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Dopamine D_1- and D_2-Receptors in Immunostimulation under Activation of Mu-Opioid Receptors in Mice with Different Psychoemotional States

Margarita Cheido, Galina Idova, Elizaveta Alperina

Laboratory of the Mechanisms of Neurochemical Modulation, State Research Institute of Physiology and Basic Medicine, Siberian Branch of the Russian Academy of Medical Sciences, Novosibirsk, Russia.
Email: lalperina@yahoo.com

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ABSTRACT

The purpose of the present study was to analyze the effect of activation of mu-opioid receptors (mu-OR) on the immune response under blockade of postsynaptic D_1- and D_2-receptors in mice of the C57BL/6J strain displaying either aggressive or depressive-like behaviors in the social conflict model. It is shown that activation of activation of mu-OR with a highly selective agonist DAGO (100 μg/kg) increased significantly IgM-immune response not only in C57BL/6J mice with an unchanged psychoemotional state but also in mice displaying aggressive or depressive-like behaviors in the social stress model (10 days of agonistic confrontations). Selective blockade of DA receptors of the D_1-type with SCH-23390 (1.0 mg/kg with DAGO administration) caused a more pronounced elevation of IgM-immune response than DAGO alone while DAGO effect was completely blocked by prior administration of D_2-receptor antagonist haloperidol (1.0 mg/kg). At the same time, both SCH-23390 and haloperidol prevented the immune response increase induced by DAGO injection in mice engaged in aggressive or depressive-like behaviors. Thus, in animals not subjected to social stress DAGO-induced immunostimulation is provided only by D_2-receptors, whereas in animals with altered psychoemotional state mu-opioid immunostimulation is mediated by both types of DA receptors—D_1 and D_2. These data provide evidence for different impacts of the main subtypes of DA receptors in the mediation of immunomodulating effects of mu-opioid system under normal and stressful conditions.

KEYWORDS

Mu-Opioid and Dopamine Receptors; Social Stress; Aggression; Depressive-Like Behavior; Immunomodulation

1. Introduction

At present there is strong evidence for the involvement of central mu-opioid system in immunomodulation [1-5]. A series of neurophysiological and neuropharmacological studies indicate that immunomodulatory effects of this system are mediated by the DAergic mechanisms [4-8] which are known to provide immunostimulation [9,10]. Our previous data have shown that the nigrostriatal (nucleus caudatus) and mesolimbic (nucleus accumbens) DAergic structures are playing an important role in immunostimulation [10] induced by a highly selective [11] agonist of mu-opioid receptors (mu-OR) DAGO [4]. These brain structures have also been found to contain significantly high amounts not only of DA D_1- and D_2-receptors [12] but also of mu-OR [13]. There is also evidence that DAGO-induced activation of immune reactivity found in mice of the CBA strain not subjected to social stress is realized with the participation of DA receptors of the D_2-type [4,7] that is consistent with other studies indicating close interconnections between mu-opioid and DA systems [14,15].

Recent data have shown that psychoemotional state of animals and humans can significantly affect immune functions [16-19]. At the same time, mu-opioid and DA mechanisms have been found to be implicated in the reg-

ulation of psychosocial stress [17,20-22].

In this connection, a role for the main types of DA receptors in DAGO-induced immunostimulation needs to be examined not only in normal healthy animals but also in animals subjected to psychoemotional stress. Therefore, the purpose of the present study was to analyze the effect of activation of mu-OR on the immune response under blockade of postsynaptic D_1- and D_2-receptors in mice of the C57BL/6J strain displaying either aggressive or depressive-like behaviors in the social conflict model.

2. Materials and Methods

2.1. Animals

The experiments utilized 122 male mice of the C57BL/6J strain weighing 22 - 24 g. The animals were maintained at the State Research Institute of Physiology and Basic Medicine SB RAMS and were housed under standard vivarium conditions and a natural light regime. Food and water were available *ad libitum*.

