

**Centre for Physiology and Biochemical Research (CPBR)
The Russian Society for BioPsychiatry (RSBP)
Ukrainian Society for Biological Psychiatry (USBP)
International Stress and Behavior Society (ISBS)
Institute of Experimental Medicine (IEM RAMS)**

CONFERENCE PROCEEDINGS

**14-th Multidisciplinary International Conference
on Neuroscience and Biological Psychiatry
“Stress and Behavior” ISBS Conference**

**Dedicated to 120th anniversary
of the Institute of Experimental Medicine (IEM)**

**St-Petersburg, Russia
May 16-20, 2010**

Welcoming Address from the Conference Chair

Dear Colleagues,

It is our great pleasure to welcome you to the 14th annual International Neuroscience “Stress and Behavior” Conference, this year hosting scientists from over 30 countries worldwide.

Back in laboratories, we hope that our research progresses, and that we make new discoveries. Sometimes though, research may falter as we find ourselves unable to grasp the proof for why or how things occur. Conferences like this help to ignite creative imagination, as hearing new ideas allows us to connect the dots or leads us on a tangent.

As time passes, we find that the tools at our disposal are rapidly improving. Because of technological advances, “omicses”, nano-biology, and neuroimaging make the analysis of brain phenomena a reality. By using special imaging tracers or ligands that bind structures and send out signals, we can observe structural, physiological, and functional changes. This can also allow us to separate normal or healthy structures and functions from abnormal ones, or to determine if a drug is effective in slowing down the progression of a disease.

As the technology improves, we must take advantage of it by finding ways to apply it to our work. This is the way to approach old problems from new perspectives, and hopefully discover potential interventions which obstruct the onset of neuropsychiatric symptoms.

Our conferences always show that many promising approaches are available for biological psychiatry research today. We all hold the hope that the collective insights will progress our understanding of how stress influences the brain, and how it impacts the lives of those who chronically struggle to overcome these debilitating diseases.

This technological progress, together with the brain being the most exciting product of nature, and scientists being very inquisitive people, will ensure that these goals will be achieved.

I look forward to welcoming you in St. Petersburg!

A handwritten signature in black ink, appearing to read "Allan V. Kalueff", with a long horizontal line extending to the right.

Allan V. Kalueff PhD, PhD

Welcoming Address from the Program Committee Chair

Dear Colleagues,

I am glad to have an opportunity to greet you in Saint-Petersburg.

As we all know, stress and its consequences are one of the most urgent problems both in the modern practice of medicine and in medical science. In the age of information avalanches and high velocities, stress affects all people: their health, their behavior, and their relationships. All this makes the reason for our meeting more than evident. We are all devoted to our work and its main purpose: to make human life happier.

By arranging the Conference in one of the most beautiful Russian cities, we have made it a good tradition to enrich our meetings with a touch of history and art. During the meeting, you will also have an opportunity to attend one of the famous Saint-Petersburg theatres, and to make a journey along the rivers and channels crisscrossing Northern Venice – as our beautiful city is called due to its Italian architecture as well as to its affinity for water.

We again would like to welcome you at the Institute for Experimental Medicine, the renowned place where an outstanding Russian physiologist I.P. Pavlov worked. This year our Institute turns 120 years old, and our conference is dedicated to this event. You will be able to visit us during the conference, and my colleagues are looking forward to see you there.

Years ago, when choosing the exact time for our first meeting held in Saint-Petersburg, we decided on the month of May because it provides participants with the pleasure of our white nights beauty. I sincerely hope that our choice was a right one, and that you will enjoy this phenomenon, making our city even more special.

Cordially,

A handwritten signature in black ink, appearing to read 'V. Klimenko', with a long, sweeping horizontal stroke at the end.

Prof. Victor Klimenko MD, PhD

IN PARTNERSHIP WITH:



Noldus Information Technology: Software for human and animal observational studies. www.noldus.com/



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Clever Sys., Inc.: High-throughput tools for automated behavioral testing, including data collection and analysis. www.cleversysinc.com



Metris B.V.: Novel automated animal behavior and sound analysis systems. www.metris.nl



OpenScience Ltd: Equipment and software for animal behavior research. www.openscience.ru

Conference Symposia

Day 1. May 16, 2010

15.30-16.30 Plenary Opening Lecture. NOVEL EXPERIMENTAL MODELS FOR DRUG ABUSE RESEARCH. A. Kalueff (USA)

16.30-17.30 Symposium 1. Alcoholism and experimental models

Day 2. May 17, 2010

Plenary lecture 1. 120TH ANNIVERSARY OF INSTITUTE OF EXPERIMENTAL MEDICINE. V. Klimenko (Russia)

10.30-12.10 Symposium 2. Genetic animal models of brain disorders

12.30-13.30 NOLDUS-OPEN SCIENCE Workshop

14.30-17.30 Symposium 3. Experimental models in biological psychiatry

Day 3. May 18, 2010

10.00-11.00 TSE SYSTEMS Workshop

11.30-12.00 Symposium 4. Translational biological psychiatry

14.00-15.00 METRIS Workshop

15.00-16.40 Symposium 5. Serotonin, Brain and Behavior

17.00-18.00 Plenary Lecture 2. NPY AND STRESS. Z. Zukowska (USA)

10.00-18.00 POSTER SESSION

Day 4. May 19, 2010

10.00-12.00 Symposium 6. Clinical aspects of Biological Psychiatry

13.00-16.50 Symposium 7. Special Symposium of the Russian Society for Biological Psychiatry (RSBP)

Day 1. May 16, 2010

Plenary Opening Lecture

NOVEL EXPERIMENTAL MODELS FOR DRUG ABUSE RESEARCH

A. Kalueff

Pharmacology Department and Neuroscience Program, Tulane University Medical School, New Orleans, USA

Drug abuse is a complex, multifaceted mental health and societal problem. To better understand how drug abuse affects brain and behavior, we need novel high-throughput experimental models of this pathogenesis. While mouse and rat models have long been used in this field, zebrafish (*Danio rerio*) emerge as a useful model species for drug abuse research. Acute sensitivity to drugs of abuse, behavioral responses to chronic treatment with these drugs, tolerance, as well as acute (single) and repeated withdrawal models, have been developed for zebrafish. This lecture will summarize the developing utility of larval and adult zebrafish models to study behavioral and physiological abnormalities associated with drug abuse.

Symposium 1. Alcoholism and experimental models

Chair: A.Y. Egorov (Russia)

THE INFLUENCE OF INDIVIDUAL EMOTIONAL CHARACTERISTICS ON ETHANOL PREFERENCE FORMATION IN RATS

E.V. Filatova, E.O. Kutcher, A.Y. Egorov, O.B. Guzhova, K.O. Kulagina

Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St-Petersburg, Russia

Introduction: It is known that a number of psychological factors (relation to problem situations, information overloading, anxiety level, etc.) influence the formation of chronic alcohol consumption in rats. The goal of the study was to investigate the influence of individual emotional characteristics on the formation of ethanol preference in rats.

Materials and Methods: Research was carried out on 24 male Wistar rats. Eighteen species were exposed to a compulsory 10% ethanol solution intake during a 12 week period. The control group was composed of 6 rats which consumed water. Before the experiment began, all rats were given the two-bottle test to estimate their ethanol preference. The emotional condition of rats was elucidated before the experiment, after 6 weeks, and after the experiment, with the open field test and the Suok-test.

Results and Discussion: After 12 weeks, all ethanol drinking rats were divided into two groups based on the results of two-bottle test: those with less (group 1) and with more (group 2) ethanol preference.. The dynamics of ethanol preference formation essentially differed in these groups. In group 1 the gradual increase of ethanol preference was found in the first weeks of experiment. In the last weeks, a sharp decrease in ethanol preference, down to the levels of control rats, was observed. On the contrary, the 2nd group had much lower levels of ethanol preference (similar to those in controls) in the first weeks, with a subsequent sharp growth of preference that resulted in levels that were twice those of the controls at the end of the experiment. The analysis of individual emotional characteristics up to the Suok-test showed that group 1 rats initially had similar motor and exploratory activity to controls, while their anxiety levels were significantly higher than in group 2 rats. Rats from the second group did not have different anxiety levels than in controls, but had significantly lower motor activity. Thus, rats which refused ethanol at the initial stage of alcohol

misuse, strongly preferred it after 12 weeks,, in comparison to the rats which preferred alcohol in the beginning. Also, indicators of motor and exploratory activity, together with anxiety levels, can serve as a prognostic marker for the formation of ethanol preference in rats.

THE INFLUENCE OF CHRONIC CAFFEINE AND ETHANOL CONSUMPTION ON ALCOHOL PREFERENCE IN FEMALE RATS

E.O. Kucher, A.Y. Egorov, E.V. Filatova, K.O. Kulagina, O.B. Guzhova

Sechenov Institute of Evolutionary Physiology and Biochemistry RAS, St-Petersburg, Russia

Introduction: The consumption of alcohol-containing energy drinks, especially among adolescents, has increased during the last few years. However, there is a lack of information regarding the interaction of ethanol with other drink ingredients, including caffeine. The few experiments about caffeine's strengthening effect on the formation of alcohol motivation have contradictory data. The purpose of this study was to investigate the long-term influence of the combined effects of ethanol and caffeine on the formation of alcohol preference in rats.

Materials and Methods: This study was carried out on 30 adult female Wistar rats. 3 individuals were kept in each standard cage and they were on a standard diet. The rats were divided into 4 groups. During the 6-month experiment, group 1 had access only to a solution containing 10% alcohol and 0.4 g/l caffeine, group 2 had access only to a solution of 10% alcohol, group 3 had access only to a solution containing 0.4 g/l caffeine, and group 4 (control) had access only to water. Prior to the study, all rats were studied for ethanol preference in a two-bottle test.

Results and Discussion: Before the experiment, the two-bottle test showed low consumption of ethanol for all four groups (about 20% or less in relation to the total fluid intake) without significant differences. After a month of the experiment the consumption of alcohol was increased in all the groups except in the control. For the second month, all the experimental groups had significantly higher alcohol consumption than the controls. In fourth months the following was observed: Group 1 (alcohol + caffeine) had the greatest preference, followed by group 2 (alcohol), then group 3 (caffeine), and the minimum preference was observed in the control group. After five months, the preference for alcohol reached 80% in group 1 and 2, and was significantly higher than in groups 3 and 4. After sixth months the alcohol preference was significantly higher in all experimental groups compared to controls. When comparing experimental groups in group 1 the alcohol preference was significantly higher than in group 2 and 3; in group it 2 was significantly higher than in group 3. Thus, the study has showed that the combination of two psychoactive substances, alcohol and caffeine, significantly increases alcohol motivation in rats. The strongest preference for alcohol was induced by the combined consumption of ethanol and caffeine. This was followed by the consumption of pure ethanol, and then pure caffeine. These data also indicate that the combined consumption of psychoactive substances has a higher addictive potential compared to their individual usage. This resonates with some clinical data that indicates there is a more rapid formation of drug dependence in polysubstance consumption compared to monosubstance intake.

THE EFFECT OF ETHANOL ON EVOKED DOPAMINE RELEASE IN THE NUCLEUS ACCUMBENS OF ALCOHOL-PREFERRING AA AND ALCOHOL-AVOIDING ANA RATS

T. Shnitko

University of Eastern Finland, Kuopio, Finland

Introduction: The dopaminergic system has been implicated in the development of addiction to drugs of abuse including ethanol. It has been shown that ethanol could increase the extracellular concentrations of dopamine in the striatum. The alcohol-preferring (AA) and alcohol-avoiding

(ANA) rats is an animal model used widely for studying the behavioral and neurochemical aspects of ethanol consumption. The effect of ethanol on different monoamine neurotransmitters in the brain of these rats was studied in microdialysis experiments. It was found that ethanol significantly increased the extracellular concentration of dopamine in the nucleus accumbens of AA and ANA rats, but the lines' differences were not found [Kiianmaa et al., 1995; Tuomainen et al., 2003]. The delicate equilibrium between such neurochemical processes as dopamine release and reuptake and effects of low and high doses of ethanol on these processes in the striatum of Alcohol-Preferring AA and Alcohol-Avoiding ANA rats have been studied in the present work.

Materials and Methods: The dopamine overflow after stimulation of the median forebrain bundle was measured by constant potential amperometry in the caudate putamen (CPu) and the nucleus accumbens core (AcbC) of anesthetized animals. Two stimulation frequencies were used. The high frequency stimulation was applied for a 2-s period at 50 Hz. The low frequency stimulation was applied for a 5-s period at 20 Hz. The rats were injected with 0,1 and 3,0 g/kg i.p. of ethanol for studying the effects of ethanol on dopamine release and reuptake in the nucleus accumbens core.

Results and Discussion: The experiments showed lower evoked dopamine release in the caudate putamen (CPu) and the nucleus accumbens core (AcbC) of AA rats in comparison to ANA rats. The intraperitoneal administration of ethanol significantly decreased the DA release in the nucleus accumbens of AA and ANA rats. No difference in DA release between these rat lines was found. However, there was a significant difference in DA reuptake between AA and ANA rats after ethanol injections. Ethanol significantly decreased DA reuptake in AA rats.

Day 2. May 17, 2010

Plenary lecture 1. 120TH ANNIVERSARY OF INSTITUTE OF EXPERIMENTAL MEDICINE.

V. Klimenko

Institute of Experimental Medicine RAMS, St-Petersburg, Russia

This lecture will summarize a unique 120-year history of the Institute of Experimental Medicine (IEM) of the Russian Academy of Medical Sciences (RAMS).

Symposium 2. Genetic animal models of brain disorders

Chair: R. Gainetdinov (Italy)

UNDERSTANDING THE NEUROCHEMISTRY OF SCHIZOPHRENIA ENDOPHENOTYPES: GENETIC ANIMAL MODELS OF HYPERDOPAMINERGIA AND NR1 DEFICIENCY

R. R. Gainetdinov, Department of Neuroscience and Brain Technologies, Italian Institute of Technology, Genova, Italy

Introduction: There is a growing understanding that abnormalities in multiple neurotransmitter systems may be involved in the pathophysiology of schizophrenia. Two major neurochemical hypotheses that are based on pharmacological observations have been proposed to explain schizophrenia. The dopamine hypothesis suggests that either an excess of dopamine or an increased sensitivity to the neurotransmitter is the underlying pathological mechanism. A competing notion, the hypoglutamatergic hypothesis of schizophrenia, suggests that decreased glutamatergic transmission underlies schizophrenia. This is based on the ability of NMDA receptor antagonists to producing certain endophenotypes of schizophrenia.

Materials and Methods: In an attempt to understand the potential contribution of various neurotransmitter systems to particular endophenotypes of schizophrenia, several genetically modified animal models have been investigated.

Results and Discussion: A model of hyperdopaminergia can be produced with a mouse that has an inactive dopamine transporter gene (DAT-KO). This mouse displays hyperactivity, perseverations in cognitive tasks and deficient sensorimotor gating. These are endophenotypes of schizophrenia related to positive symptoms, and these behavioral deficits can be corrected by antipsychotic drugs. A model for a hypofunctioning glutamate system can be produced with a mouse which carries a hypomorphic allele of the NR1 subunit of the NMDA receptor. NR1 mutant mice display more complex sets of behavioral abnormalities that include mild hyperactivity, social dysfunctions, deficient sensorimotor gating, and cognitive impairment. These aberrant behaviors can be ameliorated more effectively by atypical rather than typical antipsychotics and thus NR1 deficient mice may have translational value for understanding endophenotypes of schizophrenia related to negative symptoms. Here I will discuss how these and other recent genetic animal models of aberrant neurotransmission may be instrumental to decipher the contribution of specific neurochemical abnormalities to certain endophenotypes of schizophrenia.

