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BOOK OF ABSTRACTS



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## PLENARY LECTURES

### FROM AUTISM TO SCHIZOPHRENIA AND ALZHEIMER'S DISEASE: SHARED GENES AND HOPE

Professor Illana Gozes

*The Lily and Avraham Gildor Chair for the Investigation of Growth Factors; Department of Human Molecular Genetics and Biochemistry; Sackler Faculty of Medicine; The Adams Super Center for Brain Studies and Sagol School of Neuroscience, Tel Aviv University, Israel <http://www.brain.tau.ac.il/director.html>*

Our brains are composed of millions of nerve cells and billions of connections. While the system is operating in an excellent coordination most of the time, in the case of autism, schizophrenia and Alzheimer's disease (to name a few), the brain is not functioning as required. We are interested to uncover shared mechanisms that will lead to better diagnosis and better treatments. In this regards, we have discovered a new gene to science, encoding activity-dependent neuroprotective protein (ADNP). ADNP is essential to the formation and function of the brain and is mutated in autism (the ADNP syndrome) and deregulated in schizophrenia and Alzheimer's disease. A small fragment of ADNP, named NAP (also known as davunetide or CP201) is available by intranasal administration and is now under clinical development by Coronis Neurosciences (<http://www.coronisns.com/>) for the ADNP syndrome.

### GENOMIC BIOMARKERS FOR EARLY DETECTION OF ALZHEIMER'S DISEASE

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With the extended life span in developed countries in the 21st century, the lack of prognostics for early identification of individuals at high risk to acquire Alzheimer's Disease (AD) is becoming a major health concern. Once an individual has been diagnosed with AD, brain damage is already too widespread to cure, or at least dramatically slow, the disease progression. As a result, current AD therapeutics may only slightly slow the disease. Future AD therapeutics may hopefully be more effective, but require the development of biomarkers for much earlier identification of at-risk individuals. I will present studies on our novel approach for finding transcriptomic (RNA-based) blood biomarkers for such diagnostics at a much earlier disease stage. Initially, using human lymphoblastoid cell lines (LCLs) from healthy donors, we applied genome-wide transcriptomics and discovered that lower expression of RGS2 (Regulator of G proteins 2) is strongly associated with higher in vitro sensitivity to amyloid-beta, a peptide known since long as accumulating in AD patient brain plaques and exhibiting toxicity towards both neurons and glia. We subsequently showed that RGS2 levels are ~3-fold lower in LCLs from AD patients compared with similar cell lines from age-matched non-demented controls. Next, using bioinformatics data-mining of published Gene Expression Omnibus datasets, we showed that RGS2 levels are also decreased in postmortem brain tissues of AD patients. Moreover, we showed that RGS2 levels are also reduced in AD patient peripheral blood, as well as in patients with MCI, the prodromal phase often preceding AD diagnosis. We therefore propose that low blood levels of RGS2 may be predictive of high risk to progress to AD. Lastly, I will present a hypothesis stating that reduced RGS2 expression represents an 'attempt' of the brain to keep functioning in spite of the ongoing neurodegeneration and the reduced cholinergic and glutamatergic signaling. However, the price for this 'protective attempt' is that aggregated brain amyloid-beta becomes more toxic to brain cells. This hypothesis, while awaiting proof from AD animal model studies, indicated that amyloid-beta may not be the culprit of AD, rather, a by-stander that becomes toxic only after the neurodegenerative process has been 'ignited' by other factor(s).

# SENSORY SENSITIVITY, NEURAL NOISE AND AUTISM

David R. Simmons

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The primary effect of Autism Spectrum Disorders (ASDs) is typically thought to be difficulty with social interaction and communication. However, recent research and thinking has highlighted the importance of non-social issues such as potentially debilitating sensory sensitivities. Sensory difficulties are now thought to be so important in ASD that they are enshrined in the most recent diagnostic criteria (DSM-5), but there is a conundrum: whilst there is no question that people on the autism spectrum, and their carers, often report a bizarre combination of sensory hyper- and hypo-sensitivity across most of their senses, there is little consistent evidence for any effects on sensory thresholds. In this talk I will provide an overview of our research on sensory processing in ASD and those with higher levels of autistic traits, and go on to describe how some new ideas about the neural basis of ASD, namely higher levels of internal neural noise, might be able to explain the curious presentation of the sensory signs and symptoms in ASD, and possibly also extend to the social issues that are so characteristic of this enigmatic condition. I shall also touch on other current theories of the neural basis of ASD as well as the work we are doing to try to ameliorate the effects of sensory sensitivities in schools and residential homes.

## EFFECTS OF U373-MG ASTROCYTOMA CELLS CONDITIONED MEDIUM ON DIFFERENTIATED IMR-32 NEUROBLASTOMA CELLS SUBJECTED TO HYPOXIA

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Nervous system cells are highly dependent on adequate tissue oxygenation and are very susceptible to hypoxia, which causes mitochondrial dysfunctions involved in apoptosis and necrosis.

Astrocytes are the most numerous cell type within the central nervous system. They are not only the main source for nutrients and growth factors in the brain, but they are also communication partners of neighboring neurons. For this purpose astrocytes are equipped with several types of transmitter receptors and the capacity to release neuroactive substances. The role of astrocytes in brain function during neuronal damage caused by hypoxia is the topic of the present study. Thus, the effects of conditioned U373-MG astrocytoma cell medium on differentiated IMR-32 neuroblastoma cell subjected to 24h hypoxia (2% O<sub>2</sub>) and 24h hypoxia followed by 24 h reoxygenation, were evaluated. In particular cell viability, depolarization of mitochondrial membrane, variation of [Ca<sup>2+</sup>]<sub>i</sub>, variations of intracellular NO and phosphorylated ERK1/2 production and expression - activation of NF-κB were examined.

The NO concentration increased significantly immediately after hypoxia only in IMR-32 without astrocytes conditioned medium and returned to values similar to those of controls after the reoxygenation period. At the same time, we observed a significant increase of [Ca<sup>2+</sup>]<sub>i</sub> immediately after hypoxia, in both IMR-32 with and without astrocytes conditioned medium. Moreover, IMR-32 cell mitochondria were significantly depolarized after hypoxia, and membrane potential returned to normal value after the reoxygenation period; on the contrary, any significant modification of membrane potential was measured in IMR-32 conditioned with astrocytes medium. Phosphorylated ERK proteins increased significantly during the first 2 h of hypoxia, then decreased, and remained practically unmodified after 24 h hypoxia and the following reoxygenation period, while an increase was still present after 24h hypoxia in conditioned IMR-32. Finally, expression and activation of NF-κB after 2 h hypoxia was detected in both IMR-32 and, in lesser extent, in conditioned IMR-32. Our results show the neuroprotective role of astrocytes conditioned medium which could counteract hypoxia induced variations of NO, [Ca<sup>2+</sup>]<sub>i</sub> and subsequent mitochondrial depolarization measured in differentiated IMR-32 cells.

*Acknowledgements: Andrea Nannetti (Fineco Bank) for financial support.*

# RISKS FROM REAL LIFE EXPOSURES THE AGEING PROCESS AND ITS MODULATION

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Linking xenobiotic chemical exposure to health effects has been the subject of many experimental and epidemiological studies but still remains a matter of permanent controversies. This issue is complicated by the multiple mechanisms of xenobiotic toxicity often involved, the uncertainties related to long term and low dose xenobiotic exposure. The general population experiences uncontrolled multi-chemicals exposure from many different sources at doses around or well below regulatory limits. Therefore, traditional chronic toxicity evaluations for a single chemical could possibly miss to identify adequately all the risks as risk assessments, in general, focus on individual compounds. For this an experimental methodology comprised of a long-term toxicity study of non-commercial chemical mixtures, consisting of common everyday life chemicals at low and realistic dose levels around the regulatory limits and with the simultaneous investigation of several key endpoints has been developed. Ageing and associated chronic diseases is a multifactorial process. Main factors that interplay in the ageing process are free radicals and oxidation, insulin and insulin growth factors, sirtuins, mTOR, microbiome, lack of micronutrients and declining proteasome activity. All the above processes have in common that cellular damage is caused and accumulated. This brings to apoptosis and/or autophagy and cell replacement or repair. Telomere length shortens with age and leads to senescence. Shorter telomeres are associated with increased incidence of aging related diseases and shorter lifespan. Recently was demonstrated that telomere re-lengthening can reverse aging phenotype. Diverse lifestyle, environmental and nutritional factors influence positively and/or negatively telomere length. Telomere length at birth can vary from 5000-15000 pair bases, so the rate of telomere shortening is a more important biomarker than the absolute telomere length. Average telomere length has been used into epidemiological studies. It's not a good biomarker for a clinical evaluation because it gives no data on the percentage of short telomeres. Measurement of all telomeres through Q-FISH is necessary to evaluate single telomere length and percentage of short telomeres. The percentage and rate of increase of the percentage of short telomeres predicts longevity in mammals. We have formed a data base measuring leucocyte telomere length (LTL) of different age groups within a healthy adult population, through Q-FISH, creating a reference range based on age and percentile distribution of LTL. It is considered and partially demonstrated that a proportionality of the telomeres length distribution (TLD) in leucocytes corresponds in general to the TLD of stem cells in the body. Our study with drugs of abuse user's revealed that median of telomere length is about 1.000 base pairs lower than the median of healthy population. The user's 20% percentile was also about 1.000 base pairs lower than the one of healthy population. In general we found higher percentage of extremely low telomeres in drugs of abuse users and also absence of extremely high telomeres. In addition the telomere length was conversely related on annual opiates use. Conclusively older biological age compared as fact with chronological age, based on telomere length in drugs of abuse users. Repeated measurements at a distance of 6 months or a year can reveal the rate of change of the short telomeres, and response of patients to treatments, lifestyle, diet, supplementation and exercise modifications. The value below of 3000 pair bases for short telomeres is considered the critical one as well as the percentage of them to be lower than 3% of the total. Within our in vitro experiments in cell cultures we've been able to discover a potent natural molecule that activates telomerase up to 1300% in relation to the control cells.

