Posters

Incorporation of [^{3}H]uridine and [^{3}H]glycine in the brain of rats prenatally exposure to cadmium

Dariusz Boroń[1,2], Janusz Konecki[2], Ryszard Brus[1]

[1]Department of Nursy, High School of Strategic Planning, Kościelna 6, PL 41-303 Dąbrowa Górnicza, Poland;
[2]Department of Histology and Embriology, Medical University of Silesia, Jordana 19, PL 41-808 Zabrze, Poland

Numerous studies have demonstrated that exposure of mammalians, including humans to inorganic cadmium, result in a cascade of toxic effects. The developing mammalian brain is particularly more sensitive to cadmium then the adult brain, being affected both morphologically and neurochemically. Uridine is a precursor of RNA, and the intensity of its incorporation in tissue represents the rate of RNA and protein synthesis. Glicine is an important aminoacid, an element of many proteins and enzymes in mammalian organism. On the first day of pregnancy, Wistar rats were divided into two groups. First, control consumed filtred tap water while other half consumed filtred tap water with 50 ppm cadmium ($CdCH_3COO_2$). At eight weeks after birth both groups were injected with [^{3}H]uridine (incorporated to RNA) or [^{3}H]glycine (incorporated to protein) 1 μCi/kg IP. Four hours later rats were sacrificed by decapitation and parts of the brain were excised and examined for radioactivity in liquid scintillation counter. Results were presented as a disintegration per minute (DPM)/100 mg wet tissue weight, which expressed labeled substances incorporation. Prenatal exposure with cadmium significantly decreased [^{3}H]uridine incorporation in all examined parts of the brain (frontal cortex, striatum, thalamus with hypothalamus, pons, hippocampus, cerebellum). Neonatal exposure rats to cadmium decreased incorporation of the [^{3}H]glycine in frontal cortex, thalamus with hypothalamus, pons and cerebellum. From above we concluded and confirmed that prenatal exposure with cadmium exert a toxic effect on RNA and proteins synthesis in the brain of developing rats.

The effect of chronic pregnancy stress on depression-related behavior and immune parameters: implications for imipramine reactivity

Katarzyna Curzytek[1], Weronika Duda[1], Marta Kubera[1], Agnieszka Basta-Kaim[1], Bogusława Budziszewska[1], Monika Leśkiewicz[1], Beata Gygier[1], Anna Kurek[1], Ewa Szczęsny[1], Jan Detka[1], Wojciech Nowak[2], Michael Maes[3], Władysław Lasoń[1]

[1]Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland; [2]Department of Anatomy, Jagiellonian University, Medical College, Kopernika 12, PL 31-034 Kraków, Poland; [3]Maes Clinic & TRIA, Piyavate Hospital, 998 Rimklongsamsen Road, Bangkok 10310, Thailand

Basic research on the consequences of the chronic stress in the pregnancy for the mother is lacking in contrast to the effect of stress on the offspring. This is due to a lack of appropriate animal models for studying postpartum mood and anxiety disorders, but also reflects the general lack of research assessing the effect of chronic stress in females. Chronic stress in pregnancy may prevent behavioral, neuroendocrine, immune and neuronal adaptations specific to the reproductive status of the female and can induce long lasting behavioral and immuno-endocrine changes although this subject has not been studied yet. Therefore we aimed to characterize the long-lasting effect of chronic stress during pregnancy on depression related behavior and some immune parameters. In the last week of pregnancy stressed dams were exposed to daily restrained stress (3 × 1 h at least 3 h apart during light phase). Pregnancy stress had no effect on pup litter size or birth weight. Depression-related behavior were examined four months after delivery in Porsolt test. There were increased in immobility and decrease in climbing in group of stressed females in comparison to non-stressed group. Chronic imipramine-treatment (21-day, 10 mg/kg, *ip*) attenuated depressive behavior in chronically stressed females. Chronic imipramine treatment increased climbing with a concurrent decrease in immobility in the non-stressed dames compared with equivalent vehicle-treated group. Stressed imipramine treated animals climbed twice less and were immobile 40 % more than non stressed imipramine group. Depression related behavior was altered between vehicle-treated non-stressed and stressed females, suggesting that pregnancy stress induce long-lasting depressive-like phenotype connected with decrease in the relative thymus weight and metabolic activity of splenocytes. Imipramine reduced the passive behavior in the stressed and non-stressed females but inhibit metabolic activity of splenocytes and reduced the relative thymus weight. This studies showed that chronic pregnancy stress significantly changed reactivity to imipramine probably via down regulation of responsiveness to noradrenergic stimulation in brain but not in immune system.

