Role of Activation of the Sympathoadrenal System in the Realization of Immune Reactions during Acute Poisoning with Organophosphorus Compounds

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Experiments on Wistar rats showed that acute poisoning with organophosphorus compound dimethyldichlorovinylphosphate (0.2 and 0.8 LD_{50}) was accompanied by suppression of the major immune reactions. Increasing the concentration of epinephrine and norepinephrine in the plasma produced less pronounced opposite effects, except for the influence on natural killer activity.

Key Words: *organophosphorus compounds; immune reactions; epinephrine; norepinephrine*

An important role in the realization of immunotropic effects during acute poisoning with organophosphorus compounds (OPC) is played by the anticholinesterase mechanism underlying inhibition of esterases in immunocompetent cells [3], inactivation of acetylcholine esterase, increase in the content of acetylcholine in cholinergic synapses [13], activation of the hypothalamic-pituitary-adrenal system [2,3] and subsequent rise of blood corticosteroids and catecholamines (epinephrine and norepinephrine) [6]. The role of the anticholinesterase mechanism (inhibition of nonspecific esterases in T cells and macrophages and effects of acetylcholine and corticosteroids [2]) was established. However, the role of catecholamines (*e.g.*, epinephrine and norepinephrine) in the realization of immune reactions during OPC poisoning is poorly understood [3]. Studies of reactions to anticholinesterase poisons would allow us to evaluate poststress changes in the organism and develop new approaches to the therapy and prevention of adverse consequences [5].

Here we evaluated the role of epinephrine and norepinephrine in the realization of general immune reactions during acute poisoning with OPC.

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MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 180-220 g. Anticholinesterase insecticide dimethyldichlorovinyl phosphate (DDVP) was injected subcutaneously in single doses of 0.2 and 0.8 LD_{50} (65±6 mg/kg for rats) during immunization. Epinephrine and norepinephrine were injected subcutaneously in doses of 0.25 and 2.5 mg/kg during immunization. The activity of natural killer cells was estimated spectrophotometrically by the index of natural cytotoxicity (NC). Target cells non-destroyed in the cytotoxic test were counted 24 h after treatment with DDVP [1]. The humoral immune response was evaluated 5 days after treatment with DDVP and intraperitoneal immunization with thymus-dependent (sheep erythrocytes) and T cell-independent antigens (Vi-Ag) in doses of 2×10^8 cells and 8 μg/kg, respectively, by the number of antibody-producing cells in the spleen [10]. These tests reflect IgM synthesis by splenic B cells, which involves Th1 lymphocytes. Antibody-dependent cell cytotoxicity characterizing activity of natural killer cells was evaluated spectrophotometrically in rat splenocyte suspension 5 days after immunization with sheep erythrocytes (10^8 cells) [4]. Delayed-type hypersensitivity reflecting the cell immune response (*e.g.*, Th1 lymphocyte activity) was evaluated by the increase in the

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weight of hindlimb pads. The animals were intraperitoneally immunized with sheep erythrocytes (10^8 cells). Sheep erythrocytes in a provoking dose (5×10^8 cells) were injected subaponeurotically into hindlimb pads 4 days later. Delayed-type hypersensitivity was evaluated 24 h postinjection.

Plasma epinephrine and norepinephrine concentrations were measured 3 h after poisoning, which corresponds to the most pronounced redistribution of immunocytes in immune organs caused by catecholamines [13]. To study the effect of catecholamines on the major immune reactions epinephrine and norepinephrine were injected subcutaneously in doses of 0.25 and 2.5 mg/kg during immunization.

The results were analyzed by Student's *t* test.

RESULTS

DDVP dose-dependently suppressed test parameters of the immune homeostasis and increased plasma epinephrine and norepinephrine concentrations (Table 1). It can be hypothesized that suppression of the immune response is related to the effects of catecholamines. However, the data obtained in experiments when epinephrine and norepinephrine administered during immunization are at controversy with this assumption (Table 2).

Epinephrine and norepinephrine in a dose of 0.25 mg/kg markedly enhanced immune reactions, except for NC. However, in a dose of 2.5 mg/kg these compounds reduced test parameters of the immune response.

