PREVENTIVE AND THERAPEUTICAL ANTIULCER EFFECTS OF MINERAL MUD DEPOSITS WATER ON STOMACH IN WHITE RATS

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In a modern society, especially at the end of the XX century, a big growth of socially-significant diseases - neurosises, ulcer diseases of a gastroenteric tract and other neurotic reactions are marked. In this connection, preventive and protective search the means directed on mitigation of negative consequences stress - reactions are rather actual. Peloid - and rapatherapeutic are is used for treatment of digestive system of diseases, including stomach ulcer. In medical muds of lake Big Yashalta biologically active substances, defining therapeutic value, penetrating into an organism are included. During pelotherapeutic effective regulative influence on all parts of a homeostasis is made. The purpose of the work was to study preventive antiulcer effect of brine of this lake on stress model of ulcer formation in white rats. Stress was caused by swimming in cold water (t=20° C) for 3 hours. Preliminary animal experimental group received in the form of drink diluted brine (1:75), and the control group - usual water. It was revealed, that preliminary watering of animals, the experimental group by diluted brine considerably reduced the degree of the ulcer formation up to 70 % (the control, n=20; experiment, n=18) ($p < 0,05$)). It is possible to assume, that under influence of brine there is an increase of stability of a mucous membrane of a stomach to damaging factors due to action of specific components entering into their composition (mineral or organic) which probably stabilize the mechanisms regulating a blood-current in stomach, raising its stability to action of aggressive factors.

CYTOTOPOGRAPHY OF LECTIN RECEPTORS IN THE LIVER OF RAT IN STREPTOZOTOCIN-INDUCED DIABETES MELLITUS

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Key pathogenetic mechanisms of diabetes mellitus (DM) are disorders of the synthesis and metabolism of carbohydrates and carbohydrate-containing biopolymers. Analysis of available literature has shown that, even though liver affections play a significant role in the pathogenesis and clinical picture of DM, there are but a few research works concerned with liver investigations by the conventional morphological methods, and there are no publications on the employment of lectin histochemistry (LHC) for this purpose. The aim was investigation of cytomorphology of lectin receptors in the rats liver in experimental streptozotocin-induced DM with the use panel of 8 lectins: Con A (αDMan, αDGlc), PNA (βDGal), RCA (βDGal > βDGalNAc), SBA (DGalNAc), HPA (αDGalNAc), WGA (DGlcNAc >NeuNAc), SNA (Neu5Ac(α2-6)Gal/GalNAc), LABA (αLFuc). Staining by hematoxylin and eosin showed that development of DM is associated with lymphocyte infiltrations of hepatic lobules and portal ducts, and dilatation of sinusoidal hemocapillaries and central veins. LHC permitted to reveal modifications of carbohydrate determinants of the endotheliocytes of sinusouidal hemocapillaries, central veins of hepatic lobules and vessels of portal ducts which might reflect altered permeability of the vessels and adhesive properties of endothelium in DM. There were identified reduction

of Con A receptors and lectin LABA in the cytoplasm of centrally localized hepatocytes and their aggregations in the hepatocytes of lobular periphery that may be evidence of alterations in the synthesis and distribution of glycogen inclusions. Were noticed aggregations of the receptors of PNA, SBA and SNA in the cytoplasm of Kupffer's cells that are likely to be a sign of the activation of these cells with a change of final stages of glycosylation and modification of carbohydrate determinants in the synthesized biopolymers. These studies suggest that LHC liver is an interesting methol for future investigation for potential use in human liver diseases.

ACTION OF GLUCOCORTICOIDS DURING DESENSITIZATION OF CAPSAICIN-SENSITIVE SENSORY NEURONS IN RATS

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Accordingly to our data glucocorticoids may play a compensatory role in the maintenance of gastric mucosal integrity after desensitization of capsaicin-sensitive sensory neurons (CSN). In this study we investigated the mechanisms underlying the compensatory gastroprotective action of glucocorticoids. Methods: Male S-D rats were used after 24 h fasting. The effects of desensitization of CSN on gastric mucosa, gastric microcirculation and blood glucose levels were investigated before and after injection of indomethacin (35 mg/kg, sc) in adrenalectomized rats without or with corticosterone replacement (4 mg/kg, sc) and in sham-operated animals. Desensitization of CSN was performed with capsaicin (100 mg/kg, ip) two weeks before experiment; adrenalectomy (ADX) was created one week later. An in vivo microscopy technique for the direct visualization of gastric microcirculation was employed. Results: Indomethacin-induced gastric erosions were aggravated with similar extension by ADX or desensitization of CSN. Desensitization of CSN profoundly aggravated the erosion formation in ADX rats without corticosterone replacement. Indomethacin decreased the blood flow velocity in submucosal-mucosal microvessels, caused dilatation of superficial mucosal microvessels and increased their permeability. Desensitization of CSN potentiated the microvascular disturbances. The potentiated effects of the desensitization are profoundly promoted by ADX. In ADX rats desensitization of CSN also markedly potentiated indomethacin-induced falls in blood glucose levels. Corticosterone totally prevented all worsening effects of ADX. Conclusions: The compensatory gastroprotective action of glucocorticoids during desensitization of CSN may be provided by their maintenance of gastric blood flow and glucose homeostasis. Supported by BSciM RAS-2008, RFBR-07-04-00622, DBSci RAS-2008, Sci School RAS-1434.2008.4.

NITRIC OXIDE AND BLOOD FLOW OF GASTRIC MUCOSA IN HYPERSECRETORY, HYPOSECRETORY AND HYPERKINETIC CONDITIONS OF THE STOMACH

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Secretory function of gastric mucosa (GM) is correlated with the character of blood flow (BF). But the data reported that the role of nitric oxide (NO) in mechanisms of gastric secretion and cytoprotection have remained disputable. Experimental study was performed on white male rats with body weight of 180 -230 g. Measurement of the BF speed in GM was based on registration of hydrogen ions clearance. Contents of NO_2^- in biological liquids were estimated with Griess' reactive. Products of painting were spectrophotometrised on waves of λ = 540-550 nm. The 10-day course of once-daily intramuscular injections of histamine (5 mg/kg), famotidine (30mg/kg) and metoklopramide (2 mg/kg) modelled hypersecretory, hyposecretory and hyperkinetic conditions. BF level in GM of intact animals

was determined within the limits of 200.9 - 318.0 ml/min/l00 gr averaging 286,5 ± 6,8 ml/min/100g. The concentration of NO in GM of intact animals was 5.0 ± 0,2 mmol/l. Prolonged histamine activation of H_2-histamine receptors considerable increased BF (661,9 ± 54,0 ml/min/100g) ($p<0,05$). After prolonged blockade of H_2-histamine receptors by famotidine was observed decrease of BF to 101,5±14,1 ml/min/100g ($p < 0,01$). NO content was reduced to 3.13 ± 0.21 (by 41 %) ($p<0.05$). Acid secretion of gastric glands was decreased at 63 %. Prolonged blockade of D_2-dopamin and $5HT_3$-serotonin receptors by metoklopramide caused the reducing of BF to 187,4±20,3 ml/min/l00g ($p<0,05$), NO concentration dropped to 3,39±0,24 ml/min/100g (by 36 %). At this condition acid secretion of gastric glands was increased at 118 %. Thus, blockade of acid secretion with prolonged injection of H_2-blocker leads to decrease of BF and NO in GM. Prolonged blockade of D_2-dopamin and $5HT_3$-serotonin receptors is characterised by the increase of secretion and reduction of BF level. Obtained findings proved that NO changes are associated with BF level, but aren't related with gastric secretion.

PROTECTIVE EFFECTS OF PROLIL-GLYCIL-PROLINE (PGP) IN COMPOUND 48/80-INDUCED ANAPHYLACTOID REACTIONS

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It is known, that stress and inflammation lead to disorders in rats mesenteric microcirculatory system. These disorders are connected with mast cells (MC) activation. Activation of MC by compound 48/80 also led to microcirculatory system disorders. MC stabilization by ketotifen decreased them. Proline containing peptides (PGP, PG, GP) had a protective effect in microcirculatory dysfunction under conditions of inflammation and stress. This effect can be connected with PGP ability to stabilize MC. We supposed that PGP can have protective effect under other pathologies, such as allergic response. Effects of PGP in development of compound 48/80 (i. p., 8 or 12 mg/kg) -induced anaphylactic reaction were investigated. This reaction was characterized by appearance of writhes, itch, muzzle and paws edema, convulsive breathing and tail hyperemia. Animals died in 50% of cases. Injection of PGP (i. p., 1mg/kg) 15 min before injection of compound 48/80 led to 2-3 fold mortality decrease and reduced some of anaphylactoid reaction symptoms. There was no muzzle and paws edema, tail hyperemia. Such effects may be caused by direct MC stabilization with PGP, as well as its influence on other systems. The influence on rat peritoneal MC activity in vitro was investigated to clear possibility of direct PGP effects in MC stabilization. MC incubation with compound 48/80 (2 mg/ml, 10 mkl/aliquot) led to 2.6 fold increasing of enzyme β-hexosaminidase (β-Hex) secretion. But PGP didn't prevent MC activation by compound 48/80. These results indicate that mechanisms of PGP protective effects may be different under conditions of stress, inflammation and compound 48/80-induced anaphylactoid reactions. It is possible that PGP effect in MC stabilization doesn't play critical role in its protective attributes under conditions of 48/80-induced anaphylactoid reactions.

ORIGINAL HEMATOLOGIC EFFECTS OF ACETATE CU/ZN COMPLEX WITH ETHYLENEDIAMINE AFTER PER OS SINGLE DOSE INJECTION

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A search of new drugs promotes the synthesis of new agents, among them are coordination compounds. Novel acetate Cu/Zn complex with ethylenediamine has been synthesized in National Taras Shevchenko University of Kyiv and revealed antiphytoviral, bactericidal and fungicidal activity. In comparison

with chloride and bromide heterometallic compounds the acetate complex is more active upon interaction with artificial and nature membranes and has a higher influence on the activity of membrane enzymes. The presence of copper(II) and zinc(II) atoms in heterometallic complex plays an important role in the functioning of hematopoietic tissue. Hematoxicity and injury of blood cells caused by copper and zinc compounds are well known. Thus, the aim of our work is to investigate the original hematologic effects of acetate Cu/Zn complex with ethylenediamine (en) ($[Cu(en)_2ZnAc_4]\cdot$dmso) on blood cells in high dose (794 mg/kg). Experiments have been done on pubertal age outbred male rats. The acetate complex was dissolved in distilled water and injected per os. Blood cells were counted with hemanalyzer Sysmex F800. It has been shown that the parameters obtained in 24 hours after injection of acetate Cu/Zn complex with ethylenediamine, namely the number of red blood cells, hematocrit, haemoglobin, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume, red cell distribution width do not differ from the control group parameters. The number of leukocytes does not change. The tendency to increase in neutrophilic granulocytes number ($p=0,1$) and to decrease in lymphocytes number ($p=0,08$) has been revealed. These data probably indicate the nonspecific reaction of the organism after complex injection. No changes in platelet number and platelet volume has been shown. Thus, acetate Cu/Zn complex with ethylenediamine does not affect on blood cells in 24 hours after its injection.

THE PREVENTION OF THE ALTERATIONS OF COLONIC MUCOSA TRANSPORT FUNCTION UNDER HYPERGASTRINEMIA BY PROGLUMIDE AND PIOGLITAZONE

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Hypergastrinemia (HG) is a risk factor for arising and development of neoplasm in human colon which are accompanied by alterations of colonocytes' proliferation/differentiation ratio. The alterations of this ratio forms the basis of the changes in the colonic mucosa (CM) transport function (TF), so these processes may be responsible for the appearance of diarrhea under HG. But the studies of influence of HG on CM TF are absent. The aims of this study were to investigate the influence of long-term HG (for 4 weeks) on net water (W) and electrolyte (Na^+, K^+, Cl^-) movements (J_{net}) through the colonic epithelium and to examine the influence of nonselective CCK/gastrin receptors antagonist proglumide (PGL) and PPARγ ligand pioglitazone (PZ) on induced changes in the model of omeprazole-induced (OM) HG in rats. Adult male Wistar rats (180-250g) were used under urethane anesthesia (1,1g/kg) according to a method of isolated colonic loop perfusing technique in vivo for determining of $J_{net}W$, Na^+, K^+ and Cl^- movements. Animals were divided in 4 groups which were received the following injections for 4 weeks. The 1st group (n=5) – baseline (BG), water for injection (0,2ml; i.p.); the 2nd (n=7) – animals with OM-induced HG (14 mg/kg; i. p.); the 3rd (n=5) – OM with PGL (10 mg/kg, i.p.) and the 4th (n=5) – OM with PZ (30 mg/kg, per os). Plasma gastrin level (GL) was determined by radioimmune assay. In the 2nd group GL was significant increased *vs.* BG. There were decreased $J_{net}W$ (by 47,1%, $p<0,05$) and Na^+ (by 54,9%, $p<0,001$) and increased $J_{net}Cl^-$ (by 84,0%, $p<0,05$) and $J_{net}K^+$ (by 200,0%, $p<0,001$) *vs.* BG. In the 3rd group $J_{net}W$, Na^+ and K^+ recovered to the initial rate while $J_{net}Cl^-$ was increased by 292,43% ($p<0,01$). GL remained higher *vs.* BG ($p<0,01$). In the 4th group GL also was higher *vs.* BG ($p<0,01$). But PZ has entailed all functional indexes to the initial rate. Thereby prolonged OM-induced HG altered the CM TF. But PGL and PZ may be useful for prevention of the CM TF alterations induced by HG.

EXPERIMENTAL SUBCLINICAL HYPOTHYROSIS: METABOLIC STATES OF BLOOD, MYOCARDIUM AND LIVER TISSUES AND CORRECTION BY INTERVAL HYPOXIC TRAINING

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Subclinical hypothyroidism, defined as a mild elevation in thyroid-stimulating hormone (TSH) levels with normal serum thyroxine levels. Over past decades, a number of studies have investigated the effects of subclinical hypothyrosis on the heart, showing that this condition may be associated with important abnormalities of ardiac structure and function. The present study deals with the research of the metabolic changes of blood, myocardium, liver tissues under condition of experimental subclinical hypothyrosis. Rat blood, myocardium, and liver tissue, were investigated. The model of mild thyroid failure was induced by the administration of mercazolilum in doses of 3 mg/kg during 3 weeks. Total cholesterol (TCh), high-density lipoprotein cholesterol (HDL), low-density lipoprotein (LDL), nitriteion, under conditions of hypothyrosis were measured. According to obtained results, the subclinical hypothyrosis is associated with increased serum levels of LDL and with reduced HDL, and finally, with increased atherogenic index (0,530±0,035). The relationship between a mild thyroid failure and an atherogenic lipoprotein profile was observed. We have revealed the association between mild deficiency of thyroid hormones and parameters of nitric oxide system. The decreased level of nitriteion in rat blood, likewise the mobilization of mononitric oxide system in myocardial (25,7%) and liver tissue was shown. The content of some products of free radical metabolism was biochemically measured. Activation of lipoperoxidation (LPO) processes has been established in blood (due to the content of MDA–27%, DC–46 %.), and, in fact in all media under condition of hypothyrosis. Due to this, the activity of antioxidant protection system was depressed. Interval hypoxic training (IHT) was elaborated and tested with a purpose to correct the biochemical abnormalities. All the markers of cholesterol providing system and oxygen dependent parameters were decreased under correction by IHT.

THE ANTINOCICEPTIVE EFFECT OF LOW INTENSITY, ULTRA-HIGH FREQUENCY ELECTROMAGNETIC FIELD

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The thesis is addresses the issue of conformity to natural laws of antinociceptive effect of exposure to low intensity, ultra-high frequency electromagnetic radiation (UHF EMF) (λ=7.1cm, density of power flow 0,1mW/cm^2). Analysis of the collected experimental data, that previous both single and course expose to low intensity UHF EMF turned to result in significant antinociceptive effect on pain stress of different etiology (tonic, visceral, sharp pain), so to prove certain universal analgetic influence of UHF EMF on an organism. The antinociceptive action of UHF EMF influence the following effects: decreased duration of pain reactions; growth of pain sensitivity threshold, pain endurance level and non-pain behavior duration; restoration of correlation and cluster interrelation between different behaviour forms; modification pain sensitivity rhythmical processes in rats within high-frequency, ultra- and infradian ranges. Opioid peptides, serotonin, melatonin, dopamine - and noradrenergic systems take significant part in the mechanisms of analgetic effect of millimeter irradiation.

BIOLOGICAL ACTION OF ELECTROMAGNETIC FIELDS OF EXTREMELY HIGH FREQUENCY IN THE CONDITIONS OF OPIOID PEPTIDE RECEPTORS BLOCKING

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The thesis is devoted to study of biological action of electromagnetic fields of extremely high frequency (λ=7,1, mm, power flow density 0,1 mW/sm^2) isolated and combined with experimentally envoked stress reaction (hypokinesia) in the conditions of opioid peptide system disabling, which is the one of the main stress-limiting organism systems, by injection of naloxone that is an antagonist of all sub-types of opioid peptide receptors. Obtaind results are an evidence that one of the mechanisms of biological action of low-intensity emission of millimeter range is an increase of functional activity of opioid peptide system which is a remedy of effective prophylaxis and correction of stress-reaction development. It is realized, firstly, by means of activity limitation of sympathoadrenal system through depression of the processes of catecholamine release and reception, secondly, by means of an increase of nonspecific resistance and immunological reactivity, thirdly, by means of stimulation of generation and release of serotonin and melatonin, that is, potentiation of activity of other stress-limiting organism systems.

