DOI 10.1007/s11055-016-0311-0
Neuroscience and Behavioral Physiology, Vol. 46, No. 7, September, 2016

Functional Interactions between 5-HT_{1A} and 5-HT_{2A} Receptors in the Brain

V. S. Naumenko, D. V. Bazovkina, and E. M. Kondaurova

UDC 57.042+577.2

Translated from Zhurnal Vysshei Nervnoi Deyatel'nosti imeni I. P. Pavlova, Vol. 65, No. 2, pp. 240–247, March–April, 2015. Original article submitted July 21, 2014. Accepted December 22, 2014.

Activation of 5-HT_{1A} receptors by their agonist 5-OH-DPAT (0.1, 0.5. and 1.0 mg/kg, i.p.) produced a significant and dose-dependent decrease in the number of headshakes mediated by 5-HT_{2A} receptors, while blockade of 5-HT_{1A} receptors by their antagonist WAT-100635 (0.5 and 1.0 mg/kg, i.p.), conversely, induced a significant increase in this functional response to 5-HT_{2A} receptors. At the same time, activation of 5-HT_{2A} receptors by their agonist DOI (0.5 and 1.0 mg/kg, i.p.) prevented the hypothermic response mediated by 5-HT_{1A} receptors, while blockade of 5-HT_{2A} receptors with ketanserin (1.0 and 2.0 mg/kg, i.p.) enhanced this functional response of 5-HT_{1A} receptors. In addition, ketanserin (1.0 and 2.0 mg/kg, i.p. or 20 and 40 nmol, i.c.v.) induced a dose-dependent hypothermic response. This ketanserin (40 nmol, i.c.v.)-induced hypothermic response was significantly weakened by prior administration of the 5-HT_{1A} receptor antagonist WAY-100635 (1.0 mg/kg, i.p.). This suggests that the hypothermic response evoked by blockade of 5-HT_{2A} receptors is partially mediated by 5-HT_{1A} receptors. These data point to the existence of a bidirectional functional interaction between 5-HT_{1A} and 5-HT_{2A} receptors, such that these receptors can support the mutual regulation of functional activity.

Keywords: 5-HT_{1A} receptor, 5-HT_{2A} receptor, functional activity of receptors, functional interaction between receptors, mice.

Among the many cloned and identified serotonin (5-HT) receptors, the most intensely studied is the 5-HT_{1A} receptor. This receptor is involved in regulating a diversity of physiological functions and types of behavior and plays the key role in regulating the 5-HT system of the brain [Popova and Naumenko, 2013]. Data have been obtained on the existence of functional interactions between different types of 5-HT receptors, which have significant influences on the functions of the serotonin system of the brain. The functions of 5-HT_{1A} receptors have repeatedly been shown to be modulated by other serotonin receptors [Naumenko et al., 2010; Raymond, 1991]. At the same time, various 5-HT receptors can partially mediate their actions via 5-HT_{1A} receptors [Kondaurova et al., 2012; Naumenko et al., 2009].

Published data indicate that there is a functional interaction between 5-HT_{1A} and 5-HT_{2A} receptors. The protein kinase C (PKC) phosphorylation site is located in the third cytoplasmic loop of the 5-HT_{1A} receptor [Raymond, 1991]. As PKC is the second messenger for the 5-HT_{2A} receptor, these data suggest that the functions of 5-HT_{1A} receptors can be under the control of 5-HT_{2A} receptors [Zhang et al., 2001; Zifa and Fillion, 1992]. In fact, activation of 5-HT_{2A} receptors was found to produce a significant decrease in the functional response of 5-HT_{1A} receptors in rats [Zhang et al., 2001; Zhang et al., 2004]. At the same time, the 5-HT_{2A} receptor agonist DOI leads to the development of behavioral patterns, such as fidgeting with the forepaws and stretching, which are characteristic of activation of 5-HT_{1A} receptors [Gaggi et al., 1997]. This indicates that activation of 5-HT_{2A} receptors stimulates 5-HT_{1A} receptors, which is consistent with data on the negative effects of chronic activation of 5-HT_{2A} receptors on the functions of 5-HT_{1A} receptors [Hensler and Truett, 1998; Valdez et al., 2002]. We have previously demonstrated that activation of 5-HT_{2A} receptors in mice with a genetic predisposition to freezing reactions has an anticataleptic action, mediated mainly by 5-HT_{1A} receptors [Naumenko et al., 2010]. At the same time, activation of 5-HT_{2A} receptors has been shown to lead to signif-

Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, Novosibirsk, Russia; e-mail: naumenko2002@bionet.nsc.ru.

icant suppression of the functional activity of 5-HT_{1A} receptors, assessed in terms of the intensity of the hypothermic response to activation of 5-HT_{1A} receptors by their agonist 8-OH-DPAT [Naumenko et al., 2010], which is consistent with data reported by other investigators [Raymond, 1991].

