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1. Skorodumova L.O., Belodedova A.V., Sharova E.I., Malyugin B.E.

Search for genetic markers for precise diagnostics of keratoconus.

Keratoconus is a chronic disorder of the cornea, characterized by its progressive thinning, stretching, and conical protrusion. Diagnostics of subclinical keratoconus, as well as its early stages (forme fruste), is a complex problem. The presence of these forms of keratoconus in a patient is one of the reasons for the development of keratectasia after laser refractive surgery. Currently, the role of genetic factors in keratoconus development has been proven. This indicates the possibility of diagnostics of subclinical and forme fruste keratoconus using genetic markers. Knowledge about the patient's genetic susceptibility to keratoconus would allow correcting the tactics of treatment of refractive anomalies and avoiding serious side effects. The studies of causal mutations indicate the genetic heterogeneity of keratoconus, which complicates the development of a diagnostic panel. Selection of candidate variants from the currently known ones based on clear criteria may be one of the approaches for diagnostic markers search. In this review, we have analyzed articles on keratoconus markers in order to form a list of candidate variants for genotyping in the Russian population. The selection criteria took into account the complexes of symptoms in which a marker was found, populations in which a particular marker was investigated, the presence and results of replication studies. The analysis included markers in VSX1, SOD1, ZEB1, LOX, CAST, DOCK9, TGFBI, HGF, MAP3K19, KCND3, COL4A3, COL4A4, COL5A1, FNDC3B, FOXO1, BANP-ZNF469, MPDZ-NF1B, WNT10A genes. Based on the results of the analysis, the following candidate variants were selected for genotyping in the Russian population of patients with keratoconus: rs1536482 and rs7044529 in the COL5A1 gene, rs5745752 and rs2286194 in the HGF gene, rs4954218 in the MAP3K19 gene, rs4839200 near the KCND3 gene, rs2721051 near the FOXO1 gene, rs1324183 between the MPDZ and the NF1B genes, and rs121908120 in the WNT10A gene.

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2. Gushcha V.K., Lelevich S.V., Sheibak V.M.

Neurotransmitter disturbances in some parts of the rat brain and their correction under chronic and intermittent alcohol intoxication.

The pool of key neuromediators and some neurotransmitter amino acids in cerebellum, hypothalamus and midbrain of rats exposed to chronic and different variants of interrupted alcohol intoxication was investigated. The most pronounced changes were recorded in midbrain. Chronic alcohol intoxication caused an increase in the concentrations of tyrosine, dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), noradrenaline, tryptophan, serotonin, GABA and aspartate in this part of the rat brain. Interrupted alcohol intoxication with 4 days interval is accompanied by an increase in the content of tyrosine, and noradrenaline. Interrupted alcohol intoxication with 1 day interval leaded to an increase in the concentrations of tyrosine, DOPAC, noradrenalin, tryptophan, GABA, glycine and aspartate. The amino acids composition â€œTitacinâ€• had a pronounced normalizing effect in the midbrain under interrupted alcohol intoxication with 1 day interval.

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3. Prokopieva V.D., Plotnikov E.V., Yarygina E.G., Bokhan N.A.

Protective action of carnosine and organic lithium salts in case of ethanol-induced oxidative damage of proteins and lipids of blood plasma in healthy persons and alcoholic patients.

Organic lithium salts containing anionic components (succinate, fumarate, pyruvate and antioxidant ascorbate) were tested for protection of blood plasma proteins and lipids against ethanol-induced oxidation in vitro. We used normothymic lithium carbonate and well-known antioxidant dipeptide carnosine (b-alanyl-L-histidine) as the reference drugs. The oxidized proteins and lipids were determined by the level of carbonylated proteins (CP) and TBA-reactive products (TBA-RP), respectively. In alcoholic patients the level of oxidized proteins and lipids was higher than in healthy persons. Incubation of blood with ethanol resulted in an increase in oxidized proteins and lipids in blood plasma of healthy persons but had no influence on the level of CP and TBA-RP in blood plasma of alcoholic patients. Lithium carbonate, lithium ascorbate, and lithium succinate exhibited protective action against ethanol-induced oxidation of biomolecules of blood plasma of healthy people. These effects were comparable with carnosine action. The studied compounds had no effect on the level of CP and TBA-RP of blood plasma of alcoholic patients.

