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EXPERIMENTAL ARTICLES

Studies of the Behavioral Effects of a Novel Endogenous Modulator of the Serotonergic System, 5-hydroxytryptamine-moduline

I. P. Ashmarin†, R. A. Danilova[1], O. I. Rudko, M. F. Obukhova, L. A. Andreeva, E. M. Amelchenko, M. Yu. Zyatikova, and N. I. Sergeeva

Moscow State University, Biological Faculty, Vorob'evy Gory, Moscow, 119992 Russia

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Abstract—We studied effects of a new endogenous peptide, 5-hydroxytryptamine-moduline (5-HT-moduline), which specifically interacts with 5-HTIB auto and hetero-receptors in rats. The data from anxiety tests suggested that an increase in the endogenous level of 5-HT-moduline has an anxiogenic effect, which supports the hypothesis that 5-HT-moduline plays a major role in the development of anxious and, possibly, depressive behavior. In contrast, the induction of autoantibodies to 5-HT-moduline by active immunization of rats by covalent conjugates of 5-HT-moduline had a long-term anxiolytic and antidepressant effect, which was accompanied by an increase in the level of 5-HT in the striatum. Inhibition of the anxiogenic effect following introduction of two anxiogenic agents, 5-HT-moduline and cholecystokinin-4 (CCK-4), indicated that CCK-B and 5-HTIB receptors interacted during the modulation of anxious behavior.

Key words: 5-hydroxytryptamine-moduline, cholecystokinin-4, anxiety, depression, inverse immunoregulation

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INTRODUCTION

Endogenous regulators of dopaminergic, cholecystokininergic, and serotonergic transmission play a key role in the complex mechanism for the development of pathological anxiety and depression.[2] The 1B subtype of serotonin (5-HT) receptors (5HT-1B), which belongs to the largest group of 5-HT receptors, is important for the control of 5-HT functions. These include auto-receptors and hetero-receptors. The auto-receptors are located on the terminals of serotonergic neurons, where they inhibit the biosynthesis and release of 5-HT. The hetero-receptors are located on the non-serotonergic terminals and block the transmission of other mediators [1–5 and others]. It has been proposed that dysfunction of 5HT-1B receptors plays a role in the disturbance of adaptation mechanisms (stress, depression, and anxiety) [6–7 and others]. The Leu-Ser-Ala-Leu endogenous tetrapeptide, which can noncompetitively and specifically interact with 5HT-1B receptors as an allosteric modulator, was recently extracted from the brain and is referred to as 5-hydroxytryptamine-moduline [8–11]. Interaction of 5-HT moduline with autoreceptors on the neuronal terminals is associated with a decrease in their functional activity due to changes in their conformation. As a result, 5HT-1B receptors lose their ability to interact with serotonin. It has been shown that the local introduction of 5-HT-moduline to the prefrontal cortex decreases the extracellular level of 5-HT [4]. Intracerebral administration of the peptide to rats induced desensitization of 5HT-1B receptors in the substantia nigra [12] and eliminated the effects of agonists of these receptors, as shown by biochemical and behavioral studies on mice in social tests [9].

Several types of data indicate that 5-HT-moduline may induce such pathological states as anxiety, aggression, and depression [3, 4, 13–14]. An increase in the level of 5-HT-moduline was observed during acute stress in the cortex, hippocampus, and hypothalamus [7, 13]. Study of the functional activity of 5-HT-1B receptors during physiological stress revealed the complete desensitization of these receptors, presumably due to an increase in the content of 5-HT-moduline in the hippocampus [14]. A single introduction of polyclonal antibodies to 5-HT-moduline (passive immunization) had an anxiolytic effect on the behavior of mice in anxiety tests [3, 15], suggesting a direct involvement of 5-HT-moduline in the control of anxious disorders. On the basis of these data, some authors have hypothesized that changes in the level of endogenous 5-HT-moduline are important for the control of serotonergic activity and the development of pathological states, and that the activity of 5-HT-moduline is a key element in understanding the mechanisms of depression and fear.

