

1. Pankov Y.A.

Adipogenic function and other biologic effects of insulin.

Studies on experimental animals with knockout of the insulin receptor gene *Insr* (in the whole body or in certain tissues) and/or related genes encoding proteins involved in realization of insulin signal transduction in target cells, have made an important contribution to the elucidation of insulin regulation of metabolism, particularly fat metabolism. Since the whole insulin secreted by β -cells, together with the products of gastrointestinal tract digestion of proteins, fats, and carbohydrates reach the liver, the latter is the first organ on which this hormone acts. The liver employs released amino acids for synthesis of proteins, including apoproteins for various lipoproteins. Glucose is used for synthesis of glycogen, fatty acids, and triglycerides, which enter all the organs in very low density lipoproteins (VLDL). The LIRKO mice with knockout of the *Insr* gene in the liver demonstrated inhibition of synthesis of macromolecular compounds from amino acids, glucose, and fatty acids. Low molecular weight substances demonstrated increased entry to circulation, and together with other disorders induced hyperglycemia. In LIRKO mice blood glucose levels and glucose tolerance demonstrated time-dependent normalization and at later stages the increase in glucose levels was replaced by hypoglycemia. These changes can be well explained if we take into consideration that one of the main functions of insulin consists in stimulation of energy accumulation by means of activation of triglyceride deposition in adipose tissue. FIRKO mice with selective knockout of adipose tissue *Insr* were characterized by decreased uptake of glucose in adipocytes, and its transformation into lipids. However, the level of body fat in animals remained normal, possibly due to preserved insulin receptor in the liver and insulin-induced activation of triglyceride production which maintained normal levels of body fat stores, the effective functioning of adipose tissue and secretion of leptin by adipocytes during inhibition of glucose transformation into triglyceride in adipose tissue. Knockout of the *Insr* gene in muscles blocked glucose uptake by myocytes, but it did not induce hyperglycemia, probably due to the increase in glucose uptake by other organs, which retained the insulin receptor, and induced some increase in fat resources in adipose tissue. Similar results were obtained in mice with knockout the glucose transporter 4 GLUT4 in muscle and/or adipose tissue. Insulin microinjections in the brain, in the cerebral ventricle 4 (ICV) and mediobasal hypothalamus (MBH) did not affect the insulin levels in the general circulation, but effectively activated lipogenesis and inhibited lipolysis in adipose tissue. They induced obesity, similar to conventional obesity when the insulin levels increased. These results may serve as additional evidence for importance of the adipogenic insulin function in mechanisms of regulation of general metabolism.

DOI: 10.18097/PBMC20166201005

2. Kuzmenko D.I., Udintsev S.N., Klimentyeva T.K., Serebrov V.Yu.

Oxidative stress in adipose tissue as a primary link in pathogenesis of insulin resistance.

Obesity is a leading risk factor of diabetes mellitus type 2, impairments of lipid metabolism and cardiovascular diseases. Dysfunctions of the accumulating weight of the visceral fat are primarily linked to pathogenesis of systemic insulin resistance. The review considers modern views about biochemical mechanisms underlying formation of oxidative stress in adipocytes at obesity, as one of key elements of impairments of their metabolism triggering formation of systemic insulin resistance.

DOI: 10.18097/PBMC20166201014

3. Popov A.M., Krivoschapko O.N., Klimovich A.A., Artyukov A.A.

Biological activity and mechanisms of therapeutic action of rosmarinic acid, luteolin and its sulphated derivatives.

The review considers recent experimental studies of biological activity and mechanisms of therapeutic action of rosmarinic acid, luteolin and its sulfated derivatives in diseases associated with disorders of carbohydrate and lipid metabolism. Particular attention is focused on the results of studies showing a high therapeutic potential of these phenolic compounds in their prophylactic and therapeutic use at experimental modeling of type 2 diabetes and hyperlipidemia. Based on the analysis of our results and the literature data putative mechanisms of therapeutic action of rosmarinic acid, luteolin and its sulfated derivatives have been proposed.

DOI: 10.18097/PBMC20166201022

4. Galenova T.I., Kyznetsova M.Y., Savchuk A.N., Ostapchenko L.I.

Low molecular weight regulators of the intracellular insulin signal transduction as a correction method of the insulin resistance in the treatment of type 2 diabetes.