Acknowledgment:
This work was supported by grant POIG.01.01.02-12-004/09-00.

Abuse of psychoactive substances by school youngsters; questionnaire study

Bożena Gierdysz-Czoków, Dariusz Boroń, Ryszard Brus

Department of Nursing, High School of Strategic Planning, Kościelna 6, PL 41-303 Dąbrowa Górnicza, Poland

Many psychoactive substances acting on the central nervous system (CNS) have profound effects on emotion, mood and behavior, and are sometimes used for nontherapeutic reasons. This illicit use, termed substance abuse, often occurs with drugs categorized as stimulants (including nicotine in cigarettes), depres-

sants, opioids, and hallucinogens. Regular and prolonged use leads to addiction. Youngsters are a special at-risk group. The described study was performed on 127 male high school students, ages 16 to 20 years. All obtained the questionnaire with many questions concerning the type of substances with which they were in contact (e.g., alcohol, tobacco, marijuana, organic solvents, amphetamine, hallucinogens and others), as well as circumstances of contact and frequency of use. Results, anonymous, indicate that 81 students (64%) had contact with one or more of the above substances, mainly with alcohol (63%), tobacco (22%), but including others (40%). Respondents presented reasons and place of contact with mentioned substances (curiosity, party event, peer-pressure by colleagues, company, relaxation, etc.). Alarmingly, 12% designated the school as a place of first contact with psychoactive substances. All examined youngsters declared that contact with the above substances was sporadic or single use.

Alterations in number and functions of lymphocytes after exposure to chronic mild stress: the effect of desipramine

Beata Grygier[1], Marta Kubera[1], Danuta Wrona[2], Piotr Gruca[3], Władysław Lasoń[1,4]

[1]Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland; [2]Department of Animal Physiology, University of Gdańsk, Kładki 24, PL 80-822 Gdańsk, Poland; [3]Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland; [4]Department of Drug Management, Institute of Public Health, Jagiellonian University, Medical College, Grzegórzecka 20, PL 31-531 Kraków, Poland

The relationships between stress, anxiety, depression and the immune system has been studied in recent years extremely carefully. Nevertheless, the impact of antidepressants on immune function in aspect of diverse behavioral characteristics is still poorly recognized.

Our aim was to:

• study the changes in lymphocyte profile and NK cells cytotoxicity in Wistar rats subjected to chronic mild stress (CMS),

• establish the effect of desipramine on these parameters.

After exposure to CMS and sucrose preference test stress-highly-sensitive and stress-non-reactive rats were selected. The quantity of circulating and splenic lymphocytes (T, B, $TCD4^+$, $TCD8^+$) and NK cells as well as NK cytotoxicity was determined before and 24h after single or repeated desipramine (10 mg/kg, ip) administration.

The main observations were:

• stress-highly-sensitive rats revealing a strongly decreased sucrose intake, showed an increased immobility time in the forced swimming test;

• stress-highly-sensitive rats displayed significantly lower number of T, B, $TCD4^+$ and $TCD8^+$ cells and decreased NK cytotoxicity;

• single desipramine dose diminished the number of B, $TCD4^+$ and $TCD8^+$ cells in stress-resistant rats but increased NK cells number in stress-highly-sensitive animals;

• two weeks desipramine administration impaired NK cytotoxicity and lymphocytes quantity in stress-resistant animals but increased B and NK cells number and NK cytotoxicity in stress-highly-sensitive animals.

To sum up, rats particularly sensitive to stress reveal dysregulation of lymphocytes subpopulations. These changes may be induced by stress per se, but we cannot exclude the possibility that impaired immune function is a kind of treat-marker of hypersensitivity to stress. Under certain conditions, desipramine possesses the capacity to enhance or disturb cell mediated immunity. Identification of specific cellular and molecular mediators responsible for such desipramine effects represents important areas for further studies.