† Deceased.

[1] Corresponding author; e-mail: danilovara@mail.ru

[2] Abbreviations: BSA, bovine serum albumin; CCK-4, cholecystokinin-4; DA, dopamine; DOPAK, 3,4-dihydrophenylacetic acid; 5-HIAA, hydroxyindolylacetic acid 5-HT, serotonin; 5HT-1B, 1B subtype of serotonin receptors; 5-HT-moduline, 5-hydroxytryptamine-moduline; HVA, homovanilic acid.

However, despite rather complete biochemical characterization of 5-HT-moduline presented in a number of studies, there are no experimental data on the influence of this peptide on behavior.

Here, we publish the results of a number of studies of the behavioral effects of the new endogenous peptide. In addition to traditional approaches to this task, such as direct administration of the peptide, we used the method of inverse immunoregulation, i.e., active immunization against 5-HT-moduline, as being more promising for long-term measurements of the endogenous level of 5-HT-moduline [16].

MATERIALS AND METHODS

The study was performed with white Wistar rats weighed 150–200 g. We used the Leu-Ser-Ala-Leu tetrapeptide that is, 5-HT-moduline, synthesized in the Institute of Molecular Genetics of the Russian Academy of Sciences, and commercial CCK-4 {Trp-Met-Asp-Phe-NH_2} (ICN Biomedical Inc.). These agents were intraperitoneally administered once in doses of 20 and 100 μg per rat (volume 0.2 ml). Physiological saline in the same volume was administered to the control groups.

Immunization of rats. We used 5-HT-moduline covalently bound to antigen-carriers, BSA or tetanus anatoxin for rat immunization. Carbodiimide-1 (*N*-ethyl-*N*'-3-dimethylaminopropyl carbodiimide hydrochloride) was used as a coupling reagent at a molar ratio of 1 : 100 for the synthesis of the conjugates. The rats were immunized by the conjugates three times at intervals of 7–8 days. The injections were made at four points on the back. The first and the second immunizations were made with the use of an immunostimulator, Freund's adjuvant (ICN Biomedical Inc., United States) in a volume ratio of 1 : 1. The immunization doses were 600–800 μg of protein per kg of weight. The control group was injected with the adjuvant in physiological saline.

Immunoassay of the blood sera of the control and the experimental animals was performed with the use of the solid phase enzyme immunoassay (ELISA) in phosphate sedimentation buffer (pH 7.5).

Biochemical studies. Determination of the level of monoamines and their metabolites (DA, DOPAK, HVA, 5-HT, and 5-HIAA) in the striatum of the brain of immunized rats was performed one month after the immunization using high performance liquid chromatography with electrochemical detection.

Behavioral studies were performed at 1 and 24 h after parenteral introduction of the peptides, three-four weeks after the beginning of immunization, and later with use of the following tests.

(1) The elevated cross maze was used for studies of anxiety and fear in rat behavior. We recorded such parameters as the number of open arm entries, duration of stay in the arms, total number of transitions, risk behavior, number of rearings, freezing time etc, over a 5 min period.

(2) The dark-light test. We recorded the latent period of entry to the dark part, number of entries to light part, and time spent in the light part during a 5 min period after placing a rat in the lit part of the chamber.

(3) The susceptibility of rats to the development of a depressive-like state was evaluated using the Porsolt forced swimming test [17]. We recorded the duration of active (energetic movements by all feet) and passive (weak movements by rear feet) swimming and immobilization of an animal during a 10 min period.

(4) The motor and exploratory activity of rats, along with the recording of horizontal and vertical components, was evaluated with the use of an automatic RODEO device. The total time of testing was 5–10 min.

(5) The learning abilities of the immunized rats were evaluated with the use of the conditional food-procuring reflex in a Y-shaped maze and the conditional reflex of active avoidance in an automated installation.

Statistical analysis was performed with the use of the non-parametric Wilcoxon–Mann–Whitney or Fisher tests.

