

1. Pankov Y.A.

Genetic variations in the regulation of energetic balance.

Single nucleotide polymorphism (SNP) near certain genes revealed association of FAT (fat mass and obesity-associated gene), MC4R (melanocortin 4 receptor gene), and other genes with obesity. Participation of the FAT expression products in the regulation of energy balance remains to be clarified. The function of MC4R encoding melanocortin 4 receptor (MC4R) is somewhat better understood. $\hat{1}\pm$ -, $\hat{1}^2$ -, and $\hat{1}^3$ -MSH encoded by the POMC gene bind to MC4R, reduce food intake, and slow down fat accumulation. Expression of POMC that codes MSH is enhanced by leptin binding to the receptor (LepRb) in hypothalamic neurons. Mutations in human and animal MC4R, POMC, and LEP genes are known to be associated with obesity. More than 60 mutations in MC4R, more than 20 mutations in POMC and fewer LEP mutations have been reported. Nonsense mutations and reading frame shifts block gene expression and thereby disrupt protein synthesis. Missense mutations frequently affect protein folding in endoplasmic reticulum; unfolded or misfolded proteins remain in the cytoplasm and undergo degradation. Certain missense mutations do not interfere with gene expression and folding of proteins but impair their functioning at the periphery. P.S127L mutation in MC4R, p.E206X and p.F144L mutations in POMC as well as other mutations in homozygous and heterozygous forms account for disturbed energy balance in man. The LEP gene has been reported to contain G133fsX15, p.R105X, p.R105W, and p.S141C mutations. As a rule, they are associated with obesity and other pathological conditions only in homozygous forms. DOI: 10.18097/pbmc20105602152

2. Ansari N.A., Rasheed Z.

Non-enzymatic glycation of proteins: from diabetes to cancer.

Incubation of proteins with glucose leads to their non-enzymatic glycation and formation of Amadori products known as an early glycation product. Oxidative cleavage of Amadori products is considered as a major route to advanced glycation endproducts (AGEs) formation in vivo. Nonenzymatic glycation of proteins or Maillard reaction is increased in diabetes mellitus due to hyperglycemia and leads to several complications such as blindness, heart disease, nerve damage and kidney failure. Accumulation of the early and advanced glycation products in plasma and tissues of diabetic patients and causes production of autoantibodies against corresponding products. The advanced glycation products are also associated with other diseases like cancer. This review summarizes current knowledge of these stage specific glycated products as common and early diagnostic biomarkers for the associated diseases and the complications with the aim of a novel therapeutic target for the diseases. DOI: 10.18097/pbmc20105602168

3. Yaglova N.V., Berezov T.T.

Regulation of thyroid and pituitary function by bacterial lipopolysaccharide.

Activation of toll-like receptors-4 by bacterial lipopolysaccharide downregulates pituitary and thyroid function. Besides decrease of thyroid-stimulating hormone secretion lipopolysaccharide affects secretion in follicular thyroid cells directly. The endotoxin partially activates and inhibits different phases of follicular thyrocytes secretion. Lipopolysaccharide enhances thyroglobulin synthesis and exocytosis into follicular lumen and suppresses its resorption. It results in sharp drop of blood thyroxine concentration without decrease of deiodinases-mediated thyroxine to triiodothyronine conversion. Stimulation of the lipopolysaccharide-pretreated thyroid gland with thyroid-stimulating hormone increases resorption of thyroglobulin and thyroid hormone production. Combined stimulation of the thyroid gland increases protein bound thyroxine and triiodothyronine serum concentration unlike only TSH stimulation resulting in increase of free thyroid hormone levels. It also proves that binding capacity of thyroid hormone serum transport proteins during nonthyroidal illness syndrome remains normal. DOI: 10.18097/pbmc20105602179

4. Tolstikova T.G., Khvostov M.V., Bryzgalov A.O., Dushkin A.V., Meteleva E.S.

Improvement of pharmacological values of the nifedipine by means of mechanochemical complexation with glycyrrhizic acid.

A new water-soluble form of the calcium blocker nifedipine (NF) with glycyrrhizic acid (GA) (with molecular ratio 1:4) has been obtained by mechanochemical synthesis. Its pharmacological advantages in comparison with nifedipine were determined. An effective dose of nifedipine in complex reduced to 10 times as compared to its therapeutic dose while high antihypertensive activity preservation and pleiotropic antiarrhythmic activity enhancement. This new antihypertensive and antiarrhythmic agent (complex of NF:GA = 1:4) is chemically stable and safe for parenteral administration. DOI: 10.18097/pbmc20105602187

5. Bozhkov A.I., Sidorov V.I., Dlubovskaya V.L., Shevtsova M.Ya., Surov Yu.N.

Appearance of the imprinting effect on the specific pattern of intracellular distribution of copper ions in the liver after exposure to high concentrations of copper sulfate.

