Changed Count of CD4+ T-Lymphocytes in the Bone Marrow of Aggressive CBA Mice

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 124, No. 11, pp. 544-546, November, 1997
Original article submitted July, 30, 1996

Enhanced immune response of aggressive CBA mice after 10 daily confrontations in sensory contact on day 4 after immunization with sheep red blood cells (5×10^8) is paralleled by an increase in the count of $CD4^+$ T-cells in the bone marrow. Aggressive behavior, weight of the spleen, and count of $CD4^+$ T-helpers in the bone marrow (which is increased only in aggressors with a history of at least 3 victories) are correlated. The effect of aggressive behavior on immunity can be caused by changes of the neurochemical status of the brain and determined by an increase in the $CD4^+$ T-helper count.

Key Words: *aggression; immune response; bone marrow; $CD4^+$ T-helpers*

Immunological reactivity depends on behavior [3,4, 14,15]. Immunostimulation of aggressive CBA mice after 10 daily confrontations was observed on a model of sensory contact [3]. Intensification of immune reactions with the development of aggression can be due to increased activity of dopaminergic (DA) system of the brain, because dopamine dependence of aggression was demonstrated in neurophysiological and pharmacological studies [8]. On the other hand, DA system contributes to regulation of immune response, and its immunostimulating effect is explained by increased count of $CD4^+$ T-helpers in the bone marrow [1,4,6,10-12]. All this prompted us to investigate changes in the count of CD4 T-lymphocytes in the bone marrow during the development of aggression in a zoosocial conflict.

MATERIALS AND METHODS

Experiments were carried out on male CBA mice aged 2.5-3.0 months weighing 20-23 g. The animals were kept under standard conditions. The sensory contact model [7] was used to develop the aggressive behavior; the method is described previously [3]. The behavior of animals was tested daily for 10 days. The procedure was as follows: a perforated transparent wall dividing 2 males but not preventing their olfactory and visual perception was removed daily for 10 min, which usually led to confrontation. Fights during agonist counteractions of the animals and the type of animal behavior (aggression or submission) were recorded. After 10 days, aggressive animals were intravenously immunized with sheep red cell (SRC) suspension in a single dose of 5×10^8. Mice without history of confrontations immunized with SRC were the controls.

The immune response was assessed on day 4 post-immunization. The spleen was removed, weighed, and the counts of plaque-forming cells per 10^6 cells and per spleen were determined [9]. Simultaneously, the count of $CD4^+$ T-cells was determined in the bone marrow by the cytotoxic test with murine monoclonal antibodies (anti-L3T4/CD4, Boehringer Mannheim) [2].

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

RESULTS

The weight of the spleen was increased, and immune response was enhanced in aggressive CBA mice on

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0007-4888/97/0011-1101$18.00

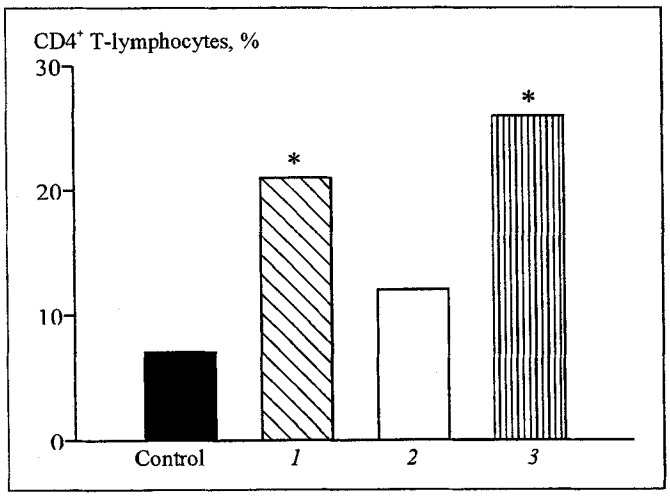

Fig. 1. Changed count of CD4+ T-lymphocytes on day 4 after immunization with sheep red cells (5×10^8) in the bone marrow of aggressive CBA mice with different number of victories in agonist confrontations (*1*), with victories in 1-2 (2) or 3 and more tests (*3*). *Changes are significant in comparison with control.

day 4 postimmunization (the peak of immune response) following 10 sensory contacts. The count of plaque-forming cells per 10^6 cells and spleen in such animals was higher than in the control (Table 1). This is in line with previous findings [3].

Aggressive behavior is paralleled by activation of DA system [7,8]. Therefore, the development of aggression can be regarded as an approach to changing the neurochemical status of the brain with the predominance of DA system. Brain DA system contributes to immunostimulation mechanisms and its effect on immunity is due to increased count of CD4+ T-helpers in the bone marrow [4,6,11]. The count of CD4 T-cells in the bone marrow of aggressive mice on day 4 postimmunization is increased in comparison with the control: 20.8±2.4 *vs.* 9.1±0.9%, $p<0.001$ (Fig. 1). Previous experiments with mice left 1-4 per cage showed that such conditions affected the production of cytokines by TH1 and TH2 T-helper subpopulations. Studies on volunteers showed a relationship between a decrease in blood CD4+ T-cells and personality characteristics when the balance of neurotransmitter systems were shifted toward activation of the serotoninergic system [14]. Study of the count of CD4+ T-cells in every aggressive mouse and assessment of its aggression (number of victories upon sensory contact) in the present investigation showed that increased percentage of CD4+ T-cells in the bone marrow and the appreciable increase of the spleen weight (143.6±14.7 *vs.* 86.9±9.4 mg in the control, $p<0.02$) were observed only in aggressive animals with a history of victories in at least 3 tests out of 10 (Fig. 1). In aggressive animals with a history of 1-2 victories, the weight of the spleen and count of CD4+ T-cells were the same as in the control (Fig. 1).

The effect of social conflict on immune response can be largely determined by migration of T-helpers to the bone marrow, as T-helpers is the most rapidly recirculating population of T-cells. Such a migration was observed in different types of stress [5]. However, this process seems unlikely in the light of previous data demonstrating an increase of the helper activity in the bone marrow but not in other immunocompetent organs during activation of DA system [4,6]. Differentiation of these cells from T-lymphocyte precursors available in the bone marrow is more probable; it is very rapid, involves no cell division, and is due to reconstruction of cell surface [13].

The increase in the count of T-helpers in the bone marrow associated with activation of DA system is mediated by the central mechanisms including the hypothalamo-pituitary complex [4,11].

These data permit a conclusion that by altering the neurochemical picture of the brain, behavioral factors affect the immunity through changing the ratio of T-subpopulations in the bone marrow. In aggressive behavior characterized by the predominance of DA system and stimulation of immune response, the count of CD4+ T-helpers in the bone marrow is increased. Probably, the number of victories reflects to a certain extent different degrees of activation of the brain DA system: no changes in the T-helper count in animals with a lesser number of victories and an appreciable increase of this value in animals with a history of many victories.

The study was supported by the Russian Foundation for Basic Research (project code No. 96-04-50030).

TABLE 1. Count of Plaque-Forming Cells and Weight of the Spleen in Aggressive CBA Mice Immunized with SRC in a Dose of 5×10^8 (*M±m*)

Group of animals	Count of plaque-forming cells		Spleen weight, mg
	per 10^6 cells	per spleen	
Control (*n*=18)	209.9±33.6	20889.2±4752.4	86.9±9.4
Aggressive mice (*n*=10)	327.9±37.4*	48947.9±7875.5**	117.1±11.2

Note. *$p<0.05$, **$p<0.01$ *vs.* the control.

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