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IN COLLABORATION WITH: THE WORLD FEDERATION OF SOCIETIES OF
BIOLOGICAL PSYCHIATRY (WFSBP)

4TH ISPNE REGIONAL CONGRESS FOR EASTERN AND CENTRAL EUROPE

“STRESS AND PSYCHOENDOCRINE
CHANGES ACROSS THE LIFE CYCLES”
PROGRAM AND ABSTRACTS





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T U R I N Y S
C O N T E N T S

4th ISPNE Regional Congress for Eastern and Central Europe
“Stress and psychoendocrine changes across the life cycles”
4th Baltic Symposium of Biological Psychiatry

INVITATION	2
PROGRAM:	5
English.....	5
Lithuanian.....	8
ABSTRACTS:	11
Plenary Lectures	11
Symposiums (Oral Presentations).....	14
Poster Sessions.....	25
Endocrine Responses to Stress (P1).....	25
Stress and Heart (P2).....	29
Stress and Psychiatric Morbidity (P3).....	31
Stress and Women Health (P4).....	33
Others (P5)	35
PROCEEDINGS:	40
Uriel Halbreich	
Treatment of Reproduction Related Disorders in Women	40
Dimiter Dimitrov	
Stress, Dietary Habits and Metabolic Syndrome.....	42
Julia Fedotova	
Effects of Mild, Moderate and Severe Stress on Depression in Female Rats: Modifications by Estrous Cycle, Ovariectomy and Estradiol Replacement.....	45
N.P. Garganeyeva, V.Ya. Semke, M.F. Belokrylova, E.V. Ryabova	
Formation of Psychosomatic Correlations in Diabetes Mellitus Type 2.....	48
Markowitsch, H.J	
Brain Imaging Correlates of Stress-related Memory Disorders in Younger Adults	50
Robertas Bunevičius	
Thyroid Gland and Mental Disorders	53
Aida Spahic-Mihajlovic, John W. Crayton, Edward J. Neafsey,	
Emotional Numbing and Salivary Cortisol in Male and Female Bosnian Refugees With PTSD	56
Fatih Tanriverdi, Fahrettin Kelestimur	
Is Polymyalgia Rheumatica (PMR) a Stress Related Disorder? ...	59
Regina C. Casper, Erika Gaylor, Barry E. Fleisher, Joan Baran,	
Allyson Gilles, Anne DeBattista, H. Eugene Hoyme	
Perinatal and Postnatal Symptoms after Late in Utero Exposure to Serotonin Reuptake Inhibitors (SSRIs).....	61
Giedrius Varoneckas	
Sleep, Depression and Cardiovascular Function in Coronary Artery Disease	63
AUTHOR INDEX	66
PSICHOFARMAKOLOGIJOS AKTUALIJOS	68

INVITATION

4th Regional Congress for Eastern and Central Europe “Stress and psychoendocrine changes across the life cycles”

June 15-17, 2006
Vilnius, Lithuania

Dear colleagues,

It is a great pleasure to invite psychiatrists, endocrinologists, psychologists, neurologists and other scientists to the 4th Eastern and Central European Regional Congress of the International Society of Psychoneuroendocrinology (ISPNE) in Vilnius, Lithuania, 15-17 June 2006.

Endocrine factors play a key role in growth, maturation and aging of the brain. Hormone changes during life cycles and stress have a great impact on brain functioning, mental state, physical health, and quality of life. The main topic of this congress “Stress and psychoendocrine changes across the life cycles” will cover endocrine-brain interactions across different life spans; from fetal brain development, to aging and neurodegenerative diseases in the elderly.

On the behalf of the ISPNE, organizer of the Congress, and the Lithuanian Society of Biological Psychiatry, host organization of the Congress, we would like to invite physicians and scientists to share research data, clinical experience and knowledge in the field of psychoneuroendocrinology in the very centre of Europe. Geographical centre of the continent is located only in a few kilometers from Vilnius, host city of the Congress, and the capital of the Lithuania. Vilnius is the largest and the most beautiful city of the country. The old town of Vilnius, recognized as UNESCO World Heritage Site and the new Vilnius, with the modern skyscrapers, is a good illustration for changes across the life cycles. We hope that scientific and social program of the Congress will make your participation not only scientifically rewarding but also as enjoyable as possible.

With kind regards,

Robertas Bunevičius
President of the Lithuanian Society of
Biological Psychiatry (LSBP)



Ned Kalin
President-elect of the International Society of
Psychoneuroendocrinology (ISPNE)



4th Regional Congress for Eastern and Central Europe
“Stress and psychoendocrine changes across the life cycles”

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International Society of Psychoneuroendocrinology (ISPNE)
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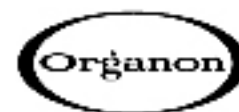
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ABSTRACTS

PLENARY LECTURES

PL-01 Oxytocin and the Intergenerational Transmission of Maternal Behavior and Stress Responses

Cort Pedersen

*The University of North Carolina at Chapel Hill,
Dept of Psychiatry, Chapel Hill, North Carolina, USA*

Clinical experience and research in humans and primates clearly show that nurturing received early in life influences parenting, other social behavior and the capacity to cope with stress during adulthood. Analogous relationships have recently been found in rats. The amount of pup-licking (PL) and arched-back nursing (ABN) received during the first postnatal wk is inversely related to the magnitude of adult responses to acute stressors (anxiety and adrenal axis activation) and is directly related to the PL-ABN adult females bestow on their own pups. Oxytocin (OT) has been implicated in a number of ways in the intergenerational transmission of similar levels of maternal behavior and acute stress responses. The effects of centrally-infused OT antagonist show that OT stimulates PL and ABN in rat mothers. Indeed, antagonist administration decreases the PL frequencies of mothers that received high rates of maternal licking during infancy to levels exhibited by mothers that received low maternal licking indicating that differences in central OT activity account entirely for their contrasting PL frequencies. This may be related to the greater central OT receptor concentrations found in adult female rats that received high rates of maternal licking. OT receptor density is higher in sites in which OT stimulates maternal behavior or decreases stress-induced anxiety and adrenal activation. OT receptor distribution is more widespread in the postnatal compared to the adult brain suggesting that OT may influence the early development of a number of neurochemical systems. If maternal behavior affects OT activity in the female pup brain, it could be a mechanism whereby the amount of PL-ABN received regulates the development of neural systems affecting adult maternal behavior and emotionality. In partial support of this hypothesis, OT and OT antagonist treatments of female rats on postnatal days 2-10 respectively increase and decrease their adult PL frequencies. In summary, OT selectively enhances rat dams' PL-ABN which may regulate central OT activity in female pups and, thereby, influence their neurochemical development including expression of brain OT receptors and, consequently, their adult PL-ABN frequencies and acute stress responses.

PL-02 Stress, Depression and the Role of the Immune System: is Depression an Inflammatory Disorder that Preludes Dementia?

Brian E. Leonard^{1,2}

¹Pharmacology Department, National University of Ireland, Galway, ²European Graduate School of Neuroscience, University of Maastricht, The Netherlands.

Key words: HPA axis, corticosteroids, pro-inflammatory cytokines, serotonin, noradrenaline, kynurenine pathway, neurodegeneration.

The impact of acute and chronic stress on the hypothalamic-pituitary-adrenal (HPA) axis is reviewed and evidence presented that corticotrophin releasing factor (CRF) is the stress neurotransmitter which plays an important role in the activation of the central sympathetic and serotonergic systems. The activity of CRF is expressed through specific receptors (CRF1 and 2) that are antagonistic in their actions and widely distributed in the limbic regions of the brain, as well as in the hypothalamus, and on immune cells.

The mechanism whereby chronic stress, via the CRF induced activation of the dorsal raphe nucleus, can induce a change in the serotonergic system, involves an increase in the 5HT_{2A} and a decrease in the 5HT_{1A} receptor mediated function. Such changes contribute to the onset of anxiety and depression. In addition, the hypersecretion of glucocorticoids that is associated with chronic stress and depression desensitises the central glucocorticoid receptors to the negative feedback inhibition of the HPA axis. This indirectly results in the further activation of the HPA axis.

The rise in pro-inflammatory cytokines that usually accompanies the chronic stress response results in a further stimulation of the HPA axis thereby adding to the stress response. While CRF would appear to play a pivotal role, evidence is provided that simultaneous changes in the serotonergic and noradrenergic systems, combined with the activation of peripheral and central macrophages that increase the pro-inflammatory cytokine concentrations in the brain and blood, also play a critical role in predisposing to anxiety and depression. Neurodegenerative changes in the brain that frequently occur in the elderly patient with major depression, could result from the activation of indoleamine dioxygenase (IDO), a widely distributed enzyme that converts tryptophan via the kynurenine pathway to for the neurotoxic and product quinolinic acid.

PL-03 Glucocorticoids: Harmful or Protective?

Ronald E. Kloet

*Leiden University, Department of Medical Pharmacology,
LACDR/LUMC, Gorlaeus Laboratory, Leiden, The Netherlands*

In psychiatric illness emotional arousal, cognitive abnormalities, psychotic episodes and physical health are often related to altered activity of the hypothalamic-pituitary-adrenal (HPA) activity corresponding to either excessive or inadequate actions of cortisol. This altered neuroendocrine reactivity pattern depends on genetic background, early life experience and the ability to cope with a stressor. In this 'Meet the Professor' session we will address the question under what conditions the life sustaining and adaptive functions of cortisol can be considered harmful. What is the cause and what are the long term consequences? In addressing this question I argue that the outcome of the neuroendocrine reaction pattern for health depends on

the balance in the two modes of operation of the stress system: activation and suppression, and the context in which the stress system operates. The discussion will proceed along the following specific issues:

1. molecular basis: the stress system balance is viewed from the actions mediated by mineralocorticoid (MR) and glucocorticoid receptors (GR) expressed in the limbic brain. These receptors convey signals over all temporal domains of the stress response from fast non-genomic to slow genomic actions.
2. Genetic basis: Genes are being discovered (e.g. the γ -secretase gene) that control developmental programs producing extreme differences in dopamine/stress responsivity.
3. Perinatal experience: the outcome of early life experience is not inevitably unidirectional (as literature suggests) but rather drives 'cognitive performance' to the extremes (impaired vs unimpaired) at the expense of the average.
4. Coping with stress: A change in neuroendocrine response patterns is always adaptive. Whether the outcome is (experienced as) protective or harmful depends on 'context'.

Karst et al. (2005) PNAS 102: 19204-19209; Coolen et al. (2005) Neuron 45: 497-503; de Kloet et al. (1999) Trends Neurosci 22, 422-426; de Kloet et al (2005) Nature Rev Neurosci 6: 463-475; de Kloet et al (in press) Nature Clin Pract Endocr & Met. Supported by the Royal Netherlands Academy of Arts and Sciences.

PL-07 Andropause: Definition, Diagnosis and Treatment

Jean-Jacques LEGROS,
Endocrine Service, Psychoneuroendocrine Unit,
University of Liege, Belgique.

«Andropause» or «male climateric» refer to the term «menopause» in the women. The parallelism between both entities is however only partial since the decrease of gonadal function in the male is very different from one individual to the other. Some men present a gonadal deficiency together with an increase gonadotropin function as early as in the 40s while others show normal testicular function at 80 or later! It appears that besides genetic factors many life events (stress, obesity, sedentarity) can «precipitate» testicular failure. Besides the major symptoms of sexual impotency and loss of libido, testosterone deficiency also induces reversible modification in lipid profile, muscle strength, bone density and on some cognitive and psychological parameters. It is therefore reasonable to treat androgen deficiency in early or late aging provided a cautious urological check-up has been realized before treatment. The mode of administration (IM, PO, or transdermal) will depend on the principal goal of the treatment and on the wish of the patient! An annual clinical and biological urological assessment is mandatory. In this presentation, we will focus on personal results based on public detection campaign and on Interdisciplinary University Andropause Clinic. We will discuss the practical guidelines recently published in that field (Europ. Urology, 48, 2005, 1-4).

PL-08 The Mystery of Hypocortisolism

Hellhammer Dirk
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A rapidly growing body of literature contra-intuitively suggests that hypocortisolism is frequently associated with a wide range of stress related disorders, including chronic daily pain syndromes, chronic fatigue, post-traumatic stress disorder, irritable bowel syndrome, fibromyalgia, etc. Although it is conceivable that insufficient glucocorticoid signalling during stress would lead to maladaptation and ultimately disease, particularly in physiologic and central systems that are targets of the regulatory effects of cortisol, the precise definition, measurement, and epidemiology of hypocortisolism, as well as its underlying mechanisms and physiological relevance remain to be explored. We will exemplify the presence and possible origins of hypocortisolism in fibromyalgia. Our recent data suggest that prenatal stress may program low adrenal capacity particularly in the female fetus and that low adrenal capacity may be considered a risk factor for fibromyalgia under stressful conditions in later life.

PL-09 Brain Imaging Correlates of Stress-Related

Markowitsch Hans J.,
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Bielefeld, Bielefeld, Germany

Stress-related memory impairments are usually confined to the autobiographical memory domain and are mainly found in younger patients with dissociative amnesias (Markowitsch, 2002; Fujiwara et al., 2006). Major traumatic events may provoke such amnesias. Data obtained with roughly a dozen patients with dissociative amnesias indicate that stress may induce reductions in brain metabolism which have a major impact on the patients' memory and social life. Static and functional neuroimaging as well as neuropsychological testing were applied to investigate consequences of a threatening environment. All patients suffered from retrograde autobiographical amnesia while other memory domains were either largely unimpaired or could be regained within a short period. Autobiographical amnesia affected year-long portions or all of their past life. Brain imaging with FDG-positron-emission-tomography revealed a reduced glucose level in frontal and temporal (or temporo-parietal) regions, affecting the right hemisphere more than the left one. fMRI or 15O-PET showed a differential activation for remembered (or reacquired) as opposed to forgotten material. Our data show that environmentally induced stress situations may change brain activity and cerebral metabolism persistently. They also indicate that the brain's circuitry in getting access to previously stored information is altered. Especially fronto-temporal regions of the right hemisphere may be sensitive to autobiographical old memory processing.

Markowitsch, H.J. (2003). Psychogenic amnesia. *NeuroImage*, 20, S132-S138. Fujiwara, E., Brand, M., Kracht, L., Kessler, J., Diebel, A., Netz, J. & Markowitsch, H.J. (2006). Functional retrograde amnesia: a multiple case study. *Cortex* (in press).

PL-10 Synergic Concept of Dependent Behavior*Sidorov Pavel**Rector, Institute of Psychology and Psychoneurology,
Psychology & Psychiatry, Northern State Medical University,
51, Troitsky Ave, Arkhangelsk, Russia*

The variety of views on mechanisms of etiopathogenesis and clinical phenomenology of dependences emphasizes the necessity of dependent behavior's multidisciplinary studies. A new methodological instrument of studying dependent behavior is synergetics, a multidisciplinary science about development and self-organization. The integrating ability of the synergic approach can be generally presented by three main levels (vectors) of a biopsychosocial model of ontogenesis. Sociogenesis of dependent behavior is to a certain extent predetermined by violation of a structure and functions of a parents, family, violation of maturation and socialization of a personality in a disharmonious millisocial milieu. To a considerable extent, psychogenesis is predetermined by a premorbid psychopathologic burden which is remarkable by its emotional and communicative defects. An important role in biogenesis (somatogenesis) is played by a non-specific hereditary burden, unfavorable intra- and perinatal influences. Generally and somewhat relatively, the synergic concept of dependent behavior with a change of fractals can be shown in the following way: predispositions - changed biopsychosocial basis latent - recollections; obsessive reminiscences; initial; obsessive phantasies; obsessive-compulsive actions (prodrome of a detailed clinical picture); a detailed clinical picture behavior with signs of dependence; initial - inverse pathokinesis. The synergic approach presupposes considerable revision of preventive and medical rehabilitation strategies of aid to dependent personalities, changes in the ideology and methodology of the traditional addictological service. A subject of preventive activity should be a new class of experts-preventologists that professionally deal with self-preserving behavior.

SYMPOSIUMS (ORAL PRESENTATIONS)

OR-01 Aging Male, Testosterone and the Central Nervous System

Birute Zilaitiene¹, Lina Lasaitė¹, Valentinas Matulevicius¹, Niels Jorgensen²

¹Institute of Endocrinology, Kaunas University of Medicine, Kaunas, Lithuania, ²Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark

Effects of sex steroids on psychological state of men are still explored insufficiently. Some evidences about the correlation of endogenous testosterone and cognitive function of young and older men could be found in the earlier studies.

The aim of our study was to explore relationship of psychological state of young men with testosterone concentration.

Methods. 206 young men, mean age 20.8±1.7 years, range 18-26 years, participating in the European Commission study no QLK4-CT-1999-01422, NAS: QLK4-CT-2001-02911 „The Reproductive Function of Estonian, Latvian and Lithuanian young men“ were invited to participate in the substudy evaluating their psychological state. The following tests were performed: Trail Making (TM) test, which shows attention, memory and psychomotoric speed; Wechsler Adult Intelligence Scale, Digit Symbol Tests (DST) – the bigger score in it denotes better cognitive function; Profile of Mood State (POMS), which is related to mood and emotional state.

Results. Mean testosterone concentration in the group of healthy Lithuanian men was 26.2±8.4 nmol/l. Mean score of TM test was 60.5±16.8, range 20-120, mean DST score – 17.6±3.6, range 7-26, total POMS – 20.7±23.4, range -31-111. There was no significant correlation between total testosterone concentration and DST scores and between total testosterone concentration and POMS scores. However TM test results correlated with total testosterone concentration significantly ($r=0.151$, $p=0.03$).

Discussion. Results from a big group of healthy young men confirm that even in a young population testosterone concentration is important for cognitive functions. The demographic data clearly demonstrates increasing percentage of older population. Also it was demonstrated by epidemiological data that a significant part of men after the age of 60 years have testosterone concentration lower than normal and experience a lot of psychological problems. Recent data demonstrate an improvement of mood, energy levels, and libido using optimal testosterone supplementation. Data on the impact of testosterone supplementation on cognitive functions is still controversial, but, the positive effect could be expected in the larger studies, because, as we demonstrated in our study, even endogenous testosterone is related to attention, memory and psychomotoric speed.

OR-02 Gestational Age at Birth Predicts Cardiovascular Stress Responses 60 Years Later

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Background. The association of size at birth with adult blood pressure is relatively modest compared with its stronger association with overt hypertension and its complications. However, most studies have used blood pressure measurements at a clinic, which may be an inaccurate indicator of blood pressure responsiveness to everyday stressors. We investigated whether gestational age and birth weight, as markers of fetal environment, predict blood pressure responses during experimentally induced psychosocial stress in late life. **METHODS.** A total of 73 men and 80 women born after 36 weeks' gestation in Helsinki, Finland, during 1934-44, underwent Trier Social Stress Test (TSST), a standardized psychosocial stress test consisting of speech and arithmetic task in front of a two-person jury. Changes in blood pressure levels were monitored continuously via non-invasive finger photoplethysmography (Finometer). **RESULTS.** Mean systolic/diastolic increments from baseline to task were 40/21 mmHg. Birth weight was weakly related to reactivity scores in men. This association disappeared after adjustment for gestational age at birth, which proved to be the most robust early determinant of blood pressure response; however, the relationship was opposite in men and women (p for interaction=0.001). In women, one week increase in gestational age at birth was associated with a decrease of 3.1 mmHg (95% CI 0.4 to 5.9) in systolic and 1.2 mmHg (-0.1 to 2.5) in diastolic response, while in men one week of increase in gestational age was associated with an increase of 4.9 mmHg (1.9 to 8.0) in systolic and 2.2 mmHg (0.8 to 3.7) in diastolic blood pressure. **CONCLUSIONS.** Cardiovascular stress responses at age 60 are predicted by normal variation in gestational age at birth, with opposing effects in men and women. Since the hypothalamic-pituitary-adrenal axis is known to be involved in the regulation of autonomic nervous system function, blood pressure and the timing of parturition, and it shows well-established sex differences, we speculate a role of early programming of this axis in explaining this finding.

OR-03 Chronic Stress, Dietary Habits and Metabolic Syndrome

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Chronic stress leads to elevated cortisol levels, which may lead to accumulation of visceral adipose tissue (VAT) and Metabolic syndrome. Stress-induced increased levels of glucocorticoids can also have a major effect on food intake. A subset of stressed or depressed humans may overeat, especially comfort food (e.g., sugar and fat), in an attempt to reduce anxiety and activity in the chronic stress-response network. This is supported by the finding that these people have decreased cerebrospinal corticosteroid releasing factor (CRF), catecholamine concentrations, and HPA activity. While comfort foods

may calm them down in the short term, they may lead to abdominal obesity if this becomes a long term "solution." The chronic elevation of systemic glucocorticoids may contribute to VAT deposition. By itself, being obese may be a stressful stimulus to overeating. A weight loss program can be stressful, which can sabotage its success by eliciting the release of stress hormones, which, in turn can make a person crave high energy foods. Feeding rats a long-term high-sucrose diet along with supplemental dexamethasone has been shown to increase fat depots and induce liver steatosis. In addition to dietary intervention, stress management may improve one's cognitive, behavioral, and physiologic responses to stress, including glycemia.

OR-04 Depression and the Metabolic Syndrome in Middle Aged Adults Population

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The metabolic syndrome is a constellation of metabolic disorders, such as obesity, dyslipidemia, hypertension, hyperglycemia, that are associated with increased risk of type 2 diabetes mellitus and cardiovascular diseases. Previous reports have suggested that depression may lead to the development of cardiovascular disease through its association with the metabolic syndrome; however, little is known about the relationship between depression and the metabolic syndrome. The aim of our study was to estimate relation of depression and the metabolic syndrome in general adults population. Methods: In cross-sectional study we analyzed clinical, anthropometric and biochemical parameters in 1115 adults (aged 45 – 96 years): 562 (50.4 %) men and 553 (49.6 %) women – randomly selected in one of the Lithuania district. Diagnosis of metabolic syndrome was based on 2005 International Diabetes Federation diagnostic criteria. A standard questionnaire – the Hospital Anxiety Depression Scale – was used for the assessment of depressive disorder. Results: The prevalence of metabolic syndrome was 42.5 % (CI 95 % 39.6 – 45.5), in men 31.1 % (CI 95 % 27.4 – 35.2), in women 54.1 % (CI 95 % 49.8 – 58.3), $p = 0.00001$. The prevalence of depression in all sample was 37.1 % (CI 95 % 34.3 – 40.1), in men 26.2 % (CI 95 % 22.6 – 30.0), in women 48.3% (44.1 – 52.5), $p = 0.00001$. In persons with metabolic syndrome prevalence of depression was 47.7 %, in persons without metabolic syndrome 29.3 %, $p = 0.0002$. In women with metabolic syndrome prevalence of depression was significantly higher, then in women without metabolic syndrome – 60.2 % and 34.3 %, $p = 0.0001$, respectively. In men we did not found significant differences between these two groups (with and without metabolic syndrome) – 26.3 % and 26.1 %, $p = 1.0$, respectively. Metabolic syndrome was associated with depression in women (OR = 2.9, CI 95 % 2.05 – 4.11), but was not significantly associated in men (OR = 1.01, 95% CI 0.67 – 1.52). Conclusion: We found, that the prevalence of depression in general middle aged adults population of one of the Lithuania district was significantly higher in women with metabolic syndrome.

OR-05 Formation of Psychosomatic Correlations in Type 2 Diabetes Mellitus

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Objective: To assess a part of factors of mental maladaptation in formation of psychosomatic correlations in patients with type 2 diabetes mellitus (DM) with methods of multivariate biostatistics, logistic regression (LR). In the Borderline States Department of SI MHRI TSC SB RAMSci 203 patients with type 2 DM, age 50.62 ± 8.07 years have been examined. Structure of mental disorders (MD): 40.0 % - depressive disorders of neurotic and affective spectrum; 32.5 % - asthenic; in 9.5 % - anxiety-phobic; in 11% - somatoform; in 7.0 % - personality disorders. Adjustment and affective disorders were notable by instability of glycaemia level (4.63 – 11.68 mmol/l). Dispersion analysis has established interrelationship between age of onset of MD, conditioned by stressor factors (life events, social, medical) ($p=0.00135$) and diabetes severity degree ($p=0.0046$). Maximum dependence was observed in diabetes, for which compensation insulin was used and diagnosed in the first six months from onset MD. Stressor factors and associated with them MD of the depressive character, promoted a quicker decompensation of type 2 DM requiring administration of insulin. LR method (Concordant from 74.5 to 92.7 %) has established predictors: glycaemia level ($p=0.0001$); MD duration ($p=0.0002$); stressor factors (life events) $p=0.0001$; body mass index ($p=0.0001$); vegetative disorders ($p=0.0005$); dyslipidemia ($p=0.0009$); age of on-set of MD ($p=0.0118$); MD ($p=0.0029$); subjective attitude of the patient toward his/her disease ($p=0.0046$); anxiety level ($p=0.0104$); changes of retina vessels ($p=0.0214$); level of SAP ($p=0.045$); family history according to DM ($p=0.0437$). Anosognosia was combined with excessive, undifferentiated anxiety. Programs of treatment and prevention of DM in general health care practice should account mental and psychosocial factors as additive criteria of stratification of risk of exacerbation of the diabetes in interaction of specialists (internist/endocrinologist, psychiatrists, psychotherapist).

OR-06 Peculiarities of Body Composition, Emotional State and Quality of Life in Obese Male and Female

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Obesity is a widespread and growing health problem. It can have serious consequences in both physical and psychological domains.

Objective of the study was to determine body composition, quality of life and emotional state in obese male and female and to compare that to the body composition, quality of life and emotional state of normal population of the same age and gender, also to find correlations between body composition, quality of life and emotional state data.

Patients and methods. 52 persons – 26 male (43.3 %) and 34 female (56.7 %) were recruited to the study. Two groups were formed of them according to the data of body mass index (BMI): research group (age 41.97 ± 12.8 years) - BMI >30 (n=22) and control group (age 40.2 ± 14.7 years) - BMI <25 (n=30). Data of body composition was assessed by body composition monitoring unit „Bodystat 1500“ (Great Britain). Height was measured by stadiometer of international standard „Holtain Limited, Crymic Dyteg“ (Great Britain), weight by electronic weights „Soehnle“ (Great Britain). Profile of Mood State (POMS) was used for the assessment of emotional state. Quality of life was evaluated by means of World Health Organisation Quality of Life questionnaire (adapted short version) (WHOQOL-100). Results. In body composition data weight (121.1 ± 25.3 kg vs. 78.2 ± 7.6 kg, $p < 0.001$), BMI (38.2 ± 7.4 kg/m² vs. 24.5 ± 1.3 kg/m², $p < 0.001$), waist-to-hip ratio (0.94 ± 0.02 vs. 0.85 ± 0.05 , $p = 0.01$), fat body mass (43.3 ± 17.3 kg vs. 14.6 ± 5.7 kg, $p < 0.001$), lean body mass (77.8 ± 10.7 kg vs. 63.6 ± 6.5 kg, $p = 0.002$), water body mass (55.3 ± 7.8 kg vs. 44.4 ± 4.2 kg, $p = 0.001$), basal metabolic rate (2286 ± 326 kcal vs. 1913 ± 194 kcal, $p = 0.004$) of obese male (n=10) were significantly higher than that of male with normal BMI (n=12). In psychological data POMS global score (32.5 ± 29.2 vs. 6.2 ± 21.8 , $p = 0.021$), POMS anger-hostility score (12.7 ± 6.8 vs. 6.7 ± 4.7 , $p = 0.04$), POMS fatigue-inertia score (10.1 ± 5.1 vs. 4.5 ± 4.1 , $p = 0.002$) were significantly higher, showing worse emotional state of male in the obese group than that of male in the control group. Differences in quality of life in the research group and the control group were not significant.

In body composition data of female weight (99.9 ± 20.7 kg vs. 64.3 ± 6.3 kg, $p < 0.001$), BMI (37.3 ± 6.4 kg/m² vs. 23.9 ± 2.1 kg/m², $p < 0.001$), waist-to-hip ratio (0.87 ± 0.04 vs. 0.79 ± 0.06 , $p = 0.015$), fat body mass (47.8 ± 14.5 kg vs. 20.9 ± 4.6 kg, $p < 0.001$), lean body mass (52.1 ± 7.6 kg vs. 43.3 ± 5.7 kg, $p = 0.002$), water body mass (38.8 ± 5.5 kg vs. 31.7 ± 3.0 kg, $p < 0.001$), basal metabolic rate (1616 ± 204 kcal vs. 1421 ± 159 kcal, $p = 0.019$) were significantly higher in the obese group (n=12) than that in the control group (n=18). In emotional state and quality of life data of female no significant differences were detected between the obese group and the control group. In male significant positive correlations were found between weight and POMS depression-dejection score ($r = 0.44$, $p = 0.03$), weight and POMS anger-hostility score ($r = 0.41$, $p = 0.049$), fat body mass and POMS depression-dejection score ($r = 0.52$, $p = 0.009$), fat body mass and POMS fatigue-inertia score ($r = 0.41$, $p = 0.05$), water body mass and POMS anger-hostility score ($r = 0.43$, $p = 0.035$), BMI and POMS depression-dejection score ($r = 0.48$, $p = 0.018$), BMI and POMS anger-hostility score ($r = 0.41$, $p = 0.047$), BMI and POMS fatigue-inertia score ($r = 0.45$, $p = 0.026$), BMI and POMS confusion-bewilderment score ($r = 0.44$, $p = 0.032$), waist-to-hip ratio and POMS fatigue-inertia score ($r = 0.58$, $p = 0.008$). In female positive correlation was found between water body mass and POMS vigor-activity ($r = 0.34$, $p = 0.005$), and negative correlation was found between quality of life and waist-to-hip ratio ($r = -0.52$, $p = 0.023$).

In conclusion, weight, body mass index, waist-to-hip ratio, fat body mass, lean body mass, water body mass, basal metabolic rate, also anger-hostility and fatigue-inertia of obese male are significantly higher than that of normal population of the

same age and gender. Weight, body mass index, waist-to-hip ratio, fat body mass, lean body mass, water body mass and basal metabolic rate of obese female are significantly higher than that of normal population of the same age and gender. Significant correlations between body composition data and psychological data are both in male and in female.

OR-07 Peculiarities of Hormone Secretion in Neuroendocrine Obesity

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Neuroendocrine obesity usually develops due to regulation disturbances at hypothalamic and pituitary level or due to disorders of peripheral endocrine glands.

Objective of the study was to investigate basal and stimulated stress hormones, taking part in fat mass metabolism regulation (cortisol, growth hormone (GH), prolactin (PRL)) concentrations in blood of female suffering of neuroendocrine obesity.

Patients and methods. 36 female of average age of 34.2 ± 11.43 years were recruited to the study. Height was 1.65 ± 0.06 m, weight was 98.0 ± 22.5 kg, body mass index was 36.4 ± 8.8 kg/m², waist-to-hip ratio was 0.86 ± 0.03 . Thyroid and gonadal functions were normal (FT4 was 15.5 ± 11.6 pmol/l, TTH was 1.5 ± 0.7 mIU/l).

20 healthy female were recruited to the control group (age 26.6 ± 9.4 years). Height was 1.67 ± 0.07 m, weight was 66.4 ± 2.4 kg, body mass index was 22.5 ± 2.4 kg/m², waist-to-hip ratio was 0.80 ± 0.02 . Thyroid and gonadal functions were normal.

Blood samples for the evaluation of basal hormone concentrations were taken in the morning for the fasting patients. After that hormone response to insulin induced hypoglycaemia was investigated after insulin injections in doses of 0.1 IU/kg. Blood samples were taken after 30 and 60 min. after the injection. The method of insulin induced hypoglycaemia allows to investigate hormone reserve in patients. Hormone concentrations were assayed by radioimmune standard kits of CEALRESORIN and BYK-MALLINCRODT companies.

Results. Basal levels of GH, PRL and cortisol in blood of all the female (research group and control group) were normal.

Lower GH response to insulin induced hypoglycaemia was noticed in the obese female than in the control group. Basal GH concentration of obese female was 3.04 ± 2.4 ng/ml, after 30 min. after insulin injection it was 4.3 ± 0.2 ng/ml, after 60 min. it was 10.4 ± 6.1 ng/ml. Basal concentration of GH of females of the control group was 2.4 ± 1.9 ng/ml, after 30 min. after insulin injection it was 21.5 ± 4.2 , after 60 min. it was 16.8 ± 2.8 ng/ml. Maximal GH response after 60 min. after insulin injection was significantly lower and later in the obese female than that in the control group ($p < 0.05$).

Lower PRL concentration as a response to insulin induced hypoglycaemia was not significant in the research group. Basal concentration of PRL in the obese female was 241.5 ± 127.5 mIU/l, after 30 min. after insulin injection it was 206.4 ± 98.1 mIU/l, after 60 min. it was 215.7 ± 113.4 mIU/l. In the control

group basal concentration of PRL was 231.6 ± 124.6 mIU/l, after 30 min. after insulin injection it was 421.5 ± 120.7 mIU/l, after 60 min. it was 321.4 ± 117.4 mIU/l. Concentration of PRL after 30 min. after insulin injection in control female was significantly higher ($p < 0.05$) than in the obese group.

Cortisol concentration after insulin injection for the obese female increased, but not significantly: basal cortisol concentration was 460.5 ± 285.7 nmol/l, after 30 min. after insulin injection it was 425.7 ± 242.7 , after 60 min. it was 626.0 ± 285.5 nmol/l. In the control group cortisol concentration increasing reaction to insulin induced hypoglycaemia was significant after 60 min. ($p < 0.05$): basal cortisol concentration was 389.9 ± 115.7 , after 30 min. after insulin injection it was 749.8 ± 93.7 , after 60 min. it was 879.5 ± 91.1 nmol/l.

BMI in female had negative correlation with GH response to insulin induced hypoglycaemia and with basal cortisol concentration. Waist-to-hip ratio in female negatively correlated with GH and PRL response to insulin induced hypoglycaemia and basal cortisol concentration.

In conclusion, in patients suffering of neuroendocrine obesity we found disturbances of growth hormone, prolactin and cortisol secretions. Lack of response to stimulant insulin test depends on regulation defects of hypothalamic level.