THE GENETICS OF TIMING MECHANISMS IN MICE

V. Tucci, Department of Neuroscience and Brain Technologies, Italian Institute of Technology, Genova, Italy

Introduction: The cognitive processes and the underlying neural functions that allow animals to evaluate time and to store, process, and retrieve temporal information are of paramount importance in a natural environment. Many neuropsychiatric and neurological interviews begin with questions about the time of day, the place where the patient is located, the year, and how long he/she has been there. This testifies to the fundamental role of our ability to localize ourselves in time. Furthermore, patients with Alzheimer's disease show attentional deficits which depend on timing characteristics and impairment. Two issues are crucial for determining how time is encoded by biological organisms. First, what is the origin of these cognitive abilities and what are the role of genes and the environment in shaping how time is encoded? Second, what are the underlying neural mechanisms? These are complex issues and, in the biological sciences, complex issues can be successfully addressed by using effective experimental paradigms in which specific and well-defined variables can be investigated in relative isolation with well-chosen animal model systems.

Materials and Methods: The identification of animal models (e.g. the mouse) with cognitive abnormalities related to timing represents the next frontier in the study of cognitive genes. Because of the complex nature of cognitive phenotypes, it is often difficult to identify appropriate models in mice. However, a successful approach in the study of gene function is the incorporation of systematic, hierarchical and high-throughput phenotypic analyses. A set of promising paradigms in phenotyping cognition in mice have been the development of temporal tasks. In timing learning paradigms, conditioning is directly evident in the timing of the conditioned response.

Results and Discussion: Recently we have developed automated systems to study mouse phenotypes and we have screened for mouse mutant models. By extracting quantitative properties of underlying timing responses we have identified phenodeviants for timing phenotypes in ENU mutagenised mice.

THE SIGNALING PATHWAYS FOR ANIMAL MODELS OF STRESS AND DEPRESSION

E.T. Tzavara

INSERM Institute, Créteil, France

Introduction: Several lines of evidence indicate that signal transduction pathways play an important role in the regulation of affect, the pathogenesis of mood disorders, and may constitute novel targets for the management of these disorders. We, and others, have shown that signaling proteins can act as molecular switches to reversibly alter the function of neuronal networks that are related to affective responsiveness and kinase/-phosphatase pathways that are important mediators of antidepressant action.

Materials and Methods: We have used novel pharmacological tools and genetically modified mice to decipher the specific role of the ERK pathway in environmental and genetic regulations relevant to depression.

Results and Discussion: Altering ERK signaling modules decreased immobility in the tail suspension and the forced swimming tests in naïve mice, and reversed blunted sucrose preference and coat degradation in chronically stressed mice. Also in chronic paradigms there was a markedly reduced delay for the onset of action for antidepressant treatments. These effects were paralleled by changes in ERK dependent synaptic activity and gene regulation, suggesting that ERK signaling is a key regulator of synaptic plasticity in response to stress and to antidepressant actions.

Research Support: INSERM

NOLDUS-OPEN SCIENCE Workshop
COMPLETE SOLUTIONS FOR BEHAVIORAL RESEARCH

D.D. Vorontsov, R.F. Roelofs

OpenScience Ltd, Moscow, Russia; Noldus Information Technology, Wageningen, The Netherlands

The OpenScience company was established in 2006 by a group of neuroscientists from the Moscow State University, to provide Russian researchers of animal behavior with non-expensive and locally made research equipment like mazes and arenas. Since then, we have diversified our activity. Currently, we offer arenas for many standard behavioral tests (like open field, plus-maze, t-maze etc; see www.openscience.ru for details), but nowadays, we also have the facilities to produce custom-made mazes and/or equipment with state-of-the-art machines and materials for scientists all over Russia and beyond. Since we are neuroscientists ourselves and have a background in animal behavioral research, we have a thorough understanding of what the researcher needs: we use recently published protocols, select appropriate materials and test the newly-developed equipment in real experiments. Our co-operation with Noldus IT enables us to offer the Russian researcher a complete solution for behavioral research – that includes the best of two worlds: Locally made hardware, state-of-the-art software and, of course, extended technical support from our Moscow based company. The fact that we produce large-scale equipment locally and that we are a reseller of the Noldus IT software (e.g. EthoVision XT, The Observer XT, Theme and Catwalk; visit www.noldus.com for more details) allows us to ship everything from within Russia and gives our customers the possibility to pay in local currency without having to worry about the difficult and expensive import of foreign equipment. Finally, this co-operation allows us to offer the Russian researchers a complete behavioral research solution for a similar price as our colleagues abroad would have to pay. During the presentation we will show our products for animal behavioral research, how they are developed and produced. And finally, I will discuss the complete solutions we can offer for stress related research in combination with Noldus software.

Symposium 3. Experimental models in biological psychiatry

Chairs: A. Kalueff (USA), V. Klimenko (Russia)

THREE-DIMENSIONAL RECONSTRUCTION OF ZEBRAFISH EMOTIONAL BEHAVIOR

J. Cachat, A. Stewart, K. Wong, S. Gaikwad, A. Kalueff

Pharmacology Department and Neuroscience Program, Tulane University Medical School, New Orleans, USA

Introduction: The use of adult zebrafish is rapidly proliferating in neurobehavioral research. As behavioral assays are developed, techniques for quantifying swimming activity are continuously improved. In the process of researching affective states in adult zebrafish, our lab has developed a technique to reconstruct individual swimming paths.

Methods: Video-tracking was performed by Noldus Ethovision ET7 (Noldus Technologies, Netherlands) and swim tracks were exported into separate Excel sheets. Track data was formatted and imported into RapidMiner 5.0 Community Edition (Rapid-I, Germany) to reconstruct swimming paths in a 3D color scatter plot. These 3D paths can be reproduced across temporal or spatial landscapes, providing an intuitive environment for examining behavioral profiles. Moreover, qualitative variables (i.e. velocity, mobility) can be represented across these paths as color variations.

Results and Discussion: With the ability to zoom in and out across the trace and apply various endpoints, these reconstructions allow for in-depth analysis of specific pharmacological or psychological treatments on zebrafish behavior. Promoting these techniques to deconstruct affective behavior in adult zebrafish improves neurobehavioral research by better characterizing natural behaviors of this species and also increasing the throughput of zebrafish behavioral assays.

Research Support: NARSAD Young Investigator Award, TU/LSU CTRECP Pilot Grant, LABOR PFund Grant, TU Intramural Research Funds

CLEVER SYS. INC. PRESENTATION:

GROOMING BEHAVIOR DETECTION USING AUTOMATED VIDEO ANALYSIS

J. Cachat, J. Goodspeed, T. Micheli, A.V. Kalueff, Y. Liang, V. Kobla, Tulane University, Clever Systems, USA

Introduction: One of the most widely recognized underlying mechanisms of numerous diseases is stress. Stress has a physiological and psychological component, affecting the organism from the onset of a perceived stressful event, through the duration, and for an undefined period thereafter, until the body returns to a state of homeostasis. Identifying whether an animal is experiencing a stressful situation is difficult, as one must interpret the animal's behaviors. The home cage is the most natural setting for a laboratory animal, and therefore is an ideal setting for assessing behavioral changes due to stress. Home cage monitoring in the past has been complex and time consuming; the mere act of having someone watch the animal and record its behavior, changes the animal's behavior. In addition, video recording and manual observation could lead to confounds due to human interpretation. Recent advances in lab automation has allowed for the observation and analysis of home cage behaviors. Since self-grooming is an intrinsic behavior within rodents, and has been shown to increase in rodents during periods of high and low stress (Kalueff & Tuohimaa, 2004), manual scoring of grooming has been compared to automated scoring using Clever Sys, Inc.'s HomeCageScan, in an effort to determine if automated systems can be a useful means of identifying stress in rodents.

Materials and Methods: All mice were exposed to a similar period of predator stress, prior to behavioral observations. For grooming behavior evaluation, mice were placed in a small clear cylinder measuring 6 inches in diameter and 10 inches in height. Mice were video-recorded for 5 minutes each. Behavioral measures were manually scored, indicating the total number of grooming bouts as well as the total self-grooming duration. For manual scoring, grooming bouts were defined as paw licking, nose and face wash, head wash, body licking, leg licking, and/or tail/genital grooming. There was no specific minimum length threshold for a groom bout for manual scoring. Videos were then analyzed using HomeCageScan (Clever Sys, Inc., Reston, VA) for grooming behaviors. HomeCageScan detects grooming behaviors by analyzing the body movement patterns of the rodent. A minimum time threshold of 3 seconds was used, implying that only grooming bouts lasting at least 3 seconds would be detected.

Results and Discussion: Initial manual scoring of the behavioral sessions produced increased bouts of grooming as well as decreased durations, as compared to automated analysis. This difference in grooming results is thought to be due to the constrained threshold of grooming exercised during the automated analysis. Mice had to remain grooming for a minimum of 3 seconds prior to the computer indicating that a grooming event was taking place. Manual analysis calculated any event in which the animal's nose or feet came into contact with any of the targeted body parts, regardless of duration. Videos are in the process of being re-analyzed manually, using the same criteria of duration as the automated system. Preliminary analysis suggests that the stringent manual scoring and automated scoring will be correlated, giving researchers another tool to identify possible stress, within their animal model.

MOTOR ACTIVITY CHANGES IN THE OFFSPRING OF FEMALE RATS INDUCED WITH EAE DURING THE GESTATION PERIOD

C.C. Chan, I.N. Abdurasulova, M.N. Karpenko, V.A. Schukina, V. M. Klimenko
Institute of Experimental Medicine RAMS, St-Petersburg, Russia

Introduction Pregnant women with multiple sclerosis (MS) have significantly reduced disease activity, especially during the 3rd trimester, and an increase of disease activity during the 3rd to the 6th month postpartum. Pregnancy delays the onset and reduces the incidence of disease, which has been shown from studies in experimental autoimmune encephalomyelitis (EAE), an animal model for MS. However, there is no investigation about their children's behavior and growth weight. Investigating the effect of pregnancy on the appearance of symptoms of EAE, the differences of growth weight and behavior between the offspring of mothers with EAE induced and those whose mothers were healthy.

Materials and Methods: 40 female Wistar rats were divided into 4 groups (10 for each): 1) pregnant rats with EAE induction, 2) pregnant rats without EAE induction, 3) non-pregnant rats with EAE induction, 4) non-pregnant rats without EAE induction. Inoculation of homological spinal cord homogenate (HSCH) with complete Freund's adjuvant was done to induce EAE in pregnant rats on day 12-14 of pregnancy. The severity of neurological disorders was estimated with a clinical index (c.i.) from 0 (without disorders) to 6 (lethality) by the existence of clinical symptoms – muscular weaknesses, pareses and paralyses. When the offspring became 1 month old, their motion activities were tested by the Reil test and the «Open field» test. The number of infant rats tested was 128(54 from control group and 74 from experimental group). In the «Reil» test, the following parameters were analyzed: 1) T1 – latency time; 2) T2 - time of running; 3) M - number of mistakes. In the «Open field» test, we estimated the horizontal and vertical locomotion activity, exploratory activity and anxiety on 11 behavior parameters. Then, the results were analyzed.

Results and Discussion: HSCH inoculation induced disease of different severity in 95.3% of non-pregnant females and in 20% of pregnant rats. There was one rat that showed the symptoms of EAE during pregnancy (c.i.=6) and one rat that showed the symptoms of EAE after giving birth (c.i.=4). The infant rats from females with EAE showed decreased growth weight in comparison with infant rats from normal rats. The growth weight of experimental rats was lower than normal rats by 20 g on day 18. In the Reil test, experimental rats showed increases in T1 in comparison with control rats. The data obtained in the open field test showed a decrease in locomotion average time duration, an increase in absolute value and total time duration in movement in situ of experimental group in comparison with control group. Also, a slight decrease in average time duration of stand with support and an increase in absolute value and total time duration of “vertical” position, absolute value of sniff round and step in “burrow” were also observed. It is suggested from the data obtained in this experiment that there are differences in growth weight and behavior between offspring from mothers with EAE and those from healthy mothers.

D1 AND D2 DOPAMINE RECEPTOR ACTIVATION NORMALIZES BEHAVIOR IN MALE AND FEMALE RATS WITH PTSD MANIFESTATIONS

S.G. Tsikunov, A.G. Pschenichnaya, A.G. Kusov, G.V. Beznin, S.G. Belokoskova
Institute of Experimental Medicine RAMS, St-Petersburg, Russia

Introduction: The investigation of mental diseases, such as depression and posttraumatic stress disorder, (PTSD) is becoming increasing important. Mental trauma is known to play a considerable role in the pathogenesis of these diseases. Some reports in the literature suggest that psychological

trauma is a risk factor for the development of PTSD. The data obtained in our laboratory showed that both male and female rats develop PTSD manifestations after being exposed to mental trauma. Despite numerous investigations of the problem, the neurophysiological mechanisms underlying pathophysiology of PTSD remain unclear. Nowadays antidepressants are extensively used for treating PTSD patients and these lead to alterations in metabolism of monoamines in brain tissue. The noradrenergic, serotonergic, dopaminergic, glutamatergic, and other stress-activating systems are known to be active in forming and maintaining the depressive mood. This led to the development of hypotheses which proposed that there is a correlation between pathological changes in behavior and disturbances of monoamine metabolism in the brain.

The aim of the study was to investigate the behavior of male and female rats following psychotraumatic experiences, and the mechanisms of emotional compensation and behavioral disturbances through analyzing the manifestation of these abnormalities by the actions of 5-HT and dopamine system receptor ligands.

Materials and Methods: The model of mental trauma utilized to manifest PTSD in rats was the experience of a cage mate's death from a predator's (python's) actions. 4 groups of 15 rats (two male and two female, 200–250 g) were exposed to a predator for 25 min. The rats which survived were then returned to their regular cages. The antidepressants were administered intraperitoneally from 2-4 p.m., for 21 days after the psychotraumatic event. Piribedil (an agonist of D1 and D2 dopamine receptors, 0.72 mg/kg) and fluoxetine (selective serotonin reuptake inhibitor, 0.64 mg/kg) were used. The same durations and volumes were used when injecting saline into the controls. The substances were given in doses similar to those used in humans for the treatment of depression. The emotional state of both male and female rats after the psychogenic trauma was examined following antidepressant treatment. The open field test, elevated plus-maze test, intruder-resident, and Porsolt's tests were used to assess behaviors and emotional states.

