Effects of New Taurine Derivatives on Primary Immune Response in Rats

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The effects of new taurine derivatives TAU-15 and TAU-60 with normal and branched alkyl chains, respectively, in a dose of 25 mg/kg on the primary immune response in rats were studied in rats. Intraperitoneal injections of test compounds for 24 days caused transient inhibition of immune reactions to thymus-dependent antigen, which was related to suppressed production of interleukin-1β playing a key role in antigen presentation. This effect was probably associated with activation of cortisol secretion. TAU-15 inhibited production of tumor necrosis factor-α and, therefore, prevented tissue damages. The immune response was normalized after withdrawal of these preparations.

Key Words: *cortisol; primary immune response; interleukin-1β; tumor necrosis factor-α; immunosuppression*

The immune system is the major target for stress factors [1,2,11]. This system maintains the antigen homeostasis by elimination or isolation of foreign agents [11]. Nearly all medicinal preparations of various chemical and pharmacological types in therapeutic doses modulate the immune system. Immunoactive compounds include antioxidants, whose immunomodulatory properties are related to the effects on lipid peroxidation [2]. The natural compound taurine possessing various pharmacological activities is a potent drug for metabolic correction and replacement therapy of many diseases [3,8]. The protective effect of taurine is associated with its participation in oxidation-reduction reactions. Mammalian tissues producing oxidants contain high concentrations of taurine. In cultured cells, taurine, neutralizes toxic hypochlorous acid (HOCl) produced by myeloperoxidase, forms stable chloramines, and prevents cells from autolysis [13,15]. Previous studies showed that taurine-chloramine complexes protect tissues from oxygen-induced damages by inhibiting production of tumor necrosis factor-α (TNF-α) [14].

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A series of N-phenylalkyl taurine derivatives was synthesized at the Department of Neuropharmacology (Institute of Experimental Medicine). One of these compounds having branched alkyl chain displays antihypoxic properties, modulates systemic hemodynamics and cardiac conduction during hypoxia [6], and produces antiischemic effects [7].

Here we studied the effects of new taurine derivatives TAU-15 and TAU-60 with normal and branched alkyl chains, respectively, on the primary immune response in rats.

MATERIALS AND METHODS

Experiments were performed on 250 male outbred rats weighing 200-220 g, obtained from the Rappolovo nursery, and kept under standard vivarium conditions.

To study the immune response, taurine derivatives TAU-15 and TAU-60 in a daily dose of 25 mg/kg were injected intraperitoneally for 24 days. Control rats received an equivalent volume of physiological saline. Half of experimental and control rats were intraperitoneally immunized with 1 ml 50% sheep erythrocytes (SE) and decapitated 5 days after immunization. The remaining animals were kept in a vivarium

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for 7 days after withdrawal of preparations and then immunized with SE. After decapitation, parameters of the primary immune response were studied in the spleen and serum. The total titer of antibodies (AB) to SE ($-\log_2 X$) and individual IgG and IgM AB titers [10] were measured by the reaction of hemagglutination [9]. The number of antibody-producing cells (APC) was estimated by the reaction of local hemolysis in gel [12] and calculated per 10^6 splenocytes and per spleen. IgM-APC (direct) and IgG-APC (indirect) were counted separately.

Functions of the pituitary-adrenocortical system were evaluated 1 h after administration of taurine derivatives by serum cortisol content, which was measured by competitive enzyme immunoassay using Al'-kor-Bio kits (St.Petersburg).

The contents of immunomodulators interleukin-1β (IL-1β) and TNF-α were measured in the supernatant of cultured splenocytes from rats intraperitoneally injected with taurine derivatives in a dose of 25 mg/kg for 7 days. IL-1β content in the supernatant of 3-day-old splenocyte culture activated with phytohemagglutinin-P and prodigiozan was estimated by stimulation of mouse thymocyte proliferation. TNF-α concentration in the supernatant was measured by the cytotoxic reaction using TNF-α-sensitive transformed mouse fibroblasts L-929. We thank Prof. A. S. Simbirtsev and collaborators for their help in this assay.

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

RESULTS

The number of APC and titers of AB to SE decreased in rats treated with TAU-15 or TAU-60 (Table 1). TAU-60 and TAU-15 decreased the number of IgM-APC per 10^6 splenocytes and per spleen by 43 and 46%, respectively. The count of IgG-APC per spleen and per 10^6 splenocytes decreased by 59 and 51%, respectively.

Changes in IgM and IgG AB titers also indicated attenuation of the immune response after 24-day treatment with taurine derivatives. This primarily concerns titers of IgG AB, whose synthesis is initiated later than that of IgM AB and associated with partial transformation of IgM- into IgG-APC. TAU-60 decreased the total titer of AB to SE and IgG titer by 17 and 20%, respectively; TAU-15 decreased these parameters by 13 and 16%, respectively ($p<0.05$).

