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1. Vekshina N.L., Anokhin P.K., Veretinskaya A.G., Shamakina I.Yu.

Heterodimeric D1-D2 dopamine receptors: a review.

This review summarizes modern data on the structure and functions ofheteromersformed by D1 and D2 dopamine receptors focusing on their role in the mechanisms of drug dependence. This article discusses potential functional significance of heterodimeric D1-D2 dopamine receptorsdue to their localization in the brain as well as unique pharmacological propertiesversus constituent monomers. It is shown that heteromerization results in dramatic changes in activated signaling pathways compare to the corresponding monomers. These studies update our current knowledge of ligand-receptor interactions and provide better understanding of dopamine receptors pharmacology. Furthermore elucidation of significance of heterodimeric D1-D2 dopamine receptors as drug targets is important for the development of new effective drug addiction treatment.

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2. Zhdanov D.D., Vasina D.A., Orlova E.V., Orlova V.S., Pokrovsky V.S., Pokrovskaya M.V., Aleksandrova S.S., Sokolov N.N.

Cisplatin-induced apoptotic endonuclease EndoG inhibits telomerase activity and causes malignant transformation of human CD4+ T lymphocytes.

Alternative splicing of telomerase catalytic subunit hTERT pre-mRNA (human Telomerase Reverse Transcriptase) regulates telomerase activity. Increased expression of non-active splice variant hTERT results in inhibition of telomerase. Apoptotic endonuclease EndoG is known to participate in hTERT alternative splicing. Expression of EndoG can be induced in response to DNA damages. The aim of this study was to determine the ability of a DNA-damaging compound, cisplatin, to induce EndoG and its influence on alternative splicing of hTERT and telomerase activity in human CD4+ Đ¢ lymphocytes. Overexpression of EndoG in CD4+ T cells downregulated the expression of active full-length hTERT variant and upregulated its non-active spliced variant. Reduction of full-length hTERT caused downregulation of telomerase activity, shortening of telomeres length during cell divisions, converting cells to the replicative senescence state, activation of apoptosis and finally cell death. Few cells survived and underwent malignant transformation. Transformed cells have increased telomerase activity and proliferative potential compare to initial CD4+ T cells. These cells have phenotype of T lymphoblastic leukemic cells and are able to form tumors and cause death in experimental mice.

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3. Yakovlev A.A., Lyzhin A.A., Khaspekov L.G., Guekht A.B., Gulyaeva N.V.

Peptide drug cortexin inhibits brain caspase-8.

Cortexin, a drug containing hydrolyzed brain peptides, has long been used in clinics, but the mechanisms of its action remain obscure. We have hypothesized that cortexin-related neuroprotection is associated with the ability of the drug to inhibit brain proteases. Cortexin effectively inhibited brain caspase-8, while its effects on caspase-1, -3, -9, cathepsin B and calpain were much less pronounced or absent. In addition, we isolated a peptide fraction from cortexin holding all the inhibitory capacity of the original drug, but with a much more simple composition. Both cortexin and its fraction prevented neuronal damage in a culture model of glutamate-induced cell death. Neuroprotective effect of Cortexin may be mediated by inhibition of the initiator caspase-8 in the brain.

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4. Chernonosova V.S., Kvon R.I., Kiseleva E.V., Stepanova A.O., Laktionov P.P.

Investigation of the surface layer of 3D-matrices for tissue engineering.

Electrospinning is a convenient and promising manufacturing method a variety of materials for tissue engineering. 3D matrices fabricated by electrospinning from solutions of polycaprolactone with human serum albumin or gelatin in 1,1,1,3,3,3-hexafluoroisopropanol were studied. The microstructure of the 3D matrices and surface of the fibers were investigated using scanning electron microscopy. Protein distribution in the surface layer was studied by modification of protein amino groups with N-(2-hydroxyethyl)phenazine and X-ray photoelectron spectroscopy. It was shown, that concentration of the proteins in the surface layer of fibers exceeded their concentration in the initial electrospun solution up to 12 times and the surface layer was enriched in the protein inversely to the concentration of the protein in solution. The minor part of the proteins was released from fibers during first 30-60 min after swelling in water. Treatment of matrices with proteinase K hydrolyzed about 1/3 of the surface exposed human serum albumin. Thus, both methods can be used to study the surface content of the materials produced by electrospinning from blends of synthetic and natural polymers, however X-ray photoelectron spectroscopy appears to be more convenient and informative.

