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The Russian Society for BioPsychiatry (RSBP)
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Proceedings

11-th Multidisciplinary International Neuroscience and Biological Psychiatry Conference "Stress and Behavior" (1st ISBS Conference)

Editors: Allan V. Kalueff, Justin L. LaPorte

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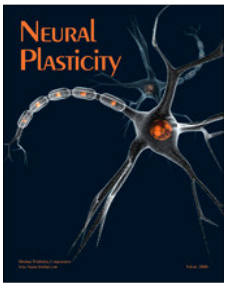


Table of Contents

Welcoming Address
from the Conference Chair

Dear Colleagues,

On behalf of the Conference Organizers, I would like to extend a warm welcome to the delegates of the 11th International "Stress and Behavior" Conference. We have researchers and clinicians from nearly 40 countries, representing every continent of the world, to join us in St. Petersburg in 2008. Our meeting has had a solid history of scientific excellence for a full decade, and I look forward to another enriching assembly this year. As there are many pertinent issues that will serve as focal points for our meeting, I would like to mention just a few of them here.

Firstly, modern developments in the clinical field are driving shifts in our conceptualization of biological psychiatry. Today, our knowledge of disorders of the brain is showing that these illnesses are not nearly as discrete as previously thought. Clearly, a more holistic, spectrum-oriented concept of brain disorders and their interrelatedness is emerging that represents a "new face" of biopsychiatry.

There have also been remarkable advances in experimental neuroscience during the last years. New genetically-altered animal models and the opportunity for novel experimental paradigms are making this an exciting time to do research. The progress in the field of psychiatric genetics has widened our understanding of the genetic contribution to both normal and abnormal brain function. Equally important for us, however, are the epigenetic, epistatic, gene x environment, gene x gene, and gene x personality factors.

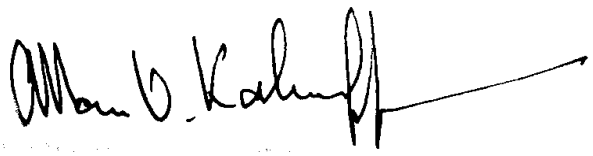
Biopsychiatry today deconstructs complex neuropsychiatric diseases into endophenotypes - objective, quantifiable, and inheritable traits that serve as biological markers of a brain disorder. This approach allows researchers to focus on endophenotypic domains more specifically to discover novel genes/alleles related to a disorder and elucidate pathogenetic mechanisms by modeling causal pathways.

In addition to these considerations, however, other emerging concepts in biological psychiatry are reinvigorating research efforts across the globe. Cross-species trait genetics concept and the domain-interplay approach are among these recent developments in our field. While clinical research is facing new challenges, such recent concepts will address them with innovative solutions, thereby ushering in a new era of effective detection and treatment of mental illness.

We recognize that constant development of new experimental models and new theories represents an essential part of neuroscience research. This notion is particularly important today, when it is becoming dangerously tempting to trade innovative research for “safer” incremental progress. Nevertheless, I strongly believe that it is our privilege, and yet our obligation, to employ our creativity, to think “outside of the box”, and to foster innovative translational research.

Because we all understand the need for inventive experimental and conceptual approaches, I am confident that our 2008 conference will provide us with a stimulating environment through collegial interaction and collaboration. Collectively, this will facilitate multidisciplinary research that will help to expand our knowledge of the pathogenetic mechanisms of stress-induced brain maladies.

Welcome to St. Petersburg!



Allan V. Kalueff, PhD Hon
Washington DC, March 12, 2008

Welcoming Address
from the Conference Program Committee Chair

Dear Colleagues!

It has always been my pleasure to welcome you to our beautiful city every year at the opening of the Conference on Neuroscience and BioPsychiatry “Stress and Behavior”. Last year we celebrated our 10th anniversary – an event that now gives us the right to consider the Conference as one of the regular scientific meetings which has already proved to be fruitful. It attracts many scientists from all corners of our planet.

Our time is one of e-mail exchanges and electronic journals. We cannot deny that modern science would not survive without computers and that the Internet helps us to gain easy and fast access to much useful information. However, all these electronic advances make us value every possibility to have face-to-face communication with friends and colleagues. This is especially true if these friends have strong common interests, and are eager to discuss new ideas and challenge the field.

Successful ventures have a tendency to develop and grow. Therefore, it is unavoidable that our Conference has obtained a satellite – the Summer School on behavioral genetics and neuroscience of stress. Young scientists from 15 different countries will be participating this year, and we sincerely hope that this Summer School will become another regular event that stimulates further scientific interaction and collaboration in our field.

Although the attraction of scientific reports and discussions is undeniable, I also hope that it is not all that matters at this meeting. I believe that those of you who attended our previous conferences could not help but return to see the beauty of Saint Petersburg again. And I am sure that our first time guests will also fall in love with our city.

Combining scientific and historic interests, it will be my pleasure to welcome you at the Pavlov Department of Physiology, where Ivan Pavlov spent 45 years of his most fruitful years that earned him the Nobel Prize.

Finally, I want to emphasize that both the city of Saint Petersburg and the participants of this event guarantee its success. I sincerely hope that this meeting inspires your research, which we always look forward discuss with our old and new friends.

Professor Victor M. Klimenko, MD, PhD
St. Petersburg, March 22, 2008

Plenary Lectures

PL1 REFOCUSING PSYCHIATRIC GENETICS: FROM DISORDERED DOMAINS TO DOMAIN INTERPLAY

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The field of biological psychiatry can greatly benefit from new perspectives on the old problems facing researchers. Previously, there have been limited techniques available for the study of emotional states in humans and animals. Behavioral neurophenotyping has been one of the field's most familiar tools. However, new experimental techniques are needed to ensure further progress in the field. The concept of domain interplay shifts the focus away from singular domains or interactions, and focuses on modeling numerous separate domains and the interface between them. By modeling these phenotypical interfaces, researchers can link domains in relation to each other, thereby modeling an extended conglomeration of interactions that will aid in characterization. In this way, interactions can be modeled across-species and used as a tool for effective translational research, thereby widening the extent of phenotypical characteristics that can be investigated and decreasing the risk of inconsistent results. The concept of domain interplay encourages research efforts away from the traditional narrow single-domain approaches, and helps alleviate some of the guesswork inherent in endophenotying and cross-species techniques. The domain-interplay concept promotes correct data interpretation in behavioral paradigms and supports the construct validity of the animal model by harnessing this inherent emotional complexity. Evaluating several domains simultaneously will distinctly improve the ability of the models to mimic the entire pathway of the disorder, instead of a single point along the continuum. Thus, the clinically-relevant aspects of brain disorders, such as comorbidity and disorder pathogenesis, can now be realistically achieved with this concept, opening new paths of research into neurological substrates of pathogenesis. The domain interplay concept provides a design for creating models that exploit the interplay of domains evident in basic and clinical research of many brain maladies. This research was supported in part by the Intramural Program of the NIH, NIMH and by a NARSAD YI Award.

PL2 POLYMORPHIC VARIATION MODULATES NEUROTRANSMITTER GENE EXPRESSION

JP Quinn, K Haddley, F Ali, S Vasiliou, VJ Bubb
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We predict that susceptibility to behavioral disorders will involve polymorphisms within transcriptional regulatory domains of many neurotransmitter genes rather than lie solely within the protein encoding exons. We are complementing bioinformatics and association studies with biochemical and transgenic analysis to determine regions that are both involved in tissue specific and stimulus regulated neurotransmitter gene expression with important correlates of clinical importance, drug response and predisposition to disease. We have demonstrated that some members of a subclass of such polymorphic domains termed Variable Number Tandem Repeats (VNTRs) have functional effects on gene expression. This suggests that individuals with a particular combination of polymorphisms may respond differently to an individual medication or environmental stress. We have demonstrated in both the human serotonin transporter gene (5HTT, SLC6A4) and the dopamine transporter gene (DAT1, SLC6A3) that specific VNTRs, correlated with predisposition to neurological and psychiatric disorders, act as transcriptional regulatory domains. These domains can act as both tissue-specific and stimulus-

inducible regulators of gene expression. Further, in vitro, the 5HTT VNTR in intron 2 is responsive to lithium and the DAT1 VNTR in intron 8 modulates a response to cocaine and amphetamine. These functional studies link the clinical findings that at risk groups have a higher incidence of a particular polymorphic variant. In the above examples, the VNTRs may alter the concentration of transporter protein in specific cells or in response to a challenge; chemical, environmental or physiological. We have demonstrated that multiple VNTRs within the same gene or distinct genes can bind the same transcription factor and therefore potentially are on the same signal transduction pathway. Therefore a more global analysis of VNTRs complemented by single nucleotide polymorphism (SNP) data correlated with disease predisposition would be a first step to understand the integrated cellular response to a specific challenge. Further, it is predicted that this data will be invaluable to enable future intelligent directed drug design. We are identifying and characterizing other regulatory domains which exhibit polymorphism, e.g. the most evolutionary conserved regions (ECRs) at a particular gene locus which are not in exons. ECRs also contain polymorphic variants, such as SNPs, that could change the function of that domain. By concentrating on genetic variation in functional regions of the genome this approach will greatly accelerate the association of SNPs and VNTRs within these regions with susceptibility to various psychiatric conditions and will lead to the development of much more effective and personalized anti-depressive drug therapies.

PL3 DEJA VU: A STUDY OF GOOD AND BAD DUPLICATION IN MEDLINE

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With little chance for discovery and decreasing budgets, yet sustained pressure to publish, the unethical practices of duplicate publication and plagiarism can be enticing to some. There are also cases where there is high similarity between citations, and these include reviews, updates, errata, etc., which are valuable additions to the scientific literature. These practices are difficult to detect and have therefore largely gone unchecked because there is a lack of robust methods to identify partial or full duplications of article text. Here we show that approximately 0.04% of Medline abstracts are plagiarized and 1.3% is duplicated. Using the text similarity engine eTBLAST, we analyzed Medline in two ways, by sampling citations and comparing them to the remainder of Medline, and by comparing related articles to each other. We have made a number of observations and have captured this information in a free, on-line database, Déjà vu. eTBLAST is freely available to all, with special functionality for editors and reviewers, as a screening tool to identify putative duplicate articles and thus may act as a deterrent. I will present the results of this work, providing individual examples and also trends.

PL4 CONVULSIONS IN FASTED ANIMALS AFTER ANTIMUSCARINIC TREATMENT AND FOOD INTAKE

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Mice treated with scopolamine after fasting for 48 h develop clonic convulsions soon after being allowed to eat ad lib. The additive effect of scopolamine treatment and access to food is essential to the induction of convulsions (Enginar et al., 1996). Food deprivation itself, but not its hypoglycaemic consequence, seems to be critical in the development of these convulsions, since prevention of hypoglycaemia by glucose intake during food deprivation had no preventive effect (Enginar et al., 2005). Development of convulsions in fasted animals pretreated with antimuscarinic drugs atropine and biperiden ruled out a specific convulsant or pro-convulsant effect for scopolamine (Enginar et al., 2005). Suppression of convulsions by the noncompetitive N-methyl-D-aspartate (NMDA) antagonist MK-801 (Enginar et al., 1997) and changes in [3H] glutamate binding induced by fasting and reversal by scopolamine treatment and food intake

have been evaluated as glutamatergic contributions to the underlying mechanism(s) (Enginar et al., 2003). Suppression of convulsions by pretreatments of alpha-2 agonists clonidine and tizanidine (Enginar et al., 1999) and by dopaminergic antagonists chlorpromazine and haloperidol (Enginar et al., 2003) also indicated adrenergic and dopaminergic hyperactivities as possible contributing factors. These convulsions, on the other hand, seemed somewhat unresponsive to conventional antiepileptic drugs, since only valproate, gabapentin and diazepam provided effective treatments (Enginar et al., 2005). Convulsions in fasted rats after scopolamine or atropine treatments and food intake indicated that antimuscarinic-induced convulsions are not specific to mice (Nurten and Enginar, 2006). The electroencephalographic characterizations of these convulsions were also described (Nurten et al., 2006). Recent studies showing convulsions in mice deprived of food for periods shorter than 48 h suggested that food deprivation itself, rather than its duration, seems to be the principal factor in the development of these convulsions and implied that putative neuroadaptations as mechanisms underlying convulsions might occur even in hours after exposure to food deprivation. In view of these findings and the differences from convulsions produced by both chemical convulsants and metabolic derangements in animals, this method may provide a new technique/model easy to produce seizures in rodents.

PL5 CYTOKINES IN THE BRAIN

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Behavior is determined by the environment and mediated by central mechanisms, evaluating incoming information and forming the most appropriate reactions. Efficiency of experience acquisition, as well as its reproduction, depends upon many factors such as the level of consciousness, motivations and emotions. Another common connection is quite evident – all these factors depend on the inter-correlation of all physiological systems and on the level of their activity or health. Interactions between the nervous and immune systems are multifaceted and have a long scientific history. The ancient saying, “mens sana in corpore sana” (a healthy mind in a healthy body), is an adequate motto for this field of research. Cytokines were discovered as messengers among various components of the immune system, but with the molecular identification of cytokines, it soon became clear that they affected the brain as well. Infections, inflammation and pro-inflammatory cytokines have been shown to disrupt exploratory behavior and learning (particularly based on spatial cues), consequently impairing the formation of the special cognitive map in the hippocampus. Cytokines mediate cellular and systems interactions in immune and nervous systems participating in both the regulation of physiological functions and in the development of brain pathology. Numerous publications and our own data reveal expression of cytokines and activation of biogenic amines in the brain induced by systemic and icv treatment with Interleukin-1β (IL-1β) or with a cytokine inductor – bacterial lipopolysaccharide (LPS). The reactions are followed by changes of communicative activity, feeding behavior, slow-wave sleep, pyrogenic reaction and by activation of HPS axis. Our experiments reveal different thresholds of physiological reactions to IL-1β or LPS injections (of pyrogenesis, of changes of feeding and social behavior), that are mediated by different neuromediator pathways and develop separately. Administration of a subpyrogenic dose of IL-1β induces a decrease of animal communicative activity and changes in dopamine and serotonin metabolism in the anterior hypothalamus. It is possible to block the effects by preliminary icv injection of Il-1 receptor antagonist (IL-1r.a.). Icv administration of parachlorphenilalanin, a selective inhibitor of serotonin synthesis, blocks feeding behavior disturbance but not communicative activity nor the pyrogenic reaction induced by IL-1β systemic treatment. Treatment with IL-1β influences the structure of rat behavior: reactions to new stimuli and working memory do change (open field intruder-resident and 12-beams maze tests) but well-trained behavior programs (maze) do not. There is much converging evidence supporting

the contention that illness-inducing agents and cytokines are capable of producing anhedonia, a finding especially relevant for linking sickness behavior to depression. Thus, cytokines express activity in the brain and initiate the complex set of symptoms defined as sickness behavior. Cytokines recognized initially as immunopeptides demonstrate distinctive influence on brain functions. They are produced by CNS cells and are ligands of neuron receptors. Moreover, taking into consideration their participation in the signal transferring from the immune system to the CNS, and their ability to induce the cascade of regulatory processes, we considered that cytokines act as regulatory peptides in the brain. Just a few first steps have been made to explore the role of cytokines in the brain. But they have already revealed cytokines involvement in the brain regulation of physiological processes that have no connection with the immune system activity, such as the processes of thermoregulation, and sleep/wakefulness cycles. These peptides transfer the signal about immune cells activation to the brain, reorganize the perception and behavior of the individual, and subordinate current functions to the strategy of survival in the wild environment. Furthermore, in the central compartment, cytokines play the same role as they do in the periphery by mediating inflammation. Further investigation of the cytokine's role in behavior is very promising. Sufficient evidence is now available to accept the concept that cytokines are interpreted by the brain as molecular signals of sickness. Sickness can actually be considered as a motivation, that is, a central state that organizes perception and action in face of this particular threat that is represented by infectious pathogens. A sick individual has priorities other than a healthy one. This reorganization of priorities is mediated by cytokines to a number of peripheral and central targets. Exploration of mechanisms involved in these effects will provide new ideas about the ways through which the brain organizes the processes of disease and healing.

PL6 EARLY SOCIAL ISOLATION INTERFERES WITH THE BEHAVIORAL EFFECTS OF ETHANOL

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The influence of early social isolation on the behavioral effects of ethanol was quantitatively investigated. Male Wistar rats were bred and reared either isolated in standard laboratory cages or grouped of five-six rats/cage (social rearing) in the same room. Four weeks later, these rats were tested for their sensitivity to ethanol using the social interaction and elevated plus-maze tests. The results from the social interaction test showed that ethanol (300 and 600 mg/kg i.p.) significantly decreased the active social interaction behavior in both isolation and socially reared rats compared with the saline treated controls $P<0.05$). This effect was more pronounced in the socially reared rats. Moreover, ethanol produced a dose-related antiaggressive effect in socially reared rats as indicated by a decrease in the aggressive interaction time. This effect of ethanol was not observed in the isolation reared rats. The results from the elevated plus-maze test demonstrated that pretreatment with ethanol (300, 600 and 1200 mg/kg i.p.) significantly produced an anxiolytic profile (increase in percentage of open arm entries and time) on the elevated plus-maze in socially reared rats ($P<0.05$). However, in the isolation reared rats, low doses of ethanol (300 and 600 mg/kg i.p.) did not produce the anxiolytic-like effect. This effect of ethanol was reached significantly only at the highest dose (1200 mg/kg). Thus, our results indicate that early social isolation powerfully interferes with both anxiolytic and antiaggressive effects of ethanol. This abnormality may reflect alterations of GABA functions in the central nervous system.

PL7a CLARIFYING THE ORIGIN OF BIOLOIGICAL ABNORMALITIES IN PTSD THROUGH THE STUDY OF IDENTICAL TWINS DISCORDANT FOR COMBAT EXPOSURE

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Introduction: A biological abnormality found to be associated with posttraumatic stress disorder (PTSD) may be, among other things, a pre-trauma vulnerability factor, that is, it may have been present prior to the traumatic event's occurrence and increased the individual's likelihood of developing PTSD. Alternately, it may be an acquired PTSD sign, that is, it may have developed after the traumatic exposure, along with the PTSD. Methods: We have studied pairs of U.S. Vietnam combat veterans and their combat-unexposed, identical twins in an effort to resolve these competing origins. Combat veterans were diagnosed as current, combat-related PTSD or non-PTSD (i.e., never had). Results and discussion: Increased heart rate responses to loud tones, lower auditory P3b event-related potential responses, increased P2 amplitude intensity slope, poorer recall of extinction of conditioned fear, and diminished gray matter density in pregenual anterior cingulate cortex were found in Vietnam combat veteran twins with vs. without PTSD, but these differences were not shared by the PTSD veterans' unexposed co-twins, whose responses were similar to those of the non-PTSD veterans' co-twins. These results suggest that the above biological abnormalities represent acquired signs of PTSD. In contrast, increased neurologic soft signs (NSSs), diminished hippocampal volume, presence of abnormal cavum septum pellucidum, and increased resting regional cerebral metabolic rate for glucose in dorsal anterior cingulate cortex were found in Vietnam combat veteran twins with vs. without PTSD as well as in PTSD veterans' co-twins vs. non-PTSD veterans' co-twins. These results suggest that the latter abnormalities represent antecedent, familial vulnerability factors for developing chronic PTSD upon trauma exposure. Conclusion: These findings support the conclusions that some structural and functional brain abnormalities found in PTSD represent pre-trauma vulnerability factors for developing PTSD upon exposure to a traumatic event, whereas others are acquired as a result of the traumatic event and/or the consequent PTSD.

PL7b ORIGIN OF PSYCHIATRIC SYMPTOMS IN POSTTRAUMATIC STRESS DISORDER: FINDINGS FROM MONOZYGOTIC TWINS DISCORDANT FOR COMBAT EXPOSURE

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VA Medical Center, Manchester, NH; Harvard Medical School, Boston, MA, USA

Introduction: Some reports in the literature have suggested that pre-trauma psychopathological traits are risk factors for the development of posttraumatic stress disorder (PTSD) in individuals subsequently exposed to traumatic stressors. However, retrospective and prospective studies to date, which have yielded conflicting results, have been unable to fully determine the role of premorbid psychopathology. The current case-control twin study attempted to clarify the origin of psychopathological symptoms in PTSD. Methods: Subjects included a convenience sample of 104 identical twin pairs discordant for combat exposure in Vietnam, with (N=50) or without (N=54) combat-related PTSD in the exposed twin. The Symptom Checklist-90-Revised (SCL-90-R), Mississippi PTSD Scale, and Clinician-Administered PTSD Scale were used to assess the presence of current mental disorder symptoms. If psychopathological traits represent an underlying familial vulnerability factor for PTSD, they should be found at elevated rates in the non-trauma-exposed, identical co-twins of trauma-exposed twins with PTSD. Results and discussion: Combat veterans with PTSD had higher scores on all scales and subscales than their own combat-unexposed co-twins, and than combat veterans without PTSD and their co-twins. There were no significant differences between the high- and low-risk, unexposed co-twins, i.e., those whose combat-exposed brothers did or did not develop PTSD. Conclusion: These findings do not support the conclusions that individuals who develop PTSD possess pre-existing psychopathological traits, or would have developed some form of psychopathology, even in the absence of a traumatic event.

Plenary Presentations

PP1 THE USE OF NOLDUS TOOLS FOR STRESS BEHAVIOR RESEACH

RF Roelofs
Noldus Information Technology, Wageningen, The Netherlands

Introduction: Since the founding of our company in 1987, NoldusIT has evolved into the market leader of behavioral research tools. Currently our software and hardware tools (e.g. The Observer® XT, EthoVision® XT, CatWalk® and Theme®) are used for the collection and analysis of behavioral data in every discipline of behavioral research (e.g. Biology, Psychology, Industrial design, etc).EthoVision® XT is the latest version of our versatile Video Tracking System designed for the collection, analysis and presentation of automatically generated position related parameters (e.g. position, orientation, distance, speed, movement, etc) of freely moving animals. Because EthoVision® XT is a video based system its special and temporal resolution is much higher and the data more versatile and reliable than with non video based systems, like photo-beam based systems. Furthermore, its restrictions on the animals' environment is far less pronounced than in any other competitive system, giving the researcher the freedom to gather behavioral data for longer periods in a wide variety of circumstances (e.g. home cage environment, enriched environment). This means it can be used for almost any test available to behavioral researchers that involves movement and position analysis. The video and behavioral data acquired with EthoVision® XT can also be used to analyze behaviors that are not automatically generated (e.g. grooming, rearing, sniffing, head dipping) giving researchers the ability to create the most detailed and refined picture of behavior in almost any situation. During my presentation I will give an overview of how The Observer® XT, EthoVision® XT and Theme® are used by various researchers around the world for gathering, analyzing and presenting stress related behaviors in non-standardized and standardized behavioral tests (e.g. Porsolt (Forced) Swimming Test, Open Field, Elevated Plus Maze, Zero Maze and their variations).

PP2 BEHAVIOR RECOGNITION—W5: THE NEXT GENERATION OF TECHNOLOGY FOR BEHAVIORAL RESEARCH

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Clever Sys Inc., Reston, George Mason University, Fairfax, VA, University of Minnesota, Minneapolis, MN, USA

Introduction: Behavioral researchers today are frequently met with the challenges of finding adequate methods to observe and record animal behavior. Neurological diseases are being characterized by the behavioral phenotypes of mouse models and targeted mutations of genes expressed in the brain are revealing the underlying mechanisms of behavior. As a result, the most comprehensive maps of the brain include molecular, cellular, system, and behavioral data. All of which are dynamic, interactive, interdependent, and complex processes. Clever Sys. Inc. (CSI), a bioinformatics software company, has devised a system that automatically recognizes and records animal behaviors in a variety of environments depending on individual research needs. Methods: For the purpose of the development of this technology, CSI roughly classifies behaviors into 4 categories: natural, simple, complex, and designed. The patented software is characterized by the ability to capture the entire animal body and discriminate between its individual parts. In addition to approaches in analyzing temporal-space relationships, such as with time sequence-analysis, CSI has developed novel algorithms to determine: what the animal

is doing, when the behavior is occurring, where the animal is doing the monitored behavior, and which is which? In specific cases, multiple animals such as mice, drosophila, or zebra fish can be observed for analysis within one apparatus. Results and Discussion: Previous attempts have been made to fulfill this need for automation, such as with the introduction of Photobeam and Video Tracking technologies. Unfortunately, both systems only provide limited information about an animal's location. This is because behaviors that go beyond the measure of location are too sophisticated for either type of technology. CSI has addressed this problem by using novel computer vision and digital video technologies to develop Behavior Recognition technology. Conclusion: Using high throughput video analysis tools allows research to be conducted on a much larger scale at a faster rate; this provides faster results and consequently a more rapid scientific discovery process. This is not to suggest that research be conducted with haste, but rather that CSI has made it is possible to collect data with less restraints, in more natural environments which reflect more unrestrained forms of behavior. This capability will advance the field of behavioral science in ways that have been previously impossible.

Conference Lectures

CL1 PRESERVATION OF HUMAN NERVOUS TISSUE IN ITALIAN SIXTEENTH CENTURY MUMMIES

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Pathological Anatomy III, Department of Surgery, Department of Arts History, University of Siena, Division of Paleopathology, Department of Oncology, Transplants and Advanced Technologies in Medicine, Pisa University, Pisa, Italy

Introduction: Few studies have been applied to ancient human soft tissues, in particular to brain tissue. This is because of the scarcity of available mummies and the rarity of preserved mummified human central nervous system. This study undertook an analysis of three naturally mummified human brains and orbital region tissues from the Basilica of San Francesco in Arezzo (Tuscany). The bodies are in good preservation state, because they were buried in very dry soil. Dresses style makes possible to establish the second half of the sixteenth century as the most probable dating for the tombs. Identification of the individuals is at present impossible, but considering the importance of the burial site, we can assume that they were eminent members of the Arezzo wealthy Renaissance class. Methods: As the first step, we examined these individuals with digital radiology and helical computed tomography (CT). Then samples of brain and orbital region tissues were taken, rehydrated and processed for structural analysis by light microscopy. Results and discussion: The light microscopy revealed an eosinophilic staining background with vascular, nerve, fat and muscle structures. The nervous tissue is recognized, despite the fact that only a few cellular elements are present. Moreover we use histochemical and immunohistochemical techniques, such as Masson's trichrome, Von Kossa, S-100 protein, Chromogranin, Neurofilament, Giemsa, Synaptophysin, GFAP, EMA, Vimentin that helped us in the recognition of the different histological structures. Conclusion: The examination of ancient human brain tissues can reveal normal and abnormal neuroanatomy, playing an important role in determining the cause of death.

CL2 BEHAVIOR OF WOMEN MEDICAL STAFF IN STRESS SITUATIONS

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Introduction: Women working in hospital wards are exposed to a significant daily stress, which can influence their health and behavior. Methods: The purpose of this study was to investigate their stressors, stress symptoms and behavior in stress situations. The sample consisted of 192 Polish women (68 physicians and 124 nurses/midwives working in a hospital in Tarnow) who filled out a specially-designed questionnaire related to stressors, health and behavior. The obtained results were calculated with the use of Chi-square analysis. Results and Discussion: In general, the main sources of stress for women members of medical staff were connected with their work routine and economic situation. More than half of respondents complained about insufficient salaries and one fifth expressed concern regarding housing accommodations. For female physicians, the major stressor was the responsibility for patients' health and life, while for nurses and midwives the major stressor was discharge threat. Family life (relationships with partner and children) stress of women doctors was reported with half the frequently of their counterparts. In stressful periods, 1 in 3 investigated members of medical staff reported insomnia and many mentioned disturbances in appetite drive (its decrease by every 4th and its increase by every 5th respondent). More nurses and midwives complained of heartburn, digestive system disorders (stomach ache and diarrhea) and profuse sweating than did physicians. In situations of stress, independent of job position, over 50% of women sought help,

1 in 4 women-doctors and one in 3 nurses/midwives smoked cigarettes, every fifth went for a walk and more than 16% read books in order to relax. Physicians consumed alcohol significantly more often, took drugs, watched television, listened to music or slept, while nurses/midwives cried in stressful situations. Some of those differences in ability to cope with stress could be consequences of the specifics of the workplace (watching TV, listening to the radio or sleeping were possible in doctor's rooms even during work hours, especially during quiet night shifts). Conclusion: The main sources of stress for Polish women-doctors and nurses/midwives working in the same hospital were connected with their workplace. In some cases their sensitivity to stressors, stress symptoms and behavior in stress situations were different and job-dependent. A great amount of strain on women medical staff could have a detrimental impact on their health and determine specific behaviors in both professional and private life. Polish physicians and nurses/midwives highly require economical and organizational strategies to manage or prevent work stress as well as stress in their private lives.

