Clinical Medicine I

A NOVEL CELLULAR MODEL FOR FUNCTIONAL STUDIES OF pH REGULATION AND ELECTROLITE TRANSPORT MECHANISMS IN AMELOGENESIS

Rácz, Róbert

Róbert Rácz, Erzsébet Bori, Gábor Varga Department of Oral Biology, Semmelweis University, Budapest, Hungary

Introduction

During amelogenesis, the formation of hydroxylapatite crystals liberates a large number of protons that requires buffering, presumably by secretion of bicarbonate. No functional data exist for mineral ion transport by ameloblasts. Therefore, we developed a novel cellular model to investigate these mechanisms, using the HAT-7 rat ameloblast cell line.

Aim

Our aims were to provide functional evidence for the role of several key transporters in pH regulation in HAT-7 cells and to test whether cells achieve transepithelial bicarbonate transport in our model. We investigated which signaling pathway plays a role in the regulation of this mechanism and also whether fluoride exposure can disturb this process.

Methods

To gain monolayers, HAT-7 cells were seeded on Transwell permeable filters and cultured in differentiation medium for 4 days. We monitored transepithelial resistance as an indicator of tight junction formation and polarization. We evaluated intracellular pH changes by microfluorometry using BCECF fluorescent indicator. The activity of transporters was tested by withdrawal of various ions from outer solutions, and by using specific inhibitors and modulating agents.

Results

We detected sodium/proton-exchanger, anion-exchanger and sodium/potassium/chloride-cotransporter activity at the basolateral side of HAT-7 cells. Measurements of transepithelial bicarbonate transport showed a significant increase in response to Ca2+- and cAMP-mobilizing stimuli (ATP and forskolin). We could not detect significant alteration in bicarbonate secretion upon acute fluoride exposure in this setting, although 1 mM fluoride induced substantial cell death when applied for at least 24h.

Conclusion

We could verify the activity of several key transporters affecting the pH regulation of HAT-7 ameloblast cells. HAT-7 cells are functionally polarized and are able to take up bicarbonate ions from the basolateral side and secrete them at the apical membrane. Our HAT-7 model can be a useful tool to conduct functional studies for the better understanding of amelogenesis.

Notes

Supported by:NIH-NIDCR 5R01DE013508 subaward:7743sc Doctoral School: Clinical Medicine Program: Dental research Supervisor: Gábor Varga E-mail address: racz62(kukac)gmail.com

Abstract type

oral

TOOTH-DERIVED STEM CELL CULTURING ON POLI(ASPARTIC ACID) (PASP) BASED HYDROGELS

Hegedűs, Orsolya

Orsolya Hegedűs1, Dávid Juriga2, Krisztina Nagy1, Angéla Jedlovszky-Hajdú2, Miklós Zrínyi2, Gábor Varga1 1 Department of Oralbiology, Semmelweis University, Budapest 2 Laboratory of Nanochemistry, Semmelweis University, Budapest

Introduction

Stem cells isolated from tooth-associated tissues have multi-differentiation potential and immunomodulatory effects. For in vitro 3D proliferation and differentiation of these cells, scaffolds are needed that could mimic the properties of the native ECM and provide optimal conditions for the cells. Amino acid-based hydrogels are capable of that, and they may increase the cells applicability in clinical processes.

Objective

Our aim is to analyse periodontal ligament derived stem cell culture (PDLSC) viability, morphology and differentiation potential on poly(amino acid) based hydrogels with different physico-chemical properties. The long-term goal is to find the ideal composition, which may subsequently be used in regenerative therapy.

Matrials and methods

Cells originated from impacted human wisdom teeth according to our previously published protocols. The cells were seeded on the PASP (polyaspartic acid) -based hydrogels having different mechanical properties and containing thiol groups or/and dopamine. After 1, 3, 7 and 14 days the morphology of the cells was examined by phase-contrast microscope. To visualize the cells growing into the gels, they were labelled with the fluorescent vital dye Vybrant DiD, then the examination was carried out with two-photon microscopy. For analysing cell viability, we used WST-1 reagent.

Results

Our cells are able to attach and grow on PASP-based hydrogels. The highest population of viable cells can be observed when cultivating PASP gels containing thiol groups or/and dopamine. We found that the increase of the hardness of the gel increases the adhesion and the proliferation of the cells. Phase-contrast and two-photon microscopic analysis also confirmed thiese results and showed that these cells can grow inside the gel matrix.

Conclusion

The thiol- and dopamine containing PASP gels proved to be suitable for culturing PDL stem cells, since they ensure the conditions for adhering, reproduction and migration. These gels would be a good candidate as a scaffold in stem cell-based tissue engineering.

Notes

Doctoral School: Clinical Medicine Program: Dentistry Supervisor: Gábor Varga E-mail address: orsolya.hegedus @iocs.hu

Abstract type

oral

Evaluation of exosomal microRNA biomarkers in adrenocortical tumours

Perge, Pál

Pál Perge 1, Henriett Butz 2, Raffaele Pezzani3, Zoltán Nagy 1, Krisztina Pálóczi4, Gábor Nyírő 2, Ábel Decmann 1, Edit I. Buzás4, Miklós Tóth 1, Marco Boscaro3, Attila Patócs 2,5, Péter Igaz 1 1 2nd Department of Medicine, Semmelweis University, 1088 Budapest, Szentkirályi str. 46. 2 Molecular Medicine Research Group, Hungarian Academy of Sciences and Semmelweis University, 1088 Budapest, Szentkirályi str. 46. 3 Endocrinology Unit, Department of Medicine, University of Padua, Via Ospedale, 105, 35128 Padova, Italy 4 Department of Genetics, Cell- and Immunobiology, Semmelweis University, 1089 Budapest, Nagyvárad tér 4. 5 “Lendület-2013” Research Group, Hungarian Academy of Sciences and Semmelweis University, 1088 Budapest, Szentkirályi str. 46.

Background

There is no available serum marker for the preoperative diagnosis of adrenocortical malignancy. In our previous study, we found that circulating microRNAs isolated from the whole plasm could be potential biomarkers for adrenocortical carcinoma (ACC). Recent trials proved that microRNAs secreted in membrane vesicles, exosomes could be more sensitive and specific as microRNAs isolated from whole plasm.

Objective

To study the expresssion of exosomal microRNAs and their potential diagnostic utility in patients suffering from adrenocortical tumours.

Methods

Exosomes were isolated from from 200 ul human plasm by Total Exosome Isolation (Life Technologies) protocol. We have evaluated the microRNA expression in the preoperative plasm samples of 6 adrenocortical adenomas (ACA) and 6 histologically verified adrenocortical carcinomas with Taqman Human Microarray A-cards. Significant microRNAs were validated with targeted RT-qPCR. Ultracentrifugation was also used to analyze the trustworthiness of the exosome isolation with the kit.

Results

Hsa-mir-101 and hsa-miR-483-5p were significantly overexpressed in adrenocortical carcinoma versus adrenocortical adenoma samples. On the other hand, hsa-mir-487b was significantly underexpressed in ACC relative to ACA. The reference was the geometric mean of hsa-miR-342-3p and hsa-miR-20a based on the results of the Taqman cards.

Discussion

As minimally invasive biomarkers, exosomal hsa-mir-101, hsa-mir-483-5p and hsa-mir-487b could be useful in the preoperative diagnosis of adrenocortical carcinoma. Nevertheless, increasing the number of patients is necessary to confirm their clinical applicability.

Notes

Clinical medicine, Hormonal regulations, Péter Igaz paul.perge@gmail.com

Abstract type

oral

Screening model for evaluation different surface modifications of intraosseous titanium devices by measuring the anchorage level in bony tissues

Farkasdi, Sándor

Sándor Farkasdi1, Gergely Hriczó-Koperdak1, Róbert Rácz 1, Beáta Kerémi1, David Pammer2, Bence Szabó5, Csaba Dobó-Nagy5, Frederic Cuisinier3, Wu Gang4, Gábor Varga1 1 Department of Oral Biology, Semmelweis University, Budapest 2 Department of Materials, Science and Engineering, BME, Budapest 3 Laboratoire de Biologie Santé et Nanoscience, Université de Montpellier, Montpellier 4 Department of Oral Cell Biology, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam 5 Department of Oral Diagnostics, Semmelweis University, Budapest

Introduction and aim

Development of titanium devices for reconstructive medicine is one of the most profitable healthcare and industrial specialisation. Strict guidelines are not developed for screening differences of titanium devices in preclinical and clinical levels. We aim to develop an animal model to evaluate osseointegration differences by detecting the differences of bone to implant anchorage after difference surface treatments.

Matrials and methods

Wistar rats (Crl(Wi)Br, CharlesRiver; 450g) were used (permission No:1799/003/2004). The bed preparation for implant placement were performed in standardised circumstances at caudal vertebrae vertically and sagittally. During sagittal implant placement we can work on vertebrae from C2-C5 vertebrae parallel handling 4 implants in one experimental animal. Vertical implant placement can be performed by using only one vertebra C4 or C5. Validation of the bone remodelling around the titanium implants was performed at 4, 8, 12, 16 weeks after surgery. Implant stability was measured using a non-invasive system utilising RFA. This test was followed by micro-CT evaluation. Biomechanical properties were further characterised by histomorphometric analyses and with measuring the maximum extraction force.

Results

The micro-CT, histomorphomtery, pull-out measurements were correlating with each other and were showing the dynamical increase of ossoeintegration on a timeline. On the other side RFA showed a week correlation with other measurment techniques. The bone to implant contact (BIC) values were at 4, 8, 16 weeks 27±13, 59±11, 74±12%. We observed statistically significant differences between the three evaluation periods. As well sagittally and as well vertically implant placement showed a reliable results in osseointegration processes.

Conclusion

Our results provide evidence that caudal vertebrae can provide a standard circumstances for preclinical screening of different surface modification of titanium devices.

Notes

Supported by the Hungarian-French TÉT-BalatonProgram (TÉT_12_FR-2-2014-0010). Doctoral School: Clinical Medicine Program: Dental Research Supervisor: Gabor Varga E-mail address: farkashdishandor@gmail.com

Abstract type

oral

Effect of a chlorhexidine/fluoride varnish on mutans streptococci colonisation and laser fluorescence readings in occlusal fissures of permanent molars. A split-mouth study

Lipták, Lídia

Lídia Lipták1, Nóra Bársony2, Melinda Madléna1 1. Department of Paedodontics and Orthodontics, Faculty of Dentistry, Semmelweis University, Budapest, Hungary 2. Department of Community Dentistry, Faculty of Dentistry, Semmelweis University, Budapest, Hungary

Aim

To examine the effect of chlorhexidine/fluoride varnishes on mutans streptococci (SM) counts and laser fluorescence (LF) readings in fissures of young permanent molars.

Methods

25 healthy volunteered schoolchildren (7-14 yrs.) were involved in the study after informed consent. Counts of SM of the plaque from the fissures of healthy permanent molar-pairs were determined (CRT Bacteria, Ivoclar-Vivadent, Schaan, Liechtenstein) at baseline and every 6th week throughout the 24-week study period. LF readings (DIAGNOdent pen, KaVo, Bieberach, Germany) were performed in fissures of permanent molars at baseline and after 12 and 24 weeks to detect demineralization. Permanent molars were randomly assigned to treatments with either the chlorhexidine-fluoride varnish (CHX-F, Cervitec© F) (Ivoclar-Vivadent, Schaan, Liechtenstein) or a chlorhexidine-thymol varnish (CHX-T, Cervitec© Plus) (Ivoclar-Vivadent, Schaan, Liechtenstein) as active control. The varnishes were topically applied in the fissures at baseline and every 6th week. SM and LF indices were created from adding SM and LF counts belonging to each tooth. For statistical analysis, descriptive statistics, variance analysis, T test were used.

Results

SM indices were significantly decreased in both groups during the study [Test: 4.32±1.65 (mean±S.D.) vs 1.78±0.79; Control: 4.32±1.70 vs 1.65±0.71] ($p<0.05$) without significant difference between the two groups. LF indices were decreased significantly in both groups (Test: 13.16±7.24 vs 4.33±2.75; Control: 12.88±7.19 vs 5.96±3.81) ($p<0.05$), the decreasing was significantly higher in the test group, comparing to the control group. The differences were 1.04±2.07 after 12 weeks and 1.625±1.952 after 24 weeks ($p<0.05$).

Conclusion

There was significant decrease in SM counts of plaque from the fissures of permanent molars due to the indirect effect of CHX. Both varnishes reduced the LF readings significantly after 6 months compared with baseline but F containing varnish resulted in higher remineralization.

Notes

The study was supported by Ivoclar Vivadent AG, Schaan, Liechtenstein who supplied the dental varnishes, chair-side tests and clinical disposals. Doctoral school: Clinical Medicine Program: Epidemiological studies and preventive procedures for maintaining oral health Supervisor: Melinda Madléna E-mail: liptakl01@gmail.com

Abstract type

oral

Predicting of short and medium-term efficacy of biosimilar infliximab therapy. Do trough levels/ADAs or clinical/biochemical markers play a more important role?

Vegh, Zsuzsanna

1 Zsuzsanna Vegh, 1Zsuzsanna Kurti 1 First Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Introduction

Biosimilar infliximab CT-P13 received EMA approval in June 2013 for all indications of the originator product and its use is mandatory in all anti-TNF naïve IBD patients in Hungary since May 2014. In the present study we aimed to prospectively evaluate the predictors of short and medium term clinical outcome in patients treated with the biosimilar infliximab in two IBD centers in Hungary.

Methods

Demographic data were collected and a harmonized monitoring strategy was applied. Clinical and biochemical activity were evaluated at weeks 14, 30 and 54. Therapeutic drug monitoring (TDM) was regularly used. Trough level (TL) and anti-drug antibody (ADA) concentration were measured by ELISA (LT-005, Theradiag, France) at baseline at 14, 30 and 54 weeks and in the above 2 centers at weeks 2 and 6 right before anti-TNF administration during the induction treatment.

Results

291 consecutive IBD patients (184 CD patients and 107 UC patients) were included in the present cohort. 24.5/14% and 62/52% of CD and UC patients received previous anti-TNF and concomitant immunosuppressives at baseline therapy. Mean TLs were 20.1, 14.7 and 5.1 μg/ml at weeks 2, 6 and 14 (n=124, 86 and 158). Cumulative ADA positivity rates were 8.7%, 19.3%, and 28.0% in IBD patients at weeks 0, 14, and 30 (ntotal= 229, 192 and 143). Early TLs at week 2 were predicting short term- (week 14 response/remission, AUCTLweek2=0.715/0.721, p=0.05/0.005,) but not medium-term (week 30 or 54) clinical efficacy. TLs measured at week 6/14 were not predicting either short or medium-term clinical outcome. In addition, early ADA status by week 14 (p=0.04-0.05, OR: 2.1-2.6 for week 14 and 30), early clinical response (p<0.001, OR: 7.7-42.8 for week 30/54) and normal CRP at week 14 (p=0.005-0.0001, OR: 3.2-7.8 for week 14 and 30) and previous anti-TNF exposure (p=0.03-0.0001, OR: 2.22-6.25, for week 14, 30 and 54) were associated with short and medium-term clinical outcomes (response and remission).

Conclusion

Early TLs were only associated with short-term clinical outcomes, while ADA development by week 14, early clinical response and normal CRP at week 14 and previous anti-TNF exposure were predicting medium-term clinical outcomes.

Notes

Clinical Medicine Doctoral School Program: Molecular Genetics, Pathomechanism and Clinical Aspects of Metabolic Disorders Supervisor: Peter L Lakatos MD PhD DsC veghzsuzsi@gmail.com

Abstract type

oral

Predictors of loss of response to adalimumab therapy; the importance of therapeutic drug monitoring in inflammatory bowel diseases

Kurti, Zsuzsanna

Zsuzsanna Kurti1, Zsuzsanna Vegh1 1 First Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Background and objectives

Therapeutic drug monitoring (TDM) measuring drug trough levels (TL) and antidrug antibodies (ADA) may aid the therapeutic decision in patients with inflammatory bowel disease (IBD) who loose response to anti-TNF therapy. Our aim was to evaluate the frequency and predictive factors of loss of response to adalimumab therapy and the role of the therapeutic drug monitoring to predict the loss of response in adalimumab treated IBD patients.

Methods

74 IBD patients (with 94 TDM measurements, CD/UC 59/15, male/female 32/42, mean age CD/UC: 38/31 years, mean duration of adalimumab therapy CD/UC: 147.6/43.7 weeks) were enrolled in this consecutive cohort from two referral IBD centres in Hungary. Demographic data were comprehensively collected and a harmonized monitoring strategy was applied. Previous and current therapy, laboratory data and clinical activity at the time of the TL and ADA measurement were recorded. Patients were evaluated either at the time of suspected LOR or during follow-up. TDM measurements were done by commercial ELISA (LISA TRACKER, Theradiag, France).

Results

Among 74 IBD patients, the probability of ADA positivity and low TL (<4.5 μg/mL) was 8.1% and 13.8% in the first year and 11.4% and 28.8% and in the second year after start of adalimumab therapy in Kaplan-Meier analysis. The frequency of previous and current steroid and azathioprine exposure were 95.9%/29.7% and 73.3%/53.3% and previous anti-TNF therapy was present in 74% (in CD 69%, in UC 93.3%) in the IBD cohort. Dose intensification was needed in 38.7% during the study period. The combination of normal TL and no ADA, normal TL and high ADA, low TL and no ADA and low TL and high ADA were observed in 63.5%, 6.8%, 23% and 6.8% at TDM measurement. Predictors of the dose intensification were female gender (p=0.06, HR: 2.1), concomitant steroid therapy (p=0.01, HR: 2.57) and ADA positivity (p=0.005, HR: 3.26) with Cox-regression model (p<0.05). Predictors of loss of response were female gender (p=0.004, HR: 4.9), dose intensification (p=0.009, HR: 3.75) and there was a positive trend for concomitant steroid therapy (p=0.06, HR: 2.71) and previous anti-TNF therapy (p=0.15, HR: 2.39). Predictors remained unchanged if the 94 TDM episodes were analysed separately.

Conclusion

Our results suggest that ADA development, low TL and need for dose intensification are frequent during adalimumab therapy and support the use of routine TDM assessment in IBD patients. Female gender, concomitant steroid therapy and ADA positivity were predictors of dose intensification and female gender and dose intensification predicted loss of response.

Notes

Clinical Medicine Doctoral School Program: Molecular Genetics, Pathomechanism and Clinical Aspects of Metabolic Disorders Supervisor: Peter L Lakatos MD PhD DsC zsuzsa.kurti@gmail.com

Abstract type

oral

Involvement of PARK7 in the pathomechanism of inflammatory bowel diseases

Lippai, Rita

Rita Lippai1, Erna Sziksz1,2, Domonkos Pap1,2, Réka Rokonay1, Apor Veres-Székely1,2, Gábor Veres1, Tivadar Tulassay1,2, Attila J.Szabó1,2, Ádám Vannay1,2 1 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary 2 MTA-SE, Pediatrics and Nephrology Research Group, Budapest, Hungary

Introduction

The therapy of inflammatory bowel diseases (IBD), beginning frequently in childhood, is still unresolved, however recent studies suggested interleukin (IL)-17 as a potential therapeutic target.

Parkinson's disease 7 (PARK7) is an antioxidant, antiapoptotic, immunoregulatory molecule, but its relation to IL-17 and role in the gastrointestinal tract is completely unknown. Thus we aimed to investigate its involvement in the pathogenesis of IBD.

Matrials and methods

The mRNA expression, protein level and localization of PARK7 were determined in colon biopsies of children with IBD, in colon of wild type and IL-17 KO mice with dextran sodium sulphate (DSS)-induced colitis and in IL-17-treated HT-29 colonic epithelial cells by real-time PCR, western blot, flow cytometry and immunofluorescence staining, respectively.

Results

The mRNA expression, protein level and localization of PARK7 were determined in colon biopsies of children with IBD, in colon of wild type and IL-17 KO mice with dextran sodium sulphate (DSS)-induced colitis and in IL-17-treated HT-29 colonic epithelial cells by real-time PCR, western blot, flow cytometry and immunofluorescence staining, respectively.

Conclusion

The mRNA expression, protein level and localization of PARK7 were determined in colon biopsies of children with IBD, in colon of wild type and IL-17 KO mice with dextran sodium sulphate (DSS)-induced colitis and in IL-17-treated HT-29 colonic epithelial cells by real-time PCR, western blot, flow cytometry and immunofluorescence staining, respectively.

Notes

Support: OTKA PD105361, -K116928, -K108688, LP2011-008/2016 Doctoral School: Clinical Medicine (2) Programe: Prevention of chronic diseases of childhood (03) The name of supervisor: Erna Sziksz E-mail address of the presenter: lippaimolnarka@gmail.com

Abstract type

oral

Involvement of the cytokines of IL-20 subfamily in the pathogenesis of coeliac disease

Rokonay, Réka

Réka Rokonay1, Erna Sziksz1,2, Domonkos Pap1,2, Apor Veres-Székely1,2, Rita Lippai1, Gábor Veres1, Tivadar Tulassay1,2, Attila J.Szabó1,2, Ádám Vannay1,2 1 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary 2 MTA-SE, Pediatrics and Nephrology Research Group, Budapest, Hungary

Introduction

Immunoregulatory role of the cytokines of interleukin (IL)-20 subfamily, IL-19, IL-20 and IL-24 was suggested, however their role in the pathogenesis of coeliac disease (CD) is completely unknown.

Matrials and methods

Expression of IL-19, -20, -24 and their common IL-20R2 receptor was investigated by real-time PCR in the duodenal biopsy samples of children with CD and controls. Localization of IL-24 and IL-20R2 was determined by immunofluorescence staining. Effect of different factors including IL-1β, IL-17, tumor growth factor (TGF)β, tumor necrosis factor (TNF)α and lipopolysaccharide (LPS) was investigated on the mRNA expression of IL-19, -20, -24 and -20R2 of duodenal epithelial and fibroblast cells. Effect of IL-24 on the mRNA expression of vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)2 and mucin (MUC)1 of the epithelial and fibroblast cells was measured by real-time PCR.

Results

We found elevated IL-24 expression in the duodenal mucosa of children with CD compared to controls. IL-1β increased the mRNA expression of IL-19, -20, -24 and -20R2 and also the IL-24 protein secretion in both epithelial and fibroblast cells. IL-24 induced VEGF, MMP2 and MUC1 mRNA expression in duodenal fibroblast cells and MUC1 mRNA expression in epithelial cells.

Conclusion

Increased presence of the members of the IL-20 subfamily in the duodenal mucosa of children with CD suggest their role in disease pathogenesis. Based on our in vitro results we suggest that IL-20 subfamily of cytokines have a potential role in the maintenance of mucosal integrity.

Notes

Support: OTKA PD105361, -K116928, -K108688, LP2011-008/2016 Doctoral School: Clinical Medicine (2) Programe: Prevention of chronic diseases of childhood (03) The name of supervisor: Ádám Vannay E-mail address of the presenter: rokonayreka@gmail.com

Abstract type

oral

Functional and cell surface molecular characteristics of PDLSC – Characterization of novel synthetic polypeptide conjugates as potential dental therapeutic materials

Khorolsuren, Zambaga

Zambaga Khorolsuren1, 2, Zsófia Kőhidai1, Orsolya Láng1, Éva Pállinger1, János Vág2, LászlóKőhidai1 1 Department of Genetics-, Cell- and Immunobiology, Semmelweis University, Budapest 2 Department of Conservative Dentistry, Semmelweis University, Budapest

Introduction

Cell–extracellular matrix (ECM) interactions are significant for survival of adherent cells;impairedcell attachment may result pathological condition or dental diseases. Adequate selection of dentalmaterials supports the physiological cell-ECM interaction based wound healing and prevents the nucleation process in and around the dental matrix. Adhesion to ECM is performed predominantly by integrins(fibronectin binds viaRGD loops). Multipotent periodontal ligament stem cells (PDLSCs) arepotential targets of dental interventions (periodontitis, tissue engineering).Synthetic biomimetic conjugates composed by substrate-coating molecules (e.g. polylysine)with adhesive peptide motifs are prospective candidates. In our work ’cycloRGD’ motive expressing peptides are investigated.

Objective

(i) To analyze adhesive and proliferative ability of 3 synthetic polypeptides with ’RGD’ motives on PDLSCs; (ii) To identify cell surface molecular characteristics of PDLSCs.

Matrials and methods

Our conjugates are composed by polylysine backbone (SAK, AK) and adhesive peptide side chain cRGDfC or AcCGRGDCSVVYGLR.PDLSCs isolated from human extracted third molars were applied and compared withepithel (HGEP) and fibroblast (MRC5) cells.Techniques applied:(i) Real time impedance assays (xCELLigence)monitored PDLSCs adhesion and proliferation on surface coated with synthetic and reference peptides. (ii) The characteristic CD markers (e.g. CD29, CD49b,CD146, CD90,) are detected by flow cytometry (FACSCalibur).

Results

(i)SAK-c[RGDfC] coated surface increasedadhesion of FBS free cultured PDLSCs after 4 hrs. Comparative adhesion inducer effects of synthetic polypeptides were also more effective in FBS freeconditions.(ii) In PDLSCs, CD49b is expressed in low level while CD29 in higher level; CD90 and CD146 expressions were high comparing to referent cells.

Conclusion

Characterization of novel peptides constructs proved to beapplicable as biocompatible dental materials as well as carriers of drugs.Characterization of PDLSC surface CD markers showdifferences to MRC-5 and HGEp cells.

Notes

Doctoral School: Clinical Medicine Program: Dental Research Supervisors: Kőhidai László, Vág János E-mail: zagi1982@gmail.com

Abstract type

oral

Basic Sciences, Cardiology and Pharmaceutical Sciences

REGULATION BY INTRINSIC MECHANISMS OF VASOMOTOR TONE OF SMALL SKELETAL MUSCLE VEINS

Szénási, Annamária

Annamária Szénási1, Gabriella Dörnyei2, Anita Rácz1, Béla Debreczeni3, ÁkosKoller1,4 1 Department of Pathophysiology, Semmelweis University, Budapest, Hungary 2 Department of Morphology and Physiology, Semmelweis University, Budapest, Hungary 3 Department of PlasticSurgery, Military Hospital, Budapest, Hungary 4 Institute of NaturalSciences, University of Physical Education, Budapest, Hungary

Notes

In many developed countries the prevalence of venous disorders and its consequences are higher than that of arterial diseases. Thus it is very important to understand the exact physiological and pathophysiological function of small veins and their control mechanisms. Small veins and venules have an important role in the regulation of capillary fluid exchange, as well as return of the venous blood into the heart. However, there only limited knowledge available regarding the role of local mechanisms controlling the vasomotor tone and diameter of small veins. In the last decade we had focused on the elucidation of these mechanismsin isolated skeletal muscle venules of rat. Our results suggest that the tone of small veins is controlled by the integration of several mechanisms, activated by the intraluminal pressure and flow/wall shear stress, in addition to numerous local mediators synthesized and released from the smooth muscle and endothelium. These mechanisms areinvolved - in a complex manner - in the control of postcapillary resistance, thus regulation of tissue blood supply, venous return and consequently in the modulation of the cardiac output, as well. Doctoral School: Basic Medicine Program: Physiology and Pathophysiology of the Regulation of Fluids and Electrolyte Homeostasis Supervisor: ÁkosKoller E-mail:szenasi.annamaria@med.semmelweis-univ.hu

Abstract type

oral

HERITABILITY OF THE FEMORAL INTIMA MEDIA THICKNESS

Fejér, Bence

Bence Fejér MD1, Ádám Domonkos Tárnoki MD, PhD1,2, Dávid László Tárnoki MD, PhD1,2, Pierleone Lucatelli, MD3, Levente Littvay, PhD4, Pál Maurovich-Horvát, MD, PhD, MPH5, Ádám Jermendy, MD5, Attila Kovács, MD, PhD5, Erika Gódor, MD1, Corrado Fagnani, MS6, Maria Antonietta Stazi, MS, PhD, DSc6, Andrea Ágnes Molnár, MD, PhD5,7,8, Fabrizio Fanelli, MD, PhD3, DSc, Carlo Cirelli, MD3, Filippo Farina, MD9, Claudio Baracchini, MD, PhD9, Giorgio Meneghetti, MD, PhD, DSc9, Giacomo Pucci, MD10, György Jermendy, MD, PhD, DSc11, Béla Merkely, MD, PhD, DSc5, Giuseppe Schillaci, MD, PhD, DSc10, Emanuela Medda MS6 Department of Radiology and Oncotherapy, Semmelweis University, Budapest, Hungary Hungarian Twin Registry, Budapest, Hungary Vascular and Interventional Radiology Unit, Department of Radiological, Oncological and Anatomo-Pathological Sciences, Sapienza University of Rome, Rome, Italy Central European University, Budapest, Hungary MTA-SE „Lendület" Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest, Hungary Genetic Epidemiology Unit, National Centre of Epidemiology, Surveillance and Health Promotion; Istituto Superiore di Sanità, Rome, Italy Research Group for Inflammation Biology and Immunogenomics of Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary Department of Cardiology, Military Hospital, Budapest, Hungary Department of Neurosciences, University of Padua School of Medicine, Padua, Italy Università di Perugia, Unità di Medicina Interna, Ospedale "S. Maria", Terni, Italy 3rd Department of Internal Medicine, Bajcsy Zsilinszky Hospital, Budapest, Hungary

Introduction

The different manifestations of peripheral atherosclerosis, such as increased femoral intima-media thickness (fIMT), has long been underestimated and underdiagnosed in the clinical practice. fIMT is a surrogate marker of coronary and other cardiovascular events and has a prognostic impact for prediction.

Aim

We assessed the heritability of fIMT of common and superficial femoral arteries (CFA, SFA) to determine the genetic, common and unique environmental effects.

Methods

388 Hungarian and Italian twins (121 monozygotic, 73 dizygotic pairs) underwent B-mode sonography of bilateral femoral arteries. IMT was measured by a semiautomated software or by calipers.

Results

Within pair correlation in monozygotic twins was higher than in dizygotics for each parameter. Age-, sex- and country-adjusted genetic effect accounted for 43.9% (95% confidence interval, CI 21.3%-65.2%) and 47.2% (95% CI, 31.4%-62.6%) of the variance of CFA and SFA IMT, and unshared environmental effect for 56.1% (95% CI 34.6%-78.5%), and 52.8% (95% CI, 37.2%-68.5%), respectively. No shared environmental effect was found. These results did not change significantly after correcting for body mass index or central systolic blood pressure.

Conclusion

To our knowledge, this is the first study which demonstrates the substantial role of the genetic factors in the determination of common and superficial fIMT; however, the influence of environmental (lifestyle) factors remains still relevant. These findings may highlight the importance of considering fIMT values in the atherosclerotic screening guidelines due to its genetic determination if further studies confirm our findings.

Notes

Doctoral School: Basic Medicine Supervisor: Dr. Ádám D. Tárnoki PhD. E-mail address: bence.fejer@gmail.com

Abstract type

oral

Risk Factors for the Recurrence of Atrial Fibrillation

Korodi, Szilamér

Korodi Szilamér, Rápolti Emese, Alina Velicu, Kovács István, Benedek Theodora, Benedek Imre
Emergency Clinical County Hospital of Targu Mures, Romania

Introduction

Atrial fibrillation is the most common sustained arrhythmia, with an increasing prevalence. There are a series of risk factors that lead to the development and recurrence of atrial fibrillation. Identification of these risk factors is necessary in order to implement effective prevention strategies.

Matrials and methods

We conducted a bidirectional observational study with 2 year follow-up in patients admitted to the Cardiology Clinic of Targu Mures County Hospital, who presented with at least one ECG confirmation of the arrhythmia. A series of risk factors for the recurrence of atrial fibrillation were evaluated: hypertension, age>75 years, stroke, COPD, heart failure, diabetes mellitus, coronary artery disease, chronic renal disease. Ecocardiographic rutine parameters were also evaluated, such as Left Atrial (LA) size, Left Ventricular (LV) size and Left Ventricular Ejection Fraction (LVEF).

Results

The study population included 216 patients (107 men, 109 women), with the mean age of 66 ± 11 years. Almost all the evaluated risk factors were not associated with the recurrence of atrial

fibrillation, except for heart failure, which was highly correlated with the recurrence of the arrhythmia (p=0.003). Regarding the ecocardiographic parameters, the increased size of the LA was the most important risk factor for the recurrence of atrial fibrillation (p=0.0001). The increased LV (p=0,029) and a low LVEF (p=0,021) were also correlated with the recurrence.

Conclusion

Heart failure was the only risk factor that was highly associated with the recurrence of atrial fibrillation. The increased LA, LV size and the altered function of the LV (low EF) were associated with a higher risk for the recurrence of atrial fibrillation.

Abstract type

oral

CORRELATIONS BETWEEN CONTRAST DENSITY GRADIENT IN CORONARY COMPUTER TOMOGRAPHY ANGIOGRAPHY AND FUNCTIONAL SIGNIFICANCE OF CORONARY ARTERY STENOSIS

Stanescu, Alexandra

Authors: Marius Orzan, Alexandra Stanescu, Diana Opincariu, Benedek Edvin, Benedek Theodora, Benedek Imre Emergency County Hospital Targu Mures

Background

Evaluating the hemodynamic significance of a coronary artery stenosis is a challenging topic, extremely important for evaluation of indication of revascularization in atherosclerotic coronary artery stenosis. The aim of this study was to evaluate the role of a new marker reflecting the functional significance of coronary artery stenosis, represented by the attenuation degree of contrast density along the stenosis by Coronary Computed Tomography (CCT).

Matrials and methods

We retrospectively assessed 30 patients with angina pectoris and coronary artery stenosis who underwent 64-slice Coronary Computed Tomography Angiography. The patients were divided into 2 groups according to the degree of the stenosis: group 1: with ≥70% coronary stenosis, group 2: with <70% coronary stenosis. We measured the intraluminal contrast density (Hounsfield units [HU]) at two levels, proximal and distal to the stenosis, and calculated the attenuation gradient.

Results

There were no statistically significant differences between the 2 groups regarding the baseline patient characteristics (age, presence of hypertension, diabetes).The average contrast density was 77,96 HU proximal and 67,6 HU distal to the stenosis. The average transluminal gradient was 10,36 HU. The mean length of the coronary lesions was 16,93 mm. Patients from group 1, that presented significant stenosis, expressed as more 70% luminal narrowing, had a significantly higher transluminal gradient, compared to those from group 2, with less than 70% luminal stenosis (6.16 +/-3.7 HU, 95% CI, 4.3-8.0 vs 16.6 +/- 8.4, 95% CI, 11.3 – 21.9). The degree of luminal narrowing was significantly correlated with the contrast attenuation gradient (r=0.71, p<0.001).

Conclusion

The assessment of intraluminal contrast density by Coronary Computed Tomography Angiography may represent a new noninvasive method to obtain relevant information about the clinical significance of a coronary stenosis.

Notes

Larger studies are requested to emphasize the benefits brought by CCTA in evaluating coronary lesions. Clinical Medicine Cardiovascular Disorders: Physiology and Medicine of Ischaemic Circulatory Diseases Benedek Imre sandy_yo15@yahoo.com

Abstract type

oral

Comparison of dobutamine stress echocardiography and fractional flow reserve in moderate coronary artery disease

Abdelkrim, Ahres

Abdelkrim Ahres, Balazs Jablonkai, Peter Andrassy Bajcsy-Zsilinszky Hospital, Department of Cardiology, Budapest

Background

Fractional flow reserve (FFR) and dobutamine stress echocardiography (DSE) are widely accepted methods to evaluate myocardial ischaemia. Limited amount of data are available about the prognostic value of these tests in case of moderately severe coronary artery disease (CAD).

Purpose

Our study was designed to examine the correlation between FFR and DSE and to compare their prognostic values on moderate CAD in terms of target vessel revascularisation (TVR), acute coronary syndrome and cardiac death as primary endpoints.

Methods

Patients were included with 30-70% CAD. FFR and DSE was regarded as positive if FFR≤0,8 and new wall motion abnormality was detected in ≥2 segments of the coronary supplying area (CSA). In comparison FFR was used as standard method. Revascularisation was indicated if both tests were positive (PCI group). In case of matching negative tests and any kind of mismatch we choose optimal medical treatment (OMT group). The planned follow-up time is 2 years.

Results

Ninety-seven CSAs (64 LAD, 13 LCx and 20 RCA) were investigated in 80 enrolled patients. Thirty-three FFR and 13 DSE were positive. Match was found in 69,07 %, mismatching in 30,93 %. Eight patients were in the PCI and 72 in the OMT group. However, there is no significant difference between FFR and DSE test results (p=0,024), just a low degree of correlation was found between them (Kappa=0,193). The positive and negative predictive value of DSE was 61,53 % and 70,23 %, respectively. Until now (average follow-up time is 8,85 months) 3 patients reached the primary endpoint (TVR) in the OMT group (4,1 %, all of them were FFR negative/DSE positive) and none of them in the PCI group.

Conclusion

In our study, there wasn't significant difference between the FFR and DSE test results. The clinical significance will be determined by the end of the follow-up.

Notes

Doctoral School of Basic Medicine, Semmelweis University Program: Physiology and clinics of the heart and coronary diseases Supervisor: Péter Andrássy E-mail address: ahresabdelkrim@gmail.com

Abstract type

oral

Design of haptenes for vaccines against drugs of abuse

Köteles, István

István Köteles, PharmD School of Ph.D Studies, Semmelweis University, Budapest

Background

Drugs of abuse are small molecules that typically do not induce an antibody response following injection or inhalation. To induce antibodies against small molecules, structural surrogates of the molecules, which were named "haptens", must be coupled to immunogenic proteins, called "carriers". These structural surrogates are typically drug-linker adducts, in which the linker has a terminal functional group that forms a covalent bond with the carrier. The efficacy of these conjugate vaccines

depends on several factors including hapten design, coupling strategy, hapten density, carrier protein selection, and vaccine adjuvant.

Results

Drugs of abuse are small molecules that typically do not induce an antibody response following injection or inhalation. To induce antibodies against small molecules, structural surrogates of the molecules, which were named “haptens”, must be coupled to immunogenic proteins, called “carriers”. These structural surrogates are typically drug-linker adducts, in which the linker has a terminal functional group that forms a covalent bond with the carrier. The efficacy of these conjugate vaccines depends on several factors including hapten design, coupling strategy, hapten density, carrier protein selection, and vaccine adjuvant.

Notes

Doctoral School: Pharmaceutical Sciences Supervisor: Sándor Hosztafi E-mail: koteles.istvan@pharma.semmelweis-univ.hu

CHRONIC AND BINGE ETHANOL CONSUMPTION CAUSES CARDIAC DYSFUNCTION, OXIDATIVE/NITRATIVE STRESS, MITOCHONDRIAL DYSFUNCTION AND MYOCARDIAL STEATOSIS

Mátyás, Csaba

Csaba Mátyás1,2, Zoltán V Varga2, Partha Mukhopadhyay2, János Pálóczi2, Tamás Lajtos2, Katalin Erdélyi2, Tamás Radovits1, Pál Pacher2 1 Heart and Vascular Center, Semmelweis University, Budapest 2 Laboratory of Cardiovascular Physiology and Tissue Injury, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

Background

Alcoholic cardiomyopathy develops in response to chronic alcohol consumption. Alcoholic cardiomyopathy is characterized by increased oxidative/nitrative stress, mitochondrial dysfunction and myocardial remodeling.

Purpose

We studied the effect of chronic and binge ethanol (EtOH) feeding on cardiac function, mitochondrial function, myocardial oxidative stress and remodeling in the modified NIAAA mouse model.

Methods

Mice were fed with 5% EtOH for 10, 20, 40 days (d) combined with single/multiple EtOH binges (5g/kgBW). Isocalorically pair-fed mice served as controls. Left ventricular (LV) function and morphology was examined by invasive hemodynamic measurements and by echocardiography. Mitochondrial complex (I, II, IV) activities, 3-nitrotyrosine (3NT), 4-hydroxy-2-nonenal (4HNE) levels, gene expression of oxidative stress markers (gp91phox, p47phox), mitochondrial biogenesis (PGC1α, PPARα), hypertrophy, fibrosis were assessed. Cardiac steatosis, hypertrophy, fibrosis and apoptosis were investigated by histological/immunohistochemical methods.

Results

Chronic and binge EtOH feeding (already in 10d plus single binge) was characterized by systolic dysfunction (decreased slope of endsystolic pressurevolume relationship, decreased preload recruitable stroke work), by impaired relaxation (decreased time constant of LV pressure decay and dP/dtmin) and by worsened vascular function (impaired arterial elastance, lower total peripheral resistance). Oxidative stress markers 3NT, 4HNE, gp91phox, p47phox were significantly increased in alcoholism combined with single/multiple EtOH binges. We observed significant deterioration of mitochondrial complex I, II, IV activities and mitochondrial biogenesis, myocardium hypertrophy (increased cardiomyocyte area) and excessive cardiac steatosis in our model. There was no difference in apoptosis and fibrotic remodeling among the groups.

Conclusion

Chronic plus binge EtOH feeding induces heart failure and increased oxidative stress coupled with mitochondrial dysfunction and cardiac steatosis.

Notes

Doctoral School: Basic Medicine Program: Cardiovascular Disorders Supervisors: Tamás Radovits
E-mail address: csaba.matyas@gmail.com

Abstract type

oral

Targeting intarcellular Mycobacterium tuberculosis bacteria with newly synthesized liposomal antituberculotic compounds

Kósa, Nikolett

N. Kósa1, B. Bőcskei-Antal 1, K. Horvát 2, Sz. Bősze 2, L. Herényi 1, I. Voszka 1 1: Semmelweis University Department of Biophysics and Radiation Biology 2: MTA− ELTE Research Group of Peptide Chemistry

Introduction

Liposomes are widely investigated nanocarriers, which are capable for incorporation of both lipid-soluble and water-soluble drugs. WHO aimed to eradicate TB disease, which is caused by Mycobacterium tuberculosis bacteria. The main reasons for death are increasing frequency of MDR (multidrug-resistant) and XDR (extensively drug-resistant) bacteria stems and inappropriate patient compliance.

Aim

Preparation and encapsulation of newly synthesized antituberculotic compound into liposomes to enhance the encapsulation efficiency and to target intracellular bacteria in the macrophages.

Methods

We have prepared two types of liposomes. Type I. consists of dipalmitoyl phosphatidylcholine (DPPC). Type II. consists of: dioleoylphosphatidylethanolamine (DOPE), cholesteryl hemisuccinate (CHEMS) and pegylated distearoyl phosphatidylethanolamine (DSPE-PEG). We used thin lipid film technology to prepare multilamellar vesicles (MLV) and henceforward both types were treated with extrusion technique to get small unilamellar vesicles (SUV). The size distribution of liposomes was determined/measured with dynamic light scattering (DLS). The change of diameter of vesicles shows the rate of aggregation. The used antituberculotic compounds were: TB 501, TB 504, TB 505 and TB 515 (chemical structure not published yet). Encapsulation efficiency was determined by measuring absorbance after size exclusion chromatography (SEC). Cellular uptake of liposomal compounds and non-encapsulated drugs was measured by flow cytometry on MonoMac6 human monocytic cell line. Intracellular fluorescence intensity and forward-scattered light (FSC) of MonoMac6 cells was monitored (488 nm (Coherent Sapphire, 22 mW) laser, which is proportional to the cellular uptake.

Results

The extrusion method resulted rather uniform and stable vesicles. Encapsulation efficiency was influenced by the physico-chemical properties of antituberculotic compounds. The in vitro activity of liposomal antituberculotic compounds was determined on M. tuberculosis H37Rv culture. Considering that M. tuberculosis is an intracellular pathogen the effect of the compounds was studied on M. tuberculosis H37Rv infected MonoMac6 human monocytes.

