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## EFFECTS OF IMMUNE MODULATORS AT METALL IMMUNOSUPPRESSION

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### Introduction

One of the major environmental problems is the environmental changes under the influence of anthropogenic human activities. In Kazakhstan, the mining and metallurgical industries emit into the environment large amounts of waste products containing metal compounds such as vanadium and chromium, which are toxic to animals and humans. Continuous influence of harmful environmental factors inhibits the immune reactivity of the organism following development of immunodeficiency states [1-5].

For correction of immune status, are widely used immune modulators. Nowadays scientists pay attention to synthetic drugs, which have a favorable effect on the body, stabilizing and bringing back to the norm functions of the immune system as well as other systems. In this regard it is urgent to search for new immune modulators, the use of which would give a minimum of side effects, not only would stimulate immune responses, but the balance of the immune system in general and its adaptive capabilities to intoxication by heavy metals. 1-(2-ethoxyethyl)-4-(dimethoxyphosphoryl)-4-hydroxypiperidine was synthesized in Institute of Chemical Sciences named after A.B. Bekturov [6]. It was used under laboratory code oxyphosphonate for the treatment of metal induced damages in comparison with the known immune modulator polyoxidonium.

### Material and methods

The investigation was carried out on 104 white male rats with mass 180-220 g., contained in standard vivarium conditions on a standard diet. 4 experimental series have been carried out: the first series - control animals; the 2nd series - animals received ammonium vanadate (AV) and potassium bichromate (PB); the 3 series - animals received AV and PB and treated with oxyphosphonate; the 4 series - animals received AV and PB and treated with Polyoxidonium (PO). Each series included 26 rats. Intoxication with salts of metals was induced in the experimental animals by the introduction of AV and PB in a dose of 5 mg/kg orally for two weeks. Correction

of the damages was being reached by using of Oxyphosphonate and Polyoxidonium in a dose of 5mg/kg beginning from the second week of the experiment. Investigated drugs dissolved in saline were being injected subcutaneously in a volume of 0.5 ml daily for a week. Control animals received an equal volume of 0.9% solution of NaCl.

The immune status of rats was evaluated at the end of the second week of poisoning and treatment, the researching of its parameters was carried out at the medical center "Immune diagnostics". We determined the following parameters of immune status: the total number of WBC, the absolute and relative content of lymphocytes, leukogram, DDN test (direct damage to neutrophils) by the method of Fradkin (1985), the concentration of circulating immune complexes (CIC) with a set of reagents "Microanalysis CIC" produced by «НПО СИНТЭКО», NBT - test (Nitroblue tetrazolium reduction test). According to these tests, the calculation of indices that reflected the phagocytic activity of neutrophils was performed: the index of neutrophil stimulation (INS), the index of absorptive activity (IAA), coefficient of stimulation (CS), % of phagocytosis, and so the index of immune reactivity (IIR), lymphocytic index (LI). These figures are mathematically processed by Student's t-criterion.

#### Results

The experimental animals received AV and PB, showed a significantly decrease in total blood leukocyte count to 1.7 times. Such leukopenia was due to decrease in relative and absolute number of lymphocytes in 1.3 and 2.2 times respectively. Detected changes of immunological parameters characterized the destabilization of the immune system. The index of immune reactivity (IIR) and lymphocytic index (LI) at animals received metal compounds, were significantly decreased in 1.5 and 2.7 times respectively. Treatment the animals received AV and PB, with Oxyphosphonate and Polyoxidonium led to the return of the relative number of lymphocytes to the initial values and significantly increased their absolute number in 1.5 times. It should be noted that, according to the IIR and LI, which were not much different from the control data, immune modulating effects of Oxyphosphonate compared with Polyoxidonium were more marked.

Phagocytosis and NBT test during the treatment with Oxyphosphonate and Polyoxidonium underwent significant changes. Under the influence of metals both spontaneous and induced by pyrogenalum activity of neutrophils in the NBT-test, and so the CS and the INS did not change significantly, indicating a lack of absorptive activity of neutrophils. At the same time phagocytic activity, both spontaneous and induced by latex, as well as IAA of neutrophils influenced by AV and PB were not significantly different from control. While IIR and LI, decreased by 32.4% and 63% respectively compared with the control.

Treatment of experimental animals with Polyoxidonium without significantly changes in INS and CS increased spontaneous and induced NBT by 32.5% and 19.2% respectively compared with control levels. Spontaneous and induced phagocytic activity of neutrophils was increased by 29.4% and 23.2% respectively. IIR and LI as compared with the untreated animals were higher in 1.2 and 2.1 times. Treatment of the animals received metal compounds, with Oxyphosphonate had a similar effect. However, should pay attention to the fact that under the influence of Oxyphosphonate IIR and LI were more significant in comparison with Polyoxidonium.

Studies of DDN showed that addition of chromium and vanadium into blood samples of control animals in vitro did not cause damage exceeding the norm (10%). However, in tests of experimental animals, damage of neutrophils by the addition of metals exceeded the control levels more than 2 times. Treatment of animals received AV and PB, with Oxyphosphonate significantly decreased the process of neutrophil destruction. So, addition chromium or vanadium in vitro led to decrease in DDN index in 1.3 times at treated animals in comparison with untreated ones. However, this figure was improved to a greater extent in the experimental animals treated with Polyoxidonium, and the index DDN for chromium declined almost doubled, whereas for vanadium in 1.3 times.

We received the triple decrease in CIC under the influence of metal compounds which was completely corrected by the treatment with Oxyphosphonate,\* whereas treatment with Polyoxidonium increased this figure only to 1.2 times.

These experimental data allow concluding that under the influence of metal compounds there is inhibition of the immune reactivity of the organism. Treatment of experimental animals with Polyoxidonium and Oxyphosphonate significantly corrects the damages. The effectiveness of Oxyphosphonate does not yield to well-known Polyoxidonium, and for some indicators has the best effect.

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