SKINNED INTESTINE SMOOTH MUSCLES. CA^{2+} - DEPENDENT MUSCLE CONTRACTION AND IT'S MATHEMATICAL MODELLING

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In our experiments in reply to the applique of Krebs hyper calcium solution (HCS) intact muscles developed isometric tension. Decreasing of [Ca^{2+}] that entered in the complement of HCS from 2.5 mM to 10^{-5}M or bringing of EGTA (4 mM) with the next applique of Ca^{2+} (10^{-6} or 10^{-5} M) not attended contractions of these muscle preparations. Unlike intact preparations saponin skinned preparations in reply to bringing in activating solution Ca^{2+} in a concentration 10^{-6}M has developed tension. Activating solution with the concentration of Ca^{2+} 10^{-4}M or 10^{-6}M has also activate the contraction. A next increase of [Ca^{2+}] to 10^{-3} M did not cause the changes of maximal value of muscle tension. Replacement of activating solution on relaxing was accompanied relaxing of muscles to the basal tension level. It was set by an experimental way that time dependence of smooth muscle contraction has the appearance of logistic (S-similar) curve. Obviously, that muscle contraction force is straight proportional the amount of complexes of actin and myosin filaments. That's why $F=k\cdot y$, where F - force of contraction, k - proportionality coefficient, which specifies what force develops one actomyosin complex, y - concentration of actomyosin complexes. Such process of change of concentration of these complexes in time can be described Verhyulst equation: $dy/dt=y\cdot(1-3\cdot y/C)$, where C is a concentration of inner cell calcium ion. We can get differential equation for the change of intracellular [Ca^{2+}]: $dC/dt=C\cdot(1 - C/Cmax) - y\cdot(1-3\cdot y/C)$, where Cmax is a maximal concentration of Ca^{2+} in cell (EPR), the element of $C\cdot(1-C/Cmax)$ - Ca^{2+} induced calcium release and it is logistic equation. Element - $y\cdot(1-3\cdot y/C)$ is responding for decreasing of intracellular Ca^{2+} concentration, as a result of contraction complex formation (3 ions Ca^{2+} for 1 complex). This system of differential equations was solved in the program Mathematica 5.0 and the graphics of time dependence of actomyosin complexes and Ca^{2+} concentrations were built.

FUNCTIONAL STATE OF RAT LIVER MITOCHONDRIA AT STRESS MODEL OF THE STOMACH ULCER

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One of the most widespread forms of gastroenterology pathology is the stomach ulcer. Other organs of the digestive tract are also involved in this process. Liver occupies an important place among them. It is the central organ of chemical homeostasis which requires bulk of energy for all metabolic processes. Oxidative phosphorylation is the key mechanism owing to which the ATP is synthesized in mitochondria. The purpose of work was to investigate the functional state of rat liver mitochondria at stress model of the stomach ulcer. Materials and methods. In experiments were used rats of Vistar line with mass of 180-230 g. Water-immersion stress was used for making stress model of stomach ulcer restraint. Mitochondria were isolated by ising standard method. Respiration of mitochondria in different metabolic states was studied by polarographic method. Succinate dehydrogenase activity was determined by ferricyanide method. Statistical processing of results was made with the use of t-criterion of Student. Results. At research of the functional state of liver mitochondria it was determined the following: stress factor increased the speed of respiration on 23% in comparison with control mitochondria; intensity of mitochondrion oxidations during phosphorylation of exogenous ADP authentically decreased on 12%; speed of respiration in the state of rest (V_4) increased on 80% in comparison with the control; at action of stress the coefficient of respiratory control of Chance in rat liver mitochondria was reduced on 52%; energy production of rat liver mitochondria at influence of the stress factor decreased (the coefficient [ADP]/[O] dropped on 31%). It was also established that enzyme activity of succinate dehydrogenase in rat liver mitochondria decreased on 70% at stress model of stomach ulcer. Conclusions. According to the results of experimental researches in stress model of stomach ulcer the functional state of rat liver mitochondria is broken to what testify disconnection of processes of oxidation and phosphorylation, reduction of succinate dehydrogenase activity and decrease of energy production of organella.

THE INFLUENCE OF GLYPROLINES ON FORMATION OF LIPID PEROXIDATION PRODUCTS AND THE ENZYME ACTIVITY OF ANTIOXIDANT PROTECTION IN GASTRIC MUCOSA OF RATS AFTER WATER IMMERSION RESTRAINT STRESS

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Glyproline peptide family includes the simplest proline-containing linear peptides PG, GP, PGP. Using rat model of gastric lesions induced by stress, ethanol, indomethacin and pylorus ligation it was demonstrated that PG, GP, PGP decrease the area of lesions and this effect was accompanied by increased gastric mucosa (GM) blood flow and decreased gastric acid secretion. However, the data about the influence of PG, GP, PGP on lipid peroxidation process and antioxidant system activity balance which are one of the main mechanism in development of gastric injury are absent. So the aim of the study was to investigate the action of PG, GP, PGP on formation of lipid peroxidation products and the enzyme activity of antioxidant protection in GM of rats after water immersion restraint stress (WIRS). Male Wistar rats, weighting 180-220 g and fasted for 24 h with free access to water were used in our studies. Acute gastric lesions were induced by WIRS for 3 h. Drugs were given intraperitoneally in dose 3,7 μM/kg (-1) body weight 15 min before stress. Determinations were made of GM injury, lipid peroxidation, superoxide dismutase (SOD) and catalase (CAT) activities. It was

established that PG, GP and PGP decreased the area of ulcers in GM evoked by WIRS by 17%, 67% and 70% accordingly. Thiobarbituric acid (TBA) reactive substances, conjugated dienes and shiff bases in GM as an index of peroxidation, was increased after WIRS and this increase was inhibited by PG, GP and PGP. WIRS didn't change SOD activity but increased CAT activity in GM. PG, GP and PGP didn't influence on SOD activity and diminished CAT activity. These results suggest that the protection afforded by simplest proline-containing peptides against WIRS gastric injury may be, in addition to other possible mechanisms, to its radical scavenging activity.

ZINC CHELATOR INJURING ACTION TO INSULIN PRODUCING CELLS

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The need to study injuring action of chelators on the cells is increasing year after year because of the mice and more extending application of these drugs in various industry branches and agriculture. The investigation of cell damaging action of chelators has been of interest since the first reports of dithizone ability to induce alteration of insulin producing cells in rabbits. Dithizone is shown to accumulate selectively in pancreatic beta cells. The accumulation of this chelator in ones is explained by it's binding to zinc, that contains in this cells in high concentrations. In experiments on mice, golden hamsters and rabbits we observed the development of intravitale cytocemical reaction in pancreatic beta cells of 8-(p-toluinesulfonylamino-quinoline) (8-TSQ) a selective reagent for zinc. The product of this reaction was revealed on pancrease frozen sections 3 min – 2h after 8-TSQ injection. The sections with chelator intravitale reaction were investigated with the aid of fluorescent microscopy (light filters V-1 and Y-18). A yellow green fluorescence was observed in pancreatic beta cell. At first the intensity of intravitale 8-TSQ reaction in pancreatic beta cells was increased. Maximum reaction was observed 15-30 min after the injection. Then a decrease of this reaction intensity was observed on the sections. Zinc chelat granules became more and more diffused and 2h after the injection the fluorescence in beta cells was almost absent.The first signs of B-insulocyte damage were discovered 2h after 8-TSQ administration. The necrosis reached a marked expression 8 to 24h after injection. The subsequent 3d a cell detritus disappearance was observed. The islet size and beta cells quantity decreased in islets. Complete and partial degranulation of these cells was accompanied by zinc disappearance in them. Dependence between intensity of intravitale 8-TSQ reaction in beta cells and the degree of subsequent alterations of these cells was observed.

DUAL ACTION OF GLUCOCORTICOID HORMONES ON THE GASTRIC MUCOSA: HOW PHYSIOLOGICAL GASTROPROTECTIVE ACTION CAN BE TRANSFORMED TO PATHOLOGICAL ULCEROGENIC EFFECT

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Glucocorticoids and gastric ulceration have been discussed in many contexts. The effects of acute and chronic treatment of patients or experimental animals with glucocorticoids as well as the action of basal and stress-induced glucocorticoid production on the gastric mucosa have been considered. It is established that administration of glucocorticoids at high pharmacological doses can induce gastric ulceration. The ulcerogenic properties of exogenous glucocorticoids were extrapolated to the properties of endogenous glucocorticoids. It has been generally accepted for several decades that glucocorticoids released during stress also caused an ulcerogenic response in the stomach. We designed

experiments to clarify the validity of this dogma. The results obtained do not support the traditional paradigm and suggest that glucocoricoids released during acute activation of the hypothalamic-pituitary-adrenocortical axis are important gastroprotective factors. We demonstrated that the glucocorticoids may contribute to gastroprotection by maintaining local gastric mucosal and general body homeostasis. Thus, beneficial action of glucocorticoids released during acute stress on the stomach is opposite to the harmful actions of exogenous glucocorticoids used at pharmacological doses. How physiological gastroprotective action can be transformed to pathological ulcerogenic effect? We hypothesized that glucocorticoid-induced disturbance of carbohydrate regulation may be responsible for the transformation. The results obtained support the hypothesis and suggest that maintenance of blood glucose levels may be responsible for the gastroprotective action of glucocorticoids, while disturbance of carbohydrate regulation during glucocorticoid-induced hyperglycemia may account at least partly for the ulcerogenic action of glucocorticoid hormones. Supported by BSciM -2008, RFBR-07-04-00622, DBSci RAS-2008, Sci School RAS-1434.2008.4.

LIVERS ANTIOXIDATIVE SYSTEM AFTER SINGLE DOZE ADMINISTRATION OF NOVEL CYTOSTATIC MALEIMIDE DERIVATE

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Novel protein kinases inhibitor maleimide derivate 1-(4-Cl-benzyl)-3-Cl-4-(CF_3-phenylamino)-1H-pyrrol-2.5-dione (MI-1) has been synthesized in ChemBioCenter (Kyiv, Ukraine). It displays cytostatic effects on transformed and cancer cell lines. Hepatic drug metabolism, often with an imbalance between the generation of reactive oxygen species, can cause liver damage. The present study was performed in order to evaluate the properties of MI-1 to affect antioxidant system. For better estimating MI-1 effect it was compared with the effect of $CoCl_2$ induced oxidative stress. The influence of MI-1 has been studied on male rats. MI-1 was injected by intragastric way in dose 5 mg/kg b.w., $CoCl_2$ was injected subcutaneously – 3 mg/kg b.w. One group of animals received both MI-1 and $CoCl_2$. Rats were decapitated 24 h later. Cytosol fraction of liver cells was prepared by ultracentrifugation method. The protection against oxidation is provided by glutathione (GSH) and antioxidant enzymes including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione-S-transferase (GST). No significant changes of CAT and SOD activity under the influence of MI-1 have been detected but in case of combined application of MI-1 and $CoCl_2$ some disturbances of enzymes activity have been noted. Gpx activity is declined by single doze administration of MI-1 alone and by its combination with $CoCl_2$. GSH and GST activities increase both in case of MI-1, $CoCl_2$ and MI-1+$CoCl_2$ administration. In the last case this increasing is mach more significant that in two previous. Those changes are statistically meaningful for GST activity. Elevation of GSH level and GST activities might suggests about increasing of the cell's resistance to injected compounds. Therefore, single doze *per os* administration of novel maleimide derivate MI-1 does not cause significant disturbances of antioxidant system in liver cells after single dose administration. It suggests that MI-1 is not apparent oxidizing agent.

EFFECT OF COX-2 BLOCKAGE AND DUAL COX/LOX INHIBITION ON LIPOPEROXIDATION PROCESSES IN HEART TISSUE AND GASTRIC MUCOSA OF RATS

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COX-inhibitors are the most commonly prescribed medications in the treatment of inflammatory states. Their use is associated with a number of side effects, the most serious are – GI irritation and increased risk of myocardial infarction. LOX pathway also plays an important role in inflammation.

Compounds that combine COX and LOX inhibition present multiple advantages. The purpose of the research was to compare changes of NO content, lipoperoxidation processes (LPP) and activity of the antioxidant protection system (APS) in heart tissue and gastric mucosa under prolonged application of inhibitor COX-2 celecoxib and thiazolidin derivatives – agents possessing dual COX/LOX inhibition. The research was performed on 27 white rats. Celecoxib (10 mg/kg), {2,5-Dioxo-3-[4-oxo-5-(3-phenyl-allylidene)-2-thioxo-thiazolidin-3-yl]-pyrrolidin-1-yl} acetic acid (agent 1) (10 mg/kg) and 4-{2,5-Dioxo-3-[4-oxo-5-(3-phenyl-allylidene)-2-thioxo-thiazolidin-3-yl]-pyrrolidin-1-yl}-benzene-sulfonamide (agent 2) (10 mg/kg) were introduced per os for 14 days. LPP were evaluated by MDA content, activity of enzymes of the APS was evaluated on basis of determination of SOD, catalase, GP, and GR activity, Griess reagent was used to measure the content of NO. COX-2 inhibition by celecoxib caused the increase of MDA content in heart tissue by 37 %. After inhibition both COX and LOX by agent 1 and agent 2 MDA concentration was also increased (by 28% and 30% subsequently). MDA content almost wasn't changed in gastric mucosa after action of these inhibitors. NO concentration was 21% higher than normal in heart tissue after COX-2 blockage, whereas agent 2 caused increase of NO concentration only by 7%. Inhibition of COX-2 as well as COX/LOX dual inhibition led to the increase activity of the APS (catalase, SOD, GP, GR) in both investigated tissues. Thus, COX-2 inhibition led to intensification of LPP in heart tissue. Changes appeared after prolonged dual COX/LOX inhibition, were less marked in both tissues, comparing with action of celecoxib.

EFFECT OF BENZIMIDAZOLE AND ITS DERIVATIVES ON ELECTRICAL NEURONAL ACTIVITY OF *HELIX ALBESCENS ROSSM.* AND RAT BEHAVIOR

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In this work studied, concentration dependence and mechanisms of bezimidazole and its new derivatives effect on electrical processes in *Helix albescens Rossm.* neurons and their influence on rat behavior. These compounds occurred to have neurotropic properties dependant on their chemical structure and types of neurons. Threshold, optimal and toxic concentration values of the tested substances determined. Benzimidazole and 2-trifluoromethylbenzimidazole influence in concentrations of 10^{-3} and 10^{-2} M turned to render both excitatory and inhibitory postsynaptic potentials on soma membrane of some pacemaker and non-pacemaker neurons and even its strong depolarization. Pacemaker neurons membrane (namely, neuron RPa2) occurred to have at least two spatially separated trigger sites with different action potential trigger mechanism. After single intraperitoneal injection (50 mg/kg) of the substance solution, as a result of discovered effects the tested compounds were divided into two groups. The first group inhibits locomotion and psychoemotional state of rats, the second group renders the opposite effect. Dosage of 100 and 150 mg/kg of all the tested substances appeared to inhibit animal's activity.

CONNECTION BETWEEN GLUTATHIONE CONTENT AND APOPTOTIC PROCESSES DURING CHRONIC ATROPHIC GASTRITIS DEVELOPMENT

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Chronic atrophic gastritis (CAG) is characterized by mucosal glands loss due to disturbances in processes of cellular proliferation and death. Among main apoptotic triggers are members of Bcl-2 fam-

ily: Bax protein is involved in mitochondrion membrane permeabilisation, but Bcl-2 acts like antiapoptotic agent. Enhanced production of reactive oxygen species (ROS) could be a signal for apoptosis. They lead to defects in protein folding and enzyme function, increase membrane lipid peroxidation. Glutathione (GSH) could neutralize effect of ROS production by reduction of these agents. According to this data we decided to investigate GSH content and level of pro- or antiapoptotical agents during CAG development. Rat model of CAG was performed by intragastric administration of sodium salicilate as damaging agent. Drinking water was replaced by sodium deoxycholate solution. GSH was determined by fluoromethric assay. Bcl-2 and Bax content was determined by Western-blot analysis. All measurements were performed on stomach parietal cells. Data was obtained on 1st, 3d and 5th weeks of model development. GSH concentration in rat parietal cells increased during 3 weeks of CAG, after which statistically significant decrease was observed on the 5th week. Level of Bcl-2 slightly increased on the 1st week of model development and reached peak values on the 3rd week. This rise of Bcl-2 content could be connected with compensatory cells functional activation responding to stress stimuli. Bax concentration was lower than control values during 1st model week possibly due to necrotic (not apoptotic) cell death. From the 3rd week Bax remained on relatively high level. According to our investigations GSH content in parietal cells is closely connected with pro- and antiapoptitic proteins. It could be argued that GSH is heavily involved in apoptotic signaling and CAG development.

PHARMACOLOGICAL EVIDENCE THAT ACTIVATION OF NMDA–NO, NMDA-ENDOMORPHIN CASCADES MAY MEDIATE GASTRIC MUCOSAL DEFENSE INITIATED CENTRALLY

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The role of dorsal vagal complex in centrally-induced gastric mucosal defense has well been documented. Since glutamatergic pathway from NTS to dorsal motor nucleus of vagus neurons was described we aimed to analyze if excitatory amino acids are involved in gastric mucosal protective effect of α_2-adrenoceptor stimulants, opioids, cannabinoids, nociceptin and nocistatin. Methods*:* Gastric mucosal damage was induced by 100% ethanol; the lesions were determined 1 hour after ethanol administration. The agonist compounds were given icv. and ic. 10 min prior to the ethanol challenge, the antagonists were injected 10 min before the administration of agonists. Results: 1. The gastroprotective effect of opioid peptides, clonidine, rilmenidine, methanandamide, nociceptin and nocistatin (NST) was reversed by dizocilpine (non-competitive antagonist of NMDA). 2. NMDA (5-10 pmol icv.) inhibited gastric mucosal lesions. 3. The gastroprotective effect of α_2-adrenoceptor stimulants, opioid peptides, nociceptin and NMDA was reversed by icv. injected nitric oxide (NO) synthase inhibitor, N^G-nitro-L-arginine. (670 nmol). 4. The gastroprotective effect of NMDA was antagonized also by naloxone and endomorphin-2 antiserum given ic. 5. Endomorphins (0.1-1 nmol icv.) also induced gastric mucosal protection. Conclusion: 1. Activation of NMDA receptors (probably by disinhibition) may mediate the gastroprotective effect of α_2-adrenocepor stimulants, opioid peptides, cannabinoid CB_1-receptor stimulants, nociceptin and NST. 2. Central NO as well as endomorphins may play a role in the gastroprotective effect of NMDA. This work was supported by ETT 529/2006.