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5. Makarenkova I.D., Akhmatova N.K., Ermakova S.P., Besednova N.N.

Morphofunctional changes of dendritic cells induced by sulfated polysaccharides of brown algae.

The effects of various sulfated polysaccharides of brown algae Fucus evanescens, Saccharina cichorioides and Saccharina japonica on the morphofunctional changes of dendritic cells have been investigated using flow cytometry and phase-contrast microscopy. The dendritic cells are characterized by larger sizes, vacuolated cytoplasm, eccentrically located nucleus, and also by the presence of numerous cytoplasmic pseudopodia of various shapes. They express surface markers, indicating their maturation (CD83, CD11c, HLA-DR, CD86). Increased production of immunoregulatory

(IL-12) and proinflammatory TNF-a, IL-6) cytokines (by dendritic cells polarizes the development of the Th-1 type immune response.
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6. Tyurenkov I.N., Popova T.A., Perfilova V.N., Prokofiev I.I., Borisov A.V., Kustova M.V., Zaypullaev G.I., Ostrovskij O.V.

Protective effects of a new glutamic acid derivative against stress after nNOS blockade.

We studied the effects of a new glutamic acid derivative, glufimet, on oxidative stress, activity of antioxidant enzymes, mitochondrial respiration, endothelial vasodilation and anti-platelet activity in female rats after exposure to 24-hour immobilization pain stress and 7-nitroindazole, a neuronal nitric oxide synthase (nNOS) inhibitor. A single dose administration of glufimet (29 mg/kg intraperitoneally) 10 minutes before stress exposure caused a decrease of NO metabolites in serum (by 27.2%) and heart homogenate (33.5% (pÂ£0.05), respectively, compared with the control group. Administration of 7-nitroindazole with glufimet also decreased the studied parameters by 14.3% in the heart homogenate and by 30,3% in the brain (pÂ£0.05) compared with stress exposed rats receiving only the nNOS inhibitor. Glufimet decreased the levels of primary and secondary products of lipid peroxidation (LPO), conjugated dienes by 20% (pÂ£0.05) and 17.3% (pÂ£0.05), ketodienes by 16% and 13.7%, malondialdehyde by 15% (pÂ£0.05) and 26.6% (pÂ£0.05) in the heart and brain mitochondria of stress exposed rats, respectively, compared with the control group. Glufimet administration also increased SOD activity (by 14.4% and 13.1%, respectively), catalase (by 19% and 26.8%, respectively) and glutathione peroxidase (GPx) activity (by 45.5% (pÂ£0.05) and 7.3%, respectively). The antioxidant effect of glufimet may be also attributed to increased coupling between the processes of mitochondria respiration and oxidative phosphorylation. This was evidenced by an increase in the respiratory control ratio (RCR) (by 46.0% (pÂ£0.05) for malate/glutamate and by 49,7% (pÂ£0.05) for succinate) in the heart mitochondria. A statistically significant increase in RCR (by 37.3% (pÂ£0.05)) was observed in stress exposed female rat brain mitochondria for succinate. RCRs differed significantly for succinate in the heart and brain of rats receiving glufimet after nNOS blockade. RCR increased by 62.3% (pÂ£0.05) in the heart mitochondria and by 72.2% (pÂ£0.05) in the brain mitochondria compared with the RCRs in stress exposed rats receiving 7-nitroindazole.
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7. Medvedeva N.V., Torkhovskaya T.I., Kostryukova L.V., Zakharova T.S., Kudinov V.A., Kasatkina E.O., Prozorovskiy V.N., Ipatova O.M.