Effect of co-administration with fluoxetine and risperidone in the forced swimming test and on the extracellular level of dopamine, serotonin and noradrenaline in rat frontal cortex

Katarzyna Kamińska, Anna Górska, Krystyna Gołembiowska, Zofia Rogóż

Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

A few clinical reports have suggested that a combination of a low dose of atypical antipsychotic drug, e.g. risperodone (RIS) and antidepressants (ADs), especially selective serotonin reuptake inhibitors, has a beneficial effect in the treatment of drug-resistant depression. RIS whose low doses block mainly 5-HT_{2A} serotonin receptors and higher ones dopamine D_2 receptors, is known to produce minimal extrapyramidal side-effects compared to classical antipsychotics. To understand the mechanism of the clinical efficacy of a combination of an AD and RIS in drug-resistant depression, we studied the effect of fluoxetine (FLU) and RIS, given separately or jointly, in the forced swimming test (an animal test of depression), as well as on the extracellular levels of dopamine (DA), serotonin (5-HT) and noradrenaline (NA) in rat frontal cortex using a microdialysis in freely moving animals. The levels of monoamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindole acid (5-HIAA) were measured in rat dialysates by HPLC with electrochemical detection. Co-treatment with RIS (0.05 and 0.1 mg/kg) and FLU (10 mg/kg), decreased immobility time in the forced swimming test, but those drugs given separately showed no such effect. RIS (0.1 and 1 mg/kg) increased the extracellular levels of DA, DOPAC and HVA. The increase in DA extracellular level induced by FLU was weaker than that evoked by either dose of RIS. A combination of FLU and the higher dose of RIS produced a stronger effect on the extracellular levels of DA, DOPAC and HVA than did those drugs given separately. Both those drugs elevated the extracellular levels of 5-HT and NA, but the effect of co-treatment with RIS and FLU was not stronger than that after their separate administration. The above findings suggest that the effect of combined administration of RIS and FLU on DA cortical release may be of crucial importance to the pharmacotherapy of drug-resistant depression.

Acknowledgment:
This study was financially supported by grant POIG.
01.01.02-12-004/09-00 from European Regional Development Fund.

Metformin has adenosine-monophosphate activated protein kinase (AMPK)-independent effects on rat primary microglial cultures

Daniela Kasprowska[1], Bożena Gabryel[1], Alicja Kost[1], Krzysztof Łabuzek[2]

[1]Department of Pharmacology, [2]Department of Clinical Pharmacology, Medical University of Silesia, Medyków 18, PL 40-752 Katowice, Poland

The results of recent studies suggest that metformin, in addition to its efficacy in treating type 2 diabetes, may also have therapeutic potential for the treatment of neuroinflammatory diseases in which reactive microglia play an essential role. However, the molecular mechanisms by which metformin exerts its anti-inflammatory effects remain largely unknown. Adenosine-monophosphate-activated protein kinase (AMPK) activation is the most well-known mechanism of metformin action; however, some of the biological re-

sponses to metformin are not limited to AMPK activation but are mediated by AMPK-independent mechanisms. For this reason, we attempted to evaluate the effects of metformin on unstimulated and LPS-activated rat primary microglial cell cultures. Our evidence supports the conclusion that metformin-activated AMPK participates in regulating the release of TNF-α. Furthermore, the effects of metformin on the release of IL-1β, IL-6, IL-10, TGF-β, NO, and ROS as well as on the expression of arginase I, iNOS, NF-κB p65 and PGC-1α were not AMPK-dependent, because pretreatment of LPS-activated microglia with compound C, a pharmacological inhibitor of AMPK, did not reverse the effect of metformin. Based on the present findings, we propose that the shift of microglia toward alternative activation may underlie the beneficial effects of metformin observed in animal models of neurological disorders.

Acknowledgments.
The work was supported by grant No NN 401 072139 from the State Committee for Scientific Research.

Influence of *mGluR7* gene knockout and behavioral changes which its causes on male mice fertility

Tomasz Lech[1], Andrzej Pilc[1,2]

[1]Department of Neurobiology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland;
[2]Faculty of Health Sciences, Jagiellonian University, Medical College, Grzegórzecka 20, PL 31-531 Kraków, Poland

Background: Metabotropic glutamate receptor 7 (mGluR7) belongs to third group of metabotropic glutamate receptors (mGlu) together with receptors mGlu4, 6 and 8. A recent study suggests that the glutamatergic system may be a relevant therapeutic target for such disorders like stress or depression. Various dates described that mGluR7 is expressed in brain and its function is implicated in emotional learning, working memory and behavioral connecting with fear.