Results and Discussion: The results of the present study demonstrate that there are changes in behavior in rats that survived a mental trauma. The behavioral manifestations of PTSD were ameliorated by the antidepressants. The administration of fluoxetine and piribedil promoted the normalization of exploratory activity and decreased anxiety. However, fluoxetine did not affect the level of aggression in either male or female traumatized rats with the doses used. On the other hand, the dopamine receptor agonist piribedil normalized aggressive behavior. The reductions in emotional disturbances in rats of both genders that are achieved by the activation of D1 and D2 dopamine receptors provide evidence for the involvement of the dopaminergic system in the development of depression and PTSD. The administration of fluoxetine after psychogenic trauma was shown to increase locomotory activity in female rats and the exploratory behavior in male rats in open field test. The levels of anxiety and immobility fluoxetine were decreased only in male rats. The introduction of piribedil increased the exploratory behavior in female rats as well as decreased the freezing pattern in males and females in the open field test. When compared to the controls, immobility in the Porsolt's test was only decreased in female rats. The introduction of piribedil following the psychogenic stress caused significant decreases in the levels of anxiety in rats of both genders in the elevated plus-maze, and in the level of aggression in the intruder-resident test.

VISUALIZATION OF A COMMON STRUCTURE OF SOCIAL BEHAVIOR DEVELOPMENT IN DOMESTIC CHICK AND COMMON MARMOSSET

M. Koshihara, M. Suzuki, K. Yamazaki, A. Seno, M. Okuya, D. Mochizuki, Y. Sugiura, K. Shimizu, Y. Shirakawa, K. Mimura, I. Aoki, I. Kanno, Y. Honda, I. Tanaka, T. Kodama, H. Tokuno, S. Usui, S. Nakamura

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Introduction: Psychiatric diagnoses are mainly based on qualitative judge of behavior expression in DSM IV or ICD 10. These diagnoses represent a collective clinical knowledge and a guideline for clinical care. The experience-based clinical knowledge, therefore, remains to be reinforced and paralleled by the scientific reasoning behind it. Although non-invasive imaging and brain activity measurement revealed the plausible neuronal basis of social behavior and cognition, animal models of psychiatric disorder are urgently needed to investigate the molecular basis of neural circuit development. Here, we have established a peer social interaction model where the cross-modal sensory-motor integration played an important role in the development of social behavior.

Methods: Animals (chicks and marmosets) were reared under either grouped or sensory cue-deprived conditions and tested for social behavior using multi-behavior parameter integration analysis based on principle component analysis. Call behavior was analyzed using syrnix software (Dr. J. Burt).

Results and discussion: Chick reared under tactile sense-deprived conditions developed quite similar social behavior (to the group-reared chicks) that was supposedly like their adaptation to each social context as stereotype patterns. However, chick under acoustic and tactile sense-deprived condition behaved anxiously like the chick reared entirely in social isolation. Two sibling marmosets in care of their parents were able to differentiate emotional calls in alert and affiliated type until adolescent age (postnatal day 210). At the same time, a single sibling with its parents, or in care of humans, showed unique behavior pattern, respectively.

Conclusion: Chick and marmoset developed a common social behavior pattern where emotional calls were differentiated into "alert" and "affiliated" type, depending on peer social interaction. This visualization suggests some homologous or unique brain mechanism over evolutionary trees.

STRESS, COGNITIVE FUNCTIONS, AND THE CEREBROPROTECTIVE EFFECTS OF NEUROPEPTIDE DRUGS IN ITS REGULATION AND COMPENSATION (THE EVOLUTIONARY ASPECT OF THE INVESTIGATION)

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Introduction: One of the most significant problems currently facing modern neurophysiology and medicine is the compensation of different stresses. It is known that the Higher Nervous System Functions (Cognitive Functions) are the first to suffer from different stresses. At present, the biologically active peptides such as Semax (Sem), Selank (Sel) and nootropes Noopept (Npt) are believed to help repair brain function disturbances. It has been known that application of Sem, Sel and Npt exert positive therapeutic effects on different neurological diseases. Currently, there is no experimental data on the compensatory influences of these drugs on disturbances of Higher Nervous System Functions in primates. Also, the evolutionary aspect of this problem has not been studied.

Materials and Methods: The present work is devoted to the study of the roles of Sem, Sel and Npt in compensating for mental disturbances (mnestic, cognitive) and vegetative functions in the phylogenetically ascending series of mammals, insectivores, rodents and primates. The experiments were carried out under the conditions of free behavior and the primatological chair (monkeys) was conducted using the multiparametrical computer registration of EEG, vegetative and motor indices. Some types of memory such as conditional, operative, short term and image memory have been investigated.

Results and Discussion: The dynamic amnestic disturbances of these types of memory were traced. Sel, Sem and Npt drugs were administered intranasally or intramuscularly, peroral (Npt) in doses of 30-100 mkg/kg, 0,5-1 mkg/kg and 1 mg/kg respectively. It has been established that the role of Sel and Sem is wholly uniform in hedgehogs with neurosis. Such effects are expressed more

with inherent forms of behavior. It has been shown that the effects of drugs on the simple forms of Higher Nervous Activity have uniform, nonspecific, facilitative characters. The compensatory effects of peptide drugs on the memory disturbances have no distinct character. Contrary to insectivores, rodents have a clear tendency to compensate for Higher Nervous Functions disturbances. At the Sem and Sel background, the delayed conditional reflexes (DCR) were restored. It has been established that the cerebroprotective effects of Sel exerted more significant influences upon the brain function disturbances in neurotic rats. Contrary to the results found in lower mammals, the application of Sel, Sem and Npt to neurotic monkeys exerted different effects upon the Higher Nervous System Function disturbances. The compensatory effects of drugs are dose dependant in nature, being more effective with intranasal administration and having different effects on the various types of neurosis. It has been shown that the intranasal administration of Sel induced long lasting changes in the behavioral disturbances of monkeys during neurosis (disappearance of aggression, the facilitation of handling-reactions and communication). The long duration compensation of the mental disturbances (the EEG and homeostatic parameters of memory processes) took place during the Sel (30-50 mkg/kg) administration. The anti-stressor effects of Sel are independent of neurotic type disturbances, and are long lasting (6 months). The cerebroprotective effects of Sem are especially significant with the administration of low drug doses (0,3-0,5 mkg/kg). With Sem administration, the operative memory and DCR are intensified. After Sem, ultra-small doses of the sedative are administered over 10-14 days. It has been shown that Npt increases attention and concentration. The application of Npt (0,5 mg per 20 days) in old (35+ years) monkeys with neurological deficits and cognitive disturbances provides long lasting positive therapeutic effects on the neurological, motor, and homodynamic disorders. Our data may serve as a neurophysiological underpinning for the differential application of Sem, Sel and Npt in neurological clinics.

SPATIAL MEMORY DERANGEMENTS INDUCED BY INCREASED LEVEL OF INTERLEUKIN-1B IN EARLY POSTNATAL ONTOGENESIS

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Introduction: Parturient injuries, brain ischemia, hypoxia, allergic and infectious diseases sustained in early childhood frequently result in cognitive disorders in children and adolescents. It is well known that the pathological states of newborns are accompanied by increased production of proinflammatory cytokines, particularly interleukin-1 β (Il-1 β), in cells of the nervous and immune systems. The aim of our study was to explore the influence of increased levels of Il-1 β in early postnatal ontogenesis on spatial memory in a mature age.

Materials and Methods: Subjects were male pups of Wistar rats. Recombinant human Il-1 β was injected in a moderate pyrogenic dose of 1 μ g/kg daily during the third week of life. Rats injected with saline in the same period were used as a control. Spatial memory of the sexually mature animals was tested in 2.5 months using the Morris water maze – a round tank, 1.5 m in diameter, filled with water mixed with milk to make it opaque. In the spatial memory experiments, rats were trained to find the location of a hidden platform, submerged 1 cm below the water surface, using visual cues located on the inner sides of the tank. Training consisted of four trials per day, with 15-minutes breaks between trials, for four days.

The conditioned activity of animals was tested on the fifth day. In the first study, the extinction reaction was evaluated: the platform was removed and the time that experimental and control rats spent in segment of the maze where the platform was situated before was measured. In the second study, the rearrangement of the conditioned reflex was investigated. The platform was placed at the fifth day in other positions of the maze. The rats had the opportunities to find the new position of the

platform during two days. The tracks of animals were recorded with a video monitoring system in a computer's memory, and the length of tracks, time of searching and speed were analyzed.

Results and Discussion: Analysis of rats' behavior revealed the rigidity of conditioned activity of the experimental animals. The extinction of the habit of movement to the position where the platform was situated in the past was lower and the time spent searching for the hidden platform was more in experimental rats compared with control animals.

Thus, the increased level of $IL-1\beta$ in early postnatal ontogenesis leads to spatial memory derangements and greater rigidity of conditioned activity in a mature age.

Research Support: Supported by RFBR Grant № 08-04-01335.

Day 3. May 18, 2010

TSE SYSTEMS Workshop

PROGRESS IN AUTOMATED MULTI-DIMENSIONAL HOME CAGE PHENOTYPING OF MOUSE AND RAT MODELS OF HUMAN DISEASES

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Introduction: Investigations into genetically modified laboratory mouse and rat strains provide valuable insight into the mechanisms of various human diseases and give new chances for drug development and therapies. The task of comparative in-vivo phenotyping of a large number of different mice strains has created specialized centers where it can be performed systematically. Behavioral phenotyping of suited mice strains is a prerequisite for understanding the mechanisms of mental illness, while metabolic phenotyping is important e.g. for fighting the epidemic of obesity.

Materials and Methods: Classical behavioral phenotyping is performed by a large set of individual tests that are dedicated to checking different individual behaviors (Karl et al., 2003). This tedious and time consuming work is performed by specialists who do not use the same test equipment or highly specialized apparatus (Nguyen et al., 2006). The risk of having an experimenter influence the results is well known. In order to increase throughput as well as to perform these investigations in environments where animals are subjected to a minimal amount of stress, within the past few years, new technologies have led to new types of automated equipment that are based on standard home cages.

Results and Discussion: We report on two complementary automated phenotyping systems and their applications: IntelliCage by NewBehavior – a unique solution for automated monitoring of stress-free behavior in social groups (Krackow et al., 2010) and PhenoMaster by TSE – multi-dimensional automated behavioral and metabolic phenotyping of mice and rats in a home cage test battery for a large number of animals in parallel (Urbach et al., 2010). IntelliCage is designed for long-term high-throughput investigations of cognitive abilities in laboratory mice. Socially housed mice (in group of up to 16 transponder-tagged mice) can perform a variety of freely programmable behavioral tasks within one common large home cage. Simple to complex conditioning tasks can be programmed in a uniquely flexible manner and controlled for each animal inside the IntelliCage. The individually tailored experimental protocols are automatically run and analyzed for these animals simultaneously in the same cage. This allows the investigation of experimentally-induced phenotypic or genotypic effects on cognitive abilities as well as activity patterns. Such behavioral screening is frequently required in biomedical and basic behavioral, neurobiological, pharmacological and genetic research, with exceptional high efficiency and standardization and minimal work load. Practically no interference by the human investigator can occur. IntelliCage offers enormous flexibility for designing a variety of behavioral and conditioning protocols. The following behavioral domains are covered by programmable tasks: Spontaneous behavior – anxiety, neophobia, exploration, behavioral stereotypies, habituation, circadian activity; Spatial and temporal behavior – place preferences and avoidance learning, reversal learning, spontaneous alternation, temporal conditioning, patrolling schedules; Discrimination learning – visual discrimination, gustatory discrimination, spontaneous drug preference or avoidance; Memory – habituation, working and reference memory, gustatory memory, procedural memory; Operant conditioning – fixed or progressive ratio conditioning, differential reinforcement of low responding (DRL). IntelliCage allows for investigations excluding animal handling induced stress, ensures high animal welfare, leads to a reduction of animal numbers needed for complex studies, a substantial reduction of routine work for technicians and scientists, and an assurance of high standardization of the procedures.

PhenoMaster is a multi-dimensional modular research platform for automated, integrative, and precise assessments of various behavioral, physiological and metabolic parameters within a home cage environment that assures an exceptionally high throughput. The PhenoMaster System enables individual, automated, and detailed short- or long-term monitoring of small laboratory animals performing various integrated behavioral assays. The modular structure of the hard- and software components allow the integration of additional hypothesis-driven paradigms and modules. Consequently, PhenoMaster distinguishes behavioral and physiological phenotype alterations induced by various genetic, epi-, nongenetic or pharmacological manipulations. Functional modules allow for automated monitoring of food and liquid intake behavior, including programmable food and liquid intake control. Automated body weight assessment is available as well as automated urine and feces monitoring (separation and quantification). Automated metabolic monitoring is performed by indirect calorimetry including exercise calorimetry. □ Automated three-dimensional home cage locomotor activity monitoring is a basis and can be combined with an assessment of running wheel activity including time, distance, and workload control. Motor functions can be screened by automated motor skill testing using special running wheels. PhenoMaster can be applied for assessments of pain sensitivity, novelty exploration, and anxiety. Cognitive functions are checked by automated and programmable operant walls inside the home cage (with different reward qualities available: pellets, liquid, wheel running) thus providing assessments of associative learning and memory. The application of PhenoMaster for rats has been performed inside the EU research project *RATstream*TM while *PhenoScale* assures development for even higher throughput and further scientific validation with selected mutant mice strains. In conclusion, the PhenoMaster System opens new dimensions for a variety of low-stress in-vivo research approaches and phenotyping in biomedical and preclinical science. The post-genomic era profits from new technological advances which will bring higher throughput and low-stress testing into rodent in-vivo phenomics, thus assuring a new quality of results in this important research field.

Symposium 4. Translational biological psychiatry

Chairs: A. Kalueff (USA), V. Klimenko (Russia)

THE EFFECTS OF MIDAZOLAM AND D-CYCLOSERINE ON THE RELEASE OF GLUTAMATE AND GABA IN THE BASOLATERAL AMYGDALA OF LOW AND HIGH ANXIETY RATS DURING THE EXTINCTION TRIALS OF A CONDITIONED FEAR TEST

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Introduction: In this paper, we attempted to answer the questions of how midazolam and D-cycloserine might regulate the tonic activity and/or phasic reactivity of brain neurotransmitter systems to fear evoking stimuli, and how this accounts for their ability to effectively modify the behavior of rats which differ in the strength of their fear responses. We used a new animal model with high (HR) and low (LR) anxiety rats, that were selected according to their behavior in the contextual fear test (i.e. the duration of a freezing response was used as a discriminating variable).

Materials and Methods: We used an animal model with high (HR) and low (LR) anxiety rats. The rats were divided according to their behavioral responses in the conditioned fear test (CFT): HR - (high responders, freezing time longer than the mean + SEM) and LR (low responders, freezing time shorter than the mean - SEM). On the 8th day after CFT, all animals were re-exposed to the testing box, and the freezing response of rats was examined without any aversive stimulation - context extinction. To assess the glutamate and GABA release in the amygdala, we used the

standard method of microdialysis in vivo. 30 min before the context extinction session, midazolam (0.75 mg/kg), D-cycloserine (15 mg/kg) or saline (0.9% wt/vol) were given intraperitoneally to animals with microdialysis probes implanted into the basolateral amygdala.