# SYNCHRONIZATION OF FRONTO-PARIETAL OSCILLATORY NETWORKS AS A SIGNATURE OF VISUAL AWARENESS

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To study signatures of visual awareness in brain networks, we used a clinical model of neglect syndrome. The perceptual deficit for contra-lesional hemi-space in neglect is viewed as a dysfunction of fronto-parietal cortical networks, the disruption of which has been described in neuroanatomical and hemodynamic studies. Here we exploit the superior temporal resolution of electroencephalography (EEG) to study dynamic transient connectivity of fronto-parietal circuits at early stages of visual perception. As reflected by inter-regional phase synchronization in a full-field attention task, two functionally distinct fronto-parietal networks in beta (15–25 Hz) and theta (4–8 Hz) frequency bands were related to stimulus discrimination within the first 200 ms of visual processing. Neglect pathology was specifically associated with significant suppressions of both beta and theta networks engaging right parietal regions. These connectivity abnormalities occurred in a pattern that was distinctly different from what was observed in right-hemisphere lesion patients without neglect. Also, both beta and theta abnormalities contributed additively to visual awareness decrease quantified by the Behavioral Inattention Test. The results provide evidence for the impairment of fast dynamic fronto-parietal interactions during early stages of visual processing in neglect pathology. Also, they reveal that different modes of fronto-parietal dysfunction contribute independently to deficits in visual awareness at the behavioral level.

## NEUROTOXICOLOGICAL STUDIES IN INSTITUTE OF PHYSIOLOGY/NEUROBIOLOGY: SOME OF THE MOST DESTINGUISH ACHIEVMENTS

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Department of Drug Toxicology in Institute of Neurobiology is a fundamental science unit building the experimental drug toxicology in Bulgaria. The main topics of research are the influence of drugs, xenobiotics and endogeneous factors on adverse drug reactions mainly based on drug-drug metabolic interactions, new facts on pharmacodynamics and pharmacokinetics of new potential drugs in normal and pathological conditions.

The present review describe some of the most distinguish results of the departmental team in the field of neurotoxicology obtained in collaboration with Bulgarian and foreign scientists.

Psychotropic drugs and vision: in a series of human experiments was shown that caused by certain psychomimetic (LSD, mescaline), stimulant (amphetamine, caffeine) and depressant (chlorazin, diazepam, phenobarbital) substances, changes in visual perception of environment were not due to changes the maximum and the mean velocity of the saccadic eye movements (peripheral vision analyzer) but in the system synthesizing the information (the cerebral cortex of the cerebrum).

1. *Benzodiazepines and isolated syndrome*: Three-month isolation housing of Wistar rats induces aggressive behavior in respect to mice which is due to significantly decreased affinity of binding and number of benzodiazepine receptors in cerebral cortex, midbrain and striatum.
2. *Blood brain barrier and phosphodiesterase inhibitors*: Glaucine (phosphodiesterase IV inhibitor) facilitate L-DOPA blood brain barrier transport and by this way potentiate its antiparkinsonian effect.

3. *Organophosphates and acylpeptide hydrolase (APH)*: APH, enzyme which regulate the turnover of neuropeptides with cognitive enhancement effects, is inhibited with higher affinity and for longer time than CHE by important organophosphates (nerve agents and pesticides).
4. *Xanthates and neuroprotection*: Selective inactivation of brain CYP 2B6 by C8-xanthate help to understand nicotine brain metabolism and mechanism of addiction.

## NEUROPHYSIOLOGY SESSION

### AUTOPHAGY AND BRAIN: THE CHALLENGES OF HOPE

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Autophagy is a complex process using similar molecular elements and machinery from yeast to humans that enables eukaryotic cells to deliver cytoplasmic constituents for lysosomal degradation, to recycle nutrients, and to overcome challenges during stress conditions such as starvation. Autophagy has been suggested to play a key role in the regulation of innate and adaptive immune responses as well as Central Nervous System aging and neurodegeneration.

The autophagy-lysosomal pathway is crucial for health and survival of neurons - post-mitotic cells known to require a high amount of energy for their normal functioning that depend upon the homeostatic and waste-recycling reactions.

The dysregulation of autophagy results in protein aggregation, generation of toxic protein species, and accumulation of dysfunctional organelles which in turn contributes to the pathophysiology of aging and neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, and prion disease.

There are data that the enhancement of autophagy may help us in the development of new therapeutic strategies for the treatment of brain pathologies.

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### EFFECTS OF CLASSICAL MUSIC ON HEART RATE VARIABILITY

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**Introduction:** There are growing number of studies demonstrating physiological changes in response to music, including blood pressure, heart rate, respiration, and etc. Thus music may modulate or trigger autonomic responses. In recent years, a fluctuation between intervals of consecutive heart beats because of different humoral and neural factors on cardiovascular system, or so called Heart Rate Variability (HRV) has been used as an indicator of autonomic nervous activity. Clinical studies revealed that the higher HRV is a mark of better functional state while the lower is connected with increased morbidity and mortality.

**Aim:** The aim of our study was to evaluate the effect of classical music over the tone of the ANS in young healthy people.

**Material and methods:** This was an experimental study done in 17 healthy students aged between 19-24 years, of either sex. HRV test was performed at rest for three minutes with no music (basal examination), then participants were asked to listen to classical for a period of 10 min. ECG recording was performed at the last 5

min of music session and 3 minutes after that for 5 min in silence. The HRV parameters were evaluated, and frequency and time domain analyses were then performed. The results were statistically assessed by Student's test. Values of  $P \leq 0.05$  were considered to indicate statistical significance.

**Results:** Our data showed that listening to classical music increases significantly HRV parameters such as RRNN, pNN50, HF nu, %HF. These results suggest that the organism has reached a better functional state than usual.

**Conclusion:** Classical music has immediate physiological effect shown by highly sensitive and specific HRV test. Thus, music can be used to regulate the mood and arousal in everyday life and to promote physical and mental health. However more studies are suggested to explore this topic in greater detail.

Keywords: heart rate variability, classical music, ECG

## INTIMATE RELATIONSHIP BETWEEN MICROGLIA AND GRAFTED DOPAMINERGIC CELLS

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Intracerebral grafting of dopaminergic cells is a viable option for treatment of Parkinson's disease. The glial reaction caused by the transplantation is, however, scarcely described. Therefore, the present study aims to give an account of the reaction of the host microglial cells following dopaminergic transplantation in a rodent model of Parkinson's disease.

By immunohistochemical methods, we assess the microglial reactivity in and around intrastriatal grafts of fetal mesencephalic tissue in the unilateral 6-OHDA model of Parkinson's disease. By comparing the characteristics of microglial reaction following transplantation with the reaction caused by the mechanical impact of the transplantation instrument, we demonstrate the relationship between neurons and glia following intracerebral transplantation.

The dopaminergic neurons within the grafts are mostly found in clusters, often associated with the graft-host interface. Reactive microglial cells are present around and inside the grafts, but are very prominently gathered in the same locations as the neuronal clusters. Careful observation of these microglial cells reveals that they retain their activated, ameboid morphology for a considerable time following transplantation. Additionally, the microglial reaction following grafting is quantitatively attenuated, when compared to the reaction following mechanical impact.

The present findings suggest a relationship between grafted neurons and microglial cells, which is not only spatially, but also functionally conditioned. Microgliaocytes are activated by grafting, however their activity seems to be neuroprotective, and not inflammatory. Better understanding of the mechanisms of this activation is needed to elucidate the basis of the neuron-glia crosstalk following transplantation.

## HOMEOPATHIC REMEDY ACTION OVER AUTONOMIC NERVE SYSTEM

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**Introduction:** Heart rate variability refers to beat-to-beat fluctuations in heart rate reflecting both sympathetic and parasympathetic functions of the autonomic nervous system (ANS). HRV is generally assessed based on time-domain or frequency-domain analysis. Analysis of time domain includes NN intervals, SDNN, pNN50



and RMSSD. The frequency domain includes Total Power (TP), High Frequency (HF), Low Frequency (LF), LF and HF ratio (LF/HF) and Very Low Frequency (VLF). The TP express the magnitude of the HRV in a global manner. HF and LF reflect the interaction between parasympathetic and sympathetic tone respectively. Generally, increased HRV is linked to good health and decreased stress.