MORPHO-FUNCTIONAL PARAMETERS OF RAT'S PANCREAS AFTER *PER OS* ADMINISTRATION THE NEW ANTINEOPLASTIC COMPAUND MALEIMIDE DERIVATIVE

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Pancreas cancer among the tumors of the digestive system belongs to difficultly treated diseases due to low efficiency of existed antitumor treatment. Protein kinase inhibitors are considered as new potentially effective substances for cancer treatment. Maleimide derivatives reveal potential antitumor activity because they combine antineoplastic effect with low toxicity. The morpho-functional status of rat's pancreas after per os administration the new derivative of maleimide (1-(4-Cl-benzil)-3-Cl-4-(CF_3-fenilamino)-1H-pirol-2.5-dion) – MI-1 were investigated. MI-1 effects were studied on rats after 5 weeks of administration at dozes of 0.00027, 0.027 and 2.7 mg/kg. Nuclei area of exocrine cells, endocrine cells, height of excretory ducts' epithelium and nuclei area of its epithelium cells were measured. Signs of inflammatory process in the exocrine parenchyma and increasing of connective elements were observed. It has been revealed nuclei area increasing into exocrine cells that depends on MI-1 doze. Analysis of these cells nuclei area variability has shown that the most cells in control group have nuclei size 22-28 mkm^2, and a quantity of cells with nuclei size above 30 mkm^2 is about 20%. If MI-1 has been applied at a doze of 0.00027 mg/kg the part of large nuclei is 40%, 0.027 mg/kg - 45%, 2.7 mg/kg – 55% from total. Increase of exocrine cells nuclei size can be caused by both inflammatory process and compensatory process in pancreas. Endocrine system and excretory ducts of gland are resistant to the investigated compound. The obtained data indicates that MI-1 is low toxic compound for status of control animal pancreas and its further research is reasonable. The final goal of future research might be the investigation of MI-1 specific toxicity and antineoplastic properties against to digestive system tumors.

INFLUENCE OF ACETIC ZINC ON THE ZINC CONTENTS IN A RATS LIVER UNDER CHRONIC ALCOHOLIC INTOXICATION CONDITION

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Today the alcoholism gets the increasing diffusion among the population of Ukraine. Alcoholism pathogenesis metabolism changes results to disturbances of a biogenesis, structure and function of different organs cells and systems. Therefore studying of ethanol metabolism system in an organism of the human and animals with the purpose of new drugs making which are used for prophylaxis and treatment of alcoholic dependence are importance for clinical and experimental biology and medicine. It is known, that under chronic alcoholic intoxication conditions is observed deficiency of Zincum (Z) in a number of organs. With the purpose of correction of the specified dissonance use Z salts among which the hypotoxicity characterizes zinc acetate (ZA). Therefore the our researches purpose was to define influence of acetic Z on the Z contents in a liver cells homogenate of rats with a chronic alcoholic intoxication. White laboratory rats-males were parted on 3 groups. 1-st group - control animals; 2-nd group - rats with a chronic alcoholic intoxication which caused behind standard procedure; 3-rd group - rats with a chronic alcoholic intoxication which follow-up administration ZA in a dose of 0,2 g on 100 g of animal mass one times into day. Liver homogenate was obtained in 1 % Triton X-100 solution in the ratio tissues-solutions 1:3 on procedure for 4, 6, 11, 16 and 21 day after the beginning of experiment. The Z content was defined behind a atomic absorption spectophotometeries method. At rats with a chronic alcoholic intoxication Z contents increase in a liver homogenate

for 7 day on 10 %, decrease for 11 day (on 15 %) and gradual rise of 16 and 21 day to control value has been shown. The research of ZA introduction influence was positioned, that the contents of Z in a liver increased for 7 day on 15 %, on 11 - dropped to control value, and for 16 and 21 day again increased on 21 % and 33 %, accordingly. Thus, ZA introduction result to normalization of the Z contents in a liver of rats with a chronic alcoholic intoxication.

LEVEL OF NUCLEAR DNA POLYMERIZATION OF GASTRIC MUCOSA CELLS AT STRESS ULCER MODEL

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Study of properties of biologically active substances (BAS) provides perspective of their use at pathologies of different genesis. Our earlier researches on factors of protection of gastric mucosa cells (GMC) (glycoproteins of gastric mucus, neutral and phospholipids of cell membranes, membrane-bounded enzymes, factors of local immunity and cytohistological characteristics of GMC) revealed protective influence of active components of Trigonella foenum graecum extract (TFGE) on regenerative potential of superficial epithelium cells. Activation of oxidative processes at stress conditions results in genome destabilization, therefore one can expect correcting effect on these processes of BAS of natural origin. The purpose of the work was comparative determination of the level of nuclear DNA (nuDNA) polymerization in GMC at stress gastric ulcer model as well as to animals by intragastrically administration of TFGE in dose 50 mg/kg within 7 days twice per day on the background of developed ulcer damages. Researches were done on 97 nonlinear male rats with mass of 230 to 240 g. 1st group of animals was control, 2nd group was decapitated in 24 h after stress model development, 3rd – in 8 days after the model creation and introduction of TFGE. Nuclei from GMC were isolated in glycerin gradient. Electrophoresis of nuDNA was carried out in 0.8% and 1.7% agarous gel. Standard markers were used as molecular mass markers. Gel electrophoresis and ethidium bromide staining showed that average molecular mass of nuDNA of intact rats was about 25000 bp. In conditions of the stress model, there were revealed the fragments of wide range of molecular masses, at that their size in low-molecular area was approximately multiple 180 bp, that indicates oligonucleosomal fragmentation of nuDNA in GMC. At introduction to the animals of Trigonella foenum graecum extract on the background of developed ulcerous damages, there was discovered substantial decrease of the level of nuDNA fragmentation.

A NEW ROLE FOR IRON IN THE PATHOGENESIS OF TISSUE INJURY: DISTURBANCES OF IRON TRANSPORT IN CYSTEAMINE-INDUCED DUODENAL ULCERATION IN RATS

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Cysteamine induces perforating duodenal ulcers in rats within 24-48 hr. This reducing aminothiol may generate hydrogen peroxide in the presence of transition metals (e.g., ferric iron), producing oxidative stress, which may contribute to organ-specific tissue damage. Since most intestinal iron absorption takes place in the proximal duodenum, we hypothesized that cysteamine may disrupt regulation of mucosal iron transport, and iron may facilitate cysteamine-induced duodenal ulceration. We show here that cysteamine-induced ulceration was aggravated by pretreatment of rats with Fe^{3+} (as ferric chloride) or Fe^{2+} (ferrous sulfate). In

contrast, feeding an iron-deficient diet was associated with a 4.6-fold decrease in ulcer formation, accompanied by a 34% decrease ($p<0.05$) in duodenal mucosal iron concentration. Administration of the iron chelator deferoxamine decreased ulceration by 65%. Cysteamine-induced duodenal ulcers were inhibited in Belgrade rats ($p<0.05$). In normal rats cysteamine administration increased the iron concentration in the proximal duodenal mucosa of rats by 33% ($p<0.05$). Cysteamine also markedly enhanced activation of mucosal iron regulatory protein 1 (IRP1) and increased the expression of divalent metal transporter-1 (DMT1) mRNA and protein. Transferrin receptor 1 (TfR1) protein expression was also increased, although mucosal ferroportin and ferritin remained almost unchanged. These results indicate an expansion of the intracellular labile iron pool in the duodenal mucosa increasing its susceptibility to oxidative stress and suggest a role for iron in the pathogenesis of duodenal ulcers.

THE STRUCTURAL STATE OF INNER MITOCHONDRIAL MEMBRANES FROM COLORECTAL ADENOCARCINOMA TISSUES OF DIFFERENT CLINICAL STAGE

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The mitochondrial membranes (MM) are the highly-organized structures with the specific distribution and spatial orientation of individual molecules. Mitochondria (M) play an important role in the molecular mechanisms of programmed cell death induction: the increase of MM permeability under the influence of different proapoptotic stimuli leads to release of apoptogenic molecules from the M that realizes in the spreading of death signals within the cell. The most essential peculiarity of tumor cells is the evasion of programmed cell death. The aim of this study was to investigate the structural properties of inner mitochondrial membranes (IMM) from colorectal adenocarcinoma tissues of different clinical stages. The samples of submitochondrial particles were isolated from the primary tumors corresponded to the I,II,III,IV stages according to the clinical and histological classifications. Membrane structural state was estimated using the method of fluorescent probes. The spatial organization of membrane was evaluated by the method of inductive resonance energy transfer from donor to acceptor in pairs of fluorophores with different localization in the membrane. It was shown the decrease of annular and bulk fluidity in IMM of tumor tissues. During the tumor progression the modification of protein macromolecules of IMM and increase of intermolecular dynamics of membrane was shown to take place. The degree of protein molecules submersion in the hydrophobic lipid bilayer of membrane was shown to be increased for the submitochondrial particles from tumor tissues. During the colorectal carcinogenesis the structural realignment of IMM is characterized by the conformational changes of the protein molecules, the decrease of structural regularity of lipid phase of membrane, the changes in protein-lipid interactions and topography that make evidence of the possible role of the M structural state modification in malignant transformation.

LIPID PEROXIDATION PROCESSES, PARAMETERS OF THIOL /DISULFIDE SYSTEM OF RED BLOOD CELLS IN RATS WITH GUERIN'S CARCINOMA UNDER INFLUENCE OF RHENIUM COMPOUNDS

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Cluster rhenium compounds are known to be antitumor substances and are modulators of cisplatin mechanism of action [Anticancer Research, 2007]. Investigation of their influence on biochemical

parameters of the living organism is of great importance for further preclinical and clinical steps. The influence of the cluster rhenium compound in liposome form and cisplatine on the activity of superoxide dismutase (SOD), on content of secondary products of the lipid peroxidation (LP) – malonic dialdehyde (MD), on the parameters of antioxidant thiol /disulfide system (SH/-S-S-) of red blood cells of rats with Guerins (T8) carcinoma has been studied. It was shown the increase of MD level (in 1,5 times in average), concentration of –S-S- groups (in 3.4 times) an decrease of SOD activity (in 1.4 times) and -SH groups concentration (in 5.6 times) under tumor development and cisplatin therapy that was the consequence of the mighty oxidative stress. Introduction of the rhenium compound led to the decrease of the concentrations of MD level (in 1,5-2 times), concentration of –S-S- groups (in 2 - 3,4 times) and increase of SOD activity (in 1,8 - 2 times) and -SH groups concentration (in 3 – 7 times) that corresponded practically to the normal parameters and confirms protective properties of rhenium compounds in the conditions of peroxide products explosion caused by malignancy. Extraordinary sensitivity of thiol-disulfide system to the introduction of the rhenium compounds should be noted and possible mechanism of the influence is the matter of discussion and further investigations.

GASTROPROTECTIVE EFFECTS OF PROBIOTICS: MYTH OR REALITY?

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Background and Aim: Probiotic bacteria exert anti-inflammatory effects in lower GI tract but their gastroprotective activity has not been assessed. The aim of the study was to study the effects of pretreatment of rats with probiotic E.coli strain Nissle (EcN) or Lacidofil on the development of acute stress-induced or ethanol-induced gastric lesions. Methods: Rats pretreated with EcN or Lacidofil were exposed to water immersion and restraint stress (WRS) or ethanol (75%). Involvement of prostaglandins (PG) was tested by the measurement of PGE2 generation in gastric mucosa and by indomethacin applied 1 h before EcN or 75% ethanol, whereas sensory nerves were assessed using capsaicin. In addition, in vitro analysis was performed with the incubation of gastric cell line (MKN-45) with ethanol in the presence of EcN. Analysis of apoptosis was performed by FACS. Results: Exposure to WRS or ethanol induced acute gastric erosions which were dose-dependently reduced by EcN or Lacidofil, accompanied by increased gastric blood flow. The protective effect of EcN and Lacidofil was abolished by indomethacin and attenuated by capsaicin-denervation. Pretreatment with EcN, raised significantly mucosal PGE2 generation, but significantly downregulated the expression of TNFα, COX-2, NFκB, while upregulating β_2-defensin expression. In in vitro experiments, EcN reduces apoptosis rate induced by exposure to ethanol as evidenced by FACS analysis. Conclusions: Probiotics protect gastric mucosa against acute gastric lesions. The gastroprotective effects induced by probiotics are due to anti-apoptotic, anti-inflammatory and vasodilatory actions, involving HSP70, prostaglandins, sensory nerves and β_2-defensin.

THE INVESTIGATION OF MECHANISMS OF INTERMITTENT HYPOXIC TRAINING (IHT) AND AMARANTH OIL ACTIONS IN ANIMALS WITH CHRONIC FLUORINE INTOXICATION AND LOW DOSES OF RADIATION

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The problem of improving the adaptation potential of an organism for maintaining homeostasis remains a priority under conditions of permanent exposure to anthropogenic factors. The aim of this

study was to determine mechanisms of amaranth oil and intermittent hypoxic training actions on ultrastructure of liver tissues including the parameters of antioxidant system of blood and tissues in rats with combined action of fluorine intoxication and low doses of radiation (total dose is 1 Gr). Fluorine intoxication was induced by oral administration of sodium fluoride (10 mg/kg) for 30 days. Radiation exposure of animals was performed after fluorine intoxication. IHT was carried out in a pressure chamber. At the same time rats were fed with concentrated amaranth oil added to food in daily dose 38 mg/kg during 10 days. Superoxide dismutase, catalase, glutathione peroxidase activities were measured spectrophotometrically in blood, liver and heart tissues. The liver tissue specimens underwent electron microscopy examination. Complex application of IHT and amaranth oil in rats with combined action of fluorine intoxication and low doses of radiation was demonstrated with the following effects: effective normalization of structure and metabolic damages of investigated tissues, complete recovery of antioxidant enzymes activities. The electron-microscopic investigation of the liver samples showed the ordered and compact position of mitochondria, peroxisomes, lipoprotein droplets with light electronic density, glycogen granules and also agranular endoplasmatic retuculum channels. The synergic influence of IHT and amaranth oil is aimed at activation of oxidation-reduction reactions in mitochondria, induction of organism's antioxidant defense and the recovery of compensatory defense mechanisms.

ROLE OF MEMBRANE PHOSPHATIDYLINOSITOL, INTRACELLULAR CALCIUM AND PROTEIN KINASE C ACTIVITY IN RAT COLONOCYTES UNDER ULCERATIVE COLITIS DEVELOPMENT

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Ulcerative colitis (UC) is a widespread chronic inflammatory large intestine disorder. The pathophysiologic mechanisms that trigger colitis are only partially understood. Brown J. F. established that increases in protein kinase C (PKC) activity have been associated with the state of UC. Most of PKC isozymes require Ca^{2+} for activation. Phosphatidylinositol (PI) cleavage and triphosphoinositol accumulation is necessary for intracellular Ca^{2+} increase and, properly, for PKC activation. The aim of our study was to determine membrane phosphatidylinositol content, level of free cytoplasmic Ca^{2+} and PKC activity under experimental colitis development. Colitis was induced by 1,5 % dextran sulfate sodium salt (DSS) solution. The membrane phosphatidylinositol content was determined by thin-layer chromatography on 1-st, 3-rd and 7-th day of DSS treatment. The probe (indo-1) was applied for intracellular Ca^{2+} measuring. The colonocyte PKC activity was assessed by the transfer of the phosphate group from [γ-^{32}P]ATP to the specific protein substrate. Significant changes of both membrane phosphatidylinositol content and intracellular Ca^{2+} were not determined on 1-st day of colitis induction. The colonocyte PKC activity was increased at this term. We suggest it could be explained by activation of Ca^{2+}-independent PKC isoforms. Temperate decrease of PI content (on 14%) and PKC activity (on 13%) occurred on 3-rd day. However maximal accumulation, exceeding of intracellular Ca^{2+} was observed at the same period of experiment. Such changes of Ca^{2+} content maintained until 7-th day of colitis development. The PKC activity had maximal value at this time point. The membrane PI level had decreased on 15% comparing with the control. These findings are supportive of a role for $Ca^{2+}$and PKC signaling pathway in mediating physiological events in colonocytes, and suggest that changed activity of this pathway may contribute to the alterations in colonocyte functions and cell cycle associated with colonic inflammation.

PRO- AND ANTI-APOPTOTIC FRAGMENTS OF FIBRONECTIN IN MYOCARDIAL INFARCTION

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Apoptosis is a distinct form of cell death that contributes to the active removal of irreversibly damaged or redundant cells in physiological and pathological processes, such as myocardial infarction and ischaemia. It has been brought to light the key role of apoptosis in the post-infarction remodelling that results in progressive myocyte loss in the periinfarct and remote myocardial regions. Recently it has been presented a number of experimental data about participation of fibronectin and its fragments in the regulation of apoptosis. Besides it was reported that RGD, CS-1 and FN-C/H-V fragments induce apoptosis in lung fibroblasts and 150 kDa fragment may elicit mesangial cell apoptosis. At the same time it was shown that native fibronectin promotes survival of cardiomyocytes. The aim of our work was to determine fibronectin fragmentation and the presence of native and pro-apoptotic fragments in blood plasma of the patients with myocardial infarction (MI) before and after the treatment with enocsaparin (EP), phondaparin (PH) and their combinations. Fibronectin fragments (fFn) were studied in 71 patients with MI by Western-blot analysis. Patients were divided into 4 groups: 1- with uncomplicated duration; 2- with total complications; 3- with thrombotic complications; 4- with hemorrhagic complications. Blood collection was made at the 1-st day (myocardial infarction), 8-21 (treatment period) and a year later. During MI pro-apoptotic fFN (40-49kDa, 125-140kDa) appeared in blood stream, simultaneously increased content of anti-apoptotic fFn 215-220kDa (native subunits of fFN). Dynamics of change of these fFN depended on chosen way of treatment. It has been revealed that administered EP results in some decreasing of 40-49 fFN at 8-th day. Other results were obtained during treatment with PH – this fFN was present in all studied patients at 8-th day, but later frequency of appearance of this fragment decreased and was present only in 57% cases. Combination of EP - PH led to significant decreasing of 40-49 fFN. Also combination of EP - PH results in decreasing of 125-140 fFN. So study of the connection between apoptosis and presence of some pro-apoptotic fFN may highlight a lot of interesting things and become useful in monitoring of the disease, remodelling process, prognosis of complications and in choice of the optimal therapy.