Notes

This work was supported by Hungarian Research Fund 104275. Doctoral School of Pharmaceutical Sciences Program: 3/1. Modern Trends in Pharmaceutical Scientific Research Supervisor: Levente Herényi email: kosa.nikolett@med.semmelweis-univ.hu

Abstract type

oral

Synhtesis and pharmacological study of 6β-pyridincarboxylic-morphinane amides

Urai, Ákos

Ákos Urai, Péter Horváth, Sándor Hosztafi, Béla Noszál Department of Pharmaceutical Chemistry, Semmelweis University, Budapest

Notes

Treatment of chronic pain is still an important area of pharmaceutical research. Researchers are trying to develop more potent analgesics with fewer side effects. We have previously reported the synthesis of a series of novel 6□-cinnamoyl-morphinamines carrying various cinnamoyl side chains. In vitro and in vivo characterization of the synthesized compounds revealed high affinity for MOR-1 receptors. Analgesic activity of 6□-cinnamoylmorphinamine was found to be comparable to morphine, but without causing respiratory depression, a major side-effect of commonly used opioids. In our research project 6β-amino derivatives of morphine were synthesized with Mitsunobu reaction then acylated with nicotinoyl chloride or isonicotinoyl chloride. We synthesized more than 10 new substances, in vitro and in vivo testes were carried out in the Memorial Sloan-Kettering Cancer Center. For structure determination mass spectroscopy, nuclear magnetic resonance spectroscopy and combination of circular dichroism spectroscopy and quantum chemical computations were utilized. Reference: 1. Design, synthesis, and biological evaluation of 17-cyclopropylmethyl-3,14b-dihydroxy-4,5a-epoxy-6b-[(4'-pyridyl)carboxamido]morphinan derivatives as peripheral selective m opioid receptor agents. Yuan, Y., Elbegdorj, O., Chen, J., Akubathini, S.K., Zhang, F., Stevens, D.L., Beletskaya, I.O., Scoggins, K.L., Zhang, Z., Gerk, P.M., Selley, D.E., Akbarali, H.I., Dewey, W.L. and Zhang, Y.: J. Med. Chem. 55 10118-10129 (2012) 1. Novel 6β-acylaminomorphinans with analgesic activity, Váradi A, Hosztafi S., Le Rouzic, Tóthh G, Urai Á, Noszál B, Pasternak GW, Grinnell SG, Majumdar S., Eur. J. Med. Chem. 2013, 69, 786-9 PhD. School: Semmelweis Egyetem Doktori Iskola, Gyógyszertudományok Program: A gyógyszerészeti tudományok korszerű kutatási irányai Adviser: Dr. Sándor Hosztafi E-mail: urai.akos@pharma.semmelweis-univ.hu

Abstract type

oral

Imaging of spatial and temporal lymphatic growth with single-cell resolution by tissue decolorization

Styevkóné Dinnyés, Andrea

Andrea Styevkóné Dinnyés1,2 and Zoltán Jakus1,2 1 Department of Physiology, Semmelweis University, Budapest, Hungary 2 MTA-SE "Lendulet" Lymphatic Physiology Research Group of the Hungarian Academy of Sciences and the Semmelweis University, Budapest, Hungary

Notes

Novel and unexpected roles of altered lymphatic fuction have recently been implicated in the pathogenesis of hypertension, atherosclerosis, myocardial infarction, obesity and metabolic diseases, but the molecular mechanisms regulating lymphatic growth remain not fully understood due to the great limitations of the available experimental systems. In our studies we aimed to develop an effective approach to monitor spatial and temporal lymphatic growth. In different experimental systems, lymphatic growth was shown by fluorescent, confocal and two-photon microscopy. First, paraffin-based histology was performed followed by immunohistochemistry. In the second set of the experiments, whole-mount immunostaining or lymphatic reporter strains were utilized to visualize the lymphatic vessels. Third, a recently described tissue decolorization approach was optimized, in which embryonic and adult tissues was made transparent using the aminoalcohol containing CUBIC cocktails followed by the immunostaining of the lymphatic vessels. Paraffin based histology combined with immunohistochemistry appeared to be efficient to visualize the lymphatic vessels, but it was greatly limited by the imaging plane in the two-dimensional approach. The whole-mount and lymphatic reporter systems made possible the rapid visualization of the lymphatics, but only on the surface due to the lack of organ transparency. The tissue decolorization approach allowed us to make both developing embryonic and adult organs completely transparent. Although tissue decolorization resulted in undetectable fluorescent reporter signals, immunostaining appeared to be efficient to show the lymphatic vessels with single cell resolution in transparent organs. Collectively, we demonstrated that whole body tissue decolorization allows us to visualize the lymphatic vessels with single cell resolution in developing organs and adult tissues. Imaging lymphatic vessels in decolorized tissues provides new perspectives for the studies focusing on spatial and temporal

lymphatic growth, which are essential for the development of novel therapeutic approaches modulating lymphatic growth and function. Semmelweis University School of PH.D studies Name of the Doctoral School: Doctoral School of Molecular Medicine Title of the program: Cellular and Molecular Physiology Supervisor: Zoltán Jakus E-mail address of the presenter: dinnyes.andrea@med.semmelweis-univ.hu

Abstract type

oral

Vectorial drug transport mediated by GFP-tagged ABCG2 in polarized epithelial cells

Bartos, Zsuzsa

Zsuzsa Bartos, Anita Schamberger, Tamás Orbán, László Homolya Institute of Enzymology, Research Center for Natural Sciences, Hungarian Academy of Science

Notes

ABCG2 is an integral membrane protein belonging to the ATP-Binding Cassette transporter superfamily, which is expressed in stem cells and in polarized cells of several physiological interfaces. Using the energy of ATP binding and hydrolysis, ABCG2 mediate the transport of numerous molecules across the plasma membrane of these cells, providing protection against endo- and xenobiotics. However, when expressed in cancer cells, ABCG2 may confer multidrug resistance in tumors. Identification of substrate molecules of ABCG2 is therefore essential for drug development and ADME/Tox screenings. Previously, a GFP-tagged variant of ABCG2 protein has been generated. Although tagging with fluorescent protein is a powerful tool for live cell studies, it may interfere with expression, localization, and function of the labelled protein. In the present work, we used an MDCK II (Madin-Darby canine kidney) cell line stably expressing GFP-tagged ABCG2. The cells were grown in Transwell inserts to obtain fully polarized cultures. The proper localization of the GFP-tagged ABCG2 to the apical cell membrane was examined by confocal microscopy. Topotecan is a known ABCG substrate with intrinsic fluorescence. This drug was used in a vectorial transport assay to study the function of the tagged ABCG2 variant. Both the apical (A) to basolateral (BL) and basolateral to the apical fluxes of Topotecan were measured in polarized MDCK II cells expressing GFP-tagged ABCG2. The calculated transport rates and efflux ratio demonstrated unidirectional (BL to A) movement of the drug through the polarized epithelial layer. These results demonstrate not only the proper functionality of the GFP-tagged ABCG2, but also provide an efficient assay system suitable for combined cell biological and transport studies. Molecular Medicine Pathobiochemistry Program Supervisor: László Homolya bartos.zsuzsa@ttk.mta.hu

Abstract type

oral

A convenient method to pre-screen candidate guide RNAs for CRISPR/Cas9 gene editing by NHEJ-cloning a "self-cleaving" GFP-expression plasmid

Tálas, András

András Tálas1,2, Péter Kulcsár1,3,4, Adrienn Borsy1, Eszter Tóth1,3, Kornélia Szebényi1, Nóra Weinhardt1,3,4, Sarah Krausz1, Krisztina Huszár1,3, István Vida1,5, Ádám Sturm1, Bianka Gordos1, Orsolya Ivett Hoffmann6, Petra Bencsura1,3, Antal Nyeste1,3 and Ervin Welker1,3,* 1 Institute of Enzymology, Research Centre for Natural Sciences of the Hungarian Academy of Sciences, Budapest, Hungary; 2 School of Ph.D. Studies, Semmelweis University, Budapest, Hungary; 3 Institute of Biochemistry, Biological Research Centre of the Hungarian Academy of Sciences, Szeged, Hungary; 4 University of Szeged, Szeged, Hungary; 5 Institute of Organic Chemistry, Eötvös Loránd University, Budapest, Hungary; 6 NARIC Agricultural Biotechnology Institute, Animal Biotechnology Section, Ruminant Genome Biology Group, Gödöllő, Hungary

Notes

The efficacies of guide RNAs (gRNAs), the short RNA molecules used by Streptococcus pyogenes Cas9 (SpCas9) nuclease to determine its sequence specificity vary dramatically, thus the selection of appropriate target sites is critical for most applications. Here, we describe a simple method for

experimentally pre-testing the activities of various gRNAs targeting a gene. The method explores the genomic integration of a GFP-expressing plasmid linearised in-cell. The use of “self-cleaving” GFP-plasmids containing universal gRNAs and corresponding targets alleviates cloning burdens when this method is applied. These universal gRNAs mediate efficient plasmid cleavage and are designed to avoid genomic targets and off-targets in 12 model species. Our approach is likely to be applicable to other Cas9 and Cpf1 nucleases as well. These experiments demonstrate that non-homologous end joining- (NHEJ-) cloning when combined with SpCas9 and a self-cleaving plasmid is a superior alternative to random integration in mammalian cells. This approach provides coupled integrations of target and marker/selectable genes at about 90%, integrates DNA-cassettes larger than 10 kb with efficiencies up to 30%, reveals five gRNAs that mediate integration to the ROSA26 locus above 10% efficiencies and achieves targeted genomic integrations equally efficient to homologous recombination by 800 base-long homologous arms. Docoral School: Molecular Medicine Program: Pathobiochemistry Supervisor: Ervin Welker e-mail: talas.andras@ttk.mta.hu

Abstract type

oral

Genetic factors have substantial influence on epicardial adipose tissue quantity: a classical twin study

Jermendy, L. Adam

Adam L. Jermendy1, Dorottya V. Horcsik1, Tamas Horvath1, Andrea Bartykowszki1, David L. Tarnoki2, Adam D. Tarnoki2, Szilard Voros3, Bela Merkely1, Gyorgy Jermendy4, Pal Maurovich-Horvat1 1Semmelweis University Heart and Vascular Center, MTA-SE Lendulet Cardiovascular Imaging Research Group, Budapest 2Semmelweis University Department of Radiology and Oncotherapy, Budapest 3Global Genomics Group, Richmond, USA 4Bajcsy-Zsilinszky Hospital, Budapest, Hungary

Notes

It has been reported that epicardial adipose tissue might have an important role in the pathogenesis of coronary artery disease because of its metabolic activity and proximity to the epicardial coronary arteries.Whether the epicardial adipose tissue depends on environmental influences or determined by genetic factors is unclear. The aim of the study was to evaluate the genetic and environmental impacts on the epicardial adipose tissue quantity within a cohort of twin pairs. We have enrolled 210 twin subjects without known cardiovascular disease of whom 63 were monozygotic (MZ) pairs (age: 55.7±9.7 years) and 42 were dizygotic (DZ) pairs (age: 58.1±8.7 years). All subjects were investigated with a 256-slice CT-scanner (Philips Healthcare, Best, The Netherlands). For each twinsubject epicardial fat volume (EFV), waist circumference (WC) andbody mass index (BMI)were assessed. To quantify phenotypic similarity, intra-pair correlations were calculated. With the use of structural equation models these correlations were broken down to additive genetic (A), common (C) and unique (E) environmental correlation components. The EFV was 98.1±45.2 cm3, the WC was 98.0±14.1 cm, and the BMI was 27.8±5.2 kg/m2(mean±SD). The intra-pair correlation between EFV, WC and BMI values were stronger in MZ twins as compared to DZ twins (rMZEFV=0.75, rDZEFV=0.27; rMZWC=0.70, rDZWC=0.40; rMZBMI=0.67, rDZBMI=0.16; all $p<0.05$), which implies a strong genetic dependence of these parameters. The structural equation models confirmed these findings: AEFV=75%, AWC=71%, ABMI=66%; EEFV=25%,EWC=29%, EBMI=34%. No role of common environmental factors was found. In this classical twin study we were able to show that genetic but not environmental factors have substantial influences on EFV, similarly to BMI and WC. As both abdominal obesity and increased volume of epicardial fat are linked to the development of cardiovascular diseases, early and sustained preventive measures are needed to reduce the amount of these pathogenic fat depots. Doctoral School: Basic Medicine Program: Physiological and clinical aspects of cardiovascular diseases Supervisor: Pál Maurovich-Horvat E-mail address: adam.jermendy@gmail.com

Abstract type

oral

PATTERN FORMATION IN THE BROMATE-SULFITE-FERROCYANIDE REACTION

Molnár, István

István Molnár1,2, István Szalai2 1. School pf PhD. Studies, Semmelweis University Budapest 2. Institute of Chemistry, Eötvös University Budapest

Notes

Mixed Landolt-type pH oscillators are versatile systems that allow the experimental study of a wide range of nonlinear phenomena including multistability, oscillations, and spatiotemporal patterns. We report on the dynamics of the bromate–sulfite–ferrocyanide reaction operated in a open one-side-fed reactor, where spatial bistability, spatiotemporal oscillations, front and Turing-type patterns have been observed. The role of different experimental parameters, like the input flow concentrations of the hydrogen and the ferrocyanide ions, the temperature and the thickness of the gel medium (which affects the rate of the diffusive feed) have been investigated. We point out that all these parameters can be efficiently used to control the spatiotemporal dynamics. We show that the increase of ionic strength stabilizes the uniform states at the expense of the patterned one. Some general aspects of the spatiotemporal dynamics of mixed Landolt type systems, which are based on the oxidation of sulfite ions by strong oxidants, are emphasized. Fundings: OTKA 100891 Doctoral School: Pharmaceutical Sciences Program: Modern Trends in Pharmaceutical Scientific Research Supervisor: István Szalai E-mail address: imolnar@chem.elte.hu

Abstract type

oral

Endoplasmic reticulum stress response in G6PC3 deficient white blood cells

Pittner, Rebeka

Rebeka Pittner1, Gergely Kriván2, Zsigmond Lédeczi1, Tamás Kardon1 Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University,Budapest, Hungary Pediatric Hematology and Stem Cell Transplantation Unit, Szent László Hospital, Budapest, Hungary

Introduction

Severe Congenital Neutropenia type 4 (SCN4) is a rare autosomal recessive disease due to mutations in the glucose-6-phosphatase beta (G6PC3) gene. G6PC3 is a typical metabolic enzyme in the endoplasmic reticulum (ER) suggested hydrolyzing glucose-6-phopshate (G6P) in glucose and phosphate. This enzyme catalyzes the final step of glycogenolysis in non gluconeogenic tissues like neutrophils. In the lumen of ER glucose-6-phosphate can be metabolized by hexose-6-phosphate dehydrogenase (H6PD) as well, which is responsible for ER redox homeostasis. The first diagnosed patient in our country has a non-sense mutation in the first exon at position W73Term causing a lack of G6PC3. Beyond severe inborn neutropenia and consequent inflammatory episodes the phenotype comprises other anomalies including congenital heart defects, urogenital anomalies prominent superficial veins, facial dysmorphism, growth and developmental delay.

Aim

The question arises as to what kind of disturbances can cause a defect of a metabolic enzyme leading to developmental malignancies - beyond affecting neutrophils? Since data are already presented in G6PC3 KO mice, we were interested in the differences or similarities between human and rodent WBC-s.

Methods

Whole blood from healthy and patient with SCN4 was collected and purified obtaining total white blood cell (WBC) fraction. Enzymatic and Western-blot measurements were made on these protein samples.

Results

Neutrophils from G6PC3-deficient WBC-s proved the lack of G6PC3 on Western blot, and also on the enzymatic level. Surprisingly we could not identify any metabolic aberrations in G6PC3-deficient WBC-s. G6PC3 deficient cells showed increased level of Grp78 and phosphorylated eIF2-α

compared to the control one. Other ER stress enzymes are still under investigation. Interestingly H6PD was also decreased in the mutant cells vs. control cells.

Conclusion

Lack of G6P reduction or hydrolysis suggests that endoplasmic reticulum stress can be responsible for increased apoptosis in G6PC3-deficient neutrophils. However, the involvement of the PERK-eIF2α-ATF4 signaling pathway in SCN4 is still unclear; these alterations may at least in part be responsible for the phenotype of G6PC3 deficiency. Our results suggest that trying to maintain the ER redox environment with small molecules, like ascorbic acid, may help in neutrophil granulocyte surviving. We continue our investigations towards this direction.

Notes

Funding: Hungarian Scientific Research Fund/OTKA 101226 Doctoral School: MOLECULAR MEDICINE Program: Pathobiochemistry Supervisor: Tamás Kardon E-mail address: pittner.rebeka@gmail.com

Abstract type

oral

Clinical Medicine II

FINITE ELEMENT ANALYSISBASED LUMBOSACRAL REVISION SURGERY USING AN INDIVIDUAL NAVIGATION TEMPLATE

Éltes, E. Péter

Péter E. Éltes1,2,Márton Bartos3, VargaPéter Pál1, Áron Lazáry1 1 National Center for Spinal Disorders, Budapest 2 School of Ph.D Studies, Semmelweis University, Budapest 3 Do3D Innovations Ltd., Budapest

Background

A revision surgery in case of a lumbosacral non-union can be challenging especially if an implant related failure (e.g. a broken S1 screw) is complicating the clinical situation. Removal of the broken screw impairs the local bony environment, jeopardizing the outcome of the revision. In this paper, we present a case suffering from a lumbosacral non-union complicated with a broken sacral pedicle screw what has been surgically managed by the application of a CT based 3D reconstruction method combined with finite element analysis (FEA) and computer assisted design (CAD).

Methods

A step-by-step approach was developed and performed to manage the clinical problem. (1) Quantitative computed tomography (QCT) based patient-specific FE model of the sacrum was created. (2) In order to plan the revision surgery CAD model of the pedicle screw was inserted in the sacrum model in a bicortical convergent and a monocortical divergent position. (3) According to the two screw insertion scenarios two static FEAs were performed using 500 N tensile load applied to the screw head. (4) A template with the two screw guiding structures designed to fit on the bone surface was created for the sacrum using 3D design and photoactive 3D printing technology. (5) The revision screw has been implanted into the biomechanically optimal position guided by the patient- and condition-specific template. Postoperative CT scan was used to evaluate the accuracy of the pedicle screw placement.

Results

Based on the FEA results the modified bicortical convergent screw had better stability resulting in optimal von Misses stress distribution and less displacement compared to the monocortical divergent placement. Preoperatively the template was found to fit exactly on a 3D printed plastic sacrum model, and screw insertion simulation was successfully performed. The design concept was proved to be accurate based on the CT scan and virtual model comparison. Intraoperatively the template also fitted on the bone surface and screw insertion was completed successfully. Postoperative CT scans confirmed that the inserted pedicle screw reached the virtually planed position.

Conclusion

The intraoperative pedicle screw navigation provided by a patient specific screw-guiding template allows the surgeon to insert the screw into its optimal position considering the local bone material property and the challenging geometrical situation. Its advantages compared to the conventional surgical navigation techniques are the relatively low cost, minimized intraoperative X-ray exposure and the possibility for the consideration of the patient-specific biomechanics. This new patient- and condition-specific approach can be widely used in revision spine surgeries or in challenging primary cases.

Notes

Doctoral School: Clinical Medicine Program: Physiology and pathology of the musculoskeletal system Supervisor: Áron Lazáry E-mail: peter.eltes@bhc.hu

Abstract type

oral

New diagnostic criteria for thrombotic microangiopathy after stem cell transplantation

Horvath, Orsolya

Orsolya Horvath1,2, Krisztian Kallay1, Gergely Krivan1, Zoltan Prohaszka2 1. United St. Istvan and St. Laszlo Hospital, Pediatric Hematology and Bone Marrow Transplantation Unit 2. 3rd Department of Internal Medicine, Fust Complement Laboratory, Semmelweis University

Introduction

Hematopoietic stem cell transplantation (HSCT)- associated thrombotic microangiopathy (TMA) is a multifactorial complication, and has variable incidence in study populations due to different criterias.

Aim

Our aim was to identify patients with TMA using classical and newly defined criteria and complement parameters.

Patients and methods

We enrolled 36 pediatric patients (median age 10,4 year, (1,8-17,5)) in this prospective study who underwent allogeneic HSCT using treosulfan based (N=31/36) conditioning therapy. Complement pathway activities, ADAMTS13 and terminal complement complex (TCC) were measured during early HSCT period. Graft versus host disease (GVHD) was diagnosed using Glucksberg criteria. TMA was defined two ways, using classical criteria (elevated LDH, hematological parameters) during our clinical practice and patients were reviewed using more sensitive new diagnostic criteria (hypertension, elevated TCC) proposed by Jodele et al..

Results

2/36 patients were defined as TMA using classical criteria during patient care. Therefore, after analyzing clinical data and complement parameters, 10/36 subjects met the new criteria for TMA. Reviewing our data showed, that patients defined as drug side effect (N=3), viral reactivation (N=2), GVHD (N=2), and relapse (N=1) also met the criteria for TMA. TMA occured in the first 100 days with elevated TCC on day 28 ($p<0,01$). GVHD was more frequent among TMA patients, TMA coexisted with acute GVHD in 7/10 cases (7/10 vs. 4/26; $p<0,01$). After a median 0,95 year (0,03-2,2) follow-up time, overall survival was 25/36. Relapse related mortality was the most common cause of death (N=7/11, $p<0,05$), while TMA was not a significant cause of mortality (N=1/11).

Conclusion

Using new diagnostic criteria, TMA has a higher incidence and can coexist with other HSCT complications. Monitoring of criteria and complement activation during HSCT can guide physicians to diagnose TMA as a complication after stem cell transplantation.

Notes

Fundings: PhD stipendium Doctoral School: Clinical Medicine Program: Basic Sciences Research in Clinical Practise Supervisor: Krivan Gergely, Zoltan Prohaszka E-mail adress: orsolyahorvath.mail@gmail.com

Abstract type

oral

RENOPROTECTIVE EFFECT OF SGLT2 INHIBITOR, Dapagliflozin IN TYPE- 1 DIABETES

Balogh, Dóra

Dora B. Balogh1,4, Judit Hodrea1,4, Lilla Lenart1,4, Adam Hosszu1,4, Sandor Koszegi1,4, Edgar Szkibinszkij1,3, Adam Vannay2,4, Laszlo J. Wagner3, Attila J. Szabo2,4, Andrea Fekete1,4 MTA-SE „Lendület" Diabetes Research Group, Budapest MTA-SE Pediatrics and Nephrology Research Group, Budapest Department of Transplantation and Surgery, Semmelweis University, Budapest 1st Department of Pediatrics, Semmelweis University Budapest

Introduction

Sodium glucose cotransporter (SGLT) 2 inhibitors act by inhibiting SGLT2 mediated glucose reabsorption in the proximal tubules. Currently these drugs are approved for type 2 diabetes (DM) and their use is limited in renal impairment.

Aim

We investigated the effect of highly selective SGLT2 inhibitor Dapagliflozin (DAPA) in the prevention of diabetic nephropathy (DNP) in monotherapy and in combination with the ARB Losartan (LOS).

Methods

DM1 was induced by streptozotocin in male Wistar rats. Immediately following onset of DM the animals were treated for six weeks with DAPA either in monotherapy (D+DAPA, 1 mg/bwkg/nap, po.) or in combination with LOS (D+DAPA+LOS, DAPA: 1 mg/bwkg/day, po.; LOS: 20 mg/bwkg/day, po. - only in the last three weeks). Blood glucose level, body weight, blood pressure and water intake were monitored. By the end of the protocol the metabolic and renal parameters were determined and the histological evaluation of glomerular and tubulo-interstitial damage characteristic to DNP was performed.

Results

In the DM group development of DNP was confirmed by decline metabolic parameters, decrease in body weight, impairment of renal function, proteinuria and structural damage of kidneys. Blood pressure was not influenced by treatments. DAPA in monotherapy and also in combination with LOS reduced the weight loss and water consumption, decreased the blood glucose level (D: 37±2,7; D+DAPA: 17,7±5,6; D+DAPA+LOZ: 18±6,1; mmol/L). There was no difference between the mono- and combined therapy. The SGLT2 inhibition decreased the DM induced mesangial matrix expansion and tubulo-interstitial fibrosis, in addition the combined treatment was more efficient.

Conclusion

DAPA improved metabolic and renal parameters and decreased the histological lesions in the kidney. The renoprotective effects of DAPA was equal to the gold standard ARB LOS. These results suggest the possibility of clinical application in the prevention/treatment of DM1 and associated nephropathy.

Notes

Fundings: LP008/2015, OTKA -K100909, -K112629, -K108688, KMR12-1-2012-0074. Doctoral School: Clinical Medicine Program: Prevention of Chronic Diseases in Childhood Supervisor: Andrea Fekete E-mail address: dorabiankabalogh@gmail.com

Abstract type

oral

ANATOMICAL VARIATIONS OF HUMAN LIVERS IN HUNGARIAN POPULATION: RELEVANCIES FOR SURGERY AND TRANSPLANTATION

Kiss, Mátyás

Mátyás Kiss1,2, András Szuák1, Károly Németh1,2, Laura Fekete1, Zsolt Pápai1, Sándor Kovács1,2, Zsuzsanna Kürti1, Ibolyka Dudás3, Csaba Korom3, László Kóbori2, Ágnes Nemeskéri1, Zoltán

Máthé2 1Department of Anatomy, Histology and Embryology, 2Department of Transplantation and Surgery, 3Department of Diagnostic Radiology and Oncotherapy, Semmelweis University Budapest

Introduction

The precise knowledge of hilar and intrahepatic biliary and vascular variations is essential to further reduce the incidence of intra- and postoperative complications of partial liver transplantation and liver resections.

Aim

Our aim was to investigate the frequency and surgical relevance of the intra- and extrahepatic anatomical variations.

Methods

A new synthetic resin corrosion cast method was worked out and more than 500 human liver casts were made and analyzed. Furthermore, for post mortem simulation of liver splitting, organs were injected with special resin mixture, then before fixation livers were CT scanned and 3D reconstruction were made.

Results

The statistical analysis of 140 biliary duct preparations revealed new variations and subvariations. We found differences in frequencies of certain biliary duct variations, compared to data available in the international literature. Investigating 55 casts, the branching patterns of hepatic veins and anastomoses between the right and middle hepatic veins were revealed and their surgical importance discussed. Patterns of intrahepatic arterial branching and extrahepatic arterial blood supply showed significant differences in comparison to data published by others (65 casts). The hilar branching of portal vein displayed normal anatomy in 60% of preparations (75 casts). Intersegmental portal venous anastomoses were observed in 13 cases out of 18 liver casts (72%). Using our unique liver model, planning of different types of splits could be simulated, like in living hepatic surgery.

Conclusion

We are the first to provide complex detailed data on the incidence of hepatic vascular and biliary variations in the Hungarian population. Description of these differences could contribute to a better planning of complex liver resections for tumor surgery and partial liver transplantation.

Notes

Fundings: TÁMOP-4.2.1B-09/1/KMR, István Apáthy Foundation Doctoral School: Basic Sciences Doctoral School Consultants:: Zoltán Máthé and Ágnes Nemeskéri E-mail address: kissmatyas@gmail.com

Abstract type

oral

THE PREVALENCE OF INTRACRANIAL HEMORRHAGE IN ASPHYXIATED INFANTS TREATED WITH THERAPEUTIC HYPOTHERMIA

Szakmár, Enikő

Enikő Szakmár1, Kata Kovács1, Ünőke Méder1, Andrea Lakatos2, Lilla Lamboy1, Márton Kolossváry3, Miklós Szabó1, Ágnes Jermendy1 1. 1st Department of Paediatrics, Semmelweis University, Budapest 2. MR Research Center, Budapest 3. MTA-SE “Lendület” Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest

Introduction

Perinatal asphyxia occurs in 3 to 5 cases per 1000 term live births and may lead to hypoxic-ischemic encephalopathy (HIE) and permanent neurological deficit. Currently, mild therapeutic hypothermia (HT) is the state-of-the-art therapy for HIE, which can improve long-term neurodevelopmental outcome. Symptomatic intracranial hemorrhage (IVH) is relatively uncommon in term newborns; however, severe asphyxia could be one of the risk factors, and the effects of hypothermia treatment in these patients are not fully understood.

Aim

Our aim was to evaluate the prevalence of IVH among asphyxiated term newborns treated with HT.

Methods

In this retrospective cohort study, medical records of 128 asphyxiated neonates treated with HT, born between 2013 and 2015 were reviewed and collected in a web-based, well-structured database ("Asphyxia Register") developed by our research group. In 106 cases (83%) brain MRI was performed to detect the radiological signs and severity of HIE. Data were compared by contingency tables.

Results

The average gestational age of infants was 38.3±2.2 weeks, gest.weight was 3149±582 g. The brain MRI was performed on the 5.8±2.9 day of life, in 78 % of the cases after HT treatment. The rate of mortality was 14/128 (9%). Neuroimaging with MRI did not show any anatomical or functional abnormalities in 29 cases (27%). HIE was detected in 52 infants (49%), the grade of HIE was severe in one quarter of the cases. The appearance of HIE and IVH together was 30% (16/52) on MRI, IVH occurred alone in 40% (19/48) (p=0.141). Furthermore, we found stroke in 6 cases (6%).

Conclusion

According to our results, IVH detected by brain MRI is common in term neonates also without the radiological signs of HIE. Early MRI examination may be warranted to aid clinical decision making regarding hypothermia treatment and allow for individualized therapy in asphyxiated newborns.

Notes

Doctoral School: Clinical Medicine Program: Prevention of Chronic Diseases in Childhood
Supervisor: Ágnes Jermendy E-mail address: drszakmareniko@gmail.com

Abstract type

oral

COMORBIDITIES IN PATIENTS WITH POLYARTICULAR OSTEOARTHRITIS- A CONTROLLED STUDY

Kovari, Eszter

Eszter Kovari 1, Zsuzsanna Kiss 2, Reka Kurucz 1, Geza Balint 1,3, Peter Vince Balint 1 1: National Institute of Rheumatology and Physiotherapy, Budapest 2: Faculty of Medicine, Semmelweis University, Budapest 3: The Bone and Joint Decade

Introduction

Osteoarthritis (OA) is the most common form of arthritis, and one of the leading causes of disability in adults. Previous studies have demonstrated that patients with OA often suffer from comorbidities.

Aim

To investigate the prevalence of comorbidities in patients with hand and knee osteoarthritis (polyarticular OA) compared to an age and sex matched control group.

Methods

A cross-sectional, observational cohort study was conducted. Consecutive patients diagnosed with polyarticular OA according to the criteria of the American College of Rheumatology (ACR) were invited to enrol in the study. Inclusion criteria for controls were absent of any musculoskeletal symptoms, diagnosed osteoarthritis and inflammatory rheumatic disease. Cardiovascular, gastrointestinal, pulmonary, endocrine, psychiatric comorbidities, obesity and cancer were recorded. Descriptive statistics, chi square and Fischer test were used for the data analysis. The study population included 170 OA and 170 control subjects. The age (68,8 ± 6,7) and sex distributions (female gender: 97%) of patients and controls were similar.

Results

In OA group the following comorbidities were observed with high prevalence compared to the control group: hypertension (85% vs 58% p<0,001), metabolic syndrome (diabetes mellitus: 21% vs 15% p=0,21 , dyslipidaemia: 58% vs 40% p=0,001), obesity (47% vs 35% p=0,03), varicose veins in the lower extremity (40% vs 20% p<0,001), depression (28% vs 6% p<0,001), gastrointestinal ulcer (26% vs 8% p<0,001), cardiovascular events (stroke: 6 % vs 3% p=0,3, myocardial infarction: 14% vs 7% p=0,05) and breast cancer (10% vs 3% p=0,01).

Conclusion

These results indicate a significant prevalence of comorbidities in patients with polyarticular OA.

Notes

Doctoral School: Clinical Medicine Program: Physiology and pathology of the musculoskeletal system Supervisor: Peter Vince Balint E-mail address: ester.kovari@gmail.com

Abstract type

oral

THE DISTRIBUTION OF ACTIVATION MARKERS AND SELECTINS ON PERIPHERAL T LYMPHOCYTES IN PREECLAMPSIA

Bajnok, Anna

Anna Bajnok, MarusiaIvanova, Gergely Toldi 1stDepartment of Obstetrics and Gynecology, Semmelweis University Budapest

Introduction

In industrialized countries preeclampsiais responsible for 18% of maternal mortality and 15% of premature births. A major factor in the pathogenesis of preeclampsia is related to impaired maternal immune tolerance, resulting in systemic inflammation. By describing activation properties of circulating T cells we could gain a better understanding of the pathophysiology of preeclampsia.

Aim

Our aim was to characterize the cell surface expression of several T lymphocyte activation markers (CD69, HLA-DR, CD62L, CD25, CD122) and theexpression of theselectins playing a role in tethering and extravasation (CD62E, CD62L, CD62P). We alsoaimedtocharacterizetheprevalence of activated (CD11c+)myeloiddendriticcells (mDCs), playing a role in T cellactivationviaantigenpresentation.

Methods

We collected peripheral blood samples from 18 preeclamptic patients and 20 healthy pregnant women as controls. We isolated the peripheral blood mononuclear cells and then administered the following conjugated antibodies:CD4 APC-Cy7, HLA-DR PerCP, CD62L PE-Cy7, CD62P PE, CD62E APC APC-Cy7, CD25 FITC, CD11c PE-Cy7, CD122 PE, CD69 APC. We measuredfluorescentdatausing flow cytometry.

Results

We found an elevated ratio of CD62E (5.77 vs 16.10%), CD62L (1.74 vs 2.91%), HLA-DR (6.19 vs 21.05%) and CD122 (1.20 vs 1.63%) expressingCD4+ T cells in preeclampsia in comparisontohealthypregnancy. No alterationswerefoundin other markers.

Conclusion

Our findings support the role of activated T lymphocytes in the pathophysiology of preeclampsia. The markers showing the most distinct elevations (CD62E, HLA-DR) play a role in T cellactivation and extravasation, however, furtherinvestigation is neededto understandtheexactmechanismthey play in pathophysiology.

Notes

Fundings: OTKA PD-109451 Doctoral School: Clinical Medicine Program: Clinical Applications of Basic Research Supervisor: Gergely Toldi MD, PhD E-mail address: bajnok.panni@gmail.com

Abstract type

oral

SKIN INTERSTITAL GLYCOSMINOGLYCANS – SODIUM HOMEOSTASIS

Sugár, Dániel

Dániel Sugár1, Róbert Agócs1, Attila J. Szabó1,2, Endre Sulyok3 1 Semmelweis University, First Department of Pediatrics, Research Laboratory, Budapest 2 HAS-SE Nephrology Research Laboratory 3 University of Pécs, Faculty of Health Sciences, Pécs

Introduction

According to the literature in case of Na+ overload reversible changes in the ratio of free/bound Na+ in subcutaneous tissue serve as a volume buffer and protect against volume expansion and the rise of blood pressure. The system consists of the negatively charged glycosaminoglycan (GAG) molecules of the skin, the macrophages sensing hypertonicity and the VEGFC protein secreted by macrophages. VEGFC secretion results in hyperplasia of the existing lymph capillary system draining liberated Na+ back to circulation. The weakness of the theory is that it does not explain the mechanism of release of the bound Na+. To address this question we measured the changes of VEGFA-levels in the skin, a signaling protein that might decrease charge density of interstitial GAGs thus playing a key role in the release of bound Na+.

Matrials and methods

Normotensive female Wistar rats aged 8 weeks were assigned to three groups (n=8) each receiving either high salt diet (HS, NaCl=8% m/m), low salt diet (LS, NaCl<0.1% m/m) for 4 weeks or high salt diet followed by low salt diet for 8 weeks (HS/LS). Na+ content of the skin was measured by flame photometry, skin hyaluronic acid and chondroitin 4,6 sulphate content was measured by high performance liquid chromatography, skin VEGFA and VEGFC mRNA levels were measured by PCR.

Results

Our results confirm that the changes in dietary sodium intake have a strong influence on skin GAG levels. Significant correlation has been found between skin sodium and GAG content.

Conclusion

We have demonstrated that in the skin of salt resistant rats the accumulation of Na+ on skin GAGs correlates with proportionate amount of water, the blood pressure remaining unchanged. The decrease of skin Na+ and GAGs in the HS/LS group supports the hypothesys of the regulated degradation of skin GAGs.

Notes

Doctoral School: Clinical Medicine Program: Prevention of chronic diseases in childhood Supervisor: Attila J Szabo E-mail: sugar.daniel@med.semmelweis-univ.hu

Abstract type

oral

A protreomic screen for alterations in psoriasis

Szél, Edit

Edit Szél1, Renáta Bozó1, Éva Hunyadi-Gulyás2, Róbert Kui1, Brigitta Gál1, Nóra Belső1, Máté Manczinger1,3, Katalin F. Medzihradszky2,4, Zsuzsanna Bata-Csörgő1,3, Lajos Kemény1,3, Gergely Groma3 1 Department of Dermatology and Allergology, University of Szeged, Hungary, 2 Biological Research Centre, Szeged, Hungary, 3 MTA-SZTE Dermatological Research Group, University of Szeged, Hungary, 4 Department of Pharmaceutical Chemistry, University of California, UCSF, USA

Introduction

Psoriasis is a chronic inflammatory skin disease affecting 2-3% of the population, whose pathomechanism is not completely understood.

Objective

This project aimed: to screen for alterations of the psoriatic non-lesional (NL) and lesional (L) samples vs. healthy (H) skin samples using a proteomic approach, to compare these results with those of other proteomic and RNA studies of psoriasis, to search for ranked pathways, associations with psoriasis GWAS study, psoriasis comorbidities and druggable target proteins.

Methods

A solubility-based, multi-step protein extraction, followed by high pH-chromatography and LC-MS/MS analysis was performed from the skin biopsies of 4 H, and the NL and L samples of 3 psoriatic individuals. Our results were compared with those of 6 independent proteomic studies, 4 RNA microarray and 1 RNA-seq analyses.

Results

Our analysis resulted in the identification of over 700 proteins, of which more than 500 showed at least two-fold change. These proteins showed approximately 70% concordant changes in comparison with independent studies of the psoriatic skin at protein and RNA levels. More than 200 proteins were found to be associated with the HGVST902 psoriasis GWAS study, more than 50 were previously linked to psoriasis comorbidities and over 20 were found to be potential drug targets.

Conclusion

The results of the pathway overrepresentation analysis are in accordance with the current concepts of the pathomechanism of the disease. These results provide a starting-point for further studies aiming to broaden the therapeutic options in psoriasis.

Notes

Doctoral School: Clinical Medical Studies, Faculty of Medicine, University of Szeged Program: Dermatology Supervisor: Gergely Groma E-mail: szeledit@hotmail.com

Abstract type

oral

Clinical Medicine

DIVERGENT MICRORNA EXPRESSION IN INFLAMMATORY BOWEL DISEASE SUBTYPES

Kiss, Zoltán

Zoltán Kiss1*, NóraJudit Béres1*, Dániel Szűcs2, Katalin Eszter Müller1, Áron Cseh1, Zsófia Sztupinszki1, Gábor Lendvai3, András Arató1, Erna Sziksz1,4, Ádám Vannay1,4, Attila J. Szabó1, Gábor Veres1 1. 1st Department of Pediatrics, Semmelweis University, Budapest, Hungary 2. Department of Pediatrics and Pediatric Health Care Center, University of Szeged, Szeged, Hungary 3. MTA-SE Tumor Progression Research Group, SemmelweisUniversity, Budapest, Hungary 4. MTA-SE Pediatrics and Nephrology Research Group, Budapest, Hungary * equally contributing authors

Introduction

MicroRNAs (miRs) came recently into focus as promising novel research targets offering new insights into the pathogenesis of inflammatory bowel diseases (IBD). Since the diagnosis of IBD is often challenging, there is a need to determine new disease biomarkers. Therefore, the aim of the present study was to identify a pediatric IBD characteristic miR profile serving as potential Crohn's disease (CD) and ulcerative colitis (UC) specific diagnostic pattern. Our next aim was to further analyze the related target genes of the miRs to reveal their complex role in the pathomechanism of IBD.

Methods

Illumina sequencing was performed on macroscopically inflamed (CD inflamed, n=4) and intact (CD intact, n=4) colonic biopsies of therapy-naive children with CD and controls (C, n=4). Selected miRs were further investigated by real-time PCR using an extended number of patients (CD inflamed, n=15; CD intact, UC, C, n=10). To analyze network connection of differentially expressed miRs and their target genes in pediatric IBD according to the MiRTarBase database and available sequencing data was used.

Results

Sequencing analysis identified 148 miRs, dysregulated in the inflamed mucosa compared to the intact mucosa of IBD patients or controls. Twenty-two miRs were differentially expressed in the intact mucosa of CD patients compared to controls. Subsequent analysis by RT-PCR revealed differently expressed miRs which could discriminate between the inflamed mucosa of CD and UC (miR-31, -142-3p, -146 and -125a). Moreover, the expression of miR-20a, -100, -185, -204, and -221 was elevated in the intact mucosa of CD patients compared to controls, referring to the differences between the non-inflamed mucosa. The target gene screening, annotation and enrichment analysis identified several IBD-related functional groups (inflammation, fibrosis and angiogenesis).

Conclusion

We demonstrated a characteristic colonic miR pattern in pediatric patients with IBD which could facilitate the deeper understanding of the pathomechanism of IBD.

Notes

Fundings: OTKA-K105530, -K108688, -K116928, -PD105361, LP008/2016. Doctoral School: Clinical Medicine Program: Prevention of Chronic Diseases in Childhood Supervisor: Gábor Veres E-mail adress: zoltan.kiss.bio@gmail.com

Abstract type

oral

MATHEMATICAL EXAMINATION OF SHAPE MUTATIONS AND GEOMETRICAL PARAMETERS OF THE SPINE

Sándor, Zoltán

Zoltán Sándor1, Gábor Ráthonyi2 1 Institute of Digital Health Sciences, Semmelweis University, Budapest 2 Orthopaedy, Health Service of Budavári Local Government, Budapest

Background

Several different methods are used to measure lumbar lordosis such as the Cobb technique (Cobb-angle), arctan middle/deep point methods and vertebral centroid methods (centroid angle), etc.

Introduction

Spinal diseases and back pain concern a lot of people. Spinal curvature differences may relate to shape mutations of the spine.

Aim

The known methods approximate the spine with a circle and characterize the spine with angles. These methods are adequate at first but the spine curvature is more complex than a simple circle. The aims of the research are to develop a new method and new geometrical parameters, to collect and to evaluate measurement data, to find a connection between new geometrical parameters and shape mutations with statistics methods and to develop a new computer program for practical applications.

Methods

A new method has been developed which is able to approximate the spinal curvature much more precisely than previously known methods. The new method uses mathematical Lagrange interpolation where the vertebrae are approximated more accurately by a polynomial, rather than by a simple circle. Only one interpolation polynomial fits indisputably onto the spine and on the examined interval it is continuous, differentiable, integrable and it has a minimum and a maximum. New geometrical parameters can be introduced by these proper attributions for better approximation. These new geometrical parameters are the Rho-angle, the Digression percentage and the Expansion percentages.

Results

We have developed a new method and three new geometrical parameters for the more precise approximation of the spine curvature. This method and these geometrical parameters have also been realized by a prototype computer program for practical applications.

Notes

Doctoral School: Pathological Sciences Program: Research in Public Health and Health Science Supervisor: Elek Dinya E-mail address: sandor.zoltan@public.semmelweis-univ.hu

Abstract type

oral

LIVER FUNCTION AS MONITORED BY HEPATOBILIARY SCINTIGRAPHY FOLLOWING PORTAL VEIN LIGATION

Kovács, Tibor

Tibor Kovács1, András Fülöp1, 1. 1st Department of Surgery, Semmelweis University, Budapest

Introduction

Risk reduction of posthepatectomy liver failure following extended tumorous liver resection often necessitates surgical induction of liver regeneration. The selective portal vein ligation (PVL) of infiltirated liver segments is a successful method in inducing ipsilateral atrophy- and contralateral hypertrophy of liver lobes. In contrast to the consensus on morphological changes following PVL, literature data on the alteration of hepatic function remains controversial.

Aim

Our goal was to evaluate the temporal characteristics of hepatic function and morphology following PVL.

Matrials and methods

PVL affecting approximately 80% liver parenchyma was performed on male Wistar rats (Σn=42). Liver weight and histopathological analysis (HE; Ki-67) was determined preoperatively and 24h/48h/72h/168 hours after surgery (n=6 each). Different animals were subjected to serial radiological diagnostics in the above time points. Indocyanine green (ICG) clearence was performed on one subset of animals (n=6), while on another cohort (n=6) MRI-volumetry visualised liver morphological changes, whereas 99mTc-mebrofenin hepatobiliary scintigraphy (HBS) quantified global (uptake: B1/2, excretion: DSTART) and regional (Tmax, T1/2) hepatic function.

Results

Ligated (L) lobes underwent atrophy (mL/mBODY%0=3,83%±0,27%; mL/mBODY%168=0,92%±0,22%), while non-ligated (NL) lobes hypertrophysized (mNL/mB%0=1,0%±0,1%; mNL/mB%168=3,29%±0,22%) and weight changes strongly correlated with MRI volumetric data ($p<0,01$). ICG-clearence (PDR, RT15) and HBS (B1/2, DSTART) both displayed transitional suppression of global hepatic function, which recovered by the 168thh. PVL decreased regional mebrofenin excretion in both lobes, however, after 72thh, NL lobes gradually retained their original values, ultimately exceeding excretion rates of L lobes by the 168thh (CpsNL/L0h=1,3; CpsNL/L168h=3,2).

Conclusion

Following PVL-induced liver regeneration, 99mTc-mebrofenin HBS verified a shift in hepatic function towards NL lobes, which is in accordance with ICG-clearence and the observed morphological changes.

Notes

Funding: OTKA- K115607. Doctoral School of Clinical Medicine Program: Hepatobiliary diseases - experimental and clinical aspects Supervisor: Szijártó Attila MD Ph.D E-mail: ktib1991@gmail.com

Abstract type

oral

ALPPS in surgical research: benefits and pitfalls of animal models

Budai, András

András Budai MD1, András Fülöp MD1 1: 1st Department of Surgery, Semmelweis University.

Introduction

ALPPS (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy) is a novel, effective yet risky two-staged hepatectomy. To better understand the working mechanics and to develop patient safety, suitable animal models must be created.

Objective

To compare the different ALPPS animal models designed and established by our research group by their applicability in surgical research.

Methods

Male Wistar rats and swine were used. The rats underwent 75-80% portal deprivation by the occlusion of the branches leading to the right and left lateral, right medial and caudal lobes, liver splitting was carried out according to the falciform ligament. As for swine the portal branches leading to the left lateral and medial lobes (involving 55-60% of liver) and medial part of the right medial lobe were ligated, and the right lateral lobe (accounting for 20-24%) was partially resected to achieve critical (~20%) remnant liver volume. The right medial lobe was transected in the midline.

Results

Critical remnant liver volume can be reached easily in both species. In swine the localization of the caval vein allows only left hepatectomies. Because of the lobular structure of the rat liver humanization by ligatures is essential to have a human-like lobe. It can only be achieved through selective portal vein ligations while leaving the portal supply of the median lobe complex (35% of the liver) intact although it is not fully applicable to human anatomy. Both species presented minuscule number of porto-portal anastomoses which makes human interpretation doubtful.

Conclusion

According to our results the rat model is superior in answering basic research questions concerning ALPPS, while the porcine model seemed to be less fitting for translational research purposes.

Notes

Funding: OTKA- K115607. Doctoral School of Clinical Medicine Program: Hepatobiliary diseases - experimental and clinical aspects Supervisor: Szijártó Attila MD Ph.D E-mail: andras.budai.md@gmail.com

Abstract type

oral

Representative Hungarian diagnostic data in Sjögren’s syndrome

Dézsi, Anna

Anna Dezsi 1, Gabor Nagy 2 1 Semmelweis University Depatment of General Dental Preclinical Practice 2 Semmelweis University Department of Community Dentistry

Introduction

Sjögren’s syndrome is a chronic, autoimmune, inflammatory disorder characterised by focal lymphcytic infiltration of the salivary and lacrimal glands. The infiltration of these glands leads to extreme reduction of salivary and tear secretion which cause the main subjective symptoms: the dry eye and dry mouth. In primary Sjögren’s syndrome the symptoms are not associated with another autoimmune disease. In secondary Sjögren’s syndrome the classic sicca complex associated with other polysystemic autoimmune disorder such as systematic lupus erythemathosus (SLE), rheumatoid arthritis (RA), progressive systemic sclerosis (PSS).

Aim

The basic aim of my research is to make a statistical data base of Hungarian patients with Sjögren’s syndrome and reveal important relationships between the different diagnostic results. In the future we

try to elaborate new non invasive salivary tests using modern microbiological methods (e.g miRNS, DNS methylation examinations) replace the invasive lip biopsy.