Aim: Our studies are designed to see how mGluR7 gene knockout and behavioral changes which it causes affect fertility in male mice.

Methods: For this purpose, we focused on checking the six main sperm parameters: sperm count, motility, viability (eosin test), maturity, sperm head morphology and cytoplasmic membrane integrity of sperm tail. Analysis of these parameters was performed in two groups of male mice from a strain of C57BL: mGluR7 (+/+) and mGluR7 (–/–) and the parameters are tested at a standard assessment of human semen.

Conclusions: During breeding our mice with mGluR7 gene knockout, we found that these animals are more susceptible to stress, and their behavior manifests anhedonia. An important observation is that these animals have reduced fertility.

Acknowledgment:
This study is supported by the Ministry of Science and Higher Education [Grant N405 055737] (to A.P.).

Chlorpromazine and clozapine affect glucose uptake and glucose transporter GLUT3 expression in the human neuroblastoma SH-SY5Y cell line

Monika Leśkiewicz[1], Agnieszka Basta-Kaim[1], Joanna Kaczanowska[1], Magdalena Regulska[1], Bogusława Budziszewska[1], Marta Kubera[1], Joanna Ślusarczyk[1], Ewa Szczęsny[1], Barbara Korzeniak[1], Wojciech Nowak[2], Władysław Lasoń[1]

[1]Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland; [2]Department of General Surgery, Faculty of Medicine, Collegium Medicum, Jagiellonian University, Prądnicka 37, PL 31-202 Kraków, Poland

Glucose is the main energy source in the brain cells. Its transport is an important regulatory step in glucose metabolism. Glucose is transported into cells by facilitated diffusion mediated by the family of glucose transporters, e.g. a neuron-specific transporter GLUT3. Modifications in the glucose metabolism may have an impact on the brain function and pathogenesis of some psychiatric disorders. Furthermore, some antipsychotic drugs contribute to changes in glucose metabolism. However, only limited attention has been devoted to the mechanisms of such their action and metabolic disturbances that may be caused by them. In the present study, we focused on the effect of two antipsychotic drugs: typical – chlorpromazine and atypical – clozapine on the glucose uptake and GLUT 3 transporter expression. Chlorpromazine or clozapine was added to the cultured cells for 24 hours. Briefly, cells were incubated in glucose free medium in the absence or presence of cytochalasin B (to account for non-specific background by blocking transport of glucose) for 30 min. ^{3}H-2- deoxyglucose was then added to the culture and the uptake was measured 5 min later. Radioactivity was estimated in a scintillation counter and the results were calculated as the percentage inhibition of uptake when compared to the control. The expression of GLUT3 was evaluated by ELISA method. Chlorpromazine and clozapine in a dose-dependent way altered glucose uptake into SH-SY5Y cells. However, exposure of the cells to the drugs for 24 h did not change the expression of GLUT3.

In summary, the inhibition of glucose accumulation by chlorpromazine and clozapine creates a state of relative glucose deprivation in the human neuroblastoma cells. In addition our observations may help to explain some of their therapeutic actions as well as some of their side effects.

Inflammation and activation of cell-mediated immunity in chronic fatigue syndrome

Michael Maes[1], Frank N. M. Twisk[2], Marta Kubera[3], Karl Ringel[4], Jean-Claude Leunis[5], Michel Geffard[6], Barbara Korzeniak[3], Katarzyna Curzytek[3], Weronika Duda[3], Agnieszka Basta-Kaim[3], Bogusława Budziszewska[3], Monika Leśkiewicz[3], Beata Grygier[3], Władysław Lasoń[3]

[1]Maes Clinic & TRIA, Piyavate Hospital, 998 Rimklongsamsen Road, Bangkok 10310, Thailand; [2]ME-de-patiënten Foundation, Zonnedauw 15, 1906 HB Limmen, Nederland; [3]Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland; [4]Immunologische Laboratorien, Beeckstr. 40, 52062 Aachen, Germany; [5]Laboratoire Ategis, Avenue des Mésanges 18, 1300 Wavre, Belgium; [6]Association Institute for Research & Development in Human Pathology and Therapy, 200 Avenue de Thouars, 33400 Talence, France