Adrenocortical hormones produce a pronounced immunosuppressive effect related to the inhibition of various stages of immunogenesis and metabolism in lymphoid cells (up to apoptosis). Corticosteroids modulate the major immune processes, differentiation and migration of lymphocytes [4]. In special experiments, we measured serum cortisol content to evaluate the mechanisms underlying immunosuppressive activity of taurine derivatives. Excretion of endogenous cortisol 60 min after administration of TAU-15 and TAU-60 increased to 25.9±2.2 and 26.4±4.2 nmol/liter, respectively, compared to 16.8±3.0 nmol/liter in the control ($p<0.05$). This suppression of the immune response to SE after 24-day treatment with TAU-15 and TAU-60 was probably related to increased secretory activity of the adrenal cortex and production of cortisol possessing antiinflammatory properties.

Parameters of the primary immune response did not differ from the control 1 week after withdrawal of test preparations (Table 1). Thus, taurine derivatives produce short-term suppression of the primary immune response, which is completely normalized after withdrawal of these preparations.

Corticosteroids inhibit the release of inflammatory mediators and cytokine synthesis and secretion by

TABLE 1. Primary Immune Response in Rats after 24-Day Treatment with 25 mg/kg TAU-15 and TAU-60 and 2 Weeks after Withdrawal (*M*±*m*)

Parameter	Control	TAU-15	TAU-60	After withdrawal		
				control	TAU-15	TAU-60
IgM-APC						
per 10^6	91.9±19.1	49.5±1.2*	52.5±13.1*	105.0±14.0	97.3±13.5	102.5±34.5
per spleen	120,422±17452	58,813±17241*	48,947±14,086*	100,025±13,891	108,362±14,756	93,066±26,687
IgG-APC						
per 10^6	85.6±20.8	72.5±32.1	71.5±18.1	117.0±37.8	106.7±17.8	114.4±42.7
per spleen	117,743±27,662	84,188±37,004*	68,267±21,392*	117,595±39,098	109,432±25,379	132,509±40,832
AB titer						
total	6.3±0.4	5.5±0.5	5.2±0.9	6.4±0.2	5.9±0.3	6.0±1.0
IgG	2.5±0.6	2.1±0.2	2.0±0.5	2.70±0.54	2.6±0.4	2.7±0.9
IgM	3.8±0.6	3.4±0.5	3.2±0.5	3.40±0.43	3.3±0.7	3.3±0.6

Note. *$p<0.05$ compared to the control.

TABLE 2. Effects of Taurine Derivatives on the Content of Cytokines in Supernatants of 3-Day-Old Splenocyte Culture Stimulated with Phytohemagglutinin-P and Prodigiozan (*M*±*m*)

Cytokine, U/ml	Control	TAU-15	TAU-60
IL-1β	39.8±2.3	12.2±7.1**	14.2±1.6*
TNF-α	23.0±3.0	≪10***	51.0±13.0*

Note. *p<0.001, **p<0.01, and ***p<0.05 compared to the control.

mononuclear cells [4,11]. Immune cytokines (e.g., IL-1β and TNF-α) are probably the major substances regulating the intensity of inflammatory processes and the relationship between nonspecific and immune reactions. It is hypothesized that interleukins serve as a link between immune and neuroendocrine mechanisms maintaining homeostasis [1,11]. IL-1β stimulates secretion of adrenocorticotropic and corticotropin-releasing hormones in the hypothalamus [5]. TNF-α and IL-1β possess a variety of systemic antiinflammatory properties, modulate neuroendocrine interactions and vascular permeability, and in high concentrations cause septic (toxic) shock [1]. These cytokines are involved in the immune response by enhancing expression of adhesive and co-receptor molecules and stimulating proliferation of lymphocytes.

TAU-15 and TAU-60 inhibited IL-1β production by 70 and 64%, respectively (Table 2). TAU-15 markedly suppressed, while TAU-60 2-fold increased production of TNF-α (Table 2). Transient inhibition of the primary immune response probably results from suppressed production of IL-1β (a key cytokine in antigen presentation), which is related to increased concentration of cortisol (IL-1β antagonist) in the blood.

Thus, 24-day treatment with TAU-15 and TAU-60 inhibits production of antiinflammatory immunomodulator IL-1β, which is related to increased blood cortisol concentration. This leads to transient inhibition of the primary immune response to thymus-dependent antigens. TAU-15 inhibits production of TNF-α and, therefore, prevents tissue damages. The immune response is normalized 14 days after withdrawal of test preparations.

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