MODULATION OF TOTAL BASE-LINE ELECTRIC ACTIVITY OF HYPOTHALAMUS IN RATS UNDER THE ACTION OF THE PROTRACTED EMOTIONAL STRESS AND APPLICATION ON ITS BACKGROUND OF SOME PSYCHOTROPIC DRUGS

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Probed the influence of the protracted emotional stress, created by limitation of animals' vital space, on the total base-line electric activity of hypothalamus and the modulating action of psychotropic drugs (Gidazepam, Amitriptyline, Pyracetam, Aminazinum or Pyroxan) on the indexes of electrohypothalogrammy (EGtG) in rats, which were in stress situation. During 21 weeks were analyzed the spectral powers of basic frequency components (mkV^2) and their rationed values to total power of all waves in EGtG (%).It was set that modulation of base-line total electric activity of hypothalamus under the action of stress was characterized by a difficult dynamics in which concordantly to the electrographic indexes it was possible to select certain periods. During the first 6 weeks of experiment in EGtG were signs of general excitation of animals under the action of external irritants: growth of indexes of beta-waves on the background of desynchronization of electrical activity in other frequency ranges. From 9 to 15 weeks of investigations the emotional tension of animals began to show up, what

increase of the rationed power of teta-waves testified about. This index attained the maximal value to the end of researches and was accompanied by synchronization of slow waves in EGtG. Application of different psychotropic drugs caused the identical modulation of EGtG in rats, which were under the stress situation. During first 6 weeks the power of all rhythms in EGtG decreased, whereupon the analyzed index sharply increased and remained high to the end of experiment. In EGtG the amount of beta-waves diminished and the representation of teta-waves increased. Such changes could specify on decline of reactivity of the cerebral systems on external stressogenical irritants and on a basic role of endogenous mechanisms in forming of EGtG, caused the synchronization of total base-line electric activity of hypothalamus in rats.

VASODILATATOR EFFECTS OF AMYLIN AS ONE OF MECHANISMS OF HIS ANTIULCEROUS ACTION

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Amylin is a hormone of peptide nature, secreted jointly with insulin by β-cells of pancreas. In our previous researches on the different models of ulcer the expressed antiulcerous effect of amylin was rotined in regard to the gastric mucosa, but the mechanisms of realization of this effect are studied it is not enough. From our data, one of such mechanisms is an improvement of terms of microcirculation in a mucosa. We have shown, that amylin has vasodilatator endothelium-independent effect on the isolated circular preparation of rat aorta. This work is devoted to the study of action of this hormone on the microcirculation of gastroenteric bed. Research of vasculomotor effects of amylin was conducted on the isolated mesenteric artery of rats, which perfuse with an indirect cost. we judged about the reaction of vessel on preparations by the changes of perfuse pressure on a degree. Initial tone of vessel was created by perfusing solution of Noradrenalinum ($5 \cdot 10^{-7}$M), that resulted increasing of pressure. Introduction to the system of perfuse amylin in a dose, near to physiological (10^{-6}M), caused decreasing of perfuse pressure on 18% ($P<0,01$), that in the conditions of this experiment corresponds expansion of vessel. A reaction on a peptide developed in the 2-3 minutes of perfuse, a maximal effect was seen at in 5 minutes. So, a presence of vasodilatation action of amylin on a mesenteric artery allows to suppose that an improvement of blood flow of tissues is one of mechanisms of increasing gastric mucosa stability at the action of this hormone.

NONSELECTIVE NITRIC OXIDE SYNTHASE INHIBITOR INFLUENCE ON PROCESSES OF GASTRIC MUCOSAL ULCER DEVELOPMENT

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Acute stress provokes alterations in acid secretion, increase in gastric motility, disturbance of gastric mucosal microcirculation and mucus production. Such pathological is attended by high risks of appearance of gastric mucosal lesions. Nitric oxide (NO) as a secondary messenger regulates mucosal blood flow and shows gastroprotective properties. However, production of excessive amount of NO has been implicated as a cytotoxic factor in a variety of pathophysiological processes. The aim of the study was to evaluate the nitric oxide synthase (NOS) activity in gastric mucosa during development of ulcer induced by stress and determine influence of nonselective nitric oxide synthase inhibitor on ulceration. Male rats weighing 270 - 280 g were starved for 24 h prior to experiments, but were allowed free access to water. Rats were restrained in a wire cage and immersed up to the depth of the xiphoid process in a 23°C water bath. The animals were killed 0,5, 1, 2, 3 h later. L- nitro-arginine

methyl ester was given intraperitoneal 5 min before the stress. NOS activity was measured in homogenate of gastric mucosa.The significant damages of gastric mucosa were not found after 30 min of stress. However, the quantity and areas of ulcer were shown increased on 1, 2, 3 hour of experiment. The elevation of NOS activity in 3, 6, 8 times was observed at these terms of experiment. The gastroprotective effect of inhibitor treatment was established. The NOS activity increased after L-NAME administration on initial stages of ulcer development, but it decreased on 3 hour of stress. These results suggest that, excessive production of NO by NOS is a additional cytotoxic factor, injuring gastric mucosa under stress-induced ulceration.

HSP90 AND HSP70 EXPRESSION LEVELS IN GASTRIC MUCOUS PARIETAL CELLS UPON ATHROPHIC GASTRITIS DEVELOPMENT IN RATS

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The protective role of heat shock proteins in gastric mucosa is well established by numerous investigations. However, it is little known about precise role of Hsp in different cell types in mucous, especially upon different stomac disorders, such as ulcer, different types of gastritis etc. In our work chronic atrophic gastritis (CAG) model in rats was used to elucidate the role of main groups of chaperones in parietal cells. CAG model in rats was established according to Si and coworkers. Male Wistar rats (230-250 g) were administered 2 % sodium salicylate (2 ml i. g.) daily for 6 weeks, and deprived of water which was replaced by 20 mmol/L sodium deoxycholate, placed in stainless cages with 5 animals in each group, at temperature near 20°C, with 12 h dark and light cycles. In order to elucidate heat shock proteins expression level during chronic atrophic gastritis development parietal cells from gastric mucous glands were taken on 1-st, 3, 4, 5 and 6-th weeks of disease progression. Changes of Hsp70 and Hsp90 expression levels were detected by Western blot analysis with polyclonal antibodies against DnaK and bovine Hsp90 respectively. It was observed significant increasing in Hsp70 expression during CAG progression. However, changes in Hsp90 expression patterns were not so obvious. It is well known that there is a high level of cooperation between Hsp70 and Hsp90 in mammalian cells. In that way these chaperones may play a role in parietal cells protection upon gastric mucosal metaplasia in CAG.

RESPONSE OF MAST CELLS ON INFLUENCE OF EXTREMELY LOW FREQUENCY MAGNETIC FIELDS

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Mast cells are the special immune cells which are located in all organs and tissues. These cells are the effector cells that secreted wide spectrum of biologically active substances by means of degranulation. Mast cells are very sensitive to state of extracellular matrix and take part in initiation of regional inflammatory reaction and also regulate functional activity tissue cells, other immune cells, processes of hemostasis et cetera. The high sensitivity of mast cells to influence of extremely low frequency magnetic field (ELF MF) *in vitro* was discovered in our researches on animals. The aim of this study was estimation of ELF MF influence on mast cells *in vitro*. It was revealed that influence of ELF MF changes the spontaneous degranulation of mast cells *in vitro*. Value and direction of these changes depend on frequency (in diapason 0-100 Hz), magnetiv field amplitude (0.02-30 μT) and time of exposure (0-3 hours). Magnetic field frequencies 2; 8-10; 50; 72-74 Hz stimulate but 32-34

Hz decrease spontaneous degranulation of mast cells. The increasing of degranulation rate can be up to 60-80% during 3-hour exposure. The minimal response (on level 5-7%) of mast cells on ELF MF can be discovered at the magnetic field amplitude 50-200 nT. The obtained experimental data allows us to put question: are the ELF MFs activator and sensibilizator of some immune processes, in particularly allergic reactions?

THE APOPTOTIC PATTERN OF THE EMRYONIC HEART: LECTINS HELP TO VISUALIZE.

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The apoptotic processes in the embryonic heart determine the further alignment of the organ and possibly show the participation of the neural crest (NC) in the developement of the heart. We have studied the normal and abnormal apoptotic patterns in chick embryo hearts. The chick embryos were treated by 0,2-0,25 ml of 50% ethanol at 72 hours of incubation and also were treated by 1 mkg of all-trans retinoic acid at the 15th HH stage. The macroscopic study of the hearts of the normal and treated embryos, and the histological and lectinhistochemical study of the serial sections were carried. The apoptotic cells were single up to the 4,5 embryonic day (ED). Activity of these processes increased rapidly and achieved a maximum on the 5-5,5 ED, whereupon gradually declined to the 8 ED. The areas with the maximal apoptotic activity were the cono-truncal part of heart (the peak of activity is on the 5-6 ED), atrioventricular septum (the peak is on 5 ED), the apex of interventricular septum (the peak is on the 6 ED), and the area of valves (peak is on the 7-8 ED). The apoptotic processes in the cono-truncal part of the heart resulted in its substantial contraction and the disappearance of the cardiac muscle layer in a trunk which is a basis for the formation of the aorta and pulmonary trunk. The treated embryons showed a diminishing number of apoptotic cells in the crucial regions, perhaps as a result of the delay of the migration of the dense mesenchyme that originated from the NC. Some lectins (RCAI, WGA, STA) clearly revealed apoptotic cells in the embryo. We suggest that the strong binding by the apoptotic cells of the lectins that were studied are the result of the exposure of the largest part of the cell membrane receptors during cell death. We conclude that the apoptotic pattern of the emryonic heart in different models of abnormal development can give the overview about participation of NC.

THE LINK BETWEEN THE HYPOACIDITY OF GASTRIC JUICE AND MORPHOFUNCTIONAL STATE OF COLONIC MUCOSA AND POLYPS FORMATION

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The implication of gastrin (G) as a trophic agent for colonic mucosa (CM) is arising. In mice with increased G serum levels (hypergastrinemia, HG) a significant increase in polyp number in colon was observed. As since the hypoacidity of gastric juice causes G secretion and the functional state of colonic mucosa tightly depends on its morphological state the aims of the study were to establish the gastric acidity in patients with anal and rectal polyps (RAP) and to study the action of the long-term HG on the morphofunctional state of the CM. The first part of our investigation included examination of 20 patients. 10 patients were healthy volunteers. In another 10 patients were diagnosed the RAP. The gastric acidity was determined by intragastric pH-metric method. The second part of the investigation consisted of the study of net water and electrolyte (Na^+, K^+, Cl^-) colonic epithelial transport (Jnet) in rats with omeprazole-induced HG (n=7) compared with the baseline (n=8) (0,2 ml of saline, i.p.). Rats were given omeprazole for 4 weeks (OM, 14 mg/kg, i.p.). Jnet water was determined by

colorimetric method, Jnet electrolyte – by ion selective electrodes. Also it was examined the trophic effect of HG on CM in rats and were used such morphometric indices as mucosa thickness (MT), crypt depth (CD) and nuclear profile area (NPI). Plasma G level (PGL) was determined by radioimmune assay. It was established that in healthy volunteers pH of gastric juice of empty stomach was 1,8-2,4 but in all patients with RAP pH was 5,9±0,6. In rats long-term injection of OM induced hyperplasia of CM. In these rats PGL was increased by 189,27%, Jnet water, Jnet Na^+ and K^+ were decreased but JnetCl^- was increased. So prolonged HG induces the appearance of hyperplastic lesions of CM along with alterations of its transport function.

BACTERIAL AND ANTIGEN-SPECIFIC SUBSTANCES ACTON ON MEMBRANE AND CELL MECHANISMS OF AGONIST-INDUCED ACTIVATION AND INHIBITION IN SMOOTH MUSCLE CELLS

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The action of cell-bound protein A (CBPA) of Staphylococcus aureus and transfer factor (TF) of immune reactivity to diphtheria-tetanus anatoxin on processes of excitation and inhibition in taenia coli smooth muscles were researched with sucrose-gap technique, tension measure and fluorescence spectrum registration. In our investigation CBPA depolarizes smooth muscle (SM) membrane and increases its tone. In presence of atropine these changes weren't noticed. CBPA enhances, in time - decreases the inhibiting action of purinergic receptors agonists (ATP and UTP) in SM, removes hyperpolarizing action of sodium nitroprusside (SNP). SM depolarizations, invoked by TEA, and by ATP against a background of SNP inhibition were not sensitive to this substance. N^{ω}-nitro-L-arginine inhibits the activating action of CBPA on nicotine-invoked relaxation of histamine activated SM. CBPA decreases the inhibiting ATP action (or SNP) on SM contraction, invoked by histamine; enhances cholinergic excitation. CBPA increases fluorescence in indo-1coated suspension of isolated SM cells in Ca^{2+}-free solution in presence of caffeine and carbocholine. Low concentrations of CBPA enhance ATP-ase activity (Mg^{2+},Ca^{2+}-; Mg^{2+}-; Mg^{2+}- in presence of EGTA) of SM actomyosin. Transfer factor (TF) modulates the low waves of depolarization, spontaneous contractile activity of non-atropinized and atropinized SM. In the presence of methylene-blue, blocker of guanylcyclase, TF increases muscle tone, which transforms into its stable relaxation under basal. This substance significantly enhances after-inhibiting SM cells depolarization invoked by ATP (or UTP). TF removes the inhibiting SNP and noradrenaline action on SM.

INHIBITION OF ACUTE ENDOGENOUS CORTICOSTEROID RELEASE MAY BE A REASON OF GASTRIC ULCEROGENIC EFFECTS OF GLUCOCORTICOIDS AT PHARMACOLOGICAL DOSES

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Glucocorticoids administered at pharmacological doses can induce or aggravate gastric injury. Based on this fact, the increase of glucocorticoids during stress was also considered to be an ulcerogenic factor. Our findings, however, suggest gastroprotective role of glucocorticoids produced in response to acute stress. The study was designed to verify the hypothesis that the deleterious effect of glucocorticoids at pharmacological doses on the gastric ulcerogenic response could be due to inhibition of acute release of corticosteroids in response to ulcerogenic stimuli. Methods: Gastric erosions were induced by 3 h cold-restraint or water immersion and restraint or indomethacin (35 mg/kg, sc) in rats after 24 h fasting. The effects of cortisol at the dose of 300 mg/kg, (ip) on the gastric erosions and

glucocorticoid production were investigated in 1 or 4 weeks after cortisol treatment. CRF-41 content in median eminence and blood ACTH level were also investigated 1 week after cortisol administration. Results: The stressors and indomethacin caused plasma corticosterone rise that was almost fully prevented in cortisol pre-treated rats 1 week after the pre-treatment. The deficient corticosterone responses observed 1 week after cortisol pre-treatment was due to inhibition of hypothalamic-pituitary adrenocortical (HPA) axis at hypothalamic and pituitary levels. The gastric erosions were significantly aggravated 1 week after cortisol pre-treatment, and an acute corticosterone replacement (4 mg/kg, sc) prevented this aggravation. Four weeks after cortisol pre-treatment both corticosterone and gastric responses to ulcerogenic stimuli were totally restored. Conclusions: Inhibition of HPA axis with consequent deficient corticosterone production may be a reason for the gastric ulcerogenic effect of glucocorticoids administered at pharmacological doses. Supported by BSciM RAS-2008, RFBR-07-04-00622, DBSci RAS-2008, Sci School RAS-1434.2008.4.

IRRITABLE EFFECT OF ASPIRIN ON THE INTESTINAL MUCOSA OF RATS

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Recently, intestinal endoscope demonstrated that NSAIDs (including enteric-coated aspirin) induces hemorrhagic lesions and ulcers in the intestinal mucosa of patients. Such intestinal lesions induced by NSAIDs are also confirmed in the animal experiments. However, aspirin is known not to damage the intestinal mucosa in laboratory animals by its chemical specificity (pKa=3.5). We studied to know whether or not aspirin induces intestinal mucosal lesions in rats when it was given directly in the small intestine thinking about the enteric-coated aspirin. Aspirin (6.3,12.5,25,50,100 mg/animal), packed in the gelatin capsule (#4,Gc-aspirin), was given intraduodenally (i.d.) to the 20hr-fasted rats (male SD,12-14wk-old), through a small hole produced in the proximal duodenum. The hole was closed by suture after administration. Gc-aspirin was also given in the stomach through the small hole produced in the forestomach. 1,3,6,24 hr after treatment, the animals were killed with ether and the entire part of small intestine (jejunum and ileum) was examined for the visible injuries. The intestinal specimen was examined by routine histological examination. Gc-aspirin at 6.3 mg/animal clearly induced severe hemorrhagic lesions in the small intestine l to 3 hr after administration at the incidence of 100%. The lesions were found both in the jejunum and ileum, sometimes even in the cecum. Although the dose was increased up to 100 mg/animal, the damaging effect was much the same. Interestingly, Gc-aspirin given into the stomach had no irritable effect on the stomach. Pretreatment with 16, 16-dimethyl PGE_2 (10 ug/animal) significantly prevented the development of Gc-aspirin-induced intestinal damage. The present study clearly demonstrated that i.d. administered Gc-aspirin could induce intestinal lesions in rats at 100% incidence, yet had no effect in the stomach. This suggests that the small intestine has very high sensitivity to aspirin than the stomach. The mechanism of action of aspirin appears due to the direct irritation of aspirin to the intestinal mucosa, yet the precise mechanism remains unknown.