**Aim of the study:** Evaluation of the influence of homeopathic remedies over the tone of the ANS by HRV measurement.

**Materials and methods:** We examined 50 patients, from 7 to 65 years. After homeopathic interview, patients lied down for 5 min in a supine position. Basal measurement of HRV parameters was performed. Second measurement of HRV parameters was done 10 minutes after individually chosen homeopathic remedy or after placebo.

**Statistical analysis:** All measurements were presented by means and standard deviation. The comparisons were conducted with t Student test for independent values ( $p < 0.05$ ).

**Results:** In experimental group TP and HF were significantly increased while there were not changes in these parameters in placebo group.

**Conclusion:** We observe certain effect of individually chosen homeopathic remedies over HRV hence these remedies change the tone of vegetative nerve system and function of the heart. Parasympathetic tone is increased that is protective for heart and other organs. This effect is basis for improvement of health as increased HRV is connected with better functional state and higher adaptability while lower HRV is seen in certain diseases.

## PLASMA NPY AND METABOLIC STATUS OF RATS AFTER SWEETENER CONSUMPTION

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Neuropeptide Y (NPY) is a significant orexigenic factor in the central appetite regulation. It has been hypothesized that in the current Western lifestyle, which influences central NPY through leptin resistance and peripheral NPY through stress, could contribute to a number of diseases such as hypertension, diabetes, and obesity. At experiments with Wistar rats we modeled metabolic disturbances with fructose, sucrose and aspartame (a sugar substitute for diabetics and obese patients). The aim of the study was to track changes in plasma NPY levels of experimental rats and to compare them with some metabolic indicators. Three groups of male Wistar rats (N=7 each) were supplemented with 15% fructose (Group F), 10% sucrose (Group S), and 0.3% aspartame (Group A) in the drinking water for a period of eight weeks, accompanied by ad libitum feed consumption. Another group was kept on a standard rodent chow diet and drinking water as a control (Group C, N=7). Plasma NPY was measured by ELISA method. Nonsignificant increase in plasma NPY levels in the groups was registered, but higher levels were observed in the fructose-fed group ( $1.13 \pm 0.057$  pg/mL), followed by the aspartame group ( $0.9 \pm 0.024$  pg/mL). Significant changes in fundamental metabolic parameters (glucose, triglycerides, total and LDL cholesterol, AST, ALT, uric acid) of Group F were registered compared with Group C, as well as some metabolic disturbances in Groups S and A. Positive correlation was found between plasma NPY and uric acid levels. The elevation of plasma NPY after fructose and aspartame ingestion suggests that a failure of these sweeteners to suppress NPY release could contribute to decreased satiety during their long-term consumption. Results from our experiment demonstrate the need to limit the intake of these sweeteners in humans as an opportunity to reduce the current global epidemic of obesity, hypertension and type 2 diabetes.

## **CHANGES IN PLASMA NPY AND IMPROVEMENT OF SOME METABOLIC INDICATORS AFTER ANTIOXIDANT TREATMENT OF RATS ON A HIGH - FRUCTOSE DIET**

Gergana Sandeva<sup>1</sup>, Aneliya Dimitrova<sup>2</sup>, Vanya Tsoneva<sup>1</sup>, Tanya Tacheva<sup>1</sup>, Rositsa Sandeva<sup>1</sup>

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Changes in plasma orexigenic hormone NPY, metabolic and oxidative status after antioxidant treatment (S-adenosylmethionine - SAM) of patients and experimental animals on a high fructose diet are not well researched. The aim of this study was to track changes in plasma NPY, the product of lipid peroxidation malondialdehyde (MDA) and some metabolic indicators in serum of 18 Wistar rats divided into 2 groups: control fructose fed (15%, 8 weeks, N= 6) - CF and experimental group ST, also fructose fed (15%, 8 weeks, N=12), but treated with 20 mg/kg bw SAM during the last 3 weeks. Group ST consisted of male (FMS) and female (FFS) subgroups of rats. Plasma NPY was measured by ELISA method and MDA - with Pasha and Sadasivadu's method. Glucose, triglycerides, total, LDL and HDL cholesterol, uric acid and liver transaminases were measured as markers of metabolic disorder. Significant difference was found in plasma NPY of FC and ST groups. Results showed that high fructose consumption caused metabolic disturbances and SAM reduced significantly plasma Gl, TG, total and LDL cholesterol, UA, liver transaminases and MDA ( $p < 0.05$ ). Significant difference was found in HDL cholesterol and uric acid between FMS and FFS subgroups of rats supplemented with SAM ( $p = 0.026$  and  $0.04$  resp.). Significant correlations, both positive and negative, were observed between various metabolic parameters and MDA. The observed changes in NPY, metabolic disturbances and an increase of MDA in experimental rats with fructose consumption demonstrate the need to limit the intake of this sweetener in humans as preventive measure against metabolic syndrome and NAFLD. SAM improves metabolic parameters in rats on a high - fructose diet and may be used to correct metabolic status of patients with obesity, hepatic steatosis and diabetes mellitus type 2.

### **POSTER SESSION**

#### **BONE AS AN ENDOCRINE ORGAN**

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The recent achievements in research of bone tissue have shown that, in addition to their involvement in mineral metabolism and hematopoiesis, they secrete biologically active substances that are relevant to a number of metabolic processes. One of the most studied bone hormones is the specific protein produced by osteoblasts called osteocalcin. Our study aims to systematize the available literature data on the effects of osteocalcin on metabolism, reproductive function and the brain. A number of authors report that osteocalcin modulates glucose tolerance and testosterone production. Receptors for this hormone are found in the pancreas, brain, skeletal, adipose tissue and testes. It has been found that the osteocalcin crosses the blood-brain barrier, affects the synthesis of monoamine neurotransmitters, inhibits gamma-aminobutyric acid synthesis, thus preventing conditions such as anxiety and depression. The researches with laboratory mice reported data for the effect of osteocalcin on brain development and cognitive function. In conclusion, it can be said that the bone is an endocrine organ, affecting by its secretion the carbohydrate metabolism and the brain function, forming the bone-brain axis.

Keywords: bone, hormone, osteocalcin

## VITAMIN D AND ITS REGULATION OF PANCREATIC SECRETION

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Insulin secretion from  $\beta$ -cells of pancreatic islets is subjected to very precise and complex regulation by metabolites, hormones and the autonomic nervous system. The aim of this study is to highlight the links between vitamin D and its regulatory effects on pancreatic secretions. In recent years, studies have shown that vitamin D was found to modulate the proliferation of rat pancreatic  $\beta$ -cells in vitro. Other studies have shown impaired insulin secretion in certain polymorphisms of the Vitamin D receptors in animal and human models. Vitamin D has also been shown to induce autophagy and suppresses apoptosis of pancreatic  $\beta$ -cells. Furthermore, it is important to note that insulin secretion is a calcium dependant process and vitamin D has been shown to play a role in the regulation of extracellular calcium flux through  $\beta$ -cells. Vitamin D deficiency may, therefore, lead to a reduction of insulin secretion and  $\beta$ -cell function.

## IDIOPATHIC PULMONARY FIBROSIS

Anton Videv, Nikolay Genov, Tsvetoslava Hristozova, Darina Mihova, Delyan Terziev

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According to WebMD Lung diseases are some of the most common medical conditions in the world. Tens of millions of people suffer from lung disease in the U.S. alone, billions are the victims all around the globe. The different types are numerous they include asthma, bronchitis, chronic obstructive pulmonary disease, pneumonia etc. Some are curable, others chronic but there is one specific example of a lung disease, one the cause of which is still a mystery, one deadly, irreversible and still incurable lung diseases-The Idiopathic Pulmonary Fibrosis.

In our study we have tried to summarize some of the main aspects of that progressive, affecting over 100 000 people in Europe, disease. Firstly, we have focused on the origin, the genesis, the cause of IPF. Secondly, we have given a detailed information about the different diagnostic methods such as X-ray, HRCT, lung biopsy, ABG, bronchoscopy. What is more, we have included some of the main strategies of fighting that illness. For instance, drug treatment, transplantation, oxygen therapy and rehabilitation. Last but not least, we have looked at the number of people diagnosed with lung diseases and the correlation between their lifestyles, working environment and how often has an IPF being reported.

In conclusion IPF is rare and severe disease. In our study we have included some of the latest information about IPF as well as the up to date methods to diagnose it. Lastly, we have presented some of the most advanced ways of fighting that incurable illness.

