Role of Corticosterone in Realization of Immunosuppressive Effects in Acute Poisoning with Toxic Chemicals

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Experiments on random-bred male rats shows that acute poisoning with metaphos and acrylonitrile inhibites mainly the thymus-dependent humoral immune response, delayed type hypersensitivity reaction, and activities of natural killers and K cells. The increase in plasma corticosterone under the effect of metaphos ensures the participation of this hormone in the realization of suppression of natural killers and thymus-dependent humoral immune response (production of IgG), the contribution of the hormone to this suppression being 35.6 and 35.1%, respectively. Suppression of immune reactions by acrylonitrile is not associated with corticosterone effect.

Key Words: *organophosphorus compounds; metaphos; acrylonitrile; corticosterone; immunity*

Corticosteroids play an important role in the realization of immunotoxic effects of toxic chemicals (TC). Due to stress reaction to acute poisoning, high concentrations of corticosteroids in the blood can suppress humoral and cell immune reactions [3]. Decreased humoral and cell immune response in poisoning with organophosphorus compounds is attributed mainly to the effect of corticosteroids [7,8,15]. It should be noted that stress reaction in poisoning with different chemical compounds can be associated with an essential increase of plasma corticosterone (CS), which causes suppression of immune reactions, or with a negligible increase in CS concentrations, which virtually does not affect the immune system, or with modification of daily fluctuations in the hormone level in the blood [6], which does not lead to the realization of immunosuppressive effects. Some TC inhibiting tissue respiratory enzymes inhibit the production of adrenocortical hormones [4,10], thus impairing corticosteroid regulation of immunogenesis, specifically, preventing the contribution of stress reaction to the formation of postintoxication immunodeficiency [4]. The role of immunosuppressive effect of corticosteroids to the realization of immunotoxic effects of TC is little known. The contribution of adrenocortical hormones in the immunosuppressive effect of TC has never been evaluated. Elucidation of the role of CS in the formation of postintoxication immunodeficiency will help to develop pathogenetically-based methods for prevention and treatment of this condition.

We evaluated the contribution of immunosuppressive effect of CS on immune reactions in acute poisoning with organophosphorus insecticide metaphos and acrylonitrile.

MATERIALS AND METHODS

Experiments were performed on random-bred male rats (180-250 g). Metaphos and acrylonitrile in olive oil (0.5 ml) were administered into the stomach in a dose of 0.8 LD_{50} (LD_{50} of metaphos and acrylonitrile for male rats are 22±3 and 85±5 mg, respectively). Acrylonitrile (aqueous solution) was injected subcutaneously in a dose of 0.8 LD_{50} (LD_{50} was 70±7 mg/kg). Controls received 0.5 ml olive oil into the stomach. Humoral immune response to thymus-dependent (sheep erythrocytes) and thymus-independent (Vi-Ag) antigens was evaluated by the number of antibody-produc-

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TABLE 1. Effects of Metaphos, Acrylonitrile, and CS on Humoral and Cell Immune Reactions in Rats (*M*±*m*, *n*=7-9)

Parameter	Control	Metaphos	Acrylonitrile	CS
APC to SE, 10^3	36.6±4.2	14.1±2.0*	19.2±2.8*	20.3±2.4*
APC to Vi-Ag, 10^3	27.3±3.4	17.1±2.4*	20.1±2.5	27.3±2.2
Increase in paw weight, %	25.1±2.3	17.2±1.3*	23.5±2.5*	24.8±2.5
Cytotoxicity, % natural	28.2±4.1	12.5±2.3*	17.4±3.2*	20.8±2.9*
antibody-dependent	12.3±1.6	4.4±0.9*	5.2±1.7*	7.2±1.7

Note. *$p<0.05$ *vs.* the control.