OR-08 Nutritional Stress in Anorexia Nervosa: Hormonally Connected Psychological Impairments

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Multiple hormonal alterations occur in Anorexia Nervosa, possibly secondary to the biochemical stress of malnutrition/starvation. The influence that the hormonal impairments exert on the development, course and prognosis of the anorexic psychopathology is relatively unknown. In 96 anorexic female patients plasma concentrations of TSH, FT4, FT3, IGF-1, estrogens and testosterone were significantly lower and those of GH significantly higher than in 30 sex and age matched controls. In parallel in the patients we looked for correlations between hormonal and psychopathological aspects monitored by the EDI-2 and HSCL-90 rating scales. Significant correlations were observed between hormonal impairments and EDI-2 subitem alterations (perfectionism, body dissatisfaction, sense of ineffectiveness, interceptive awareness, interpersonal distrust, maturity fear) and HSCL-90 alterations (depression, somatization, hostility). The significance of these correlations will be discussed.

OR-09 Metabolic Inflexibility, Stress and Psychopathology in Anorexia Nervosa During Weight Restoration

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In anorexia Nervosa there appears to be a metabolic inflexibility whereby fat oxidation during moderate exercise is not suppressed as it is in lean healthy subjects. Like the relatively increased diet induced thermogenesis, this might constitute an impediment to weight gain. A stress response to exercise was also seen in which glucose was increased. As expected, scores on the EAT inventory for eating disorders and the EEE-C quality of life scale were negatively correlated with leptin and positively correlated with adiponectin levels, respectively. Anxiety levels on STAIS were related to vomiting. These phenomena were shown in 10 patients with anorexia nervosa following 8 weeks of nutritional rehabilitation during which time they had gained a mean of 5 kg. In the previous 12 months there had been net weight changes ranging from +7 kg to -10 kg

OR-10 Neurosteroids in Eating Disorders, Implications for Psychopathology

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Neurosteroids are synthesized in the central nervous system, particularly but not exclusively in myelinating glial cells, from cholesterol or steroidal precursors imported from peripheral sources. They include several compounds, such as allopregnenolone or $3\alpha,5\alpha$ -tetrahydroprogesterone ($3\alpha,5\alpha$ -THP), dehydroepiandrosterone (DHEA) and its sulfate metabolites (DHEA-S) (1). The secretion of these compounds occurs also in the adrenal gland, especially in response to stressors. Anorexia nervosa (AN) and bulimia nervosa (BN) are eating disorders of unknown pathogenesis, which can be considered chronic stress conditions with potentially serious somatic consequences. Therefore, it is likely that neurosteroids may play a role in the pathophysiology of these syndromes. To assess whether the secretion of DHEA, DHEA-S, and $3\alpha,5\alpha$ -THP is altered in AN and BN and to explore whether such alterations are related to some aspects of the eating disorder psychopathology, we measured plasma levels of these neuroactive steroids, cortisol, testosterone, and 17β -estradiol in 30 drug-free women with AN, 32 women with BN and in 30 age-matched healthy control subjects. We found that, compared with healthy women, both AN and BN patients exhibited increased plasma levels of $3\alpha,5\alpha$ -THP, DHEA, DHEA-S, and cortisol but reduced concentrations of 17β -estradiol variable. These results support the idea that the enhanced production of these neurosteroids in patients with eating disorders may represent an attempt to counteract a neurotransmitter dysfunction potentially involved in the genesis or maintenance of the aberrant eating behavior. References Rupperecht, R., 2002. Neuroactive steroids: mechanism of action and neuropsychopharmacological properties. *Psychoneuroendocrinology* 28, 139–168.

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OR-11 Biological Age Paradoxes by Alcohol Dependence

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The social stress that continues in Russia is accompanied by appearance of a number of negative social phenomena, in particular, an increase in the number of adult and elderly persons abusing alcohol. One of the important aspects of alcoholization development in adult and elderly persons is somatic troubles. Apart from the fact that the disease increases progressively with age physiological changes at the background, it also strengthens and brings new kinds of pathologies characteristic of such people. Somatic stress caused by alcohol is the reason of a change in biological age (BA) – index of the level of the organism's wear calculated by way of correlation of individual biomarkers with corresponding indices of healthy people at this age. According to the proposals of different authors, BA determination is based on comprehensive medical and anthropological studies including evaluation of a metabolism change including development of hyperlipemia, diabetic type of metabolism, hyperuremia etc. With the goal of BA comparison of adult and elderly persons with symptoms of alcohol dependence, we have examined patients of a mental hospital. We have used both physiological-biological criteria and subjective evaluations of their own health. The results have shown a mismatch of BA and calendar age in most of the examined persons. In particular in the men, a tendency has been traced of precipitated aging with BA exceeding over calendar age as a result of an unbalance between interacting functional systems of an organism. The BA analysis helps to determine rate of aging of persons with alcohol dependence, what is important for evaluation of their life quality and planning of medical-rehabilitation measures.

OR-12 Emotional Numbing and Salivary Cortisol in Male and Female Bosnian Refugees With PTSD

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Emotional numbing is an important symptom of PTSD, but it is not clear whether it affects both positive and negative affect equally or not. To address this question we administered Lang's Looking at Pictures test, in which a series of pictures are rated for valence (pleasant--unpleasant) and arousal (high--low), to 10 male and 11 female Bosnian refugees suffering from PTSD (DSM-IV criteria) and to control groups of 11 male and 10 female Bosnian refugees with similar trauma exposure but without PTSD or any other major mental illness. All subjects were also characterized using Foa's PTSD Symptom Scale and the Hamilton Rating Scale for Depression. In addition, male subjects provided salivary cortisol samples at 8AM on two

consecutive days, with a 0.5 mg tablet of dexamethasone taken at 11PM of the first day (between the two saliva samples). The mean change in 8AM cortisol levels was not different between the control (-0.067 µg/dl) and PTSD (-0.137 µm/dl) male subjects ($t=-0.6277$, $df=12.92$, $p=0.54$). The mean valence ratings for unpleasant, neutral, and pleasant pictures of control males and females and of PTSD males were similar to normal ratings, but PTSD females rated neutral and pleasant pictures as significantly less pleasant than control females (ANOVA). Likewise, the mean arousal ratings for unpleasant, neutral, and pleasant pictures of both control males and females were similar to normal, with both unpleasant and pleasant pictures rated more arousing than neutral pictures. In contrast, in both PTSD males and females pleasant pictures were rated as almost completely non-arousing and significantly lower than controls (ANOVA). Thus, in Bosnian refugees affective numbing is seen primarily with pleasant or positive stimuli. Emotional numbing in PTSD is pervasive and subtle and merits more research and more attention in therapy as well.

OR-13 Increased Psychosocial Strain in Lithuanian Versus Swedish Men: Concomitant Cross Sectional Study of Men Aged 50.

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One of the most important causes of death in any European member state is coronary heart disease (CVD). As an example of these differences is mortality in ischemic heart disease (ICD 410-414) where in 1994 four-fold differences were found between 50 year old men in Lithuania and Sweden. To investigate possible mechanisms, a joint research - LiVicordia (Linköping-Vilnius coronary artery disease risk assessment) study – was planned. This is a cross-sectional survey comparing 150 randomly selected 50 year old men in each of the two cities, Vilnius, Lithuania and Linköping, Sweden. We compared a broad range of traditional and new possible risk factors for CHD. There were small differences in traditional risk factors between the groups: Vilnius men had higher blood pressure, Linköping men had higher levels of serum cholesterol, smoking habits did not differ. However, Vilnius men had signs of more oxidative strain than Linköping men: they had shorter lag phase for LDL oxidation and serum levels of several fat soluble antioxidant vitamins were lower. In addition, other measures, indicating oxidative stress, such as plasma 7-beta-hydroxycholesterol and urinary excretion of 8-hydroxydeoxyguanosine were higher compared to Linköping men. More signs of sub clinical atherosclerosis were found in Vilnius men as measured by intima media thickness and amount of plaque in the carotid and femoral arteries by ultrasound examination. These results suggest that the antioxidant status in Vilnius men is less favorable than for Linköping men, possibly contributing to CHD development. In addition we investigated cortisol and cardiovascular reactivity to a standardized laboratory stress test. Samples for cortisol

analysis were taken in serum and saliva. We found that Vilnius men had lower cortisol responses to the stress test than Linköping men, both in serum and saliva samples. A low peak cortisol response was significantly related to high baseline cortisol, current smoking and to vital exhaustion. This finding suggests a physiological mechanism of chronic stress, which may contribute to increased risk for cardiovascular death.

OR-14 Posttraumatic Reactions and Coping Among Lithuanian Survivors of Soviet Repression

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Between 1940 and 1958 more than 300,000 Lithuanians were arrested and deported to Siberia. Conditions of imprisonment in Gulag camps were extremely harsh and mortality rate from exhaustion and disease was high. Victims who managed to return to Lithuania suffered from persistent persecutions. Traumatic experiences of former political prisoners were neglected for decades; they had to keep in secret the fact of the imprisonment. Our study aimed to examine traumatic experiences and posttraumatic reactions among non-clinical sample of former Lithuanian survivors of political repression. The group of former political prisoners with a history of deportation to Gulag camps was compared with an age and sex matched control group. Semi-structured interviews were used to measure experiences during and after imprisonment and also coping factors. Posttraumatic effects were measured using self-rating scales: Harvard Trauma Questionnaire (HTQ), Impact of Event Scale - Revised (IES-R), Trauma Symptom Checklist (TSC-35). Victims of political repression reported significantly more lifetime traumatic events. 72% of survivors stated that they were persecuted upon return to Soviet occupied Lithuania. Results suggest that traumatic experiences dealing with political imprisonment and exile have long-term posttraumatic effects on Lithuanian survivors of the soviet repression: compared with control group they had significantly more PTSD intrusive recollection symptoms, more sleep disorders symptoms, poorer subjective rating of health. Belief in God, mutual support of survivors as well as support of family members, political activity and hope were indicated by survivors as main coping factors.

OR-15 Post Tsunami - Early Mental Health Intervention

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Introduction. Some of the coastal areas in Penang and Kedah were affected by Tsunami disaster or the killer waves on the 26th of December 2004 which had devastating effect on the residents of the Coastal area and also those picnicking in the beaches. Such disasters would lead to development of Post Traumatic Stress Disorder (PTSD) among affected people. An

Early Mental Health Intervention programme was carried out in Balik Pulau, Penang, which was one of the badly affected spots. **Objective** The objective of the intervention programme was to identify the victims, counsel them, make references if necessary and segregate help resources to make sure that they do not develop Post Traumatic Stress Disorder (PTSD). **Methodology** Penang residents identified as the tsunami victim by the local health authorities were recruited. A group of Health care workers, school teachers, village authorities and volunteers were trained to carry out the crisis intervention programme and become trainers, by health care workers experienced in crisis interventions. The recruited subjects were then subjected to crisis intervention programme. Follow up assessments were made 6 months after the intervention programme to identify the victims who were still having problems. **Results.** The early psychiatric intervention programme included 299 adult victim. Outcomes of the follow up assessment showed that only 1% of the victims (n= 3) had problem. The victims with problems were referred to doctors. This shows that the intervention programme which was done in the first week after tsunami disaster with reference to medical services had helped to stabilise the victims such that 6 month later only 1% had psychiatric problem.

OR-16 Migration and Stress Among Adult Foreigners in Vilnius City

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Foreigners coming from abroad to Lithuania on the basis of business, work or studies were exposed to long lasting stress, unstable surrounding, new people with their habits, tradition, culture, language, their way of thinking and working, they have language problems and they needed to cope with new problems and adopt themselves to new circumstances. The stress from workload, relations and time pressure had a great impact on their quality of life, mental state and physical health, leading to depression. The main purpose of the survey was to assess migration as a risk factor among adult foreigners in Vilnius city. A central aspect of the study was to investigate the foreigners lifestyle and evaluate migration as a risk factor in itself that could affect their health in negative way. Migration by itself is one of the most important risk factors for foreigners quality of life and it was not identified and assessed in previous studies. In this survey foreigners were defined as foreign born persons with another cultural, religious and linguistic background, having lived in Lithuania more than three months according the Law on status of foreigners in Lithuania (1999). Comes from former Soviet Union countries were excluded. **Method.** The tool for survey was Questionnaire about Health Behaviour and Migration as Risk Factor Among Adult Foreigners in Vilnius city, which consisted of 34 questions. The method of sampling – non-probability quota sampling. Sample group reflected the general population of foreigners in Lithuania of 2000 by age and sex. The transactional model of stress explains the nature of stress and coping in terms of transactions between a person and the environment. Nearly all foreigners suffered from stressors but not all developed deterioration of health status, symptoms of ill health and depression. In our work we investi-

gated the opinion of deterioration of health status, frequency of symptoms of ill health and depression. However constitutional predisposition, health practices, coping, personality and social support were moderating factors of stress for them. Coping with new environment are to be found in a sense of coherence.

OR-17 Cortisolemia in First - Episode Schizophrenia

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Background: Dexamethasone test (DST) non-suppression occurs frequently also in schizophrenia. Higher rates of DST nonsuppression have been attributed to depressive symptoms, suicidality and negative symptoms. Available data suggest that phase of illness and medication status influence rates of DST nonsuppression and may partially account for some discrepant findings in the literature. No study concerning first-episode schizophrenia has yet been published.

Aim of the study: To assess cortisolemia and DST in first-episode schizophrenia and search for clinical correlates.

Methods: In patients hospitalised for the first time with first-episode schizophrenia The DST has been performed before, at the end of the acute treatment and after one year. At the same time the clinical evaluation with PANSS was performed. A cortisol value greater than 5 microgram/dl in either of the post-dexamethasone samples indicated nonsuppression of cortisol. For statistical analysis descriptive statistics and nonparametric methods (Spearman's correlation) were used.

Results: Totally 56 males (mean age 22 years, mean duration of illness 0.6 years). 18% of pts were DST nonsuppressors at medication-free baseline, 5 % and 16% after acute treatment and after one year respectively. After 1 year 42/56 of patients fulfilled the criteria of remission. The rate of nonsuppression was 21%, 5% and 17 % in remitters and 7%, 7% and 14 % in nonremitters. Significant differences in the whole group were found between postdexamethasone cortisolemia at discharge on the one hand and on admission and at the one-year follow-up on the other. Significant correlations were observed between postdexamethasone cortisolemia and negative symptoms at the end of acute treatment.

Conclusions: In first-episode schizophrenia the short-term treatment led to decrease of cortisolemia and rates of nonsuppression and an increase at a one-year follow-up. The DST nonsuppression in the early phase phenomenon (alteration of illness may be of prognostic value and further correlates or this hippocampus) should be studied.

OR-18 Effects of Mild, Moderate and Severe Stress on Depression in Female Rats: Modifications by Estrous Cycle, Ovariectomy and Estradiol Replacement

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It is widely accepted that stress may be involved in the clinical manifestation of depression. Also, it is well documented that women are more susceptible to depression than men. However, it is not known whether and in which extent stressors of different strength might influence the response of female animals in experimental model of depression. The aim of present work was to evaluate different stressors effects on behavior in forced swim test using intact females during the estrous cycle, ovariectomized (OVX) and OVX-estrogen treated rats. Also, a possible correlation between behavioral response in females and corticosterone response was assessed. The intact cycling rats, OVX and OVX-estrogen treated rats were received electric shocks of different intensity and duration (mild, moderate and severe) 24 h and 1 h before being subjected to forced swim test. At the end of behavioral procedures corticosterone plasma levels were measured by ELISA kit. Statistical processing of the received data was carried out using two-way ANOVA test and post-hoc Dunnett's test at $p < 0.05$. Immobility time appeared to be generally higher when mild (0.1 mA, 5 ms), moderate (1 mA, 5 ms) or severe (1.0 mA, 10 ms) shocks were applied prior to behavioral testing in proestrus and estrus animals, while the behavioral response of diestrus and metestrus animals did not differ from that of non-shocked rats. Application of severe shock significantly decreased immobility time in OVX rats as compared to non-shocked OVX rats. On the contrary, application of mild shock had no effect on immobility time in OVX rats as compared to non-shocked OVX rats. Application of mild shock significantly reduced immobility time in E2-treated OVX rats as compared to E2-treated non-shocked OVX rats. Stress-induced plasma corticosterone levels surge correlated with intensity and duration of shocks in rats. Thus, these results suggest that duration and intensity of stressors profoundly affect the behavioral response of female rats with imbalance of estrogen in forced swim test. Hormonal response correlates with the behavioral response indicating that reactivity of hypothalamus-pituitary-adrenal axis to stress may be involved in the mechanisms of depression in female rats. Supported by RFBR, grant 04-04-49025.

OR-19 Stress Hormones and Anabolic Balance in Depression: Influence of Antidepressants.

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Objectives: Some researchers suppose that cortisol/DHEAS ratio and growth hormone (GH) are important markers of anabolic balance. The aim of the study was to investigate cortisol, DHEAS and GH levels in depressed patients with antidepressant treatment. **Methods:** There were examined 39 patients with depressive episode (F 32.2). Patients in the first group (n=25) had antidepressant treatment of tianeptine during three weeks in the average dose of 37.5 mg per day. Patients in the second group (n=14) had treatment of sertraline in the average dose of 50 mg per day. Depressive symptoms were evaluated by the Hamilton Depression Scale (HDS). Blood samples were drawn two times: before antidepressant treatment, and on 21 day of the treatment. Serum DHEAS, cortisol and growth hormone levels were measured using immune-enzyme method. **Results:** There was a negative correlation between DHEAS level and

score by the HDS before treatment ($r_s = -0.47$, $p=0.037$). Cortisol/DHEAS ratio in patients after tianeptine treatment was significantly low than before treatment (accordingly 258 and 394, $P = 0.002$). In patients under sertraline treatment these differences were also significant (accordingly 339 and 419, $p=0.04$), but after tianeptine treatment cortisol/DHEAS ratio was significantly low than after sertraline treatment (accordingly 258 and 339, $p=0.003$). Decrease in the cortisol/DHEAS ratio was correlated with improvement of depressive symptoms, measured by HDS ($r_s = 0.42$, $p=0.045$). GH level on the 21st day of therapy significantly increased both in patients under tianeptine treatment ($p=0.83$ ng/ml) and sertraline treatment ($p=0.6$ ng/ml) in comparison with GH levels in these groups before treatment (accordingly $p=0.2$ and $p=0.35$ ng/ml, $p=0.03$). Conclusions: Our results demonstrate that antidepressants influence on anabolic balance in depression, decreasing cortisol/DHEAS ratio and increasing GH level. The influence of the tianeptine on cortisol/DHEAS ratio is marked more than sertraline.

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OR-20 Psychiatric Morbidity and Autoimmune Thyroid Disease

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Autoimmune thyroid disease (AITD) is frequently related to thyroid dysfunction and it is suggested that even marginal thyroid dysfunction may be associated with mood and anxiety disorders. However, recent studies in general population, in psychiatric population and in medical population found no statistical association between clinical or subclinical thyroid dysfunction, and the presence of depression or anxiety disorders. Moreover, several studies reported an association between depression and increased levels of thyroid antibodies and found that depression was not related to thyroid dysfunction. It may be that it is not marginal thyroid dysfunction, but rather thyroid autoimmune processes, frequently responsible for this dysfunction, are responsible for co-morbidity with mood disorders. Involvement of thyroid immunity in brain functioning was reported by several neuro-imaging studies, demonstrating a higher prevalence of brain perfusion abnormalities in euthyroid patients with autoimmune thyroiditis and higher levels of anxiety and depression in these patients. These abnormalities are similar to those observed in cases of severe Hashimoto's encephalopathy and may suggest a higher than expected involvement of the brain in AITD.

OR-21 Depression and Thyroid Function During Pregnancy

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The aim of the study was to examine depressive symptoms, thyroid function and to assess their relationship during pregnancy. Material and methods: 199 women, attending antenatal clinic at the Kaunas University of Medicine and Silainiai Primary Health Care Center, three times during pregnancy: in the first, in the second, and in the third trimester fulfilled Edinburgh Postnatal Depression Scale for the assessment of depressive symptoms. At the same assessment points blood was drawn for the measurement of thyroid function parameters: thyroid stimulating hormone (TSH) and free thyroxine (FT4). Results: Frequency of intense depressive symptoms was 9.5 % in the first trimester, 4.5 % in the second trimester and 6.5 % in the third trimester of pregnancy. No one participant of the study was diagnosed as having clinical thyroid dysfunction. There was no correlation between results of the Edinburgh Postnatal Depression Scale and TSH or FT4 concentration during any trimester of pregnancy. Conclusions: intense depressive symptoms were most frequent in the beginning of pregnancy. There was no relationship between depressive symptoms and parameters of thyroid function during pregnancy.

OR-22 Late Pregnancy Exposure to Serotonin Reuptake Inhibitors (SSRIs) is Associated With Neonatal Adjustment Problems and Subtle Motor Changes in Infancy Compared to Early Pregnancy Exposure to SSRIs

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Antidepressant drug treatment during pregnancy, specifically with Serotonin Reuptake Inhibitors (SSRIs) has been associated with a reduced acute pain response, motor symptoms in the newborn and motor changes in the infant at follow-up. The primary objective of the present study was to compare newborn functioning and the developmental outcome of children of depressed mothers who took SSRIs during the first trimester only, or took SSRIs during the third trimester or longer in pregnancy. Methods: Information regarding delivery and neonatal course of 78 newborns were collected from obstetric and neonatal medical records. At follow-up, mean age 15.5 months, children underwent neurologic and dysmorphology examinations and were tested using the Bayley Scales of Infant Development (BSID-II). Children (N=13) exposed during the first trimester were compared to children (N=41) exposed during the third trimester or longer in gestation to SSRIs. Results: The mothers' demographic and clinical characteristics were similar. Birth outcome: No between group differences were observed for stillbirths, preterm births, major and minor malformations, or birth weights and lengths. Newborns with late exposure had significantly lower Apgar scores at 1 min and at 5 min than newborns with first trimester exposure. Among the newborns with third trimester exposure 27 % were admitted to neonatal care units as opposed to none with first trimester exposure. Follow-up: Infants in the three groups were not different in their mental development but children with late SSRI exposure were different from early exposure children in their psychomotor development. Children with late exposure showed lower scores on the Behavioral Rating Scale for behavioral motor

quality, specifically they had lower scores on the subscales for gross and fine motor movements compared to the children with first trimester exposure

Conclusions: The higher rate of neonatal adaptation problems in children, who were exposed to SSRIs during late gestation as opposed to those exposed during the first trimester emphasizes the need for close neonatal monitoring of newborns of mothers taking SSRIs prenatally and the need to reduce or discontinue maternal SSRI medications before delivery to avoid adaptation problems in the newborn

OR-23 Is Polymyalgia Rheumatica a Stress Related Disorder?

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The hypothalamo–pituitary–adrenal (HPA) axis plays a pivotal role in the physiological response to stress, including the inflammatory and pain states of some rheumatic diseases. Most of the previous studies have applied to patients with rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome and fibromyalgia. But there are only a few studies evaluating the HPA axis in PMR. This presentation will provide an overview of the studies regarding HPA axis in PMR and discuss the impact of HPA axis in the pathogenesis of PMR. PMR is characterized by a constellation of symptoms in elderly people and is typically associated with certain laboratory abnormalities, such as an elevated erythrocyte sedimentation rate, pain and morning stiffness affecting the neck, shoulder girdle, and pelvic girdle. The etiopathogenesis of PMR remains unknown, although genetic, autoimmune and environmental factors have been implicated. There is also relation between PMR and a chronic vascular disease called Giant-cell arteritis. Because of the effectiveness of steroids in the treatment of PMR, the role and status of the HPA axis in the pathogenesis or course of PMR need to be clarified. In a recent study from our clinic, significant low cortisol responses to ACTH stimulation were detected in the patients with PMR. In addition, a negative correlation after the 1 mg ACTH stimulation test between peak cortisol levels and disease duration was detected. These findings may indicate hypoactivation in the HPA axis. However it is too early to consider PMR as a stress related disorder. Therefore more data are warranted to clarify the impact of HPA axis in the pathogenesis of PMR.

OR-24 Adult Attachment and Cardiovascular Responses to Psychological Stress

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Background. Several studies have shown that lack of social support predicts cardiovascular morbidity and mortality. Individuals with insecure adult attachment styles may be less able to use support and so be at increased risk of developing dis-

ease. In two recent studies, we investigated the proposition that insecure adults respond to challenging situations with exaggerated cardiovascular responses.

Methods. We examined cardiovascular responses (blood pressure, heart rate, total peripheral resistance and cardiac output) to a stressor. In study 1, 56 undergraduate students completed a driving task and, in study 2, 36 undergraduate students completed a public speaking task. Attachment was assessed using the Revised Adult Attachment Scale (Collins & Read, 1990). Scores were used to categorize respondents into secure and insecure groups. Measures of social support and hostility were also taken. Results. In study 1, secure participants showed smaller systolic blood pressure responses and larger decreases in total peripheral resistance to driving compared with insecure participants. In study 2, secure participants showed smaller systolic blood pressure responses to speaking compared with insecure participants. Social support and hostility did not account for the physiological differences we observed. Conclusions. In these studies we found that secure participants displayed smaller cardiovascular responses to laboratory stressors. This patterning of physiological responses may help to explain how supportive ties protect some individuals from cardiovascular disease.

OR-25 Plasma Oxytocin, Stress and Cardiovascular Reactivity in Mothers of Infants

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Background. Oxytocin (OT) has been termed the ‘bonding hormone’ and has been hypothesized to mediate some of the health benefits of supportive social relationships. Mammalian animal models have linked greater oxytocin levels to reductions in blood pressure (BP), sympathetic and HPA axis activity. In a study of cohabiting couples we have reported higher oxytocin in both men and women reporting greater partner support, and correlations between higher OT and lower BP, heart rate (HR) and plasma norepinephrine (NE) in women only. In a study of mothers of young infants, we have also previously reported lower ambulatory BP at home in mothers showing greater plasma OT responses to laboratory stress. In the current study we investigated the effects of OT and feeding method on cardiovascular responses to stress in new mothers who were exclusively breast- or formula-feeders. Methods. Subjects were 37 mothers of infants. An IV was used to assess OT during tasks, and vascular resistance and cardiac output (VRI, CI) were calculated with impedance cardiography during baseline, speech, speech replay, cold pressor (CP) and recovery. Results. Plasma OT was higher in breast vs. bottle-feeders ($F=8.36$, $p<.01$). BP levels were similar across feeding groups however hemodynamic determinants of BP response differed. Repeated measures ANOVA’s revealed that although feeding groups did not differ in baseline VRI or CI, formula-feeding mothers exhibited greater VRI increases and smaller CI responses to speech task (Time x Feed: VRI $F=7.43$, $p<.01$; CI $F=3.89$,

$p < .05$). Formula-feeding mothers had greater VRI responses to cold pressor (Time x Feed $F = 3.62$, $p < .05$): with 30% increase in VRI vs. 12% increase in breast-feeders. Greater VRI was maintained during 8-min recovery (VRI 14% GT baseline vs. 1% in Breast-feeders). Greater OT across the protocol, computed as area under the curve, was correlated with lower VRI during speech, replay, and CP (r 's = -0.48 to -0.41) and greater CI during speech, CP and recovery (r 's = 0.41 to 0.54). Conclusion. These data suggest that, compared with formula-feeders, breast-feeding mothers have reduced vasoconstriction or greater vasodilation responses to certain stressors, which may be related to higher circulating levels of plasma oxytocin.

OR-26 Stress Reactivity in Hostile Cardiac Patients

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The correction of hostility may be a new target for coronary heart disease (CHD) prevention in order to decrease cardiovascular and psychological reactivity to stressogenic factors. However little is known about hostility impact on stress reactivity. Methods. 51 pts with CHD were assessed for psychological stress before stressful event - one day before cardiac surgery. They were measured for three global indicators of distress, for anxiety and depression according to SCL-90-R scales scores. Also the quality of life was evaluated by SF-36 coefficients. Hostility was assessed using SCL-90-R scale. Results. 18 (33 %) patients (pts) had increased hostility scale's score ($> 60T$). There were significantly more pts with psychological distress (the score > 90 %) in this subgroup: 12 (67 %) pts had increased global severity index, when only 5 (15 %) non-hostile pts had increased one ($p = 0.000$); increased positive symptom total was found in 11 (61 %) hostile pts and in 9 (27 %) non-hostile pts ($p = 0.018$). Also more pts had increased depression scale's score ($> 60T$) in hostile pts' ($n = 14$ [78 %] and $n = 11$ [33 %] respectively, $p = 0.024$) and increased anxiety ($n = 13$ [72 %], $n = 6$ [18 %] respectively, $p = 0.000$). The hostile pts had worse quality of life in some aspects: the means of pain and mental health scales' coefficients were significantly lower (34.39 ± 19.85 in hostile pts and 52.82 ± 30.43 in pts without hostility, $p = 0.025$; 55.78 ± 17.78 and 66.91 ± 19.32 , $p = 0.049$). Multiple regression analysis have shown significant hostility scale's relation with global severity index ($\beta = 0.564$, $p = 0.000$), positive symptom distress index ($\beta = 0.339$, $p = 0.015$), positive symptom total ($\beta = 0.51$, $p = 0.000$), depression ($\beta = 0.514$, $p = 0.000$), anxiety ($\beta = 0.471$, $p = 0.000$), mental health ($\beta = -0.47$, $p = 0.000$), pain ($\beta = -0.4$, $p = 0.004$), role limitation due to emotional problems ($\beta = -0.31$, $p = 0.03$). Conclusions. These data support to the hypothesis that hostility adversely affects stress reactivity and confirm that identification of hostility should be emphasize in prevention programs. Further studies are needed in order to determine if psychotherapy in reducing hostility might improve patients' cardiovascular and psychological reactivity to stressogenic factors and impact to cardiac events.

OR-27 Emotional Changes in Patients with Ischaemic Heart Diseases

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The prevalence of major depressive disorder (MDD) among patients with cardiovascular disease is around three times that of total population. Depression increases morbidity and mortality of patients with cardiovascular disease. Depressed patients report more stress and are slower to return to work. The goal of this study was to evaluate depressive symptoms in patients with ischaemic heart disease (IHD) and their prognostic meaning of developing MDD.

Methods: We analysed 159 inpatients (mean age 53.94 ± 0.856) with IHD: 78 with comorbid major depressive disorder (MDD), 81 with sporadic depressive symptoms. No significant differences between age ($p = 0.73$) and gender ($p = 0.21$) in both groups was observed. Patients were screened for MDD using Mini-International Neuropsychiatric Interview (ICD-10), HDRS-17. Mood/cognitive, somatic, insomnia, anxiety clusters of depression were evaluated. The correlation between age and sporadic symptoms of depression also clusters of depressive symptoms was made. Odds ratio was calculated using method of logistic regression.

Results: Somatic cluster of depressive symptoms was common in both groups. Under them in patients with MDD were mood/cognitive, insomnia, anxiety clusters and in patients free from MDD were insomnia, anxiety, mood/cognitive clusters. Patients age was positively correlated with depressed mood, initial insomnia, loss of work and interest, loss of appetite, anergia, loss of libido, hypochondriasis. Negative correlation was found between age and guilt feeling also insight. Anxiety symptoms has no significant positive or negative correlations with age. Age was positively correlated with mood/cognitive, somatic and insomnia clusters of depression. Conclusions: Somatic symptoms of depression were common in patients with IHD. Patients with IHD having mood/cognitive (OR=30.90), anxiety (OR=7.847), insomnia (OR=6.016), somatic (OR=3.676) symptoms of depression have more chance to developing MDD as comorbide with IHD.

OR-28 Sleep, Depression and Cardiovascular Function in Coronary Artery Disease

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Background. Depression and insomnia often occur in coronary artery disease patients (CAD pts) and have negative impact on the latter development. The goal was an investigation of depression and sleep quality in CAD patients in relation to their cardiovascular functional state. Methods. Polysomnography was used for objective evaluation of sleep quality: total sleep time (TST), sleep efficiency (SE), wakefulness after sleep on-

set (WASO), body movements, REM sleep, and 1, 2, 3 and 4 sleep stages. Subjective sleep quality was evaluated by means of Pittsburgh sleep quality index (PSQI). Anxiety and depression was investigated using Hospital Anxiety and Depression Scale. Fifty healthy subjects (H Ss) and 1086 CAD pts were investigated using clinical and instrumental evaluation of cardiovascular function: NYHA class I – 49 pts, II – 627, III – 405 pts. There were 229 pts with anxiety, 64 pts with depression and 171 pts with both, anxiety and depression. Restoration of cardiovascular function during sleep was evaluated using heart arte variability analysis during different sleep stages and active orthostatic test at evening- and morning-time. Full restoration was seen in 279 pts, partial restoration - in 662 pts and no restoration – in 18 pts. Results. CAD pts, as compared with H Ss, demonstrated reduced TST, SE, REM sleep and stages 3-4 as well as increased WASO. Subjective quality of sleep was worse in CAD pts, too. Leading pathology and complications were followed by a worsening of objective and subjective sleep quality: hypertension - by decrease of TST, SE and stages 3-4, while CHF and diabetes II - by reduction of REM sleep and increase in PSQI. Frequent ventricular premature beats were worsening sleep quality. Decreased stages 3-4 were found for CAD pts with partial restoration of cardiovascular function during sleep. Depression alone, or depression and anxiety being together, were followed by worsening objective sleep quality, while anxiety alone – by worsening subjective sleep. Conclusions. CAD and its complications are disturbing objective and subjective sleep quality. Depression and anxiety showed negative impact to sleep quality as well. Restoration of cardiovascular function during sleep was positively related to total sleep time and slow wave sleep.

OR-29 Dietary Supplements for Stress and Obesity Co-Morbidities Reduction.

Dimitrov Dimiter

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Metabolic syndrome (Met-S) is determined using clinically evident diagnostic criteria (abdominal adiposity, dislipidemia, hypertension, hyperglycemia). The diet of patients exposed to stress had been shown to be low in fibre, low in fruit and vegetables, low in vitamins C and E, and beta-carotene, high in sugar, and high in saturated fat. The implications of these findings were two-fold: the diet associated with stress is similar to those in patients with features of the Met-S. There is evidence for an adaptive role of the omega -3 fatty acid, docosahexaenoic acid (DHA), magnesium and soybean oil during stress. Mechanisms of action may involve regulation of stress mediators, such as the catecholamines and proinflammatory cytokines. They may also have other heart health benefits, including the ability to reduce the oxidation of LDL cholesterol and promote vascular relaxation, physiological effects which are emerging as important risk factors for heart disease. Scientific researchers and health professionals should agree that the public should be encouraged to incorporate a variety of anti-stress supplementation products into a heart healthy diet and lifestyle plan.