Influence of doxorubicin inclusion into phospholipid nanoparticles on tumor accumulation and specific activity.

The specific activity of drug formulation of doxorubicin embedded into phospholipid nanoparticles with diameter less than 30 nm (â€œDoxolipâ€•) was studied in mice LLC carcinoma. Doxolip was prepared according to technology that was elaborated in Institute earlier. Doxorubicin tumor accumulation after intraperitoneal administration (at 4 h) was 4.5 times higher for Doxolip, than for free doxorubicin. The study of doxorubicin antitumor activity in developing tumor after single intravenous administration, 48 h after inoculation, showed, that: 1) tumor growth inhibition of Doxolip was observed at 6th day, while it was only at 11th day for free doxorubicin and revealed in less extent; 2) there was no antitumor effect of free doxorubicin at 8 days after administration of doses 2 and 4 mg/kg, but it was observed for Doxolip in dose-dependent manner, 10% and 30% correspondently. In experiment with developed tumor weekly Doxolip intraperitoneal administration (5 mg/kg, 3 weeks beginning from 7 days after inoculation) resulted in 56% decrease of tumor volume as compared with control. This parameter for free doxorubicin was 2.8 times lower. The obtained data indicate, that incorporation of doxorubicin into phospholipid nanoparticles with size up to 30 nm as delivery system increases its tumor accumulation and results to increase of specific activity both in intraperitoneal and in intravenous administration.
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8. Pokrovskaya M.V., Zhdanov D.D., Eldarov M.A., Aleksandrova S.S., Veselovskiy A.V., Pokrovskiy V.S., Grishin D.V., Gladilina Ju.A., Sokolov N.N.

Suppression of telomerase activity leukemic cells by mutant forms of Rhodospirillum rubrum L-asparaginase.

The active and stable mutant forms of short chain cytoplasmic L-asparaginase type I of Rhodospirillum rubrum (RrA): RrA+N17, D60K, F61L, RrA+N17, A64V, E67K, RrA+N17, E149R, V150P, RrAE149R, V150P and RrAE149R, V150P, F151T were obtained by the method of site-directed mutagenesis. It is established that variants RrA-N17, E149R, V150P, F151T and RrĐ•E149R, V150P are capable to reduce an expression hTERT subunit of telomerase and, hence, activity of telomeres in Jurkat cells, but not in cellular lysates. During too time, L-asparaginasĐµs of Escherichia coli, Erwinia carotovora and Wolinella succinogenes, mutant forms RrĐ•+N17, D60K, F61L and RrĐ•+N17, A64V, E67K do not suppress of telomerase activity. The assumption of existence in structure RrA of areas (amino acids residues in the position 146-164, 1-17, 60-67) which are responsible for suppression of telomerase activity is made. The received results show that antineoplastic activity of some variants RrA is connected both with reduction of concentration of free L-asparagine, and with expression suppression of hTERT telomerase subunit, that opens new prospects for antineoplastic therapy.
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9. Chesnokova N.B., Beznos O.V., Lozinskaya N.A., Volkova M.S., Zaryanova E.V., Zefirov N.A., Grigoryev A.V.

Novel agonists of melatonin receptors as promising hypotensive and neuroprotective agents for therapy of glaucoma.

Melatonin is a pineal hormone that has a capacity to lower intraocular pressure; it exhibits neuroprotective and antioxidant properties that make it possible to use melatonin in the therapy of glaucoma. Analogs of melatonin having affinity to melatonin receptors are promising candidates for application as antiglaucomatous drugs. Chemical modification of the melatonin structure can in-crease efficiency, bioavailability and selectivity of these analogs. We have designed and synthe-sized a number of new 2-oxindole derivatives â€“ ligands of melatonin MT3 subtype receptors that displayed ability to lower intraocular pressure in normotensive rabbits and high antioxidant activity against hydroxyl radical and superoxide anion-radical. The antioxidant activity of new ligands was several times higher than one of melatonin that makes them prospective therapeutic tools for the diseases that include oxidative stress. The maximal hypotensive effect of analogs was comparable to that of melatonin itself but prolonged. Combination of these properties gives an opportunity of using the presented melatonin analogs in complex therapy of glaucoma.
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10. Popovtseva A.V., Suzopov E.V., Korenovsky Yu.V.