CL3 CONTEMPORARY APPOACH TO THE DIAGNOSTICS AND CORRECTION OF EMOTIONAL STRESS FOR CHILDREN WITH ATTENTION DEFICIENCY SYNDROME WITH HYPERACTIVITY

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Introduction: One of the most characteristic disturbances of childhood development is attention deficiency syndrome with hyperactivity (ADSH). The teaching of hyperactive children is an urgent problem in school. Children with ADSH have problems with self-estimation, excessive risk behavior, social difficulties and trouble with learning. Early studies of nervous system disturbances in many cases give the ability to improve the behavior of hyperactive children. The aim of current research was to investigate age peculiarities of psychoemotional stress to various sensory irritants for preschool and primary school age children with ADSH, as well as to determine the connection of this phenomenon with their cognitive functions. Methods: The intensity of psychoemotional stress was assessed by the dynamics of peripheral blood flow. 90 5-6 year old preschool age children and 120 7-8 year old first form children were used. Periphery blood flow was ascertained by the parameters of photoplethysmogram (PPG). Registration of PPG was carried out from forefinger of the left hand with "Reacor" equipment, using a "stress test" computer program. This program gives the ability to assess the amount of psychoemotional reactivity of children during phone and various other irritations: verbal, visual, auditory, and the possibility of children for adaptation as well. The peculiarities of children's cognitive functions were assessed by sensorimotor reactions. The reaction time for common sensor signals and reaction time of selection between two different geometrical figures was assessed. Results and discussion: It was ascertained that periphery blood flow parameters of both age group children with ADSH changed in comparison with the control group. 5-6 year old children with ADSH have unstable parameters of PPG with individual typological parameters. The most characteristic type of PPG in this group is an increase of PPG amplitude as from phone and later on during verbal, visual and auditory irritations. The majority of 7-8 year old children with ADSH have the highest amplitude of PPG on the phone and later on it stabilizes. They can better regulate their functional state in comparison with the younger group of children. Children of both groups have high levels of psychoemotional stress. The reaction time of selection between two different geometrical figures was longer for children with ADSH and they made more mistakes during the geometrical figure determination. Conclusion: The computer "stress test" program is as an effective method of clarifying high levels of emotional stress in children. It can be used as a screening method for detecting at-risk children.

CL4 IMPACT OF INDIVIDUAL HOUSING ON EXPERIMENTAL BEHAVIOR OF MALE MICE

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Introduction: Rodent models play a major role in biomedical- and behavioral research. Inappropriate social housing conditions, which might be considered as chronically stressful for the animals, will affect the reliability of these models, since stress is known to influence emotionality fundamentally. Due to territoriality, social housing might lead to an increase in interindividual aggression, especially in male mice, resulting in a modulation of the emotional state of the animals. Since systematic research on the effects of social housing conditions on experimental behavior is lacking, we compared experimental behavior and peripheral stress hormone levels of single housed individuals with that of animals housed in social groups. Methods experiment 1: After two weeks of distinct housing, the animals were behaviorally tested in the modified hole board test for 5 minutes. This test reliably monitors a variety of motivational systems in rodents, such as anxiety-related behavior, exploration, locomotor activity and social affinity. In a first experiment, male C57BL/6 mice were housed either singly or socially in groups of 2, 3, 4 or 5 individuals per cage. Socially housed individuals were tested in the presence of their group-mates throughout. Results: No behavioral signs of stress were found in the individually housed mice and notably, basal corticosterone levels did not differ between groups. After exposure to the modified hole board test however, animals housed in groups of 3 to 5 individuals were characterized by an increased corticosterone-response when compared to the individually housed animals. Methods experiment 2: Since the order of behavioral testing might have caused the response in the first experiment, we excluded this parameter in an otherwise similar, second experiment by behaviorally testing only one animal per social group. Groups of 3 individuals were compared with individually housed males of the strains C57BL/6, BALB/c and A. Results experiment 2: Neither behavioral nor hormonal signs of stress were found in the individually housed animals. Conclusion: Individual housing appears to be non-stressful for male mice and does not impact experimental behavior.

CL5 HEAT SHOCK PROTEINS IN NEUROSCIENCE RESEARCH

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CL6 PARTICIPATION OF GABA(A) RECEPTORS OF VENTROLATERAL PREOPTIC AREA IN REALIZATION OF THE SOMNOGENIC EFFECTS OF HEAT SHOCK PROTEIN 70

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Multifactorial regulation of sleep is a fundamental requirement for the stability of all physiological processes during sleep. The currently known sleep factors in slow-wave sleep (SWS) regulation are involved. These substances include hormones, prostaglandins, peptides, cytokines and neuromodulators [Obal and Krueger, 2003]. However, it still remains unclear which of the endogenous factors is the basic in SWS regulation. We have recently shown that heat shock protein 70 kDa (Hsp70) may act as an important hypnotic substance in the brain. Microinjections of Hsp70, liberated from contaminants, into the 3-d brain ventricle (b.v.) and ventrolateral preoptic area (VLPA) of hypothalamus, which plays an important role in promoting and maintaining SWS, induced an increase in SWS, a decrease in wakefulness and rapid sleep during inactive phase of the day in rats and pigeons [Pastukhov et al., 2005, 2008; Ekimova, 2007]. Mechanism of realization of the somnogenic effect of Hsp70 is unknown. Earlier, we showed that the onset of SWS is linked to an increase in GABA(A)- receptor activity in VLPA in

pigeons [Ekimova, Pastukhov, 2005]. We made the hypothesis that the somnogenic effects of Hsp70 may be related to a mediated activation of GABA(A) - receptors in the VLPO [Pastukhov, Ekimova, 2005]. In order to verify this hypothesis we microinjected pigeons with antagonist GABA(A) receptors bicuculline (Sigma) at a dose of 1 mkg/1.0 mkl into VLPO of hypothalamus 15 min before the microinjection of Hsp70 or vehicle (control). It was elicited that bicuculline induced for the first hour following the injection an increase in total time of wakefulness and a decrease in SWS in comparison with control. Microinjections of bicuculline into VLPO prevented somnogenic effects of microinjections of exogenous Hsp70 into the 3-d. b.v. and into VLPA. These experiments revealed a decrease in SWS and rapid sleep and an increase in wakefulness for 5 hours since the moment of microinjections. Our findings permit us to hypothesize that Hsp70 and, perhaps, other molecular chaperones having neuroprotective properties contribute to the maintenance of SWS by activation of GABA(A)-receptors primarily in theVLPO of the hypothalamus. This research was supported by the Russian Foundation for Basic Research (Project N 08-04-00922).

CL7 CORTICOLIBERIN MRNA EXPRESSION IN HYPOTHALAMUS AND AMYGDALA AFTER GRADUAL ADMINISTRATION OF PSYCHOACTIVE DRUGS IN RATS

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Wistar rats were injected intraperitoneally for 4 days in elevated doses with: 1) physiological saline (control; 0.1-0.2-0.4-0.8 ml/rat), 2) amphetamine (0.5-1.0-2.0-4.0 mg/kg); 3) fentanyl (0.00625-0.0125-0.025-0.05 mg/kg), 4) ethanol 40% solution (0.5-1.0-2.0-4.0 g/kg), 5) sodium ethaminal (2.5-5-10-20 mg/kg) or 6) dexamethasone (0.5-1.0-2.0-4.0 mg/kg). The forced regimen of drug administration led to gradual load of the organism and prevented drug tolerance. This method was actively used for formation of drug dependence (or its features) from different narcogens. The biggest mRNA expression for corticoliberin was registered in amygdala after administration of dexamethasone (0.46 units compared with β-actin), and the minimal one was after sodium ethaminal (0.07) and fentanyl (0.037). In hypothalamus, sodium ethaminal produced elevated mRNA expression (0.8 unit), then were ethanol (0.37) and fentanyl (0.039). Amphetamine did not activate mRNA expression for corticoliberin nor in hypothalamus, nor in amygdala for all of the drugs studied. The mRNA expression for vasopressin did not register for all drugs both in hypothalamus and amygdala. Therefore, the reinforcing system of the hypothalamus supports the typical reaction on narcogens administration, where as the extended amygdala includes both the proper reinforcement and stress reactivity elements. Supported by RFBI grant #07-04-00549a.

CL8 THE EVOLUTIONARY PECULIARITIES OF BRAIN FUNCTION DISTURBANCES: NEUROPETIDE COMPENSATION AND POSSIBLE NEUROCHEMICAL MECHANISMS

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The question of how an organism adapts, remains stable, and compensates in an environment full of stressful influences, and of differential consequences those influences have on brain function (especially mnestic and cognitive processes) presents a prominent problem for modern neurophysiology and medicine. Neuropeptides and neurohormones play a very important role in an organism's stress compensation. At present, studying the influence of the neurohormones of Hypothalamus (Hyp), such as Thyroliberin (TRH) and ACTH (especially nervous and visceral), on the brain functions disturbances are the most encouraging candidates in this research. For the last few years, drugs such as the synthetic analog ACTH – ACTH4-7 (Semax – Sem) have

been clinically utilized for many diseases of the central nervous system (CNS), including vascular and vegetative disturbances. It was shown that the application of Sem exerted a positive therapeutic effect in certain cases of brain trauma (Gusev et al., 2007). The experimental data on the regulatory effects of TRH and Sem have been obtained mainly from behavioral rat research. This main bulk of research has not approached the problem from an evolutionary perspective. Nor have the studies focused on the neurochemical mechanisms related to the different etiology of stresses. The present work is devoted to the comparative study of the role of TRH and Sem in Higher Nervous and Homeostastic Functions/disturbances. We examined these in the ascending row of mammals (insectivores, rodents and primates) to specifically study the influential mechanisms of Hyp and Hippocampal (Hipp) structures on new cortical activity. These experiments were performed in two series, using the food model and multiparametrical registration of objective (electroencephalographic (EEG), vegetative and motor) components of Higher Nervous Activity. The first series was done with freely moving animals, while the second one used monkeys placed into a primatological chair. Besides the positive conditional reflexes, the following types of memory were investigated: conditional (the delayed conditional reflexes – DCR), short-term, long-term, working, and operative memory. The TRH and Sem drugs were administered intranasally or intramuscularly at a dose of 3-5 mkg/kg and 0.01-5.0 mg/kg respectively. Emotional stress was provoked by overloading the analytico-synthetic brain activity (hedgehogs), prolonged (1-1.5 hour) fixation into immobilization machine-tool (rats) or by extremities (monkeys). The stimulation of Hyp and Hipp structures were performed by implanted electrode resistance of 10-20 kOm. It has been established that the compensatory role of TRH and Sem in hedgehogs with neurosis is mainly the same. Such effects are more expressed in the inherited forms of behavior. However, detailed analyses have shown that some differences do take place. The compensatory effect of TRH is more significant in hedgehogs with an inhibitory type of neurosis. On the TRH background, the motor-oriented and food activity are restored and increased. The TRH effects on the respiratory system were significant and had some specific features. For example, the respiratory rate was restored, the amplitude was increased, and the pattern was increased. The compensatory influence of TRH and Sem on the simple form of Higher Nervous Activity was generally uniform. The food conditional reflexes were restored. It was established that the compensatory effects of TRH and Sem on the disturbances of Higher Nervous Function have different character. The small (3 mkg/kg) doses of TRH exerted inhibitory effects on the motor and visceral components of memory. On the Sem background, the delayed conditional reflexes (DCR) were facilitated and restored within 1-3 days. However, the pattern of reaction and the time delay did not change. It was found that the preliminary TRH administration, followed by Hyp stimulation, led to a potentiation effect and exerted facilitatory influence on Higher Nervous Activity. The preliminary administration of TRH with the following Hipp stimulation did not provoke any definitive changes. Contrary to TRH, the preliminary Sem administration followed by Hipp stimulation had a significant facilitating effect on all Higher Nervous System parameters studied. It has been established that the compensatory effects of Sem are especially significant in the destruction of Hipp structures (model of organic pathology). The Sem administration exerted a significant compensatory effect on the different parameters of Higher Nervous Activity, an influence that is especially evident on the motor and respiratory parameters. This phenomenon is particularly apparent in cases when the Sem is first introduced at the earlier stage of Hipp destruction. In comparison with hedgehogs, the Sem role in the compensation of brain function disturbances is increased in rodents (rabbits, rats). The preliminary Sem introduction prevented the development of the inherent and acquired forms of pathological changes in the Higher Nervous Activity through conditions of immobilization stress. On this background, observed for a short time (2-3 days), there was a normalization of all parameters of Higher Nervous Activity. At the administration of small Sem doses (0.1 mkg/kg) in rats, significant restoration of brain function disturbances took place. In rats, compared to hedgehogs, the facilitatory effect of Sem

introduction followed by Hipp stimulation brought about a significant effect on all indicators of Higher Nervous Activity. Contrary to hedgehogs, the Sem compensatory role at Hipp destruction conditions is more expressed in rats and rabbits. On the Sem background, the phone and conditional indicators are restored. The expression of respiratory and heart rate parameters also increased. It was found that, contrary to lower mammals (hedgehogs and rats), the application of TRH and Sem to neurotic monkeys exerts different characteristics of compensatory influence on the different kinds of memory and their various parameters. The compensatory effects of monkeys depended upon the type of neurotic disturbances (excitatory or inhibitory). The compensatory effects of TRH were more highly expressed with the inhibitory type of neurosis. On the TRH background, the EEG was the same as during the awake state. The image memory is intensified for a long time (5-7 days). In contrast to TRH, the Sem compensatory effects were more expressed with excitatory type of neurosis. The cerebroprotective effects of small doses (0.3-0.5 mg/kg) of Sem are especially significant. The background EEG and the reaction of desynhronization also normalized. On the Sem background, the operative memory and DCR were intensified. EEG indicators of DCR were recorded mainly at the delay phase. After ultra-small doses of Sem were administered, sedative effects were observed for 10-14 days. Thus, the data obtained show that the compensatory role of TRH and Sem at the disturbances of Higher Nervous Functions is increased in the process of evolution and have specific features. The influence of TRH and Sem on neocortical activity are spread throughout different limbic structures. These data may serve as a neurophysiological background for differentiated application of TRH and Sem in clinical neurology.

CL9 THE PAVLOV DEPARTMENT OF PHYSIOLOGY: A SCIENTIFIC HISTORY

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The organization of the brain and the exploration and understanding of its activity is the boldest challenge for the human intellect, as the brain is the most complicated and highly developed structure created by nature. Throughout history, the challenge of understanding the brain has been taken up by many outstanding people of different nations. However, no final conclusions have been reached, as the questions were too multiple and the means for their exploration were limited. Although the world of science accumulated more and more knowledge about the brain during the 19th century, the activity of higher compartments of the cortex, psychic activity above all, was still out of reach of natural science. Russian physiologist Setchenov was one of the first to lead the way towards solutions in his work *Reflexes of the Brain.* He was followed by Pavlov and his colleagues who studied the same questions in the Department of Physiology at the Imperial Institute for Experimental Medicine in St. Petersburg (IIEM).

The Institute of Experimental Medicine. In 1890 in St. Petersburg, the official opening of the Imperial Institute of Experimental Medicine took place. This organization was initiated by Prince Oldenburgsky and was the first Russian scientific research institution in the field of biology and medicine. Pavlov was drawn into the development of the Institute, which included Departments of Chemistry, General Bacteriology, Pathologic Anatomy, Epizootology, and Syphilidology. Pavlov was invited to head the Department of Physiology and guide their researchers - a job he successfully performed for 45 years from 1890 until 1936. In April of 1890, Pavlov accepted the position as Head of the Pharmacology Department at the Military Medical Academy (MMA), which he left in 1895, when he became the Head of the Physiology Department of the MMA. Since the Department did not have sufficient facilities for his studies, students of the Academy practiced at the Department of Physiology headed by Pavlov at the IIEM. At that time, the IIEM constructed a new building, specifically equipped for scientific research. Young students evolved into researchers here, under the guidance of Pavlov. Therefore, it can be said that Pavlov's physiological school was actually formed at the Department of Physiology of the IIEM. With the aid of the permanent fistulae technique, the Department at the IIEM studied the activity of the gastro-intestinal tract,

determined the mechanisms of the digestive glands activity, and elucidated the role of the nervous system in regulating these activities. The classic operations of oesophophagotomy, isolation of the gastric pouch, pancreatic and bile fistulae and a number of other experimental techniques were developed. Also, the innervations of gastric glands and the physiology of the pancreas were investigated here. In the spring of 1895, Pavlov delivered lectures on digestion at the IIEM. During these presentations he reviewed the achievements of the Department in this area of physiology. Those lectures were an important step in bringing order to the vast field of information on nervous regulation of the digestive glands, on the laws ruling the production of digestive juices, and on the interaction of stomach secretion with the functions of the liver, pancreas, and small intestines, as well as with the functions of other parts of the digestive tract. Pavlov demonstrated that the wide use of experimental surgery in long-term experiments on animals gave the opportunity to investigate interactions between the functions and mechanisms of the digestive glands. It was a new group of studies in digestion: exploration of physiological mechanisms of the digestive glands under conditions of long-term experiments on healthy animals with complete and continuously working digestive systems. Pavlov summarized all these achievements in this field in his book *Lectures on the Work of the Chief Digestive Glands* (1897). In this book he added his eighth lecture, "Physiological Data, Human Instinct and Medical Empiricism." A year later the book was published in German after being translated by Valter. By 1904, when Pavlov was awarded with the Nobel Prize, he had been engaged in scientific and pedagogical activities for 25 years. His studies made a large impact on the scientific community; never had physiology helped clinical medicine so significantly. In his lectures, Pavlov regarded the process of digestion as a physiological conveyer which combined separate organs of the digestive tract into a system. Such an approach helped to create a complete picture of the mechanisms of digestion. At every stage of his research, Pavlov paid great attention to the connection of physiological investigation and clinical medicine. Elaborating on questions regarding the physiology of digestion, he systematically studied the pathology of digestive organs as well. Between 1898 and 1904, studies of the digestive function of the liver and transport of food from the stomach to intestines were carried out under Pavlov's direction. The general coordination of all parts of the digestive tract was revealed as well. Special research was devoted to bile, pancreatic, and gastric juice secretion into the stomach. Conditions for such secretion and its relevance to digestion were determined. Pavlov's research formed the basis for the modern concept of disturbanced gastro-intestinal tract function and facilitated the development of adequate therapeutic methods for their treatment. The highest form of appreciation during the period of Pavlov's research was the Nobel Prize which was first given to a Russian scientist in 1904 as a token of acknowledgement of his works on physiology of digestion, which reformed and widened the knowledge in this field. Pavlov's work on the physiology of digestion was a separate and complete set of systemic studies which was internationally acknowledged in 1904. It served as a starting point for a large series of studies that laid the foundation for a new area of physiology—physiology of higher nervous activity, or the theory of conditioned reflexes. The phenomena of "psychic secretion" of digestive glands attracted Pavlov's closest attention. Pavlov endeavored to fill in this "white spot" on the map of knowledge and decided to explore the psychic aspect of the digestive glands activity. This decision was followed by 35 years of tenacious work devoted to the exploration of special brain reflexes which Pavlov termed "conditioned" reflexes. As the history of science shows us, his work on conditioned reflexes brought him more success, popularity and fame than his work on the physiology of digestion, for which he was awarded the Nobel Prize. It is necessary to note that it was Bidder and Schmidt, from Derpt University, who for the first time in 1852 described gastric secretion from the gastric fistula conditioned by food demonstration. However, at that time the theory of psychic secretion of gastric juice did not attract the serious attention of scientists. The data gained in the Physiology laboratory at the MMA by von Anrep went unnoticed as well, though he was one of the first who, before Pavlov's work, came to understand the role of the nervous system in gastric secretion. Questions were finally answered by Pavlov and Shumova-Simanovskaia and results were

published in the article "Gastric Gland Innervation in Dogs." A study carried out by Glinsky, who was a temporary member of the Department of Physiology at the IIEM, played a crucial role in the exploration of salivary glands and nervous regulation. It also played a basic role in the physiology of conditioned reflexes. He invented the operation of implanting fistula into the ducts of salivary glands in 1895, and he also performed the first experiments with reflective salivation in dogs. His work was not published because of unknown reasons, but on May 13, 1895, Pavlov presented the results of Glinksy's study at the meeting of the Society of Russian Physicians. Pavlov also wrote in 1902 about the same matter in an article on Dr. Glinksy's technique. From then on, Glinsky's technique was accepted all over the scientific world as the most convenient method of precise and full registration of secreted saliva in long-term experiments. Early in the 20th century, Pavlov's investigations attracted the attention and interest of specialists. In his letter to Prince Oldenburg, curator of the IIEM, Pavlov remarked that the Department of Physiology had become a significant attraction for brilliant and loyal scientists not only from Russia, but from other counties. In 1902, Doctors Stensma (Amsterdam), Straub and Fridental (Berlin University), Gross and Professor Konheim (Heidelberg University), and Professor Chermak (University of Halle) worked in the Department under the direction of Pavlov. Pavlov's *Lectures on the Work of the Chief Digestive Glands* (which had been translated into both German and English), along with his lecture delivered at the XIII International Congress of Physicians (where he addressed an international audience for the first time in July, 1900), were the reasons for the growing interest in his work. In his report "Experimental Therapy as a New and Fruitful Technique of Physiological Studies" he did not limit himself to the contents of his latest works. He concentrated on the questions related to "experimental therapy" and announced that physiology, with its special resources and its chances for success, is aimed at such scientific work that completely coincides with the modus operandi of medicine in its treatment of sick human beings. In natural science, one obstacle to understanding the activity of the higher processes of the brain was the initial problem of comprehending the relationship between physical and psychic processes in nature. That is (in a philosophical approach) the question of material and spiritual, or objective and subjective. Throughout the history of science we can find evidence of this debate.

The Birth of a New Era: Conditioned Reflexes. The theory of psychic excitation of salivary glands was elaborated between 1896 and 1901 by Pavlov in co-operation with Wolfson and Snarsky. In Wolfson's dissertation on salivary glands (1899), which was given at the Department of Physiology at the IIEM, the psyche was regarded as a special entity regulating the process of salivation. In the dissertation given by Snarsky (1901) on salivary glands functioning, (which was also carried out at the Department of Physiology), the facts were explained from the point of view of zoo-psychologists. Discussing the mechanism of "psychic" salivation, the author compared animals and human beings with their subjective inner world. That approach was not accepted by Pavlov. Snarsky insisted on looking for explanations of the phenomena in the field of the subjective. Pavlov, in his own words, "was astonished by scientific unfruitfulness of such an approach to the problem," and he began to look for another solution. After many hours of speculation and "hard intellectual struggle" he decided to treat psychic excitation as a "pure" physiologist, that is, as an objective external observer and experimenter who deals exclusively with external phenomena and their interactions. This decision was made in 1901. Pavlov was sure that a physiological approach to psychic phenomena exploration would allow the fruitful development of brain physiology, which would explore the role of the brain in organizing interactions between the organism and its environment. The moment in which Pavlov stated his "physiological" approach to the phenomenon of "psychic salivation" is regarded as the birth date of a new notion called the "conditioned reflex." The first work on conditioned reflexes was carried out, after Pavlov suggested it, by Tolotchinov (1902) who temporarily formed a part of the Department of Physiology. The results were presented in 1902 at the Congress of Physicians and Natural Scientists of the Northern Countries of Europe in Helsingfors (Finland). Tolotchinov described some external conditions under which temporary connections appear in the cortex. He also established the natural reflex

generating the natural reflex, its dissipation and restoration, and the possibility of external inhibition of a newly elaborated reflex. The experiments registered not only secretion, but also a motor conditioned reaction. Pavlov, just as many other scientists who were looking for the explanation of the essence of life, was interested in the way in which the brain generated the mind and mentality. All his life he longed to explore the depth of the human psyche. In his first report on the theory of conditioned reflexes, delivered in Madrid at the XIV International Medical Congress in 1903, he said, "Relying on the likeliness and sameness of external phenomena, all objective data obtained in experiments will be used by future science to explain our subjective world. Thus our mysterious nature will be illuminated, and the mechanism of the most interesting human function—of his mind, torments of his mind—will become clear" (p. 119).The varied and in-depth methods of exploring conditioned reflexes chosen by Pavlov in 1901 provided natural science with the opportunity to regain its unconstrained development and enabled it to tread into the "last facet of life"— the mechanisms of the brain's higher activities. The theory of conditioned reflexes developed at the Department of Physiology at the IIEM pre-ordained the field of future scientific activities for Pavlov, his practicians and colleagues. The formation and development of Pavlov's work on the physiology of higher nervous activity were permanently linked with the Physiological Department at the IIEM. It was there that Pavlov and his disciples carried out research which permitted Pavlov to give the first lecture on the theory of conditioned reflexes at the Medical Congress of Madrid in April 1903. In his lecture, he demonstrated an objective method of study for higher nervous activity in animals and humans. "Only by the way of objective investigations," Pavlov (1903) stated, "step by step we will reach the complete analysis of that infinite device as a whole, which forms the life on the Earth" (p. 120). The Congress lasted from March 30th until April 26th and there were 6,961 delegates who participated. The Russian delegation consisted of 297 members. Pavlov and his wife were well acquainted with many European capitals, but in Madrid they were deeply impressed by an exposition of Fancisco Goya's works in The Prado. They spent a lot of time standing in front of the pictures. Pavlov and his wife also visited Escorial, Toledo and some places in Seville. Beginning in 1904 all efforts of the Department staff were focused on the methodological aspects of exploring the conditioned reflexes. According to Pavlov, high speed accumulation of accurate facts and their easy interpretation presented a drastic contrast with the uncertain and questionable results provided by the subjective approach. It was in 1905 that the method of "artificial" conditioned reflexes was introduced into practice in research. The technique allowed quantitative analysis of the processes of higher nervous activity. As a result, Pavlov formulated the main principle of the conditioned reflex theory according to which the magnitude of the response depends on the intensity of the stimulus. By 1906, almost all types of cortical inhibition had been discovered: conditioned, differentiating, retarding, external and sequential. Basic ideas of the conditioned reflex were formed and conditioned trace reflexes were discovered. Under Pavlov's guidance, investigations were carried out after removing different areas of cerebral cortex (in dogs) to reveal the link between conditioned salivary reflexes and cerebral cortex. Pavlov presented his most important findings in his lecture dedicated to Huxley, which he delivered in London in 1906. At the conclusion of his presentation he felt it necessary to stress his strong belief in the inevitable unity between physiology and medicine. "If the doctor in reality and even more so in ideal is a mechanic repairing a human organism," Pavlov remarked "then any new physiological achievement will sooner or later inevitably expand his power over the mechanism, the power to maintain and repair it" (p. 915). In 1907, Pavlov's disciple Krasnogorsky obtained data on the role of conditioned reflexes in the formation of behavior as he worked with children. In 1908, Nikiforovskiy took the first steps towards the application of the conditioned reflex technique to pharmacology. Beginning in 1908, investigations in the field of physiology of higher nervous activity under Pavlov's direction were conducted not only at the Physiological Departments at the IIEM and MMA, but in the Physiological Laboratory at the Academy of Sciences. However, the Physiology Department remained the main center of scientific work and the experimental base for the development

of studies at Pavlov's physiological school. From 1891 to 1917 more than 110 persons worked there under the direction of Pavlov. Dissertations and studies at the Department of Physiology were accomplished by Babkin, Zelioniy, Savich, Orbeli, Krasnogorsky, Zavadsky, Folbort, Tsitovitch, Krestovnikov, Kupalov, Deriabin, Rozhansky and many others. In connection with the development of research on the physiology of higher nervous activity at the IIEM, a problem of establishing a special laboratory equipped with soundproof chambers arose. Since the IIEM did not have sufficient funds, Pavlov turned to the Ledentsov Fund for monetary assistance. In 1910, at the Society Council Session in Moscow, Pavlov gave a lecture about tasks and arrangement of a model laboratory for studying higher parts of the central nervous system in higher animals. The Society granted Pavlov 50,000 rubles and in 1913 the "Tower of Silence," a three-story building with three soundproof chambers, was built. Five more chambers were added by 1917. In 1911, Pavlov started a broad investigation of cortex inhibition and formulated the major laws of the development of neural processes in the brain cortex. He also defined the notion of two main mechanisms operating in the central nervous system: the mechanism of temporary connection and the mechanism of analyzation. Further on in his scientific investigations, he returned to these definitions repeatedly. Ten years after his first presentation on conditioned reflexes, Pavlov delivered a report called "Investigation of HNA" (higher nervous activity) at the IX International Physiological Congress in Groningen (Holland). Outstanding physiologists such as Sherrington, Starling, Gemmeter, and Fisher participated in the work of the Congress. In his report, Pavlov substantiated his idea that analyzers were a special part of the nervous system. He also presented his research with this perspective based on the idea of a unified center and periphery. In addition, he mentioned the possibility of conditioned reflexes being hereditary, an idea that was later transformed into the question of the genetics of high cerebral functions. During World War I, the two revolutions that followed, and the Civil War, scientific work continued at the DEM. The period between 1918 and 1920 was especially difficult because the country was in ruins, and as a result of starvation and cold it was impossible to experiment on dogs.

