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ABSTRACTS

The authors are solely responsible for the scientific content and linguistic presentation of the abstracts.

SOCIAL, EMOTIONAL AND COGNITIVE REPRESENTATIONS OF AUTISM: INTERDISCIPLINARY PERSPECTIVE

THE ROLE OF TESTOSTERONE AND ITS METABOLITES IN AUTISM ETIOLOGY

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The higher prevalence of autism in boys supports the theory that testosterone plays a significant role in its etiology. Increased prenatal testosterone is according to the theory of the hypermale brain in autism (Baron-Cohen, 2005) supposed to affect brain development and consequently cognition and personal characteristics (1).

The objectives of the study were to compare testosterone levels in children with autism and control children and to determine the contribution of genes related to testosterone metabolism. Second-to-four digit length ratio was measured as it was found to be a reliable marker of prenatal testosterone. The lower the ratio the higher prenatal androgenic effect.

82 boys aged 7–12 participated in the study. Their hormonal levels and the results of genetic analyses were compared with 93 boys from general population of the same age. Testosterone levels were found to be higher in autistic children and genetic analysis revealed the increased androgenic effect in our patients.

We have confirmed the prenatal androgenic influence via the measurement of 2D:4D ratio which was found to be lower in autistic patients. Future research should be focused on molecular mechanisms behind non-genomic effects of testosterone and on the behavioral "geno-endocrinology" of autism.

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OXYTOCIN ROLE IN AUTISM

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Deficit in oxytocin signaling might result in impairments of social perception and social interactions. Autism is pervasive developmental disorder characterized by social deficits. Several studies found decreased levels of oxytocin in autistic children. Genes encoding oxytocin receptor (OXTR) and oxytocin have been linked with autism diagnosis.

The aim of the present study was to reveal differences in plasma levels of oxytocin between autistic and healthy population in Slovakia. 108 autism patients were recruited into the study (83 males, 25 females). 131 healthy children were recruited as a control group (106 males, 25 females). Blood samples were obtained and plasma oxytocin levels were measured using ELISA. Children were divided into groups according to age and gender; boys into three groups (under 6 years, prepubertal group – 7–13 years, pubertal group – more than 14 years) and girls into two groups (under and above 12 years).

Oxytocin levels were significantly lower in prepubertal and pubertal boys in comparison to controls ($p<0.05$ in both cases; mean 187.8±44.0 pg/mL (autism) and 320.8±42.5 pg/mL (control); 173.9±63.8 pg/mL (autism) and 309.4±33.9 (control), respectively).

We have found no significant differences in plasma oxytocin levels neither in boys under the age of 6 and nor in girls of both age groups. We have found decreased oxytocin levels in plasma of autism boys which may be related to decrease sociability and social interactions.

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THE EFFECTS OF PROBIOTIC ADMINISTRATION ON GASTROINTESTINAL FUNCTIONS IN CHILDREN WITH AUTISM

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The autism symptoms may be exacerbated or even partially due to the underlying gastrointestinal (GI) problems. Probiotics are live microorganisms with positive effects on GI functions.

Aim of the presented pilot study was to determine the effects of a probiotic supplementation on GI functions in a sample of subjects with autism. The study involved 26 cases and 13 controls aged 3–22 years. Personal history of GI disorders was obtained by a questionnaire. A supplement containing 6 probiotic strains was administered to the cases

The results show a higher frequency and severity of GI problems in subjects with autism when compared to the controls, hard stools and voluminous stools being the most common disorder indicated by 76.9% and 73.1% of subjects, respectively. After the 4-month probiotic administration a decrease in prevalence of GI symptoms was found.

The results indicate that probiotics may be an effective supporting therapy for the individuals with autism. Future research will be focused on effects of probiotic supplementation on markers of the intestinal flora and behaviour.

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COENZYME Q10 STIMULATES BRAIN FUNCTION IN CHILDREN WITH AUTISM

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Autism is a range of complex neurodevelopment disorders with multifactorial reasons which manifests within 3 years after the birth. The metabolic changes may involve antioxidants, oxidative stress and energy production in brain mitochondria. Characteristic manifestations of autism include behaviur problems (hyperactivity, destruction, self-harm, aggression), sleep and eating disorders.

Aim of the study was to develop a new diagnostic test and to examine the effect of supplementary therapy with ubiquinol (reduced CoQ_{10} – QH) on behavior, physiological functions, antioxidant status and lipid peroxidation in children with autism.

Material and methods: Twenty four patients, aged 3–6 years, were included in the study. Antioxidants ($CoQ_{10\text{-}TOTAL}$, γ-tocopherol, α-tocopherol, β-carotene) and lipid peroxidation were estimated. Children with autism were on Li-QH™ supplementary therapy for three months, at a daily dose of 2 x 50 mg QH.

Results: Significant improvement in autistic children was observed, in communication with parents and friends, verbal communication, activity, decreased destruction, self-harm, aggression.

Conclusion: Ubiquinol supplementation was beneficial when concentration of the $CoQ_{10\text{-}TOTAL}$ increased over 2,5 μmol/L. Improvement was in behavior problems, in sleep and eating. Plasma concentration of $CoQ_{10\text{-}TOTAL}$ could by used as metabolic marker of QH supportive therapy.

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REDOX STATUS AND POTENTIAL PROTECTIVE EFFECT OF METHYLCOBALAMIN IN AUTISM

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Oxidative stress has been suggested to be one of the key elements in the pathophysiology of autism. Oxidative stress is produced by the high level of free radicals, which are in physiological conditions under control of multiple antioxidative mechanisms. It has been proposed that the loss of this control participates in the autism pathogenesis. The aim of our project was to examine whether potentiated antioxidative mechanisms would affect the autistic disorder symptoms.

50 patients (3–21 years old) with autistic disorder were enrolled. Exclusion criteria for subject selection were: Asperger syndrome, high-functioning autism, epilepsy, selected pharmacotherapy affecting CNS. Methylcobalamine was given daily at dose 500 μg. Venous blood was collected at d0 and d100 and redox status of glutathione and levels of homocystein and cobalamine were determined. The psychological profile was defined at d0 and d100 by psychologist using scale in combination with parent observations.

Oral application of methylcobalamine at the dose 500 μg per day influences glutathione redox status. Based on combination of parent and psychologist observations, language and social skills were affected in patients using methylcobalamine. Social interaction was increased, including social responsiveness and eye contact.

Oral application of methylcobalamine in patients with autism seems to potentiate antioxidative mechanisms and leads to the changes in the psychological profile of the patients.

NEUROPSYCHOLOGY

PHYSIOLOGICAL CORRELATES OF NON-VERBAL IQ IN INTELLECTUALLY GIFTED GIRLS

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The nature–nurture debate assumes a center role in the arguments surrounding the origins of giftedness. Balanced perspective acknowledges that giftedness is likely a manifestation of a relationship between genes and environment. Testosterone can be assumed to be one of the possible etiological factors of intellectual giftedness affecting the brain organization and function.

The aim of our study was to analyze associations between prenatal or actual testosterone levels and non-verbal IQ in intellectually gifted girls. Fifty one gifted girls aged 10–18 years with IQ>130 were enrolled. Saliva samples were collected and used for ELISA of actual levels of salivary testosterone. The 2D/4D finger length ratio as an indicator of prenatal testosterone was measured on both hands and averaged. IQ parameters were assessed by a professional psychologist using standardized set of tests. The CAG repeat polymorphism in exon 1 of the androgen receptor gene was analyzed using PCR and capillary electrophoresis.

Multivariate analysis of covariance proved the effect of 2D/4D ($F=5.73$, $p<0.0.5$), genetic variability in androgen receptor ($F=4.39$, $p<0.0.5$) and also actual testosterone level

(F=5.47, p<0.0.5) on non-verbal IQ in gifted girls. Future studies should focus on other genetic determinants of non-verbal IQ, potentially on genes involved in testosterone metabolism.

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VERBAL-MANUAL DUAL TASKS INTERFERENCE IN TWO NEURODEVELOPMENTAL DISORDERS

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The dual-task paradigm is used as a means of investigating attentional allocation and hemispheric cognitive processing (1, 2). In the present study the dual-task paradigm was employed to examine lateralization of interference between reading and finger tapping in two neurodevelopmental disorders that differ in patterns of overall intellectual ability and of language abilities impairments.

The studied samples were composed of twenty-three right-handed individuals with developmental dyslexia, and seven right-handed persons with Williams-Beuren syndrome. Right-handed individuals from the non-clinical population participated as control subjects. Verbal-manual dual tasks were individually administered to all participants in four interference conditions: two oral reading tasks (composed of real words and pseudowords) during unimanual finger tapping with right hand and with left hand. Single tasks finger tapping with right hand and left hand were used as control baseline conditions.

In the group with developmental dyslexia the results showed that both reading tasks interfered to a greater degree with right-hand tapping than with left-hand tapping. Reading of pseudowords disrupted the finger tapping more than the reading of real words. The interference patterns did not differ significantly from those of the controls. In the group with Williams-Beuren syndrome, similar patterns of asymmetry of interference were observed but the amount of interference tended to be greater in comparison with the control group, namely in right-hand tapping during the reading of real words.

The findings suggest that verbal-manual interference reflected the predominance of left-hemisphere processing of reading, as well as differences in processing resources as a function of the reading task characteristics and of executive capacities.

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PROMOTING POSITIVE PSYCHOLOGICAL FUNCTIONING: COMPARISON AMONG THREE GROUP TRAININGS

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Positive Psychology suggest a positive approach to mental health based on strengths and resources of individuals and, in according with the Keys's Model of mental health, curing or eradicating mental illness will not guarantee a mentally healthy population (Keys, 2007). Different ways to promote positive functioning worked out in the last decades (Goldwurm, Colombo, 2010).

Aim of our research is to compares three different group trainings to promote positive psychological functioning and well-being in people from the general population. The group interventions are: a) Subjective Well-being Training, b) Self-esteem training, c) Stress management.