5-HT_{1A} receptors are known to be involved in the mechanism of thermoregulation. Despite data on the influences of 5-HT_{2A} receptors on the function of 5-HT_{1A} receptors, information on the role of 5-HT_{2A} receptors in controlling body temperature are fragmentary and contradictory. Activation of 5-HT_{1A} receptors has been shown to lead to the development of a hypothermic response [Mazzola-Pomietto et al., 1995]. At the same time, studies have been reported demonstrating the absence of such an influence [Takao et al., 1997]. Blockade of 5-HT_{2A} receptors with ketanserin has also been shown to lead to both hyper [Won and Lin, 1988] and hypothermic responses [Abdel-Fattah et al., 1995].

There is very little information on the influences of 5-HT_{1A} receptors on the function of 5-HT_{2A} receptors. However, stimulation of 5-HT_{1A} receptors has been shown to be able to suppress the function of 5-HT_{2A} receptors [Chaiseha et al., 2010; Herremans et al., 1999], while indirect activation of 5-HT_{2A} receptors mediated by blockade of presynaptic 5-HT_{1A} receptors increases the number of 5-HT_{2A} receptor-mediated headshakes [Fox et al., 2010].

Thus, data on the functional interaction between 5-HT_{1A} and 5-HT_{2A} receptors in the brain are scanty and contradictory. The aim of the present work was therefore to identify the nature of the functional interaction between 5-HT_{1A} and 5-HT_{2A} receptors in the brain.

Methods

Animals. Experiments were performed on adult (8–9 weeks, weight about 25 g) male mice of the inbred strain CBA-Lac, kept at the animal house of the Collective Resource Facility of the Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences. This strain was selected because of its high functional activities of 5-HT_{1A} and 5-HT_{2A} receptors, as seen in our previous studies [Naumenko et al., 2010]. Mice were kept in standard laboratory conditions with a natural illumination cycle (12 h light and 12 h dark) with free access to food and water. All experimental procedures were performed in compliance with the *Guide for the Care and Use of Laboratory Animals* of the National Institutes of Health (NIH Publication No. 80-23), 1996.

Drugs. The selective 5-HT_{1A} agonist 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin, Research Biochemicals Inc. USA) was dissolved in physiological saline and given i.p. at doses of 0.1, 0.5, and 1.0 mg/kg. The selectivity of 8-OH-DPAT for 5-HT_{1A} receptors was confirmed by data showing that blockade of 5-HT_7 receptors by the selective antagonist SB269970 had no effect on hypothermia evoked by administration of 8-OH-DPAT [Naumenko et al., 2011].

The selective 5-HT_{1A} receptor antagonist WAY-100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl cyclohexanecarboxamide maleate, Sigma Aldrich, USA) was dissolved in physiological saline and given i.p. at doses of 0.5 and 1.0 mg/kg.

Experiments with prior blockade or activation used 5-HT_{1A} receptors WAY-100635 or 8-OH-DPAT given 10 min before DOI or ketanserin. When ketanserin was given, WAY-100635 was used at a dose of 1.0 mg/kg.

The 5-HT_{2A} receptor agonist DOI ((±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride, Sigma, USA) was dissolved in physiological saline and given i.p. at doses of 0.5 and 1.0 mg/kg.

The selective 5-HT_{2A} receptor antagonist ketanserin (Sigma, USA) was dissolved in physiological saline and given i.p. at doses of 1.0 or 2.0 mg/kg (180 or 360 μmol). The effects of blockade of peripheral 5-HT_{2A} receptors were avoided by giving ketanserin centrally into the left lateral ventricle of the brain (i.c.v.) (AP: –0.5 mm, L: –1.6 mm; DV: 2 mm [Slotnick and Leonard, 1975]) at doses of 20 and 40 nmol. Before central administration, animals were anesthetized with diethyl ether for 20–30 sec. Animals of the control group received i.c.v. physiological saline. The volume given was 5 μl.

In experiments with prior blockade of 5-HT_{2A} receptors, ketanserin was given 30 min before 8-OH-DPAT. In experiments with prior blockade of 5-HT_{1A} receptors, ketanserin was given centrally at a dose of 40 nmol 10 min after administration of WAY-100635 (1.0 mg/kg, i.p.).