Methods

After a routine dental examination (both cariological and periodontal), sialometry is performed, which measure the quantity of saliva. We measure non stimulated saliva. The non stimulated saliva collected for 10 minutes normal ratio is 0,3 ml/min and under the value of ≤ 0.1 ml /min regarded as hyposalivation. In case of clinical suspicion minor salivary gland biopsy is performed Focus score≥1 (focus: minimum 50 aggregated lymphocytes in 4 mm2 gland tissue) regarded as positive for Sjögren's syndrome. We are working in strong collaboration with the Semmelweis University Departmnt of Ophtalmology and National Rheumatology and Physiotherapy Institute. At the Department of Ophtalmology brake-up time of lacrimal film (BUT) is examined, (under 10 seconds is considered abnormal), then the erosions of the conjunctiva and cornea are visualised. At the National Rheumatology and Physiotherapy Institute specified Anti-Sjögren's-syndrome-related antibodys A/B (aSSA/SSB), rheumatoid factor (RF) and antinuclear antibody (ANA).

Results

We already have more than one thousand sialometrical data and approximately 150 immunological and ophthalmological data of the corresponding patients. We try to give a guidance both dentists, ophthalmologists and general practitioners to make easier the diagnosis of Sjögren's syndrome patients thereby they probably will spend less time in the labyrinth of the Hungarian healthcare.

Notes

Doctoral School: Clinical Medicine Dental Research Program: General disorder's stomatological and immunological aspects Supervisor: Gábor Nagy FSzOI E-mail address: drdezsianna@gmail.com

Abstract type

oral

"ASPHYXIA REGISTRY" – A NOVEL ONLINE DATA COLLECTION PLATFORM FOR CLINICAL RESEARCHERS

Kovács, Kata

Kata Kovács1, Márton Kolossváry1,2, Enikő Szakmár1, Ünőke Méder1, Zsuzsanna Élő1, Lilla Lamboy1, Miklós Szabó1, Ágnes Jermendy1 1. 1st Department of Paediatrics, Semmelweis University, Budapest 2. MTA-SE "Lendület" Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest

Introduction

The incidence of perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE) is around 150-200 cases per year in Hungary. One third of the asphyxiated newborns are treated in the NICU of the 1st Department of Paediatrics. Due to the large patient load, we aimed to build a new online database system to facilitate scientific research and guide clinical decision-making.

Methods

The Asphyxia registry, called "Biobankok", is an online database and structured reporting tool, developed with bioinformatics assistance. As a first test of the system, we conducted a retrospective cohort study of asphyxiated newborns with standard hypothermia treatment, who were born between 2013 and 2015.

Results

Currently, a total of 84 patients (gestational age 38.6±1.9 weeks, 66% males) are registered in the database. Our preliminary results show that the asphyxiated neonates were born with 3208±522g, with average Apgar scores of 2.4/4.5/5.7 at the 1st/5th/10th minutes of life. The average age of the mothers was 32.6±5.9 years, 60.7% of the newborns were born with cesarean section, and in 21.4% of the cases a prolonged fetal expulsion occurred. After establishing HIE criteria (within the first 6 hours of life), hypothermia treatment was started during neonatal transportation, in 57.1% of cases with active cooling, in 35.7% with passive cooling, and only 7.1% of newborns started the cooling

treatment in the NICU. The median time spent with intensive care was 11.8 days [IQR 9;19]. Asphyxia is often associated with multiorgan failure, it was present in 86% of the patients, and in 31% of patients further hospital treatment was required after intensive therapy.

Conclusion

Automatic collection of descriptive data is feasible using our in-house developed structured reporting-registry tool. Critical analysis of patient outcomes of recent years could help to optimize clinical care. In addition, our results may provide guidance to other perinatal centers on treating asphyxiated newborns.

Notes

Doctoral School: Clinical Medicine Program: Prevention of Chronic Diseases in Childhood
Supervisor: Ágnes Jermendy E-mail address: mail.kata.kovacs@gmail.com

Abstract type

oral

THE ROLE OF CONTRAST ENHANCED ULTRASOUND IN THE FOLLOW-UP OF KIDNEY TRANSPLANT PATIENTS

Korda, Dávid

Dávid Korda, Pál Ákos Deák, Veronika Kozma, Gergő Kiss, Attila Doros All the authors are from Department of Transplantation and Surgery, Semmelweis University, Budapest

Introduction

Contrast-enhanced ultrasound (CEUS) combines the advantages of native ultrasound and other contrast-enhanced imaging modalities. In selected cases it can be preferable to CT scan among kidney transplant recipients.

Methods

We performed a retrospective study involving patients of Semmelweis University Department of Transplantation and Surgery who underwent a CEUS examination between 2011 and 2015. During this period 251 CEUS examinations were performed, including 45 ones on kidney transplant patients. A Toshiba Aplio XU ultrasound device was used, and 1-1,5 ml SonoVue contrast agent was administered intravenously for each patient. The patients' eGFR value was measured before the CEUS examination as part of the routine lab tests. The indications of these evaluations can be divided into three groups: characterisation of circumscribed kidney lesions, control after radiofrequency ablation (RFA) therapy and examination of graft perfusion.

Results

Fully 93% of the examinations were conclusive. The eGFR value was below 60 ml/min/1,73 m2 in 84% of the patients. In the first group out of the 37 cases where tumour suspect lesions were investigated, 13 examinations suggested the presence of a space-occupying lesion. Out of the 13 cases two patients had a negative biopsy. Nephrectomy was performed in 11 cases and the histological evaluation verified a tumour in 9 samples. In the second group, the RFA control examination detected a residual tumour in none of the 6 cases. Finally, in the third group where the circulation was investigated blood flow was satisfactory in one of the two patients, in the other it was low.

Conclusion

The CEUS examination was conclusive in most cases. The low average eGFR value of the patients' means that a contrast-enhanced CT-scan would have been contraindicated in many cases and contrast enhanced MR would have been risky as well. The applied contrast material is not nephrotoxic and the method uses non-ionizing radiation. These features make CEUS highly suitable for the examination of kidney transplant patients.

Notes

Doctoral School: Scientific Medicine Program: Radiology of Transplantation Supervisor: Attila Doros MD PhD E-mail address: kordadavid@t-online.hu

Abstract type

oral

THE EFFECT OF MATERNAL WEIGHT GAIN BEFORE THE DIAGNOSTIC OGTT ON THE RISK OF GESTATIOANL DIABETES

Szili-Janicsek, Zsófia

Zsófia Szili-Janicsek1, Ádám Gy. Tabák1,2 1 1st Department of Medicine, SemmelweisUniversitiy Faculty of Medicine, Budapest, Hungary 2 Department of Epidemiology and Public Health, UniversityCollegeLondon, London, UK.

Background and aim

Body mass index measured in the 1st trimester(bBMI) is an important predictor of gestational diabetes (GDM), however effect of BMI change during the first two trimesters is unknown.Therefore we hypothesized that larger BMI change until the OGTT (dBMI) would predict GDM.

Methods

Between 2002-2005, n=5335 pregnant women participated in a universal population-based screening at SzentImre Hospital. Body weight was measured at 6-8 and 24-28 gestational week (first prenatal visit and at the time of the 75g OGTT). GDM was diagnosed based on both the WHO-1999 (n=296) and the WHO-2014 (n=648) diagnostic criteria. Hierarchical logistic regression models were used to investigate the association between GDM risk and (1) dBMI and then (2) adjusted for bBMI.

Results

The age of participants was 29.3±4.22 (mean±SD) years, bBMI 22.80±4.25 kg/m2, dBMI2.51±1.50 kg/m2. Later GDM women had a smaller BMI increase compared to controls, and there was a negative correlation between bBMI and dBMI (r=-0.21, p<0.0001). In univariate analysis a larger BMI increase seemed to be protective against GDM development (OR: 0.89 95%CI: 0.84-0.94, p<0.001), however this association was completely abolished after adjustment for bBMI (OR: 0.97 95%CI: 0.91-1.03, p=0.261). A similar (but weaker) negative association was found between the risk of GDM based on the WHO-1999 recommendation and dBMI (OR: 0.91 95%CI: 0.84-0.99, p=0.023), that was also reduced to nonsignificance after adjustment for bBMI (OR: 0.98 95%CI: 0.90-1.06, p=0.558).

Conclusion

Our results suggest that weight gain between early pregnancy and the 2nd trimester has little effect on the risk of GDM determined by early pregnancy obesity and thus lifestyle counselling at early pregnancy is unlikely to substantially decrease the risk of GDM development.

Notes

Fundings: OTKA 68575/2007. DoctoralSchool: Clinical Medicine Program: Molecular Genetics, Pathomechanism and Clinical Aspects of Metabolic Disorders Supervisor: Ádám Gy. Tabák E-mail address: zsofi1101@gmail.com

Abstract type

oral

INTEGRATED ANALYSIS OF MIRNA- AND MRNA EXPRESSION PROFILES IN PREECLAMPSIA

Biró, Orsolya

Orsolya Biró1, Bálint Nagy1,2, JánosRigó Jr.1 1 1st Dept. of Obstetrics and Gynecology, Semmelweis University, Budapest, Hungary 2 Dept. of Human Genetics, University of Debrecen, Hungary

Introduction

Preeclampsiais the leading cause of maternal and fetal morbidity and mortality, affecting 3-8% of all pregnancies worldwide. Unfortunately, the pathogenesis of preeclampsia is still not clear. miRNAsare

small, non-coding RNA molecules, which negatively regulate gene expression. They are associated with several pathological conditions including pregnancy complications such as preeclampsia. The aim of our study was to find preeclampsia-relatedmiRNA regulatory mechanisms usingbioinformatics approaches.

Methods

We analyzed miRNA (GSE57050) and mRNA (GSE73374) expression datasets, which were created under similar experimental circumstances. Differentially expressed miRNAs were identified for the estimation of their inhibitory effect. We integrated miRNA and gene expression profiles with the MAGIA web tool, and created abipartite network from the significant miRNA-mRNA pairs using theCytoscape software. Two subnetworks were expanded by protein-protein interactions from the HPRD database. We analyzed the network elements using different bioinformatics tools and through literature research.

Results

We created a network, which consists of 85 nodes and 80 edges signalizing the connections between 52 regulated genes and 33 miRNAs. 11 of the genes are preeclampsia-related and 9 of them were targeted by multiple miRNAs. 8 miRNAs are associated with preeclampsia, and 13 miRNAs regulated more than one mRNA. Hsa-mir-210 was the highest degree node in the network and its role in preeclampsia is well-known.

Conclusion

We identified several miRNA-mRNA interactions which may contribute to the pathogenesis of preeclampsia. Further investigations are needed to validate these mechanisms and to unfold the possibilities of identifying potential biomarkers for the disease.

Notes

Doctoral School: Clinical Medicine Program: Reproductive Medicine Supervisor: János Rigó Jr., Bálint Nagy E-mail: biro.orsolya@noi1.sote.hu

Abstract type

oral

Effects of perinatal impairments on the development of extremely low birth weight newborns

Nagy, Anett

Anett Nagy1,2, Anna Mária Beke2, Rózsa Gráf1, Magda Kalmár3, János Rigó jr.2 Eötvös Loránd University, Faculty of Special Education, Special Education Institute of Atypical Behaviour and Cognition. Budapest Semmelweis University 1st Department of Obstetrics and Gynaecology. Budapest Eötvös Loránd University, Faculty of Pedagogy and Psychology. Budapest

Introduction and aim

The purpose of the study is to judge the early and the late outcome in this risk-group of newborns. The increasing rate of survival of newborns with extremely low birth weight (BW≤1000 grams) raises many questions. The authors ask whether the changing in neonatal state, neonatal morbidity resulted in changing in late outcome prognosis too. Can we observe the signs of immaturity in the late outcome?

Participants

67 extremely low birth weight preterms born in years 1990-2012 in 1st Department of Obstetrics and Gynaecology Semmelweis University.

Methods

The authors investigate the developmental outcome of preterms, which are influenced by perinatal impairments (Bronchopulmonary displasia (BPD), Intraventricular haemorrhage (IVH) and Retinopathy of prematurity (ROP)). The early and late developmental disabilities were assessed. The age-specific examinations were performed with standardized tests and methods. The infants 1 year of age and 2 years of age were tested by Brunet-Lezine test.

Results

The authors found correlation between the birth weight, gestational age, neonatal morbidity, sex, maternal education at the developmental test.

Discussion

The developmental outcome of patients suffering in different disorders depends on early pathological and biological factors. This outcome (including results of subtests) in patients without serious impairments can suggest long term effects of immaturity in this extremely low birth weight group.

Notes

Doctoral School: Eötvös Loránd University, Faculty of Pedagogy and Psychology Program: Clinical Child Psychology Program Supervisor: Magda Kalmár email: anett.barczi@gmail.com

Abstract type

oral

Primary sensory neuron desensitization by resiniferatoxin increases the severity of L-ornithine-induced acute pancreatitis in rats

Bálint, Emese Réka

Emese Réka Bálint1, Zsolt Balla2, Andrea Molnár1, Chloé Marsollier3, Romane Marc4, Péter Hegyi1,5, Lóránd Kiss2, Zsuzsanna Helyes4, Zoltán Rakonczay Jr.1 1 First Department of Medicine, 2 Department of Pathophysiology, 3 University of Angers, Angers, France, 4 University of Nantes, Nantes, France, 5 Department of Translational Medicine / 1st Department of Medicine, 6 Department of Pharmacology and Pharmacotherapy 1-2 University of Szeged, Szeged, Hungary 5-6 University of Pécs, Pécs, Hungary

Introduction

Transient receptor potential vanilloid 1 (TRPV1) is a nociceptor predominantly expressed by primary sensory neurons. TRPV1 participates in neurogenic inflammation and thus to have a major role in the pathogenesis of inflammatory disorders. Therefore, we aimed to examine if desensitization of TRPV1 neurons affects the severity of experimental acute pancreatitis (AP) in rats.

Methods

To induce AP, Sprague-Dawley rats were injected intraperitoneally (i.p.) with 3 g/kg L-ornithine. 4 weeks before the induction of AP, primary neurons expressing TRPV1 were desensitized by resiniferatoxin (RTX), an agonist of TRPV1. RTX was administered by three i.p. injections (30 μg/kg, 70 μg/kg and 100 μg/kg, 30, 29 and 28 days before the induction of AP, respectively). Rats treated with L-ornithine and/or RTX were compared to their respective control groups treated with physiological saline. To determine AP severity, laboratory and histological parameters were measured.

Results

L-ornithine induced necrotizing AP caused decreased pancreatic amylase activity and increased serum amylase and pancreatic myeloperoxidase activities, water content and heat-shock-protein 72 expression. RTX administration in itself did not significantly influence any of the measured parameters compared to the absolute control group (physiological saline instead of both RTX and L-ornithine). Most laboratory and histological parameters demonstrated that primary sensory neuron desensitization increased AP severity vs vehicle-pretreated L-ornithine-induced AP.

Conclusion

Defunctionalization of TRPV1 neurons in the L-ornithine-induced AP model demonstrated an exacerbation of disease severity. Interestingly, our findings indicate that primary sensory neurons have a protective role in L-ornithine induced AP.

Notes

Doctoral School: SZTE ÁOK Elméleti Orvostudományok Doktori Iskola Program: Neuroendocrinology, Pancreatology E-mail address: bioemese@gmail.com

Abstract type

oral

Supporting rehabilitation of patients post-stroke with application of task-specific exercises in high repetition number

Tavaszi, Ibolya

Ibolya Tavaszi (1), Gabor Fazekas (1) (2), Beata Karlik (1), Rahel Lukacs (1), Renata Steigervald (1), Ferenc Szerencses (1) (1) National Institute for Medical Rehabilitation, Budapest, Hungary; (2) Szent Janos Hospital, Budapest, Hungary

Introduction

Upper-limb functions are often impaired as a consequence of stroke. The improvement of these functions involves not only the increase of the muscle power and range of motion, but also the improvement of manual dexterity. Task specific, goal oriented exercises can help to fulfil this aim. Executing such tasks in high repetition number can be exhausting for the therapist, for this reason more and more frequently robots are used for this purpose. In case of patients, whose upper limb function is moderately impaired, it is not necessary to use expensive robots. It seems to be reasonable to execute exercises with weight support of the upper limb without electromechanical assistance.

Methods

Authors executed a cross-over pilot study with a gravity-supporting exoskeleton device (ArmeoSpring®) involving 12 patients post-stroke. All of them received a four-week-long rehabilitation programme. It consisted of two parts: through two weeks each subject got only traditional physiotherapy, during the other two weeks they also underwent 10 sessions with the device. The improvements seen in the two parts of the trial were compared. The subjects' mean age was 56 (24-86) years, the mean time since onset of the stroke was 32 months (12-50). Upper limb subsection of Fugl-Meyer (FM), Modified Ashworth Scale, Functional Independence Measure, Bathel Index were assessed before and after each phase of the therapy programme. Applying this device requires a relatively good upper limb function.

Results

FM (maximum score 66) improved in 5 patients (3-8 points) during the experimental phase and in 2 cases (7-7 points) during the control phase, while in 5 cases there were no improvement. There were no considerable changes in the other scores (regarding the functional scales patients have quite high scores even at the inclusion). All subjects found this therapy useful and they would take part in such trial again with pleasure.

Conclusion

This pilot study suggests that supplementation of the traditional rehabilitation programme of patients post-stroke with goal-oriented repetitive exercises applying a gravity-supporting exoskeleton may present some further advantages for patients even those with moderate impairments. A limitation of this study is the relatively low number of training sessions. For this reason a trial with higher numbers of subjects and more therapy sessions are required to verify these results.

Notes

Doctoral School: Clinical Medicine Program: Physiology and Pathology of the Musculoskeletal System Supervisior: Gabor Fazekas E-mail address: tavaszi.ibolya@gmail.com

Abstract type

oral

Some psychological features related to the craniomandibular disorders. A cross-sectional study

Albert, Luminița Elena

Luminița Elena Albert 1, Sorin Popșor2 1 clinical psychologist at the Tîrgu Mureș County Hospital, PhD student 2 University of Medicine and Pharmacy, Tîrgu Mureș

Introduction

The involvement of the psycho-emotional factors in the craniomandibular disorders onset, as well as in its perpetuation and treatment, is well-known and broadly accepted. Numerous psychometric tools have been proposed to assess the association between the craniomandibular parameters and the psychological ones. The purpose of this cross-sectional study was to assess the association between some psycho-emotional features and the craniomandibular disorder severity expressed by Helkimo Di and Ai indexes.

Matrials and methods

Forty subjects (28m and 18 f, mean age 24,4 years) presented for various prosthetic treatments and without any subjective complaint of dysfunction agreed to participate in this study. We used for the epidemiological evaluation the well known Helkimo indexes for dysfunction. To assess some psychological characteristics we applied the tests for the temperament and behavioral phenotypes, as well as for the evaluation of the stress level . We used the EPI INFO version 6.03-1995 statistical program to evaluate the association between the selected psychological factors and the craniomandibular disorder severity expressed by the Di and Ai values. We took into consideration the values up to 50% of credibility and correlation and the significant difference ($p<0.05$) between the D<i and the Ai values for the psychological items.

Results

Eight from the forty investigates subjects(20.00%) had DiO, 53.33% DiI,20.00% DiII and 6.77% DiIII. From the entire patient group 53.33% had AiO, 20.00% AiI and 26.67% AiII. There are significant differences ($p=0.02$) when to compare the Di score regarding the behavioral phenotype (type A and B). The same significant difference is present regarding the Ai score versus the psychological parameter ($p= 0.0320$).

Conclusion

The findings of this study support the role of the psychological factors in the craniomandibular dysfunctions development and its perpetuation, as well as the multifactorial cause of this disorder.

Notes

University of Medicine and Pharmacy Doctoral School, Tîrgu Mureș, Romania Dental Medicine Program Supervisor : Sorin Popsor E-mail address of the presenter: albertluminita04@gmail.com

Abstract type

oral

Characterization of pancreatic ductal fluid and bicarbonate secretion in wild type ferrets

Tóth, Emese

Emese Tóth1, Petra Pallagi1, József Maléth1, Viktória Venglovecz2, Zoltán Jr. Rakonczay1,3, Péter Hegyi4,5 1. First Department of Medicine, University of Szeged, Szeged, Hungary 2. Department of Pharmacology and Pharmacotherapy, University of Szeged, Szeged, Hungary 3. Department of Pathophysiology, University of Szeged, Szeged, Hungary 4. MTA-SZTE Momentum Translational Gastroenterology Research Group, University of Szeged, Szeged, Hungary 5. Institute for Translational Medicine/1st Department of Medicine, University of Pécs, Pécs, Hungary

Introduction

Cystic fibrosis (CF) is a lethal genetic disease affecting several organs, including the pancreas. Although animal models are available to study the CF related tissue damage they have clear limitations. Recently a cystic fibrosis transmembrane regulator (CFTR) knock out ferret model was generated. This model would be the first available one to study pharmacological prevention of the disease development.

Aim

We aimed to characterize the fluid and bicarbonate secretion of wild type (WT) ferret pancreatic ducts.

Methods

Expression of CFTR was detected by immunohistochemistry. Intra/interlobular pancreatic ducts were isolated from the WT ferret pancreas. Resting pH, buffer capacity and Cl-/HCO3 exchange activity were evaluated by microfluorometry. Fluid secretion was examined by video microscopy.

Results

CFTR was expressed on the luminal membrane of ferret pancreatic ducts. The resting intracellular pH of pancreatic epithelial cells is lower (7.17±0, 08) in ferrets compared to mice (7.31) or to guinea pigs (7.36). Concerning the bicarbonate influx mechanisms, functionally active sodium/hydrogen exchanger and sodium/bicarbonate cotransporter were detected. Anion exchanger activity measured by NH4Cl- technique, Cl— removal and inhibitory stop methods indicated that ferret pancreatic ducts secrete similar amount of bicarbonate as mice and guinea pigs. Video microscopy revealed a significant increase in fluid secretion to HCO3- and to 5μM forskolin stimulation.

Conclusion

Ferret pancreatic ductal epithelial cells express the major epithelial ion transporters. Our results indicate that ferret could be a suitable model organism to study the CF related pancreatic damage. Moreover this model open up the possibilities to test pharmacological interventions in the disease development.

Notes

Doctoral School: SZTE-ÁOK Elméleti Orvostudományok Doktori Iskola Program: Neuroendocrinology /Pancreatology/ Supervisors: Péter Hegyi, Petra Pallagi, József Maléth Email address of the presenter: tothemesem@gmail.com

Abstract type

oral

INCREASED placental tissue factor pathway inhibitor-2 (TFPI-2) expression in women with preeclampsia and HELLP syndrome: RELEVANCE TO IMPARED TROPHOBLAST INVASION?

Karaszi, Katalin

Katalin Karaszi1,2, Barbara Kocsis-Deak2, Szilvia Szabo3, Ilona Kovalszky1, Nandor Gabor Than1,2 1 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest 2 Systems Biology of Reproduction „Lendület” Research Group, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest 3 Department of Morphology and Physiology, Faculty of Health Sciences, Semmelweis University, Budapest

Introduction and aim

Tissue factor pathway inhibitor-2 (TFPI-2) is an extracellular matrix-associated Kunitz-type serine proteinase inhibitor predominantly expressed by the placenta. It is also produced by various tumors and plays a role in tumor growth, invasion and metastasis, presumably through plasmin-mediated matrix remodeling. Preeclampsia is a severe pregnancy complication originated from the failure of trophoblast invasion and the consequent malfunctioning of the placenta. This placental pathology is extensive in early-onset preeclampsia, while it is less pronounced in later developing late-onset preeclampsia. The altered placental pathologic pathways leading to impaired trophoblast invasion include proteinases and their inhibitors; however, their contribution to these pathologic events has not been fully elucidated in these various subforms of preeclampsia.

Aim

Our aim was to examine how placental TFPI-2 expression is altered in the placenta in preeclampsia with or without hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.

Methods

Tissue microarrays (TMAs) were constructed from formalin-fixed paraffin-embedded placentas obtained from pregnant women in the following groups: 1-2) early-onset preeclampsia with (n = 8) or without (n = 7) HELLP syndrome; 3) late-onset preeclampsia (n = 8); 4-5) preterm (n = 5) and term (n

= 9) controls. TMA slides were stained for TFPI-2 and immunostainings were semi-quantitatively evaluated using virtual microscopy.

Results

TFPI-2 expression was localized to the cytoplasm of syncytiotrophoblast. TFPI-2 immunoscores were higher in both late-onset preeclampsia and early-onset preeclampsia, irrespective of the presence of HELLP syndrome, than in respective preterm and term controls.

Conclusion

In conclusion, increased TFPI-2 expression may lead to abnormal placentation and inadequate trophoblast invasion partly responsible for the development preeclampsia and HELLP syndrome. Our findings may also suggest that TFPI-2 plays a key role in the physiological regulation of trophoblast invasion, similarly to inhibiting tumor growth, invasion and metastasis.

Notes

Funding: Systems Biology of Reproduction „Lendület” Grant Doctoral School: Pathology Program: Oncology Supervisor: Prof. Dr. Ilona Kovalszky E-mail address: tika0604@gmail.com

Abstract type

oral

Antidrug antibody formation against biological agents in psoriasis

Herszényi, Krisztina

K. Herszényi, H. Jókai, N. Wikonkál, F. Rencz, V. Brodszky, S. Kárpáti, E. Nagy, P. Holló

Introduction

Nowadays biological agents are used in the treatment of psoriasis with great efficacy but in some cases antidrug antibody (ADA) formation can occur and may stand behind primary and secondary inefficacy. These can be neutralizing or non-neutralizing antibodies - may bind to the active cytokine binding place of the agent, can change the pharmacokinetics and pharmacodinamical parameters of the drugs, they can form immunocomplexes with the biologicals and lead to an accelerated clearance.

Patients and methods

In our study 64 patients on adalimumab, 49 on infliximab and 46 patients on etanercept treatment were examined. Bridging ELISA was used to evaluate ADA-s in patients sera, the serum drug concentration at the time of sample collection, PASI was calculated at the same time and the need of drug switch was registered as well.

Results

In case of adalimumab (n=64) 18.4% of the patients had ADA formation (p=0.009), the serum drug concentration was significantly higher in the ADA negative group and the necessity for drug switch was significantly more common in ADA positive patients (p=0.02).In patients receiving infliximab (n=49) 30.6% of them had ADA in their sera, the serum drug concentration was significantly higher in the ADA negative group (p<0.001) and the need for drug switch was significantly higher in ADA positive patients (p=0.016).We can not identify any ADA in case of etanercept treated patients (n=46), among them 40 patients had measurable drug concentration. The mean PASI value was 2.45, in case of ADA positive patients it was 3.2 (p=0.717). In the group of ADA positive patients the need of drug switch for more than one time, guttate exacerbations were more common and more patients belonged to the Type I. psoriasis group (data are not significant).

Conclusion

In the background of poor efficacy or efficacy lost after a good response in the treatment of psoriasis with biological agents we should properly search for ADA formation beside other causative factors. It can become a great tool for optimizing and trying to make a more personalized therapy, avoiding unnecessary therapeutical changes and maintaining cost- effectivity as well.

Notes

Clinical Sciences Dermatology and Venereology Tutor: Dr. Péter Holló
krisztina.herszenyi@gmail.com

Abstract type

oral

Steroid receptor expression in pregnancy-related melanoma cases

Fábián, Melinda

Melinda Fábián1, Petra Balogh2, Tibor Krenács2, Fanni Rencz3, Sarolta Kárpáti1 1. Department of Dermatology, Venereology and Dermatooncology, Semmelweis University 2. 1st Department of Pathology&ExperimentalCancer Research, Semmelweis University 3. Department of Health Economics, Corvinus University of Budapest, and Semmelweis University, Doctoral School of Clinical Medicine

Background

Most publications define pregnancy-associated melanoma (PAM) when it is diagnosed during pregnancy or after delivery within one year (postpartum melanoma). Beside breast, ovarian and prostate cancer, part of the scientific community considers melanoma also as a hormone dependent malignancy, while the role of estrogen receptor (ER) and progesterone receptor (PR) in PAM development and prognosis is still controversial.

Methods

The database of the Dermatology, Venereology and Dermatooncology Clinic of the Semmelweis University (DVDSE) was retrospectively reviewed and all the recorded PAM cases diagnosed between 2003 -2015 were analyzed in this study. The expression of ERα, ERβ and PR was examined by immunohistochemistry (IHC) and the slides were subjected to whole slide digitalization using Panoramic Scanner (3DHISTECH). The IHC was evaluated on 81 melanoma samples (38 PAM and 43 NPAM as controls) who underwent surgery for the primary tumor at the DVDSE during this period.

Results

The purpose of our study was to evaluate the presence of ER subtypes and PR on the tumor cells and on the inflammatory cells within the melanoma microenvironment. In contrast with many other publications, we detected cytoplasmic ERβ positivity of the tumor cells together withan intensive nuclear labeling in a subpopulation of inflammatory cells. The protein expression of ERβ was significantly higher in PAM than in NPAM group. In contrast, melanoma tissue samples remained negative for both ERα and PR.

Conclusion

The presence of ERβ in the tumor cells is suggesting an active estrogen driven signaling via the classical, nuclear pathway, while the cytoplasmic expression of the ERβ pool is indicating more some non-classical signaling cascades, that has an emerging role in tumour progression and development. Further functional studies are needed to define the exact role of cytoplasmic ERβ expression in melanoma, but the striking differences in cytoplasmic and nuclear steroid receptor status is indicating a new focusof future research on this area.

Notes

Doctoral School: Clinical Medicine Program: Dermatology and Venereology Supervisior: Prof.Dr. Sarolta Kárpáti email address: fmelindee@gmail.com

Abstract type

poster

Neurosciences

The outcome of fMRI language mapping is affected by patient fatigue

Kiss, Máté

Máté Kiss, Gabor Rudas, Lajos Rudolf Kozák

Purpose

Proper patient cooperation is very important for successful task-based clinical functional MRI (fMRI). Careful paradigm design can help maintaining the patients' attention, but fatigue may still affect the outcome. We aimed to investigate the possible effects of fatigue in 4 different fMRI language mapping paradigms.

Matrials and methods

Nineteen healthy volunteers performed picture naming, synonym matching, speech comprehension and auditory decision tasks in separate 576s runs (12-12 active and passive 24s blocks). Data analysis was performed by means of generalized linear model in SPM12 and connectivity analysis in CONN, both with standard preprocessing steps. To investigate the effects of fatigue we compared the first and second halves of each run in both analyzes on the single subject and on the group level using parametric statistics.

Results

All paradigms yielded the expected task activation maps, but the spatial distribution of activations shifted towards the default mode (DMN) and the attentional (ATT) networks for the second halves of the runs, in a paradigm-dependent fashion. Task-related connectivity analysis confirmed this shift by showing more prominent overall connectivity of DMN and ATT.

Conclusion

While longer paradigms lead to better model fit theoretically, effects of fatigue can change the outcome of fMRI mapping. The observed increased DMN involvement may be consistent with losing attention or day-dreaming, while increased ATT involvement may represent recruitment of additional neural circuits to maintain processing performance. Further investigation may elucidate the effects of paradigm design on decreasing fatigue while keeping proper attention for longer mapping runs.

Notes

Doctoral School: Neurosciences (János Szentágothai Clinical Medicine Doctoral School) The title of the Program: Clinical Neurological Research Supervisor: Lajos Rudolf Kozák E-mail address of the presenter: kissmate20@gmail.com

Abstract type

oral

Data-driven identification of white matter (WM) changes can help finding hard-to-identify malformations of cortical development (MCDs)

Gyebnár, Gyula

Gyula Gyebnár, Zoltán Klimaj, Gábor Rudas, Péter Barsi, Lajos R Kozák Magnetic Resonance Research Center, Semmelweis University

Purpose

MCDs are important causes of drug-resistant epilepsy. Some subtypes, e.g. focal cortical dysplasias (FCDs) pose serious challenge to identify in MRI. We aimed to develop an automated post-processing tool for the identification of such lesions by the examination of WM microstructure, based on T1 and diffusion weighted MRI data.

Matrials and methods

18 patients with MCDs and 31 controls were involved. MCD subtypes included polymicrogyria (7) schizencephaly (2), subependymal heterotopia (2), FCD (12). Diffusion weighted (32 directions with b=800s/mm2, one b=0 image) and high resolution 3D T1W images were acquired at 3Tesla. We used ExploreDTI for data processing (e.g. corrections and robust tensor-fitting) and calculation of tensor-based diffusion metrics (fractional anisotropy, mean, axial and radial diffusivity), and SPM12 for anatomical segmentation and spatial normalization. The diffusion metrics were used as dimensions in the composition of multivariate probability distributions; thereby each WM voxel was

assigned 4 numbers in each subject. Patients were compared to controls by calculating the multi-dimensional voxel-vise Mahalanobis-distance. Significance of distances was assessed using Chi-squared based statistics with False Discovery Rate control. MCD ROIs were marked by an automated toolbox (MAP07) and reviewed and corrected by experienced radiologists for validation purposes.

Results

We found significant ($p<0.001$) alterations of white matter microstructure adjacent to the lesions in 15 of 18 cases, with 12 of 18 patients showing changes in contralateral white matter, as well.

Discussion

Our novel, data-driven approach can serve as an aid in the identification of minute structural changes in MCDs, however further research is needed to improve the specificity of the method.

Notes

This study was supported by the Hungarian National Brain Research Program grant KTIA/NAP_13-1-2013-0001 and by the MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group. L.R.K. also received support from the Bolyai Research Fellowship Program of the Hungarian Academy of Sciences. Doctoral School: Neurosciences (“János Szentágothai”) Program: Clinical Neurological Research Supervisor: Lajos R Kozák E-mail: gyebnargyula@gmail.com

Abstract type

oral

Stuctured reporting in neonatal hypoxic-ischemic encephalopathy – preliminary results

Lakatos, Andrea

A. Lakatos1; M. Kolossvary1,3; M. Szabo2; M. Kiss1; G. Gyebnar1; Z. Bagyura3; G. Rudas1; L.R. Kozak1 1 MR Research Center, Semmelweis University, Budapest, Hungary; 2 First Dept. of Paediatrics, Semmelweis University, Budapest, Hungary; 3 MTA-SE „Lendület” Cardiovascular Imaging Reseach Group, Budapest, Hungary

Introduction

The radiology report is a tool to communicate information to the referring physicians and record data for follow-up or research purposes. The aim of our work was to develop a structured MRI reporting template for neonatal hypoxic-ischemic encephalopathy (HIE) in collaboration with neonatologists and information technologists.

Patients and methods

A systematic reporting template (iSORT for HIE) was developed on the basis of published evidence and the retrospective analysis of MRI examinations of 106 asphyxiated neonates. MRI studies were performed with a Philips Achieva 3T MR scanner between 2013-2014. A web-based reporting template was created based on T1-, T2, T2*/SWI, DWI MR images and SVMR-spectroscopy. The development and improvement of the system was followed by a feasibility study including data input on all the 106 patients and data analysis aiming to find out whether the diffusion changes show an evolution in time and space.

Results

The tree-structured iSORT outline directs focus on the most characteristic imaging findings seen in HIE. The three sections of the template contain the patient data, the technical aspects of the MRI examination and record signal intensity changes in nested anatomic landmarks. As a feasibility study, our search for infants presenting with restricted diffusion resulted 36/106 patients. Partitioning the patients regarding the age at the MRI examination and the affected anatomic area showed that diffusion restriction in the thalami has a steady decline, while the involvement of the optic radiations increased until the 7-8th day, followed by dicrease over the subsequent days.

Conclusion

The iSORT for HIE is a structured reporting system dedicated to report MRI examinations of asphyxiated neonates. Getting used to the system, the data recording is faster and the information is more detailed compared to a conventional report. The sytem is particularly beneficial in research, enabling bulk data input, arrangement and search.

Notes

Name of the Doctoral School: Semmelweis University, János Szentágothai Doctoral School of Neurosciences, Clinical Medical Sciences. Title of the Program: Changes of functional and structural networks of the brain in disorders affecting the central nervous system. Name of the Supervisor: Lajos R. Kozák Presenter's e-mail address: drea820317@gmail.com

Abstract type

oral

Microglia protect against brain injury via shaping neuronal activity and spreading depolarization in vivo

Martinecz, Bernadett

Gergely Szalay1*, Bernadett Martinecz2*, Nikolett Lénárt2*, Zsuzsanna Környei2, Barbara Orsolits2, Linda Judák1,3, Eszter Császár2, Rebeka Fekete2, Brian L. West4, Gergely Katona3, Balázs Rózsa1,3# and Ádám Dénes2# Two-Photon Imaging Center, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary Laboratory of Neuroimmunology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary Faculty of Information Technology and Bionics, Pázmány Péter University, Budapest 1083, Hungary Plexxikon Inc., Berkeley, CA 94710, USA *Joint first authors; #Joint senior authors

Introduction

Microglia are the main immune cells of the brain and contribute to common brain diseases. Altered microglial activity is associated with migraine, stroke, dementia, traumatic injury, epilepsy and Parkinson's disease. However, it is unclear whether microglia regulate neuronal survival after injury via shaping the activity of complex neuronal networks in vivo.

Matrials and methods

We have developed a precisely controlled model of brain injury induced by cerebral ischemia to combine fast in vivo two-photon calcium imaging with selective microglial manipulation. Microglia-neuron interactions were investigated in real time, followed by super-resolution microscopy to study brain injury-induced changes at the nanoscale level.

Results

We show that neuronal network activity is monitored and controlled by microglia. Selective elimination of microglia leads to a striking, 60% increase in infarct size, which is reversed by microglial repopulation. Microglia-mediated protection includes reduction of excitotoxic injury, since an absence of microglia leads to dysregulated neuronal calcium responses, calcium overload and increased neuronal death. Furthermore, incidence of spreading depolarization (SD) is markedly reduced in the absence of microglia, both in the evolving infarct and in the non-ischemic brain. We also show that microglia-neuron interactions are markedly altered in the injured brain that could be mediated by changes in purinergic signaling.

Conclusion

We identify microglia as major regulators of neuronal activity and SD in vivo that could have important implications for common brain diseases.

Notes

Doctoral School: János Szentágothai Neuronal Doctoral School Program: Neuromorphology and Cell Biology Supervisor: Adam Denes E-mail: martinecz.bernadett@koki.mta.hu

Abstract type

oral

METHYLENE BLUE, THE POTENTIAL NEUROPROTECTIVE AGENT, WHICH INCREASES MITOCHONDRIAL SUBSTRATE LEVEL PHOSPHORYLATION

Komlódi, Tímea

Tímea Komlódi1, Vera Ádám-Vizi1,2, László Tretter1,2 1 Department of Medical Biochemistry, Semmelweis University, Budapest 2 Laboratory for Neurobiochemistry, Hungarian Academy of Science, Budapest

Introduction

Methylene blue (MB), a potential neuroprotective agent is efficient in Alzheimer's and Parkinson models. The mitochondrial effects of MB were explained by the alternative electron transfer model which means MB can transfer electrons from NADH to cytochrome c when the complex I or complex III are inhibited.

Aim

In the present study the effect of MB was investigated on mitochondrial substrate-level phosphorylation (SLP). SLP is partially independent from the mitochondrial protonmotive force and involves reaction catalyzed by succinyl-CoA ligase in the citric acid cycle.

Methods

Measurements were carried out on isolated guinea-pig brain mitochondria respiring on α-ketoglutarate, glutamate, glutamate plus malate (GM) or succinate. It is known that the former substrates support mitochondrial SLP while succinate does not favor it. The following protocol was used throughout the experiments to detect mitochondrial SLP: oxidative phosphorylation was inhibited by the ATP synthase inhibitor, oligomycin. This step was followed by the addition of MB. At the end of each experiment adenine nucleotide translocator was blocked. In order to characterize mitochondrial bioenergetics the rate of ATP synthesis, oxygen consumption, mitochondrial membrane potential, and NADH autofluorescence were followed.

Results

Our experiments demonstrated that ATP synthesis was stimulated by MB in the presence of complex I dependent substrates, but no stimulation of ATP synthesis was detected in mitochondria supported by succinate. The order of stimulation was α-KG > glutamate > glutamate + malate. Oxygen consumption was increased by MB added after oligomycin with each substrate, demonstrating that respiration enhancement and ATP production does not run parallel.

Conclusion

It is concluded that MB mediated stimulation of SLP can be an important factor to maintain energetic competence of mitochondria.

Notes

Fundings: OTKA (NK 81983), TAMOP (4.2.2./B-09/1), MTA (MTA TKI 2013), and Hungarian Brain Research Program (Grant No. KTIA_13_NAP-A-III/6) Doctoral School: János Szentágothai School of Neurosciences Program: Functional Neurosciences Supervisor: László Tretter E-mail address: komlodi.timea@med.semmelweis-univ.hu

Abstract type

oral

ANALYSIS OF THE INTRA- AND INTERAREAL CONNECTIONS IN THE PRIMATE SOMATOSENSORY CORTEX

Pálfi, Emese

Emese Pálfi1, László Zalányi2, Mária Ashaber3, Cory Palmer4, Robert M. Friedman5, Anna W. Roe5,6, László Négyessy1,2 1 Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, H-1094 Hungary 2 Complex Systems and Computational Neuroscience Group, Wigner Research Centre for Physics, Hungarian Academy of Sciences, Budapest, H-1121 Hungary 3 Department of Physiology and Biochemistry, Szent István University, Faculty of Veterinary Science,

Budapest, H-1078 Hungary 4 Department of Mathematical Sciences, University of Montana, Missoula, MT, USA 5 Division of Neuroscience, Oregon Health and Science University, Portland. OR 6 Zhejiang University Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University, Hangzhou, China

Notes

Areas 1 and 3b are the two most important regions in the primary somatosensory cortex where elementary perceptual processing takes place. After combining tract tracing and functional mapping by intrinsic signal imaging and electrophysiology, we compared the connectivity of distal finger-pad representations following tracer injections in areas 1 and 3b.The size of injections matchedthe size of submodality specific tactile modules in both areas. In all cases retrograde and anterograde labeling exhibited supragranular dominance, making these layers the main site of somatosensory cortical interactions. Density analysis of the retrograde labeling showed that similar size of neuronal populations provide input to column-size cortical regions within and between areas 3b and 1.However, the inter-areal spread of anterograde labeling was a larger after area 1 injectionthan after injection of area 3b. Connections within and between the two areas were highly anisotropic dominated by a medio-lateral orientation across the finger representations. In conclusion, intrinsic connections play a dominant role in integrating information across the functional maps within each area.However, regarding inter-areal connecivity feedback projection exhibit larger horizontal spread than that of feed forward. Supported by: FIRCA NS059061 (to A.W.R. and L.N.), NS044375 (to A.W.R.) and the Hungarian Scientific Research Fund OTKA NN79366 (to L.N.). Doctoral School: Neurosciences “János Szentágothai” Program: Neuromorphology and Cell Biology Supervisor: László Négyessy, PhD Email adress: palfi.emese@med.semmelweis-univ.hu

Abstract type

oral

mtDNA alterations and autism associated nuclear gene variants in the background of autism spectrum disorder

Varga, Á. Noémi

Noémi Á. Varga1*, Klára Pentelényi1, Péter Balicza1, Viktória Reményi1, Vivien Hársfalvi1, Renáta Bencsik1, Anett Illés1, Csilla Prekop2, Mária J. Molnár1 1) Institute of Genomic Medicine and Rare Disorders, Semmelweis University 2) Vadaskert Foundation for Children’s Mental Health,

Introduction

Autism spectrum disorder(ASD) is a neurodevelopmental disorder, with an unclear ethiological background. Mitochondrial dysfunction (MD) is one of the most common metabolic abnormality associated to ASD.

Aim

Our aim was to estimate in our ASD cohort the prevalence of mtDNA alterations, the mutation frequencies in genes associated with mtDNA maintenance and the alterations of genes associated to ASD.

Methods

We screened 60 ASD patients and 98 healthy individuals for the most common mtDNA disorders (mtDNA deletions, m.A3243G, m.A8344G, m.T8993C/A). Next generation sequencing (NGS) was performed with TruSight Autism Rapid Capture Kit (Illumina) to detect 103 ASD associated nuclear gene variations and SureSelect QXT Kit (Agilent) to detect 51 nuclear gene variations responsible for mtDNA maintenance.

Results

In 16.6% (10) of 60 ASD patients the genetic testing confirmed mtDNA deletions (MD-ASD cases). In this 10 MD-ASD cases we performed NGS testing, which identifies in 4 cases pathogenic mutations in genes responsible for mtDNA maintenance, and in 2 cases pathogenic mutations in genes related to ASD.One syndromic autism form could be identified. In 50% of cases, beside the ASD associated genetic risk factors, mutations responsible for mtDNA maintenance were detected. Phenotypically

some MD specific symptoms were most frequently present in MD-ASD patients than in pure ASD cases.

Conclusion

Among patients with ASD the presence of mtDNA alteration is more common than in control persons. The mtDNA deletion is usually not a single genetic alteration in ASD, it coexists both in syndromic and non-syndromic ASD forms either with other ASD associated genetic risk factors and/or alterations in genes responsible for intergenomial communication.

