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1. Rusetskaya N.Y., Fedotov I.V., Koftina V.A., Borodulin V.B.

Selenium compounds in redox regulation of inflammation and apoptosis.

Monocytes and macrophages play a key role in the development of inflammation: under the action of lipopolysaccharides (LPS), absorbed from the intestine, monocytes and macrophages form reactive oxygen species (ROS) and cytokines, this leads to the development of oxidative stress, inflammation and/or apoptosis in all types of tissues. In the cells LPS induce an â€œinternalâ€• TLR4-mediated MAP-kinase inflammatory signaling pathway and cytokines through the superfamily of tumor necrosis factor receptor (TNFR) and the â€œdeath domainâ€• (DD) initiate an â€œexternalâ€• caspase apoptosis cascade or necrosis activation that causes necroptosis. Many of the proteins involved in intracellular signaling cascades (MYD88, ASK1, IKKa/b, NF-kB, AP-1) are redox-sensitive and their activity is regulated by antioxidants thioredoxin, glutaredoxin, nitroredoxin, and glutathione. Oxidation of these signaling proteins induced by ROS enhances the development of inflammation and apoptosis, and their reduction with antioxidants, on the contrary, stabilizes the signaling cascades speed, preventing the vicious circle of oxidative stress, inflammation and apoptosis that follows it. Antioxidant (AO) enzymes thioredoxin reductase (TRXR), glutaredoxin reductase (GLRXR), glutathione reductase (GR) are required for reduction of non-enzymatic antioxidants (thioredoxin, glutaredoxin, nitroredoxin, glutathione), and AO enzymes (SOD, catalase, GPX) are required for ROS deactivation. The key AO enzymes (TRXR and GPX) are selenium-dependent; therefore selenium deficiency leads to a decrease in the body's antioxidant defense, the development of oxidative stress, inflammation, and/or apoptosis in various cell types. Nrf2-Keap1 signaling pathway activated by selenium deficiency and/or oxidative stress is necessary to restore redox homeostasis in the cell. In addition, expression of some genes is changed with selenium deficiency. Consequently, growth and proliferation of cells, their movement, development, death, and survival, as well as the interaction between cells, the redox regulation of intracellular signaling cascades of inflammation and apoptosis, depend on the selenium status of the body. Prophylactic administration of selenium-containing preparations (natural and synthetic (organic and inorganic)) is able to normalize the activity of AO enzymes and the general status of the body. Organic selenium compounds have a high bioavailability and, depending on their concentration, can act both as selenium donors to prevent selenium deficiency and as antitumor drugs due to their toxicity and participation in the regulation of signaling pathways of apoptosis. Known selenorganic compounds diphenyldiselenide and ethaselen share similarity with the Russian organo selenium compound, diacetophenonylselenide (DAPS-25), which serves as a source of bioavailable selenium, exhibits a wide range of biological activity, including antioxidant activity, that governs cell redox balance, inflammation and apoptosis regulation.

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2. Shevchenko K.V., Nagaev I.Yu., Andreeva L.A., Shevchenko V.P., Myasoedov N.F.

Stability of prolin-containing peptides in biological media.