Results and Discussion: The results showed that a pre-extinction session administration of D-cycloserine (15 mg/kg, i.p.) significantly enhanced the inhibition of an aversive context-induced freezing response observed during the extinction session in the HR and LR rats, whereas midazolam (0.75 mg/kg, i.p.) accelerated attenuation of fear responses only in the HR rats. The less anxious behavior of LR animals given saline was accompanied by an elevated concentration of glutamate and GABA in the BLA in comparison with HR rats, and a stronger elevation of GABA in response to the contextual fear. In the more anxious HR animals, the pretreatment of rats with D-cycloserine and midazolam significantly increased the local concentration of GABA and inhibited the expression of contextual fear. The previous and present findings suggest that animals which are more vulnerable to stress, might have innate deficits in the activity of brain systems that control the activity of the prefrontal cortex, and enhanced reactivity of limbic structures that would normally allow them to cope in a balanced way with stressful situations. These results may help to better understand the mechanisms of individual differences in the effects of anxiolytic drugs, found among the patients with anxiety disorders.

Research Support: The study was supported by statutory Grant No. 5010308050 from the Institute of Psychiatry and Neurology, and by Grant No. 0440/B/P01/2009/36 from the Ministry of Science and Higher Education (ML), Warsaw, Poland.

DIFFERENCES IN THE DENSITY OF GABA(A)R ALPHA-2 SUBUNIT AND GEPHYRIN IN THE BRAIN STRUCTURES OF LOW AND HIGH ANXIETY RATS IN BASAL AND FEAR-STIMULATED CONDITIONS

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Introduction: The aim of the present paper was to examine differences in the density of GABA-A-R alpha-2 subunits and gephyrin (postsynaptic scaffolding protein at GABAergic synapses) in the brain structures of low and high anxiety rats.

Materials and Methods: In experiments we used an animal model using high (HR) and low (LR) anxiety rats. The rats were divided according to their behavioral responses in the conditioned fear test (CFT): HR - (high responders, freezing time longer than the mean + SEM) and LR (low responders, freezing time shorter than the mean - SEM). 7 and 14 days after the test, the animals were exposed again to the aversive context (extinction sessions). On the 20 and 21st days, animals were retrained and reexamined in the conditioned freezing test. We analyzed the expression of the alpha2 subunit of the GABA-A receptor and gephyrin in basal conditions, (7 days after contextual fear conditioning test) and 1.5 h after retesting, with the Western blot technique.

Results and Discussion: We found that HR rats showed a marked decrease in the conditioning of fear responses in the conditioned fear test (CFT) over the course of two extinction sessions (7 and 14 days after), in comparison to the control and LR groups. After re-testing, the freezing response of HR rats almost returned to the pre-extinction value. The behavior of the LR group remained unchanged at different stages of the experiment. There appeared to be no differences in the basal expression of examined proteins, except for overexpression of alpha-2 subunits of GABA-A receptors in the amygdala in the HR(vs. control rats). After retesting, the density of alpha-2 subunits were significantly increased in HR animals in the amygdala and prefrontal cortex (vs. control, not fear conditioned animals, and LR rats), and in the hippocampus (vs. LR rats). The expression of gephyrin was increased in the hippocampus of HR animals (vs. LR rats), but remained unchanged in the amygdala and prefrontal cortex. Moreover, there was a significant negative correlation

between the expression of alpha-2 subunits in the amygdala and the duration of freezing time in the HR group. The current data indicate that the neurochemical profiles of both groups of animals were qualitatively different, with distinct brain structures involved in the organization of a response to the conditioned aversive stimulus. This finding supports other data on the role of alpha-2 subunit in the basolateral amygdala in the expression of anxiety-like behavior. The animals more vulnerable to stress (HR) might have innate disturbances in the activity of intracellular systems controlling the trafficking of GABA-A receptors in the limbic structures (hippocampus and amygdala), involved in the control of emotional behavior.

Research Support: The study was supported by statutory Grant No 5010308050 from the Institute of Psychiatry and Neurology and by Grant No. 0440/B/P01/2009/36 from the Ministry of Science and Higher Education (ML), Warsaw, Poland.

EMOTIONALLY CHALLENGED BEHAVIOR IN γ -SYNUCLEIN KNOCK-OUT MICE

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Introduction: Gamma(γ)-synuclein is a member of the synuclein family of cytoplasmic and predominantly neuronal proteins that appeared late in evolution and only in vertebrates. In the axons and presynaptic terminals of neurons located in regions that are involved in emotions, substantial amounts of γ -synuclein have been detected during learning and memory. The role of γ -synuclein in these brain functions has not been previously assessed. We have demonstrated for the first time that the loss of γ -synuclein results in a significant increase of orientation responses in new situations, an elevated risk tolerance, and a decreased state of anxiety.

Materials and Methods: Behavioral tests: novel cage, dark-light box, o-shaped elevated maze, open field. Molecular techniques: PCR.

Results and Discussion: We identified significant differences in emotional behavior between the γ -synuclein knockout mice (γ -KO) and the control group. The lack of γ -synuclein gene has the following consequences. Mice lacking the γ -synuclein gene were determined to have an increase in the orienting responses during the "Novel Cage" test and "O-shaped elevated maze". Secondly, the distinguishing feature of γ -KO mice was their high risk tolerance which was evident because of the increased time that mice spent in the non-fenced segment of the elevated O-shaped maze. This parameter was also confirmed by the amount of time that the group of γ -KO mice spent in the center of open field after a single presentation of stress factors (i.e. high illumination). The study of the general anxiety of γ -KO mice indicates their reduced level of anxiety in the relation to those of the control animals. These findings were confirmed by the results obtained in the O-maze test and the motor activity in the open-field test. We found that γ -synuclein is directly involved in regulating the functions of higher nervous activity.

Research Support: The research was supported by the Russian Foundation for Basic Research grants No. 09-04-01412-a and by the project of Russian Academy of Sciences "Fundamental Sciences for Medical Research".

QUANTITATIVE TRAIT LOCI (QTL) ANALYSIS OF BEHAVIOR IN THE ZEBRAFISH.

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Introduction: Domestication selection has been performed in several different animal species, and has led to numerous differences between the selected populations and their wild counterparts (termed the 'domestication syndrome'). Principally these have included changes in growth,

reproduction, and time to sexual maturity, though behavioral differences are also ubiquitous throughout such domesticates, leading to a decrease in anxiety-related traits and anti-predation behavior (close association with conspecifics, extreme vigilance, etc). Such changes may be brought about unintentionally, simply by prolonged breeding in captive conditions, where increases in fecundity are desirable, and with an absence of any predators. Though not classically a domesticated species, the zebrafish has nevertheless been maintained in controlled laboratory conditions for many generations and as a variety of different strains. Such strains often show strong differences in growth and behavior as compared to their wild-derived progenitors.

Materials and Methods: Population differences between a laboratory strain, AB, and a wild-derived population from Bangladesh were used as the basis for a Quantitative Trait Loci (QTL) study, to determine the genetic basis for the phenotypic differences. An F2 intercross was performed, comprising of 184 individuals genotyped with 65 fully informative microsatellite markers. Individuals were assayed for shoaling tendency (a conspecific association test) and predator inspection (a boldness-related explorative behavior).

Results and Discussion: Standard Interval Mapping analysis revealed two significant and one suggestive behavioral QTL, whilst a more advanced 2 x 2 digenic epistatic analysis revealed one significant and two suggestive epistatic pairs of loci. These results serve to identify some of the underlying genetic architecture of anxiety-related behavior in the zebrafish and also act as a proof of principle as to the amenability of the zebrafish to such types of analysis.

METRIS Workshop

ANIMAL BEHAVIOR AND THE MATRIX METHOD FOR AUTOMATED BEHAVIOR ANALYSIS. LABORAS SYSTEM – THE MATRIX PARAMETERS AND INTEGRATION OF PHYSIOLOGICAL RESULTS WITH TELEMETRY PARAMETERS

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Metris B.V., The Netherlands

Introduction: The study of animal behavior, particularly from evolutionary and ecological viewpoints, has been one of the major growing areas in biology over the last 15 years. Animal behavior is an interpretation of internal and external factors (stimulus).

BEHAVIOR = Function {Internal stimulus, external stimulus}; Where the “internal stimulus” is a process or function in the animal body, and the “external stimulus” is a function, process, or parameter from the environment, outside of the animal’s body. Behavioral pharmacology is an area in preclinical research that investigates the effects of drugs on the behavior of a laboratory animal. The drugs produce specific effects in the body in terms of stimulus and energy changes (e.g. biochemical energy, internal energy, entropy). Changes in the potential energy of the body of an animal will result, after some time, in changes in the kinetic energy of the animal, which will be amongst others expressed in the behavior. Goal of the behavioral study - **Behavior = Function {Dynamic Internal Stimulus/Drugs effects}; if external stimulus = constant**

- A constant environment is essential for building a reliable behavioral study and analysis
- To enhance the quality of the study and have better statistic probability, it is important to analyze many parameters from the same behavior (i.e. group of parameters or matrix)

Most experiments in preclinical research involving observation of the laboratory animal behavior are still based on either direct observation by humans or the use of video recording systems. Both these methods use the visual cue as a parameter to determine the behavior of the animal. This also applies for automated methods that are based on video and only look at the position changes of the animal (tracking). These methods lack the possibility to determine and analyze ‘more’ parameters from the same behavior, and offer limited possibilities. Therefore, this paper proposes an alternative

and comprehensive method for analyzing matrix parameters of animal behavior in in-vivo experiments.

Materials and Methods: Force measurement vs. Observation methods - The movements accompanying behaviors that result in oscillations of energy are often short, weak, fast and highly repetitive, and therefore difficult or impossible to observe or record on video (such as head shakes, scratches, chewing). Metris has developed the LABORAS system that is able to measure total movements (kinetic energy) in a reliable and non-invasive way by using force transducers under the cage of the animal.

Matrix method for Behavior Analysis - Acquiring the proper analysis and statistics from the data is very important in in-vivo experiments. The use of many independent parameters for the automated recognition of an animal's behavior is therefore crucial. To recognize a behavior automatically, LABORAS applies the 'Matrix Method', which involves the analysis of several parameters that are derived from the measurement system. **Your specific behavior = matrix / X1, X2, X3 - - - - - Xn; Y1, Y 2, Y 3 - - - - - Y n; E1, E2, E3 - - - - - En/** The above matrix shows an example of the different parameters for a specific behavior. Where X1, X2, X3 - - - - - Xn, ; E1, E2, E3 - - - - - En are functions from the specific behavior (e.g. amplitude, frequency, total energy, locomotion energy, locomotion energy / oscillation energy, etc.).

Results and Discussion: Measuring matrix parameters in in-vivo experiments are very important for obtaining a full ethogram of all behaviors shown by the laboratory animal. Traditional methods based on observation or video analysis only offer limited information. The Metris LABORAS system enables measurements of all types of kinetic energy while other non-invasive automated systems for behavior detection can only measure the locomotion component of the kinetic energy (e.g. locomotion energy $mv^2/2$). In addition, the matrix method and technology used in Laboras provides a way to measure more behaviors and to recognize them completely automatically and more precisely than ever before. Laboras is globally considered as the best method for Animal Behavioral Research. Laboras system can integrate with telemetry systems and analyze Physiological and Behavioral parameters in one result summary. The best and quickest results from your pre-clinical study:

- For behavioral studies, use matrix parameters from behavior, not only tracking parameters / use Laboras system for behavior recognition and analysis;
- For ultrasound vocalization studies, use the Sonotrack system and integrate it with Laboras results.
- Integrate telemetry parameters with Laboras results to get the best analysis tool;
- The bigger your analysis matrix (group of parameters) is, the better your statistics and results from the experiments will be.

Symposium 5. Serotonin, Brain and Behavior

Chairs: Z. Zukowska (USA), A. Kalueff (USA)

EARLY POSTNATAL STRESS AFFECTS 5-HT_{1A} RECEPTOR FUNCTION IN EMOTION-RELATED BRAIN REGIONS IN ADULT RATS

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Introduction: Traumatic events in early life are associated with an increased risk of psychiatric diseases in adulthood. 5-hydroxytryptamine (5-HT)_{1A} receptors are known to play a pivotal role in the 5-HTergic mechanisms associated with the etiology of stress-related disorders. The goal of the

present study was to investigate whether early postnatal stress influences 5-HT_{1A} receptor function in emotion-related brain regions in adult rats.

Materials and Methods: Rats were subjected to aversive foot shock (FS) during the third week of the postnatal period (3wFS group). During the post-adolescent period (10-14 weeks postnatal), immunohistochemical and neurochemical experiments were carried out to investigate 5-HT_{1A} receptor function in the medial prefrontal cortex (mPFC), dorsal hippocampus and amygdala.

Results and Discussion: In the mPFC, c-Fos expression induced by the 5-HT_{1A} receptor agonist 8-OH-DPAT in the 3wFS group was significantly attenuated compared to that in the non-FS control group. We also found that local perfusion of 8-OH-DPAT via a dialysis probe decreased extracellular 5-HT levels in the mPFC of the non-FS group, but not in the 3wFS group. 5-HT_{1A} receptor numbers detected by [³H]WAY-100635 binding and 5-HT_{1A} receptor mRNA detected by quantitative PCR in mPFC were not different between the non-FS and 3wFS groups. In the dorsal hippocampus, bilateral local injection of 8-OH-DPAT significantly reduced freezing behavior, a kind of anxiety reaction induced by contextual fear conditioning. However, in the 3wFS group, local injection of 8-OH-DPAT failed to reduce freezing. 5-HT_{1A} receptor numbers significantly decreased in the dorsal hippocampus of the 3wFS group, but 5-HT_{1A} receptor mRNA did not change. In the amygdala, bilateral local injection of 8-OH-DPAT reduced freezing behavior both in the non-FS and 3wFS groups equally. There were no differences in 5-HT_{1A} receptor numbers and mRNA between the non-FS and 3wFS groups. These results suggested that 3wFS attenuates 5-HT_{1A} receptor function in the mPFC and dorsal hippocampus in adulthood. 3wFS did not affect 5-HT_{1A} receptor numbers in the mPFC, whereas 3wFS decreased 5-HT_{1A} receptor numbers in the dorsal hippocampus in adulthood. Therefore, aversive stress in juvenile period has lasting effects on brain 5-HT system.

SEROTONERGIC SYSTEM INVOLVMENT IN THE CRITICAL PERIOD OF PEER SOCIAL BEHAVIOR DEVELOPMENT IN CHICK

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Introduction: We have established an animal model for the development of social behavior with the domestic chicken (*Gallus gallus domesticus*). Chicken social behavior develops through three steps, imprinting to conspecific cage-mates, fear learning, and social affiliation learning. The sensitive (critical) period for affiliation learning starts from around day 5 and ends up around day 9 after hatching. Chickens reared under socially isolated conditions during this period, fail to develop social affiliation even after having acquired imprinting to cage mates. For this experiment, we explored the possible role of the serotonergic system during this period of social affiliation, and if it is affected by developmental disorders.

Materials and Methods: Chickens were reared either in groups or were socially isolated from hatching. They were tested for social behavior using multi-behavior parameter integration analysis based on principle component analysis. The brain area specific extract from socially grouped or isolated chickens was examined for monoamine contents by HPLC as well as for gene expression patterns by DNA microarray. Milnacipran(5mg/kgwt) was subcutaneously administered daily from P5 for 10 days with or without social interaction training.