BOWEL MICROFLORA IS NOT INFLUENCED BY HELICOBACTER INFECTION IN PATIENTS WITH GERD

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Introduction. H. pylori role in ethiology and pathogenesis of many gastro-duodenal disorders is well known. At the same time, it is not known how H. pylori infection influences the quantity and quality of

bowel microflora. Changes in microflora can be one of the factors provoking development of posteradication syndrome. The aim of the study was to investigate bowel microflora in patients with GERD depending on presence of H. pylori infection. Materials and methods. Bowel microflora was studied in 2 group of patients. First group consisted of 15 patients with GERD and H. pylori infection, the second group consisted of 15 patients with GERD without H. pylori infection. Diagnosis of GERD was verified by endoscopic examination, 24-hour esophageal-pH monitor and urea breath test with 13C-marked urease. The patients from both groups did not receive anti-helicobacter treatment before. The microflora of stool samples was examined. Results. The quantity and quality of bowel microflora in those 2 groups of patients was statistically even ($p>0.05$). In group of H. pylori infected patients with GERD general quantity of E. coli was $1.72\cdot10^8\pm8.9\cdot10^7$; β-glucosidase lactose negative E. coli – $4.61\cdot10^7\pm3.1\cdot10^7$; enterohaemorrhahic E. coli – $1.42\cdot10^7\pm9.5\cdot10^6$; lactobacterium and bifidobacterium – $7.65\cdot10^9\pm7.1\cdot10^9$. In group of H. pylori negative patients with GERD general quantity of E. coli was $8.7\cdot10^7\pm4.9\cdot10^7$; β-glucosidase lactose negative E. coli – $1.2\cdot10^7\pm6.9\cdot10^7$; enterohaemorrhahic E. coli – $3.8\cdot10^7\pm2.2\cdot10^7$; lactobacterium – $9.2\cdot10^8\pm6.2\cdot10^8$ and bifidobacterium – $6.71\cdot10^9\pm6.2\cdot10^9$. Conclusion. In this study no dependence between bowel microflora in patients with GERD and H. pylori infection was found.

CHANGES OF PANCREATIC ALPHA-AMYLASE ACTIVITY IN BLOOD AND LIPOPEROXIDATION PROCESSES UNDER COX-2 BLOCKAGE IN RATS WITH DIABETES MELLITUS

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Objective: Pathogenesis of diabetes mellitus (DM) is associated with increased contents of endogenous prostaglandins (PGE2), nitric oxide (NO) and intensified lipoperoxidation processes (LPO) in the pancreatic tissue. Purpose of the work was to investigate changes of LPO processes, NO content, α-amylase activity in rats with DM type 1 under COX-2 blockage with selective inhibitor celecoxib. Methods: investigation was conducted on 6-8 male rats in two series: 1) on the 4th week after streptozotocin (STZ) injection (60 mg/kg); 2) 2 weeks after STZ injection, celecoxib was introducing perorally (10 mg/kg) for 14 days. Contents of TBARS and NO, activity of antioxidant enzymes – SOD and catalase were studied in the tissue and blood serum and α-amylase activity in the serum. Nitric oxide content was measured with the use of Griess reagent and evaluation of α-amylase activity was performed by means of the set of reagents manufactured by the company "Pliva – Lachema Diagnostika". Results: Due to the action of STZ, content of TBARS increased by 60 % ($p < 0.05$), NO content decreased by 26%. Activity of the antioxidant protection enzymes SOD and catalase enhanced by 60 % ($p < 0.05$) and 16 %, respectively. Activity of α-amylase in the blood decreased sharply by 61 % ($p < 0.05$). COX-2 blocker celecoxib in diabetic animals caused decrease of TBARS by 17 %, NO - by 7 %, SOD activity by 53 % ($p < 0.05$), catalase - by 9 %. In contrast, activity of pancreatic α-amylase increased in serum by 19 %. Conclusion: Thus, blockage of COX-2 by celecoxib in rats with DM caused reduction processes of LPO and antioxidant enzymes activity in pancreatic tissue. Introduction of celecoxib causes enhancement of α-amylase in the blood thereby contributing to the improvement of digestive processes in the intestines in DM.

PRO- AND ANTIOXIDATIVE PARAMETERS IN RAT BLOOD AND LIVER MITOCHONDRIA UNDER HEMIC HYPOXIA AND PREVIOUS APPLICATION OF AMARANTH OIL

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Changes of pro- and antioxidant processes in blood and liver mitochondria under condition of hemic

hypoxia maximal development (1 hour after injection of sodium nitrite in dose 20 mg/kg) and previous introduction of amaranth oil (38 mg/kg, during 10 days) was investigated. Lipid peroxidation (LPO) according to content of thiobarbituric acid reagent substances (TBARS) in studied tissues of high resistant (HR) and low resistant (LR) to hypoxia animals at hemic hypoxia was differed. TBARS content in liver mitochondria and blood of HR animals exceeded a norm, but in LR rats this parameter was decreased in comparison with control. Activity of superoxide dismutase (SOD) and catalase (CAT) – antiradical link of antioxidant defense system was increased in liver mitochondria of both groups rats comparison with control. Reliable decrease of SOD in the blood of HR and LR rats in comparison with control was revealed. CAT activity in blood of HR rats was increased only by 15 %, and in LR animals significant was decreased, compared with norm. Depression of glutathione peroxidase (GPx) and I_{AOA} – antiperoxide links of antioxidant activity (AOA) – in liver mitochondria of HR rats, in relation to control, was associated with elevated LPO. Increase of GPx in mitochondria of LR rats was correlated with increase of I_{AOA}, activation of antiradical mechanisms and supported level LPO close to control. Elevation of GPx, I_{AOA} and reduced glutathione level in blood of HR rats in comparison with norm, unlike LR animals was revealed. Changes of studied parameters of LPO-AOA system at previous application of amaranth oil, in comparison with introduction only sodium nitrite, in blood and liver mitochondria of HR and LR rats testified of redox processes intensification. In blood and liver mitochondria of LR rats LPO activation, with closing to norm, and antioxidative defense system links was determined. The study was supported by WUBMRC (West-Ukrainian BioMedical Research Center).

THE EFFECT OF HYPERGASTRINEMIA ON ESOPHAGOPATHIC CONSEQUENCES IN HYPOTHYROID RATS

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Prolonged proton pump inhibition has led to hypergastrinaemia (HG) and it has been presumed that HG in itself increases the risk of neoplasia in humans. It has been reported that dilation of the intercellular space in esophageal mucosa (EM) was observed in patients with esophageal damage and possibly contributed to pain and the onset of the abnormal sensation. We previously reported of the role of thyroid hypofunction (TH) as a risk factor of oxidative stress on gastro-intestinal abnormality and showed that EM epithelial glycoforms play specific and distinct functional roles during development injury and repair onset. The aim of the present study is to examine if the inhibition of gastric acid secretion by proton pump inhibitor (PPI) treatment influence on intercellular, matrix-cellular epithelial and stromal components in EM with experimental hypofunction of thyroid gland. The study was conducted on rats without/with experimental HG induced by omeprasol (20 mg/kg/day) and generally accepted merkazolil-induced TH. Rats were sacrificed at 28 days to analyze the damage by esophageal epithelial thickness, leukocyte infiltration and proliferation index and the expression of oligosaccharide residues of peroxidaseconjugated *Helix promatia* (HPA), snail agglutinin (SNA), wheat germ agglutinin (WGA), and peanut agglutinin (PNA) lectins in (A) the upper, (B) the middle and (C) EM areas. Cell-to-cell and cell-to-matrix spaces of non-erosive EM of TH rats were significantly dilated in comparison to intact rats. HG evoked epithelial hypertrophy in C area by increased proliferation index, but in rats with HG&TH combination were dislocalization of EM epithelial layers and disorganisation of matrix component and mosaic increased of NAcDGlc, NAcDGal i DGal, NAcDGlc expression in superficial, spinosum and basal layers that we interpreted as the defense reaction. The results of the present study suggested that hypothyroidism may be a potential source of esophageopathic changes and HG is one of the most important risk factors for the development of esophageal epithelial hyperplasia.

PROTECTIVE AND DELETERIOUS ACTIONS OF DEXAMETHASONE AGAINST STRESS- AND INDOMETHACIN-INDUCED GASTRIC ULCERATION: DEPENDENCE OF THE ACTION ON TIME INTERVAL BETWEEN THE HORMONAL INJECTION AND ONSET OF ULCEROGENIC STIMULUS

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Administration of glucocorticoids can induce or aggravate and in some cases attenuate gastric erosion formation. The aim of the study was to investigate the factors responsible for manifestation of protective or deleterious actions of dexamethasone on the gastric mucosa. Methods: Gastric erosions were induced by 3 h cold-restraint or indomethacin (35 mg/kg, sc) in male S-D rats after 24 h fasting. Dose- and time-dependent effects of dexamethasone on the gastric erosions as well as corticosterone and blood glucose levels, somatic parameters were examined after single injection of dexamethasone. In the dose-dependent study, the animals were given an injection of dexamethasone at various doses (0.01, 0.1, 1, 10 mg/kg, ip) or its vehicle and 1 h later they were underwent the ulcerogenic stimulus. In the time-dependent study, the animals were given an injection of dexamethasone at a dose of 1 mg/kg or its vehicle and they were underwent the ulcerogenic stimulus at various time points after the injection (15 min; 1, 6, 12, 18, 24 h). Results: Dexamethasone at the doses of 0.1, 1, 10 mg/kg decreased the gastric erosion area dose dependently in the case of its injection 1 h before the ulcerogenic stimulus. Gastroprotective action of dexamethasone (at a dose of 1 mg/kg) was also observed in the case of its injection 6 and 12 h before the ulcerogenic stimulus. The further increase in the time interval (24 h) caused transformation of gastroprotective action of dexamethasone to ulcerogenic one. Conclusions: Manifestation of protective or deleterious actions of dexamethasone on the gastric mucosa may be dependent on the time interval between the hormonal injection and onset of ulcerogenic stimulus. Supported by BSciM RAS-2008, RFBR-07-04-00622, DBSci RAS-2008, Sci School RAS-1434.2008.4.

THE INFLUENCE OF TRANSECTION OF RAMUS PYLORICUS NERVI VAGI ON GASTRIC EMPTYING OF CARBOHYDRATE AND FAT FOOD IN DOGS

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Transection of ramus pyloricus nervi vagi (RPNV), the branch of nerve vagus, which innervates pylorus, often is part of whole series of operating intervention in humans such as pancreato-duodenal resection. That's why it is important to investigate consequences of this transection on gastric emptying (GE). So, the aim of the study was to investigate the influence of transection of RPNV on gastric emptying of carbohydrate food (CF) and fat food (FF). The investigation were carried out in chronic experiments on dogs (n=6) with fistulas of fundul part of stomach and duodenum. The animals of 1st group (3 dogs) were with intact nervous system (INS). The animals of the 2nd group (3 dogs) were after operation of transection of RPNV. GE from stomach was investigated by the method of draining of the duodenal fistula with CF (100 g bread = 21,5 kkal/kg) or FF (100 g bread + 25 g margarine = 33,7 kkal/kg) mixed with 600 rubber corpuscles, which were markers. The volume of each corpuscle was not more than 1mm^3. In every 25 minutes we drained the duodenal fistula and during 5 minutes collected the chyme with rubber corpuscles. It was established that transection of RPNV didn't change the time of GE of CF but decreased duration of the 1st phase of evacuatory process by 30 min. In results duration of the 2nd (exponential) phase is increased by 30 min. In dogs with transection of PRNV FF was evacuated by 23.8 % faster in comparison to dogs from control group. Transection of RPNV evoked

appearance of exponential character of dynamic of GE of FF which was absent in dogs with INS. We concluded that some postoperative disturbances in digestive disease in patients with transection of RPNV are connected with acceleration of GE of FF and these patients are in need of low-fat diet.

PROTECTIVE ACTION OF PEPTIDE PRO-GLY-PRO-LEU ON ETHANOL-INDUCED GASTRIC ULCER

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Glyprolines are a family of endogenous regulatory peptides, which have already shown wide range of biologic activities. Their formation may be a part of collagen metabolism and maturation. One of these peptides, Pro-Gly-Pro (PGP) demonstrated significant protective effect on different (stress-, ethanol- substance 48/80- and indometacine-induced, acetic, pylorus ligation) gastric ulcer models and curative effect on acetic ulcer model. Peptide Pro-Gly-Pro-Leu (PGPL) can be viewed as PGP modification and may also have an endogenous source. Moreover, peptide Gly-Pro-Leu (GPL) proved to be an effective angiotensin-converting enzyme inhibitor. This may be very important for support of gastric mucosa homeostasis, as angiotensin II is one of essential factors of ischemia development during ulcerogenesis. The aim of our study was to explore the possible protective effects of PGPL on gastric mucosa homeostasis disrupted by ethanol. PGPL (3,7 mkmol/kg, i/g) was administered 1 hour prior to 96% ethanol (5 ml/kg, i/g). Our results showed that PGPL failed to increase gastric mucosa homeostasis resistance to ethanol. While biological activity of GPL suggested the possible existence of protective antiulcer effect, it was absent. PGP had significant antiulcer effect and decreased lesions size on 64%, but PGPL only showed tendency towards lowering lesions size on 18,05%. Conclusions: PGP and PGPL antiulcer effects on ethanol-induced gastric ulcer highly differ; PGPL is ineffective on this model, despite the known GPL bioactivity.

REGULATION OF THE COLONIC MUCOUS COAT'S STATE CHANGES, CAUSED BY LONG-TERM HYPERGASTRINEMIA, USING THE MULTIPROBIOTICS "SYMBITER® ACIDOPHILIC" AND "APYBACT®"

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Influence of the multiprobiotics "Symbiter® acidophilic" (S) and "Apybact®" (A) on the morphometric characteristics of colonic epithelium in the presence of the long-lasting hypergastrinemia (28 days) was investigated. A total of 37 rats (the control group – 7 rats, the second group received omeprazole (O), the third – O and S, and the last one – O and A (10 rats in every group) were used in the study. The height of the colonic mucous coat, the cross-sectional area of the epithelial cells and their nuclei, and nucleocytoplasmic index were evaluated. It was shown that long-lasting hypergastrinemia causes hyperplastic alterations with increase of mucous coat height, cross-sectional area of epithelial cells and decrease of cross-sectional area of nuclei, as well as decrease of nucleocytoplasmic corellation. It is generally known, that hypergastrinemia causes the increase of gastrin level, and alterations observed may be given by the trophic action of gastrin. The administration of S to rats promoted restitution of mucous coat height and nucleocytoplasmic corellation to normal level, cross-sectional area of epithelial cells decrease and cross-sectional area of their nuclei increase as well, but did not reach normal level. However, the administration of A caused less significant restitution of the characteristics

investigated: all of them exhibited tendency to normalization, but no one did not reach the normal level. Taking into consideration results of the investigation, S and A may be recommended with preventive goal in patients with hypoacidity, and during long-term use of antisecretory drugs in patients with duodenal ulcers, pancreatitis, gastroesophageal reflux etc to avoid hyperplastic alterations of colonic mucosa.

ESTIMATION OF ANTIOXIDANT ACTION TO MALIGNANT GROWTH IN RADIOTHERAPY

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Our researches aim was investigation of LP and PAS superscripts in tissues of organs (brains, livers, spleens), tumor and blood in rats with Geren carcinoma within the dynamics of tumor growth under the conditions of local radiation treatment and a grape seed proanthocyanidin extract (Acti Vin) treatment. 102 white laboratory rats-males (weight 130 ± 10 g) kept to standard vivarium diet were used in experiments. Geren carcinoma was transplanted to the animals by subcutaneous injection of 20% tumor cells suspension of 0.9% NaCl solution into back extremity hip. Tumor cells were taken from the rat-donor. 8 days after inoculation tumor was exposed to X-radiation at the rate of 1 Gr on the RUM-17. Some animals took antioxidant preparation Acti Vin™ (InterHealth Nutritionals Incorporated, Concord, CA) per oral at the rate of 25 mg/kg every day during 7 days between tumor inoculation and local radiation treatment. Acti Vin™ contains natural antioxidants grape seed proanthocyanidins from polyphenol bioflavonoids group. Cancerous process and radiation treatment promote even greater increase of quantity of LP-products in the healthy organs of animals and especially in the brains. SOD and catalase activities mainly decrease. These changes characterize negative effects of cancerous growth and radiotherapy on the organism state. The effects of antioxidant preparation being investigated on the oxidant-antioxidant tumor homeostasis are small but taken data are evidence that antioxidant doesn't stimulate cancerous process. At the same time the preparation treatment improves the state of the healthy organs in rats with tumor substantially, especially in the brains where negative after-effects are the most expressed. Quantity of LP-products decreases in the organs substantially and activities of antioxidant enzymes rise significantly. These data characterize appropriateness of utilization of present biologically active substance in the complex therapy of tumor particularly.