New data on peptide drugs have been summarized; their high stability is due to both the introduction of Pro-Gly-Pro in various amino acid sequences and the modification of the glyproline fragment itself. Pro-Gly-Pro-Leu, ACTH(6-9)Pro-Gly-Pro, 5-oxo-Pro-Arg-Pro and 5-oxo-Pro-His-Pro-NH2 were used as proline-containing peptides. Tritiated peptides were obtained: Pro-Gly-Pro-Leu with specific radioactivity of 135 Ci/mmol, ACTH(6-9)Pro-Gly-Pro â€“ 26 Ci/mmol, 5-oxo-Pro-Arg-Pro â€“ 60 Ci/mmol and 5-oxo-Pro-His-Pro-NH2 â€“ 75 Ci/mmol. The concentration of Pro-Gly-Pro-Leu, ACTH(6-9)Pro-Gly-Pro, 5-oxo-Pro-Arg-Pro and 5-oxo-Pro-His-Pro-NH2 in the blood was found to be about 200 times more than in the brain for intranasal administration, and in average 600 times more for intravenous administration. The stability of proline-containing peptides in vitro experiments was determined using different commercially available peptidases (leucine aminopeptidases, dipeptidases, carboxypeptidases B and Y), and using nasal mucus, microsomal fraction of the rat brain (IMPC) and rat blood plasma. During peptidase hydrolysis of Pro-Gly-Pro-Leu, the main metabolites were Gly-Pro-Leu, Pro-Gly-Pro, Gly-Pro and Pro-Gly. For ACTH(6-9)Pro-Gly-Pro, the main metabolites were Phe-Arg-Trp-Pro-Gly-Pro and Trp-Pro-Gly-Pro. In peptidase hydrolysis of 5-oxo-Pro-His-Pro-NH2, the major metabolite was 5-oxo-Pro-His-Pro. It was shown that with different methods of peptides administration the composition of the metabolites formed is different. Based on the data obtained, resistance to enzymatic cleavage of peptides and their metabolic pathways were evaluated. Thus, these new data have shown that the above approaches can be used to prolong the action of glyprolines in living objects. In this case, the degradation of proline-containing peptides occurs mainly not due to the action of proteases, but due to other ways of degradation. In general, the data presented in the review indicate the promise of intranasal way of introducing biologically active peptides into the brain of living organisms.

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3. Rak A.Ya., Trofimov A.V., Ischenko A.M.

Mullerian inhibiting substance type II receptor as a potential target for antineoplastic therapy.

The review considers properties of the type II anti-Mullerian hormone receptor (mullerian inhibiting substance receptor type II, MISRII), a transmembrane sensor with its own serine/threonine protein kinase activity, triggering apoptosis of the Mullerian ducts in mammalian embryogenesis and providing formation of the male type reproductive system. According to recent data, MISRII overexpression in the postnatal period is found in cells of a number of ovarian, mammary gland, and prostate tumors, and anti-Mullerian hormone (AMH) has a pro-apoptotic effect on MISRII-positive tumor cells. This fact makes MISRII a potential target for targeted anti-cancer therapy. Treatment based on targeting MISRII seems to be a much more effective alternative to the traditional one and will significantly reduce the drug dose. However, the mechanism of MISRII-AMH interaction is still poorly understood, so the development of new anticancer drugs is complicated. The review analyzes MISRII molecular structure and expression levels in various tissues and cell lines, as well as current understanding of the AMH binding mechanisms and data on the possibility of using MISRII as a target

for the action of AMH-based antineoplastic drugs.
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4. Antonova O.A., Shustova O.N., Golubeva N.V., Yakushkin V.V., Alchinova I.B., Karganov M.Y., Mazurov A.V.

Coagulation properties of erythrocyte derived membrane microparticles.

Membrane microparticles (MP) produced upon cell activation and/or damage possess coagulation activity, i.e. ability to accelerate blood clotting. They contain on their surface phosphatidylserine (PS), a substrate for assembling coagulation enzymatic complexes, and some of them tissue factor (TF), the initiator of clotting cascade reactions. In this study coagulation properties of MP derived from erythrocytes have been investigated. These MP were obtained from donor's erythrocytes activated with ionophore A23187 as well as from outdated erythrocyte concentrates for transfusion. MP were counted by flow cytometry. Coagulation activity of MP was examined by modified plasma recalcification assay. Involvement of PS and TF in this reaction was assessed using PS blocker lactadherin and anti-TF antibodies. TF activity in MP was measured by its ability to activate factor X in a chromogenic assay. Size of MP was evaluated by dynamic light scattering. Properties of erythrocyte MP were compared with previously characterized (using the same methodological approaches) MP derived from platelets and monocytic THP-1 cells, lacking and containing TF, respectively. Erythrocyte MP accelerated plasma clotting, but less actively than MP from platelets and MP from THP-1 cells, which demonstrated maximal activity. Lactadherin completely inhibited coagulation activity of all MP. Anti-TF antibodies did not affect clotting parameters in the presence of platelet and erythrocyte MP, but slowed clotting in the presence of MP from THP-1 cells. TF activity was not detected in erythrocyte and platelet MP, unlike MP from THP-1 cells expressing active TF. MP derived from erythrocytes were smaller than MP from platelets and THP-1 cells, with average diameter about 200 nm and 400 nm respectively. Thus, MP from erythrocyte possess less ability to accelerate plasma clotting in comparison with MP from platelet and THP-1 cells. The data obtained suggest that lesser coagulation activity of erythrocyte MP in comparison with MP from THP-1 cells is due to the absence of TF in erythrocyte MP (in contrast to MP from THP-1 cells) and to their smaller size, and in comparison with MP from platelets (which as erythrocyte MP do not express TF) is due to their smaller size only.