Results and Discussion: The grouped chickens which were temporally separated from cage mates emitted isolation calls and 5-HT level concomitantly increased in medial prefrontal areas including nucleus accumbens. Dopamine and noradrenaline levels decreased in the same region. Long term social isolation gave rise to chickens which were not affiliated to other chickens, but this

behavior was improved by combinatorial treatments of SNRI's during the sensitive period and with social interactions after this period.

Research Support: This work was supported by MEXT KAKENHI (Grant-in-Aid for Scientific Research on Innovative Areas 21200017).

STRESS-REACTIVITY IN WINNER AND LOSER RATS AFTER CHRONIC SOCIAL STRESS

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Introduction: The behavioral consequences of social stress for loser animals are well-studied, but the behavioral reactions of winner rats still remain unclear. On the other hand, we were interested in examining not only the behavior after stress, but also the reactions of rats with opposite social experience on behavioral parameters yet. So, the aim of our experiment was to evaluate the anxiety levels and learning abilities of rats subjected to social stress.

Materials and Methods: A novel model of social stress in rats was used in order to give equal possibilities for animals to become a winner or a loser. Before the stress, animals were tested in the Open Field (OF) test and Black-White box (BW) test to detect initial locomotor and anxiety levels in rats. To evaluate stress-reactivity in "winner" and "loser" rats, some rats were subjected to acute foot-shock stress after social stress. All rats were divided into 4 groups: control(C), acute foot-shock stress (approximately 1mA, 20min)(AFSh), social stress group (14 days of social stress)(SS) and combined stress group (rats were subjected to acute foot-shock stress after social stress) (Comb). The elevated Plus maze (EPM), Social interaction test (SI), Defensive burying test (DB) and Radial maze (RM) were used to examine behavioral activity.

Results and Discussion: There were no observed differences between anxiety levels of winner and loser rats in OF and BW tests. Rats from the AFSh group demonstrated decreased exploration in EPM and SI tests, increased social anxiety in the SI test, and decreased working memory mistakes in the RM. Winner rats from both the SS and Comb groups demonstrated increased urination in the EPM, and decreased levels of social anxiety in SI test. It was higher level of exploratory activity in EPM test and higher level of social anxiety in SI test in winner rat from Comb group. Loser rats from the SS group demonstrated lower levels of exploratory activity in the SI test, immobility in the DB test, and decreased general activity and productivity in RM. Loser rats from the Comb group demonstrated increased urination in the EPM, decreased exploratory activity in the SI test, and no difference in the RM. Thus, one can conclude that social stress differentially affects winner and loser rats. Moreover, changes in behavior depend on the subsequent stress experienced by animal.

A BIOLOGICAL AND BEHAVIORAL PROFILE FOR INHIBITED BEHAVIOR

K.J. Fomalont, J.C. Earnheart, C.M. Ragan, B. Luscher, S.A. Cavigelli
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Introduction: In humans, an inhibited temperament in infancy is predictive of the development of an anxiety disorder in adulthood. Using a rat model, this study aims to find patterns in the biological underpinnings of the inhibited temperament. We have analyzed rat behavior in novel situations and determined if inhibited behavior is correlated with increased corticosterone release reactivity in response to a stressor, and with a smaller number of GABAA receptors in the hippocampus and limbic regions.

Materials and Methods: 24 Sprague-Dawley outbred rats were exposed to the elevated plus maze, a novel social task, and a novel environment task twice. The rats were weighed and handled by an experimenter daily until behavioral testing began on Post-Natal Day (PND) 30. A blood

sample was taken immediately, 40 minutes, and 120 minutes after tail clipping. On PND 125, the rats were sacrificed. The brains were dissected and the sections were incubated in a radioactive benzodiazepine agonist. Autoradiography was performed to visualize benzodiazepine receptor concentration and location.

Results and Discussion: Rank analyses showed that behavioral measures were not correlated to blood corticosterone measured after the introduction of a physical stressor. There was a significant positive correlation between inhibited behavior and radioligand binding in the hippocampus and in limbic areas. There was no correlation between blood corticosterone and GABAA receptor concentration in any regions of the brain. Inhibited behavior did not predict corticosterone release reactivity or GABAA receptor concentration. Most research supports the link between the inhibited temperament and high reactivity in corticosterone release. The discrepancy between our results and the consensus of previous research may be attributed to early handling of rat pups which disrupted HPA axis development. An unexpected positive correlation between latency to a novel object and radioligand binding in some areas of the brain was found. Research in primates suggests that the amygdala is involved in the processing of learned fear, but it is not necessarily involved in the behavioral inhibition associated with temperament. Our data support this conclusion. Future research should use inbred rats or a rat strain bred to exhibit anxiety-like behavior to study the biological underpinnings of inhibited behavior.

Research Support: PSU, Pennsylvania, USA, National Institute of Mental Health B/STARTR03

Plenary Lecture 2. NPY AND STRESS

Z. Zukowska

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Prenatal stress, psychological and metabolic (e.g. low 8% protein diet, LPD), has been linked to increased risk of obesity and anxiety in the progeny, sometimes in a gender-specific manner. While mechanisms remain unclear, epigenetic changes in the HPA axis have been implicated. Here we studied the effects of stress on another stress system - sympathetic nerves and their non-adrenergic co-transmitter, neuropeptide Y (NPY) - on adipogenesis and obesity in various in vitro and in vivo models. In adult mice fed high fat (HF) diet, stress activated NPY and its Y2 receptor (R), specifically in the abdominal fat and its stromovascular fraction enriched in adipose stem cells (ASCs). This increased de-novo adipogenesis and angiogenesis leading to abdominal obesity and metabolic syndrome; in addition, stressed/high fat-fed mice were more anxious. Similarly in vitro, epinephrine-induced "stress" augmented adipogenesis in murine embryonic stem cells proportionally to the level of expression of NPY and inversely proportional to DNA methylation of its gene at CpG regions corresponding to NGF-RE and CAM-RE. These results suggested that stress may epigenetically up-regulate NPY expression in ASCs leading to greater development of abdominal adiposity when animals are placed in pro-adipogenic environment, such as over-nutrition. To test this hypothesis in vivo, we subjected mice to prenatal stress of LPD followed by 9 weeks of post-weaning HF diet. While both male and female LPD offspring were born smaller, only females had faster growth rate on HF diet than the control group, and by 9 weeks developed abdominal adiposity and impaired glucose tolerance. In contrast, male LPD offspring had improved glucose tolerance and decreased abdominal fat content. No significant differences were found in expression of NPY in either gender and groups but Y2R was up-regulated specifically in the visceral fat in the LPD-stressed females already at weaning, while Y1 was down-regulated as compared to the control group. While the study continues, data so far suggest that stress may induce epigenetic changes in the NPY and/or its receptor genes, specifically in ASCs of the visceral fat and thus

program for future development of abdominal obesity and metabolic syndrome. Why the effect is sex-specific is unclear but may be related to sex steroid-dependent regulation of NPY expression, as previously reported.

10.00-18.00 POSTER SESSION

THE EFFECTIVENESS OF A MEDITATION-BASED STRESS MANAGEMENT PROGRAM IN PATIENTS WITH ANXIETY DISORDERS

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Introduction: Meditation includes techniques such as listening to breathing, repeating a mantra, detaching from thought processes, focusing attention, and bringing about a state of self awareness and inner calmness. The objective of this study was to examine the effectiveness of a meditation-based stress management program in patients with anxiety disorder.

Materials and Methods: Patients with anxiety disorder were randomly assigned to an 8-week clinical trial of either a meditation-based stress management program and/or an anxiety disorder education program. The Hamilton Anxiety rating scale the Hamilton Depression Rating Scale, the Stait-Trait Anxiety Inventory, and the Beck Depression Inventory were used to measure outcomes after 0,2,4,6, and 8 weeks of the program.

Results and Discussion: Compared to the education group, the meditation-based stress management group showed significant improvement in score on all anxiety scales(HAM-A, $P=.02$, STAI state $P=.01$, STAI trait, $P=.001$). This study shows that meditation-based stress management programs can be effective in relieving anxiety symptoms in patients with anxiety disorders.

THE A1 ALLELE OF D2 DOPAMINE RECEPTOR (DRD2) GENE IS ASSOCIATED WITH POSTTRAUMATIC STRESS DISORDER SYMPTOMS IN KOREAN VETERANS OF THE VIETNAM WAR

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Introduction: Evidences from recent studies supports the role of genetic factors in the development of Posttraumatic Stress Disorder (PTSD). The primary aim of this study is to investigate the association between the dopamine D2 receptor (DRD2) TaqI A polymorphism and PTSD. The second aim is to examine the association between the DRD2 TaqI A polymorphism and clinical symptoms in patients with PTSD.

Materials and Methods: We recruited 189 Vietnam veterans for participation in this study, among whom 99 were PTSD patients and 90 were control subjects. The presence of the DRD2 TaqI A polymorphism was determined by polymerase chain reaction (PCR). Several standardized research scales were used in the clinical assessment of PTSD, including the Combat Exposure Scale (CES), Clinician Administered PTSD Scale (CAPS), Beck Depression Inventory (BDI), and Clinical Global Impression (CGI).

Results and Discussion: There was no significant difference in the distribution of the DRD2 genotype, frequency and prevalence of the A1 allele, or the frequency of heterozygotes between the patients with PTSD and the controls. In the PTSD group, the patients with the A1 allele (A1A1, A1A2) scored higher on the CAPS-total ($p=0.044$), CAPS-avoidance symptoms($p=0.016$) and BDI ($p=0.024$) than those without the A1 allele (A2A2).

We could not find an association between the dopamine D2 receptor (DRD2) TaqI A polymorphism and PTSD. However, the A1 allele of DRD2 seems to influence avoidance symptoms in patients with PTSD.

Research Support: This study was supported by a grant from Korea Institute of Medicine.

THE RATIO OF THETA AND BETA RHYTHMS IN FRONTAL BRAIN AREAS (AN INDEX OF INATTENTION) IN CHILDREN WITH ADHD DURING THE COURSE OF BIOACOUSTIC CORRECTION

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Introduction: Two kinds of quantitative EEG are most common among the patterns of bioelectrical activity in attention deficit hyperactivity disorder (ADHD) patients. The first kind typically increase in intensity of slow-wave activity, mainly theta-rhythm, in frontal parts of a brain, including premotor and sensorimotor areas, as well as reduction of beta-rhythm in these areas, pointing to down-regulation of frontal lobe activity. The second kind is characterized by increase in capacity of beta-rhythm in frontal areas, and it is connected with excessive activation of frontal lobes of the brain. For treatment of children with ADHD, the most often used is the concept of directed local correction of parameters EEG, in particular apply beta/theta training.

Materials and Methods: Applied in the present work is a new method of ADHD treatment - bioacoustical correction (BAC). The correction is achieved by listening to an acoustic image of one's own brain bioelectrical activity in a real time mode, which is produced with an online computer transformation of the EEG into sounds by transposition of the oscillation spectrum to the acoustic sector of frequencies. With this method of EEG transformation, the initial ratios of the main parameters of the EEG signal (amplitudes, frequencies, and phases of oscillations of the whole physiologically significant range) remain completely the same in the sound image of the brain's bioelectrical activity, and so does the integrity of the space-temporal structure of the EEG. Data from 53 children was received as a result of research (41 boys and 12 girls) with a diagnosis of ADHD, during a course of the EEG- acoustic correction. Middle age of the children was $8 \pm 0,74$ years. For each child in the investigated group, the self-regulation has been 12 sessions on average . During the analysis of data from each session, theta a rhythm and beta a rhythm indices were calculated in frontal assignments. During a rate, the EEG- acoustic biofeedback analyzed reorganization of these rhythms and estimated their correlation with clinical displays.

Results and Discussion: Before carrying out procedures of bioacoustical correction, the given parameter children were distributed into 2 subgroups: 1 subgroup of 37 children (69,81 %) - in bioelectric brain activity, in frontal assignments domination theta range, with an index of $30,8 \% \pm 1,72$ was observed; the index of beta activity was $20,37 \% \pm 1,8$. In 2 subgroup of 16 children (30,19 %), in frontal assignments it was registered $\Theta\Gamma$ with raised beta activity levels. The index beta a rhythm was $34,56\% \pm 6,18$; expression of a share of the periods theta, a rhythm of $19,69 \% \pm 3,3$. After carrying out procedures of bioacoustical correction on the given parameter in the group (37 children) with dominating theta, a range, it has been revealed that the index of theta a rhythm authentically ($p < 0,01$) decreased from $30,8 \% \pm 1,72$ to $22 \% \pm 1,51$, and the index of beta a rhythm authentically ($p < 0,01$) increased from $20,37 \% \pm 1,8$ up to $24,73\% \pm 2,06$. In the group (16 children) with dominating beta a rhythm, it has been established that the index of beta a rhythm authentically ($p < 0,03$) decreased from $34,56 \% \pm 6,18$ to $27,75$ as a whole on group. The theta index changed doubtfully, from $19,69 \% \pm 3,3$ to $19,38 \% \pm 2,43$.

Change in theta and beta rhythm indices was accompanied by authentic change in clinical syndrome attributes: carelessness of $5,37 \pm 0,69$ to $2,26 \pm 0,64$ ($p < 0,01$), impulsiveness of $2,83 \pm 0,87$ to $1,26 \pm 0,78$ ($p < 0,01$), hyperactivity of $3,35 \pm 0,76$ to $1,46 \pm 0,61$ ($p < 0,01$) and authentic reduction of

the average values of the parameters of scale SNAP-IV: carelessness of $2,03 \pm 0,35$ to $1,52 \pm 0,34$ ($p < 0,01$); hyperactivity of $1,83 \pm 0,51$ to $1,34 \pm 0,42$ ($p < 0,01$); impulsiveness of $1,59 \pm 0,64$ to $1,01 \pm 0,45$ ($p < 0,01$). During the EEG- acoustic biofeedback procedures, an observed parity change in indices of theta and beta rhythms authentically correlates with reduction of the quantity of clinical attributes of ADHD and a degree of expression of symptoms of the disease.

MORPHOLOGICAL AND FUNCTIONAL CHANGES IN THE BRAINS OF RATS THAT EXPERIENCED ACUTE MENTAL TRAUMA

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Introduction: Psychogenic affective disorders are common in various psychoemotional disturbances and structural changes in brain. Mental traumatic experiences in humans and animals may result in structural alterations of the brain and abnormalities in immune and endocrine system functions. Extremely stressful experiences, as shown in our investigations, contribute to chronic sustained aberrations in animal behavior (e.g. anxiety, depression), imbalances in lipid metabolism, and dysfunctional neurotransmission (Tsikunov et al., 2005, 2006). In the DSM-IV, this is defined as posttraumatic stress disorder (PTSD). Furthermore, massive structural lesions in tissue of the adrenal glands, mucous tunic of stomach, and duodenum were found in traumatized animals. The aim of the present study was to detect and characterize morphological, cytochemical, and functional changes in the brains of rats that experienced an acute psychotraumatic situation.