Notes

Fundings: KTIA_AIK_12-1-2013-0017 Doctoral School: Szentágothai János Doctoral School of Neuroscience, Program: Clinical Neurosciences Supervisor: Prof. Dr. Molnár Mária Judit E-mail address: noemiagnesvarga@gmail.com

Abstract type

oral

Increased spectral entropy dynamics with outlier spectral patterns associated with clinical seizure onset zone on the interictal ECoG recordings of epilepsy patients

Nánási, Tibor

Tibor Nánási1, Bálint File2, István Ulbert1, László Entz3, Loránd Erőss3, Dániel Fabó4 1. Institute of Cognitive Neuroscience and Psychology, RCNS, HAS, Budapest, Hungary 2. Faculty of Information Technology and Bionics, Pázmány Péter Catholic University, Budapest, Hungary 3. Department of Functional Neurosurgery, National Institute for Clinical Neurosciences, Budapest, Hungary 4. Epilepsy Centrum, Dept. of Neurology, National Institute of Clinical Neurosciences, Budapest, Hungary

Notes

The advent of computerization bought a plethora of autonomous and semi-autonomous tools to aid the diagnosis of multiple brain anomalies, including epilepsy. Bi- and multivariate methods rooted in graph theory becoming increasingly popular in this field. In the same time, approaches which could deliver meaningful results from individual electrode data tracks are relatively scarce and despite their robustness and simplicity, generally considered inferior. Spectral entropy has a long history in many fields dealing with time series analysis, however its potential to aid seizure onset zone detection from interictal ECoG recordings was not extensively explored yet. In this pilot study, we have analyzed ECoG data from 3 patients waiting for epilepsy surgery who were implanted with subdural grid arrays over the temporal lobe with 1 cm spacing between electrodes. We used interictal recordings preferably free from any obvious epileptic activity (except of spikes) with at least 1 hour of temporal separation from actual seizures. The patients were sleeping during the acquisition. We used multilevel wavelet decomposition on the basis of the ‘Daubechies 20’ wavelet to acquire dyadic frequency bands from 512 Hz to 2 Hz. Then, for every sampling point, an approximation of spectral entropy was calculated and the extent of dynamics of the entropy changes trough time was measured as its standard deviation. Channels marked by high values of this measurement overlapped significantly with the clinical seizure onset zone determined by expert neurologists in all three cases. Spectral dynamics profiles were defined as the standard deviation of the normalized power spectra through time, meaning this measurement was sensitive for the modulation of power on the given frequency bands but not to their mean power itself. The zones highlighted with elevated spectral entropy shown outlier profiles with weak resemblance to the supposedly healthy tissue, and the graph of the extent of similarities between this kind of spectral profiles between channels exhibited a separation of the marked channels from their surroundings. To verify our results, we performed the same analysis with high resolution continuous ‘Morlet’ (‘Gabor’) wavelet decomposition (100 frequency bands instead of the dyadic approach), with and without corrections for the 50 Hz power grid artefacts. Regardless to the wavelet basis and the corrections applied, conclusions remained the same. Taken together with the previous findings, spectral entropy based approaches are showing a great promise to become computationally effective, especially robust and light-weight tools for epilepsy surgery preparation. In contrast to many other approaches, they are free from manual

thresholding, which could be a significant advantage in a clinical setting where the temporal and computational resources may be limited. Doctoral School: Neurosciences “János Szentágothai” Program: Functional Neurosciences Supervisor: István Ulbert E-mail address: nanasitibor@gmail.com

Abstract type

oral

CRYSTAL STRUCTURE OF THE D444V DISEASE-CAUSING MUTANT OF HUMAN DIHYDROLIPOAMIDE DEHYDROGENASE

Szabo, Eszter

Eszter Szabo1*, Reka Mizsei1*, Zsofia Zambo1, Beata Torocsik1, Manfred S. Weiss2, Vera Adam-Vizi1, Attila Ambrus1 1 Department of Medical Biochemistry, Semmelweis University, Budapest, Hungary 2 Helmholtz-Zentrum Berlin für Materialien und Energie, Berlin, Germany *these authors contributed equally to this work

Introduction

Our research group addresses the pathogeneses by disease-causing mutants of dihydrolipoamide dehydrogenase, the third subunit (E3) of the human alpha-ketoglutarate dehydrogenase complex (hKGDHc), a rate-limiting enzyme in the Krebs cycle. hKGDHc is considered to be a major producer and a very sensitive target of reactive oxygen species (ROS). ROS generation by and dysfunctions of the hKGDHc are implicated in senescence/aging, neurodegenerative diseases and E3-deficiency, among other pathologies. hKGDHc generates ROS via the E3 subunit, the pathogenic mutations of which cause the often lethal human disease, the E3-deficiency.

Aim

Our main objective is to determine the crystal structures of the 14 disease-causing hE3 mutants (as many as attainable) by X-ray diffraction analysis with emphasis on those which produce ROS at a significantly higher rate relative to hE3.

Methods

A BL21(DE3)/pET-52b+ expression system combined with a one-step Strep-tag/Streptactin affinity chromatography purification protocol has been developed and optimized to produce and purify the mutant proteins. The first crystallization trials were carried out using commercially available screens, whereas generally the final successful conditions were the results of further optimizations. X-ray diffraction data were collected using synchrotron radiation in Helmholtz-Zentrum Berlin, Germany.

Results

We isolated all the 14 pathogenic mutants of the hE3. From these the following mutants were successfully crystallized: D444V, R447G, P453L, G194C, I358T, I318T, K37E, R460G and I445M. Hitherto, the crystal structure of the D444V mutant has been determined at 1.8 Å resolution.

Conclusion

Our major achievement is the determination of the crystal structure of the isolated hE3-D444V.

Notes

Fundings: MTA 02001, OTKA 112230, KTIA_13_NAP-A-III/6[all to A-V.V.], Bolyai and EMBO Fellowships to A.A., Erasmus Scholarships to Sz.E. and M.R. Doctoral School: János Szentágothai Doctoral School of Neurosciences Program: Functional Neurosciences Supervisor: Dr. Attila Ambrus Email address: szabo.eszter1@med.semmelweis-univ.hu

Abstract type

oral

Three novel mutations and genetic epidemiology analysis of the Cx32 gene as the cause of CMTX1 among Hungarian patients

Milley, György Máté

György Máté Milley1, Edina Tímea Varga1,2, Zoltán Grosz 1,Benjamin Bereznai1, Zsuzsanna Arányi3, Anna Süveges1, Anikó Gál 1 and Mária Judit Molnár1 Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary Department of Neurology, University of Szeged, Szeged, Hungary MTA-SE NAP B Peripheral Nervous System Research Group, Dept. of Neurology, Semmelweis University, Budapest, Hungary

Introduction

Charcot-Marie-Tooth neuropathies (CMT) belong to the most common hereditary neurological diseases. Pathogenic variants of the connexin 32 (Cx32) geneare responsible for the X-linked inherited CMT subgroup (CMTX1). In this study we estimate the mutation frequency of Cx32among Hungarian CMT patients and compare the phenotypes between male and female CMTX1 patients.

Patients and methods

Detailed neurological and neurophysiological investigation was performed in 210 patients suffering from hereditary motor and sensory neuropathy.The Cx32 gene was analyzed by Sanger sequencing.The novel alterations were tested in 350 healthy individuals by PCR-RFLP methodology.

Results

Altogether 13 missense substitutions were found in the Cx32 gene. Among them, ten have been already described as pathogenic variants (Arg15Trp, Val63Ile, Leu89Val, Ala96Gly, Arg107Trp, Arg142Gln, Arg164Trp, Arg164Gln, Pro172Ala and Asn205Ser), while 3 were novel,likely pathogenic alterations (Val13Gln, Glu186Gly, Met194Ile). These alterations were not detected in the control cohort and were predicted as disease causing by in silico analysis. The frequency of the variants was 6.7% in our cohort.

Conclusion

Among our positive cases, the statistical analysis revealed significant differences between the two genders regarding age of onset, CMT neuropathy and examination scores. In addition to the classical peripheral neuropathy phenotype, CNS involvement was proved in 26.1% of the patients. The Cx32 pathogenic alterations are a common cause of hereditary neuropathy among Hungarian patients. Cx32 mutations were found mainly in males but were also detected in female probands. The affected female individuals had a significantly higher age of onset and lower CMT neuropathy score than males.

Notes

Fundings:This study was supported by the Hungarian Brain Research Program (KTIA_13_NAP-A-III/6 to V.A-V.) grant.ZsuzsannaArányi was supported by the Hungarian National Brain Research Program (NAP B) (KTIA_NAP_13-2-2014-0012). Doctoral School: School of Ph.D.studies János Szentágothai Doctoral School of Neurosciences Supervisor: Anikó Gál E-mail address: milley.gyorgy@med.semmelweis-univ.hu

Abstract type

oral

Signaling via P2Y12 mediates microglial recruitment and defense against neurotrophic virus infection in the brain

Fekete, Rebeka

Rebeka Fekete1, Beáta Sperágh2, Ágnes Kittel2, Szilamér Ferenczi3, Előd Méhes4, Valéria Németh4, Zsolt Boldogkői5, Barbara Orsolits1, Bernadett Martinecz1, Nikolett Lénárt1, Balázs Rózsa6, Zsuzsanna Környei1, Ádám Dénes1 1 IEM HAS, Laboratory of Neuroimmunology 2 IEM HAS, Laboratory of Molecular Pharmacology 3 IEM HAS, Laboratory of Endocrinology 4 ELTE, Department of Biological Physics 5 University of Szeged, Department of Medical Biology 6 Femtonics

Introduction

Understanding immune mechanisms that are initiated in response to viral infectioninthe CNS is essential to develop appropriate therapies to diseases such as herpes simplex virus enchephalitis or viral meningitis. Microglial cells are known to be rapidly recruited to the sites of brain injury or

infection. In previous studieswe have demonstratedthat microglia form barriers around virus infected cells in the brain. However,the functional role of microglia in defense against neurotrophic viral infection and mechanisms controlling microglia recruitment to infected neuronsremained unclear.

Matrials and methods

We studied retrograde, transsynaptic spread of an attenuated pseudorabies virus (PRV) strain in the brain of wild type, P2X7 and P2Y12 knock out (KO) mice. Early and late stages of neuronal infection in different brain areas were discriminated and correlated with microglial activation and recruitment.In vivo two-photon imaging and super-resolution microscopy were performed to investigate mechanisms of rapid microglial responses to viral infection.In vitro cultures of microglia and PRV- infected neurons and astrocytes were used to study how altered purinergic signaling contributes to microglial responses. Cytokine responses were measured by quantitative PCR and cytometric bead array.

Results

Viral infectionwas associated with release of ATP and increased Ecto-ATPase activity, which resulted in rapid activation and recruitment of microglia both in vitro andin vivo. In contrast, the expression of inflammatory chemokines that facilitate the recruitment of monocytes and macrophages was negligible. P2Y12-positive microglia were rapidly recruited to infected neurons in the brain and phagocytosed cells showing signs of late infection. Microglial cells were resistant to virus infection. We found reduced microglia recruitment around infected neurons in P2Y12 KO mice, which was associated with enhanced spread of viral infection in P2Y12 KO, but not in P2X7 KO mice.

Conclusion

Our results suggest that ATP released from infected neurons and/or nearby cellscould mediate rapid recruitment of microglia to sides of neurotrophic viral infecion in the brain. Therapeutic interventions facilitating the phagocytosis of virally infected neurons by microglia could be used to support the elimination of viral particles and infected neurons from the CNS.

Notes

Doctoral School: János Szentágothai Neuroscience Doctoral School Program: Neuromorphology and cell biology Supervisor: Zsuzsanna Környei & Ádám Dénes E-mail: fekete.rebeka@koki.mta.hu

Mental Health Sciences

PARENTAL ATTACHMENT AND BODY SATISFACTION ON A LARGE HUNGARIAN STUDENT SAMPLE

Szalai, Tamás Dömötör

Tamás Dömötör Szalai1, Edit Czeglédi1 1 Semmelweis University, Institute of Behavioural Sciences, Budapest

Notes

Insecure attachment contributes to various mental health problems, among them to body dissatisfaction. It has not been clarified, whether attachment anxiety, or avoidance predicts lower body satisfaction, relationships with maternal and paternal patterns have not been distinguished yet. Aim: Our aim was to test the relationship of body satisfaction with paternal and maternal attachment traits like anxiety or avoidance in Hungarian adolescents. Methods: A large cross-sectional survey investigated health-related variables of Hungarian school-aged children and adolescents (N = 5214 respondents, 51.6% males, mean age 14.8 years, SD = 2.6 years). Measures: Sociodemographic and self-reported anthropometric data (weight, height), body satisfaction (five aspects), Hungarian version of Experience in Close Relationships Scale – Relationship Structures, Hungarian version of Child Depression Inventory. Results: Boys had significantly higher body satisfaction, and worse maternal attachment than girls, who showed worse paternal attachment and higher depression. Higher paternal anxiety and avoidance, and maternal avoidance predicted lower body satisfaction in both genders adjusted for age and BMI (R2 = 6.1–12.5%). Depression significantly mediated the relationship between dysfunctional parental attachment and lower body satisfaction in both genders (R2 = 55.6–92.9%). Conclusions: Dysfunctional parental attachment was associated with lower body dissatisfaction, mediated by the level of depression. The importance of paternal attachment was

highlighted in boys' body concerns. Results suggest that handling negative moods and parental attachment issues such as anxiety or avoidance may be useful in the case conceptualizations and therapies related to adolescents' body dissatisfaction that requires further assessment. Doctoral School: Mental Health Sciences Program name: MENTAL HEALTH SCIENCES Supervisor: Ferenc Túry E-mail address: szalai.domotor@gmail.com

Abstract type

oral

VISUALLY IMPAIRED CHILD IN THE FAMILY: PATERNAL COPING STRATEGIES OF PARENTS RAISING VISUALLY IMPAIRED CHILDREN

Kiss, Erika

Erika Kiss1, Péter Pál Tóth1,2 1 Institute of Mental Health, Semmelweis University, Budapest, Hungary 2 Hungarian Central Statistical Office, Budapest

Introduction

The aim of my research was to answer the question how parents raising visually impaired children adapt to their specific situation. I also endeavour to identify factors that increase the parents' positive adaptation (protective factors) and factors that enhance their difficulties (risk factors). Based on the cited research findings (Eddy-Engel, 2008, Danis-Kalmár, 2011, Garai-Kovács, 2013.) I presume that visual impairment is an aggravating circumstance that brings about changes in the family functioning. My hypothesis is that the efficiency of the adaptation in families raising visually impaired children is a multifactoral process in which, besides the socioeconomic status, (SES), social (external support, resources within the family) and personal characteristics (the intellect of the child, the nature and severity of the impairment, additional impairments or illnesses) play an important role.

Methods

In my research I use quantitative and qualitative analytical methods: based on an investigation of demographic features retrieved from the anamnestic data of 1707 visually impaired (blind and low vision) children aged 0-16, I attempt to describe the changes that the presence of such children might bring about in the family (e.g. discontinuing relationship, moving to different locations, not having more children etc.). Furthermore, emphasis will be laid on how the personal characteristics of the child (the severity of the visual impairment, additional disabilities) influence the family functioning. I also plan to ask more than a hundred concerned couples and single parents alike (in groups matched by main demographic data) to fill in a questionnaire in which I aim to identify the protective and risk factors that affect the acceptance of the visually impaired children.

Conclusion

From the quantitative analytical section of the research undertaken so far it is clear seen that the discontinuation of parental relationships has a far greater likelihood in families with low vision children than in those with blind children, and furthermore, that beyond the severity of the visual impairment the additional disabilities (e.g. mental and physical disabilities) also exert a strong influence on the quality of the family relations. The data obtained clearly indicate that, besides the above factors, the place of residence and the age and education of the parents also play a significant role in the adaptive functioning of the families.

Notes

Key words: parents of visually impaired children, coping strategy, family functioning, blindness, low vision, protective factors , risk factors, SES Doctoral School: Mental Health Sciences Program: Sociological and mental health approaches to resources for individuals and communities Supervisor: Pál Péter Tóth E-mail: kiss.erika@mental.usn.hu

Abstract type

oral

RELATIONSHIP EXPERIENCES AND MOTIVATIONAL PATTERNS OF WOMEN BATTLING BREAST CANCER – AN INTERPRETATIVE PHENOMENOLOGICAL ANALYSIS

Désfalvi, Judit

Judit Désfalvi, Viola Sallay, Tamás Martos Judit Désfalvi – Institute of Mental Health, Semmelweis University, Budapest, Hungary Viola Sallay dr., Tamás Martos dr. - University of Szeged, Institute of Psychology, Department for Personality, Clinical and Health Psychology

Notes

Theoretical background: Contemporary oncologists refer to breast cancer as a chronic illness, however the diagnosis of this condition is usually still a very traumatic experience for both the patient and her partner (Balog, Dégi, 2005). The illness often leads to partial or complete removal of breasts, or to chemotherapy, which leads to loss of hair on the scalp, the brow area and the eyelashes, not to mention the occasional fits accompanying these treatments. In such situations reducing stress and anxiety is undoubtedly of high importance, even though the quality of support as perceived by the patient is hard to measure (Holland, 2010). Personal goals and a certain representation of one's future play a crucial role when coping with cancer (Martos, 2009). Goals: Our study aims to discover how women suffering from cancer perceive and process the psychological reasons they think caused their illness, and how this process helps them cope with the illness. Methods: Two female patients coping with breast cancer were selected. The criteria included diagnosis at least a year prior to the study and living with their partners for at least two years. In the case of both patients the treatment included breast operations, chemotherapy and radiotherapy. The patients are 49 and 61 years old and had been married for 26 and 34 years, respectively. A half structured interview was implemented in both cases, during which we aimed to learn about their personal plans and goals, and how these factors were related to their coping with their illness and their relationships. The specific analytical method was Interpretative Phenomenological Analysis (IPA). Results: The main topics that emerged during the analysis of the interviews indicate important milestones in the lives of patients battling breast cancer: (1). the necessity of change, (2). the illness, as a milestone, (3). the disposition towards fear, (4) the destructive relationship, (5). defenselessness, (6). lack of confrontation, (7) resources. Conclusion: With the IPA method we can get closer to the innermost motivations, fears and expectations that are intertwined with personal plans of female patients suffering from breast cancer. Keywords: Breast cancer, coping, goals, plans, relationship, interpretative phenomenological analysis Doctoral School: Mental Health Sciences Program: Sociological and mental health approaches to resources for indivials and communities Supervisor: Tamás Martos dr. Email: desfalvijudit@gmail.com

Abstract type

oral

Folate pathway gene MTHFD1L exerts an effect on ruminative response style independently of depression

Eszlari, Nora

Nora Eszlari1,2, David Kovacs1,2, Peter Petschner1,2, Dorottya Pap1,2, Xenia Gonda1,2,3, Rebecca Elliott4,5, Ian Muir Anderson4,5, John Francis William Deakin4,5,6, Gyorgy Bagdy1,2, Gabriella Juhasz1,2,4,5,7 1 Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary; 2 MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary; 3 Department of Clinical and Theoretical Mental Health, Kutvolgyi Clinical Center, Semmelweis University, Budapest, Hungary; 4 Neuroscience and Psychiatry Unit, School of Community Based Medicine, Faculty of Medical and Human Sciences, The University of Manchester, Manchester, UK; 5 Manchester Academic Health Sciences Centre, Manchester, UK; 6 Manchester Mental Health and Social Care Trust, Manchester, UK and 7 MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary

Introduction

Ruminative response style (or shortly rumination) denotes an inflexible and passive thinking about one's own depressed mood, thus predicts future depression. Altered function of the folate-linked one-carbon cycle has been studied in the background of both depression and inflexible cognition, but not in that of rumination.

Aim

In this study, we examined the relationship of rumination with the rs11754661 polymorphism of the MTHFD1L gene coding the mitochondrial monofunctional 10-formyl-tetrahydrofolate synthetase enzyme, which have proven to be an important factor in several neuronal mechanisms from neural tube closure to late-onset Alzheimer's disease. Our European white participants from Budapest (n=862) and Manchester (n=1258) filled out the NewMood questionnaire pack and were genotyped for rs11754661. We used regression models to explore the effect of rs11754661 on rumination and on two distinct depression phenotypes, and tested if this genetic effect on rumination is mediated by depression, and / or if this genetic effect on depression is mediated by rumination.

Results

In our combined Budapest + Manchester sample, we observed a significant association between rs11754661 and rumination, and this finding could be replicated both in the Budapest and Manchester subsamples. The association of rs11754661 with the depression phenotypes was absent in Manchester, but was significant or trend in Budapest and in the combined sample. In both Budapest and the combined sample, we found that rumination totally mediates the effect of rs11754661 on the depression phenotypes, but depression only partly mediates this genetic effect on rumination.

Conclusion

Our findings indicate that the shared variability of rs11754661 and rumination may be an important background factor not only in depression, but in other mental and physical disorders that have an association with rumination. These results may have therapeutic implications regarding the role of folate supplementation in disease prevention.

Notes

Doctoral School: Doctoral School of Mental Health Sciences Program: PSYCHIATRY Supervisor: Gabriella Juhasz Email: eszlari.nora@gmail.com

Abstract type

oral

THE 'LEAP OF COURAGE' – DEATH ANXIETY AND SOCIAL TRUST

Mújdricza, Ferenc

Ferenc Mújdricza1 1 Institute of Mental Health, Semmelweis University, Budapest

Notes

In this paper I present the results of my investigations concerning the definition of trust and its relationship with death anxiety on social theory background. Since theorists of trust have not agreed on how to define trust yet, I have to explain both competing sides: cognitive and non-cognitive ideas. Although non-cognitive concepts seem to catch the core of the phenomenon much better, they still have major weaknesses. Therefore, a new approach seems to be necessary that goes beyond the common relationship between trust and anxiety. Although existing theories of trust claim that anxiety disrupts trust, I argue that it is more complicated than that. Death anxiety not only destroys trust, but, together with courage, it can be the very background for trust to emerge! To prove this statement, we need to look into relevant sociological, psychological, philosophical, even biological studies, and, above all: Paul Tillich's Courage to Be. The conclusion is that trust is interrelated with death anxiety, both being 'built-in' human traits. The 'mediator' between them seems to be courage: anxiety, in the presence of courage, can result in societal, trusting behaviour, while lack of courage leads to the decline of existing trust. Based on this dynamic correlation, I present improved definitions of trust and some related notions, like distrust and naïvety. I can also solve some problems of non-cognitive concepts of trust by elaborating a new interpretation of cognitive trust. To sum up, courage is the power that makes possible the 'Leap of Faith': trusting in spite of all the uncertainties, risks, fears, terrors, anxieties, and finitudes of human existence. Supported by courage, trust rises even in the greatest despair because of and in spite of death anxiety. Doctoral School: Mental Health Sciences

Program: Sociological and Mental Health Aspects of Individual and Community Resources Supervisor: Endre Nagy E-mail address: mujdricza.ferenc@mental.usn.hu

Abstract type

oral

Patterns of aggression in adolescents with externalization problems

Vida, Peter

Peter Vida1,2, Judit Balázs2,3, Lili Olga Horváth4, Ágnes Keresztény2, Mónika Miklósi2,5, Dóra Szentiványi4, József Halász3,6 1 Semmelweis University, PhD School of Mental Health Sciences, Budapest; 2 ELTE PPK, Institute of Psychology, Department of Developmental & Clinical Child Psychology, Budapest; 3 Vadaskert Child Psychiatric Hospital, Budapest; 4 ELTE PPK, PhD School of Psychology, Budapest; 5 Heim Pál Children's Hospital, Centre of Mental Health, Budapest; 6 Óbuda University, AMK, Székesfehérvár

Introduction

Problems of aggressive behavior can be detrimental in social life.Aggressive behaviorcan have different patterns across various psychiatric diagnoses and have heterogenous background mechanisms. In this research, we aim to describereactive and proactive aggression in a clinical sample of adolescents, and to examine the difference between them in groups with or without externalizing diagnosis.

Methods

82 adolescents (39 with externalizing diagnosis; age: 13 - 17 years; girls: n=33; mean age=14.6; Standard Error of Means SEM=0.2) were recruited from the inpatient care system of Vadaskert Child Psychiatric Hospital. The sample is part of "Dimensional Approach in Externalization Disorders" research. We assessed aggression with Reactive and Proactive Aggression Questionnaire and psychiatric diagnoses with the M.I.N.I. Kids Diagnostic Interview. Statistical analyses were performed with ANOVA.

Results

Within the sample, means of reactive and proactive aggressions were 9.5 and 2.4, respectively (SEM = 0.47 and 0.32). Reactive aggression means were 10.5 (SEM=0.7) in the diagnosed group and 8.6 (SEM=0.7) in the group without diagnosis.According to ANOVA, there was a significant difference between groups with/without externalizing diagnosis in reactive aggression ($F=4.06$; $p<0.05$).

Discussion

Data from this study shows that levels of aggression are elevated if compared to typically developing sample from previous studies of our research group. There is a difference between levels of reactive aggression in regard to types of psychiatric disorders, while hierarchical characterization of comorbidities and aggression types might have major importance in outlining differences and more precise behavioral patterns in the above conditions.

Notes

Doctoral School: Semmelweis University, PhD School of Mental Health Sciences, Budapest Program: Psychiatry Supervisor: József Halász Email: fitz026@yahoo.co.uk

Abstract type

oral

ORGANIZATIONAL FACTORS AS PREDICTORS OF BURNOUT AMONG YOUNG UNIVERSITY HOSPITAL PHYSICIANS IN HUNGARY AND SWEDEN, THE HOUPE STUDY

Nistor, Anikó

Anikó Nistor1, Katalin Nistor1, Lise Tevik Løvseth2, Ann Fridner3, Szilvia Ádám1 1 Semmelweis University, Institute of Behavioural Sciences, Budapest 2 St. Olavs University Hospital, Department of Research and Development, Trondheim 3 Karolinska Institute, Centre of Gender Medicine, Stockholm

Background

The HOUPE study aims at assessing the work related mental health of university hospitals physicians across Europe.

Aim

Determining the relationship between organizational factors and burnout among young (age<44) Hungarian and Swedish university hospital physicians.

Methods

97 Hungarian (56.7% male, 43.3% female) and 251 Swedish (45.7% male, 54.3% female) physicians below the age of 44 filled in the HOUPE questionnaire. The average age of the sample was of 39.4 years (SD=3) in Hungary respectively of 37 years (SD=3.9) in Sweden. For the assessment of burnout (exhaustion and disengagement) the MOLBI questionnaire was used. The following organizational factors were assessed using the scales of QPS-Nordic: human resource primacy, empowering leadership, innovative climate, role conflict, control of work pacing respectively harassment at work. Controlling for age and gender, stepwise multiple regression analysis was used to test whether organizational factors significantly predicted burnout among the Hungarian and Swedish physicians.

Results

Burnout levels, exhaustion (U=11594,rankHUN=177.73,rankSWE=171.19,Z=-.49,p=.624) and disengagement (U=10804.5,rankHUN=185.95,rankSWE=168.72,Z=-1.45,p=.147), did not differ significantly between the two countries. Firstly, concerning exhaustion, role conflict was a significant predictor in case of both Hungarian (βHUN-EXH=.25,t(91)=2.36,p=.020) and Swedish (βSWE-EXH=.38,t(241)=6.64,p=.000) physicians. Furthermore human resource primacy (βHUN-EXH=-.29,t(91)=-2.4,p=.018), empowering leadership (βHUN-EXH=.34,t(91)=3.13,p=.002) and control of work pacing (βHUN-EXH=-.24,t(91)=-2.53p=.013) significantly predicted exhaustion among Hungarian physicians (R2HUN-EXH=26.5, F(4,91)=8.2,p<.001), while innovative climate (βSWE-EXH=-.23,t(241)=-3.86,p=.000) and gender (βSWE-EXH=.13,t(241)=2.29,p=.023) were predictors of exhaustion among the Swedish (R2SWE-EXH=29.5,F(3,241)=33.59,p<.001). Secondly, significant predictors of disengagement among both the Hungarian and Swedish physicians were role conflict (βHUN-DIS=.30,t(92)=3.04,p=.003;βSWE-DIS=.17,t(241)=2.95,p=.004) and human resource primacy (βHUN-DIS=-.28,t(92)=-2.83,p=.006;βSWE-DIS=-.32,t(241)=-4.75,p=.000). Additional predictors of disengagement were age (βHUN-DIS=-.19,t(92)=-2.91,p=.031) among the Hungarian (R2SWE-DIS=31.9,F(3,92)=14.4,p<.001) respectively empowering leadership (βSWE-DIS=-.24,t(241)=-3.87,p=.009) among the Swedish (R2SWE-DIS=32.4,F(3,241)=38.44,p<.001) physicians.

Conclusion

Among both the Hungarian and Swedish physicians two major organizational factors emerged related to burnout: role conflict, as a risk factor and human resource primacy, as a protective factor. Optimizing these factors can contribute to efficient burnout prevention.

Notes

Doctoral School: Doctoral School of Mental Health Sciences Program: Mental Health Sciences Supervisor: Szilvia Ádám E-mail address: aniko.nistor@gmail.com

Abstract type

oral

Effectiveness of cognitive training in elderly population

Sirály, Enikő

Enikő Sirály, MD 1, Zsuzsanna Fodor 1 , András Horváth, MD 2 , Pál Salacz, MD 1,3, Zoltán Hidasi, MD, PhD 1 , Éva Csibri, MD 1 , Gábor Csukly, MD, PhD 1 1 Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary 2 National Institute of ClinicalNeurosciences, Budapest, Hungary 3 Department of Neurology, Hospitalat Péterfy Sándor Street

Introduction

Some of the mechanisms of neuroplasticity are functional changes or modifications of neurons' inner qualities or structural changes such as changes in numbers or localization of synapses. (Johnston 2009). This plasticity gives the scientific background to theories that suggest that cognitive training may slow down mental decline.Screening the population at risk is backed by literature data, according to which treatment during the pre-dementia prolongs this phase and also prolongs the time when the patient is able to take care of themselves (Budd et al., 2011). The effect of cognitive training on cognitive performance were examined.

Methods

The study included 32 participants, aged between 49 and 74, dementia was an exclusion criteria. The cognitive changes of the participants were examined as a result of a four week cognitive training. For the objective evaluation of changes CogState package was used.For four weeks, 5 days a week, participants played an hour with the selected set of cognitive games.The games trained the following skills: visuospatial memory, planning, working memory, executive functions, attention and psychomotor speed.

Results

There was a significant ($p<0.05$) increase by the end of the training in the following skills:short term memory, executive functions, and social cognition.

Conclusion

Regular use of computer games can improve the cognitive functions and may prevent or slowing the cognitive decline in elderly population.

Notes

Doctoral School: Mental Health Program: Psychiatry Supervisor: Gábor Csukly E-mail address: esiraly@gmail.com

Abstract type

oral

PSYCHOTHERAPISTS' EXPERIENCES OF PROFESSIONAL COLLABORATION REGARDING SPRITUALITY

Jáki, Zsuzsanna

Zsuzsanna Jáki1, Teodóra Tomcsányi1, András Ittzés, Edit Kiri, Viola Sallay, Tünde Szabó1 1 Institute of Mental Health, Semmelweis University, Budapest

Introduction

In my presentation I report the partial results of a qualitative study, which examines the professional collaboration of Hungarian psychotherapists regarding issues of spirituality. The Institute of Mental Health, Semmelweis University started a research project in 2009 on the topic of spirituality and psychotherapy, this study is a part of that research. Six different issues were investigated, the question of professional collaboration is one of these.

Aim

The aim of the study is to unfold what experiences do psychotherapists have today in Hungary on the fields of professional collaboration regarding the issue of spirituality. We gathered and analyzed psychotherapists' experiences of the following questions: in what extent and what form has been the question of spirituality present in their training, in their collegial relationships, and on the occasions of supervision and scientific forums. We present furthermore the experiences of the collaboration with professionals of theology (spiritual leader).

Methods

Thirty-three in depth interviews were taken with thirty-one psychotherapists (two of these are re-questioning of the same subjects) belonging to various schools of psychotherapy: psychoanalysis, cognitive-behavioral therapy, family-therapy, relaxation and symbol therapy, hypnosis, psychodrama.

The texts of the interviews were analyzed with the method of grounded theory (GT). GT is a method of content analysis, in which the texts in the theme of the research question are organized in a three level category-system, formulating the final result of the research: the code-tree and the grounded theory itself.

Results

The data was regularized in two different code-trees: the first shows the experiences of collaboration strictly among the professionals of psychotherapy, the second shows the patterns of collaboration between professionals of psychotherapy and of spirituality, such as spiritual leaders or pastoral care providers. The code-trees are not yet in final forms, the stages of settlement and recoding are still ahead. The outcomes so far show, that psychotherapists are parted regarding the question of collaboration on this field. Only in a few training is the question of spirituality brought up, and the same can be said of professional relations as well. However, when the issue of spirituality is named in professional contacts, it is often surrounded by misunderstanding, uncertainty and conflicts. At the same time there is a growing interest, the number of those who seek after professional forums, events on the theme of spirituality is evolving. The patterns of collaboration with the spiritual leader show what are some background factors of the missing collaboration, and which are the forms of realized collaboration, including the ones with personal contact, and the ones without – this later means a parallel work with the same patient, whereas the two professional know of each-other but do not get in touch with each-other.

Notes

Doctoral School: Mental Health Sciences Program: Sociological and mental health approaches to resources for individuals and communities Supervisor: Teodóra Tomcsányi, András Ittzés E-mail address: zsuzsannajaki@gmail.com

Abstract type

oral

THE PHYSICAL AND MENTAL HEALTH OF HOSPICE WORKERS WITH SPECIAL FOCUS ON THE DIFFERENCE BETWEEN NURSES AND OTHER PROFESSIONALS

Kegye, Adrienne

Adrienne Kegye1, Edit Czeglédi1, Ágnes Zana1, Edit Révay2, Katalin Hegedűs1 1. Institute of Behavioural Sciences, Semmelweis University, Budapest 2. Department of Sociology, Sapientia College of Theology, Budapest

Introduction

Healthcare workers dealing with terminally ill patients are exposed to significantly higher physical and mental burden than healthcare professionals working in other healthcare fields or non-healthcare workers. Annual reports show an increase in hospice services and the number of terminally ill patients, while the number of health professionals working in hospices is decreasing, resulting in increased burden and burnout among hospice workers, and employee turnover.

Aim

This study aims to assess the physical and mental health of hospice workers, comparing nurses and other professionals.

Methods

The sample of the cross-sectional questionnaire survey consisted of hospice team workers (response rate ~14%, N=195, 16 men and 179 women; mean age 46.0 years, SD=10.77). Measurements: questions related to physical symptoms, health problems, life satisfaction, WHO Well-being Index, Vital Exhaustion Questionnaire. Time of data collection: 2013–2014.

Results

The respondents reported an average of 2.7 work places (SD=2.18), and 40.8% work at least 12 hours per day. The exhaustion indicators: disabling fatigue, lack of energy (65.1%), sleep problems (42.1%). The prevalence of fatigue and lack of energy is significantly higher among nurses (N=82)

than other hospice workers (χ2(1)=5.727, p=0.017). Of respondents 46.9% suffer from disabling physical pain that at tendency level occurs less often among nurses (χ2(1)=3.315, p=0.069). According to our results the well-being of nurses (t(182)=2.978, p=0.003, Cohen's d=0.44) and their life satisfaction (t(182)=2,987, p=0.003, Cohen's d=0.45) is significantly lower and their vital exhaustion is higher (Z=2.453, p=0.014, Cohen's d=0.39) than that of other hospice professionals.

Conclusion

Our results support that compared to other hospice professionals hospice nurses are overburdened and have worse mental health while the co-occurrence of compassion fatigue and compassion satisfaction make it worthwhile for them to work in end-of-life care. Therefore a prospective study is needed to validate the Professional Quality of Life Scale (ProQOL).

Notes

Doctoral School: Mental Health Sciences Program: Mental Health Sciences 4/2 Supervisor: Katalin Hegedűs E-mail address: kegyepalfi@t-online.hu

Abstract type

oral

STUDENT'SSUCCESS INDEX THE TIME OF ENTRY TO UNIVERSTY

Dinyáné Szabó, Mariann

Mariann Dinyáné Szabó, Gabriella Pusztai Institute of Digital Health, Semmelweis University, Budapest Education Department, University of Debrecen

Introduction

My research is focused on implementing the conception of social capital posited by Coleman in higher education.Coleman defined the resources owned by humans „as capitals" and indentified them as economic capital, human capital and social capital. As every form of capitals have the ability to be accumulated and transform, this explains why may play social capital such a big part at processing human capital.Social capital coming from their familar and communal background therefore enables students to better utilize other resources for their personal development.My focus is on those factors that may influence of the success and efficiency of students starting their higher education atUniversity. The first university year has a largerole in student's successin their education. In this period of their study can be developeda commitmentto qualification and university.

Aim

The research aimsto examinethe factors thatestimate thesuccessof studentsat the time ofentry into theUniversity.

Methods

A questionnaire surveywas carried outonlinedownloadoption, at all faculty of SemmelweisUniversity. Data processing was done by SPSSsoftware package.

Results

My dataset has 512 students' data: 1st year student 377 (74%) and 135 (26%) students are upper year. I only investigated the 1st year students. The distribution of this dataset: 114 male (30%) and 263 female (70%) students. By age: 19.7±1.5 year and 19.4±1.1 year. I adopted different contingency tables for Student's Success Index: and found no significant difference among four faculties (Chi-square=2,9, df=3, p=0,401), similar to the results concerning father's qualifiation (Chi-square=3,2, df=2, p=0,203), mother's qualifiation (Chi-square=1,5, df=2, p=0,477) or parents' qualification (Chi-square=1,4, df=2, p=0,513). Gender-based results only show borderline significance regarding fathers' qualifications (p=0,055): father's higher school education significantly impacts male student achievement. Concerning the different types of localities, I did not find significant differences among them, but I found that the larger localities (county towns and capital cities) are more beneficial for theStudent's Success Index.By logistic regression the significant variables raising academic achievement are: level of father's secondary education (OR=1,6), one parent model,living with mother

(OR=2,4), sport activity (OR=2,5), religion (OR=1,4), non-campus students living with thefamily (OR=1,3).

Conclusion

This study is the first step to evaluate the student's success factors in the first year which determine their university career. Some factors as godliness, sport activity, family model or coexistence with family forcefully influence their future studies and success.Further examinations are necessary to confirm these results on different university samples.

Notes

Doctoral School: Mental Health Science Program: Sociological and mental health approaches to resources for individuals and communities Supervisor: Gabriella Pusztai E-mail: dinyane.mariann@public.semmelweis-univ.hu

Abstract type

oral

Risk and protective factors in ragweed pollen allergy based on a cross-sectional study among schoolchildren in Hungary

Vörös, Krisztina

Krisztina Vörös1, János Bobvos2, János Mihály Varró2, Tibor Málnási2, Tamás Kói3, Donát Magyar2, Annamária Mácsik2, Péter Rudnai2, Anna Páldy2 (1) Semmelweis University, School of PhD studies, Budapest, Hungary (2) National Public Heath Centre, Department of Environmental Health, Budapest, Hungary (3) Budapest University of Technology and Economics, Budapest, Hungary

Background and aim

Hay fever is a major public health concern all over the world. Hungary is one of the heavily infested areas by ragweed pollen in Europe. Ragweed pollen is the most important cause of seasonal allergic rhinoconjuntivitis in our country. Sensitization rate of the population has doubled between 1990 and 2004 resulting significant public health burden. The aim of this analysis was to examine the risk and protective factors known in national literature on domestic pediatric population and to assess the impact of other possible factors unknown so far on the outcome.

Matrials and methods

The National Institute of Environmental Health carried out a cross-sectional study named National Children Health Respiratory Survey (NCHRS) between 2005 and 2006 to estimate the prevalence of chronic respiratory and allergic symptoms and possible promoting factors for these conditions in the 3rd grade schoolchildren throughout the country. A standardized questionnaire was used in this survey based on the International Study of Asthma and Allergies in Childhood. In this study we processed the data of ragweed pollen allergy of NCHRS. The pollen load of the settlements were calculated from data of daily ragweed pollen concentrations in the atmosphere monitored by 19 measuring stations of National Public Health Service Network covering the country. Descriptive and analytical (binary logistic regression) methods were applied to identify possible risk and protective factors of ragweed allergy by SPSS 23.0 for Windows. We considered $P<0,05$ significant.

Results

25,013 (49.3% male; 50.7% female) 8-9 year-old children's data were analysed who have not changed the place of residence since their birth. The average prevalence of ragweed pollen allergy diagnosed by a doctor was 6.6% in the country. Allergy was significantly more frequent among boys ($p=0.002$) and 9 year-old children ($p=0.001$). Atopic diseases of parents ($p=0.000$), lower respiratory infections in the first two years of life ($p=0.000$) and mould inside the house ($p=0.036$) showed positive association, but higher paternal educational level ($p=0.039$) and getting social aid ($p=0.002$) had negative associations with health outcome.

Conclusion

Genetic predisposition, environment in early childhood and the socio-economic state of the family play a determinant role in the allergy development.

Notes

Doctoral School: Pathology Program: Public Health Supervisor: Anna Páldy email address: krisztinavoros86@gmail.com

Abstract type

oral

Oncology

9-CIS RETINOIC ACID AS A NOVEL AGENT IN THE TREATMENT OF ADRENOCORTICAL CANCER?

Nagy, Zoltán

Zoltán Nagy1, Kornélia Baghy2, Éva Hunyadi-Gulyás3, Gábor Nyírő4, Henriett Butz4, Ábel Decmann1, Ilona Kovalszky2, Katalin F. Medzihradszky3, Károly Rácz1,4, Attila Patócs4,5, Peter Igaz1* 1 2nd Department of Medicine, Semmelweis University, 1088 Budapest, Szentkirályi str. 46. 2 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, 1088 Budapest, Üllői Str. 26. 3 Biological Research Centre, 6726 Szeged, Temesvári krt. 62. 4 Molecular Medicine Research Group, Hungarian Academy of Sciences and Semmelweis University, 1088 Budapest, Szentkirályi str. 46. 5 “Lendület-2013” Research Group, Hungarian Academy of Sciences and Semmelweis University, 1088 Budapest, Szentkirályi str. 46.

Background

The drug treatment options for adrenocortical carcinoma (ACC) are limited, and therefore it is essential to find novel, effective agents. In our previous studies, in vitro 9-cis retinoic acid (9-cisRA) had an inhibitory effect on NCI-H295R adrenocortical carcinoma cell line and in vivo had antitumoral effects in a small pilot xenograft study.

Objective

To investigate the antitumoral effect of 9-cisRA and its combination with mitotane on a large-scale xenograft model.

Methods

43 male severe combined immunodeficiency (SCID) mice were xenografted with NCI-H295R cells, and treated in four groups (i. control, ii. 9-cisRA, iii. mitotane, iv. 9-cisRA+mitotane) for 28 days. Tumor size follow-up, histological and immunohistochemical (Ki-67) analysis of the excised tumors and gene expression microarray (4x44K Agilent Whole Genome Microarray) were performed, and microarray results werevalidated with quantitative reverse transcription PCR (Taqman). Circulating plasma microRNAs were detected also with qRT-PCR. The protein expression changes were investigated with proteomic analysis, and results were confirmed by Western-blot.

Results

Mitotane and 9-cisRA+mitotane treatment resulted in a significant decrease in tumor volumes. The Ki-67 index was significantly reduced in both 9-cisRA and combined treated groups. Only modest alterations in gene expression were found by microarray, i.e. only two genes (APOA4 and PDE4A) could be validated as significantly differentially expressed. The level of circulating microRNA hsa-miR-483-5p was significantly decreased in the combined treatment group relative to control. By proteomics, the significant decrease of protein SET was found also in the 9cisRA+mitotane treated group relative to control.

Conclusion

These data support that 9-cisRA might be a helpful additive agent in the treatment of ACC patients. hsa-miR-483-5p might be utilized for treatment efficacy monitoring, and our proteomics findings might raise the relevance of SET in ACC biology.

Notes

Doctoral School: Clinical Medicine Program: Hormonal Regulations Supervisor: Péter Igaz E-mail address: zoltan.nagy.md@gmail.com

Abstract type

oral

Presence of immune cells and low expression of PD-L1 correlate with better survival of patients with lung cancer brain metastasis

Téglási, Vanda

Vanda Téglási, Judit Moldvay, Katalin Fábián, Irén Csala, Attila Bagó, Zoltán Szállási, József Tímár, Lilla Reiniger 1st Department of Pathology and Experimental Cancer Research

Notes

Metastatic brain lesions are the most common intracranial tumors in adults. The majority of brain metastases originate from lung cancers. Survival of patients with brain metastases is generally poor even with a multi-disciplinary therapeutic approach. Novel immune checkpoint inhibitors are in advanced clinical development, however, the pro- and anti-tumor effects of the immune system are still controversial. We examined 292 surgically resected brain metastatic tissues from lung cancer patients. The infiltration pattern of the metastasis, the amount of stromal tumor infiltrating lymphocytes (sTIL) and the mononuclear ring (MR) around the tumor were measured on HE sections. Expression of PD-L1 and PD1 on tumor cells (TC) and immune cells (IC) was evaluated by immunohistochemistry on tissue microarrays. The findings were correlated to overall survival (OS) and survival from brain metastasis surgery (BS). Better OS and BS appeared in cases showing massive sTIL (p=0.021 and 0.015) and pushing/papillary infiltration pattern (p=0.019 and 0.005). Better BS was also associated with the presence of MR (p=0.02). Moreover, cases with massive sTIL or MR combined by decreased PD-L1 expression showed better BS (p=0.028 and 0.003) compared to the rest of the cases. Massive sTIL and the presence of MR were associated with higher PD-L1 (p<0.001 in both) and PD1 (p<0.001 in both) expression of IC. Sparse sTIL was associated with lower PD-L1 expression of TC (p=0.007) and IC (p=0.004). Pushing/papillary infiltration pattern was associated with low expression of PD-L1 of TC (p=0.022). Our results show that the presence of larger amount of immune cells within and around the brain metastasis of lung carcinomas, especially with very low or no PD-L1 expression is associated with better BS of patients, indicating a significant role of the immune system in controlling tumor growth. Doctoral School of Pathological Sciences, Experimental Oncology Program Supervisor: Lilla Reiniger email: vanda.teglasi@gmail.com

Abstract type

oral

THE ROLE OF CD49d EXPRESSION IN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

Kriston, Csilla

Csilla Kriston1, Márk Plander2, Ágnes Márk1, András Matolcsy1, Gábor Barna1 1 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest 2 Department of Hematology, Markusovszky Hospital, Szombathely

Introduction

Chronic lymphocytic leukemia (CLL) is the most common B-cell leukemia of adults in Western countries. The disease is characterized by variable clinical courses, which can be predicted by various prognostic factors. One of the strongest flow cytometry based predictor is the CD49d molecule. The high CD49d expression associated with poor outcome. The CD49d, also known as the α4 integrin subunit, is associated with the CD29 (β1) molecule and binds VCAM-1 and fibronectin. The CD49d/CD29 can be present in multiple activation state, which determines the binding affinity to its ligands. It is well known that CLL cells resist apoptosis as a result of their interaction with the microenvironment.

Aim

We investigated the role of CD49d-VCAM-1 axis in the survival, cytoskeleton-remodelling and surface molecule expression of CLL cells with different CD49d expression. We determined the conformation of CD49d/CD29 complex on the surface of CLL cells.

Results

Peripheral blood mononuclear cells from CLL patients with different CD49d expression were cultured on VCAM-1 coated plates or in a co-culture with bone marrow stromal cells (BMSCs), to mimic the tumor microenvironment. BMSCs reduced the spontaneous apoptosis of CLL cells after 7 days, while VCAM-1 alone did not. The protective effect of the BMSCs was independent of the CD49d level, but showed correlation with CXCR4 expressed on CLL cells. The CLL cells co-cultured with BMSCs have increased expression of CD5, CD49d, CD19, CD126 and decreased CXCR4; the VCAM-1 did not change the surface antigen levels. VCAM-1 stimulation resulted in enhanced F-actin-formation by CLL cells with high CD49d expression. We detected only the low affinity conformation of CD29 on the CLL cell surface. Our results suggest that the CD49d do not mediate direct survival signals. Through cytoskeleton-remodelling the CD49d can have important role in migration to protective lymphoid niches and adhesion to supportive microenvironmental cells.