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5. Prozorovskii V.N., Ipatova O.M., Tikhonova E.G., Zakharova T.S., Druzhilovskaya O.S., Korotkevich E.I., Torkhovskaya T.I.

Prednisolone in phospholipid nanoparticles: prolonged circulation and increased antiinflammatory effect.

Along with modern new drugs, many therapeutic schemes also include known effective drugs, particularly, glucocorticoids. One of the most distributed of them is prednisolone that has pronounced anti-inflammatory properties. Its disadvantage is short-term circulation, resulting in a number of side effects. For this reason the development of its more effective and safe formulations is carried out. We have obtained the formulation of prednisolone included in nanoparticles from soy phosphatidylcholine with an average diameter of 20 nm. With oral administration to rats and analysis by HPLC an increase in prednisolone maximal concentration in of plasma and the duration of circulation as compared with free drug administration were shown. The experiment with mice with conconavalin A induced inflammation was also carried out: conconavalin A was injected subplantary in an hour after oral administration of both prednisolone formulations in several doses. The index of the inflammatory reaction (determined by the edema degree) was suppressed more effectively in the case of prednisolone in nanoparticles. Maximal suppression (62.2% as compared with 49.6% for free prednisolone) was observed even at a minimal dose (2.5 mg/kg), at which the free drug did not act at all. The results indicate an increase in the efficiency of prednisolone included in phospholipid nanoparticles, that makes it possible to diminish its administered doses and thereby reduce the risk of side effects.

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6. Klyueva N.N., Okunevich I.V., Parfenova N.S., Belova E.V., Ageeva E.V.

Effect of lipid-lowering activity of the natural original enzyme preparation in the experiment.

The experimental study in vivo was aimed at evaluation of hypolipidemic action of the original natural microbial enzyme preparation of cholesterol oxidase (CHO). In preliminary chronic experiments in rats, rabbits, dogs, low toxicity, good tolerability, and anti-atherosclerotic activity of the CHO preparation were established. To assess the effect of CHO under conditions of moderate, nutritional, atherogenic dyslipoproteinemia, experiments were carried out in rats, guinea pigs, and rabbits. It was shown that administration of CHO had the pronounced lipid-lowering effect in models of atherogenic dyslipoproteinemia induced in these animals.

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7. Serebryakova L.I., Studneva I.M., Ovchinnikov M.V., Veselova O.M., Molokoedov A.S., Arzamastsev E.V., Afanasyeva E.Yu., Terekhova O.A., Sidorova M.V., Pisarenko O.I.

Cardiometabolic efficacy and toxicological evaluation of a pharmacological galanin receptor agonist.

The goal of this study was to examine effects of a novel galanin receptor agonist GalR1-3 [bAla14, His15]-galanine 2-15 (G), obtained by automatic solid-phase synthesis, on the metabolic state of the area at risk and the size of acute myocardial infarction (MI) in rats in vivo and evaluate its toxicity in BALB /c mice. In anesthetized rats, regional ischemia was simulated by coronary artery occlusion and then coronary blood flow was restored. The peptide G was administered intravenously (i.v.) with a bolus after a period of regional ischemia in the dose range of 0.25-3.0 mg/kg. The sizes of MI and the activities of creatine kinase-MB (Đ¡K-MB) and lactate dehydrogenase (LDH) in blood plasma were estimated. The effect of administration of the optimal dose of G (1.0 mg/kg) on myocardial content of adenine nucleotides (AN), phosphocreatine (PCr), creatine (Cr) and lactate was studied. I.v. administration of G to rats at a dose of 1.0 mg/kg slightly affected hemodynamic parameters, but reduced MI size by 40% and decreased plasma LDH and CK-MB activity by the end of reperfusion compared to control. These effects were accompanied by a significant improvement in energy state of area at risk (AAR) â€“ an increase in myocardial content of ATP, Ã¥AN, PCr and Ã¥Cr, and combined with a decrease in myocardial lactate level compared with the control. Toxicity of peptide G was studied with a single intraperitoneal injection of 0.5-3.0% solution of the peptide substance to mice. The absence of signs of intoxication and death of animals after G injection in the maximum possible dose did not allow determining the value of