Materials and Methods: Here we used a model of PTSD. Experiments were performed on Sprague Dawley rats (200–250 g, 5 months old). The animals were exposed once to an acute psychotraumatic situation. The rats experienced the threatening situation by witnessing the death of a cage mate from the actions of the black-tailed python, a predator of rats. 25 days later, the rats were sacrificed, their brains removed, and fixed via immersion in zinc-ethanol-formaldehyde. Paraffin sections were stained by the Nissl's method, PCNA staining, and NeuN with the astra blue counterstain. Thus, the influence of a single psychotraumatic situation may be seen after 25 days via structural and cytochemical alterations in various regions of rat brain (especially in hippocampus and basal nuclei). The probable mechanisms of onset and development for structural and cytochemical alterations are the hypersecretion of glucocorticoids, lesions of neurons due to excitotoxicity, oxidative stress, decreased proliferation of a neuronal progenitor cells, decreased level of synthesis of neurotrophic factors, decreased survival of cells, and pathological remodeling of dendritic arbors.

Results and Discussion: In brains of animals that did not experience the psychotraumatic situation, very few shrunken cells were found. In brains fixed on the 25th day after the acute psychotraumatic situation, we observed alterations. In the Nissl's stain, shrunken cells and hyperchromatic cells were detected in many regions of brain in large quantities. The highest quantities of shrunken cells were revealed in the hippocampus and basal nuclei. Few shrunken cells were found in the cerebral cortex. The pattern of cytoarchitecture in the hippocampus layers were significantly altered in comparison to the controls. Large quantities of shrunken cells were observed in the supraoptic nucleus. With the PCNA staining, increased proliferation was revealed in some areas of brain tissue. We considered this phenomenon to be a nonspecific glial reparative reaction that accompanied neuronal cell death. However, suppression of proliferation in the dentate gyrus of the hippocampus was found. In staining to NeuN, we observed a lack of synthesis of this protein in the pyramidal cells of some areas in the hippocampal formation.

TREATING DEPRESSIVE BEHAVIORS WITH CELLULAR THERAPY IN FEMALE RATS WITH BRAIN INJURY

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Institute of Experimental Medicine RAMS, St-Petersburg, Russia

Introduction: The high frequency of cerebral traumas and heavy complications induced by them impel neurologists to develop new ways of brain injury treatment. We have a stab of the pathology treatment with mesenchymal stem cells (MSCs) method.

Purpose: Evaluation of influence of intravenous transplantation of MSCs on the behavior and structure of brain tissue of the primary motor cortex around the removed locus of cortex.

Materials and Methods: Experimental animals consisted of groups: 1- the control (n=30); 2 - the negative control (n=25); 3 - group of cellular therapy (n=45). A small part (about 1 mm³) of brain sensorimotor cortex area from female rats was removed under ether narcosis. Animals were injected with 5 million MSCs in 100 mcl α MEM culture into a caudal vein just after operation.

The emotional and locomotor status of the rats was estimated in the open field test (OF-test) in 2 and 4 weeks after a brain injury. MSCs were allocated from rats' bone marrow, proliferated in vitro up to the necessary quantity, and were characterized by staining with antibodies against CD45 + and CD90 + cells.

Experimental animals were killed in 2 and 4 weeks after a brain injury. Segments of brain tissue with an injury zone from 8 animals were fixed in formalin, and brains of 3 rats were subjected to cryofixation. All samples were stained with an immunohistochemical method against PCNA, NeuN, and vWF.

Results and Discussion: Flow cytofluorometric subpopulation analysis of MSCs culture detected 97% of CD90+ (hemopoietic cells) and 3% of CD45+ (MSCs). Ablation of the primary motor cortex area of the brain led to significant disturbances in locomotor and investigative behaviors of animals in the OF test. Spontaneous recovery of behavior did not occur during 4 weeks. In the cellular therapy group, quantity and duration of the basic behavioral acts corresponded to the level of control animals. Analysis of transplanted MSCs' distribution on cryopreparations revealed them in the tissue adjoining the defect. The quantity of vessels in the border zone of the cellular therapy group was 1,6 times more than in the negative control group. Also, the quantity of intact neurons in the boundary zone of brains with injury was 1,8 times more than in the negative controls. Transplantation MSCs stimulated proliferation of the cells in the subventricular zone. Treatment of female rats' brain injury by MSCs led to recovery of behavior in short terms, in our opinion, due to preservation of neurons' viability and maintenance of microcircumambience at the boundary of the injury zone.

Research Support: Trans-Technologies Ltd, S. Petersburg, Russia

THE CORRELATION OF DREAM RECALL AND CLINICAL VARIABLES IN NARCOLEPSY

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Introduction: Narcolepsy is a sleep disorder characterized by abnormal rapid eye movement(REM) sleep. The relationships between the REM sleep, dream and clinical manifestations of narcolepsy have been reported by many sleep researchers. This study was designed to investigate the relationship between the clinical features and frequency of DQB1*0602 in narcoleptics with dream recall, to those without dream recall, during the sleep onset REM period by using the multiple sleep latency test (MSLT).

Materials and Methods: From March 2004 to August 2009, we selected 126 patients who visited the Sleep Disorders Clinic of St. Vincent's Hospital, Catholic University of Korea and suffered excessive daytime sleepiness. All subjects were tested by nocturnal polysomnography and the multiple sleep latency test. Subjects were divided into a dream recall group (N=66) and a non-dream recall group (N=60), and the clinical symptoms, sleep patterns, and frequency of HLA-DQB1*0602 were compared.

Results and Discussion: Among the two groups which were classified by dream recall during the multiple sleep latency test, no significant differences were found regarding the demographic features. But for clinical symptoms, daytime sleepiness was more severe and cataplexy was more frequent in the dream recall group than the non-dream recall group. In polysomnography tests, latency to sleep and latency to REM sleep in the dream recall group proved to be shorter than in the non-dream recall group. In the MSLT, mean latency to sleep for the dream recall group proved to be shorter than in the non-dream recall group. No significant difference in the relationship between dream recall and the frequency of HLA-DQB1*0602 was identified. In this study, we found that the dream recall was related to daytime sleepiness and cataplexy, which are symptoms of narcolepsy. We may need more comprehensive and in-depth studies to find the pathogenesis of narcolepsy associated with dream recall.

FACTORS ASSOCIATED WITH PSYCHIATRIC VISITS AFTER EMERGENCY ROOM TREATMENT FOLLOWING SUICIDE ATTEMPTS

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Introduction: Suicide is a serious potential outcome that is associated with many psychiatric disorders, such as depression, schizophrenia, and alcoholism, etc. Psychiatric evaluation and intervention is critical to reduce further suicide attempts. In the present study, we investigated factors that can predict follow-ups at psychiatric outpatient clinics after initial medical care at the emergency room.

Materials and Methods: Medical records of patients who were treated at the emergency room following suicide attempt from Jan 1, 2009 to July 31, 2009 were reviewed. The data of a total of 145 patients were analyzed. Age, sex, past psychiatric history, numbers of previous psychiatric episodes, impulsiveness of suicide attempt, medical severity of suicide attempt, risk-rescue rating scores, reasons for suicide attempts and methods of suicide were examined. Psychiatric diagnoses were made using DSM-IV-TR by psychiatric residents at the initial interview with patients at ER. Logistic regression analysis was used to identify significant predictors that are related to psychiatric follow-up after emergency medical care.

Results and Discussion: The mean age of the patients was 42.9 years (range, 15–92 years), and 99 (68.3 %) were women and 46 (31.7%) were men. Psychotropics were the most commonly used suicide method (n=69, 69%), and ingestion of pesticides was the second most frequent method (n=28, 19.3%). Interpersonal problems were the most common precipitating event of the suicide attempts (n=84, 57.9%). Depression was the most common psychiatric disorder (n=129, 89%). About a half of the patients (n=74, 51%) had previous psychiatric disorders and about one third of the patients (n=39, 26.9%) had more than one previous suicide attempt. Fifteen patients (10.3%) attempted planned suicide and 124 patients (85.5%) attempted impulsively. The mean risk rating score was 8.6, and the mean rescue rating score was 12.3. About one third of patients (n=52, 35.9%) had a follow-up visit at the psychiatric outpatient clinic. The most important predictor of psychiatric follow-up was the risk rating scores by logistic regression (b=0.402, p <0.05). In conclusion, this study suggests that female patients with interpersonal problems should be carefully

monitored for suicidal ideation. Early detection and intervention of depression is also important to reduce suicide attempts.

MULTI-DISCIPLINARY BEHAVIOR MODIFICATION PROGRAM FOR POST-MYOCARDIAL INFARCTION PATIENTS

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Introduction: A short multi-disciplinary intervention targeted at working-age patients with a history of myocardial infarction was developed to manage their complex needs. Cardiovascular disease can activate various coping strategies in the affected individuals. Often the illness itself, and illness-related emotional changes, may inhibit those patients' motivation and capability of returning to work. Interventions are needed to focus on increasing the participants' awareness of the emotional impact of their illness, allow them to reevaluate their capacities, and to foster reintegration into their habitual social and vocational environment. The aim of the 6-day-long rehabilitation program was to minimize the psychosocial risk factors interfering with recovery, and thereby improve quality of life and encourage participants to follow lifestyle-changing strategies and continue their vocational and personal pursuits.

Materials and Methods: The intervention consisted of group physiotherapy and psychoeducative group sessions about stress management, coping with illness, relaxation training and conflict management. In addition, patients received individually combined psychotherapy sessions, ergotherapeutic counseling, nutrition counseling and career counseling for 3-6 hours daily. Family counseling was offered on the 6th day, in order to increase the social support needed to maintain lifestyle changes. Before and after the program, the working status, emotional well-being (EEK-2), and awareness of stress and conflict management (a short self-developed questionnaire) of the patients was measured. Patient satisfaction ratings were obtained immediately after the end of the program. Motivation was measured through personal goal-setting abilities and during a one-month follow-up, the fulfillment of those goals was measured on a 0-100 % scale.

Results and Discussion: The mean age of participants was 47 years (from 35 to 55). All six participants were men. Four of the six patients had returned to work one month after the end of the program. Increased awareness and slight increases in patients' emotional well-being were immediate outcomes. Patient satisfaction ratings were high. In a follow-up session one month later, 70-100 % of the goals were fulfilled. Due to the small size of the sample, statistical significance of the changes could not be assessed.

This study was conducted as a pilot program, but because the results are promising and the satisfaction of participants was high, hopefully further studies with more participants will confirm the need for developing this kind of rehabilitation program.

DECREASED IFN-GAMMA ACTIVITY IN ANXIETY DISORDERS

R. Tukul, B.A. Arslan, B.A. Ertekin, E. Ertekin, S. Oflaz, U Zeybek, S. E. Kuruca, T. Isbir
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Introduction: Immune system and inflammatory responses may be related to the pathogenesis of anxiety disorders. The aim of this study is to assess the measures of proinflammatory cytokines in patients with panic disorder and social anxiety disorder (SAD) in comparison to healthy subjects.

Materials and Methods: Twenty three patients with panic disorder with or without agoraphobia, 23 with SAD and 23 controls who were group-matched to the patient groups for age and sex, were recruited for the study. Plasma samples of all subjects were analyzed for TNF- α , IFN- γ , IL-1 β , IL-2,

IL-6, and IL-12 concentrations using a commercially available enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's manual. NK-cell activity against K562 cells (in effector/target (E/T) ratios of 1:1, 5:1, 10:1, 25:1 and 50:1) was measured in the peripheral blood samples of the subjects by using a MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay.

Results and Discussion: The mean values of the IFN- γ and IL-12 were found to be significantly lower in the group with anxiety disorders (panic disorder and SAD), compared to the controls (respectively, $t=2.67$, $p=0.013$; $t=2.27$, $p=0.027$). There was no difference between the two groups in terms of mean values for NK activity, TNF- α , IL-1 β , IL-2, and IL-6. IFN- γ values were significant predictors for the development of the anxiety disorders ($B = -0.48$, $SE = 0.17$, $p = 0.002$) as well as of anxiety levels ($r^2 = 0.12$, $F = 8.95$, $B = -0.18$, $SE = 0.06$, $\beta = -0.34$, $p = 0.004$). Our results support previous animal research which suggested that there is a relationship between anxiety and low levels of IFN- γ .

Day 4. May 19, 2010

Symposium 6. Clinical aspects of Biological Psychiatry

Chair: T.N. Sollertinskaya (Russia)

OPEN LABEL TRIAL OF ESCITALOPRAM IN MOTOR VEHICLE ACCIDENT SURVIVORS WITH POSTTRAUMATIC STRESS DISORDER

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Introduction: Selective serotonin reuptake inhibitors (SSRIs) have generally been associated with good clinical responses in patients with anxious and/or depressive disorders. Escitalopram, an S-enantiomer of citalopram, may have a favorable role in the treatment of Post Traumatic Stress Disorder (PTSD), a disabling illness which is frequently seen in motor vehicle accident (MVAs) survivors, although there is a lack of data on this specific subject.

Materials and Methods: One hundred and fourteen adult MVA survivors with PTSD entered a 16 week, open-label trial of escitalopram treatment. One-hundred and five subjects (92.1%) completed the 16 weeks of treatment. The primary efficacy measure was the Davidson Trauma Scale (DTS).

Results and Discussion: There was a significant reduction in PTSD symptoms during escitalopram treatment: the mean DTS score was reduced from 74.3 (SD=16.0) at baseline, to 32.3 (SD=20.5) at the 16-week study endpoint ($P<0.001$). Secondary measures of depression (Hamilton Depression Rating Scale) and of global status (Clinical Global Impression Scale) also improved significantly. Escitalopram was well tolerated, with only 3 patients (2.6%) dropping out of the study due to adverse effects. Data from this open-label study suggest that escitalopram may be effective for reducing the key symptoms of PTSD in MVA survivors. However, randomized double-blind controlled studies are needed to confirm these findings.

Research Support: David Suarez was supported by a research grant from both the Instituto de Salud Carlos III, the Ministry of Health and Consumer Affairs, Spain and the Departament de Salut, Generalitat de Catalunya (FIS ECA07/041).

CHILDHOOD VICTIMIZATION EXPERIENCES AMONG YOUNG ADULTS IN ST. PETERSBURG, RUSSIA

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Introduction: Childhood victimization is a term that refers to the broad range of negative experiences which are related to the exposure of children and adolescents to crime and violence. Modern research links certain types of childhood victimization (e.g. child sexual abuse) to the development of chronic PTSD as well as other mental health and adjustment difficulties. Victimization in childhood and adolescence is a serious stress factor (often chronic, as in child maltreatment) which affects brain development and impairs intellectual and social skills. A growing body of international research indicates that childhood victimization is prevalent across many cultures. Knowledge of the local rates of childhood victimization provides important information for the development of effective prevention and intervention services. In Russia, this area of research is only beginning to develop, and information about the types and frequency of victimization experienced by local populations is largely unavailable. The goal of this study was to assess and describe childhood victimization experiences in a sample of university students in St-Petersburg, Russia.

Materials and Methods: Cluster sampling was used and 743 students from 15 universities participated in the study (63% female). The mean age was 20.47 (SD = 0.89, range = 19 – 25). Childhood victimization experiences were assessed with an adult self-report version of the Juvenile Victimization Questionnaire. Participation in the study was anonymous.