Notes

Doctoral School: Pathological Sciences Program: Experimental Oncology Supervisor: Gábor Barna E-mail: kristoncsill@gmail.com Our results suggest that the CD49d do not mediate direct survival signals. Through cytoskeleton-remodelling the CD49d can have important role in migration to protective lymphoid niches and adhesion to supportive microenvironmental cells.

Abstract type

oral

IBRUTINIB DRIVEN CLONAL EVOLUTION IN CHRONIC LYMPHOID LEUKEMIA

Marosvári, Dóra

Dóra Marosvári MTA-SE Lendulet Molecular Oncohematology Research Group, 1st Department of Pathology and Experimental Research, Semmelweis University, Budapest, Hungary

Notes

Chronic lymphocytic leukemia (CLL) is the most frequent mature B-cell non-Hodgkin lymphoma in the Western countries. In the majority of cases, CLL shows an indolent course and patients do not require therapy. However, treatment is indicated in advanced cases of CLL. Besides the standard chemo-immunotherapy novel monoclonal antibodies and novel kinase inhibitors have recently been approved for treatment of CLL. The irreversible Bruton tyrosine kinase inhibitor ibrutinib, has been shown to be highly effective in relapsed and refractory CLL patients, including those with del(17p) and/or TP53 mutation. We aimed to examine the effects of ibrutinib treatment on clonal architecture of CLL by performing next generation sequencing (NGS) analysis of a selected panel of target genes (n=34) previously found to be mutated at least in 2% of the cases. Targeted resequencing was performed on 21 sequential peripheral blood samples obtained from 5 patients treated with ibrutinib. These were collected longitudinally, before initiation of the ibrutinib therapy, and at 4, 8 and 12 months on therapy. Our preliminary findings show that all patients achieved at least partial remission and are still on ibrutinib with an average follow up of 8 months. Despite the fact that our patients had an aggressive course of CLL only one patient (P1) carried a baseline TP53 mutation which demonstrated a reduction upon treatment with ibrutinib. The other recurrent mutation targets included components of the DNA damage (ATM), RNA processing (ZNF292, XPO1), wnt1 signalling (FAT1), chromatin structure (HIST1H1E) and NFkB signalling (NFKBIE) with heterogeneous clonal dynamics observed across the individual patients with the same mutation demonstrating reduction in a patient while expansion in another one. In summary, our preliminary findings demonstrate heterogeneous clonal evolution patterns in CLL patients treated with ibrutinib in terms of the affected pathways as well as dynamics of the individual mutations. Doctoral School: Doctoral School of Pathological Sciences Program: Oncology Supervisor: Csaba Bödör and Lilla Reiniger E-mail address: marosvari.dora@med.semmelweis-univ.hu

Abstract type

oral

ADVANTAGE OF MULTIPLE ASSAYS TO CHARACTERIZE METABOLIC PROFILE AND RELATED REGULATORS IN HUMAN TUMOUR CELLS

Hujber, Zoltán

Zoltán Hujber1,2, András Jeney1, Gábor Petővári1, Noémi Nagy1, Norbert Szoboszlai2, Júlia Oláh1, Titanilla Dankó1, Ágnes Márk1, Anna Sebestyén1,3 1 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest 2 Laboratory of Environmental Chemistry and Bioanalytics, Department of Analytical Chemistry, Institute of Chemistry, Eötvös Loránd University, Budapest 3 Tumour Progression Research Group of Joint Research Organization of Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary

Notes

The altered bioenergetics is a hallmark of cancers. Genetic alterations induce reprogramming of tumour metabolism microenvironment dependently. High glucose uptake and glycolytic activity even in the presence of oxygen (Warburg effect) and/or impaired mitochondrial functions were described as metabolic changes previously. The metabolic profiles of individual cancers show a great variety. There is an increasing demand to introduce appropriate bioenergetics assays to characterize metabolic alterations of tumours at the diagnosis and during the therapy. Our assays describe the bioenergetics substrate utilization and oxidation with 1-14C-glucose and 1-14C-acetate labelling. We can also detect the extreme utilization of glucose and acetate and follow the incorporation of 13C atoms into the metabolites in tumour cell lines by using U-13C-glucose, 2-13C-acetate and LC-MS (liquid chromatography - mass spectometry). Our results showed that different cell lines have different cell type independent metabolic profiles and substrate preferencies. HT-1080 and ZR75.1 cell lines were deeply characterized with different ratio of 13C lactate/13C malate and 13C ribose-5-phosphate/13C malate related high glucose utilization, glycolysis dominancy in HT-1080 or functioning TCA cycle in ZR-75.1 cells. To observe the relevance of metabolic characterization the expression of certain bioenergetic enzymes (GAPDH, GLUT1, beta-F1-ATPase), mammalian target of rapamycin complexes – as key regulator of cellular metabolism – and related targets as important elements at the cell signalling network were also investigated and confirmed the alterations. The applied methods of energy substrate utilisation represent simple assay system using 14C-or 13C-acetate and glucose to characterize dominant bioenergetic pathways in tumour cells. supported by K84262, Bolyai Grant, Medinprot Synergy 2016 Doctoral School: Pathological Sciences Program: Oncology Supervisor: Anna Sebestyén consulent: András Jeney E-mail address: zoltan.hujber56@gmail.com

Abstract type

oral

ELECTRO-HYPERTHERMIA INDUCED PROGRAMMED CELL DEATH AND IMMUNE RESPONSE IN A C26 COLORECTAL CANCER ALLOGRAFT MODEL

Vancsik, Tamás

Tamás Vancsik1, Éva Kiss1, Dr. Csaba Kővágó2, Nóra Meggyesházi1 1 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary 2 Department of Pharmacology and Toxicology, Szent Istvan University Faculty of Veterinary Science, Budapest, Hungary

Introduction

Modulated electro-hyperthermia (mEHT) using capacitive impedance-coupled radiofrequency and the concomitant heat (<42oC), can selectively target malignancies due to their elevated glycolysis, ion concentration and conductivity compared to normal tissues. The mEHT has been used as a complementary to radio- or chemotherapy of human cancer. In colorectal cancer xenografts of athymic mice mEHT provoked programmed cell death through apoptosis inducing factor (AIF) activation and damage associated molecular pattern (DAMP) signals compatible with a potential immunogenic cell death (ICD).

Aim

Here we tested the mEHT related tumor damage and immune response in colon-26 (C26) colorectal cancer allografts in immunocompetent (Balb/C) mice.

Results

mEHT induced significant and progressive cell damage in the treated right-leg tumors of the animals compared to their symmetrical but untreated left-leg tumors. The programmed cell death response proved to be caspase-dependent causing significant increase in cleaved/activated caspase-3 levels, besides elevated cytochrome-c release from the mitochondria but without AIF activation, or major mitochondrial accumulation of Bcl-2-associated X protein (BAX). Significant increase in TUNEL positive cell nuclei also indicated apoptosis. Elevated release of stress-associated Hsp70, calreticulin and HMGB1 proteins was also observed in mEHT treated tumors related to DAMP signaling and for an ICD response. In line with this, the number of S100 positive dendritic cells and CD3 positive T-cells was significantly elevated in the treated tumors, at low number of FoxP3 positive regulatory T cells. In addition, mEHT supplemented with a flavonoid rich CD8+ T-cell promoting agent induced cell death also in the untreated left-leg tumors indicating a systemic anti-tumor effect. In conclusion, mEHT can induce caspase-dependent programmed cell death in CT26 colorectal cancer allografts and the release of stress associated DAMP proteins calreticulin, Hsp70 and HMGB1, which may support dendritic cell activation and T cell mediated tumor immunity for a potential ICD response.

Notes

Doctoral School: Pathological Sciences Program: Experimental Oncology Supervisor: Dr. Tibor Krenács E-mail address: vancsik.tamas@gmail.com

Abstract type

oral

THE PROGNOSTIC IMPACT OF KI-67 PROLIFERATION INDEX IN BREAST CANCER: DOES THE ANTIBODY MATTER?

Acs, Balazs

Balázs Ács 2nd Department of Pathology, Semmelweis University

Introduction

Although several antibodies are available for immunohistochemical (IHC) detection of Ki-67, even the most commonly used MIB-1 has not been validated yet.Our aim was to compare 5 commercially available antibodies for detection of Ki-67 in terms of agreement and also to investigate their prognostic significance in breast cancer.

Methods

Tissue microarrays were constructed from 388 breast cancer patients' representative FFPE tumor blocks. Five antibodies were used to detect Ki-67 expression as follows: MIB-1, SP-6, 30-9, N1574, B56. The IHC reactions were evaluated on digitized slides. Semi-quantitative assessment was performed by two pathologists independently. To compare Ki-67 proliferation index (KIPI) of the five antibodies, intra-class correlation coefficient (ICC), Cohen's Kappa, concordance correlation coefficient (CCC) were used. KM plots with log-rank test were performed to correlate KIPI with clinical outcome.

Results

Significant difference occurred between the KIPI scores by the five antibodies and they also showed a moderate concordance (ICC=0.645). The highest concordance was found betweenMIB-1 KIPI and N1574 KIPI (CCC=0.785), although significant bias was found between them (p=0.001). Dichotomizing KIPI at 20% and 30% thresholds, no significant difference was found between MIB-1 KIPIandN1574 KIPI (p=0.052), although they showed only moderate agreement (κ=0,564). For prognosis prediction, KIPI by all the five antibodies was able to perform statistically significant division of our patients into two cohorts with distinct DFS at 20% threshold ($p< 0.05$ for all comparisons). At

30% cut-off, B56 KIPI (p=0.288) failed, while KIPI scores by the other antibodies were able to separate good and unfavorable patients' cohorts (p< 0.05 for all comparisons).

Conclusion

Our results showed that there are considerable differences between the different Ki67 antibodies in their capacity to detect proliferating tumor cells. Also, we could show that the capacity of various Ki67 antibodies to identify low-risk and high-risk patients is variable.

Notes

Doctoral School: Pathological Sciences Program: Alteration of cell and extracellular matrix in cardiovascular- and certain neoplastic diseases. Experimental and diagnostic pathomorphological examinations. Supervisor: A. Marcell Szasz E-mail address: acs.balazs.se@gmail.com

Abstract type

oral

RAS/RAF/PI3K signaling network combination inhibition leads to additive inhibitory effect in tumor cell lines with oncogenic BRAF and concomitant RAS or PTEN/PI3K mutation

Molnár, Eszter

Eszter Molnár1, Tamás Garay1,2, Dominika Rittler1, Walter Berger3, Balázs Döme 3,4, József Tímár1,2, Balázs Hegedűs 2,3 1 2nd Department of Pathology, Semmelweis University, Budapest, Hungary 2 HAS-SE Molecular Oncology Research Group, Budapest, Hungary 3 Institute of Cancer Research, Medical University of Vienna, Vienna, Austria 4 National Korányi Institute of TB and Pulmonology, Budapest, Hungary 5 Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria

Background

Growth factor signaling cascade components (e.g BRAF, RAS, PI3K, PTEN) are often impaired in tumors. Since oncogenic BRAF mutation can occur simultaneously with RAS or PI3K/PTEN mutations we evaluated how these mutations effect on RAS/RAF/PI3K signaling network inhibition sensitivity in a panel of human cancer cell lines with BRAF and concomitant RAS or PTEN/PI3K mutations.

Methods

We investigated the effect of panRAF, mutant BRAF specific, MEK and PI3K/mTOR inhibitors on 12 human cancer cell lines divided into 3 groups according to their mutational status: BRAF-mutant with no PTEN/PI3K/RAS mutations (A375, WM35, SK-MEL-28, CRL5885), BRAF + PTEN-PI3K (A2058, WM239, HT29, SW1417) and BRAF + RAS double mutant (WM3629, WM3670, MDA-MB-231, CRL5922). Effect of inhibitors on cell viability and signaling pathway activation were investigated via SRB/clonogenic assays and immunoblot assay, respectively. Both single agent and combination treatments were applied.

Results

In single agent treatments mutant-BRAF and MEK specific inhibitors were the most effective in cells without concomitant PTEN/PI3K or RAS mutations. Interestingly, not only the combination of RAF + MEK inhibitors but the combination of PI3K/mTOR + MEK or PI3K/mTOR+RAF inhibition showed additive inhibitory effect on proliferation in all subgroups.

Conclusion

BRAF mutant cells carrying concomitant PTEN/PI3K or RAS alterations display distinct sensitivity to RAS/RAF/PI3K network inhibition. Our data suggests that combination inhibition acting concurrently on different targets of the RAS/RAF/PI3K network can be more effective than single therapies.

Notes

Doctoral School of Pathological Sciences Oncology Balázs Hegedűs m.molnareszter@gmail.com

Abstract type

oral

Aquaporin 1 protein expression is associated with BRAF V600mutation in cutaneous melanoma

Imrédi, Eleonóra

Eleonóra Imrédi1, Béla Tóth2, Viktória Doma1, Tamás Barbai 1, Erzsébet Rásó1, István Kenessey1, József Tímár 1,3 1. Second Department of Pathology, Semmelweis University 2. Department of Dermatology, Venerology and Dermatooncology of Semmelweis University 3. Molecular Oncology Research Group, Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary

Introduction

In a previously published meta-analysis of gene expression arrays, we have identified several genes potentially influencing the progression of cutaneous melanoma.

Aim

We studied the expression of AQP1 protein in cutaneous melanoma, correlated our findings with standard histological and genetic markers, and long-term clinical follow-up.

Methods

The AQP1 protein expression was evaluated in 78 melanoma patients, representing two predefined risk cohorts using immunohistochemistry technique with commercially available anti-AQP1 antibodies on routinely formalin-fixed and paraffin-embedded tumor tissue samples. BRAF V600E mutation was identified in 70 patients using PCR and RFLP analyses, followed by confirmatory analysis with the Sanger sequencing technique.

Results

AQP1-expressing melanoma cells were found in 52 cases (66.7%, median H-score=124.24). Significantly higher AQP1 H-scores (P=0.047) were found in the ‘high-risk’ patients. No correlations were found with the established histological markers, such as mitotic index (P=0.42), Clark level (P=0.95), and Breslow thickness (P=0.51). BRAF V600 mutation analyses were successful in 89%, and showed a two times higher mutation frequency in the ‘high-risk’ group. BRAF V600 mutations were significantly associated with AQP1 expression (P=0.014). Long-term follow-up represented a reduced progression-free survival (P=0.036) and overall survival (P=0.017) for the AQP1-positive cutaneous melanoma patients.

Conclusion

AQP1 expression is likely to be associated with an adverse prognosis in cutaneous melanoma. We believe that our findings enhance the understanding of melanoma progression and our results certainly call for further experimental and clinical investigations of the AQP1 expression to determine the eventual value of this interesting molecule as a potential prognostic marker or therapeutic target in cutaneous melanoma.

Notes

Fundings: This work was supported by OTKA K-112371 and by the Hungarian Academy of Sciences. Doctoral School: Pathology Program: Oncology Supervisior: Prof. Tímár József PhD DSc E-mail: nora.imredi@gmail.com

Abstract type

oral

CLINICAL SIGNIFICANCE OF CYP2C9-STATUS GUIDED VALPROIC ACID THERAPY IN CHILDREN

Bűdi, Tamás

Tamás Bűdi1, Katalin Tóth2, Andrea Nagy3, Zsuzsa Szever3, Ádám Kiss2, Manna Temesvári2, Edit Háfra2, Miklós Garami1, Adrienn Tapodi3, Katalin Monostory2 1 2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary 2 Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary 3 Heim Pál Children's Hospital, Budapest, Hungary

Introduction

Valproic acid (VPA) induced adverse effects, which are sometimes serious in children, can be associated with alterations in VPA metabolism. VPA-evoked toxicity is attributed to both the parent compound and its unsaturated metabolites, primarily formed by CYP2C9 enzyme.

Aim

Association between children's CYP2C9-status and serum valproate concentrations or dose-requirements was evaluated. Testing CYP2C9-status may contribute to the improvement and rationalization of VPA therapy in children.

Methods

The contribution of CYP2C9 genotype and CYP2C9 expression in children with epilepsy to valproate pharmacokinetics was analyzed. We have also evaluated the effect of CYP-status guided valproic acid therapy. CYP2C9-status was estimated by the identification of defective CYP2C9 allelic variants and current CYP2C9 expression in patients' leukocytes which reflects hepatic CYP2C9 activities. Combining the results of CYP2C9 genotyping and CYP2C9 expression, the patients' VPA-metabolizing capacity was predicted, and VPA dosing was adjusted to the patients' CYP2C9-status. Clinical and biochemical parameters, such as VPA serum levels, blood cell counts, liver function parameters, adverse effects in patients of CYPtest group were compared with those of the control group treated with VPA according to conventional clinical practice.

Results

Valproate concentrations were significantly lower in normal expressers with CYP2C9*1/*1 than in low expressers or in patients carrying polymorphic CYP2C9 alleles. Consistently, the dose-requirement was substantially higher in normal expressers carrying CYP2C9*1/*1 (33.3 mg/kg vs 13.8–17.8 mg/kg, $p < 0.0001$). Low CYP2C9 expression significantly increased the ratio of poor metabolizers predictable from CYP2C9genotype. CYP2C9-guided treatment significantly reduced VPA misdosing and consequently decreased the ratio of patients out of the range of target VPA blood concentrations. In CYPtest group of children receiving CYP2C9-status adapted dose, serum alkaline phosphatase (ALP) and the ratio of patients with abnormal ALP levels were substantially lower than in the control group. The incidence of serious side effects, notably hyperammonemia, was reduced in CYPtest group; however, some other side effects, such as weight changes and somnolence, could not be avoided.

Conclusion

Due to the substantial downregulation of CYP2C9 expression in epilepsy, inferring patients' valproate metabolizing phenotype merely from CYP2C9 genotype results in false prediction. The knowledge of pediatric patients' CYP2C9-status can contribute to the optimization of VPA dosing and to the avoidance of misdosing-induced side effects.

Notes

Fundings: GOP-1.1.1-09/1-2009-0001, GOP-1.1.1-11-2012-0027, K104459 Doctoral School: Pathological Sciences (+Pharmaceutical Sciences) Program: Oncology Supervisor: Katalin Monostory, Miklós Garami E-mail address: drbdtamas@gmail.com

Abstract type

oral

Neurosciences and Mental Health Sciences

Relationship between cognitive flexibility and symptom presentation in adult ADHD

Bálint, Sára

Bálint, Sára1; Bitter, István1; Czobor, Pál1, 1-Semmelweis University Department of Psychiatry and Psychotherapy

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed childhood psychiatric disorders, which persists into adulthood in 30-50% of the cases. ADHD is characterized by three core symptoms: impulsivity, hyperactivity, and inattention. Cognitive flexibility, which is the mental ability to switch between thinking about two different concepts, has been considered as one of core dysfunctions of ADHD; nonetheless, the relationship between the symptom presentation and the deficit in cognitive flexibility is not well understood.

Objective

Our aim was to examine whether there is an association between the presentation of the three core symptoms of ADHD and the performance on a task-switching test.

Methods

We examined 36 ADHD patients (mean age= 31.1 years, SD=10.7). Symptom severity on core ADHD symptoms was measured by the Conners Adult Rating Scale (CAARS). Cognitive flexibility was examined by a task switching paradigm (SWAT- Switched Attention Task).

Results

We found a significant negative association between impulsivity and reaction time for correct answers on the SWAT (Spearman-rho=-0.35, $p<0.05$). Regarding the switch cost, our results showed positive correlation between the symptom severity on impulsivity and task-switching accuracy. Specifically, ADHD patients with higher severity on impulsivity made more commission errors after the switch (Spearman-rho=0.36, $p<0.05$). Furthermore, we found a negative association between the switch cost for reaction time and the severity on the CAARS self-concept scale (Spearman-rho=-0.38, $p<0.05$).

Conclusion

Our results show that ADHD patients with more impulsive symptoms not only respond faster but make more commission errors on the SWAT than patients with less impulsivity, indicating that patients with more impulsive symptoms display deficits with regard to the flexible suppression. This supports the idea that the neuropsychological basis of impulsive symptom presentation in ADHD goes beyond disinhibition, and involves an impairment in cognitive flexibility, as shown by the poor performance on the SWAT.

Notes

Fundings: Hungarian National Brain Research Program (Nemzeti Agykutatási Program - KTIA_NAP_13-1-2013-0001 projekt). Doctoral School: Mental Health Science Program: Psychiatry Supervisor: Pál Czobor E-mail address: balint.sara@med.semmelweis-univ.hu

Abstract type

poster

THE VALIDATION OF THE FEAR AVOIDANCE QUASTIONNAIRE IN HUNGARIAN

Simoncsics, Eszter

Eszter Simoncsics Egyesített Szent István és Szent László Kórház Rehabilitáció Centrum, Budapest

Introduction

Fear avoidance makes the treatment of chronic low back pain difficult. The avoidance of physical activity impairs the quality of life, self-sufficiency, and leads to social isolation. Patients don’t take part actively in a healing process.

Aim

The aim of the study was to validate the Fear Avoidance Questionnaire (FAQ) in Hungarian.

Methods

Waddell (1993) and colleagues put together the FAQ which consists of 16 items. The items can be divided in to two parts: the fear of physical activity (4) and survey on work-related beliefs (7), the remaining 5 items are omitted from the evaluation. The responses are rated on 7 point Likert scale.

The internal consistency (Cronbach alpha) test of the questionnaire was based on 10 health care workers and 10 patients. The clinical validity was examined on the basis of 50 chronic low back pain patients' data. Correlation was analysed between the fear avoidance questionnaire and the 11 points pain visual analogue scale, the Oswestry Low Back Pain Questionnaire and Zung depression questionnaires.

Results

The first group of questions had Cronbach's alpha value of 0.82, the second of 0.8, which indicates good consistency. The main score of the clinical sample on the pain scale was 6.48 ± 1.82. The correlation of the FAQ with the Oswestry questionnaire was r = 0.188 (p=0,197), with Zung Questionnaire was r=0.058 (p=0,7) and with the pain scale was r= 0, 221(p=0,140). None of them were significant. This indicates that the FAQ questionnaire is an independent indicator of the specific cognitions intervening between low back pain and disability.

Conclusion

We found a good consistency of the FAQ subscales. Clinical use is justified by the fact that other dimension is measured as in present clinical practice used functional, anxiety and pain questionnaires.

Notes

Mental Health Science Name of supervisor: Dr Adrienne Stauder Email: esimoncsics@gmail.com

Abstract type

oral

ANALYSIS OF THE CURRENTLY APPLIED PRACTICES OF PERINATAL AND INTRAUTERINE DEATH AND THEIR EFFECTS ON HEALTH CARE PROFESSIONALS

Zsák, Éva

Zsák Éva1 1. Institute of Behavioural Sciences, Semmelweis University, Budapest

Introduction

The sorrow caused by perinatal loss is a phenomenon of pathological mourning, a burden for the parents, their environment, the medical personnel, yet, it is a less researched, studied field.

Aim

(1) To present the applied practice in pre-chosen healthcare institutions, to compare the valid protocol with the effective help provided. (2) To study how these events affect the helping personnel professionally and psychologically.

Methods

(1) To present the applied practice in pre-chosen healthcare institutions, to compare the valid protocol with the effective help provided. (2) To study how these events affect the helping personnel professionally and psychologically.

Results

(1) To present the applied practice in pre-chosen healthcare institutions, to compare the valid protocol with the effective help provided. (2) To study how these events affect the helping personnel professionally and psychologically.

Conclusion

The results can serve to create trainings aiming at helping the patients with adequate support, at improving coping strategies.

Notes

Doctoral School: Mental Health Sciences Program: Mental Health Sciences Supervisors: Dr. Katalin Hegedűs, PhD, Dr. Kovácsné Dr. Török Zsuzsa, PhD E-mail address: eva_zsak@hotmail.com

Abstract type

poster

COPING WITH STRESS IN COUPLES: THE SIGNIFICANCE OF PERSONAL GOAL RELATED DYADIC COPING FOR RELATIONSHIP SATISFACTION AND WELL-BEING

Szabó, Evelin

EVELIN SZABÓ, TAMÁS MARTOS

Background and objectives

Theory of dyadic stress and coping is an extension of stress and coping model of Lazarus (1984) to systemic couple interactions (Bodenmann, 1995, 1997, 2005). It was repeatedly shown in scientific studies that better dyadic coping in general is related to higher relationship satisfaction, well-being and lower perception of stress in couples. However, there is much less research on dyadic coping processes in specific life domains.

Aim

Within the framework of an ongoing OTKA research (PI: TamásMartos), we seek to answer the questions: 1) how stress in one partner's personal goal is connected to the dyadic coping processes associated with these goals and 2) how these processes correlate with the well-being of couples in committed relationships.

Methods

We used a sample of 149 Hungarian adult couples living in committed relationships (marriage or cohabitation). The questionnaire pack was administered to both partners and consisted of the assessment of personal goals, ratings of dyadic coping experiences with a chosen goal and well-being indices (satisfaction with life, relationship satisfaction).

Results

Dyadic coping (r=0,195 p=0,05) has a positive correlation with well-being, and there is a negative correlation (r=-0,463 p=0,01) between the personal goal's difficulty and well-being.

Conclusion

We presented a new approach to dyadic coping assessment, results reinforce the significance of dyadic coping. Our analysis shows,thatdyadiccopingwereassociatedwithhigherquality of life and higherlevel of well-being. The higherthecoupleperceivedthedifficulty of personalgoals, thelowerthecouple's well-being.

Notes

Keywords: Dyadic coping, relationship satisfaction, personal goals, well-being Doctoral School: Mental Health Sciences Program: Sociological and mental health approaches to resources for individuals and communities Supervisor: Tamás Martos E-mail: szabo.evelin@mental.usn.hu

Abstract type

oral

Nonsuicidal self-injury (NSSI) and its psychopatological correlates among adolescents – status report

Mészáros, Gergely

Gergely Mészáros1,2 1 Vadaskert Child Psychiatry Hospital and Outpatient Clinic 2 Semmelweis University School Of Ph.D.

Background

During the last decade there is a growing interest in nonsuicidal self-injury (NSSI). During my PhD work at first a systematic literature search was made to examine the prevalence and psychopathological correlation of NSSI. Additional aim was to review terminology and measurements of self-injurious behaviour. Altogether 49 papers were included. There is large diversity both of the terms for self-injury and instruments. There were 9 expressions for self-injurious behaviour, NSSI was the most common (it was found in 28 publications), and 12 methods for measuring it. Prevalence of NSSI was 19-67% in clinical samples and 3-43% in normal population.

Aim

The main objective of my PhD study is the examine NSSI and its association with psychopathology.

Methods

Adolescents aged 13-18 are involved in the study. The clinical group is enrolled in the Vadaskert Child Psychiatric Hospital, while the control group is enrolled in high schools of Budapest. Instruments: structural interview: Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) for psychiatric diagnoses; self-reported questionnaires: Deliberate Self Harm Inventory (DSHI) for measuring NSSI, Strength And Difficulties Questionnaire (SDQ) for externalizing-internalizing dimensions and symptoms.

Results

At the time of submission of this abstract there are 174 participants in the clinical group. From 225 possible participants 20 adolescents or their caregivers refused participation, in the case of 20 adolescents we couldn't contact their caregivers for consent to our study, 11 adolescents were unable to fill the self-report questionnaires, because of the severity of their psychopathology. From 192 possible participants 74 caregivers gave their consents, and 62 adolescents agreed to take part in our study. The data entry runs parallel with the data collection.

Notes

Clinical Medicine Psychiatric Disorders Judit Balázs meszaros.gergely.83@gmail.com

Abstract type

oral

Update on ECT use in Hungary

Asztalos, Márton

Márton Asztalos, Semmelweis University, Budapest and Aalborg Universitetshospital, Aalborg Gábor Gazdag, Clinic of Addictology and Psychiatry, Szt. László Hospital, Budapest

Objective

There has been no systematic evaluation of ECT use in Hungary since 2002. In 2005 a National Guideline on ECT use was published. Since 1994, the collaboration of a specialist in anesthesiology is a legal obligation. However, the introduction of the new antipsychotic and antidepressant drugs expanded the possibilities in psychopharmacological treatment. These events basically influenced ECT use. The aim of this study was to obtain an overview of ECT practice in Hungary.

Methods

Two questionnaires were sent to all psychiatric departments in Hungary (exceptions: child- and adolescents ward, rehabilitation and addiction). One with 25-questions about ECT practice for those departments that perform ECT, and another questionnaire for non-using departments, to explore the reasons of reluctance.

Results

All departments except four replied by mail, by phone, or by e-mail. Twenty-one departments indicated the use of ECT, but only nineteen departments applied ECT in 2014. The average number of treated inpatients was 9 on ECT using departments. The rate of ECT treated patients was 0,174 per 10.000 population. The indication for ECT was schizophrenia in 32,2% of the patients and affective disorder in 48,3% of the cases. Mostly bitemporal electrode placement was used usually thrice weekly. Most commonly used sleep induction agents was propofol.

Conclusion

The rate of ECT use in Hungary significantly decreased since the nationwide survey in 2002, the number of treated patients was nearly halved. Diagnostic distribution of ECT treated patients also significantly changed. Affective disorders have become the main indication to 2014 which is in accordance with international guidelines. Comparing with other Central-European countries, Hungary has one of the lowest rate of ECT treatments with a decreasing tendency in the last decade.

Notes

Doctoral School of Mental Health Sciences, 01. Psychiatry Gábor Gazdag asztalos.marton@gmail.com

Abstract type

oral

Oscillatory gamma band activity in spontaneous EEG in schizophrenic patients

Baradits, Máté

Máté Baradits1, István Bitter1, Pál Czobor1 1. Semmelweis University Department of Psychiatry and Psychotherapy

Introduction

Patients with schizophrenia show altered neural oscillatory activity compared to healthy controls. Electrophysiological studies found modulation of synchronous gamma-band oscillation in schizophrenia during sensory-evoked, cognitive as well as resting-state conditions. Animal models suggest that altered modulations in gamma activity could be responsible for cognitive deficits in schizophrenia.

Aim

The goals of our study were to investigate (1) whether resting state gamma oscillation in patients with schizophrenia differs from that of controls and (2) to delineate using high-density EEG recording those brain areas where disturbances in gamma activity are manifested.

Methods

Data were acquired with a high-density, 256 channel Biosemi-EEG system, in rest with closed eyes. We investigated 26 patients with schizophrenia and 26 healthy controls, individually matched by gender, age and education level. Fast Fourier Transformation was used to determine spectral power in the gamma frequency range, separated into low gamma (31-48Hz) and high gamma (52-70Hz) bands. We used random regression hierarchical linear modelling (HLM) for statistical analysis to identify group differences between schizophrenic and healthy subjects.

Results

We identified several brain areas where pronounced group-differences emerged, based on the alpha-level of 0.005 that we adopted for statistical significance due to the multiple comparisons. Specifically, in the low gamma-band we found significant decrease at lateral anterior regions in the right hemisphere and significant increase at posterior midline regions. High gamma band activity yielded similar significant differences with a similar regional-distribution.

Conclusion

Changes in gamma activity in the right anterior region may reflect neurophysiological alterations in the dorsolateral prefrontal cortex, which is involved in executive control network, while changes in posterior regions could manifest dorsal attention network activity. These networks, which have been incriminated in symptoms of schizophrenia, are part of resting state networks; changes in gamma power may alter their operations, thereby contributing to the pathophysiology of schizophrenia.

Notes

Fundings: KTIA_NAP_13-1-2013-0001. Doctoral School: Mental Health Science Program: Psychiatry Supervisor: Pál Czobor E-mail address: baradits.mate@gmail.com

Abstract type

oral

Hidden relationship forces in the family businesses: their role in well-being and well-functioning

Gubányi, Mónika

Mónika Gubányi1, Tamás Martos1,2 1 Institute of Mental Health, Semmelweis University, Budapest 2 Department of Health, Personality and Clinical Psychology, University of Szeged, Szeged

Introduction

In business families, the functioning of the family and the business are connected by the relationships of family members. Therefore, a systemic approach is needed to assess the relationship experiences of the family members for understanding business families. The theory of psychological contracts (Sager, 1976; Rousseau, 1989) rooting in psychodynamic and learning theory is an excellent approach to describe the complex, transactional and intrapsychic aspects of the relationships. There are specific psychological contracts in business families. Relationships of the business partners are based on strong personal and committed emotions which not only affects business benefits but it is in interaction with the relationship of the family members to the business. In turn, experiences with the family business may have an impact on family relations.

Aim

The aim of the study is to examine the relationship experiences of the families concerned with their own businesses, the patterns how family and business relationships develop in time, and to explore the specificity and similarity of the families in this regard. We can support both well-being and well-functioning of business families with the examination of the ways how their psychological contracts.

Methods

In the first phase of the qualitative research we interviewed the adult members of 7 business families from Budapest and surrounding areas. A semi-structured interview schedule was developed and assessed in 1 to 1,5 hour interviews for studying the research questions.

Results

The research methodology applies the Grounded Theory (GT) which allows the theory to emerge during the research. This way the analysis process may lead to the description of variations in the dynamic relationships of business families and their business. The presentation shows the developing code tree and examples from the interviews.

Discussion

First results will be interpreted with regard to the challenges but also the well-being potential of business families.

Notes

Doctoral School: Mental Health Sciences Program: Sociological and Mental Health Approaches to Resources for Individuals and Communities Supervisor: Tamás Martos E-mail address: gubanyi.monika@mental.usn.hu

Abstract type

oral

PACIFIER USE AND BREASTFEEDING PATTERNS - SURVEY AMONG MOTHERS IN A DISTRICT WITH EXCEPTIONALLY HIGH BREASTFEEDING RATES COMPARED WITH A CONTROLL GROUP RECRUITED WITH SNOWBALL METHOD

Ungváry, W. Renáta

Renáta W. Ungváry Semmelweis University, Institute of Mental Health, Budapest

Notes

Breastfeeding is the biological norm, and has many short and long term advantages for the breastfeeding dyad. It is an important health issue to identify factorsnegativelyinfluencingduration and exclusivity of breastfeeding. Observational studies, historical studies and expert opinions show that pacifier use is one of the prevalent and oldest known breast/nipple substitutesworldwide.Breastfeeding is naturally multifunctional: it provides the most appropriate, human-specific food, immunological defence, helps satisfy the infant’s sucking needs naturally, helps the infant fall asleep, provides a feeling of security and human proximity. But all these functions,

except the feeding aspect, disappeargo an increasing extent in our bottle-pacifier culture. As a result, breastfeeding rates and duration are droppingworldwide. Research suggests that early use of artificial nipples is associated with decreased exclusive breastfeeding rates and shorter duration of breastfeeding – but it is not clear, if artificial nipples cause this issue, or if pacifiers serve as a solution to existing breastfeeding problems. The purpose of my survey was to identify factors leading breastfeeding mothers to use pacifiers instead of breastfeed their infants on demand – using and utilizing all the functions of breastfeeding. Method: structured questionnaire with possibility to share personal opinions and stories if the mother wishes to do so. Results clearly show that mothers' decisions to use a pacifier do not depend on possible, known or unkknown health risks or advantages of pacifiers, but merely on the need to calm the crying or colic infant without breastfeeding. One of the most important underlying purposes is the fear of negative reactions when breastfeedingpublicly. Despite these maternal attitudes, results show that health visitors and paediatricians can hold the pacifier-use rates low and breastfeeding rates exceptionally high, when congruently recommending breastfeeding on demand, and if they do not mention artificial nipples as solution for breastfeeding- or infant care problems, but offer different, natural solutions. Doctoral School: Mental Health Sciences Program: Sociological and mental health approaches to resources for individuals and communities Supervisor: Szabolcs Török E-mail adress: ungvary.renata@gmail.com

Abstract type

oral

The topographical distribution of EEG power in the age range of 4-8 years

Szakadát, Sára

Sára Szakadát1,*, Piroska Sándor1, Róbert Bódizs1,2 1 Institute of Behavioural Sciences, Semmelweis University, Budapest 2 PázmányPéter Catholic University, Budapest

Notes

NREM slow wave activity (SWA, EEG spectral power between 0.5-4.5 Hz) decreases during childhood in parallel with a back-to-front shift in its topographical distribution cohering with the global concept of caudo-rostral pattern of cortical maturation. Our previous resultscould not confirm the robust changes of delta power topography with age in the narrow age range of 4-8 years. Recently,the anteroposterior developmental shift was confirmed in the age group of 0-4 year olds widening the range of frequencies involved in this maturational process. Upper alpha activity was found to show changing maxima from occipital to frontal regions.Inspired by these recent results and the earlier recognition of ours that we need a more subtle approach to analyse our data, we planned to follow a new data analysing strategy. We study the spectral analyses of the first 1 hourof NREM sleep from all night 10/20 polysomnographic recordings (EEG, EOG, EMG, ECG) of 27 healthy subjects between 3.8-8.4 years (6.17±1.5 years; n=27, 14 females). We evaluate the regional differences in EEG activity across the antero-posterior axis investigating the entire frequency range of 0.5-15 Hz with the resolution of 1 Hz instead of using the traditional and arbitrary frequency ranges of delta, theta, alpha and sigma. We are interested in the topographical distribution of the power of these narrower frequency ranges across the antero-posterior axis. With this fine tuned methodology we hope to grasp the above described maturational pattern of sleep-related cortical functioning in our sample. Fundings:OTKA-K105367 Doctoral School: Mental Health Sciences Program: Mental Health Sciences Supervisor: Róbert Bódizs E-mail address: szurtrikk@gmail.com

Abstract type

oral

PUSH AND PULL FACTORS OF COMPLEMENTARY AND ALTERNATIVE MEDICINE USE

Zörgő, Szilvia

Szilvia Zörgő, Dr. Ágnes Zana Institute of Behavioural Sciences, Semmelweis University, Budapest

Introduction

In the intercultural milieu of medical pluralism, an increasing amount of patients choose to treat their illness with various modalities of naturopathy. The aim of this research is to investigate motivations

behind complementary and alternative medicine (CAM) use, as well as to understand illness-interpretations that are altered vis-à-vis CAM concepts among patients and practitioners primarily socialized in a biomedical setting. Reasons underlying CAM use can be categorized in the dichotomy of factors “pushing” the patient away from biomedicine, and factors “pulling” the client toward CAM.

Methods

The research is primarily a qualitative, medical anthropological analysis, which signifies fieldwork (participant observation) that began in September 2014 at a clinic of Traditional Chinese Medicine. Thus far the fieldwork involves 163 patients and entails participating in everyday work, observing admittance of patients, conducting unstructured and in-depth interviews with patients/staff. The interviews are coded with Interpretative Phenomenological Analysis; all information is aggregated employing Atlas.ti software.

Results

Therapy choice must be interpreted in the arena of greater societal phenomena, e.g. globalization, information production and related information-seeking behavior, yet individual responses to such phenomena can be reduced to a dichotomy concerning reasons for CAM use. “Push factors” include issues that are experienced as shortcomings of biomedicine, such as failing to obtain diagnosis, effective treatment, or retaining unmet needs in the doctor-patient relationship. “Pull factors” essentially denote various areas of “philosophical congruence:” the patient espouses convictions (concerning world, man, illness, health, therapy) that a certain CAM modality also holds true.

Comments

The foundation for therapy choice lies in the patient’s subjective response to biomedicine and large-scale societal changes, which form a reciprocal relationship with their explanatory model of illness. This medical anthropological inquiry aids our understanding of culture’s determining role in patient behavior.

Notes

Doctoral School: Mental Health Sciences Program: Mental Health Sciences Supervisor: Ágnes Zana, PhD Email address: zorgoszilvia@gmail.com

Abstract type

oral

The practice of clinical nutrition in Hungarian nursing homes compared to other countries

Kovács, Ágota

Kovács Ágota1,2,3, Kovácsné Balogh Judit2,4, Gaál Péter1 1 Semmelweis Egyetem Egészségügyi Menedzserképző Központ 2 Semmelweis Egyetem Egyetemi Gyógyszertár Gyógyszerügyi Szervezési Intézet 3 Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet 4 Semmelweis Egyetem Egészségtudományi Kar

Notes

In Hungary, more than 70.000 elderly live in nursing homes, where they are cared for an extended period of time. However, it is barely known how the assessment of nutritional status and the supply of clinical nutrition are implemented in Hungarian nursing facilities. Based on a profound literature review of e.g. Danish, Dutch, German and Austrian publications, I tried to summarize the most up-to-date researches on the international practice of nutrition in nursing homes. Several investigations are published concerning the malnutrition prevalence and the description of nutritional status in nursing homes; furthermore, the influence of nutritional supplement and physical activity on the morbidity and mortality of the elderly is also investigated. Some researches examine the impact and the cost-effectiveness of multidisciplinary nutritional support involving physiotherapist, dietitian and occupational therapist. Based on the reviewed publications, an exploratory research was performed in nursing homes in the capital of Hungary and in regional centres. Data were collected from questionnaires completed by nurses and dietitians as well as from patients’ medical documentations. As a summary of the results, it can be concluded that the assessment and monitoring of the nutritional status in the nursing homes are more widespread in the western countries than in

Hungary. Often the nutritional supplement of Hungarian older people cannot be carried out due to financial problems and there is a lack of adequate equipment and health care workers e.g. nurses and dietitians. However, it is promising that no side effects associated to the clinical nutrition occur in the Hungarian nursing homes. The multidisciplinary approach of western countries should be implemented in Hungary as well and adequate education should be provided to the health care workers in order to improve the quality of nutritional care in nursing homes. Doctoral School: Mental Health Sciences Program: Mental Health Sciences Supervisor: Péter Gaál E-mail address of the presenter: agota_55@hotmail.com

Abstract type

oral

DISORDERED EATING AND BODY IMAGE OF CHILDREN AND ADOLESCENT WITH CHRONIC ILLNESS

Major, Melinda

Melinda Major1,2 1 Semmelweis University, Institute of Behavioural Sciences, Budapest 2 Semmelweis University, Ist Department of Pediatrics, Budapest

Notes

Chronic illnesses are common problem in childhood and in adolescent. The puberty is a big challenge also in case of a normal development; but chronic health conditions can cause more difficult adaptation to changing or may delay puberty. Serveral illnesses require a special diet (type 1 diabetes, inflammatory bowel desease, cystic fibrosis). More findings reflects that adolescent with diet related health conditions may be at risk of disordered eating and may have worse body image than healthy peers. Theese adolescents deal more with their dietary restriction, body shape and weight. Disordered eating behavior can lead to the diagnosis of an eating disorder. Because of the lacking data on prevalence and risk factors of disordered eating in chronic health conditions, the topic is very actual and important to investigate. The dissatisfaction with body image in the context of medical conditions should be better understood because of the connection with quality of life. The study reflects related scientific data on disordered eating and dissaticfaction with body image of children and adolescent with chronic illness. Another aim was to assess the possibility of a study in this topic in Hungarian children and adolescent, and to evaluate the available methods. Doctoral School: Mental Health Sciences Program name: MENTAL HEALTH SCIENCES Supervisor: Irena Szumska E-mail address: major_melinda@yahoo.com

Abstract type

oral

Interleukin-6 polymorphism influences physical aspects of depressive symptoms when interacts with stress.

Kovacs, David

David Kovacs 1,2, Nora Eszlari 1,2,Peter Petschner 1,2, Dorottya Pap 1, Szilvia Vas 1,2, Peter Kovacs 1,3,4, Xenia Gonda 1,2,5, Gabriella Juhasz 1,2,6,7, Gyorgy Bagdy1,2 1.) Department of Pharmacodynamics, Semmelweis University, Budapest, Hungary, Nagyvarad ter 4. 2.) MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Hungarian Academy of Sciences, Budapest, Hungary, Nagyvarad ter 4. 3.) National Institute of Oncology, Budapest, Hungary, Rath Gyorgy u. 7-9, 4.) PhD school of Mental Health Sciences, Semmelweis University, Budapest, Hungary, Balassa u. 6, 5.) Department of Clinical and Theoretical Mental Health, Kútvölgyi Clinical Center, Semmelweis University, Budapest, Hungary, Kútvölgyi u.4 6.) Neuroscience and Psychiatry Unit, University Manchester, Manchester M13 9PT United Kingdom 7.) MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest, Hungary, Nagyvarad ter 4.