There is evidence that Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is accompanied by inflammation, activation of cell mediated immunity (CMI) and increased IgA and IgM responses against lipopolysaccharides (LPS) of intestinal commensal bacteria. Inflammation is indicated among others by an increased levels of pro-inflammatory cytokines, including interleukin (IL-1)α, IL-1β, IL-6, IL-8 and tumor necrosis factor (TNF)α; increased IgM responses against a number of neoepitopes formed by oxidative and nitrosative stress; and increased serum elastase, a neutrophil-derived protease that cleaves the outer membrane of gram negative bacteria, elastin, immunoglobulines, cytokines, etc. Activation of CMI in ME/CFS is indicated among others by increased serum neopterin, which indicates activation of interferon (IFN)γ-induced pathways; higher IL-12 levels, and increased expression of activation markers, such as CD38+ and HLA-DR+ . ME/CFS is also accompanied by increased prevalences and median values for plasma IgA and IgM against the LPS of commensal bacteria. These results indicate an increased translocation of gram negative commensal bacteria subsequent to a weakening of the intestinalmucosal or tight junction barrier (leaky gut) in ME/CFS. This allows otherwise poorly invasive bacteria to exploit lipid raft-mediated transcytotic pathways to cross the intestinal mucosa. This mechanism allows LPS, a component of the outer membrane of gram-negative bacteria, to be translocated from the gut to the interstitium and the mesenteric lymph nodes and eventually the blood. The aims of the present study are to examine the relationships between bacterial translocation, inflammation, CMI activation and ME/CFS symptoms in patients with ME/CFS, based upon the working hypothesis that bacterial translocation may cause systemic inflammation and CMI activation and that these three factors may be associated with the onset of fatigue and somatic (F&S) symptoms. Therefore, we examine whether F&S symptoms, such as fatigue, sadness, a flu-like malaise, autonomic symptoms, muscle pain, gastro-intestinal symptoms, etc., are positively correlated to IgA/IgM responses to LPS, IL-1, TNFα, elastase and/or neopterin circulating levels. In present study patients with an abnormally high IgA response show increased serum IL-1, TNFα and neopterin levels, and higher ratings on irritable bowel syndrome (IBS) than subjects with a normal IgA response. Serum IL-1, TNFα and neopterin are significantly related to fatigue, a flu-like malaise, autonomic symptoms, neurocognitive disorders, sadness and irritability. It is concluded that increased translocation of commensal bacteria may be responsible for the disease activity in some ME/CFS patients.

Identification and characterization of new 5-HT_7 receptor inverse agonists

Marcin Marciniak[1], Grzegorz Burnat[1], Piotr Brański[1], Andrzej Pilc[1,2]

[1]Department of Neurobiology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland; [2]Faculty of Health Sciences, Jagiellonian University, Medical College, Grzegórzecka 20, PL 31-531 Kraków, Poland

Background: The 5-HT_7 receptor is a seven-transmembrane-domain G-protein-coupled receptor that is positively linked to adenylyl cyclase. It was found by the application of molecular cloning and has been identified in rat, mouse, human, pig and guinea pig. 5-HT_7 receptors have been localized in brain limbic and cortical areas. Although the biological functions of the 5-HT_7 receptors are poorly understood, preliminary evidence suggests that it may be involved in thermoregulation, circadian rhythm, learning and memory, hippocampal signaling, sleep and endocrine regulation. For these reasons, the 5-HT_7 receptors have become a target for the development of novel drugs.

Aim: Identification novel chemical scaffold possessing 5-HT_7 antagonistic activity.

Methods: The screening study and activity of potential 5-HT antagonists was determined using cAMP production in the presence of 5-carboxytryptamine, in a HEK-293 cell line stably expressing 5-HT_7 receptor protein. The direct quantitative determination of cyclic AMP was based on homogeneous time-resolved fluorescence (HTRF) technology. Tested compound was added to the 96 – well plate containing cells suspended in the HHB buffer. After 5 min incubation in 37°C 2000 cells were transferred to the white opaque 384 – well plate containing 5 ul per well of labeled d2 cAMP in lysis buffer and then 5 ul per well of anti-cAMP antibody, were added to each well using of Evo 2000 liquid handling system (Tecan, Warszawa, Poland). After 1 h incubation in room temperature plates were measured using the Infinitive M1000 (Tecan, Warszawa, Poland) with excitation at 350 nm and emission of 620 and 655 nm. Data was calculated as a 655/620 nm ratio.