Pavlov after the Revolution. Between 1921 and 1923, scientific work in the Department of Physiology at the IIEM gradually returned to normal and investigations began again. In Pavlov's report "Normal Activity and General Constitution of Cerebral Cortex", delivered in 1922 at the meeting of the Society of Finnish Physicians in Helsingfors, he distinguished 6 types of events which "embraced the whole HNA without residue". Those 6 events included excitation, inhibition, movement (irradiation and concentration), mutual induction, connecting and disconnecting, and, finally, analysis. It was a report which summarized two decades of the most important results from his work. In 1923 Pavlov published a new book. It was comprised of his articles, reports, lectures and speeches presented in chronological order, so that it reflected the course of development of the theory of conditioned reflexes. Placing special significance on the sixth edition of this book, the last one published during his lifetime, Pavlov wrote in January of 1936 that the book was enriched abundantly—12 new works had been added to it. According to Pavlov, those works clearly demonstrated how immensely the horizon of research had extended. Physiology, psychology (with its practical applications) and pathology (with therapy of the cortex of the brain) had started to join and merge so that they became the same field of scientific work. Judging by the results, this combination has been to their mutual benefit. Between 1925 and 1927, much attention was paid to investigating nervous system types and to studying different kinds of internal inhibition and mutual induction. In 1927 Pavlov published a book on the functions of the hemispheres. In the same year, he suggested that nervous system types be studied on dogs while researching other questions. The years between 1922 and 1935 were a time of active development of the Physiological Department at the IIEM and in-depth study of the physiology and pathology of higher nervous activity under the supervision of Pavlov. In 1923 Pavlov received land to build a special facility for breeding and keeping experimental animals in the vicinity of Koltushi, a village near St. Petersburg. A short time later, Pavlov decided to organize a Biological Station for experimental investigations there. The Station was officially opened in 1926 and it became a

base for investigation of conditioned reflexes in dogs in connection with inborn peculiarities of their nervous systems. The stonework laboratory building was completed in 1933. In the same year, the first studies of the higher nervous activity of anthropoids were carried out at the Biological Station under Pavlov's direction. Koltushi became known world wide as the "Capital of Conditioned Reflexes" after the XV International Physiological Congress which took place in Leningrad and Moscow in 1935. Several days before the Congress started, Pavlov initiated the building of a monument dedicated to the dog not far from the Physiological Department building on the premises of the IIEM. The statue was created by the sculptor Bespalov. American physiologist and Harvard University Professor Cannon wrote about his meetings with Pavlov in his memoirs: "The last time I saw Pavlov was in Leningrad and Moscow at the conferences of the Physiological Congress in 1935. He was 86 years old then but he looked lively, full of his former energy. I will never forget the day we spent together in the environments of Leningrad, in the huge new buildings of the Institute built by the Soviet Government for Pavlov's experimental works. During our talk Pavlov heaved a sigh and said regretfully that he did not have such huge possibilities 20 years before" (Cannon, 1945, p. 229). In 1918 Pavlov resumed his visits to a mental hospital with the aim of studying the physiological mechanisms of cortical cerebral activities in humans. In those years, Pavlov and his team paid more attention to studies in psychiatric hospitals, which they had started in 890 with the aim of exploring the physiological mechanisms of human cerebral cortex activity. In 1923, Pavlov decided to investigate natural psychopathological syndromes and psychic diseases. In 1931, Pavlov initiated the establishment of two clinics: One based on the neuropsychiatry dispensary and another based on a mental hospital at the Physiology Department. Neurasthenia, hysteria and psychasthenia, narcolepsy, schizophrenia and circular psychosis were investigated in these clinics. The types of higher nervous activity of patients with different neurotic and psychotic sickness dynamics were studied, as well as potential methods of therapy. It should be noted that investigations in the physiology and pathology of higher nervous activity reached their peak in the 1930s. Positive and negative induction phenomena and their temporal and spatial features were discovered with the conditioned reflex method. A concept of sleep, as well as sleeping control methods, was elaborated there. The possibility of producing conditioned reflexes to complexes of irritants working concurrently, or one after another was discovered, as well as producing reflexes to time intervals ("time reflex"). The research on conditioned reflex activity in cases of disturbances in normal higher brain functioning, and understanding the conditions that induce such disturbances, led Pavlov to the elaboration of the concept of four main types of nervous systems. This later formed one of the most important ideas of higher nervous physiological activity. Based on the results of the behavioral investigations on anthropoids, Pavlov proposed the concept of conditioned sensory and signal temporal associations. The latter meant the possibility of forming genetic causative relations between subjects and events in anthropoids. Pavlov stated his belief that it is incorrect to interpret the behavior of highly developed animals relying on the mechanism of conditioned reflex only.

Pavlov and his School. The formation and development of Pavlov's scientific school between 1903 and 1925 was characterized by the dedication of Pavlov and his disciples. For the most part, it was based on questions related to the physiology of higher nervous activity. With Pavlov's guidance and personal participation, the mechanisms of conditioning and the closing function of the brain were studied. The research stated the idea of analyzation and synthesizing activities of the higher brain levels. The role of conditioned stimuli strength was formulated, the main nervous processes (excitation and inhibition) were characterized, the phenomenon of beyond-limits-inhibition and mutual induction was discovered during this time. Also, the theories of dynamic stereotyping, experimental neuroses, and types of higher nervous activity evolved. The questions of experimental pathology of the higher nervous activity were worked on at the Department of Physiology, and pharmacological substances restoring nervous activity were studied. Results of the work performed at neurological and mental clinics provided a physiological basis for the mechanisms of a number of nervous and mental diseases in humans. Under Pavlov's

guidance, Anokhin, Biriukov, Bykov, Ivanov-Smolensky, Mayorov, Orbeli, Razenkov and Speransky worked at the Department of Physiology as well as many other scientists and disciples of the Pavlov physiological school. It was a period when many prominent scientists and representatives of Pavlov's school left the Department of Physiology at the IIEM and began to work independently. Among them were scientists who influenced the development of physiology abroad, von Anrep for example . After 1920, von Anrep worked at London and Cambridge Universities, became a Member of Royal Society and for more than 20 years headed the Department of Physiology at the Egyptian University of Cairo. Babkin, who introduced Pavlov's ideas into physiological research in England and Canada, was a Member of Canadian Royal Society. Boldyreff emigrated to Japan in 1918 and in 1922 moved to the USA, where he headed the Pavlov Laboratory at the Sanatorium in the State of Michigan until 1940. In Poland, Konorsky developed neurophysiology, as did Ten-Kate who worked in Holland. Gantt, who worked at Pavlov's laboratories from 1925 to 1929, played a key role in the subsequent development of Pavlov's ideas in the USA. Within Gantt's archives, there is a rich collection of documents connected with Pavlov. Among other things, he organized the Pavlov Scientific Society in the USA. Besides the wide field of investigations in physiology and pathology of higher nervous activity, Pavlov contributed to the development of new trends of research at the Physiology Department. It was because of the physiology and pathology of cortical-visceral relations, first and foremost, that a trend originated at the intersection of physiology of higher nervous activity and physiology of autonomic functions. Investigations in this field began with the work *Development of Urinary Excretion Conditioned Reflexes,* which was carried out in 1926 by Pavlov's disciple Bykov in collaboration with Alekseev-Berkman. By 1931, significant experimental material on cortical regulation of the activities of the internal organs had been accumulated. The second trend of research initiated by Pavlov was the first Russian systematic study of the influence of different health factors in animal and human organisms. In 1931, the further development of these two trends was passed on to the Department of Applied Physiology, which was newly organized at the IIEM. In 1931, it was called the Department of Common Physiology and headed by Bykov. It is now called the K.M. Bykov Department of Visceral Systems. In 1933, Orbeli, one of Pavlov's oldest disciples and collaborators, organized the third physiological department within the IIEM - the Department of Special and Evolutionary Physiology. The systematic study of some branches of physiology, which had not yet been studied in the Soviet Union, as well as the theories of the evolution of functions of animal and human organisms, were the subject of study in this department. It is interesting to note that Orbeli became successor to Pavlov as the Head of the Physiology Department at the MMA, when Pavlov left in 1925. By the end of Pavlov's life, two physiological departments at the IIEM besides the Physiological Department and the Biological Station had been established and were headed by Pavlov's disciples. Both were geared towards the study of physiology and pathology of higher nervous activity. By that time, Pavlov was an Honorary Member of more than 100 Scientific Societies in many countries of the World, including Cambridge University. Pavlov died on February 27, 1936. The last time he visited the Department of Physiology at the IIEM, on February 18th of the same year, is commemorated by a calendar on the desk in his office which is now a memorial. The coffin with the body of the Honorary Director of the IIEM and Nobel Laureate, was placed for its last farewell in Tavritchesky Palace, the former sitting place of the Duma -Russian Parliament before the Revolution. He was buried in the Academician Yard of the Memorial Cemetery "Litterateurs' Brow." According to the decision made by the Government, his name was given to the Department of Physiology at the IIEM which was founded by him, to the 1st Leningrad Medical Institute (now the St. Petersburg State Medical University named after Pavlov), to the Physiological Institute of the USSR AS (now called the Institute of Physiology named after Pavlov by the Russian Academy of Science), and also to many other research and educational medical institutions. To perpetuate the memory of the organizer and first Head of the Department, Pavlov's office was preserved as a memorial in the Department of Physiology at the IIEM, and

Pavlov's museum was opened in his apartment on Vassilievsky Island, which is a part of St. Petersburg.

From Pavlov to the XXI Century. After Pavlov's death, the Department at the IIEM was headed by Academicians of the USSR AMSci Orbeli (1936 to 1937), then by Kupalov (1937 to 1964), Khananashvili (1965 to 1976) and Vartanian (1978 to 1995). Since 1995 the Department has been headed by Professor Klimenko. Kupalov was the closest disciple and colleague of Pavlov, about whom Pavlov said, "Kupalov is my alter ego." Under the guidance of Kupalov, new regularities were revealed in brain functions. Shortened conditioned reflexes were discovered, the mechanisms of the tonus regulation were found in the cortex, properties of long-term neural processes were studied under normal and pathological conditions and properties of cortical representation of the unconditioned reflexes were characterized. Thanks to the technique of situational conditioning suggested by Kupalov, general regularities of higher nervous activity were studied in animals under conditions of unrestrained behavior and some new causes for experimental neuroses and their mechanisms were revealed. During the same time period another disciple of Pavlov, Abuladze, carried out his investigations. He is the author of original investigations based on the outward extension of the tongue's symmetrical areas. This was used to study the conditions of joint and separate functioning of the brain hemispheres, and of unilateral conditioned reflexes. The experiments carried out under the guidance of Academician Khananashvili resulted in the formation of the concept of integrated systems of conditioned reflexes as the functional units of general behavior. The experiments also helped develop the concept of informational neuroses in animals and humans, as well as ways of their prophylaxis and treatment. Influence of various forms of animal interspecies communication upon the mechanisms of higher nervous activity was studied under normal and pathological conditions. In 1976, Khananashvili left the Department of Physiology to accept the position of Director of the Beritashvily Institute of Physiology in Tbilisi, the capital of Georgia. For two years, the investigations in the Department were continued under the guidance of Professor Silakov. Scientists used microelectrode techniques to reveal the mechanisms of formation of temporal connections. It appeared this was due to the activity of a special group of unspecific neurons called "the learning neurons." Their unique feature involves the ability to establish new functional connections among themselves in the course of conditioning. The concept of microsystems of these neurons as the structural-functional basis had been advanced. Later, when the Department was headed by Vartanian, attention was focused on the question of reinforcement and the role of emotional mechanisms and unconditioned reflex mechanisms in the brain's reinforcement functions. New details were revealed concerning the role environmental agents in neurophysiological and psychophysiological mechanisms of emotional behavior. A number of main structural and functional patterns of the brain's emotional mechanisms were described for animals bred under the conditions of communicative deprivation. Currently, there are three laboratories at the Physiological Department at the IIEM: a) The Laboratory of Neurobiology of Integrative Brain Functions, b) The Laboratory of Psychophysiology of Emotions, and c) The Clinical Laboratory of Neurodynamic Correction of Psycho-Neurological Pathology.

Laboratory of Neurobiology of Integrative Brain Functions (Head: Klimenko). The main interests of the laboratory include investigating the conditions through which physiological processes in the brain may transform into pathological conditions. We explore the central mechanisms of nervous and immune system interactions by means of afferent signals involving cytokines and transmission through nervous and humoral pathways from an activated immune system. Cytokines recognized initially as immunopeptides demonstrate distinctive influence on the brain's functions. They are produced by CNS cells and are ligands of neuronal receptors. Moreover, taking into consideration their participation in the signal transferrence from the immune system to CNS, and their ability to induce the cascade of regulatory processes, one has every reason to consider that cytokines in the brain act as regulatory peptides. These peptides transfer the signal about immune cell activation to the brain, reorganize the perception and behavior of the

individual, and subordinate the current functions to the strategy of survival in the environment. Furthermore, in the central compartment, cytokines play the same role as they do on the periphery, that is—as the mediators of inflammation. Techniques used in exploring the brain's functions cover the subject from the level of conditioned reflexes and integral behavior to the mRNA level of peptides and receptor expressions and of neuropeptide production in the brain. Our experiments include studies of neuromediators and cytokine system interaction in autoimmune neurodegenerative processes in the EAE (experimental autoimmune encephalomyelitis). Completely original data has been obtained regarding the enhancing role of pro-inflammatory cytokine levels in blood circulation and in the brain tissue due to hypoxia, trauma, infection, etc. during critical periods of early postnatal ontogenesis. The increase in cytokine levels correlates with the development of psycho-neurological pathology in these adult animals or during the period of their maturation.

The Laboratory of Psychophysiology of Emotions (Head: Tsykunov). This laboratory's work is directed towards investigating the mechanisms of emotions, emotional disorders and solving the problems of anxiety and depressive conditions. Pavlov was one of the first who introduced the concept of reinforcement into scientific literature. Nowadays, the phenomenon of reinforcement is the central point in different theories of emotions and behavior. Main principles of forming conditioned reflexes—a specially directed control of emotional state—are employed by the staff during investigations of dolphin's purposeful activity in free behavior. Adequacy and agility of emotions are destroyed in affective disorders, especially in depression. While working with our models of depression in rats (as a result of mental trauma, caused by a threat to life, or zoo-social conflicts), it was shown that there were two forms of depressive-like disorders. Those disorders have common depressive symptoms, but they were divided in their structure of modified investigation and aggressive behavior as well as by the level of anxiety. It was shown that those conditions are characterized by opposite shifts in lipid turnover. One result of mental trauma is a decrease in Alfa-cholesterol. Disclosure of the mechanisms of those disorders will enhance our understanding of the pathogenesis of depression and will provide the basis for the development of new drugs.

Clinical Laboratory of Neurodynamic Correction of Psycho-Neurological Pathology (Head: Jakovlev). The role of generating conditioned reflexes in the formation of children's behavior was the subject of exploration by Pavlov's disciple Krasnogorsky. The study was carried out when Pavlov was still alive. On the basis of this research it is possible to conclude that the mechanisms of the feedback a person maintains with the environment play an essential role in developing healthy behavior. Conditions of informational deficit, due to poor environment, often result in brain dysfunctions in children <7-10 years old. A risk factor of alcohol and drug addiction, which has the widest distribution among teenagers, is attention deficit syndrome and hyperactivity disorders (ADHD). Pathogenesis of ADHD, and alcohol/drug addiction is based on the deficit of emotional reinforcement which, in turn, results from an imbalance in the systems of neuromediators, peptides and opioids in mesocortical-limbic structures of the brain. A technique involving outer computerized biofeedback for training children with ADHD was developed at the Department of Physiology. As a result of training with biofeedback, all patients demonstrated positive dynamics of vegetative, emotional, and motor reactions. It has been discovered that the kind of guided parameter (for example: EEG, ECG, breathing, etc.) chosen to work out adaptive self-regulation does not matter. A new stereotype of function regulation is formed in the CNS and new functional nervous connections are established.

Conclusion. Summarizing the scientific history of Pavlov's Physiological Department at the IEM in St. Petersburg, the authors would like to emphasize the importance of Pavlov's contribution to the world of science. He has created a new system of knowledge and introduced new notions which have become an inherent part of physiology, medicine, psychiatry, psychology and pedagogy.

CL10 INTERLEUKIN-1β AND LEARNING

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Proinflammatory cytokine interleukin-1β (IL-1β) is known as a mediator of neuroimmune interaction. The increase of IL-1β level in the blood and brain results in pyrogenic reaction, an activation of hypothalamic-pituitary-axis and in a motivated state disturbance. The influence of IL-1β on cognitive function was demonstrated by Goshen et al. (2007). Matsumoto and colleges (2004) reported the working memory impairment induced by IL-1β. We investigated the effect of IL-1β on long-time memory in 12-arm radial maze. A high pyrogenic IL-1β dose did not influence the behavior of a trained rat (the augmentation of errors number was not fixed). To sum up, IL-1β has more effect on the short- time than the long-time memory. To evaluate an involvement of hippocampal IL-1β in learning process the expression of cytokine mRNA after the fear-conditioning test was investigated. Rats were trained during 7 days (20 trials/day). 30 minutes after the last test, the level of IL-1β mRNA expression in hippocampus was less in trained rats as compared with intact. The effect of IL-1β injection on forming of memory mechanisms was studied in early postnatal ontogenesis. The pyrogenic dose of cytokine was administrated daily during the third week of life (1 injection/day). The behavior of adolescents was tested in the age of 50-70 days in the open field, Y-maze and fear-conditioning (two-way active avoidance) tests. Experimental rats demonstrated disturbance of habituation in the open field after 3 training days. They studied worse in fear-conditioning test. The measure of learning was achievement of 70% correct trails. 25% rats of control group respond to criterion on the 3rd, 37 % on the 4th, 50% on the 5th days of learning. Rats of the experimental group did not respond to criterion on days 3-4, and only 18% the 5th day. The learning in the Y-maze did not reveal any abnormalities. Conclusion: Pyrogenic doses of IL-1β influence learning and memory processes.

Conference Symposia (S)

S 1. GENOMICS AND POLYMORPHISMS
Chair: John Quinn (UK)

GENOME-WIDE ASSOCIATION STUDIES OF PSYCHIATRIC DISORDERS
G Breen, I Pedroso, S Campos, P McGuffin, D Collier, J Knight.
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Recently there has been an explosion of interest in the area of Genomewide Association Studies (GWAS). Many have now been published or have been funded and are beginning to reveal the genetic architecture of psychiatric and other complex diseases. They add to the existing literature of replicated disorder associated genes for schizophrenia, bipolar disorder, ADHD and other traits while also revealing the considerable flaws and occasional strengths of the candidate gene approach. We have performed in depth haplotypic and pathway analyses of the Wellcome Trust Case Control Consortium Bipolar Case Control cohort which yield two more genomewide positive loci for bipolar disorder. Similarly we have conducted, via DNA pooling, the first GWAS for cocaine addiction, the first results of which will be presented here. However, the current weaknesses of GWAS in terms of lack of coverage of some common variation, rare variants and VNTRs are serious and suggest that our genomewide coverage is significantly less than commonly stated with many studies capturing information from less than 60% of variants. However, many of these issues will be addressed in the next generation of GWAS experiments by increased redundancy, and various array and resequencing strategies, one example of which we will present the design of.

A GLOBAL SURVEY OF MICROSATELLITE CONTENT IN GENOMES USING A CUSTOM MICROARRAY
H Garner
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We have developed a new microarray that contains every possible 1-mer to 6-mer and mismatch probes, every known transcription factor binding site, every known RepBase probe and controls. This array, containing 7 copies of each probe for a total of 385,000 probes, is made by Nimblegen. We have hybridized a number of species as well as a variety of matched normal/cancer samples to study the total content of these regions in various genomes and in the evolving cancer genome. Some specific results are: 1) there are some specific motifs that differentiate the species, especially humans and chimpanzees, 2) in comparing humans and chimpanzees, the genes in which these motifs fall are in ontologies that can account for the differences in the species. The data and their implications to evolution, speciation, forensics, phylogenic analysis, and disease biomarker discovery will be discussed.

GENE REGULATION, SNPs AND DISEASE
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The causal link between stress and depression has been well established. Determining the mechanistic basis for this linkage is a priority in understanding the causes of depressive disorders such as post traumatic stress disorder (PTSD). The well known tachykinin; substance P (SP), is expressed in the amygdala and has been found to increase fear and anxiety related behaviors. However, recent efforts in developing novel antidepressants based on antagonism of

the SP receptor NK1 have been inconclusive. Instead of blocking its receptor, an alternative approach to blocking the effects of SP in the amygdala may involve targeting its transcriptional regulation. In an effort to understand the mechanisms controlling SP transcriptional regulation in the amygdala we used comparative genomics and transgenic analysis to identify an enhancer sequence (ECR1) that supports the expression of the TAC1 gene (That encodes SP) in the medial and central amygdala (CA) regions. Sequence analysis of ECR1 demonstrated the presence of highly conserved glucocorticoid receptor (GR) binding sites. In the present study we have used a combination of ChIP analysis on primary amygdaloid neurones to demonstrate the increased/decreased binding of GR to ECR1 in the presence of GR agonists/antagonists. We further demonstrate, using organotypic and whole transgenic animal studies and QrtPCR, that activation of GR increases the expression of ECR1 activity and TAC1 expression in parallel. Furthermore, using immunohistochemistry on CA brain sections we detect significantly greater cellular co-localisation of GR, SP and ECR1 activity following induction of GR in whole transgenic animals. The link between GR activation and the activation of ECR1 in the CA is the first mechanistic linkage between the physiological stress response and the expression of a peptide known to modulate fear and anxiety related behavior in the amygdala. Understanding this linkage may provide a platform for understanding PTSD and lead to alternative approaches to developing novel therapies.

S 2. PROGRESS IN EXPERIMENTAL NEUROSCIENCE RESEARCH

Chair: Allan Kalueff (USA)

HABITUATION TO NOVELTY AS INDICATOR FOR ANXIETY PHENOTYPE IN INBRED MICE

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Introduction: Pathological anxiety in animals might be distinguished from normal anxiety as a persistent and uncontrollable emotion triggering physiological and behavioral responses which lack adaptive value. Non-pathological anxiety in animals can be assessed, for example, by behavioral responses towards novelty, which will habituate over time. However, inappropriate responses might result in non-adaptive anxiety, for example reflected by impaired habituation after repeated exposure to a novel stimulus. In addition, since anxiety interacts with cognitive processes, it is crucial to take multiple behavioral dimensions into consideration when testing for anxiety related behavior. Methods: Male individuals of the two inbred mouse strains BALB/c and 129P3/J were repeatedly exposed to a novel environment, the modified hole board test. The animals were tested in 20 sessions (4 trials of 5 minutes each/day). A second experiment was performed using a one trial object recognition task. In both experiments, several behavioral categories were observed such as anxiety related behavior, exploratory and locomotor behavior and the ability to discriminate between the novel and familiar object. Results and discussion: The results revealed that the BALB/c mice initially demonstrated significantly more anxiety related behavior than the 129P3/J mice. The initially higher anxious BALB/c individuals subsequently habituated to the test situation. In contrast, the 129P3/J strain initially characterized by a lower anxiety level compared to the BALB/c mice showed no habituation in anxiety related behavior. Interestingly, anxiety related behavior even increased during the experimental period. In BALB/c mice, habituation was also observed in other parameters such as exploratory activity and locomotion, whereas no obvious changes were seen in the 129P3/J strain during the test period. No differences in object memory were found between the strains, and both were able to discriminate between a novel and a familiar object. This implies that the lack of habituation as observed after repeated exposure to a novel environment in the 129P3/J strain is not caused by impaired cognitive processing. Conclusion: Impaired habituation as seen

in the 129P3/J strain indicates a non-adaptive anxiety-related profile. Further investigation of this behavioral profile is necessary.

INHIBITOR OF HSP70 EXPRESSION QUERCETIN ABOLISHES ANXIOLYTIC EFFECT INDUCED BY THERMAL PRECONDITIONING IN RATS

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Stress protein, or heat shock protein, 70 kDa (HSP70) is one of the most conservative systems of cell and organism protection from various damaging factors (review: Pastukhov, Ekimova, 2005). The most effective method of the enhancement of HSP70 expression in various organs and tissues, including CNS, is a thermal preconditioning (TP) approach. Protective effects of TP have been elicited in different biological levels, however, so far there is no data related to behavioral studies. The purpose of the present study was to examine an effect of the TP in two standard behavioral tests for anxiety in rats. In order to verify the HSP70 mechanism underlying possible behavioral effects we used an injection of inhibitor of HSP70 expression quercetin. Experiments were carried out in adult male Wistar rats. The TP procedure was conducted inside a thermal chamber in anesthetized animals for 15 min since the moment of the rise of rectal temperature at 41° C. Control group was also anesthetized, but not placed inside the chamber. Quercetin injections were peritoneally performed 4 h before the TP procedure. 24 h later all groups were submitted to the behavioral tests. In the elevated plus maze test, TP group compared to control exhibited a pronounced decrease in the level of anxiety-like behavior scored by percentage of open arm entries (the number and the duration) and the number of unprotected head dips. At the same time, this group exhibited an increase in the levels of exploratory and locomotor activities scored by the number of protected head dips, the number and the duration of open/close arm entries, the number of open arm sectors, the number of transitions between open/close arms, the number and the time of central platform entries. No effect of the TP was elicited in the level of emotionality scored by the number of defecations/urinations, grooming patterns (correct/incorrect), rearing activity and different latencies. In the open field test, TP group compared to control exhibited only an increase in the level of locomotor domain scored by the number of wall ambulations and rearing activity. Treating animals with quercetin abolished or attenuated all the effects induced by the TP. Thus, the results of the study showed that the prior TP procedure may induce an anxiolytic effect against a background of the increased level in exploration and locomotion, with the specifics depending on the behavioral test and indicating the heterogeneity of anxiety manifestation. The inhibition of the behavioral effects by quercetin may prove the implication of HSP70 expression underlying the TP biological protective mechanism.

STRESS-INDUCED RAPID HIPPOCAMPAL CORTICOSTERONE RELEASE MODULATES MEMORY RETRIEVAL

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Introduction: This study provides the first evidence that the stress-induced rapid corticosterone release into the dorsal hippocampus specifically modulates serial contextual retrieval via non genomic mechanisms. Numerous studies have shown that the hippocampus is involved in mediating the glucocorticoids' (GCs) action on learning and memory consolidation processes under stress condition. GCs differently affected memory systems and classically involved a delayed genomic mechanism by cytosolic receptor activation. However, rapid GCs effects on retrieval processes are scarcely studied. Therefore, we recently developed an original behavioral protocol (CSD test) that allows to evaluate simultaneously the effects of an acute stress (3 inescapable electric footshocks) on retrieval of stable (spatial) and flexible (contextual

and serial) information in mice. Methods: Aims of the present study were to determine i) by microdialysis technique the kinetics of corticosterone release into the dorsal hippocampus after acute stress administration ii) the functional impact of the rapid corticosterone release on memory retrieval by pre-test metyrapone (a corticosterone synthesis inhibitor) administration, and iii) whether the injection of corticosterone-BSA (that can not enter the cell membrane) into the dorsal hippocampus mimics the fast effects of stress on memory retrieval. Results and discussion: Results showed that i) corticosterone release into the dorsal hippocampus increase 15 minutes after the acute stress delivery ii) the inhibition of the rapid stress-induced corticosterone increase into the hippocampus by metyrapone laid off stress effects on contextual retrieval iii) corticosterone-BSA injected into the dorsal hippocampus produced an inversion of the memory retrieval pattern in the CSD similar to that resulting from the acute stress. Conclusion: Overall, the present study indicates that the hippocampus underlies the interaction between stress and memory retrieval for contextual information, and provides the first evidence showing that corticosterone mediates the fast effects of acute stress on contextual retrieval probably by hippocampal membranar receptor activation.

LONG-LASTING BEHAVIORAL EFFECTS OF CARBETOCIN ON WISTAR RATS

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Introduction: In our previous studies we demonstrated that carbetocin (1-butanoic acid-2-/O-methyl-L-tyrosine/1-carbaoxytocin), a long-acting analog of a neurohypophyseal nonapeptide hormone oxytocin, improved the deteriorating effects of restraint/immobilization stress when tested the behavior of Wistar rats in the open-field device. Moreover, these effects seemed to last for several days without repeated treatment of animals with carbetocin. Methods: The aim of this study was to compare the effects of several doses of carbetocin on untreated Wistar rats in the open-field device and to see whether the observed changed behavioral parameters after acute application survived for some following days. We used male Wistar rats (Velaz, Czech Republic) and the tests were performed in the large (150 cm diameter) circular arena; behavior was recorded by AnyMaze software (Stoelting Co, USA). Carbetocin was administered i.p. in four doses ranging from 0.1 to 3.0 mg/kg b.w. 60 min before the open-field test. Results and discussion: After acute treatment, all of the used doses (with the exception of dose 3.0 mg/kg), significantly increased most measured behavioral parameters (total movement distance, total time active, rearing, entry in the inner one etc.). The open-field test was repeated 3 and 7 days after carbetocin application without any additional treatment. We obtained a surprising result; the enhanced behavioral parameters lasted for the whole week without any changes in the controls. Conclusion: Findings of long-lasting effects of carbetocin seem to be of great importance, mainly in the light of possible therapeutic use of this drug for the treatment of autism and some other psychiatric disorders. Acknowlegements: Supported by grants MSM 0021620806 and GACR 309/06/0121. Authors thank Dr. M. Flegel, PhD, for a kind supply of carbetocin.