About eighty adults followed the different courses in according with their preferences. The evaluation included six self-report questionnaires repeated at the beginning and at the end of the respective training: a) the Rosenberg Self-Esteem Scale, b) the Cognitive Behavioral Assessment (CBA-VE), c) the Satisfaction With Life Scale by Diener, d) The Psychap Inventory by Fordyce, e) The Happiness Measures by Fordyce, f) the Psychological Well-being Scales by Ryff.

Participants from every group trainings significantly increased their well-being level as measures by self-report questionnaires. Differences were found among different conditions and variables.

This study provides evidence that group trainings to promote positive psychological functioning might increase well-being in subjects from the general population

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MEMORY MECHANISMS AND EMOTIONAL EVENTS

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Anxiety disorders belong to the most prevalent mental disorders and cause severe suffering to affected subjects. Unfortunately, pathophysiology of anxiety is still little understood. Biased cognition is considered to play a central role in the development of anxiety. We investigated the mechanisms of long-term memory to negative thread-arousing stimuli in subjects with high or low trait anxiety.

In our experiment, subjects were presented horror and emotionally neutral film clips and were asked to recollect these movies one week later. During both sessions, electro-

dermal activity (EDA) and electroencephalogram (EEG) were measured. Compared to individuals with low anxiety, subjects in the high anxiety group used higher number of emotionally valenced words for describing the memories of the horror movie.

There was no difference between groups in the number of emotional words used to report the memory of the neutral movie (1). No group difference was found in the total number of memories for either of the movies. In the low compared to high anxiety group, we found stronger positive association between EDA during horror watching and subjective ratings of emotional intensity of the memories to the horror film. During both watching and recalling the horror movie, the markers of physiological arousal, EDA and hemispheric asymmetry of EEG power in the alpha band over parieto-temporal scalp region, were lower in the high anxiety group compared to the low anxiety group.

The findings indicate that relationship between bodily arousal and emotional memories is disrupted in anxious subjects.

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EXPERIMENTAL PSYCHOPHYSIOLOGY

EEG INVESTIGATION OF ATTENTION AND DECISION MAKING COGNITIVE FUNCTIONS BY "DOUBLE STEP" EXPERIMENTAL SCHEME

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In 17 healthy subjects we studied the latencies of saccades to the two short (50 or 150ms) successive visual stimuli and EEG potentials related to the first visual stimulus switched on or its expectation. Stimuli were presented at the opposite semifield (pulse – overshoot scheme).

An increase of saccade latency and the number of single saccades to the short (50ms) second stimulus was shown (p<0.0001). This fact may reflect inhibitory influence of automatic attention shift from the first stimulus to the second one that makes difficult the early stage of saccade programming.

Comparison of timing and topography of positive components of ERP potentials depending on the first stimulus duration and "pattern" of saccade responses permits us to suppose that positive potential *P100* may be *EEG* correlates of decision making in the case of two saccades response.

Analysis of slow negative waves in the expectation period revealed that expectation and motor readiness influence on the pattern of saccade response. Parameters and topography of ERP potentials reflect activation of top-down mechanism of fronto – media-thalamo-parietal systems of attention that may influence on the selection of saccadic goal and decision making. The pattern of saccade responses in double step scheme may be defined by direction of covert attention in the period of expectation.

The study was supported by the RFBR (the projects 11-06-00306, 12-04-00719)

SACCADE LP AT THE PRESENTATION OF TARGET AND DISTRACTING STIMULI TO THE DOMINANT AND SUBDOMINANT EYE

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The stimulus choice as a saccadic target for the directed movement includes inhibition of other possible answers, insignificant in a situation of current behavior.

The aim of this study was to estimate dependence of saccadic latency during stimulation of the dominant and subdominant eye in various conditions of presentation of target and distracting stimuli. 13 healthy subjects participated in the experiment.

In 70% of cases under identical conditions of stimulation saccade latency was shorter at the presentation of stimuli to the dominant eye (p<0.05). Saccade latency of correctly executed saccades increased when the distance between target and distracting stimuli reduced and reached a maximum (near 242 ms) when stimuli were shown in different visual hemifields. Minimum of saccade latency was near 208 ms, when stimuli were presented in one visual hemifield at the distance 5 degrees each from other. But the quantity of errors in this case increased to 60 % when the subjects can't inhibit saccades on distracting stimulus.

The results specify that saccadic latency depends first of all on the brain hemisphere where primary visual information on stimulus comes. The leading role of the right hemisphere responsible for spatial attention in a situation of a visual choice is supposed.

The work is executed at support of the RFBR (the projects № 11-06-00306 and № 12-04-00719)

POLYPHENOLS CAN AFFECT THE CARDIOVASCULAR FUNCTIONS VIA THE NON VEGETATIVE BUT HIGHER BRAIN REGULATORY MECHANISMS ALSO

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The beneficial effects of natural polyphenols (PPs) upon hypertension are explained by complex biochemical, pharmacological and physiological interventions with complex cardiovascular (CV) regulatory mechanisms (1). As neural CV regulatory mechanisms the sympathetic and parasym-

pathetic are taken into account. The effects of higher brain functions upon CV regulatory mechanisms are usually thought over as psychosomatic component of certain CV problems. The question remains whether the higher brain regulatory mechanisms could be affected by PPs also (2, 3).

The red wine PPs were administered to healthy undergraduate volunteers (4 mg/kg of body weight). The blood pressure, EEG and accuracy of eye movements in the visual and memory space tasks were registered before and 2 hours after drug administration. The accuracy of eye movements as well as the EEG power spectra were analyzed.

The performance of subjects in experimental tasks was significantly better (higher accuracy of eye movements, less number of corrections, diminished extent of inaccuracy) after polyphenols administration. The EEG alpha spectra pointed to changed level of overall CNS activation. As expected, the single dose of polyphenols did not affect the blood pressure.

The PPs increased the overall CNS activation as well as positively affected the cognitive function. The question remains whether is this a specific effect or rather general effect upon the integrative brain functions (e.g. attention). The results clearly suggest that the effects of natural PPs upon CV functions may be complex and include the higher brain regulatory mechanisms as well.

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CORAZOLE-INDUCED CHANGES IN SEIZURE PRONENESS AND POSTICTAL MUSCLE TONUS IN TWO STRAINS CONTRASTING IN AUDIOGENIC EPILEPSY

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The effects of chemoconvulsant corazole i.p injections on seizure proneness and postictal muscle tonus in rats of two genotypes were analyzed. KM rat strain displays the most intensive audiogenic seizures (AS). Rats of strain "0", selected for the absence of AS (descendants of KM × non-prone Wistars hybrids), were used as the controls.

The sub convulsive drug dose (40 mg/kg) induced typical corazole seizures in 87.5% KM strain rats, although the postictal catalepsy occurred in 28.6% of cases only. In others the fit ended by motor exitation, myoclonic jerks, and posture collapse.

The corazole dosage used did not induce seizures in strain "0" rats, although, being exposed to loud sound after the injection they developed the typical AS in 50% of cases, the attack starting as a typical "wild run" stage. The postictal catalepsy had been expressed in "0" strain rats.

Thus, the pattern of seizure fit and postictal state were directly determined by the stimulant "trigger". In AS prone KM rats the seizures developed in response to sub convulsive drug dose, these data confirm the deficit of GABA-ergic system in KM rats. Although in "0" rat strain corazole made these animals susceptible to AS only, it means that in non-AS prone "0" strain rats the brain system responsible for AS fit development stayed active although has the increased threshold.

The work was partly supported by RFBR (grant N 12-04-00360-a)

INFLUENCE OF VISUAL INPUT DURING STANCE WITH INCREASED POSTURAL THREAT

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In the study we examined influence of visual stimulation during stance on support surface heights above ground level, which means a stance with higher postural threat. Also stance on tilted support surface with eyes open and closed was analyzed.

In the first part 12 young subjects stood quietly on a force plate at level 40 cm or 200 cm above ground level. Each standing trial was performed with visual stimulation consisted of a rotating disc with a diameter of 125 cm. The scene rotated to left (LOW threat) or to the right side (HIGH threat) with an angular velocity of 60 deg/s and duration 20 s. In second part subjects stood on support surface with 20 degree slope angle which was placed on force platform. Dual-axis accelerometers were placed on the lumbar (L5), the thoracic (Th4) vertebra for measurements of trunk tilts (1). Subjects were asked to lean as far as they could using ankle strategy.

The results demonstrated that postural response to visual stimulation measured by centre of pressure (COP) displacement decreased as postural threat increased from LOW to HIGH. The central nervous system progressively tightened control of posture as postural threat increased. Also during stance on inclined support surface maximal amplitude of body tilt decreased as postural threat increased.

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THE PSYCHO-ACOUSTIC TRANSITIONAL (PAT) APPROACH CAN REDUCE COGNITIVE-EMOTIONAL DISTRESS ASSOCIATED WITH TINNITUS

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Recent f-MRI findings showed that the "default network" is altered in subjects experiencing chronic tinnitus. The Psycho-Acoustic Transitional (PAT) approach is hypothesized

to increase neural communication inducing a general cortical synchronization that seems to be involved in restoring the correct "default network" when brain is at rest.

Ten subjects with chronic tinnitus accepted voluntarily to participate in an experimental trial consisting of 24 consecutive PAT sessions twice a week. Each PAT session is structured in 20 minutes of listening to the standard PAT micro-synchronized sound stimulus, followed by 30 minutes of clinical interview with an expert therapist. At beginning as at end of each session, subjects were administered with the State-trait Anxiety Inventory (Stai-Y). The Cognitive-Behavioural Assessment (CBA) scale was administered at beginning as at end of the whole trial. Spontaneous descriptions of tinnitus evolution were also considered.