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4. Chistyakov D.V., Azbukina N.V., Goriainov S.V., Chistyakov V.V., Gancharova O.S., Tiulina V.V., Baksheeva V.E., Iomdina E.N., Philippov P.P., Sergeeva M.G., Senin I.I., Zernii E.Yu.

Inflammatory metabolites of arahidonic acid in tear fluid in UV-induced corneal damage.

The ultraviolet (UV) B-induced damage of the eye surface of experimental animals (rabbits) includes loss of corneal epithelium, apoptosis of keratocytes and stromal edema. These changes are accompanied by clinically and histologically manifested corneal inflammation, neutrophil infiltration, and exudation of the anterior chamber of the eye. According to mass spectrometric analysis, UV-induced corneal damage is associated with pronounced changes in the lipid composition of tears, including a decrease in the amount of arachidonic acid and prostaglandin E2 and an increase in the concentrations of prostaglandin D2 and its derivative 15d-PGJ2. In addition, it is accompanied by an alteration in the levels of hydroxyeicosate tetraenic acid derivatives, namely upregulation of 12-HETE and downregulation of 5-HETE. The revealed changes indicate the activation of metabolic pathways involving 5-lipoxygenase, 12-lipoxygenase, cyclooxygenase 1 and 2, and prostaglandin-D-synthase. These findings contribute to understanding mechanisms of UV-induced keratitis and point on feasibility of selective anti-inflammatory therapy for improving corneal regeneration after iatrogenic UV

damage.
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5. Grishin D.V., Gladilina Ju.A., Zhdanov D.D., Pokrovskaya M.V., Toropygin I.Yu., Aleksandrova S.S., Pokrovskiy V.S., Sokolov N.N.

Preparation and characterization of a new mutant homolog of chemotaxis protein CheY from anaerobic hyperthermophilic microorganism Thermotoga naphthophila.

Using genetic engineering methods the expression vectors structures have been designed to produce recombinant proteins TnaCheY and Tna CheY-mut, the homologues of the chemotaxis protein CheY from the hyperthermophilic organism Thermotoga naphthophila in Escherichia coli BL21(DE3) cells. The cultivation conditions of transformed strains were optimized. The influence of episomal expression of the heterologous chemotaxis protein CheY on growth kinetics parameters of the culture of mesophilic bacteria E. coli was studied. The optimal purification flowchart of the obtained proteins using thermolysis is proposed. Using the E. coli BL21(DE3) laboratory strain as an example, the possibility of employment the episomal expression of such proteins to control the cultivation and production time of pharmaceutically and industrially valuable metabolites due to the impact on some stages of the bacterial chemotaxis is experimentally proved.
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6. Studneva I.M., Palkeeva M.E., Veselova O.M., Molokoedov A.S., Lubimov R.O., Ovchinnikov M.V., Sidorova M.V., Pisarenko O.I.

Protective action of a modified fragment of galanine in rats with doxorubicin-induced heart failure.