Measurement of body temperature. Body temperature was measured using a KJT thermometer (Hanna Instruments, Singapore) with a copper rectal probe for mice (Physitemp Instruments, USA). In experiments with 8-OH-DPAT, body temperature was measured before administration of physiological saline, DOI, or ketanserin, at 30 min, immediately before administration of 8-OH-DPAT, and 20 min after administration of 8-OH-DPAT. In experiments with ketanserin, body temperature was measured before and 30 min after drug administration. In experiments with WAY-100635 and ketanserin, body temperature was measured before administration of physiological saline or WAY-100635, at 10 min, immediately before administration of ketanserin, and 30 min after administration of ketanserin. The hypothermic response was expressed as the difference between body temperature measured 30 min after drug administration and baseline body temperature (Δt, °C).

Assessment of receptor functional activity. The functional activity of 5-HT_{1A} receptors was evaluated in terms of the intensity of the hypothermic response evoked by i.p. administration of 8-OH-DPAT (1 mg/kg) [Overstreet et al., 1996].

The functional activity of 5-HT_{2A} receptors was evaluated in terms of the number of 5-HT_{2A} receptor-mediated headshakes evoked by i.p. administration of DOI (1 mg/kg) [Green and Heal, 1985]. The number of headshakes was measured over 20 min starting 5 min after drug administration.

Statistical analysis. Results were presented as $m \pm$ SEM and compared using unifactorial analysis of variance for analysis of variance for repeat measures and post hoc multiple comparison using Fisher's test.

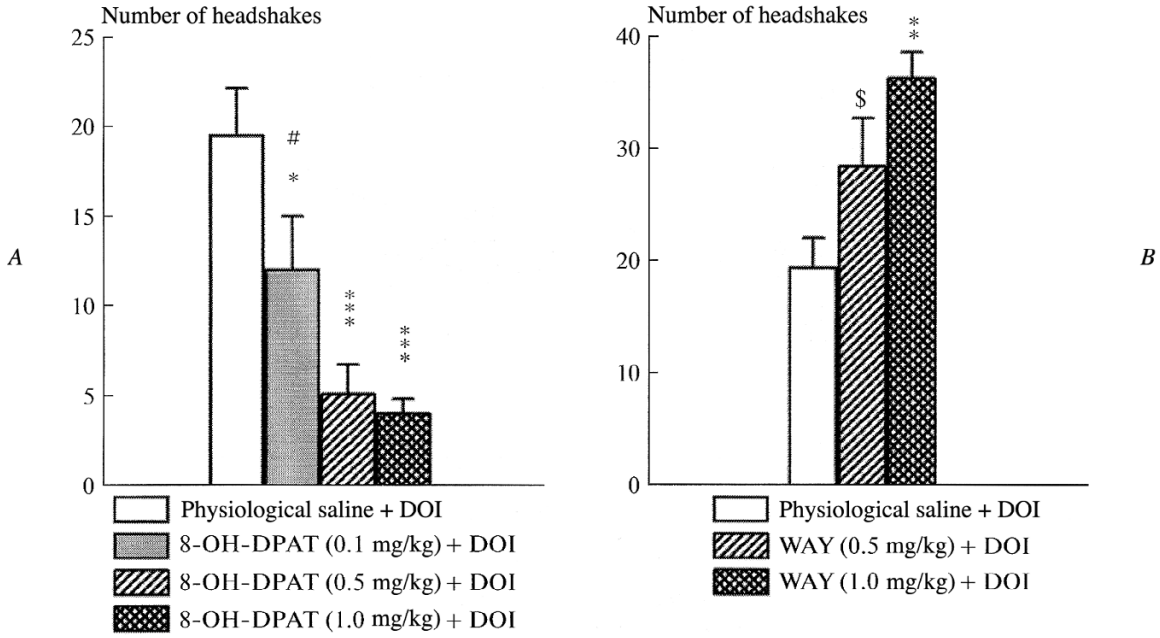

Fig. 1. Effect of activation (*A*) and blockade (*B*) of 5-HT$_{1A}$ receptors on the functional activity of 5-HT$_{2A}$ receptors. The functional activity of 5-HT$_{2A}$ receptors was assessed in terms of the number of 5-HT$_{2A}$ receptor-mediated headshakes evoked by administration of DOI (1 mg/kg, i.p.). $n \geq 6$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared with the group given physiological saline and DOI; $^{\#}p < 0.05$ compared with the 8-OH-DPAT (0.5 and 1 mg/kg) + DOI group; $^{\$}p = 0.06$ compared with the physiological saline + DOI group.

