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Mgr. Dominika Besterciová

How can noninvasive brain stimulation help us in research and therapy of neuropsychiatric disorders?

In recent years noninvasive brain stimulation (NIBS) has become widely used in research and clinical practice. It allows us to safely and effectively study various brain functions while also shows therapeutic effects on symptoms of neuropsychiatric disorders such as depression or schizophrenia. NIBS consists of several techniques with the same main principle, which is a modulation of brain activity using ultrasound, electric current or magnetism delivered via surface stimulating electrodes attached over the target brain area. While the exact mechanisms of action of these techniques on the brain tissue are still largely unknown, in general, there are three levels of alternations that NIBS can induce in the stimulated area: neuroelectrical, neurochemical and oscillatory. Each of these effects can manifest locally, but it can also alter the neuronal pathway connecting two separate brain regions or it can affect the whole brain activity. Therefore it is of great use in studying not only functions of one specific region, but whole neuronal networks, thus allowing us to better understand the functional relationship between many regions associated with complex brain functions. Many of these functions are often dysfunctional in neuropsychiatric disorders which are becoming more and more prevalent in our society. One of the areas of interest is linguistic processing in the brain. Deficits in lexical-semantic processes are a common symptom in neuropsychiatric diseases and yet it is still unclear how exactly are these executive functions processed by the brain. Our research aims to investigate lexical-semantic functions such as word generation, verbal fluency, semantic memory retrieval or semantic prediction using transcranial electrical stimulation. We aim not only to broaden the knowledge about the role of prefrontal brain networks in these processes but also to bring a new view about a contribution of the cerebellum, a structure not associated with these complex functions in the past.

Mgr. Jakub Benko

Psychoplastogens – a promising concept in psychiatry

Increasing prevalence and burden of major depressive disorder presents an unavoidable problem for psychiatry. Existing antidepressants exert their effect only after several weeks of continuous treatment, often producing serious side effects. Moreover, approximately 30% of patients fail to respond to any class of antidepressants. Recent advances have given rise to the concept of psychoplastogens. These compounds are capable of fast structural and functional rearrangement of neural networks by targeting mechanisms previously implicated in the development of depression. This group has been expanding and includes various substances, such as ketamine, *N*,*N*-dimethyltryptamine, and 7,8-dihydroxyflavone. It was shown that effect of these substances converges on activation of mTOR, a key regulator of synaptic plasticity. Furthermore, evidence shows that they exert a potent acute and long-term positive effects, reaching beyond the treatment of psychiatric diseases.

Mgr. Vladimír Heger PhD.

Drug Interactions with the Ca2+-ATPase from Sarco/endoplasmic Reticulum (SERCA) and Calcium Homeostasis.

The maintaining of optimal calcium concentrations under physiological conditions is essential for life. Calcium homeostasis is complex and tightly regulated by the amount of enzymes and hormones. One of the most important enzymes mantaining calcium homeostasis is the Ca2+ ATPase from the sarco/endoplasmic reticulum (SERCA). Its main function is the transport of calcium from the cytosol to the lumen of the sarco/endoplasmic reticulum. Natural compounds are able to reduce or stimlate SERCA activity thus preventing calcium homeostasis impairment. Recently, novel natural molecules able to stimulate SERCA activity have been found.

SERCA activators may offer an innovative and promising therapeutic approach to treat diseases, such as heart failure, diabetes and metabolic disorders. In the present review the effects of compounds on SERCA transport activity are introduced.

Mgr. Lea Kissová

Impairment of skeletal muscle sarco/endoplasmic reticulum Ca 2+ -ATPase in Zucker Diabetic Fatty rats is protected by cemtirestat.