Insulin resistance is the characteristic feature of type 2 diabetes. This condition is manifested in the reduction of peripheral tissues sensitivity to the biological action of insulin and is expressed in the inhibition of cellular glucose absorption and metabolism in response to hormonal stimulation. At the cellular level, disorders which are realized both at the receptor and the postreceptor levels can serve a prerequisite to the formation of insulin resistance and are associated with a change in the amount or dysfunction of major molecular signaling cascade. Thus, the insulin receptor, as well as the other related signaling molecules can be considered as ideal therapeutic targets for the correction of insulin resistance and thus low molecular weight effectors which act on the individual links of insulin signaling cascade may be positioned as a new generation of anti-diabetic agents. This report provides information on the regulators of insulin receptor cascade, main advantages and disadvantages of their impact on biological targets and prospects for their therapeutic use as anti-diabetic drugs.

DOI: 10.18097/PBMC20166201031

5. *Stulov S.V., Dugin N.O., Zharkova M.S., Shcherbinin D.S., Kuzikov A.V., Shumyantseva V.V., Misharin A.Yu., Veselovsky A.V.*

Interaction of novel oxazoline derivatives of 17(20)e-pregna-5,17(20)-diene with cytochrome P450 17A1.

In order to find novel inhibitors of 17 α -hydroxylase-17,20-lyase (cytochrome P450 17A1, CYP17A1), a key enzyme of biosynthesis of androgens, molecular docking of six new oxazoline-containing derivatives 17(20)E-pregna-5,17(20)-diene has been carried out to the active site of the crystal structure of CYP17A1 (pdb 3ruk). Results of this study indicate that: 1) complex formation of docked compounds with CYP17A1 causes their isomerization in energetically less favorable 17(20)Z-isomer; 2) the localization of the steroid moiety of all compounds in the active site is basically the same; 3) the structure of the oxazoline moiety significantly influences its position relative to heme as well as the energy of complex formation; 4) coordination of the nitrogen atom of the oxazoline moiety and the heme iron is only possible in the 17(20)Z-conformation with anti oriented double bonds 17(20), and C=N; 5) the presence of two substituents at C4' of the oxazoline moiety significantly impairs ligand binding; 6) oxazoline - and benzoxazole-containing derivatives 17(20)E-pregna-5,17(20)-diene can effectively inhibit the catalytic activity CYP17A1 and may be of interest as a basis for the development of new drugs for the treatment of androgen-dependent cancer.

DOI: 10.18097/PBMC20166201038

6. *Shomurotov Sh.A., Mamadullaev G., Turaev A.S.*

Medical and biological properties of polysaccharide complex of isoniazid and ethambutol.

The polymeric anti-tubercular drug systems β -Biophthizoetham-K α and β -Biophthizoetham-P α have been obtained by chemical modification of parent compounds isoniazid and ethambutol with carboxymethylcellulose and polygalacturonic acid. These systems were less toxic than the parent compounds; they exhibited prolonged anti-tubercular action at a dose sixfold lower than isoniazid. Pharmacokinetic studies have shown that after administration of β -Biophthizoetham-K α and β -Biophthizoetham-P α , therapeutic concentration of active substances (isoniazid and ethambutol) in blood remained longer than after administration of active substances alone. Introduction of isoniazid in the polysaccharide matrix decreased its metabolism into the therapeutically inactive form "acetylisoniazid".

DOI: 10.18097/PBMC20166201045

7. *Ketsa O.V., Shmarakov I.O., Marchenko M.M.*

Lipid peroxidation in cardiac mitochondrial fraction of rats exposed to different supplementation with polyunsaturated fatty acids.

The effect of diet supplementation with polyunsaturated fatty acids (PUFAs) used at different ratios of w-6/w-3 was studied on the content of primary (diene conjugates, DC; triene conjugates, TC), secondary (ketodienes, CD; coupled trienes, CT; TBA-active products) and terminal (Schiff bases) lipid peroxidation products (LPO) and generation of superoxide anion-radical in rat heart mitochondrial fraction. It was shown that diet supplementation with high doses of w-6 or w-3 PUFAs increased the content of primary, secondary and terminal LPO in rat heart mitochondrial fraction. Lipid peroxidation was accompanied by the intensification of superoxide anion-radical generation in rat heart mitochondrial fraction. During diet consumption with the PUFAs leading factor affecting the intensity of lipoperoxidation in rat heart mitochondria is fatty acid composition, rather than the level of their saturation.