The study was performed in compliance with principles of the declaration of Helsinki and was approved by the local Ethics Committee of the State Research Institute of Physiology and Basic Medicine SB RAMS.

2.2. Behavioral Procedure

To produce aggressive and submissive behaviors in C57BL/6J mice, the model of sensory contact was used [23]. Males were weighed and individually caged for 5 days to abolish group-living effects. Pairs of animals of nearly the same weight were placed in a steel 28 × 14 × 10-cm cage divided in half by a transparent partition with holes. This permitted animals to see and smell each other but prevented physical contact. After 2 days of adaptation to the housing conditions and sensory contact a test started. Every morning (11:00 a.m., local time), a steel cover of cage was replaced by a transparent one and, 5 min later (a period of individual activation) the partition was removed for 10 min, allowing an agonistic interaction between mice. Agonistic interactions were observed in an overwhelming majority of cages (90% - 100%). A daily test of social confrontations continued for 10 days; if animals did not fight, they were excluded from the experiment. Clear superiority of one partner was evident within two or three tests in daily social encounters in the same cage. One partner demonstrated aggression, attacking, biting and chasing the other one which displayed defense behaviors (sideways, upright postures, and "on the back" or "freezing") during the tests. Submissive mice with experience of defeats during 10 tests of encounters have been shown to display depressive-like behavior and a high level of anxiety [20]. The control for wounding during the aggressive encounters did not show severe injuries in submissive or aggressive mice that could alter the immune parameters.

The group with an unchanged psychoemotional state comprised the group-housed males, after 5 days of individual housing, since, in this case, the submissiveness of grouped C57BL/6J had already disappeared while the repeated experience of aggression had not yet been acquired [20,23].

2.3. Drugs

Selective activation of mu-OR was performed by a structural analogue of enkephalin DAGO [D-Ala^2, N-Me-Phe^4, Gly^5-ol]enkephalin (Sigma, Germany) at a dose of 100 μg/kg. To block postsynaptic DA D_1- or D_2-receptors their highly specific antagonists SCH-23390 [R(+)-7-hloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepinehydrochloride] (Sigma, Germany) and haloperidol (Gedeon Richter A.O., Hungary) respectively were used, both drugs at a dose of 1.0 mg/kg. Drugs were dissolved in saline and injected once intraperitoneally in a final volume of 0.2 ml. DAGO was administered 30 min prior to immunization, SCH-23390 or haloperidol—5 - 10 min before DAGO. The doses for each drug and the routs of their administration used in the present study were chosen based on those previously reported to affect the corresponding receptor and immune reactivity [9].

Animals not subjected to social stress and mice engaged in aggression or depression were divided into groups receiving: 1) Vehicle (control); 2) DAGO alone; 3) Combination of SCH-23390 + DAGO; 4) Combination of haloperidol + DAGO.

2.4. Immunization

All groups of mice were immunized with sheep red blood cells (SRBC), which were suspended in saline and injected in the tail vein at a dose of 5×10^8 cells in 0.5 ml.

2.5. Immunological Assay

The immune response was assessed by measuring the number of antibody-forming cells (IgM-AFC) [24] in mouse spleen at the peak of the immune response (the fourth day after immunization).

2.6. Data Analyses

The significance of the mean differences between experimental groups (set at $p < 0.05$) was first analyzed by one-way analysis of variance (ANOVA) with subsequent multiple comparisons by the Student *t*-test using Statistics for Windows ver.10.0. All data are expressed as the mean ± SEM.

3. Results

3.1. Effect of Mu-Opioid Receptor Activation on the Immune Response under Blockade of Postsynaptic D_1- and D_2-Receptors in Mice with an Unchanged Psychoemotional State

Activation of mu-OR with a highly selective agonist DAGO (100 µg/kg) produced a significant increase of IgM-immune response ($F(1,12) = 79.99$; $p < 0.001$) in C57BL/6J mice having no experience of social encounters when compared to the vehicle-injected group (**Figure 1**).