Keywords: Idiopathic Pulmonary Fibrosis, IPF, deadly, treatment, lung disease, HRCT, X-ray

## EFFECTS OF DEHYDRATION ON BRAIN FUNCTIONS

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Dehydration is a condition that occurs when body fluids are lost, predominantly water, exceeding the amount entering the body. This process has a critical effect on brain structure and functions, as indicated by recent advances. Some of the most studied effects of dehydration are mood swings, cognitive and motor abilities and

changes in brain structure, including increase in cerebral ventricle volume. Maintaining fluid homeostasis has a critical impact on brain function. As such the effects of severe dehydration are well researched. However there is insufficient evidence of the effects of a low level of acute dehydration that occurs in ordinary day-to-day activities. The purpose of this study is to systematize published data regarding the effect of acute dehydration on brain function. Slight dehydration is the first degree of loss of body fluids, which is quickly compensated after adequate intake. In contrast, acute dehydration is characterized by severely reduced turgor of the skin and serious consequences. It is not compensated by a short-term adequate fluid intake. There are differences between the effects of acute dehydration on the functions of the male and female brain. Studies assessing women experiencing acute dehydration, indicate that participants share a feeling of aggression, difficulty in taking on new tasks, headaches and low concentration. Studies of men subjected to acute dehydration also provide an evaluation of the effects of this condition. They indicate that with or without physical activity, negative effects are observed, including fatigue, tension, adverse changes in vigilance and working memory-To conclude, it can be observed that dependent on gender, different symptoms arise as a result of acute dehydration; in order to create an algorithm for its appropriate treatment, further research is required.

Keywords: dehydration, brain functions, treatment

## **POST-CONCUSSION SYNDROME**

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Concussion: a common cranial brain trauma, which is considered to be one of the smallest brain injuries. It is not associated with a cranial cavity fracture or hematoma. However, it is usually related with problems such as a brief loss of consciousness and dizziness. It is interesting to know that the causes of the cerebral concussion could be numerous but in general they occur as a result of a stroke with a blunt and hard object.

Although, concussion is not considered as a severe injury and in most cases it has no health consequences, occasionally some negative effects may show and we generalize them as the Post-concussion syndrome. In our study, we have synthesized the reasons behind that syndrome which symptoms may continue within weeks, months or even years. What is more, we have highlighted most of the negative effects which that syndrome has on people's quality of life. Last but not least, we have included a specific examples of professions that have the highest risk of Post-concussion syndrome.

In conclusion we have based our study on a syndrome which most of the people do not consider as threatening or dreadful as all the other illnesses. Yet, we think that its impact on people's quality of life is significant. As a result we have established our work on a syndrome the cause of which are still unknown.

Keywords: Concussion, Post-concussion syndrome, threatening, life quality, significant impact, cranial fracture

## **THE ROLE OF MIRROR NEURONS IN BUILDING A MENTAL SIMULATION**

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The aim of the following study is to explain what "mirror neurons" are. In addition we will categorize and describe the mechanisms of the possible processes that they take part in.

A mirror neuron is a neuron that fires both when an animal acts and when the animal observes the same action performed by another. It excites the same neurons that would otherwise perform the said task however it does not cause a motion to be performed by the observer.

This allows the neurons to take part in learning new motions and aids in understanding languages as a child. A more complex function of mirror neurons is their supposed connection with building a simulated sensation, desire or motion in a person's mind. This can then be used to predict another's actions, much like mind reading, or to form the feeling of empathy, as you would try to mimic the targets experiences.

This system is highly dependent on neuron inhibitory mechanisms. It has been noted that patients with prefrontal lesions compulsively imitate gestures or even actions performed in front of them by an experimenter. This behavior can be explained with the impairment of inhibitory control normally governing motor schemas. Taking all that into account, the activity in mirror neurons can be linked with building mental simulations, as that would explain how people can have experiences and movements, without them being translated into real actions.

Key words: Mirror Neurons, learning motions, mental simulations

## **GAZE DISTRIBUTION IN OLDER ADULTS DURING WALKING IN A VIRTUAL REALITY PEDESTRIAN PRECINCT**

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Human gaze pattern changes with advancing age. Our previous study revealed prolonged viewing at traffic lights in older adults while walking in a virtual reality pedestrian precinct (Bock et al, 2015). Here, we examined whether older adults look longer than young adults not only at upcoming traffic light, but also at regions that are crucial for safe walking like uneven pavement or fellow pedestrian on a collision course. 17 young (mean age  $24.51 \pm 3.58$  years) and 16 older adults ( $66.15 \pm 5.73$ ) participated in the test. By starting to walk on a treadmill the individuals advanced the rendering of a virtual world presented on a screen situated in front of them. The virtual world presented shopping precinct with buildings, still and moving objects like pedestrians, cat crossing, flying papers, trees, mailboxes, benches and etc. Some of the events required a response such as stop walking in order to wait for a cat crossing or announcing the gender of an oncoming pedestrian. The eye position was recorded by means of a video-based system. We calculated the following gaze parameters: total gaze time, relative total gaze time, longest glance time, number of re-glances and mean glance time for the regions of visual space with high and little behavioral relevance. The results revealed that older adults looked longer than young adults not only at upcoming traffic lights, but also at pedestrians passing by and cats crossing the path. The results also revealed a reduced gaze time in the regions of low behavioral relevance that could be life-threatening for older adults.

## **PSYCHOPHYSIOLOGY SESSION**

### **DRIFT DIFFUSION MODELING OF REACTION TIME: EFFECTS OF INFORMATION RELIABILITY AND AGE ON DECISION MAKING**

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Decision making in perceptual tasks is considered as a process of accumulation of evidence for a particular response that depends on the task difficulty, the instruction and the non-decisional processes. We performed a study on discrimination of simulated heading direction in which we manipulated the need for spatial and temporal integration. Four conditions were used. In the static condition the direction of heading is based on the

orientation of dot pairs and requires spatial integration. In the motion condition the heading direction is determined by the motion trajectory of dots. In the flicker condition a sequence of static patterns was presented and the heading direction depends on the temporal integration of the information about the orientation of pair of dots. In the combined condition the heading direction is determined by both the orientation and trajectory of dot pairs. In all conditions except the static one, the dots had limited lifetime of 100 ms. Seven heading directions to the left or to the right of the screen center were simulated. 31 observers (20-84 years) classified in three age groups had the task to indicate whether the heading direction was to the left or to the right. The results confirmed that the reaction time increased with age. The discrimination performance depended on the reliability of the spatial and temporal information. The older group had greater difficulty to temporally integrate the orientation information in the flicker condition as compared to the other age groups. Applying a hierarchical drift diffusion modeling on the reaction time and the observers' responses we showed that the conditions requiring temporal integration increase the time for the non-decisional processing, while the information reliability changes the rate of evidence accumulation for a particular response. Moreover, age affects the amount of necessary evidence for making a decision and the non-decisional time.

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## **EXCESSIVE NEURAL VARIABILITY IN SOME DEVELOPMENTAL DISORDERS**

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Everyone experiences difficulties in trying to recognise a friend in a crowded shopping centre but this difficulty is accentuated in some neurodevelopmental disorders. Presumable excessive from moment to moment brain function variability interacts with the noisy environment and markedly degrades the neural processes. Excessive neural variability is described in several developmental disorders such as Autism Spectrum Disorder (ASD), Developmental Dyslexia (DD), and Attention Deficit Hyperactivity Disorder (ADHD). Each of the disorders refers to a specific pattern of behavioural and learning difficulties with different core defining features. There is however a common feature in neuronal mechanisms functioning in the three disorders. It is connected to the performance efficiency which is limited by external noise in the sensory signals as well as by internal neuronal noise associated with random variations of neuronal activity. In the present work psychophysical and neurophysiological studies are reviewed that demonstrate increased neural variability (internal noise) in ASD, DD and ADHD. We discuss the internal noise origin in relation to separate or common pathophysiological mechanisms and the possibility to determine unique key features of the three developmental disorders. We further motivate a necessity to study neural variability by a combination of psychophysiological approaches and state-of-the-art techniques for brain activity visualization and to develop mathematical diagnosing model.

## **SPOTLIGHT ON NEW CONCEPTS IN SLEEP AND COGNITIVE NEUROSCIENCE: THE ROLE OF DISSOCIATIVE CONSCIOUSNESS AND PREDICTIVE CODING**

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Dissociative consciousness (DC) and predictive coding (PC) are new psychological concepts. DC refers to fragmentation of perceived experiences and is characterized by dream-like mentality during wake as observed in many psychiatric disorders. PC is a neurocognitive concept, according to which the brain does not process the whole qualia of external information, but only residual mismatches occurring between incoming information and an individual, inner model of the world. It has been recently proposed that the inner model is

updated during rapid eye movement (REM) sleep thus affecting PC functioning and probably contributing to DC states. Although revealing the latter mechanisms may deepen our understanding of the cognitive functions of sleep in both normal and psychiatric conditions, the implications of DC and PC for cognitive science and psychopathology are still loose. Here, we summarize recent psychological, neurophysiological and neuroimaging evidence pointing to a crucial role of DC and PC for psychopathology, cognition and successful adaptation. We conclude that both DC and PC appear as useful and relevant concepts in psychiatric research, cognitive science, sleep medicine, and social psychology.

## **MOTION DIRECTION DISCRIMINATION AND EYE MOVEMENTS BEHAVIOR OF CHILDREN WITH DEVELOPMENTAL DYSLEXIA**

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Deficits in visual information processing and visual spatial attention are commonly observed in children with dyslexia. The aim of the present study was to evaluate whether such deficit occurs in tasks that require to ignore irrelevant visual information.