MATERNAL SEPARATION SEX-SPECIFICALLY AFFECTS NEURO-DEVELOPMENTAL APOPTOSIS IN THE SUBSTANTIA NIGRA AND THE VENTRAL TEGMENTAL AREA OF RATS

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Introduction: There is a growing body of evidence that stressful experiences in early life alter brain development, and consequently increase the risk for such psychiatric disorders like, e.g., depression, anxiety, drug abuse, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD). Many of the above mentioned disorders are characterized by abnormalities in

dopaminergic neurotransmission and there are numerous preclinical studies showing that early life manipulations affect this monoaminergic system. However, data presenting the specific impact of early stress on development of the dopaminergic system are still limited. The above findings prompted us to apply one of the models of early life stress, i.e. prolonged maternal separation (MS) and investigate its impact on neurodevelopmental processes occurring in rat midbrain dopaminergic nuclei, i.e. in the substantia nigra (SN) and the ventral tegmental area (VTA). Methods: In the first part of the study we examined the effect of MS on survival of cells generated on embryonic (E) days 12-14 (presumably dopaminergic neurons). The pregnant females received an injection of BrdU (30 mg/kg) once daily on E12-E14. After birth, the rat pups were separated from the dams once daily for 180 min, on each of postnatal (P) days 1-14 (MS animals) or were left undisturbed (controls). On P15 the incorporation of BrdU was revealed in the SN and the VTA by immunohistochemical (IHC) methods. In the next stage (also on P15) we examined the impact of MS on the expression of active caspases 9 and 3 – the chief initiator and executor caspases of apoptotic pathways, respectively (IHC methods). Additionally, we applied double-labeling immunofluorescence and examined the phenotypes of cells expressing caspases 9 and 3 and BrdU in the SN and the VTA. Finally, we measured the enzymatic activity of caspase 3. Results: MS increased survival of cells generated on E12-E14 in the SN pars compacta (SNc) and the VTA of males but not in females. BrdU-positive nuclei were neuronal and co-localized with tyrosine hydroxylase (TH) – marker of dopaminergic neurons. Moreover, only MS male rats exhibited decreased number of caspase 9 – immunoreactive (IR) elements in the SNc, SN pars reticulata (SNr) and in the VTA and decreased activity of caspase 3 in the SN. Caspase 9 – IR elements displayed typical apoptotic morphology. Finally, MS increased number of caspase 3 – IR cells in the SNc (in males only) as well as in the SNr and VTA (in both males and females). Caspase 3 was mainly expressed by glial cells. Conclusion: Our results indicate that MS sex-specifically effects neurodevelopmental apoptosis in the SN and the VTA. Neurodevelopmental abnormalities in these midbrain structures can be responsible for some behavioral and neurochemical aberrations observed in adult animals with a history of early life stress.

BEHAVIORAL STUDIES ON THE ROLE OF CRF IN RAT FRONTAL CORTEX

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Corticotropin-releasing factor (CRF) is a 41 amino acid peptide, which takes part in stress responses. Its role in the modulation of anxiety states is well documented after intracerebroventicular and intra-amygdalar injections, but its role in the cerebral cortex still remains unknown. The aim of our study was to investigate the effect of CRF on anxiety on rats in elevated plus maze when it is bilaterally injected into rat frontal cortex. We examined the effect in two different experimental groups, 5 and 30 min after CRF microinjections. We also tested whether that effect was actually connected with activation of CRF receptors. Therefore, we injected α-helical CRF (a CRF 1&2 receptors antagonist) or NBI27914 (a CRF1 receptor antagonist) before CRF administration. Behavioral experiments showed that CRF in a dose of 0.2 µg/µl/site produced a significant anxiolytic-like effect in both times of administration. We also found that both antagonists significantly prevented the CRF-induced anxiolysis. The obtained results suggest that, in the frontal cortex, CRF may have anxiolytic-like effect. This effect is mediated by CRF receptors, mainly of the CRF1 type.

EFFECT OF MORPHINE ON THE ANXIETY IN THE VENTRAL TEGMENTAL AREA (VTA) AND NUCLEUS ACCUMBENS (NAC) IN ADULT MALE RAT

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Anxiety is a complex phenomenon with different social and psychological causes. In fact, anxiety is a biological process that has repetitive biological and physiological effects on the biological structure of the brain. Since long ago, anxiety and fear have been recognized as important physiological issues and different drugs with different mechanisms were used for their control. In this study, the effect of morphine on anxiety in adult male rats was studied in the ventral tegmental area (VTA) and nucleus accumbens (NAc). The elevated plus maze (EPM) method was used in this research. Adult male rats weighing 200 to 240 grams after canola placement surgery were allowed to recover for five days. Then, they were injected with saline (control) or one of three different doses of morphine (2.5, 5, and 7.5 µl/rat) and behavioral tests were done after 12-16 hours. Each animal was tested only once. The first experiment was done once in the VTA. The saline and three doses of morphine were injected. After statistical analysis, it was shown that the doses of morphine have no effect on the OAE% but that a dose of 5 µl/rat of the drug can cause increase of the OAT% and decrease of the anxiety in studied animals. However, it did not cause a significant effect on animal activity (locomotion). In the second experiment, which was performed in the NAc, saline and three doses of morphine were injected. After statistical analysis, it was shown that injection of the 2.5 µl/rat dose significantly increased the OAT% and OAE% but decreased anxiety in the animal and did not cause significant changes in the animal's activity. As a result of these two experiments, morphine can be said to decrease anxiety probably through interaction of the GABAergic system.

S 3. CLINICAL ISSUES IN STRESS RESEARCH – PART I

Chairs: Viktor Klimenko (Russia), Allan Kalueff (USA)

CHANGES IN LIFESTYLE BEHAVIOR AMONG BASHKORTOSTAN REGION POLICEMEN WITH NON-COMMUNICABLE DISEASES AFTER A STRESSFULL SITUATION IN CHECHNYA

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Introduction: Behavioral risk factors of the development of non-communicative diseases such as smoking, sedentary life-style, alcohol consumption, unhealthy eating, and psychological problems have a high level of frequency among policemen. Understanding the influence of stressful situations in changing these factors among policemen is very important. Methods: The interview (by special questionnaire) was conducted with 60 policemen who have somatic diseases and had participated in a Chechnya combat visit. Results and discussion: Most of the policemen did not change their behavioral habits concerning lifestyle after a Chechen combat visit: 80.0% did not change smoking status while 5% smoked more, 15% stopped smoking. 15% drink less alcohol, and 15% pay more attention to physical training and sports. Most participants have the same eating habits as before the visit, though 5% eat less salt, 10% eat less sugar and cakes, 11.6% began to visit physicians and take medicine more attentively for treatment, and 23.3% spend more time with their families. After a Chechnya trip, the health conditions become bad and a small percentage of the policemen began to take an active interest in their health. Conclusion: Most Chechnya combat participants do not change their habits concerning alcohol consumption, tobacco use, eating or other behaviors. Policemen who improved their lifestyle were those with deteriorated behavioral risk factors.

PREJUDGEMENT IN THE TREATMENT OF CHRONIC CANCER PAIN

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Introduction: About 90% of patients in the terminal stage of the malignant neoplastic disease suffer from pain that significantly interferes with the life quality. In our institution the team that is dealing with chronic cancer pain consists of a medical oncologist, anesthesiologist, psychologist and the nurse. Apart from pharmacotherapy, invasive methods (epidural catheter, neurolysis) and supportive program for the family members are also applied. The purpose of the study was to estimate if the reflectivity of the patients to the syrup of morphine influences on the treatment success. Methods: The study included 21 patients with chronic cancer pain, 62% women and 38% men, average age of 63. All patients were in the terminal stage of malignant disease (clinical stage IV) and opioid treatment was administered (transdermal fentalin and morphine syrup). As for the academic level, 68.4% of patients graduated secondary school, 21% graduated from a university and 10.6% primary school. No satisfactory halting of the cancer pain was noted in 36.8% of patients. The questionnaire was used to evaluate the attitude of patients to opioid treatment and potential reflectivity. Results: The reflectivity to morphine was present in 33% of patients while in 21% of patients treated with tramadol. The side effects of the opioids were the reason of reflectivity in 48.5% of patients, mainly due to potential harmful effect on other systems, vertigo, addiction and personality changes. 79% of patients knew that severe pain had to be treated with strong opioids, 66% of patients unequivocally accepted the advice of the oncologist, while 12.5 % of patients would have never agreed to take morphine. The prejudgment regarding the opioid treatment was present in 50% of examinees, 52.6% of patients had the association between the taking of morphine and close death. Conclusion: The prejudgement regarding the opioid medications might have been related to inadequate pain control in patients during the terminal stage of the neoplastic disease. This pilot study needs to be continued in order to establish education programs for minimizing the prejudgement that would potentially enable the improvement of the life quality in patients in the terminal stage of malignant diseases.

POST-WAR STRESS INCREASES MENTAL AND BEHAVIORAL DISORDERS IN CHILDREN AND ADULTS IN CENTRAL KOSOVO AFTER NATO BOMBING

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Introduction: After the NATO operation in Serbia during 1999, only small number of Serbs stayed in Kosovo, being constantly under attack from local nationalist extremists, and living in extremely poor housing environments.The influence of chronic stress and living in dangerous situations can increase the likelihood of developing mental disorders. The aim of this study is to clarify mental and behavioral disorders in Serbian population in Kosovo after NATO arrival 1999. Methods: We tracked registered cases of mental and behavioral disorders in the post-war period from 1999-2007 in the central Kosovo area (with domicile Serbian population). Results and Discussion: In 2000, 1196 cases of mental and behavior disorders were registered, whereas in 2007, this number increased to 3698. 680 cases of neurotic, stressogenic and somatoform disorders were found in 2000, rapidly increasing to 2239 by 2007. Affective disorders also demonstrated an increase from 280 cases in 2000 to 808 in 2007. In 2000, we found 149 cases of serious mental (schizophrenia, schizopathic, etc.) disorders. After 7 years the number had grown to 562 cases. The number of patients with psychosomatic disease also increased in this time interval. According to the available data, we can note a rise of phobic conditions in pre- and school-children. Increases in alcohol and drug abuse are also typical. Conclusion: The high-stress environment after the arrival of NATO has led to a very unsafe situation for the Serbian population. Constant life endangerments from extremist attacks, low socio-economical status and lack of access to medical care were basic factors influencing the appearance of mental illness.

SEX-RELATED DIFFERENCE AS A FACTOR OF POST-STROKE DEPRESSION

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Introduction: The notion of sex-related difference in interhemispheric processing of emotion has received increased attention. Although the brain areas with sex-related differences, as well as the sex steroids, remain understudied, the neuroactive steroids are believed to be important endogenous modulators of depression- and anxiety-related behavior. Methods: This study included a total of 20 first-stroke patients, with either cortical or subcortical lesions, 2-18 months after the stroke. The patients were subdivided according the sex (8 females, 12 males). All patients were tested by self-rating depression scale Beck Depression Inventory (BDI)-II, a very useful screening instrument for depression with high reliability. A paired t-test was performed to evaluate differences between two groups. Results and discussion: Seven patients (29%) in our sample met clinical criteria for depression. The results demonstrated that male patients had significantly increased BDI-II scores and rate of PSD compared to female patients (probability value less than 0.05). Reproductive hormones are thought to be involved in emotional regulation and the development of depression. A significant functional interaction between estrogen and serotonin are acknowledged, suggesting a possible role for estrogen in the treatment of postnatal psychiatric disorders or depression during perimenopause. In conclusion, details of this relationship between depression and sex in post-stroke patients require further investigation.

ANALYSIS OF GENES CODING FERMENTS RESPONSIBLE TO DEVELOPMENT OF UNIPOLAR DEPRESSION

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Introduction: Unipolar depression (UD) is a heterogeneous mental disorder and the leading cause of worldwide disability among individuals between 15 and 44 years old. According to the data of family, twin and adoption studies heritability of UD ranges from 40% to 70%. Abnormalities in the functioning of the monoaminergic systems are believed to be involved in the pathogenesis of depressive illness. The enzymes play a highly important role in the metabolism of biogenic amines in the brain. The monoaminooxidase A and B are mitochondrial enzymes involved in the degradation of biogeonic amines and neurotransmitters. Dysfunction of methylentetrahydrofolate reductase (MTHFR) enzyme may lead to a reduction in monoamine neurotransmitter function and greater risk of UD. The aim of our study was to examine the association of 3 polymorphisms of genes coding ferments that may be responsible to development of UD, namely: C677T of MTHFR, rs6651806 in MAOB and MAOA-LPR in MAOA genes. Materials and Methods: 174 patients of Russian and Tatar descent (age 19-72 years) with UD (according to ICD-10 diagnostic criteria) and 331 healthy controls with corresponding ancestry (age 18-69 years) from the Republic of Bashkortostan (Russia) were included in the study. In our investigation, we used the following methods: extraction of genomic DNA from whole blood, PCR-, RFLP-analyses, gel electrophoresis of PCR products. Statistical analysis of results was conducted using a BIOSTAT program, an interactive table of conjugation 2x2 (http://www.biometrica.tomsk.ru). Results and discussion: There were significant differences in the distribution of genotype ($\chi 2$=6.006, P=0.05) and allele ($\chi 2$=4.603, P=0.03) frequencies in the MTHFR gene between depressive patients and controls in total samples. For the Tatars the *T/*T (OR=3.21, 95%CI=1.04-9.93) and the *T (OR=1.87, 95%CI=1.19-2.94) are risk markers; the *C/*C (OR=0.51, 95%CI=0.29-0.90) and *C (OR=0.53, 95%CI=0.34-0.84) are protective markers. For the Russians, only *T/*T genotype (OR=2.56, 95%CI = 1.01-6.48) is a possible risk marker of UD. We found significant differences in MAOA-LPR distribution of genotype frequencies ($\chi 2$=19.25, P=0.000) between patients and controls of Tatar descent, but not between individuals of Russian descent. An increase of the *209/*239 genotype (OR=2.74, 95%CI=1.61-4.58) frequency and decrease of the *239/*239 genotype (OR=0.42, 95% CI=0.24-

0.72) frequency were registered in the depressive group compared to those in the control group. No significant differences in genotype or allele frequency distribution in the rs6651806 of the MAOB gene were found between UD patients and control groups in individuals of Russian or Tatar descent. Conclusion: Our study supported the hypothesis of the involvement of polymorphisms of MTHFR and MAOA genes in the development of unipolar depression in Russian and Tatar descents. We conclude that the polymorphisms of the MAOB genes are unlikely to have a major role in the pathogenesis of UD. The research was supported by the Russian Humanitarian Research Fund (the grant № 06-06-00163a) and Russian Science Support Foundation.

AUDITORY INFORMATION PROCESSING (ODDBALL PARADIGM): AN IMPACT OF COMT POLYMORPHISM

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Introduction: The aim of the study was to determine to what extent the different stages of auditory information processing were influenced by a molecular-genetic factor (catechol-o-methyl transferase (COMT) gene polymorphism), which was shown to modulate the dopamine activity in the prefrontal cortex. Considering the role of dopamine in the pathogenesis of some mental illnesses, the study was also conducted in patients with schizophrenia and schizoaffective psychosis. Methods: 57 patients (F20, F25, ICD-10) and 52 mentally healthy relatives of the patients (controls) were examined. Auditory ERPs in the “active” oddball paradigm were recorded on the Brain Atlas mapping system (Bio-logic, USA), with 80% of non-targets (1000 Hz, 60dB) and 20% of targets (2000 Hz, 60dB) stimuli. Peak amplitudes and latencies of N100, P200 (ERP to non-targets), N100, N200, P300 (ERP to targets), MMN (difference wave) were analyzed. DNA was extracted from the white cells of venous blood by Master Pure kit (Epicenter, Madison WI). The COMT Val158Met polymorphism was assayed using an ABI SnaPshot ddNTP Primer Extension kit and the products were analyzed in an ABI 310 DNA analyzer. An impact of different COMT genotypes on ERP was assessed statistically separately for each group (all tested subgroups were matched for age, sex and, in case of patients, for the diagnosis). Results and discussion: In both groups, COMT polymorphic variants were associated with ERP to targets. In patients, the carriers of the Val/Met genotype had the longest N100 and N200 latencies, while in controls the Met/Met genotype was associated with the shortest N100, N200 latencies and largest P300 amplitudes. Also in controls, the carriers of the Val/Val genotype had the longest P200 (ERP to non-targets) latencies. There was no statistically significant association between the COMT polymorphism and MMN. The findings show the relationship between the higher dopamine activity in the prefrontal cortex (due to the tested genetic factor) and “better“processing of significant auditory information in norm with deterioration of such correlation in schizophrenia. The specific impact of prefrontal cortex dopamine activity on generation of different waves of auditory ERP, in respect to “involvement” of latencies in case of the earlier components and amplitudes - for P300, also merits attention. The study was partially supported by RFH grant N08-06-00084a.

MENTAL STATUS AND HEART RATE VARIABILITY

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Introduction: A number of studies have shown that heart rate variability (HRV) and especially power of high frequency spectral range (0.15 – 0.5 Hz) relates to mental status. But, there are not reliable psycho-diagnostic techniques based on analysis of HRV so far. “Complex and largely undiscovered physiology” (Taylor & Studinger, 2006) of HRV is a probable reason of this. The purpose of this study was to discover the features of heart rate variability which are

actually related with mental status. Methods: Three groups of 64, 39 and 19 healthy volunteers were in study. Actual mental status was evaluated by the Russian questionnaire technique POMS (Profiles of Mood States). In order to avoid a contradiction when series of time intervals (RR) are analyzed as a function of the same time, we analyze them as a function of number. 150 harmonics were defined by digital Fourier transformation technique. In order to normalize the distribution of frequency values they were transformed logarithmically. To investigate the frequency structure of heart rate oscillations, the factor analysis of the frequencies was performed. Results and discussion: The results in each group were similar. The factor loadings diagrams of the four first factors have forms like a wave. If the waves were interpreted as physiological phenomena of periodical modulation of heart rate, we can conclude that there are at least three such phenomena in high frequency range instead of the one mainly being discussed now. The second factor has the wave at about 0.14 – 0.24 1/beat and peak at 0.18 1/beat. This may only be the frequencies of respiratory sinus arrhythmia. The next two factors have not yet been physiologically interpreted. The wave of the third factor is about 0.21 – 0.31 1/beat with peak is at 0.26 1/beat. The first factor which has a grates eigenvalue has the wave at frequencies from 0.25 up to 0.5 1/beat and peak 0.35 1/beat. The periodogram values at the frequencies of the first factor have significant positive correlations with the POMS scale of Vigor. Stepwise methods of multiple regression analysis allow for a good model with R-square equal to 0.83. Conclusion: The results let us suppose that there are at least three periodical phenomena of HRV in frequency range related with mental status. Two of them have not been discovered and physiologically explained yet. The most powerful of these phenomena relates to mental status. It has frequencies from 0.25 to 0.5 1/beat and peak 0.35 1/beat. Despite the difference of the peak frequencies, the waves of factor loadings are overlapped. Therefore, regression models would be more fit for useful evaluation of mental status, rather than the power of spectral density within any frequency range.

S 4. ANIMAL MODELS OF BRAIN DISORDERS

Chairs: Yuriy Pastuhov (Russia), Irina Ekimova (Russia)

BEHAVIORAL DIFFERENCES BETWEEN GENDERS IN ANIMAL MODELS OF DEPRESSION IN MICE

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Introduction: One of the most prevalent psychiatric diseases is depression, with an incidence nearly two times higher among women than men.The goal of our study was to determine whether this difference between genders in humans can also be detected in mice using two animal models of human depression: tail suspension and forced swimming. Materials and methods: Male and female NMRI and DBA mice were used with normal or reversed light-dark diurnal cycle to examine contingent differences between inbred and outbred strains. The effects of two well known antidepressants: citalopram (SSRI) and imipramine (TCA) have been tested in these models. Results: In the tail suspension test, no difference was found between genders in NMRI mice housed in normal light-dark cycle. However, a significant difference has been detected within groups housed with a reversed diurnal cycle: females spent significantly more time in immobility (average: 54 s, $p<0.05$) than males. Male DBA mice displayed similar behavior to male NMRI mice, as there was no difference in time spent in immobile state between the two strains. Experiments with DBA female mice were not evaluated, since these animals displayed an atypical behavioral response (climbing up on the tail). Citalopram (5 mg/kg) and imipramine (25 mg/kg) showed antidepressant-like effect in both strains following intraperitoneal administration. In the forced swimming test, there was no difference in immobility between control groups of NMRI and DBA mice. Conclusion: This is the first study to report

behavioral differences between genders in mice with reversed cycle in the tail suspension model. Our results indicate a tendency of female NMRI mice to spend more time with immobility in a despair state, than corresponding males. However, the effect seems strain and model specific, since behavior of female DBA mice could not be evaluated in tail suspension, and investigations in the forced swimming model could not reveal any difference at all between genders in the two tested strains. Further investigations are necessary to thoroughly describe gender and strain effects in other strains as well as on antidepressant treatment in mice.

THE STUDY OF IMPAZA ANXIOLYTIC PROPERTIES IN EXPERIMENTAL MODELS OF ANXIETY IN RATS

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Introduction: Earlier preclinical and clinical studies of impaza (ultra-low doses of antibodies to endothelial NO-synthase) showed its proerectile action. Impaza is reported to be successfully used in the treatment of erectile dysfunction (ED) of different origin. The maximal efficacy was observed in patients with psychogenic ED (78.5% patients showed improvement). The aim of the study was to assess impaza's anxiolytic properties. Methods: 120 white outbred male rats (230-250 g) were used in the study. Anxiolytic effect was estimated in Vogel conflict test (60 animals) and elevated plus-maze test (60 animals). In Vogel conflict assay the number of punished water intakes was counted during 10 minutes (0.25 mA). In the elevated plus-maze the number of entries into the open arms and the time spent there was registered during 5 minutes. 6 groups (n=60) were administered intragastrically once (n=30; 40 minutes before experiment) or for 5 days (twice a day) (n=30) with following drugs: impaza (4 ml/kg), diazepam (comparative drug; 2 mg/kg) or distilled water (control; 4 ml/kg). Results and Discussion: In Vogel conflict test impaza demonstrated anxiolytic activity comparable to diazepam. Impaza increased the number of punished water intakes by 1.5 times ($p<0.05$) after single administration and by 1.55 times ($p<0.05$) after course administration (diazepam – by 1.55 and 1.6 times, respectively, $p<0.05$). In elevated plus-maze test animals of control group did not enter into the open arms at all. Single and course impaza administration resulted in 0.8±0.63 and 1.5±0.7 entries into the open arms respectively (time spent in the open arms was 24.9±12.2 sec and 34.4±8.5 sec, respectively). Diazepam on single and course administration produced a similar effect, resulting in 1.0±0.9 and 0.9± 0.6 entries into the open arms, respectively (time spent in the open arms was 26.5±12.8 and 29.2±17.1 sec, respectively). Conclusion: The present study demonstrated impaza's anxiolytic activity (4 ml/kg) comparable to diazepam (2 mg/kg). The anxiolytic effect of impaza provides explanation for high drug efficacy in patients with ED of psychogenic origin.

EFFECTS OF STRESS IN C57BL/6N MICE SUBJECTED TO TWO DIFFERENT CHRONIC STRESS PROCEDURES

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Introduction: Chronic stress is the major environmental factor contributing to the development of depression. In experimental animals, the unpredictable chronic mild stress paradigm, based on the exposure to different mild stressors in an unpredictable manner, was developed to model the chronic stress exposure in humans. We investigated the effects of two different stress protocols with different stress intensities on C57Bl/6N mice. Methods: The first unpredictable chronic mild stress (UCMS) stress protocol consisted of stressors immobilization stress (2h), exposure to tilted cage or cage without bedding (12h), wet bedding (12h), paired housing with another stressed mouse and rat exposure (3h), of which three were applied in a pseudo-randomized manner each day for six weeks. As an additional stressor, the light-dark cycle was

inversed weekly. In the second unpredictable chronic stress procedure (UCS), emotional stress was enhanced. Therefore, mice were exposed to a rat for 10h to 14h, and the paired housing procedure was replaced by a 10 min social defeat paradigm using aggressive CD-1 males. In both UCMS and UCS stress procedures, the body weight and preference to 1% sucrose solution (as a measurement of hedonic state) were measured weekly. After completing the six weeks stress procedure, food consumption was assessed and the open field (OF) test, the tail suspension test (TST), forced swim (FST) tests and shuttle-box test were performed. Results and discussion: Despite of reduction in sucrose consumption in the stressed mice, there was no reduction in sucrose preference in both of groups. Stress caused a long lasting reduction of body weight gain in the UCMS group, even though food consumption increased. The UCS stress group showed a similar effect until the 3rd week of stress. Then, in parallel to sucrose consumption, body weight increased. In the OF test, UCMS mice showed increased locomotion. Mice in both stress groups showed higher numbers of jumping and rearing. In TST but not in FST, stressed mice showed higher mobility. In addition, mice from both UCMS and UCS groups showed reduction of electric shock avoidances in Shuttle-box-test, indicating cognitive impairments. Conclusion: Both UCMS and UCS stress protocols induce hyperlocomotion and learning impairments. The stress procedures in C57Bl/6N mice did not induce “depressive-like” phenotypes like anhedonia or lower mobility in FST or TST. Thus, long-term exposure of C57Bl/6N mice to UCMS or UCS chronic stress is not suitable as models of stress induced depression.

DELETION OF THE PRODYNORPHIN GENE INCREASES ANXIETY-LIKE BEHAVIORS AND MODIFY POMC, CRF AND CB1 RECEPTOR GENE EXPRESSIONS IN RESPONSE TO RESTRAINT STRESS

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The aim of this study was to evaluate the role of the prodynorphin gene (PDYN) in the emotional responses induced by different anxiogenic stimuli. To this purpose, PDYN knockout mice (PDYN KO) and their correspondent wild type mice (WT) were used. The response of PDYN KO mice to the anxiety stimuli was measured by using different behavioral paradigms (open field, light-dark box, elevated plus-maze, and social interaction tests). The response to stress was evaluated by measuring POMC (arcuate nucleus), CRF (paraventricular nucleus) and CB1 receptor (R) gene expressions (hippocampus, amygdala, ventromedial nucleus) by in situ hybridisation after restraint stress. In addition, the response of PDYN KO and its corresponding WT mice was measured in the light dark box test after administration of bromazepam (50 and 100 μg/kg, p.o.). PDYN KO mice presented increased peripheral distance and increased speed in the central area of the open field, spent less time in the lighted box (light dark box) and in the open arms (elevated plus maze) and decreased social interaction compared to WT mice. The anxiolytic action of bromazepam was significantly reduced compared to WT mice. Basal levels of CRF gene expression and CB1 R (CA2, CA3) were lower and POMC and CB1R (amygdala) were higher in PDYN KO than in WT. Restraint stress revealed an enhanced sensitivity in POMC (PDYN KO 72%; WT (31%) and CRF (PDYN KO 37%; 22% WT) gene expressions. CB1 R gene expression decreased after stress in a similar manner in WT and PDYN KO mice. These findings reveal that deletion of PDYN gene increased anxiety-like behaviors, reduced the anxiolytic response to benzodiazepines and increased the sensitivity in POMC and CRF gene expressions in response to restraint stress. Furthermore, these results suggest that functional alterations of PDYN gene may be associated to the emergence of anxiety disorders and affect the efficacy of anxiolytic drugs. Supported by a grant from Spanish Ministry of Health FIS 05/0429 to J.M.

OVEREXPRESSION OF CANNABINOID CB2 RECEPTORS DECREASED THE RESPONSE OF EMOTIONAL BEHAVIORS TO ANXIOGENIC STIMULI AND IMPAIRED THE ANXIOLITIC ACTIONS OF BENZODIAZEPINES

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The purpose of this study was to analyze the role of the cannabinoid CB2 receptor in the emotional responses induced by different anxiogenic stimuli. To this aim, transgenic mice overexpressing the cannabinoid CB2 receptor (CB2Xp, developed in our laboratory) were used. The response of CB2Xp to the anxiety and depression stimuli was evaluated by using different behavioral tests (light-dark box test, elevated plus-maze paradigm, tail suspension and novelty suppressed feeding tests). The response to stress was evaluated by measuring CRF gene expression in the paraventricular nucleus of the hypothalamus (PVN) after restraint stress. In addition, the response of CB2Xp and its corresponding WT mice after administration of alprazolam (45 μg/kg, p.o.) was measured in the light dark box test and after ethanol (2 g/kg, p.o) in the elevated plus maze. Mice CB2Xp spent more time in the lighted box and in the open arms and reduced time of immobility compared to WT in the tail suspension test. The time of latency to initiate consumption is lower and the amount of consumption is significantly higher in CB2Xp compared to WT mice. The administration of alprazolam in the light dark box was without effects in CB2Xp and presented reduced anxiolytic action after ethanol administration in the elevated plus maze compared to WT mice. Restraint stress significantly increased (85% from control) CRF gene expression in the PVN of WT mice whereas was without effects in CB2Xp mice. The results of this study suggest that increased expression of the CB2 receptors significantly decreased anxiety and depression related behaviors. Furthermore, these results point out the cannabinoid CB2 receptor as a new potential key target in the treatment of anxiety and depression related disorders.