RESULTS AND DISCUSSION

Effects of the direct action of 5-HT-moduline. No anxiogenic effect was observed during testing of rats in the cross maze 1 h after the parenteral introduction of 5-HT-moduline at a dose of 20 μg/rat. A small anxiogenic effect was observed after an increase in the peptide dose to 100 μg/rat. A well pronounced anxiogenic effect was observed during both primary and repeated testing in the cross maze 24 h after the introduction of doses of 20 μg/rat and, especially, 100 μg/rat. We noted a decrease in the characteristics that indicate the presence of anxiogenic effect (number of entries, duration of stay in the open arms, and risk behavior (Fig. 1). The figure shows that none of the rats treated with 100 μg of 5-HT-moduline entered the open arms. Some decrease in the characteristics of motor (the number of entries to closed arms, 69% of the control) and exploratory activity (the number of rearings, 46% of the control) in the cross maze could also indicate the presence of anxiogenic effect, because we noted no changes in the motor activity in the automated open field (under conditions close to natural). The anxiogenic effect was also demonstrated in another anxiety test (the dark–light test) where a significant decrease in the number of entries to the light part and duration of stay in this part were observed (Fig. 5).

In addition, in this experimental group, we noticed a significant increase in the freezing time in the cross maze (Fig. 1) which pointed to a possible depressive effect. The Porsolt test showed that the immunized rats really had pronounced and significant components of depressive behavior, a decrease in the time of active

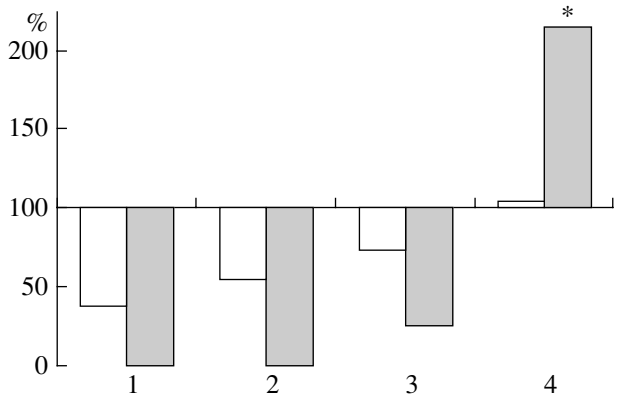

Fig. 1. Characteristics of rat behavior in the elevated cross maze after parenteral introduction of 5-HT-moduline (% of control). Bright bars and dark bars correspond to 5-HT-moduline in doses of 20 and 100 μg/rat, respectively. 1, the number of entries to the open arms; 2, time spent in the open arms; 3, risk behavior; 4, freezing time. *$p < 0.05$ according to the Wilcoxon–Mann–Whitney test.

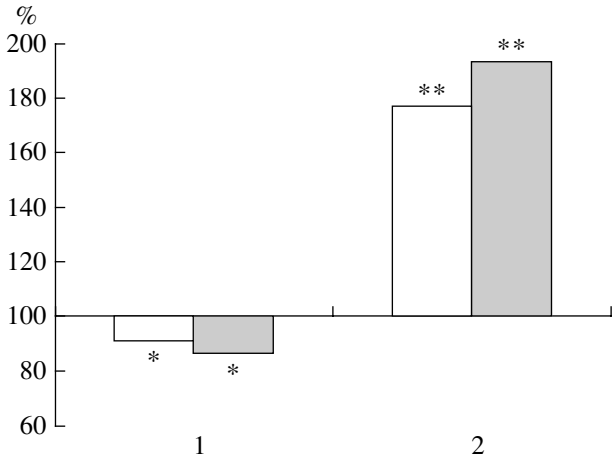

Fig. 2. Characteristics of rat behavior in the forced swimming test after parenteral introduction of 5-HT-moduline (% of control). Bright bars and dark bars correspond to 5-HT-moduline in doses of 20 and 100 μg/rat, respectively. 1, time of active swimming; 2, time of immobilization. *$p < 0.05$ and **$p < 0.005$ according to the Wilcoxon–Mann–Whitney test.