A motion direction encoding was studied by estimating of coherent motions thresholds in children with developmental dyslexia (DD) and controls. Motion coherence thresholds were measured using a random dot kinematogram consisting of a patch of 100 white dots (0.1°) randomly distributed within a 23 x 23° region on a black background. A variable proportion of these dots moved coherently, at a velocity of 4.4 deg/s amongst the remaining randomly moving noise dots. Four types of coherent motion were used: horizontal and vertical translation, radial motion and rotation. On each trial, the child indicated the perceived direction of motion by manual response. A two up, one down adaptive staircase procedure was used.

The motion coherence thresholds in the DD children were higher than controls for all types of coherence motion and the discrimination was performed differently depending on the type of coherence motion due to poor global pooling of motion signals or imprecision in local direction estimates.

In addition, assuming that abnormal eye movements occur independently from the reading process, we investigated eye movement behavior of the children reading a fairytale, listening to a recorded reading from another child and visual-spatial attention task in which in a sequence of color squares either the cued or the uncued square changed color. We found a high number of saccades in DD children, short saccade amplitudes for the aloud reading task and high eye velocity for the listening task. For visual spatial attention task, the large saccades showed higher velocities than small saccades toward targets. Small and large saccades, respectively, subserved different perceptual and cognitive strategies and may rely on different programming modes.

Keywords: coherent motion, direction discrimination, eye saccades, dyslexia  
*The study was supported by SNF DN05/13 – 2016.*

## **STUDY OF AUDITORY PROCESSING OF CHILDREN WITH DYSLEXIA**

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In the present research, we focus on auditory processing of non-linguistic and sub-lexical stimuli in dyslexia. We investigate frequency discrimination of non-speech stimuli in order to explain the basic auditory deficits that could account for the observed phonological processing deficits in dyslexia. Individual abilities of

7-10 year-old children with developmental dyslexia and children with normal language function were evaluated during an auditory sensory-motor task. A random auditory sequence, consisting of two tones differing by about 150 Hz with tone duration 50 ms and inter-stimulus intervals 1.5-2.5 s, was presented to 17 children of each group. When hearing the low-frequency tone (900 Hz) the children responded by pushing a button with the right hand and when hearing the high-frequency tone (1050 Hz) they responded with the left hand. The tone-frequency discrimination task showed a deficit in the dyslexic group for frequency difference of 150 Hz, the dyslexic children also had slower RTs than the controls for the low-frequency tone.

In another experiment, audio recordings of sub-lexical stimuli (words/pseudo-words with length of 3 and 4 letters) were played and the children were instructed to respond with the right hand when hearing a word and with the left hand when hearing a pseudo-word. The individuals with dyslexia performed worse than the controls and had slower RT for the 4 letter task. The lack of between-group differences in RT can be attributed to the compensatory mechanisms serving to increase arousal and readiness, and which help the early stimulus feature analysis in order to counteract perceptual impairments.

Thus, this study further strengthens the view that children with dyslexia are characterized by auditory processing deficits when processing non-speech stimuli and highlights a further dimension that these deficits can manifest.

Keywords: language competence, sensor-motor regularities, child development

*The study was supported by SNF DN05/13 – 2016.*

## **CONTRAST SENSITIVITY TO SINUSOIDAL GRATINGS AND VISUAL-SPATIAL ATTENTION IN DEVELOPMENTAL DYSLEXIA**

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The purpose of our study is to examine the relationship between visual sensory dysfunction and visual spatial attention in the context of developmental dyslexia (DD). Individual abilities were evaluated in 17 children (7-10 year-old) with DD and children with normal reading skills.

We carried out two different experiments. In the first experiment we determined the contrast thresholds of detection of gratings with high temporal and low spatial frequency and gratings with low temporal and high spatial frequency. The thresholds were also measured using the same type of gratings with doubling of their spatial frequency. All gratings were embedded in external noise. The contrast threshold was determined by two-alternative forced choice method combined with double staircase procedure.

The results show that the dyslexic children had higher contrast thresholds and difficulties detecting normal sinusoidal gratings and they were also less sensitive to the frequency-doubling illusion than normal readers.

In the second experiment, we study a visual-spatial attention in one-shot color-change detection task using a cue. The cue (black rectangle) appeared on the blank screen at a viewing distance of 50 cm. An array of four colored squares, one of which was located within the cue, appeared 200 ms after the cue. The squares and cue remained onscreen for 300 ms, after that they both disappeared simultaneously and the screen remained blank for 1.2-2.5s. For valid streams, the square inside the cue changed color (right-hand response). For invalid streams, one of the uncued squares changed color (left-hand response).

For visual-spatial attention task, dyslexic readers had responding with less success and more slowly than the controls. The results have been interpreted as evidence for visual spatial attention deficits in relation to orienting and focusing in dyslexic readers in comparison with control group.

Keywords: sinusoidal gratings, visual-spatial attention, dyslexia

*The study was supported by SNF DN05/13 – 2016.*



# HEMISPHERIC SPECIALIZATION IN IMPLICIT SEQUENCE LEARNING IN 6-8 YEAR-OLD CHILDREN

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Hemispheric specialization in implicit sequence learning in pre-school and first grade children is of interest in the context of the implicit-explicit model of language (Ullman, 2004). According to this model, phonological, morphological and syntactic aspects of language are dominated by structured regular patterns which are incorporated implicitly in language functions. In the present research, the associations between language competence and individual abilities of implicit learning of sensorimotor regularities with the right or the left hemisphere were evaluated in 6-8 year-old typically developing children with normal language function. Language competence was assessed using a standardized test for phonologic awareness (Shtereva, 2012). Individual abilities for implicit learning were evaluated in an auditory serial response time task, which was trained implicitly with the right and the left hand. Implicit learning with the left and right hand reveal different associations with language competence indicating specific roles for the left and right hemisphere in integrating implicit sensorimotor memories in language competence. The results support the implicit-explicit model of language acquisition during development and provide evidence for hemispheric specialization in this process.

## DEVELOPMENTAL GENDER DIFFERENCES IN SELECTIVE ATTENTION: AN ERP STUDY

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*Objectives:* The aim of the present study was to explore the neurophysiological grounds of the developmental gender differences during auditory selective attention by analyzing event-related potentials (ERPs). *Methods:* Fifty-five boys and 55 girls aged 9-16 years, pairwise matched for age, were studied in a selective attention task, in which target (2000 Hz) and non-target (1000 Hz) tones appeared with equal probability in the right and in the left ear in two conditions (attend right and attend left). Targets required motor responding only when appearing on the attended side. Auditory ERPs to four stimulus types (target-attended, non-target-attended, target-unattended, non-target-unattended) were recorded at bipolar and midline frontal, central and parietal electrodes and analyzed for main and interactive gender effects. Reaction times also were measured. *Results:* Response speed was not affected by gender. Independently of stimulus processing conditions and age, the latencies of early (N1, P2, N2) ERP components were shorter in girls than boys indicating overall faster neurophysiologic processes during early auditory selection. Notably, girls manifested larger peak-to-peak amplitudes of N1-P2 component over the left parietal hemisphere for unattended stimuli, pointing to gender-dependent differences during early auditory selection, as well as larger N2-P3 amplitudes over parietal regions for attended stimuli, indicating gender differences in late selective attention mechanisms. *Conclusions:* Both early and late neurophysiological mechanisms of auditory selective attention depend on gender in 9-16 year-old children by being overall faster and more intensive for the unattended channel during early auditory selection, and more intensive for the attended channel during late selective attention in girls as compared to boys.

# APPROPRIATE SEMANTIC PRIMING COULD IMPROVE ADAPTATION OF VISUAL SACCADES IN SENIORS

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The human sensorimotor adaptation to visual distortions consists of two components: sensorimotor recalibration and workaround strategies. Sensorimotor adaptation reduction that was found in old age was suggested to occur mainly due to cognitive decline (Bock & Girgenrath, 2006). However, literature showed that different semantic primings had positive effect on sensorimotor reactions, e.g. locomotion, handwriting etc. even in old age.

Therefore, we aimed at examining whether two types of semantic priming, which positive effect on arm movement adaptation was found, would had similar effect on adaptation of reactive visual saccades in older persons. Half of the examined seniors were manipulated by priming with age stereotype (positive/negative) to old age while the rest half were primed for spatial selective attention (wide/narrow). They were divided equally into five groups with respect to the applied priming: 1) positive age stereotype; 2) negative age stereotype; 3) wide attention focus; narrow attention focus; 5) controls (without priming).

Priming was performed by scrambled sentence task (Bargh, Chen, & Burrows, 1996) just before saccade adaptation. The participants, who were naïve to the purpose of the experiment, were instructed to select from 20 sentences consisting of five words, four words and formulate a meaningful sentence as the fifth, non-fitting word, had to be crossed out. One of the four words was priming (e.g., “wisdom” versus “decay” or “large” vs. “small”). Saccade adaptation was performed by modified double-step paradigm of McLaughlin (1967) to adapt saccade direction (Bock et al, 2008).

The outcomes showed magnitude increasing of saccade adaptation benefit after priming with: *positive age stereotype* and; *wide attention focus*. Aftereffects magnitudes did not differed between different primings. It was suggested that: not all semantic primings improved saccade adaptation; appropriate primings influenced only workaround strategies that occurs at cortical level and; cognitive decline in older persons could be increased by appropriate semantic priming.