As is seen in **Figure 1**, selective blockade of DA receptors of the D_1-type with SCH-23390 (1.0 mg/kg with DAGO administration) caused a more pronounced elevation of IgM-immune response than DAGO alone ($F(1,17) = 6.17$; $p < 0.02$). In contrast, effect of DAGO was completely blocked by prior administration of a selective antagonist of D_2-receptors haloperidol (1.0 mg/kg). In this case, the number of IgM-AFC did not differ from that of control ($F(1,12) = 1.62$; $p > 0.05$) and was significantly lower compared to animals receiving only mu-receptor agonist ($F(1,12) = 73.7$; $p < 0.001$) (**Figure 1**).

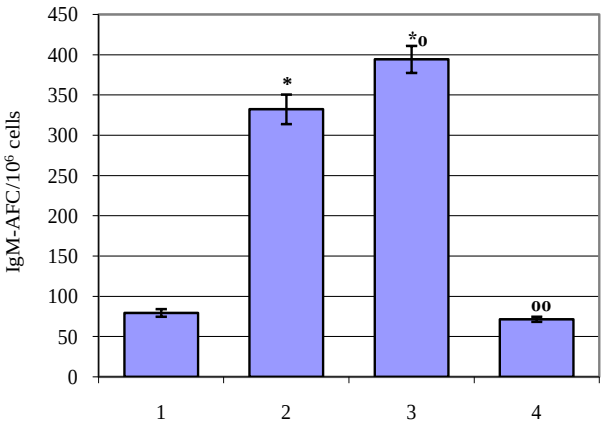

Figure 1. Effect of the blockade of DA D_1- and D_2-receptors on immunostimulation caused by mu-opioid receptor (mu-OR) agonist DAGO in mice having no experience of social encounters. Activation of mu-OR with DAGO at 100 µg/kg (2) increased the number of IgM-AFC in C57BL/6J compared to the vehicle-injected control (1). Blockade of DA of the D_1-receptors with SCH-23390 (1.0 mg/kg) enhanced DAGO induced immunostimulation (3). An antagonist of D_2-receptors haloperidol (1.0 mg/kg) completely blocked DAGO-induced immunostimulation (4). All drugs were dissolved in saline and injected once intraperitoneally in a volume of 0.2 ml. DAGO was administered 30 min prior to immunization (SRBC 5×10^8), SCH-23390 or haloperidol—5 - 10 min before DAGO. IgM-AFC number was tested on the 4th day after immunization. Each value indicates the mean ± SEM. Number of animals—7 - 10/group. $^{*}p < 0.001$—statistical significance compared to the control. $^{o}p < 0.002$, $^{oo}p < 0.001$—compared to the DAGO.

3.2. Effect of Mu-Opioid Receptor Activation on the Immune Response under Blockade of Postsynaptic D_1- and D_2-Receptors in Aggressive Mice

DAGO at 100 µg/kg administered alone have been also found to increase IgM-immune response in mice conditioned to display aggressive behavior during 10 tests of daily confrontations ($F(1,13) = 28.22$; $p < 0.001$) compared to aggressive animals that did not receive the drug (control) (**Figure 2(A)**). The immune response level was also significantly higher the control values after co-administration of DAGO with either the selective D_1-receptor antagonist SCH-23390 ($F(1,12) = 23.11$; $p < 0.001$) or D_2-receptor antagonist haloperidol ($F(1,12) = 14.88$; $p < 0.01$), although the combination of the two drugs caused a less pronounced immunostimulatory effect than that of produced by DAGO (**Figure 2(A)**). An elevation of IgM-AFC numbers in aggressive mice resulting from combining SCH-23390 and DAGO ($F(1,14) = 14.63$; $p < 0.002$) or haloperidol and DAGO ($F(1,15) = 15.40$; $p < 0.001$) was two times lower than DAGO alone values.