Sarco/endoplasmic reticulum (SR) Ca^{2+}-ATPase (SERCA1) in skeletal muscle is responsible for majority of the whole body glucose disposition mediated by insulin. Herein, impairment of SERCA1 of Zucker Diabetic Fatty (ZDF) rats in a model of type 2 diabetes was studied for the first time. Decreased activity and expression of SERCA1 were observed in the skeletal muscle of fatty ZDF rats in comparison with the lean animals. The dysfunction of SERCA1 was associated with increased protein carbonylation and tyrosine nitration, as well as elevated peroxidation of SR lipids. Levels of SH-groups and conformational states in the cytosolic and transmembrane regions of SERCA1 were without any alterations. Treatment of fatty ZDF rats with cemtirestat (2.5 or 7.5 mg/kg/day by oral gavage) resulted in partial recovery of activity and significant restoration of SERCA1 expression. These protective effects of cemtirestat were accompanied by significantly decreased levels of SERCA1 protein carbonyls and nitrotyrosine, as well as by marked drop in SR TBARs products. The findings comply with the previously reported antioxidant action of cemtirestat.

MSc. Aydemir Gunes Basak

The Effect of Metformin Use on Chemerin's Level in Non Alcoholic Fatty Liver Patients

Non-alcoholic fatty liver disease (NAFLD) expresses a broad spectrum that develops based on steatohepatitis after the development of non-alcoholic steatohepatitis (NASH) with simple fat and it can progress to cirrhosis and hepatocellular cancer. This study aimed to evaluate the effects of metformin on the chemerin levels in the NASH subgroup that were diagnosed with a liver biopsy of NAFLD. **Materials and Methods**: Recruited from the Gastroenterology Outpatient Clinic of Şişli Hamidiye Etfal Training and Research Hospital, a total of 52 patients (35 females, 17 males) who were diagnosed with NAFLD and underwent liver biopsy were enrolled in the study. NAS Score was calculated for each patient according to their biopsy and patients were divided into two groups depending on metformin use. The control group consisted of 26 (20 females and 6 males) healthy volunteers. Body mass index was calculated for patients and healthy volunteers. Two tubes of blood were taken from the patients and chemerin, fasting plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and fasting plasma insulin values were measured. Insulin resistance was also calculated. **Results:** The group receiving Metformin treatment was assigned as Group 2, the group that did not receive treatment, Group 3, and the control group as Group 1. The chemerin levels of Group 2 and Group 3 were significantly higher than Group 1 ($p < 0.001$). There was no statistically significant difference between the chemerin values of Group 2 and Group 3. When the biopsy results were evaluated according to the averages of chemerin levels, there was a statistically significant difference in inflammation and NAS score ($p < 0.001$, $p = 0.013$, respectively). For the factors determining the level of chemerin, the inflammation score was found to be the most significant factor ($p < 0.001$) in the univariate model, which was $p < 0.250$ and was calculated from the biopsy results. **Conclusion:** Collectively, these results show that chemerin is increased in inflammatory processes and serum elevation in NAFLD may be consistent with the severity of the disease. In this context, it is thought that NAFLD might be a biomarker compatible with its diagnosis and severity.

Key words: Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis, Metformin, Chemerin

Mgr. Drahomír Michalko, PhD.

Time-dependent involvement of controlled processing in semantic retrieval

Theoretical accounts view automatic and controlled processes in semantic retrieval during verbal fluency (SVF) as uniformly distributed across the performance. We tested the proposal that rapid automatic retrieval exploiting stable associative structure in the early stages of the performance (or easier categories) is followed by slower, more executively-demanding retrieval in later stages (or difficult categories). Eighty-five young and healthy adults completed SVF protocols varying in semantic difficulty that were assessed for retrieval rate, response typicality, and inter-response similarity across three consecutive stages. Additional executive functioning measures served to estimate the involvement of controlled processing over the course of SVF. We confirmed that the slowing of responding in time is associated with lower typicality and weaker semantic similarities among the responses, especially at the initial stages and easier categories. Critically, the time-dependent decrement in fluency was steeper in individuals with less efficient interference control, particularly in difficult semantic categories. Poorer interference control also predicted slower overall retrieval fluency only in difficult categories. Our findings show that the relative involvement of automatic and controlled processes in semantic retrieval changes with associative sparsity over time and across category difficulty and provide clinical implications for SVF in neuropsychological evaluations.