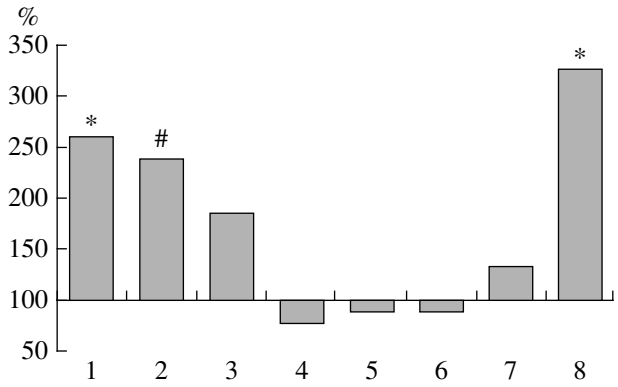

Fig. 3. Behavior of rats in the elevated cross maze after immunization against 5-HT-moduline (% of control). 1, number of entries to the open arms; 2, time spent in the open arms; 3, risk behavior; 4, freezing time; 5, number of looks at the open arms; 6, number of transitions in the closed arms; 7, number of rearings; 8, latent period of entry to the closed arm. *$p < 0.05$ according to the Wilcoxon–Mann–Whitney test and #$p < 0.05$ according to the Fischer test.

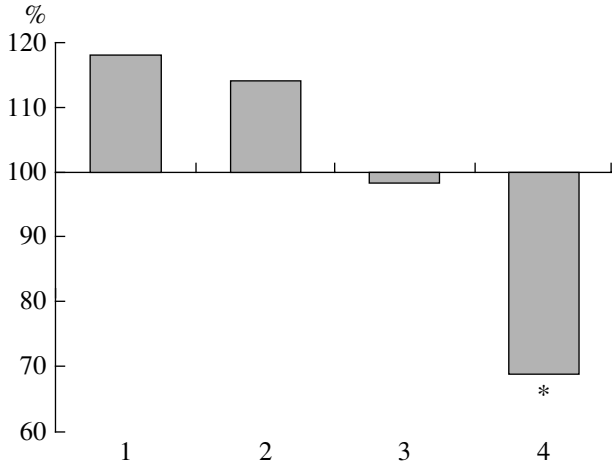

Fig. 4. Characteristics of behavior of rats immunized against 5-HT-moduline in the forced swimming test (% of control). 1, time of first immobilization; 2, time of active swimming; 3, time of passive swimming; 4. time of immobilization. *$p < 0.05$ according to the Wilcoxon–Mann–Whitney test.

swimming and an increase in immobilization time (Fig. 2).

Thus, we found a number of effects of single parenteral introduction of the new endogenous peptide, 5-HT-moduline, suggesting the dose-dependent and delayed anxiogenic and depressive effects of this peptide. The most effective dose was 100 μg/rat. We also observed delayed anxiogenic and depressive effects in experiments with the use of the well-known anxiety inductors, CCK-3 (Met-Asp-Phe-NH_2) and CCK-4 (Trp-Met-Asp-Phe-NH_2) [18, 19] These results helped us to propose some mechanisms for this phenomenon. This is in agreement with the hypothesis that long-term hyposensitization of the receptor system occurs during action of the exogenous peptide, i.e., a long-term change in the excitability of receptors after the initial introduction of the regulatory peptides [20].

The results of these studies of the anxiogenic effect of 5-HT-moduline support hypotheses on the major role of 5-HT-moduline in the development of anxious and, possibly, depressive behavior. However, the dose-dependency of the effect of 5-HT-moduline and the dif-