The use of the anticancer drug doxorubicin (Dox) is limited due to its cardiotoxic effect. Using the method of automatic solid-phase peptide synthesis, we obtained a synthetic agonist of galanin receptors GalR1-3 [RAla14, His15]-galanine (2-15) (G), exhibiting cardioprotective properties. It was purified by high performance liquid chromatography (HPLC). The homogeneity and structure of the peptide was confirmed by HPLC, 1H-NMR spectroscopy and mass spectroscopy. The purpose of this study was to study the effect of G on the metabolism and cardiac function of rats with chronic heart failure (CHF) caused by Dox. Experiments were performed using male Wistar rats weighing 280-300 g. The control group of animals (C) was intraperitoneally treated with saline for 8 weeks; the doxorubicin group (D) of rats was intraperitoneally treated with DoÑ…; the group of DoÑ… + peptide G (D+G) received intraperitoneally injections of DoÑ… and subcutaneously injections of peptide G; the peptide G group (G) was subcutaneously treated with G. At the beginning and at the end of the study, the concentration of thiobarbituric acid reactive substances (TBARS) and the activity of creatine kinase-MB (CK-MB) were determined in blood plasma; the animals were weighed, and cardiac function was assessed using echocardiography. At the end of the experiments, the hearts were used for determination of metabolites and assessment of oxidative phosphorylation in mitochondria. After 8-week treatment, animals of group D were characterized by severe heart failure, the lack of weight gain and an increase in plasma TBARS concentration and CK-MB activity. These disorders were accompanied by a decrease in the content of myocardial high-energy phosphates, a reduction inmitochondrial respiratory parameters, accumulation of lactate and glucose in the heart, and disturbances in the metabolism of alanine and glutamic and aspartic acids. Coadministration of G and Dox prevented the increase in plasma CK-MB activity and significantly reduced the plasma TBARS concentration. At the end of the experiments animals of group D+G had higher myocardial energy state and the respiratory control index of mitochondria than animals of group D, there was a decrease in anaerobic glycolysis and no changes in the amino acid content compared to the control. The peptide G significantly improved the parameters of cardiac function and caused weight gain in animals of group D+G in comparison with these parameters in group D. The obtained results demonstrate the ability of a novel agonist of galanin receptors GalR1-3 to attenuate Dox-indiced cardiotoxicity.
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7. Voronkina I.V., Irtyuga O.B., Smagina L.V., Adamova P.E., Zhiduleva E.V., Malashicheva A.B., Sibagatullina Y.S., Kruk L.P., Gordeev M.L., Moiseeva O.M.

Expression of osteoprotegerin and soluble ligand of receptor of kappa-B transcription factor activator in the calcification of aortic valve.

The mechanism of valve calcification that is the main cause of aortic stenosis formation and progression is not yet clear. In recent years, the role of the OPG/RANKL/RANK system is considered as one of possible variants of pathogenesis of valve calcification. In presented work the differences in OPG and sRANKL levels involved in the calcification processes in tissues of patients with severe aortic stenosis have been examined. The study was performed using three groups of patients: group 1 â€“ patients with aortic stenosis, group 2 â€“ patients with aortic aneurysm, and group 3 â€“ patients with aortic stenosis and aortic dilatation. In patients with aortic stenosis, the level of RANKL was significantly higher, and the level of RANKL was higher in valve than in tissue. The negative correlation between aortic dilatation and RANKL level indicated the lack of RANKL influence on pathogenesis of aortic dilatation. The obtained data confirm the increased expression of RANKL in patients with aortic valve calcification. The results of this study confirm importance of the OPG/RANKL/RANK system in calcification in patients with aortic stenosis. Athough patients of all groups had comparable values of OPG (including patients with aortic dilatation), the RANKL level increased only in patients with aortic stenosis. This suggest involvement of some additional mechanisms influencing the increase of RANKL expression.
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8. Gnedenko O.V., Yablokov E.O., Ershov P.V., Svirid A.V., Shkel T.V., Haidukevich I.V., Strushkevich N.V., Gilep A.A., Usanov S.A., Ivanov A.S.

Interaction of prostacyclin synthase with cytochromes P450.

Biosensor experiments on investigation of interaction between prostacyclin synthase (PGIS) and different proteins of the cytochrome P450 monooxygenase systems were perfomed. Interaction of PGIS with microsomal (CYP21A2, CYP2E1) and mitochondrial (CYP27A1, CYP11B1, CYP11B2, CYP11A1) cytochrome P450s was detected. Kinetic and equilibrium parameters of protein complexes formation were determined. Data obtained suggest an essential role of these hemoproteins interaction in regulation of prostacyclin and thromboxane A2 biosynthesis.
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