LONG TERM EFFECTS OF INTRACAUDATE ADMINISTRATION OF LACTACYSTINE ON MOTOR, EMOTIONAL AND COGNITIVE BEHAVIORS AND THE EXPRESSION OF TYROSINE HYDROXYLASE IN THE BASAL GANGLIA

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The purpose of this study was to examine the long term effects of intracaudate administration of lactacystin, a proteosome inhibitor, on motor, emotional and cognitive behaviors and the neurochemical alterations associated underlying these changes. To this aim, lactacystin (16 μg/4 μl) or its corresponding vehicle were injected under stereotaxic surgery in two injections in the caudate-putamen of Swiss albino mice. Motor impairment (neurological severity score, contralateral rotations induced by apomorphine), emotional behaviors (light dark box, elevated plus maze) and cognitive alterations (step down inhibitory avoidance and object recognition) were evaluated at various times between 2-8 weeks after administration of lactacystin. In addition, 8 weeks after the administration of lactacystin mice were anesthetized, perfused and brains were sliced at 40 μm using a vibratome. Tyrosine hydroxylase (TH), glial fibrilary acid protein (GFAP), and α-synuclein (α-SN) were examined by immunocytochemistry. Lesion with lactacystin produced a moderated motor deterioration (increased neurological severity score and contralateral apomorphine rotations) accompanied by significant loss of TH in the substantia nigra and caudate-putamen compared to vehicle treated mice. As soon as two weeks after lactacystin administration, an increased in the time spent in the lighted area (light dark box

test) and in the time in the open arms (elevated plus maze) was detected suggesting decreased anxiety-like behaviors that were maintained up to 8 weeks. The analysis of cognitive behaviors revealed an impairment in memory consolidation (short and long term) in the step down inhibitory avoidance and in the object recognition test. An increase in GFAP and α-SN immunoreactivities were observed in various brain areas.These results revealed that administration of lactacystin produced a moderated motor impairment, decreased anxiety like-behaviors and significant short and long term cognitive deterioration. These behavioral alterations are accompanied by loss of TH in the basal ganglia and cingulate cortex and increased α-SN in the hippocampus, cingulate cortex and caudate-putamen.

MOLECULAR IMAGING OF ENHANCED CALCIUM EXPRESSION IN THE AREA POSTREMA OF TOTAL SLEEP DEPRIVED RATS

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Introduction: Calcium is a key ion involved in numerous metabolic activities ranging from intracellular signaling to impending excitotoxicity. Given that homeostatic regulation of calcium may play an important role in regulation of metabolic function, the present study was aimed at determining the in vivo calcium expression in tissue levels of adult rats subjected to total sleep deprivation (TSD), a stressful condition known to harm the metabolic activities. Methods: TSD was performed by the disc-on-water method. After five days of TSD, the area postrema (AP, an integrative site for metabolic/cardiovascular regulation in lower brainstem) was removed and processed for time-of-flight secondary ion mass spectrometry (ToF-SIMS) molecular imaging analysis. In the meanwhile, with the aim of assessing intracellular pathways for calcium reaction, the calcium binding protein [calmodulin, (CaM)] immunohistochemistry was further carried out in the same section following spectrometric analysis. Results and discussion: In normal rats, the calcium intensity was estimated to be 0.5×105 at m/z 40.08. However, following TSD, the intensity for calcium was greatly increased to 1.2×105 and the signal for the calcium image was strongly expressed in AP neurons with clear profiles. Immunohistochemical staining correlated well with molecular image findings in which a majority of CaM positive cells co-localized with calcium-containing neurons. The functional significance of enhanced calcium was demonstrated by augmented mean arterial pressure (MAP) that may serve as clinical manifestation for metabolic dysfunctions. Conclusion: It was suggested that increased calcium expression in AP would injure many biochemical reactions related to metabolic regulation via calcium-CaM complex pathways. Significant activation of these pathways would render AP neurons more vulnerable to calcium-mediated neurotoxicity, which may subsequently act as a critical mechanism for the development or formation of TSD relevant metabolic dysfunctions.

S5. PROGRESS IN BIOPSYCHIATRY RESEARCH

Chair: Allan Kalueff (USA)

MORPHOLOGICAL AND CYTOCHEMICAL ALTERATIONS IN THE RAT BRAIN AFTER EXPOSURE TO ACUTE MENTAL TRAUMA

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Introduction: Mental traumatic experience in human can results in many psycho emotional disturbances, indelible structural alterations in the central nervous system (especially in

hippocampus) and abnormalities in immune and endocrine system function. In the DSM-IV, this is defined as posttraumatic stress disorder (PTSD). Extreme psychotraumatic influences in rats, as demonstrated in our experiments, leads to sustained non-arresting PTSD-like abnormalities in animal behavior, imbalance of lipid metabolism, dysfunction of neurotransmission and hormonal dysfunction (Tsikunov et al. 2005, 2006). Furthermore, in traumatized animals massive structural lesions were found in tissues of the adrenal glands, the mucous tunic of stomach, and the duodenum. The aim of the present investigation was to detect and characterize morphological and cytochemical alterations in brain of the rats that were exposed to the acute psychotraumatic situation. Materials and methods: Here we used a model of PTSD. Experiments were made on Sprague-Dawley rats (200–250 g, 4 months old). Animals were single-exposed to the acute psychic trauma. The rats were exposed to a threatening situation by witnessing the death of a cagemate by a black-tailed python, a predator of the rat. 9 days later, the rats were sacrificed, the brain was taken out and fixed via immersion in the zinc-ethanol-formaldehyde. Preparations were made by the method of paraffin sections. Then preparations were stained by the Nissl's method and also to the revelation of PCNA with and without the background astra blue stain. Results: In animals that were not exposed to the psycho-trauma, very few wrinkled cells were found. In rat brain that was fixed on the 9th day after acute psychotraumatic situation, the following alterations were observed. In the Nissl's stain, wrinkled cells and hyperchromatic cells were detected in many regions of brain at high quantities. A maximum of wrinkled cells were revealed in the hippocampus and basal nuclei. Many wrinkled cells were found in the cerebral cortex. Patterns of cytoarchitecture of hippocampus layers were significantly altered compared with controls. Decreased ordering of neurons and chaotic arrangement of axons and dendrites were also found. A high quantity of wrinkled cells was discovered in the suprachiasmatic nucleus. In staining to PCNA with background astra blue stain, the intensification of proliferation was revealed in some locations of brain tissue. This phenomenon we considered as a nonspecific glial reparative reaction that accompanied neuronal cell death. Conclusion: Thus, the influence of a single psychotraumatic situation can results in structural and cytochemical alterations in various regions of rat brain, especially in hippocampus, basal nuclei and cortex of cerebrum after 9 days. Probable mechanisms of the structural development and cytochemical alterations are hypersecretion of glucocorticoid hormones, lesions of neurons due to excitotoxicity, oxidative stress, a decrease of neuronal progenitor proliferation, disturbances in synthesis of neurotrophic factors, decreased surviving of cells in neurogenesis, and remodeling of dendritic arbor.

CORRECTION OF BEHAVIOR MANIFESTATIONS OF THE POSTTRAUMATIC STRESS DISORDER BY MODULATION OF MONOAMINE SYSTEM ACTIVITY OF THE FEMALE RAT BRAIN

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Introduction: Currently, the importance of investigating mental diseases such as depression and posttraumatic stress disorder (PTSD) is increasing. Mental trauma is known to play a considerable role in the pathogenesis of these common disorders. Despite the numerous studies, the neurophysiological mechanisms underlying PTSD remain unclear. Most of the neurobiological investigations on the consequences of psychogenic trauma are performed in male animals. At the same time, there are reports demonstrating sex differences in responses to stress. The data obtained in our laboratory show that both female and male rats develop PTSD after exposure to mental trauma. The disorders in female rats are retained during not less than 2 months and depend on the estrous cycle phase. The noradren-, seroton-, dopamin-, glutamate-ergic and other stress-activated systems are implicated in depression. Numerous

data suggest the influence of estrous cycle, not only on reproductive function, but in non-reproductive behavior. The aim of the present study was to investigative mechanisms of compensation of behavioral and emotional disturbances by analyzing the action of receptor ligands on different neuromediator systems in female rats. Methods: A model of mental trauma – the experience of partner death from a predator (python) was used for the formation of PTSD manifestations in rats. A group of female rats (200–250 g) was exposed to the predator for 25 min, and rats who survived this situation were returned to their regular cages. The antidepressants were injected i.p. from 2 to 4 p.m. 1-21 days after the psychotraumatic event. Piribedil (a dopaminergic agonist, 0.72 mg/kg) and fluoxetin (a selective inhibitor of serotonin reuptake, 0.64 mg/kg) were used. 0.9% NaCl was used as a control. The substance was given in doses compared with those used in humans for the treatment of depression. The emotional state of female rats was estimated after psychogenic trauma against the background of the introduction of antidepressants. For assessment of behavioral and emotional state, the following tests were used: open field, elevated plus-maze, intruder-resident and Porsolt tests. Results: Injection of piribedil after mental trauma increased the investigative behavior as well as decreased freezing in the open field test. The immobility in the Porsolt test decreased vs. control group. In female rats, a significant inhibition in the elevated plus-maze, and in aggression level in the intruder-resident test was revealed after psychogenic stress following the introduction of piribedil. Fluoxetin in the doses used did not change the behavior of the traumatized rats. Conclusions: The results of the present study demonstrate changes in the behavior of female rats that have survived a mental trauma. PTSD-like behaviors were corrected by antidepressants. Administration of piribedil promoted normalization of exploratory activity, and decreased anxiety and aggression. Thus, positive results in correcting emotional disorders in female rats were achieved through activation of dopamine receptors. This suggests the involvement of the dopaminergic system in depression and PTSD.

THE INFLUENCE OF SLEEP DEPRIVATION ON THE NEURONS CONTAINING OREXIN A IN RATS

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Introduction: The hypothalamus has a major role in regulation various behaviors that contribute to homeostasis such as arousal, feeding and thermoregulation by integrating external and internal stimuli. Orexins could be involved in the regulation of feeding, blood pressure, hormonal release, temperature and arousal. Neurons in the lateral hypothalamus area have been involved in the maintenance of waking state. Orexin fibers were seen in numerous structures involved in the sleep-waking cycle such as the locus coeruleus, the tuberomammillary nucleus, the pontine reticular formation, the rape nuclei, the preoptic area and the laterodorsal tegmental nucleus. The high density of fibers in the locus coeruleus and the tuberomammillary nucleus of the hypothalamus, nuclei containing neurons responsible for the maintenance of the waking stage, suggest that orexins might have an effect on arousal. To characterize this peptide further and to help understand what physiological functions it may serve, we undertook an immunohistochemical study to examine the distribution of orexin A -immunoreactive neurons and fibers in the rat brain under stress conditions -sleep deprivation in ontogenesis. Methods:14 -days and 30-days old Wistar rats were undertaken sleep deprivation during 2 hours. After decapitation the brain was fixated in Buen fluid. Immunohistochemistry detection of orexin A was done on paraffin slices (6 mkm) in orexin A antiserum raised in rabbit (1:4000 in PBS). The orexin A staining appeared as dark brown punctuate granules in somata and processes of orexin A neurons. Mapping of neurons and fibres immunoreactive to orexin in rat brain was done using a light microscope equipped with a video camera connected to a computerized image data analysis system. Results: Immunohistochemistry against orexin A showed the decrease of immunoreactive material in cell bodies in the dorsal and lateral hypothalamic areas,

caudate nucleus, and in fibers in hypothalamic region in comparison to the control group. More over the changes are stronger in the group of 30 -day rats than in 14 day - old animals. Thus, orexin A neurons are involved in sleep-deprivation reaction and the level of their reactivity depends on the age.

PSYCHOPHYSIOLOGICAL CORRELATES OF PRE- AND POST-SURGERY STRESS IN CARDIOSURGICAL PATIENTS

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Introduction: Pre- and postsurgical periods are extremely stressful for cardiovascular surgery patients. The emotional component of stress prevails in presurgical period, while surgery is a strong physiological stress. One of its main components which could have long-term consequences is global brain ischemia (GBI) developing due to the long period of artificial blood circulation. In this present research we studied pre- and post-surgical stress using set of psychophysiological tests, psychological questionnaires and event-related potential (ERP) recording. Methods: 6 patients with acquired heart diseases (49+-8 years, 1 female, 5 males) and 6 healthy age-matched controls participated in the study. Patients were tested twice – before surgery and 14-21 days afterwards. Controls were tested once. Anxiety levels were assessed by Spielberger Stait-Trait Anxiety Inventory (STAI). Reactions on emotional faces were measured by a specially developed program. Psychophysiological testing was realized using NS-Psychotest complex, 2-channel ERPs were recorded according to oddball paradigm. In ERP we measured latencies of P1, N1, P2, N2 and P3 peaks and P2-N2 and N2-P3 peak-to-peak amplitudes. Statistical comparisons were made using the non-parametric Wilcoxon test. Results and discussion: Presurgical patients evaluated facial expressions with extreme scores, differing both from control group and post-surgical measures. High emotional stress leads to inadequate evaluation of human facial expression. Surprisingly, presurgical patients had relatively low scores on state anxiety questionnaire. It could evidence that they use repressive coping style to overcome presurgical stress. Reaction times in sensorimotor tests increased and amplitude of target N2 ERP peak decreased after surgery, pointing on impairments of selective attention. Conclusions: (1) Level of emotional stress could be assessed using measures of facial expression evaluation. (2) Verbal tests on anxiety level did not provide correct absolute measure of a patients' state, but could be used for obtaining relative dynamics of this parameter. (3) The consequences of GBI lead to a reduction of selective attention level, which could be measured by the speed of somatosensory reactions and changes in target N2 ERP peak amplitude.

BEHAVIORAL CHANGES AND ALTERATION OF SKIN CONDUCTANCE IN RATS AFTER EXPOSURE TO CHRONIC SOCIAL STRESS

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Introduction: Social stress is widely distributed through the population and plays a crucial role in numerous illnesses. Thus, it is important to investigate stress-induced and stress-related alterations in an organism, including behavioral changes. On the other hand, numerous experiments show the necessity of finding effective indicators of stressed state of the organism. Indicators such as skin electrodermal activity can be used to detect conditions of sympathetic division of vegetative nervous system. The aim of this study was to investigate stress-induced behavior of rats and to use parameters of electrodermal activity as an indicator of the condition of an organism. Methods: The behavioral procedure of social defeat consisted of five daily conditioning sessions that involved the same pairs of residents and intruders. The 45 min conditioning sessions started at 10:00 A.M. They were divided into two consecutive periods.

During period I (30 min), intruders were placed singly inside the resident home cage, but were separated from them by the protective grate that allowed unrestricted visual, auditory, and olfactory contacts with the resident, but precluded close physical contact. During period II (15 min), the protective grate was removed with the resident present, allowing physical confrontation with the intruder. After the fifth conditioning session (i.e., on the sixth day), intruders and control rats were tested in the Elevated plus maze (EPM). On the second and third days after last stress exposure rats were tested in Open field test and Suok test, accordingly, to investigate the stress-induced behavior. After all the behavioral testing was done, the electrodermal activities of rat's palm were measured. On the same day the skin potentials were measured, the weights of rat's adrenal gland were evaluated. Results and discussion: Decreased locomotor and exploratory activity was shown in the Open field test and Suok test in stressed group. However, behavioral activity in control group of rats did not show such alterations. In the EMP, the stressed group of rats spent significantly less time in open arms compared with non- stressed rats. This data suggest that 5-days chronic stress exposure results in more stress-related behavioral patterns. The adrenal gland weight was more, on average, in stressed rats (20%) compared to control animals. They also registered significantly lower skin potential response frequency compared to control rats. In our experiments, we demonstrated that lower SPRF correlates with a lower level of locomotor activity in Suok test, indicating a higher level of anxiety. Conclusion: Our data suggest that chronic social stress results in a higher level of noophobic behavior and behavioral alterations, such as elevated numbers of escapable behavioral acts. On the other hand, in our experiment we showed that measuring electrodermal activity can be a good indicator of stress.

NEUROPEPTIDE VASOPRESSIN HAS EFFECTIVE INFLUENCE ON POST-STROKE DEPRESSION

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Introduction: Depressed mood is one of the common psychiatric consequences after a stroke. The prevalence of depression is 20-60% among patients with cerebrovascular problems. This makes the search for new ways of treatment for post-stroke depression an important goal. Previous investigations revealed that vasopressin improves memory (Wide et al., 1993), speech and motor functions in patients with stroke (Belokoskova et al., 2002). The aim of this work was to investigate the influence of vasopressin on clinical depression after stroke. Methods: The study was performed in 48 patients with stroke and post-stroke depression, >1 year after the onset of the brain lesion at the time of research. Neurological diagnoses were made using the Stroke Date Bank criteria, which are based on both computed tomographic scan and clinical examinations. Psychiatric diagnoses were based on DSM-IV and ICD-10. The initial interview included two standardized measures of depression: the Hamilton Depression and the Zung Self-Rating Depression Scales. Cognitive impairments were assessed using the Mini-Mental State Examination. Statistical analysis was performed using means and standard deviations, analysis of variance, and Student's t-test. 17 cases of organic mood disorders were revealed. Minor depression was found in all cases. There were no significant cognitive and aphasia impairments in the group. 12 patients with affective disorders have been treated with sub-endocrine doses of 1-desamino-8-D-arginin-vasopressin, adiuretin-sd, (DDAVP) daily by intranasal application for 3 weeks. Results: The comparison between the onset and completion of therapy revealed that patients with depression significantly improved their scores on all two scales. DDAVP positively influenced mood of patients. After the course of treatment, the absence of feeling blame, suicidal thoughts and enhanced self-estimation was noted, along with improved sleep. Ideatory and motor inhibition, feelings of helplessness and asthenic symptoms were all significantly reduced. There were no significant shifts in scores in the 5 patient placebo control group. The

medication was well-tolerated and without side effects. Conclusions: Our data suggest that vasopressin has psychotropic properties, showing thymoanaleptic, anxiolytic and activating effects in patients with depressed mood. The results of this preliminary study demonstrate the potential efficacy of a selective agonist of vasopressin V2 receptors, DDAVP, in therapy of post-stroke depression.

S 6. CLINICAL ISSUES IN STRESS RESEARCH, PART II

Chairs: Nelli Tolmacha (Latvia), Juris Porozovs (Latvia), Viktor Klimenko (Russia)

FEEDBACK SELF-REGULATION TO COPE WITH STRESS OF SPEECH ACTIVITY

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Psychoemotional stress, fear, anxiety, physiological outgoings of organism, heritable factors as well as congenital abnormalities negatively influence human speech breathing, speech, and speech behavior. This causes much suffering for children, and their speech pathology grows each year, both in Russia and abroad. Among adults there is a considerable risk group of persons whose occupation requires speech and vocal skills: singers, actors, radio and TV announcers, lecturers, teachers, and tutors. Vocal and speech pathology negatively influences human psychosomatic and physiological functions, interpersonal communication, the effectiveness of studies, professional activities, and, eventually, the level of social adaptation. Speech breathing, differing in the parameters and mechanisms of regulation from usual breathing (deeper and more rare, with a short inspiration and a lengthened expiration, depending on the speech material pronounced, subject to voluntary control, etc.), is known to be the physiological and energetic basis of speech. An important role in the formation of the speech breathing pattern is played by effective diaphragmatic breathing, which, along with providing the gas exchange required for the body, is a basis for the activity of the speech-forming apparatus. It promotes the development, coordination, and normal activity of the speech functions, is used for avoiding excessive psychoemotional and muscular tension and hypo- or hyperventilation, and maintains human health on the whole. However, the mechanisms of speech breathing have not been studied in sufficient detail yet, and the works on their study in health and in pathology are few. Most of these works do not take into account objective physiological parameters of the intersystem cardiorespiratory interactions, such as respiratory sinus arrhythmia (RSA), i.e., changes in the heart rate connected with the phases of the respiratory cycle (an increase in inspiration and a decrease in expiration). To solve the problems of speech breathing and speech, we developed a new methodology for the study of the parameters of these functions, as well as for their correction and optimization, using adaptive self-regulation (ASR) for an objective parameter of intra- and intersystem integration of the cardiovascular and respiratory systems of the body, RSA (ASR-RSA). The optimization and correction of speech breathing and speech using ASR-RSA were performed gradually (from simpler to more complex tasks). At first, subjects were taught a new stable stereotype of diaphragmatic breathing using RSA; after that, they worked up a lengthened, uniform, smooth expiration on its basis using RSA again, subsequently developing a new dynamic stereotype of speech breathing at speech loads differing in complexity. As a result of speech breathing and speech in apparently healthy subjects and persons with disordered speech breathing and speech (more than 500 subjects of 8 - 65 years) it was revealed, that speech breathing disorders in the process of reading prose aloud were accompanied by a number of characteristic signs: the predominance of upper-chest (often shallow) breathing over the diaphragmatic type, a shorter respiratory cycle (and, especially, a shortened expiration), sympathicotonia, high energy requirements of the cardiorespiratory and speech-forming systems, and changes in the biorhythm structure of cardiac contractions unsynchronized with

the respiratory phases (the absence or minimization of RSA). This was especially distinct in individuals with a high level of neurotization and anxiety and with panic states, social phobias, and marked autonomic and neuroendocrine dysfunction, under speech load. It was found that ASR of speech breathing with an RSA-based external feedback facilitates restoration of disrupted mechanisms of self-regulation of speech breathing and speech, broadening of the range of interactions between the cardiovascular and respiratory systems, and gradual (from simple to more complex) formation of a new dynamic stereotype of diaphragmatic breathing, speech, and speech behavior. The consistency of the new habit of breathing was expressed in its stability during the session and from lesson to lesson, its reproducibility by the subjects under subjective self-control, and its successful application to counteracting autonomic dysfunction, emotional stress, and muscular tension. In all the groups studied, the hart rate significantly decreased by twofold on average compared to the first diagnostic examination, while RSA increased by a factor of at least 1.5.Thus, the use new habit, based on RSA, an objective physiological criterion of intersystem integration, is effective and justifiable for the study, diagnosis, and optimization, correction of speech breathing, speech, and speech behavior and for increase of adaptive ability as well as socialization.

INFLUENCES OF SEASONAL MOOD VARIATION ON POSTPARTUM DEPRESSION

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Objective: We compared the social demography and clinical characteristics between a group of women with postpartum depression (PPD) and postpartum control (non-depressed) group. Also we aimed to find the factors related to the seasonality to get data for pertinent prevention. Methods: We categorized 50 postpartum depressed women and 67 postpartum control women by DSM-IV criteria for PPD. Applying the Seasonal Pattern Assessment Questionnaire (SPAQ) and the Korean version of the Edinburgh Postnatal Depression Scale to each group, we identified significant statistical differences in social demographic and clinical characteristic factors. Results: We identified no significant differences in factors such as age, body weight, and level of education between postpartum depressed group and postpartum control group. When we compared clinical characteristic factors in SPAQ, there were significant differences in seasonal mood change ($p=0.001$), seasonal appetite change ($p<0.001$), seasonal energy change ($p<0.001$), global seasonality score ($p<0.001$), and seasonal affective disorder ($p=0.028$). But, no significant differences were found in seasonal sleep length change, seasonal social activity change, or seasonal weight change between postpartum depressed and normal women group. Using multiple logistic regression analysis after controlling for age, weight, and educational level, Seasonal mood change ($p=0.002$), seasonal appetite change ($p=0.001$), seasonal energy change ($p=0.001$), and existence of past history of seasonal affective disorder ($p=0.038$) were identified as significant risk factors for the postpartum depression. However, seasonal sleep length change, seasonal social activity change, and seasonal weight change were not identified as significant risk factors. Conclusion: We identified the global seasonality score, seasonal mood, appetite and energy change as risk factors for postpartum depression, and there is especially a risk for those with a past history of seasonal affective disorder. So we must be cautious in caring for the women with these factors.

THE ASSOCIATION GENE POLYMORPHISM OF RENIN ANGIOTENSIN SYSTEM (RAS) AND BEHAVIOR

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Introduction: The brain RAS has been found to be involved in the modulation of cardiovascular and fluid-electrolyte homeostasis. The RAS has additionally been implicated in other brain-

specific functions, such as memory, cognition and stress. The physiologically active octapeptide angiotensin II in the brain, mediated by angiotensin receptor type 1 (AT1) and type 2 (AT2), involves modulations of neuronal activity. It is well-known that neuronal AT1 receptors mediate the stimulatory actions of Ang II on blood pressure, water and salt intake, and secretion of vasopressin, but the function of AT2 receptors remains controversial. There are a few studies about influence of AT2 receptor on personality. Methods: In the current investigation, 160 healthy persons (male=78; female=82) participated. Their mean age was 19±2 years. The individual's level of aggression was assessed with Buss-Durkee Hostility Inventory (BDHI). Personality traits were studied with 16 factories R. Kettell scale, Eysenck Personality Inventory, Five-Factor Nonverbal Personality Questionnaire. Venous blood was collected from each subject, and genomic DNA was isolated. There was determination of gene polymorphism C3123A of AT2 receptor. Gene using the polymerase chain reaction (PCR). The results of PCR were documented with gel electrophoresis. Statistical calculations were performed using the program "STATISTICA" for Windows (StatSoft Inc., USA). Results and discussion: We found an association between AT2 receptor gene polymorphism and any type of aggression: assault (physical aggression) (p=0.04), verbal aggression (p=0.05), and negativism (p=0.03). Interestingly, heterozygotes have a lower level of aggression than homozygotes. They are not so impulsive as homozygotes. It is very intriguing that heterozygote are more anxious (p=0.03; p=0.02) and have a higher level of emotional labiality (p=0.05, p=0.01). The cause of this effect is that some RAS components can affect neurotransmitters (norepinephrine, dopamine, serotonin), which influence behavioral characteristics. Conclusion: In our investigation we studied the relationship between gene polymorphisms of AT2 receptor and personality characteristics that can indicate the influence of renin angiotensin system components on neurotransmitter signaling.

ASSOCIATION ANALISIS OF MTHFR AND HTR1A GENES WITH SUICIDAL BEHAVIOR IN TWO DIFFERENT POPULATIONS OF BASHKORTOSTAN (RUSSIA)

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The basis of suicidal behavior (SB) is complex and multifactorial. Numerous risk factors have been identified. Epidemiological genetics studies (family studies, twin studies, adoption studies) suggest that there is a genetic basis to SB and that this genetic basis is specific and independent from the genetic factors implicated in the predisposition to psychiatric disorders associated with SB (bipolar disorder, schizophrenia, alcoholism). It has been reported that a functional single gene polymorphism 677C>T (rs1801133) of methylenetetrahydrofolate reductase gene (MTHFR) is involved in pathogenesis of depression, and also of schizophrenia and bipolar disorder. 1019C>G polymorphism of HTR1A gene was associated with a number of psychiatric disorders including major depression and anxiety-related traits and also with antidepressant response. The aim of our study was to examine the association of 677C>T polymorphism of MTHFR gene and 1019G>C polymorphism of HTR1A gene and suicidal behavior in two different ethnic groups. We genotyped DNA samples of 312 cases (Russians- 150, Tatar-120) who had suicide attempts and 434 healthy volunteers (Russians- 169, Tatar - 248) from Bashkortostan (Russia) using PCR-RFLP technique. The distribution of allele and genotype frequencies was in accordance with the Hardy-Weinberg equilibrium. The statistical analysis was carried out with accordance to ethnic origin. We found no significant differences in allele and genotype frequencies of MTHFR 677C>T polymorphism between suicidal and control groups in Russian population. However, there is a significant association of MTHFR*T allele (X2 = 16,48; p<0,001; df = 1; OR = 2,13; 95%CI 1,47-3,08) and MTHFR*C/*T genotype (X 2 = 21,14; p <0,001; df = 1; OR = 2.95; 95%CI 1.85-4.737) and suicidal behavior in Tatar population. Moreover MTHFR*C allele ($\chi 2$ = 16,48; p<0,001; df = 1; OR = 0,47; 95%CI 0,33-0,68) and MTHFR*C/*C genotype ($\chi 2$ = 21,95; p<0,001; df = 1; OR = 0,33; 95%CI 0,21-0,53)

are protective markers of suicidal behavior in Tatar population. A strong association was found for the allele HTR1A*C (X2=8,5; p=0,004; OR=1,78; 95%CI=1,21–2,64) and genotype HTR1A*C/*C (X2 =5,22; p=0,02; OR=2,04; 95%CI=1,101–3,79) of HTR1A 1019G>C polymorphism and suicide attempts in Russians. Controversially, both the genotype HTR1A*G/*G (X2=8,89; p=0,003; OR=0,28; 95%CI=0,12-0,67) and allele HTR1A*G (OR=0,56; 95%CI=0,37–0,83) of the HTR1A 1019G>C polymorphism are protective markers of suicidal behavior in Tatar population. The results suggest contribution of investigated polymorphisms of HTR1A and MTHFR genes in predisposition to suicidal behavior; and it is shown that the effect is influenced by ethnicity. The work was supported by RSCI grant 06-06-00163 and Russian Science Support Foundation to DG and AK.