Results and Discussion: The results of the study showed that the rate of victimization in this sample is rather high. More than half of the sample (51.2%) indicated that they have experienced some sort of child maltreatment (34.59% of the sample stated that they experienced physical violence and 3.77% indicated that they suffered sexual abuse on behalf of an adult they knew). Almost 21% of study participants reported experiencing sexual assault (completed or attempted) before the age of 18. Peer victimization also appeared to be prevalent in this sample: 12.38% indicated sexual harassment and violence on behalf of peers. Exposure to conventional crime and witnessing violence were reported by the majority of study participants. The data is consistent with similar international research, but further studies are warranted to explore victimization rates in different community groups and assess the psychological sequelae of such victimization.

HEART RATE VARIABILITY AS A MEASURE OF MENTAL WORK CAPACITY

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Introduction: We have previously shown that the amplitude of heart rate modulation at the frequency of approximately 0.33 modulations per cardiointerval is associated with the level of frontal cortex activation, arousal level, and mental mobilization readiness. The aim of this study is to investigate the association between mental work capacity and heart rate variability.

Materials and Methods: The total score of the computer game tetris was taken as an integral measure of mental work capacity. In a group of 13 males, before and during tetris, 300 cardiointervals were recorded with an ECG equipment. Then frequency analysis of these records was performed with the discrete Fourier transform.

Results and Discussion: Correlation analysis showed that there is positive association between tetris scores and the amplitude of heart rate periodograms within the frequency bound by 0.26-0.31 modulations per cardiointerval. This association was tighter for the rest records than for the records obtained during the Tetris test. The strongest correlations were found at the frequency of approximately 0.29 modulation per cardiointerval ($r=0.94$). Multiple correlation analysis results (R-square = 0.88; $p<0.0001$) showed that the amplitude of the heart rate periodogram at the frequency of 0.29 modulations per cardiointerval should be taken as a measure of mental work capacity.

EFFORT-REWARD IMBALANCE, OVERCOMMITMENT, AND MENTAL ILLNESS IN CHINESE NURSES – CROSS-SECTIONAL AND PROSPECTIVE ASSOCIATIONS

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Introduction: So far, there is little evidence from China about the association between work stress and mental illness. The aim of this study was to test whether work stress increases the risk of mental illness in a sample of Chinese nurses.

Materials and Methods: A total of 3088 registered female nurses working in hospitals were recruited in a baseline survey, 1744 nurses without mental illness at baseline were followed-up for one year. Work stress at baseline was defined in terms of non-reciprocity between high efforts spent and low rewards received. In addition, a personal coping style, overcommitment, was

measured, which may aggravate the stress experience. Mental illness (e.g. depression, burnout, anxiety or insomnia) was self-reported, based on physician's diagnosis.

Results and Discussion: At baseline, 2.69% of nurses had reported mental illness, which was associated with high imbalance between effort and reward (OR=1.46, 95% CI 1.13-1.88), and with high overcommitment (OR=1.62, 95% CI 1.26-2.09). At follow-up, the incidence of mental illness was 2.98%, and high overcommitment predicted the onset of mental illness (RR=1.54, 95% CI 1.13-2.09). The findings indicate that overcommitment is a risk factor of incident mental illness in Chinese nurses, and work stress in terms of effort-reward imbalance is an additional risk factor at baseline. Improving coping skills and reducing work-related stress may contribute to improved mental health among nurses.

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DEPRESSION IN NEWLY DIAGNOSED TYPE 2 DIABETES PATIENTS

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Introduction: Depression and type 2 diabetes are closely related. Depression is a risk factor in anticipating diabetes as one of its comorbidities or consequences. The depressed diabetic patient presents with poor control of his/her diabetes and a low adherence to diet and physical exercise, all of which have a negative effect on his/her quality of life and cost of care.

Materials and Methods: The association between type 2 diabetes and depression in newly diagnosed patients was studied in one hundred patients who were consecutively registered during one month in the Clinical Centre of Diabetes, Nutrition and Metabolic Diseases of Iasi, Romania. We established the diagnoses according to 1999 WHO criteria completed with HbA1c. The record for each of these patients includes: an interview, review of previous medical reports, the complete clinical exam, and laboratory tests. Depression was assessed using the Hamilton Depression Rating Scale (HDRS 1986). This group of patients was compared with another group of non-diabetics, including first degree relatives, for which similar medical records and depression tests were completed. Interviews with the members of both groups were taken by the same specialists who were trained to perform the test. The t test or χ^2 test was used to investigate differences, characteristics, and depression as measured by HDRS between type 2 diabetes and the nondiabetic group.

Results and Discussion: Depression was found in 23% of newly diagnosed diabetic patients and in 12% of the control group. Associations between depression and sex, age, social and economic status, educational level, associated chronic diseases and their complications were also assessed. Several factors were correlated with depression in type 2 diabetes but the analyses demonstrated that they were not significant.

Symposium 7. Special Symposium of the Russian Society for Biological Psychiatry (RSBP)

Chairs: Y.V. Ekimova (Russia), Yu.F. Pastuhov (Russia)

STRESS, BEHAVIOR, AND AGING OF THE HPA AXIS

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Introduction: The incidence of stress-related diseases dramatically increases with aging. However, there are individual peculiarities in susceptibility and resistance to stresses and stress-related

pathologies. The purpose was to investigate potential differences in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis in young adult and old monkeys that have different behavior under stress.

Materials and Methods: Plasma cortisol (F) and dehydroepiandrosterone sulfate (DHEAS) levels were measured in 35 young adult and 35 old healthy female rhesus monkeys with various types of adaptive behavior (aggressive, depression-like, and average type) 1-2 months after their transfer from cages designed to group housing in individual metabolic cages both in the basal conditions and under acute psycho-emotional stress (moderate restraint for two hours). Eight of these animals were exposed to maternal deprivation during the neonatal period.

Results and Discussion: We have found that the age-related changes in the HPA axis of monkeys with depression-like behavior were accompanied by the maximal absolute and relative hypercortisolemia in the basal conditions as well as in the stress conditions. Moreover, the young aggressive monkeys, in comparison with the young monkeys of other behavior groups, demonstrated the highest levels of DHEAS and the smallest molar ratios between F and DHEAS levels. For the old animals with aggressive behavior, these inter-group differences were not exhibited. The minimal age-related changes in HPA have been revealed for the monkeys of average behavioral types. Seventy-five per cent of animals exposed to neonatal stress, showed the depressive-like behavior. Thus, our results testify that the age-related disturbances of HPA axis exhibit individual features that are associated with the peculiarities of the adaptive behavior of animals, and that neonatal stress sharply increased probability of developing depression-like behavior and neuroendocrine age-related alterations.

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PRENATAL SOCIAL ISOLATION AFFECTS COGNITIVE FUNCTION DURING THE ADOLESCENT PERIOD

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Introduction: Despite extensive research on the relationship between prenatal social isolation stress and learning and memory performance, it is not known whether prenatal social isolation effects an offspring's learning and memory performance during the adolescent period of life. This experiment investigated the effects of prenatal social isolation stress on cognitive functions during the adolescent period of life.

Materials and Methods: In this study, pregnant rats were divided into two groups. Rats in one group were kept in separate cages for social isolation, while those in the other group were left in normal laboratory conditions to serve as the control group. Offspring from both groups were held in standard laboratory conditions until adolescence. For both groups of adolescent rats, the eight arm radial-maze test was used to measure spatial memory performance, and the passive avoidance test was used to measure associative learning and consolidation.

Results and Discussion: The rats subjected to social isolation stress showed fewer errors than the non-isolated rats on each point of radial maze testing. When rats were tested for retention with the passive avoidance test after 24 and 48 hours, it was also found that social isolation slightly caused a longer latency to enter to the dark compartment. These results indicate that prenatal social isolation stress may affect performance of learning and memory during the adolescent period of life.

Research Support: This study was supported by "The Research Support Ünit of İstanbul University" as the project no T-801/27122005

STRESS PROTEIN Hsp70 AS A POTENTIAL ANTICONVULSANT IN ANIMAL MODELS OF EPILEPSY

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Introduction: Nowadays major attention is concentrated on the search for natural molecules that are able to interfere in key links of epileptogenesis. In this respect, one of the potential direction may be the stress proteins of the family of Heat Shock Proteins 70 kDa (HSP70). The aim of this study was to explore the effects of a pure Hsp70 preparation on generalized seizures in rats. The Hsp70 preparation was delivered into the third ventricle of the brain and seizures were induced in rats by intracerebroventricular (i.c.v.) microinjection of NMDA (80 ng) or systemic injection of pentylenetetrazole (PTZ, 80 mg/kg).

Materials and Methods: Male Wistar rats (180–220g) were used in experiments. Experimental rats received microinjections (i.c.v.) of Hsp70 or boiled Hsp70 2h before the induction of seizures. Control animals were injected with the same volume of phosphate-buffered saline 2h before seizure initiation. The intensity of seizures was registered using a modified Racine's scoring system (Racine, 1972).

Results and Discussion: Our results indicate that the delivery of pure Hsp70 significantly decreased the brain epileptiform activity, the duration of motor seizures and the muscle tonus in model NMDA-induced seizures. In the model of PTZ-induced seizures, Hsp70 corrected motor components and extended the latent period of seizures; this was manifested by the delay of seizure onset, reduced duration of generalized clonic seizures and disappearance of tonic seizures, as observed in about half of the animals. Pretreatment of animals with boiled Hsp70 did not affect the latency to seizures or the duration of motor seizures induced by NMDA- and PTZ. Taken altogether, these data prove the anticonvulsant effect of exogenous Hsp70 administered to the cerebrospinal fluid of the brain in two animal models of generalized tonic-clonic seizure activity. The data recently obtained indicates, that exogenously administered Hsp70 is able to pass through the cerebrospinal fluid-brain barrier and penetrate into the neurons and terminals of the limbic seizure complex of the brain [Ekimova et al., 2010]. In these regions of the brain, Hsp70 interacts with the GABA-synthesizing enzyme, L-glutamic acid decarboxylase 67. We suggest that the anticonvulsant property of exogenously delivered Hsp70 is closely related to its ability to modulate GABA neurotransmission, which in turn contributes to the maintenance of the excitatory-inhibitory balance of the CNS.

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GAP-43 PROTEOLYSIS BY CALPAIN IN CNS TISSUE OF WISTAR RATS WITH EXPERIMENTAL ENCEPHALOMYELITIS

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Introduction: The object of this research is protein GAP-43 (Growth Associated Protein 43), which is a major protein of the nerve endings. In adult neurons, a large amount of this protein is contained in the synaptic terminal at the end of the axon, and it is expressed at high levels in the neuronal growth cones during development of the neurite. Its expression is directly related to growth and regeneration of axons, new synaptic connections during the development of the nervous system, and with synaptic plasticity in adult organism. GAP-43 is also takes part in induction of certain kinds of apoptosis. It was recently demonstrated that GAP-43 is a substrate of Ca^{2+} -dependent cysteine

proteinase m-calpain. GAP-43 loses its 40 N-ended amino acids as a result of proteolytic cleavage by calpain. The generated C-end fragment of GAP-43 is called GAP-43-3. The functions of GAP-43-3 have not been studied, but they must differ from the intact protein functions because proteolysis affects the functionally significant GAP-43 domain, which includes the phosphorylation site and the membrane attaching domain. It is known that during the development of neurodegenerative diseases (Alzheimer's disease and Parkinson's disease), including those of autoimmune origin (multiple sclerosis), m-calpain hyperactivation in CNS cells. Consequently, as these diseases develop, the amount of GAP-43-3 increases in CNS cells. This hypothesis was tested on the multiple sclerosis model – experimental autoimmune encephalomyelitis (EAE).

Materials and Methods: Disease was induced in Wistar rats with a single inoculation of homologous spinal cord with complete Freund's adjuvant (CFA), while control animals were inoculated with CFA. As a result, we observed the progression of different EAE forms: light, medium, severe and extremely severe (with fatal outcome). The extent of neurologic malfunction in the rats was evaluated daily throughout the experiment by using a score system based on clinical signs: 0.5, muscle weakness of one limb; 1, paresis; 1.5, paralysis. On the disease peak, the animals were decapitated and the lumbar spine was removed. Extraction of GAP-43 and GAP-43-3 from the lumbar spine cell homogenate was performed with a 1% triton X-100 and 5% perchloric acid extraction. After extraction, proteins were divided by electrophoresis in an acetic acid/urea system using the Panim and Choeli method and the released proteins were transferred from polyacrylamide gel to nitrocellulose filter with the «surface print» method. Statistical comparisons were made using one way ANOVA, Tukey's post hoc test. Differences were considered significant at $p < 0.05$.

Results and Discussion: We observed an increase of GAP-43 proteolysis by calpain in the cells of the lumbar spine of all rats with visible neurological disorders at the peak of their disease. It appeared that in the intact and control groups an average of 37% of GAP-43 took the GAP-43-3 form, but in animals with benign and medium clinical course 60% was in the GAP-43-3 form. In severe cases, 85% was in GAP-43-3 form. In thoracic and cervical spines, only animals with severe forms of EAE had a higher percentage increase of GAP-43-3 compared to controls. Indeed, normally about 40% of GAP-43 was in the GAP-43-3 form. During the development of benign and medium forms, the portion of GAP-43-3 did not change, but in severe and extremely severe forms, it made up 65% and 85% accordingly. Therefore, the level of GAP-43 proteolysis in the spinal cord of rats with EAE may be related to the severity of the disease, and the proteolysis of GAP-43 may disrupt the capability of axons to regenerate.

COMPENSATORY MECHANISMS IN A PRECLINICAL MODEL OF PARKINSON'S DISEASE

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Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease. It develops as a result of the impairment of chaperone and ubiquitin proteasome systems (UPS), which are responsible for the packing and elimination of spatial proteins. It is known that preclinical stage of PD may take up 20-30 years before the loss of dopamine (DA)-ergic neurons in the substantia nigra pars compacta (SNpc) reaches 70-80% (Ugrumov, 2008). Most animal models of PD, including those in which inhibitors of the cell protective systems are used, are aimed at reproducing the clinical stage of the disease (Fornai et al., 2003; Subhankar, 2008). The aim of our research, was to develop a preclinical model of PD in rats by using a natural bacterial blocker of the UPS lactacystin (LC), and to investigate the brain's endogenous compensatory systems.

Materials and Methods: The experiments were carried out on male Wistar rats (240–250 g). 0.4 μ g of LC, or a phosphate buffer, were injected twice, at a one week interval, using a conducting

cannulae bilaterally into the SNpc (AP = -5 mm, L = 2.0 mm, V = 8.5 mm) at a rate of 0.1 μ L/min for 10 min (atlas Paxinos and Watson, 1998). The effects were assessed one week after the second injection. Electrophysiological, behavioral and immunohistochemical (using the first polyclonal antibodies to tyrosine hydroxylase (TH); 1:2000; Abcam, UK) methods were used to evaluate the model's characteristics.

Results and Discussion: LC injections induced a 25-35% decrease in the number of DA-ergic neurons in the SNpc, which was not accompanied by the impairment of fine motor skills or changes in locomotory, exploratory, and emotional activity of animals; these findings are consistent with the preclinical stage of PD. There was a tendency for TH levels to increase in neurons of the SNpc which survived, and whereas there was a negative correlation ($r = -0.8$, $p < 0.05$) between the number and the optical density of neurons that were immunopositive for TH, indicating a compensatory production of DA in the SNpc. A Polysomnographic assessment showed an increase in the number of episodes, a 33.8% increase in the total time spent in rapid eye movement (REM) sleep, and a tendency for the total time of wakefulness to increase in experimental animals compared to controls. The data obtained indicates an activation of compensatory processes which are directed towards the enhancement of DA production in the developed model of the preclinical stage of PD, and proposes that REM sleep is involved in the brain's protective mechanisms.