Mgr. Kristína Ferenczyová, PhD.

Effects of quercetin on cardiovascular system in Zucker diabetic fatty rats, model of type 2 diabetes

Quercetin (QCT) is a natural plant polyphenol with antioxidant properties. Previously it was shown to have beneficial effects in cardiovascular system; particularly it exerted antihypertensive, vasculoprotective, as well as cardioprotective effects against I/R injury in young healthy animals. The aim of the current study was to explore the effects of long-term administration of QCT on cardiac I/R injury and vascular function in ageing Zucker Diabetic Fatty (ZDF) rats, an animal model with associated comorbidity - type 2 diabetes.

Six-month- and 1-year-old lean (fa/+) and obese (fa/fa) ZDF rats were administered with QCT at a dose of 20 mg/kg/day for 6 weeks. Blood pressure, vascular relaxation, as well as recovery of myocardial function and infarct size after 30 min ischemia and 120 min reperfusion (I/R) were evaluated. In addition, molecular mechanisms were analyzed by Western blotting.

Our results showed that QCT administration significantly reduced blood pressure in 6-month-old lean and obese, while no effect was observed in 12-month-old rats. Vascular relaxation was significantly reduced in diabetic rats compared to lean animals in both age groups. QCT prevented impairment of relaxation in obese 6-month-old rats, but even accelerated impaired vasorelaxation in obese 12-month-old rats. QCT had no effect on vascular relaxation in lean rats. QCT exerted no cardioprotective effects against I/R injury. In 1-year-old rats, even negative effect of QCT on post-ischemic heart recovery was documented. Finally, no complex activation of the cardioprotective RISK pathway was induced.

In summary, QCT exerted beneficial effects on blood pressure and vascular relaxation in ZDF rats, but these vasculoprotective effects were eliminated by aging and/or the development of diabetes. Cardioprotective effects of QCT in I/R injury were not documented in the study, likely due to failure of RISK pathway activation in ZDF rats.

Mgr. Natália Andelová

Mitochondrial proteomics: a tool for the characterization of signaling pathways of cardioprotective stimuli

Mitochondria are key in maintaining the energy balance needed to preservation of a sufficient cardiac energy in pathological conditions. Preconditioning (PC) as one of the forms of non-invasive cardiotherapy is an effective tool for increasing myocardial tolerance to load. Understanding the mechanisms of signaling pathways and cardioprotective processes at the level of cardiac mitochondria by using proteomic analysis offers us new possibilities to study their therapeutic potential. The state of reduced oxygen utilization in the cardiac mitochondria induced by acute streptozotocin diabetes mellitus (D) can be compared to the state of partial or complete absence of oxygen in the ischemic PC. Processes of inhibiting mitochondrial permeability transition pores (mPTP) opening and thereby keeping an oxidative phosphorylation in process, which would lead to the maintenance of adequate ATP production, represent an essential and beneficial cardioprotective strategy. Detailed proteomic analysis of cardiac mitochondrial respiratory chain complexes in conjunction with mPTP plays an important role in identifying cardioprotective compensation and ensuring myocardial survival during its increased energy requirements.

The obtained results showed a significant protein stimulation of respiratory chain complex I and complex II in the D group compared with the healthy control group (C). These changes at the level of respiratory chain complexes may be an effective regulator of energy sustainability in pseudohypoxic conditions. The diabetic conditions significantly increased the abundance of mPTP proteins as a whole in comparison with the C group. The mPTP protein expression levels were not significantly altered in the D group except for ATP5H, ATP5J and KCRS.

Our study has shown that stimulation of proteins forming mitochondrial respiratory chain complexes and mPTP is involved in endogenous compensatory mechanisms leading to the preservation of myocardial function under increased energy load represented by acute D. The achieved results may be helpful in the eventual PC´s therapy, the principle of which is associated with short hypoxic impulses.