Acute hypoxic hypoxia increases lactate concentration in amniotic fluid of rabbits on 27-28th day of pregnancy.

We evaluated the influence of hypoxic hypoxia on lactate, creatinine and urea concentrations in the amniotic fluid (AF) of rabbits on 27-28th day of pregnancy. Rabbits were randomly sudivided into two groups: experimental (n=9) and control (n=6). Rabbits of experimental groups were placed in a hypoxic chamber containing 10Â±2% oxygen and 90Â±2% nitrogen for 1 h and then were euthanized, AF was extracted from the amniotic sacs via disposable syringe. Acute hypoxic hypoxia had no effect on the AF volume, increased (1.4-fold) lactate, (1.3-fold) creatinine and (1.1-fold) urea concentrations in AF. In contrast to animals of the control group, lactate concentration in the groups with hypoxic hypoxia correlated with the creatinine ($r=0.71$, $p<0.0001$, $n=35$) and urea concentrations in the AF ($r=0.81$, $p<0.0001$, $n=35$). These results suggest that acute hypoxic hypoxia in late pregnancy causes changes in the biochemical composition of AF; these changes are characterized by high lactate concentrations, and the fetus and uterus can be the source of increased lactate level in AF.

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11. Lupatov A.Yu., Saryglar R.Yu., Chuprynin V.D., Pavlovich S.V., Yarygin K.N.

Comparison of the expression profile of surface molecular markers on mesenchymal stromal cell cultures isolated from human endometrium and umbilical cord.

Endometrial mesenchymal stromal cells (eMSCs), along with mesenchymal stromal cells (MSCs) isolated from other tissues, are promising for use in regenerative medicine. The benefits of eMSCs include their presence in adults, simplicity of isolation, high proliferative and differentiation capacity. In this study, we have employed the flow cytometry technique to assess expression of 28 molecular markers on the surface of two eMSCs cultures. The culture of MSCs isolated from Wharton's jelly of the umbilical cord (uMSCs) was used as a reference, because uMSCs were studied in details earlier and demonstrated their effectiveness in vivo. Both types of MSCs demonstrated similar expression profiles. They included stem cells surface molecules, cell adhesion molecules and their ligands, some receptor molecules responsible for cell metabolism and proliferation, as well as immunological response molecules.

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12. Grigor'eva A.E., Dyrkheeva N.S., Bryzgunova O.E., Tamkovich S.N., Chelobanov B.P., Ryabchikova E.I.

Contamination of exosome preparations, isolated from biological fluids.

The aim of our study was to attract the attention of researchers at the problem of contamination of exosome preparations. Using a transmission electron microscope JEM-1400 (â€œJEOLâ€•, Japan) we have examined exosome preparations, isolated according to the conventional scheme of sequential centrifugation from different biological fluids: plasma and urine of healthy persons and patients with oncologic diseases, bovine serum, and culture fluid (MDCK, MDA-MB Ð¸ MCF-7 cells). All exosome preparations (over 200) contained exosomes, which were identified by immuno-electron microscopy using antibodies to tetraspanins CD63 or CD9. Besides exosomes, all the studied preparations contained contaminating structures: distinct particles of low electron density without limiting membrane (â€œnon-vesiclesâ€•). Two main kinds of the â€œnon-vesiclesâ€• species were found in exosome preparations: 20-40 nm in size, representing 10-40% of all structures in the preparations; and 40-100 nm in size (identical to exosomes by size). Morphology of the â€œnon-vesiclesâ€• allowed to identify them as lipoproteins of intermediate and low density (20-40 nm), and very low density (40-100 nm). The highest level of the contamination was detected in exosome preparations, isolated from blood samples. The results of our study indicate the need to control the composition of exosome preparation by electron microscopy and take into account the presence of contaminating structures in analysis of experimental data.

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