IMMUNOLOGY AND MICROBIOLOGY

Immune Response in Mice of a New Strain ASC (Antidepressants Sensitive Catalepsy)

E. L. Alperina, A. V. Kulikov, N. K. Popova, and G. V. Idova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 144, No. 8, pp. 188-190, August, 2007
Original article submitted May 8, 2007

Inherited predisposition of ASC mice with depressive behavior to catalepsy was accompanied by a significant decrease in the immune response to sheep erythrocytes (compared to parent strains CBA and AKR). The degree of immunosuppression was highest on day 5 after immunization.

Key Words: *catalepsy; immune response; psychoneuroimmunology*

Increasing interest in psychoneuroimmunology studying the relationships between nervous, mental, and immune processes can be explained by the fact that impairment of these interrelations can induce nervous disturbances, mental disorders, and secondary immune deficiency [6,10]. The search for new models of psychopathological conditions is of considerable importance. Experiments on animals allow us to evaluate the mechanisms of interaction between neurochemical systems of the brain, behavioral reactions, and immune function.

Freezing response, or catalepsy, is a natural form of passive and defensive behavior. This behavior of laboratory animals is associated with severe neurochemical and physiological changes. Catalepsy in humans is a symptom of severe nervous and mental disorders (*e.g.*, schizophrenia and depression) accompanied by significant changes in the immune status [5,6].

A new mouse strain ASC (antidepressants sensitive catalepsy) was selected from a backcross population of CBA and AKR strains at the Laboratory for Neurogenomics of Behavior (Institute of Cytology and Genetics). These animals are characterized by high predisposition to catalepsy (85% mice demonstrate freezing response), depressive behavior, and increased sensitivity to chronic administration of antidepressants [1,9].

Here we compared the immune response in ASC mice and in mice of the parent strains (CBA and AKR).

Laboratory for Mechanisms of Neurochemical Modulation, Institute of Physiology, Siberian Division of the Russian Academy of Medical Sciences; Laboratory for Neurogenomics of Behavior, Institute of Cytology and Genetics, Siberian Division of the Russian Academy of Sciences, Novosibirsk. ***Address for correspondence***: liza@iph.ma.nsc.ru. E. L. Alperina

MATERIALS AND METHODS

Experiments were performed on 36 male ASC/Icg mice aging 2.5-3.0 months and weighing 28-32 g (generation 10 of selection). The study also involved the animals of parent strains of similar age and weight (CBA/Lac, n=47; AKR/J, n=32). Experimental animals were obtained from the vivarium of the Institute of Cytology and Genetics.

The animals were immunized with sheep erythrocytes (SE, 5×10^8 cells, single injection) in 0.5 ml physiological saline into the caudal vein. The immune response was studied in the spleen on days 4 and 5 after immunization by the number of plaque-forming cells (PFC, IgM antibody-producing cells) [11] and rosette-forming cells (RFC) [2].

The results were analyzed by Student's *t* test for independent samples (Statistica software).

RESULTS

Differences in the primary immune response to SE were revealed between mice of parent strains CBA and AKR on day 4 after immunization. In the early stage of the immune response, the intensity of plaque formation and rosette formation in AKR mice was lower than in CBA mice. It is known that CBA mice exhibit the highest titter of antibodies against SE (Table 1). The ability of inbred mice to respond to the antigen depends not only on the type and dose of this antigen, but also on genetic characteristics and neuroendocrine status of animals [15]. These factors probably determine more rapid reaction of CBA mice to SE.

In immunized ASC mice, the numbers of RFC and PFC on day 4 of the immune response were much lower than in CBA mice (Table 1). At the same time, ASC mice did not differ from AKR mice by the number of RFC and were even superior by the level of plaque formation. However, after 1 day the immune response in ASC mice was lower than in parent strains CBA and AKR. Parent strains did not differ in the immune response on day 5 after immunization (Table 2).

Thus, ASC mice with inherited predisposition to catalepsy are characterized by a lower immune response to SE compared to parent strains CBA and AKR. These differences are most pronounced on day 5 after immunization.

The decreased immune response in ASC mice is not associated with inherited predisposition to catalepsy. Cataleptic mice of the parent strain CBA demonstrated a strong immune response to SE, which was not lower compared to that in non-cataleptic AKR animals.

A characteristic feature of ASC mice is depressive behavior. It is manifested in the decreased locomotor activity and exploratory behavior in the open-field test and longer immobility in the forced swimming and tail suspension tests [1]. Moreover, catalepsy in ASC mice was sensitive to chronic, but not acute administration of the antidepressant imipramine. These data are consistent with clinical observations that the therapeutic effect develops only after long-term treatment with antidepressants [9]. These specific features determine the use of ASC mice as an experimental model of depression [1].

Another specific feature of ASC mice is a decrease in the immune response. This condition is observed not only in depressive patients [6], but also in mice when the depressive state results from repeated defeats in intermale confrontation [2].