Mgr. Martin Chrastina

M. Chrastina, S. Poništ. K. Bauerová, A. Tchorbanov

ADMINISTRATION OF CROCUS SATIVUS EXTRACT IN MONOTHERAPHY AND IN COMBINATION WITH METOTREXATE IMPROVED THE CLINICAL MANIFESTATION OF ADUJVANT ARTHRITIS IN RATS.

Background: Crocus sativus is known for his benefit effect in depression and hypertension. It also start gain some attention because of its immunomodulatory and anti-inflammatory properties, thus we decided to use it in adjuvant-induced arthritis, a model for human rheumatoid arthritis. Methotrexate is the first line antirheumatic drug. The present study aimed to investigate if an extract of a Crocus sativus (SF) can improve methotrexate treatment in rat adjuvant arthritis. Methods: The study lasted 21 days and included healthy animals, untreated arthritic rats and arthritic rats treated with: SF (daily dose of 25 mg/kg SF1 and 50 mg/kg SF2) and methotrexate (twice a week dose of 0.3 mg/kg) in single treatment or in combination with SF. Arthritic score and changes in body weigh were measured during the treatment while inflammatory marker (MMP9) and biochemical parameters (gamma-glutamyl transferase (GGT)) at the end of the experiment.

Results: The combination of methotrexate and the saffron extract has significantly reduced biochemical marker such as MMP9. Also changes of the weight and changes in hind paw volume were improved by combination of methotrexate and SF and moreover on day 14 by saffron extract itself. Activity of GGT was not therapeutically changed by extract itself nor by combination treatment of saffron extract and methotrexate.

Conclusions: The results suggest that long-term administration of SF in higher dosage of SF itself and in combination with methotrexate (50mg/kg) can positively affect weight gain, hind paw volume and other parameters in arthritic rats.

Mgr. Barbora Bajzová

B. Bajzová, T. Senko, L. Kršková

BEHAVIOUR OF EURASIAN WOLF (CANIS LUPUS LUPUS) IN CONDITION OF ZOO BRATISLAVA

Background: Eurasian wolf *(Canis lupus lupus)* belongs among very common species in zoos. At present, therefore, zoos strive to create enclosures reminiscent of their look and size natural environment of animals. Individuals living in these big enclosures spend most of their time by undisturbed comfort behaviour, which was in the past connected with boredom. However, now it is one of the criteria reflecting the quality of the environment and the welfare. Our observations were realised at two neighbouring enclosures in two phases of observation. We used the method of behaviour sampling and chosen forms of behaviour were recorded continuously. The main aim of our thesis was monitoring the behaviour of five Eurasian wolves in the condition of ZOO Bratislava, while more attention was paid to comfort behaviour and motor activity.

Result: Comfort behaviour was the most common activity in both enclosures in both phases of monitoring. It was realised in the largest quantity was realised in enclosure 1 in the second phase of monitoring. In all categories and all expressions of behaviour were individual differences. Even though close contact of enclosures 1 and 2, there are significant differences between them. The impact of temperature on realised behaviour is just in some categories, mainly in behaviour conditioned by metabolic processes.

Conclusion: We can say that the large amount of comfort behaviour monitored in individuals of Bratislava ZOO can indicate appropriate conditions and good welfare. To confirm this statement should be realised other researches aimed for example at abnormal behaviour.

Mgr. Barbora Boťanská

Barbora Boťanská, Kristína Ferenczyová, Monika Barteková, Miroslav Barančík

EFFECT OF QUERCETIN ON MYOCARDIAL MATRIX METALLOPROTEINASES AND SUPEROXIDE DISMUTASES IN PATHOLOGICAL CONDITIONS ASSOCIATED WITH DIABETES DEVELOPMENT AND TOXICITY INDUCED BY DOXORUBICIN.