Notes

Interleukin-6 levels found to be consequently elevated in depressed individual’s peripherial plasma samples. This proinflammatory cytokine also has major role in the development of depressive

symptoms as side effects of immune therapies such as IFN-α treatment. A promoter polymorphism marked rs1800795 modulates greatly the expression rate of this cytokine, especially under stressful conditions. In our study we examined the interactions of this IL-6 polymorphism with painful medical conditions, and stressful life events happened in the near past. We included two different depressive symptom measuring scales, Brief Symptom Inventory (BSI), and Zung Self-Rating Depression Scale (ZSDS), in order to distinguish between the features of depressive symptoms, since ZSDS is proved to be more sensitive to somatic aspects of depression compared to BSI. We used additive, dominant, and also recessive heritability models for the analysis. We found no main effects of the polymorphism on both depressive symptom scales. At nominal significance level we found both painful conditions, and recent life stress to interact with the polymorphism, significantly changing depression scores. However after correction for multiple testing, only one result remained significant in the BSI scale influencing group, while four out of six interaction remained significant when the outcome measure was the ZSDS scale. Therefore we suggest that including interacting factors in the examination of IL-6 polymorphism rs1800795's effect on depression is necessary to achieve replicable results. Also we found that mainly somatic aspects of depressive symptoms are influenced by the interactions, so using an appropriate measuring scale is also crucially important. ??Doctoral??School????Mental??Health??Sciences??Program????Psychiatry??Supervisor????Pro f??Bagdy??György????Email????thadeoussmith@gmailcom

Abstract type

poster

Transgenic mice with partial SUCLA2 deficiency exhibit increases in SUCLG2 expression, GTP-forming succinate-CoA ligase activity and blood carnitine esters

Kacso, Gergely

Gergely Kacso, Dora Ravasz, Judit Doczi, Beáta Németh, Ory Madgar, Ann Saada, Polina Illin, Chaya Miller, Elsebet Ostergaard, Iordan Iordanov, Daniel Adams, Zsuzsanna Vargedo, Masatake Araki, Kimi Araki, Haruka Ito, Aniko Gál, Mária J Molnár, Vera Adam-Vizi and Christos Chinopoulos Department of Medical Biochemistry, MTA Lendület Neurobiochemistry Research Group

Notes

Succinate-CoA ligase (SUCL) is a heterodimer enzyme composed of an invariant SUCLG1 and a substrate-specific SUCLA2 or SUCLG2 subunit yielding ATP or GTP, respectively. We generated mice lacking either one SUCLA2 or SUCLG2 allele. SUCLA2 heterozygote mice exhibited tissue- and age-dependent decreases in SUCLA2 expressionassociated with decreases in ATP-forming activity and rebound increases in SUCLG2 expression and GTP-forming activity. Bioenergetic parameters including substrate-level phosphorylation were not different between wild type and SUCLA2 heterozygote mice unless a submaximal pharmacological inhibition of SUCL was concomitantly present. mtDNA contents were moderately decreased, but blood carnitine esters of short- and long-chain fatty acids were significantly elevated in SUCLA2 heterozygote mice. SUCLG2 heterozygote mice exhibited decreases in SUCLG2 expression but no increases in SUCLA2 expression. Our data suggest that a partial reduction in SUCLA2 elicits rebound increases in SUCLG2 expression, pleiotropically affecting metabolic pathways associated with SUCL. Szentágothai János Doctoral School of Neuroscience Functional Neurosciences Christos Chinopoulos gergelykacso@gmail.com

Abstract type

oral

Lack of evidence of NQO1 participating in the SKDCC axis

Ravasz, Dora

Dora Ravasz, Gergely Kacso, Christos Chinopoulos Department of Medical Biochemistry, Semmelweis University, Budapest

Notes

The SKDCC axis consists of Succinyl CoA ligase, KGDHC, DT-diaphorases, Complex III and Cytochrome C, producing high-energy phosphates through substrate-level phosphorylation in the

mitochondrial matrix in the absence of oxidative phosphorylation. Here we tested the hypothesis that NQO1 is the DT-diaphorase producing NAD+ for KGDHC under anoxic conditions and inhibition of complex I. We compared adenine nucleotide translocase directionalities during anoxia or pharmacological inhibition of complex I in liver mitochondria from wild-type versus Nqo1-/- mice, implying substrate-level phosphorylation, thus interrogating the state of the SKDCC axis. We found that substrate-level phosphorylation of Nqo1-/- mice was indistinguishable from that of WT mice. Furthermore, inhibitors as well as substrates of DT-diaphorases were equally effective in WT and Nqo1-/- mice. We conclude that NQO1 is not the DT-diaphorase of the SKDCC axis.
Neurosciences (”János Szentágothai”) Doctoral School Functional Neurosciences Program Supervisor: Christos Chinopoulos E-mail address: ravasz.dora@med.semmelweis-univ.hu

Abstract type

oral

SUCCINATE DEHYDROGENASE REGULATION VIA OXALOACETATE IN BRAIN MITOCHONDRIA

Horváth, Gergő

Gergo Horvath1, Gergely Svab1, Vera Adam-Vizi1, Laszlo Tretter1 1. Department of Medical Biochemistry, MTA-SE Laboratory for Neurochemistry, Semmelweis University

Introduction

Succinate dehydrogenase (SDH) a mitochondrial enzyme participates in the respiratory chain and in the citrate-cycle. SDH has a well-known metabolic role but according to recent studies it also participates in hypoxia-induced cellular reactions and tumorigenesis. We have observed earlier that at low concentrations of succinate ADP inhibited oxygen consumption in brain mitochondria, but this phenomenon was not detected in kidney and liver mitochondria.

Aim

Our goal was to investigate the SDH organ specific regulation. In our experiments we examined which regulatory mechanism stands behind the ADP induced respiratory depression.

Methods

Our experiments were done on isolated brain and kidney mitochondria from guinea pigs. The mitochondrial respiration was measured by Clark-type electrode. The SDH, malic enzyme, phosphoenolpyruvate-carboxykinase (PEPCK) and hydroxy-oxoglutarate aldolase (HOGA) was determined spectrophotometrically.

Results

Oxygen consumption measurements pointed out that the maximal respiration in the presence of succinate was similar in both organs at saturating conditions. We assumed the cause of inhibition at lower succinate concentration was the endogenously produced oxaloacetate (OA). The OA inhibited SDH in both organs to a similar extent. Addition of rotenone a respiratory chain inhibitor abolished the ADP-mediated repiratory inhibition. Mitochondria supported with low succinate and pyruvate also increased oxygen consumption after adding ADP. The mitochondrial malic enzyme activity was five times higher in brain mitochondria. Threefold higher PEPCK enzyme was measured in kidney mitochondria.

Conclusion

The reason behind the organ specificity of ADP-mediated inhibition of succinate respiration could be the different mechanism and efficacy of oxaloacetate elimination in the two organs. Our results showed, that PEPCK and HOGA enzymes participate in the regulation of OA concentration. OA is the main metabolic inhibitor of SDH.

Notes

Fundings OTKA (NK 81983), MTA (MTA TKI 2013), Hungarian Brain Research Program (KTIA_13_NAP-A-III/6) to V.A-V. Doctoral School: János Szentágothai School of Neurosciences

Program: Functional Neurosciences Supervisor: Tretter László E-mail address: horvath.gergo@med.semmelweis-univ.hu

Abstract type

poster

Effect of spontaneous migraine attack on periaqueductal grey connectivity measured by resting state functional magnetic resonance imaging: a case report

Édes, Andrea Edit

Andrea Edit Édes 1,2, Lajos Rudolf Kozák 1,3, Terézia Zsombók 1,2, György Bagdy 2,4, Gabriella Juhász 1,2,4,5 1 MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group, Budapest, Hungary 2 Department of Pharmacodynamics, Faculty of Pharmacy, Semmelweis University, Budapest, Hungary 3 Semmelweis University, MR Research Center, Budapest, Hungary 4 MTA-SE Neuropsychopharmacology and Neurochemistry Research Group, Budapest, Hungary 5 Neuroscience and Psychiatry Unit, The University of Manchester, UK and Manchester Academic Health Sciences Centre

Introduction

Migraine is the most prevalent neurologic disorder, and its pharmacological treatment is not satisfactory still. Over the past centuries several different theories have been proposed to explain the disease pathophysiology and the complexity of its symptoms. According to the literature the periaqueductal grey plays an important role in the pathophysiology of migraine. To our knowledge, no studies have been investigated so far spontaneous migraine attack with resting state functional magnetic resonance imaging (fMRI).

Methods

Using blood oxygen level dependent (BOLD) fMRI, we assessed a 24 years old woman affected by migraine without aura at two different times: during the spontaneous migraine attack, and in interictal phase. We compared the two conditions with Statistical Parametrical Mapping 12 (SPM12) and the CONN toolbox for MATLAB to identify differences in functional connectivity of the periaqueductal grey (PAG).

Results

The analysis showed connectivity changes of PAG during the migraine attack compared to the migraine free scan in areas related to pain network. We found increased connectivity with visual cortices, caudate, thalamus and other pain related areas. Other brain regions responsible to control pain network, e.g. subgenual anterior cingulate cortex showed decreased connectivity with PAG.

Conclusion

We observed significant connectivity changes of PAG with several cortical and subcortical areas in a patient during spontaneous migraine attacks. A single case cannot answer the question of whether PAG is the key structure in pathophysiology of migraine or whether it is only a piece of a puzzle. However, our findings can verify the importance of resting state fMRI technique in investigation of acute migraine attack.

Notes

Doctoral school: Doctoral School of Mental Health Sciences Program: Psychiatry Supervisor: Gabriella Juhász E-mail: edes.andrea88@gmail.com

Abstract type

oral

Frequency characteristics of tremor in patients with cerebellar and/or brainstem lesions

Kovács, Andrea

Andrea Kovács1,2, Zsuzsanna Farkas3, Nándor Pintér1, Anita Kamondi1,3 1 – National Institute of Clinical Neurosciences 2 - JánosSzentágothai Doctoral School of Neurosciences 3 – Semmelweis University, Department of Neurology

Background and objectives

The cerebellum and the brainstem, which are functionally interrelated structures, play a key role in the pathogenesis of tremor. Although there are only scarce data on quantitative parameters of tremor due to cerebellar or brainstem lesions, it is generally accepted that cerebellar lesions may cause intentional and/or postural tremor of less than 3-4 Hz frequency. The aim of our study was to investigate the characteristics of tremor in patients with cerebellar or brainstem lesions.

Methods

49patients suffering from stroke or cerebral tumour with cerebellar or brainstem lesions proved by CT or MRI were investigated.15 patients were excluded because of the presence of concomitant conditions that are known to induce tremor.Tremor was recorded with biaxial accelerometers bilaterally simultaneouslyin resting, postural and intentional position. Patients were divided into subgroups according to the localisation and duration of their lesion, and the intensity and peak frequency of tremor. The subgroup of patients with normal tremor intensity was statistically compared to healthy controls.

Results

None of the 34 patients had pathologic tremor at rest. 2of 7 patients with chronic, 7 of 11with acute stroke, and 7 of 16with tumour presented pathologicalpostural/intentional tremor. Peak frequency of the pathological tremor ranged between 2-3 Hz (11 of 16 patiens) or8-9 Hz (4 of 16 patients).Tremor intensity was increased only in 7 patients.Patientswith peak frequency between 2-3 Hz and normal tremor intensity hadlowerfrequency dispersion, higher harmonic index (0,97), proportional power in the 0-3 Hz range (45%)on the affected side than healthy controls. In 2 post-strokepatientstremor became normal after 1 and 2 months.

Conclusion

Acute/chronic cerebellar lesions might induce pathological tremor with increased or normal tremor intensity. Further investigations are needed to clarify the role of the cerebellum and brainstem in tremorgenesis.

Notes

Name of the doctoral school: János Szentágothai Doctoral School of Neurosciences, Semmelweis University Title of the program: Clinical research in neurosciences Supervisor: Anita Kamondi

Abstract type

oral

CAUSALITY ANALYSIS FOR BRAIN RESEARCH

Benkő, Zsigmond

Zsigmond Benkő1, Zoltán Somogyvári1 Wigner Research Centre for Physics of the Hungarian Academy of Sciences, Department of Theory, Complex Systems and Computational Neuroscience Group

Introduction

The vast amount of neural data opened a new era of brain research where new data analysis methods are highly needed for taking a full advantage of the resources we have. Such methods for example the causality detection methods, which try to extract causal relations from data based on observations without any experimental intervention.

Aim

In this poster we attempt to review mainstream causality analysis methods.

Methods

In the first part we present methods based on Norbert Wiener's notion of causality on stochastic systems. We start with the first formalization of the Wiener-principle, namely Granger causality. Then we continue with the exact information-theoretical formulation (Schreiber) by introducing Transfer Entropy, which measures predictive information transfer between two variables. In the second part

we present state-space methods. This approach applies for deterministic dynamical systems and based on Takens theorem. In one hand we show how Convergent Cross-Mapping works and review enhanced versions of it since of its invention in 2012. The other hand we present how complexity and causality are related.

Results

We show the methods in work on simulation examples, discuss the capabilities and draw the borders of applicability.

Conclusion

The stochastic and deterministic dynamical system views are complementary approaches and the simultaneous application of the two to neural data bears the promise of a new level of understanding of the information processing and the underlying dynamics.

Notes

Fundings: Hungarian Scientific Research Grant (OTKA) K113147 Doctoral School: János Szentágothai Doctoral School of Neuroscience Program: Functional Neuroscience Supervisor: Zoltán Somogyvári E-mail address: benko.zsigmond@gmail.com

Abstract type

oral

Pre-hospital RSI – efficiency and patient safety

Burány, Béla

Béla Burány1, Péter Temesvári2, Márton Radnai3, Ákos Sóti2, László T Hetzman2 MH EK Military Hospital1, Hungarian Air Ambulance2, National Ambulance Service3

Introduction

Rapid Sequence Intubation (RSI) is gold standard for advanced emergency airway management in many countries. As opposed to other (nonRSI) methods, with RSI, muscle relaxants are used. At the National Ambulance Service (NAS), RSI is practiced since 2013. Safety and efficiency of the procedure is yet unknown.

Objective

To compare RSI to nonRSI regarding efficiency and complication rate and determine underlying factors.

Matrials and methods

Clinicians of the NAS are required to complete a structured data sheet after intubation. We've studied intubations performed between September 2013 and July 2015. We looked at rate of intubation at first attempt, medication used and serious complications with every level of training of the clinicians. For statistical analysis we used the $\chi 2$ test with SAS software.

Results

Out of the 5836 involved, RSI was used in 2751 (47,14%) cases, while nonRSI in 3085 (52,86%) cases. Overall success rate did not differ significantly between the two study groups (RSI vs. nonRSI: 97,20 vs. 96,34%; p=0,06). First attempt success rate was significantly higher in the RSI group (85,5 vs. 74,42 %; p<0,0001) and the rate of intubations without complications significantly favorable (69,76 vs. 56,53%; p<0,0001). In the non-RSI group. first attempt success rate was significantly higher if intubation was performed by specialist physicians compared to paramedics (82,85 vs. 73,45%; p=0,0007); specialist physicians had a lower complication rate as well (67,52 vs. 55,55%; p=0,0001). With RSI there was no significant difference between clinician groups with different levels of training regarding efficiency and safety.

Conclusion

RSI at the NAS is notably more efficient and significantly safer compared to nonRSI. First pass success rate and complication rates of RSI are similar to those found in other studies. When intubating with RSI, clinicians with different levels of training achieved identical efficiency and safety.

Notes

Doctoral School: Mental Health Sciences Program: Mental Health Sciences Supervisor: Éva Belicza E-mail: burany@monornet.hu

Abstract type

poster

Molecular Sciences

A comparative study of dUTPase inhibition by StI, a staphylococcal repressor protein

Benedek, Andras

Andras Benedek1,2, Istvan Poloskei2, Beata G. Vertessy1,2 1Institute of Enzymology, RCNS, HAS, Budapest, Hungary 2Department of Applied Biotechnology, Budapest University of Technology and Economics, Budapest, Hungary

Notes

The enzyme dUTPase plays a key role in maintaining sufficiently low cellular dUTP/dTTP ratio via effective hydrolysis of dUTP into dUMP and pyrophosphate. This enzymatic reaction is thought to be evolved in order to prevent hyperactivation of the base excision repair process which carries the risk of DNA double strand brakes or even cell death [1]. As dUTPase activity is already proven to be essential in several species, it is a potential therapeutic target in certain infectious diseases like malaria or tuberculosis [2] and even from some aspects of cancer treatment [3]. Though small molecule dUTPase inhibitors do exist, an effective proteinaceous inhibitor of the enzyme may promote identification of a potentially alternative synergistic inhibition site at the dUTPase surface. StI is a pathogenicity island repressor protein in Staphylococcus aureus. Its primary function is abolished upon complexation with the Staphylococcal Φ11 phage dUTPase [4, 5]. Subsequent quantitative characterization of this interaction revealed that StI acts as a highly potent inhibitor of the Φ11 phage dUTPase, vice versa [5]. In addition, it also shows cross-species effects by inhibiting mycobacterial dUTPases both in vitro and in vivo. In hope of identifying StI as a broad-spectrum dUTPase inhibitor, we tested its in vitro effect on both the eukaryotic Drosophila melanogaster and on the prokaryotic Escherichia coli dUTPases. Using steady-state activity assay we observed approximately 40% decrease in enzymatic activity of the Drosophila dUTPase but we did not detect any change in E. coli dUTPase activity. We further confirmed a strong interaction between D. melanogaster dUTPase and StI by native gel electrophoresis. Surprisingly, the native gels showed that StI also forms a protein complex with the E. coli dUTPase despite of the fact that no inhibitory effect of dUTPase activity was detected. 1. Vertessy, B.G. and J. Toth, Keeping uracil out of DNA: physiological role, structure and catalytic mechanism of dUTPases. Acc Chem Res, 2009. 42(1): p. 97-106. 2. Pecsi, I., et al., The dUTPase enzyme is essential in Mycobacterium smegmatis. PLoS One, 2012. 7(5): p. e37461. 3. Ladner, R.D., The role of dUTPase and uracil-DNA repair in cancer chemotherapy. Curr Protein Pept Sci, 2001. 2(4): p. 361-70. 4. Tormo-Mas, M.A., et al., Moonlighting bacteriophage proteins derepress staphylococcal pathogenicity islands. Nature, 2010. 465(7299): p. 779-82. 5. Szabo, J.E., et al., Highly potent dUTPase inhibition by a bacterial repressor protein reveals a novel mechanism for gene expression control. Nucleic Acids Res, 2014. 42(19): 11912–11920. George Olah Doctoral School (Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics). Functional and biochemical characterization of uracil recognizer and metabolizer enzymes playing a role in DNA repair. Supervisor: Beata G. Vertessy. Email: benedek.andras@ttk.mta.hu.

Abstract type

oral

DNA methylation analyses in a pilot study of patients with borderline personality disorder

Kruk, Emese

Emese Kruk Semmelweis University, Department of Medical Chemistry, Molecular Biology and Pathobiochemistry

Background

Increasing number of studies have been using peripheral tissues (blood, saliva) for DNA methylation analyses in psychiatric disorders, since brain samples are hardly accessible. Importantly, epigenetic marks can be cell-type-specific, which can create technical heterogeneity in the collected samples. Interestingly, an easily accessible biological sample, the epithelial cells' DNA methylation patterns are more similar to the brain samples, compared to blood samples, possibly because of common ectodermal origin. Therefore, buccal swab samples could serve as more relevant peripheral tissue in psychiatric disorder related epigenetic studies.

Methods

We investigated candidate gene regions of the catechol-O-methyltransferase (COMT), serotonin transporter, glucocorticoid receptor, FK506 Binding Protein 5 (FKBP5) genes. Moreover, we investigated 2 tissue specific CpG sites, the epithelial specific (PTPN7 cg18384097) and neutrophil granulocyte specific (POR cg20748065). Four different type of biological samples (blood, saliva, bucca, mouthwash) were collected from patients with borderline personality disorder (n=10) and from control persons (n=11). Furthermore, blood was processed to obtain peripheral blood mononuclear cells. DNA samples were first bisulfite-treated, than analyzed by pyrosequencing.

Results

The DNA methylation level of the PTPN7 cg18384097 varied widely (ranging from 2.40-82.71) among the collected mouth-related samples. The DNA methylation levels of serotonin transporter and glucocorticoid receptor promoter regions showed little variance, whereas the alternative promoter of COMT and the intronic region of FKBP5 gene showed large variance. The methylation levels of these candidate gene regions showed an inverse correlation to the PTPN7 and POR CpG marker sites (R2=0.8-0.9) in mouth-related samples.

Discussion

Our results show that DNA samples obtained from the mouth can be quite heterogeneous, containing different amount of epithelial cells and leukocytes. Therefore, in epigenetic analyses cell composition should be taken into account as a technical variable, especially in the case of the tissue-specific alternative promoters.

Notes

Doctoral School of Molecular Medicine Program of Pathobiochemistry Supervisor: Zsófia Nemoda
kruk.emese@med.semmelweis-univ.hu

Abstract type

oral

TREK-1 and TREK-2 two-pore domain K+ channel subunits form functional heterodimers

Lengyel, Miklós

Miklós Lengyel Department of Physiology, Semmelweis University, Budapest

Introduction

Usually the K2P background K+ channels are assembled as homodimers. Sequence similarity and coexpression of TREK-1 and TREK-2 K2P channel subunits in different native cells raised the question whether they can form heterodimers, which can increase the diversity of background K+ currents, leading to a finer regulation of the resting membrane potential and cell excitability.

Methods

Mutant versions of TREK-1 and TREK-2 were created using site-directed mutagenesis. A concatenated TREK-1/TREK-2 'tandem' channel construct was created by PCR-based cloning to force the assembly of the different subunits. Channel constructs were expressed in Xenopus laevis oocytes, their currents were measured in whole cells and in excised membrane patches.

Results

Currents of TREK-1, TREK-2 and the tandem channel can be pharmacologically distinguished on the basis of their sensitivity to extracellular acidification and RR. Coexpression of TREK-1 and TREK-2 subunits results in a current with pH and RR sensitivity suggesting spontaneous heterodimer formation. The tandem can be also distinguished from the homodimers on the basis of its intermediate single channel conductance. Coexpression of TREK-1-L and TREK-2-S resulted in channels with conductances characteristic for the heterodimer. The effects of extracellular acidification, RR and the selective TREK-1 blocker, the sortilin-derived neuropeptide spadin (considered to be an endogenous antidepressant) were examined in outside-out membrane patches. The effect of extracellular acidification and RR on TREK was confirmed at the single channel level. TREK-1 was inhibited by spadin, while TREK-2 was not effected. The tandem was also sensitive to spadin.

Conclusion

TREK-1 and TREK-2 subunits form functional heterodimers when coexpressed in Xenopus oocytes. The heterodimer has an intermediate single channel conductance and is inhibited by extracellular acidification and spadin. We propose that the heterodimer may play a role in the sensing of changes in extracellular pH and the antidepressant effect of spadin.

Notes

TREK:TWIK-related K+ channel RR: Ruthenium red Doctoral School: Doctoral School of Molecular Medicine Doctoral Program: Cellular and Molecular Physiology Supervisor: Péter Enyedi E-mail: lengyel.miklos@med.semmelweis-univ.hu

Abstract type

oral

The regulation of human in-vitro Th17 cell differentiation in healthy donors and in autoimmune patients

Baricza, Eszter

Eszter Baricza1, Nikolett Marton1, Barbara Érsek-Molnár1, Edit Buzás1, György Nagy1,2 Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest Department of Rheumatology, Semmelweis University, Budapest

Background and objectives

Th17 cells have a central role in the inflammation by producing pro-inflammatory cytokines such as interleukin (IL)-17A, -17F, -21, -22, and tumor necrosis factor-α. We studied in vitro Th17 cell differentiation in healthy donors and in patients with autoimmune diseases.

Matrials and methods

Naive (CD45RO-) and memory (CD45RO+) T cells were isolated from the peripheral blood of healthy volunteers and rheumatoid arthritis (RA) patients with a two-step negative magnetic separation method. The cells were activated with anti-CD3 and anti-CD28 antibodies and treated with different combinations of TGFβ (2.5ng/ml), IL-6 (25ng/ml), IL-1β (10ng/ml) and IL-23 (10ng/ml) cytokines with an anti-IL-4 (10μg/ml) blocking antibody. After 5 days IL-17 and IL-22 production were measured by ELISPOT and ELISA; the RORc and Tbet expression were measured by quantitative real-time PCR. Cell viability was monitored by an impendance-based cell analyzer (CASY-TT).

Results

T cell activation increased the IL-17 and IL-22 production but did not alter the RORc expression of the naive T cells in healthy controls. In healthy donors, memory T cells expressed higher RORc and T-bet without stimulation or cytokine treatment and produced higher IL-17 compared to the naive T cells. There was no difference between the RORc and Tbet expression of naive and memory T cells in RA patients. After differentiation, the highest RORc expression was induced by TGFβ+IL6+IL1β+anti-IL4. However, the highest Tbet expression was induced by the IL-1β+IL23+IL-6+anti-IL4 treatment in controls. In RA patients the IL-1β+IL23+anti-IL4 treatment increased the

expression of both the RORc and Tbet, while TGFβ+IL6+IL1β+anti-IL4 increased only the RORc expression.

Conclusion

The IL-17 and IL-22 production are differently regulated during human Th17 differentiation. These data suggest that the increased baseline of RORc and Tbet expression in naive T cells and the difference in Th17 cell differentiation development may contribute to the accelerated inflammation in RA.

Notes

Doctoral school: 7. Molecular Medicine Program: 7/4 Basis of Human Molecular Genetics and Gene Diagnostics Name of supervisor: György Nagy Presenters email: bekyca86@gmail.com

Abstract type

oral

DOWN-REGULATION OF AUTOPHAGY BY NRF2 CONTROLED AMPK EXPRESSION DURING PROLONGED OXIDATIVE STRESS

Kurucz, Anita Andrea

Anita Andrea Kurucz1, Diana Papp2, Mónika Kosztelnik2, Barna János2, László Földvári-Nagy2,Orsolya Kapuy1, Gábor Bánhegyi1, Tibor Vellai1, Tamás Korcsmáros2 1 Semmelweis University, Department of Medical Chemistry, Molecular Biology and Pathobiochemistry, Budapest 2 Eötvös Loránd University (ELTE), Department of Genetics, Budapest

Notes

Keywords: NRF2, AMPK, autophagy, oxidative stress NRF2 (NF-E2-related factor 2, NFE2L2) transcription factor is a master regulator of oxidative and xenobiotic stress response and it is also important in cell homeostasis maintenance.Besides regulating phase I and phase II drug metabolism genes, it canalso influence cellular responses to DNA damage, intermediary metabolism and mitochondrial function. Previous studies have shown that there is a link between autophagy dependent self-eating and NRF2.Under normal conditions NRF2 is bound to its repressor Keap1 (Kelch-like ECH associating protein 1), in the cytosol to facilitate its degradation. When the level of ROS and electrophiles increases Keap1 gets inactivated by oxidation and NRF2 becomes free. The active NRF2 translocates into the nucleusand promotes transcriptions of its target genes. Our study is based on previous experiments by ELTE,Department of Genetics that confirm a negative regulatory loop between NRF2 and AMPK(Caenorhabditis elegans ortholog skn-1 and aak-2, respectively). AMPK(AMP-activated protein kinase)is a key cellular energy sensor and highly conserved in eukaryotic organisms. AMPK is activated by nutrient deprivation caused increased intracellular AMP levels. This kinase caninhibit cell proliferation and biosynthetic processes meanwhile autophagy gets activated. Collaborating with ELTE,Department of Genetics we investigate the same regulatory loop in Homo sapiens.First we silenced Nrf2 in HEK293T cells(human embryonic kidney). Then oxidative stress was induced by TBHP (tert-Butyl hydroperoxide)or starvation was mimicked with 2DG(2-Deoxy-D-glucose). The expression of AMPK (AMPKα1, ULK1 Ser 555) autophagy (LC3) and apoptotic markers (pro-Casp3, PARP, CHOP) were followed by Western blot. We verified the efficiency of silencing with quantitative PCR. We observed that siNRF2 results inhyper-activation of autophagyviahyper-phosphorylation of AMPK, meanwhile mTOR getsinactivatedAccording to our results permanentoxidative stress results in NRF2-dependent transcripitionaldown-regulation of AMPK.We can conclude thatNRF2 negatively regulates autophagy through AMPK inhibition with respect to either oxidative stress or starvation in human cell line as well as their orthologs in C. elegans. Doctoral School: Molecular Medicine Program: Pathobiochemistry Supervisor: Gábor Bánhegyi, Orsolya Kapuy E-mail address: kurucz.anita88@gmail.com

Abstract type

oral

Analysis of the expression of lipid-droplet associated proteins in skeletal muscle disorders

Erdei, Lilla

Lilla Erdei 1 – BeateK.Straub2 – Benjamin Bereznai1 –Mária Judit Molnár1 1. Institute of Genomic Medicine and Rare Disorders, Semmelweis University, 1083 BudapestTömő u. 25-29,Hungary, 2. Department of General pathology, Institute of Pathology, University Clinic Heidelberg, Heidelberg, Germany,

Introduction

According to proteomic studies there are more than one hundred proteins associated to lipid droplets, among them, the PAT family of proteins are the most studied. The PAT family of protein includes perilipin (perilipin-1), adipophilin (perilipin-2, synonymous with adipose differentiation-related protein, ADRP), TIP47 (perilipin-3, synonymous with 47 kDa mannose 6-phosphate receptor-binding protein), S3-12 (perilipin-4) and MLDP (perilipin-5, Oxpat). It is already proved that the expression of the lipid droplet-associated proteins of the PAT-family are different in different cell types such as adipocytes, hepatocytes, smooth, heart and skeletal muscle cells, and also in the case of many diseases altered expression of the PAT proteins can be observed.

Aim

Analysis of thelipiddroplet-associatedprotein'sexpressionwasperformedinthemuscle specimen of patientswithdifferent muscledisorders.

Methods

Muscle specimens of patients with different types of skeletal muscle disorders have been investigated including Duchenne muscular dystrophy, mitochondrial myopathies, and inflammatory myopathies. Immunohistochemistry and Western blot analysis were perfomed using antibodies against: Perilipin, ADRP, TIP47, S3-12 and MLDP.

Results

Four member of the PAT family of proteins, adipophilin (perilipn-2), TIP47 (perilipin-3), S3-12 (perilipin-4) and MLDP (perilipin-5) were identified in skeletal muscle.In the different muscle disorders variable altered expression of PAT proteins can be detected presumably due to the diverse disease related metabolic changes in the different muscle disorders.

Conclusion

By understanding the importance of the perilipins' expression and their association to disease pathomechanism may promote a more targeted treatment of skeletal muscle disorders.

Notes

Doctoral school: Molecular Medicine Program: Basis of Human Molecular Genetics and GeneDiagnostics Supervisor: Dr. Molnár Mária Judit e-mailaddress: erdei.lilla.l@gmail.com

Abstract type

oral

Epigenetic changes following striatal 6-OH-dopamine lesion and L-DOPA treatment in a rodent tic model

Pagliaroli, Luca

Luca Pagliaroli1,2, Borbala Veto2, Ester Nespoli3, Piroska Devay2, Bastian Hengerer3, Csaba Barta1 and Tamas Aranyi2

Introduction

Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by multiple repetitive involuntary movements ie. motor tics and at least one vocal tic. The cause of TS remains elusive but dopamine (DA) appears to have a central role through the nigrostriatal pathway.TS has a complex genetic background, but environmental factors also play animportant role in the development of the disease, which may take place through epigenetic mechanisms. The aim of this project is to investigate DNA methylation at CpG dinucleotides in a juvenile animal tic model.

Methods

Animal Model: Juvenile male Wistar rats receivedstereotaxic injections of 6-hydroxydopamine (6-OHDA) or vehicle in the left medial forebrain bundle. This results indegeneration of nigrostriatal neurons. Chronic application of L-dopa after the lesion leads to the development of motorticsas a consequence of the striatal hypersensitivity to DA. This isa putative pathological mechanism of TS and the model is obtained by prior deprivation of the neurotransmitter. Samples: Striatum, cerebellum, prefrontal cortex and hippocampus were collected from the lesioned as well as the contralateral side.

Results

We analyzed methylation changes by Reduced Representation Bisulfite Sequencing (RRBS). We pooled 2 lesioned striata and 2 contralateral striata to analyze the methylation pattern by Next Generation Sequencing after bisulfite treatment of the most CpG rich regions of the genome. We observed a striking difference in methylation levels between lesion and control. We identified differentially methylated regions and we characterized their distribution across the genome. We also performed pathway analysis on the top CpG sites and identified candidate TS genes for further studies.

Discussion

This project is a combined epigenetic study on Tourette Syndrome. It is a new field of research and will provide a possible link that may help to better explain the pathophysiology of TS.

Notes

Doctoral School of Molecular Medicine Program: Pathobiochemistry Supervisor: Csaba Barta pagliaroli.luca@med.semmelweis-univ.hu

Abstract type

oral

The association of geneticmutations in PARK2, PINK1 and LRRK2 geneswiththeearly-onset Parkinson's diseaseinHungarianpatients

Illés, Anett

Anett Illés1, Anna Kékesi1, Péter Balicza1, Anikó Gál1, Benjámin Bereznai1, Annamária Takáts2, Péter Klivényi3, György Dibó3, Eszter Hidasi4, István Balogh5, Mária Judit Molnár1. 1. Institute of GenomicMedicine and Rare Disorders, Semmelweis University, Budapest, Hungary. 2. Department of Neurology, Semmelweis University, Budapest, Hungary. 3. Department of Neurology, University of Szeged, Szeged, Hungary. 4. Department of Neurology, University of Debrecen, Debrecen, Hungary. 5. Department of Laboratory Medicine, Medical and Health Science Center, University of Debrecen, Debrecen , Hungary

Introduction

According to current knowledge,mutations and copy number changes in PARK2, PINK1, and DJ-1 genes related to the autosomal recessive, SNCA and LRRK2 to the autosomal dominant early-onset Parkinson’s disease (PD), however this list is continuously expanding by identifying new mutations and associated genes.

Aim

According to current knowledge,mutations and copy number changes in PARK2, PINK1, and DJ-1 genes related to the autosomal recessive, SNCA and LRRK2 to the autosomal dominant early-onset Parkinson’s disease (PD), however this list is continuously expanding by identifying new mutations and associated genes.

Patients and methods

98 Hungarian patients (48 female, 50 male; age of onset: 41.6) with early-onset PD were analyzed. The complete sequences of PARK2 and PINK1 genes and the hot spots (28% of the coding regions) of the LRRK2 gene were directly sequenced by Sanger method. Exon dosage was determined by multiplex ligation-dependent probe amplification. The most common LRRK2 mutation (G2019S) has been excluded by PCR-RFLP method.

Results

The presence of Q34R and C446S pathogenic mutations in heterozygous genotype were found in 2 unrelated patients in the PARK2 gene. The I803T mutation was found in heterozygous genotype in 1 patient in LRRK2 gene. The common LRRK2 G2019S mutation was not present in the Hungarian patients, but a modifying factor (S1647T) was present in homozygous genotype in 10 patients, which is a PD risk factor based on the literature. In the PINK1 gene no pathogenic mutation was detected. Furthermore, the mutation frequencies in the Hungarian population are similar to other European populations.

Conclusion

The monogenic form of the early-onset PD was very rare in Hungarian patients. The prevalence of heterozygous mutations in PARK2 observed in our cases support the concept that single heterozygous mutations in recessive PD may play a pathogenic role in the Hungarian patients. Although could not be excluded the possibility that the mutations of other genes, even unknown or undetermined, or epigenetic factors stand behind the clinical phenotype.

Notes

Fundings: Hungarian Brain Research Program - Grant, No. KTIA_13_NAP-A-III/6 Doctoral School: Molecular Medicine Program:Basis of Human Molecular Genetics and Gene Diagnostics Supervisor: Mária Judit Molnár MD E-mail address: netty.illes@gmail.com

Abstract type

oral

Regulation of monocyte function by preeclampsia-associated extracellular vesicles

Kovács, Árpád

Á. Kovács1, O. Láng1, L. Kőhidai1, J. Rigó2, N. Fekete1, E.I.Buzás1, É.Pállinger1 1 Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary 21st Department of Obstetrics and Gynaecology, Semmelweis University, Budapest, Hungary

Introduction

Preeclampsia(PE) is a serious, pregnancy-specificmultisystem disorder which can be also characterized by the imbalanced activity of the maternal monocyte-macrophage (Mo-Mph system. Numerous microenvironmental factors including extracellular vesicles (EVs)regulate the activity of Mo-Mph system. The aim of our study was to characterize the effects of preeclampsia-associated circulating EVs (P-EV) onmonocytes.

Methods

THP-1 cell line was used as a monocyte model system. P-EV induced adhesiveness of THP-1 cells was characterized by both multicolourimmunophenotyping ofcell surface adhesion proteins (CD44, integrin alfa 2, integrin beta 1, integrin beta7) and also byanimpedance-based real-time method(xCELLigence SP). The effects of P-EVs on the migratory activity of THP-1 cells were documented by holographic microscopy(Holo Monitor M4). The uptake of PKH-labelled P-EVs by phagocytosis was evaluated by flow cytometry. The P-EV induced proinflammatory cytokine production (IL-6, TNF□) of THP1 cells were quantified by real time PCRin a time dependent manner.EVs isolated from the plasma of healthy pregnant women (HP-EV) were used as biological controls.

Results

Although P-EVs and HP-EVs bound to THP-1 cells equivalently, the cells internalized significantly lower amounts of P-EVs by phagocytosis. On the one hand the P-EVs induced adhesion molecule expression, migratory activity and adhesiveness of THP-1 cells were reduced.P-EV induced chemotaxis was significantly lower. On the other hand we detected elevated TNF□mRNA level after P-EV treatment, which remained significantly higher after 24 hours.

Conclusion

Circulating preeclampsia-associated EVs exert significant long range effects on THP-1 cells, which is reflected by i)a differential cell surface adhesion protein distribution, ii) a reduced cell motility,iii) decreased phagocytosis and iv) induction of proinflammatory cytokines. Consequently, interaction ofP-EVs – monocytes is mediated via the down-regulation of the effector functions and the up-regulation of regulatory mechanismsof monocytes.

Notes

Doctoral School of Molecular Medicine Program: Human Molecular genetics and basics of gene diagnostics Supervisor: Pállinger Éva E-mail: dr.arpad@yahoo.com

Abstract type

oral

High-throughput analysis of the dynamics of the CD103+ cytotoxic resident memory T cell responses during influenza reinfection

Bencsik, András

András Bencsik1,2, Nikolett Lupsa1,2, Barbara Molnár-Érsek1,2, István Jankovics3, János Matkó4, Edit Irén Buzás2, Zoltán Pós1,2 1 Hungarian Academy of Sciences - Semmelweis University ”Lendület” Experimental and Translational Immunomics Research Group, Budapest 2 Semmelweis University, Dept. of Genetics, Cell and Immunobiology, Budapest 3 National Center for Epidemiology, Division of Virology, Budapest 4 Eötvös Loránd University, Dept. of Immunology, Budapest

Notes

CD8+ resident memory T cells (Trm) are sentinel-like memory cells maintaining an early warning system and also constituting the first line of defense against various recurring viral infections in diverse tissues. Nonetheless, the exact contribution of CD8+ Trm cells to recall antiviral immune responses is still elusive, in part because it seems to be fine-tuned by both the viral entity in question, and local tissue environs. This study aims at a better understanding of the earliest response mechanisms initiated by lung-resident murine CD8+ Trm cells activated by influenza reinfection in vivo. Lung resident CD8+ Trm cells were generated in naïve C57Bl/6J mice by intranasal infection using sublethal dose (150xTCID50) of mouse-adapted influenza A/PR/8/34 (H1N1), and subsequently activated by lethal dose viral challenge (150.000xTCID50) six weeks later. Successful viral infection was confirmed by monitoring weight loss, performing lung histology, and influenza-specific immunohistochemistry. Next, lungs were subjected to automated tissue dissociation using a GentleMACS Octo platform, and establishment of virus-specific CD8+ resident memory was validated by enumerating nucleoprotein-specific Trm cells with MHC tetramer staining. Finally, live CD8b+CD69+CD103hi (Trm) cells were FACS-sorted from dissociated lungs, harvested on days 0, 1, 2, and 3 after reinfection. Isolated CD8+ Trm cells were analyzed by transcriptome profiling, Q-PCR and ELISPOT. CD8+ Trm-specific changes were identified by using non-Trm CD8b+ cells as reference. In line with others’ findings our data demonstrate that CD8+ Trm cells react to influenza reinfection via multiple mechanisms, however, Trm response apparently does not involve classical cytotoxic effector functions, e.g. granzyme B secretion. Doctoral School: Molecular Medicine Program: Basis of Human Molecular Genetics and Gene Diagnostics Supervisor: Zoltán Pós E-mail address: bencsikandras89@gmail.com

Abstract type

oral

Mapping the genetic backgrounds of the Neurodegeneration and Brain Iron Accumulation (NBIA) in the Hungarian population

Bencsik, Renáta

Renata Bencsik 1 – Zoltan Grosz1 – Peter Balicza1 – Aniko Gal1 – Vivien Harsfalvi1 – Gertrud Tamas2 – Peter Ács 3– Peter Klivenyi4- Bernadett Kalman5, Judit Maria Molnar1 1 Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary 2 Department of Neurology, Semmelweis University 3 Department of Neurology, University of Pécs 4 Department of Neurology, University of Szeged 5 Markusovszky County Hospital, Szombathely

Introduction

The rapid development of sequencing technologies is greatly facilitated to study the genetic backgrounds of the Neurodegeneration and Brain Iron Accumulation (NBIA). Currently, 9 genes have been associated with NBIA (more commonly affected genes: PANK2, PLA2G6, C19orf12 (MPAN), CP; rarely affected: WDR45 (BPAN) FA2H, ATP13A2, DCAF17, FTL, CoAY). These genes are related to autosomal recessive pattern except of the WDR45 gene, which is X-linked dominant inheritance.

Objective

Our goal was the identification of phenotype-genotype correlations of Hungarian NBIA patients in order to understand the dysfunction of proteins which are associated with NBIA and the pathomechanism of the disease.

Patients and methods

We examined 32 patients (mean age 45.2 years) who have extrapyramidal motion dysfunction and cerebral brain iron accumulation confirmed by MRI. The entire coding regions of the PANK2, PLA2G6, MPAN, CP, FA2H, CoASY and WDR45 genes were bidirectionally sequenced with Sanger method. In one case haplotype analysis is done, as well.

Results

In the examined 32 cases the background of the disorder was cleared in 17 cases. Pathogenic MPAN mutations was verified in 6 patients, the mutation of PLA2G6 gene in three patients, the mutation of PANK2 gene in 5 patients, while the mutation of the coeruloplasmin gene was verified for three patients. In one Gypsy proband the PANK2 gene p.T528M pathogenic mutation was found in homozygous form. The same mutation has been identified in Gypsy patients in Spain.

Conclusion

According to our observation in the Hungarian population the mutations of MPAN gene are more frequent than in other populations. Genotype-phenotype correlations are complex in NBIA disorders. Several genetic test, led by clinical picture and gene mutational frequency, is necessary in order to identify the genetic background of the disease. Identification of PANK2 p.T528M mutation in several Gypsy patient suggest the presence of a new Gypsy founder mutation in this population.

Notes

This work was supported by the project KTIA_13_NAP-A-III/6 Molecular Medicine Doctoral School Basis of Human Molecular Genetics and Gene Diagnostics Supervisor: Prof. Dr. Molnár Mária Judit e-mail: bencsikrenata14@gmail.com

Abstract type

oral

ANALYSIS OF SKIN-HOMING CD8+ T CELLS IN ACUTE GVHD REVEALS INVOLVEMENT OF THE CAP SUPERFAMILY IN CUTANEOUS T CELL HOMING

Lupsa, Nikolett

Nikolett Lupsa1,2, Barbara Ersek1,2, Andras Bencsik1,2, Andor Horvath1 , Peter Remenyi3, Janos Matko4, Tamas Masszi3, Edit Buzas2 and Zoltan Pos1,2 1 Hungarian Academy of Sciences - Semmelweis University ”Lendület” Experimental and Translational Immunomics Research Group, Budapest, Hungary, 2 Dept. of Genetics, Cell and Immunobiology, Semmelweis University, Budapest, Hungary, 3 Dept. of Hematology and Stem Cell Transplantation, St. Istvan and St. Laszlo Hospital Budapest, Hungary 4 Dept. of Immunology, EötvösLoránd University, Budapest, Hungary

Notes

Here we sought a better understanding of the biology of CD8+ T cell subsets homing to distinct tissues of the host. To this end, we conducted an in-depth, comparative survey of the biomarkers of skin-homing and gut-homing CD8+ T cellsactivated in cutaneous and gastrointestinal acute graft versus host disease (aGVHD), in that activation of these subsets has been reported to occur

frequently, in parallel, and to be instrumental indisease pathology. Peripheral blood-derived CLA+/CD8+ (skin-homing), and ITGB7+/CD8+ (gut-homing)T cellswere collected from matched groups of patients not developing aGvHD,developing cutaneousaGvHD, gastrointestinal aGvHD, or bothforms of aGvHD upon allogeneic hematopoietic stem cell transplantation, by FACS sorting, and compared with each other. In all studies, CLA-/ITGB7- CD8+ T cells served as reference, and respective subsets of healthy blood donors were also analyzed as additional controls. Global transcriptome profiling disclosed thataGVHD affects gene expression patterns of circulating CD8+ T cells in a disease subtype-, and/orhoming subset-dependent manner. Of particular interest was a massive overexpression of a less known member of theCAP superfamily (Cysteine-Rich Secretory Proteins, Antigen 5, and Pathogenesis-Related 1) inskin-homing CLA+/CD8+ T cells (p=0.003), a finding successfully validated by Q-PCR, and also confirmed by flow cytometry. Also, attempts were made to analyze the subcellular distribution andbiological function of this marker byconfocal microscopy and co-immunoprecipitation studies, as well. Our data indicate that the CAP superfamily may include previously undocumented markers of CLA+/CD8+ T cells potentially involved in cutaneous T cell homing. Fundings: Lendület LP2012-49/2012, OTKA 2015/1K 116340 Doctoral school: Doctoral School of Molecular Medicine Program: Basis of Human Molecular Genetics and Gene Diagnostics Supervisor: Zoltan Pos E-mail address: lupsa.nikolett@gmail.com

Abstract type

oral

Basic Sciences and Cardiology

Complex assessment of vulnerability markers associated with neoatherosclerotic plaques in patients with in-stent restenosis using Cardiac CT, OCT and VH-IVUS

Mester, András

Nyulas Tiberiu, Mester András, Benedek Theodora, Benedek Edvin Levente, Orzan Marius, Morariu Mirabela, Benedek Imre Emergency Clinical County Hospital of Târgu-Mureș, Romania

Introduction

In-stent restenosis (ISR) is associated with neointimal hyperplasia. The term of "neoatherosclerosis" has been recently introduced to describe the new atheromatous process within the implanted stent. We aimed to assess correlations between Cardiac Computed Tomographic Angiography (CCTA) markers associated with unstable plaques, and Optical Coherence Tomography (OCT) or Virtual Histology Intravascular ultrasound (VH-IVUS) markers of vulnerability in ISR.Emergency Clinical County Hospital of Târgu-Mureș, Romania

Matrials and methods

We included 28 patients with 36 coronary bare metal stents, having symptomatic ISR, defined as >50% stenosis inside the implanted stent identified by CCTA and coronary angiography, 6-12 months after stent implantation. Qualitative and quantitative analysis of 30 ISR lesions was performed with CCTA, OCT and VH-IVUS. Group A: 21 lesions, where CCTA qualitative analysis identified dark spots representing very low plaque density areas, and group B: 9 lesions without dark spots inside the restenotic tissue.