DOI: 10.18097/PBMC20166201050

8. *Bolbasov E.N., Antonova L.V., Matveeva V.G., Novikov V.A., Shesterikov E.V., Bogomolova N.L., Golovkin A.S., Tverdohlebov S.I., Barbarash O.L., Barbarash L.S.*

Effect of radio frequency discharge plasma on surface properties and biocompatibility of polycaprolactone matrices.

Surface modification of bioresorbable polymer material (polycaprolactone, PCL) with abnormal glow discharge, initiated during radio-frequency magnetron sputtering of a hydroxyapatite target was investigated. Plasma treatment resulted in an increase of surface roughness of PCL, crystallite size, the surface free energy and hydrophilicity. Increased treatment time (30, 60, 150 seconds) provoked the polymer surface saturation with the sputtering target ions (calcium, phosphorus). The assessment of plasma exposure of PCL surface on bone marrow multipotent mesenchymal stromal cells behavior (BM MSCs) has been performed. Modification of the polymer surface with the abnormal glow discharge stimulated adhesion and subsequent proliferation of BM MSCs; thus, maximum values were achieved with the surface treatment for 60 s. This type of plasma modification did not affect cell viability (apoptosis, necrosis). Thus, the surface modification with abnormal glow discharge, initiated during radio-frequency magnetron sputtering of a hydroxyapatite target, appear to be a promising method of surface modification of bioresorbable polymer material (PCL) for tissue engineering.

DOI: 10.18097/PBMC20166201056

9. *Stepovaya E.A., Shakhristova E.V., Ryazantseva N.V., Nosareva O.L., Yakushina V.D., Nosova A.I., Gulaya V.S., Stepanova E.A., Chil'chigashev R.I., Novitsky V.V.*

The role of oxidative protein modification and the glutathione system in modulation of the redox status of breast epithelial cells.

The effects of the SH-group blocker N-ethylmaleimide (NEM) and thiol group protector 1,4-dithioerythritol (DTE) on the redox status of cells HBL-100 cells, oxidative modification of their proteins and the state of glutathione and thioredoxin systems have been investigated. Breast epithelial cells cultivated in the presence of NEM were characterized by decreased redox status, increased glutathione reductase activity, and increased concentrations of products of irreversible oxidative modification of protein and amino acids. Cultivation of HBL-100 cells in the presence of DTE resulted in a shift of the redox status towards reduction processes and increased reversible protein modification by glutathionylation. The proposed model of intracellular redox modulation may be used in the development of new therapeutic approaches to treat diseases accompanied by impaired redox homeostasis (e.g. oncologic, inflammatory, cardiovascular and neurodegenerative disease).

DOI: 10.18097/PBMC20166201064

10. *Pogorelova T.N., Linde V.A., Gunko V.O., Selyutina S.N.*

The imbalance of metal-containing proteins and free metal ions in the amniotic fluid during fetal growth.

The levels of zinc, copper, iron, and magnesium ions, and some of their binding proteins have been investigated in an amniotic fluid under the fetal

growth retardation (FGR). FGR, developed under conditions of placental insufficiency, is characterized by a decrease in the content of zinc, iron, and magnesium ions and by an increase in the copper content in the amniotic fluid in the II and III trimesters of pregnancy. During these trimesters the levels of ceruloplasmin, ferritin, and Ca²⁺, Mg²⁺-ATPase were lower in FGR, while the level of zinc- α -2-glycoprotein was higher than during the same periods of normal pregnancy. Changes in the parameters studied in the amniotic fluid were associated with developmental disorders of the newborns. These changes obviously have a pathogenetic importance in the development of FGR, and the levels of metal ions and their ratio in the amniotic fluid can be used as markers of the pre- and postnatal pathology.

DOI: 10.18097/PBMC20166201069

11. *Yaglova N.V., Yaglov V.V.*

The effect of long-term exposure to low doses of endocrine disruptor ddt on serum levels of thyroid protein autoantigenes and antithyroid autoantibodies.