At about the 6–8th sessions, 9 out of 10 subjects described an "objective" amplitude modulation of the tinnitus, that is a reduction of the level and/or a modification of the frequency. A trend of long term amplitude modulation, with a monthly peak lasting for 1–3 days, also emerged.The perceived distress remarkably decreased within the first 6 sessions for 8 subjects, as suggested also from Stai-Y scores. After the end of the trial, 7 out of 10 subjects referred that the distress related to tinnitus was remarkably decreased, together with the improving of CBA results for six of them. The tinnitus was often described as "moved" to the background of the perception field. In some cases, tinnitus was completely disappearing for hours.

These results could sustain the hypothesis that PAT approach can restore the neural network related to the default state of brain at rest. In particular, this effect can reduce or fix distress and emotional networks in chronic tinnitus experiences.

ELECTROPHYSIOLOGY OF HIGHER BRAIN FUNCTIONS

SYNCHRONIZED ACTIVATION OF FRONTAL AND TEMPORAL REGIONS DURING TARGET VARIANT OF VISUAL ODDBALL TASK

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Remote brain regions within cognitive networks are known to cooperate during sensorimotor coupling, i.e. during cognitive operations associated with the processing of a sensory signal up to the processes linked to a given motor action. Considering that such a sensorimotor coupling takes place in the target variant of the visual oddball task, the question arose, whether also in this cognitive task a synchronized activation of remote brain areas can be found.

In present study we searched for synchronization in activity of frontal and temporal regions. Electrical activity from frontal (145) and temporal (184) cortical sites of 8 epileptic patients was recorded during a visual oddball task by means of depth electrodes. For each subject we averaged 1800 ms long EEG periods free of epileptic activity.

Sections of highly correlated activity were detected either in the early or middle phase or even in the whole length of the evaluated record in frontal/temporal structures of 6 patients: (1) left medial frontal, right middle frontal, right rectal frontal gyri / left superior temporal gyrus, (2) left orbital gyrus/ left medial temporal gyrus, (3) right rectal gyrus/ right medial temporal gyrus, (4) right middle frontal gyrus / right hippocampus; right anterior cingulate gyrus/ right fusiform gyrus, (5) right anterior cingulate gyrus / right hippocampus, (6) right anterior cingulate gyrus / left parahippocampal gyrus.

These results imply that frontal and temporal regions could be engaged in the cognitive task studied in a synchronized manner.

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FRONTAL AND PARIETAL EARLY PRE-MOVEMENT ACTIVATION DURING SELF-PACED HAND MOVEMENT

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The system controlling volitional actions is thought to consist of functionally distinct frontal and parietal parts. The possibility to dissociate early and late Bereitschafts potential (BP) components allowed us to ask whether the early pre-movement activations in these locations are simultaneous or sequential.

The early BP components recorded by depth electrodes in six epilepsy surgery candidates (2 men, 4 women; aged from 18 to 39 years) during self-paced clenching movements of the hand opposite to the explored hemisphere were analyzed in the study.

In each individual the early BP responses from frontal and parietal electrodes had identical latency, were of relatively short duration and were recorded from neighboring contacts of one electrode with almost identical configuration and latency. The mean amplitude of the record calculated before and after the early BP was significantly different in all cases ($p<0.001$, t-test). The calculation of phase synchrony of records by running correlation technique showed the highest r-values shortly before or before and during the period of early BP components.

In conclusion, the data demonstrated the simultaneous activation and increased functional linkage of frontal and parietal loci during the early pre-movement period of the voluntary movement.

VARIABILITY OF HIPPOCAMPAL COGNITIVE POTENTIAL RECORDED DURING A SIMPLE SENSORI-MOTOR TASK (INTRACEREBRAL STUDY).

R. Roman, J. Chládek, M. Brázdil, I. Rektor, M. Kukleta

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CONTRIBUTION OF SHORT-TERM MEMORY RETENTION TO ROTATION-RELATED ERP NEGATIVITY

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Rotation of a visual image in mind is associated with a late posterior negative deflection of the event-related potential (ERP), termed rotation-related negativity (RRN). Retention of a visual image in short-term memory is also associated with a late posterior negative ERP, termed negative slow wave (NSW).

We assessed whether short-term memory retention contributes to the RRN. ERPs were recorded in two tasks performed by the same subjects (N = 24, healthy adults, 19 females, age = 25.8 ± 3.5 years) within one EEG recording session. One task involved mental rotation of characters (90, 135 and 180 deg). The other task was a delayed orientation discrimination (DOD) task, a version of a delayed match to sample task, requiring precise retention of character's visual image in short-term memory (1). In a regression analysis, the NSW recorded during the delay interval in the DOD task was used as predictor of the RRN.

Over both right and left posterior cortices, the effect of the NSW on the modulation of the RRN by rotation angle (the slope of the RRN rotation function) was insignificant. Furthermore, eliminating the variance associated with NSW had no effect on a significant association between the slope of the rotation function for reaction time and slope of the rotation function for RRN.

Our resuls suggest that RRN reflects manipulation but not retention of the visual image in short-term memory.

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NEUROSCIENCES – REGULATORY MECHANISMS

SEX DIFFERENCES IN DELAYED EFFECT OF CROWDING STRESS ON OPEN FIELD BEHAVIOUR OF YOUNG NORMOTENSIVE RATS

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Chronic stress is considered to be a significant risk factor of various behavioural disorders. This study investigated delayed effect of crowding stress on open field behaviour of young male and female Wistar-Kyoto (WKY) rats.

Male and female WKY rats, 5-weeks-old, were divided into two groups: controls (four rats per cage, 200 cm2/rat) and crowding stress-exposed rats (five rats per cage, 70 cm2/rat). After two weeks of crowding rats were returned back to standard cage for additional two weeks. Exploratory behaviour was observed in the open field (100x100 cm with the central zone 55x55 cm, 10 min/session) two weeks after stress exposure and analysed using ANY-maze software.

Exposure to crowding stress did not alter open field behaviour (total and central part distance travelled, average speed, time spent in central zone) 2 weeks post-stress in males but it increased it in females vs. the respective control. All the parameters mentioned above were increased significantly in post-stress females vs. males. Additionally, post-stress females spent less time in the peripheral zone and corners than males.

Crowding stress produced different effect on post-stress motor activity in young females and males. Additionally, post-stress females showed less anxiety than males. These results suggest different sensitivity of young female rats on stress as compared to males.

Study was supported by the grants Nos. APVV-0523-10 and VEGA 2/84/10

QUANTITATIVE TRAIT LOCUS (QTL) ANALYSIS OF THE RAT HXB/BXH RECOMBINANT INBRED STRAINS REVEALS GENETIC DETERMINANTS OF SPATIAL LEARNING AND BEHAVIORAL FLEXIBILITY IN ACTIVE PLACE AVOIDANCE TASK

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The study investigated spatial learning in 30 HXB/BXH recombinant inbred (RI) rat strains derived from SHR/Ola and BN-Lx/Cub strains in the active place avoidance task.

The task involved avoidance of an unmarked sector defined with respect to fixed distal cues on a rotating circu-

lar arena. Four daily acquisition sessions were conducted, followed by a non-reinforced retrieval session and three sessions, in which the shock sector was reversed. This hippocampus-dependent test requires the spatial learning, cognitive coordination and behavioral plasticity. The number of errors, maximum time avoided latency to first entrance into a shock sector served as measures of spatial performance. We also recorded open-field behavior and beam-walking performance in the RI strains to exclude any non-specific effects on learning. A one-way ANOVA showed significant differences between strains. Genetic determinants and correlations were analyzed using web-based tool www.genenetwork.org.

We observed significant correlations between avoidance learning and several published somatic and metabolic parameters. Importantly, performance on the beam-walking test did not correlate with spatial learning, suggesting that motor deficits were not sufficient to explain differences in spatial learning. However, some exploratory parameters in the open-field ethographs correlated positively with the number of errors in the retention test (with shock off, i.e., related to exploration). The study showed QTLs on chromosomes 4,10 and 20; however, learning was generally determined by many loci rather than oligogenetically.

The results show longer segments of chromosomes (QTLs), comprising of many genes, which significantly regulate learning.

This study was supported by grant GACR P303/10/J032

CENTRAL EFFECTS OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR, CAPTOPRIL IN EXPERIMENTAL HYPERTENSION

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Since lowering of blood pressure by the inhibition of the renin-angiotensin-aldosterone system within peripheral but also central nervous system was documented, it seems that brain angiotensin II may play a key role in the contribution of CNS to hypertension (1).

The aim of our study was to analyze central effects of angiotensin converting enzyme (ACE) inhibitor, captopril on the development of spontaneous hypertension and to determine molecular mechanisms of the drug actions in the brain. Six-week-old SHR were divided into two groups: controls and group receiving captopril in the dose of 50 mg/kg/day for 6 weeks.

At the end of experiment, systolic blood pressure in the captopril group (121±5 mmHg) was significantly lower than that in the controls (186±7 mmHg). Captopril increased significantly brain NO synthase activity, however, it was not able to elevate expression of eNOS or nNOS. Moreover, captopril increased the level of nitrosothiols and antioxidant activity measured by TEAC assay. Captopril decreased the level of superoxides and expression of nuclear factor kappaB subunits.

In conclusion, captopril, beside inhibition of ACE, increased NO synthase activity and nitrosothiols with simultaneous decrease of oxidative stress in the brain. This together may contribute to the prevention of blood pressure increase in SHR. Moreover, in human study, captopril reduced body sway (2) which could reflect a better sensory-motor integration playing the significant role not only in the central control of posture but improved overall human sensory-motor interactions.

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FREE COMMUNICATIONS 1

DEVELOPMENT OF BIOCHEMICAL PARAMETERS PATTERN IN CORE AND PENUMBRA DURING THE INFARCT EVOLUTION AFTER TRANSIENT MCAO IN RAT

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The period from stroke initiation up to end of damage spreading represents the therapeutic window of expansion alleviation. Some biochemical parameters helpful for infarct evolution estimation were studied in present work.