Background: For flavonoid Quercetin (Q) were described various biological functions including anti-oxidative and radical-scavenging. The mechanism underlying Q effects may be associated with affecting antioxidant enzymes and matrix metalloproteinases (MMPs). Aim of our study was to determine influence of Q on cardiac superoxide dismutases (SODs) and MMPs during development of diabetes and toxicity induced by doxorubicin (Dox). Methods: In the study we used Wistar rats with Dox (cumulative dose 15 mg/kg for 3 weeks) and/or Q (20 mg/kg/day for 6 weeks) treatment and lean and obese Zucker diabetic fatty (ZDF) rats with or without Q treatment. Protein levels of MMP-2, MMP-9, MMP-28, SOD-1, and SOD-2 we analyzed by Western blot analysis in left ventricular tissue samples.

Results: We found significant decrease of MMP-28 in obese ZDF rats but Q did not modulate these diabetes-induced changes. On the other hand, Q treatment down-regulated MMP-28 in control Wistar rats. We also found that Q increased 63 kDa form of MMP-2 in lean and also in obese ZDF rats. MMP-9 was not influenced by Q application and that neither in Dox-treated nor in diabetic rats. Administration of Q potentiated the anti-oxidative response systems by upregulating of SODs in ZDF rats and also in animals exposed to effects of Dox.

Conclusions: Our data showed that effects of Q in both experimental models are associated with modulation of antioxidant defense and MMPs. Decrease of MMP-28 in diabetic rats point to important role of this enzyme during diabetes development. The alterations in SODs protein levels prove the involvement of this anti-oxidative system in realization of potential protective effects of Q.

Hande Özbaşak

SELF-INTRODUCTORY PRESENTATION: MY PAST RESEARCH AND FUTURE PLANS FOR PHD STUDY

This is the introductory presentation of myself as a new PhD. student at the CEM IEPhT SAS enrolled in the program Biochemistry organized by the Faculty of Natural Sciences CU in Bratislava.

I was born and raised in Istanbul, Turkey. I have graduated with a Bachelor's degree in Biology from Istanbul University and obtained my Master's degree in Pharmacology at the Faculty of Pharmacy Hacettepe University in Ankara, Turkey. The topic of my Master's thesis was "The Effect of Atorvastatin on Sestrin-2, Sirtuin-1, TPP1 and LC3B in Amyloid Beta Induced Alzheimer's Disease Model in Human Neuroblastoma Cell Culture." The aim was to investigate the pathogenesis of the relationship between Aβ-cholesterol pathways and autophagy-related pathways. During my Master's thesis time, I have got experience in cell culture techniques and created the cell culture-based Alzheimer's disease model. Furthermore, I performed the experimental acute systemic toxicity assay using lab animals and cytotoxicity assays according to ISO standards at the Department of Pharmacology, Faculty of Pharmacy. I have 2 publications from my Master's work.

After the graduation, I worked at Acıbadem Hospital molecular pathology laboratories and learned the routine laboratory techniques such as DNA-RNA isolation from paraffin embedded tissues and oncogene detection. At the start of the pandemic, I started to work at the company Genmark Biotechnology and gained experience on SARS-CoV-2, oncogene, genetic diseases, and microorganism detection with qPCR and played a central role in company's activities. In May 2021, I started my position as the Early-Stage Researcher (ESR12) within Horizon2020 LogicLab project at the CEM IEPhT SAS. At the same time, I was admitted for a PhD study. The title of my PhD project is "Toxicology of new molecular sensors and NO donors and their application in cellular models". In my study, I am evaluating the cytotoxicity and efficacies of novel substances such as NO-releasing compounds developed by my colleagues and other ESRs in the LogicLab project.

Samuel Golas

The Role of Perivascular Adipose Tissue and Hydrogen Sulfide in Thoracic Aortas of Normotensive and Spontaneously Hypertensive Rats

Perivascular adipose tissue (PVAT) plays an important role in the regulation of cardiovascular system. One of the crucial substances produced by both vascular wall and PVAT is hydrogen sulfide (H_2S) which reveals a biphasic vasomotor effect on cardiovascular system. The vasoregulatory role of PVAT and its mutual interaction with endogenous and exogenous H_2S in the thoracic aorta (TA) in condition of essential hypertension could play an important role in the regulation of vascular tone. Moreover, H_2S can be involved in vascular tone regulation via interaction with other signaling pathways, and the crosstalk between H_2S and NO signaling has been con-firmed by several authors.