## ERP CORRELATES OF MEMORY LOAD DURING PRO-ACTIVE MODE OF PROCESSING

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The purpose of this study is to investigate the neurophysiological mechanisms by which the executive control system would optimize human behavior while actively maintaining task-relevant internal models with different complexity. This aim was approached (1) by using audio-motor tasks with structured regularity and different levels of complexity, and (2) by employing the method of the event-related brain potentials (ERP). A total of 16 young adults (mean age 25.6 years, 4 males) performed auditory serial response time tasks (SRTT), in which determined sequences of targets (800 Hz, L) and non-targets (1200 Hz, H) were delivered. The subjects were asked to attentively listen and identify a repeated sequence of tones in an easy (6-item sequence) and in a heavy (10-item sequence) condition. ERPs to target and non-target tones were recorded at frontal, central and parietal electrodes and compared between the easy and heavy SRTTs after explicit sequence comprehension to guarantee a pro-active mode of processing. Results show that the proactive mode of processing in both conditions was associated with a significant amplitude reduction and latency increase of the early ERP components (N1 and P2). Notably, these effects were only observed for non-targets. Also, proactive mode of processing was associated with a significant amplitude enhancement and latency increase of the late cognitive P3 ERP component. In contrast to early ERPs, P3 effects were observed for both non-targets and targets, and

increased as a function of model complexity. It was concluded that maintaining an active internal task representation influences both sensory and cognitive stages of processing: (1) The anticipation of sensory information is minimized for the irrelevant stimuli (non-targets) and re-allocated to support processing of the relevant stimuli (targets); (2) On the other hand, cognitive processing intensifies for each stimulus regardless of its task relevance as function of internal model complexity.

## NEUROPHARMACOLOGY & NEUROTOXICOLOGY SESSION

### INFLUENCE OF THE CHRONIC LOSARTAN TREATMENT ON THE TYPE 2 DIABETES MELLITUS-INDUCED BEHAVIORAL CHANGES IN WISTAR AND SPONTANEOUSLY HYPERTENSIVE RATS

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The Renin-Angiotensin System plays a role both in the development of essential hypertension and in the mechanism of the pathological consequences of diabetes mellitus (DM). Based on literature data, we have formulated the hypothesis that angiotensin AT1 receptors are involved in the behavioral changes provoked by type 2 DM (T2 DM). The aim of the study was to investigate the role of the antihypertensive agent, angiotensin AT1 receptor antagonist losartan on the behavioral changes induced by an experimental T2 DM in normotensive Wistar and spontaneously hypertensive rats (SHRs).

The experimental T2 DM was induced by a combination of long-term high fat diet and a low dose (30 mg/kg) of streptozotocin. We studied the effects of metabolic disorder alone and combined with the antihypertensive drug (given 10 days before and 10 days after the streptozotocin) on the locomotor and exploratory activity (open field test), anxiety (open field test and elevated plus maze test), nociception (paw pressure test) and working memory (novel object recognition test).

T2 DM provoked a decrease in the locomotor activity both in Wistar rats and SHRs, increased the anxiety level and pain threshold, and decreased the working memory in SHRs. Losartan normalized the motor activity, increased the pain threshold and improved the recognition memory in the diabetic rats.

Taken together these data show that T2 DM induced weak but significant changes in some behavioral characteristics and that losartan exerts a protective and beneficial effect on these changes.

Key words: Type 2 diabetes mellitus, SHRs, Losartan, Nociception, Anxiety, Memory

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### AGOMELATINE EXERTS A NEUROPROTECTION AGAINST KAINATE-INDUCED EPILEPTOGENESIS WITHOUT PREVENTING DEVELOPMENT OF STATUS EPILEPTICUS AND SPONTANEOUS SEIZURE ACTIVITY IN WISTAR RATS

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The novel antidepressant agomelatine, which is a mixed MT<sub>1</sub> and MT<sub>2</sub> melatonin receptor agonist and 5HT<sub>2C</sub> serotonin receptor antagonist was shown to possess an anticonvulsant and neuroprotective action. Our preliminary data suggests that it may have potential to contribute against epileptogenesis and epilepsy-induced neuronal loss. In order to ascertain whether protection of some brain structures could suppress epileptogenesis,

in the present study, we evaluated the effect of repetitive injection with agomelatine during kainate (KA)-induced status epilepticus (SE) on epileptogenesis and neuronal damage in Wistar rats. Latency for onset of spontaneous motor seizures (SMS) and their frequency was detected by a 24-h video-recording and EEG registration. Our results revealed that this melatonin analogue is unable to prevent development of KA-induced SE and concomitant epileptogenesis. However, agomelatine induced a neuroprotection in the dorsal hippocampus, specifically in the CA1, septal CA2 and partially in the CA3c region, the hilus of the dentate gyrus, piriform cortex and septo-temporal and temporal basolateral amygdala. Our findings suggest that the beneficial impact against SE-induced neuronal loss exerted by agomelatine is not crucial for the suppression of epileptogenesis and its deleterious consequences in KA model of temporal lobe epilepsy.

Key words: Agomelatine, Kainate, Epileptogenesis, Neuronal loss; Wistar rats.

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## **OXIDATIVE STRESS PARAMETERS IN MDBK CELLS, INFECTED BY *HERPES SIMPLEX VIRUS-1***

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Increased risk of viral infections is observed during neurodegeneration. On the one hand viral infections can cause increased generation of reactive oxygen species and thus changes in the redox-state of host cells. On the other hand it has been suggested that oxidative stress is one of the mechanisms of neurodegenerative diseases development. Whether the redox imbalance is the cause or effect of increased propensity of brain cells to infection remains unclear. The present study aimed to evaluate changes in the oxidative status of host cells after virus infection. In this research the MDBK cells are used, since they are a simple and adequate in vitro model of herpes virus type 1 (HSV-1) infection.

The goal of this study was to determine the changes in oxidative status of MDBK cells infected by HSV-1. HSV-1 was replicated in monolayer MDBK cells for 48 h. After sonication of both control and infected cell suspensions the oxidative stress markers lipid peroxidation (LP) level, total glutathione (tGSH) concentration and the activities of glutathione peroxidase and catalase were evaluated spectrophotometrically. Our results showed a significant increase (more than 3 times) of LP and decreased level of tGSH by 24%, in cells infected by HSV-1 compared to the control cells. As a result of viral invasion it was found a threefold increase of the antioxidant enzymes' activities.

HSV-1 provokes marked imbalance redox parameters in host cells. These findings would be useful for developing of new therapeutic strategies to target redox/inflammatory markers in brain inflammation and neurodegenerative disorders.

## EVALUATION OF THE ANTIOXIDANT POTENTIAL OF LYOPHILIZED EXTRACT OF *CLINOPODIUM VULGARE* (LAMIACEAE) IN THE BRAIN OF SPONTANEOUSLY HYPERTENSIVE RATS (SHRs)

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The aim of this study was to evaluate the antioxidant potential of lyophilized extract from *Clinopodium vulgare* (LECV) in the brain of spontaneously hypertensive rats (SHR). Hypertension is a socially significant disorder and oxidative stress is regarded as one of the main pathophysiological mechanisms. LECV was administered at a dose of 100 mg/kg bw (1/20 LD<sub>50</sub>) for 14 days. The activity of acetylcholine esterase (AChE) and the following antioxidant enzymes: superoxide dismutase (SOD), catalase (CAT), glutathione-peroxidase (GPx), as well as the biomarkers of oxidative stress malondialdehyde (MDA) and reduced glutathione (GSH) have been measured in the brain of SHR. In comparison to normotensive Wistar rats, in control, non-treated SHRs the GSH level and the activity of GPx and AChE were lower, while the activity of CAT and SOD, as well as the level of MDA were higher in the brain. Compared to the control SHRs, LECV exerted antioxidant activity, discerned by statistically significant increased activities of all measured antioxidant enzymes and decreased production of MDA. The AChE activity remained unchanged. The observed effects on tissue level were consistent with the histopathological observations of the brain.

Based on the results of our study we could conclude that the lyophilized extract of *Clinopodium vulgare* showed antioxidant potential in the brain of spontaneously hypertensive rats – a model of essential hypertension in humans.

## NEUROTOXICITY OF SOME HEAVY METALS - LEAD, MERCURY, MANGANESE

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A lot of heavy metals have a toxic effect on the central (CNS) and peripheral nervous system (PNS). Contamination of various ecological systems with heavy metals, especially food products, is a prerequisite for their entry into the body and damage to the nervous system. Heavy metals are toxic for humans over the doses of the acceptable concentrations.

It has been found that heavy metals, such as lead, mercury and manganese, pass through the hematoencephalic barrier easily and that defines their effects on the CNS and the PNS. The most common disorders they cause in the CNS are various brain damages, reduced neurophysiological functions and brain tumors. Data suggest that changes in PNS due to elevated concentrations of heavy metals in the blood are: abnormal movements and reflexes, peripheral neuropathies, polyneuritis.

According to a large number of authors, the easy passage of lead through the haematocephalic barrier is mainly due to its ability to replace calcium ions. Lead leads to damage to the prefrontal cortex, hippocampus and cerebellum, resulting in various neurological disorders.