THE ULCEROPROTROPIC EFFECT OF N-URONOYLDERIVATIVE AMINO ACID

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In previous researches is it set by us, new N-uronoylderivative β-alanine (DAGU-Ala), glycyl-D,L-glutaminic acid (DAGU-Glu) и glycyl-glycine (DAGU-Gly) in stress-models render a certain psychotropic action. The presence of ulceroprotective action at these connections was probed with the use of Sel'e's offered model of the forced swimming. In this test the index of stress is an ulcerous defeat of mucous membrane of stomach (MMS). Research was conducted on white outbred rats-males mass of a 200-220 gram. Connections dissolved in physiologic saline and introductioned the rats of main groups intraperitoneal introduction. in a volume 0.2 ml, in a dose 50 mgs/kg 20 minutes before the experiment. Physiologic saline was introductioned the rats of control group in the same volume. Statistical treatment of results was conducted with the use of non-parametric criterion Manna-Whitney. Reliable distinctions of parameters of the main and control groups were considered at $p<0,05$. At research of MMS of rats after one hour of the forced swimming found out subepithelial and epithelial

hemorrhage or expansion of capillaries of punctate or linear form. The dimensions of these injuries fluctuated from a spot (1 mm^2) to 3-5 mm in length (3-5 mm^2). The total area of ulcerogenic affection of gastric mucosa at control rats has on average formed 10,2±2,1 mm^2. At preliminary introduction of DAGU-Ala at animals decreases up to 7,3±2,4 $мм^2$ the area of MMS affection. At introduction DAGU and DAGU-Glu, on the contrary, inauthentically increases (up to 13,2±3,9 $мм^2$ and 11±1,2 $мм^2$ accordingly) a total affection area of mucous a stomach. Only at introduction of DAGU-Gly connection at animals authentically ($p < 0,05$) in comparison with the control group decreases (up to 2,5±0,5 $мм^2$) a total area of defeat mucous a stomach, i.e. the datum connection possesses antiulcerogenic action. Viewed the possible mechanisms of antiulcerogenic action of DAGU-Gly.

NEW CLASS OF REGULATORY PEPTIDES - GLYPROLINES, GASTRIC MUCOSA HOMEOSTASIS AND ORGANOPROTECTION

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Glyprolines (GPs) are a new family of biologically active peptide drugs containing Gly-Pro in their structure. GPs are fragments of collagens. Considering these peptides as endogeneous we supposed that they can be released during catabolism and some special stages of collagen synthesis too. Collagen maturation is partly associated (20-40%) with proteolysis of already assemled polypeptides. As a result small peptide containing less then five amino acid residues are secreted from collagen-synthetizing cells [Bienkowski et al., 1978-89]. GPs have a broad spectrum of action from antiulcer and antiaggregative to anxiolytic and nootropic. GPs protect gastric mucosa, increasing its stability, against such ulcerogenic factors as ethanol, indomethacin, stress, pylorus ligation, compound 48/80. They reveal not only protective antiulcer properties, but also decrease the formation of acetic ulcer and accelerate the healing of full-grown ones. As it was shown before PGP normalized many physiological functions and affected a number of mechanisms that caused gastric mucosa ulceration. It's important to emphasize that PGP prevents or eliminates post-stress behavior disorders accompanied by decreasing of anxiety. GPs can prevent disorders of the functional state of the mesenteric microcirculation bed during both inflammation and stress. This property is associated with their stabilizing effect on mast cells. It could be one of the mechanisms of PGP protective effect not only during stress or inflammation but also during other pathologies. The administration of tritium-labelled PGP was shown that degradation of PGP is realized gradually with mainly formation of GP to 12 minute. The presence of radioactive PGP or GP and PG was shown in some organs, including stomach, intestine and brain. Intranasal injection is the most optimal way for the peptide penetration to the rat brain. The greatest quantity of radiotracer was discovered in gastric tissues after different ways of administration, sometimes exceeding labeled peptide concentration in blood.

LEUKOTRIENS ARE IMPLICATED IN INDOMETHACIN- INDUCED SMALL INTESTINAL LESION FORMATION IN CATS

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Recent progress in endoscopic techniques, such as capsule endoscopy, has revealed that some NSAIDs often caused lesions in the small intestine in addition to the upper GI tracts in humans. Several different factors related to pathogenesis of NSAID-induced small intestinal lesions have been proposed.

However, the role of leukotriens (LTs) in the pathogenesis remains unclear. In the present study, we examined the role of LTs and cholinergic pathway in the hypermotilities and lesion formation in the small intestine induced by indomethacin (IND) using a 5-lipoxygenase (LOX) inhibitor (AA-861), a cysLT1 receptor antagonist (pranlukast) and an anti-cholinergic agent (atropine). Both male and female cats (2.5–3.5 kg) were used (4 or 5 cats per group). Gastrointestinal lesions: Pellets of dry food were given to animals twice a day during the experiment. IND was administered orally once a day after a morning meal for 3 days. The animals were sacrificed 24 h after the final dosing of IND, and mucosal lesions in the GI tract were examined. AA-861, pranlukast or atropine was given p.o. or s.c. twice a day, i.e., 1 h before and 7 h after IND administration. Gastrointestinal motility: GI motility was recorded in conscious cats implanted with force transducers in the stomach, duodenum, jejunum and ileum using a telemetory system. The effects of AA-861, pranlukast and atropine on the hyper-motility induced by IND were investigated. RESULTS: Effect on GI mucosa: IND (3 mg/kg, p.o.) caused many lesions in the lower half of the small intestine; the mean lesion area (MLA) was 7.7 ± 2.0 cm^2 ($n = 5$). Pretreatment with AA-861 (30 mg/kg, p.o.), pranlukast (100 mg/kg, p.o.) or atropine (0.3 mg/kg, s.c.) obviously inhibited the lesion formation by IND; the MLAs were 1.3 ± 0.5 cm^2 ($P < 0.05$) , 2.0 ± 0.5 cm^2 ($P < 0.05$) and 0.6 ± 0.5 cm^2 ($P < 0.05$), respectively. Effect on GI motility: IND (3 m/kg, p.o.) increased the motility in the lower small intestine by 50-80% starting from 2 h after the dosing of IND, and the effect continued for 4-5 hrs. The stimulatory effect of IND on the lower intestine was markedly inhibited by pretreatment with AA-861 (30 mg/kg, p.o.), pranlukast (100 mg/kg, p.o.) and atropine (0.3 mg/kg, s.c.). Present results suggest that both LTs and cholinergic pathways are implicated in the hyper-motility and the lesion formation in the small intestine caused by IND.

SOLUBLE DIETARY FIBERS PROTECT THE SMALL INTESTINE FROM INDOMETHACIN- INDUCED LESIONS IN CATS

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Recently we reported that both insoluble dietary fibers, such as cellulose, and intestinal hypermotility play an important role in the pathogenesis of small intestinal lesions induced by indomethacin (IND) in cats. In the present study, we examined the effects of soluble dietary fibers (SDFs; pectin, guar gum and polydextrose) and mucin on IND-induced intestinal lesions, and found that all of the SDFs and mucin can prevent the lesions. We also examined viscocities of the SDFs and mucin to elucidate the mechanism of protective effects of the SDFs. Both male and female cats (2.5–3.5kg) were used (4 or 5 cats per group). Pellet of dry food (PDF) or PDFs added pectin, guar gum, polydextrose or mucin from pig stomach were given to animals twice a day during the experiment. IND was administered orally once a day after a morning meal for 3 days. The animals were sacrificed 24 h after the final dosing of IND, and mucosal lesions in the small intestine were examined. Viscocities of the SDFs and mucin were measured by a rotation viscocimeter. In cats given only PDF, IND (3 mg/kg) produced many lesions in the lower half of the small intestine; the mean lesion area (MLA) was 7.7 ± 2.0 cm^2 ($n = 5$). The addition of pectin (1, 3 and 10%) to the PDF prevented the lesion formation in a dose-dependent manner. The lesions by IND were also markedly decreased in cats given PDF added guar gum, polydextrose or mucin. The inhibitory activity was more potent in guar gum, than pectin, polydextrose and mucin; the MLAs in cats given PDF containing 3% guar gum, pectin, polydextrose or mucin were 0.0 ± 0.0 cm^2, 0.6 ± 0.3 cm^2, 1.3 ± 0.8 cm^2 and 1.6 ± 0.5 cm^2 ($n = 4$), respectively. The inhibitions were significant ($p < 0.05$ vs PDF alone). Viscocities of the SDFs and mucin (0.03-30%) were increased in a concentration dependent manner, and the viscocities (mPa-S) of guar gum, pectin, polydextrose and mucin at the concentration of 3% were >1200, 414, 1 and 4, respectively. We con-

clude that SDFs and exogenous mucin can prevent the formation of intestinal lesions by NSAIDs, probably by protecting the mucosa like endogenous mucin from aggressive factors. As there is a good correlation between the protective activities and viscocities of the SDFs, viscocity may relate, at least in part, to the protective effects of the SDFs on the small intestine.

NEW DATA ABOUT THE HUMORAL REGULATION OF THE FAST MOTILITY OF THE STOMACH AND DUODENUM

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In the fasting state there is a cyclic migrating myoelectric complex (MMC) initiated in the stomach (S) and duodenum (D) that regularly propagates through the small intestine, clearing the intestine of contents. The mechanisms of the MMC are not known completely and are investigated very intensively at nowadays. The aim of our investigation was to study the blood glucose and insulin levels during different phases of MMC and investigate the influence of the agonist and antagonist of H_3-HR and PP on the duration of these phases. Periodical motility was recorded by ballonographic method. The blood glucose and insulin levels were measured by radioimmunology method. It was established that H_3-HR agonist R-α-metylhistamine (R-α-MEH, 0,2 mg/kg, i/v) diminished the duration of the III phase of MMC in S and D. R-α-MEH prolongated the duration of the I phase in S and in D. H_3-HR antagonist thioperamide (0,07 mg/kg, i/v) decreased the duration of the I phase in S and in D. Thioperamide increased the duration of the III phase in S and the II phase in D. PP (200 pmol/kg/h, i/v) diminished the duration of the III phase and prolongated the duration of the I phase in S. In D PP increased the duration of the II phase and decreased the duration of the I phase of MMC. PP decreased the blood glucose level. The high blood glucose and insulin level at the beginning of the III phase of the MMC. It was concluded that endogenous histamine is the physiological factor which limited the duration of the phase of work of the S and D through the activation presynaptic H_3-HR. It was established the interrelationship between the fluctuation of the PP, insulin and blood glucose level during MMC. Hypoglycemia during the I phase evoked the secretion of the PP which stimulated the appearance of the II phase of the MMC of the D. It is obvious that glucagon increases the blood glucose level during the III phase, which evoked the secretion of the insulin. Insulin decreases the blood glucose level and this lead to the excretion of PP.

THE INFLUENCE OF NITRIC OXIDE ON WATER AND ELECTROLYTE TRANSPORT DURING ACETIC ACID COLITIS IN RATS

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Formerly we established that in physiological conditions L-arginine (L-Arg) had no significant effect on the net water and electrolyte flux. To take into account that in inflamed colon nitric oxide (NO) stimulates electrogenic chloride secretion, the aim of the study was to investigate the action of NO synthesis substrate L-Arg on water and electrolyte transport in dynamics of development of ulcerative colitis in colon. Net water and electrolytes movements were evaluated by isolated colonic loop perfusion technique in vivo on anaesthetized adult male Wistar rats at 1, 3 and 7 days after acetic acid enema. Experimental colitis was modeled by means of rectal injection of 1 ml 4% acetic acid in 0,9% NaCl (groups 2-6) or vehicle 1 ml 0.9% NaCl (group 1). Groups 5 and 6 was given L-arginine (500 mg/kg, i.p.) in 60 min after beginning of colonic perfusion. At the beginning of CD (in a day after acetic acid injection) net water absorption didn't change. In 3 days after acetic acid injection it

was shown net water secretion. In 7 days after beginning of colitis development (CD) we could see the recovery of net water absorption to the control rate. At the beginning of CD Na^+ absorption was changed to secretion into the lumen. In 3 days after acetic acid injection net Na^+ absorption stayed at the decreased rate. In 7 days after beginning of CD we could see the increase of Na^+ absorption in comparison with 1 and 3 days of experiment. At the beginning of CD K^+ secretion was increased but in 3 days after acetic acid injection it changed into absorption. In 7 days after beginning of CD K^+ absorption decreased in comparison with 3 days of experiment In 1, 3 and 7 days after acetic acid injection Cl^- absorption didn't change. L-Arg didn't influence on net water movements and on K^+ secretion in all terms of experiment. L-Arg increased Na^+ absorption only in 7 days and increased Cl^- absorption only in 3 days after the beginning of CD Thus, we concluded that NO might have slight pro-secretory properties in the mechanisms of colonic water and electrolyte transport via regulation of active Na^+ absorption during experimental colitis.

TEICHOIC ACID FROM *STAPHYLOCOCCUS AUREUS* INCREASES ANTITUMOUR AND ANTIMETASTATIC EFFECTS OF THE HETEROMETALLIC CU/CD COMPLEX

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Earlier we showed that the influence of teichoic acid (TA) – one of the main biopolymers of the cell wall of *Staphylococcus aureus* – on the initial tumour and its dissemination of implanted Lewis lung carcinoma depends on the time of TA administration. It was found that administration of TA on the day of the tumour implantation the percent of animals (mice) with tumour was of 75, with dissemination of tumour – 66% relative to the control. Whereas administration of TA on the 7th day after the tumour implantation led to 100% output of the tumours and metastatic damage in the experimental animals as well as to the hyper activation of the growth of the initial tumour and metastasis. Upon administration of TA on the 7th day a volume of the initial tumour outnumbered the one in the control 1.5-2.5 times, while the level of the metastatic damage increased ten times more relative to the control group. We have also found that the heterometallic complex $[Cu(En)_2][Cd_2(CH_3COO)_6]$ (PO244) possesses antimetastatic and antitumour effects towards the implanted carcinoma. We have studied antimetastatic and antitumour effects of PO244 against a background of the tumour growth activation and metastasis induced by TA. The antimetastatic and antitumour effects of the compound were found to increase in conditions of the immune system activation by TA. The antitumour effect of PO244 in monotherapy appears in the following: 50% of mice show no tumours and 63% - no metastases relative to the control. Upon simultaneous administration of TA and PO244 the antitumour effect was exemplified: 67.5% of mice show absence of tumours and 75% - absence of the metastatic damage relative to the control group of animals. Therefore combined application of TA along with PO244 reliably increases the antimetastatic and antitumour effects of the coordination compound.

ADAPTING BY R.WEIGL'S OF LICE AS LABORATORY ANIMALS FOR CULTIVATION OF *RICKETTSIAE PROWAZEKII* IN THE MIDGUT

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Rudolf Weigl (1883-1957) has made several major contribution to medical biology and parasitilogy by adapting different insects, lice, to serve as laboratory animals. In 1920th-1940th years, scientific achievements of Lviv's professor R.Weigl were appreciated and became famous all over the world.

During Human's history typhus was a dreadful disease killing millions and affecting world history. From Charles Nicolle's and Rocha-Lima's studies, R.Weigl knew that lice are the vector of the typhus and that *Rickettsiae* propagates in louse intestines, but there was no way at that time to cultivate the typhus agent, *Rickettsiae prowazekii*. Therefore, R.Weigl has decided to use lice as an experimental animal to propagate the *R.prowazekii* bacteria and to develop a life-saving vaccine. R.Weigl decided to infect lice through their "other end annus" using a very fine capillary. Besides of introduction of an insect, lice, as the experimental animal, R.Weigl has "developed" their special strain, *Pediculus vestimenti,* which was easy to breed, and was well adapted to the production of typhus vaccine. The strain was a Caucasus-African cross between lice isolated from the WW1 Russian prisoners (captured by Austrians) and Ethiopian lice received in 1939 by R.Weigl from the Laboratory for rickettsiosis in Addis Ababa. This cross was designated as "Weigl strain". Cultivation and passaging of *R.prowazekii* in the midgut of Weigl's strain of lice (*P.vestimenti* or *P.humanus corporis*) was resulting in the most potent and reliable anti-typhus vaccine. Significance of Weigl's vaccine was enormous, at that time (before and during WW2), and Weigl's scientific heritage retains a great importance in the history of world medicine.

URSODEOXYCHOLIC ACID IS MORE EFFECTIVE IN LEPTIN INHIBITION THAN ATORVASTATIN IN OBESE PATIENTS WITH HYPERTENSION

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Introduction. Among common disorders associated with obesity hypertension and hyperlipidemia are in prevalence. The purpose of this study was to compare lipids and leptin level in obese patients with hypertension who received the basic ACE-inhibitor-lisinopril and ursodeoxycholic acid or atorvastatin. Methods. 43 obese patients with arterial hypertension were included in clinical investigation with median blood pressure SBP > 140 mm.hg, DBP > 90 mm.hg. Age varied from 50 to 73 years old, body mass index 27-32. The 1st group of patients (23) received treatment (atorvastatin 10 mg daily and lisinopril 20 mg daily) for a month. The 2nd group of patients (20) received treatment (ursodeoxycholic acid 360 mg daily and lisinopril 20 mg daily) for a mounth. Lipids (general cholesterol, HDL, triglycerides) and Leptin was measured before and after management for a month. LDL cholesterol was determined by Friedewald method. Results. The results of the study showed that admission of atorvastatin allowed to lower cholesterol concentration by 11%, triglycerides by 15.3%, LDL by 16%. At the same time Leptin concentration did not change significantly (6.6%). Admission of ursodeoxycholic acid allowed to lower cholesterol concentration by 7.4%, triglycerides by 8.4%, LDL by 7.0%. Leptin concentration was decreased by 25%. Conclusion. Correction of hyperleptinemia is considered to be the serious problem in obese patients with hypertension. Ursodeoxycholic acid can be recommended as a hypoleptinemic drug addition to standard therapy for management obese patients with hypertension.