OR-30 Antenatal Thyroid Status Correlates with Postpartum Depression

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In an earlier study, we found significantly higher T3-resin uptake and nearly significantly lower total thyroxine concentrations at 38 weeks of pregnancy in women with higher postpartum depression ratings. The current study further examined the relationship between thyroid status during late pregnancy and antenatal and postpartum depression scores. Thyroid measures were obtained at 32-35, 36, and 37 weeks of pregnancy in 31 euthyroid women. Subjects rated their mood at these antenatal time points and every other week between postpartum weeks 2 and 24 on the Edinburgh Postnatal Depression Scale and the Beck Depression Inventory. Mean antenatal thyroxine concentrations and free thyroxine indices correlated significantly and negatively with mean depression scores during each of three postpartum time periods (postpartum weeks 2-6, 14-18, 20-24). Women with total and free thyroxine concentrations that were respectively $<10.1 \mu\text{g/dl}$ and $<1.06 \text{ ng/dl}$ at all 3 antenatal time points had significantly higher mean depression scores during all postpartum time periods. Women with antenatal total and free thyroxine concentrations in the lower euthyroid range may be at greater risk of developing postpartum depressive symptoms. Our results have two important clinical implications. First, thyroid hormone measures during late pregnancy may help identify women who are more likely to develop postpartum mood disorders especially when these hormone measures are combined with other factors known to increase risk such as prior depression history and psychosocial stressors. Second, thyroid hormone supplementation of women with low normal thyroxine concentrations during late pregnancy may protect them from postpartum mood deterioration. If studies in larger populations confirm our findings, examination of the mechanisms whereby antenatal thyroid status influences postpartum mood may provide new insights into the pathophysiology of mood disturbances during the puerperium.

POSTER SESSIONS

ENDOCRINE RESPONSES TO STRESS (P1)

P1-01 Potential Role of DHEA in Anxiety Severity in Drug-Free Patients Experiencing a Major Depression Episode

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Objectives: Although a number of studies have demonstrated the correlation between dehydroepiandrosterone (DHEA) and anxiety or depression, findings remain controversial. This study determined whether a correlation exists between depression or anxiety severity and DHEA concentrations in blood plasma in drug-free patients experiencing a major depression episode. **Experimental design:** Thirty-four patients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) diagnostic criteria for major depressive disorder were examined during a severe episode of depression (17-item Hamilton Rating Scale for Depression (HAM-D 17) (total score, ≥ 17) were enrolled consecutively in this study. Depression was assessed using HAM-D 17 and the Hospital Anxiety and Depression Scale (HADS) depression sub-scale. Anxiety was assessed using the HADS anxiety sub-scale. Subject plasma levels of DHEA were measured promptly after the HAM-D 17 and HADS assessments on the same day in the morning. **Principal observations:** A significant, positive correlation existed between HADS anxiety sub-scale total score and morning DHEA concentration in blood plasma ($p=0.027$). No statistically significant correlations existed between depression ratings and DHEA concentrations. **Conclusions:** This preliminary experimental result is the first clinical evidence identifying the potential role of DHEA in anxiety severity in patients experiencing a major depression episode. This study demonstrated that morning DHEA concentrations in blood plasma were significantly and positively correlated with HADS anxiety sub-scale total score after controlling for age, gender and body mass index (BMI).

P1-02 Stress- Related Hormone Status in Patients With Psoriasis

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Psoriasis is a chronic, erythematous disease of as yet unexplained etiology. In patients with psoriasis many different stimuli produce a psoriatic reaction, including stress, skin injury and infection. The role of stress in the pathophysiology of psoriasis has been widely accepted. Therefore, we were interested in identifying what happens to the hypothalamic-pi-

tuinary-adrenal (HPA) axis and cortisol, a stress-related hormone, in psoriasis. The aim of our study was to compare the blood and urine values of cortisol in psoriatic patients before and after naphthalene (a mixture of polycyclic carbohydrates) watering place therapy. The study included 19 male patients and 17 healthy volunteers. Twenty-four-hour free urinary cortisol, circadian cortisol rhythm at 8 a.m. and 5 p.m., and cortisol in dexamethason suppression test (DST) were determined by standard radioimmunoassay in all study subjects. Results of the study showed lower cortisol levels in psoriatic patients before therapy (mean values 150 ± 98 nmol/24h urine, 404 ± 138 nmol/L at 8 a.m., 187 ± 80 nmol/L at 5 p.m., and 23 ± 5 nmol/L in DST), compared with control subjects (mean values: 590 ± 87 nmol/24h urine, 590 ± 53 nmol/L at 8 a.m., 402 ± 31 nmol/L at 5 p.m., and <86 nmol/L in DST), corresponding to the cortisol level in a state of chronic stress. After 3 weeks of naphthalene therapy, there was a statistically significant increase in urinary cortisol (193 ± 94 nmol/24h urine) but not in blood cortisol (338 ± 94 nmol/L at 8 a.m. and 148 ± 74 nmol/L at 5 p.m., and cortisol in DST 23 ± 9 nmol/L). However, pretherapeutic plasma cortisol showed a „stronger“ circadian rhythm than after therapy, pointing to the improvement in the hormonal status with higher cortisol supplies during the day. It is concluded that psoriatic patients exhibit a different psychoendocrine response from normal subjects, demonstrating that psoriasis, as an example of stress-related disorder, leads to HPA axis alteration, which might be an important fact in the disease persistence, and also that stress-related hormone status improves after therapy with naphthalene.

P1-03 Psychological Stress and Body Temperature: Effects of Alprazolam and Flupentixol

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We here explored effects of psychological stress under laboratory conditions (Trier Social Stress Test) on body temperature, as verified by an infrared camera and ear thermometer. Skin and ear temperature, respectively, were analyzed in three groups, which either received placebo ($n=23$), 1mg Alprazolam ($n=23$) or 0.5mg Flupentixol ($n=23$). Under placebo conditions, ear temperature was highest in anticipation of the stressor, but this effect was significantly lower under Alprazolam. The average skin temperature of the probands' faces during the psychosocial stress test continuously increased under all 3 conditions, while this effect was significantly blunted by Alprazolam. In sum, our data show a dissociation in the progression of ear and skin temperature. Furthermore, Alprazolam reduced temperature measures independent of the locus of assessment.

P1-04 Endocrine and Cardiovascular Stress Responses Following Psychological Challenge in Women with Borderline-Personality-Disorder

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Borderline-Personality-Disorder (BPS), a severe psychiatric disorder, is characterized by a pervasive pattern of instability in affect regulation, impulse control, frequent experience of tension, self mutilating behavior, and multiple suicide attempts. About 70% of BPS patients show comorbidity with post-traumatic stress disorder (PTSD). In contrast to PTSD, there is a paucity of data on HPA and cardiovascular stress reactivity in BPS patients. One study showed increased cortisol awakening responses and higher daily cortisol levels in BPS patients compared to healthy controls. Therefore, we are currently investigating cortisol, heart rate, and blood pressure reactivity following a psychological challenge conducted during the first two weeks of an inpatient therapy program in 20 young women with BPS. All women are free of oral contraceptives and tested during the luteal phase. All tests are conducted in the afternoon. The psychological challenge is a 15-minutes lasting interview concerning the last suicide attempt or self injury focussing on cognitive and emotional aspects. As a control situation, a non-challenging interview was conducted. Additionally a first session without any challenge was conducted to get familiar with sampling methods. Till now we analysed data of the first 13 patients with the following results: During control and the adaptation session no significant increase in cortisol reactivity was observed, while the psychological challenge resulted in a slight increase ($F=5.6$; $p<0.001$), however compared to the control sessions we observed only a tendency to significantly higher levels ($F> 2.3$; $p<0.09$). Moreover, we observed in the total group in all sessions very low cortisol levels compared to usual observed levels in healthy controls after psychosocial stress tests. While heart rate and diastolic blood pressure raised significantly during the psychological as well as the non-stressful interview control session ($F> 4.8$; $p<0.05$), psychological challenge resulted not in higher reactivity compared to control sessions ($F<3.1$; $p=n.s.$). Till now data are not influenced by comorbidity of PTSD or early Trauma. Since data collection is still in progress, final results will be presented at the meeting.

P1-05 Effects of Immobilized Stress on Sexual Behavior of Male Rats Exposed Prenatally to Cholinolitics

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Influence of different neurotropic drugs at prenatal period is the cause of brain sexual differentiation disorder at neonatal period and behavioral abnormalities at sexually mature age. In some cases, these effects are mediated by brain cholinergic system injury. The aim of the current work was to study the effect of immobilization stress on the sexual behavior (SB) of male rats subjected prenatally to the action of selective M-

and N-cholinoblockers. Pregnant female Wistar rats at 9–11, 12–14, and 17–19 days of pregnancy (the group 1, the group 2, and the group 3 correspondingly) were injected with cholinotropic drugs of the central action — methylbenactyzine (MeT) (2.0 mg/kg) and ganglerson (GnL) (12.0 mg/kg). Gonadal hormones were analyzed in peripheral blood in some of offsprings at the age of 2 months. Testosterone level was significantly decreased in all groups with GnL. The matured male rats from these groups showed less spontaneous sexual activity and slow dynamics of acquisition of sexual experience in comparison with the animals from the control group. The male rats from the group MeT, possessed low spontaneous sexual activity, showed more fast dynamics of acquisition of sexual experience as compared with such behavior in control group of animals. Quantity of setting, intromissions, and ejaculation was significantly decreased (accordingly on 19.7%, 23.4% and 25.1%, $p<0.05$) and SB time components were considerably limited. The male rats from the MeT group showed comparable with the control group dynamics of sexual activity after stress exposure, except the group 1, which ejaculatory component was decreased more greatly (44.3%). Quite differing data from the control and MeT groups were found in the GnL-treated male rats' offsprings: SB motivational components were decreased more then twice at all groups. The ejaculatory component was decreased more then 1.5 times as distinct from the group 3 (reduction on 27.3%). Sexual activity after stress exposure was totally suppressed in 25% of male rats from the 1st GnL group. Thus, prenatal exposure to cholinergic blockers of N-type and to a lesser degree of M-type exerts long-term effects on sexual hormone level of male rat's offsprings and on sexual activity of the matured offsprings.

P1-06 Anxiety Symptoms and Hypo-Echoic Thyroid Pattern in Primary Care Patients.

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Mood and anxiety disorders are highly prevalent in the primary care. Autoimmune thyroid disease may be related to emotional disorders. The aim of this study was to evaluate impact of the thyroid immunity, assessed by the hypo-echoic thyroid ultrasound pattern, on depression and anxiety symptoms, in primary care setting. In cross-sectional design 474 consecutive primary care patients were screened for depression and anxiety symptoms using the Hospital anxiety and depression scale (HADS) and ultrasonographic imaging of the thyroid gland was performed. Patients were divided into two groups, the first group consisted of patients with normal echoic pattern of the thyroid gland ($n=352$) and the second group consisted of those with hypo-echoic pattern of the thyroid gland ($n=122$) indicating autoimmune involvement of the thyroid gland. After adjusting for age women with hypo-echoic thyroid pattern in comparison to women with normo-echoic thyroid pattern had significantly higher scores on the subscale of anxiety of the

HADS (9.0 $p=4.6$ vs. 7.8 $p=4.4$, respectively; $p=0.05$). This difference was most significant in mid-age peri-menopausal women (10.6 $p=4.3$ vs. 7.8 $p=4.8$, respectively; $p=0.02$). There were no significant differences in mood state of men or in mood state of post-menopausal women in regard to echoic thyroid pattern. The results of this study confirm an association between thyroid immunity and anxiety symptoms in peri-menopausal women, but not in post-menopausal women or men. Ultrasonographic evaluation of the thyroid gland is relatively simple and cost-effective instrument for the evaluation of the autoimmune involvement of the thyroid gland.

P1-07 Clonidine in Premenstrual Dysphoric Disorder

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Pharmacological studies have demonstrated that medications augmenting noradrenergic activity are not effective for the treatment of premenstrual dysphoric disorder (PMDD). In contrast, some data demonstrate that medication suppressing sympathetic nervous system, such as alpha-2 receptor agonist clonidine, has some positive effects in PMDD. Objectives: The aim of this study was to evaluate effects of clonidine on premenstrual symptoms, mood scores and norepinephrine (NE) level in women with PMDD. Methods: Twelve women with prospectively confirmed PMDD were randomly assigned to oral 0.3 mg/day clonidine, or to 10 mg/day loratadine, as an active placebo, for two months each, using a double blind, crossover design. NE concentration, premenstrual symptom rating and mood scores on Beck Depression Inventory (BDI) and Spielberger State Anxiety Inventory (SSAI) were measured at pretreatment, after clonidine treatment and after placebo treatment. Results: There were no significant differences between effects of clonidine and placebo on premenstrual symptoms and mood scores on BDI and SSAI, but, as expected, clonidine significantly suppressed NE concentration in comparison to placebo ($p<0.05$). This suppression was related to a history of sexual abuse, in women with sexual abuse clonidine was not able to suppress NE secretion. The majority of subjects reported significantly more side effects while receiving clonidine, such as dry mouth ($p<0.01$), sedation ($p=0.05$), and tended to experience more irritability ($p=0.06$), in comparison to placebo. Conclusion: Clonidine demonstrated no beneficial changes in mood and premenstrual symptoms, in women with PMDD, but caused more side effects in comparison to active placebo. History of sexual abuse was related to alterations in suppression of NE secretion by clonidine.

P1-08 Cortisol and Cytokine Profiles in Depressed Women Following Psychosocial Stress

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Background: Depression has been associated with an activation of the immune system and the endocrine system. Some studies have shown increased levels of pro-inflammatory cytokines as well as increased levels of cortisol in patients with major depressive disorder (MDD), but conflicting results also have been described. Further studies have shown that both systems play an important role in maintaining homeostasis during stress, mounting large cytokine and cortisol responses following strain. However, it is unclear whether acute stress elicits similar reactions in patients with MDD. The aim of our study was therefore to (i) reliably assess the hypothalamic-pituitary-adrenal axis (HPAA) function in depressed women, (ii) evaluate whether depression was associated with changes in cytokine production, and (iii) assess the acute modulation of HPAA activity and cytokine production in the respective sample. Methods: Thirty-nine outpatient women diagnosed with major depression and thirty-eight healthy controls took part in the study. Salivary cortisol was measured 0, 0.5, 1, 4, 9 and 11 hours after awakening on three days to determine the basal hormone profiles as well as -3, +5, +17, +30, +40 and +50 minutes after a psychosocial laboratory stressor, the TSST. LPS-induced cytokine production (IL-6 and TNF- λ) was measured in vitro under rest and -3, +17 and +50 minutes after the stress protocol. Results: Basal cortisol levels were lower in depressed women. Remarkably, patients showed no significant cortisol increase in response to the stressor. Depressed women had elevated basal TNF- λ concentrations compared to controls while cytokine levels increased in response to the stress test irrespective of the depression status. Conclusions: Our results show that depression is associated to a decreased endocrine and an increased immune function under rest as well as to a damped endocrine stress response. This pattern might be especially true for mild clinical profiles as tested in the present study. Thus, endocrine and immune function may vary according to the psychological profile of the depressive disorder. However, our findings indicate that cortisol and cytokine production are dysregulated in depressed patients and may matter in the origin of the disease.

P1-09 The Influence of Psycho Emotional Status and Sleep Quality on Health-Related Quality of Life in Coronary Artery Disease Patients

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Background: Health-related quality of life (HRQL) represents the effect of an illness and its treatment as perceived by the patient and is affected by the person's physical health, psychological state, level of independence and social relationships. The aim of the study was to assess the influence of anxiety, depression and sleep disturbances on HRQL in coronary artery disease patients. Methods: The contingent was 2011 CAD patients (mean age - 57.9 years, 73.2% male). HRQL was assessed using SF-36. Anxiety and depression were assessed using Hospital Anxiety and Depression Scale. There were 58.9% of patients without anxiety, 21.3% with moderate and 19.8% with severe

anxiety; 76.0% of patients without depression, 15.6% with moderate and 8.4% with severe depression. Pittsburgh Sleep Quality Index was used for subjective sleep quality assessment. Thirty one point nine percent of patients have no sleep problems. Student's t-test was used to determine the significance of the differences between the means. The effect of anxiety, depression and poor sleep on HRQL was evaluated by means of multiple logistic regressions. Results: According to severity of anxiety and/or depression paralleled diminished HRQL, especially mental component summary. Poor sleep had a negative impact on HRQL; patients who reported good sleep quality had significantly higher scores on all domains of the SF-36. They also had significantly lower depression and anxiety scores. The biggest negative influence on HRQL had poor sleep, which one was associated with twofold-threefold increase in odds of worse all domains. Anxiety and depression increased odds ratio of relatively worse mental health scales (OR 1.0-2.4), than physical ones (OR 0.9-1.8). Conclusions: The biggest negative influence on HRQL had poor sleep. Depression and anxiety as well as worse sleep quality cause significant decrease in HRQL.

STRESS AND HEART (P2)

P2-01 Sleep Quality in Coronary Artery Disease Patients Across Life Cycles

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Background: Age and cardiac pathology are the factors having negative impact to sleep quality. Assessment of the sleep quality using both, objective and subjective methodologies, is more complex and accurate. The goal of this study was to investigate influence of age on sleep quality in coronary artery disease patients (CAD pts). **Methods:** Contingent of the study was 1708 CAD pts. Sleep structure was assessed using objective parameters, obtained from polysomnography: total sleep time (TST), sleep efficiency (SE), wakefulness after sleep onset (WASO), sleep stages 1, 2, 3, and 4, REM sleep, and body movements (BM). The Pittsburgh sleep quality index (PSQI) was used for subjective sleep quality assessment. Patients (pts) were divided into 4 groups according to their age: in the 1st age group from 35-44 yrs were 125; in the 2nd age group from 45-54 yrs - 441, in the 3rd age group 55-64 yrs - 672 and in the 4th age group 65-74 yrs - 470 CAD pts. To determine the significance of the differences between the means Student's t-test was used. **Results:** Significant shortening of duration of TST in CAD pts groups with ageing was found. Longest duration of TST was observed in age group 35-44 yrs (348±60.7 min.); while shortest one – in age group 65-74 yrs (322±66.7 min.). Statistically significant worsening of SE in all aging groups was observed. SE has highest values in group 35-44 yrs (90.7±8.29 %), and lowest ones in group 65-74 yrs (83.3±12.11 %). Duration of the WASO also was increasing in parallel with aging. Shortest duration of the WASO found in CAD pts with age 35-44 yrs (33.7±3.10 min), and longest duration in CAD pts with age 65-74 yrs (63.6±4.73 min). Length of the REM sleep also was significantly higher in youngest CAD pts group with age 35-44, as compared with older CAD pts groups. Sleep quality, measured by PSQI, was significantly worse in age group 65-74 yrs, as compared with other ones. A decrease of objective sleep quality in CAD pts with aging might be caused mainly by two factors, age and progressing cardiovascular pathology. **Conclusions:** Objective sleep quality was significantly decreased with aging in CAD patients; while subjective evaluation of sleep quality in different age groups did not differ significantly.

P2-02 Relationship of the Fatigue with the Physical Work Capacity in Coronary Artery Disease Patients

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Background. The term fatigue refers to a normal, every day experience that most individual reports after sleep or rest, after physical exertion or mental effort or when they lack the moti-

vation to initiate activities or describes a symptom considered to indicate the presence of illness as well as cardiac disease. The aim of study is to evaluate the association of the fatigue with the work capacity level in coronary disease patients during cardiovascular rehabilitation. **Methods.** The total contingent was 395 patients after myocardial infarction, mean age 56.5 years. Bicycle ergometry test with increasing workload by 25 W every 3 min until exercise - limiting symptoms was performed. Multidimensional Fatigue Inventory (MFI-20) for evaluation of the fatigue was used. Five factor model allowed to estimate value of general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. The differences between parameters was considered to be significant at $p < 0.05$. **Results.** The relation between expression of general fatigue (66.4, 64.4, 55.1, 56.5, 36.5, 41.9) and the level of the threshold workload (25 W, 50 W, 75 W, 100 W, 125 W, 150 W) was evaluated ($R = 0.70 - 0.76 - 0.60$). Negative association between physical fatigue and threshold workload during exercise test was estimated. In the cases with the high total work capacity (>1800 kgm) the values of general fatigue (48.9 vs. 56.3), physical fatigue (56.1 vs. 62.4), reduced activity (55.2 vs. 60.7) and reduced motivation (39.7 vs. 43.9) were less expressed than in cases of the low total (<1800 kgm) work capacity ($p < 0.05$). **Conclusion.** Fatigue model data of general fatigue, physical fatigue, reduced activity and reduced motivation are associated with total work capacity level in coronary artery disease patients. Though, the question, how often the fatigue is the real reason for prediction of the threshold workload and what the role plays an impact of experimenters motivation, remain open.

P2-03 Alexithymia and Sleep Structure in Coronary Artery Disease Patients

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Objective: Alexithymia as a deficiency in the ability to identify and describe emotions is one of the most common factors associated with coronary artery disease and poor sleep quality. The goal was an investigation of sleep structure in coronary artery disease patients (CAD pts) with alexithymia. **Methods:** Toronto Alexithymia Scale with the 20-item was used for assessment of alexithymia. Sleep structure was assessed using objective parameters obtained from polysomnography: total sleep time (TST), sleep efficiency (SE), wakefulness after sleep onset (WASO), sleep stages 1, 2, 3, and 4, REM sleep, and body movements (BM). The contingent was 436 CAD pts (from 22 to 80 yrs, mean age 57.2 (SD=9.7) yrs). All pts were distributed into two groups: 1st group, 170 nonalexithymic pts, mean age 56.3 (SD=11.0) yrs, 44 ♀, 126 ♂; 2nd group, 266 alexithymic pts, mean age 57.9 (SD=8.7) yrs, 74 ♀, 192 ♂). Age, sex, and cardiovascular functional status did not statisti-

cally differ between the groups. To determine the significance of the differences between the means Student's t-test was used. The nonparametric Mann-Whitney rank sum test was used in cases where the studied items had a non-normal distribution. The χ^2 test with a Yates correction test was used for the comparison of proportions between groups. A value of $p < 0.05$ was considered statistically significant. Results: Alexithymic pts, as compared with nonalexithymic one, were characterized by disturbed sleep structure. A statistically significant increase of sleep stage 1 (13.8 % (10 - 20) and 13 (9 - 18) %, correspondingly in alexithymic and nonalexithymic pts) and a significant decrease of stage 4 (1.8 % (0.8 - 3.3) and 3.8 % (1.5 - 6.8), correspondingly) was observed in CAD pts with alexithymia. Duration of TST, SE, WASO, sleep stages 2 and 3, REM sleep as well as BM did not differ significantly between the groups. Alexithymia, characterized by the disability to identify feelings and to distinguish them from physical sensations, might result an increase of anxiety level which can be important factor disturbing sleep in CAD pts. Conclusions: Sleep structure in CAD pts with alexithymia, as compared to patients without one, is more disturbed. These pts demonstrated more increased stage 1 and decreased stage 4

P2-04 Association Between Depression and Thyroid Axis Functioning in Patients with Coronary Artery Disease: Impact of Gender.

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Despite increasing information about links between depression and heart disease there is no accepted model that accommodates the mechanisms that may be involved. Moreover, some potentially important mechanisms are not studied yet. Dysfunction in thyroid hormone metabolism is such a mechanism. The main goal of this study was to examine relationship between depression and thyroid axis function in patients with coronary artery disease (CAD) and to determine the role of gender in this relationship. Eighty-seven patients with CAD were enrolled to the study. There were no significant correlations between mood variables and hormonal variables in total sample of study patients. However, we found significant correlations within the group of men as well as within the group of women. In men higher scores of depression were related with lower total T3 concentration ($r = -0.302$, $p = 0.017$) and with higher NT-pro BNP concentration ($r = 0.385$, $p = 0.002$). In contrast to men in women higher scores of depression were related with lower NT-pro BNP concentration ($r = -0.538$, $p = 0.018$) as well as with higher cortisol concentration (0.612, $p = 0.005$). These data suggest that severity of cardiac dysfunction in patients with CAD is related with alterations in thyroid hormone concentrations and with greater scores on depressive symptoms scale. These relationships are evident in men, but not in women.

P2-05 Influence of the Psychoemotional Status to the Efficacy of Cardiovascular Rehabilitation During Long Term Follow-up Study

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Background Psychoemotional risk factors in coronary artery disease patient's are associated with increased mortality, worse adaptation to environment factors and quality of life. The aim of the study was assessment relationship of psychoemotional status with cardiovascular functional status, rehabilitation efficacy, and autonomic control in myocardial infarction patients during 2 year follow-up study. Methods. 170 patients with myocardial infarction was taking part in self – administered, cardiovascular rehabilitation program with repeated clinical, biochemical and instrumental evaluation of cardiovascular and psychoemotional status, and heart rate (HR) variability through every 6-month, during follow-up. Psychological status was assessed with using Hospital Anxiety and Depression Scale, Beck Depression Inventory. On the basis of the rhythmogram, the heart rate (HR) variability parameters during rest were evaluated. Prepared computerized method for quantitative evaluation of the functional status and efficiency of rehabilitation (ER) process was used. Results. During early rehabilitation and 2 years follow-up periods in patients with anxiety and depression poorer cardiovascular status was estimated ($p < 0.05$). Significant not marked relationship between psychoemotional disturbances and cardiac status, heart failure, angina pectoris and inverse relation with efficiency of rehabilitation was evaluated ($p < 0.05$). During long-term follow-up in patients with anxiety and depression ER was significant lower than in other psychological status groups. Relationship between ER and psychoemotional status during 6 month period was positive ($R = 0.35$), and became stronger and negative ($R = -0.59$) after 6-month, especially in patients with poor cardiovascular status. In post-MI patients with anxiety and depression significant predominance of sympathetic control of HR regulation (LF-14.7 and 19.8%), if compared with patients without disturbances, during functional tests was determined. Conclusion. In post myocardial infarction patients with anxiety and depression poorer cardiovascular status and lower efficacy of rehabilitation, with predominance of sympathetic control of heart rate regulation, during 2 year was evaluated.

STRESS AND PSYCHIATRIC MORBIDITY (P3)

P3-01 Interdisciplinary Approach: Therapy of Anxiety and Depressive Disorders in Women With Premenstrual Syndrome

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Objective: To study comorbidity of psychopathological disorders in nervous-mental form of the premenstrual syndrome for founding a complex method of treatment. **Materials and methods:** under conditions of an outpatient reception on the base of gynecological clinic 75 female patients with neuro-mental form of premenstrual syndrome (Premenstrual Dysphoric Disorder according to DSM-IV at the age of 18-41) were examined. Case story, clinical-psychopathological methods were used, for rating the severity of the anxiety and depression Hamilton Rating Scales were applied, for self-report – Scales by Tsung. **Methods** were presented to female patients during folliculinic and luteinic phases of the menstrual cycle before the onset of treatment and after the end of the therapy. **Results:** two variants of neuro-mental form of premenstrual syndrome have been distinguished. The first variant is characterized by presence of anxiety-depressive disorders in folliculinic phase that becomes more severe in luteinic phase of the menstrual cycle: a high level of comorbidity has been revealed with neurotic, stress-related disorders (65%). The second variant has been presented by cyclically emerging anxiety-depressive in luteinic phase; in 45% of cases interrelationship with demonstrative type of the accentuation of the personality has been revealed. In clinical structure in 755 of cases such symptoms are found as irritability, touchiness, low self-esteem, forgetfulness and somatic – mastodynia, hydropness and headache. Determining mental status in the first variant anxiety-depressive syndrome is, in the second – anxiety syndrome. A complex method of treatment including the intake of a tranquilizer (grandaxin, EGIS) with cyclic courses on day 14 till day 1 of the next menstrual cycle and administration of UHF-therapy on points of acupuncture V-H from day 14 of the menstrual cycle 8 procedures every cycle during two months. According to data of remote catamenesis (after 6 months) stability of therapeutic effect constituted 100% for removal of such symptoms as uneasiness, mood fluctuation, decrease of the interest in surroundings, aggressiveness, conflict temper, fatigue, low back pain and headaches.

P3-02 Prevalence of depressive mood and sleep complaints across the life cycles and the relations between emotional status and sleep complaints in the population of the West part of Lithuania

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Background. There is evidence to suggest a close relationship between depression and disturbed sleep. The aim was to estab-

lish the prevalence of depressive mood and sleep complaints across the life cycles and to assess relations between emotional status and sleep complaints in the population of Palanga, located in the West part of Lithuania. **Methods.** The design of the study was population-based, epidemiologic cross-sectional study. In a period of 16 months the data of randomly selected 1602 persons, 600 males and 1002 females, aged 35-74, was collected. Respondents according to the age were divided into 4 groups: 35-44, 45-54, 55-64 and 65-74 years. Depressive mood was assessed using WHO (5) Well-being Index (WHO, 1998) questionnaire. Sleep complaints were evaluated by Basic Nordic Sleep Questionnaire (Partinen, Gislason, 1995). Statistical analysis was performed using the SPSS 11.5 statistical package. **Results.** Prevalence of depressive mood among the respondents aged 35-44, 45-54, 55-64 and 65-74 years did not differ significantly, respectively 27.6% (95% CI 23.2-32.0), 32.6% (95% CI 27.9-37.2), 28.8% (95% CI 24.6-33.0) and 23.4% (95% CI 19.1-27.7). Persons aged 65-74, as compared with respondents aged 35-44 years, more often complained about regular difficulties falling asleep, respectively 10.5% (95% CI 7.4-13.6) vs. 4.0% (95% CI 2.1-5.6), $p < 0.05$, as well as regular night-time awakenings and too early morning awakenings, respectively 46.8% (95% CI 41.7-51.9) vs. 22.1% (95% CI 18.1-26.2), $p < 0.001$ and 8.9% (95% CI 6.0-11.8) vs. 3.7% (95% CI 1.9-5.6), $p < 0.05$. Respondents, who had depressive mood, as compared with persons whose mood was considered normal, more often complained about regular difficulties falling asleep, night-time awakenings and too early morning awakenings, respectively 11.5% (95% CI 8.5-14.4) vs. 5.1% (95% CI 3.8-6.4), 46.7% (95% CI 41.9-51.3) vs. 33.5% (95% CI 30.8-36.2), and 10.6% (95% CI 7.8-13.6) vs. 5.7% (95% CI 4.5-7.2), $p < 0.001$. **Conclusions.** Prevalence of depressive mood did not differ with respect to the age, while proportion of the respondents who had sleep complaints increased across the life cycles. Depressive mood more often was observed among the persons with sleep complaints.

P3-03 Depression, Sleep and Quality of Life in Post-Stroke Patients

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Background: Stroke as the third leading cause of death and the most common disabling disease has an enormous emotional impact on patients. Depressive disorders often follow a stroke and influence stroke rehabilitation, recovery and quality of life. This study aims to investigate the frequency of post-stroke depression at late stages of stroke recovery and its correlates with neurological impairment and quality of life.

Subjects and methods: A cross-sectional, descriptive correlational design was used. Subjects were identified from records of consecutive discharges of stroke survivors during 2000-2003 periods from Klaipeda hospital-based stroke register. One hundred ninety nine randomized stroke survivors (a mean

age 67.9 (SD 9.4), a range 29-89 yrs) were interviewed 1 to 4 (average 2.7) yrs after acute stroke. Psychological state was assessed with the HADS (Hospital Anxiety and Depression Scale score ≥ 8).

Results: Depression was found in 138 (69.4%) (20.1% middle expressed and 49.3% strongly expressed, HAD score ≥ 11) patients, anxiety in 125 (64.8%) (21.8% middle expressed and 43.0% strongly expressed). This study confirms quite a strong linear correlation ($r=0.71$, $p<0.01$) between scores on the two subscales of the HAD. The symptoms of depression and anxiety coexisted in 54.6% of all patients (44.4% in age group till 65 years and 59.7% in older). Gender was not associated with depression. The depressive patients were older than non-depressive ones, the mean age of non/major depressive patients being 63.9/70.1 yrs ($p<0.05$). Anxiety was most common among patients aged ≤ 65 yrs and women. Women with depression had coexisted anxiety frequently than men. The depressive patients were more dependent in activities of daily living function and had more severe impairment and handicap evaluated by the Barthel Index, the MMSE and the Rankin Scale than the non-depressive patients. There was a strong correlation between depression, sleep quality, and overall quality of life for stroke survivors.

Conclusion: These findings call for multidimensional evaluation of stroke patients and provide new challenges for stroke rehabilitation.

P3-04 The Vulnerability to Stress in Medical Students: an Association With Mood Symptoms and Personality Traits

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High level of vulnerability to stress has negative and significant effect on students' academic achievements. In this study we hypothesized that in population of students higher level of vulnerability to stress is linked with higher levels of depression, anxiety and neuroticism. Students of the Kaunas University of Medicine were evaluated for vulnerability to stress by the Stress Vulnerability scale (SVS), for symptoms of anxiety and depression by the Hospital Anxiety and Depression scale (HADS) and for prevalent personality trait by the Big Five Personality Dimensions (BFPD). A total of 338 sets of questionnaires were filled correctly by 73 (22%) male students and by 265 (78%) female students. The mean age of study population was 21 ± 1 years. We found that students who scored 8 or more on the HADS depression subscale (HADS-D) had higher scores on the SVS when compared to those students who scored less than 8 on the HADS-D (36 ± 11 and 24 ± 9 respectively, $p<0.001$). The score on the HADS-D correlated significantly with the score on the SVS ($r=0.44$, $p=0.01$). Students who scored ≥ 8 points on the HADS anxiety subscale (the HADS-A) had higher scores on the SVS when compared to those students who scored <8 on the HADS-A (30 ± 11 and 23 ± 9 respectively, $p<0.001$). The score on the HADS-A correlated significantly with the score on the SVS ($r=0.38$, $p=0.01$). The score on the SVS correlated positively with the score of

the neuroticism ($r=0.27$, $p=0.01$) and correlated negatively with the score of the extraversion ($r=0.21$, $p=0.01$), with the score of the consciousness ($r=0.13$, $p=0.01$), with the score of the agreeableness ($r=0.29$, $p=0.01$) and with the score of the openness ($r=0.11$, $p=0.02$) on the BFPD. This study shows that in population of medical students vulnerability to stress is associated with symptoms of depression and with symptoms of anxiety as well as with personality trait of neuroticism. Other personality traits such as extroversion, consciousness and openness have negative association with vulnerability to stress.