Epinephrine in a dose of 0.25 mg/kg was more potent than norepinephrine in activating immune reactions, which was related to stimulation of β-adrenoceptors on immunocytes [12]. Epinephrine in a dose of 0.25 mg/kg less markedly stimulated T cell-dependent antibody formation compared to thymus-independent processes (by 1.72 and 2.45 times, respectively).

It should be emphasized that after injection of epinephrine and norepinephrine in a dose of 0.25 mg/kg their plasma concentrations 10- and 20-fold surpassed those observed during acute poisoning with 0.8 LD_{50} DDVP. These values could be lower, if we take into account biotransformation of compounds, their interaction with receptors, and excretion. Intensive differentiation of immature lymphoid cells [6], in particular, B lymphocytes [9], induced by activation of β-adrenoceptors contributes to stimulation of antibody formation to T cell-independent antigens caused by epinephrine and norepinephrine in low doses.

The stimulating effects of catecholamines are realized through α- and β-adrenoceptors on immunocytes, which triggers cAMP synthesis and production of interleukins involved in the regulation of immune reactions [11]. cAMP stimulates differentiation of immature lymphoid cells [6], *e.g.*, B lymphocytes [9]. The activation of β-adrenoceptors on immunocompetent cells over the first 12 h after antigenic stimulation (inductive phase of the immune response) potentiates antibody formation. It can be hypothesized that the increase in blood epinephrine and norepinephrine levels during acute poisoning with OPC is accompanied by a decrease in their contents in the brain and adrenal glands due to the influence of acetylcholine. Catecholamines in high doses activate B cells, but decrease T helper cell activity [8], which results in suppression of immune reactions [2]. Reduction of NC on the next day after injection of 0.25-2.50 mg/kg catecholamines is determined by increased cAMP/cGMP ratio [7]. Previous studies showed that activity of natural killer cells increases after adrenalectomy [11]. It can not be excluded that administration of catecholamines in the in-

TABLE 1. Effects of DDVP on the Major Immune Reactions and Plasma Epinephrine and Norepinephrine Concentrations in Wistar Rats (*M*±*m*, *n*=7-9)

Parameter	Control	DDVP	
		0.2 LD_{50}	0.8 LD_{50}
NC, %	29.8±4.3	17.1±3.9*	13.1±2.2*
Number of antibody-producing cells, 10^3			
to sheep erythrocytes	31.2±3.7	23.2±2.8	17.3±2.3*
to Vi-Ag	22.4±3.1	16.4±2.1	12.4±1.9*
Antibody-dependent cell cytotoxicity, %	8.5±1.9	6.3±1.3	4.1±1.0*
Increase in limb weight, %	29.5±2.8	24.1±2.0	19.8±1.5*
Epinephrine, μg/liter	6.7±1.2	10.4±1.8	20.1±2.3*
Norepinephrine, μg/liter	2.1±0.8	4.8±1.0*	10.5±1.7*

Note. Here and in Table 2: *p<0.05 compared to the control.

TABLE 2. Effects of Epinephrine and Norepinephrine on the Major Immune Reactions in the Plasma of Wistar Rats (*M*±*m*, *n*=7-9)

Parameter	Control	Epinephrine, mg/kg		Norepinephrine, mg/kg	
		0.25	2.5	0.25	2.5
NC, %	29.8±4.3	21.1±2.9	15.2±2.2*	23.5±2.5	13.3±2.3*
Number of antibody-producing cells, 10^3					
to sheep erythrocytes	31.2±3.7	53.7±4.6*	20.0±2.1*	43.3±3.1*	21.1±2.2*
to Vi-Ag	22.4±3.1	54.9±3.3*	11.0±1.5*	35.8±2.9*	9.7±1.0*
Antibody-dependent cell cytotoxicity, %	8.5±1.9	15.1±1.4*	4.7±0.9*	13.7±1.1*	4.0±0.8*
Increase in limb weight, %	29.5±2.8	37.4±3.1*	20.5±2.1*	34.5±2.5	18.5±1.7*

ductive phase of the immune response can modulate immune reactions, which is at controversy with published data [11].

Our findings suggest that immunosuppression during acute poisoning with OPC is not associated with the increase in plasma epinephrine and norepinephrine concentrations. Exogenous catecholamines in low doses stimulate immune reactions, while in high doses these compounds cause immunosuppression.

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