THE RELATIONSHIP BETWEEN EXECUTIVE ATTENTION AND POLYMORPHISM 2756C/T MGLUR8 IN MALE

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The glutamatergic signaling pathway represents a candidate susceptibility system involved in the mechanism of forming attention and working capacity. One of the attractive candidates for studying the molecular physiology of attention is the glutamatergic receptor subtype 8 (mGluR8). Expression of mGluR8 was observed in the olfactory system, the neocortex, and the limbic cortex including the hippocampus and the amygdala. Using an electron microscope, mGluR8 was largely observed on the axon terminals. Especially in several regions of the hippocampus, it was found in the active zone of both asymmetrical and symmetrical synapses where mGluR8 may regulate glutamate release as an autoreceptor or GABA release heterosynaptically. Influence of mGluR8 polymorphism located 29 bp after the termination codon (2756C/T) on executive attention was conducted on volunteers. 108 students of Moscow state university (mean age 20±2, females = 61, males = 47) were tested by the Schulte tables. Genetic analysis consisted of follow steps: extracting DNA from whole blood, PCR analysis, restriction of the products PCR with BstMAI and detection of the fragments using 3% agarose gel. Association between markers and executive attention was estimated with ANOVA. We found a significant association of mGluR8 polymorphism with executive attention only in males. Carriers of T allele (TT, CT) implemented the test faster than CC group (p=0.02). It is known that the hippocampus plays an important role in cognitive function in humans. Glutamate is major excitatory neurotransmitter in the hippocampus. The mGluR8 is located within the presynaptic grid of the glutamatergic synapse and thus may provide significant control of glutamatergic synaptic transmission. We showed that polymorphism 2756C/T mGluR8 affects executive attention only in males.

DOPAMINERGIC SYSTEM GENES (DAT1, DRD2, DRD4) AND THEIR RELATION TO PERSONALITY TRAITS IN HEALTHY INDIVIDUALS

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Introduction: Personality traits are highly inherited (30-40%) and, early in life, tendencies are manifested that have a constitutional basis. Since the psychobiological model of temperament (TCI) was proposed, molecular-genetic studies have focused on genes involved in neurotransmitter pathways. According to Cloninger's model, Novelty Seeking is influenced by the dopaminergic system. We aimed to define a single genotype effect of DAT1 MspI and 3'-VNTR, DRD2 TaqIA and DRD4 5'-VNTR polymorphisms on personality traits. Materials and Methods: The present study sample was comprised of 587 healthy individuals (mean age±SD, 19, 85±2.43 years) from Bashkortostan (Russia) and included Tatars (143 men and 234 women) and Russians (54 men and 156 women). Personality traits were assessed using the Russian version of psychological inventories EPI and TCI. Genotyping was performed using

PCR, PCR-RFLP technique. Analysis of variance (ANOVA) under SPSS 13.0 was carried out in order to investigate the single genotype effect of all polymorphic loci on personality traits. Results and discussion: The distributions of allele and genotype frequencies of all investigated markers were consistent with the Hardy-Weinberg equilibrium. Since population and gender differences in personality traits were proposed, stratification analysis was performed in 4 groups (Tatars male, Tatars female, Russians male, Russians female). One-way ANOVA showed that in the Russian female group DAT1 A-allele or 10/10-genotype carriers scored significantly higher on Novelty Seeking (P = 0,018; F = 5,737 and P = 0,048; F = 3,986 correspondingly) and DAT1 A-allele carriers had significantly higher scores on Reward dependence (P = 0,047; F = 4,011). While conducting ANOVA in the Tatars male group, association of DRD2 A1-allele and higher Reward Dependence (P = 0,033; F = 4,622), DRD4 S-allele and higher Novelty Seeking (P = 0,027; F = 5,024) was detected. Reported results are in accordance with those of Van Gestel et al. (2002) indicating that female carriers of lower expressing allele (9-allele) of DAT1 VNTR polymorphism had lower Novelty Seeking. Although no studies involved DAT1 MspI polymorphism and personality traits, Ling et al. (2004) reported an association between DAT1 A-allele and smoking (characterized by higher Novelty Seeking). Rogers et al. (2004) demonstrated the association of DRD4 S/S-genotype (resulting in high expression of the gene) and higher Novelty Seeking, which is at odds with ours. Conclusion: Our findings suggest that the variance in sociability-related traits (such as Novelty Seeking and Reward Dependence) is related to specific genotypes of DAT1, DRD2, DRD4 gene polymorphisms. Moreover, these associations are gender- and ethnicity specific. This work was supported by RSCI grant 06-06-00163a and Russian Science Support Foundation to AVK and DAG.

FEATURES OF ADAPTIVE RESPONSE TO FIRST INTERACTION WITH DOLPHINS IN HEALTHY CHILDREN 6-7-YEAR OLD

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Introduction: Tactile interaction (TI) with dolphins in and outside the water environment is included into a number of modern animal-assisted therapy methods for the correction of emotional and cognitive abnormalities in children and adults. Methods: Results of the investigation of adaptive response to first TI with dolphins in 42 healthy children of 6-7 years old are presented here. This research used integrative psychophysiologic approach including the estimation of: a) a level of active wakefulness (registered in vertex-tenar leads, using one of the type of superslow biopotentials – steady potential, omega-potential, OP, in millivolt range, from 0 up to 0,05 Hz); b) autonomic tone (Kerdo's autonomic index) and central hemodinamics (systolic blood pressure and cardiac outpet). The resistance to endogenous transitory hypoxia assessed by the duration of the voluntary threshold apnea is an integral index of oxygen – depended systems for energy supply. An emotional condition and motivation for effective activity was estimated on parameters of Lusher's test. Conclusion: Thus, the results of this research has shown, for the first time, an interrelation between the type of adaptive response at first TI with dolphins and equilibration (first group) or disintegration (second, third groups) in superslow regulation systems in first-graders of comprehensive schools. The study was supported by RHSF Grant (project № 06-06-00051a) and Grant SS №6359.2006.4

INTERACTION BETWEEN BEHAVIORAL PARAMETERS AND SKIN POTENTIALS IN ADULT RATS

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Introduction: The aim of this study was to discover the relationship between the level of skin potentials and individual parameters of behavioral activity of rats (intensity of locomotor and

exploratory activity, processes of arousal and inhibition, emotionality). Our investigation can help to describe functional states of organisms and, the in the future, in human beings by analyzing parameters of electrodermal activity of the skin. Methods: This investigation was done on white male rats. The level of behavioral activity was measured in such behavioral tests as the Open field test, Suok test, Elevated plus maze (EPM). Also, electrodermal activity was measured from the left hind leg of the rat and indifferent electrodes at the bottom of the tail. Skin potential level (SPL), skin potential response frequency (SPRF), and skin potential response amplitude (SPRA) was registered in this method. In the behavioral tests, we registered locomotor activity, exploratory activity (horizontal and vertical), grooming (number and frequency), and time spent in open and closed arms in EPM. All behavioral tests were 5 min in duration and skin potentials were measured during a 10 min period. Results and discussion: A positive correlation was shown between behavioral activity and electrodermal activity of rats. The level of SPRF correlates with parameters of values of grooming (emotional activity and anxiety). SPL and SPRA correlates with the number of crossed segments in the Suok test (locomotor activity) and also the value of SPRA concerns the time spent in open arms of the EPM (indicating the level of anxiety). Because electrical potentials admittedly depend on sudoriferous gland activity and the level of sympathetic nervous system activation, electrodermal activity may represent functional activity of the organism on the system level. Various emotional states may cause the different physiological answers that affect potential values. That is why fluctuations of skin potentials may suggest a different level of activation in rats (may be used as a stress test) and correlate with individual behavioral parameters such as level of anxiety and emotional activity. Conclusion: Thus, the method of measuring electrodermal activity gives us the possibility to appreciate the functional state of organism on the more system-defined level, this is a methodological approach that gives allows us to take more system results and decrease the variables. Electrodermal potentials are used in clinical research for diagnosing the state of the patient. In our investigation, we showed that potentials may be used to evaluate the individual differences in behavioral activity and changes in its level after different influences.

S 7. RECENT ADVANCES IN TRANSLATIONAL RESEARCH

Chairs: Roza Czabak-Garbacz (Poland), Allan Kalueff (USA)

INHIBITION OF CARDIOPULMONARY CARDIAC REFLEX RESPONSES BY DIRECT STIMULATION OF PERIAQUEDUCTAL GRAY AND CUNEIFORMIS NUCLEUS IN RATS

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Dorsal periaqueductal gray (dPAG) stimulation in anaesthetized rats elicits "arousal-like" and cardiovascular events characteristic of stressful situations (i.e. defence reaction). In particular, we showed previously that dPAG stimulation inhibits the cardiac response (bradycardia) of a reflex critically involved in cardiovascular homeostasis, the baroreflex. Underlying mechanisms involve cascade of events including GABAA and 5-HT3 receptors activation in the nucleus tractus solitarius (NTS), the latter receptors being activated by serotonin released from afferences originating from the B3 region (which includes the raphe magnus and paragigantocellularis nuclei). Whether dPAG stimulation also inhibits, through B3 activation, the cardiac component of the Bezold-Jarisch reflex, another vital cardiovascular reflex, has been the first question addressed in our studies. Because neuro-anatomical studies showed that cuneiformis nucleus sends direct projections to dPAG, the second aim of our studies was to asses whether this nucleus could be implicated in the B3-mediated inhibition of cardiac reflex responses during the defence reaction. First, we analyzed, in urethane-anaesthetized rats, the effect of electrical (50 Hz, 1 ms pulse duration, 70 µA) and chemical (D,L-homocysteic acid, 5

mM) stimulation of dPAG on the Bezold-Jarisch reflex bradycardia evoked by phenylbiguanide (20 µg/kg, i.v.), before and after microinjections into the NTS of 5-HT3- and GABAA -receptor antagonists, granisetron (175 pmol) and bicuculline (5 pmol), respectively. In addition, similar experiments were conducted after B3 chemical blockade by muscimol. Second, we analyzed the effects of electrical and chemical stimulation of the cuneiformis nucleus on the cardiac responses of Bezold-Jarisch reflex and baroreflex (evoked by phenylephrine, 20 µg/kg, i.v.). The Bezold-Jarisch reflex bradycardia was strongly inhibited (- 80%) during dPAG electrical stimulation. Intra-NTS microinjections of granisétron and bicuculline prevented the inhibitory effect of dPAG stimulation as well as Muscimol microinjection into B3. On the other hand, electrical and chemical stimulation of the cuneiformis nucleus also produced the same "arousal-like" and cardiovascular (i.e. inhibition of the baroreflex [75 %] and Bezold-Jarisch reflex [80 %] bradycardia) responses as those occurring during the defense reaction. Altogether, these results suggest that activation of the cuneiformis nucleus may produce dPAG neuroexcitation, which causes (i) B3 activation at the origin of 5-HT release within the NTS, (ii) local 5-HT3 receptor stimulation and (iii) consequent inhibition, via local GABAA receptor activation, of cardiac reflex bradycardia.

INFLUENCE OF THE C1473G POLYMORPHISM IN TRYPTOPHAN HYDROXYLASE-2 GENE ON THE ENZYME ACTIVITY, INTERMALE AGGRESSION AND IMMOBILITY IN THE FORCED SWIM TEST IN MICE

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Introduction: The neuromediator serotonin is implicated in the regulation of various physiological functions and types of normal and pathological behavior. Tryptophan hydroxylase 2 (TPH2) is the key enzyme of brain serotonin synthesis. The C1473G polymorphism in TPH2 gene leads to the replacement of Pro447 by Arg447 in the enzyme molecule and a decrease in serotonin synthesis rate in cell cultures. Earlier we demonstrated an association between the C1473G polymorphism and inter-male aggression in inbred mouse strains. The aim of the present study was to investigate the influence of the C1473G polymorphism on brain TPH2 activity, intermale aggression and immobility in the forced swim test. Methods: Experiments were carried out on the inbred strains C57BL/6 (B6, C/C genotype) and CC57BR/Mv (BR, G/G genotype), their F1 hybrids (B6 x BR) and F2 intercrosses (F1 x F1), as well as on lines B6-1473C (C/C genotype) and B6-1473G (G/G genotype) bearing a relatively equalized genome close to that of the B6 strain. These lines were obtained after three successive back-crossings, starting from F1 hybrids, onto the parental strain B6. Genotyping for the C1473G polymorphism was performed with the help of allele-specific PCR. TPH2 activity was assessed fluorometrically in the midbrain extracts. Intermale aggression was measured in a resident-intruder test and characterized by number of attacks. The forced swim test lasted for 3 min after a 40 sec adaptation period. The difference between groups was analyzed by one-way ANOVA. Results and discussion: BR mice had lower TPH2 activity, intensity of intermale aggression and forced swim immobility as compared to B6 mice. TPH2 activity was significantly lower in F2 mice with G/G genotype as compared to C/C genotype. Nevertheless, the F2 intercrosses did not differ in the studied behavioral patterns, which was likely to result from the complex nature of the traits and a highly uncontrolled variability of the F2 genome. At the same time, there was a significant difference between the B6-1473C and B6-1473G lines in aggression intensity (lower in B6-1473G) and immobility in the forced swim (lower in B6-1473G), but not in the open-field locomotor activity. Conclusion: The results obtained indicate that the C1473G polymorphism is an essential factor determining the hereditary variability of TPH2 activity in mouse brain. Moreover, this polymorphism is linked to intensity of intermale aggression and immobility in the forced swim test in mice.

ANALYSIS OF EXPRESSION AND DISTRIBUTION OF GLUCOCORTICOID RECEPTORS AND AVP NEURONS IN THE HYPOTHALAMIC PARAVENTRICULAR NUCLEUS

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Introduction: Investigation of the expression and distribution of GR (glucocorticoid receptor), AVP neurons and the coexpression of both in the anterior (PAAP) and medial (PAMP) parvocellular subdivisions of PVN after manipulations of HPA axis in male rats with immunofluorescence technique. Methods: Male Wistar rats weighing 250 10G were housed individually, acclimated for 5 days and divided into 6 groups: normal (groups I/II), sham adrenalectomized (groups III/V), andrenalectomized bilaterly (groups IV/VI). On the sixth day at 19 H the animal received intraperitoneal injection of NACL-0,15 M (groups I, III, IV) or dexamethasone – 2 mg/100 g (groups II, IV, VI). After 12 hours, these animals were anesthetized and the brains were removed after perfusion, postfixed, quickly frozen and cut into frontal sections and the blood was collected for corticosterone measurements. The sections were stored at -70 C before imimunohistochemistry. Results and discussion: The expression of AVP neurons in the PAAP increased in the adrenalectomized rats with dexamethasone. The expression of AVP neurons increased in the PAAP but decreased in the PAMP fromadrenalectomized rats treated with dexamethasone. On the other hand, the expression of GR increased in both PVN regions from these animals but it was higher in the PAMP than the PAAP. The coexpression of AVP and GR was found only in the PAMP. Conclusion: These findings suggest that glucocorticoids can have a direct action onto AVP neurons in the PAMP. Finally, the coexpression of AVP and GR in this region indicates a possible role of those neurons in the control of the HPA axis.

INFLUENCE OF THERMAL PRECONDITIONING ON ANTICONVULSIVE EFFECTS OF VALPROATE AND MEMANTINE

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Epilepsy is one of the common chronic diseases of human brain. Among the most urgent issues, there are side-effects of modern drugs and a resistance of one third patients to the medication. It indicates the importance of analysis of the molecular mechanisms of epilepsy and search for new approaches to its treatment. Data on neuroprotective functions of chaperones family Heat Shock Protein 70 kDa (HSP70) and their strong therapeutic potential were the base to validate our investigation [review: Pastukhov, Ekimova, 2005; Ekimova et al, 2008]. The purpose of our investigation is to find out whether thermal preconditioning (TP), inducing massive HSP70 expression in the brain, is capable to considerably enhance anticonvulsive effect of modern drugs valproate and memantine. The investigation was conducted in the model of pentylentetrazole (80 mg/kg)-induced seizures in Wistar rats, which is close to several forms of human epilepsy by the mechanism of pathogenesis. TP (the rise of rectal temperature at up to 40.5-410C) was performed 24 h before initiation of seizure convulsion, and convulex (valproic acid derivative) and memantine were intraperitoneally injected 15 min before the convulsion. Convulex at a dose of 300 mg/kg was shown to increase 4 times more the latent period of seizure, eliminated clonic and tonic convulsions and decreased the severity of seizure. Convulex at a dose of 150 mg/kg and TP had less pronounced anticonvulsive effect. A combined treatment with TP and convulex (150 mg/kg) resulted in a complete absence of convulsions in 50 % rats as well as in a decrease of clonic convulsions and the severity of seizure in other animals. Blockade of HSP70 expression by quercetin attenuated the effects of TP. Single memantine decreased tonic convulsions, the severity of seizure and animal mortality, but increased the duration of clonic convulsions by almost 2 fold. Memantine combined with TP in 75 % rats induced complete elimination of all components of epileptic seizure and a decrease

of the severity. TP was shown to decrease and eliminate neurological disorders initiated by convulsive seizure, valproate and memantine. Hence, TP, inducing an increase in the content of brain HSP70, is capable to enhance the efficacy of antiepileptic drugs. Our results indicate the participation of molecular chaperones HSP70 in epilepsy pathogenesis.

NOOTROPIC AND PEPTIDE DRUGS POSSESS METEOADAPTOGENIC PROPERTIES IN HEALTHY VOLUNTEERS

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The meteoadaptogenic properties of pharmacological drugs of both peptide (cortexin, noopept, dilept) and nonpeptide (vinpotropil) structures were investigated in climate termobarocomplex Tabaj (Japan) in healthy volunteers aged 20-22. All of the drugs studied possessed meteoadaptogenic action. Its power was dependent on the environment conditions to be used (overcooling, overheating, hypobaric hypoxia). Vinpotropil, the optimizing physiological component of the functional state, could be recommended as a meteoadaptogen for both the cold and the hot climate as well as for hypobaric hypoxia, where it elevated the psychological component of the functional state. Cortexin was qualified as an adaptogen and actoprotector only for hypobaric hypoxia conditions (uplands). Noopept, which affected the psychological component of the functional state positively, could be used for rapid adaptation to the cold and hot climate. In the hot climate, noopept enhanced physical efficiency. Dilept elevated the psychological component of the functional state preferably and could be considered as a psychomotor enhancer and adaptogen. Therefore, all the drugs studied (vinpotropil, cortexin, noopept and dilept) can be recommended as the drugs of activation, support and recovery of physical and psychological efficiency in rapidly changing environment conditions.

HYBRIDIZING ANIMAL MODELS IN NEUROBEHAVIORAL RESEARCH

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Traditional use of single-domain test batteries for neurophenotyping research is associated with a number of methodological challenges that could be improved using innovative testing techniques. Using “hybrid” protocols that assess multiple domains in parallel may be an effective method of combining experimental paradigms to address these issues by maximizing the number of tested phenotypes per experimental manipulation. Multi-domain models could be created by including a combination of several traditional single-domain models into new research contexts to target additional domains and their interplay. There are numerous benefits to this approach. First, hybrid models require fewer stress exposures than a combination of single-domain models by assessing multiple domains in the same test, saving time and laboratory resources. Using this method will also diminish some undesirable conditioning or stress effects on the animals, which will promote more valid data and limit chances for experimental confounds. Also, when testing distinct domains such as anxiety and depression, this method will allow researchers to model and investigate clinically relevant aspects like comorbidity that single-domain models cannot dissect. The hybridizing approach also enhances the ability to observe a larger spectrum of behavioral phenomena, a fact that aids in the investigation of complex neurophenotypes. This is particularly important when screening pharmaceutical drug compounds or when testing new transgenic or mutant animals. Another very important advantage of using hybrid method is that it can model the “continuum” nature of brain pathogenesis (e.g. transmission from anxiety to depression), which will become increasingly useful considering the new developments in clinical psychiatry. In conclusion, the hybridization strategy offers new developments in behavioral analyses that are lacking in the standard single-domain tests. As such, they enable innovative modeling of neuropsychiatric disorders by more thorough and broader investigation of complex phenotypical characteristics

and may represent a solution for today's neurophenotyping research. This research was supported in part by the Intramural Program of the NIH, NIMH and by a NARSAD YI Award.

ANTIDEPRESSANT LIKE EFFECT OF BIEBERSTEINIA MULTIFIDA DC. ROOT EXTRACT IN MICE

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Introduction: Depression is a common psychological disorder and recent data confirm the high prevalence of the disease in the world. So far, antidepressant effects of many plants have been evaluated and some are accepted in the clinic. Methods: In the present research, the antidepressant effect of Biebersteinia multifida DC root extract was studied and compared with Fluoxetine in mice, using forced swim, tail suspension and open-field tests. The anti-inflammatory and analgesic activity of the root extract has been studied before. Results and Discussion: Oral administration (Gavage) of the root extract (4, 7, 10 mg/kg) after 1, 7 and 14 days, like Fluoxetine, significantly reduced the immobility time in tail suspension test. Also the significant reduction in immobility was observed by 4mg/kg of the root extract and Fluoxetine, after 1 and 7 days as compared with the control group. Conclusion: Therefore, it is possible that the antidepressant effect of root extract is induced by the variation of monoamine (especially serotonin) release in the central nervous system. However, further studies are needed to highlight the exact antidepressant mechanisms of Biebersteinia multifida root extract.

S 8. COGNITIONS AND EMOTIONS

Chairs: Yuriy Pastuhov (Russia), Irina Ekimova (Russia)

THREE WEEKS OF SOCIAL STRESS LEADS TO LONG-LASTING DEFICITS IN PRE-PULSE INHIBITION OF STARTLE RESPONSE IN INDIVIDUALLY, BUT NOT IN GROUP HOUSED MICE

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Introduction: Psychotrauma (stressful life events) is an environmental co-factor that is believed to play an important role in the development of many psychiatric disorders, e.g. schizophrenia and mood disorders. Social support (the possibility for helpful social interactions), on the other hand, is supposed to be a protective factor that contributes to the prevention of these diseases. The present study examined the late effects of chronic social stress exposure on pre-pulse inhibition (PPI) of startle response, a measure of sensorimotor gating abnormalities that are associated with several psychiatric and neurological disorders, including schizophrenia. We investigated group and individually housed mice in order to determine to which extend social support influences the effects of chronic social stress on pre-pulse inhibition. Methods: Young, 28 day old, group versus individually housed C57Bl6 mice were subjected daily to social defeat in a resident-intruder paradigm for 3 weeks. The pre-pulse inhibition test was performed 3 months after the stress exposure. Results: Only in the individually housed condition social defeat had a clear late effect on sensorimotor gating deficits. Three months after the stress exposure mice showed significantly reduced pre-pulse inhibition as compared to non-stressed control mice ($p<0.05$). However, in the group housed condition, stressed and control mice did not differ significantly. Discussion: These results demonstrate that chronic social stress occurring at very young age may cause impairment in basic information processing in adulthood. Most importantly, the results suggest that the deleterious effects of chronic social stress are counteracted by rewarding interactions within a familiar social group. This indicates

the importance of social support for preventing stress-induced information processing deficits in psychiatric diseases.

EARLY ONTOLOGY STRESS WITH CRF INVOLVMENT MODULATES BEHAVIORAL RESPONSES IN ADULT RATS

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Wistar rat pups in age groups of 4,10, and 17 days were injected intraperitoneally with corticotropin releasing hormone (CRH; 0.5, 1.0, 2.0 μg/rat respectively, single administration for each rat), activating stress system, or heat shock proteins 70 kDa (HSP-70; 5-10-20 μg/rat respectively), intracellular shaperons, possessing antistress properties. In adult rats of 90-100 days old, the emotional and motor behavior in 5 tests (open field, elevated plus-maze, intruder-resident, Porsolt's test on depression and rotation test) were assessed. The activation of stress or antistress systems with CRH or HSP-70 respectively changed the behavior of adult rats. These effects were different in males and in females and depended on animal gender: males were more sensitive in Porsolt's test on depression, elevated plus-maze test of anxiety and the rotation test. The open field and intruder-resident tests were less sensitive. Therefore, the basal sensitivity to CRH or HSP-70 was different in males and in females. These data were correlated with morphological findings of the limbic structures of the brain. In particular, CRH increased relief (volume) of neurons of substantia nigra and ventral tegmental area without changing its density, but HSP-70 produced mild degeneration of neurons, decreasing its density. It is suggested the data obtained is necessary to consider in the planning and realization of experimental investigations concerning the influence of pharmacological agents on behavior. Supported by RFBI grant #07-04-00549a.

APPLICATION OF BRAIN AND ABDOMINAL MRI IN MONITORING THE CONSEQUENCES OF DELAYED RECOGNITION OF WILSON'S DISEASE

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Introduction: Wilson's disease (WD) is a rare genetic disorder of copper metabolism initially presenting with neurologic, hepatic or psychiatric symptomatology. The purpose of this study was to detect the abnormalities in the brain parenchyma in WD, to evaluate the rate of morphologic abnormalities in patients with predominantly neurological clinical presentation and to estimate the possible significance of time latency from the initial symptoms to the introduction of chelating therapy. Methods: Brain MR examination was performed in 37 patients with WD, presenting psychiatric and neurologic (cerebellar, pseudoparkinsonian and dystonic) symptomatology, while control MR reexamination 3.5-7 years after initial scanning, associated with additional abdominal MRI, was performed in 14 of them. Results: The symmetric putaminal involvement was noted in all patients with dystonic and in a majority of patients with cerebellar and pseudoparkinsonian clinical presentation of WD. The second most frequently involved structure was the pons, affected in 54% of patients. Normal findings of abdominal MRI were seen in 80% of patients in whom the chelating treatment started within 18 months from the first symptoms, while significant splenomegaly was noted in 44% of patients in whom the correct diagnosis was established 24-60 months after initial neurologic/psychiatric symptoms. A markedly significant difference in complete brainstem lesions regression was evident between these two groups of patients on control MR examination 3.5-7 years after initial scanning. A statistically significant difference between these two groups of patients in partial/complete resolution of putaminal lesions was also present. Conclusion: Putamen and pons are the most

frequently involved structures in patients with neurological presentation of WD. The likelihood of resolution of these lesions appears to be significantly higher if appropriate treatment is initiated in the earlier course of the disease. Our results also suggest that portal hypertension and liver damage in patients with neurologic presentation of WD might be reversible or even do not develop if chelating treatment is initiated within 18 months of the disease onset.

BRAIN MECHANISMS OF BEHAVIORAL CONTROL IN SUBJECTS WITH DIFFERENT ANXIETY LEVELS: STOP-SIGNAL PARADIGM STUDY

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Introduction: Influence of anxiety level on EEG/MEG oscillatory activity in conditions of stop-signal paradigm (SSP) was studied in non-clinical subjects. Anxiety is usually defined as inclination of the subject to perceive the environment as dangerous and to develop corresponding emotional, physiological and behavioral reactions. Studies of anxiety allow relating this trait with behavioral inhibition and activation systems. Highly anxious people are simultaneously inclined to suppression of behavior directed on external stimuli and to increase of internal attentional control over consequences of behavior. It could be suggested, that the differences in brain activity between high- and mid-anxious subjects would be found in conditions, when they have to realize or stop motor activity. The experimental stop-signal paradigm is usually applied for exploration of processes associated with activation and inhibition of motor reactions. Here, SSP is used as experimental model for exploration of brain mechanisms underlying behavioral control in subjects with different anxiety level. Methods: 15 healthy right-handed subjects (26±3.0 years, 13 men) participated in the study. Anxiety levels were measured by Chinese version of Spielberger State Trait Anxiety Inventory. EEGs were recorded by 132-channel “Neuroscan” amplifier. MEGs were recorded by 157-channels Yokogawa Electric Corporation SQUID. Neuronal dynamics were analyzed using independent component analysis (ICA) and event-related spectral perturbations (ERSP). In the procedure, one of two pictures appeared on the monitor – a deer or a tank. Subjects should choose a weapon to strike a target and shoot (Go). In 30 from total of 130 trials, target presentation was followed by signal indicating that subject shouldn’t shoot (Stop). The same experiments were conducted independently in the EEG and MEG sessions. Results: Wide-band desynchronization (8-25 Hz) was found in Go condition before button-press. It was prolonged after pressing, but with decreasing frequency. Also, synchronization in 15-30 Hz band occurred in 200-800 ms after button-press. In stopping condition, synchronization in lower frequencies (4-8 Hz) was found during 0-500 ms after stop-signal onset. Significant desynchronization in 8-18 Hz was found in 400-600 ms after stop-signal. Significant differences between high- and mid-anxious subjects were found for both Go- and Stop conditions. In Go condition, highly-anxious subjects showed desynchronization in 13-37 Hz in 0-300 ms after button-press, whereas mid-anxious ones showed synchronization. In 0-600 ms after Stop-signal, desynchronization in 8-13 Hz was observed in highly-anxious subjects, whereas mid-anxious demonstrated synchronization or weak desynchronization. Conclusion: Trait anxiety is reflected in EEG/MEG-reactions, recorded in conditions of stop-signal paradigm. This finding supports connection of anxiety with systems of behavioral inhibition and behavioral activation. However, influence of anxiety level was not found in components of EEG/MEG-reactions, which are directly linked with motor response activation or inhibition. Instead, trait anxiety modulates attentional control on and subjective evaluation of motor task execution. This research was supported by grant NSC 96-2413-H-001-MY3 from the National Science Council (Taiwan).