Results

Activation of 5-HT$_{1A}$ receptors with 8-OH-DPAT significantly ($F_{3,22} = 11.5$, $p < 0.001$) and dose-dependently ($p < 0.05$ for 0.1 mg/kg and $p < 0.001$ for 0.5 and 1.0 mg/kg) decreased the functional activity of 5-HT$_{2A}$ receptors (Fig. 1, *A*). At the same time, blockade of 5-HT$_{1A}$ receptors with WAY-100635 led to a significant ($F_{2,19} = 6.4812$, $p < 0.01$) and dose-dependent ($p = 0.06$ for 0.5 mg/kg and $p < 0.01$ for 1 mg/kg) increase in the functional activity of 5-HT$_{2A}$ receptors (Fig. 1, *B*).

Activation of 5-HT$_{2A}$ receptors with DOI completely blocked the 5-HT$_{1A}$ receptor-mediated hypothermic response, indicating a decrease in the functional activity of 5-HT$_{1A}$ receptors (Fig. 2, *A*). Analysis of variance for repeat measures revealed an effect for the dose factor ($F_{2,29} = 3.9$; $p < 0.05$) and an effect for the interaction between the dose and measurement factors ($F_{4,52} = 17.5$, $p < 0.001$). At the same time, analysis of variance for repeat measures in the experiment with preliminary blockade of 5-HT$_{2A}$ receptors with ketanserin followed by activation of 5-HT$_{1A}$ receptors with 8-OH-DPAT revealed an effect for the DOI dose factor ($F_{2,24} = 29.4$, $p < 0.001$), the measurement factor ($F_{2,48} = 102.5$, $p < 0.001$), and the interaction between these factors ($F_{4,48} = 22.2$, $p < 0.001$). Thus, blockade of 5-HT$_{2A}$ receptors enhanced the functional activity of 5-HT$_{1A}$ receptors. In addition, we observed a significant hypothermic response to administration of ketanserin ($p < 0.001$ for both of the doses used) (Fig. 2, *B*).

To avoid the vascular effects of blockade of peripheral 5-HT$_{2A}$ receptors [Delaney et al., 2011] on body temperature, we repeated this experiment but with ketanserin given into the left lateral ventricle of the brain. Central administration of ketanserin also induced a significant ($F_{2,12} = 4.74$, $p < 0.001$) dose-dependent ($p < 0.001$ for both of the doses used) hypothermic response 30 min after substance administration (Fig. 3), as shown for peripheral administration of ketanserin.

It should be noted that blockade of 5-HT$_{1A}$ receptors with WAY-100635 (1 mg/kg, i.p.) led to a significant ($F_{1,15} = 4.8$, $p < 0.05$) decrease in the hypothermic response evoked by administration of ketanserin (40 nmol, i.c.v.) (Fig. 4).

Discussion

The present study yielded new information on the functional interaction between 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors. In our studies, like those of Takao et al., [Takao et al., 1997], activation of 5-HT$_{2A}$ receptors had no significant effect on body temperature. However, blockade of 5-HT$_{2A}$ receptors led to the development of a marked hypothermic response which, according to data from Abdel-Fattah et al. [Abdel-Fattah et al., 1995], indicates that 5-HT$_{2A}$ receptors had an inhibitory effect on other receptors able to induce the hypothermic response.