The gene responsible for predisposition of ASC mice to catalepsy is linked with 5-HT_{1A} receptor gene [7]. 5-HT_{1A} receptors probably play an important role in the general neurochemical mechanism

TABLE 1. Number of PFC and RFC in the Spleen of CBA, AKR, and ASC Mice on Day 4 of the Immune Response to Immunization with SE in a Dose of 5×10^8 (*M*±*m*)

Mouse strain	Number of PFC×10^6 cells	Number of PFC per spleen	Number of RFC×10^3 cells
CBA	392.1±34.6 (*n*=20)	68 027.4±14 362.4 (*n*=20)	17.3±0.9 (*n*=18)
AKR	102.1±20.8** (*n*=20)	700.7±174.1** (*n*=20)	10.8±1.7** (*n*=13)
ASC	231.2±52.4*+ (*n*=18)	1805.5±453.7*++ (*n*=18)	8.8±0.9* (*n*=17)

Note. Here and in Table 2: *n*, number of animals per group. *$p<0.01$ and **$p<0.001$ compared to CBA; +$p<0.05$ and ++$p<0.001$ compared to AKR.

TABLE 2. Number of PFC and RFC in the Spleen of CBA, AKR, and ASC Mice on Day 5 of the Immune Response to Immunization with SE in a Dose of 5×10^8 (*M*±*m*)

Mouse strain	Number of PFC×10^6 cells	Number of PFC per spleen	Number of RFC×10^3 cells
CBA	353.3±42.9 (*n*=27)	3393.7±353.7 (*n*=27)	27.8±1.5 (*n*=16)
AKR	260.4±24.2 (*n*=10)	2394.4±408.3 (*n*=10)	27.6±1.6 (*n*=12)
ASC	183.2±27.8*+ (*n*=17)	1255.1±236.0*++ (*n*=17)	15.8±1.7**++ (*n*=18)

for catalepsy. Our conclusion is derived from the fact that 8-OH-DPAT, a selective agonist of these receptors, decreases the severity of inherited catatonia and neuroleptic-induced catatonia in rats and mice [8,14]. Previous experiments with highly selective agonists and antagonists showed that this type of serotonin receptors is involved in modulation of the immune response [4]. It can be hypothesized that the serotoninergic mechanisms realized via 5-HT_{1A} receptors mediate the development of immunosuppression in ASC mice.

The haloperidol model is extensively used in the studies of the mechanisms of catalepsy and effect and clinical effectiveness of antipsychotic drugs. Blockade of postsynaptic dopamine receptors with haloperidol in catalepsy-inducing doses of 0.5-12.5 mg/kg is followed by a decrease in the immune response [12,14]. $CD8^+$ and T cells with suppressor function are similarly redistributed between immunocompetent organs and accumulated in the bone marrow during activation of the serotoninergic system (serotonin administration) or inhibition of the dopaminergic system (haloperidol administration) [3].

Decreased immunoreactivity of ASC mice can be related to dysfunction of cell populations, change in migration activity of T and B lymphocytes, and redistribution of these cells between the immunocompetent organs.

We conclude that ASC mice can serve as a convenient model to study the molecular mechanisms of depression and immunoreactivity.

REFERENCES

1. D. V. Bazovkina, A. V. Kulikov, E. M. Kondaurova, and N. K. Popova, *Genetika*, **41**, No. 9, 1-6 (2005).
2. L. V. Devoino, E. L. Alperina, N. N. Kudryavtseva, and N. K. Popova, *Fiziol. Zh. SSSR*, **77**, No. 12, 62-67 (1991).
3. G. V. Idova, *Byull. Sib. Otd. Ros. Akad. Med. Nauk*, No. 4, 52-56 (1994).
4. G. V. Idova M. A. Cheido, and S. M. Davydova, *Eksper. Klin. Farmakol*., **68**, No. 1, 42-44 (2005).
5. V. G. Kolpakov, A. V. Kulikov, T. A. Alekhina, *et al*., *Genetika*, **40**, No. 6, 1-7 (2004).
6. A. V. Kulikov, *Ibid*., **40**, No. 6, 779-786 (2004).
7. G. N. Kryzhanovskii, S. V. Magaeva, S. V. Makarov, and R. I. Sepiashvili, *Neuroimmunology* [in Russian], Moscow (2003).
8. N. K. Popova, A. V. Kulikov, D. F. Avgustinovich, *et al*., *Byull. Eksp. Biol. Med*., **68**, No. 12, 633-635 (1994).
9. M. A. Tikhonova, V. V. Lebedeva, A. V. Kulikov, *et al*., *Ibid*., **141**, No. 1, 53-55 (2006).
10. H. O. Besedovsky and A. D. Rey, *Brain Behav. Immun*., **21**, No. 1, 34-44 (2007).
11. A. J. Cunningham, *Nature*, **207**, No. 5001, 1106-1107 (1965).
12. L. Devoino, G. Idova, E. Alperina, and M. Cheido, *Brain Res*., **633**, Nos. 1-2, 267-274 (1994).
13. J. M. Petitto, *Psychoneuroimmunology*, New York (2001), pp. 173-186.
14. E. P. Prinssen, F. C. Colpaert, and W. Koek, *Eur. J. Pharmacol*., **453**, Nos. 2-3, 217-221 (2002).
15. P. Scott, *Cur. Opin. Immunol*., **5**, No. 3, 391-397 (1993).