We designed control group and three groups of animals after MCAO with reperfusion 2 hours, 1 or 3 days. In the ischemic core and penumbra, fluorimetric and spectrophotometric methods for investigating total and MnSOD, MAO-AB activity and glutamate concentration were used. Protosynthesis was assessed by measuring of ^{14}C-leucine incorporation.

In core, the proteosynthesis was transiently inhibited two hours and three days after ischemia (36%). Glutamate and total SOD activity peaked first day, but on the third day after attack rapidly decreased by about 44%, 33.6%, respectively. In penumbra, transient ischemia led to higher proteosynthesis (78%), elevation of excitotoxic gluatamate and rapid activation of MnSOD (8.8 times increase) one day after insult. At third day the proteosynthesis and MnSOD is still significantly elevated (36%, 38.8% respectively) while glutamate level returned to base line. Additionally, the impact of ischemia on MAO-AB activity in penumbra was confirmed.

In conclusion, biochemical parameters screening could be helpful for cell damage progress and rescue possibility estimation. Both regions reflect different biochemical pattern that seems to be clearly established following the first day after MCA occlusion. Moreover, first postischemic day in present stroke model seems to be breakpoint up to the

time when expanding cell death from the infarct core to penumbra could be at least partially eliminated.

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POSSIBLE THERAPEUTIC APPROACH TO THE TREATMENT OF TRAUMATIC SPINAL CORD INJURY.

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Traumatic spinal injury has devastating impact on human health and quality of life. Despite intensive effort, there is still no effective clinical therapy to treat injured spinal cord. The aim of our project is to find an effective treatment of injured spinal cord, mainly by reducing secondary neuronal damage.

In our experiment we use unique model of traumatic spinal cord injury in minipigs, where the trauma is induced by a computer controlled spinal compression aparatus located at the lower thoracic level, which results in paraplegia of lower extremities.

After injury, a special spinal perfusion chamber is implanted over the site of injury, which allows local perfusion of injured tissue by oxygenated media solution containing growth factors and others factors reducing secondary spinal injury. The fabrication of perfusion chamber is quite unique – the site of laminectomy is scanned by 3D laser scanner. 3D scans are then processed by 3D software to design chamber, which fits injury site. The actual plastic chamber is then printed in 3D printer. To monitor neurological status of experimental animals, we use neurological scoring system and spinal

cord is removed and tissue is analyzed histologically, mainly for axonal quantification. The project is designed so that in the case of success can be transfered to the clinical practise.

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CYCLIC GMP IN DIAPHRAGM AFTER THE C2-C3 HEMISECTION AND AFTER THE PHRENIC NERVE INJURY

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It is known that endogenous nitrogen oxides modulate excitation-contraction coupling in diaphragm (Abraham et al., 1998). Because cyclic guanosine monophosphate (cGMP) is a second messenger for nitric oxide (NO) we tested the hypothesis, that NO acts via cGMP in diaphragm.

Concentration of cGMP was measured by ELISA using a cGMP-specific polyclonal antibody in control muscle (in the subsarcolemmal region) and in the ipsi-/contralateral part of the diaphragm after the C2-C3 hemisection, phrenic nerve ligation or transection and 8 days of survival.

We can point out, that the hemisection at the C2-C3 level decreased the concentration of cGMP at the side of the hemisection. In the case of changes on contralateral side, there were no significant changes in comparison to the control. Significant decrease of cGMP level was seen on ipsilateral side of the diaphragm after the phrenic nerve injury (particularly after the phrenicotomy). Changes in cGMP level can be coupled with the fact, that the cGMP is synthetised not only by soluble guanylyl cyclase, but also by particulate guanylyl cyclase.

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IMMUNOHISTOCHEMICAL AND BEHAVIORAL STUDY IN RATS AFTER SPINAL CORD INJURY AND BACLOFEN TREATMENT

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The interruption of important connections between supraspinal centers and spinal cord causes sensitive and motor impairment which often leads to spasticity. Our study was focused on effect of baclofen on changes in motor activity, nNOS, PV and GFAP immunoreactivity in spinal cord of Th9-transected rats.

The experiment was performed on 17 male Wistar rats divided into 5 groups: 1) control (n=5); 2–4) transected animals without baclofen treatment surviving for 1 (n=3), 6 (n=3) and 9 weeks (n=3); and 5) transected animals surviving for 9 weeks, repeatedly treated with baclofen (n=3). Baclofen (30mg/b.w., p.o.) was administered daily for 6 days, starting firstly 1 week and secondly 4th week after injury. Animals were subjected to immunohistochemical and behavioral analyses by using tail–flick test and BBB-locomotor rating scale.

Strong nNOS- and PV-IR was seen in α - motoneurons of lumbar spinal cord 6 and 9 weeks after transection. Repeated baclofen treatement decreased both nNOS- and PV-IR in motoneurons at 9th week of animal´s survival. Hypertrophied astrocytes were also detected 6 and 9 weeks post-injury. Baclofen had no effect on astrocyte´s expresion. The tail-flick test values did not reveal a significant decrease of reflex activity after the treatment. BBB score values showed significant improvement of motor function in baclofen treated animals 3–6 weeks postoperatively.

Our results indicate the role of NO and PV in proceses related with motor functions and the improvement in locomotion of transacted animals after repeated baclofen treatment.

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THE EXPRESSION OF ANGIOTENSIN II RECEPTORS IN THE SPINAL GANGLIA AFTER CHRONIC CONSTRICTIVE NERVE INJURY

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Angiotensin II (Ang II) is a neuropeptide that is a fundamental factor in regulation of blood pressure and blood volume. Ang II produced locally in the central nervous system (CNS) can increase the neuronal excitability and neurotransmission. To clarify the role of Ang II in the regulation of peripheral sensory system, we initiated a study of the expression and localization of Ang II receptor types in the rat sciatic nerve pathway under physiological conditions and after unilateral ligation of the sciatic nerve.

Study of rat dorsal root ganglion sections incubated with labeled ligand [^{125}I]-Sarcosine1-Ang II and selective ligands for both receptors showed predominant AT1 receptor binding. In situ hybridization using sense and antisense riboprobes revealed the presence of both AT1A and AT1B receptor subtype mRNAs. Based on emulsion autoradiographic technique, mRNA localization of AT1 receptors was detected and subsequently confirmed by immunofluorescent method in almost all primary sensory neurons, mostly in small ganglion cells (more than 40% of total). Statistically significant increase of AT1 – immunoreactive cells (about 10%) was found after sciatic nerve ligation.

Increased number of AT1+CGRP-immunoreactive neurons after sciatic nerve ligation suggests, that Ang II can play an important role in pain transmission mainly through peptidergic neurons of spinal ganglia.

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USING ACCELEROMETERS IN VISUAL BIOFEEDBACK FOR IMPROVING HUMAN BALANCE CONTROL

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The aim of the study was to examine effectiveness of visual biofeedback (VBF) signals (1,2) from accelerometers, which measure inclination of different body segments to the vertical.

The study was performed on 20 young subjects during stance on firm and foam surface with eyes open and with VBF using signals from force platform (CoP-VBF) or from two accelerometers placed at lower trunk (L5-VBF) and upper trunk (Th4-VBF). VBF signal was presented as a moving red point on the monitor screen controlled by tilt of body segment. Amplitudes (Ax, Ay) and root mean square (RMS) of body sway were evaluated.

ANOVA revealed that VBF had significant effect on each parameter and body segment. Amplitudes and RMS showed decrease on both types of surface due to VBF. L5-VBF and CoP-VBF significantly reduced CoP displacements and lower trunk tilts. Th4-VBF reduced only upper trunk tilts.

Reduction of body sway was the most significant in the segment from which the signal was sensed. CoP and L5 segments seem to be the best locations for VBF because upper trunk showed high variability of Th4 displacements. Using accelerometers offers new opportunities to optimize VBF systems (3), make VBF devices less expensive and perspective for rehabilitation of posture impairments.

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HOW DOES WEARING HIGH HEEL SHOES INFLUENCE POSTURAL STABILITY

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Measuring the limits of stability is a way how to quantify postural balance. The limit of stability evaluates the maximum displacement of person's center of body mass. To investigate limits of stability in the absence of external perturbations, the maximum voluntary tilted body posture can be used.

In the study participated 25 young healthy women (average age 23.2 ± 2.1 years). Subjects stood on the force platform and two dual-axis accelerometers (ADXL203) were situated on the fifth lumbar (L5) and the fourth thoracic (Th4) vertebra (1). Participants were instructed to make a maximal voluntary lean after hearing auditory signal and persist in this position till the next auditory signal. Body tilt was performed in forward direction, using ankle strategy. Each trial lasted 10s and was repeated 3 times. We evaluated amplitude and velocity of centre of pressure (CoP) and trunk tilts. Analysis of variance with 2-way repeated measures was used as a statistic method.

In conditions with high heel shoes 42% (eyes open) and 38% (eyes closed) decrease of amplitude of CoP displacement was recorded. We observed also significant decrease of amplitude of trunk tilts ($p<0.001$) in L5 and Th4 levels. The velocity of CoP responses was significantly reduced by 35% in eyes open and by 23% in eyes closed condition. In L5 and Th4 levels also significant decrease of velocity ($p<0.001$) was recorded.

The present study showed that wearing high heel shoes reduced significantly the range of functional limit of stability in forward direction.

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POSTURAL STABILIZING EFFECT OF VITAMIN D IN ELDERLY OSTEOPENIC AND OSTEOPOROTIC WOMEN

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Deficiency of vitamin D may cause muscle weakness, increased body sway and falls. On the other hand, supplementation with vitamin D may improve bone mineral density, and also may decrease the risk of falls, which are caused by impaired posture. The aim of the study was to compare balance control in osteopenic/osteoporotic women before and after vitamin D supplementation.