Mercury also disturbs the normal development processes in human brain seriously. It has a high binding affinity to the element selenium found in proteins that protect cells from damage by free radicals. By associating with selenium, mercury blocks this chain of defense processes, which explains why it is neurotoxic even at low doses.

It has been proven that the brain is extremely sensitive to excess manganese and this leads to the neurodegenerative diseases, one of which is known as manganism. An important characteristic of the disease are parkinson-like symptoms. It is considered that the common between the two diseases is that manganese is mostly accumulated in the basal ganglia and this is the etiology of both diseases.

The examined heavy metals disrupt the structures and functions of the CNS and the PNS through different mechanisms which is a result from their neurotoxicity.

## **JANUS KINASE INHIBITORS AND BONE REMODELING**

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Rheumatoid arthritis (RA) is characterized by the infiltration and proliferation of various inflammatory cells in the synovial tissue, forming pannus tissue, which invades and next destroys adjacent cartilage and bone. A number of cellular and molecular responses are involved in the pathogenesis of RA. JAK kinases are intimately involved in signal transduction by various cytokine receptors and, considering the role of cytokines in rheumatoid arthritis their inhibition is expected to dampen the overall inflammatory process. Possessing enzymatic activity, tyrosine kinases are relatively easy to target by small molecule inhibitors that usually inhibit the kinase by competing for ATP in the ATP-binding site. Most of the tyrosine kinase inhibitors are of limited specificity towards their target molecule and rather inhibit a broader range of tyrosine kinases. During the multi-step pathogenesis of RA, kinases participate in initiation, inflammation, and bone resorption, including Janus kinase 1/3 (JAK1/3) in T cells and, in B cells. Thus, RA has been a disease of interest for tyrosine kinase modulation, with small molecule JAK inhibitors, leading to the clinical treatment of patients with RA. Jak2 inhibitor AG490 and a selective Jak1/2 inhibitor baricitinib are currently in clinical use. They negatively influence osteoclast differentiation and formation being capable to prevent bone resorption. Therefore, the inhibition of tyrosine kinases could be the next step in the treatment of patients with RA. In this short review are summarized data on Jak inhibitors in regard to bone remodeling processes.

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## **POSTER SESSION**

### **EFFECTS OF ANGIOTENSIN II AND LOSARTAN INFUSED INTO AMYGDALA ON LEARNING AND MEMORY IN RATS WITH A MODEL OF DEPRESSION**

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Angiotensin II (Ang II) is the most important angiotensin peptide, which binds selectively AT1 and AT2 receptors. Major depressive disorder is one of the world's major causes of disability. Bilateral olfactory bulbectomy (OBX) is a widely used animal model of depression. The effects of Ang II (0.5 µg) and losartan (100 µg), specific antagonist of Ang II type I (AT1) receptors, infused uni- or bilaterally into the central nucleus of the amygdala (CeA) on learning and memory (step through) in the depressive state induced by OBX in rats were studied. In non-OBX group, it was found that Ang II microinjected bilaterally or into the left CeA impaired the memory as compared to the saline-treated controls. Right-side Ang II infusions did not affect learning criteria. Losartan microinjected bilaterally or into the left CeA improved the learning and memory, while right-side losartan administration did not affect it compared to the respective controls. The bilateral or left CeA infusions of Ang II on the developed depression background impaired the memory, while losartan applied

bilateral or left-side improved the memory of OBX rats compared to the respective OBX controls. The memory was improved after inhibition of the AT1 receptors in the left amygdala as compared to the right amygdala. It was found that losartan reverses memory deficits induced by bulbectomy unlike Ang II which deepens it. In conclusion, the data point to a lateralized modulatory effect of losartan infused into the CeA on the memory deficits in OBX rats. The left CeA was predominantly involved in the positive effect of losartan on learning and memory. A possible role of the AT1 receptors is suggested.

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## **MODULATION OF NOCICEPTION BY ANGIOTENSIN II TYPE 1 RECEPTORS ANTAGONIST LOSARTAN INFUSED INTO AMYGDALA OF RATS WITH A MODEL OF DEPRESSION**

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The effects of angiotensin II (Ang II) and losartan (specific antagonist of Ang II type I receptors) infused unilaterally or bilaterally into the central nucleus of the amygdala (CeA) on nociception of male Wistar rats with a model of depression (bilateral olfactory bulbectomy-OBX) were investigated. Nociception was examined by applying mechanical pressure on the paw of the rat (analgesy-meter). The OBX rats were divided into three groups: 1<sup>st</sup> group – bilaterally microinjected into CeA with Ang II (0.5 µg), losartan (100 µg.) or saline; 2<sup>nd</sup> group - unilaterally (left- or right-side) microinjected into CeA with Ang II (0.5 µg), losartan (100 µg.) or saline and 3<sup>rd</sup> group - sham-operated rats. It was found that Ang II microinjected bilaterally and into right-side CeA decreased the pain threshold (nociceptive effect). The inhibition of AT1 receptors by losartan microinjected uni- or bilaterally into CeA of bulbectomized rats, increased pain threshold (antinociceptive effect) compared to the respective OBX controls; the antinociceptive effect was more pronounced in the right-side.

In conclusion, this study for the first time provides information on a lateralized nociceptive effect of Ang II and antinociceptive effect of losartan and involvement of AT1 receptors in nociception of rats with a model of depression. These findings point to the predominant involvement of the right CeA in nociceptive responses of OBX rats, suggesting an asymmetry of the Ang II-connected behavior responses of the left or right CeA and a different distribution of AT1 receptors in the two hemispheres.

*Acknowledgements: This study was supported by CMS Medical University of Sofia, Grant №16/2016.*

## **CHRONIC AGOMELATINE TREATMENT ATTENUATES ANHEDONIA, MEMORY IMPAIRMENT AND BETA-AMYLOID ACCUMULATION IN A RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE**

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The newly developed antidepressant agomelatine, which mechanism of action involve a combined agonism on MT1/MT2 melatonin receptors and antagonism on 5-HT<sub>2C</sub> serotonin receptor, has been considered to have advantages compared to SSRIs as a circadian phase-shifting agent. Our previous studies suggest that this melatonin analogue has a potential role in the protection of the central nervous system. Therefore, we tested the hypothesis that agomelatine can be used as a therapeutic agent for reducing the severity of Alzheimer's disease (AD), a progressive neurodegenerative disease characterized by behavioral deficit and memory dysfunction. In the present study, we demonstrated that chronic agomelatine intraperitoneal administration, at a dose of 40 mg.kg<sup>-1</sup>, starting three months following the induction of AD, by intracerebroventricular injection of streptozotocin (STZ) corrected anhedonia in sucrose preference test and decreased working memory errors

during the last two sessions in radial arm maze. Correction of behavioral deficit exerted by agomelatine correlated with its efficacy to attenuate the amyloid beta (A $\beta$ ) burden in the hippocampus of STZ-treated rats. Taken together, our findings suggest that agomelatine administration could alleviate the burden of AD and may be considered a promising pharmaceutical treatment of the disease.

Key words: Agomelatine; Alzheimer's disease; Memory; amyloid beta; Wistar rats.

Acknowledgement: This research was supported by the Medical University – Pleven (grant No. 17/2016).

## **AGOMELATINE TREATMENT CORRECTS DEPRESSIVE-LIKE BEHAVIOR INDUCED BY CHRONIC CONSTANT LIGHT EXPOSURE THROUGH MODULATION OF CIRCADIAN RHYTHM OF MELATONINE RELEASE**

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**Abstract.** Exposure to chronic constant light (CCL) affects diurnal rhythms and provokes depression in experimental animals. The aim of the present study was to explore the effect of continuous treatment with the clinically used antidepressant agomelatine, a potent melatonin MT<sub>1</sub> and MT<sub>2</sub> receptor agonist and serotonin 5HT<sub>2C</sub> receptor antagonist, on depressive symptoms induced by CCL and diurnal rhythm of plasma corticosterone concentration. Male Wistar rats exposed to CCL for three weeks showed symptoms typical for depressive behavior with decreased grooming in splash test, anhedonia in sucrose preference test and despair-like behavior in forced swimming test during the subjective dark period of day/light regimen. This behavioral deficit correlated with loss of circadian patterns of corticosterone and melatonin in plasma. Chronic agomelatine treatment, injected at a dose of 40 mg/kg for three weeks, prevented depressive behavior and restored disrupted rhythm of melatonin but not in corticosterone release. Taken together, CCL caused a depressive-like behavior accompanied by a disrupted rhythm of corticosterone and melatonin level in plasma in Wistar rats. Agomelatine exerted a beneficial chronotropic effect on depression induced by CCL through correction of diurnal rhythm of melatonin in plasma.

Key words: Chronic constant light; Agomelatine; Depression; Corticosterone; Wistar rats.

Acknowledgement: This research was supported by the National Science Fund, Bulgaria (grant No. DH 03/10/2016).

## **THE RELATIONSHIP BETWEEN VITAMIN D AND THE RENIN-ANGIOTENSIN SYSTEM**

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In the following study we have tried to show the main functions of vitamin D and the renin-angiotensin-aldosterone system. Vitamin D is both a hormone and a fat soluble vitamin. Vitamin D, both the orally taken and endogenously synthesised in the skin, undergoes a complex, multistage metabolism.