Changes in secretion of thyroid autoantigenes and production of antithyroid autoantibodies after long-term exposure to low doses of DDT were studied. Changes in serum levels of antithyroid peroxidase antibodies and thyroid peroxidase, attributed to disruption of thyroxine production by DDT were found. Long-term exposure of rats to low doses of DDT revealed no specific impact on serum autoantibodies to all thyroid autoantigenes studied. The increase of the ratio of autoantibody/autoantigen for thyroid peroxidase and thyroglobulin was rather small and thus could not be considered as a significant symptom of thyroid autoimmunity.

DOI: 10.18097/PBMC20166201073

12. *Savilov P.N.*

Urea formation in the after operational liver.

The effect of resection of the left lobe of the liver (LR, 15-20% of the organ weight) on hepatic urea formation was investigated in 84 albino rats. The objects of study were the surgery left (LLP), inoperable middle (MLP) lobe of the liver, blood (aorta, v. hepatica, v. porta) and choledochal bile. They studied the urea content. Arginase activity was examined in liver homogenate. On the day 3 and day 7 after resection reduced arginase activity was detected. LR caused a decrease of urea in v. hepatica, but increased urea content in the arterial blood and v. porta. Increase in bile urea on day 7 it was replaced by a decrease observed on day 14 of the postsurgery period. The concentration of urea in the liver on the 3rd day after LR was below the norm, and on the 7th and 14th day was within it. The results indicate a violation of urea operated by hepatocytes of the liver and extrahepatic activation mechanisms of the formation of urea.

DOI: 10.18097/PBMC20166201079

13. *Habriyev R.U., Kamayev N.O., Danilova T.I., Kakhoyan E.G.*

Peculiarities of the action of hyaluronidase of different origin to the connective tissue.

The lecture is devoted to consideration of mechanism of therapeutic action of the enzyme hyaluronidase in hyperplastic connective tissue. Drugs based on hyaluronidase increase bioavailability of other drugs used in adjuvant therapy; they significantly increase effectiveness of treatment, and also provide targeted synthesis of hyaluronic acid, thus regulating the regeneration process of connective tissue.

DOI: 10.18097/PBMC20166201082

14. *Gerasimovich E.S., Yakovlev A.A., Druzhkova T.A., Grishkina M.N., Guekht A.B., Gulyaeva N.V.*

Activation of caspases in lymphocytes of patients with depression and anxiety.

The processes in the nervous and immune systems are closely interrelated. In particular, increased apoptosis was reported in lymphocytes of patients with depression. The aim of this study was to assess activities of proteases associated with cell death in lymphocytes of patient with personality disorders accompanied by depression and anxiety. In patients with personality disorders associated with organic brain dysfunction caspase activities were reduced in patients with depression and increased in patients with anxiety. The results may be useful for elucidation of pathogenetic mechanisms of personality disorders and in search of new biomarkers of these diseases.

DOI: 10.18097/PBMC20166201089

15. *Kolyovska V.*

Serum IgG antibodies to GD1a and GM1 gangliosides in elderly people.

Nowadays, the percentage of elderly people in society grows. Good nutrition and medical care help older people to have a normal life over 80 to 90 years. In the last ten years it is of critical importance to establish the clinical significance of serum IgG anti-GD1a and anti-GM1 ganglioside antibodies as potential biomarkers for neuronal damage in neurodegenerative diseases and immune-mediated neuropathies and demyelination. In the current study, the diagnostic values of IgG anti-GD1a and anti-GM1 antibodies were determined by the ELISA method in serum samples of 18 elderly patients (71-91 years). Significantly elevated serum IgG anti-GD1a and anti-GM1 antibodies titers were detected only in patients over 80 years. These data suggest that the immune-mediated neuropathies, neurodegeneration and demyelination in healthy elderly occur after 80 years old. Therefore, IgG anti-GD1a and anti-GM1 antibodies can serve as biomarkers, showing the nervous system dysfunction.

DOI: 10.18097/PBMC20166201093

16. *Korenovsky Yu.V., Remneva O.V.*

Reference ranges of matrix metalloproteinase-1, -2, -9 and tissue inhibitor of matrix metalloproteinases-1 concentrations in amniotic fluid in physiological pregnancy.

