calization. According to published data [8,14], the affinity of only the D_3 receptors for DA and haloperidol is similar in the nanomolar range. This suggests their key role in the mechanism of haloperidol catalepsy development.

The results of this investigation attest that a rise of the extracellular DA content in the striatum prevents the development of haloperidol catalepsy in rats.

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Pharmacological Correction of Immune Disorders during Acute Poisoning with Dimethyl Dichlorovinylphosphate

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Experiments on mice revealed that the cholinesterase reactivator dipiroxime in a single dose of 15 mg/kg and retinol acetate in a dose stimulating thymus-dependent antibody production (3000 U per os daily for 3 days after poisoning) reverse the suppression of the main immune reactions caused by dimethyl dichlorovinylphosphate.

Key Words: *organophosphorus compounds; immunity; dipiroxime; retinol acetate*

Organophosphorus compounds (OPC) characterized by an anticholinesterase effect are among the xenobiotics causing widespread acute and chronic poisoning because of their extensive agricultural and household use as pesticides. There is also the possibility of OPC intoxication at chemical plants where they are produced. In addition, intoxication with anticholinesterase poisons may occur on a mass scale during accidents at chemical plants, specifically, at those engaged in the destruction of toxic OPC. Recently many publications have appeared that are devoted to studies of the immunotoxic effects of OPC [2,3,5,9]. The principal mechanisms of these effects have been disclosed [5], thus permitting a targeted pharmacological correction of postintoxication immunodeficiency in order to prevent various infectious complications and diseases. Our studies [5] suggest that reactivation of T-lymphocyte acetylcholineste-

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rase [11] and of nonspecific esterases of macrophages, cells determining natural and antibody-dependent cytotoxicity [12], is one method of reducing the immunosuppressive effect of OPC. In addition, agents boosting antibody production due to other mechanisms, such as interferon inducers [8] or retinol acetate [7], may be used. We investigated the possibility of correcting immune disorders during acute poisoning with OPC by means of an antidote of the cholinesterase reactivator dipiroxime and retinol acetate.

MATERIALS AND METHODS

Experiments were carried out on male CBA mice and Wistar rats weighing 18-22 and 180-220 g, respectively. The anticholinesterase insecticide dimethyl dichlorovinylphosphate (DDVP), an OPC, was administered in a dose of 1.0 LD_{50} subcutaneously. Dipiroxime was injected intraperitoneally in a single dose of 15 mg/kg after the animals developed tremor and convulsions. Retinol acetate (oily solution) was given orally in a dose of 3000 U/animal daily for 3 days. Antibody-producing cells in the spleen were counted on day 5 after immunization of mice with sheep red cells injected intravenously in a dose of 10^8 cells according to a method described elsewhere [10]. The titer of antibodies to *Salmonella typhi* thymus-independent Vi antigen was assessed in rats by the indirect hemagglutination test 8 days after intravenous immunization with this antigen in a dose of 8 μg/kg. The immunization was carried out 1 h after injection of DDVP.

The capacity of macrophages to induce a humoral immune response was assessed by the titer of antibodies to sheep red cells 5 days after poisoning with OPC. Macrophages which had processed the sheep red cells were transferred from donor rats to recipient rats one day after intoxication. To donors dipiroxime and retinol acetate were administered in a single dose 1 h after DDVP, and the recipients were administered retinol acetate 30 min after intraperitoneal injection of donor macrophages. Natural cytotoxicity was assessed in mice spectrophotometrically 24 h after intoxication, as described previously [4]. Antibody-dependent cell cytotoxicity (ADCC) was assessed 5 days after immunization of mice with sheep red cells in a dose of 10^8 [6]. The data were statistically processed using Student's t test.

RESULTS

Table 1 shows that dipiroxime injected after DDVP negligibly increased the number of antibody-producing cells in the spleen in comparison with that during intoxication, the value being statistically reliably ($p<0.05$) lowered in comparison with the control. When dipiroxime was used after DDVP, the titer of antibodies to Vi antigen was less decreased in comparison with the control, in contrast to the thymus-dependent humoral immune response to this antigen. The detected effect of dipiroxime was due, first, to a lesser suppression of the thymus-independent humoral immune response by DDVP, that is, to a greater effect of OPC on T helpers (a negligible decrease of the production of antibodies to Vi antigen under the effect of DDVP was detected only 8 days after poisoning, whereas 5 days after exposure to OPC the titer of antibodies to Vi antigen was virtually the same — 4.0±0.2 *vs.* 4.2±0.2 in control, $p>0.05$); and second, this effect might be due to recovery of the capacity of macrophages to produce interleukin-1, which affects the synthesis of antibodies to thymus-independent antigens by B lymphocytes [13].

The cholinesterase reactivator restored the DDVP-reduced capacity of macrophages to induce a humoral immune response, natural cytotoxicity, and ADCC. The decrease of the OPC immunosuppressive effect due to dipiroxime is apparently due not only to reactivation of immunocyte esterases, but also to a reduction of the severity of intoxication as

TABLE 1. Effects of Dipiroxime and Retinol Acetate on the Parameters of the Immune System during Acute Poisoning with Dimethyl Dichlorovinylphosphate (DDVP)

Agents	Number of antibody-producing cells, 10^{-3}	Titer of antibodies to Vi antigen, $-\log_2$	Induction of humoral immune response by macrophages, $-\log_2$ of antibody titer to sheep red cells	Natural cytotoxicity, %	ADCC, %
Control	26.7±3.4 (10)	4.2±0.2 (8)	2.5±0.2 (7)	27±4 (10)	8.8±1.4 (9)
DDVP, 1.0 LD_{50}	12.3±3.1 (8)*	3.5±0.2 (6)*	1.7±0.3 (5)*	8±2 (7)*	2.7±0.9 (7)*
DDVP+dipiroxime, 15 mg/kg	17.3±3.2 (10)*	3.9±0.2 (8)	2.2±0.2 (6)*	19±3 (10)**	6.2±1.1 (8)**
DDVP+retinol acetate, 3000 U	21.8±2.9 (8)**	3.3±0.3 (6)*	2.0±0.1 (6)**	7±2 (6)*	4.6±1.3 (6)*
DDVP+dipiroxime+retinol acetate	24.2±3.5 (8)**	4.0±0.3 (7)	2.7±0.3 (6)**	21±5 (9)**	7.7±1.5 (8)**

Note. The number of animals is shown in parentheses; $p<0.05$: *vs. the control, **vs. the value during DDVP poisoning.

a result of the known antidote properties of this compound. However, if we bear in mind the capacity of acetylcholine to boost the humoral immune response [1] and the ability of this transmitter to reduce the suppression of antibody production during OPC poisoning [5], we must admit the possibility that the reactivation of macrophage and T-lymphocyte esterases is the main factor responsible for the immunoprotective effect in OPC poisoning.

Administration of retinol acetate after DDVP poisoning led to an increase of the count of antibody-producing cells in the spleen virtually to the control level and did not affect the thymus-independent production of antibodies (titer of antibodies to Vi antigen), the macrophage function, or the natural cytotoxicity. ADCC was negligibly increased by retinol acetate. The results are in line with a previous report [7] describing the capacity of vitamin A in a dose of 3000 U to boost antibody production to thymus-dependent antigen.

Combined use of dipiroxime and retinol acetate virtually normalized the studied parameters of the immunity system after OPC poisoning.

Hence, the cholinesterase reactivator dipiroxime and retinol acetate in a dose stimulating thymus-dependent antibody production (3000 U) reversed the suppression of the main immune reactions caused by DDVP.

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