Results: Via in vitro screening of compound collection we have identified chemical scaffold possessing 5-HT_7 receptor potential antagonistic activity with inverse agonist properties.

Acknowledgments:
This study is supported by project POIG.01.01.02-12-004/09 co-financed by European Union from the European Fund of Regional Development (EFRD).

Influence of sildenafil on the anticonvulsant effect of vigabatrin and gabapentin in the timed pentylenetetrazole infusion test in mice

Dorota Nieoczym[1], Katarzyna Socała[1], Jarogniew J. Łuszczki[2,3], Stanisław J. Czuczwar[2,4], Piotr Wlaź[1]

[1]Department of Animal Physiology, Institute of Biology and Biochemistry, Maria Curie-Skłodowska University, Akademicka 19, PL 20-033 Lublin, Poland; [2]Department of Pathophysiology, Medical University of Lublin, Jaczewskiego 8, PL 20-090 Lublin, Poland; [3]Isobolographic Analysis Laboratory, Institute of Rural Health, Jaczewskiego 2, PL 20-950 Lublin, Poland; [4]Department of Physiopathology, Institute of Rural Health, Jaczewskiego 2, PL 20-090 Lublin, Poland

Sildenafil, a selective phosphodiesterase 5 (PDE5) inhibitor, is used in the treatment of erectile dysfunctions. Animal studies have revealed that sildenafil displays both pro- and anticonvulsant effects [Nieoczym et al., Pharmacol Rep, 2010]. Furthermore, sildenafil affects activity of some antiepileptic drugs in experi-

mental models of seizures [Nieoczym et al., Pharmacol Rep, 2010; Nieoczym et al., Epilepsia, 2010; Nieoczym et al., J Neural Transm, 2012].

We investigated the influence of sildenafil on the anticonvulsant activity of gabapentin (GBP) and vigabatrin (VGB) in the intravenous (iv) pentylenetetrazole (PTZ) test in mice. Our results revealed that GBP increased the threshold for forelimb tonic extension in this test. Moreover, co-administration of GBP at a sub-effective dose of 12.5 mg/kg with sildenafil at doses of 10 and 20 mg/kg significantly raised the threshold for tonic convulsions in mice. The anticonvulsant properties of VGB in the iv PTZ test were noted in case of myoclonic and generalized clonic seizures. Co-administration of VGB at a sub-effective dose of 200 mg/kg with sildenafil (5 mg/kg) caused significant increases in thresholds for myoclonic and generalized clonic seizures in mice. Sildenafil did not significantly change plasma and brain concentrations of the studied antiepileptic drugs in mice.

The results from this study indicate that sildenafil enhances the anticonvulsant action of GBP and VGB in the PTZ iv test in mice. Moreover, the interactions between GBP, VGB and sildenafil are pharmacodynamic in nature. It seems that co-administration of sildenafil with GBP or VGB in male epileptic patients with co-existing erectile dysfunctions may be beneficial and worthy of consideration from a preclinical point of view.

Potential antidepressant and anxiolytic properties of new phenylpiperazine derivaties

Karolina Pytka[1], Jacek Sapa[1], Barbara Filipek[1], Anna Partyka[2], Magdalena Jastrzębska-Więsek[2], Anna Wesołowska[2]

[1]Department of Pharmacodynamics, [2]Department of Clinical Pharmacy, Jagiellonian University Medical College, Medyczna 9, PL 30-688 Kraków, Poland

More and more cases of depression, as well as limited efficacy and numerous side effects of drugs used in the treatment of this disease are the reason for searching new chemical structures as potential antidepressants. The discovery that some phenylpiperazine deriatives can act within the CNS and may posses dopaminergic, serotoninergic, adrenergic properties was significant. As a continuation of studies on developing new drugs acting within the CNS, potential antidepressant and anxiolytic activity of three phenylpiperazine derivatives: HBK-10, HBK-14 and HBK-15 was investigated.