We examined 14 elderly osteopenic/osteoporotic women (mean age 69.1±1.5 yrs) during quiet stance under the static conditions: at stance on firm and foam surface with eyes either open or closed and at semi-tandem stance with eyes open. Duration of each trial was 50 sec. Body sway was recorded by a force platform and quantified by displacement of the centre of foot pressure (CoP) in anterior-posterior (AP) and medial-lateral (ML) directions and by two accelerometers fastened on upper (Th4) and lower (L5) trunk. Subjects were measured before and 4 months after vitamin D (cholecalciferol) supplementation. Paired comparison of sway parameters before/after supplementation were made using Student´s t-test, $p<0.05$ was consideredsignificant

We found that amplitude and RMS (root mean square) of upper trunk tilts were significantly decreased when comparing elderly subjects before and after vitamin D supplementation during the stance on firm surface with eyes either open or closed. At the stance on foam surface and semi-tandem stance, velocity of lower trunk tilts were also significantly decreased in both, AP and ML directions. Our results suggest that postural stability was improved after vitamin D treatment in elderly women with osteopenia/osteoporosis.

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SHIFTS IN VISUAL SPATIAL ATTENTION AFFECT DICHOTIC LISTENING

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Salient peripheral visual targets induce shifts in spatial attention, accompanied by gaze shifts. It is not known whether shifts of visual spatial attention affect processing in other modalities (1). We investigated whether visual spatial orienting affects auditory processing.

Horizontal visually guided saccades were executed during dichotic listening test. Sixty right-handed healthy volunteers (age 18–26 years) participated in the study. Saccades were elicited by visual targets, which made unpredictable steps from the center of the screen toward the right or the left.

In the first group of subjects (n=30), small amplitude saccades (10 deg) were elicited; in the second group (n=30), the amplitude was 45 deg (large amplitude saccades). We observed that only large amplitude saccades affected dichotic listening: right ear advantage was significantly lower during leftward saccades then during rightward saccades ($p<0.01$).

Our data suggest that **s**hifts in visual spatial attention are accompanied by automatic shifts in auditory attention, which result in altered performance in the dichotic listening test.

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THE CONTRIBUTION OF WISDOM AND ITS COMPONENTS TO HEALTH AND PSYCHICAL RESISTANCE

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In the past, wisdom was a part of philosophical and theological studies. Its potential for the human development generates interest of researchers also in the last decades (1). Recently, articles including the neurobiology of wisdom and psychotherapeutic use of wisdom in psychosomatic patients with the Post-Traumatic Embittertment Disorder occur .

For the next research of this complex and potentially supporting phenomenon, it is important to find a common definition of wisdom with its components and to deal with methodological problems of its measurement. The aim of this study was, therefore, to investigate the relationship of wisdom and especially its dimensions to health, psychical resistance (hardiness) and psychopathology.

Data were obtained from 46 respondents (26 psychosomatic patients and 20 patients of the control group) using three scales of wisdom: Three-Dimensional Wisdom Scale (3D-WS), Self-Assessed Wisdom Scale (SAWS), Adult Self-Transcendence Inventory (ASTI) and by Hardiness questionnaire (PVS) with Symptom Checklist-90 (SCL-90).

The results showed significantly higher scores in humor, emotional regulation, openness, reflective and cognitive dimensions in the control group; negative relationship of these components to subscales of SCL-90 and excepting emotional regulation their positive relationship to hardiness dimensions.

Identifying the key wisdom dimensions as well as its independence on age and education may have implications for psychotherapeutic practice.

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CEREBELLAR NUCLEAR FACTOR KAPPAB, NITRIC OXIDE AND BEHAVIOURAL ACTIVITY: DIFFERENCES IN HYPERTENSIVE AND OBESE RATS

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Alterations in cerebellar nuclear factor kappaB (NF-κB) and nitric oxide (NO) isoforms expressions were documented to be associated with increased locomotor activity in spontaneously hypertensive rats (1,2).

We aimed to analyze whether changes in cerebellar NF-κB pathway in hypertension associated with metabolic syndrome (MS) may affect locomotor activity of MS rats. Furthermore, the age-dependent changes were investigated as well. Male Wistar Kyoto rats (WKY, 9 weeks old), spontaneously hypertensive rats (SHR, 9 weeks old), and rats with MS aged 9 and 12 weeks were analyzed. Blood pressure was measure by tail-cuff plethysmography. Locomotor activity was tested by the open field method. Protein expression of NF-κB (p65 subunit), inducible NOS (iNOS) and NOS activity were determined in the cerebellum.

In SHR, despite no changes in NOS activity, increased NF-κB (p65) expression was associated with increased of both horizontal and vertical motor activities. Similarly, in young MS rats, increased NF-κB (p65) expression led to increased horizontal motor activity despite decreased NOS activity. On the other hand, no significant changes in NF-κB (p65) expression were demonstrated in adult MS rats. Horizontal and vertical motor activities as well as NOS activity were markedly reduced in this group of rats.

In conclusion, increased cerebellar NF-κB (p65) expression was associated with increased horizontal motor activity in both SHR and young MS rats, despite the obesity which accompanied also young rats with metabolic syndrome. Downregulated NF-κB pathway together with increased weight of rats may belong to the causes of decreased locomotor activity of adult MS rats.

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ENWHP INTRODUCTORY WORKSHOP: RISK FACTORS

LIFESTYLE AND HEALTH

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Maintaining a healthy society is contemporary major challenge. Public health programmes are designed to ensure that the potential health problems are tackled before they become a burden. In recent past a significant growth in non-communicable diseases cost governments worldwide millions. The Institute of Normal and Pathological Physiology SAS takes the post of National Contact Office of the European Network for Workplace health Promotion for eight years. In such a manner we fulfil the EP and EC Decision that the research institutes should participate at performing the public health policies as well.

In prevailing majority the following health risk factors are taking into account: High blood pressure, Alcohol consumption, Cigarette smoking/tobacco use, Elevated cholesterol/diet, Physical activity/inactivity, Overweight/obesity and Illicit drug use. Usually, they coexist and interact with one another. The individual lifestyle is more than diminishing/eliminating the seven main health risk factors (1). When planning the programs for individual behaviour modification the Behavioural and biomedical risk factors, Personality traits factors, Mental ill health factors, Family-related, Social, Genetic, Demographic and Environmental factors should be assessed – not only at least but as much as possible. Concerning the leading causes of deaths in 2030 ratings point to negative change in rank for several types of cancers, nephritis and nephrosis and hypertensive heart disease. All of them can be positively affected by a proper healthy lifestyle. The transfer of lifestyle scientific knowledge to public is an imperative need.

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FUNCTIONAL FOODS; FOCUS ON BIOACTIVE TRIPEPTIDES AND BERRIES

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Cardiovascular diseases, such as hypertension, heart infarction and stroke, as well as cancer, infectious and inflammatory diseases and diabetes are the most common direct or indirect causes of mortality in many countries. Despite development of new drugs, prevention is still important in reducing morbidity and mortality

In addition to dietary recommendations, functional foods are popular worldwide and research evidence is needed for their marketing claims. A food can be regarded as "functional", if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects. Functional foods must remain foods (not a pill or capsule) and they must demonstrate their effects in amounts that are normally consumed.

During the last 15 years our research group has concentrated in the following: Milk casein derived bioactive tripeptides lower mildly elevated blood pressure both in animal models and in man. They also improve vascular endothelial function mainly by inhibition of angiotensin converting enzyme (ACE -1), but also other interesting mechanisms have been suggested. Probiotics (e.g.*Lactobacillus rhamnosus* GG) prevent antibiotic induced diarrhoea, traveller´s diarrhoea and acute viral gastroenteritis in children. They may also diminish some allergic symptoms and improve immunologic responses. Our most recent interest has been in Finnish berries of which especially lingonberry (*Vaccinium vitis-idaea*) juice normalizes vascular dysfunction in hypertensive rats.

To conclude, functional foods should be taken into consideration in the prevention of diseases as supporting but not substituting drug therapy.

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PROBIOTICS IN HEALTH AND DISEASE

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FAO/WHO defines probiotics as "Live micro-organisms which when administered in adequate amounts confer a health benefit on the host. Prebiotics are nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or limited number of bacteria in the colon. The criteria for acceptable probiotics are 1)tolerance to gastric and bile acids 2) adhesion to mucosa 3)safety in clinical use 4)health effects proven in scientific clinical trials 5) technological feasibility.

Intestinal infections and disorders, oral health, urinary infections, candidiasis, but also systemic effects e.g.in allergy and respiratory infections are potential clinical applications for probiotics. Recently, there has been discussion on the role of microbiota in obesity. FAO/WHO has issued recommendations to evaluate probiotic safety.

The EFSA legislation on health claims is one of the challenges for the development of probiotic therapy. Until now no probiotic claim has been accepted in Europe. Demonstrating the requested efficacy in health is not an easy. The Human Microbiome Project and the metatranscriptomic and transproteomic approaches will certainly reveal more detailed data on the role of probiotics in health and diseases and lead the way to more targeted probiotics. Gene-modification is an appealing possibility for the future probiotics.

CHANGED FOOD ADMINISTRATION AND PHASE DELAY SHIFTS OF LIGHT RESULTS IN DISTURBANCE OF CIRCADIAN RHYTHMS IN CARDIOVASCULAR SYSTEM

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Our previous experiments revealed that 12 weeks lasting phase shifts of photoperiod (phase advance and phase delay) did not induce an increase in blood pressure (BP) but disturbed circadian rhythms of BP and heart rate (HR). In addition to light/dark (LD) cycle, the feeding regimen can entrain biological rhythms. Therefore, we designed phase delay shifts of light (PDS) with food available only during the passive phase of 24h cycle (F).

Male Wistar rats were exposed to PDS for 6 weeks. Cardiovascular parameters (CVP) and locomotor activity (LA) were measured by radiotelemetry (DSI, USA). Fresubin (isocaloric liquid energy drink; Fresenius, KABI, Germany) was available during the passive (L) phase of the day. Food and water consumption were measured on daily basis.