P3-05 Effect of Exercise Training on Quality of Life in Patients With Depression

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Background: A number of studies are showing that exercise training help people simply feel good and may even fight clinical depression. Regular physical activity being a potent mood-booster may be helpful in depression treatment for some patients. The goal was to investigate the impact of regular physical exercise on psychological state, sleep and quality of life (QoL) in patients with depression. Methods. The contingent was 59 women (a mean age 39.3 (SD 3.1), a range 22-51 yrs) with diagnosed clinical depression distributed into 2 groups: 1 group, 36 patients (a mean age 41.1 SD9.6 yrs), with regular exercise training; and 2 group, 23 control patients (45.8 SD13.3 yrs) without training. The QoL was assessed using the Medical Outcomes Study Short Form Health Survey (SF-36). This is a 36-item questionnaire generating component scores for physical function (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), emotional role (RE) and mental health (MH). Psychological state was evaluated using Hospital Anxiety and Depression Scale. Pittsburgh Sleep Quality Index (PSQI) was used for evaluation of sleep quality. Testing was performed four times: before treatment and at 1, 3, 6 months of follow-up. Results: Scores on depression subscale decreased from 15.1 ± 3.9 to 7.9 ± 1.9 ($p<0.05$) and PSQI from 15.1 ± 2.7 to 9.5 ± 1.6 ($p<0.05$) after 1 month of regular physical training in patient group with exercise. These characteristics remain constant during further follow-up. Before treatment QoL in all domains did not differ significantly between both groups, with and without exercise training. In patients with regular physical activity QoL was statistically significantly improved in all domains of SF-36 survey, except RE and GH after 1 month of treatment. The further improvement was observed after 3 and 6 months of treatment in all domains of QoL. In patient group without exercise training the scores of QoL, PSQI, and HADS did not differ significantly through all follow-up periods. Conclusion. Involvement of regular physical exercises into the treatment of patients with depression significantly improves their quality of life and psychological status.

STRESS AND WOMEN HEALTH (P4)

P4-01 Altered Female Sex Hormone Effects on Adrenocorticotropin Secretion in Women with Adverse Childhood Experiences

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Adverse childhood experiences (ACEs) predispose individuals to the development of mental and stress-related bodily disorders in adulthood, including depression and premenstrual dysphoric disorder (PMDD). In humans, a variety of studies have examined ACE-related changes in activity of the hypothalamic-pituitary-adrenal axis. However, little is known about whether ACEs also affect other hormonal systems and their interactions with the HPA-axis. Animal research suggests that ACEs lead to long-term changes in estrogen receptor sensitivity. Given that depression is more common in women, we were interested in exploring ACE-related changes in the interaction between the HPA-axis and sensitivity to female sex hormones. Methods: Plasma adrenocorticotropin (ACTH) and cortisol concentrations during a low-dose arginine vasopressin (AVP) stimulation test were analyzed in 18 women with childhood physical or sexual abuse experiences and 20 controls. Approximately 25% of the women in each group were taking oral contraceptive (OC) medication. Results: Overall, women taking OCs showed significantly higher plasma cortisol concentrations during the AVP stimulation test, with no effect of ACEs. However, looking at ACTH concentrations, there was a significant interaction effect between ACEs and OC medication. In the ACE group but not in the controls, women taking OCs showed significantly lower ACTH concentrations compared to those not taking OCs. Conclusions: These results provide preliminary evidence that in women, ACEs are associated with long-term changes in female sex hormone effects on ACTH. The findings should be further evaluated in studies specifically designed to assess ACE-related changes in the female sex-steroid system. Changes in female sex hormone receptor sensitivity in women with ACEs may underlie the association between ACEs and an increased vulnerability to estrogen-related illnesses, such as PMDD, or other illnesses that are more prevalent in women than in men.

P4-02 Particular Features of Depressive Episodes in Patients With Bipolar Disorder After Menopause

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The female reproductive lifecycle introduces many challenges in the evaluation and treatment of bipolar disorders. Aims: To analyze the features of depressive episodes of bipolar patients

before and after menopause and finding the optimal treatment doses. Material and Methods: We assessed 20 patients with min 10 years history of bipolar disorder which are in physiological climax. We used Menopausal Raters Scale (MRS) to assess the menopausal status, Freiburg (FPI) Personality inventory to assess emotional lability nervousness, receptivity, sociability and aggressiveness, and Hamilton Test for Depression (HAMD) to assess the severity of depressive episodes. MRS and FPI have been performed during the first depressive episode since menopause and again after 12 months. HAMD has been performed during last depressive episode before menopause, during the first depressive episode in menopause and after six months of treatment with similar doses of antidepressive treatment, and after 12 months when the treatment doses were increased. Results: Before menopause, patients have had an average of 2 annual episodes, and after menopause an average of 4.65 episodes of depressive episodes. HAMD before menopause was 29.6/episode/patient, after menopause was 40/episode/patient, after 6 months with the same treatment 39/episode/patient and after increased doses for 6 months was 35.5/episode/patient. FPI scores was increased After menopause, FPI scores regarding emotional lability, nervousness and aggressiveness and MRS were increased with a significant decrease only after high doses of antidepressive treatment. Conclusions: In bipolar patients, after menopause, increasing the doses of antidepressive treatment alleviates the psychiatric symptoms more effectively than the doses administrated before menopause.

P4-03 Does Migration in Pregnancy Influence on Perinatal Outcomes?

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Objective. To evaluate the influence of instable socioeconomic status and acute stress, that is related to migration during pregnancy, on perinatal outcomes. Methods. From November 1, 2005 to March 31, 2006, 1153 women who delivered in the Department of Obstetrics and Gynecology of Kaunas University of Medicine were asked about migration during pregnancy. 31 of them used to live abroad during pregnancy and they completed questionnaire which was aimed to find out demographic, social, behavioural, and biomedical factors. The control group was made up from women, who during pregnancy lived in Lithuania and delivered at the same day as control. The medical records were analyzed for data about pregnancy and delivery complications and perinatal outcomes Result. Most of reemigrants were from West European countries (26/31). The main socio-demographic and behavioural characteristics (age, education level, marital status, parity, smoking and alcohol consumption habits) didn't differ between groups. Migrant women more frequent worked manually during pregnancy (53.3% vs. 36.7%, respectively, $p < 0.001$). The significant difference in diet peculiarities, frequency of domestic violence and experienced stress in pregnancy was not observed between groups.

Lack of antenatal care was noticed in 57% of migrant women, compare to 10% in control group ($p < 0.001$). The proportions of premature births and low birth weight were higher but showed no statistically significant differences between migrant and control group women (23.3% vs. 6.7% and 10% vs. 6.7%, respectively, $p = 0.07$). Other perinatal complications, including an Apgar score < 8 (10% vs. 0%, respectively) and 1 case of stillbirth were found only in migrant women group ($p = 0.08$). Premature rupture of membrane was strongly associated with migration during pregnancy (46.7% vs. 20.0%, $p < 0.05$). Conclusion. Migration during pregnancy and immigrant status has association with a period of stress that slightly influences perinatal complications. The most of migrant women had healthy pregnancies and healthy birth outcomes despite of frequent lack of antenatal care but the least small part is a high risk subpopulation.

OTHERS (P5)

P5-01 Effect of the Treatment With Atypical Antipsychotic Agents on Condition of Thyroid Axis

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The aim of our study was to investigate condition of thyroid axis on the treatment with atypical antipsychotics. Method: 97 patients were included in this study, age ranging from 18 to 48 years, 25 males and 72 females. All patients met DSM-IV criteria for paranoid schizophrenia and schizoaffective disorder and took the single-drug therapy by quetiapine (Ist group), amisulpride (IInd group) and clozapine (IIIrd group). The levels of TSH and T4 in peripheral blood were determined before the initiation of neuroleptic therapy (Ist phase), after 3-4 weeks (IInd phase) and after 6-8 weeks of treatment (IIIrd phase) by ELISA method. Results: There was a significant decrease of TSH level on male patients in Ist group from IInd to IIIrd phase (II – 1.5 ± 0.24 μ IU/ml p III – 0.75 ± 0.41 μ IU/ml; $p=0.025$), whereas T4 level was increased from phase to phase, arrived at statistically important differences between Ist and IInd phases (10.7 ± 0.39 pmol/l and 14.5 ± 0.58 pmol/l accordingly; $p=0.02$). There was a significant decrease of free T4 (FT4) level on female patients from Ist to IInd phase (15.25 ± 0.99 pmol/l and 13.71 ± 0.96 pmol/l accordingly; $p=0.03$). In the IInd group of male patients there was founded a weak tendency to decrease of TSH level to IInd phase and significant increase to IIIrd phase (1.26 ± 0.24 μ IU/ml p; 1.52 ± 0.36 μ IU/ml; $p=0.01$) and differently directed fluctuations of the TSH level on female patients (1.58 ± 0.44 μ IU/ml, 1.39 ± 0.4 μ IU/ml p; 1.48 ± 0.36 μ IU/ml), but this differences were not statistically significant. The TSH level on male patients in IIIrd group had weak tendency towards increase, whereas the level of free T4 (FT4) had an opposite tendency to decrease although in both of that cases the differences was not statistically significant. There was a significant increase of TSH level during the therapy of clozapine on female patients from Ist to IIIrd phases (0.95 ± 0.16 μ IU/ml; 1.42 ± 0.3 μ IU/ml [$p=0.035$]; 1.61 ± 0.27 μ IU/ml; [$p=0.00009$]). The dynamic of free T4 (FT4) had an opposite tendency to decrease from phase to phase. Conclusion. The results of research show that the most expressive influence on central and peripheral hormones of female patients treated by clozapine.

P5-02 Symptoms of Anxiety and Depression with Relation to Personality Traits in Medical Students

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Symptoms of depression and anxiety are prevalent in general population, especially in young adults. The aim of this study was to evaluate the prevalence of depression and anxiety symptoms and their relationship with personality traits in population of students of the Kaunas University of Medicine. For symptoms of anxiety and depression students were evalu-

ated using the Hospital Anxiety and Depression scale (HADS). Students who scored 8 or more on the HADS anxiety subscale (HADS-A) and/or on the ADS depression subscale (HADS-D) were considered to be positive for anxiety and/or depression symptoms. Personality traits were assessed using the Big Five Personality Dimensions (BFPD). A total of 338 sets of questionnaires were filled by 73 (22%) male students and by 265 (78%) female students. The mean age of study population was 21 ± 1 years. We found that 145 (43%) students had anxiety symptoms and 48 (14%) students had depression symptoms. Co-morbidity of anxiety and depression symptoms was 10%. The mean score on the HADS-A was 8 ± 4 and the mean score on the HADS-D was 5 ± 3 . The score on the HADS-A and the score on the HADS-D did not differ significantly according to the sex, age and years studying at the university. The score on the HADS-A correlated positively with the score of the neuroticism ($r=0.46$, $p=0.01$) and correlated negatively with the score of the agreeableness ($r=-0.24$, $p=0.01$) on the BFPD. The score on the HADS-D correlated positively with the score of the neuroticism ($r=0.26$, $p=0.01$) and correlated negatively with the score of the extroversion ($r=-0.19$, $p=0.01$), with the score of consciousness ($r=-0.15$, $p=0.01$) and with the score of agreeableness ($r=-0.31$, $p=0.01$) on the BFPD. This study shows that depression and anxiety symptoms are prevalent in population of medical students. Symptoms of anxiety and depression have positive relationship with personality traits of neuroticism and negative relationship with personality trait of agreeableness. Depression symptoms also have negative relationship with personality traits of extroversion and consciousness.

P5-03 Distribution of Pituitary Tumors in Republic of Croatia

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Over the 10 percentage of all intracranial tumors are pituitary tumors. Clinical manifestations of pituitary tumors depend on their localisation and hormonal activity. They are either hormonally functional or nonfunctional, respectively. By location tumors are intrasellar or extrasellar. By biologic behavior tumors are non invasive or invasive (then this tumors are of malignant behavior, although they are histologically benign). Regarding the size there are microadenomas (smaller than 10 millimeters) and macroadenomas (10 millimeters or more). In the Center for Clinical Neuroendocrinology and Pituitary Diseases Clinical Hospital «Sestre milosrdnice» Zagreb, Croatia, in the last working 10 years, there have been examined and treated 504 patients with pituitary tumors. Patients came from the whole territory of Republic of Croatia. All patients were analysed by tumor type: 182 patients with prolactinomas, 137 patients with acromegaly, 70 patients with Cushing's disease and 115 patients with non-functional pituitary tumors. They were also separated on the regional base: Continental and Mediterranean (coast) Croatia. The aim of our study was to see if the natural, climatic conditions and different life style (includ-

ing food, water, or war events) have any impact on appearance and distribution of pituitary tumors. In continental region were found 377 patients (because of the largest number of inhabitants). Prolactinoma had 140 (37%), acromegaly 101 (27%), Cushing had 51 patients (14%), and nonfunctional tumor had 85 patients (22%). In Mediterranean region of Croatia were found 127 patients with pituitary tumors. Prolactinoma had 42 (34%), acromegaly 36 (28%), Mb Cushing had 19 (15%), and nonfunctional tumors had 30 patients (23%). Our results show there is no statistically significant difference among presentation between this two regions. The incidence of pituitary tumors is very similar to data we found in the literature. So, the natural, climatic and life conditions have no impact on appearance and distribution of some types of tumors in Republic of Croatia.

P5-04 The Impact of Growth Hormone Replacement Therapy on the Risk Factors for Atherosclerosis in Patients with Cushing's Disease

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Our retrospective study included ten female patients aged 29-44 (mean age 37.6±8.6) years, who had undergone adenectomy for pituitary tumor and Cushing's disease. Postoperatively, all patients had developed panhypopituitarism, and conventional hormonal replacement therapy (HRT)- hydrocortison, L- thyroxine and ovarian hormones, was started. After six months of therapy, endocrinological and other testing were performed, including plasma cholesterol, triglycerides, blood glucose, body weight, body height, waist-to-hip ratio, systolic and diastolic blood pressure and pulse at rest, and body mass index (BMI). All patients answered the questionnaire on their general condition. Although endocrinological test results (serum cortisol, ACTH, T3, T4, TSH and gonadal hormones) showed that conventional HRT was correctly performed, both subjective and objective recovery of all patients was quite poor. Additional laboratory tests (basal growth hormone-GH, IGF-1, insulin tolerance test and TRH test) were determined and revealed the lack of growth hormone. Therefore, we added GH in the replacement therapy, at a dose of 1-2 IU/day s.c. After subsequent six months all patients felt much better subjectively. Great improvement was recorded in the objective parameters as compared with the conventional HRT alone. The mean plasma level of total cholesterol decreased from 6.95±1.05 to 4.9±1.8 mmol/L, triglycerides from 4.39±1.61 to 1.94±0.76 mmol/L, plasma glucose from 7.83±3.17 to 5.12±1.22 mmol/L, mean body weight from 80.2±5.2 to 74.7±4.7 kg, waist-to-hip ratio from 0.827±0.093 to 0.814±0.064 m, systolic blood pressure from 148.5±11.5 to 141±9.0 mm Hg, diastolic blood pressure from 89±16.0 to 84.5±5.5 mm Hg, pulse from 82.2±7.8 to 71±11.0 per min, and mean BMI from 29.1±2.1 to 26.8±1.6 kg/m². It was concluded that the introduction of GH in standard hormone replacement therapy led to noticeable better patient recovery as compared with standard HRT alone. The values of many risk factors for atherosclerosis such as a total cholesterol,

triglycerides, blood glucose, waist-to-hip ratio, blood pressure, and BMI were considerably reduced after growth hormone was added in therapy.

P5-05 Pituitary and Pancreatic Endocrine Tumors

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Multiple endocrine neoplasia (MEN) syndrome often includes neoplasms of parathyroid glands, anterior pituitary and pancreatic islets cells, but also adenomas of the adrenal and thyroid gland can occur. Pituitary tumors develop in 15%-20% of patients with MEN 1 and the most common type of pituitary tumor is prolactinoma. We present a young girl at the age of 16 appeared with headache, galactorrhoea, primary amenorrhoea and low height for her age. Endocrinological evaluation revealed an increased prolactin level exceeding 400 ng/ml. Computed tomography (CT) scan of the pituitary gland discovered a tumor mass 1.5x0.9 cm in size. Transnasal selective partial adenectomy was performed as most appropriate surgical procedure. Postoperative pathologic examination showed a prolactinoma (chromophobic adenoma). The patient has developed hypopituitarism postoperatively and hormonal replacement therapy including levothyroxin and hydrocortison was started. Laboratory test showed decreased blood glucose levels which have never been explained because the patient selfinitatively left the hospital and lost further contact. Four years later she presented with recurrent episodes of confusion, excessive sweating, weakness with tremor and significant increase in body weight of 90 kg since last exam. She was extremely overweight, with body mass index exceeding more than 63 kg/m², due to extreme carbohydrate intake caused by hypoglycemia. Laboratory tests revealed severe hypoglycemia with high plasma insulin and C-peptide level. A tumor secreting insulin or insulin-like growth factor were presumed. CT and magnetic resonance (MR) of the abdomen could not be performed because of the patient's extreme overweight. Abdominal ultrasonography showed a tumor mass measuring 26 mm in the distal part of the tail of the pancreas and consecutively hemipancreatectomy and splenectomy were performed in one act. After the surgery, clinical symptoms disappeared but the patient developed transitory diabetes which required temporary insulin in treatment. Her body weight was gradually normalized, losing 54 kg in one year. Postoperative MR of sellar region and CT of the abdomen showed no pathologic changes. Patient presenting with prolactinoma and hypoglycemia is suspected on existing MEN 1.

P5-06 Depression Revealed Gigantic Pituitary Tumor

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Center for Clinical Neuroendocrinology and Pituitary Diseases Clinical Hospital „Sestre milosrdnice“ Zagreb, Croatia Nonfunctional pituitary tumors due to their slow growth and wide modality of clinical appearance very often are lately and hardly diagnosed. Diagnosis is most often setted when tumor affects surrounding anatomical structures so they act local invasively or they cause hypopituitarism. Gigantic pituitary tumors are extremely rare because they are reached in earlier phase of their growth with supreme diagnostic methods. We represent 55-year old male patient, intellectual, who presented us with heavily impaired general condition, severe right hemiparesis, right opthalmoplegy and ptosis of right eye lid, who was hospitalised at neurology department due to instability and fall during the walk. From his medical history is known he has been for 20 years in psychiatric treatment due to depression. Computed tomography (CT) revealed expansive tumor process in sellar region. Afterwards magnetic resonance (MR) of sellar region indicated 9 cm large pituitary macroadenoma spreading in both cavernous sinuses filling sphenoidal sinus, with erosion of dorsum sellae and spreading in suprasellar region. Clinical features of panhypopituitarism were confirmed by endocrinological evaluation, therefore complete hormonal replacement therapy was started. Transphenoidal microsurgical maximal tumor reduction was done. Pathological analysis revealed acidophile pituitary adenoma. Postoperative course was slowed with significant residual neurologic failure and control CT and MR of brain showed no acute bleeding but showed noted tumor residue, so irradiation therapy on tumor residue was delivered. On performed rehabilitation and complete hormonal replacement therapy patient showed significant recovery in physical and mental condition. This case represents treatment due to secondary manifestation of main disease which was for a long period of time unsuspected. Diagnosis of gigantic pituitary tumors itself often indicates previously unrecognized symptoms and signs of underlying pituitary disease.

P5-07 Peculiarities of Bipolar Disorder in Adolescents

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Background: Bipolar disorder (BD) is a serious illness in children. Its prevalence in adolescents is estimated to be about 0,1-1%. There are only about 3 new cases of BD diagnosed per year in Lithuania. Adolescent's BD in this age group has developmentally distinct presentation from that in adults, high comorbidity, with relatively poor outcome. objective: To analyze demographic characteristics, course, comorbidity, clinical symptoms and treatment of adolescents with BD in Clinics of Kaunas University of Medicine (KMUK) Children and Adolescent Psychiatry department. Methods: We studied all case histories of 14-18 years old patients, hospitalized in KMUK Children and Adolescent Psychiatry department during 2000-2005 year, with diagnosis of BD. RESULTS: We analyzed cases of 5 girls (83%) and 1 boy (17 %), whose average age was 16 years. Most often diagnosis was BD without psychosis (3cases). BD with psychosis, BD with hypomania and BD with

depression were distributed equally. Childhood-onset bipolar disorder was comorbid with emotionally instabile personality disorder 33 p, adaptation disorder and struma diffusa. We found that depressive disorders were diagnosed previously for 83% patients and mania for 33%. Parents of 83% of patients were healthy and 17 % of parents were ill with schizophrenia. 33% of patients parents had impulsive character and unstable mood. Most frequent symptoms were rapid changes of mood without any reasons, which was observed in 4 patients. There were also symptoms of dysphoric mood, oppositional or impulsive behaviour, decreased need for sleep. Euphoric mood was accompanied by increased energy. All patients were treated with antipsychotics. Carbamazepin was administered for 3 patients and lithium was given for 4 patients. Psychotherapy was practised as a relapse-prophylactic intervention with strategies to improve interpersonal relationships and stress management. Conclusions: BD in adolescents has insidious onset, is highly comorbid and characterized by high rates of irritability, rapid cycling of symptoms, increased energy, euphoric mood. Antipsychotics with mood stabilizer is usual treatment of BD in KMUK Psychiatry Clinic.

P5-08 Quality of Life in Patients with Different Severity of Graves' Ophthalmopathy

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Many features of Graves' ophthalmopathy (GO) are considered to be stressful because cause pain, disfigures the appearance due to proptosis, redness, swelling of eyelids and invalidate due to diplopia, permanent streaming eyes, sometimes - blindness. Objective: to compare the quality of life (QL) in patients ill with mild and moderately severe GO. Methods: We included 80 patients ill with GO (42 ill with mild and 38 patients - with moderately severe GO) who were scheduled for endocrinologist consultation. The disease specific questionnaire developed by C. Terwee was used; information on disease characteristics was obtained also. GO-QOL contained 16 questions concerning visual functioning and psychosocial consequences of changed appearance. For the evaluation the disease impact on visual functioning the patients were asked to indicate the degree to which they were impaired in activities like driving, reading, watching TV and etc. For the evaluation of psychosocial consequences of changed appearance patients were asked indicate how much they felt their appearance had changed, how much they felt they got unpleasant reactions from others, how much they felt the disease influenced their self confidence, friendship and etc. Results: QL was in patients with mild GO was 84.6±14.7 comparing to 54.5±13.2 for moderately severe in visual functioning scale and for appearance scale 78.6±14.3 in patients with mild GO compare to 55.7±15.0 for moderately severe (p<0.01). There were found no correlations between OL and age, sex in patients with mild GO. It was found that QL for females was worse compare to males (49.9±16.9 vs 60.1±18.0; p<0.05) because of changed appearance. The correlation between age and QL due to impaired visual functioning was detected (r=-0.5). Conclusions: 1. GO has a big impact on quality of life. 2. The quality of life is worse in patients ill with

more severe GO. 3. Psychosocial consequences of changed appearance have bigger impact on female's QL compare with males. 4. Impaired visual functioning compare to changed appearance has bigger impact on QL for elderly people.

P5-09 CRF Distribution and its Effects in Rat Frontal Cortex

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Corticotropin releasing factor (CRF) is a neuropeptide widely distributed in the brain. The role of CRF in the modulation of anxiety states in several brain structures is well documented, but its function in the cerebral cortex still remains unknown. Our previous studies showed that CRF in doses of 0.05, 0.1, 0.2 $\mu\text{g}/\mu\text{l}/\text{site}$ decreased locomotor and exploratory activity during a 40-min session in the open field test. In the elevated plus maze test, an anxiogenic tendency was observed after a low dose of CRF(0.05 $\mu\text{g}/\mu\text{l}/\text{site}$) and an anxiolytic tendency after its dose of 0.1 $\mu\text{g}/\mu\text{l}/\text{site}$. The aim of our study was to investigate the behavioral functions of CRF in the rat frontal cortex, as well as the distribution of CRF-containing neurons and terminals in that structure. The study was carried out by immunohistochemical and behavioral methods. Immunohistochemical studies showed that CRF was present in the frontal cortex mainly in bipolar neurons in layers II and III, and in terminal varicose fibers scattered over all cortical layers, the density of fibers being higher in outer layers, though. In behavioral studies, male Wistar rats with chronically implanted cannulae in the frontal cortex were bilaterally injected with CRF in a dose of 0.2 or 0.4 $\mu\text{g}/\mu\text{l}/\text{site}$; additionally, some rats received alpha-helicalCRF (a CRF1&2 receptors antagonist) in a dose of 0.5 $\mu\text{g}/\mu\text{l}/\text{site}$ and NBI27914 (a CRF1 receptor antagonist) in dose of 1 $\mu\text{g}/\mu\text{l}/\text{site}$. The animals were placed in the elevated plus-maze to examine effects of CRF on anxiety. Behavioural experiments showed that CRF in dose of 0.2 or 0.4 $\mu\text{g}/\mu\text{l}/\text{site}$ produced significant anxiolytic-like effects in elevated plus maze test, that effect being prevented by CRF receptor antagonists. The obtained results suggest that: 1) CRF-immunoreactive nerve cell bodies and terminals are distributed in rat frontal cortex; 2) CRF injected into the frontal cortex decreases locomotor and exploratory activity and may play a modulatory role in anxiety behavior.

P5-10 Cognitive Dysfunction in Patients With Eating Disorders

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Background: The recent studies have showed that patients with eating disorders have disturbed food, body shape and weight related information processing. The purpose of the study was to investigate the cognitive function in women with eating disorders. Methods: Auditory event related potentials were recorded and analyzed in 10 female subjects with eating disorders and

in 10 normal women using "oddball" paradigm and the verbal disorder-related stimuli (food and neutral words). Results: The P300 amplitude was significantly lower at all three sites (Fz, Cz, Pz) in bulimic group compared with that in controls and in patients with anorexia. Whereas the patients with anorexia nervosa responded to food stimuli significantly faster than patients in other groups. These effects were only found when auditory evoked potentials were recorded using verbal stimuli. The P300 latency or amplitude of three groups of patients did not differ at any site when two-tone discrimination task was used. Conclusions: The results show changes of P300 parameters in women with eating disorders. The main limitation of the study is the small sample size that could affect the results. Further study is being done to test these results.

P5-11 Role of Alcoholization in Diabetes Clinical Picture

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The primary purpose of the research was detection of the role of alcoholization in the clinical picture of diabetes mellitus (DM). 120 patients with DM (39 men and 81 women) that were treated at the Arkhangelsk Regional Clinical Hospital have been examined - 58 persons with DM type 1 and 62 persons with DM type 2. The clinical and physiologo-biochemical methods of research, a questionnaire have been used. According to the results of the questioning, all patients were divided into 4 groups concerning their use of strong drinks: I – 10 persons (8.3%) - practically did not use strong drinks; II – 74 (61.6%) - using alcohol on the average with frequency 1 time per a month (in doses up to 100 ml of 40 % alcohol) - "using rarely"; III – 20 (16.7%) – with frequency 1-4 times per a month (up to 500 ml) - "using moderately"; IV – 16 (13.3 %) patients – with clear symptoms of alcohol abuse. During the research in the patients that abused alcohol, more pronounced changes have been revealed in albuminous, lipid and carbohydrate metabolism, microelement composition, hyperenzymia of transaminases; for them, long non- compensated state of ketoacidosis was typical at a background of insignificant dynamics of glycemia level decrease. They used reliably bigger doses of insulin that can be explained by the presence of insulin resistance during alcohol abuse. The terms of DM compensation achievement and duration of patients' stay in the hospital were inversely proportional to intensity of strong drinks use. At the same time, direct dependence of frequency of cases and pronouncedness of DM somatic complications (micro- and macroangiopathies) with an increase in the degree of patients' alcoholization has been revealed. Thus, alcoholization is one of the factors that makes the clinical picture of DM significantly more serious, contributing to its decompensation and early development of complications. The detection of the role of alcoholization by DM allows to develop differentiated approaches to rendering aid to patients directed at improvement of their quality of life.

P5-12 Neuroimmunologic Stress of Epileptic Syndrome of Alcoholic Genesis

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Epileptic syndrome (ES) as a non-specific response of an organism to toxic impact of alcohol is one of the leading disturbances of the nervous system by chronic alcoholic intoxication (CAI). Certain neuroimmunologic mechanisms underlie ES alcoholic genesis. In this case, alcohol is a powerful stress factor leading to ionic, energetic, immunologic and endocrine shifts in an organism, causing changes in brain neuronal activity that becomes abnormal, excessive, periodic. As a result of influence of the stress factor – alcohol, the hematoencephalic barrier's permeability increases and immunologic reactions with formation of anticerebral antibodies and autoantibodies to glutamate receptors start up what causes a decrease in nerve cells and cerebral tissue hypotrophy. As the main condition for beginning of epileptic abstinent seizures is CAI, all the shown shifts appear at a background of immunodeficit state and endocrine dysfunction (hypercorticism, hypogonadism) that exist by alcoholic disease. We have examined 167 patients with ES divided into two groups – of alcoholic (89) and non-alcoholic (78) genesis and 84 patients of a neurologic clinic without ES (group of comparison). In 100% of cases of ES alcoholic genesis, low bioelectric activity, dysrhythmia and diffusive changes on electroencephalograms were revealed what can be considered as a manifestation of the median-truncal structures' dysfunction and a reduction of brain functional ability. These disturbances result in immunologic changes, production of cerebral antibodies. In the group with ES of non-alcoholic genesis and the group of comparison, similar changes were revealed in less than a half of the observations. On the brain computer tomograms of patients with ES of alcoholic genesis in 82% of cases, signs of mixed hypotrophic hydrocephalus existed, in cases of non-alcoholic genesis – only in 64.3%. It has been also detected that development of brain hypotrophy went quicker at the young age in the group of patients with alcoholic attacks (in 10.1% of cases).

PROCEEDINGS

PROCEEDINGS

Treatment of Reproduction Related Disorders in Women

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Introduction

According to the World Bank and the World Health Organization (WHO) report on global burden of disease. (Murray and Lopez, 1996), in women of ages 15-44 (roughly corresponding to women of reproductive age) depression is the leading cause of disease – burden and disability in developed as well as emerging economies. Women are at least twice as likely as men to suffer from recurrent major depressive disorder (MDD). Lifetime prevalence of MDD in women is reported to be 7%-21% as compared to 2.6%-13% in men (Kessler et al 1994). The higher prevalence of depression is not limited to MDD but has also been reported for seasonal affective disorder (SAD), Dysthymic Disorder, General Anxiety disorder (GAD), panic disorders, and most phobias, as well as obsessive compulsive disorder (OCD) and post-traumatic stress disorder (PTSD). It is of interest that the gender difference in prevalence of depression is mostly in “atypical depression” and “anxious depression” as well as “somatic depression” but not in “endogenous depression” (or “melancholia”) (Ernest and Angst, 1991, Silverstein, 2002).

There are consistent epidemiologic reports that the gender difference in affective disorders emerges at adolescence (Angold et al 1998), persists throughout reproductive life and may decrease after menopause (though this may be debatable-Angst et al 2002). These epidemiologic studies suggest association between at least a subgroup of affective disorders and reproductive related processes, and fluctuations in levels or activity of gonadal hormones. The main gonadal hormones – estrogen and progesterone, influence numerous Central Nervous system (CNS) processes including those that are putatively important for regulation of mood, cognition and behavior: the serotonergic, norepinephrine, dopaminergic, cholinergic and the GABA systems. Furthermore specific periods in women’s life have been demonstrated to be associated with increased prevalence of affective disorders, or Reproductive related dysphoric disorders (RRDDs). These periods are mostly pregnancy, the post partum period (the first 6 weeks post partum), the pre (peri) menstrual period and the perimenopause or the menopause transition. It is of interest that once the menopause stable state is achieved, the prevalence of dysphoric disorders decreases. This phenomenon underscores the notion that RRDDs are associated with periods of change or instability. Probably the most important process during these periods is the decrease in levels and activity of gonadal and other hormones which may be abrupt, as is the case immediately following delivery (which is actually related to the delivery of the placenta and not the baby), or may be more gradual as is the case with the perimenopause. The relative rate of change in activity of gonadal and other hormones (e.g. CRF) may be of importance – and may cause a state of instability and impaired homeostasis

which may lead to the emergence of symptoms. (Halbreich et al, 1987, 1988)

Due to the bidirectional interactions between changes in gonadal hormones and changes in neurotransmitters, and impairment related to the gonadal hormones’ trigger and/or neurotransmitters’ activity - RRDDs may be treated in two main ways: a) stabilizing or limiting the changes in activity of estrogen and/or progesterone, and: b) enhancing activity of neurotransmitters that are putatively involved in the pathobiology of RRDDs. Another clue for interventions is the phenomenology of RRDD, which is mostly consistent with “anxious depression”, irritability, “atypical depression” and “somatic depression” or a mixture of somatic and mental symptoms. It is still undocumented if relevant subtypes of RRDDs exist and if specific treatment modalities may be more efficient for specific phenotypes.

Here we focus on the treatment of 3 of the RRDDs: Post partum depression, premenstrual syndrome (PMS) with an emphasis on Premenstrual dysphoric disorder (PMDD) and depression during the perimenopause period.

Post partum depression (PPD)

The prevalence of PPD is probably culturally-dependent (Halbreich, Karkun, 2006). It varies between 0.5% in Singapore to 60.8% in Taiwan. In Western countries the widely-cited rate is 10-15% but prevalence is higher among poor, inner city, single mothers or minorities. In women with high socioeconomic risk the prevalence may be over 40%. Since the DSM IV criteria of PPD are based on MDD with a time qualifier (6 weeks post partum) the prevalence of post partum disorders, including stress, distress and anxieties, that may warrant treatment - may be even higher.

Since the symptoms of PPD are presumably similar to MDD and since the most prevalent hypothesis concerning its pathobiology is the abrupt withdrawal of gonadal hormones in the context of psychosocial stress, not surprisingly most prevalent treatment modality of PPD is by antidepressants – mostly selective serotonin reuptake inhibitors –SSRIs. Surprisingly the specific efficacy of SSRIs for PPD is not yet established, and it is unclear if it differs from their efficacy for MDD in general. When prescribing SSRIs to lactating women one should bear in mind that they are secreted into the mother’s milk and then to the breast-fed baby, though in a lower levels than in the mother’s blood. Probably there may be a short term influence of mother’s SSRIs on the baby’s behavior and mood. However, the long-term impact on the offspring’s serotonergic system and the relevant mood, cognition and behavior affects are still unclear.

It is also still unclear if SSRIs are less or more efficacious than the tricyclic antidepressants (TCA), or serotonin-norepinephrine reuptake inhibitors (SNRI). Probably dopaminergic agents like bromocriptine are ineffective for most women with PPD, though their prolactin decreasing effect may suggest some benefit.