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THE EFFECTS OF INDUCIBLE AND CONSTITUTIVE HSP70 ON CONVULSIVE ACTIVITY IN KRUSHINSKII-MOLODKINA STRAIN RATS

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Introduction: The anticonvulsant effects of natural Heat shock protein 70 kDa (Hsp70), which includes two members of the HSP70 family, stress-inducible Hsp70i and constitutive Hsc70, have been previously revealed in rats of the Krushinskii-Molodkina (KM) strain with inheritable audiogenic epilepsy [Khudik et al., 2006, 2008]. Hsp70i and Hsc70 have similar molecular structure and biochemical functions [O'Malley et al., 1985]. Hsp70i content increases in glial cells, neurons, and in pre- and postsynaptic elements under stress, while Hsc70 levels in the nerve tissue of mammals, stays high in non-stress conditions and do not increase after stress [Chen, Brown, 2007]. However in stress conditions, Hsc70 moves to areas rich with synapses, allowing us to propose that both chaperones may display protective activity. It remains unclear whether Hsp70i and Hsc70 possess anticonvulsant effects.

Materials and Methods: Convulsive activity in an inbred population of KM rats was induced by the sound (intensity 50 dB, frequency 8 kHz) from a generator. The registered parameters were the latency to seizure onset and the duration of the wild running phase, and clonic-tonic seizures. Video surveillance and computer registration systems (Logitech, Switzerland) were used to record and analyze convulsive activity.

Results and Discussion: Microinjections of Hsp70i (6 μ g) in the 3rd brain ventricle of KM rats induced changes in seizure activity, similar to those induced by Hsp70, which consisted of the mixture of Hsp70i and Hsc70. Hsp70i initiated significant decrease in the duration (by 32%) and severity of the tonic phase, but did not affect the latency to seizure onset or wild running phase duration. Hsc70 and thermodenatured Hsp70i and Hsc70 (used as control) did not exert any significant influence on the components of audiogenic seizures in KM rats. We propose that Hsp70 anticonvulsant effects are connected primarily to the Hsp70i activity. It has been previously shown that the physiological effects of Hsp70 are connected to its action on the inhibitory GABA(A)-ergic mechanisms [Pastukhov et al., 2008, 2009]. The results of this research confirm the proposition that

inducible Hsp70i is able to reinforce inhibitory processes in brain against a background of excitatory processes in rats with an inheritable form of audiogenic epilepsy.

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THE INFLUENCE OF ANXIETY LEVELS ON THE LEARNING ABILITY OF RATS WITH DIFFERENT ALCOHOL MOTIVATION

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Introduction: The aim of this work was to identify differences in anxiety levels of rats with different alcoholic motivation and to evaluate the influences of these differences on their learning ability in Radial maze.

Materials and Methods: The experiment was performed on the white male rats. Before alcoholization, rats were trained in the radial maze for 14 days. After training, rats were divided into 2 sub-groups: "well-trained" and "poorly-trained". Before and after the alcoholization period, rats were tested in the elevated plus-maze. Chronic alcoholic intoxication was carried out in two stages:

1) Animals were trained to voluntarily drink an alcohol solution (15%) over 2 weeks. 2) Animals had alcohol as the only drinking fluid available for the month. Statistical analysis was done with the Statistica 7.0 program.

Results and Discussion: The expressed anxiolytic effect of ethanol appeared in the AP group of rats during the EPM test, whereas ethanol consumption in the AN group of rats increased anxiety levels during the EPM. In the AN group, anxiety levels before alcoholization were higher in "well-trained" rats than in "poorly-trained" rats, and alcohol consumption resulted in an increase of anxiety in both sub-groups. In the AP group, anxiety levels were higher in "poor-trained" rats compared to "well-trained" rats both before and after alcoholization. Thus, differences in anxiety levels in "poorly-trained" and "well-trained" rats with different dispositions to alcohol were revealed. The expressed anxiolytic effect of ethanol in the AP group, and the increased levels of anxiety after alcohol abuse in the AN group, confirms that a high level of anxiety is one of the main factors underlying alcohol dependence.

THE INFLUENCE OF LIKOPID ON DOPAMINERGIC BRAIN SYSTEM ACTIVITY IN MALE WISTAR RATS

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Introduction: Likopid is an immunomodulator and its use in the psychoneurology has only just begun. The aim of our study was to investigate the functional activity of the dopaminergic brain system in rats under influence of likopid. Tyrosinhydroxylase is known to be the main enzyme in dopamine synthesis, thus immunohistochemical studies of tyrosinhydroxylase were conducted.

Materials and Methods: There were three groups of animals: 1) the control group that received physiological saline (NaCl 0,9%), 2) the experimental group that received 0.2 mg/rat likopid (low dose), 3) the experimental group treated with 0.4 mg/rat likopid (high dose). After 14 days, animals were decapitated and their brains were fixed in the Buen fluid. The immunohistochemical assay of tyrosinhydroxylase was performed using paraffin slices (6 mcm). The level of immunoreactive materials was analyzed in neurons in several brain structures.

Results and Discussion: In the low dose experimental group, a decrease in the immunoreactive materials in the cell bodies and axons was shown. In the caudate nucleus, there was a significant decrease of immunoreactive materials compared to the control group. In the “high” dose experimental group, it was shown that the level of immunoreactive materials in cells bodies and axons was the same as in the control group. In the caudate nucleus, the level of immunoreactive materials was larger than the “low dose: group, yet it decreased compared to the control group. Thus, our study showed that lipoid modulates the functional activity of the dopaminergic brain system in rats after 14 days of the experiment, and that the “low dose is effective. We plan to continue this work in animals by utilizing different kinds of stress and pathological condition models.

THE EFFECTS OF THERMAL PRECONDITIONING AND EXOGENOUS HSP70 ON MOTOR DISORDERS AFTER CHEMICALLY INDUCED SEIZURES

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Introduction: In our previous investigations, we showed that thermal preconditioning (TP) increased the amount of Heat shock protein 70 kDa (Hsp70) in structures of the central nervous system which are responsible for the initiation of generalized seizures. Furthermore TP was able to decrease the severity of seizures induced by N-methyl-D-aspartic acid (NMDA) or by pentylenetetrazole (PTZ) [Pastukhov et al., 2005, Nitsinskaya et al., 2006]. Injections of bioflavonoid quercetin resulted in decreased amounts of Hsp70 in the same brain structures and increased the severity of seizures in NMDA and PTZ models of generalized epilepsy [Nitsinskaya et al., 2010]. Exogenously delivered Hsp70 was able to decrease the severity of seizures [Ekimova et al., 2008]. There were severe motor disorders after the chemically induced seizures. It was unknown how TP and exogenous Hsp70 affected the motor disorders which were observed after convulsions. The aim of this study was to investigate the effects of thermal preconditioning and exogenous Hsp70 on motor disorders induced by NMDA and PTZ.

Materials and Methods: Male Wistar rats were used in the present study. Seizures were induced either by the microinjection of NMDA (80ng/2µl) into the third ventricle of rats brain, or by intraperitoneal injection of PTZ (80 mg/kg). Thermal preconditioning performed 24h before seizure initiation was used to enhance Hsp70 expression. The bioflavonoid quercetin (5 mg/kg) was injected intraperitoneally 4h before NMDA- or PTZ-induced seizures in order to block Hsp70 expression. The exogenous Hsp70 preparation used in our experiments was isolated from bovine muscles and purified from contaminants at the Institute of Cytology, Russian Academy of Sciences. It contained a mixture of the inducible and constitutive isoforms at a ratio of 3:2. Hsp70 preparation was microinjected into the third brain ventricle 2h before seizure onset. In all groups, motor disorders were observed for 30 min after seizure initiation.

Results and Discussion: The injection of NMDA resulted in motor disorders such as ataxia (in 43% of rats) and stereotypic activity (in 64% of rats). Thermal preconditioning reduced the amount of rats with ataxia symptoms (2-fold). No changes in stereotypic activity were observed after TP. Exogenous Hsp70 resulted in a complete absence of rats with ataxia symptoms. Also, there were no changes in the number of animals with stereotypic activity, but the duration was significantly reduced (5-fold). PTZ-induced seizures resulted in ataxia symptoms and death in 90% of the rats. TP reduced the amount of animals with ataxia symptoms (by 40%) and the duration (1.5-fold). The mortality rate in this group was reduced by 50%. Exogenously injected Hsp70 decreased the number of animals with ataxia symptoms, and mortality rate by 45%. The data obtained indicates that TP and exogenous Hsp70 are able to intensify the recovery process of motor functions that are disturbed by NMDA and PTZ.

THE EFFECTS OF HYDROALCOHOLIC EXTRACT OF *ZIZIPHORA TENUIOR* ON THE VISCERAL PAIN WITH WRITHING TEST IN MICE

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Introduction: *Ziziphora tenuior* is a traditional herbal medicine widely used as a mild sedative, spasmolytic and antibacterial agent. In this study, the effect of hydroalcoholic extract of *Ziziphora tenuior* on visceral pain was investigated.

Materials and Methods: This experimental study performed on 40 N-MRI male mice ($28 \pm 3g$). Animals were randomly grouped into control, positive control, and receivers of *Ziziphora tenuior* extract. Control and positive control groups received normal saline and indomethacin (5mg/kg), respectively. Treatment groups were injected with 50, 75 and 100 mg/kg of hydroalcoholic extract of *Ziziphora tenuior*. All injections were performed intraperitoneally (ip). 30 min after of each intraperitoneal administration, animals were injected with 0.6% acetic acid (10ml/kg) to induce visceral pain,. Antinociceptive effects were recorded by counting the number of writhes during 30 minutes. The data were analyzed by the One- Way ANOVA test using SPSS statistical software . Significance was set at $p \leq 0.05$.

Results and Discussion: Hydroalcoholic extract of *Ziziphora tenuior* at 50, 75 and 100 mg/kg and Indomethacin (5mg/kg) induced a significant reduction in pain responses when compared to the control group. The 75mg/kg of extract showed the most effect ($p < 0.05$). This study confirms the antinociceptive properties of *Ziziphora tenuior* in comparison to Indomethacin, however further studies are necessary to determine an optimal indication for the antispasmodic effect of *Ziziphora tenuior*.

Published Communications:

RISK FACTORS FOR POST-STROKE DEPRESSION

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Introduction: Post-stroke depression is a common psychiatric complication of stroke. However, depression is often not diagnosed, and patients do not receive appropriate treatment. It is known that these disorders increase mortality and reduce the effectiveness of rehabilitation for patients after stroke. In this regard, determination of risk factors for post-stroke depression can predict their development, allowing time to begin treatment of patients after stroke.

Materials and Methods: An investigation was conducted on 42 patients in residual periods after stroke. The study involved patients with a newly evolved local supratentorial stroke. The severity of strokes was assessed using stroke scales from the National Institutes of Health (NIHSS). Differentiation between left-and right strokes was based on data from a computer and/or magnetic resonance imaging and clinical manifestations. Functional motor asymmetries and hemispheric dominance for motor function was assessed using standard methods (Bragina, Dobrokhotova, 1988). We used the Hamilton Depression Scale (Hamilton, 1967) in the diagnosis of depression. Personality characteristics of patients were assessed using the Eysenck Personality Inventory (EPI) (Eysenck, 1963). The relationship between the presence of depressive disorders, damage to the hemisphere, and temperament were analyzed using contingency tables and Fisher's exact test. For all the statistical calculations the computer program SPSS was used.

Results and Discussion: Post-stroke depression was found in 12 patients (33 %). Nine patients with depression had a choleric temperament before the stroke, three had a sanguine temperament and two patients had a phlegmatic temperament. The presence of depressive disorders was correlated with the localization of strokes in the dominant hemisphere of motor function and the choleric temperament. Patients with post-stroke depression had higher levels of neuroticism ($p < 0,001$) in comparison to patients without depression disorders.

ANXIETY LEVEL OF THE PERSONALITY AND PSYCHOPHYSIOLOGICAL RATES OF HUMAN HEALTH.

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Introduction: This research involved 84 volunteers ranging from 21 to 48 years of age.

Materials and Methods: The indices of personal and reactive anxiety (Spielberger-Hanin test), verbal anxiety (Erikson test), subjective self-esteem and depression (Depression scale test), emotionality (Suvorova method), neurotization (Wassermann method), neurosis (Hek and H. Hess method), subjective evaluation of time and vegetative dysfunctions (Vein Questionnaire) were analyzed. The heart rate (H.R.), rate of respiration per minute, and respiratory sinus arrhythmia, were estimated while participants were in a resting state or reading a text aloud. Besides the quality of speech, the duration of the phonation for the sound “a” and the indices of s/z pronunciation were analyzed.

Results and Discussion: According to the results of the Spielberger-Hanin test, all the participants of the experiment were divided into two groups: a) 50 people (44 women and 6 men) with of personal anxiety (P.A.) levels that were high (45+ points), b) with moderate level of P.A. (from 30 to 44 points) – 34 people (23 women and 11 men). The research showed that participants with moderate P.A. levels performed better on all the psychological tests (except subjective self-esteem and the sense of time) and the emotionality and vegetative dysfunction ($p < 0.01-0.0001$) test than those with high personal anxiety. The presence of high levels of P.A. was accompanied by high and increased levels of speech anxiety, conditions similar to depression, occurrences of latent (masked) depression and neurotic genesis depression, neurotization, presence of neurosis, emotionality, and lower self-esteem. The data indicates that the personalities with high P.A. levels form the high risk group because of their psychological health rates, adaptation, and socialization. These people need to work upon improving their personal relationships, individual responses, and behavior. During the physiological indices research, reliable distinctions were only made with the phonation rates. The duration of the sound “A” in the high P.A. group was lower than those of the moderate P.A. group ($p < 0,01$), and the s/z rate was higher ($p < 0,02$) for the high P.A. group. People with high P.A. (unlike the persons with the moderate P.A.) did not have indices which corresponded to the normal standards. This reflected the presence of excessive tension in vocal organs during phonation and indicated that there was a risk for the occurrence of vocal pathologies. The heart rate, respiration rate, and evidence of respiratory sinus arrhythmias during resting state and the vocal act, did not differ very much between the groups with different P.A. levels. This indicates that these indices depend mostly on the personal and behavioral features, neuroendocrine regulation, condition of the vegetative nervous system, and adaptive properties of the organism, as opposed to the P.A. level. It would be worthwhile to stress that vegetative dysfunctions were diagnosed in 76% of participants and disturbance of the vocal respiration technique and some speech components were seen 72% of the participants. The representatives of the both groups demonstrated sympathicotonia and excessive psychoemotional tension during the speech tests due to the adaptive character of the organ and the presence of stress. The research proved the presence of an inverse relationship

between the indices of personal anxiety and psychophysiological characteristics. The higher the personal anxiety levels are, the worse are psychological and even some physiological personality health rates.

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