Rats exposed to the control 12L:12D regimen consumed twice more calories than the PDS group and F rats on control LD and PDS regimen. Water consumption was five times lower in rats consuming the liquid diet in comparison with control rats. BP did not increase in the experiment. CVP and LA were synchronized during LD conditions, with higher values during D in comparison with L. As expected, F rats exposed to PDS exhibited significant disturbances of circadian rhythm in CVP and LA . Moreover, F rats kept on LD showed an earlier desynchronization with different pattern than PDS F rats.

We demonstrate that food is a strong Zeitgeber for circadian rhythms of BP, HR and LA and irregular food consumption can disturb circadian rhythms similarly as PDS.

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ISCHEMIA AS CARDIOVASCULAR RISK FACTOR

INFLUENCE OF RISK FACTORS ON CARDIOPROTECTIVE SIGNALING: HYPERLIPIDEMIA

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Ischemic pre- and postconditioning are well described endogenous adaptive responses to protect the myocardium against ischemia/reperfusion injury. Most experimental studies on cardioprotection have been undertaken in animal models, in which ischemia/reperfusion is imposed in the absence of other disease processes. However, isch-

emic heart disease in humans is a complex disorder caused by or associated with known cardiovascular risk factors including hypertension, hyperlipidemia, diabetes, insulin resistance, atherosclerosis, heart failure, and aging.

The pathological processes related to the risk factors include fundamental molecular alterations that can potentially affect the development of ischemia/reperfusion injury and responses to cardioprotective interventions. Hyperlipidemia causes massive alteration in cardiac gene expression profile and among several possible mechanisms, the pathological increase in reactive oxygen and nitrogen species, alteration in matrix metalloproteinase activation, and reduced expression of connexin-43 may disrupt major cytoprotective signaling pathways thereby significantly interfering with cardioprotective signaling. Moreover, the use of statins in hyperlipidemia may further interfere with cellular mechanisms of cardioprotection.

This presentation reviews the evidence that risk factors (focusing on hyperlipidemia) modify responses to cardioprotection and emphasizes the critical need for mechanistic preclinical studies that examine cardioprotection in the presence of risk factors and complicating disease states. These are now essential to for successful development of rational approaches to therapeutic protection for patients with ischemic heart disease developing as a consequence of comorbid conditions.

HYPERTENSION AND DYSLIPIDEMIA ALTER CARDIAC RESPONSE TO ISCHEMIA VIA SUPPRESSION OF INNATE CARDIOPROTECTION

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Lifestyle-related risk factors (RF), such as hypertension and dyslipidemia have a negative effect on the cardiac response to ischemia. On the other hand, moderate stress including ischemia(hypoxia), hyperglycemia and/or free radicals, may trigger adaptive processes increasing resistance to ischemia/reperfusion injury (IRI) known as preconditioning (PC), which is also observed in the diabetic heart.

We hypothesized that RF may exacerbate tolerance to ischemia via interference with mechanisms of intrinsic cardioprotection. While acute STZ-induced diabetes or high-fat diet alone reduced cardiac susceptibility to ischemia, combination of RF markedly exacerbated IRI in the adapted hearts promoting pro-oxidative and apoptotic processes. Accordingly, severity of arrhythmias and infarct size were increased in preconditioned or diabetic SHR and diabetic-hypercholesterolemic animals.

Research shows that although innate cardioprotection is still retained in the pathologically altered myocardium, its potential is lower. Thus, a higher intensity of adaptive stimulus is required to reach a similar level of protection as in the „healthy" heart. Cardioprotective pleiotropic (independent of primary) effects of PPAR agonists indicate a promising approach to improve ischemic tolerance in the „diseased" myocardium.

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CARDIAC ISCHEMIC TOLERANCE IN RATS ADAPTED TO CHRONIC CONTINUOUS NORMOBARIC HYPOXIA

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Chronic reduction of oxygen availability evokes complex adaptive responses resulting in improved cardiac tolerance to acute ischemia/reperfusion injury. The aim was to find out whether brief daily reoxygenation during adaptation to chronic continuous hypoxia (CCH) affects protective cardiac phenotype.

Adult male Wistar rats were kept at CCH (inspired oxygen fraction 0.1) for 5, 15 or 30 days; a subgroup of animals was exposed to room air daily for a single 60-min period. While 5 days of CCH did not affect myocardial infarction induced by 20-min coronary artery occlusion and 3-h reperfusion, 15 days reduced infarct size from 62% of the area at risk in normoxic controls to 52%, and this protective effect was more pronounced after 30 days (41%). Susceptibility to ischemic ventricular arrhythmias exhibited reciprocal development: the marked suppression of arrhythmias was observed already after 5 days of CCH, vanishing with the prolongation of hypoxic exposure. CCH increased myocardial abundance of mitochondrial superoxide dismutase (MnSOD) without affecting malondialdehyde concentration. Daily reoxygenation abolished the infarct size-limiting effect of CCH, worsened arrhythmias, prevented MnSOD up-regulation, and increased malondialdehyde (by 53%). Ventricular cardiomyocytes isolated from CCH rats exhibited better survival and lower lactate dehydrogenase release caused by simulated ischemia/reperfusion than cells from normoxic and daily reoxygenated groups.

Results suggest that CCH is cardioprotective and brief daily reoxygenation blunts its salutary effects likely by interfering with mitochondrial antioxidant defense, resulting in oxidative stress.

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INVOLVEMENT OF MEMBRANE FLUIDITY IN REGULATION OF SYSTEMS EMBEDDED IN CARDIAC SARCOLEMMA AND MITOCHONDRIA IN ISCHEMIA, DIABETES AND HYPERTENSION

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Physical state of lipid bi-layer of the membranes is termed liquid crystal. Most membrane receptors and transport systems are embedded in the lipid layer and their molecules are even spanning the cell membrane. However, all membrane receptors and transporters request to their activity certain movement that may be determined by fluidity of the liquid crystal. Therefore, membrane fluidity (MF) becomes a specific regulatory property of membrane systems. It has been accumulated much evidence that diverse physiological and pathological impulses targeting the membranes may increase or decrease the MF. In addition, chemical compounds including drugs may immerse into the membrane, depending on degree of the hydrophobicity of their molecule and in this way artificially modulate the MF. Finally, changes in chemical composition of membranes may also alter MF. This enormous sensitivity to diverse influences may be the reason why the normal physiological range of changes in fluidity of single subcellular membrane systems was not yet determined satisfactorily. Nevertheless, our experimental findings obtained on heart sarcolemma and mitochondria indicate that when estimated parallel with the changes in some important membrane-embedded sytems, such as enzymes, data about MF may offer unique information and explanation for the mechanisms of processes induced by hypoxia, diabetes, hypertension and different drugs in cardiac subcellular membranes.

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MITOCHONDRIA FROM DIABETIC RAT HEARTS ARE ACTIVELY INVOLVED IN INCREASED TOLERANCE OF THE MYOCARDIUM TO ISCHEMIA/REPERFUSION INJURY

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Due to damage to the respiratory chain diabetic (DIA) heart mitochondria (MIT) are unable to utilize oxygen normally and they are also permanently exposed to increased calcium transients. Permanent exposure to these pathological impulses leads to partial adaptation of the DIA heart to hypoxia and to certain degree of overload with calcium as well as to increased resistance to ischemia/reperfusion injury (IR). Relatively little data are available about participation of MIT in mechanisms of adaptation of the myocardium to acute DIA and via it to increased resistance to IR. This particularly concerns the involvement of the MIT Mg-ATPase and the possible alterations in MIT membrane fluidity (MF), which may play decisive role in adaptation of ATP production and delivery to the myocardial cells in both DIA and the IR.

On the day 8 after streptozotocin application, the isolated hearts were subjected to Langendorff perfusion with the following protocol: 15 min normoxic stabilization perfusion, 30 min global ischemia, 40 min reperfusion.

Results revealed considerably better postischemic recovery in the DIA hearts. After ischemia, isolated MIT exhibited significant decrease in both the Mg-ATPase activity and MF and this decrease also followed after the reperfusion indicating the lack of any adaptation. A significant ischemia-induced decrease in MF was also observed in DIA heart MIT, but after reperfusion it was continuing less pronounced and in contrary to controls, the Mg-ATPase activity was increasing considerably.

Results indicate that DIA heart MIT are actively involved in resistance of the myocardium to IR injury.

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NITRIC OXIDE AND CARDIOVASCULAR RISK FACTORS

THE ROLE OF OXIDATIVE STRESS IN ACUTE ISCHEMIC STROKE

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Reactive oxygen species (ROS) act physiologically as signaling molecules. In pathological conditions, such as ischemic stroke, ROS are released in excessive amounts and upon reperfusion exceed the body's antioxidant detoxifying capacity. This process leads to brain tissue damage during reoxygenation. Consequently, antioxidant strategies have long been suggested as a therapy for experimental stroke, but clinical trials have not yet been able to promote the

translation of this concept into patient treatment regimens. As an evolution of this concept, recent studies have targeted the sources of ROS generation-rather than ROS themselves.

The objective of the present study was to estimate parameters of oxidative status in the blood and cerebrospinal fluid in the course of ischemic stroke and in the prediction of recovery of neurological functions. Experimental studies provide evidence of an association between ischemic stroke and increased oxidative stress, but data in humans are still limited and controversial. Concentration of superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) as a marker of antioxidant adaptation, the secondary lipid peroxidation products reacting with thiobarbituric acid (TBARS), nitrite, superoxide anion radical (O_2^-) and hydrogen peroxide (H_2O_2) release as a marker of oxidative stress were studied.