Fractions of copper-binding protein (CBP) specifically bound copper ions were extracted from the rat liver cell cytosole. These fractions of 10-14 kDa proteins are involved in specific pattern of intracellular distribution of copper ions. The imprinting effect of specific pattern of copper ions intracellular distribution has been found. The effect was detected 30 days after sequented injections of copper sulfate into the body. It was shown, that after primary injection of copper the ability of CBP to bind copper ions could increase tenfold, regardless of schemes of copper sulfate injection.

6. *Sumbul S., Khan M.S., Bano B.*

Effect of curcumin on the nitric oxide induced structural and functional modifications of high molecular mass goat brain cystatin.

Cystatins are thiol proteinase inhibitors ubiquitously present in the mammalian body. In brain, they prevent unwanted proteolysis and are involved in several neurodegenerative diseases. Under physiological conditions nitric oxide can be found in almost all the tissues, but under pathological conditions NO has damaging effects. Its increased concentration, under various neural diseases leads to cell damage through formation of highly reactive peroxynitrite. Our present study was designed to investigate the protective effect of curcumin against NO induced damage of HM-GBC. NO caused intensive structural and functional damage of HM-GBC, resulting in 89% loss of its antiproteolytic activity after 2 h of incubation. Structural damage occurs in the form of protein degradation. Curcumin significantly protected HM-GBC against this damage. This suggests that curcumin has a significant potential in the treatment of diseases caused by nitrogen free radicals and this potential must be further explored for the development of novel drugs.

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7. *Tsvetikova L.N., Popova T.N., Rakhmanova T.I., Iskusnykh I.Y.*

Expression and catalytic properties of rat liver nadp-isocitrate dehydrogenase under normal conditions, after administration of tumor necrosis factor- α and at thioctic acid action.

Development of apoptosis is accompanied by a decrease in transcripts of NADP-isocitrate dehydrogenase (NADP-IDH, E.C. 1.1.1.42.), and also alterations of catalytic properties from the rat liver enzyme in comparison with control. Administration of thioctic acid is increased the level of expression towards normal values. Enzyme preparations NADP-IDH were obtained from rat liver at norm conditions, after introduction of tumor necrosis factor and thioctic acid action under apoptosis. Molecular weight of homogenous preparations of NADP-IDH purified from livers of control and experimental rats was 112 ± 5.8 kDa, however Km values and pH-optimum changed in apoptosis. Regulation of NADP-IDH activity under effect of some intermediates of the tricarboxylic acid cycle also differed in these groups.

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8. *Logashenko E.B., Kuznetsova I.L., Ryabchikova E.I., Vlassov V.V., Zenkova M.A.*

Mechanism of the toxicity of the artificial ribonucleases for the different human cancer cell lines.

The ability of artificial ribonucleases to cause in the concentration-dependent manner death of cancer cells has been studied. The cytotoxic activity of artificial ribonucleases is observed at rather low concentration of these compounds (10^{-5} μM). Analysis of the mechanism of artificial ribonucleases cytotoxicity revealed that compounds under the study exhibit membranotropic activity in addition to ribonucleases activity found earlier. This activity is responsible for effective penetration of these compounds inside cells. The results obtained show that artificial ribonucleases induce cell death via damage of cells membrane, detachment of plasmalemma and derangement its macromolecular organization. In the case of short-term exposure of cells to the compounds, cells, even with damaged membrane, survive.

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9. *Kuchmenko E.B., Petukhov D.N., Donchenko G.V., Mkhitarian L.S., Tymoshchuk S.V., Strutynskaya N.A., Vavilova G.L., Sagach V.F.*

Effect of complexes of precursors and modulators of coenzyme q biosynthesis on functional state of old rats and heart mitochondria.

Our research demonstrate that ageing leads to changes in activity of electron-transporting enzyme complexes in myocardial mitochondria of old rats and to increased sensitivity of mitochondrial permeability transition pore to inductors of its opening - Ca^{2+} and phenylarsine oxide. We also observed activation of lipid and protein free-radical peroxidation processes. Administration of a complex of biologically active substances that included precursors and modulators of coenzyme Q biosynthesis (α -tocopherol acetate, 4-hydroxybenzoic acid, and methionine) we observed the increase in coenzyme Q content, correction of functional activity of mitochondrial electron-transport chain enzyme complexes, the decrease in intensity of lipid and protein free-radical peroxidation in the heart and the decrease in sensitivity of mitochondrial permeability transition pore to inductors of its opening. This complex may be used to treat mitochondrial dysfunction under numerous pathologies of cardiovascular system, as well as in ageing.

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10. *Indutny A.V., Bykov D.E., Vysokogorsky V.E.*

The level of free radical oxidation products in heart and blood plasma by diabetes mellitus with chronic alcohol intoxication.