MODIFYING THE EFFECT OF SEROTONIN TRANSPORTER GENE (5-HTTLPR) – BRAIN-DERIVED NEUROTROPHIC FACTOR GENE INTERACTIONS ON EMOTIONAL DISTRESS IN PARENTS OF PSYCHOTIC PATIENTS

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Introduction: Recently, an interaction between the 5-HTTLPR polymorphism and the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene was reported to moderate the development of depression in response to experiences of stress. Taking into account this finding, we assumed that 5-HTTLPR and Val66Met polymorphisms might contribute to distress in subjects experiencing the burden of having a mentally-ill family member. Methods: A sample included 235 psychiatrically-well parents of psychotic patients and 102 age-matched controls. The Minnesota Multiphasic Personality Inventory (MMPI) was administered to assess the response to stress. After being informed about the goals of the investigation, each subject gave a written consent for participation in the study. The study was approved by the Ethics Committee of Mental Health Research Center. All subjects were ethnic Russians. Results: There was a significant effect of the 5-HTTLPR x BDNF genes interaction on scores of Depression ($p=0.02$) and Psychasthenia ($p= 0.03$) in the group of parents, but not in the control group, with carriers of the Val/Val x SS genotype scoring higher as compared to other allelic combinations. Discussion: We revealed an effect of BDNF x 5-HTTLPR genotype interactions on D and Pt MMPI scales. Scale D reflects anxiety and depression symptoms and scale Pt taps obsessive-compulsive features, as well as abnormal fears, self-criticism, difficulties in concentration, and feelings of guilt. The interactions were seen in parents of psychotic patients but not in the controls. This finding is in accordance with our assumption that response to chronic stress related to the burden of having the affected child can be mediated by genetic factors. The association obtained in our report is in predicted direction, i.e. parents with the Val/Val x SS genotype combination have the highest score on MMPI scales D and Pt. Our study differs from the prior one in many ways including outcome measures, a nature of stressful factor and sample characteristics, which, taken together, may explain the opposite genotype results obtained in the study, i.e. that the highest distress was observed in carriers of the SS and the Val/Val genotypes. Of note, the results were in accordance with the assumption based on the previous reports on higher neurotic traits in subjects with the Val allele. It should be mentioned that our study has a limitation concerning the specifics of the group used for a G x E study. It is well known that relatives of schizophrenic patients can share some features predisposing to psychosis. Thus, this left the possibility that the results of our study would just reveal the association between genetic polymorphism and some intermediate phenotypes emerging in relatives. To minimize this possibility, we included in the study only psychiatrically-well parents of psychotic patients who had been examined by the psychiatrist. Mean scores for all MMPI scales in this group were within normal limits. The average MMPI profile of parents did not feature elevations on scales which were thought to be characteristic of high-risk individuals for psychosis, e.g. scales Pd and Sc. In our study, the genetic variant predicted elevations on scales D and Pt, i.e. the scales related to anxiety and depressive symptoms. A molecular-genetic variant likely plays a modifying role between objective and subjective burden and may be taken into account in elaboration of psychosocial programs aimed at helping informal caregivers to cope with the stressful situation. Conclusions: The results obtained revealed that 5-HTTLPR x BDNF genes interactions might moderate the level of anxiety and depression caused by stressful situation. This finding can be considered as additional evidence for the modifying role of genetic factors in individual responses to stressful life events.

THE INFLUENCE OF EMOTIONAL STRESS ON COGNITIVE PROCESSES IN PRIMATES

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Introduction: Emotional stress can affect the cognitive processes, thereby influencing an individual's adaptive social behavior. To study such cognitive processes, we used a model of conditioned spatio-temporal stereotype - eating behavior of primates in their natural hierarchy. Methods: Subjects were 5 adult and 2 baby Macaco Javansk primates. The hierarchical structure of the group included the leader (dominant male), 2 sub-dominant females (one with a baby, who inherited high rank) and subordinant animals (2 males and the baby of the second sub-dominant female). The formation of conditioned spatio-temporal stereotype was created through different stages. Stage I: forming stable conditioned spatio-temporal stereotype in the leader. Stage II: forming conditioned spatio-temporal stereotype in the first, and then the second sub-dominant female. Stage III: forming conditioned spatio-temporal stereotypes in the subordinant animals. The stable conditioned spatio-temporal stereotype of eating behavior included several steps: 1) realization of individual program of positive and negative conditioned reflex in the leader animal; 2) programming of the first sub-dominant animal through changing the meaning of certain conditioned stimuli (support and non-support); 3) programming of the second sub-dominant animal; and 4) other animals. In the present study, the primates were also given alcohol (1.2 g/kg) for 21 days. Results and discussion: The conditioned spatio-temporal stereotype of group eating behavior had formed by the 10th experimental day, starting with the leader, then the first sub-dominant monkey, followed by the second, and then the other members of the group. With regards to the alcohol abstinence syndrome, there was a disturbance of stable conditioned spatio-temporal stereotype and also the individual stereotype in each animal. Bio-adaptive regulation (photo-stimulation) in the rhythm of brain bio-potential (alpha- and theta-rhythms) restored conditioned spatio-temporal stereotypic behavior. Our data confirm that chronic alcoholization leads to disordered cognitive functions in primates, which may be corrected by biofeedback modulation.

S 9. TOWARDS INTEGRATIVE BIOLOGICAL PSYCHIATRY

Chairs: Petr Shabanov (Russia), Allan Kalueff (USA)

NEUROTOXIC LESION OF ROSTRAL PART OF THE RAT PERIRHINAL CORTEX BLOCKS STRESS-INDUCED BEHAVIORAL CHANGES

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Introduction: Exposure to stress leads to adaptive responses including both behavioral and physiological changes. This process is induced by the activation of different brain regions. In the present study, we examined the role of rostral perirhinal cortex (rPRh) in the expression of behavioral stress responses. Methods: In the present study, the rPRh was lesioned by local microinjections of 10 µg NMDA and the effects of these lesions on foot shock (0.7 mA, 1 s) induced behavioral stress responses were tested in the open field and the light-dark box. Results and discussion: Stressed and sham-lesioned rats showed several well-known behavioral changes in the open field (e.g., immobility, reduction of exploratory activity) and the light-dark box (e.g. reduction of time spent in the lit compartment). All these stress-induced behavioral changes were blocked by neurotoxic lesions of the rPRh. Furthermore, rPRh lesions did not affect the behavior in the open field and the light-dark box in unstressed animals. Conclusion: These data clearly indicate that the rPRh is crucially involved in the processing of foot shock stress induced behavioral changes.

CENTRAL EFFECTS OF PYRIDOSTIGMINE TREATMENT IN CHRONICALLY STRESSED RAT

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Introduction: Since their return from the first Persian Gulf War, some veterans have reported various symptoms designated as “Gulf War Illness” (GWI). Pyridostigmine bromide (PB), an anticholinesterase drug used as a prophylaxis treatment against nerve agent poisoning, has been proposed by many authors as a cause of dysfunction related to GWI. The aim of our study was to evaluate the effects of PB pre-treatment on cognitive and social behavior in rat under chronic stress. Methods: To induce chronic stress, rats were submitted to Pole Climbing Avoidance (25 min per day) for 10 days (D1 to D5, then D8 to D12). 30 min before each stress session, animals received PB (1,5 mg/kg, p.o.). Non-stressed and/or not treated animals were used as controls. Two types of behavioral experiments were conducted from D15 to D19 then D52, D113 and D199. Learning and memory capacities were studied using the water-maze test and social behavior was evaluated by electric fight test. A second experiment was conducted in order to evaluate the change of gene expression. Immediately after the last stress session (D12), brains were removed and molecular biological assessments were performed on two brain areas (hypothalamus and hippocampus). These genes were chosen because of their implication in memory or stress processes. Results: Behavioral results show that stress induces learning disorders and aggressiveness. These effects were increased by the association with PB. However in stressed animals receiving PB, the expression of various genes as Il1α, NF-κB or the activation of CamKIIα pathway favoured the development of learning and memory. It is hypothesized that PB protects organisms against stress actions. This could explain why stressed animals receiving PB are slower in water-maze but keep on learning. Moreover, molecular results demonstrate that PB preferentially stimulates the mineralocorticoid pathway while the expression of glucocorticoid receptors is not modified by PB treatment. Conclusion: Behavioral results suggest that PB induces central side effects when it is orally administered to chronically stressed rats. The molecular biology study is in agreement with behavioral disorders induced by chronic stress or by its association with PB.

ROLE OF CHAPERONES 70 KDA IN PATHOGENESIS OF SEIZURES WITH DIFFERENT ETIOLOGY

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One of the most pressing problems of epilepsy research is to find endogenous regulators which possess neuroprotective properties and are able to interfere in the crucial link of convulsive activity generation. It is determined that thermal preconditioning (TP) (method of an increase in concentration of Heat Shock Protein 70 kDa (HSP70)) can possess protective action under stress and in many disorders [review: Pastukhov, Ekimova, 2005]. The aim of the present investigation is to study effects of an increase in concentration of endogenous HSP70 by TP on the severity of seizures and neurological disturbances in rats not predisposed to epilepsy and rats genetically predisposed to epilepsy. To make a comparative analysis we used two models of epilepsy, which are similar to some human epileptic disorders: 1) a model of pentylentetrazole (PTZ, 80 mg/kg)–induced seizures in Wistar rats and 2) a model of hereditary audiogenic epilepsy in Krushinskii-Molodkina (KM) rats. Changes were determined in seizures components in Wistar rats 24 hrs after TP and concentration of inducible Hsp70 (by electrophoresis in polyacrilamide gel and immunoblotting with monoclonal antibody to Hsp70) 6 and 24 hrs after TP. It was found that TP increased Hsp 70 concentration in the following Wistar brain areas: senso-motor cortex, corpus callosum, thalamus, hypothalamus, cerebellum, midbrain, piriform cortex and amygdale; the highest increase was observed in hippocampus 24 hrs after TP. TP resulted in an increase in the latent period (by 2 fold) of seizures and a decrease in their severity, lethality (by 50%) and the duration of the ataxia symptoms in 48% of rats. Investigation in KM rats revealed an increase in concentration of Hsp70 in hippocampus

and piriform cortex 1st day after TP (duration - 7 min) and in midbrain and inferior colliculus 1st and 4th days after TP. TP in KM rats caused a significant increase in the duration of the latent period of seizures induced by sound (intensity 50 dB, frequency 8 kHz) during the 2nd -7th days. The maximum effects were observed on the 4th day (2.7 fold increase) after heat. TP did not reduce the duration of components of audiogenic seizures and neurological disturbances in KM rats. Thus, significant changes in the components of generalized seizures and neurological disturbances induced by PTZ in Wistar rats can be linked to an increase in the level of Hsp70 in many brain areas. An essential delay in seizures in KM rats is associated with the highest increase in the concentration of Hsp70, predominantly in brain areas which are responsible for the initiation of audiogenic seizures. It can be related to abnormalities of the neuromediator brain systems and, possibly, to the production of the regulatory gene dysfunction in KM rats.

THE USE OF BENZODIAZEPINES IN THE EMERGENCY DEPARTMENT OF HEALTH CENTERS IN NORTHERN GREECE. A COMPARATIVE STUDY BETWEEN URBAN AND RURAL AREAS

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Introduction: The use of benzodiazepines in the emergency department of primary care institutions is a common practice. The aim of this study is the research of the use of benzodiazepines in emergency care in two Health Centers in Greece and the comparison of the data between rural and urban areas. Method: Retrospective study. Data was collected from the records of the Health Centre of Ionia, Thessaloniki (urban area) and Health Centre of Litochoro, Pieria (rural area) for a period of one year. Results: Benzodiazepines were administered as an emergency remedy in a total of 830 patients (N=830), 58% of which (N=488) were residents of rural area and 42% (N=421) residents of urban area. 36.3% of the studied population (N=301) were male and 67.3% (N=529) were female and the mean age of the group 50.26 years (SD ±17.7). The most common causes of administration were somatomoform and stress disorders (27.2% and 26,0% respectively) followed by hypertension (21,4%) and tachycardia (4.1%). It is interesting to notify the statistically significant difference regarding the frequency of benzodiazepine administration between rural and urban areas (5% versus only 0.8% respectively of the total number of patients presented to the emergency department for any reason). Conclusions: The use of benzodiazepines in emergency Primary Care, although being an everyday practice is not always justified, as these drugs are often given to female patients for reasons other than psychiatric concerns (e.g. hypertension). Further effort is needed to inform the general practitioners as well as other specialties occupied in Primary Care about the orthological use of benzodiazepines in cases of medical emergencies.

CENTRAL CHOLINERGIC CORRELATES OF ANXIETY AFTER STIMULATION OF VENTROMEDIAL HYPOTHALAMUS IN RATS AND ZOOSOCIAL CONFLICTS

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Introduction: In recent years, much attention has been paid to the role of monoaminergic systems in the development of anxiety, but cholinergic system functioning has ceased to be the object of detailed analysis. Among various methods for modeling anxiety states, we focused our attention on the model of sensory contacts, which make it possible to form the anxiety in animals as a result of zoosocial conflicts that have always been accompanied by the formation of negative emotion. Another way to model negative emotions and anxiety in rats is the direct electrical stimulation of ventromedial hypothalamus nucleus. The aim of the present study was to compare the effects of these different impacts on cholinergic activity in various brain structures in rats. Methods: The experiment was carried out in 38 male rats aged 4-5 months. In some, the electrodes for electrical stimulation were implanted into the ventromedial

hypothalamus nucleus, according to the stereotaxic atlases [Fifkova, Marshall, 1967]. In other rats, we used the model of sensory contacts [Kudryavtseva, 2002], as a result of which the animals with anxiety were chosen. The activity of acetylcholinesterase (AChE), reflecting the intensity of cholinergic processes, was determined in 11 brain structures by Ellman e.a. (1971). Results and Conclusion: Stimulation of negative emotional areas forms two different types of avoidance, active and passive, which were differentially manifested through changes in cholinergic activity in the brain structures. The reaction of passive avoidance correlated more highly with the state of anxiety caused by zoosocial conflicts. What they have in common is the increase of cholinergic activity in reticular formation of the middle brain. However, they have their own specific features: the increase of AChE activity in olfactory bulbs and in frontal cortex in rats after zoosocial conflicts and the decrease of this index in hypothalamus and septum of animals that react with passive avoidance after brain stimulation. The rats with a reaction of active avoidance did not have the increase of AChE activity in reticular formation. However, in the septum this index was enhanced. The obtained results suggest that endogenous and exogenous stimuli provoking the development of anxiety eventually affect the same central cholinergic mechanisms. The difference is in the degree of the involvement of cholinoceptive mechanisms in neocortex and hippocampus which evidently work to supplement and compensate functions. Septum is one of the key structures on the way of hippocampus function regulations in the process of anxiety formation.

LEFT-HEMISPHERIC LATERALIZATION: PSYCHOMETRIC STUDY

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Introduction: A systemic approach in physiology provides a concept of asymmetric activity of large hemispheres and the peculiarities of their interaction. This promotes a revision of traditional representations of the domination of one hemisphere, accentuating the functional specialization of each. It is established that the left hemisphere begins to dominate only at a certain stage of ontogenesis. Thus, the process of transitioning function from the right hemisphere into the left one is characterized by successive organizational shifts called left-hemispheric lateralization. The aim of this research was to study the association between signs and emotional - personal sphere characteristics of latent left-handedness with an analysis of their transformation in aspects of age and gender. Methods: 408 respondents have been involved in research (157 men and 251 women) distributed according to age into three groups: 1st group – 234 respondents (middle age (M) 22.7 years ±SD=2.8), 2nd – 81 (38.7±6.2 years), 3rd – 93 (57.4±4.4 years). Psychometric examination has been carried out by Eysenck Personality Inventory, Rotter I-E Locus Control Scale, Toronto Alexithymia Scale, Spielberger State-Trait Anxiety Inventory, Beck Depression Inventory tests. An estimation of laterality structure has been carried out by tests for revealing latent left-handedness (L-H). The statistical programs GraphPad Prism 4 and STATISTICA 6.0 were used for Correlation, Multiple Linear Regression, Cluster Analysis, Factor Analysis. Results and discussion: Signs of latent L-H were revealed in 82.4% of respondents. 26.0% of the subjects had one sign, 30.4% had two signs, 14.0% had signs, and 12.0% four signs. In the community sample, it was revealed that there was a tendency for the number of persons without signs of latent L-H and with a single sign to progressively increase with years. There was also a progressive marked reduction in the number of respondents with two or more signs of latent L-H. There is a progressive increase in the number of introverts and a reduction of extraverts with the years, as well as an increase in the number of persons with external personal type and reduction in those with internal type. In parallel, there is a marked progressive increase with the years in the number of persons with high level of personal and, especially, reactive anxiety on the background of relatively uniform alexithymia distribution and light level of depression. Statistical analysis has revealed a positive correlation connection and character of association between investigated psychometric

parameters in respondents exposed to the certain modifications. Conclusion: Thus, it is established, that alongside with an increase of interhemispheric asymmetry, there occurs an original transformation of respondents' emotional-personal characteristics which can be considered as one of the parameters of left-hand brain lateralization.

THE RELATIONSHIPS BETWEEN NEURONS CONTAINING DOPAMINE AND NITRIC OXIDE SYNTHASE IN THE ENCEPHELON OF CYPRINID TELEOST

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The presence and distribution of nitric oxide synthase (NOS)-like neurons as well as tyrosine hydroxylase-immunoreactive (TH) neurons in the diencephalon of the teleost Rhodeus sericeus are well established. As the topographical patterns of NOS and TH coincide in many teleosts, the aim of this study was to determine the possible coexistence of both substances in the diencephalic nuclei of the Rhodeus sericeus. Immunohisthochemical labelling was employed on the same sections as well as a morphological study. NOS- and tyrosine hydroxylase- containing neurons were observed in all the nuclei under study (hypothalamus, posterior tuberculum, ventral thalamus, pretectum) and telencephalon (preoptic region). Although most neurons showing the coexistence of both substances were mainly located in the preoptic nucleus and hypothalamus, isolated-labelled neurons were found in the posterior tuberculum and ventral thalamic nuclei. Although both substances have previously been shown to be modified in hypothalamic neurons after osmotic stimuli, the range of functions of NOS in the teleosts CNS is only beginning to be understood. Further studies are needed to elucidate the functional role that NOS/TH neurons play in the nervous system.

STRESS-INDUCED HEMISPHERIC DIFFERENCES IN PHOSPHOLIPID COMPOSITION IN RAT BRAIN SYNAPTOSOMES

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There is abundant evidence about a morphological, neurochemical, functional and pharmacological inequality of animal and human brain hemispheres. However, in comparison with intensive studies of morphological and functional brain hemisphere differences, neurochemical basis of brain asymmetry is yet poorly explored. The purpose of the study was to estimate a contribution of left and right brain hemispheres in neurochemical mechanism underlying the central stress disordering and adaptation. From the role of phospholipids as universal "molecules of adaptation", phospholipid composition in synaptosomes were isolated separately from each brain hemisphere of rats subjected to immobilization (for 3 hours) and were analyzed by two-dimensional thin-layer micro-chromatography. The results showed no initial differences in the phospholipid composition between the brain hemispheres. At the same time, opposite shifts in the relative amount of choline-containing phospholipids (phosphatidylcholine, PC; sphingomyelin, SPM) and phosphatidylethanolamine (PE) of the brain hemispheres have been found due to stress. For example, an increase of SPM with a parallel decrease of PE in the left hemisphere was accompanied, on the contrary, by the decrease of PC with concomitant increase of PE in the right hemisphere. Stress-induced synaptosomal enrichment in most saturated phospholipids (SPM) and in most unsaturated phospholipids (PE) could promote the rigidity of nerve-ending membranes in the left hemisphere and the fluidity of nerve-ending membranes in the right hemisphere, respectively, that may produce different effects on the functional ability of the brain hemispheres. We suggest that illustrated differentiation of the neurochemical mechanisms of stress adaptation in the brain hemispheres may be associated with their inequal functional domination (R>L) at the stress.

S10: RECENT ADVANCES IN NEUROPSYCHO-IMMUNOPHYSIOLOGY

STRESS AND AUTOIMMUNE DISEASES OF CNS

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Introduction: Stress provokes many diseases, including exacerbation and the subsequent development of brain lesions in patients with multiple sclerosis (MS). MS is a chronic autoimmune disease of a central nervous system with unknown etiology, and it often manifests the first clinical symptoms during young adulthood. Experimental allergic encephalomyelitis (EAE) is the main *in vivo* tool for the investigation of MS. EAE has common pathogenic mechanisms and clinical symptoms with MS. In EAE, as well as in MS, antigen specific $CD4^+$ T-cells enter the nervous system where they stimulate the production and release of pro-inflammatory cytokines into the extracellular milieu prompting an inflammatory response. In EAE animals, paralysis is followed by spontaneous symptomatic recovery. The mechanisms underlying resolution of the disease are not fully understood. Recovery is thought to represent a switch in the cytokine profile from pro- to anti-inflammatory, and it coincides with an increase in endogenous steroid levels at the peak of disease. Stressfull events result in activation of the hypothalamic–pituitary–adrenal (HPA) axis and increased levels of cortisol production. Inflammation can also activate the HPA axis. Thus, both stress and inflammation are realized through similar mechanisms. For many MS patients, stressful life events coincide with the onset of the disease. However, the role of stress in MS is poorly understood. The aim of this work was to analyze the effect of vital stress on the severity of EAE and immune cells activity. Methods: EAE was induced in female Wistar rats by inoculation of homological spinal cord homogenate with complete Freund's adjuvant. The severity of neurological disorders was estimated by clinical index (CI) from 0 (without disorders) to 6 (mortality). The vital stress was induced before 1 month of inoculation of encephalitogenic mixture or during the inductive phase of EAE, on the 7^{th} day after inoculation (d.a.i.). The leukocyte activity was estimated for spontaneous and stimulated migration ability at 10 d.a.i. The intracellular level of defensins was determined in lisosomal-cationic test (LCT) at 0, 8, 11, 16 d.a.i. Results: 78% of animals in the control group revealed clinical symptoms of EAE. The experimental group of animals that underwent vital stress 1 month before induction demonstrated the same symptoms in 28%, and in 100% - those animals who were stressed during the inductive phase ($p<0,05$). Biological markers - RTML on PHA - were revealed in 81% of control rats and in 28% of the animals stressed 1 month before induction of EAE. Migration activity of the cells in the media with spinal cord extracts demonstrated the same ratio: 50% for control and 14% for stressed rats. The data show that sensibilization to encephalitogenic antigen developed in 50% of control rats and in 80% of sick animals. A decrease in the number of sick animals in the severely stressed rats, was followed by marked diminution of RTML to spinal cord antigens. RTML to PHA in those animals was three times lower than in others. This fact points to the strong immunosuppressive influence of stress, especially on cell immunity. During the convalescence phase, accompanied with immunosuppression, one more stress application did not lead to EAE augmentation. However, animal skins became ulcerated in places of EGM injunctions. The ulcers persisted for 45 d.a.i. Stress applied during the EAE inductive phase caused sickness in 100% of animals as well as augmentation. For 33% of sick rats, the disease was lethal. At the same time, there was no prominent immunosuppression in experimental animals. The defensines level in the control group decreased on the 8 d.a.i. to 1.2, and it remained at the same level until16 d.a.i. In the group of animals stressed during the inductive phase, defensines decrease took place on the 11 d.a.i. By the 15 d.a.i., this indicator increased to the level of 1.4. Conclusions: The obtained results showed that stress applied during the inductive phase of EAE makes the disease more severe, probably through Th-1 lymphocytes stimulation. On the contrary, immunosuppression developed as a result of stress inhibited EAE. The results of this study suggest that interrelation between phases of stress

reaction and autoimmune processes plays an important role in the development of neurodegenerative autoimmune diseases.

CALPAIN EXPRESSION IN CNS AND PERIPHERAL CELLS ASSOCIATED WITH EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS

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Multiple sclerosis (MS) is a chronic T cell-mediated autoimmune inflammatory disease which causes neuronal demyelination in the CNS. The corresponding animal model, experimental allergic encephalomyelitis (EAE), is used in evaluating the autoimmune response in CNS and peripheral organ systems. As the calpain family of proteases is implicated in cellular processes such as demyelination, apoptosis and cell migration, we assume that it participates in EAE development. In this study, the calpain expression was evaluated by RT-PCR at the transcriptional level in spleens and spinal cords of animals with EAE. We observed an increase of calpain expression in spleens of rats during the latent period of EAE in comparison with control animals. In spleens of rats with clinical symptoms (paralysis of limbs), calpain expression was decreased to the level of the control group. In spinal cords of rats with severe EAE, calpain expression was significantly increased. We believe that a better understanding these processes could provide avenues for novel therapeutic strategies to treat MS.

EFFECT OF HEAT SHOCK PROTEIN 70 KDA ON BASIC CHARACTERISTICS OF BLOOD DURING THE ENDOGENOUS STRESS IN RATS

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A rise of the level of bacterial endotoxin lipopolysaccharide (LPS) in blood evokes changes in different physiological systems and biochemical characteristics of living organisms. This kind of stress can be classified as endogenous, and often leads to very serious disorders, such as endotoxaemia and sepsis. Recently we have shown that preliminary injection of heat shock proteins 70 kDa (Hsp70) in rats and pigeons can decrease brain temperature and contractile muscular activity during endotoxaemia [Lapshina, Ekimova, 2007]. Probably, Hsp70 can be considered as the endotoxin antagonist. The goal of our study was to investigate the influence of exogenous Hsp70 on basic characteristics of blood during the endogenous stress caused by LPS in rats. Investigations were carried out in freely moving male Wistar rats. LPS (Escherichia Coli 0111:B4 (Sigma) was injected intravenously in a dose of 100 μg/kg. Exogenous Hsp70 (obtained at the Institute of Cytology RAS) was also injected intravenously 15 min before LPS (80 mkg/kg). In the control vehicle, the same volume was injected. Blood samples for the assessment of the number of red and white blood cells, hematocrit and acid resistance of red blood cells were taken an hour after the beginning of the experiment. The number of blood cells was counted using Goryaev chamber, and white blood cells were stained by methylene blue. Acid resistance of erythrocytes was investigated by colorimetric method. It was shown that injections of LPS, Hsp70 and its combined action evoked an increase in the number of red and white blood cells and the hematocrit level. LPS noticeably reduced the acid resistance of erythrocytes, whereas Hsp70 increased resistance in comparison with the control level. After the combined action of Hsp70 and LPS, acid resistance increased in comparison with LPS alone. We supposed that similar changes in blood cells number, hematocrit and fast destruction of erythrocytes may appear due to emotional stress and LPS-induced endogenous stress. The capability of Hsp70 to increase acid resistance can be explained by the release of more resistant young forms of erythrocytes [Maslova et al., 2005, Pastukhov et al., 2005]. In this case, the increase of resistance after the combined action of Hsp70 and LPS may be evidenced by the appearance of young forms of erythrocytes in the blood. The mechanism of this effect is unknown, and requires further experiments.

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LIFE EVENTS AND DEPRESSION: MYTH OR SCIENTIFIC FACT?
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Although traditionally life events are considered to play an important role in the development of depression, empirical data are controversial. Most studies fail to find any difference between depressed patients and controls, they find only magnitude differences or they attribute any differences found to the lack of social support for patients. Some studies suggest that life events are important with increasing age, but require interaction with predisposing factors in order to lead to depression; others argue that adverse events are at least partly the result and not the cause of depression. Personality factors may predispose to the development of depression but also personality traits, like high sensation-seeking, are associated with a higher rate of life events. Conclusively, many authors insist that psychosocial factors are relatively unimportant in the subsequent course of severe and recurrent depressions, in contrast to their contribution to onset of such depressions and subsequent outcome of milder depressions.

THE RELATIONSHIP BETWEEN WORK-RELATED STRESSORS, MAJOR DEPRESSION, AND SUICIDALITY
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Introduction: Work-related stressors are defined as chronic daily problems, in contrast with the one single dramatic stressor-event seen in post traumatic stress disorder (PTSD). Method: Studies in which major depression have been defined with reference to DSM-IV, as well as studies in which self-reported depression scales have been used have been included in this review. Work-related stressors have been measured with different self-reported scales, including lack of social support, role overload, role conflict, lack of meaningfulness, lack of information, and lack of influence. Results: Among the work-related stressors it seems that lack of social support (lack of social bounds) is the most important factor for the development of depression. Conclusion: Lack of social support is the single most important factor among the work-related stressors causing depression. High working load can be tolerated if social bounds are operating.

PERSONALITY, PSYCHOBIOLOGY AND LIFE EVENTS IN THE DEVELOPMENT OF MAJOR DEPRESSION
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It is well known that patients suffering from major depression also suffer from a comorbid personality disorder significantly more often than the general population. Specific personality traits might influence and modify the expression of depressive symptomatology and correlate with the reactivity of the patient to the environment. Life events are considered to be the factor relating personality characteristics with the manifestation of depression. It seems that subgroups of depressive patients are characterized by the presence of stressful life events. However, it is unclear whether this is a true fact or if these patients (which have higher personality psychopathology and interpersonal rejection sensitivity) tend to over-report life events.