Transdermal estradiol was reported to be efficacious for treatment of PPD (Gregoire et al 1996) even though treatment was initiated 2 months following delivery, when the immediate effect of the estrogen withdrawal was probably already over. Progesterone suppositories were reported by Dalton and her disciples to be highly effective treatment. However, I am unaware of double blind placebo controlled trials to confirm their clinical experience. The development of risk factors for PPD and the predictability of time of episode may suggest successful preventive modalities. Alas, this has not been developed yet.

PMS/PMDD

Premenstrual dysphoric disorder (PMDD) affects 5.6% (between 3-8%) of women of reproductive age. The prevalence of clinically relevant dysphoric PMS (subsyndromal symptoms severe enough to warrant treatment) is about 20%. The burden of disease of PMDD/PMS, calculated according to the Disability Adjusted Life Years (DALY) lost (Murray & Lopez, 1996) is substantial. Even when the prevalence of PMDD is estimated as only 5.3%, the total DALYs, or lost years of healthy life, is over 15,000,000 in the USA and over 18,000,000 in the European Union Countries. The impairment and decrease in quality of life due to PMDD (during the luteal phase of the menstrual cycle) is similar to that of MDD (Halbreich, 2004). The symptoms of PMS and even those of PMDD are diversified and subtypes have been suggested, but not confined yet. Symptoms are consistent within each individual but their severity may fluctuate from cycle to cycle. Since phenotypes are not yet established, their association with genotypes or other vulnerability factors is unclear.

PMS/PMDD may be attributed to ovulation-related fluctuations in gonadal hormones that cause changes in CNS processes and symptoms - in vulnerable women. The severity of symptoms may be influenced by the psychosocial environment. Therefore three main treatment modalities have been pursued. Especially for women with mild PMS – good healthy life style measures e.g. decreased stress, healthy diet, dietary supplements and behavior modifications, may be sufficient as a first line treatment. In more severe cases of PMS/PMDD the most widely-used treatment options are SSRIs which have been shown to be effective also as intermittent luteal-phase-only treatment. The dosages of SSRIs needed for treatment of PMDD are usually lower than those needed for MDD and the time to response is shorter, indicating a possibility of more sensitive serotonergic system in women with PMDD, or a combination of traits and state serotonergic dysregulation. Probably with most SSRIs treatment should be administered for the entire luteal phase, commencing immediately following ovulation. There are suggestions that with some SSRIs, treatment may be initiated a week before the menses or when symptoms appear, but this has not been confirmed yet, with most SSRIs the initiation of treat-

ment at time of emergence of symptoms is ineffective, indicating the importance of early luteal processes for later symptoms and a time-lag of 4-7 days between hormonal-neurotransmitter changes and symptoms' formation.

SSRIs are effective in about 60% of women with PMDD as compared to efficacy of 30%-40% of placebo, implying that SSRIs are not the perfect answer for all women with PMDD/PMS and other treatment modalities are still needed.

GABA-ergic medications, e.g. alprazolam—have been shown by some but not all studies to be an affective treatment of PMDD even when they are given only during the symptomatic period and discontinued immediately when the symptoms subside. No withdrawal effects were reported in these studies, suggesting different GABA processes in women with PMS as compared with MDD or anxieties.

The GABA system in PMS is of interest due to the suggested influence of GABA-ergic progesterone metabolites, like allopregnanolone which has been shown to be anxiolytic, but the treatment value of these modalities is still to be studied.

Probably the broader scope of treatment efficacy of PMS/PMDD is by suppression of ovulation. Studies of ovulation-suppression for PMS have been conducted with GnRH analogues, high doses of estrogen (sufficient to suppress ovulation), danazol, and recently-with hormonal contraceptives. Previously, hysterectomy with ovariectomy have been shown to be effective but same effect is achieved by “chemical menopause” which is irreversible, rendering the drastic castration unjustifiable.

Not all hormonal contraceptives are effective for treatment of PMS though all suppress ovulation. Some – e.g. –medroxyprogesterone acetate (MPA) actually induce PMS-like symptoms as adverse effects. Some, e.g. triphasic dosing schedules simulate the cyclic hormonal fluctuations and therefore may worsen PMS. A discriminating selective use of hormonal preparations is still in its infancy, but probably this is currently the most promising avenue of development of treatment modalities for PMS (Halbreich 2005)

Perimenopause related disorders

A transition from reproductive age to menopause is characterized by decreasing levels of estrogen/progesterone, increase in FSH levels, irregular menstrual cycles, until complete cessation of ovulation and cycles. Symptoms are due to hormonal and neurotransmitters instability, most noted are hot flushes and mood liability.

The prevalence of MDD during this period is about 15-20%, but there are other mental disorders and situations that may surface, their prevalence is still unclear. It has been shown that women with history of PMDD/PMS, PDD or other reproductive related disorders are more vulnerable to develop dysphoric disorders perimenopausally. As is the case with all RRDDs, vulnerability plays a major role in the appearance of episodes during the menopause transition.

Treatment with SSRIs is not always effective and sometimes augmentation strategies are needed. Due to frequency of hypothyroidism (at least 10% of perimenopausal women) many menopausal and perimenopausal women may benefit from ad-

dition of thyroid hormones. The definition of clinically-relevant hypothyroidism in women vulnerable to depression is different from that of most endocrinologists. E.g. –in many women who show TSH levels of 2.5-5.0, augmentation of SSRIs with thyroid hormones may be beneficial, although the TSH levels are considered to be within normal limits.

Probably the most effective augmentation of antidepressants for perimenopausal women is by estrogen, especially by transdermal estradiol.

Estradiol has been shown to be effective also as monotherapy (e.g. Soares et al, 2002, Schmidt et al 2000) for perimenopausal women with MDD.

It is of importance to note that estrogen is probably not effective for treatment of MDD or other dysphorias in menopausal women, though their normal state is of very low levels of estrogen.

Conclusion

Estradiol is probably effective as a monotherapy antidepressant only in periods when dysphoria is probably associated with hormonal change, mostly post partum depression, premenstrual dysphoria and depression during the perimenopause. During those periods, it is probably acting as a homeostatic agent. A sole treatment with estrogen is probably ineffective during other periods, e.g. for depressed menopausal women.

The role of other hormones or hormonal interventions for RRDDs is still awaiting classification

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Stress, Dietary Habits and Metabolic Syndrome

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The extent of the obesity problem in Europe-consequences and costs

Obesity is the most prevalent nutritional disorder in Europe. There is increasing alarm, as the enormous implications for health, mortality and quality of life associated with the dramatic increase in obesity in recent decades have become apparent. A quarter to more than half of the adult population of Europe is overweight (i.e. have a body mass index –BMI- greater than 25, with 10-40% clinically obese (BMI>30). Overweight and obesity are clearly linked to an increased risk of type-2 diabetes, cardiovascular disease and several other co-morbidities, which comprise Metabolic syndrome. By 2010 about 31 million people in Europe will require treatment for type-2 diabetes and its related complications. For the most part this is directly related to obesity and metabolic syndrome^[Zimmet PZ et al. 2001]. The WHO and national health organisations throughout Europe have declared obesity to be the 21st century epidemic, set to double by 2025 hence the growing concern about its consequences for public health and social welfare costs^[WHO/NUT/NCD/98.1 1998]. At this moment, in a number of EU countries, up to 7% of direct health care costs can be attributed to obesity, but

the cost is likely to increase in line with the rapidly increasing prevalence of obesity. The East European states that are currently integrating into the European community have even higher rates of obesity and little or no public health strategies to address this. For example in Bulgaria the prevalence of obesity is 23 %. However, the prevalence of obesity varies widely among different continents and countries, ranging from almost one third of the whole population in Yugoslavia and Greece to a prevalence below 10% in the Netherlands and Switzerland. Obviously, beyond the genetic background there are some other influences, namely cultural and life style, which could explain these differences.

Metabolic Syndrome

Metabolic syndrome (Met-S) is determined using clinically evident diagnostic criteria (abdominal adiposity, dislipemia, hypertension, hyperglycemia). Met-S is defined by NCEP as having at least 3 of the following metabolic abnormalities: fasting glucose >110 mg/dl or taking medication for diabetes, abdominal obesity (waist circumference >102 cm in men or >88 cm in women), or high blood pressure (>130/>85 mm

Hg). Met-S is defined by WHO as having one of the following metabolic abnormalities: hyperinsulinemia, abdominal obesity, dyslipidemia (triglycerides >150 mg/dl) and/or low HDL-cholesterol (<35 in men and <39 in women). Although estimates of prevalence depend on the exact definition used, Met-S, like obesity, has reached epidemic proportions^[Kereciakes DJ et al., 2003]. A recent cross-sectional health examination survey among nationally representative sample of non institutionalized civilians of the US found the age-adjusted prevalence rate of the metabolic syndrome to be 23.9%^[Ford ES, 2003]. Among Caucasians in Europe it is approximately 16%^[Beck-Nielsen, H., 1999] though there are substantial regional variations and it is associated with socio-economic status.

Environmental adaptation

Our genetic background which has provided our efficient capacity to store energy as fat is maladapted to our current environmental circumstances, where, in the developed world, there is an abundance of available food and a decrease in energy expenditure because of our increasingly sedentary lifestyles. It is these factors which have produced the obesity epidemic and its health consequences. Similarly, our highly specific stress reactivity, controlled by the hypothalamic pituitary adrenal (H-P-A) axis, which instigates activity to cope with short term stressful situations, by increasing vascular tone and glucocorticoid availability is also poorly adapted to deal with exposure to chronic stress which is common in our lifestyles. The by products of chronic stress exposure e.g. increased corticosteroids such as cortisol may exacerbate and be exacerbated by obesity and metabolic syndrome via effects on oxidative stress, fat distribution, inflammatory responses and behavioural responses.^[Rosmond R, 2005] For instance, after exposure to stress, most animals decline food and this response is seen in some humans. However, there are individuals whose behavioural response to stress is altered and their food choices may precipitate further abdominal weight gain, with elevated likelihood to develop metabolic syndrome.

Central obesity

There are two main types of obesity regarding the fat distribution pattern: android or central type obesity with the majority of fat depots located in the abdominal area, both subcutaneous and visceral, and gynoid or peripheral obesity in which the fat depots are mainly located subcutaneously in the lower body (hips and lower extremities). The difference between both types is fundamental, because the metabolic and cardiovascular complications of obesity are almost exclusively related to visceral fat depots. Central type obesity leads to an imbalanced production of several metabolic products, hormones and cytokines (adipocytokines), with a variety of local, peripheral and central effects. These fat cell-derived products include leptin, resistin, adiponectin, free fatty acids (FFA), tumor necrosis factor- α (TNF- α) and interleukin 6 (IL-6). Two measures of central obesity are waist circumference (WC) and waist-hip ratio (WHR).

Psychological stress, neuroendocrine and behavioural/appetite responses

There is an association between lifestyle, stress, cortisol and abdominal girth (WHR). Individuals with highest levels of chronic stress also had the highest levels of cortisol and visceral adipose tissue (VAT)^[Rosmond R et al., 1998]. Even brief episodes of mental stress, such as those encountered in daily life, may cause transient endothelial dysfunction even in young, healthy individuals^[Ghiadoni L et al., 2000]. Psychological stress has also been demonstrated to acutely reduce clearance of triglycerides, which could contribute to CNS leptin resistance^[Banks WA et al., 2004]. Psychological stress may therefore increase the likelihood of developing metabolic syndrome and type 2 diabetes. **Chronic psychological stress is related to central activation of the HPA axis and the sympathetic nervous system (SNS).** Psychological stress also induces IL-6, TNF α , and other cytokine secretions from macrophages^[Black PH, 2002]. Repeated stress which produces prolonged exposure to corticosteroids can damage the hippocampus, which is involved in the downregulation of corticosteroid production by corticosteroid feedback. Impairment of this feedback mechanism can lead to persisting elevated circulating cortisol levels, which might play a role in inducing VAT accumulation. The hippocampus plays a crucial role in memory and this mechanism may suggest potential cognitive effects of stress exposure and metabolic syndrome.

Corticotropin-releasing factor (CRF)/one of the urocortin family of neuropeptides, appears to mediate not only the endocrine but also the autonomic and behavioral responses to stress^[Heinrichs SC et al., 2004]. Considerable evidence from animal models suggests a role for endogenous brain CRF systems in appetite regulation, energy balance and **potentially in the aetiology of eating disorders.** Evidence from both clinical and preclinical studies strongly supports the view that CRF may be hypersecreted from both hypothalamic and extrahypothalamic neurons during stress. Thus, the well documented hyperactivity of the HPA axis observed in stressed subjects may be largely driven by increased secretion of hypothalamic CRF; elevated CSF concentrations of CRF appear to reflect hyperactivity of extrahypothalamic CRF neurons.

Similar changes have been found in adult animals that have been subjected to early-life stress, i.e. hyperreactive HPA axis in response to stress, increased concentrations of hypothalamic and extrahypothalamic CRF, and elevated CSF CRF concentrations compared with control animals. Central administration of the CRF antagonist CRF9–41 potentiates appetite induced by neuropeptide Y and attenuates stress-induced appetite suppression but does not alter intake in nondeprived or food-deprived subjects. This observation suggests a physiological role for CRF in the induction of negative energy balance not at steady state but rather under conditions of exaggerated hunger/weight gain, which may be counteracted by anorectic and sympathomimetic effects of activated CRF systems. Indeed, brain CRF content is dependent on feeding/weight status in animal models of dysregulated energy balance in stress-induced changes in appetite. Based on these observations, some investigators have postulated that CRF systems may be suitable targets for anti-obesity drugs.

Macronutrient effects on the HPA axis

Dietary carbohydrate has been known to stimulate SNS activity though a number of studies have emphasized the role of insulin in this effect. Recent studies in rats have demonstrated that adding glucose to the basic diet increased SNS activity in peripheral tissues and increased GLUT 4 activity in interscapular brown adipose tissue and retroperitoneal fat [Young JB et al. 2004]. Overfeeding results in high insulin levels. In the presence of glucose, insulin acts on the brain to increase the SNS tone, which, in turn enhances thermogenesis and dissipation of excess calories [Landsberg L, 2001]. There is a close relationship between postprandial insulinemia, SNS activation, and adipose tissue blood flow (ATBF). ATBF increases in response to stress states such as exercise or mental stress, and also in response to nutrient intake [Karpe F et al. 2002]. High insulin levels and increased SNS tone are useful for the maintenance of caloric balance, but in the long term they are conducive to CHD, hypertension, sudden death, and obesity as the SNS receptors become down regulated.

Chronic stress leads to elevated cortisol levels, which may lead to accumulation of VAT and metabolic syndrome [Bjorntorp P, 2001]. Stress-induced increased levels of glucocorticoids can also have a major effect on food intake. A subset of stressed or depressed humans may overeat, especially comfort food (e.g., sugar and fat), in an attempt to reduce anxiety and activity in the chronic stress-response network [Dallman MF et al., 2003]. This is supported by the finding that these people have decreased cerebrospinal CRF, catecholamine concentrations, and HPA activity. Eating fat and carbohydrate rich "comfort food" would be expected to reduce the activity in the HPA axis. However, although "comfort foods" may be calming in the short term, repeated consumption during periods of HPA activation may lead to abdominal obesity. The chronic elevation of systemic glucocorticoids may also contribute to VAT deposition. Simply being obese may be a stressor which encourages further food consumption. A weight loss program can be stressful, sabotaging its potential success by eliciting the release of stress hormones, which, in turn can make a person crave highly palatable energy dense foods. Feeding rats a long-term high-sucrose diet along with supplemental dexamethasone has been shown to increase fat depots and induce liver steatosis [Franco-Colin M et al. 2000].

To date, there are few known predictors of stress-induced eating. The purpose our project will be to identify those physiological and psychological variables that predict behavioural and appetitive response to stress given the relations between cortisol with both psychological stress and mechanisms affecting hunger. Specifically, we hypothesize that high CRF/urocortin reactivity in response to stress will be associated with increased appetite and food intake after stress, and that this may be mediated by psychological state such as perceived stress and physiology e.g. WC or WHR.

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Effects of Mild, Moderate and Severe Stress on Depression in Female Rats: Modifications by Estrous Cycle, Ovariectomy and Estradiol Replacement

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Introduction

Both basic and clinical studies document the importance of estrogen in a number of hormone-related affective disorders in women, such as premenstrual dysphoric symptoms, postpartum depression, and perimenopausal and, possibly, postmenopausal depression (Goodwin and Gotlib, 2004; Rubinow et al., 1998). The decrease in levels of estrogen that occurs in menopause has been correlated with depressive disorders, probably due to estrogen direct and/or indirect effects in the brain, where these hormones act through both genomic (i.e. interaction as transcription factors with nuclear receptors alpha and beta) and non-genomic (i.e. binding with cell-membrane receptors) mechanisms (McEwen, Alves, 2000). Estrogen replacement therapy appears to decrease vulnerability to depression in some cases and appears to be affective in augmenting the effects of conventional antidepressants, to enhance and shorten time to response, and to counter resistance to such treatment (Epperson et al., 1999; Rubinow et al., 1998). Nevertheless, the efficacy of such treatment remains controversial, in part because little is known about the precise mechanism or sites of action of these therapies in the brain (Rubinow et al., 1998).

It well known that hypothalamus-pituitary-adrenal axis is fundamental for the response to stress (De Kloet, 2003). Corticosteroid hormones are implicated in acute response to stressor and facilitating behavioral adaptation through their high affinity to mineralocorticoid receptors and lower affinity glucocorticoid receptor. Imbalance induced by chronic stress in two systems modes changes specific neural signaling pathways underlying psychic domains of behavior, including mood (De Kloet, 2003). Besides, changes of the hypothalamus-adrenal hormones have been described in depressed patients (Seckl et al., 1990; Gehris et al., 1991). However, it is not known whether and in which extent stressors of different strength might influence the response of female animals with imbalance of estrogen in experimental models of depression.

The present study was performed for evaluating the influence of different strength stressors on behavior using intact cycling female rats at three stages of the estrous cycle, ovariectomized (OVX) rats, OVX-estrogen treated female rats in forced swim test. Among various experimental models, the forced swim test was selected as well-established behavioral paradigm typically used to test the efficacy of antidepressants (Porsolt et al., 1977). In order to precise evaluation of stress influence on behavioral performance, variable electric shocks with different intensity and duration were used. Acute shock paradigm followed by forced swim test was selected in order to distinguish the stress procedure from experimental model of behavioral despair. In this manner, shock variables (duration and/or intensity) without affecting the behavioral procedure are modified.

Methods

Animals

A total number of 80 female Wistar rats, weighing 180-210 g, were housed in groups of six per cage in a temperature-controlled vivarium, with a 12 h light period beginning at 0800 h, and free access to food and tapwater.

Vaginal smears were taken daily from 40 intact female rats determine the different stages of the estrous cycle. Only rats exhibiting at least three consecutive regular 4-day cycles were included in this study.

Bilateral ovariectomy was performed on 40 female rats under light ether anesthesia. Fourteen days after surgical removal of the ovaries, rats were randomly divided into two groups that received either 0,5 µg 17β-estradiol (17β-E₂) in 0,1 ml corn oil or corn oil vehicle (0,1 ml/rat) for 14 days, injected subcutaneously into the dorsal region of the neck. Vaginal smears were taken for at least 4 days before commencement of 17β-E₂ administration. It should be noted that we used such dose of 17β-E₂ for recent report showing that long-term administration of low doses of estradiol benzoate reduced depression behavior in rats (Rachman et al., 1998). The intact cycling rats were received saline in the same volume.

Forced swim test

Rat were individually forced to swim inside vertical plexiglas cylinders containing 15 cm of water maintained at 25 °C (Porsolt et al., 1977). After 15 min in the water, they were removed and allowed to dry for 15 min in a heated container before being returned to their home cages. They were placed in the cylinders 24 h later and total duration of immobility (immobility time) was measured during a 5-min test. A rat was judged to be immobile whenever it remained passively floating in the water in a slightly hunched but upright position, its head just above the surface.

Experimental design

Two different experiments were carried out. In the first experiment, groups of intact rats were selected according to phase of their estrous cycle. They were subjected to electric shocks 24,5 and 1 h prior to behavioral testing. Duration of shocks was 5 or 10 ms and intensity was 0,1 or 1 mA. Rats received three such shocks through an electric grid put in a box with transparent walls. A group of non-shocked animals was considered as control. In the second set of experiments, groups of OVX and OVX-E₂ treated rats were subjected to electric shocks 24,5 and 1 h prior to behavioral testing. A group of non-shocked animals was considered as control.

Statistical analysis

For each experimental group (n = 10 rats) the results are expressed as mean ± SEM. All data were analyzed by two-way analysis of variance (ANOVA) followed by posthoc Newman-Keul's multiple comparison test. A value of p < 0,05 was considered to be statistically significant.

Results

Influence of different stressors in behavioral despair of intact cycling rats

The results of the forced swim test in intact cycling female rats are shown in Fig.1. Two-way ANOVA revealed a significant effect of estrous cycle on the behavioral despair [$F(14,9) = 4,45$, $p < 0,05$]. A group of non-shocked animals in estrous phase exhibited an immobility time shorter than that in diestrous phase. On the contrary, intact females in proestrous phase demonstrated an immobility time longer as compared with rats in diestrous phase.

Application of mild (5 ms, 0,1 mA), moderate (5 ms, 1,0 mA) or severe (10 ms, 1,0 mA) shocks prior to behavioral testing induced an altered response in females depending on the ovarian phase. Data analysis revealed that stressors exert a statistically significant effect on the behavior in forced swim test of cycling rats significant effect [$F(3,72) = 5,97$, $p < 0,05$]. In particular, proestrous and estrous rats showed an increased immobility time, while the behavioral response of diestrous animals did not differ from that of non-shocked controls. The only exception was represented by diestrous rats subjected to moderate shocks that exhibited an immobility time in forced swim test lower than that of corresponding controls.

Influence of different stressors in behavioral despair of OVX and OVX-estrogen treated rats

The results of the forced swim test in OVX and OVX- E_2 treated female rats are shown in Fig.2. Two-way ANOVA revealed a significant effect of hormonal status on the behavioral despair for OVX rats [$F(3,31) = 3,32$, $p < 0,05$] and for OVX- E_2 treated rats [$F(3,72) = 2,88$, $p < 0,05$]. Ovariectomy increased an immobility time ($p < 0,05$ compared with diestrous rats) and this effect was reversed by 17β - E_2 treatment ($p < 0,05$ compared with OVX rats).

Shocks application of various duration and intensity prior to behavioral testing induced a modified behavioral response in OVX and OVX- E_2 treated females. Newman-Keul's tests revealed a statistically significant effect on the behavior in forced swim test for OVX rats [$F(3,72) = 6,92$, $p < 0,05$] and for OVX- E_2 treated rats [$F(3,72) = 9,40$, $p < 0,05$]. Application of moderate (5 ms, 1 mA) or severe shocks (10 ms, 1 mA) reduced immobility time of OVX rats as compared to the non-shocked OVX rats. On the contrary, application of mild or moderate (5 ms, 0,1 or 1 mA) decreased immobility time of OVX- E_2 treated rats as compared to the non-shocked OVX and OVX- E_2 treated rats.

Conclusion

Thus, the results presented here support previous evidence that behavioral despair is influenced by the female's estrous cycle and by estradiol administration to OVX rats. Also, these results

suggest that duration and intensity of stressors profoundly affect the behavioral response of female rats with imbalance of estrogen in forced swim test. Data suggest that reactivity of hypothalamus-pituitary-adrenal axis to stress is an important for manifestations of depression in female rats. Furthermore, the finding that moderate and severe stressful stimuli may facilitate a depressive response in OVX rats tested in forced swim test deserves more attention at the clinical level. Besides, capability of mild and moderate stressful stimuli reduces a depressive behavior in OVX rats treated by low dose of 17β -estradiol in more extent than 17β -estradiol alone has significance for using estrogen replacement treatment.

Acknowledgment

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Immobility time in intact female rats

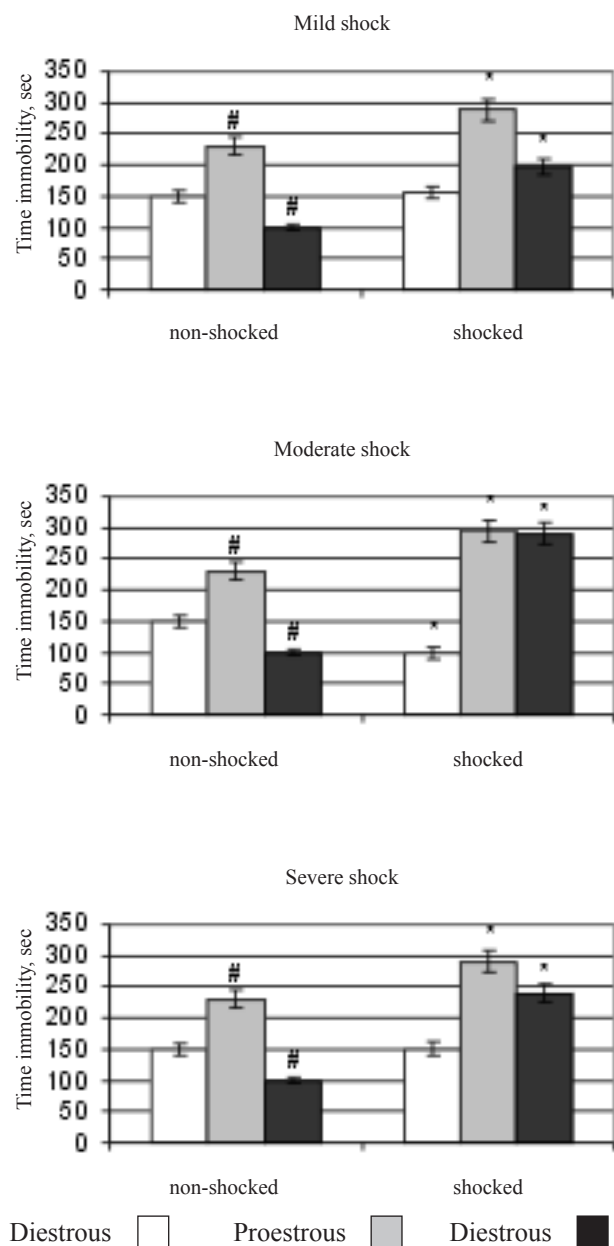


Fig.1. Effects of application of stressors of various duration and intensity on behavior of intact cycling rats in forced swim test. # - significantly different as compared to non-shocked diestrous control ($p < 0,05$, Newman-Keul's test for multiple comparisons). * - significantly different as compared to non-shocked corresponding controls ($p < 0,05$, Newman-Keul's test for multiple comparisons). Values are mean \pm SEM.

Immobility time in OVX and OVX-E₂ treated female rats

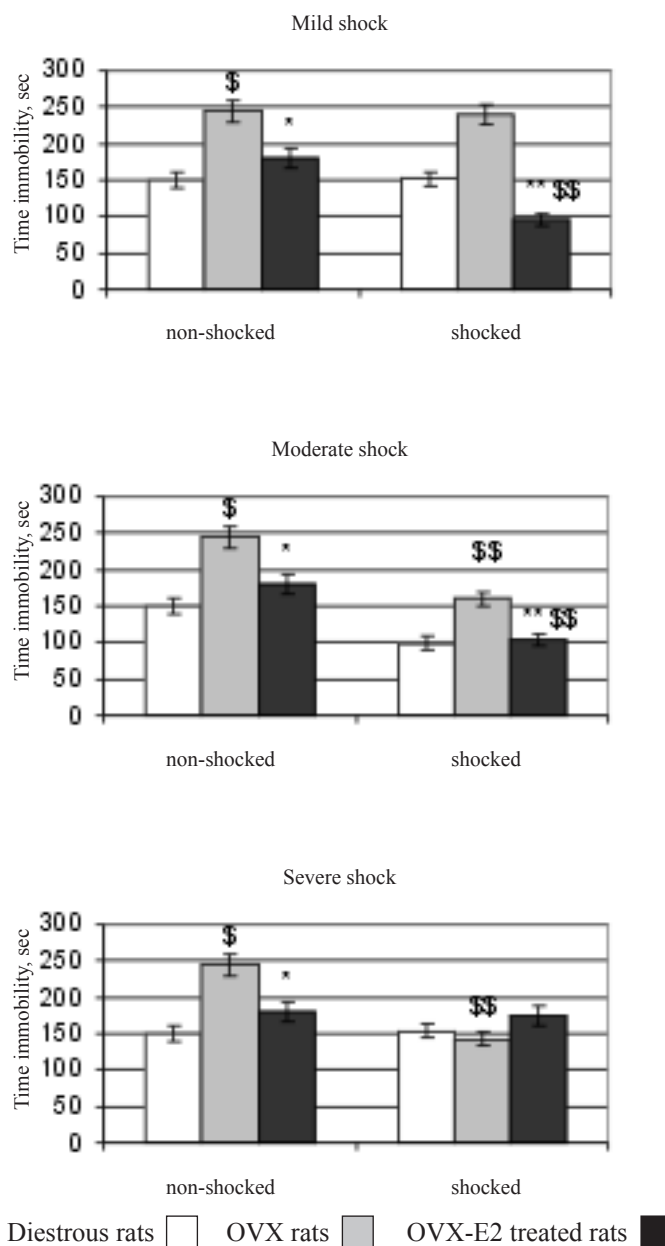


Fig.2. Effects of application of stressors of various duration and intensity on behavior of OVX and OVX-E₂ treated rats in forced swim test. \$ - significantly different as compared to non-shocked diestrous control ($p < 0,05$, Newman-Keul's test for multiple comparisons). * - significantly different as compared to non-shocked OVX control ($p < 0,05$, Newman-Keul's test for multiple comparisons). \$\$ - significantly different as compared to non-shocked OVX control ($p < 0,05$, Newman-Keul's test for multiple comparisons). ** - significantly different as compared to non-shocked OVX-E₂ treated control ($p < 0,05$, Newman-Keul's test for multiple comparisons). Values are mean \pm SEM.

Formation of Psychosomatic Correlations in Diabetes Mellitus Type 2

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Diabetes mellitus (DM) is one of the most prevalent severe metabolic diseases. As a heterogeneous one in its nature, conditioned by absolute or relative deficit of insulin, DM eventually results in disturbance of all kinds of metabolism. Attention paid to problem of diabetes in addition to its high prevalence throughout the world and in the area of Russia is associated with high risk of development of late complications which reflect indices of sick rate, disability and lethality (Dedov I.I. et al., 2000).

To present, there is not any simple opinion whether DM predisposes to formation of mental disorders or, to the contrary, mental disorders (MD) promote diabetes mellitus occurrence¹. Mechanisms of DM development reflect influence both of organic (somatogenic), and psychogenic factors. On B.E.P. Murphy's opinion (1994), situation of stress is an indicator of relationship between mental domain and endocrine regulation. Recent papers are devoted to study of psychosocial aspects of the diabetes, interrelationship of stress factors and the level of glycemia (Garganeyeva N.P., Semke V.Ya. et al., 2002, 2005; Sidorov P.I. et al., 2001; Garay-Sevilla M.E. et al., 2000; Herpetz S. et al., 2000; Surwit R.S. et al., 2002). The investigation of J.D. Lane, C.C. McCaskill et al. (2000) conducted the analysis of the interrelationship of personality correlates with variations of the glycemic control in patients with DM type 2. Risk of development of depressions in diabetes increases from 9 to 28,8% (Goodnick P.A., 1997; Lustman P.J. et al., 2000). Up to 64% of patients according to data of W.W. Eaton et al. (1996), had a depressive episode 12 months before the DM development. Several authors (Smulevich A.B., 2003; Antsiferov M.B. et al., 2003) indicate the development in patients with DM of depressions within an nosogenic reaction to the chronic disease resulting in abrupt changes of usual life style, some limits, danger of complications, invalidation as well as decrease of the level of quality of life. Psychological problems of patients with DM are discussed also in the other literature reviews (Trigwell P., Peveler R., 1998).

Of relevance is study of the interrelationships of somatic, mental and psychosocial factors what supposes the possibility of their influence on formation of psychosomatic correlations in DM type 2.

Material and methods of the investigation: In the Borderline States Department of Clinic of the Mental Health Research Institute TSC SB RAMSci 203 patients have been examined (127 women and 76 men, middle age $50,62 \pm 8,07$ years) with DM type 2 and disturbance of tolerability to glucose (DTG). Diagnosis was made according to classification of DM (WHO, 1999). The assessment of mental state used clinical-psychopathological, paraclinical and experimental-psychological

methods. Study of interrelationship of DM and mental disorders (MD) was conducted with the use of multidimensional models of biostatistic. In all the procedures of the statistical analysis critical level of significance p was accepted as equal to 0,05. Sample average values of quantitative signs have been presented in text as $M \pm SD$, where M – sample average, SD – standard deviation.

Results of the investigation: Multifactorial dispersion analysis has established an association between the level of glycemia on an empty stomach and current mental disorders depending on presence or absence of DM at achieved levels of significance ($df=11$; $F=89,11$; $p=0,0001$ and $df=3$; $F=4,04$; $p=0,0071$), as well as has detected the influence of the interaction of MD and degree of severity of DM type 2 on the indices of the glucose level in blood ($df=6$; $F=3,38$; $p=0,0026$). Maximum level of glucose on an empty stomach was observed in patients with DM type 2 of the middle degree of severity, which current mental state was determined by symptoms of depression. Adjustment disorders and reactions on severe stress as well as affective disorders (depressive episode, dysthymia, recurrent disorder) with the leading depressive symptoms were characterized by changeable content of glucose in blood what manifested in fluctuations of average indices from 4,63 to 11,68 mmol/l as compared with the group of patients without DM. In personality disorders and dissociative (conversion) disorders glucose level fluctuations were not so significant (from 4,65 to 6,80 mmol/l). In dominating in current state organic disorders maximum average indices of blood glucose level achieved 8,59 and 9,43 mmol/l in patients with DM type 2 of various degree of severity.

In 19,8% of cases in patients with earlier made diagnosis DTG (in 20 patients against the background of depressive and in 5 – anxiety disorders) a stable increase of glucose level significantly exceeding the normative limit was observed (6,1 mmol/l), indicating the development of DM type 2. In addition, in 21,7% of cases diagnosis of DM type 2 for the first time was verified in the period of admission of patients in Borderline States Department. In the structure of MD in patients with DM type 2 and DTG in 40% of cases depressive disorders of neurotic and affective spectrum were diagnosed; in 32,5% - disorders of asthenic circle; in 11% - somatoform; in 9,5% – anxiety-phobic, in 7% – personality disorders. It should be noticed that depressive disorders exerted the most adverse influence on the course of DM type 2.