The research results of level glycemia, contents of free radical oxidation products (thiobarbiturate-reactive substances, oxidized-modified proteins) in blood plasma and heart of diabetes mellitus rats with chronic alcohol intoxication are presented. It is shown, that at presence of a diabetes mellitus the chronic alcohol consumption does not change blood plasma levels of the oxidized-modified proteins, thiobarbiturate-reactive substances and glucose. However the contents of thiobarbiturate-reactive substances and oxidizing modification of proteins products in animals heart is more considerably increased at combination of the diabetes with chronic alcohol consumption, in comparison with changes at the diabetes mellitus outside of alcoholization and with changes at the isolated chronic alcohol influence. Found out alcohol-induced free radical processes hyperactivation in heart at the diabetes is capable to render additional injuring influence.

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11. *Marchenko M.M., Kopylchuk G.P., Ketsa O.V.*

Low doses x-ray irradiation influence on liver detoxication system in rats with transplanted guerin's carcinoma.

The activity of detoxication enzymes in liver microsomal fraction of preliminary radiation-exposed rats was investigated. It was shown that preliminary organism exposure to radiation reduced cytochrome P-450 and glutathione-S-transferase activity in liver microsomal fraction in the latent and logarithmic

phases of oncogenesis compared with the unirradiated rats with tumor. Low level of cytochrome P450 activity can be caused by transition of microsomal cytochrome P450 in P420 inactive form. The preliminary radiation does not influence the enzyme activity of liver cytochrome P450 and glutathione-S-transferase on terminal stages of Guerin's carcinoma growth.

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12. Venediktova A.A., Falameeva O.V., Kolosova N.G., Sadovoj M.A., Korolenko T.A.

Cathepsin K and matrix metalloproteases activity in bone tissue of OXYS rats with osteoporosis development.

The comparative study of activity of cysteine protease cathepsin K and matrix metalloproteases (MMPs) in bone tissue of accelerated senescent OXYS rats with early ageing comparatively to Wistar rats of the same age was performed. Early development osteoporosis is a typical feature of OXYS rats. In bone tissue of 3 month old OXYS rats, before appearance of osteoporosis manifestation cathepsin K activity was higher, whereas MMPs activity was lower than in Wistar rats. In Wistar rats (3 and 14 months old) cathepsin K activity of spine was shown to increase, and MMPs activity to decrease. In OXYS rats age-related change of cathepsin K and MMPs activity in bone tissue had the opposite direction. As a result of this there were no differences between Wistar and OXYS rats 14 months old despite the marked osteoporosis in OXYS rats as revealed our early researches. Serum β_2 -macroglobulin activity was higher in 14 months old OXYS rats. The role of activation of cathepsin K in bone resorption in the development of osteoporosis in early ageing OXYS rats is discussed.

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13. Serebrov V.Yu., Kuzmenko D.I., Burov P.G., Sapugoltseva O.B.

Activity of enzymes of a sphingomyelin cycle and concentration of products of sphingomyelin degradation in the liver of rats in dynamics of the acute toxic hepatitis.

Activity of key enzymes of a sphingomyelin cycle and the maintenance of its components (sphingomyelin, ceramide and sphingosine-1-phosphate) have been studied in livers of rats in dynamics of the acute toxic hepatitis caused by hypodermic introduction of an oil solution of CCl₄. Sphingomyelinase activity significantly increased already on early terms and remained increased over the whole period of observation. Activity of ceramidase insignificantly differed from the control level. The levels of sphingomyelin and sphingosine-1-phosphate did not undergo marked changes while ceramide content significantly increased. Thus, balance between liver content of ceramide (proapoptotic) and the sphingosine-1-phosphate, being the antiapoptotic factor, was shifted towards ceramide. In sphingomyelin molecules there was a significant decrease in the content of fatty acids Δ_1 18:1 and Δ_1 22:2, while in ceramide molecules and sphingosine-1-phosphate only fatty acid Δ_1 22:2 changed. In spite of significant decrease in content of some unsaturated fatty acids, calculated unsaturation coefficients of the fatty acid component of the sphingomyelin cycle metabolites. Thus, our results together with literature data suggests involvement of ceramide-mediated apoptosis in the pathogenesis of acute toxic hepatitis. Elimination of damaged hepatocytes facilitates realization of repair processes and optimization of cellular community of a liver.

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14. Kostyushov V.V., Bokal I.I.

Role of thiol-disulfid of system in mechanism of oxidative stress and distress at HIV of infection.

In the article general conformities to law and features of violation of the thiol-disulfid an redox system of whey of blood are described for patients with the without a symptom transmitter of HIV and manifestly forms AIDS. The role of her components is grounded - general, protein and non protein -SH, -S-S- groups in the mechanism of forming of oxidative stress and distress at HIV of infection. The clinic and laboratory criterions of expressed of peroxides processes are specified on the indexes of violation of redox transformations of -SH, -S-S- groups, neutralization and utilization of MDA and stability of LPC in the whey of blood at HIV of infection. Found out intercommunication between expressed of violation of the studied indexes, oxidative stress and distress and features of clinical flow of HIV of infection, allowed authors to attribute this pathology to "free radical diseases". In this connection, indicated analytic it is suggested to use as additional biochemical markers of oxidative stress and distress, and also for the ground of setting of antioxidants and their combinations in complex prophylactic or therapeutic application at HIV of infection.

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