Neurobiological research has pointed to the combined presence of self-directed aggression and higher arousal level or disinhibition of self-directed aggressive thoughts in order for a patient to become suicidal. Further research is needed to clarify the extent to which our current status of knowledge can assist in the therapeutic planning and monitoring of response to treatment.

GENETIC DETERMINANTS OF RESPONSE TO STRESSFUL EVENTS

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Stressful life events contribute to the development of affective disorders to a large extent in the majority of cases. Not all individuals, however, manifest depressive illness as a consequence of acute or accumulating stress. This suggests that there are several mediating variables which determine and influence the effects of stress and stressful life events in the development of major depression. Research concerning the genetic influence in the development of psychiatric disorders has been vastly expanding in the past decade, and gene x gene and gene x environment interactions are thought to be crucial factors in determining the manifestation of these disorders.

Presence of the s allele of the 5-HTTLPR polymorphism of the serotonin transporter gene has been associated with neuroticism and neuroticism-related traits and characteristics as well as with corresponding psychiatric disorders. 5-HTTLPR has also been related to resilience and coping with stress, and the role of the 5-HTTLPR s allele in response to stressful events has been well established in both animal and human studies. Caspi et al. (2003) described that the s allele is associated with the development of major depression as a consequence of stressful life events. In case of animal studies it has also been described that both abnormal behavior and biochemical changes occur following a stressful event if the s allele of the 5HTTLPR is present. Therefore it seems likely that the s allele increases vulnerability to stress and thus the risk of the manifestation of affective disorders by giving rise to personality characteristics associated with poorer stress resiliency and poorer coping abilities with life stressors. This would also explain the increased frequency of the s allele generally observabled.

OLD AND NEW ANXIETIES: EXPECTATIONS AND DISCONTENTS IN A BIOLOGISED WORLD

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Anxiety eludes precise, univocal definitions. It is often considered as a natural, intrinsic response, built into the human design, to certain environmental and psychological factors. However, while anxiety is a universal functionality of an organism, the contexts in which it is experienced, the interpretations of its meanings, and the responses to it are influenced by historical contingencies, cultural permutations and practices of a given time. I will sketch a historical outline of the definitions of anxiety and its nosology, the current ramification of its diagnosis and the various attempts to classify this complex phenotype. I will reflect on whether anxiety can be defined as a historical constant, in alignment with the universalism of its biological components, and on how different times and cultures display distinct ways of representing, promoting or managing this trait. I will do this in light of the progressive biologisation (and geneticisation) of anxiety that has given origin to new ways of representing it and created new ‘objects’ (e.g. anxiety susceptibility genes, anxiety laboratory tests in animal models, etc.) that reify this behavioral disorder and make it shuttle between the social context and the laboratory. During the 50s-70s, the minor tranquillizers had a determining impact on the medicalisation and management of daily tensions and anxieties. The introductions of SSRIs and

increasing knowledge in the genetic and biochemical components of anxious behavior have intensified the process. By drawing data from the latest neuroscience literature on anxiety, the spectacle of anxiety drug advertisements and the dynamics of anxiety patients organizations, I will attempt to delineate whether in the past fifty years or so the nature of this condition, as well as the promises and expectations to overcome it, have remained unchanged, and finally whether the promises have been met with fulfillment or disillusion. This is an interdisciplinary paper aimed at framing the nosology of anxiety, the most recent understanding of its biological mechanisms and treatment in a broad societal context.

POLYMORPHISMS OF THE GENES 5-HTR2A AND 5-HTT AT NEUROTIC, STRESS-RELATED AND SOMATOFORM DISORDERS

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Introduction: Neurotic, stress-related and somatoform disorders are of concern as they comprise a number of the most universal manifestations of mental desadaptation. Their occurrence and development depend on genetic, biological and external factors. The purpose of this research was the study of polymorphic variants of locus T102C and A-1438-G of gene 5-HTR2A and locus VNTR-17 and 5 '-HTTLPR of gene 5-HTT among patients with neurotic, stress-related and somatoform disorders. Methods: 60 patients with dissociative (conversion) disorders (ISD-10, F44), 43 patients with adjustment disorders (ISD-10, F43.2) and mentally healthy persons (85 persons) were investigated. Polymorphic gene variants of serotonin receptor 2A (5-HTR2A) and serotonin transporter (5-HTT) were studied. Results and discussion: Authentic distinctions between distribution of genotypes A1A1 and A1A2 of locus T102C of gene 5-HTR2A is characteristic for patients with adjustment disorders in comparison with mentally healthy people (χ^2=4.26; df=1; p=0,04). The distribution of genotypes AA and GG of locus A-1438-G of gene 5-HTR2A among patients with dissociative (conversion) disorders differs from distribution of corresponding genotypes in control at a level of the tendency (χ^2 =2,1; df=1; p=0,07). We have observed statistically significant distinctions between frequencies of genotypes AG and GG of locus A-1438-G of gene 5-HTR2A at patients with dissociative (conversion) disorders and mentally healthy people (χ^2 =3.3; df=1; p=0,03). Dissociative (conversion) and adjustment disorders characteristically have the distinct tendency for distribution of genotypes with locus VNTR-17 of gene 5-HTT. The distribution of genotypes LL, LS and SS of locus 5'-HTTLPR of gene 5-HTT among patients with dissociative (conversion) disorders did not differ from distribution of these genotypes among patients with adjustment disorders. Conclusion: Patients with dissociative (conversion) disorders and adjustment disorders and mentally healthy persons differ in the distributions of genotypes of genes 5-HTR2A and 5-HTT. The locus T102C of gene 5-HTR2A are associated with adjustment disorders, the locus A-1438-G are associated with dissociative (conversion) disorders.

PHARMACO-CORRECTION OF LATENT HERPES INFECTION: STRESS-INDUCED REACTIVATION CONTAMINATIONS AT THE ACUTE ISCHEMIC STROKE

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Introduction: The aim of this study was to reactivate latent herpetic infection in patients with acute ischemic stroke (AIS). Methods: Patients of both sexes (age 55-85 years) with primary AIS, in which the DNA of herpes simplex virus (HSV) was marked by polymerase chain reaction (PCR), were included in the study. These patients were divided in 2 groups: basic (receiving standard therapy and Cerebrolysin) and control (receiving standard therapy). Neurologic deficit was assessed by means of NIH-NINDS, modified Rankin scale and Barthel index. Infectious complications were defined by SIRS. HSV in blood was assessed by PCR method and enzyme

multiplied immunoassay (EMIA). The immune status was assessed. CT MRI of brain and laboratory tests was made. Results and discussion: PCR on HSV in blood was positive in 98 (27.7%) of 353 patients with acute ischemic stroke. These 98 patients were included in the study and divided in 2 groups: basic and control. Cerebrolysin was injected in the dose of 10ml intravenously during 10 days, in the first 12-hours from the onset of the disease. To the 10th day of AIS in the basic group, there was markedly accelerated restoration of neurologic dysfunctions, reduction of infectious syndrome level by SIRS scale, reduction of quantity of positive PCR and EMIA on HSV, and normalization of the disturbed indexes of immune system ($p<0.01$). Conclusion: With patient AIS, in terms of immunodepression, the reactivation of latent herpetic infection is marked in 27.7%. Cerebrolysin is the effective drug due to neuroimmunoresolving action.

SPECIFICITY MANIFESTATION OF EDUCATIONAL STRESS IN SENIOR PUPILS OF SECONDARY SCHOOL DURING EXAMINATIONS

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Introduction: The purpose of this study is to show the level of stress in secondary school pupils during the examining season. Methods: f3 groups of pupils (11 classes) were selected from school №2, №5, №7 of Pereyaslav-Khmelnitskiy that were the same age (16-17 years) and same educational experience. For diagnosis we used methods which analyzed the separated symptoms of stress together with education using a test of personal anxiety (the method of Spielberger-Hanin), filing activity and mood (FAM), and the level of stress adaptability (the combined method of V.I.Rozova). The methods were selected for their efficient and user-friendly style, and for their ease of interpretation. Result and discussion: The experiment consisted of three testing groups: 1) The experimental group (EGi); 2) The second experimental group (EG2); 3) The final group (FG). The research was performed in three stages: 1) Holding the diagnose fail in all three groups (EGb EG2, FG) for elucidate the primary result dates in the beginning term; 2) The realization of diagnostic shearing during the beginning an examination period the whole of groups changes educational on account of syndrome dates on beginning of the term and in the period of preparation to finals; 3) Holding the correction work of overcoming stress in senior pupils. Conclusion: psychological correction works are highly effective due to prevention of the education stress at the 37.6% of senior stress sensitive pupils of secondary school. This result was received during final summer examinations and was very effective to protection of earlier post stress health complications and brain nonorganic disorders.

ASSOCIATION BETWEEN OCCUPATIONAL STRESS FACTORS AND MENTAL HEALTH IN NURSES

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Introduction: Nursing is a stressful occupation, and because of these stresses multiple negative consequences (especially psychological) can develop. The present research was performed to investigate the role of nurses' general health, especially their mental health, in nursing services. Methods: This study is a kind of correlative research that was performed in 170 nurses in Isfahan Medical Sciences hospitals. The sampling method was stratified randomization. The tools for gathering data were Toft-Anderson Nurses Stress Scale and GHQ28. Data analysis was done by spearman correlation statistical test, using SPSS software. Results: The findings have shown that 88.8% of participants were female and 11.2% male. The level of stress was moderate among nurses (76.5%). The findings showed that there were moderate levels of anxiety in 43% participants and moderate levels of depression in 18.8%. Overall, the findings showed significant and positive association between occupational stress and mental health in

nurses (P<001). Conclusion: According to these findings, because of the nature of the nursing occupation, nurses are at risk for many stresses. This problem can affect the quality of nursing services and the improvement of public health. Therefore, in order to improve the general state of health (especially mental health) in nurses, we suggest there are both individual and organizational aspects to the necessary interventions.

THE EFFECT OF SELF-CARE ON PSYCHO-SOCIAL AND COGNITIVE FUNCTIONING OF MULTIPLE SCLEROSIS PATIENTS

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Introduction: Psycho-cognitive and physiologic signs of long term diseases affects various aspects of patients' lives. Multiple sclerosis (MS), as a long-term life threatening disease, can cause acute disabilities affecting patients' life trends. Self care diminishes the disease extension and complications, provides the patient with a better life quality, and gives the family a better coping ability against new conditions. This study was carried out with the above title. Methods: This study was quasi-experimental. Twenty eight MS patients referring to private and clinical practice of Isfahan Alzahra hospital were selected by convenient sampling. The subjects were asked to attend three educational sessions. After that, the subjects started self-care programs for three weeks and then psycho-cognitive and social function questionnaires were filled out by the patients. The findings were analyzed through descriptive and inferential statistics. Results: Findings showed a noticeable increase in mean score in psycho-cognitive (P<0.001) and social function (P<0.001) after self-care program. Conclusion: The findings showed that self-care activities promote psychological and social functions because patient participation in self-care behaviors may lead to improved self-esteem, enhanced mood status, and can eventually promote the quality of life. It is hoped that by forming educational supportive associations for the patients, they can be provided with facilities for self-care as well as a condition in which this self-care can be carried out.

EVALUATION OF STRESS AND PSYCHOLOGICAL COMPLICATIONS DUE TO CONSUMPTION OF ANTIEPILEPTIC DRUG IN EPILEPTIC CHILDREN

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Introduction: It has been reported that children with epilepsy have more behavioral problems that children with other chronic illness and children in the general population. Psychiatric disturbances, including depression and anxiety, have been reported more frequently. The aim of this study was assessment of the psychosomatic complications of antiepileptic drugs in epilepsy children of school age. Methods: This study has been done as a clinical trial study. We assessed patients of 1-20 years old that used Carbamazepine and valproate and collected demographic data including age, sex, seizure frequency, epilepsy duration, age of seizure onset, and medication histories that were collected by questionnaires and checklists. Also, information on complications with drugs of stress, behavioral and psychological problems that were collected by questionnaires and checklist of (State Trait Anxiety Inventory) (STAI) and Children's Depression Inventory (CDI) were applied to all the children. Results and Discussion: The results indicated that the mean age was 13 years old, 57% female. 47% were in primary school, 36% were the first child and the mean of history of epilepsy was 4 years. The most common complications were fatigue, impatience, abstraction, dizziness, confusion, dullness of vision and psychological problems (stress, depression and anxiety). Also, there was a significant correlation between the consumption of numerous drugs and complications. Conclusion: Our findings indicated that psychiatric disturbances, including anxiety and

depression, are seen more frequently in epileptic children. Also, patients who are using multiple drugs are exposed to drug interaction risk.

Basic Research

THE EFFECTS OF DIFFERENT TYPES OF STRESSORS ON MEMORY RETRIEVAL IN MICE
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Introduction: Modern psychological research on memory developed from work on learning, and this shift resulted in an emphasis on processes of encoding or acquisition; very little thought was given to the equally important problems of memory retrieval. However, it has been shown that retrieval of memory requires the simultaneous intervention several brain regions. It thus becomes clear that hippocampal function is essential for the acquisition, consolidation, and retrieval of spatial memory and high circulating levels of glucocorticoid hormone and the adrenal steroid hormones secreted during stress have been shown to impair or enhance acquisition, consolidation and retrieval depending on experimental conditions. The aim of the present study was to verify the effects of different types of acute stressors on memory retrieval evaluated by the plus-maze discriminative avoidance task (PM-DAT) in mice. Methods: In the first experiment, mice were submitted to the training sessions on the PM-DAT and tested in different days: 7, 15, 30, 45 and 60 days later. After the training sessions, all animals were kept in their home-cages until the test session. In the second experiment after PM-DAT training session, all animals were again kept in their home-cages until the test session. However, 12 or 24 h prior the test session the mice were continuously submitted to two different types of stressors: social isolation and crowing until the test session. Test session was performed 30 days after the training session. Results and Discussion: The results showed that all animals learned the task in the training session in both experiments. In the first experiment, in the test session, mice that had been trained 7 or 15 days before the test session did not present memory deficit. On the other hand, mice that had been trained 30, 45 and 60 days before the test session presented memory deficit. On the second experiment, we verified that both 12 or 24 h of social isolation (but not 12 or 24 h of crowding) reversed the memory deficit induced by the longer periods of time between training and session. Conclusion: The data suggest that certain stressful stimuli prior to the memory retrieval phase can be able to promote a recall of relevant memory traces that were present but not accessible by means of the experimental condition cues.

OXIDATIVE STRESS INDUCED CHANGES IN SEXUAL BEHAVIOR OF AGED RAT
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Introduction: A direct or indirect involvement of oxidative stress has been suggested in the development of human depression. In animals, oxidative stress has been shown to induce changes in a wide range of behavioral parameters including changes in exploratory, drinking and sexual behavior, as well as impairment of feeding,. Aging cells are exposed to more oxidative stress. Oxidative stress induced changes in the aged brain plays a crucial role in male sexual behavior. The objective of this study was to analyze oxidative stress induced alteration in male sexual behavior. Methods: The animals were divided into two groups as young (group I) and aged (group II). The test of libido and potency were measured through an analysis of the mating behaviors erection, quick flip, long flip, and total reflex. The pituitary gonadal axis, antioxidant and ROS of the hypothalamus were estimated. Apoptosis, caspase- 3, and NF kB in the medial pre-optic area (MPOA) were detected by immunohistochemistry. Tyrosine hydroxylase and glyoxylic acid methods were used for monoamine detection. Results and

discussion: Mating behavioral scoring indicated a significant reduction in the mounting and intermission latency, whereas there was an increase in ejaculation latency, post ejaculatory interval, number of intromission and mounts, and inter intromission interval in the aged animals. There was a decrease in the enzymatic and non-enzymatic antioxidant levels, and a high amount of reactive oxygen species (ROS) and mitochondrial dysfunction in the hypothalamus. The apoptosis observed in MPOA may be due to the increased exposure of MPOA neurons to oxidative stress and to the reduction in the free radical scavenging system. This affects the mitochondrial membrane permeability and leads to mitochondrial mediated apoptosis. The resulting dopamine deficiency alters sexual behavior, especially in delaying ejaculation latency. Conclusion: Through aging, the high ROS leads to altered mitochondrial function, synaptic transmission, and apoptosis in MPOA and low dopamine levels. Alterations in sexual behavioral and the underlying physiological mechanisms in these animal models may be useful in obtaining more insight into human disorders involving aging under oxidative stress.

INTERMEDIATE FILAMENT LOSS IN ASTROCYTES AND NEURONS OF THE HIPPOCAMPUS AND CORTEX OF ADULT RATS INDUCED BY CHRONIC ETHANOL INTAKE CORRELATES WITH BEHAVIORAL IMPAIRMENTS: BENEFICIAL EFFECTS OF THE HYDRATED FORM OF FULLERENE C60

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Introduction: Alcoholism is a common form of drug abuse (toxicomania) with a complex origin and outcome. It is well known that chronic ethyl alcohol (EtOH) consumption is capable of injuring brain cells and causing essential abnormalities in behavioral characteristics of animals addicted to alcohol. Astrocytes exhibit a considerable capacity to tolerate changes in the neuron-glial relationship induced by central nervous system (CNS) injury or neuropathological disorders to govern neuronal survival. Glial fibrillary acidic protein (GFAP, the major intermediate filament protein in astrocytes) and a triplet of neurofilament proteins were used as markers of astrocyte reaction and neuronal response, respectively, to EtOH-induced injury. Pristine C60 fullerene and some of its water-soluble derivates act as highly-efficient free radical scavengers in several biological systems and may possess neuroprotective effects. Methods: Adult Wistar rats were trained to drink ethanol (EtOH) solution by progressively increasing the EtOH concentration (5 – 15% v/v) in drinking water for 12 weeks. Some of the alcoholised animals were given water-soluble C60 fullerene (30 nM/L) in the same EtOH solution. Homogenates of brain sections were processed by immunochemical analysis using antibodies to the triplet of neurofilaments and GFAP. For studying EtOH-induced behavioral disturbances, the rats were examined in the “open field” test. Results and Discussion: EtOH consumption caused a decrease in the total GFAP level as well as in 210 kDa neurofilament subunit in hippocampus and cortex of the treated rats. The hippocampus, which has been particularly identified as one of the targets for neurotoxic effects, is more sensitive than other regions and plays a prominent role in memory and learning processes. Our data indicates that long-term EtOH exposure causes primarily glial loss. Astrocyte deficiency results in neuronal death, and a failure to give rise to new neurons, and recover neuronal pool in hippocampus of alcoholic rats. In agreement with the degree of loss of cytoskeletal markers (i.p. neuronal and glial cell loss), EtOH-induced behavioral impairments were found. Fullerene treatment has been shown to promote normalization of cytoskeletal protein level, thus being a sign of glial and neuronal viability. Fullerene was also found to have sedative effects that eliminate symptoms of any hyperexcitement exhibited by alcohol-abused rats. Conclusion: Our findings illustrate the involvement of cytoskeletal structures of neurons and glia in the development of EtOH-induced neuropathology and provide the possibility to apply the water-soluble form of fullerene for therapy of CNS dysfunctions caused by alcohol.

BEHAVIORAL REPONSE TO A HOMOTYPIC NOISE STRESS IN MALE WISTAR RATS

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Introduction: Auditory stress, commonly called noise, is traumatic to the auditory system but also has extra-auditory effects which are expressed as physiological and behavioral changes. Whereas the effects of the noise on these parameters are clearly established, it remains of interest to investigate how the organism responds the first time, and then, how it interacts with the same (homotypic) noise over a longer time. Methods: Male Wistar rats were exposed to noise stress (frequency: 2.64 kHz; intensity: 95 dB), for 15 minutes, over 7 consecutive days. On the first and last days, the rats were filmed 15 minutes before the noise onset, 15 minutes during noise exposure; and 15 minutes following noise termination. The film was divided into 5s segments. During each time segment six pre-defined behaviors were recorded: sleeping/resting; exploring; sniffing; rearing; grooming; and freezing. Statistical analysis: The difference in frequency, according to the observation period relative to the noise, was compared using the Student-Fisher test, for each behavioral category. Results and discussion: A noise of 15 min caused reduced exploration ($p<0.01$) and this reduction was accentuated once the noise stopped ($p<0.001$). The amount of freezing increased dramatically during the noise ($p<0.01$), and continued to be very high following noise termination ($p<0.01$). Sleeping/resting, rearing and grooming did not present any significant variations from their baseline values. Sniffing, which did not change during the 15 min of noise, was significantly reduced after the noise terminated ($p<0.05$). These results were a consequence of the stressful aspect of the noise, the effects of which lasted even after its cessation, as revealed by the persistence of the behavioral changes. After 7 days of the repeated noise stress, freezing no longer showed any variation compared to pre-noise levels, whereas exploring still remained significantly reduced during the stress period ($p<0.05$), and following this stress period ($p<0.01$). Conclusion: The changes we observed corresponded to a general disturbance of the behavior of rats subjected to 15 min of noise stress, and reveal the establishment of a fear and anxiety state. Although the rats no longer displayed freezing in response to the stress, after 7 days of repeated auditory stress the noise remained stressful as shown by the maintained reduction of exploration.

ASSESSMENT OF MODULATORY EFFECTS OF ACUTE STRESS AND GLUCOCORTICOID RECPETORS ON ANXIETY RELATED BEHAVIOR IN MICE

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Introduction: Previous studies indicated that stress or glucocorticoid receptors are probably involved in anxiety reactions. This study was designed to evaluate the modulatory effects of acute stress and Corticosterone on anxiety related behavior in mice. Methods: In this study, 50 male albino mice (25 – 30 g) were used. Also, we used a standard Elevated Plus Maze (EPM) model for the assessment of anxiety. Corticosterone as a glucocorticoids receptor agonist (0.5, 1, 3 mg/kg) or vehicle were injected IP, or we used a 10 min restraint stress 30 min before the test. The first time, for increasing animals' activity, we placed them inside a black-walled box for 5 min. Then the animals were transferred to the EPM and evaluation of their anxiety reaction was measures, including of number entrances and time spent in the open arm during a 5 min period. Results and Discussion: Results indicated that injection of Corticosterone in doses of 0.5 and 1 mg/kg, or acute stress, reduced reaction anxiety and have a higher number of entrances and spent more time in open arms ($P<0.05$) in the test group animals compared to the control group. However, a dose of 3 mg/kg had no significant effect. Conclusion: It is concluded that the glucocorticoid receptor or stress plays an important role in fear and anxiety related behavior.

COMPARISON OF THE EFFECTS OF AQUEOUS EXTRACT OF GLYCYRRHIZA GLABRA, DEXAMETHASONE, AND STRESS ON ACUTE AND CHRONIC PAINS IN MICE

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Introduction: Our previous investigation showed that Glycyrrhiza Glabra (GG) modulates pain in mice. The aim of this work was to examine the role of GG on acute and chronic pain and compare its effect with dexamethasone (Dex) and stress (ST) using formalin test in mice. Methods: In this study male albino mice (25-30 gr.) in 7 groups (n=49) were used. GG (200, 500 and 1000 mg/kg), Dex (0.5, 1 and 2 mg/kg) and vehicle were injected 30 min before test. Stress was applied through a 1 min period of swimming in cold water (18 – 22°). Acute (5 min) and chronic pains (5-40 min) were assessed after injection of formalin 5% (25µl) in right paw using standard scores. Results and Discussion: Results indicated that GG, Dex and ST have analgesic effects both on acute and chronic pains ($P<0.01$ in comparison with control group). Further, the analgesic effect of a higher dose of GG was significantly greater than Dex and ST. Conclusion: The finding above showed that GG extract, Dex and ST have modulatory effects on both acute and chronic pain formalin test. Further research is required to determine the mechanisms by which GG extract has an inhibitory effect on pain sensation.

THE ROLE OF ACUTE STRESS AND GLUCOCORTICOIDS ON SLEEPING TIME AND DURATION IN MICE

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Introduction: Sleep is a biological rhythm that is probably controlled by many structures, hormones and neurotransmitter systems in brain. Previous evidences suggested that glucocorticoid (Glu) receptors or stress is involved in sleeping time and duration. The aim of this study is to determine the role of peripheral injection of Corticosterone, as a Glu agonist, or acute stress on sleeping time in mice. Methods: Male albino mice (n=60, 25-30 g) were used in this experiment. At first the sleeping time was assessed by Angel behavioral method in intact animals, and then animals classified randomly to six groups. Treatment groups (n=40) received Corticosterone as a glucocorticoid agonist in doses of 0.3, 1, 2 and 5 mg/kg. The control group (n=10) received the same volume of vehicle IP and stress group received 10 min restraint stress 30 min before the sleep assessment. Then we assessed and measured again the sleeping time and duration by the same methods in those animals. Results and Discussion: Results indicated that peripheral injection of Corticosterone in doses of 2 and 5 mg/kg and acute stress significantly reduced sleeping time ($P<0.01$). But doses of 0.3 and 1 mg/kg had no significant effects. Conclusion: Our findings show that stress or glucocorticoids may play an important role on the regulation of sleep in mice.

DYNAMICS OF APOPTOSIS, SYNTHESIS OF THE APOPTOS-ASSOCIATED PROTEINS AND FUNCTIONAL ACTIVITY OF HYPOTHALAMIC NEUROSECRETORY CELLS IN AGEING

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Introduction: Changes in the neuroendocrine and immune systems are involved in the mechanism of ageing. The work of a gene tnf is linked to proteins of the Bcl-2 family and the cascade of caspases. The product of this gene TNF-a (tumor necrosis factor) takes part in the regulation of proliferation, apoptosis, activation of immune cells, inflammation, carcinogenesis and embryogenesis. Our aim was to study the dynamics of apoptosis and altered synthesis of vasopressin, proteins Bcl-2 family (Bcl-2, Mcl-1, Bax) and caspase-8 in neurosecretory cells of hypothalamus in ontogeny. Methods: We examined neurosecretory paraventricular and supraoptical nuclei of tnf-knockout mice (tnf-/-) (2, 9, 13 mo), wild type mice (wt) (4, 12, 15, 24

mo), as well as white outbred mice (4, 18 mo) of different ages. We performed immunohistochemistry reactions with antibodies to investigate the proteins. Densitometry was used for the definition of optical density. The level of apoptosis was defined with the use of luminescent microscopy. Results and discussion: Overall, apoptosis increased in the paraventricular and supraoptical nuclei in mice of all genetic lines through the ageing process, and was accompanied by a high concentration of caspase-8 in neurosecretory cells of old mice in all investigated lines. We also found genotype differences in expression of apoptos-associated proteins of the Bcl-2 family in hypothalamus. The age-related changes in expression proteins of the Bcl-2 family did not influence the activation of apoptosis in neurosecretory cells of tnf-/- ageing mice. The mechanisms of regulating Bcl-2 family synthesis proteins in different neurosecretory centers were discerned. The expression of vasopressin in the hypothalamus of white outbred mice was much higher in comparison with the linear mice at all stages of ontogeny. Wt and tnf-/- mice had increased vasopressin production, which was unaltered in white outbred mice. Conclusion: We found that the age-related activation of apoptosis occurs in both the nuclei of animal s in all investigated lines. Initiation of apoptosis of white outbred mice was associated with altered expression of Bcl-2 family proteins. However, such changes were not revealed in tnf-/- mice. The high level of synthesis of caspase-8 in neurosecretory cells of tnf-/- mice suggests the participation of other factors in the regulation of apoptosis that seem to activate caspase cascade without participation of tnf-alpha.

Our Forthcoming Events

- 12th "Stress and Behavior" Conference - 2nd ISBS congress (May 16-20, 2009, St. Petersburg, Russia)
- 2nd ISBS Summer School on behavioral genetics and neuroscience of stress (May 22-27, 2009, Riga, Latvia)

Conference Secretariat:

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Presenting Authors Index

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Lasko, Natasha
Lebedeva, Irina
Levin, Evgeny A.
Lezheiko, Tatyana
Liang, Yiqing
Lozova, Viktoriia
MacKenzie, Alasdair
Makina, Daria M.
Manzanares, Jorge
Manzhosova, Galina
Morina, Irina Y.
Mukhin, Valery
Netzer, Florence
Noskova, Tatyana
Novoselova, Nina
Osipova, Daria
Pastukhov, Yuriy
Pavlov, Konstantin
Pitman, Roger K.
Porozovs, Juris
Pushchina, Eugenya V.
Quinn, John
Roelofs, Reinko
Salomons, Amber
Schulz-Klaus, Brigitte
Sekoyan, Irene
Shabanov, Petr D.
Shchegolkova, Julia
Shim, SH
Shleptsova, Varvara
Sollertinskaja, Tatjana N.
Titkova, Anna
Tolmacha, Nelli
Tronche, Christophe
Tsai, Arthur C.
Tzikunov, Sergey
Utevska, Svitlana
Vaezi, Gholamhassan
Vorobyova, Tamara
Vovk, O.N.
Wongwitdecha, Noppamars
Zhavbert, Ekaterina

Zieba, Barbara
Zubareva, Olga