Results

OCT analysis identified significantly lower thickness of the fibrous cap in gr.A (35.5 μm vs 94.5 μm, p<0.0001). Restenotic tissue presented heterogeneous aspect in 80,95% of gr.A vs 22.22% in gr.B, (p=0.004), an irregular shape 76.19% vs 33.33% (p=0.04), and multilayered appearance 85.71% vs 44.44% (p=0.03). Microvessels were identified 80.95% vs 22.22% (p=0.004). Rupture of the neointima was associated with lower density plaque (76.19% vs 11,11%, p=0.01). VH-IVUS identified significantly larger necrotic core in lesions with low density neoatheroma (44.5% vs 21.2%, p<0.0001). Multivariate analysis identified the presence of a low density plaque by CCTA (OR 3.2) and >40% necrotic core (OR=2.4) as the most powerful predictors for plaque rupture.

Conclusion

Very low CT density area within the restenotic tissue, identified as a dark spot, is associated with a significantly lower thickness of the fibrous cap and with a higher risk for plaque rupture, thus representing a new potential marker for noninvasive assessment of plaque vulnerability in patients with ISR.

Notes

Clinical medicine Cardiovascular Disorders: Cardiac imaging Imre Benedek andras.mester@yahoo.com

Abstract type

oral

Pharmacological preconditioning with gemfibrozil preserves cardiac function after heart transplantation

Benke, Kálmán

Benke Kálmán, Sayour Alex Ali, Mátyás Csaba, Oláh Attila, Németh Balázs Tamás, Ruppert Mihály, Fischinger Tímea, Hartyánszky István, Merkely Béla, Szabolcs Zoltán, Radovits Tamás Heart and Vascular Center, Semmelweis University, Budapest

Introduction

The incidence of terminal heart failure is continuously growing, thereby increasing the clinical importance of its definitive treatment, heart transplantation. Pharmacological activation of soluble guanylate cyclase (sGC), thus increasing cGMP-signalling has been reported to have cardioprotective effects, however, potent sGC activator compounds are still under development thus they are not available for the clinical setting. Gemfibrozil, a widely used lipid-lowering fibrate has recently been shown to exert sGC activating properties in vitro. The aim of the present study was to investigate whether pharmacological preconditioning of donor hearts with gemfibrozil could protect against ischemia/reperfusion injury and preserve myocardial function in a heterotopic rat heart transplantation model.

Methods

Donor Lewis rats received p.o. gemfibrozil (150mg/kg BW) or vehicle for 2 days. The hearts were explanted, stored for 1h in cold preservation solution, and heterotopically transplanted. 1h after starting reperfusion, left ventricular (LV) pressure-volume relations and coronary blood flow were assessed to evaluate early post-transplant graft function. Additional histological and molecular biological measurements were performed.

Results

After 1h reperfusion, LV contractility (LV systolic pressure: 178±10 vs. 87±7Hgmm, $p<0.001$; dP/dtmax: 4595±472 vs. 2348±306Hgmm, $p<0.001$ at 180µl LV volume, active relaxation (dP/dtmin: -2473±216 vs. -1273±138Hgmm, $p<0.001$ at 180µl LV volume) and coronary blood flow (2,7±0,2 vs. 2,1±0,2ml/min/g, $p=0.02$) were significantly improved in the gemfibrozil pretreated hearts when compared to controls.

Conclusion

Pharmacological preconditioning with gemfibrozil reduces reperfusion injury and preserves graft function after heart transplantation, which could be the consequence of enhanced myocardial cGMP-signalling. Gemfibrozil might represent a useful tool for cardioprotection in the clinical setting of heart transplantation surgery in the future.

Notes

Doctoral School: Basic Medicine Program: Cardiovascular Disorders Supervisors: Zoltán Szabolcs, Tamás Radovits E-mail address: kalman.benke@gmail.com

Abstract type

oral

Assessing the value of novel biomarkers in predicting clinical outcomes after cardiac resynchronization therapy

Perge, Péter

Péter Perge1; András Mihály Boros1; Szabolcs Szilágyi1; Endre Zima1; Levente Molnár1; László Gellér1; Éva Fórizs1; Béla Merkely1; Gábor Széplaki1 1Heart and Vascular Center, Semmelweis University, Budapest

Purpose

Cardiac resynchronization therapy (CRT) improves mortality in chronic heart failure (HF) patients with ventricular dyssynchrony, although some patients do not improve clinically despite correct CRT indications. In this study we investigated a set of novel heart failure biomarkers associated with various pathways of heart failure pathophysiology, our purpose was to assess their ability to predict clinical outcomes after CRT.

Methods

We enrolled 136 chronic HF patients undergoing CRT implantation to our prospective single-center observational study. We measured the plasma levels of fractalkine, pentraxin-3, hepatocyte growth factor, CA-125 and MMP-9 before and six months after CRT with commercially available assays. The primary endpoint of the study was five year all-cause mortality, we considered six month reverse remodelling defined as at least 15% decrease in end systolic volume as secondary end-point.

Results

During five years of follow-up 58 patients (43%) deceased, 66 were considered as non-responder. From investigated baseline clinical variables age, NYHA class III-IV and NT-proBNP were predictive of reverse remodelling. Five years all-cause mortality was significantly related to left brundle branch block, beta blocker therapy and increasing NT-proBNP levels. After adjusting to all significant baseline parameters HGF was the only independent predictor of reverse remodelling (OR: 0.54, CI for OR: 0.32-0.90, p=0.01) and 5-year mortality (HR: 1.35, CI for HR: 1.11-1.64, p=0.003). The reclassification analyses revealed that HGF reached a reclassification improvement of 39 % [NRI= 0.39 (0.07-0-71), p=0.01] in reverse remodeling and 69 % [NRI= 0.69 (0.39-0.99), p<0.0001] in 5-year mortality prediction. Moreover, discrimination development was 3 % [IDI= 0.03 (0.00-0.06), p=0.02] in reverse remodelling and 6% [IDI=0.06 (0.02-0.11) in 5-year mortality prediction.

Conclusion

Of all studied biomarkers HGF, the pleiotropic cardioprotective agent was the only independent predictor of clinical outcomes in HF patients undergoing CRT, reclassification analyses showed that it may be useful in refining patient selection.

Notes

Doctoral School: Basic Medicine Program: Physiology and Medicine of Circulatory Diseases Supervisor: Gábor Széplaki E-mail address: peter.perge@gmail.com oral / poster presentation

Abstract type

oral

Integrated score of ST segment resolution following primary PCI - a new predictor of 1 year- mortality in STEMI

Morariu, Mirabela and Opincariu, Diana

Morariu Mirabela, Opincariu Diana, Benedek Theodora, Chitu Monica, Rat Nora, Benedek Edvin, Benedek Imre Emergency Clinical County Hospital Tîrgu Mureș, Romania

Introduction

ST-segment resolution after primary percutaneous coronary intervention (pPCI), for ST-elevation myocardial infarction (STEMI), is a surrogate for tissue reperfusion. However, little is known on the correlation between the ST segment resolution after pPCI, calculated as a global ECG score, and the future cardiovascular risk. The study aim was to evaluate the relationship between ST-segment

resolution, designed as an integrated score that includes all the 12 ECG leads where any elevation was present, and one-year mortality or MACE in patients undergoing pPCI.

Methods

580 patients with STEMI who underwent pPCI were included in the study. The ECG integrated score was calculated by summing all the ST segment elevations, from all the leads where they were present. Calculation was performed upon admission and at 1 hour after reperfusion. Patients were divided into 2 groups: gr. 1 - 477 patients (82.2%) with>50% ST segment resolution and gr. 2 - 103 patients (17.7%) with <50% ST-segment resolution

Results

Total amplitude of ST-segment elevation at baseline did not differ significantly between the 2 groups (ST score 7.4 mm in gr. 1 vs. 7.6 mm in gr. 2, p=0.002). Lack of >50% decrease in the ECG integrated score was associated with higher mortality (15.5% vs. 4.8%, p=0.0002), reinfarction (19.2% vs. 4.4% p<0.0001) and revascularization (21.15% vs. 5.8%, p<0.0001) at 1 year. Multivariate logistic regression demonstrated that lack of ST segment score resolution predicted the occurrence of a MACE event in one year (OR 3.43, p = 0.002).

Conclusion

Global decrease in ST segment elevation was associated with significantly lower death and MACE rates in STEMI patients undergoing pPCI. The lack of resolution of the integrated score of ST-segment elevation showed to be directly correlated with the risk of future cardiac events, thus being a new risk stratification method in STEMI patients.

Notes

Clinical Medicine Cardiovascular disorders Imre Benedek diana.opincariu@yahoo.ro

Abstract type

oral

Signal transduction of lysophosphatidic acid induced vasoconstriction

Dancs, Péter

Péter Dancs1, Éva Ruisanchez1, Margit Kerék1, Andrea Balogh2, Stefan Offermanns3, Gábor Tigyi2, Zoltán Benyó1 1Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Budapest, Hungary; 2Department of Physiology, and Department of Pharmacology, University of Tennessee Health Sciences Center, Memphis, Tennessee, USA; 3Department of Pharmacology, Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

Introduction

We have reported recently that lysophosphatidic acid (LPA) induces endothelium-dependent vasorelaxation mediated by LPA1 receptors, phospholipase C and nitric oxide (1). Removal of the endothelium not only abolished this effect but converted it to vasoconstriction. Here we aimed to analyze the signaling pathways of the vasoconstrictor action of LPA.

Matrials and methods

Aortic segments were isolated from wild type (WT) and knockout (KO) mice deficient in LPA1 or LPA2 receptors, cyclooxygenase-1 (COX1) or thromboxane receptors (TP). Vessels of mice subjected to smooth muscle specific deletion of Gαq/11 or Gα12/13 were also tested. Isometric tension of de-endothelialized vascular segments was measured via myography. Expression of LPA receptors in aortic vascular smooth muscle (VSM) was analyzed by qPCR. Thromboxane A2 (TXA2) release from aortae was measured by TXB2 ELISA.

Results

LPA1, LPA2, LPA4 and LPA6 transcripts were abundantly detectable in VSM. LPA elicited dose-dependent vasoconstriction in endothelium-denuded abdominal segments. The LPA1-3 agonist VPC31143 mimicked, whereas the LPA1/3 antagonist Ki16425 alleviated this effect. Lack of LPA1

but not that of LPA2 abolished VPC31143-induced vasoconstriction. Genetic deletion of Gαq/11 or Gα12/13 as well as inhibition of Gi/o by pertussis toxin also attenuated vasoconstriction. Gi/o signaling is often coupled to phospholipase A2 and COX1 activation, thus the potential involvement of autocrine/paracrine TXA2 release in the LPA1-mediated vasoconstriction was tested. Vessels lacking COX1 or TP showed diminished vasoconstrictor responses to VPC31143. Furthermore, VPC31143 increased TXA2 production in WT and TP KO but not in COX1 KO vessels.

Conclusion

In the absence of endothelium LPA induces vasoconstriction. This effect is mediated by LPA1 receptors, which facilitate COX1-mediated release of TXA2 resulting in TP activation. Underlying pathways involve Gq/11, Gi/o and Gα12/13 proteins. Our present and previous findings indicate that the summated effect of endothelial and VSM LPA1 activation depends on the functional integrity of the endothelium.

Notes

Doctoral School: Doctoral School of Basic Medicine Program: The Mechanisms of Normal and Pathologic Functions of the Circulatory System Supervisor: Zoltán Benyó e-mail: peti.dancs@gmail.com oral 1. Ruisanchez, Dancs, Kerék, el al., FASEB Journal 28: 880-890, 2014.

Abstract type

oral

The role of inhibition of renin-angiotensin-aldosterone system (RAAS) in diabetes induced fibrosis

Szkibinszkij, Edgar

Edgar Szkibinszkij 1,3, Sandor Koszegi1,4, Lilla Lenart1,4, Dora B. Balogh1,4, Judit Hodrea1,4, Adam Vannay2,4, Laszlo J. Wagner3, Attila J. Szabo2,4, Andrea Fekete1,4 1. MTA-SE „Lendület" Diabetes Research Group, Budapest 2. MTA-SE Pediatrics and Nephrology Research Group, Budapest 3. Department of Transplantation and Surgery, Semmelweis University, Budapest 4. 1st Department of Pediatrics, Semmelweis University Budapest

Introduction

Diabetic nephropathy (DN) is the leading cause of chronic kidney disease however its treatment is unsolved and the pathomechanism is yet unknown. During DN increased RAAS contributes to renal fibrosis. The platelet-derived growth factor (PDGF) plays key role in fibrosis, its relevance in DN is still not clarified.

Objective

We investigated in vivo and in vitro the effect of hyperglycaemia on development of fibrosis and we studied the potential anti-fibrotic effects of RAAS blockers.

Methods

In vitro: Proximal tubular cells were maintained in DMEM which was changed and supplemented with normal, high glucose, and as osmotic control, mannitol. We measured the protein level of PDGF. To verify the fibrosis inductive effect of PDGF, fibroblast cells were treated with PDGF, and α-smooth muscle actin (α-SMA) level was detected. In vivo: Five weeks after streptozotocin induced diabetes male Wistar rats were treated for two weeks per os with RAAS blockers. Healthy or diabetic animals served as controls. Blood pressure and the renal metabolic parameters were determined and fibrotic damage of kidneys was evaluated as well the renal amount of α-SMA and PDGF.

Results

Due to hyperglycaemia the PDGF levels were increased in tubular cells, it was not observed in case of mannitol. The PDGF treated fibroblast cells showed elevated α-SMA protein level. In diabetic animals, the deterioration of renal function was ameliorated by RAAS inhibitors. The enhanced mesangial matrix, interstitial fibrosis and the level of fibronectin were attenuated by various RAAS blockers. Increased level of α-SMA and PDGF in DN were reduced by RAAS inhibitors.

Conclusion

High glucose increases the PDGF production of proximal tubular cells, which induces the αSMA production in renal fibroblast, contributing to the development of fibrosis. RAAS blockers ameliorate this process by directly acting on renal fibroblasts. These results suggest the novel renoprotective feature of RAAS inhibitors.

Notes

Doctoral School: Basic Medical Sciences Program: Clinical and experimental transplantation Supervisor: Laszlo Wagner E-mail: szedgar@gmail.com

Abstract type

oral

Correlations between the severity of peripheral artery disease and the severity of coronary artery disease

Rapolti, Emese

Rapolti Emese, Benedek Imre, Benedek Edvin, Korodi Szilamer, Sebastian Condrea, Benedek Theodora Emergency Clinical County Hospital Targu Mures Cardiomed Medical and Research Center, Targu Mures

Introduction

Peripheral artery disease and coronary artery disease are the most important consequences of atherosclerosis. In most of the cases patients with peripheral artery disease present coronary artery disease too. Angio CT can provide relevant information related to the severity of stenosis and the amount of calcifications of the coronary and peripheral arteries.

Matrials and methods

The study population consisted in 24 patients suffering from peripheral artery disease who underwent angio CT of the lower limbs and coronary CT too. We analyzed the following parameters: cardiovascular risk factors, Fontain classification, TASC score, SYNTAX score, calcium score, presence of a left main stenosis and three-vessel coronary disease.

Results

Our patients were between 39 and 84 years old, out of which 56 % were in Fontaine class 2B, 12,5 % in Fontaine class 3 and 25 % in Fontaine class 4. Assesment of the severity of peripheral artery disease showed that 12,5 % of patients presented TASC class A, 33,3 % presented TASC class B, and 54,2 % TASC class C. We found low calcium scores in the coronary arteries in 16,6 % of these patients, intermediate calcium scores in 41,8 %, and high calcium score in 41,6 % of patients. SYNTAX score was low in 54 % of patients, intermediate in 37,5 % of patients, and high in 8,5 % of patients. Only 12 % of patients presented no significant coronary lesions, while 88 % of patients presented peripheral artery disease and associated significant coronary lesions too. We found a significant correlation between coronary calcium score and SYNTAX score (p=0,03), and a significant correlation between TASC classification and SYNTAX score (p=0,005).

Conclusion

The severity of peripheral artery disease, characterized by TASC classification, presents a good correlation with the severity of coronary artery disease determined by the SYNTAX score.

Notes

University of Medicine and Pharmacy of Targu Mures Doctoral School, Clinical Medicine Cardiovascular Disorders: Physiology and Medicine of Ischaemic Circulatory Diseases Supervisor: Benedek Theodora rapoltie@yahoo.com

Abstract type

oral

ALCOHOL CONSUMPTION AND PRESENCE OF CORONARY ARTERY DISEASE

Karády, Júlia

Júlia Karády1, Bálint Szilveszter1, Zsófia Dóra Drobni1, Márton Kolossváry1, Dalma Danicska1, Gabriella Marosi1, Andrea Bartykowszki1, ÁdámLeventeJermendy1, Mihály Károlyi1, Alexisz Panajotu1, Zsolt Bagyura1, Béla Merkely1, Pál Maurovich- Horvat1 1 MTA-SE Cardiovascular Imaging Research Group, Heart and Vascular Center, Semmelweis University, Budapest

Objective

The aim of this prospective clinical study was to investigate the association between alcohol-consumption and the presence of CADas detected by coronary computed tomography angiography (CTA).

Aim

Several observational studies suggestedthat light alcohol consumption decreases cardiovascular risk.However, the data regarding regular alcohol consumption and its association with coronary artery disease (CAD) still remain controversial.

Matrials and methods

Consecutive patients who were referred for coronary CTA due to suspected CAD were enrolled in our study. We excluded patients under the age of 18 years and patients with history of stroke, acute myocardial infarction or coronary revascularization. The weekly alcohol consumption was registered using a questionnaire.Alcohol units were calculated as follows: 1 unit equals 2 dl beer or 1 dl wine or 4 cl spirit. Based on the presence or absence of any plaque on coronary CTA we classified the patients into CAD and no CAD groups.

Results

In total, 1925 patients were enrolled (mean age 57.3±16.1 years, females 43.1%).61.3% participants had hypertension (HT), 13.7% had diabetes mellitus (DM), 40.7% had dyslipidemia (DLP) and 40.1% of the patients were current smokers. Atherosclerotic plaque was present in at least one coronary segment in 74.3% of the patients. Alcohol consumption was reported by 37.3% of the patients with a median of 6.7 (IQR: 3.3;10.8,range: 0.2-66.7) units weekly. Using univariate analysis to compare CAD positive patientsand CAD negative patients we found significant difference regarding cardiovascular risk factors ($p<0.001$) but no difference in alcohol consumption ($p=0.35$). After adjusting for age, gender, HT, DM, DLP and smoking with logistic regression we found no association between alcohol consumption and the presence of CAD (OR:1.00;CI:0.98-1.02;$p=0.76$). We performed a secondary analysis to assess the relationship between alcohol consumption and CAD among no drinkers and light drinkers (maximum 14 units per week; 82.7% of alcohol drinkers) and found no association(OR:1.02;CI:0.98-1.06;$p=0.33$). Furthermore, we have analyzed the effect of different alcohol types (wine, beer, spirit)on the presence of CAD, but no relationship was found between any of the alcohol types and CAD (all p□0.05).

Conclusion

Our study suggests that the amount of weekly alcohol consumption does not show association with the presence of CAD. We could not detect anyassociation between alcohol consumption and CAD among light drinkers either. In addition, we did not find any association between the different alcohol types and the presence of coronary atherosclerosis.

Notes

Doctoral School: Doctoral School of Basic Medicine Program: Cardiology Supervisor: Pál Maurovich-Horvat E-mail address: karadyjulia@gmail.com

Abstract type

oral

Differentiation of physiological sport adaptation from hypertrophic cardiomyopathy with cardiac magnetic resonance

Czimbalmos, Csilla

Csilla Czimbalmos, Ibolya Csécs, Nóra Sydó, Orsolya Kiss, Zsófia Dohy, Beáta Horváth, Eszte rSzima-Mármarosi, Hajnalka Vágó, Béla Merkely Semmelweis University, Heart and Vascular Center

Notes

Physiological cardiac adaptation including left ventricular (LV) hypertrophy due to intensive training may create diagnostic overlap with hypertrophic cardiomyopathy (HCM). Distinguishing HCM from athlete's heart is crucial, because HCM is the most common cause of sudden cardiac death in young athletes. Our goal was to compare the LV parameters of professional athletes and HCM patients and establish cut-off values to differentiate HCM and athlete's heart. We carried out CMR examinations on 101 male (25±6y) and 49 female (24±6y) professional athletes free of complaint, 108 male (48±15y) and 86 female (53±16y)HCM patients. We determined LV ejection fraction, end-diastolic, end-systolic volume indices, stroke volume index, mass index (LVMi) and trabecular mass index (TrMi) using MedisQMass 7.6 software. Derived parameters were calculated to evaluate the hypertrophic pattern: trabecular mass percentage: TrM% (Trabecular mass/LVM*100) andLV maximum end-diastolic wall thickness and end-diastolic volume index ratio (EDWT/LVEDVi). The new quantification method resulted lower LVEDVi, LVESVi, LVSVi and higher LVMi values (p<0,001). Comparing male and female data, we found that males LV volumes,LVMi, TrMi and EDWT were higher both in athletes and HCM patients.TrMi and TrM% were higher in males both in the athlete and HCM group (p<0.01). Athlete's LV volumes were higher compared to HCM patients. EDWT/LVEDVi and andLVMi/EDVwere significantly higher in the HCM group compared to athletes both in the male (0.248 vs. 0.104 mm×m2×ml;1.079 vs. 0.753 g/ml) and female groups (0.252 vs. 0.098 mm×m2×ml;0.967 vs. 0.617 g/ml). Using a receiver operating curve-determined cut-off value for EDWT/LVEDVi of less than 0.14 mm/m2xmlmale athletes' heart could be differentiated from HCM with 99% sensitivity and 97% specificity; female athlete's heartless than 0.13 mm/m2xml with 100%sensitivity and 100%specificity. Gender specific cut-off values for EDWT/LVEDVi seems to play an important role in distinguishing athlete's heart from HCM. Doctoral School: Basic Medicine Program: Cardiovascular Disorders: Physiology and Medicine of Ischaemic Circulatory Diseases Supervisor: Béla Merkely Presenter's email address: csilla.czimbalmos@gmail.com

Abstract type

oral

Professional athlete's left ventricular magnetic resonance parameters determined by trabecula quantification in different types of sport

Csécs, Ibolya

Ibolya Csécs, Csilla Czimbalmos, Zsófia Dohy, Beata Horvath, Eszter Szima-Mármarosi, Orsolya Kiss, Nóra Sydó, Béla Merkely, Hajnalka Vágó

Notes

Cardiac magnetic resonance (CMR) imaging is the gold standard method of evaluation left ventricular volumes, ejection fraction and mass. A new CMR software enables semi-automatic quantification of myocardial trabeculation. Our goal was to evaluate left ventricular magnetic resonance parameters for athletes and to examine how these parameters change with quantitative analysis of left ventricular trabeculation. CMR examination was performed on 159 top athletes (121male, 38female; 25±7y) and on 68 healthy volunteers (41male, 27female, 27±6y). The following types of sports were examined: canoe and kayak (n=40), water-polo (n=29), rower (n=17), cyclists (n=9), kick-box (n=9), football (n=6) and ultra-marathon (n=5). Left ventricular parameters were determined using QMass quantification software which is able to analyze quantitatively the left ventricular trabeculae mass (TrM). Comparing athletes and sedentary controls, left ventricular volumes indexes and mass index (LVMi) were higher in athletesboth with and without quantifying the TrM (p<0.001). When TrM was included in the measurement, myocardial mass indices were higher, volumes were lower both in athletes and in sedentary controls (p<0.001). TrM index (TrM(g)/BSA) was higher in athletes (male: 20.8g/m2±4.3 vs 18.3g/m2±3.1; female: 16.9g/m2±3.5 vs 13.6g/m2±4.1), however TrM% (TrM(g)/LVM(g)*100) was higher in control group (male: 20.9%±2.5 vs 19.2%±3.9; female: 22.2%±5.8 vs 19.7%±4). This suggests a more pronounced hypertrophy of the compact myocardium. LVMi corrected with TrM was higher in canoe-kayakers (121.5g/m2±16.6) compared to water-polo players (108.2g/m2±16.9), cyclists (101.2g/m2±13.1), ultra-marathon runners (100.3g/m2±9.8) and kick-boxers (88g/m2±12.3). Moreover, kick-boxers had lower left ventricular end-diastolic

(87.8ml/m2±12.4 vs 103.9 ml/m2±12.3) and stroke volume index (58.1ml/m2±6.5 vs 68.3ml/m2±7.7) compared to canoe-kayakers, and lower LVMi compared to rowers (110.8g/m2±11.6) and water-polo players. This suggests a less intense cardiac adaptation in kick-boxers. Quantitative analysis of myocardial trabeculation could fundamentally alter the normal left ventricular parameters. Measuring trabecular mass could help us to better know the cardiac adaptation in different types of sport. Doctoral School: Basic Medicine Program: Cardiovascular Disorders: Physiology and Medicine of Ischaemic Circulatory Diseases Supervisor: Hajnalka Vágó Presenter's email address: ibolyacsecs@gmail.com

Abstract type

oral

Mechanical properties of the fibrin network on the macroscopic and microscopic scales

Feller, Tímea

Tímea Feller1, Balázs Kiss1 Jolán Hársfalvi1, Miklós S.Z. Kellermayer1 1 Department of Biophysics and RadiationBiology, and MTA-SE MolecularBiophysics Research Group, Semmelweis University

Notes

The scaffold of the thrombus is a three-dimensional network of fibrin, a fibrous protein that determines the mechanical properties of the whole clot and plays thereby an important role in hemostasis. With our atomic force microscope (AFM)-based force spectroscopy, called nano-thrombelastography, we followed the nanoscale changes in the viscoelastic properties during fibrin network formation and streptokinase (STK)-induced fibrinolysis in human plasma-derived clot.During nano-thrombelastography we measure the forces acting on an AFM cantilever which is submerged into a plasma or fibrinogen droplet during its cyclic vertical travel. Viscous and elastic properties become more understandable through examining maximal force difference and hysteresis area on the cantilever travel curves.The time-dependent evolution of force resembles well a macroscopic thrombelastogram: force increases gradually with the formation of the elastic fibrin network during coagulation. By measuring the area of the hysteresis loop formed by the cyclic force curves we could follow the changes in the viscous properties of the fibrin network. Effect of STK manifests in a rapid decrease in thrombus elasticity, whereas thrombus viscosity only decayed with a delay. For morphological experiments, clot formation was initiated by adding thrombin in 0,5-1 IU final concentration to fibrinogen solution on mica surface. In dried samples, scanning AFM images of mature fibrin fibers appeared as 17-nm-high and 12–196-nm-wide filaments. Upon lowering the sodium and chloride concentration of the solution, we observed fibrin networks wherein fibers had increased diameter. We carried out force mapping on native fibers with a diameter between 100-250 nm in Hepes-buffer. Force curves were recorded for each 100-μm2 area previously scanned. The local Young-modulus was calculated by using the Hertz model. The force-volume maps revealed that fibrin fibers with a diameter exceeding 200 nm have a dense surface layer and a loose core, suggesting that the thickening of the fibrils involves a distinct mechanical maturation. Plasmindigests fibrin clotbyfirstlooseningthedensecrust and releasingtheinnersoftcore, thereforecausingtheelongation of thefibers. Furtherdigestioncutsfibersintosmallfragments.Theseresultsalsosupportthemodel of a densercrust and loosercore. DoctoralSchool: Basic Medicine Program: Cellular and molecularbiophysics Supervisor: Miklós S.Z. Kellermayer E-mail address: timea.feller@gmail.com

Abstract type

oral

Predictors of Mortality in Patients with ST-Segment Elevation Acute Myocardial Infarction and Resuscitated Out-Of-Hospital Cardiac Arrest

Benedek, Edvin

Edvin Benedek, Andreea Barcan, Nora Rat, Szilamer Korodi, Mirabela Morariu, Ciprian Blendea, Marius Orzan, Monica Chitu, Istvan Kovacs

Introduction

In patients with out-of-hospital cardiac arrest (OHCA) complicating a ST-segment elevation myocardial infarction (STEMI) the survival depends largely on the restoration of coronary flow in the infarct related artery. The aim of this study was to determine clinical and angiographic predictors of in-hospital mortality in patients with OHCA and STEMI, successfully resuscitated and undergoing primary percutaneous intervention (PCI).

Methods

Our study included 78 patients with STEMI, presenting with OHCA, successfully resuscitated, who were treated with primary percutaneous coronary intervention.

Results

The clinical baseline characteristics of the study population showed no significant differences between the survivors and non-survivors regarding age, gender, hypertension, dyslipidemia, obesity, smoking status, diabetes, a history of myocardial infarction or stroke. Compared to survivors, the non-survivor group exhibited a higher incidence of cardiogenic shock (50% vs. 24%), renal failure (64.3% vs. 30%) and anemia (35.7% vs. 12%). Three-vessel disease rate was higher in the non-survivor group (42.8% vs. 20%). The time from the onset of symptoms to revascularization was significantly higher in deceased patients compared to survivors, as was the time from the onset of cardiac arrest to revascularization. Multivariate analysis identified the presence of cardiogenic shock, multi-vessel coronary disease, renal failure, anemia, need for mechanical ventilation >48 hours and a duration of stay in the ICU longer than 5 days as the most significant independent predictors for mortality in patients with OHCA and STEMI.

Conclusion

In patients surviving an OHCA in the early phase of myocardial infarction, the presence of cardiogenic shock, renal failure, anemia or multi-vessel coronary disease, as well as a longer time from the onset of symptoms or of cardiac arrest to revascularization, are independent predictors of mortality. The most powerful predictor of death is the duration of stay in the ICU and the requirement of mechanical ventilation >48 hours.

Abstract type

oral

Oncology

The effect of imatinib in various thioacetamide-induced mouse liver fibrosis models

Rókusz, András

András Rókusz1, Edina Bugyik1, Vanessza Szabó1, Armanda Szücs1, Sándor Paku1,2, Péter Nagy1, Katalin Dezső1,3 1Ist Department of Pathology and Experimental Cancer Research, Semmelweis University; 2Tumor Progression Research Group, Joint Research Organization of the Hungarian Academy of Sciences and Semmelweis University; 3TÁMOP 4.2.4. A/1-11-1-2012-0001 ‘National Excellence Program’

Background

The deposition of collagenous extracellular matrix is an obligate consequence of chronic hepatic injury. The resulting fibrosis is mostly mediated by PDGF-driven hepatic myofibroblasts. The tyrosine kinase inhibitor imatinib efficiently suppresses the activity of PDGFR, thus it is a promising candidate for the treatment of hepatic fibrosis. In our recent experiment we investigated the influence of imatinib on the dynamics of matrix deposition and several related parameters in thioacetamide-induced mouse liver fibrosis models.

Methods

Thioacetamide (300mg/l in drinking water) was given for 18 weeks to male C57Bl/6 wild type and transgenic mice, overexpressing TGF-β1 in the liver (PNAS 1995;92:2572-6). For the test animals imatinib was given daily (25mg/kg per os). In an additional “therapeutic” experiment thioacetamide (300 mg/l) was given to wild type mice for 27 weeks. In the test group imanitib treatment was started on the 19th week. Animals were sacrificed in three week intervals. The extent of fibrosis and ductular

reaction was monitored on Picro Sirius stained and cytokeratin 19 labeled sections, respectively. The proliferative activity of hepatocytes and ductular cells was analysed by bromodeoxyuridine incorporation.

Results

Imatinib treatment resulted in transient inhibition of fibrosis progression in wild type mice, but the difference between the control and treated group disappeared by the 18th week. Imatinib failed to achieve even this temporary result in transgenic mice and in the “therapeutic” experiment. In each group the extent of ductular reaction changed in parallel with the extent of fibrosis, while the proliferation of hepatocytes remained constant.

Conclusion

Imatinib didn’t show lasting antifibrotic effect in wild type mice, and it was completely inefficient besides TGF-β1 overproduction or preceding fibrosis. Our results do not support the proposed decreasing regenerative activity of hepatocytes during chronic hepatic injury. However, the correlation between ductular reaction and fibrosis in various experimental groups underlines their close relationship.

Notes

Financial support: Hungarian Scientific Research Fund (OTKA K1116301 and PD109201). Doctoral School of Pathological Sciences Program: Oncology Supervisor: Katalin Dezső email address: rokusza@hotmail.com

Abstract type

oral

Mid-infrared imaging as a promising tool to characterize cell lines

Kontsek, Endre

Kontsek E.1, Gergely Sz.2, Salgo A.2, Schaff Zs.1, Kiss A.1 1 2nd Department of Pathology, Semmelweis University Budapest, 2 Department of Applied Biotechnology and Food Science, Budapest University of Technology and Economics

Introduction

The goal of our project is to develop a spectroscopy based diagnostic tool, revolutionizing medical diagnostics, especially cancer identification. Life science associated mid- and near-infrared based microscopic techniques are developing exponentially, especially in the past decade. This is a potential non-destructive approach to investigate malignancies.

Aim

Our goal was to observe detectable differences by infrared imaging between tumorous cell lines, since cell culture models are the first step to study complex biological systems, finally the pathological alterations of the human.

Matrials and methods

A-375 melanoma cell line, HT-29 colon tumour cell culture and MDA-MB-231 breast cancer cell line were selected. The effect of paraformaldehyde and ethanol fixation was investigated by transflectance mid-infrared imaging under dye-fee condition. Further, selection of spectra was carried out by mean transmittance optimization and principal component analysis.

Results

Fixation methods by each cell lines could be identified and separated by mathematical handling of the spectra. Further, using the same fixation method the infrared imaging features and their analysis enabled us to differentiate the various tumorous cell lines from each other. The best results were found in the fingerprint region (1800-750 cm-1).

Conclusion

Mid-Infrared imaging could be used to differentiate cell lines and might be a promising tool to image tumors in vivo in animal models. This is a key step to the final goal that this dye-free technique could be used during intraoperative surgical procedures. Altogether, our results project the feasibility of infrared imaging to identify different tissues under in vivo conditions. Therefore, the technique might be applied to judge the resection margins of malignancies.

Notes

Acknowledgement: This work was supported by OTKA grants K101435 and K108548 from the National Scientific Research Foundation. Doctoral School of Pathological Sciences Alterations of Cells, Fibres and Extracellular Matrix and Diagnostic Pathomorphological Studies in the Course of Heart and Vascular Diseases and in Certain Tumours. Experimental and Diagnostic Pathomorphological Studies András Kiss

Abstract type

oral

Tumor-stroma interaction of hepatomas with slow or fast proliferation rate

Rada, Kristóf

Kristóf Rada1, Katalin Kiss1, Alexandra Fullár1, Eszter Regős1, Kornélia Baghy1, Ilona Kovalszky1 1. Semmelweis University, 1st Department of Pathology & Experimental Cancer Research

Notes

Tumor phenotype is greatly influenced by the synthesized tumor microenvironment. This non-tumorous component includes inflammatory cells, tumor associated fibroblasts, blood vessels, and the macromolecules of the extracellular matrix. In the presented research we addressed the question if fibrogenic response of Ito cells for the presence of hepatoma cells is homogenous, or it is influenced by the phenotype of hepatocellular carcinomas? Hepatoma cell lines were received from the Pathology Department of Heidelberg University. A fast growing dedifferentiated (HLE), and a slowly growing, more differentiated (Huh-7) cell line was selected for our experiments. Immortalized LX-2 Ito cell line was a kind gift of Scott Friedman (USA). The increased invasiveness of HLE cells were proved by their high proliferation rate, and their faster migration both in would healing assay and in Boyden chamber for Matrigel compared to Huh-7 cells.Both cell lines express vimentin, an intermedierfilament described in hepatomas with poor prognosis. They also express syndecan-1 and CXCR4 chemokine receptors. When hepatoma cells were put in coculturewith Ito cells we witnessed changes in their matrix protein synthesis. However, the proteins synthesized by the two cocultures differed from each other. The coculture of LX-2 cells with the more aggressive HLE cells produced more laminin β1, TIMP1, type IV collagen, and more pronounced shedding of syndecan-1ans CD-44, whereas fibronectin, thrombospondin1 and type IV collagen were the characteristic matrix components in the LX2-Huh-7 coculture. Our results indicate that the response given by the stromal cells is determined by the biological characteristics of tumor cells. Fundings: OTKA 100904 DoctoralSchool: Pathology Program: Oncology Supervisor: Dr. Ilona Kovalszky E-mail address: rada.kristof@hotmail.com

Abstract type

oral

DETECTION AND PROGNOSTIC IMPACT OF HIGH RISKHPV INFECTION IN ADVANCED STAGE, CHEMOTHERAPY TREATED ORAL AND OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

Bilecz, Ágnes

Ágnes Bilecz1, Ildikó Szirtes1, Martin Filipits2, Balázs Hegedűs3 1 2nd Department of Pathology, Semmelweis University, Budapest 2 Institute of Cancer Research, Medical University of Vienna, Vienna 3MTA-SE Molecular Oncology Research Group, Hungarian Academy of Sciences, Budapest

Introduction

High risk human papillomavirus (HPV) has been established as a causative agent in head and neck squamous cell carcinomas (HNSCC). SinceHPV associated oropharyngeal cancer patients have significantly better prognosis at presentation and after disease recurrence compared to non-HPV related HNSCC cases, detection of HPV is of clinical relevance, and knowledge of HPV status is necessary for meaningful comparison of treatment responses in clinical studies. Prevalence of HPV infection in HNSCC has been shown to be 25.9% globally by a meta-analysis, however prevalence differs significantly among different geographical locations. HPV16 and HPV18 has been found to have the highest prevalence in HNSCC, and no other known oncogenic HPV has had a prevalence higher than 1%.

Aim

We tested a DNA PCR method suitable for HPV detection in paraffin fixed formalin embedded (FFPE) samples. We evaluated if HPV statusdetermined by this method had a prognostic impact.

Methods

In our cohort of 38 advanced stage chemotherapy treated HNSCC patients 15 of the tumors were localized to the root of the tongue, 12 to the tonsilla, 5 to the uvula and soft palate and 5 to the oral cavity. We isolated DNA from formalin fixed paraffin embedded samples. We carried out PCR amplification of the HPV16 and HPV18 E7 gene (amplicon length was 196 and 172 bp respectively). We performed immunostaining for p16.

Results

10 (26.3%) of the p16 immunostained samples were positive, all the p16 positive tumors were localized to the oropharynx. We found that 8 (21.05%) tumor samples were positive for HPV16 DNA, all of which have been p16-positive, as well. We found no HPV18 DNA positive sample. HPV positivity was seen to have a significant positive impact on overall survival: p16 positive patients had a median survival of 1999 days, while p16 negative patients had a median survival of 615.5 days (p=0.0042). HPV16 DNA positive patients had 1362 days median survival while HPV16 DNA negative patients had 704.5 days median survival (p=0.0477).

Conclusion

We found that HPV positivity had a prognostic impact on survival in advanced stage oropharyngeal squamous cell carcinoma patients, and this impact was independent of the detection method.

Notes

Doctoral School: Pathology Program: Oncology Supervisor: Balázs Hegedűs E-mail address: bilecz.agnes@med.semmelweis-univ.hu

Abstract type

oral

Pharmacogenetics of central nervous system toxicity in acute lymphoblastic leukemia

C. Sági, Judit

Judit C. Sági1, Nóra Kutszegi1, Andrea Kelemen1, Bálint Egyed2, András Falus1, Gábor T. Kovács2, Csaba Szalai1,3,, Dániel J. Erdélyi2, Ágnes F. Semsei1 1 Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary 2 2nd Department of Paediatrics, Semmelweis University, Budapest, Hungary 3 Heim Pal Children Hospital, Budapest, Hungary

Notes

The combined chemotherapy used in the treatment of paediatric acute lymphoblastic leukemia (ALL) acquired a favourable prognosis, however, we still need to count on serious side effects. Methotrexate, vincristine and cytarabine all have toxic encephalopathy as their side effects. In this study, we focused on toxic encephalopathy, a severe, progressively worsening neurological condition developing after drug administration. It can be observed as central nervous system toxicity with widely appearing, mostly reversible symptoms like e.g.: depressed level of consciousness, seizures, palsies, aphasia. Interindividual differences could be detected as the character or the grade of the symptoms differ in every patient. We hypothesized genetic polymorphisms can have importance in

these toxic events modifying function of enzymes and transporters in the pharmacokinetics, and -dynamics of the above- mentioned drugs. Our study population consisted of 300 paediatric patients with ALL. Clinical data were collected retrospectively from the patients' medical records. Currently new data collecting is ongoing to set up a validation cohort with an estimated number of 300 new cases. Symptoms were graded according to the Common Terminology Criteria for Adverse Events v3.0. DNA was isolated from blood collected in remission using QIAmpBlood DNA Maxi Kit. Genotyping was performed in a previous project with a Sequenom technology. We studied the association between 137 single nucleotide polymorphisms (SNPs) and toxic encephalopathy. Logistic regression adjusted for potential confounders was performed using SPSS 20. Toxic encephalopathy was occured in 9% of the patients. GSTP1 rs1695 G allele (p=8,54E-04; OR=0,15; CI95%=0,05-0,45) and GSTP1 rs749174 A allele (p=1,88E-03; OR=0,2; CI95%=0,07-0,55) protected against the toxic event. These variations attend to have an effect on predisposing the lack of toxic encephalopathy. Our results suggest that SNPs in GSTP1 might have an impact on toxic encephalopathy. SNPs are recommended to apply as genetic markers for evaluating risks in personalised medicine. 7/4.Molecular Medicine, Basis of Human Molecular Genetics and Gene Diagnostics Ágnes Félné dr. Semsei sjudit08@gmail.com

Abstract type

oral

Isolation and characterization of primary cells from a conditional mouse model of hereditary breast cancer

Hámori, Lilla

Lilla Hámori1, András Füredi1, Gyöngyi Kudlik1, Kornélia Szebényi1, Ferenc Uher2, Veronika Nagy1, József Tóvári3, Gergely Szakács1 1 Institute of Enzymology, Hungarian Academy of Sciences 2 Hungarian National Blood Transfusion Service 3 National Institute of Oncology

Notes

Drug resistance evoked by doxorubicine treatment of genetically engineered Brca1- /- , p53- /- FVB mice developing spontaneous mammary tumours is linked to the increased expression of the Abcb1 multidrog transporter (Rottenberg et al., PNAS, 104, 12117-22). In the present study our aim was to isolate and characterize tumor-infiltrating stromal cells as well as cancer cells from treatment-naive and drug resistant tumors. Tumor fragments isolated from Brca1- /- , p53- /- mice (a kind gift from Sven Rottenberg, NKI) were implanted into the mammary fat pad of wild-type FVB mice. We isolated stromal (mesenchymal stem cell (MSC)-like) and tumor cells from the engrafted tumors and established primary cultures. The MSC-like "stromal" cells showed characteristic mesenchymal stem cell properties, as reflected by cell surface marker expression patterns and differentiation capabilities. Strikingly, genotyping revealed that the "stromal" cells were also Brca1-negative, indicating that they were also derived from the inoculated tumor, and not from tumor infiltrating host cells. Our results indicate that p53/Brca1 negative cancer cells can produce MSC-like cells by epithelial-mesenchymal transition (EMT). Doctoral School of Molecular Medicine Pathobiochemistry Gergely Szakács hamori.lilla@ttk.mta.hu

Abstract type

oral

Orai1 and extended synaptotagmin 1 stimulate cyclic adenosine monophosphate production

Fanczal, Júlia

Júlia Fanczal1, Tamara Madácsy1, Péter Hegyi1,2, Ahuja Malini3, Shumel Muellem3, József Maléth1 1 First Department of Medicine, University of Szeged, H-6720 Szeged, Hungary, 2 MTA-SZTE Lendület Gasztroenterológiai Multidiszciplináris Kutatócsoport H-6720 Szeged, Hungary, 3 Epithelial Signaling and Transport Section, Molecular Physiology and Therapeutics Branch, NIDCR, NIH, Bethesda, Maryland 20892, USA.

Introduction

The cyclic adenosine monophosphate (cAMP) and Ca2+ signaling play central role in the regulation of the secretory functions of epithelial cells. The two signaling system have multiple synergistic interactions helping to optimize the cellular response to stimulation. One of the interferences includes the interaction between the store operated Ca2+ entry (SOCE) channel Orai1 with adenylyl cyclase 8 (AC8) that increase cAMP production, however its exact molecular mechanism is not known.

Aim

In this project we wanted to characterize the interactions of cAMP and Ca2+ signaling further focusing on the molecular components of SOCE.

Methods

Human embrional kidney (HEK) cells were transfected with plasmids encoding the proteins of interest. Cellular cAMP production was measured by fluorescence resonance energy transfer (FRET) using the cAMP reporter Epac1.

Results

The stimulation of the cells with 5μM forskolin and 100μM 3-isobutyl-1-methylxanthine (IBMX) resulted in reversible elevation in cAMP production. The expression of AC8 significantly elevated the cAMP response. Whereas, Orai1 induced spontaneous cAMP production and a massive increase in the stimulated cAMP production. The effect of Orai1 was completely Ca2+ independent. Extended synaptotagmin 1 (E-Syt1), a recently described endoplasmic reticulum-plasma membrane tethering protein, increased the cAMP response, similarly to Orai1.

Conclusion

Our results showed that Orai1 and E-Syt1 play an important role in the regulation of cAMP production. However further studies are required to clarify the mechanisms of the interaction.

Notes

Doctoral school: Basic Medicine SZTE-ÁOK Programme: Neuroendocrinology-Pancreotology Supervisor: József Maléth email: julia.fanczal@gmail.com

Abstract type

oral

The effect of FOPNL genomic variant on the prognosis of multiple myeloma

Kiss, Katalin Piroska

Katalin Piroska Kiss1, Gergely Varga2, Gábor Mikala3, Andras Bors1, Katalin Balassa1, Attila Tordai4, Peter Remenyi3, Tamas Masszi2,3, Hajnalka Andrikovics1 1 Laboratory of Molecular Diagnostics, Hungarian National Blood Transfusion Service, 2 3rd Department of Internal Medicine, Semmelweis University, 3Department of Haematology and Stem Cell Transplantation, St. Istvan and St. Laszlo Hospital, 4 Institute of Pathophysiology, Semmelweis University, Budapest, Hungary

Background

In a recent genome-wide association study of multiple myeloma (MM), the FOPNL (fibroblast growth factor receptor 1 oncogen partner N terminal like) gene rs72773978 single nucleotide polymorphism was identified as an adverse prognostic factor.

Aim

The aim of our study was to investigate the role of FOPNL polymorphism on clinical characteristics (sex, age, ISS, cytogenetic abnormalities) as well as progression free survival and overall survival (PFS and OS) in a cohort of 280 MM patients.

Methods

LightCycler melting analysis was applied to identify rs72773978 polymorphism.