3.3. Effect of Mu-Opioid Receptor Activation on the Immune Response under Blockade of Postsynaptic D_1- and D_2-Receptors in Mice with Depressive-Like State

Mu-OR activation with DAGO (100 µg/kg) also led to immunostimulation in mice with experience of 10 defeats in daily confrontations compared to depressive animals not treated with DAGO (control) ($F(1,13) = 124.65$; $p < 0.001$) (**Figure 2(B)**). A similar effect was found in C57BL/6J mice characterized by a high level of depression resulting from a long-term exposure (during 20 days) to the social defeat stress [21].

According to the present data, C57BL/6J mice at early stage of depression (10 days of confrontations) showed increased IgM-immune response when DAGO was combined with one of the DA antagonists: ($F(1,12) = 38.4$; $p < 0.001$) for SCH-23390 and ($F(1,12) = 19.75$; $p < 0.001$) for haloperidol compared to the control (**Figure 2(B)**). However, despite the fact that IgM-AFC numbers were elevated above control values after DAGO co-administration with either selective DA antagonist, their levels were significantly lower compared to the group receiving only DAGO (**Figure 2(B)**).

4. Discussion

It is well established that neuromediator/neuromodulator mu-opioidergic system is playing an important role in psychoneuroimmunomodulation. There is increasing evidence that activation of mu-OR by agonists of different

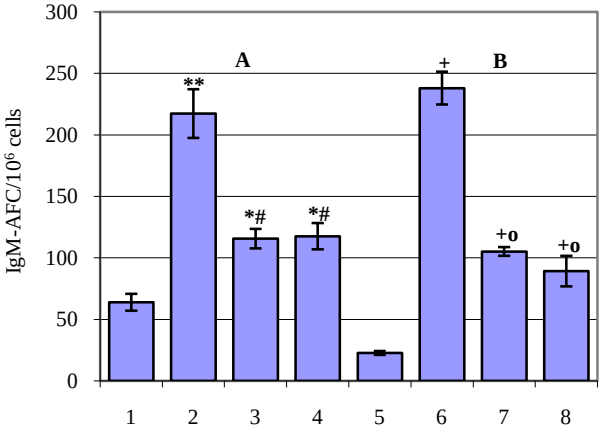

Figure 2. Effect of the blockade of DA D_1- and D_2-receptors on immunostimulation caused by mu-opioid receptor (mu-OR) agonist DAGO in aggressive (A) and depressive (B) C57BL/6J mice. Activation of mu-OR with DAGO at 100 μg/kg increased the number of IgM-AFC in aggressive (2) and depressive (6) mice compared to the vehicle-injected control (1 and 5 respectively). The blockade of DA D_1-receptors with SCH-23390 at 1.0 mg/kg partially abolished DAGO effect both in aggressive (3) and depressive (7) mice. The blockade of D_2-receptors with haloperidol at 1.0 mg/kg also partially abolished DAGO effect in aggressive (4) and depressive (8) mice. All drugs were dissolved in saline and injected once intraperitoneally in a volume of 0.2 ml. DAGO was administered 30 min prior to immunization (SRBC 5 × 10^8), SCH-23390 or haloperidol—5 - 10 min before DAGO. IgM-AFC number was tested on the 4th day after immunization. Each value indicates the mean ± SEM. Number of animals—7 - 10/group. $^*p < 0.01$, $^{**}p < 0.001$—statistical significance compared to the group 1; $^\#p < 0.001$—compared to the group 2; $^+p < 0.001$—compared to the group 5; $^op < 0.001$—compared to the group 6.

origin may produce a wide variety of effects on immune parameters [2,3,25-27]. It has been shown earlier that administration of the most widely used agonist of mu-OR DAGO significantly increased the intensity of the immune response in mice of the CBA strain and Wistar rats with an unchanged psychoemotional state [1,4,9,26]. According to our previously reported data, the immunostimulatory effect of DAGO is mediated by central mechanisms via the hypothalamus-hypophysis complex [1,4].

