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CELL THERAPY OF ROTENONE-INDUCED EXPERIMENTAL PARKINSONISM MODEL

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Among other novel therapeutic approaches mesenchymal stem cells (MSC)-based therapy seemed the most promising in Parkinson's disease animal model. In this abstract the effect of intranasal infused MSC on behavioral and neurological status of rats with experimental parkinsonism was estimated.

Keywords: Parkinson's disease, rotenone, experimental model, mesenchymal stem cells.

Parkinson's disease (PD) is a progressive neurodegenerative disorder, characterized by the loss of 50 to 70% of dopaminergic neurons located in the substantia nigra and resulted in tremor, postural instability, rigidity and cognitive impairment [1]. Current methods of diagnosis, prevention and therapy of PD are not fully effective. A novel therapeutic approach of PD treatment is based on mesenchymal stem cells (MSC) cell therapy which are characterized with neuroreparation, transdifferentiation and immunomodulation potential [2].

The aim. To establish the valid rotenone-induced experimental model of parkinsonism in rats and estimate their behavioral and neurological status after intranasal MSC infusion.

Materials and methods. The object of the study was the female Wistar rats weighing 300-350 g (n = 40). The experimental parkinsonism was induced by subcutaneous injection of a rotenone at concentrations of 1 mg/kg (group 1, n=10), 1,5 mg/kg (group 2, n=10) and 2 mg/kg (group 3, n=10) daily. The control group (n=10) was administered lipovenose. Bone-marrow derived MSC were infused intranasal (1×10^5/animal) to rats from group 3 (n=5) on day 15 of parkinsonism development. Parkinsonism features in treated and untreated rats group were observed for 3 weeks after cell therapy using "open field" test, neurological examination (oligokinesia, postural instability, gait instability, restless tremor and muscular rigidity), body weight monitoring and survival of animals. Statistical analysis was carried out using Statistica8.0.

Results. Parkinsonism developed in all three experimental groups but the dynamics of symptoms manifestation were differed. In "open field" test, a decrease in the index of locomotor activity and the investigational behavior were shown: group 1 – the decrease in grooming, vertical and research activity (day 4) and the increase in inactive time (day 14); group 2 – the decrease in vertical and research activity (day 4 and 7) as well as grooming (day 14), and the increase in inactive time (14 days); group 3 – the decrease in the number of vertical and research activities (day 2 and 4) and grooming throughout the study and the increase in inactive time (day 7) compared to the control group ($p<0.05$). A more pronounced deficiency of motor activity was registered in group 3. The evaluation of neurological status was revealed two peaks of maximum manifestation of the total symptoms (day 7 and 14) in group 1 and 2, while in the group 3 the most expressed signs were registered on day 4. Muscular rigidity characterized with the decrease in the withers-tail base sizes was detected on day 2 and registered throughout the experiment (group 1 – by 2,5 cm, group 2 – by 3 cm, group 3 – by 4 cm, $p<0.05$).

After MSC infusion it was established the short-term increase in research activity on day 3 and stable rise in grooming by 67% on day 7 as well as significant increase in vertical activity mainly due to rearing without support from day 14 and during the whole period of monitoring in treated rats compared to untreated animals ($p<0.05$). Moreover, it was shown the reduction in inactive time period from day 7 after MSC administration ($p<0.05$) without any changes in the untreated rats. However, MSC-based therapy didn't significant affect the weight indices as well as frequency of urination and rigidity rates during the entire follow-up period.

The conclusion. Considering the survival of animals, the dynamics of deficiency in motor activity and neurological symptoms, the optimal rotenone dose for experimental parkinsonism model was 2 mg/kg. MSC-based therapy of rats with experimental parkinsonism resulted in stable improvement of locomotor activity, the investigational behavior and neurological status on day 7 after administration what may be used for further design of new therapeutic protocol for PD patients.

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THE EFFECT OF GENE POLYMORPHISM OF XENOBIOTIC DETOXIFICATION ENZYMES GCLM ON URINE MERCURY CONTENT

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Mercury is removed as conjugated glutathione (GSH). The production of GSH is mediated by glutamylcysteine ligase (GCL) and conjugation using S-transfer as a glutathione (GST). This study was tested if polymorphism in the GCL and GST genes changes mercury retention in people exposed to mercury.

Keywords: mercury, polymorphism

Mercury is an ecotoxicant that causes a wide range of changes in the body and has a harmful effect on human health. It is widely used in industry, agriculture, and medicine. In Kazakhstan, in the city of Temirtau, there is a high level of contamination with mercury from the acetaldehyde plant.

Glutathione-S-transferase (GST) is an important family of enzymes involved in the detoxification of enzymes that are part of the redox cycle of glutathione and are precursors in the synthesis of glutathione also play xenobiotics, including heavy metal ions [1]. GCLM is involved in the synthesis of glutathione playing an important role in protecting against oxidative stress. GCLM contains a polymorphism in the 5'-flanking region (-588C / T) [2]. The inheritance of mutant variants in these detoxification genes can alter the metabolism and elimination of xenobiotics from the body, which may explain the different susceptibility to adverse health effects of various forms of mercury.

The goal of our study was to determine the polymorphisms of xenobiotic detoxification genes to the GCLM of people living in areas contaminated with mercury.

Materials and methods. We surveyed 180 people, 90 of them (main group), living in the mercury-containing territory (Temirtau region), and 90 – healthy people (control group, people living in Vozdvizhenka, Akmola region).

Genomic DNA was isolated from the venous blood of research participants by salting out [3]. The quantitative content of DNA was evaluated on a spectrophotometer (Nanodrop 1000). The concentration of the isolated DNA varied within 10-130 ng / μl. The polymorphism of the GCLM was 329 bp, covering -588C / T determined by PCR methods. The content of mercury in the urine of the examined was determined by stripping voltammetry.

Results. A statistically significant difference was found between the test groups for urine mercury content. Main results are on the frequency of occurrence of genotypes of GCLM genes in the studied groups. The distribution of genotypes did not deviate from the Hardy-Weinberg equilibrium.

The TT, CT, and CC genotypes of the GCLM gene were found in 2 (2.2%), 4 (4.4%), and 84 (94.4%) samples in the main group, respectively, and 0 (0.0%), 1 (1.1%), 89 (98.9%) were present in the control group, respectively. It should be noted that the results of genotyping a part of the GCLM gene were partially confirmed with the results of restriction. According to the results of 31 genotyped samples, only 9 individuals coincided with the results of restriction.

Conclusion. In the study region, the pathological effect of mercury remains on the population. The toxic effects of mercury can be related to the duration of the population's residence in the affected area. The detected elevated levels of inorganic mercury in the urine of exposed individuals indicate that its harmful effects on public health remain.

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