The aim of this study was to determine reference values of matrix metalloproteinase-1 (MMP-1), MMP-2, MMP-9 and tissue inhibitor of matrix

metalloproteinases-1 (TIMP-1) in the amniotic fluid at the first stage of labor in physiological pregnancy. 89 women at the first stage of term labor have been examined. Samples of amniotic fluid were taken at the first period of labor by vaginal amniotomy. Concentrations of MMP-1, MMP-2, MMP-9, and TIMP-1 were investigated in amniotic fluid by ELISA kits. We have determined normal concentration ranges for MMP-1, MMP-2, MMP-9, TIMP-1, and ratios of concentrations of MMPs and TIMP-1 (MMP-1/TIMP-1, MMP-2/TIMP-1, MMP-9/TIMP-1) in the amniotic fluid at the first period of labor in physiological pregnancy. These included: MMP-1 - 5.1-16.8 pg/mg of protein, MMP-2 - 238.3-374.1 pg/mg of protein, MMP-9 - 66.1-113.3 pg/mg of protein, TIMP-1 - 4.7-13.6 pg/mg of protein, ratio of MMP-1/TIMP-1 - 0.1-2.2, ratio of MMP-2/TIMP-1 - 19.9-55.7, ratio of MMP-9/TIMP-1 - 4.2-17.2. DOI: 10.18097/PBMC20166201096

17. GrigorTMeva A.E., Tamkovich S.N., Eremina A.V., Tupikin A.E., Kabilov M.R., Chernykh V.V., Vlassov V.V., Laktionov P.P., Ryabchikova E.I.

Characteristics of exosomes and microparticles discovered in human tears.

Exosomes represent a sort of extracellular vesicles, which transfer molecular signals in organism and possess markers of producing cells. Our study was aimed at search of exosomes in the tears of healthy humans, confirmation of their nature and examination of exosome morphological and molecular-biological characteristics. The tears (110-340 ml) were collected from 24 healthy donors (aged 46-60 years); individual probes were centrifuged at 20000 g for 15 min to pellet cell debris. The supernatants were examined in electron microscope using negative staining; and they were also used for isolation and purification of the exosomes by filtration (100 nm pore-size) and double ultracentrifugation (90 min at 100000 g, 4°C). The pellets were subjected to electron microscopy, immunolabeling. The RNA and DNA were isolated from the samples, and their sizes were evaluated by capillary electrophoresis, the concentration and localization of nucleic acids were determined. Sequencing of DNA was performed using MiSeq (Illumina, USA), data were analyzed using CLC GW 7.5 (Qiagen, USA). Sequences were mapped on human genome (hg19). Electron microscopy revealed in supernatants of the tears cell debris, spherical microparticles (20-40 nm), membrane vesicles and macromolecular aggregates. The pellets obtained after ultracentrifugation, contained microparticles (17%), spherical and cup-shaped EVs (40-100 nm, 83%), which were positive for CD63, CD9 and CD24 receptors (specific markers of exosomes). Our study showed presence of high amount of exosomes in human tears, and relation of the exosomes with RNA (size less than 200 nt) and DNA (size was 3-9 kb). Sequencing of the DNA showed that about 92% of the reads mapped to human genome.

DOI: 10.18097/PBMC20166201099

18. Lvovskaya E.I., Derginskyi N.V., Sadova V.A., Symnaya D.B.

Prognostic value of the parameters of free radical oxidation in traumatic brain injury.

The dynamics of lipoperoxides content and activity of antioxidant (glutathione peroxidase, superoxide dismutase, catalase) and prooxidant (xanthine oxidase) enzymes were investigated in the blood and cerebrospinal fluid of patients with traumatic brain injury of various severity depending on the left- or right-hemisphere localization of injuries. Reciprocal relationship between lipid peroxidation and oxidative modification of proteins from first to 14th day, increase of the level of total antioxidant activity, accompanied with the growth of GP and catalase activity, against the background of decrease in SOD activity from 1 to 7 day have been revealed. Were set lower average content of lipid peroxides in the blood and cerebrospinal fluid of patients with the subsequent development of lethal results in compare with cases of favorable outcomes, decrease of heptanofilic lipid peroxides in serum below the reference level, as well as the reduction of antioxidant activity in the blood and cerebrospinal fluid, associated with a sharp falling in superoxide dismutase activity and a significant increase of xanthine oxidase activity, which preceded the lethal results.

DOI: 10.18097/PBMC20166201107