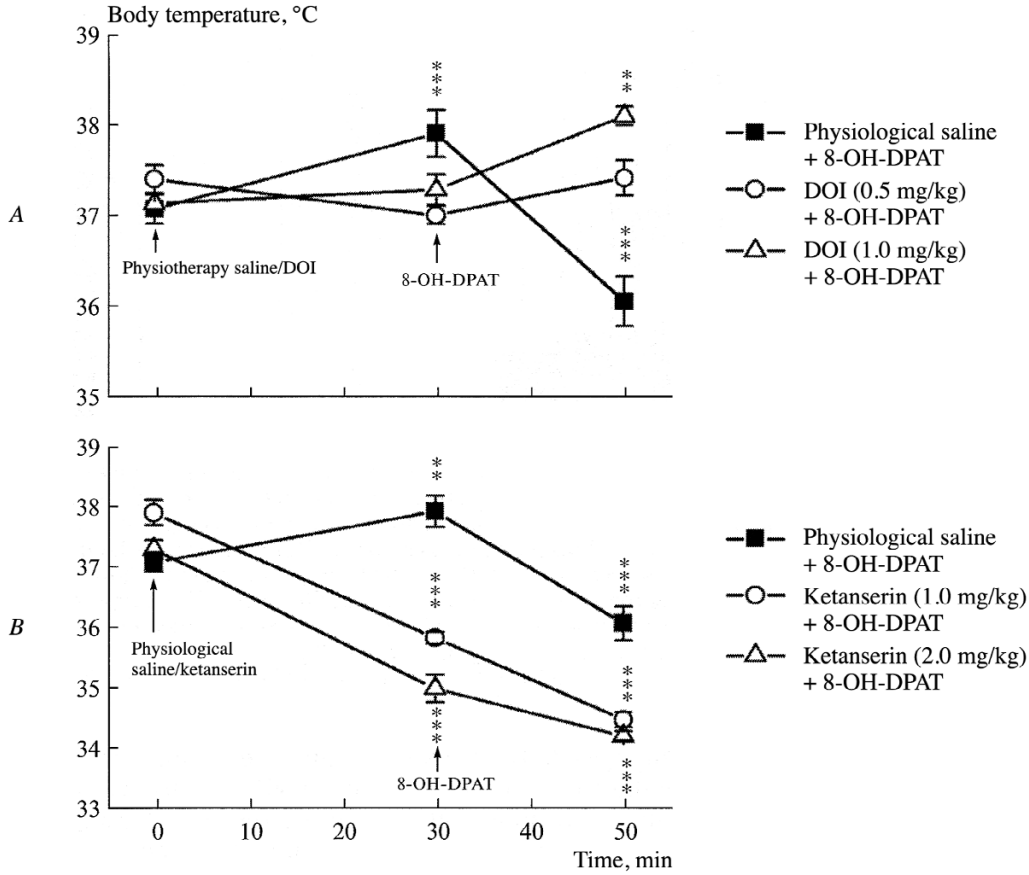

Fig. 2. Effects of activation (*A*) and blockade (*B*) of 5-HT_{2A} receptors on the functional activity of 5-HT_{1A} receptors. The functional activity of 5-HT_{1A} receptors was assessed in terms of the extent of the hypothermic response to acute administration of 8-OH-DPAT (1 mg/kg, i.p.). $n \geq 6$. $^{**}p < 0.01$, $^{***}p < 0.001$ compared with the physiological saline + 8-OH-DPAT group.

Blockade of 5-HT_{1A} receptors was shown to weaken the ketanserin-induced hypothermic response. Experimental data led to the conclusion that the hypothermic effect induced by blockade of 5-HT_{2A} receptors is at least partially mediated by 5-HT_{1A} receptors.

Activation of 5-HT_{2A} receptors was shown to suppress the functional activity of 5-HT_{1A} receptors. These results are in good agreement with previous reports [Naumenko et al., 2010; Raymond, 1991]. At the same time, these results at first glance contradict the data reported by Gaggi et al., indicating that activation of 5-HT_{2A} receptors leads to the development of patterns of behavior mediated by 5-HT_{1A} receptors – fidgeting with the forepaws and stretching [Gaggi et al., 1997] – which is evidence that 5-HT_{2A} receptors stimulate 5-HT_{1A} receptors. Furthermore, we have recently demonstrated that activation of 5-HT_{2A} receptors in mice with a genetic predisposition to freezing reactions has an anticataleptic effect linked with activation of 5-HT_{1A} receptors [Naumenko et al., 2010]. Thus, activation of 5-HT_{2A} receptors evidently leads to simultaneous inhibition and activation of 5-HT_{1A} receptor function. On the basis of this contradiction, we suggested that activation of 5-HT_{2A} receptors leads firstly to activation of presynaptic 5-HT_{1A} receptors, apparent as a decrease in the spike activity of neurons and the anticataleptic effect, and, secondly, to inhibition of postsynaptic 5-HT_{1A} receptors, which is apparent as a decrease in the intensity of the hypothermic response to 8-OH-DPAT [Naumenko et al., 2010]. This suggestion was supported experimentally by, on the one hand, the cataleptogenic effect of the 5-HT_{2A} receptor antagonist ketanserin [Egashira et al., 29007; Kalkman et al., 1998] and, on the other, data on the role of postsynaptic 5-HT_{1A} receptors in the mechanisms of hypothermia evoked by 8-OH-DPAT [Blier et al., 2002]. Our suggestion explains both the development of the anticataleptic effect [Naumenko et al., 2010] and the behavioral patterns [Gaggi et al., 1997] associated with activation of 5-HT_{1A} receptors on stimulation of 5-HT_{2A} receptors and the inhibitory effect of 5-HT_{2A} receptors on 5-HT_{1A} receptor-mediated hypothermia. Thus, 5-HT_{2A} receptors evidently act on pre- and postsynaptic 5-HT_{1A} receptors in opposite ways.