All three tested compounds showed statistically significant activity in forced swimming test (FST) and the effect was stronger than the effect of reference drugs: imipramine and escitalopram. Radioligand binding studies showed high affinity of tested compounds for serotoninergic 5-HT_{1A} (K_i = 6.9 – 23.6 nM) and adrenergic α_1 receptors (K_i = 13.1 – 22.8 nM). To evaluate whether the activity of tested compounds in FST was associated with agonism for 5-HT_{1A} receptor, FST was performed in the presence of WAY100635 (antagonist for 5-HT_{1A} receptor). None of the compounds showed activity in FST in the presence of WAY100635. Moreover, two of the studied compounds: HBK-14 and HBK-15 showed statistically significant activity in four plate test and plus maze test, which can indicate their potential anxiolytic properties. Furthermore, none of the tested compounds affected ECG in rats at the highest dose active in FST and the compound HBK-15 did not lower blood pressure at the doses 1.25 and 2.5 mg/kg. The results of this preliminary study fully justify taking further experiments for these structures to determine their full pharmacological profile.

Acute changes in values of serum high-sensitive C-reactive protein levels during switching of antipsychotics to aripiprazole in patients with schizophrenia

Jarosław Sobiś, Piotr Gorczyca

Department of Psychiatry, Medical Faculty in Zabrze of the Medical University of Silesia in Katowice, Pyskowicka 49, PL 42-600 Tarnowskie Góry, Poland

Schizophrenia is associated with approximately 20% reduced life expectancy and the mortality rate from coronary heart disease is significantly higher compared to the general population. The main risk factor for this higher rate of mortality are impaired glucose regulation/insulin resistance, dyslipidemia, obesity, and hypertension, which collectively constitute "metabolic syndrome". Most studies reporting an elevated prevalence of metabolic abnormalities in schizophrenics since the increase in the use of second-generation antipsychotics.

C-reactive protein – inflammatory marker is stable for potential use in the long-term prediction of coronary heart disease. CRP is synthesized and secreted mainly by hepatocytes in response to cytokines such as interleukin-6, interleukin-1 and tumor necrosis factor-alpha.

Very little is know about the effects of psychotropic agents (antipsychotics in particular) on CRP levels. It has been suggested that atypical antipsychotics via obesitogenic capacity interact with complex system of adipose tissue-derived cytokines, cause the liver to increase production of acute phase reactants.

Based on clinical observations, reducing the burden of cardiovascular diseases during long-term antipsychotic therapy, aripiprazole could be ideal candidate for switching.

The impact of lipopolysaccharide on the IGF-1 expression in frontal cortex in an animal model of depression

Ewa Szczęsny[1], Joanna Ślusarczyk[1], Agnieszka Basta-Kaim [1], Agnieszka Zelek-Molik[2], Katarzyna Rafa-Zabłocka[2], Katarzyna Głombik[1], Monika Leśkiewicz[1], Bogusława Budziszewska[1], Marta Kubera[1], Irena Nalepa[2], Władysław Lasoń[1]

[1]Department of Experimental Neuroendocrinology, [2]Department of Brain Biochemistry, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Changes in the pro-inflammatory cytokine levels and increased glucocorticoid action may be connected with disturbances observed in depression, especially in the central nervous system.

Additionally, it has been found that the weaker activity of growth factors, e.g. insulin-like growth factor (IGF) plays a key role in pathogenesis of depression. Proinflammatory cytokines and glucocorticoids are the main factors suppressing IGF expression in the periphery.

The goal of the present study was to find out if in the animal model of depression there are changes in IGF-1 levels in the frontal cortex after peripheral lipopolysaccharide (LPS) administration.

Pregnant Sprague-Dawley rats were subjected daily to 3 stress sessions from day 14 of pregnancy until delivery. At 3 months of age the control and prenatally stressed males were tested for behavioral changes in the Porsolt test and elevated plus-maze test. After that the animals were divided into 4 groups: control, control +LPS, prenatally stressed, prenatally stressed +LPS. LPS was injected once ip and four hours later rats were killed by rapid decapita-

tion. The frontal cortexes were dissected out and stored at –80°C for ELISA study, or immediately placed in the RNA later solution and stored at 4°C prior to total RNA extraction. The expression of mRNA was measured by two-step real-time quantitative RT-PCR assay.