Results

Applying a dominant model (AA: 243/280, 87% vs. AT&TT: 37/280, 13%), we found no significant difference in ISS stage or citogenetics stratified subgroups. In our cohort FOPNL polymorphism showed difference in the prognostic effect depending on the treatment applied. Carriership of the minor allele was significantly associated with better PFS among patients treated with proteasome inhibitor (PI) (p=0.027). Performing a multivariate analyzes by Cox regression considering sex, age and ISS the difference remained significant (log rank test p=0.018; HR: 0.535, 95%CI: 0.32-0.89). Interestingly in the non-PI treated group, adverse prognosis was observed in minor allele carriers (log rank test p=0.015; multivariate analysis p=0.085; HR: 2.3, 95% CI: 0.89-5.96). There was no difference in OS in the different genotype groups, probably due to the alternating application of PI-based or non PI based second and third line treatments.

Conclusion

In the present study we showed that FOPNL rs72773978 polymorphism influence progression free survival of MM patients depending on the treatment applied.

Notes

Doctoral School of Clinical Medicine Clinical Haematology Hajnalka Andrikovics kisskatalin84@yahoo.com

Abstract type

oral

Targeting multidrug resistent tumor cells with MDR-selective compounds

Nagy, Veronika

Veronika Nagy, András Füredi, Kornélia Szebényi, Szilard Tóth, Lilla Hámori, Gergely Szakács Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences, Budapest, Hungary

Notes

Development of multidrug resistance (MDR) represents a major challenge in the chemotherapy of malignant tumors. One of the most widely studied mechanisms contributing to cellular resistance is the increase in the expression of ATP binding cassette (ABC) transporters. The most prominent of these proteins is P-glycoprotein (Pgp, ABCB1), which transports chemotherapeutic compounds into the extracellular space using the energy of ATP. A previous study from our group has shown that Pgp-expressing MDR cells exhibit a paradoxical hypersensitivity against so called MDR-selective compounds such as BB090. The aim of the present work was to explore the effect of BB090 treatment on the expression of P-gp. Parental MES-SA uterine sarcoma cells and a Pgp-expressing MDR derivative, MES-SA/Dx5 were treated with different concentrations of BB090. Pgp function was assessed by the CalceinAM test before and after treatment. Surprisingly, 16 days after single treatment with BB090 with a concentration corresponding to IC20 (killing 80% of the cells) Pgp-expression was completely lost in 98.3 % of the MES-SA/Dx5 cells as observed at the mRNA, protein and functional levels. As a consquence of the loss of Pgp, MES-SA/Dx5-BB090 cells regained sensitivity to doxorubicin. While the Pgp-dependent toxicity of MDR-selective compounds can lead to the selective destruction of multidrug resistant cells, the rapid change in the phenotype shows the exceptional adaptive capability of tumor cells. Doctoral School of Molecular Medicine Pathobiochemistry Gergely Szakács nagy.veronika@ttk.mta.hu

Abstract type

oral

The role of ATP-depletion in the mechanism of action of MDR-selective compounds targeting ABCB1-expressing cancer cells

Cserepes, Mihály

Mihály Cserepes1,2,3, József Tóvári3, Dóra Türk2, Gergely Szakács2 1 Semmelweis University, Budapest 2 Institute of Enzymology, RCNS, Hungarian Academy of Science, Budapest 3 National Institute of Oncology, Department of Experimental Pharmacology, Budapest

Notes

Multidrug resistance of cancer cells (MDR) is one of the major obstacles in the treatment of malignant diseases. The MDR phenotype is often mediated by the energy-dependent active efflux mediated by the plasma membrane transporter protein, ABCB1/P-glycoprotein. Although ABCB1 is widely known as a protein defending cancer cells from a huge variety of chemotherapeutic agents, our group identified numerous MDR-selective agents, which show increased toxicity to transporter-expressing cancer cells. The mechanism of action underlying MDR-selective toxicity is unknown. Elevated ATP consumption in cells expressing ABCB1 may lead to intracellular ATP depletion, and the change in the energy-metabolism of the cells. To test if ATP depletion of MDR cells is linked to their collateral sensitivity, we characterized the cytotoxicity and ATP-modulating effects of metabolic inhibitors and MDR-selective agents. Our in vitro cellular system consisted of parental A431 (epidermoid carcinoma) and Mes-sa (uterine sarcoma) cell lines and their MDR derivatives engineered to overexpress ABCB1 by a lentiviral system (A431-B1 and Mes-sa-B1). Intracellular ATP levels were measured by a luciferase-based luminescent ATPLite kit (PerkinElmer). Cell numbers were quantified by Sulphorhodamine B assay. As expected, treatment with the glycolytic inhibitor 2-deoxy-glucose (2DG) resulted in a concentration and time-dependent ATP depletion in each cell line. While the 2DG-induced ATP depletion was more pronounced in MDR cells, the cytotoxicity tests did not show selective toxicity against ABCB1-transfected cells. Treatment with the LDH-inhibitor oxamate resulted in a strong ATP-depletion, while the effect of mitochondrial inhibitors (CCCP, Rotenone, Antimycin A, Oligomycin) on intracellular ATP levels was marginal. The MDR-selective agents (SZ1079, BB090) induced weak and non-selective ATP-depletion in our cellular models. Our results indicate that ATP-depletion per se does not result in MDR-selective toxicity. The MDR-selective compounds analyzed in this study did not induce a significant reduction of intracellular ATP levels. However, the energy metabolism is quite complex, and ATP levels are influenced by ATP synthesis as well as ATP consumption. MDR may be linked to a difference in the metabolic state, which may ultimately result in the collateral sensitivity of the cells. Our plans include the study of further MDR models including MCF-7 cells that we found to have different metabolic activity, and are suggested by other studies to show ABCB1-dependent sensitivity to metabolic inhibition. Further cellular metabolic approaches are being tested to reveal the intracellular mechanisms underlying MDR-selective cytotoxicity. Personal data: name: Cserepes Mihály school: Doctoral school of Pathology programme: Oncology PIs: József Tóvári, Gergely Szakács e-mail: cserepestm@gmail.com

Abstract type

oral

Expression signature driven by somatic KRAS mutations display prognostic power in NSCLC

Nagy, Ádám

Ádám Nagy1,2, Lőrinc S. Pongor1,2, Balázs Győrffy1,2 1MTA TTK Lendület Cancer Biomarker Research Group, Budapest, Hungary 2Semmelweis University 2nd Dept. of Pediatrics, Budapest, Hungary

Notes

In non-small cell lung cancer (NSCLC) the most important mutated genes include EGFR, ALK, VEGFR2, and KRAS. These genes serve as predictive markers and play crucial role in targeted anticancer therapy. Somatic mutations in KRAS are common, but it is unclear whether these mutations per se are related to poor survival and treatment resistance. Our aim was to examine the effect of mutational transcriptomic fingerprint driven by somatic KRAS mutations on survival in NSCLC. We downloaded raw exome sequencing data from the TCGA repository. We identified somatic mutations using MuTect algorithm. Gene expression data – RNAseq and Affymetrix – was obtained from TCGA and NCBI GEO, respectively. We applied MAS5 and DESeq algorithms to normalize the raw expression data. We identified metagenes whose expression were significantly correlated with KRAS mutation status by performing ROC analysis with mutation and gene expression data. Finally, we examined the correlation with survival for each metagene using Cox proportional hazards regression and by plotting Kaplan-Meier survival plots. The statistical computations were performed in the R statistical environment. We processed the exome sequencing

data of 555, RNAseq data of 555, and gene chip data of 2,437 patients. In the exome dataset, 61 patients had a somatic KRAS mutation. As a result of the ROC analysis we selected the best five genes most strongly correlated to somatic KRAS mutations. These include a set of up-regulated (PTPRE,AUC=0.74,p=1.37E-09, TOP1,AUC=0.74,p=1.44E-09, RUFY1,AUC=0.74,p=1.62E-09, ATP11A,AUC=0.73,p=3.84E-09, LTA4H,AUC=0.73,p=6.93e-09) and a set of down regulated genes (FOXRED2,AUC=0.75,p=2.14E-10, TBCCD1,AUC=0.75,p=2.55E-10, GABRA3,AUC=0.73,p=5.07E-09, SKP2,AUC=0.73,p=6.93E-09, SLCO1A2,AUC=0.73,p=7.42E-09). Cox regression analysis using the combined (up and down) signature of genes delivered highly significance (OS: HR=1.8,p=3.4E-013). By linking different levels of data we demonstrate the prognostic role of somatic mutations of KRAS. Our results emphasize the need to investigate somatic mutations in prognostic predictions. Doctoral School: Pathology Program: Oncology Supervisor: Dr. Balázs Győrffy E-mail address: n.adam044@gmail.com

Abstract type

oral

Examination of mTOR activity of post-transplant renal cell carcinomas in patients' own kidney

Krencz, Ildikó

Ildikó Krencz 1, Anna Sebestyén 1, 2, Gyula Végső 3, Nóra Buthi 1, Lilla Hancz 1, Titanilla Dankó1, Judit Pápay 1 1: 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest 2: Tumor progression Research Group Joint Research Organization of Hungarian Academy of Sciences and Semmelweis University, Budapest 3: Department of Transplantation and Surgery, Semmelweis University, Budapest

Introduction

Dysregulation of the mTOR pathway is identified in several tumor types, including clear cell renal cell carcinomas. The mTOR kinase exsists in two different multiprotein complexes – mTORC1 (markers: p-mTOR, p-S6) and mTORC2 (markers: p-mTOR, Rictor) – which differ in function and their sensitivity to rapamycin. In the treatment of post-transplant tumors the immunosuppressant therapy was often converted from calcineurin inhibitors to mTOR (mammalian target of rapamycin) inhibitors.

Methods

The expressions of the mTOR signaling related proteins (p-mTOR, p-S6, Rictor) were investigated in post-transplant clear cell (n=11) and papillary (n=13) renal cell carcinomas (CCRCC, PRCC) by immunohistochemistry on tissue microarrays. As control, we examined CCRCCs (n=10) and PRCCs (n=5) from patients without transplantation. Statistical analysis was performed using Mann-Whitney test.

Results

High mTOR activity was observed in both transplanted and non-transplanted groups. The cancers developed during immunosuppressive treatment are heterogeneous; they can be classified into two groups based on their mTOR activity. There was no significant difference regarding to p-mTOR expression in the different subgroups. In tumors developed after transplantation the expression of p-S6 (mTORC1 activity) was significantly higher (p=0.00365) in CCRCCs than in PRCCs; however, the expression of Rictor (mTORC2 activity) was higher (p=0.0188) in PRCCs. The expression of Rictor was significantly higher (p=0.0045) in post-transplant PRCCs than in PRCCs developed in normal kidneys.

Conclusion

The increased mTOR activity is characteristic of renal cell carcinomas both in patient with or without transplantation. The mTORC1 activity is higher in carcinomas of non-transplanted patients; however, the mTORC2 activity was higher in post-transplant cancers which may indicate emergence of resistant clones and decreased sensitivity to rapalogs. It is important to characterize the activity of the mTOR complexes in post-transplant tumors before applying mTOR inhibitors.

Notes

Supported by K84262, Bolyai Grant, Medinprot Synergy 2016. Doctoral School: Doctoral School of Pathological Sciences Program: Oncology (01) Supervisor: Judit Pápay E-mail address: krencz.ildiko@gmail.com

Abstract type

oral

IDENTIFYING GENES LINKED TO COPY-NUMBER VARIATION AND AFFECTING SURVIVAL IN BREAST CANCER

Pongor, S. Lőrinc

Lőrinc S. Pongor1,2, Ádám Nagy1,2, Balázs Győrffy1,2 1. 2nd Dept. of Pediatrics, Semmelweis University, Budapest, Hungary 2. MTA TTK Lendület Cancer Biomarker Research Group, Budapest, Hungary

Introduction

Copy number variations affect large sections of chromosomes. Since many genes are involved simultaneously, identifying genes affecting survival within these regions is a challenging task.

Aim

Our aim was to create an analysis pipeline capable to identify genes linked to both copy-number variations and survival in breast cancer patients.

Methods

Copy-number variation data analyzed with GISTIC as well as the RSEM normalized RNA-seq data was acquired from the TCGA Firehose repository. Samples were split into four subgroups based on HER2 and ER status (HER2+, ER+HER2-, ER-HER2- and all). Survival analysis using microarray data was performed using our previously published database (PMID: 26474971). Correlation and survival analysis of RNA-seq and CNV status was performed in the R programming language using the survival() package.

Results

Our analysis identified multiple CNV events that had a significant effect on survival. These events clustered to chromosome 17 in the genome. As CNV events affect large chromosome segments, we selected genes whose expression had a significant correlation to copy-number alterations. In total, expression of 109 genes correlated to CNV status. To identify genes with significant effect on survival, survival analysis was performed based on their expression using both the TCGA RNA-seq data and the independent microarray data. The analysis identified multiple genes in the selected subtypes. In HER2+ samples the best performing genes were CDH1 (HR=0.53, p=8e-04), RBM25 (HR=0.55, p=0.0021). In HER2-ER+ samples, the best genes were SCUBE2 (HR=1.7, p=19e-10), TMEM9B (HR=1.3, p=0.0057). In the HER2-ER- samples, the strongest genes were GIGYF2 (HR=1.4, p=0.011), EI24 (HR=1.3, p=1.5e-06).

Conclusion

We created an analysis pipeline that can identify genes linked to copy-number variation and survival in breast cancer patients. Our future plans involve refining the analysis method and analyzing other tumor types available in the TCGA repository.

Notes

Fundings: OTKA K108655 and the MTA Lendület programme. Doctoral School: Doctoral School of Pathological Sciences Program: Oncology Supervisor: Dr. Balázs Győrffy E-mail address: pongorlorinc@gmail.com

Abstract type

oral

THE NEWLY DEVELOPED CLAUDIN-1 BASED DUAL-STAINING TEST HIGHLY CORRELATES WITH ONCOGENIC TRANSFORMATION IN CERVICAL SAMPLES

Szekerczés, Tímea

Tímea Szekerczés (1), Márta Benczik (2), Ádám Galamb (3), Róbert Koiss (4), Gábor Lotz (1), Balázs Járay (1), András Kiss (1), Csaba Jeney (2), Zsuzsa Schaff (1), Gábor Sobel (3) 1. 2nd Department of Pathology, Semmelweis University, Budapest, Hungary 2. CellCall Kft, Budapest, Hungary 3. 2nd Department of Obstetrics and Gynecology, Semmelweis University, Budapest, Hungary 4. Department of Obstetrics and Gynecology, Saint Stephen Hospital, Budapest, Hungary

Background

Cervical cancer is the fourth most common cancer in women worldwide. It is the ninth most common cause of tumor deaths among women in Hungary. Pap smear is a cytological test designed to detect abnormal cervical cells. The method is highly specific, however, only of moderate sensitivity. There is a need to develop new auxiliary diagnostic methods to improve efficiency of cytological diagnostics.

Aim

We demonstrated increased expression of claudin-1 in cervical squamous intraepithelial neoplasia and invasive carcinoma. This protein is one of the major components of tight junction structure. Our aim was to develop a claudin-1 based dual-staining method featuring as good specificity and sensitivity as of CINtec Plus(Roche), which is a p16ink4a and Ki67 dual expression test

Matrials and methods

For the study, 2845 cervical samples from a randomized group of women were collected by gynecologists and were kept in preservation solution for subsequent liquid-based cytology, which is an accepted alternative to conventional Pap test. Immunochemical reactions were performed on 1342 liquid based smears including both CINtec Plus test and Claudin-1/Ki-67 test. The two methods were compared statistically by a McNemar's and Kappa test.

Results

1101 samples provided acceptable results. 899 liquid based cytological analyses detected normal stage and 202 showed premalignant or malignant stage. The positivity obtained by either the CINtec Plus or Claudin-1+Ki-67 tests corresponded well to cytological evaluation. 202 Claudin-1+Ki-67 positive cases displayed the following cytological distribution: 41/165 (24.8%) ASCUS and LSIL; 18/30 (60%) CIN 2; 3/4 (75 %) CIN 3 and 3/3 (100%) of invasive cervical carcinoma. The specificity (79.9 %) and sensitivity (68.8 %) of CINtec Plus test was comparable with the specificity (84.9 %) and sensitivity (64.9 %) of Claudin-1+Ki-67 test. There was no statistically significant difference between the two tests.

Conclusion

Our newly developed claudin-1 based dual-staining test showed comparable specificity and sensitivity with the results of CINtec Plus test. Therefore, the new method might prove to be the basis for a new auxiliary method for cytodiagnostics and to be applied as triage test in HPV detection. Furthermore, claudin-1+Ki-67 test might assist gynecologists in decision making for patients with CIN2.

Notes

The name of the Doctoral School : Doctoral School of Pathological Sciences The title of the Program: Alterations of Cells, Fibres and Extracellular Matrix and Diagnostic Pathomorphological Studies in the Course of Heart and Vascular Diseases and in Certain Tumours. Experimental and Diagnostic Pathomorphological Studies The name of the Supervisor: Zsuzsa Schaff The E-mail address of the presenter: szekerczes.timea@med.semmelweis-univ.hu

Abstract type

oral

The role of LAPTM4B copy number alterations in hormone receptor negative breast cancers

Papp, Orsolya

Orsolya Papp1, Kristóf Csaba Bende1, Laura Vízkeleti1,2, Zoltán Szállási1,2, Gábor Lotz1, Janina Kulka1, Anna-Mária Tőkés1 1 II. Department of Pathology, Semmelweis University, Budapest 2 MTA-SE NAP, Brain Metastasis Research Group, Semmelweis University, Budapest

Notes

We have only limited information about the role of LAPTM4B gene in breast cancer progression. A recent study revealed an association between LAPTM4B overexpression and resistance to anthracycline (AC) chemotherapy, examining only a few triple negative breast cancers (TNBC). Our goal was to determine the possible associations between LAPTM4B copy number alterations, metastasis, distant metastasis free survival (DMFS) and the applied adjuvant chemotherapy in hormone receptor negative (HR-) primary breast cancer. Seventy-one invasive breast carcinomas (38 TNBC, 25 HER2+ and 8 with uncertain HER2 status) with reliable follow-up data were involved in the study. Interphase FISH technique was applied on tissue microarrays, using custom-made probes (LAPTM4B/CEN8q). The average age of patients was 52 years (32-81 years). Twenty-four patients (33.8%) formed distant metastasis during follow-up period. The composition of adjuvant therapy was heterogeneous; 52 patients received AC-containing treatment. LAPTM4B amplification was observed in the average of 23.1% of tumor cells per sample (1.2%-83.1%, median: 17.6%). The average gene copy number was higher in metastatic lesions, comparing to the non-metastatic ones (2.9 vs. 2.5; p=0.043). Similarly, the proportion of LAPTM4B amplified cells was higher in metastatic samples (26.4% vs. 21.9%), but this association was not proven to be significant. Regarding DMFS, three different LAPTM4B copy number cut-off points (2.2, 2.5 and 3.0) were determined. In all cases, lower DMFS was observed when LAPTM4B copy number was increased (p=0.012, p=0.033 and p=0.040, respectively). In case of AC-containing therapy, association was found between higher gene copy number and unfavorable prognosis (p=0.040). In summary, our results confirm the possible role of LAPTM4B gene in AC resistance. Extra copies of LAPTM4B gene are associated with metastasis formation and shorter DMFS in HR- breast cancers, independently from the subtype. However, further FISH experiments are ongoing to strengthen these results. Doctoral School: Pathological Sciences, Oncology program Supervisor: József Tímár e-mail: papp.orsolya@med.semmelweis-univ.hu

Abstract type

poster

METABOLIC ALTERATIONS AND QUANTITATIVE ANALYSIS OF 2-HYDROXYGLUTARATE IN DIFFERENT TUMOUR SAMPLES

Petővári, Gábor

Gábor Petővári1, Zoltán Hujber1, Titanilla Dankó1, Norbert Szoboszlai2, Noémi Nagy1, Júlia Oláh1, László Kopper1, András Jeney1, Anna Sebestyén1,3 1 First Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary 2 Laboratory of Environmental Chemistry and Bioanalytics, Department of Analytical Chemistry, Institute of Chemistry, Eötvös Loránd University, Budapest, Hungary 3 Tumor Progression Research Group Joint Research Organization of Hungarian Academy of Sciences and Semmelweis University, Budapest, Hungary

Notes

Metabolic shifts correlate to the bioenergetics background of tumour cell division, survival and resistance to typical therapeutic treatments. Previously we characterized substrate utilization of many different types of tumour cells with a developing LC-MS method (liquid chromatography-mass spectrometry). In these cell lines the amount of different metabolites of glycolysis, TCA (tricarboxylic acid) cycle, pentose phosphate pathway were studied and based on these their metabolic profiles were described well in the studied cell lines. We have observed special peaks of specific oncometabolites of the metabolic spectrum analysis in certain cases, as well. We tested that these metabolites/oncometabolites can be detected in various samples (tumour cell lines, cellular supernatant, microvesicle fractions, peripheral circulating and bone marrow leukaemia cells, tumour tissue samples, blood serums). This measurement has several advantages: cost-, time-effective and low demand of samples. We could detect high level of 2-hydroxyglutarate oncometabolite in several

samples using LC-MS. The role of 2-HG in tumour progression was described previously in acute myeloid leukaemia, glioma, colon carcinoma and breast cancer cells. 2-HG oncometabolite was detectable in different types of samples (such as tissue, isolated tumour cells, extracted vesicles and serum). In parallel, mutations of IDH1 (isocitrate dehydrogenase enzyme isoform 1) were found in AML samples and certain cell lines with high level of 2-HG. We could also detect that different in vitro treatments could alter the production of 2-HG and other metabolites. We confirmed that the presented methods are suitable for the detection and quantification of oncometabolites (2-HG, succinate, fumarate). Beside these we can characterize the metabolic profile of different tumour cells and tumour samples. supported by K84262, Bolyai Grant, Medinprot Synergy 2016 Doctoral School: Pathological Sciences Program: Oncology Supervisor: Anna Sebestyén E-mail address: gaborpetovari@gmail.com

Abstract type

oral

VALIDATION OF RNAI SILENCING EFFICIENCY USING GENE EXPRESSION MICROARRAYS

Sztupinszki, Zsófia

Zsófia Sztupinszki1, Gyöngyi Munkácsy2,3, Péter Herman2, Bence Bán1, Zsófia Pénzváltó2, Nóra Szarvas2, Balázs Győrffy1,2 2nd Dept. of Pediatrics, Semmelweis University, Budapest, Hungary MTA TTK Lendület Cancer Biomarker Research Group, Budapest, Hungary MTA-SE Pediatrics and Nephrology Research Group, Budapest, Hungary

Introduction

Small interfering RNA (siRNA) are widely used to silence the expression of specific genes in cell culture models. The combined utilization of siRNAs and gene expression microarrays is an emerging field. However, remaining technological difficulties include a large variation of silencing efficiency of siRNAs and the occurrence of unintended off-target effects leading to high false positive rate. In many of these studies no independent cross-validation of gene silencing has been completed.

Aim

Our goal was to conduct large scale validation and comparison of siRNA techniques, to assess the influence of experimental parameters including cell line, transfection technique, validation method, and housekeeping genes.

Methods

We searched the GEO public database for paired samples with whole transcriptome analysis before and after gene silencing and evaluated the efficiency for the target and off-target genes using the array-based expression data. Wilcoxon signed-rank test was used to assess silencing efficacy and Kruskall-Wallis tests and Spearman rank correlation were used to evaluate study parameters.

Results

All together 1,643 samples representing 429 experiments published in 218 studies were included in the analysis. Fold change (FC) of down-regulation of the target gene was below 0.7 in 81.5% and below 0.5 in 61.3% of experiments. Silencing efficiency was lowest in MCF7 cells (FC=0.59) and highest in SW480 cells (FC=0.30). Studies utilizing Western blot for validation achieved higher power (FC=0.43) than those with qPCR (FC=0.47) or microarray (FC=0.55). There was no correlation between type of control, transfection method, publication year and silencing efficiency. Expression of conventional housekeeping genes (e.g. GAPDH, B2M) proved to be independent of silencing.

Conclusion

In summary, gene silencing is a robust feature successfully cross-validated in more than three-quarter of the experiments. Selection of cell line model and validation method has the highest influence on silencing proficiency.

Notes

Fundings: OTKA K108655 and the MTA Lendület programme. Doctoral School: Doctoral School of Pathological Sciences Program: Oncology Supervisor: Dr. Balázs Győrffy E-mail address: sztup@hotmail.com

Abstract type

oral

PRODUCTION AND CRYSTALLIZATION OF THE PATHOLOGICAL MUTANTS OF HUMAN DIHYDROLIPOAMIDE DEHYDROGENASE

Nagy, Bálint

Bálint Nagy1, Ágnes Hubert1, Eszter Szabó1, Zsófia Zámbó1, Vera Ádám-Vizi1, Attila Ambrus1 1. Department of Medical Biochemistry, MTA-SE Laboratory for Neurobiochemistry, Semmelweis University, Budapest

Introduction

The human alpha-ketoglutarate dehydrogenase complex (hKGDHc) has a key role in the energy production of the cell by catalyzing an irreversible step in the citric acid cycle. Although its activity is sensitive to reactive oxygen species (ROS), interestingly under pathological conditions hKGDHc is also a significant source of the oxidative stress.

Aim

Our research group addresses the mechanism of ROS generation by the hKGDHc. Currently, our major objective is to find the structural and mechanistic explanation for the altered ROS-producing capacity of the hKGDHc mediated by pathogenic mutations of the E3 component (dihydrolipoamide dehydrogenase, hLADH). Our goals include the crystallization and the high-resolution X-ray analysis of the pathogenic hLADH mutants. We would also like to find the optimal conditions for the heterologous expression in E. coli of the two other complex components E1 or E2 (E1: alpha-ketoglutarate dehydrogenase, E2: dihydrolipoamide succinyltransferase). Possessing all the three isolated components of the hKGDHc, we would be capable of investigating the biochemical and biophysical characteristics of reconstituted hKGDH complexes (including ones with pathogenic E3 variants).

Methods

Our research group developed and optimized an expression and purification system which is based on the BL21(DE3) strain of E. coli and a pET expression plasmid vector (pET52b+). For FPLC protein purification affinity chromatography is routinely used in our laboratory. Crystallization of proteins is carried out using commercially available crystallization screening kits, the solution conditions of which are further optimized when needed.

Results

I successfully accomplished the expression and the purification of two disease-causing hLADH mutants (K37E, E340K), which was followed by their crystallization trials. These trials proved to be successful hitherto in case of the K37E mutant only. Besides the high-level expression of hE2, we were also able to achieve the purification of this component to its homogeneity; expression optimization is underway for hE1.

Conclusion

Purification of the K37E-hLADH and the E340K-hLADH were successful. Crystals for X-ray analysis of the K37E-hLADH were grown. The E2 subunit of the hKGDHc was successfully expressed and purified.

Notes

Fundings: MTA 02001, OTKA 112230, KTIA_13_NAP-A-III/6. Doctoral School: János Szentágothai Ph.D. Doctoral School of Neurosciences Program: Functional Neurosciences Program Supervisor: Attila Ambrus E-mail address: nagy.balint@med.semmelweis-univ.hu

Abstract type

oral

Pharmaceutical Sciences

Cirsium boujartii fruit and its in vitro callus culture: the specific sources of antiproliferative neo- and sesquineolignans and dicaffeoylquinic acid

Könye, Rita

Rita Könye1,2, Anna Sólyomváry1,, Zsolt Mervai3, Gergő Tóth4, Ágnes Alberti1, Péter Horváth4, Béla Noszál4, Kornélia Baghy3, Ilona Kovalszky3, Szabolcs Béni1, Imre Boldizsár2 1Department of Pharmacognosy, Semmelweis University, Üllői út 26, Budapest 1085, Hungary 2Department of Plant Anatomy, Institute of Biology, Eötvös Loránd University, Pázmány Péter sétány 1/C, Budapest 1117, Hungary 31st Department of Pathology and Experimental Cancer Research, Semmelweis University, Üllői út 26, Budapest 1085, Hungary 4Department of Pharmaceutical Chemistry, Semmelweis University, Hőgyes Endre utca 7, Budapest 1092, Hungary

Notes

Secondary plant metabolites represent a rich and promising source of new bioactive compounds, among which lignans are one of the most potent candidates as cytotoxic agents. We aimed at characterizing the lignan profile of Cirsium boujartii fruit and to determine their bioactivity. Unique neolignans (balanophonin, BA and prebalanophonin, preBA) and sesquineolignans (picrasmalignan, PI and prepicrasmalignan, prePI) were determined for the first time in C. boujartii fruit using complementary spectroscopic methods. Analysis of separated fruit tissues i.e., the wall and embryo, demonstrated a fruit part-specific accumulation of compounds, since they were exclusively found in the wall allowing their high-yield isolation by preparative HPLC. The isolated compounds were tested for their antiproliferative activity (APA) against the SW480 colon adenocarcinoma cell line, confirming for the first time the (i) APA of preBA and prePI and (ii) a relation between the structure of compounds and their APA. Our results demonstrate that BA and PI are significantly more effective (IC50 of both BA and PI ≈ 50μM) than preBA and prePI. In vitro cultures established from the fruit, were found to produce dicaffeoylquinic acid as the main compound contrary to the neo- and sesquineolignans identified in the fruit. Doctoral School: Doctoral School of Pharmaceutical Sciences Program: 01. Modern Trends in Pharmaceutical Scientific Research Supervisors: Szabolcs Béni, Imre Boldizsár E-mail address: rita.konye@gmail.com

Abstract type

oral

Role of mild intracellular stress and autophagy in the cytoprotective effect of resveratrol

Ulakcsai, Zsófia Éva

Zsófia Éva Ulakcsai, Fruzsina Bagaméry, Éva Szökő, Tamás Tábi Semmelweis University, Department of Pharmacodynamics

Background

The natural polyphenolic compound resveratrol was shown to prevent serum deprivation induced caspase 3 activation. The aim of the present study was to investigate the potential molecular targets and mechanisms playing an important role in this cytoprotective effect of resveratrol. Namely, the involvement of estrogen, aromatic hydrocarbon receptors and autophagy were examined.

Methods

Apoptosis was induced by serum deprivation in primary mouse embryonic fibroblasts. Caspase 3 activation was assayed by using its fluorogenic substrate. Reactive oxygen species production and depolarization of the mitochondrial membrane were measured by fluorescence methods. The involvement of the receptors and autophagy in the effect of resveratrol were also analyzed using special agonists and antagonists.

Results

We found that neither aromatic hydrocarbon receptors nor estrogen receptors play an important role in the cytoprotective effect of resveratrol. Chloroquine, an autophagy inhibitor eliminated the

preventive effect of resveratrol, which shows the importance of autophagy. Reactive oxygen species production was elevated by serum deprivation and further increased after resveratrol treatment. In the presence of serum deprivation resveratrol also induced a significant depolarization in mitochondrial membrane potential.

Conclusion

Resveratrol was shown to protect primary mouse fibroblasts against serum deprivation induced apoptosis via provoking mild cellular stress and increasing autophagy.

Notes

Doctoral School: Pharmaceutical Sciences Program: Experimental and Clinical Pharmacology Supervisor: Tamás Tábi E-mail address: ulakcsaizs@gmail.com

Abstract type

oral

Characterization and identification of isoflavonoid derivatives in the root of Spiny restharrow (Ononis spinosa L.)

Gampe, Nóra

Nóra Gampe1, András Darcsi1, Szabolcs Béni1, László Kursinszki1 1. Semmelweis University, Department of Pharmacognosy, Üllői út 26, H-1085 Budapest, Hungary

Notes

Restharrow root has been used in traditional medicine for thousands of years as a diuretic agent; however, the active ingredients responsible for this effect are still unknown. Previous studies have proved that the root extract contains isoflavonoids, however only few derivatives were identified, mostly relying on retention times or UV data. The aim of our work was to perform a detailed structural characterization of the complete isoflavonoid profile in the aqueous-methanolic extract of Ononis spinosa root by high-performance liquid chromatography coupled to electrospray ionization accurate-mass quadrupole time-of-flight and tandem mass spectrometry in positive ionization mode (HPLC-ESI-QTOF-MS/MS) and nuclear magnetic resonance spectroscopy (NMR). On the basis of the accurate masses and fragmentation patterns isoflavones (formononetin, calycosin and pseudobaptigenin) and pterocarpans (maackiain and medicarpin) were identified. Two further dihydroisoflavone aglycones, namely onogenin and sativanone and a unique glucoside, spinonin, were isolated and their structures were elucidated by NMR experiments. The presence of biochanin A and tectorigenin were not confirmed despite of numerous literature data however their isomeric structures, calycosin and sativanone, were identified by detailed aglycone fragmentation pathways. In the same extract new nitrogen containing compounds were found as a result of thorough MS investigations. Based on the ESI-QTOF-MS/MS spectra the new compounds were elucidated as isoflavonoid glucosides esterified by proline betaine and its homologue. Proline betaine is a well-known osmoprotectant in plants; however, its isoflavonoid complexes were not described in the literature till date. The secondary metabolite profile of in vitro hairy root cultures from the Agrobacterium rhizogenes mediated genetic transformation of O. spinosa were compared to that of the intact roots. Doctoral School: Pharmaceutical Sciences Program: Modern Trends in Pharmaceutical Scientific Research Supervisors: László Kursinszki, Szabolcs Béni gampe.nora@gmail.com

Abstract type

oral

Synthesis and biological activity of pyrazolo[1,5-a]pyrimidine derivatives as potential antineoplastic agents

Czudor, Zsófia

Zsófia Czudor a, b, Rita Garamvölgyi a, b, Judit Dobos b, Anna Sipos b, Nóra Breza b, Sándor Boros b, Eszter Illyés b, Péter Markó b, Péter Bánhegyi b, Csaba Szántai-Kis b, György Kéri b, c, László Őrfi a, b a Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary b

Vichem Chemie Research Ltd., Budapest, Hungary c MTA-SE Pathobiochemistry Research Group, Department of Medical Chemistry, Semmelweis University, Budapest, Hungary

Notes

Nowadays, beside cardiovascular diseases, cancers are the most frequent illnesses with fatal outcome. According to surveys of Hungarian Central Statistical Office, cancer claimed 33 292 victims in Hungary in year 2014. In medical practice, possible treatments are surgery, radiotherapy and chemotherapy. Chemotherapeutic agents can be divided into two groups: cytotoxic and cytostatic agents. Cytostatic agents are part of targeted cancer therapy, they are treatments with less side effects in comparison to cytotoxic agents. Such agents are B-Raf kinase inhibitors functioning in the Ras-Raf-MEk-ERK signal transduction. B-Raf is one of the enzymes most likely to mutate in the cascade, in 90% of the cases the mutation occur on V600E (change of valine for glutamic acid). There are several mutant B-RafV600E enzyme inhibitors applied in cancer therapy. Non-hinge binder pyrazolo[1,5-a]pyrimidine derivates play key role in medical treatment among known B-Raf inhibitors. In this presentation 27 synthesized compounds, published pyrazolo[1,5-a]pyrimidine type B-Raf inhibitors and their novel analogues will be introduced . In order to determine structure activity relationships (SAR) these compounds were studied with computer docking, their kinase inhibitor activity were determined in parallel with the synthesized reference compounds, and their antiproliferative effect was measured on wilde type and mutant cancer cell lines. Our novel compounds showed close, and in some cases better, kinase inhibition and antiproliferative activity than the public reference substances. Further research will focus on the synthesis of pyrazolo[1,5-a]pyrimidine derivatives with altered core structures based on the structure activity relationships we present here. Doctoral School: Pharmaceutical Sciences Program: Modern Trends in Pharmaceutical Scientific Research Supervisor: László Őrfi E-mail address of the presenter: czudor.zsofi@gmail.com

Abstract type

oral

DNA binding of amino acid conjugated daunorubicin derivatives

Orosz, Ádám

Ádám Orosz1, Péter Horváth2, Gábor Mező3, Gabriella Csík1 1. Semmelweis University, Department for Biophysics and Radiation Biologya; 2. Semmelweis University, Department of Pharmaceutical Chemistryb; 3. MTA-ELTE Research Group of Peptide Chemistryc

Notes

Daunorubicin is an effective chemotherapeutic antibiotic crucial in the treatment of cancer types like leukemia and breast cancer. It intercalates between base pairs and inhibits topoisomerase II. However, its lack of selectivity can induce serious side effects. Our group studies GnRH-III as carrier to facilitate selective targeting of the compound. We synthesized lysine, arginine and leucine conjugate of daunorubicin, three potential enzymatic metabolites of the larger conjugate, to evaluate the impact of these amino acids on the binding. Investigation of DNA structure alterations upon interaction is imperative in the characterization of the biological effect of these new derivatives. We conducted absorption, fluorescence, CD and optical melting measurements, using B-form DNA and T7 bacteriophage as nucleoprotein complex (NP). Absorption and fluorescence studies verify the intercalative binding of the derivatives to DNA. With the help of the fluorescence spectra binding constants were calculated. None of the conjugates bind with the same affinity as the unmodified compound, with slight differences arising also between the conjugates. Binding can be observed with NP as well, but the binding constants are smaller than with isolated DNA. CD spectroscopy reveals alterations in the DNA structure. Upon binding of the conjugates, major intensity changes of the B-form DNA spectra can be observed, at higher concentrations also with shifting and splitting of some bands. These changes can be attributed to the loss of stacking between adjacent base pairs, and at higher concentrations of the drug, distortion of the B-conformation. Changes of DNA CD bands within the NP also indicate the loss of helicity upon interaction. The binding increases the thermal denaturation temperature of the DNA, meaning that the interaction stabilizes the two stranded structure. In the case of NP, the measurements also imply binding to the capsid proteins. Doctoral

School of Pharmaceutical Sciences Modern Trends in Pharmaceutical Scientific Research Supervisor: Gabriella Csík E-mail address of the presenter: orosz.adam@med.semmelweis-univ.hu

Abstract type

oral

Design and synthesis of new imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrazine derivatives with antiproliferative activity againstmelanoma cells

Garamvölgyi, Rita

Rita Garamvölgyi a, b, Judit Dobos b, Anna Sipos b, Sándor Boros b, Eszter Illyés b, Ferenc Baska b, László Kékesi b, István Szabadkai b, Csaba Szántai-Kis b, György Kéri b, c, László Őrfi a, b a Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary b Vichem Chemie Research Ltd., Budapest, Hungary c MTA-SE Pathobiochemistry Research Group, Department of Medical Chemistry, Semmelweis University, Budapest, Hungary

Notes

Melanoma is an aggressive form of skin cancer and it is generally associated with poor prognosis in patients with late-stage disease. Due to the increasing occurrence of melanoma and the emerging resistance against the currently used treatments, there is a need for the development of novel therapies. A new series of diarylamide and diarylurea derivatives containing imidazo[1,2-a]pyridine or imidazo[1,2-a]pyrazine scaffold was designed and synthesized to investigate their in vitro efficacy against the A375P human melanoma cell line. By developing the appropriate synthetic routes the planned derivatives could be synthesized in 5-6 steps from commercially available reagents. The structure-activity relationships were explored based on the antiproliferative activity of the synthesized derivatives. Several compounds were found that express submicromolar IC50 values against the A375P cells, from which the most active derivatives showed IC50 values below 0.06 μM. The best compounds exhibited superior activity compared to both the closest structural analogue described in the literature and to vemurafenib, a currently used therapeutic agent against melanoma. Doctoral School: Pharmaceutical Sciences Program: Modern Trends in Pharmaceutical Scientific Research Supervisor: László Őrfi E-mail address of the presenter: rita.garamvolgyi@gmail.com

Abstract type

oral

Flowering tops of Crataegus: general quality evaluation.

Sagaradze, Valentina

V.A. Sagaradze Department of basic medicine, Lomonosov Moscow State University, Russia

Notes

Crataegus herbal drug preparations are widely used for supportive treatment of cardiovascular disorders due to its comprehensive cardiotonic, antiarrhythmic and hypotensive action. Various parts of Crataegus plant are officially permitted to derivation of pharmaceuticals: berries, leaves and complex leaf and flower drug material are listed in foreign Pharmacopoeias and other international monographs. Although the quality standards and the analytical techniques differ. During the last decades, this has caused numerous changes in scientific and regulatory assessment, when attempting to harmonize quality standards for Crataegus herb. The problem is still in the hot of the discussion refer to variation and heterogeneity of raw material related with wild origin of plant, the appropriate species, suitability of different plant organs.Thus, we intended to evaluate general qualitative characteristics of Crataegus raw material according to current European Pharmacopoeia requirements and conduct a comparative study of pilot samples of leaves, flowers and flowering tops of Crataegus collected in Moscow region. The obtained values of moisture and total ash were at the same rate for all investigated morphological groups and conformed to pharmacopoeial requirements. The flavonoid profiles were qualitatively analyzed by HPLC method. The leaf and flower mass ratio in bathes of complex leaf and flower material was evaluated. These findings can be applied for monograph “Crataegi Flores cum folia” in updated version of Russian State Pharmacopoeia. •

Doctoral School of Pharmaceutical Sciences • Program Pharmaceutical chemistry and pharmacognosy • Supervisor: Elena Babaeva • valentinka.k92@gmail.com

Abstract type

oral

PURINERGIC SIGNALLING IN DEITERS'CELLS OF THE ORGAN OF CORTI IN HEMICOCHLEAE OF HEARING

Berekméri, Eszter

1Eszter Berekméri, 3Ádám Fekete, 2Tamás Horváth, 4,1E. Sylvester Vizi, 4Beáta Sperlágh, 1László Köles, 1,4Tibor Zelles 1 Department of Pharmacology and Pharmacotherapy, Semmelweis University, Budapest, Hungary 2 Department of Otorhinolaryngology, Head and Neck Surgery, Bajcsy-Zsilinszky Hospital, Budapest, Hungary 3 Program in Neurosciences and Mental Health, The Hospital for Sick Children, Toronto, ON, Canada 4 Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary

Introduction

Although supporting cells in the Organ of Corti are important in both physiology and pathophysiology of hearing, their precise function and regulation remained unclear. Our method of loading individual Deiters' cells (DCs) with Ca2+ dyes by electroporation in acute hemicochlea preparation provides the suitable signal to noise ratio for subcellular measurements of intracellular Ca2+ in hearing mice (>P15). The polar DCs are innervated and, additionally to their hair cell supporting functions, they are also supposed to play a role in cochlear amplification. Extracellular ATP and the ATP mediated intracellular Ca2+ increase are believed to regulate these processes and also contribute to the mechanisms that protect hearing against noise exposure.

Matrials and methods

In our experiments ATP was applied to the perfusion buffer and the fluorescent signals were detected by a cooled CCD camera based imaging system.

Results

Measuring the Ca2+ transients in different subregions of the polarized DCs, showed that the ATP response in the phalangeal process preceeds the one in the soma by seconds. The delay was detected in three mouse strains and was independent from the direction of the perfusion flow. This delay was inhibited by the non-specific ATP-receptor antagonists PPADS and by omission of Ca2+ from the perfusion buffer. But its increased in the presence of the endoplasmic reticulum Ca2+-ATPase inhibitor cyclopiasonic acid. The delay was not affected in P2X7 and P2Y12 receptor KO mice.

Conclusion

Our results suggest the synchronized action of the ionotropic P2X and the metabotropic P2Y receptors in DCs which presumably contribute to the multiple function of this supporting cell type of the organ of Corti.

Notes

Doctoral School: Pharmaceutical Sciences Program: Experimental and Clinical Pharmacology Supervisor: Tibor Zelles E-mail: berekmeri.eszter@med.semmelweis-univ.hu

Abstract type

oral

The beneficial effects of modern antihypertensive medication on depression and other psychometric parameters: a cross sectional and prospective study

Kőrösi, Beáta

Beáta Kőrösi MD1, Dóra Batta1, Andrea László MD1, Dániel Eörsi MD1, Orsolya Cseprekál MD, PhD2, András Tislér MD, PhD2, Ádám Tabák MD, PhD2, Xénia Gonda MD, PhD3, Zoltán Rihmer MD, PhD, DSc3,4, Zsófia Nemcsik-Bencze5, János Nemcsik MD, PhD1 1 Department of Family

Medicine; 2 1st Department of Internal Medicine; 3 Department of Clinical and Theoretical Mental Health; 4 Department of Psychiatry and Psychotherapy; 5 Department of Radiology and Oncotherapy, Semmelweis University Budapest

Background

Hypertension and affective disorders both increase the risk of cardiovascular events. Previously mostly negative effects were found in relation with the use of antihypertensive medications and psychiatric side effects, however, less data are available with novel calcium channel blockers or ACE-inhibitors.

Aim

Hypertension and affective disorders both increase the risk of cardiovascular events. Previously mostly negative effects were found in relation with the use of antihypertensive medications and psychiatric side effects, however, less data are available with novel calcium channel blockers or ACE-inhibitors.

Methods

In this study, 34 hypertensive patients (HT1) and 22 healthy controls (CONT) were involved. Amlodipine and/or perindopril compounds were preferred medications. Measurements were repeated in the HT1 group after 3 months of antihypertensive therapy (HT2). The following questionnaires were used: Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Autoquestionnaire (TEMPS-A), Beck Depression Inventory (BDI), Scl-90 autoquestionnaire, Hamilton Anxiety Scale, The Pain Vigilance and Awareness questionnaire, Berkeley Expressivity Questionnaire , The Big Five Inventory, Life Events Questionnaire. Arterial stiffness parameters were evaluated with the tonometric PulsePen device.

Results

Brachial systolic blood pressure, as well as pulse wave velocity were significantly lower in HT2 group compared with HT1 (129,2±9,7 vs 152,7±15,7 mmHg and PWV 8,0±1,7 vs 9,1±1,9 m/s, respectively). Several psychometric parameters that were significantly increased in HT1 group compared with CONT, had been significantly improved in HT2 group (BDI: CONT: 3,7 (0-5,5), HT1: 6,1 (2-8), HT2: 4,2 (0-7); TEMPS-A depr: CONT: 6,5 (4,75-8,25), HT1: 6,88 (4-9), HT2: 6,1 (3-9); Scl-90 depr: CONT: 0,38 (0,12-0,54), HT1: 0,47 (0-0,58), HT2: 0,37 (0-0,56)).

Conclusion

Our results suggest positive psychosomatic impact of modern antihypertensive medications. These compounds might have pleiotropic beneficial effects.

Notes

Doctoral School: Doctoral School of Pharmaceutical Sciences Program: 3.2 Experimental and Clinical Pharmacology Supervisor: János Nemcsik MD, PhD E-mail address: beataz.korosi@gmail.com

Abstract type

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