CHANGES OF THE ACTIVITY OF ANTIOXIDANT PROTECTION ENZYMES AND NITRIC OXIDE CONTENT IN THE STOMACH AND LARGE INTESTINE OF RATS WITH DIABETES MELLITUS UNDER THE ACTION OF PROKINETIC METOCLOPRAMIDE – –

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Introduction. Development of diabetes mellitus is accompanied by a sharp decline of the digestive organs motility resulting from the appearance of neuropathy. Hyperglycemia changes activity of

NO-synthases and induces oxidative stress. Methods: Investigation was conducted on 18 male rats in two series: 1) on the 4th week after streptozotocin (STZ) injection (60 mg/kg); 2) two weeks after STZ injection. Metoclopramide was introduced per orally (2 mg/kg) for 14 days. Then were studied TBARS and NO contents and activity of antioxidant eznymes – SOD and catalase in the mucous and muscle membranes of the stomach and large intestine. Nitric oxide content was measured with the use of Griess reagent. Results: Due to the action of STZ, the stomach, small and large intestines were visually filled with their contents, TBARS concentration increased by 60 % ($p < 0.05$), NO content decreased by 26 %, activity of SOD and catalase enhanced by 60 % ($p < 0.05$) and 16 %, respectively. Injection of metoclopramide caused emptying of the stomach and small intestine while processes of evacuation in the large intestine were less intensive. NO content were increased in gastric mucosa by 48 % and in the muscle membrane – by 92 %; in the mucous membrane of large intestine – by 200 %, in the muscle membrane – by 25 % as compared to the hyperglycemic condition. SOD activity in gastric diminished by 55 %, in the muscle membrane – by 24 %, in the mucous membrane of large intestine SOD activity reduced by 43 % ($p < 0.05$) and in the muscle membrane – by 24 %. Catalase alterations were insignificant. Conclusion. Prokinetic metoclopramide, under the action of streptozotocin, caused the increase of nitric oxide content in the stomach and large intestine, at that, SOD activity diminished and changes of catalase activity were insignificant.

ROLE OF COX-2 AND CCK-2 RECEPTORS IN LARGE INTESTINE IN THE CONDITION OF HYPERGASTRINEMIA

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Introduction: Lansoprazole (H^+,K^+-ATPase blocker) inhibits secretion of gastric glands that results in a sharp increase of gastrin level in the blood, it being a causative factor for cancerogenesis in the mucous membrane of large intestine (MMLI). Purpose of the research was to identify early morphofunctional changes in the MMLI under the solitary and combined action of lansoprazole, proglumide and celecoxib introduced to the rats. Methods: Investigation was carried out on 38 white rats, with a 14-day per os intduction of lansoprazole (30 mg/kg), lansoprazole combined with proglumide (250 mg/kg), and lansoprazole combined with celecoxib (10 mg/kg). Then were evaluated content of malonic dealdehyde (MDA), activity of enzymes of the antioxidant protection system - SOD and catalase, and content of nitric oxide (NO). Morphological alterations in MMLI were investigated by the electron microscopy and histological methods. Level of blood gastrin was measured by the radioimmunoassay method with use of MP Biomedicals, LLC (the US). Results: Lansoprazole caused a 25% decline of MDA content and enhancement of SOD and catalase activity (by 71% and 26 %, respectively). NO content decreased by 11 %. Morphology of epithelial and goblet cells width of the mucous membrane changed. Level of gastrin plasma increased 3 – fold. Due to a simultaneous action of lansoprazole with proglumide, MDA content increased by 32%, as compared to lansoprazole action. SOD and catalase activity reduced and was at the level of control rats. NO content remained unaltered. Level of plasma gastrin decreased. Combined action of celecoxib with lansoprazole induced increase of MDA content by 24 %, whereas under lansoprazole solitary action, SOD and catalase activity reduced. NO content in the MMLI increased by 14%. Conclusion: Blockage of COX-2 with celecoxib and H^+,K^+-ATPase with lansoprazole causes functional MMLI changes, impaired processes of apoptosis and proliferation that are likely to induce enteropathies and cancerogenesis.

ROLE OF VITAMIN E AND NO-SYNTHASE SYSTEM IN CYTOPROTECTIVE MECHANISMS OF GASTRIC MUCOSA

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Background. Numerous factors, including Vitamin E (Vit E) and nitric oxide (NO) affect on the cytoprotective processes in gastric mucosa. Vit E reduces lipoperoxidation processes and ulcer index but its effect under a combined action with the substrate for NO-synthases L-arginine and under iNOS blockage with L-canavalin has remained a lot to study. Methods. Ulcerogenic lesions were modeled in 22 white rats by intraperitoneal injection of adrenaline (2mg/kg); Vit E (150 mg/kg), L-canavalin (100 mg/kg), and L-arginine (300 mg/kg) were injected intramuscular 30 min prior to adrenaline. Changes of lipoperoxidation processes were evaluated by MDA content, activity of enzymes of the antioxidant protection system was investigated by the activity of SOD and catalase, and content of NO – with the use of Griess reagent. Results. Under the effect of Vit E, adrenaline impact decreased, structure-hemorrhagic lesions relieved, MDA content decreased by 9 %, and NO changed insignificantly. SOD activity reduced by 34 % as compared to that affected by adrenaline, and catalase activity remained almost unaltered. Solitary action of L-arginine caused decrease in MDA and NO contents, in SOD and catalase activity. Due to combined action of Vit E and L-arginine, NO content decreased and SOD activity enhanced. Under blockage of iNOS with L-canavalin simultaneous with Vit E injection, MDA content dropped by 41 % ($p<0.05$), NO content – by 37 % ($p<0.05$) as compared to Vit E effect under adrenaline impact. SOD activity enhanced and catalase activity reduced by 12 % each. Conclusions. Under blockage of iNOS or L-arginine action, Vit E manifested its modulatory antioxidant effect. Blockage of iNOS, simultaneous with Vit E injection, failed to influence gastroprotection, lipoperoxidation reduced, with NO action being predominant. Combined action of L-arginine with Vit E induced enhancement of gastroprotection due to decreased NO content and intensified activity of SOD.

EFFECT OF ANTIOXIDANT VITAMINS E AND C ON THE PROCESSES OF LIPOPEROXIDATION IN PANCREATIC TISSUE UNDER STRESS

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Background. Vitamins E (Vit E) and C (Vit C) are capable of exerting both antioxidant and pro-oxidant dose-related action depending on their dose. Stress exposure of the pancreas is one of the pathogenetic factors contributing to the development of pancreatitis. Material and methods. Investigation was conducted on 36 white male rats with the body weight of 150-200 g. Stress condition was modeled with adrenaline injected intraperitoneally in a single dose of 2 mg/kg, Vit E (150 mg/kg) and Vit C (200 mg/kg) were injected 30 min prior to adrenaline. There after were determined content of thiobarbituric acid (MDA), activity of superoxide dysmutase (SOD) and catalase, NO content in the pancreatic tissue, L-arginine level, and activity of pancreatic б-amylase in the serum of blood. Results. Vit E injected at the background of adrenaline impact failed to cause any changes in MDA content, NO content decreased by 38%, activity of SOD and α-amylase reduced by 70% ($p<0,05$) and 45% ($p<0,05$), respectively, and L-arginine content decreased by 39%. Due to the action of Vit E, MDA content increased by 13%, NO content decreased by 48% ($p<0,05$), SOD activity diminished by 57% ($p<0,05$), and activity of б-amylase in the blood enhanced by 41% ($p<0,05$). Due to a combined action of Vit E and Vit C, NO content decreased by 52% ($p<0,05$), SOD activity reduced by 33%, and б-amylase activity diminished by 11% as compared with the indeces of intact animals. Conclusions. Action of Vit E and VIt C, both separate and combined, causes decrease of NO content and reduction of SOD

activity. Vit E and Vit C exert a unidirected action on the activity of α-amylase in the blood – under the effect of Vit C and its combined action with Vit E, activity of α-amylase becomes intensified and under the effect of Vit E, injected at the background of adrenaline impact, it becomes reduced.

CELL SWELLING-INDUCED PEPTIDE HORMONE SECRETION, PATHOPHYSIOLOGICAL IMPLICATIONS

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Maintenance of cell volume is a prerequisite for survival and functioning of the cell. Cell volume changes could be stimuli for a variety of functions including secretion. In general way cell swelling evokes and shrinking inhibits exocytotic secretion. Dynamics of secretion is indistinguishable from that induced by natural secretagogue. Peculiarities of swelling-induced secretion indicate involvement of unique signalling pathway resistant to physiological inhibitors. Cells specifically engaged in water and salt regulation retain their specific response to osmotic stimuli; hypotonic medium does not evoke oxytocin (OT) release from hypothalamic paraventricular nucleus (PVN|). Specific response (release after hyperosmotic stimulation) of intranuclear OT secretion in the PVN and the supraoptic nucleus could be obviated by $GdCl_3$ and at these conditions OT release to swelling-inducing stimuli emerged. Pathophysiological implications: A shift to anaerobic glycolysis and production of metabolites occurring in ischemia results in increased intracellular osmolarity and swelling followed by uncontrolled release of peptides and proteins. They could play role in the pathophysiology of ischemia and be a source of mediators of local or remote preconditioning against ischemia-reperfusion injury. Disruption of mechanosensitive gating in magnocellular neurosecretory cells results in an inadequate secretory response (e.g. stimulation instead of inhibition and vice versa) of hormones engaged in water and salt regulation and development of the syndrome of inappropriate secretion of antidiuretic hormone. *Acknowledgements: The work was supported by the project 2/6158/26 (VEGA), project APVV 0235-06 and project of CE SAV CENDO.*

KEY ELEMENTS OF CELL/TISSUE INJURY & CYTOPROTECTION: HISTORIC PERSPECTIVES

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The seminal papers on “gastric cytoprotection” of Andre Robert were published 30 years ago, when cell injury&cytoprotection research flourished because of organ transplantations, e.g., kidney (1954), lung (1962), liver & heart (1967). Here we focus on (1) stages of cell/tissue injury, (2) modern definition of cytoprotection & (3) contemporary mechanisms of protection in the stomach. (1) Organ transplantation required preservation of organs and distinctions of reversible (cell membrane & endoplasmic reticulum e.g., blebbing, vacuolization) & irreversible (mitochondrial or nuclear damage resulting in cell death by necrosis or apoptosis) stages of cell injury. Necrosis is followed by acute/chronic inflammation that may also aggravate tissue injury, e.g., in gastroduodenal ulceration & IBD. (2) The initial “gastric cytoprotection” was criticized because A. Robert did only gross evaluation of gastric lesions & the first microscopic/histologic review (S. Ito) revealed that protection by prostaglandins was relative, i.e., surface epithelial cells were dead&only the hemorrhagic erosions were prevented. Hence, we proposed (1982) the term gastroprotection instead of “cytoprotection”. (3) The main mechanisms of gastroprotection include the preservation of endothelium & microcirculation

that allow the surviving gastric foveolar cells to migrate (restitution) & proliferate (regeneration) to replace the lost surface epithelial cells. Apparently a mild tissue injury results in slightly increased vascular permeability &"histodilutional barrier" that dilutes toxic chemicals & delay their absorption. Exogenous phospholipids also decrease the absorption of toxic chemicals, hence preserve mucosal microcirculation & integrity. Conclusion: The concept of "gastric cytoprotection" (1978) was based on wrong premises, in part because of the initial lack of histologic evaluation, but it stimulated extensive research that lead to better understanding of cell/tissue injury & to the discovery of new pathways of gastroprotection.

NOVEL MOLECULAR MECHANISMS OF ESOPHAGEAL AND GASTRIC ULCER HEALING: STATE OF THE ART 2008

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Ulcer healing, a genetically programmed repair process, includes inflammation, cell proliferation, re-epithelialization, formation of granulation tissue, angiogenesis, matrix and tissue remodeling, all resulting in scar formation. All these events are controlled by the cytokines and growth factors (EGF, PDGF, HGF, TGFβ, trofoil peptides, VEGF, angiopoietins and others) and transcription factors activated by tissue injury in a spatially and temporally coordinated manner. They trigger mitogenic, motogenic and survival pathways utilizing Ras, MAPK, PI-3K/Akt, PLC-γ and Rho/Rac/actin signaling. Hypoxia activates angiogenic genes (e.g. VEGF, PDGFβ and angiopoietins) via hypoxia induced factor-1α (HIF-1α), while serum response factor (SRF) is critical for VEGF-induced angiogenesis, re-epithelialization and muscle restoration. EGF, its receptor, HGF and Cox2 are important for gastric epithelial cell proliferation, re-epithelialization and reconstruction of gastric glands. Cox2 generated PGE_2 exerts ulcer healing action via transactivation of EGF receptor and by stimulation of EP-R4. VEGF and angiopoietins, are important for angiogenesis, vascular remodeling and microvessel restoration within ulcer scar. Circulating bone marrow-derived progenitor cells are also important for the ulcer healing process. Healing of esophagel ulcers is similar to gastric ulcers with a major difference that keratinocyte growth factor (KGF) plays a greater role and that re-epithelialization involves migration of sheets of interconnected cells rather than single cells. Esophageal ulceration triggers activation of KGF and its receptor (KGF-R) genes and proteins. KGF expression is strongly increased in stromal cells of the lamina propia, while KGF-R in epithelial cells of the basal layer, reflecting mesenchymal-epithelial interactions. Cox2 and VEGF are strongly overexpressed in ulcerated area. Local therapy with KGF increases epithelial cell proliferation and accelerates by >50% esophageal ulcer healing. Local gene therapy with VEGF + Ang1 and/or SRF cDNAs accelerates esophageal and gastric ulcer healing and improves quality of mucosal restoration within ulcer scar. Future directions to accelerate and improve ulcer healing include local gene therapy, the use of stem cells implantation, transplantation of tissue-engineered autologous mucosal epithelial cells and tissue engineering.

ROLE OF VEGF IN EXPERIMENTAL ULCERATIVE COLITIS: IMPLICATION OF INTESTINAL VASCULAR PERMEABILITY IN TISSUE INJURY

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Levels of VEGF correlate with disease activity in human and experimental ulcerative colitis (UC). In this study we tested hypothesis that VEGF may have a mechanistic role in the pathogenesis of exper-

imental UC. METHODS: UC was induced in Sprague-Dawley rats by 6% iodoacetamide (IA) or vehicle - 1% methylcellulose (0.1 ml/rat, given i.c.). Neutralizing anti-VEGF antibody (50 ug/rat), IgG (50 ug/rat) or saline (0.1 ml/rat) were injected i.m. on 3rd and 5th days after IA enema. Body weight and diarrhea were recorded daily. Rats were euthanized on the 7th day. Colonic vascular permeability was measured by the extravasation of Evans blue. RESULTS: VEGF protein and mRNA expressions increased as early as 0.5 hr after IA and were further elevated in the active phase of disease. Administration of anti-VEGF antibody markedly improved the clinical and morphologic features of UC. Colonic lesion areas (mm2) were significantly decreased from 370+140 and 311+170 in saline or IgG-treated groups to 122+57 in anti-VEGF-treated rats ($p<0.05$). Mucosal levels of VEGF, PDGF, bFGF were also reduced in anti-VEGF group. Increased colonic vascular permeability was attenuated by pretreatment with anti-VEGF antibody (100 ug/rat, i.m., $p<0.05$) or Src inhibitor PP1 (2 mg/100g in DMSO, s.c., $p<0.01$). Treatment with anti-VEGF antibody didn't change blood vessel density but significantly decreased the number of neutrophils ($p<0.001$) and lymphocytes ($p<0.01$) in the lesion area. CONCLUSION: Anti-VEGF antibody decreased the severity of UC. This beneficial effect may be due to attenuation of enhanced vascular permeability, prevention of excessive vascular leakage, decreasing inflammatory cells infiltration and an apparent switch of abnormal angiogenesis toward normal. Thus, modulation of VEGF activity may be a new approach to UC treatment.

PREVENTIVE ACTION OF MULTIPROBIOTIC "SYMBITER®" ON OMEPRAZOLE INDUCED CHANGES IN GASTRIC MUCOSA

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It is known that probiotics inhibit NSAIDs/aspirin-induced small intestinal damage (Arakawa T, Watanabe T, et al, 2008) and enhances gastric ulcer healing in rats (Lam E, Yu L, et al, 2007). We examined the effects of probiotic on changes of gastric acid output (BAO) and morphometric indices in gastric mucosa evoked by long term use of omeprazole in rats. The study was carried out on 43 male Westar rats. They were divided into three groups. The animals of the first (control) group were injected with 0,2 ml H_2O (i.p.). The rats of the second group were injected with OM (14mg/kg, i.p.). The rats of the third group were injected with same dose of OM and multiprobiotic "Symbiter® acidophilic" (S) (limited company "O.D.Prolisok") in dose 0,14 ml/kg (per os). All drugs were injected during 28 days. S is concentrated fluid biomass of bioplasts of symbiosis of 14 microorganisms strains. BAO was determined in 24 hours after last injection of drugs in acute experiments by method of isolated stomach perfusion by Ghosh and Shild. Tissue sections of the stomach was fixed in 10% formalin, embedded in paraffin, stained with hematoxylin and eosin. For morphometric analysis depth of epithelium, area of nucleus section of parietal cells and area of nucleus section of endocrine cells in fundus were estimated. It was established that in 28 days of OM injection depth of epithelium, area of nucleus section of parietal cells and area of nucleus section of endocrine cells in fundus were accordingly increased by 54%, 84,2% and 59,2% in comparison to control. BAO was increased by 328,0%. We concluded that OM evoked hypergastrinemia which leads to the general hyperplasia and hyperplastic mucosa has an increased capacity to produce acid. After 28 days of S and OM treatment BAO was diminished by 42,9% in comparison to second group of rats. S also removed the negative action of OM on morphometric indices of gastric mucosa. Thus use of probiotics could be perspective for prophylaxis of side effects of long term use of proton pump inhibitors and for prophylaxis of gastric mucosal hypertrophy in people with hypoacidity or achylia.