In our study prenatally stressed rats shown increased immobility time and decreased climbing behavior in the Porsolt test. Moreover, ELISA study showed that the level of IGF-1 in the frontal cortex of prenatally stressed animals was diminished. Acute LPS ip administration enhanced supresson of IGF-1 level and IGF-1 mRNA expression in the frontal cortex of stressed and control animals.

In summary, an appropriate balance between the immune and IGF systems is requisite for normal development and behavior.

Acknowledgments:
This work was supported by the Operating Program of Innovative Economy 2007–2013, grant No. POIG.01.01.02-12-004/09.

Indole-like heterocyclic compounds as a new core structure in search of potential allosteric modulators of group III metabotropic glutamate receptors

Marcin Trela[1]*, Piotr Brański[2], Andrzej J. Bojarski[1]

[1]Department of Medicinal Chemistry, [2]Department of Neurobiology, Institute of Pharmacology Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland; *e-mail: trela@if-pan.krakow.pl

Allosteric modulation of metabotropic glutamate receptors is new and attractive approach in research of GPCR targets. The third group of mGluRs (subtypes: 4, 7 and 8) are especially promising, however, they were significantly less studied due to insufficient amount of known modulators so far. Main advantages of allosteric mechanism, over traditional orthosteric agonists/antagonists, is that they exert their effects only in the presence of the endogenous ligand, and provides the possibility for more selective interaction with different subtypes of mGluR family. Moreover, the probability of receptor desensitization can be reduced, that gives hope for the development of new, safer treatments for central nervous system diseases [Williams et al., Bioorg Med Chem Lett, 2009].

The first step of the research was to create the compounds database with confirmed allosteric activity toward group III mGluR (more than 650 compounds) and grouping them into clusters of similar structure. A new derivatives of heterocyclic systems were designed based on the pattern of one group from the cluster. Indole, azaindole, indazole and other heterocyclic rings used as the central core were combined with appropriately substituted benzoyl and arylsulfonyl moieties. Pharmacophore models were developed from the known active ligands and mapping was performed for all proposed structures. The compounds of the best match were synthesized and then tested for the activity towards mGluR group III.

Acknowledgments:
This study is supported by project UDA-POIG.01.03.010-12-100/08-00 co-financed by European Union from the European Fund of Regional Development (EFRD). http://www.modall.pl

Dose-finding studies of orally-administered DHEA on the pain threshold. Attempt to explain its antinociceptive effect

Emilia Trzaska, Magdalena Bujalska-Zadrożny, Helena Makulska-Nowak

Department of Pharmacodynamics, Medical University of Warsaw, Krakowskie Przedmieście 26/28, PL 00-927Warszawa, Poland

Dehydroepiandrosteron (DHEA) plays an important role as a hormone and a neurosteroid. It is known that DHEA modulates pain mechanisms. It was shown that acute administration of DHEA to rats causes a rapid pro-nociceptive effect, whereas chronic treatment with this neurosteroid results in the antinociceptive effect. The aim of this study was to select the best dose of DHEA on pain nociception in rats after chronic oral administration. Furthermore, we tried to explain the mechanism of this antinociceptive effect. Male Sprague Dawley rats were given 1, 3, 10 and 30 mg/kg DHEA per os once daily for 14 days. Pain threshold was determined by modified method of Randal-Sellito (mechanical stimuli). After choosing the best dose of DHEA the next group of rats was given DHEA for 7 days and subsequently injected intraperitoneally with naloxone at a dose of 10 mg/kg. The pain threshold measurements were done after 15, 30, 45, 60, 75, 90, 105 and 120 min. Each dose of DHEA tested displayed an anti-nociceptive effect on pain threshold in rats, but after 1 and 3 mg/kg the changes not always were statistically significant during the whole period of observation. The best dose for increasing the pain threshold was 10 mg/kg, the effect was statistically significant (*vs*. control group) during 14 days of administration. The dose of 30 mg/kg did not show any meaningful differences *vs*. the dose of 10 mg/kg, the effect was unstable and the rats were much more aggressive than after lower doses. Concomitant administration of DHEA and naloxone completely abolished the antinociceptive effect of DHEA. In conclusion, the best dose of DHEA for increasing the pain threshold in rats is 10 mg/kg. The possible mechanism of this effect is activation of the opioidergic system in the central nervous system.