The objective of this study was to investigate the vasoregulatory effect of PVAT and its mutual interaction with endogenous and exogenous H_2S in the TA of adult normotensive Wistar rats and spontaneously hypertensive rats.

Heart failure in basic research

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There are hundreds, if not thousands, of more or less scientific articles that state that cardiovascular disease is one of the biggest problem of modern times. The World Health Organization states that cardiovascular disease is the number one cause of death in the world. The task of our experimental work is to partially contribute to the discovery of possible signaling pathways and therapeutic targets in the regression of heart failure, or possible cardioprotection.

Heart failure (HF) is a clinical syndrome in which the heart is unable to pump enough blood to meet the body's metabolic requirements. The pathophysiology of heart failure includes physiological, neurohormonal, molecular and cellular changes that result in activation of compensatory mechanisms aimed to maintaining cardiac function. In condition of increased pressure or volume overload of the heart, the chambers undergo various structural and functional changes.

The extracellular matrix (ECM) is a highly dynamic structure that affects the proper functioning of various tissues. ECM plays important role in the cell signaling, participates in the origin and development of the various of pathologies and its influence can result in improved disease. ECM critically affects the structure and function of the heart. The pathophysiology of ECM also affects intercellular communication, which results in various arrhythmias in the heart. In our work, we focused on signaling pathways involved in cardiac remodeling due to heart failure from volume overload. The aortocaval fistula (ACF) model served as our model. The solution of the given problem revealed further possibilities of using the ACF model, whether in various genetic models or in research of possible cardioprotection at the molecular level.

The results of our work can contribute to the knowledge of cellular signaling in the pathologies we are monitoring, the results of the combination of pressure and volume overload in the TGR ACF group of rats are original. The results of our work also pointed out the cardioprotective effects of ACEi and ARB on individual parameters, and possible therapeutic goals and mechanism of action of these drugs.

In conclusion, we can state that our selected proteins are involved in signaling pathways, whether in ECM remodeling processes or in the formation of an arrhythmogenic substrate. The solution of the given problem revealed further possibilities of using the ACF model, whether in different stages of HF, genetic models or in research of possible cardioprotection at different levels.

Metabolic transformations of cemtirestat (in vivo and in vitro)

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Cemtirestat, a derivative of indol-1-yl acetic acid, is the low molecular weight compound that is effective inhibitor of an aldose reductase (ALR2). ALR2, from group of oxidoreductases, is the first enzyme of polyol pathway and its contributes to the development of diabetic complications (macro- and microangiopathy, neuropathy, nephropathy, cataract, retinopathy). Activity of ALR2 in these diseases is also associated with areduced concentration of intracellular NADPH which serves as a cofactor for ALR2 in reducing glucose to sorbitol. In diabetic patients, the increased flow of glucose through the polyol pathway may contribute to oxidative stress. Inhibition of ALR2 can prevent diabetic complications and improve the quality of life of patients with diabetes mellitus.

Cemtirestat is currently undergoing a comprehensive preclinical evaluation. The results obtained so far from in vitro and in vivo experiments point to cemtirestat as an effective bifunctional agent combining the ability to inhibit ALR2 with antioxidant activity. At the same time no toxic effects of cemtirestat have been reported, which may indicate the pharmacological use of cemtirestat in the prevention and treatment of diabetic complications.

An important part of the development of a new drug is the elucidation of its pharmacokinetics. The dissertation is aimed at studies of bioavailability, metabolic changes and pharmacokinetic behavior of cemtirestat in vitro and in vivo. Cemtirestat contains two functional groups in its structure, thiol and carboxyl, which are expected to be reactive centers. Attention will be paid to possible chemical changes in these functional groups (most likely the oxidation of the thiol group and in the case of the carboxyl functional group the formation of conjugates).

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