MODULATION OF GASTRIC ACID SECRETION BY PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR γ

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Peroxisome proliferator-activated receptor gamma (PPARγ) play important role in the regulation of lipid and carbohydrates metabolism, energy homeostasis, cell differentiation and proliferation. Accordingly, metabolic activity of PPARγ might substantially affect function of the digestive system, however, PPARr functions in the digestive system have not been studied yet, although it has been supposed that PPARr involved in the development and regulation of digestive organs. This study was designed to determine the long-time effect of different dozes of pioglitazone (Pg), agonist of PPARr, on basal or induced gastric acid secretion (GAS) in rats. The study was carried out in acute experiments on 30 white rats under urethane anesthesia. The animals were divided into three groups: I – rats were fed with vehicle, II and III – rats treated with Pg in doze 5 and 15 mg/kg, respectively, for 75 days. Basal GAS and GAS stimulated by carbachol (10 μg/kg, i.p.) was investigated by method of isolated stomach perfusion by Ghosh and Shild. Pre-treatment with Pg in doze 15mg/kg significantly enhanced the total acid secretion stimulated by carbachol on 40%. Contrary, Pg given in both doses didn't influence on basal GAS and GAS stimulated by carbachol in rats treated with Pg in doze 5mg/kg. We suppose that mechanism of stimulatory action of Pg on carbachol-stimulated GAS in rats might be realized through the several known actions of PPARγ: increased release of nitric oxide by eNOS and vasodilatation; decreasing of leptin (GAS-down hormone) level; and also, affecting of blood glucose levels during carbachol action, due to inhibitions of gluconeogenesis. Obtained data should have take into account with medication by thiazolidindiones.

PIOGLITAZONE, PPAR-GAMMA LIGAND, INHIBITS OMEPRAZOL-INDUCED GASTRIC ANTRAL MUCOSAL INJURY IN RATS.

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Hypergastrinaemia, resulted from hypochlorhydria/achylia, is typical in patients with atrophic gastritis and may develop to gastric cancer. The mechanisms imply high levels of gastrin, which cause mucosal proliferation and dysplasia. Recently, peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a member of the nuclear hormone receptor superfamily, has been implicated as a regulator of overall anti-cancer responses in various cell types, possibly due to its anti-proliferative, pro-differentiation and pro-apoptotic activity. The aim of this study was to evaluate the cancer-preventive action of pioglitazone, a specific PPAR-gamma ligand, in experimental hypergastrinaemia in rats. Long-term hypergastrinaemia in male adult Wistar rats was induced by daily i.p. injections of omeprazole (14 mg/kg), with gastrin levels regularly checked using radio-immuno assay (RIA). Pioglitazone (30 mg/kg) was given per.os to omeprazol-treated rats daily during 28 days. The response of gastric antral mucosa was evaluated after histological examination and morphometry. The chronic administration of omeprazole was found to induce acute inflammation and some dysplasia in rat antral mucosa, including lymphocytic infiltration, glandular atrophy and appearance of undifferentiated cells, local thickenings or damages of epithelial layer. The data described reflect the early stages of tumorogenesis in the mucosa. Levels of gastrin gradually increased during the experiment, up to 4-fold at the 28th day of administration. Pioglitazone injections to omeprazol-treated rats were found to result in significant thinning of epithelial layer, normalization of morphometrical properties, while gastrin concentration remained increase. Based on data obtained, pioglitazone significantly inhibits the

effects of omeprazole in rat gastric antral mucosa, and may be a promising pharmacological agent in the search of anti-cancer drugs.

SOMATIC PAIN SENSITIVITY IN AWAKE RATS DURING FORMATION AND HEALING OF ACETIC ACID-INDUCED GASTRIC ULCERS

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A classical feature of visceral pain is its referring to somatic locations. Gastric ulcer is a source of visceral pain. The aim of the present study was to investigate whether gastric ulcer may trigger the changes in somatic pain sensitivity. Methods: For this aim somatic pain sensitivity was estimated under conditions of gastric ulcer development and healing. Gastric ulcers were induced by luminal application of acetic acid accordingly to Okabe method ("kissing" gastric ulcers) with our modification under surgical condition. The stomach of anesthetized rats was exposed and the corpus area was clamped with ring forceps (ID 5 mm). A 60% acetic acid solution was injected into the luminal side at the clamped portion for 45 s. Controls received an identical injection of saline instead of the acid. The sizes of acetic acid-induced kissing gastric ulcers, somatic pain sensitivity (tail flick latency), plasma corticosterone level, adrenal and thymus weight were investigated before the acid application, on the day of ulcer formation (3 days after the acid application) as well as during the healing of gastric ulcer (1 and 2 weeks after the ulcer formation). Results: The application of the acid resulted in the formation of kissing gastric ulcers, the increase of somatic pain sensitivity (the decrease of tail flick latency) as well as the appearance of typical signs of chronic stress: long-lasting increase of plasma corticosterone level, adrenal gland hypertrophy and thymus involution. The chronic ulcers almost completely healed after 2 weeks. Natural healing of gastric ulcers was accompanied by restoration of pain sensitivity, corticosterone production, adrenal and thymus weight. Delay of ulcer healing by indomethacin (2 mg/kg once daily for 2 weeks) prevented the restoration of somatic pain sensitivity. Conclusions: The results suggest that chronic gastric ulcer may trigger the changes in somatic pain sensitivity: somatic hypersensitivity. Supported by BSciM RAS-2008, RFBR-07-04-00622, DBSci RAS-2008, Sci School RAS-1434.2008.4.

STRUCTURE-ACTIVITY ANALYSIS OF NITROSATIVE STRESS ON ORAL EPITHELIAL BARRIER ABNORMALITIES IN EXPERIMENTAL EROSIVE ESOPHAGITIS

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The reflux esophagitis is a global disease rapidly increasing among world population. Reflux of gastric acid and pepsin secretion also induced extraesophageal disturbances. Oral mucosa (OM) has increased susceptibility to injury and delayed healing during reflux esophagitis. Nitrosative stress is unique factor which may contribute to the initiation and progression OM lesions. Excessive loss of damaged epithelial cells results in OM erosions or ulcers, but the cellular targets and the mechanisms are not fully defined. The aim of study was to investigated the role of NO/NOS signaling pathways in OM resistance. We compared the effects of vehicle, melatonin (20 mg/kg/day) without/with combination of indomethacin, a non-selective cyclooxygenase (COX)-2 inhibitor, L-NNA, non-selective NO/NOS inhibitor, on the healing of OM damage induced in male rats by the 7-days of intraesophageal perfusion of acid-pepsin solution. Plasma NOx concentration was assessed by Griess method. Histomorphological analysis used for determination signs of ulcerogenesis on OM and lower third esoph-

ageal biopsies. Administration of L-NNA resulted in extensive macroscopic and microscopic esophageal lesions accompanied by OM erosins and the significant reduction in plasma NOx concentration, indomethacin significantly attenuated the OM lesions. Co-treatment with melatonin added to L-NNA restored the healing of OM injury, decreased leucocytes infiltration and involved significantly increase of plasma NOx. We conclude that 1) OM lesions induced by erosive esophagitis may mediated by activity of NO/NOS signaling pathway and 2) this beneficial action of melatonin on OM probably *via* release of vasodilatory mediators such as NO and increased trophic influence and mucus thickness.

ROLE OF NO-SYNTHASE SYSTEM IN CYTOPROTECTIVE MECHANISMS OF THE ACTION OF OPIOID PEPTIDE – DALARGIN

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Background. Endogenous opioid peptides (leu-enkephalin, met-enkephalin) localized in gastric mucosa (GM), manifest their cytoprotective action in response to stress factors. But research on the role of NO-synthase system in the mechanisms of cytoprotection under the action of synthetic leu-enkephalin cannot be considered exhausting. Material and methods. Investigation was conducted on 38 Wistar line rats in acute experiment. Ulcerogenic lesions of GM were modeled by injecting adrenaline in the dose of 2.0 mg/kg. Changes of lipoperoxidation processes in GM were determined by the contents of MDA and NO, and by the activity of antioxidant protection enzymes –SOD and catalase. Results. Dalargin (0.1 mg/kg) action, at the background of ulcerogenic impact of adrenaline, caused decrease in the area of GM lesions by 32% ($p<0.05$) and improvement of its qualitative characteristics – by 50%. Action of dalargin L-canavaline (100 mg/kg) resulted in a pronounced decrease of the area of ulcerogenic lesions – to 2-3% ($p<0.01$) and positive 90% changes in the character of lesions. MDA content decreased by 15%, SOD activity - by 40%, catalase activity – by 43%, and NO content - by 33% ($p<0.05$). Due to the effect of injected L-arginine (300 mg/kg) and dalargin – versus the action of dalargin, the area of structural lesions in GM decreased by 18%, and character of the disorders was evaluated 20 scores. At that, MDA content increased (by 41%), NO concentration decreased (by 57%), SOD activity diminished by 57% ($p<0.05$), catalase activity – by 64% ($p<0.05$). Summary. Both L-arginin injection and blockage of iNOS with a selective blocker L-canavaline simultaneous with dalargin effect enhanced cytoprotection processes. But changes of lipoperoxidation processes, NO content and activity of antioxidant defense enzymes are evidence of the different roles of eNOS and iNOS in the protective processes of gastric mucosa.

NOCISTATIN-INDUCED GASTRIC MUCOSAL PROTECTION AND ITS INTERACTION WITH NOCICICEPTIN AND OPIOID SYSTEM

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Nociceptin/orphanin FQ (N/OFQ) and nocistatin (NST) are two neuropeptides derived from preproN/OFQ. N/OFQ is the endogenous ligand of the NOP receptor and has been reported to induce several actions in the gastrointestinal tract after both central and peripheral administration. In contrast, NST has originally been described as a functional antagonist of N/OFQ, which does not bind to NOP receptor. Recently, however, agonist actions of NST have been reported, which – in contrast to the original assumption – indicates that NST may also have regulatory functions. The present experiments aimed to study 1. the gastroprotective effect of NST compared with that of N/OFQ, 2. whether central opioid

system is involved in the gastroprotective effect of these peptides. Methods: Gastric mucosal damage was induced by acidified ethanol in rats. Compounds were given i.c.v. 10 min (agonists) or 20 min (antagonists) before the ethanol challenge. Results: 1. Both N/OFQ and NST reduced the mucosal lesions in the doses of 0.2 – 1 nmol/rat, but in higher doses (2 – 5 nmol/rat) their effect was highly diminished. 2. The effect of N/OFQ was reduced by J-113397 (69 nmol/rat), a competitive antagonist of NOP receptor. 3. When NST was given in the dose of 0.2 nmol/rat prior to N/OFQ (0.6 nmol/rat), the gastroprotective effects were added, whereas higher dose of NST (1 nmol/rat) injected prior to N/OFQ (1 nmol/rat) resulted in an inhibition of gastroprotective action. 4. The effect of both peptides was reduced by naloxone (27 nmol/rat), naltrindole (5 nmol/rat) norbinaltorphimine (14 nmol/rat) and β-FNA (20 nmol/rat), as well as by bilateral cervical vagotomy. Conclusions: Both N/OFQ and NST initiate centrally a series of events which result in gastric mucosal defense. The gastroprotective effect of both N/OFQ and NST is likely to be mediated by endogenous opioids and conveyed to the periphery by a vagal-dependent mechanism. This work was supported by ETT 529/2006.

GLYCOMICS – AN EFFICIENT TOOL OF CELLULAR ACTIVATION IN PHYSIOPATHOLOGY OF ESOPHAGEAL DAMAGE

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Esophageal mucosa (EM) barrier dysfunction is common disorder that closely related to preneoplastic diseases the incidence of which is on the rise. Current diagnostic is directed toward elimination of the lost EM integrity and failure of the lower esophageal sphincter, however is still hard to diagnosed the differences between non-erosive and erosive EM damage. Previously we identified several mechanisms involved in the physiopathology of EM disorders, standing out are oxidative stress, abnormal prostaglandin synthesis, endothelial dysfunction and malfunction of local neuromediators. However, there is shortness of ideal markers, which could be detectable early changes in EM resistance. We hypothesize either that the gradual deterioration of glycosylation *via* different agents causes degradation of the EM cell-to cell or cell-matrix junctions and the present study was designed to investigate the detectable esophageal glycomic profile (GP) changes as early diagnostic markers of EM resistance. Were enrolled several rat groups without/with streptozocin-induced noncontroled hyperglycemia and modulation activity of NO/NOS system by L-arginine (L-arg) and indometacin (INDO) pretreatment. All rats were sacrificed and (1) survival rate, (2) destruction occurrence ratio, (3) the size of EM lesions, and (4) the number of EM lesions was investigated. To access the GP of EM used HPA, SNA, WGA, PNA labeling. Glycemia was monitored daily, plasma level of end products of NO (NO_n) by generally accepted Grease's reagent. Peri-experimental mortality accounted for 7 deaths evenly distributed across all groups. INDO induced more severe EM damage and plasma NO_n was significantly higher than in L-arg-treated animals. Histological and histochemical analysis presented different profiling of EM lesions and expression of HPA, SNA, WGA and PNA. The changes of EM GP during abnormal glycosylation is efficient tool for investigation cellular activation in multistress conditions of esophageal resistance.

MORPHOFUNCTIONAL CHANGES IN THE OVARIES OF PATIENTS WITH POLYCYSTIC OVARY SYNDROME (PCOS)

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The frequency of PCOS currently constitutes 1,5–18 %. Medical literature reflects insufficient data on morphofunctional Y changes in this pathology. In conjunction with this fact, it was decided to par-

tially fill this blank spot. The data on morphofunctional changes, including electronic microscope st research of the ovarian tissue of 30 patients with PCOS are submitted. The material for the research was obtained via laparoscopy (partial ovarian resection). The phenomena of apoptosis with the presence of the characteristic phenomenon of he condensation of nuclear structures and the occurence of seraps; as well as picnotic pads in the location of nuclei and attributes of vacuolisation of endoplasmic structures are revealed. The given changes are determined in kept follicles and in thekaluteal tissue. Using electronic microscopes, the formation of apoptosis bodies are revealed in the homogeonization of cytoplasma, vacuolisation o and perinuclear condensation of chromatin. The number of cases with apoptosis in research tissues correlate to the number of atretic follicles and is variable, can be related to different functional ovarian conditions in patients of this group and requires greater analysis. Revealed morphofunctional changes can be considered characteristic for ovarian tissue in PCOS patients and can be one 3 more criterion for confirmation.

SOME ASPECTS OF IMMUNE-HORMONAL INTERRELATIONSHIPS IN WOMEN SUFFERING THE POLYCYSTIC OVARIE SYNDROME (PCOS)

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The immunologic state and hormone production have been studied in 30 women with PCOS suffering infertility and 15 healthy women as check group. Levels of CD_{4+} CD_{8+} CD_{3+} CD_{22+} were identificated by flow cytofluorometry using monoclonal antibodies. The data of common and humeral immunity (IgA, IgM, IgG) of tested women have been also studied in peripheral blood and in follicular, and peritoneal fluids. All patients with PCOS were made a laparoscopy as a surgical treatment. Three women's groups have been studied: the 1st – (n=ll) duration PCOS – 1 year; the 2nd – (n=19) duration PCOS – 2–5 years. The hormonal production (LH,FSH, prolactin PL, progesterone P, testosterone T, estradiol E) in dynamics of natural(check group) and stimulation cycles (7th, 13th, 14th, 15th, 16th, 17th, 21st, 26th days) were examined. Concentration of gonadal steroids and gonadotropins were detected with fluoroimmune analysis in serum blood. Day 0 denoted the LH peak. We have studied 30 women with PCOS suffering infertility with out the inflammatory diseases of genitals. An hormone – immunological investigation and humeral immunity has demonstrated labiality of immune homeostasis associated with hormone status and durations of illness (PCOS). It was revealed the main changes of immune-hormonal status in preovualatory period (13th–14th days): 1) decreasing of CD_{4+} lymphocytes levels and CD_{4+}/ CD_{8+} ratio, most pronounced at 0 day; the level CD_{22+} check for control group; the P,LG,E contents were much less than normal indexes; the level of FSG was within the limits of normal oscillations, decreasing the ratio LG/FSG; the level of PL was on upper limit of the norm; the T content was much higher than the norm and check group; the levels of secretory IgA, IgM were significant decrease in follicular and peritoneal fluids as compared with check group; the constant number of IgG in healthy women and patients with PCOS. The immune homeostasis showed the decrease IgM in serum blood as compared with check group and the constant number of IgA and IgG (the 1st group – (n=ll)). 2) increasing of CD_{4+} lymphocytes levels and CD_{4+}/ CD_{8+} ratio; increasing of CD_{22+} level as compared with check group; the LG concentration was much higher than the norm and the ratio LG/FSG increasing; an average FSH, PL, P, E levels in peripheral blood corresponded to normal values and did not essentially differ from the level of check group; the level of T was either heightened or was on upper limit of norm(the 2nd group – (n=l9). According to the given facts patients with PCOS are characterized by lymphocetosis which is accompainied by decrease in general amount of T lymphocytes. In the same time the level of B lymphocytes is rather high in comparison. The activation of immunity helperlink was accompanied by significant insufficiency P production for all cycle and LH production for periovulatory period.

THE MAIN APPROACHES TO STUDY OF THE ROLE IMMUNE SYSTEM DURING PATOLOGUCAL PRELIMINARY PERIOD

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The patologycal preliminary period attracts attention of many scientists in connection with progressively rising number of ill, suffering from the given pathology. According of the data of the literature, the PPP frequency makes up from 10% up to 47 %. During the last years pronounced efforts were undertaken in order to evaluate immunity alteration at the systemic level in women with PPP. However, these efforts were not completely successful and, unfortunately, still attract large scientific and material sources. The great number of investigations of cellular and humeral components of immunity, utilizing such modern techniques as flow cytometry with monoclonal antibodies conjunct with fluorescent probes, did not possess to get convincing evidence about relationship between development of immune system and PPP. Nevertheless, there are some data indicating for local immunity alterations in women with PPP. In this regard, it would be important to concentrate on the analysis of the following items: 1). peculiarities of local immunity function in woman reproductive tract; 2). the role of serotoninergic system as well as system of catecholamines , opioid peptides and prostaglandins in mechanisms of immune system regulation.