In the present study DAGO-induced immunostimulation has been found in C57BL/6J mice having no experience of social confrontations or conditioned to display aggressive or depressive-like behavior during 10 tests of daily social encounters. This effect was more pronounced in depressive mice than that of unconditioned (control) or aggressive animals.

To date, the immunomodulatory effects of mu-agonists are known to be mediated by the DAergic mechanisms with the involvement of brain D_1- and D_2 receptors [4,5,7,8]. It should be noted that close mu-opioid/DA interconnections in the brain structures have been shown to be particularly important for the regulation of different physiological functions including behavioral [28,29] and immune responses [4,5,7-9].

Our earlier data and results presented here demonstrate a significant role for the DA D_2-receptors in mediating DAGO-induced activation of immune responsiveness in mice of the CBA [4,7] and C57BL/6J strains, which were not subjected to social stress. This conclusion is confirmed by the finding that the immunostimulatory effect of DAGO was completely blocked by D_2-receptor antagonist haloperidol (1.0 mg/kg) while it remained unaffected after the blockade of D_1-receptors with SCH-23390 (1.0 mg/kg). At the same time, previous animal studies have indicated that both antagonists, which are known to block central DA receptors [9], produced the immune response suppression [4,7,9].

Unlike mice having no experience of social confrontations, the effect of DAGO on immunity was prevented by antagonists for the two receptor types in C57BL/6J mice showing either aggressive or depressive-like behaviors. Although, co-administration of DAGO with either D_1- or D_2-receptors antagonist (SCH-23390 and haloperidol, respectively) did not completely block the effect of activation of mu-OR on the immune response in animals with aggressive and depressive behaviors, these results indicate the requirement for D_1- and D_2-receptors in the mediation of DAGO-induced immunostimulation under psychoemotional stress.

Aggressive and depressive-like behaviors are known to be associated with changes in the level and distribution of serotonin (5-HT) and DA and their metabolites over brain structures [17,20,30-32], which appeared to be involved in the mechanisms of immunomodulation [9,10, 17]. There is also evidence for significant differences in immune reactivity of C57BL/6J mice engaged in aggression or depressive-like behavior [17,33]. Numerous data indicate that aggression is characterized by increasing activity of the DAergic system, known to stimulate immune functions, while depressive behavior is accompanied with changes in activity of the 5-HTergic system providing an inhibitory mechanism of immunomodulation [17,31,32].

Consistent with previous results [17,21,33], the present study has demonstrated that aggressive animals showed a higher immune responsiveness compared to animals with depressive-like behavior. At the same time depressive-like behavior is associated with the decreased immune function relative to that of controls and aggressive mice.

Despite the existing facts on the differences of the neurochemical pattern of the brain as well as the immune system functioning in animals displaying aggressive or depressive-like behaviors, our data indicate that the acti-

vation of mu-OR produced similar immunostimulatory effect in C57BL/6J mice with opposite types of behavior.

The enhanced immune response induced by the mu-OR agonist in aggressive animals is likely to be associated with further activation of the DAergic system. Immunostimulation found in mice with depressive-like behavior after DAGO injection seems to be also DA-dependent due to the changes in the balance between functionally linked 5-HT- and DAergic systems with the domination of the latter. Moreover, as is shown in the present study, DAGO-induced stimulation of immune response observed in mice with the opposite types of behavior is mediated by DA receptors of the D_1- and D_2-types.

Thus, our results provide evidence for different impact of the main subtypes of DA receptors in the mediation of immunomodulating effects of mu-opioid system under normal and stressful conditions. In animals not subjected to social stress DAGO-induced immunostimulation is provided only by D_2-receptors, whereas in animals with altered psychoemotional state mu-opioid immunostimulation is mediated by both types of DA receptors—D_1 and D_2. These data give a new insight in the receptor mechanisms of the interactions between mu-opioid and DA systems, in which changing activity may contribute to a variety of neurological and psychiatric diseases [34,35], known to be associated with immune dysfunctions [36,37].

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