During the study of comorbid states, in particular DM type 2 in patients with MD, analysis of correlations of long-standing and duration of DM and MD appeared to be purposeful. As a comparison (control) group a group of DM type 1 patients

¹Still in 1674 T. Willi on of the first indicated the relationship of diabetes with mental experiences underlining evidence that diabetes mellitus occurrence is proceeded by "long-standing distress". Cited according to Mendelevich V.D. Clinical and medical psychology. Pract. Manual. – Moscow: "MEDpress", 1998. – 592 p.

was considered not included into this investigation. Dispersion analysis has revealed a statistically significant interrelationship between the age of the onset of clinical psychopathological manifestations conditioned by stress factors (life events, social, medical), DM types and degree of severity ($df_1=7$; $df_2=195$; $F=3,56$; $p=0,00135$) ($df_1=3$; $F=4,47$; $p=0,0046$). Evidence worth to pay attention is that manifestation of mental disorder in all the

vegetative disorders ($p=0,0005$); dislipidemia ($p=0,0009$); age of onset of MD ($p=0,0118$); psychopathological state of the patient ($p=0,0029$); subjective attitude of the patient toward his/her disease ($p=0,0046$); level of anxiety ($p=0,0104$); alterations of vessels of retina ($p=0,0214$); family history on DM ($p=0,0437$). Anosognosia toward explicit signs of somatic disease combined in patients with excessive anxiety regard-

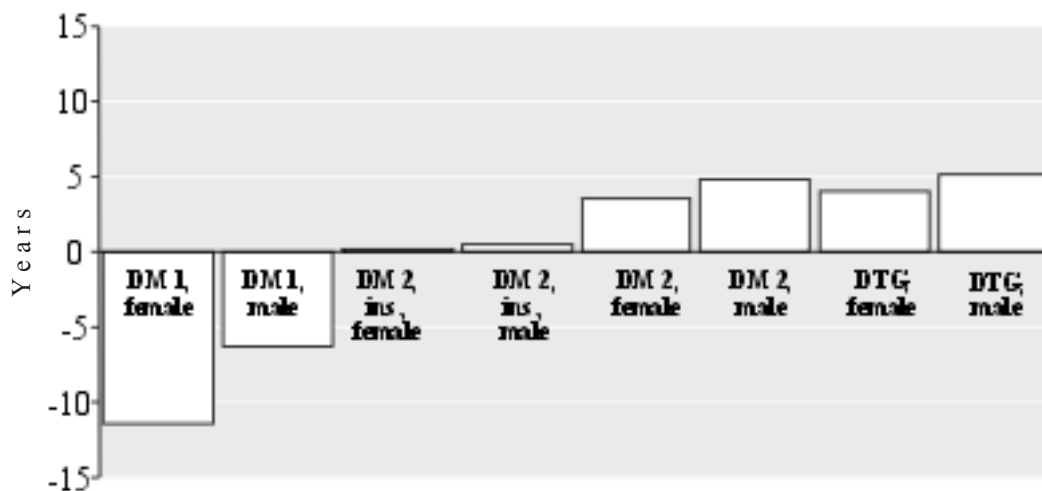


Fig. 1. Development of diabetes mellitus regarding the onset of psychopathological manifestations (zero line relatively symbolizes the onset of a mental disorder).

cases preceded to development of DM type 2 and DTG (Fig. 1). The most distinct dependence between terms of onset of MD and clinical manifestations of the diabetes was observed in patients with DM type 2 (symbolized in Fig. 1 as DM 2 ins.), for which compensation administration of preparations of insulin was required. The given evidence indicates that stress factors and related affective disturbances promote faster development or de-compensation of DM type 2 (insulin-dependent) in the course of the first 6 months from the on-set of development of MD. It is known that in persons with preceding DTG risk of development of DM increases significantly for the nearest 5 years.

Under influence of various stress factors both psychogenic and somatogenic activity of sympatic section of nervous system, level of content in blood of catecholamines, glucocorticoids and the other hormones of contrinsular action increases (Habib K.E. et al., 2001). According to data of S. Herpertz et al. (2000), level of glycemia is associated with the severity of psychosocial stress and need for insulin, but not with type of DM. Construction of models of the interrelationship of somatic and mental state and prognosis of DM in patients with MD has used a method of logistic regression where per se of distinct prognosis (Concordant) and coupling coefficient (Somers'D) fluctuated from 74,5 to 92,7% depending on the number of examined (155-203 persons) and number of introduced predictors at achieved level of statistic significance of Hosmer and Lemeshow test in all the total equations (0,7-0,9), what testified to high degree of adequacy of created models to real data. Of most important value were the following indices: level of glycemia ($p=0,0001$); long-standing of MD ($p=0,0002$); body mass index ($p=0,0001$); stress factors (life events) ($p=0,0001$);

ing their health as a whole, fear of death, dissatisfaction with their own state, decrease of activity, low self-esteem of their own possibilities. In the other variant of the equation of logistic regression at maximum per se of right prognosis (Concordant=80,5%; Somers'D=0,656) the leading one was sign "pessimism": ($p=0,0002$), that from the first step has provided 28,6% of probable development of DM. In the procedure of step-wise selection predictor "level of glycemia" ($p=0,0001$) was included by the algorithm into the given equation only at step 3. Among differentiated prognostic signs characterizing current psycho-pathological disorder the most frequent were hypothyria, anxiety, asthenia, vegetative dysfunction, depressive state.

The investigation allowed concluding that the most adverse course of DM type 2 was observed in patients with affective disorders (depressive episode of various degree of severity), organic affective disorder and neurotic disorders associated with stress (prolonged depressive reaction, mixed anxiety and depressive reaction, nosogenic and the other reactions on a severe stress).

Stress factors and associated with them MD, preferably of depressive character, serving as a cause of admission of patients in mental hospital, promoted faster development or decompensation of DM type 2. Cases of DM (insulin-dependent) for which compensation administration of preparations of insulin is required are revealed in women during the first month, in men – during the first 6 months from the onset of mental disorder.

Thus, group of high risk of development of diabetes is constituted by patients with depressive disorders in whom increased level of glycemia is associated with the influence of stress factors conditioning the development of mental disadaptation

and formation of mental disorders of neurotic and affective spectrum.

Comparative analysis of the interrelationship of the blood glucose level and mental disorders confirms participation of factors of mental impact on DM exerting adverse influence on concentration of blood glucose, clinical course and progression of DM type 2 as well as early development of diabetes in patients with preceding disturbance of tolerability to glucose. During development of programs of treatment and prevention of diabetes mellitus in general health care one should take into account mental and psychosocial factors as complimentary criteria of stratification of risk of complication of the diabetes, and envisage interaction of various specialists (internist, psychiatrist and psychotherapist).

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Brain Imaging Correlates of Stress-Related Memory Disorders in Younger Adults

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Remembering one's own past and the ability of foresight most likely differentiate man from beast. This capacity may, however, be selectively impaired in patients with dissociative amnesic states. Due to major stress or trauma related experiences such patients may suddenly lose access to their personal past (Markowitsch, 2003a; Markowitsch et al., 1999b; Fujiwara et al., 2006) or may become unable to store new episodic-autobiographic information long term (Markowitsch et al., 1999a). While it was traditionally assumed that this condition is transient and may disappear when the patients are confronted with reality (i.e., with life partners, relatives, their personal surroundings etc.), our experience with altogether more than two dozen patients with dissociative amnesic states indicates that the amnesia may persist for years, though most patients are able to "relearn" their past. This relearning lacks, however, the emotional colorization which is inherent in consciously reflected autobiographic events: The patients remain unable to synchronize emotional and cognitive attributes of memories. As a consequence, they may manifest unspecific emotional feelings ("It was a bad time and I was full of fear"), or they may retrieve neutral facts without attributing these to their own self ("It was an Eastersunday").

The possibility to study such patients in detail was facilitated by several factors: First, by the differentiation in several long-term

memory systems (Fig. 1) of which only the episodic one allows mental time travelling into the past and future and is dependent on self-reflection (autonoesis; Markowitsch, 2003b). Secondly, by the availability of valid, finely tuned differentiating neuropsychological tests (Markowitsch, 2003c), and thirdly by the advent of functional neuroimaging techniques (Reinhold et al., 2006). The evidence for neuroanatomically and functionally distinct long-term memory systems provides a basis for understanding why patients with dissociative amnesias may appear normal with respect to everyday functioning – they know how to read, write, or calculate, or how to behave socially appropriately, and they even may manifest proper general world knowledge, such as the names of prominent actors, politicians, etc. – while they are totally unaware even of their closest relatives, of their own childhood, youth, and adulthood.

These memory systems are considered to be ordered hierarchically – procedural memory appearing most early in childhood and being usually processed without conscious reflection, episodic memory appearing only lately in childhood and being.

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These memory systems are considered to be ordered hierarchically – procedural memory appearing most early in childhood and being usually processed without conscious reflection, episodic memory appearing only lately in childhood and being dependent on a conscious self-reflection and the evaluation of emotions, that is on the synchronous activation of regions such as the amygdala and the hippocampal formation (Markowitsch, 2003a). Tulving (personal communication, 2003) defines episodic memory in the following words: “Episodic memory is a recently evolved, late-developing, and early-deteriorating brain/mind (‘neurocognitive’) memory system. It is oriented to the past, more vulnerable than other memory systems to neuronal dysfunction, and probably unique to humans. It makes possible mental time travel through subjective time – past, present, and future. This mental time travel allows the ‘owner’ of episodic memory (‘self’), through the medium of auto-noetic awareness, to remember one’s own previous “thought-about” experiences, as well as to ‘think about’ one’s own possible fu-

ture experiences. The operations of episodic memory require, but go beyond, the semantic memory system. Retrieving information from episodic memory (‘remembering’) requires the establishment and maintenance of a special mental set, dubbed episodic ‘retrieval mode’. The neural components of episodic memory comprise a widely distributed network of cortical and subcortical brain regions that overlap with and extend beyond the networks subserving other memory systems. The essence of episodic memory lies in the conjunction of three concepts – self, auto-noetic awareness, and subjective time.”

Principally, procedural memory and priming act on the subconscious or semi-conscious level, while the other three memory systems require conscious processing of information. With reference to individuals with brain damage or to subjects having been exposed to major stress or trauma situations, portions of memory may be impaired in two time directions – forward (“anterograde amnesia”) and backward (“retrograde amnesia”) (Fig. 2).

With respect to the neural networks engaged in autobiographical memory retrieval, we found that patients with brain damage to right-hemispheric fronto-temporal regions become unable to retrieve autobiographical events from their past life (Markowitsch et al., 1993; Kroll et al., 1997), while, vice versa normal subjects activate this regional combination in functional imaging studies (Fink et al., 1996) (inferior lateral prefrontal cortex, temporo-polar cortex and the bilateral interconnection between the two, the uncinate fascicle). When using radioactive fluor-based positron-emission-tomography (FDG-PET), we found in a number of patients with lasting psychogenic (dissociative) amnesic states that their glucose metabolism was reduced in temporo-frontal brain regions, including the anterior hippoc-



Figure 1. The five principal memory systems important for human information processing. Procedural memory is largely motor-based, but includes also sensory and cognitive skills (“routines”); examples are playing cards, skiing, driving a car, playing a piano. Priming refers to a higher likelihood of re-identifying stimuli which were perceived previously in the same or a related form. Perceptual memory allows distinguishing an object, item, or person on the basis of distinct presemantic features, based on familiarity judgements. Semantic memory is context-free and refers to general facts. It is also termed the knowledge system. The episodic memory system is context-specific with respect to time and place. It allows mental time travel and includes emotional colorization of the remembered events. Examples are events such as the last vacation or the dinner of the previous night. Episodic memory is largely coincident with autobiographic memory and constitutes the conjunction of subjective time, auto-noetic consciousness and the experiencing self (Markowitsch, 2003a).

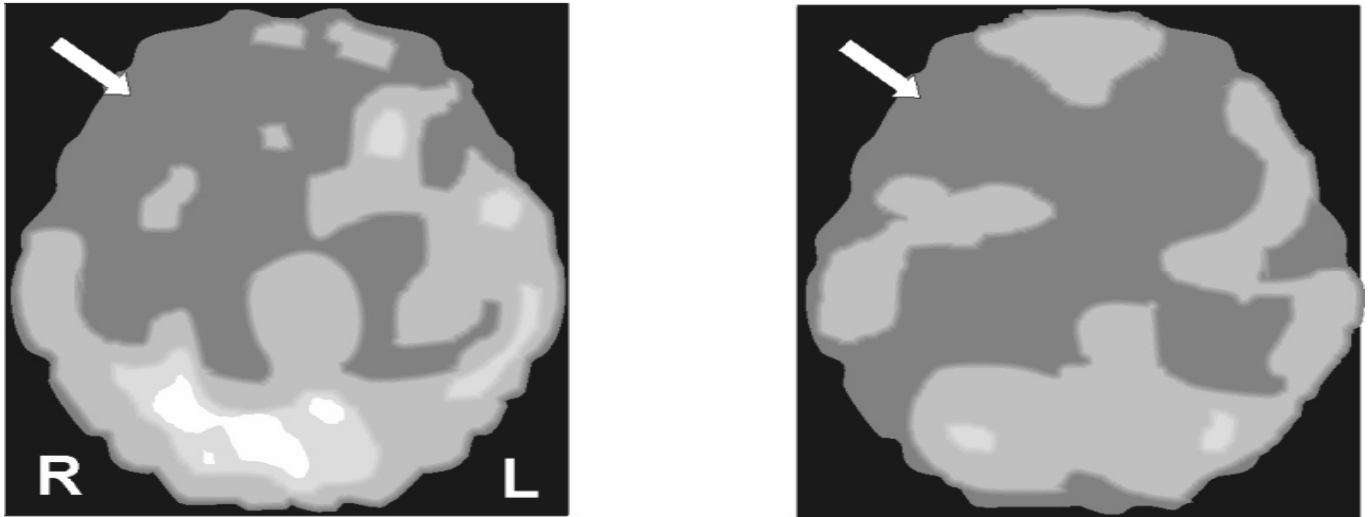


Figure 3. Sketches of horizontal views of the brains of a patient with organic brain damage (left) and of another one, in whom any evidence for “organicity” was lacking. Hypometabolic zones (arrows, dark) are nevertheless seen in the right temporo-frontal zone of both patients.

Thyroid Gland and Mental Disorders

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Introduction

Secretion of thyroid hormones is controlled by pituitary thyroid-stimulating hormone (TSH), which in turn is stimulated by hypothalamic thyrotropin-releasing hormone (TRH) and suppressed by negative feedback from serum thyroid hormones¹ (Figure 1). The thyroid gland secretes several hormones, including thyroxine (T4), triiodothyronine (T3) and reverse T3 (rT3). The main secretion of the thyroid gland is T4 and the thyroid gland is the only source of this hormone. In contrast, no more than 20% of the more biologically active hormone T3 is secreted by the thyroid gland. The remainder of T3 is produced in other tissues by removal of iodine from the T4 molecule by enzymes, called deiodinases, which exist in several forms². Type-I deiodinase is located primarily in liver and kidney and is responsible for producing as much as 80% of T3. Type-II deiodinase is located primary in the brain and muscles and contributes to tissue T3 concentration. Type-III deiodinase converts T4 into rT3, which is inactive, and degrades T3. More than 99% of T3 is bounded to specific proteins, but only free T3 is active. T3 penetrates cell membranes and is responsible for the majority of genomic and nongenomic effects of thyroid hormones.

In humans thyroid hormones are critical for brain development during fetal and postnatal life. Thyroid dysfunction in adults is frequently accompanied by mental disorders. In the DSM-IV classification and in the ICD-10 classification hyperthyroidism and hypothyroidism are considered as causal factors for mental disorder. Mental disorder caused by thyroid dysfunction is considered to be secondary to endocrine state (Figure 2). In primary mental disorder Euthyroid Sick syndrome (Low T3 syndrome) as well as autoimmune thyroid disease is frequently reported.

Hyperthyroidism

Thyroid hormone enhances the β -adrenergic receptor mediated psychiatric effects of catecholamines through increased density and sensitivity of these receptors in the brain³. Overactivity of adrenergic system may explain the precipitant role of hyperthyroidism in development of mania and anxiety disorder⁴. The relationship between hyperthyroidism and depression is less clear. Depression is usually linked to hypothyroidism not hyperthyroidism. On the other hand, blunted TSH response to TRH stimulation is found in up to one third of depressed patients⁵, has several explanations, including possibility of subclinical hyperthyroidism⁶. Another explanation of relationship between hyperthyroidism and depression may be an exhaustion of noradrenergic transmission caused by prolonged and excessive stimulation of central noradrenergic system by thyroid hormone. Such a possibility may be extrapolated to bipolar disorder, when in the initial phase of hyperthyroidism causes mania, and later, when noradrenergic neurotransmission is exhausted, depression. Several clinical studies have demonstrated high prevalence of history of mania in early presentation of Graves' hyperthyroidism and high prevalence of depression after a long course of the disease⁷.

Hypothyroidism

In adults hypothyroidism is frequently related to cognitive symptoms as well as to mood disorders. A depressive disorder seems especially related to thyroid impairment. Even subclinical hypothyroidism may predispose to depression⁸. Thyroid deficit is frequently observed in bipolar patients, especially in women with malignant, rapid-cycling form of the disease⁹. In elderly hypothyroidism may cause cognitive deficits that respond to thyroid hormone replacement.

In brain thyroid hormone contributes not only to regulation of the activity of norepinephrine as it was mentioned earlier; it also affects serotonergic neuro-transmission³ that regulates our mood and acetylcholinergic neuro-transmission that regulates our cognition. Moreover it is well established that transcription of peptides involved in mood regulation such as TRH and brain-derived neurotrophic factor is influenced by thyroid hormone. Non-genomic mechanism of action, proposed by Dratman and Gordon,¹⁰ suggests that active thyroid hormone, T3, in adult brain acts as neurotransmitter or neuromodulator with antidepressive properties.

Low T₃ syndrome

A decrease in serum T3 concentration and a parallel increase in reverse T3 (rT3) concentration are common findings in many illnesses, in trauma, starvation and after surgical operations. These changes in HPT axis function, taken together, are referred as the low T3 syndrome or euthyroid sick syndrome. It is found in up to 20% of depressed patients¹¹. In the state of fasting, this shift from the production of the metabolically potent thyroid hormone, T3, to production of the metabolically inactive thyroid hormone, rT3, suggests a compensatory role. However, in chronic illnesses, such as depression low T3 concentration can produce its own ill consequences and may contribute to depressive state.

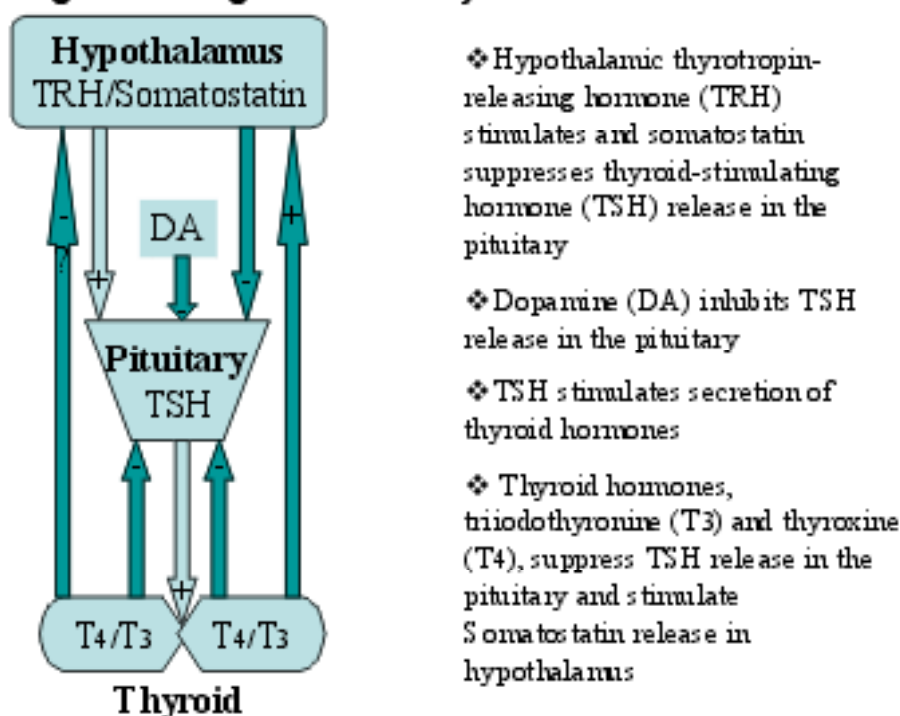
Thyroid autoimmunity

Involvement of thyroid immunity in brain functioning was reported by several neuro-imaging studies, demonstrating a higher prevalence of brain perfusion abnormalities in eu-

thyroid patients with autoimmune thyroiditis¹² and higher levels of anxiety and depression in these patients¹³. These brain perfusion abnormalities are similar to those observed in cases of severe Hashimoto’s encephalopathy¹⁴ and may suggest a higher than expected involvement of the brain in autoimmune thyroid disease. It was suggested that immune process, rather than altered thyroid state may be responsible for brain impairment in these patients. Treatment with glucocorticoids, that are powerful suppressors of immune systems, is most effective in patients with Hashimoto’s encephalopathy¹⁴.

This possibility is indirectly supported by a recent large epidemiological study that found no statistical association between clinical or subclinical thyroid dysfunction, and the presence of depression or anxiety disorders in a large unselected population¹⁵. Moreover, several studies reported an association between depression and bipolar disorder and increased levels of thyroid antibodies.¹⁶ Some studies showed that depression was related not to thyroid dysfunction but to autoimmune thyroid process¹⁷. It may be that it is not marginal thyroid dysfunction, but rather thyroid autoimmune processes, frequently responsible for this dysfunction¹⁸, are responsible for co-morbidity between autoimmune thyroid disease and mood disorder. It is not clear do these possible brain reactions in autoimmune thyroid disease are specific for thyroid autoimmunity or it is an expression of a larger autoimmune process where thyroid and brain reactions are parts of it.

Figure 1. Regulation of thyroid hormone secretion



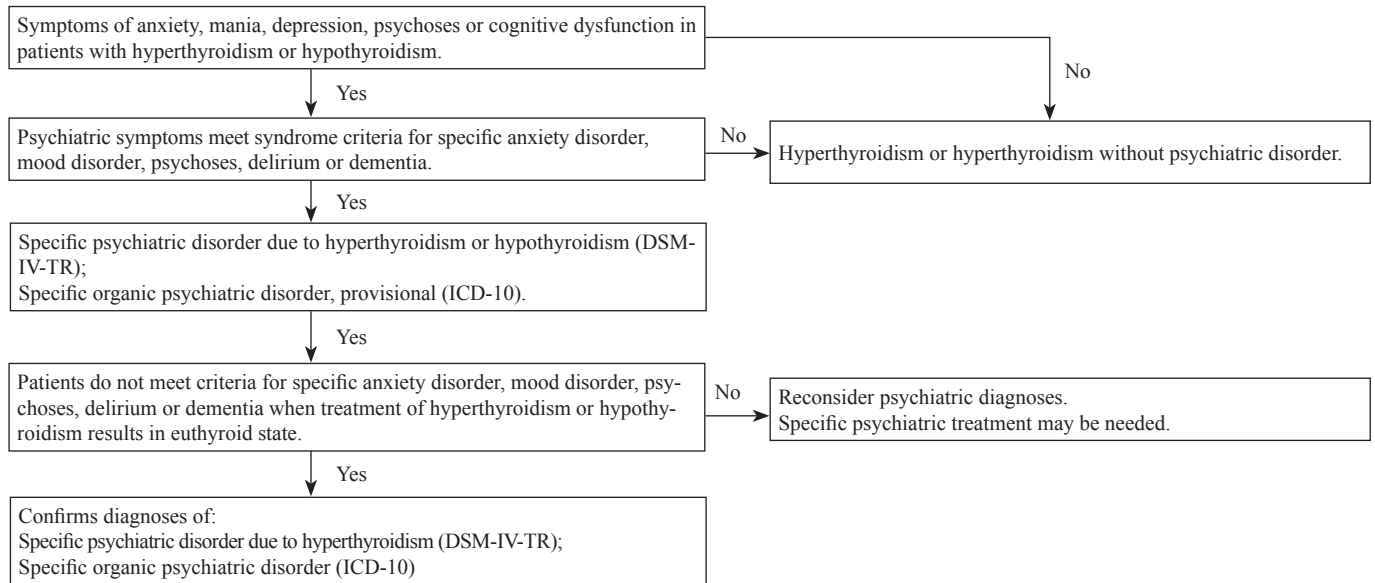


Figure 2. Diagnoses of mental disorders in patients with hyperthyroidism or hypothyroidism according to DSM-IV-TR criteria and ICD-10 criteria.

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Emotional Numbing and Salivary Cortisol in Male and Female Bosnian Refugees with PTSD

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A important affective symptom of chronic posttraumatic stress disorder (PTSD) is numbing of general responsiveness (American Psychiatric Association, 1994), which refers to the profound withdrawal from even ordinary, everyday human contacts as well as from activities that were formerly considered pleasant. Numbing distinguishes between those with and without PTSD (Foa et al., 1995), yet it remains a vague, ill-defined concept. Two recent studies (Amdur et al., 2000; Litz et al., 2000) assessed emotional numbing in Vietnam veterans with PTSD using the "Looking at Pictures" test in which subjects rate a series of pictures for their emotional valence (pleasant-unpleasant) and emotional arousal (high-low) (Lang et al., 1993). Surprisingly, neither study found any difference in emotional valence or arousal ratings between Vietnam veterans and normal controls. The absence of any difference actually suggests further investigation of affect in PTSD is warranted, especially in groups not composed of Vietnam veterans. The experiments reported here were done to quantify numbing in groups of Bosnian refugees with and without PTSD using the same Looking at Pictures test (Lang et al., 1993). In addition, because urinary (Yehuda et al., 1996) and plasma (Boscarino, 1996) cortisol levels are lower in PTSD subjects than in healthy subjects or patients with major depression, we also measured salivary cortisol levels in male Bosnian control and PTSD subjects both before and after administration of dexamethasone.

Methods

Subjects: Groups of 10 adult male and 11 adult female Bosnian refugees diagnosed with PTSD due to traumatic war experiences were recruited from the patients at community mental health clinics in Chicago and Wheaton, IL. For comparison purposes control groups of 11 adult male and 10 adult female Bosnian refugees exposed to similar traumatic events during the Bosnian war but who were without a diagnosis of PTSD or other mental illness were also recruited. All male subjects were studied in 1999, and all female subjects were studied in 2001. The treaty ending the Bosnian war was signed in December of 1995. Diagnosis of PTSD was based on a non-structured clinical interview by an experienced psychiatrist (Aida Spahic-Mihajlovic) using DSM-IV criteria; no other Axis I diagnosis besides PTSD was found in these subjects. In addition, a Bosnian version (Weine et al., 1998) of Foa's PTSD Symptom Scale (PTSDSS) and our own Bosnian translation of the Hamilton Rating Scale for Depression (HAMD) (Hedlung and Vieweg, 1979) were administered to all subjects. After description of the study to the subjects, written informed consent was obtained.

Looking at Pictures: Looking at Pictures (Lang et al., 1993)

is an experimental paradigm for studying emotion in which the examiner presents the subject with a series of 21 photographs taken from the Florida International Affective Picture Set (IAPS). Each picture is displayed to the subject for 6–8 seconds, and then the subject describes his or her feelings about the picture by marking the appropriate figure in each row of the Self Assessment Manikin (SAM, see scales in middle part of Figure 1). The top row of the SAM is used to rate emotional valence (pleasant-unpleasant feelings) and the bottom row to rate emotional arousal (high-low emotional intensity). Typical valence and arousal ratings for each picture based on the mean responses of a large sample of undergraduate students from the University of Florida have been published; these are the "normal responses" referred to in the rest of this paper. The pictures used comprised "Set A" of Lang's original paper (Lang et al., 1993)

Protocol: Each subject was first questioned by an examiner fluent in Bosnian for basic demographic information such as name, age, and years of education. The PTSD Symptom Scale and Hamilton Rating Scale were then administered. The subject was then instructed on how to use the SAM to rate his or her feelings about the pictures. The pictures and SAM scales were then presented by turning the pages of a binder containing the photos.

Salivary Cortisol: Baseline samples were collected in Salivette tubes by the subject at 8:00 AM and 4:00 PM on two consecutive days. In order to evaluate the sensitivity of feedback inhibition in our subjects, the dexamethasone suppression test was performed subsequent to the first day's baseline measurements. Subjects took a 0.5 mg tablet of dexamethasone at 11:00 PM of the first day, and the second set of cortisol samples was collected on the following day. The Salivette tubes were centrifuged at 1000g for 2 minutes to extract clear salivary filtrate. Salivary cortisol was determined by radioimmunoassay using the Cort-A-Count kit following the manufacturer's instructions (Diagnostic Products Corporation, Los Angeles, CA). Assay sensitivity is 6 nM. Salivary cortisol correlates well ($r = .9$) with plasma cortisol levels (Harris et al., 1990).

Statistics: Age, years of education, and summary statistics consisting of total sum scores on the PTSDSS and HAMD were analyzed by two-way analysis of variance (ANOVA) using as factors DIAG (control or PTSD) and SEX (male or female); post-hoc comparisons were by Bonferroni t-tests. Valence and arousal ratings from the Looking at Pictures test were analyzed in a variety of ways. In order to gain some idea of which pictures differentiated the groups, the non-parametric Wilcoxon rank sum test (the SAM rating scale is ordinal) was used to com-

pare control and PTSD group ratings for each picture within each sex. Given the number of comparisons made, these results should not be seen as indicating statistically significant differences, but they were useful for exploratory data analysis. The overall mean valence and arousal ratings for each picture by control and PTSD groups were also computed and plotted for male and female subjects. To assess possible group differences related to unpleasant, neutral, or pleasant pictures, each subject's mean valence and arousal ratings for the four most unpleasant (A-D), four most neutral (I-L), and four most pleasant (R-U) pictures (as defined by their normal valence ratings) were calculated and then analyzed by three-way ANOVAs, using as factors DIAG, SEX, VALNORMCAT (unpleasant, neutral, and pleasant), and their interactions; post-hoc comparisons were by Bonferroni t-tests. Data are presented as mean ± SEM. A significance level of $p < .05$ was used for all statistical analyses, and all statistical test comparisons were two-tailed.

Results

Subjects: Table 1 describes the ages, years of education, PTSDSS sum scores, and HAMD sum scores in the four groups of subjects. A two-way ANOVA of mean years of education in the four groups was significant ($F_{3,37} = 9.1, p = .00012$), with a significant main effect of DIAG. Post-hoc Bonferroni t-tests found that male controls had significantly more years of education than male PTSD, female controls more years than female PTSD, and combined male and female controls more years than combined male and female PTSD (all p 's $< .0167$).

Group	n	Age	Education	PTSDSS	HAMD
Male controls	11	*33.8 ± 4.1	13.0 ± 1.2	3.9 ± 1.2	5.2 ± 1.4
Female controls	10	44.4 ± 4.3	14.2 ± 1.1	2.5 ± 0.9	2.3 ± 1.1
Male PTSD	10	47.9 ± 4.3	*8.8 ± 0.5	*30.8 ± 1.7	*25.8 ± 2.2
Female PTSD	11	50.4 ± 3.9	*6.7 ± 1.5	*46.5 ± 1.9	*28.6 ± 1.9

Table 1: Mean ± SEM for age, years of education, PTSDSS sum score, and HAMD sum score of four groups studied. Asterisks (*)denote PTSD groups significantly different ($p < .05$) from their same-sex controls by Bonferroni t-tests after significant ANOVAs.

Symptom Scales: The mean total sum scores on the PTSDSS and HAMD for the four groups are also listed in Table 1. For the PTSDSS a two-way ANOVA (DIAG*SEX) for the four groups was significant ($F_{3,38} = 217.2, p = 2.2 \times 10^{-16}$), with significant main effects for both DIAG and SEX and a significant DIAG:SEX interaction as well. Post-hoc Bonferroni t-tests found that male and female PTSD subjects had higher scores than their corresponding controls and that combined male and female PTSD subjects had higher scores than combined male and female controls (all $p < .01$). In addition, female PTSD subjects had higher total scores than male PTSD subjects ($p < .01$). For the HAMD a two-way ANOVA (DIAG*SEX) for the four groups

was significant ($F_{3,38} = 63.8, p = 6.72 \times 10^{-15}$), with a significant main effect for DIAG. Post-hoc Bonferroni t-tests found that both male and female PTSD subjects had higher scores than their corresponding controls and that combined male and female PTSD subjects had higher scores than combined male and female controls (all p 's $< .01$). Despite that fact that all subjects with high PTSDSS scores also had high HAMD scores (comorbidity), it is important to note that none of the PTSD subjects were diagnosed with Major Depressive Disorder.

Looking at Pictures: Male Looking at Pictures: Figure 1's upper left graph of mean male control and PTSD picture valence ratings illustrates that the valence ratings produced by both groups were relatively normal. Note that when male PTSD ratings for each picture are compared to those of controls using Wilcoxon tests, only four pictures (marked with x's) had a rating where $p < .05$, and for two of these pictures (T, U) the PTSD mean was actually closer to normal than the mean control rating. When rating pictures for arousal, however, many PTSD subjects gave consistently lower ratings than controls to the pleasant pictures, as can be seen in Figure 1's lower left graph of the mean arousal responses of male control and PTSD subjects. Note that almost all of the pleasant pictures (x's above M, N, O, P, Q, R, S, T) were rated lower by PTSD subjects than by control subjects.

Figure 1: Group mean picture valence (top) and arousal (bottom) rating scores for male (left) and female (right) control and PTSD subjects. Pictures A–U are identified in the text. For reference normal ratings are also shown, as is SAM rating scale in middle of figure. x's indicate pictures where $p < .05$ for Wilcoxon rank sum tests comparing PTSD and control ratings.