ing cells in the spleen [1,11] 5 days after administration of TC and intraperitoneal immunization with these antigens in doses 2×10^8 cells and 8 μg/kg, respectively. These tests reflect IgM production by splenic B cells. The animals were immunized with sheep erythrocytes in a dose of 10^8 cells intraperitoneally 30 min poisoning. The resolving dose of sheep erythrocytes (5×10^8) was injected under the hind paw aponeurosis after 4 days. Delayed type hypersensitivity reaction reflecting cell immunity, specifically, type 1 T-helper (Th1) activity, was evaluated after 24 h by the increase in the hind paw weight. Natural cytotoxicity characterizing the function of natural killers (NK) was assessed spectrophotometrically by the number of intact target cells in the cytotoxicity test 24 h after poisoning [2]. Antibody-dependent cell cytotoxicity characterizing the function of K cells was evaluated in rat splenocytes by spectrophotometry 5 days after immunization with sheep erythrocytes in a dose of 10^8 cells (intraperitoneally) [5]. The concentrations of CS were measured fluorometrically 2, 12, and 24 h after administration of TC [12]. For determining the dose of CS ensuring its plasma concentration similar to that observed after poisoning, CS (ICN Pharmaceuticals) was injected subcutaneously 3 times at 5-h intervals in doses of 2 and 4 mg/kg with due consideration for its pharmacokinetics [9] and the time course of CS concentrations in the plasma after poisoning with organophosphorus compounds [6]. The concentration of CS in the plasma was measured at the same terms as in animals administered metaphos and acrylonitrile. Measurements of CS in the plasma after 2 and 24 h were performed in the daytime (10.00), and measurement after 12 h was performed at night (22.00). For evaluating the role of CS in the postintoxication changes of immune reactions, these reactions were studied after CS injection in concentrations corresponding to its plasma level after acute poisoning with TS.

The data were statistically processed using Student's *t* test.

RESULTS

Metaphos and acrylonitrile suppressed humoral and cell immunity (Table 1). Intoxication with metaphos caused a more pronounced decrease in immune reactions and natural cytotoxicity. Both test TS reduced the thymus-dependent humoral immune response, which indicates inhibition of IgM synthesis and suppression of Th1 regulating this synthesis [13].

Acute poisoning with metaphos was associated with marked increase in the concentration of CS after 2, 12, and 24 h in comparison with the control (Table 2). Changes in CS levels in the control group reflected daily fluctuations of the plasma CS level, associated with changes in rat activity [9]. The maximum increase in CS concentration (4.8 times) was observed after 2 h. Acute poisoning with acrylonitrile decreased

TABLE 2. Plasma Concentration of CS (ng/ml) after Subcutaneous Injection and Poisoning with Toxic Substances (*M*±*m*, *n*=5-7)

Substances	Term after administration, h		
	24	12	2
Control	25.1±3.6	191.3±14.8	31.3±2.8
Metaphos	120.5±10.4*	270.0±18.4*	48.5±5.2*
Acrylonitrile	30.5±3.1*°	128.8±13.1*°	15.7±1.7*°
CS (3 injections), mg/kg 2	137.6±11.8*+	241.2±15.6*+	40.2±4.5+
4	275.7±19.3*+°	459.2±20.1*+°	38.5±3.0+

Note. $p<0.05$: *vs.* the control, +*vs.* acrylonitrile, °*vs.* metaphos.

CS concentration in the plasma after 12 and 24 h. Two and 12 h after injection plasma concentration of CS increased in a dose-dependent manner. Comparison of plasma concentration of CS in acute poisoning and after exogenic administration of CS in various doses showed that the increase in CS concentration induced by metaphos corresponded to 3 injections of this hormone in a dose of 2 mg/kg.

Three injections of CS in this dose at 5-h intervals suppressed thymus-dependent antibody production (Table 1). In addition, CS in the studied dose essentially decreased NK activity ($p<0.05$) and negligibly decreased the function of K cells ($p>0.05$). CS in the studied dose virtually did not affect the thymus-independent antibody production and delayed type hypersensitivity reaction during the inductive phase of the immune response.

These findings allow us to estimate the contribution of CS to suppression of NK function and thymus-dependent humoral immune response (IgM production) in acute metaphos poisoning by the formula:

$$(1\text{-}CS/C)\times 100\%,$$

where C and CS are immune responses in the control and under the effect of corticosterone, respectively.

The contribution of immunotoxic effects of metaphos to the realization of immune suppression, not associated with the effect of CS, can be evaluated by the formula:

$$(1\text{-}M/C)\times 100\%,$$

where C and M are immune responses in the control and under the effect of metaphos, respectively.

Our estimations indicate that the contribution of CS to the realization of NK suppression and inhibition of thymus-dependent humoral immune response (production of IgM) in metaphos poisoning is 35.6 and 35.1%, respectively. Immunotoxic effects of metaphos not associated with CS ensure a decrease in NK function and thymus-dependent humoral immune response by 20 and 26.4%, respectively. Acrylonitrile induced a negligible decrease in CS concentration (it remains within the normal range of daily fluctuations — 5.9-132.0 ng/ml [9,10]), and therefore CS does not participate in the realization of immunosuppressive effect of this compound in acute poisoning.

Hence, acute poisoning with metaphos and acrylonitrile leads to a decrease in humoral and cell immune reactions; CS contributes to the realization of suppression of NK function and thymus-dependent humoral immune response in metaphos poisoning, while suppression of immune reactions by acrylonitrile is not associated with the effects of CS.

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