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Immune Response of Submissive and Aggressive Mice under Conditions of Opioid Receptor Activation

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Experiments on the model of paired sensory contact demonstrated that stimulation of immune response in aggressive CBA and C57Bl/6J mice with 10- and 20-day experience of victories, respectively, was prevented by selective δ_2-opioid receptor agonists DSLET and κ-opioid receptor agonists rimorphin in a dose of 100 μg/kg. In C57Bl/6J mice with depression-like behavior, normalization (but not suppression) of the immune response under conditions of μ-opioid receptor stimulation (100 μg/kg) was observed. Selective modulation of activity of a certain type of opioid receptors can normalize the immune function modified during the formation of a certain behavioral type.

Key Words: *immunomodulation; aggression; submission; opioid receptors and their agonists*

The μ-, κ-, and δ-opioid systems are involved in the regulation of immune function [5-7,10,14]. Some classes of opioid, dopamine, and serotonin receptors also participate in the formation of behavioral types of animals [11,12], which is associated with modification of the immune response. Immunostimulation is characteristic of aggressive behavior, while depression-like behavior is associated with immunosuppression [2].

Taking into account the differential contribution of central μ-, δ- and κ-opioid receptors (OR) into immunomodulation [5,6,10], it was interesting to evaluate the possibility of modulating the direction of the immune response in animals with different behavioral types via pharmacological modulation of these receptors.

MATERIALS AND METHODS

The study was carried out on 2.0-2.5-month-old male C57Bl/6J (n=68) and CBA (n=73) mice (22-24 g) from Breeding Center of Research Laboratory of Experimental Biosimulation, Russian Academy of Medical Sciences, which were kept under standard vivarium conditions. The studies were carried out in accordance with the humanity philosophy presented in the Directives of the European Community (86/609/EC) and approved by the Committee for Biomedical Ethics of Institute of Physiology.

Opposite behavioral types in mice were modeled and maintained using paired distant sensory contact [3].

Highly selective agonists of κ-OR decapeptide amide (1-10) rimorphin (Institute of Organic Chemistry, Latvia), δ_2-OR DSLET (Sigma), and μ-OR DAGO (Sigma) were used in pharmacological analysis. All drugs were intraperitoneally injected in a dose of 100 μg/kg in saline 30 min before immunization with sheep erythrocytes (5×10^8, into the caudal vein). Control animals (without experience of victories and defeats) received 0.2 ml solvent. Each group consisted of at least 10 animals.

The immune response was tested on day 5 by the counts of IgM-producing (IgM-APC) and rosette-forming cells (RFC) in the spleen [9].

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The significance of differences between the groups was evaluated using Student's *t* test.

RESULTS

The immune process became more intense in aggressive CBA mice immunized with sheep erythrocytes after 10 daily agonistic contacts: the counts of IgM-APC and RFC doubled in comparison with the corresponding values in the control group (Table 1).

Injection of DSLET induced immunosuppression (Table 1). According to published data, δ-OR can be involved in the regulation of some forms of aggressive behavior [13]. In our study, stimulation of δ-OR with DSLET in aggressive CBA males completely abolished the stimulation effect in comparison with the control. This was paralleled by a virtually 2-fold drop of IgM-APC and RFC counts in comparison with aggressive animals not treated with DSLET (Table 1).

There are interstrain differences in the formation of the immune response in aggressive animals: in contrast to CBA mice, the immune response in C57Bl/6J mice could be modified after longer (20-day) confrontations with submissive partners [2]. In our experiments, the immune reaction in these mice was significantly higher than in controls and particularly than in submissive males (Fig. 1), which was in line with the previous data [2]. Subsequent treatment with κ-OR selective agonist rimorphin suppressing (similarly to DSLET) the immune process [6], modified the direction of the immune response in immune animals, reducing it in comparison with the controls and even more so in comparison with aggressive animals not treated with rimorphin (Fig. 1).

Analysis of the immune status of C57Bl/6J mice with submissive behavior after 20 days of confrontations and evaluated as a depression-like state [1], revealed pronounced inhibition of the immune process (Fig. 1). The effect could be abolished by DAGO, a potent μ-OR selective agonist characterized by immunostimulatory effect [10], on the one hand, and involved in the formation of agonistic behavior [4], on the other. In addition, μ-OR are involved in the development of depression [8]. DAGO treatment of C57Bl/6J mice with a 20-day history of defeats during the stage of pronounced depression not only normalized the immune response, but even stimulated it, its values surpassing those in submissive mice not treated with DAGO (Fig. 1).

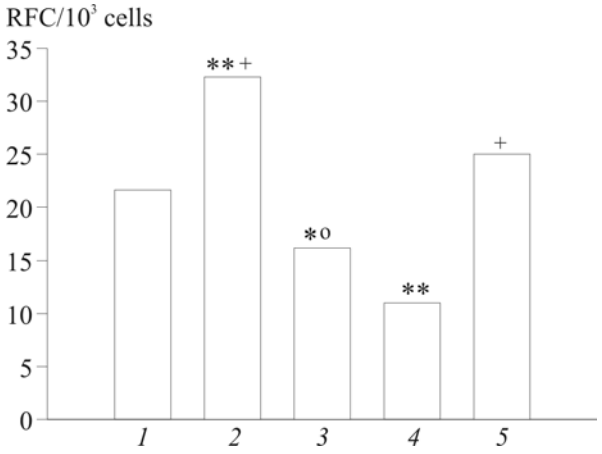

Fig. 1. Effects of κ- and μ-OR selective agonists on immune response of aggressive and submissive C57Bl/6J mice after 20-day social confrontations. *1*) control; *2*) aggressive mice; *3*) aggressive mice+rimorphin; *4*) submissive mice; *5*) submissive mice+DAGO. **p*<0.05, ***p*<0.001 compared to the control; °*p*<0.001 compared to aggressors; +*p*<0.001 compared to submissive mice.

TABLE 1. Effect of DSLET (δ_2-OR Selective Agonist) on Immune Response of Aggressive CBA Males after 10 Days of Confrontations (*M*±*m*)

Group	IgM-APC/10^6 cells	RFC/10^3 cells
Control	208.9±10.7	30.5±0.7
DSLET	67.7±3.3*	17.7±1.4*
Aggressive mice	428.2±77.9*	4.9±1.3*
Aggressive mice+DSLET	241.2±13.1+	37.7±0.7+

Note. **p*<0.001 compared to the control; +*p*<0.001 compared to aggressive mice.

Our previous pharmacological analysis showed that the intensity of the central immunostimulatory effect of DAGO was associated with activation of the dopaminergic mechanisms [5,10]. Presumably, the interactions between the μ-opioid and dopaminergic systems at the receptor level underlie the DAGO-induced modification of the immune reaction in submissive C57Bl/6J mice with a history of 20-day defeats.

On the other hand, it was shown that inhibition of immunological reactivity with rimorphin and DSLET is a serotonin-dependent process [6,7]. This suggests that DSLET- and rimorphin-induced immunosuppressive effects in aggressive CBA (10 days of confrontations) and C57Bl/6J mice (20 days of confrontations) are associated with activation of the serotoninergic system.

These data suggest extending the search for approaches to correction of the immune status in animals with different behavioral patterns via drug modulation of activities of the μ-, δ-, and κ-opioid systems.

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