Female Looking at Pictures: Figure 1's upper right graph of mean female control and PTSD picture valence ratings illustrates that females with PTSD appeared to produce consistently lower valence ratings than controls, as evidenced by the ten pictures where the PTSD valence ratings were less than control ratings (x's). These pictures included both pleasant and unpleasant pictures. Figure 1's lower right graph shows that, when rating pictures for arousal, many female PTSD subjects, like males with PTSD, gave consistently lower ratings to the pleasant pictures (x's for O, Q, R, U). Note, however, that female PTSD subjects also rated many unpleasant pictures (x's for E, F, G, H, I) as more arousing than controls.

ANOVAs for Valence and Arousal of Unpleasant, Neutral, and Pleasant Pictures: Separate 3-way ANOVAs for valence and arousal were carried out using each subject's mean valence and mean arousal ratings for the four most unpleasant (A-D), four most neutral (I-L), and four most pleasant pictures, as determined by the normal ratings. The three factors were the normal valence category of the pictures (VALNORMCAT: unpleasant, neutral, pleasant), the subject's diagnosis (DIAG: control, PTSD), and the subject's sex (SEX: m, f). Overall, the pictures used were judged by subjects in all our groups to have significantly different valence ratings for the three categories, with female PTSD subjects showing lower valence ratings overall than female controls. Unpleasant ratings were significantly higher than neutral ratings for both control ($p = 1.07 \times 10^{-9}$) and PTSD ($p = 8.98 \times 10^{-10}$) groups. For pleasant pictures, however, PTSD subject, unlike controls, did NOT

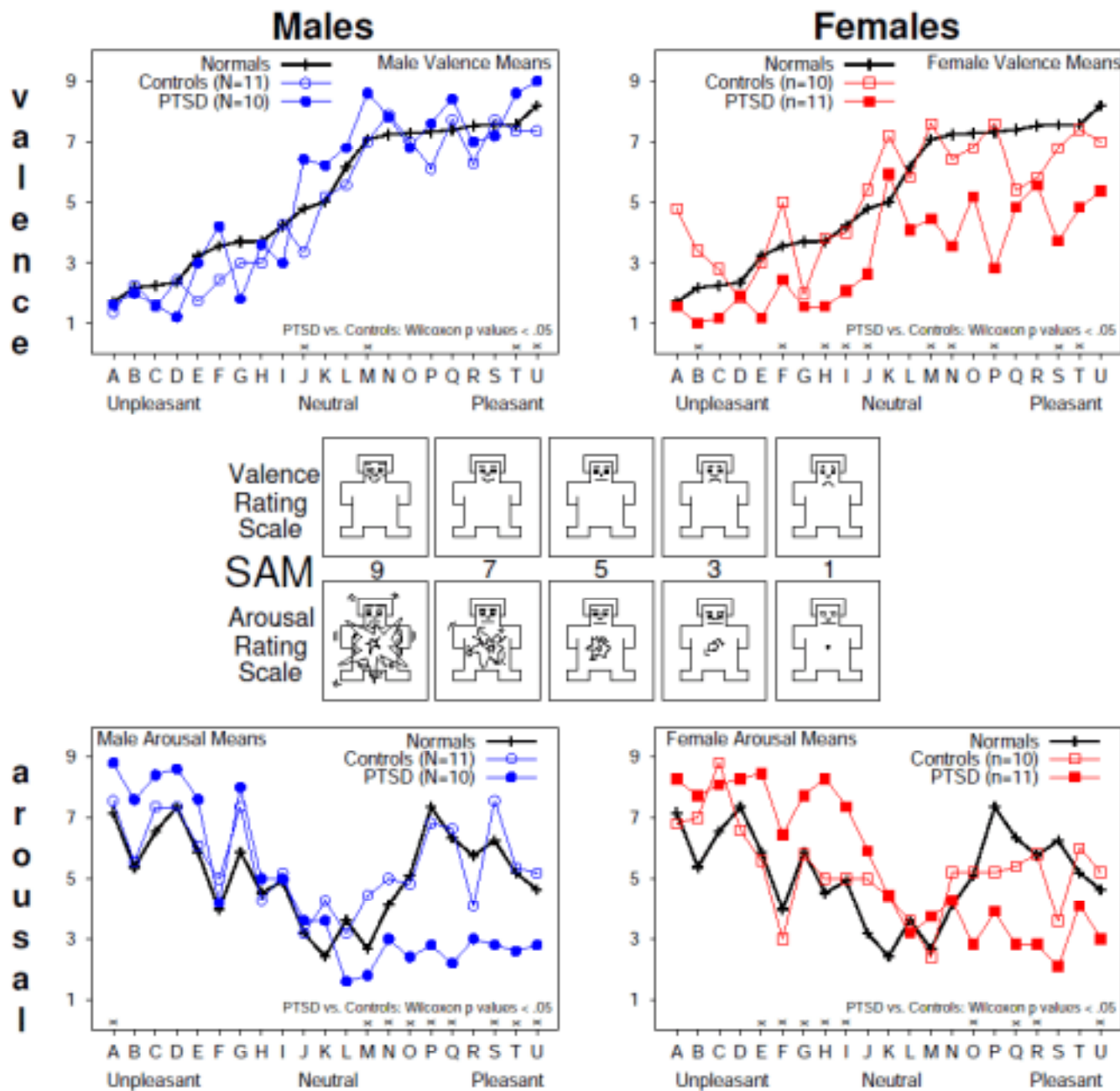
show higher arousal ratings compared to neutral pictures ($p = .028$). PTSD subject did tend to show higher arousal ratings for unpleasant pictures than for neutral pictures in PTSD subjects ($p = .023$).

Salivary Cortisol: Salivary cortisol measurements were made in 15 control and 12 PTSD subjects (several additional subjects were available for this element of the study). The salivary cortisol levels were similar to those found in other studies (Reynolds et al., 1998). A three-way ANOVA (group x day x time) was significant ($F_{7,90} = 3.286, p = 0.0037$), with significant main effects for both group (PTSD < control, $F = 8.43, p = 0.0048$) and day (day 2 < day 1, $F = 5.787, p = 0.0181$), where day 2 was post-dexamethasone. This is consistent with previous work reporting lower cortisol levels in PTSD and heightened sensitivity to dexamethasone (Kellner et al., 1997). Salivary cortisol levels from 4:00 PM on day 2 showed significant negative correlations with total scores on the PTSDSS ($r = -.519, p = 0.047$)

and on the HAMD ($r = -.556, p = 0.031$), with higher symptom scale scores (PTSD) associated with lower cortisol values.

Discussion

The most interesting observation made in the present study is that there appears to be a deficit in “pleasant arousal” in PTSD. There are precedents for such a selective disturbance of one type of affect, as seen in reports of highly specific deficits in experiencing negative, fear-related emotion after bilateral amygdala lesions. Such subjects are impaired at recognizing the presence or intensity of fearful facial expressions but are relatively normal in recognizing facial expressions of happiness, surprise, sadness, disgust, or anger (Adolphs et al., 1999). Our findings that positive affective arousal can be selectively impaired in PTSD provide further support for the hypothesis that there may be separate, distinct, selectively vulnerable brain systems for positive and negative aspects of emotion and, pos-



sibly, for even specific, individual emotions themselves (Sackeim et al., 1982). We have also confirmed that lower cortisol levels are associated with PTSD symptoms.

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Is Polymyalgia Rheumatica (PMR) a Stress Related Disorder?

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The hypothalamo-pituitary-adrenal (HPA) axis plays an important role in the physiological response to stress, including the inflammatory and pain states of some rheumatic diseases. Most of the previous studies have applied to patients with rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome and fibromyalgia.

Polymyalgia rheumatica (PMR) is a common chronic inflammatory disease in the elderly characterized by aching and morning stiffness in the neck, shoulders and pelvic girdle. But there are only a few studies evaluating the HPA axis in PMR. Here the diagnosis and pathogenesis of PMR will be summarized briefly. And an overview of the studies regarding HPA axis in PMR and the impact of HPA axis in the pathogenesis of PMR will be discussed in particular.

Diagnosis of PMR:

PMR is a common chronic inflammatory disease of unknown etiology in elderly people. Bruce provided the first definition of PMR in 1988 and called this clinical condition "senile rheu-

matic gout". Later Barber proposed to use the term "polymyalgia rheumatica" (Barber HS 1957). PMR is a common illness in certain populations, with an incidence rate 2.6 per 100 000 in the age group 50-59 yr and incidence rate 44.7 per 100 000 in the age group 80 yr and older (Machado et al. 1988). Women are affected twice as often as men.

PMR and giant-cell arteritis (GCA) are closely related conditions. GCA is a chronic vasculitis of large and medium-sized vessels. Some authors claim that these conditions are different phases of the same disorder. Population based studies of PMR have showed the occurrence of biopsy proved GCA in 16 to 21 % of patients. Conversely, symptoms of PMR have been observed 40-60 % of patients with GCA (Salvarani C et al. 1995).

The diagnosis of PMR is based on mainly clinical and laboratory findings. The current diagnostic criteria (Table 1) for PMR were formulated in 1984 (Healey LA 1984). The combination of persistent pain for at least one month with aching and morning stiffness in the neck, shoulder and pelvic girdles that lasts

30 minutes, and an increase in the erythrocyte sedimentation rate is strongly suggestive of PMR in elder patients. Systemic signs and symptoms are present nearly one third of patients and include fever, malaise or fatigue, anorexia, and weight loss. The diagnosis is usually made within 2 or 3 months after the onset of symptoms.

Table 1: Criteria for the diagnosis of PMR

* Age of 50 years or older
* Bilateral aching and stiffness for one month or more and involvement of the following areas: neck or torso, shoulders or proximal arms, and hips or proximal thighs
* Erythrocyte sedimentation rate > 40 mm/h
* Exclusion of all other diagnoses except giant-cell arteritis
* Rapid response to prednisone (≤ 20 mg/day)

Pathogenesis:

Although the exact pathogenesis of PMR is unknown it is probably polygenic disease in which multiple genetic and environmental factors influence susceptibility and severity (Salvarani et al. 2002). A viral cause (parainfluenza virus type 1, Mycoplasma pneumonia, parvovirus B19, Chlamydia pneumoniae) has been suspected but not confirmed.

The most frequently studied genetic association is with HLA complex genes. HLA-DRB1 * 04 and DRB1 * 01 alleles are associated with susceptibility to PMR and GCA (Weyand et al. 1994).

In situ production of cytokines can be documented in the temporal arteries of patients with PMR who do not have histologic evidence of arteritis suggesting a subclinic vasculitis.

All these above mentioned factors may have contribution in the pathogenesis of PMR. But little is known regarding the mechanisms of the elder onset of the disease, female dominance and responsiveness to steroids in PMR.

HPA axis in PMR:

A current body of evidence suggests that a disruption in the endocrine-immune system plays a major role in the pathogenesis of rheumatic diseases (Tanriverdi et al. 2003). As the HPA axis is important in the physiological response to the inflammatory and pain states of some rheumatic diseases, studies evaluating changes in the HPA axis are needed for understanding of the pathogenesis of these diseases.

The abrupt onset of PMR and the dramatic and rapid disappearance of symptoms following corticosteroid treatment are reminiscent of both the steroid withdrawal syndrome such as myalgia, malaise, fever, depression, anorexia, etc. and the mild to moderate crises of adrenocortical insufficiency (Cutolo M et al. 2000).

In a previous study, serum levels of IL-6 were found to be elevated in patients with PMR as compared with normal subjects. In PMR patients, the levels were positively correlated with serum levels of androstenedione, cortisol and dehydroepiandrosterone sulfate irrespective of glucocorticoid treatment. Serum levels of cortisol in PMR patients with or without corticosteroid

were lower than would have been expected considering their inflammatory status (IL-6 levels were increased). These data clearly imply that there is a change in the responsiveness of HPA axis to inflammatory stimuli such as IL-6 during PMR (Straub et al. 2000). In another study, Cutolo et al. evaluated HPA axis function in patients with recent-onset PMR not previously treated with glucocorticoids. Serum DHEAS levels in all patients were significantly lower than in the controls at baseline. In female PMR patients a significant correlation was found between baseline cortisol levels. After ovine corticotrophin-releasing hormone and ACTH stimulation tests, a similar cortisol response was found in the patients and controls. By contrast, ACTH induced a significantly higher peak of 17-OHP and higher area under the curve (AUC) in PMR patients than in controls. They concluded that the defect seemed to be related mainly to altered adrenal responsiveness to the ACTH stimulation, at least in untreated patients (Cutolo et al. 2002).

In a recent study from our clinic, the levels of basal hormones including cortisol, ACTH, 17-OHP, 11-S, DHEAS, A, prolactin and TSH were similar in patients with new onset untreated PMR patients and controls. Additionally cortisol and DHEAS levels after the low-dose dexamethasone suppression test were not significantly different between the patient and control groups. However, cortisol/CRP and ACTH/CRP ratios were significantly lower in the patient group. Significant low cortisol responses to low dose ACTH stimulation were detected in the patients with PMR. In addition, a negative correlation after the 1 µg ACTH stimulation test between peak cortisol levels and disease duration was detected. These findings may indicate hypoactivation in the HPA axis (Demir et al. 2006).

Conclusions:

A group of disorders including fibromyalgia, chronic pelvic pain, chronic fatigue syndrome, post-traumatic stress disorder and irritable bowel syndrome falls into the spectrum of what might be termed “stress-related syndromes” because of the increase in symptoms associated with physical and emotional stress. The involvement of HPA axis hormones in the pathogenesis of the stress related disorders are well documented.

Although there are not enough data recent studies suggest that there are some changes in HPA axis in PMR. But the levels of these changes are still unclear. There are several similarities between the stress-related syndromes and PMR such as presence of fatigue and pain, and HPA axis involvement. However it is too early to consider PMR as a stress related disorder. Therefore more data are warranted to clarify the impact of HPA axis in the pathogenesis of PMR.

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Perinatal and Postnatal Symptoms After Late in Utero Exposure to Serotonin Reuptake Inhibitors (SSRIs)

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The introduction of the new class of selective serotonin reuptake inhibitors (SSRIs) antidepressants in the late eighties and early nineties facilitated the treatment of depressive disorders and anxiety disorders. Ease of use and the lower incidence of side effects compared to the tricyclic antidepressants ensured very quickly that the SSRIs were widely distributed, particularly to women.

The drugs' classification by the FDA as category C, indicating the lack of adequate and well-controlled studies in pregnant women to document safety did not prevent use in pregnancy. In point of fact, in nearly half of women conception occurs without the woman's knowledge. It is well documented that SSRI medications readily cross the placenta and the blood brain barrier exposing the embryo and developing fetus fully to maternal drug levels.

Surveys involving over 2000 live births following exposures found that rates of major structural malformations in infants exposed in utero to SSRIs during the first trimester did not exceed the expected rates of major anomalies in the general population (Pastuszak et al. 1993; Chambers et al. 1966).

A decade later, however, a review from databases at the FDA, the WHO and birth outcome studies suggested a neonatal toxicity and /or withdrawal syndrome (Casper et al. 2003; Moses-Kolko et al. 2005). Newborns exposed to average doses of SSRIs and selective serotonin/norepinephrine reuptake inhibitors (SNRIs) were found to have a greater than threefold risk to experience respiratory distress, tremor/increased muscle tone, sucking problems, agitation, sleep disturbances, temperature instability and, rarely, convulsions. Drug manufacturers have recently included a warning label.

The present study was designed to examine whether the timing of SSRI exposure during pregnancy might influence birth outcome and mental and motor performance in infancy.

Methods

Women who were undergoing treatment for major depressive disorder (MDD) in the Womens' Wellness Clinic or were referred for pregnancy, postnatal care or consultation were invited to participate. Women (N=55) who met DSM-IV criteria (DSM 1994) for Major Depressive Disorder during pregnancy signed consent forms containing a description of the purpose and procedure of the study, one form for themselves and one for the participating child. The study was approved by the Human Subjects Committee.

Medication use during pregnancy.

Of the fourteen women, who took SSRIs during the first trimester, 29 % took sertraline (average dose 64.2 mg; 22 % took fluoxetine (average 10mg/d) ; 36 % took paroxetine (average 16 mg) and 7 % took either citalopram (20mg/d) or fluvoxamine (75mg/d) for 6.3 ±3.2 weeks. In the late exposure group, timing of exposure was continuous for N= 23 or 56% of the women, or second/third trimester for N=11 (27%), and third trimester for N=7 (17%). Forty-two percent took sertraline, 34% took fluoxetine, 17% took paroxetine and 7.2% took citalopram. Average daily doses of sertraline, fluoxetine and paroxetine were 107.4 mg, 20 mg, and 17.2 mg, respectively and 20 mg for citalopram. All women received supportive psychotherapy.

Diagnostic assessments.

Women were interviewed in person using the Structured Clinical Interview for DSM-IV Axis I Disorders to confirm the diagnosis of MDD, to assess the number of prior MDD episodes and the occurrence of a postpartum depressive disorder. Each woman completed a questionnaire to collect socio-demographic information and a medical, family, and psychiatric history. Information regarding delivery and neonatal course was col-

lected from the mother and from obstetric and neonatal medical records.

Follow-up evaluation: Children ranged in age from 6 months to 40 months. All children underwent a neurological examination performed by a pediatric neurologist (Amiel-Tison 1976) and a standardized dysmorphology examination by a pediatric geneticist. The child's level of mental and motor development was tested by two developmental psychologists using the Bayley Scales of Infant Development-Second Edition, BSID-II (Bayley 1993). The two psychologist raters were reliability certified on the BSID-II annually as part of a NIH-funded collaborative neonatal outcome study.

Data analysis: Statistical analyses were performed using the SPSS system, version 10.0.

Results

Mothers: Ninety percent of the women were Caucasian and all received early and regular prenatal care. More women in the early exposure group were unmarried. No between group differences were found for age at delivery, education, prenatal vitamin use, miscarriages, gravidity, parity, illnesses or weight gain during pregnancy, or number of C-sections. Women in the late exposure group spent more hours in labor than women in the early exposure group ($p < .05$).

Substance use: One woman in the late exposure group smoked and five women reported having more than 9 drinks during the pregnancy as opposed to none among the early exposure group.

Offspring

There were no stillbirths. The groups did not differ in the number of premature births or in birth weights and lengths at birth. Newborns with third trimester exposure had significantly lower Apgar scores at 1 and at 5 minutes than newborns with early exposure (both at $p < .001$). Twenty seven percent of children with third trimester SSRI exposure were admitted to neonatal intensive care units compared to none with early SSRI exposure. Reasons for admission included respiratory distress in six newborns and meconium aspiration in four.

Breastfeeding and drug exposure

About 90 % of mothers nursed their infants for an average duration of 8- 9 months. Significantly more mothers, about two thirds in the late exposure group compared to the early exposure group, about one third, used medication while breastfeeding.

Physical and neurological examinations of the children at follow-up

No differences in weight, height and fronto-occipital head circumference expressed as percentages were found between the two groups of children.

Genetic examination

No major malformation was found in the children with first trimester exposure to SSRIs. A small asymptomatic ventriculoseptal defect was observed in a child exposed to SSRIs throughout gestation. Rates of minor malformations were similar in the two groups.

Mental and psychomotor developmental outcomes assessed by the Bayley Scales for Infant Development, BSID II (Bayley 1993)

There were no significant differences in mental development (MDI) or psychomotor development (PDI) between children with first and third trimester exposure to SSRIs. On the Bayley Infant Behavioral Rating Scale (BRS) children with third trimester exposure were rated significantly lower than first trimester exposure children and they rated lower on behavioral motor quality, fine motor movements, and gross motor movements. Between group differences for motor quality and for fine motor movement remained significant after covariation for Apgar scores at 5 minutes.

In the third trimester group children whose mothers took no SSRIs during nursing showed significantly higher (better) psychomotor (PDI) development scores than children who were exposed to SSRIs through breastfeeding ($p = .005$).

Discussion

This study compared children who were exposed to SSRIs in utero during the first trimester to children who in most cases were exposed to SSRIs throughout pregnancy and in all cases in the last three months. Late SSRI exposure, but not early exposure to SSRIs, was associated with neonatal adjustment problems. Infants and children with late SSRI exposure also rated lower on fine motor control than children with first trimester exposure. The findings suggest that late gestational drug influences rather than influences during embryonic development might affect neonatal adjustment. Furthermore, exposure to SSRIs during breastfeeding, i.e. postnatal influences might contribute to less optimal motor control in the late exposure group.

The results concerning postnatal adjustment problems, specifically the occurrence of serotonergic symptoms in neonates of mothers treated with SSRIs in late pregnancy support observations by other investigators (Laine et al. 2003; Casper et al. 2003; Zeskind et al. 2004). Recently, Chambers et al. (2006) reported an increased risk of persistent pulmonary hypertension in neonates exposed to SSRIs in utero.

Few studies have examined possible long-term effects of in utero exposure to SSRI medication. Nulman et al. (2002) and Mattson et al. (1999) found no differences between SSRI exposed children and children of control mothers in their mental or motor development. However, neither study assessed motor control using the Behavioral Rating Scale.

It is reassuring that the children's mental development following in utero SSRI exposure was similar in both groups. Our results highlight the importance of including comprehensive assessments of motor development in follow-up studies of children with intrauterine exposure to SSRI antidepressants.

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Sleep, Depression and Cardiovascular Function in Coronary Artery Disease

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Introduction

Depression and insomnia often occur in patients with coronary artery disease (CAD) and have negative impact on the latter development (Carney et al., 2000). From the other hand it have been shown that CAD as well as depression are related to reduced autonomic control which reflects the functional state of cardiovascular system (Zemaityte et al., 1999). However, the role of depression and disturbed sleep in the development of cardiovascular pathology is not completely clear. The goal was to investigate a relationship between psycho-emotional status (depression and anxiety), objective and subjective sleep quality and cardiovascular functional state in CAD patients.

Contingent and Methods

Fifty six healthy subjects and 1335 CAD patients were investigated using clinical and instrumental evaluation of cardiovascular function. NYHA functional class I was in 64, functional class II – 758, and functional class III – 513 patients. Hypertension was in 348, heart failure in 650 and diabetes in 116 CAD patients.

Objective sleep quality was evaluated using polysomnography: total sleep time (TST), sleep efficiency (SE), wakefulness after sleep onset (WASO), stages 1, 2, 3, and 4, REM sleep and body movements (Rechtschaffen & Kales, 1968). Subjective sleep quality was assessed using Pittsburgh Sleep Quality Index (PSQI); a global PSQI score > 5 yielded a diagnostic sensitivity of 89.6 percent and specificity of 86.5 percent in distinguishing good (PSQI<5) and poor (PSQI>5) sleepers (Buysse et al., 1989).

Hospital Anxiety and Depression Scale was used for psychological testing (Zigmond & Snight, 1983; Bunevicius & Zilėniene, 1991). The patients were distributed into the following groups, randomised according cardiovascular status: 1) without anxiety or depression - 456; 2) with anxiety - 229; 3) with

depression - 64; 4) with depression and anxiety - 171 patients. Autonomic heart rate (HR) control was evaluated by HR variability analysis using Poincare plots during sleep (Zemaityte et al., 2001). Mean RR interval, minimal (RR_{min}) and maximal (RR_{max}) HR frequencies, the difference between of them as maximal HR response ($\Delta RR_r = RR_{max} - RR_{min}$), maximal HR variability (RR_r) as maximal width between of tangential lines of square, parallel to diagonal, general HR variability (P) as the plot of all square were measured.

Statistical comparison of investigated group data was performed using Student's criteria (with $p < .05$) and λ^2 test. The randomisation was made by using random number generator.

Results and Discussion

CAD patients, as compared with healthy subjects, demonstrated significantly reduced TST, SE, stages 3 and 4, and REM sleep and increased WASO (Table 1). Subjective sleep quality was worse for CAD patients. Worsening of NYHA functional class in CAD patients was paralleled by decreased quality of sleep (Table 2). The shortest TST and lowest SE as well as decreased stages 3-4 and REM sleep and increased WASO were observed in patients with NYHA functional class III. Worsening of objective sleep quality paralleled an increase of PSQI. Concomitant pathology was followed by a worsening of objective and subjective sleep quality: hypertension - by a decrease of TST, SE and stages 3-4, while heart failure and diabetes – additionally by a reduction of REM sleep and an increase in PSQI (Table 3).

Objective sleep quality was worse in CAD patients with depression, while only subjective one - in patients with anxiety or both, anxiety and depression (Table 4). Patients with depression, as compared with anxious patients, demonstrated significantly reduced stages 3-4, REM sleep, and TST. PSQI was higher in patients with depression, reflecting worse subjective sleep quality, than in patients with anxiety alone. However, the mostly disturbed objective and subjective sleep quality was ob-

served in patients with both, depression and anxiety. HR variability analysis during sleep was made in CAD patients groups with different psychoemotional status, randomised according cardiovascular status. CAD pts with anxiety, as compared to those without anxiety, demonstrated significantly lower HR variability (σ RR) and higher mean HR frequency (RR) while measured from Poincare plot of all sleep record (Table 5). However, this tendency was not significant at the level of minimal frequency (RR_{min}) and shows a non-significant tendency at maximal HR frequency level (RR_{max}), what was followed by a tendency to decrease of maximal HR response (ΔRR_p) during sleep. CAD patients with depression demonstrated increased ($p > .05$) level of mean HR frequency and decreased ($p < .05$) maximal HR frequency level (RR_{max}), measured from Poincare plot. Because of that, the maximal RR interval response (ΔRR_p) during sleep becomes reduced, as compared with patients without anxiety and depression. HR variability (σ RR) during sleep was lower in depressed patients as well. CAD patients with both, depression and anxiety, demonstrated significantly lower HR variability (sRR) during sleep and maximal HR frequency level (RR_{max}), while mean HR frequency (RR) and maximal RR interval response (ΔRR_p) during sleep show only tendency ($p < .1$) to increase.

Reduction of parasympathetic HR control in anxious subjects without somatic diseases was demonstrated also by Moser and co-authors (1998), while an increase of sympathetic impact in youngsters was observed by others (Duprez et al., 1995; Lesperance & Frasere-Smith, 2000). Presence of depression was followed by a further reduction of HR variability in CAD patients characterized by initially decreased HR variability because of impact of somatic disease (Stein et al., 2000). CAD or anxiety and/or depression, possibly have similar deteriorating impact on autonomic control, because of that we randomized investigated persons according to the expression of cardiovascular pathology and found a clear negative impact of depression and anxiety.

Impact of anxiety alone in CAD pts indicated a tendency of

Table 1. Sleep structure and PSQI in healthy subjects (H Ss) and CAD patients.

	H Ss	CAD pts
TST, min.	352.2	318.1*
SE, %	90.7	85.9*
WASO, %	9.3	14.1*
REM Sleep, %	12.9	12.2
S1, %	7.8	9.5
S2, %	50.6	53.1
S3, %	11.0	7.0*
S4, %	6.1	1.3*
BM, %	2.4	2.7
PSQI	5.2	7.8*

TST, Total sleep time; SE, Sleep efficiency; WASO, Wakefulness after sleep onset; S1, Stage 1; S2, Stage 2; S3, Stage 3; S4, Stage 4; BM, Body movements; PSQI, Pittsburgh Sleep Quality Index.

* $p < .05$.

HR variability reduction and significant increase of HR minimal frequency during sleep. This is caused by the reduction of maximal HR responses to the shifts of sleep stages and might be seen as a reflection of reflex HR control component. Impact of depression on HR variability during sleep was similar. Both, anxiety and depression acting together have much more evident impact to autonomic HR control, especially if evaluated by means of parameters of RR interval Poincare plot during sleep. The reduction of autonomic HR control at all levels was evident as well as at tonic and reflex control, the latter being reduced due to depression of both parasympathetic (increased minimal HR frequency) and sympathetic (decreased maximal HR frequency) control level during sleep.

It might be presumed that psychoemotional status, especially depression and anxiety together, are reducing autonomic HR control and making negative impact on the development of somatic cardiovascular diseases. Sleep disturbances might be having a complimentary negative impact to this process due to disturbing a cardiovascular function.

Conclusions

CAD and concomitant pathology disturb subjective and objective sleep quality reducing total sleep time as well as stages 3-4 and REM sleep. Anxiety is related to worsening subjective sleep quality assessed by PSQI, while depression – to changes in sleep structure and reduced total sleep time measured by polysomnography. Both, depression and anxiety, demonstrate negative impact on autonomic HR control during sleep.

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Table 2. Sleep structure and PSQI in CADpatients with different NYHA Functional class.

	NYHA Functional class		
	I	II	III
TST, min.	335.8	313.8*I	313.8*I
SE, %	89.1	84.9*I; II	84.9*I; II
WASO, %	10.9	15.1*I; II	15.1*I; II
REM Sleep, %	13.3	10.9*I; II	10.9*I; II
S1, %	9.4	9.4	9.4
S2, %	52.3	53.9	53.9
S3, %	9.6	6.8*I	6.8*I
S4, %	2.1	1.1*I	1.1*I
BM, %	2.4	2.7	2.7
PSQI	5.9	9.0*I; II	9.0*I; II

Abbreviations: see Table 1; * $p < .05$.

Table 3. Sleep structure and PSQI in CAD patients' groups with different concomitant pathology.

	CAD pts	CAD pts with		
		Hypertension	Heart failure	Diabetes
	1	2	3	4
TST, min.	326.4	326.6	317.1	308.0
SE, %	87.4	88.0	84.1* ^{1,2}	86.3
WASO, %	12.6	12.0	15.9* ^{1,2}	13.7
REM Sleep,%	13.8	13.4	11.8* ^{1,2}	11.8* ¹
S1, %	8.5	11.0* ¹	9.1* ²	10.4
S2, %	52.5	51.6	52.8	55.4
S3, %	7.9	7.4	6.7	4.9* ^{1,3}
S4, %	1.9	1.7	1.1* ¹	0.65* ¹
BM, %	2.8	2.9	2.6	3.1* ³
PSQI	7.1	6.5	8.2* ^{1,2}	8.8* ^{1,2}

Abbreviations: see Table 1; *p<.05.

Table 4. Sleep structure and PSQI in CAD patients' with different psychoemotional status.

	CAD patients			
	No Anxiety/Depression	Anxiety	Depression	Anxiety & Depression
	1	2	3	4
TST, min.	322.5	314.6	304.3* ¹	316.5
SE, %	86.4	86.5	84.9	84.7
WASO, %	13.6	13.5	15.1	15.3
REM Sleep,%	12.8	12.4	10.3* ^{1;2}	10.6* ¹
S1, %	9.3	9.6	11.2	10.1
S2, %	52.9	53.0	55.3	54.2
S3, %	7.3	7.4	4.5* ^{1;2}	5.9* ^{1;2}
S4, %	1.4	1.4	0.45* ¹	1.2* ²
BM, %	2.7	2.6	3.1	2.8
PSQI	6.5	8.7	7.4	10.7

Abbreviations: see Table 1; *p<.05.

Table 5. HR variability during sleep evaluated by means of Poincare plots of RR intervals in CAD patients with different psychoemotional status.

	CAD Patients			
	No Anxiety/Depression	Anxiety	Depression	Anxiety & Depression
RR; ms	1040.0	1009.0+	1015.9	1004.6+
sRR; ms	78.5	71.4*	70.0+	71.0*
RRmin; ms	718.3	708.4	701.4	703.3
RRmax; ms	1275.3	1234.3+	1221.6+	1225.1*
DRRr; ms	557.1	525.8+	520.1+	521.9+
DRRt; ms	150.5	144.4	137.1	137.0
P; ms ²	76656.6	69718.1	64897.8+	67759.7

Abbreviations: see Table 1; * p<.05; + p<.1.

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AUTHOR INDEX

Abraham S.	17	Grewen K.	22
Adomaitiene V.	23	Gudiene D.	37
Aleknaviciute A.	38	Halbreich U.	40
Alonderis A.	29	Hart S.	17
Andersson S.	14	Hellhammer J.	25
Andruskiene J.	31	Hellhammer D.	12, 33
Asadauskiene J.	31	Heilbronn L.	17
Baran J.	61	Heim C.	33
Barker DJP.	14	Hinderliter A.L.	27
Babarskiene R.M.	23	Hoyme E.H.	61
Belokrylova M.F.	31, 48	Janusonis V.	31
Beresnevaite M.	23	Jorgensen W.	14
Beltikova K.V.	20	Kajantie E.	14
Brambilla F.	17	Kazlauskas E.	19
Branski P.	38	Kazlauskas H.	31
Brian E. L.	11	Kazanavicius G.	37
Brozaitiene J.	29, 30	Katkute A.	32, 35
Bunevicius A.	32, 35	Kasperek T.	20
Bunevicius R.	15, 21, 26, 27, 30, 53	Kelestimur F.	59
Buneviciute J.	35	Klimavicius D.	37
Burba B.	37	Kochetkov Y.A.	20, 35
Butnoriene J.	16	Krishnaswamy S.	19
Campbell L.	17	Kusminskas L.	21
Cheng-Cheng H.	25	Kucinskiene D.	19
Caregaro L.	17	Kucinskiene Z.	18
Castaldo E.	17	Lasas L.	16
Casper R.C.	21, 61	Lasaite L.	14, 15, 16
Ceskova E.	20	Lasiene J.	15
Cerina V.	35, 36	Lasiene D.	15, 16
Crayton J.W.	56	Legros J.J.	12
Danilevicius J.	37	Leskauskas D.	37
Danileviciute V.	23	Light K.C.	27
DeBattista A.	61	Litvinov A.V.	35
Dimitrov D.	14, 24, 42	Manea M.	33
Di Filippo C.	17	Matovinovic M.	25, 35, 36
Doko M.	36	Maric A.	25, 35, 36
Domin H.	38	Markeviciute A.	37
Duoneliene I.	29	MarKowitsch M.J.	12
Elistratova T.	39	Martinkenas A.	29, 31, 37
Ermoleava L.G.	35	Maj M.	17
Eriksson I.G.	14	Matulevicius V.	14
Favaro A.	17	Meinlschmidt G.	33
Fedotova J.	20, 45	Mickuviene N.	21, 26
Feldt K.	14	Mihajlovic A.S.	17
Fleisher B. E.	61	Minkauskiene M.	33
Garaza A.	18	Monteleone P.	17
Garganeyeva N.P.	15, 48	Murgic J.	36
Gailiene D.	19	Neafsey E.J.	56
Gaylor E.	61	Nica L.	33
Gherman E.	33	Novikova I.	38
Gilles A.	61	Norkus A.	15
Gintauskiene V.	30	Osmond C.	14
Girdler S.S.	27, 30	Panzaru C.	33
Gorobets L.N.	20, 35	Peceliuniene J.	26

AUTHOR INDEX

Pecina H.I.	36
Pedersen C.A.	24, 27
Phillips DIW	14
Pilc A.	38
Podlipskyte A.	29
Pop VJ.	21
Prikryl R.	20
Radziuviene R.	31
Radosevic V.	36
Raikkonen K.	14
Rapalaviciene R.	29
Raskauskiene N.	31, 32
Russell J.	17
Ryabova E.V.	48
Saudargiene S.	32
Santonastaso P.	17
Sapronov N.	26
Schommer N.C.	26
Schmidt I.	33
Sidorov P.	13
Sheffield D.	22
Semke V.Ya	48
Skultinaite K.	33
Smialowska M.	38
Soloviev A.	18
Solter M.	25, 35, 36
Spahic-Mihajlovic A.	56
Statkeviciene A.E.	23
Staniute M.	27
Stankus A.	29
Striskaite J.	29
Sumskiene A.	33
Tanriverdi F.	22, 59
Tegethoff M.	27
Tortorella A.	17
Uchacz T.	38
Ustohal L.	20
Valyte G.	29
Varoneckas G.	23, 27, 29, 30, 31, 32, 63
Velickiene D.	37
Vrkljan M.	25, 35, 36
Zah T.	25
Zakarevicius L.	29
Zieba B.	38
Zilaitiene B.	14
Wagner D.	33
Wilronska JM.	38
Wingenfeld K.	33

Cipralex - ASRI grupės antidepresantas

Artūras Gudelis

Respublikinė Vilniaus psichiatrijos ligoninė

Straipsnis apžvelgia serotoninerginės sistemos funkcionavimo ypatumus bei svarbą, serotonininio transmisiją gerinančių vaistų poveikį ir išskirtines escitalopramo – naujos kartos alosterinio serotonininio reabsorbcijos inhibitoriaus (ASRI) – savybes.