65 patients with hemispheric ischemic stroke admitted to a hospital during the first 72 h after stroke were examined. It has been shown that the development of cerebral infarction is accompanied by increased concentrations of oxidative stress markers. Progressive ischemic stroke was characterized by the significantly prolonged increase in TBARS and nitrite, while other oxidative stress markers were note significantly changed. Furthermore, it was present increasing processes of antioxidant adaptation, expressed in the growth of SOD concentrations, can be considered as a criterion for the prediction of recovery of disturbed neurologic function.

These results suggest that the majority of other antioxidants are reduced immediately after an acute ischemic stroke, possibly as a consequence of increased oxidative stress. A specific antioxidant profile is associated with a poor early outcome.

The role of gasotransmitters in the effects of homocysteine-related compounds in isolated rat heart

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Considering the dilemma about the toxic effects of homocysteine (Hcy), the aim of this study was to estimate the effects of different homocysteine compounds on cardiac contractility, coronary flow, and oxidative stress markers in isolated rat heart.

The hearts of male, Wistar albino rats (n =48, age 8 weeks, b.m. 180–200 g), were retrograde perfused (Langendorff technique) at CPP of 70 cmH_2O, then administered with three isoforms of 10 M homocysteine, i.e. DL-Hcy, DL-Hcy thiolactone-hydrochloride (TLHC) or L-Hcy TLHC. The roles of NO, H_2S and CO were estimated through administration of compounds blocking their synthesis, i.e. L-NAME (30 μM), DL-propargylglycine (10 μM) or PPR-protoporphyrin IX (10 μM), respectively. Markers of oxidative stress: index of lipid peroxidation measured as TBARS, nitric oxide measured through nitrites (NO_2^-), superoxide anion (O_2^-), and hydrogen peroxide (H_2O_2) from coronary venous effluent were assessed spectrophotometrically.

The obtained results showed that administration of different Hcy-related compounds induced depression of cardiac contractility, decreased coronary flow and surprisingly they had no effects on oxidative stress markers acutely. These effects of different Hcy-related compounds are in part mediated by NO while H_2S was not involved in it. In addition blocker of CO synthesis administered alone significantly depressed cardiodynamic variables of isolated rat heart. Further investigations are in progress regarding the role of gasotransmitters in homocysteine-related compounds induced cardiotoxicity in rats.

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EXPERIMENTAL MODELS OF METABOLIC SYNDROME: FOCUSED ON NO AND ROS BALANCE.

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Metabolic syndrome (MS) is characterized as a cluster of risk factors in which impaired nitric oxide-(NO)-dependent signaling pathways and icreased production of reactive oxygen species (ROS) were documented. Consequently, oxidative stress may lead to activation of nuclear factor kappa B (NFkB) (1,2).

We aimed to study blood pressure changes, NO and ROS generation in two different models of MS: obese spontaneously hypertensive rats [SHR/NDmcr-cp(cp/cp)] and hereditary hypertriglyceridemic rats (HTG). Animals were divided into four groups: male young 9-week-old normotensive control Wistar Kyoto rats (WKY) and age-matched spontaneously hypertensive rats (SHR), SHRcp and HTG rats. We measured blood pressure, nitric oxide synthase (NOS) activity, expression of endothelial NOS (eNOS) and NFkB in the heart, kidney and brain. Concentration of conjugated dienes (CD) and activity of superoxide dismutase (SOD) were measured in the same tissues.

Blood pressure was significantly enhanced in SHR, SHRcp, and HTG rats. NOS activity in the heart, kidney and brain was decreased in both models of MS. While expression of eNOS protein was significantly increased in HTG rats, expression of NFkB was increased in all tissues of both MS models. But increased CD concentration along with decreased SOD activity were determined in HTG rats only.

Our data clearly showed elevated blood pressure and decreased NOS activity in the tissues of both models of

MS. Since increased markers of oxidative stress were documented in HTG rats only, we hypothetised that other mechanisms, different from increased ROS production, might be responsible for incresed blood pressure and decreased NOS activity in the model of SHRcp.

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BENEFICIAL EFFECTS OF WY14643 IN ISCHEMIA-REPERFUSION INJURY IN ISOLATED RAT HEART: INVOLVEMENT OF ROS.

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Peroxisome proliferator-activated receptors (PPAR) are transcription factors, regulating fatty acid metabolism, inflammatory response and oxidative stress. Recent studies showed that stimulation of PPARα isoform may result in increased generation of reactive oxygen species (ROS) which is in contrast with the evidence that PPARα ligands reduce ischemia/reperfusion (I/R) injury. The study aimed to explore the effects of PPARα activator WY14643 (WY) on I/R-induced ROS production.

Male Wistar rats were treated with WY (3mg/kg, 5 days, p.o.). Langendorff-perfused hearts of treated animals and untreated controls were subjected to 30-min global I and 2–h R for evaluation of infarct size (IS, in % of area of risk; TTC staining), post-I/R recovery of left ventricular developed pressure (LVDP, in % of baseline values), and R-induced arrhythmias. Samples from left ventricle tissue were taken before I and after 40-min R for determination of levels of conjugated dienes (CD).

Treatment with WY improved postischemic recovery of LVDP (61 ± 9% vs. 24 ± 3% in controls, $p<0.05$) and reduced IS by 51% ($p<0.05$). In addition, susceptibility to R-induced arrhythmias was reduced in these hearts ($p<0.05$). Despite increased myocardial baseline levels of CD in the WY-treated group, post-I/R CD levels in this group were significantly lower as compared with the controls.

Treatment with PPARα agonist attenuated postischemic stunning, occurrence of malignant arrhythmias and lethal injury possibly due to decreased ROS production during I/R in the hearts of normocholesterolemic rats indicating non-metabolic effects of PPARα activation.

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FREE COMMUNICATIONS 2

OBESITY AND AGING ARE ASSOCIATED WITH ALTERATIONS IN PLASMA OXYTOCIN LEVELS AND OXYTOCINASE ACTIVITY

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Oxytocin (OT) is well known for its´ role in reproduction and social behavior. This peptide participates also in regulation of energy homeostasis because of its anorexigenic effects. Lack of oxytocin action is associated with development of obesity and insulin resistance. Therefore, the aim of our study was to determinate plasma oxytocin level in obese and insulin resistant Zucker rats.

Plasma oxytocin level in 12-week-old and 33-week-old male obese Zucker rats and their lean littermates was assessed by an enzymatic immunoassay. Fluorometric assay was performed to evaluate plasma oxytocinase activity. Expression of oxytocin receptor gene was determined by real-time PCR.

Oxytocin level in plasma significantly varies with obesity and age ($p=0.013$). We observed 3-fold higher plasma OT concentration in 12-week-old obese Zucker rats when compared to their lean littermates. Obesity and insulin resistance in 33-week-old obese Zucker rats was associated with a 4-fold reduction in plasma oxytocin level in comparison with younger obese rats. Activity of enzyme involved in oxytocin degradation was decreased only with respect to age ($p<0.001$). In addition, changes in gene expression of oxytocin receptor in epididymal adipose tissue displayed the same pattern as plasma oxytocin.

Our results clearly demonstrate variability in oxytocin secretion and sensitivity of epididymal adipose tissue to this peptide hormone during different stages of obesity and development of related disorders. Presented results provoke a question about possible role of oxytocin in human obesity.

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EFFECT OF HIGH FAT DIET-INDUCED OBESITY ON THE EXPRESSION OF RENIN-ANGIOTENSIN SYSTEM COMPONENTS IN RAT ADIPOSE TISSUE

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Beside Ang II, other important functional heptapeptide Ang-(1–7), formed primarily by ACE2, has been recognized. Ang-(1–7) acts through specific Mas receptor and induces responses opposing those of Ang II. Furthermore, recent identification of functional renin receptor (RenR) opened new perspectives on the role of local RAS in control of adipose tissue metabolism.

We studied the effect of high fat diet-induced obesity (42% fat, 8 weeks) on the gene expression of RAS components in white adipose tissue in rats. In obese rats the body weight, energy intake and adiposity index were significantly higher. Fasting serum insulin and glucose concentration, and serum lipid profile did not differ from controls. Serum leptin concentration was elevated and adiponectin was decreased in obese rats. The level of RenR mRNA was significantly increased in epididymal adipose tissue in obese rats while the gene expression of other RAS componets (angiotensinogen, ACE, ACE2, AT1 and Mas receptors) was not altered.

We demonstrated gene expression of Mas receptor and RenR in white adipose tissue of rats and our data suggest that RenR might play a role in early stage of adipose tissue mass accumulation during high fat diet-induced obesity in rats. Our data on RenR expression prompt to study metabolic effects of renin inhibitors currently used in treatment of human hypertension.

The study was supported by grants VEGA 2/0089/11 and CE NOREG.

Alibernet red wine extract INCREASES NITRIC OXIDE AND SUPEROXID DISMUTASE ACTIVITIES IN spontaneously hypertensive rats: potential mechanismS behind.

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Polyphenols found in red wine particularly are thought to have antioxidant and antihypertensive properties (1,2). We aimed to perform a chemical analysis of an alcohol free Alibernet red wine extract (AWE) and to investigate the effects of AWE on nitric oxide and reactive oxygen species production as well as blood pressure development in normotensive Wistar Kyoto (WKY) and spontaneously hypertensive rats (SHR).

Total antioxidant capacity together with total phenolic and selected mineral content were measured in AWE. Furthermore, young 6-week-old male WKY and SHR were treated with AWE (24,2 mg/kg/day) for 3 weeks. Total NOS and SOD activities, eNOS and SOD1 protein expressions and superoxide production were determined in the tissues.

Both antioxidant capacity and phenolic content were found to have a high level in AWE. From the minerals Zn, Mg, and Ca, especially, reached the most important levels. The AWE increased NOS activity in the left ventricle, aorta and kidney of SHR, while it did not change NOS activity in WKY rats. Similarly, increased SOD activity in the plasma and left ventricle was observed in SHR only. There, however, were no changes in eNOS and SOD1 expressions. Since both NOS and SOD1 activities are Zn-dependent, we assume this mineral may directly increase the activities.