the average lethal dose. The results indicate therapeutic potential of the peptide G for preventing myocardial ischemia and reperfusion injury and feasibility for further study of its pharmacological properties and mechanisms of action.
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8. Dyleva Yu.A., Gruzdeva O.V., Belik E.V., Akbasheva O.E., Uchasova E.G., Borodkina D.A., Sinitsky M.Yu., Sotnikov A.V., Kozyrin K.A., Karetnikova V.N., Barbarash O.L.

Expression of gene and content of adiponectin in fatty tissue in patients with ischemic heart disease.

The purpose of the study was to investigate the features of expression and adiponectin content in the adipocyte culture of subcutaneous, epicardial, and perivascular adipose tissue and the effect of various doses of rosuvastatin on these processes. 29 patients with coronary artery disease were examined. Adipocytes were isolated from the samples of SAT, EAT and PVAT which were taken during coronary artery bypass surgery, followed by cultivation in the presence of rosuvastatin and evaluation of gene expression and adiponectin concentration. Adipocytes SAT, EAT and PVAT differed in the level of adiponectin secretion and expression of its gene. On day 1 of cultivation the expression of the adiponectin gene in the EAT was 2.3 times lower than in the PVAT. On day 2 of cultivation the expression of the adiponectin gene was reduced both in the EAT and the PVAT as compared to the SAT. When rosuvastatin was added at a concentration of 1 mmol/L, adiponectin gene expression in PVAT was higher than when rosuvastatin was added at a concentration of 5 mmol/L, in the adipocyte culture of SAT effect was opposite. Thus, the adipocytes of EZhT and, to a greater extent, PAS, can be a therapeutic target for statins in the case of the pathological activation of adipose tissue.
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9. Pogorelova T.N., Krukier I.I., Gunko V.O., Nikashina A.A., Alliluev I.A., Larichkin A.V.

The imbalance of vasoactive components and arachidonic acid in the placenta and amniotic fluid in preeclampsia.

The content of vasoactive compounds and arachidonic acid in the placenta and amniotic fluid was studied in full-term (39-40 weeks) physiological pregnancy and preeclampsia (PE). The content of metabolites of nitric oxide (NOx), endothelin-1, thromboxane B2 (TxB2), prostacycline (PGI2) and arachidonic acid was estimated using spectrophotometric, immunoenzyme methods and gas-liquid chromatography. It was found that in PE the content of vasoconstrictors, of endothelin and TxB2, increased in the placenta and amniotic fluid, while the content of vasodilators, PGI2 and NOx decreased. Despite the same directionality of changes in both studied objects, the degree of changes differed and was more pronounced in the placenta. A direct or inverse correlative relationship was found between various vasoactive components (depending on their effect on vascular tone). In the case of arachidonic acid changes in its content in PE correlated with the level of vasoactive compounds, the source of which it is. The revealed differences in the ratio of vasoactive components obviously play a pathogenetic role in the development of PE and its subsequent complications.
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10. Kisrieva Y.S., Petushkova N.A., Samenkova N.F., Kuznetsova G.P., Larina O.B., Teryaeva N.B., Usachev D.Yu., Zgoda V.G., Karuzina I.I.

Comparative analysis of post-translational modifications in plasma proteome of patients with cerebral ischemia based on HPLC-MS/MS method.

The relative differences between post-translational modifications (PTM) of proteins in blood plasma samples of patients with cerebral ischemia (CI) and healthy people were investigated using of the method of label-free comparative proteomic analysis based on the technology of tandem HPLC-MS/MS. For PTM detection we used multiple MS/MS search in the database Mascot for variable PTM and Progenesis LS-MS software. In the CI plasma samples, we observed an increase in the proportion of peptides with such PTM as phosphorylation of serine, threonine, and tyrosine, acetylation of lysine and protein N-term, ubiquitination of lysine and deamidation of glutamine related to clinically significant processes were revealed.
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