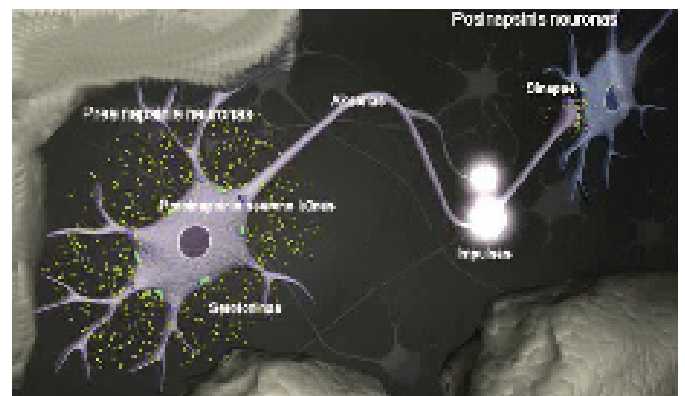
Serotonino svarba depresijos patogenezėje

Serotoninas – neuromediatorius, reguliuojantis įvairias svarbias organizmo funkcijas ir nulemiantis daugelį žmogaus elgsenos ypatumų. Nustatyta, kad serotonininio apykaitos sutrikimas galvos smegenyse turi tiesioginę įtaką depresijos, nerimo, valgymo, miego ir kitų psichikos ir elgsenos sutrikimų išsivystymui. Kiekvienais metais šiuolaikinio mokslo žinios pasipildo naujais duomenimis, įrodančiais serotonininio svarbą ir reikšmę. Atskleidžiami įvairialypės ir sudėtingos serotoninerginės sistemos funkcionavimo aspektai ir ypatumai. Remiantis teoriniais neuropsichofarmakologijos mokslo atradimais, kryptingai kuriami vaistai, reguliuojantys serotonininio apykaitą galvos smegenyse. Kaip žinome, pati svarbiausia serotonininio neurotransmisiją gerinanti šiuolaikinių vaistų grupė yra selektyvieji serotonininio reabsorbcijos inhibitoriai (SSRI). Vis gilėjančios žinios apie serotonininio sistemą leido žengti kitą žingsnį: sukurtas ir jau sėkmingai vartojamas naujos kartos anti-depresantas escitalopramas (*Cipralex*). Jo farmakodinaminės savybės yra išskirtinės ir gerokai skiriasi nuo kitų SSRI grupės medikamentų.

Serotoninerginės sistemos neuroanatominiai ir neurofiziologiniai aspektai

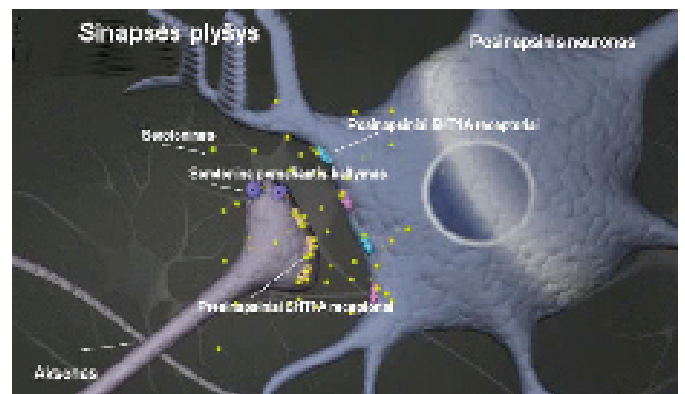
Serotonino sistema yra labai sudėtinga ir įvairialypė, todėl paminėsime tik kai kuriuos pagrindinius duomenis apie ją. Šią sistemą sudaro dvi pagrindinės grandys: presinapsinė ir posinapsinė. Presinapsinei grandžiai priklauso raphe dorsalis sritis. Šioje srityje yra išsidėstę pagrindiniai serotoninerginiai branduoliai. Joje gaminasi žmogaus galvos smegenų serotoninas. Serotoninerginiuose branduoliuose esančiuose neuronų kūnuose cheminė energija virsta elektros impulsu, ir ši aksonais kaip elektros laidais plinta į įvairias kitas smegenų sritis (1 pav.). Kad impulsas patektų į posinapsines sritis, jis turi įveikti sinapsės plyšio barjerą (2 pav.). Sinapsės plyšyje šis impulsas perduoda neuromediatorius serotoninas (2 pav.). Impulsas, perėjęs sinapsės plyšį, plinta toliau posinapsinėmis struktūromis. Ypač svarbi smegenų struktūra yra hipokampus. Hipokampus tiesiogiai nulemia žmogaus atminties, kognityvinius gebėjimus. Nustatyta, kad depresijos metu hipokampus sumažėja. Kuo ilgesnis depresijos epizodas, tuo labiau hipokampus degeneruoja. Atlikus bandymus su eksperimentiniais gyvūnais nustatyta, kad gydant antidepresantais neuronai hipokampe regeneruoja. Sergant depresija, elektrinė pulsacija į hipokampą susilpnėja. Teoriškai, norint sureguliuoti sutrikusią serotonininio neurotransmisiją, galima veikti daugelį serotonininio sistemos grandžių. Labai svarbu – užtikrinti elektrinio impulso perdavimą į posinapsines struktūras sinapsės plyšyje. Kaip žinome, šį impulsą sinapsės plyšyje perduoda serotoninas. Yra

žinoma keliolika serotonininio receptorių tipų ir potipių. Visi jie vienaip ar kitaip reguliuoja serotonininio neurotransmisiją. Labai svarbus serotonininio receptorių potipis – 5-HT_{1A} receptoriai (2 pav.). Jie pagal savo išsidėstymo vietą (presinapsiniame neurone kūno, aksono, aksono galo srityse ar posinapsinio neurono pradžioje) atlieka skirtingas funkcijas normalizuojant serotonininio apykaitą. Pažymėtina, kad presinapsinėje membranoje išsidėstę 5-HT_{1A} receptoriai „sugeria“ išsiskyrusį į



1 pav. Impulsų plitimas neuronais

[Pagal prof. Pierre Blier, Otavos universitetas, Kanada, Lundbeck]



2 pav. Sinapsės plyšys

[Pagal prof. Pierre Blier, Otavos universitetas, Kanada, Lundbeck]



3 pav. Serotoniną pernešantis baltymas

[Pagal prof. Pierre Blier, Otavos universitetas, Kanada, Lundbeck]

sinapsės plyši serotoniną atgal, todėl jų padidėjęs aktyvumas yra žalingas. Labai svarbus serotonino neurotransmisijai yra serotoniną pernešantis baltymas (3 pav.). Jis taip pat grąžina atgal išsiskyrusį į sinapsės plyšį serotoniną, todėl, samprotaujant teoriškai, depresijų metu jį reikia slopinti.

SSRI veikimo fazės

Paskyrus SSRI grupės vaistų, terapinis antidepresinis jų poveikis išryškėja ne iš karto. Remiantis šiuolaikiniais psichofarmakologijos duomenimis, yra išskiriamos trys gydymo SSRI fazės: ankstyvoji, vidurinė ir vėlyvoji. Nustatyta, kad tik trečioje gydymo fazėje pasireiškia visas terapinis atsakas.

Pirmoje gydymo fazėje serotonino kiekis padidėja tik presinapsinėse neurono kūno dalyse. Posinapsinėse struktūrose serotonino kiekio nenustatoma dėl kelių priežasčių. Vienos iš svarbių priežasčių yra tai, kad posinapsinių 5-HT_{1A} receptorių ir serotoniną pernešančio baltymo blokavimas yra nepakankamas. Išsiskyręs į sinapsės plyšį serotoninas vėl grąžinamas atgal į presinapsinį neuroną ir neatlieka savo funkcijos.

Antroje gydymo SSRI fazėje (2–4-tą sav.) pradeda ryškėti terapinis SSRI poveikis. Neurobiologinė terapinio SSRI poveikio pradžios priežastis – vidurinėje gydymo fazėje pasireiškęs 5-HT_{1A} receptorių, esančių presinapsinėse srityse, blokavimas ir dalinis nujautrinimas.

4–6-tą gydymo savaitę, t.y. trečioje gydymo fazėje, pasireiškia visas terapinis antidepresinis SSRI poveikis. Šioje gydymo fazėje pasireiškia visiškai 5-HT_{1A} receptorių blokada ir nujautrinimas, jų aktyvumas tampa optimalus. Taip pat labai sumažėja serotoniną pernešančio baltymo funkcinis aktyvumas. Verta pažymėti, kad vėlyvojoje gydymo fazėje labai padidėja posinapsinių 5-HT_{1A} receptorių aktyvumas (2 pav.). Jie, skirtingai negu presinapsiniai, yra „naudingi“, nes absorbuoja išsiskyrusį serotoniną į posinapsines struktūras, t.y. hipokampą.

Escitalopramas – kitoks negu tradiciniai SSRI

Gydant depresiją, labai svarbu atnaujinti elektros impulso perdavimą pro sinapsės plyšį. Escitalopramas, panašiai kaip ir SSRI, blokuoja ir nujautrina presinapsinius 5-HT_{1A} receptorių, aktyvuoja posinapsinius 5-HT_{1A} receptorių, todėl pagerina šio impulso perdavimą. Kaip minėta, norint atnaujinti elektros impulso perdavimą, labai svarbu slopinti serotoniną pernešančio baltymo aktyvumą. Serotoniną pernešantis baltymas turi 2 svarbias sritis, prie kurių jungiasi escitalopramas ir blokuoja jo aktyvumą: alosterinę ir reabsorbcinę (ši dar vadinama pirmine). Visi tradiciniai SSRI bei serotonino

ir noradrenalino reabsorbcijos inhibitorių grupės antidepresantai prisijungia tik prie reabsorbcinės srities, ją užblokuoja. Todėl susilpnėja serotoniną pernešančio baltymo veiklumas. Bet alosterinė sritis, stiprinanti ir ilginanti prisijungimą prie pirminės srities, lieka neužblokuota. Tik vienintelis escitalopramas vienu metu prisijungia ir prie pirminės, ir prie alosterinės sričių. Tai nulemia ilgesnį ir stipresnį serotoniną pernešančio baltymo užblokavimą. Taigi escitalopramas, palyginti su kitais tradiciniais SSRI grupės vaistais, veiksmingiau užblokuoja šį „žalingą“ baltymą ir užtikrina stipresnio elektros impulso perdavimą į posinapsines smegenų struktūras. Tai išskirtinė ir labai svarbi escitalopramo savybė. Todėl šiuolaikinėje psichofarmakologijoje escitalopramas, įvertinus šią unikalią jo savybę, vadinamas ne SSRI, bet ASRI – alosteriniu serotonino reabsorbcijos inhibitoriumi.

Nustatyta, kad raceminis RS citalopramas susilpnina teigiamas escitalopramo savybes. Kitaip tariant, citaloprame esantis R-citalopramo enantiomeras pasižymi inhibuojamuoju poveikiu ir stabdo escitalopramo prisijungimą prie serotonino pernešėjo. Kai kartu su escitalopramu skiriama kitų SSRI grupės vaistų, konkuruojančių dėl prisijungimo prie serotoniną pernešančio baltymo, escitalopramo atsiskyrimo nuo šio baltymo greitis taip pat padidėja. Ir atvirkščiai, skiriant žymėto radioaktyvaus escitalopramo kartu su nežymėtu, jo atsiskyrimo greitis nuo serotoniną pernešančio baltymo labai sulėtėja. Taigi escitalopramas pasižymi unikalia savybe pats pasiilginti prisijungimo prie serotoniną pernešančio baltymo trukmę ir ilgiau jį blokuoja. Išskirtinės escitalopramo farmakodinaminės savybės nulemia klinikinio poveikio ypatumus: veiksmingumą, greitą veikimo pradžią, gerą toleravimą.

Išvados

- Escitalopramas pasižymi unikaliu farmakodinaminio veikimo būdu – pats pasiilgina prisijungimo prie serotoniną pernešančio baltymo trukmę.
- Raceminiame RS mišinyje esantis R-citalopramas silpnina escitalopramo poveikį.
- Skirtingai negu tradiciniai SSRI grupės antidepresantai, escitalopramas vienu metu jungiasi prie reabsorbcinės (pirminės) ir alosterinės serotoniną pernešančio baltymo sričių, ir tai nulemia ilgesnį ir stipresnį šio baltymo slopinimą. Todėl jis vadinamas naujos kartos antidepresantu – ASRI (alosteriniu serotonino reabsorbcijos inhibitoriumi).
- Farmakodinaminio veikimo būdo ypatumai nulemia escitalopramo klinikines savybes: veiksmingumą, greitą veikimo pradžią, gerą toleravimą.

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DALINIAI DOPAMINO AGONISTAI – NAUJA ANTIPSICHOZINIŲ VAISTŲ KARTA

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Antipsichozinio vaisto (APV) veiksmingumas ir galimi šalutiniai poveikiai priklauso nuo jo prisijungimo prie receptorių ir poveikio jiems. Vienam iš naujausių atipinių APV aripiprazoliui būdingas dvejopas poveikis dopamino ir serotonino receptoriams: agonistinis ir antagonistinis. Manoma, kad daliniai dopamino agonistai yra trečios kartos APV.

APV VEIKIMO SPEKTRO IR GALIMŲ ŠALUTINIŲ POVEIKIŲ SVARBA

Šizofrenija serga apie 1–1,5 proc. pasaulio gyventojų. Ši lėtinė liga pasireiškia pozityviaisiais ir negatyviaisiais simptomais, kognityvinių procesų ir nuotaikos sutrikimais, neigiamai paveikia pacientą, jo šeimos narius ir visuomenę. Šizofrenija gydoma tipiniais (pirmos kartos) ir atipiniais (antros kartos) APV. Įvairių APV poveikis skirtingiems simptomams yra nevienodas, be to, vaistai gali sukelti šalutinių poveikių. Paprastai sėkmingiau gydomi psichozės ir negatyvieji simptomai, o kognityviniai – dažnai visai nesėkmingai.

Gydant tipiniais APV daugeliui pacientų išlieka šizofrenijos simptomų ir/ar pasireiškia šalutinių poveikių, pvz., ekstrapiramidinė simptomatika (EPS), hiperprolaktinemija. Atipiniai APV yra platesnio veikimo spektro, rečiau sukelia EPS, tačiau gali sukelti sedaciją, pailginti QTc intervalą, padidinti svorį, gliukozės ir lipidų koncentraciją serume. Šalutiniai poveikiai išvargina pacientą, padidina kitų ligų išsivystymo riziką, pvz., nutukimas gali paskatinti lipidų apykaitos sutrikimų, cukrinio diabeto, širdies ir kraujagyslių sistemos ligų, kvėpavimo sutrikimų, osteoartrito išsivystymą; hiperprolaktinemija gali sumažinti libido, estrogenų kiekį, sukelti menstruacinio ciklo sutrikimus, hirsutizmą, osteoporozę (dėl to didėja kaulų lūžių rizika), galaktorėją, o vyrams – erekcijos, ejakuliacijos sutrikimus, sumažinti spermatogenezę, testosterono kiekį; QTc intervalo pailgėjimas gali būti staigios mirties priežastis. Reikia prisiminti ir tai, kad dėl EPS papildomai skiriama anticholinerginių vaistų, o jiems yra būdingas neigiamas poveikis kognityviniams procesams.

Netinkamai parinktas vaistas ar jo dozė gali pabloginti paciento bendradarbiavimą, dėl to didėja atkryčių, hospitalizacijų, suicidinio ir/ar asocialaus elgesio tikimybė, blogėja ligos baigtys, padidėja ekonominiai ir socialiniai ligos kaštai. Siekiant veiksmingo ir saugaus gydymo, kuriami vis naujesni atipiniai APV. Manoma, kad vienas iš naujausių atipinių APV aripiprazolis yra trečios kartos vaistas nuo psichozės, pasižymintis unikaliu veikimo mechanizmu.

ARIPIPRAZOLIO VEIKIMO MECHANIZMAS (DALINIS DOPAMINO AGONIZMAS)

Farmakologinės vaisto savybės priklauso nuo jo prisijungimo prie receptorių ir poveikio jiems. Visiškas dopamino receptorių agonistas, prisijungdamas prie D₂ receptorių, aktyvina juos, o visiškas antagonistas (tipiniai ir atipiniai APV) – blokuoja. Dalinis agonistas (aripiprazolis) sumažina dopamino aktyvumą per didelio aktyvumo srityse ir padidina – per mažo aktyvumo srityse.

Aripiprazolis dar vadinamas dopamino ir serotonino neurotransmisinių sistemų stabilizatoriumi. Jo poveikis (skirtingai nuo visų kitų APV) dopamino ir serotonino receptoriams dvejopas: agonistinis ir antagonistinis. Dėl aripiprazolio agonistinių savybių D₂ presinapsiniams receptoriams sumažėja intrasinapsinio dopamino kiekis. Šis vaistas taip pat blokuoja postsinapsinius D₂ receptorių. D₂ receptorių blokavimas (mezolimbiniame dopamino take) siejamas su veiksmingu pozityviųjų simptomų gydymu, o agonizmas D₂ receptoriams (mezokortikaliniam dopamino take) – su veiksmingu negatyviųjų, kognityvinių simptomų gydymu. Aripiprazolis palaiko normalų dopamino aktyvumą nigrostriatiniame ar tuberoinfundibuliniame dopamino takuose, siejamuose atitinkamai su EPS ir padidėjusia prolaktino koncentracija. Dėl savo agonistinio poveikio serotonino 5-HT_{1A} receptoriams jis veiksmingai gydo nerimą, depresiją, kognityvinius ir negatyvius simptomus, o dėl antagonistinio poveikio 5-HT_{2A} receptoriams – negatyvius, kognityvinius simptomus, sujaudinimą, agresiją, rečiau sukelia EPS.

Aripiprazolis silpnai veikia histamino H₁ ir α₁ adrenerginis receptorių, neveikia muskarininių cholinerginių receptorių. Dėl to atitinkamai sukelia minimalius svorio pokyčius, mažesnę sedaciją, retas ortostatinės hipotenzijos būkles, nebloginą kognityvinių procesų.

Aripiprazolis gerai absorbuojamas, maksimali koncentracija plazmoje (*t max*) susidaro po 3–5 val. Metabolizuojamas kepenyse citochromo P450 izoenzimų (CYP2D6 ir CYP3A4). Eliminacijos pusperiodis (*t* ½) – maždaug 75 val.

ARIPIPRAZOLIO VEIKSMINGUMAS

Klinikinių tyrimų duomenimis, aripiprazolis yra:

- veiksmingesnis už placebo;
- panašaus veiksmingumo, kaip ir kiti APV (tiek tipiniai, tiek atipiniai), gydant pacientus, sergančius šizofrenija (ūminių atkryčių ar stabilios būsenos laikotarpiais). Gydant aripiprazoliu reikšmingai palengvėja pozityvieji, negatyvieji, kognityviniai ir depresijos simptomai.
- Pasižymi ilgalaikiu veiksmingumu [2, 3, 4].

Aripiprazolis veiksmingai gydo ūmines psichozes

Atliekant trumpalaikį (4 sav.) tyrimą, pacientams, sergantiems šizofrenija/šizoafektiniu sutrikimu, skiriant aripiprazolio (20 mg/p. ar 30 mg/p.) ir risperidono (6 mg/p.), nustatyta, kad

ABILIFY® (aripiprazolis)



abu šie vaistai yra reikšmingai veiksmingesni, palyginti su placebo, vertinant pagal Pozityviųjų ir negatyviųjų simptomų skalės (angl. *Positive and Negative Symptom Scale* – PANSS) bendrą, pozityviųjų balų bei Bendro klinikinio vertinimo–ligos sunkumo skalės (angl. *Clinical Global Impressions-Severity of Illness* – CGI-S) balų pokyčius [5].

Gydant ūmines būklės svarbus greitas APV poveikis, nes pacientai dažnai būna psichomotoriškai sujaudinti, pavojingo sau ir/ar aplinkiniams elgesio. Greitą aripiprazolio veikimą ūminiu šizofrenijos/šizoafektinio sutrikimo atkryčio periodu patvirtina apibendrinti 4 trumpalaikių (4–6 sav.) dvigubai aklių placebo kontroliuojamų tyrimų duomenys [1]. Jau po pirmos stacionarinio gydymo aripiprazoliu (15 mg/p., 20 mg/p. ir 30 mg/p.) savaitės reikšmingai pagerėjo PANSS bendri, pozityvieji balai, palyginti su placebo.

Medikamentų keitimo tyrimo metu pacientai teikė pirmenybę aripiprazoliui

Praktinio klinikinio (8 sav.) tyrimo metu pacientams, sergantiems šizofrenija/šizoafektiniu sutrikimu, anksčiau skirtą gydymą kitu APV pakeitus aripiprazoliu, nustatytas stabilus Bendro klinikinio vertinimo–ligos pagerėjimo skalės (angl. *Clinical Global Impressions Scale for Improvement of Illness* – CGI-I) balų gerėjimas. 64 proc. pacientų suteikė pirmenybę gydymui aripiprazoliu, palyginti su anksčiau skirtu [1]. Atviro žymėjimo (8 sav.) tyrimo metu stabilios būklės pacientams kitus APV pakeitus aripiprazoliu (30 mg/p.) nustatyta, kad nuolat mažėja PANSS bendri, pozityvieji ir negatyvieji balai.

Palaikomojo gydymo ir atkryčių prevencijos tyrimai įrodo ilgalaikį aripiprazolio veiksmingumą

Išanalizavus dviejų ilgalaikių (52 sav.) palyginamųjų atsitiktinės atrankos dvigubai aklių tyrimų duomenis, nustatytas panašus aripiprazolio ir haloperidolio ilgalaikis veiksmingumas praėjus ūminio atkryčio epizodui, vertinant pagal PANSS bendrą, pozityvių simptomų balų, CGI-I ir CGI-S balų pokyčius. Aripiprazolis buvo veiksmingesnis už haloperidolį pagal PANSS negatyviųjų ir Montgomerio-Asberg depresijos vertinimo skalės (angl. *Montgomery-Asberg Depression Rating Scale* – MADRS) balų pokyčius [2].

Gydant aripiprazoliu (15 mg/p.) sergančius lėtine šizofrenija stabilios būklės pacientus nustatytas reikšmingai ilgesnis laikotarpis ir reikšmingai mažesnis atkryčių pasikartojimas, palyginti su placebo grupe (atitinkamai 34 proc., 57 proc.) [4]. Be to, aripiprazolis buvo reikšmingai veiksmingesnis vertinant pagal PANSS bendrą, pozityviųjų balų (rezultatai ypač gerėjo nuo 6 gydymo sav.), CGI-I ir CGI-S balų pokyčius (26 sav. trukmės atsitiktinės atrankos placebo kontroliuojamo dvigubai aklo tyrimo duomenys).

ARIPIPRAZOLIO POVEIKIS KOGNITYVINIAMS PROCESAMS

26 sav. trukmės atviro žymėjimo atsitiktinės atrankos tyrimo metu buvo palygintas aripiprazolio ir olanzapino poveikis kognityviniams procesams [3]. Tirti stabilios būklės pacientai, sergantys šizofrenija/šizoafektiniu sutrikimu. 8-ą sav. abiejose gydymo grupėse nustatytas reikšmingas bendrų pažintinių gebėjimų pagerėjimas. Aripiprazolio grupėje reikšmingai labiau pagerėjo verbalinė atmintis, palyginti su olanzapino grupe (8-ą ir 26-ą sav.).

SAUGUMAS IR TOLERAVIMAS

Klinikinių tyrimų duomenimis, aripiprazolis yra saugus ir gerai toleruojamas tiek ūminių būklių, tiek palaikomojo gydymo periodais [1, 3, 4]. 26 sav. trukmės placebo kontroliuojamo tyrimo duomenimis, aripiprazolio sukeltų šalutinių poveikių dažnumas panašus į placebo sukeltų šalutinių poveikių dažnumą [1, 3]. Aripiprazolis dažniau, palyginti su placebo, sukėlė nemigą, tremorą, pykinimą, vėmimą, akatiziją (≥5 proc. pacientų) [4]. Šio vaisto sukelti nepageidaujami poveikiai nepriklausė nuo pacientų amžiaus, lyties ar rasės, buvo įvairaus sunkumo laipsnio, trumpalaikiai (nyko po pirmos savaitės) [1, 3].

Svorio padidėjimas

Gydant aripiprazoliu svoris nedidėja arba didėja minimaliai [1, 3]. 52 sav. trukmės tyrimo duomenimis, aripiprazolio sukeltų svorio pokyčių vidurkis buvo panašus į haloperidolio. 26 sav. trukmės dvigubai aklo tyrimo duomenimis, kliniškai reikšmingas svorio padidėjimas ir bendras svorio padidėjimas reikšmingai dažniau pasireiškia gydant olanzapinu, palyginti su aripiprazoliu [6]. Be to, pakeitus olanzapiną ar risperidoną aripiprazoliu pastebėta, kad reikšmingai mažėja svoris [3].

Hiperprolaktinemija

Trumpalaikių ir ilgalaikių tyrimų duomenimis, aripiprazolis nedidina prolaktino koncentracijos serume [1, 2, 3, 4, 5]. 5 trumpalaikių (4–6 sav.) dvigubai aklių placebo kontroliuojamų tyrimų metaanalizė nustatė, kad prolaktino koncentracija gydant aripiprazoliu išliko normali [1]. Dar daugiau, nustatyta, kad pacientams, kuriems padidėjusią prolaktino koncentraciją serume (pradžioje) sukėlė anksčiau vartotas APV, prolaktino koncentracijos serume vidurkis normalizavosi 6 sav. laikotarpiu ir 26 sav. laikotarpiu (26 sav. trukmės placebo kontroliuojamo tyrimo metu) išliko normalus. [4].

Ekstrapiramidiniai simptomai

Tiek trumpalaikių, tiek ilgalaikių tyrimų duomenimis, aripiprazolis pasižymi menku polinkiu sukelti EPS [2]. 4 sav. trukmės (lygintas aripiprazolis, haloperidolis su placebo) [1] ir 26 sav. trukmės placebo kontroliuojamo tyrimo duomenimis, aripiprazolio sukeltos EPS paplitimas buvo panašus į placebo [4]. Ilgalaikio (52 sav.) tyrimo metu nustatyta, kad gydant aripiprazoliu gauti reikšmingai geresni Simpson-Angus skalės (angl. *Simpson-Angus Scale* - SAS), Barnes akatizijos vertinimo skalės (angl. *Barnes Akathisia Rating Scale* – BAS), Sutrikusių nevalingų judesių skalės (angl. *Abnormal Involuntary Movement Scale* – AIMS) rezultatai, palyginti su haloperidoliu. Be to, haloperidolio grupėje vienam pacientui nustatyta vėlyvoji diskinezija [2].

Išanalizavus 5 trumpalaikių tyrimų duomenis nustatyta, kad aripiprazolio ir placebo grupėse pastebėtas panašus EPS dažnumas (atitinkamai 21,1 proc., 19,4 proc.), o haloperidolio grupėje – daug didesnis (43,5 proc.) Aripiprazolio grupėje reikšmingai labiau sumažėjo AIMS balai, palyginti su placebo. Abiejose grupėse pastebėti panašūs SAS balų pokyčiai. Aripiprazolio grupėje BAS balų pokyčiai buvo maži ir nepriklausė nuo vaisto dozės. Tuo tarpu haloperidolio grupėje reikšmingai blogėjo SAS, BAS rezultatai, palyginti su placebo [3].



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QTc intervalo pailgėjimas

Trumpalaikių ir ilgalaikių tyrimų metu nustatytas panašus QTc intervalo vidurkio pokytis tiek aripiprazolio, tiek placebo grupėse [3]. Potkin S.G. ir kolegos palygino QTc intervalo pokyčių vidurkius skirdami placebo, aripiprazolio (20 mg/p. ir 30 mg/p.), risperidono (6 mg/p.). Aripiprazolis nedarė įtakos QTc intervalo pailgėjimui [1].

Kiti šalutiniai poveikiai

Nustatyta, kad aripiprazolis pasižymi tik minimaliu sedaciniu poveikiu [1] (dalis autorių teigia, kad tai vienintelis šalutinis poveikis, galbūt susijęs su vaisto doze [3]), nedarė įtakos lipidų apykaitos sutrikimų atsiradimui [1, 3, 4], nesukelia kliniškai reikšmingų gliukozės (nevalgius) koncentracijos pokyčių [3, 4].

BŪDAI, KAIP IŠVENGTI ARIPIPRAZOLIO SUKELTŲ ŠALUTINIŲ POVEIKIŲ

Aripiprazolio šalutiniams (dažniausiai trumpalaikiams) poveikiams gydyti skirti papildomų vaistų tenka retai.

Jei pacientas skundžiasi lengvais virškinamojo trakto sutrikimais, rekomenduojama skirti aripiprazolio po valgio; jei tai neveiksminga, rekomenduojama sumažinti jo dozę. Jei minėti sutrikimai sunkūs, skiriama vaistų nuo vėmimo, pvz., antihistamininių vaistų arba 5-HT₃ antagonistų, nes dopamino antagonistai gali susilpninti aripiprazolio farmakologinį poveikį.

EPS gali išnykti savaime. Jei atsiranda akatizijos požymių, rekomenduojama sumažinti aripiprazolio dozę ar papildomai paskirti beta blokatorių, benzodiazepinų.

Atsiradus nemigai, pvz., pakeitus ankstesnį, pasižymintį sedaciniu poveikiu APV aripiprazoliu, gali atsirasti nemigos simptomų. Tada rekomenduojama aripiprazolio skirti rytais, išaiškinti pacientui miego higienos taisykles. Jei šios priemonės neveiksmingos, papildomai skiriama hipnotikų, benzodiazepinų.

KAŲ REIKTŲ ŽINOTI PRADEDANT GYDYTI ARIPIPRAZOLIU

Rekomenduojama pradinė ir palaikomoji dozė yra 15 mg vieną kartą per dieną, neatsižvelgiant į valgį.

Rekomenduojama pradėti nuo mažesnės dozės pirmas 7 dienas, jeigu:

- pacientai priklauso didesnio jautrumo grupei, pvz., nustatytas pirmas šizofrenijos psichozės epizodas; ilgai gy-

dytas kitu APV; anksčiau blogai toleravo gydymą kitais APV; senyvo amžiaus ir jaunesni nei 18 m. pacientai;

- kai kitas APV keičiamas aripiprazoliu; rekomenduojama 2–6 sav. laikotarpiu ankstesnio APV dozę po truputį mažinti, tuo pat metu aripiprazolio dozę padidinti iki 15 mg/p. APV depo formą keičiant aripiprazoliu, rekomenduojama šio vaisto vartojimą nutraukti, tuo pat metu paskiriant aripiprazolio (15 mg/p.).

Skiriant kartu su kitais vaistais, prisiminti, kad:

- fluoksetinas ar paroksetinas padidina aripiprazolio kiekį kraujyje,
- tarpusavio sąveikos tikimybė su ličiu, valproatais maža, tačiau karbamazepinas sumažina aripiprazolio kiekį kraujyje,
- aripiprazolis gali sustiprinti antihipertenzinių vaistų poveikį, nes pasižymi α_1 adrenerginiu antagonizmu.

Kartu su kitu APV rekomenduojama skirti tik vaistų keitimo laikotarpiu.

Aripiprazoliui būdingas daugiau raminamasis, o ne sedacinis poveikis, todėl psichomotoriškai sujaudintiems pacientams rekomenduojama papildomai skirti benzodiazepinų.

Aripiprazolio skilimo pusperiodis ilgas, todėl nutraukimo sindromas neišsivysto.

IŠVADOS

Aripiprazolis (15 mg/p., 20 mg/p. ir 30 mg/p.) yra:

- Veiksmingesnis už placebo ir yra panašaus veiksmingumo, kaip kiti APV (tiek tipiniai, tiek atipiniai), gydant pacientus, sergančius šizofrenija/šizoafektiniu sutrikimu (stabilios būsenos ar ūminių atkryčių periodais). Reikšmingai palengvėja pozityvieji, negatyvieji, kognityviniai simptomai.
- Ūminio atkryčio periodu aripiprazolis veikia greitai.
- Šis APV yra saugus ir gerai toleruojamas (ūminių būsenų ar palaikomojo gydymo laikotarpiais). Šio vaisto sukelti šalutiniai poveikiai nepriklauso nuo pacientų amžiaus, lyties ar rasės, būna įvairaus sunkumo laipsnio, trumpalaikiai (nyksta po pirmos savaitės). Jų dažnumas panašus į sukeltų placebo.
- Šis vaistas minimaliai didina svorį, retai sukelia sedaciją, EPS, nesukelia QTc intervalo pailgėjimo, hiperprolaktinemijos, gliukozės, lipidų koncentracijos pokyčių.
- Unikalus aripiprazolio veikimo mechanizmas nulemia jo ilgalaikį veiksmingumą, saugumą ir gerą toleravimą.

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