First of all Vitamin D plays a major role in the regulation of the calcium-phosphorus turnover and the bone metabolism. This function is realised by an intranuclear receptor. Secondly a membrane receptor has been reported to be responsible for the nongenomic effects of vitamin D. What is more, the pleiotropic effects of vitamin D are closely associated with the immune system, carbohydrate metabolism, cardiovascular system and obesity. Mounting evidence from clinical studies has demonstrated an inverse relationship between circulating vitamin D levels and blood pressure and / or plasma renin activity, but the mechanism is not understood.

The renin-angiotensin-aldosterone system (RAAS) is a hormone system that is involved in the regulation of the plasma sodium concentration and arterial blood pressure. RAAS plays a pivotal role in renal progression and its complications. If the RAAS is abnormally active, blood pressure will be too high.

Key words: Vitamin D, regulation, membrane receptor, pleiotropic effects, RAAS;



## **IN VITRO MOTOR ACTIVITY OF LONGITUDINAL AND CIRCULAR MUSCLES IN NORMAL RAT DISTAL COLON AND DNBS-INDUCED COLITIS**

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Inflammatory bowel disorders are associated with structural and functional changes in the enteric nervous system and muscle cells. Abnormal intestinal motility is a common feature of colon inflammation. The aim of the study was to evaluate spontaneous activity of longitudinal (LM) and circular (CM) muscles in colonic preparations from rats with experimental colitis.

**Material and methods.** Colitis was induced in Wistar rats by intrarectal administration of 30 mg 2,4-dinitrobenzenesulfonic acid hydrate (DNBS) in 0.25 ml of 50% ethanol. On day 6 we evaluated SMA in colonic segment of controls and DNBS-treated rats in the presence of atropine, L-arginin and N-nitro-Larginine (L-NNA), using partitioned organ bath.

**Results.** Spontaneous activity of LM and CM in proximal and distal part of preparations were characterized by irregular high-amplitude contractions with a frequency of 8-10/10 min and contractions of LM were more expressed compared to CM. Frequency of contractions of LM and CM in preparations with ulcerations (macroscopic score 4-5) were 6-7/10 min and their amplitudes in affected distal part of preparation were significantly lower (controls: LM 9.9±1.8 mN and CM 5.5±1.5 mN; DNBS-treated rats: LM 6.5±0.8 mN and CM 3.82±0.3 mN; p<0.05). Atropine decreased control SMA of LM and CM in proximal and distal part with more than 50%, while in affected distal part high-amplitude contractions were inhibited about 30%. In the presence of L-NNA, SMA of LM and CM in preparations from DNBS-treated rats displayed significantly greater enhancement compared to controls.

**Conclusion.** A reduction of frequency and amplitudes of spontaneous high-amplitude contractions of LM and CM in colonic preparations during DNBS-induced colitis can be attributed to an alteration of excitatory cholinergic control.

## **NEW METHODS FOR THERAPY OF CARADIOGENIC SHOCK**

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Cardiogenic shock is categorised by heart failure (HF) due to weakened pumping; it is severely developing resulting in a fatal reduction in cardiac minute volume and hypoperfusion of important vital organs. Cardiogenic shock is the most severe form of impaired pumping function of the heart. There are a number of symptoms suggestive of the development of cardiogenic shock. In acute myocardial infarction and in advanced phases of chronic heart disease, cardiogenic shock has a very poor prognosis: with fatal outcome, observed in 85 to 100% of cases. Cardiogenic shock involves neurohormonal mechanisms to maintain tissue perfusion. Activation of the sympathetic nervous system leads to tachycardia, systemic vasoconstriction and increased myocardial contractility, which manifests as a healthy myocardial hyperkinesia. Science is continually exploring for new methods directed towards cardiogenic shock therapy. The aim of our study is to review the trends of modern therapy and to systematize the effects of the representatives of different groups of drugs. As an inotropic agent, dobutamine may be co-administered with norepinephrine in an attempt to improve cardiac contractility, this is often performed in clinical practice. Other isotopes such as levosimendan or phosphodiesterase inhibitors are of interest in cardiogenic shock therapy as they improve myocardial contractility without increasing oxygen requirements and vasodilatation potential. As a result of long-term administration, phosphodiesterase inhibitors have a proven safety profile: they do not increase the incidence of adverse cardiovascular events even in patients with coronary artery disease (IBS) or HF, and can be safely combined with most other classes of

medication (contraindicated only with nitrates and should be used with caution when taking alpha-blockers). Levosimendan increases the efficacy of beta-adrenoreceptor agonists by 0.5 log units in weakened human myocardium, but not in the presence of cilostamid. Any inotropic response to levosimendan is associated with a lusitropic response. According to studies of the British Pharmacopoeia, the PDE3-inhibiting property of levosimendan is sufficient to account for its inotropic effect, leaving little effect, if any, on the calcium-sensitizing component.

Keywords: cardiogenic shock, treatment, levosimendan, phosphodiesterase inhibitors

## THE SPACE METHOD FOR TUMOUR TREATMENT

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Cancer, one of the most hated words nowadays. An illness that makes millions people suffer. A curse that can change lives. Cure, a word filled with hopes and smiles. But is there a real cure for the plague of 21<sup>st</sup> century. In our study we have turned our heads up and tried to summarize the basic human knowledge about curing cancer with the help of microgravity.

Up in the sky a large group of scientists are working hard to develop better methods of using microencapsulation technology in order to enable injection/transplantation into damaged tissues as well as enhancement of human tissue repair.

What is more, in the following study we have tried to show some of the benefits of microencapsulation including direct tumour targeting as well as reducing all the negative effects associated with chemotherapy.

Last but not least the microcapsules that are going to be used contain a contrast agent that enables C-T, X-ray or ultrasound imaging to monitor the distribution within the tissues to ensure that the entire tumour is treated with the drug contents.

In a nutshell our presentation is based on the latest studies about a technology that is still in development. We have tried to show the new step forward in medicine that could improve the quality of life of each person diagnosed with cancer.

Keywords: Space, microgravity, new age, cancer, step forward, microcapsule, microencapsulation, chemotherapy.

## EFFECTS OF NEWLY SYNTHESIZED DERIVATIVES OF CAFFEINE-8-THIOGLYCOLIC ACID ON HUMAN NEUROBLASTOMA CELL LINE SH-SY5Y

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Oxidative stress is implicated in the pathogenesis of many diseases, such as neurodegenerative, cancer and others. The increased production of reactive oxygen species (ROS) lead to damage of number of biomolecules: lipids, proteins, DNA etc.

Caffeine is the most commonly used psychostimulant, which revealed protective effects in conditions of chronic liver and neurodegenerative diseases.

The aim of the study was to evaluate the effects of newly synthesized derivatives of caffeine-8-thioglycolic acid (in concentration 100 µM) on neuroblastoma cell line SH-SY5Y.

SH-SY5Y cells are often used as *in vitro* models of neuronal function and differentiation. They are adrenergic in phenotype but also express dopaminergic markers and as such, have been used to study Parkinson's disease.

On human neuroblastoma cell line SH-SY5Y, administered alone, most of the derivatives didn't show statistically significant neurotoxic effects, compared to the control (non-treated cells).

Only JTA-2Ox, JTA-11, JTA-12 and JTA-13 decreased cell viability, measured by MTT-test. JTA-2Ox decreased cell viability by 41 %, JTA-11 – by 25 %, JTA-12 – by 37 % and JTA-13 – by 39 %, compared to the control.

In conditions of 6-hydroxy dopamine (6-OHDA) (at concentration 100 µM)-induced oxidative stress, only JTA-1 and JTA-2 revealed stronger statistically significant neuroprotective effects on SH-SY5Y cell line. JTA-1 preserved cell viability by 78 % and JTA-2 – by 71 %, compared to 6-OHDA.

## MICROSURGERY MODEL IN SMALL LABORATORY ANIMALS FOR EXPERIMENTAL RESEARCH OF SUBSTANCES WITH NATURAL ORIGIN AND NERVE AGENTS

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**Introduction.** Safety environment in the modern world terrorism is determined to be global threat. In the arsenal of terrorist organization takes place specific weapons. Particular attention needs to be paid to biological and chemical weapons.

**Goal.** The main goal of this study being to elaborate surgical model for small laboratory animals, implemented in preliminary study of biological and chemical compounds with toxic effects and potential antidote treatment.

For the purpose of the current study cannulation of femoral vein in small laboratory animals was performed. This provides prolonged monitoring and toxicological evaluation of the testing compounds.

**Materials and methods.** Experiments were carried out on 20 male small laboratory animals. A surgical method for cannulation of *v. femoralis* was developed. Physiological data of selected parameters (heart rate, respiratory rate, neuromuscular transmission) were digitized and recorded with a S.P.E.L. Advanced Haemosys system (Experimetria Ltd., Hungary).

**Results and conclusion.** In conclusion as a result a protocol for cannulation of *v. femoralis* has been developed for long term monitoring and prolonged experimental study. Accordingly, it is feasible to use intravenous route of administration thus entire administered dose of testing compounds reaches the systemic circulation immediately and could be applied for assessment of toxic effects of poisons from different origin and their antidotal treatment.