We observed that blockade of 5-HT_{1A} receptors enhances the functional activity of 5-HT_{2A} receptors. These results

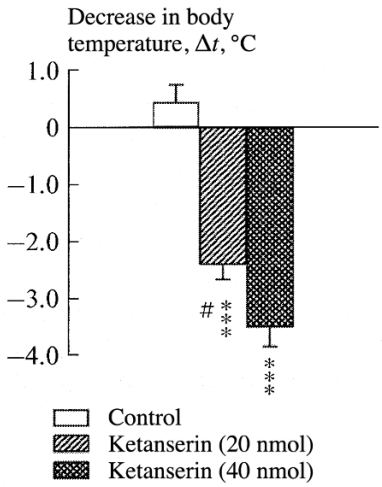

Fig. 3. Effects of central administration of ketanserin on body temperature. $n = 5$. $^{***}p < 0.001$ compared with controls; $^{\#}p < 0.05$ compared with the dose of 40 nmol.

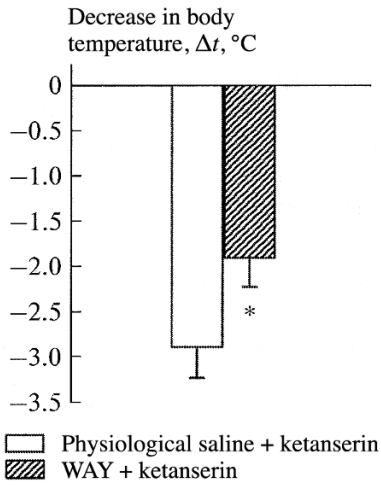

Fig. 4. Effect of prior administration of WAY-100635 (1 mg/kg) on the hypothermic response evoked by administration of ketanserin (40 nmol, i.c.v.). $n \geq 8$. $^{*}p < 0.05$ compared with the physiological saline + ketanserin group.

are consistent with data reported by Fox et al., [Fox et al., 2010]. We have also demonstrated that activation of 5-HT$_{1A}$ receptors suppresses the functional activity of 5-HT$_{2A}$ receptors, which is consistent with information reported by the groups led by Chaiseha and Herremans [Chaiseha et al., 2010; Herremans et al., 1999]. Thus, activation of 5-HT$_{1A}$ receptors suppresses and blockade enhances the functional activity of 5-HT$_{2A}$ receptors. Our data lead to the conclusion that 5-HT$_{1A}$ receptors inhibit the function of 5-HT$_{2A}$ receptors, while a decrease in this negative influence enhances the operation of 5-HT$_{2A}$ receptors, its strengthening, conversely, suppressing the function of 5-HT$_{2A}$ receptors.

The existence of a functional interaction between 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors significantly hinders our understanding of the mechanisms of the development of 5-HT-dependent behavioral pathologies and the actions of clinically effective agents directed at correcting these pathologies. However, at the same time, understanding of the nature of functional interactions between 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors provides some degree of prediction of the consequences of intervention in the disease development process. For example, it is well known that chronic treatment with classical antidepressants – serotonin reuptake inhibitors – leads to a decrease in the function of presynaptic 5-HT$_{2A}$ receptors [Albert and Lemonde, 2004]. However, this decrease, acting via a functional interaction, may lead to an increase in the function of 5-HT$_{2A}$ receptors, which, in turn, may lead to the development of other behavioral pathologies [Franklin and Carrasco, 2013].

Conclusions

Thus, the data obtained from the present studies indicate that 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors affect each other's functional activity via a two-way functional interaction: 5-HT$_{1A}$ receptors inhibit the functioning of 5-HT$_{2A}$ receptors and, conversely, 5-HT$_{2A}$ receptors suppress the function of 5-HT$_{1A}$ receptors. At the same time, 5-HT$_{2A}$ receptors evidently act on pre- and postsynaptic 5-HT$_{1A}$ receptors in opposite ways.

This study was supported by the Russian Scientific Foundation (Grant No. 14-15-00025).

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