In conclusion, our study documented that phenolics and minerals presented in AWE extract, and zinc especially, may contribute directly to increased NOS and SOD activities in the tissues of spontaneously hypertensive rats. Nevertheless, 3 weeks of AWE treatment failed to affect blood pressure of SHR yet.

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INFLUENCE OF MATURATION AND GENDER ON RESPONSE TO ISCHEMIC PRECONDITIONING IN THE RAT HEART: DISTINCT ROLE OF PI3K/AKT PATHWAY.

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Gender and maturation are important factors determining differences in cardiovascular morbidity and mortality in human population, where men are generally at higher risk than age-matched premenopausal women. The study aimed to investigate the impact of maturation on the response to ischemia/reperfusion in male and female hearts and to explore a potential role of the PI3K/Akt pathway in the cardioprotective effects of ischemic preconditioning (IPC) in the myocardium of younger and older males (M) and females (F).

Langendorff-perfused non-preconditioned control and preconditioned hearts of 12- and 18-week-old M and F Wistar rats were subjected to 30-min regional ischemia and 2-h reperfusion with or without prior perfusion with PI3K inhibitor wortmannin (100 nM) for the evaluation of ischemia-induced arrhythmias and the size of myocardial infarction (IS).

Maturation did not modify IS in both genders, however, it increased susceptibility to ventricular arrhythmias. Although IPC effectively reduced IS in males as well as in F of both ages, only the hearts of males and 18w F benefited from its antiarrhytmic effect. In the preconditioned 12w females and in M of both ages, wortmannin blunted IS-limiting effect of IPC. In contrast, inhibition of PI3K/Akt did not influence antiinfarct protection by IPC in elder F.

Maturation partially affects the response to I/R in both genders. Activation of PI3K/Akt plays an important role in protection against lethal I/R injury conferred by IPC in males irrespective of age, while IS-limiting effect of IPC appears to be PI3K/Akt-dependent only in younger F.

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EFFECT OF MOLSIDOMINE AND SILDENAFIL ON ISCHEMIC TOLERANCE IN CHRONICALLY HYPOXIC RAT HEARTS

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Chronic hypoxia causes pulmonary hypertension (PH) and improves myocardial tolerance to acute ischemia/reperfusion injury. Hypoxic PH can be attenuated by the enhanced availability of nitric oxide (NO). Therefore, the aim of this study was to find out whether chronic administration of NO donor (molsidomine, MOL; 15 mg/kg/day) or phosphodiesterase 5 inhibitor (sildenafil, SIL; 1.5 mg/kg/day) in drinking water affects i) the development of PH and ii) the ischemic tolerance of chronically hypoxic hearts.

Adult male Wistar rats were adapted to chronic continuous hypoxia (CCH; 10% O_2, 4 weeks) in a normobaric chamber. Subgroups of the animals were treated with either MOL or SIL.

Adaptation to CCH significantly decreased infarct size (induced by 20-min regional ischemia and 3-h reperfusion). MOL significantly decreased infarct size only in the normoxic group, while SIL protected both normoxic and CCH groups. CCH decreased myocardial ratio of reduced-to-oxidized glutathione (GSH/GSSG), increased 3-nitrotyrosine (3-NT) and malondialdehyde (MDA) concentrations compared with normoxic group. MOL and SIL reduced MDA and increased 3-NT in normoxic hearts without affecting GSH/GSSG ratio. Only 3-NT was increased by MOL and SIL treatment in the CCH group. Neither MOL nor SIL affected the degree of hypoxic PH.

In conclusion, chronic treatment with NO donor or phosphodiesterase 5 inhibitor reduced infarct size in normoxic rats, likely by improving NO availability and decreasing oxidative injury. The potential role of NO in ischemic tolerance of CCH hearts remains to be elucidated.

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INFLUENCE OF AGING AND HIGH-FAT DIET ON MYOCARDIAL ISCHEMIC TOLERANCE IN MICE WITH AMP-ACTIVATED PROTEIN KINASE α2-SUBUNIT DEFICIENCY

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AMP-activated protein kinase (AMPK) plays an important role in metabolic regulation under stress conditions and inadequate AMPK signaling may be also involved in processes associated with aging. AMPK is rapidly activated during myocardial ischemia.

The aim of our study was to find out whether α2-subunit deficiency can influence heart function and ischemic tolerance of aged mice. We compared infarct size in transgenic AMPK $\alpha2^{-/-}$ (TG) and wild type (WT) male and female mice at the age of 6 and 18 months. Effects of high-fat diet during aging were examined in females. Isolated Langendorff-perfused hearts were subjected to 45-min global no-flow ischemia and 60-min reperfusion. Infarct size normalized to the size of the left ventricle (LV) was similar in both strains and sexes at the age of 6 months.

Aging did not significantly affect infarct size in males, whereas 18-month-old WT females exhibited markedly improved ischemic tolerance compared with age-matched TG mice and 6-month-old mice of both strains and sexes. The high-fat diet increased infarct size in aged WT females. The main echocardiographic parameter of heart function, fractional shortening was significantly lower in TG males and females compared with WT and this difference was more pronounced after high-fat feeding. No difference in AMPK α1 protein level was detected between the strains. On the other hand, AMPK α2 level and AMPK phosphorylation status were decreased in old WT hearts.

These results suggest that AMPK α2-subunit deficiency can negatively influence changes in heart function and ischemic tolerance associated with aging and high-fat diet.

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AGE-DEPENDENT CHANGES OF NITRIC OXIDE GENERATION IN EXPERIMENTAL METABOLIC SYNDROME

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A number of studies have suggested the different nuclear factor kappaB (NF-κB) activation by nitric oxide (NO) in central nervous (CNS) and cardiovascular systems (CVS) (1–3).

We aimed to study NF-κB and inducible NO synthase (iNOS) expressions as well as NO generation in the brain and cardiovascular system of young (9 weeks) and adult (12 weeks) rats with metabolic syndrome (MS). Blood pressure was measured by tail-cuff plethysmography. NOS activity and NF-κB (p65) and iNOS expressions were determined in the brain, heart and aorta.

There were no significant changes in NF-κB (p65) or iNOS expressions in young and adult rats with metabolic syndrome. However, NOS activity of adult MS rats decreased significantly in all tissue investigated in comparison with young MS rats. This decrease, however, did not affect blood pressure of adult MS rats (young MS rats: 173±6 mmHg; adult MS rats: 179±5 mmHg).

Since decreased NOS activity in the brain and cardiovascular system did not affect blood pressure of adult rats with metabolic syndrome, we concluded that other mechanisms

than NO-dependent pathway may be responsible for blood pressure maintenance in rats with metabolic syndrome.

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DIFFERENT NO-DEPENDENT ACTIVATION OF NF-KB IN THE CENTRAL NERVOUS SYSTEM.

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Objective: Several studies have suggested the different nuclear factor kappaB (NF-κB) activation by nitric oxide (NO) in central nervous (CNS) and cardiovascular systems (CVS) (1,2).

Design: We aimed to study NO and NF-κB generation at the level of CNS and CVS in normotensive and hypertensive rats. Male 9-week-old rats were divided into two groups: control Wistar Kyoto rats (WKY) and spontaneously hypertensive rats (SHR). Blood pressure (BP) was measured by tail-cuff plethysmography. NO synthase activity was determined in the aorta, heart, cerebellum, brain cortex and brain stem. Protein expressions of endothelial NOS (eNOS), neuronal NOS (nNOS) and NF-κB were determined in the same tissues.

Results: BP increased by 55% in SHR in comparison with age-matched normotensive controls. In SHR, NOS activity was decreased significantly in the aorta and there was a decreased tendency in the heart. On the other hand, NOS activity was increased in the brain cortex and brain stem. While the expression of eNOS and NF-κB was not changed in CVS, the expression of the same parameters was enhanced significantly in CNS. No changes in nNOS expression were determined either in CVS or CNS.

Conclusion: Increased level of NO in CNS may directly induce NF-κB activation and expression which consequently increase the expression of eNOS. Increased generation of NO seems to be however insufficient to counterbalance increasing BP in hypertensive rats.

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AMBIVALENT EFFECTS OF CURCUMIN: MODEL OF EXTRAHEPATAL BILIARY ATRESIA AS AN EXAMPLE

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Curcumin, like different polyphenolic compounds (1,2) belongs among effective scavengers of reactive oxygen species. In addition to direct antioxidant activity, curcumin may function indirectly as an antioxidant by inhibiting the activity of inflammatory enzymes or by enhancing the synthesis of glutathione, an important intracellular antioxidant. However, side – prooxidative effect of curcumin was described as well.

We aimed to determine effects of curcumin on liver fibrosis and to clarify the role of NF-κB and iNOS in the model of extrahepatal biliary atresia. Male Wistar rats, 12-week-old, were divided into six groups (n=8, each): sham operated rats; rats that received curcumin (200 mg/kg/day); biliary duct ligated group (BDL); biliary duct ligated group that received curcumin (BDL curc). After 3 weeks of the treatment the animals were sacrified and the liver, kidney and blood samples were analysed.

Curcumin treatment did not modify blood plasma markers like alkaline phosphatase and aspartat aminotransferase activities, total protein, albumin, total bilirubin and conjugated bilirubin concentrations as well as iNOS and p65 NF-κB expressions in the liver species of sham group. Interestingly, there were significant increase in both liver and kidney fibrosis extents. On the other hand, despite decrease in iNOS and p65 NF-κB expressions, cucrcumin treatment did not affect fibrosis enlargement elevated due to bile duct ligation in the liver. In BDL, curcumin treatment also decreased the levels of blood plasma markers.

In conclusion, curcumin treatment was able to improve functional properties of hepatocytes and to inhibit both NF-κB and iNOS upregulations in BDL, however, without beneficial effect on the liver fibrosis developed in this model of cholestasis. Thus, in our conditions other factors, different from NF-κB and iNOS are responsible for fibrotic process in the liver.

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