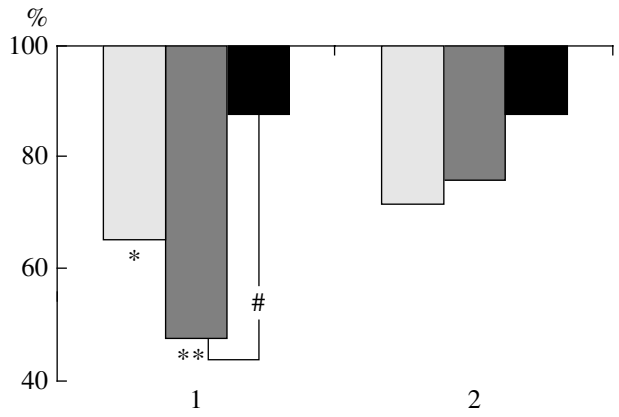

Fig. 5. Characteristics of rat behavior in the dark-light test (% of control). Bright bars, gray bars, and black bars, correspond to CCK-4 (100 μg/rat), 5-HT-moduline (100 μg/rat), and combined treatment, respectively. 1, number of entries to the light part; 2, time spent in the light part. *$p < 0.05$ according to the Wilcoxon–Mann–Whitney test; **$p < 0.005$ according to the Wilcoxon–Mann–Whitney test; #$p < 0.05$ according to the Fisher test.

ference in its direction during the first hours after its introduction and during delayed testing are subjects for further studies with wider ranges of doses and times of testing. The presence of an anxiogenic effect, along with an increase in the endogenous content of the peptide, suggests that binding of endogenous 5-HT-moduline by antagonists or during active immunization by covalent conjugates of 5-HT-moduline with antigenic carriers (the method of "inverse immunoregulation") may result in pronounced anxiolytic effects.

Inverse effects of 5-HT-moduline. In order to perform these experiments, we synthesized conjugates of 5-HT-moduline covalently bound to different antigenic carriers, tetanic anatoxin, or BSA. Immunization of rats with these conjugates induced the formation of antibodies against 5-HT-moduline. This fact indicates that immunization of rats against this endogenous peptide is possible, although it has never been performed. The immunological studies showed that the immunization efficiency was higher with the use of BSA as an antigen carrier according to the titer (Table 1), hence we used rats immunized by these conjugates in our further behavioral experiments.

Studies on the behavior of rats one month after immunization (or later) in the elevated cross maze demonstrated an increase in the basic parameters of anxiolytic components of rat behavior, which is the opposite of the direct anxiogenic effects of 5-HT-moduline. This included a significant increase in the number of entries into the open arms, the time of stay in these arms, and other parameters (Fig. 3). The effects observed in the immunized rats in the forced swimming test were opposite to those observed during a single introduction of 5-HT-moduline. Thus, the immobilization time of the immunized rats was significantly smaller than that in the control and the first immobilization occurred later, which suggests that depressive components were absent in the behavior of the immunized rats (Fig. 4).

Table 1. Level of antibodies in the blood sera of the immunized rats

Control	Conjugate of 5-HT-moduline with tetanic anatoxin	Conjugate of 5-HT-moduline with BSA
1 : 80	1 : 400 $p < 0.001$	1 : 6400 $p < 0.001$

Studies on the elaboration of conditional reflexes with positive or negative reinforcements in the immunized and control rats did not show any significant differences in learning abilities, except for a small stimulating effect during formation of the conditional food-procuring reflex.

Biochemical analysis of the levels of biogenic amines in the striatum of the brain of immunized and control rats revealed a significant decrease in the level of 5-HT and an increase in the 5-HIAA/5-HT ratio. The level of dopamine and its metabolites in the striatum of the brain of immunized rats did not differ from that in the control (Table 2).

Thus, induction of autoantibodies against 5-HT-moduline resulted in pronounced anxiolytic and antidepressive effects, which is in agreement with the results of passive immunization against 5-HT-moduline [3, 15] and the anxiolytic effects observed in three anxiety models in experiments with endogenous tetrapeptide HGL, an antagonist of 5-HT-moduline, [21].

The data on the anxiogenic effect of 5-HT-moduline during its direct administration and the anxiolytic effect during immunization against this peptide are similar to the data that we obtained during studies on the effects of another well known endogenous anxiogenic tetrapeptide, CCK-4 [22, 23] (Table 3). However, immunization against 5-HT-moduline was accompanied by changes in the biochemical characteristics of the serotonergic system and immunization against CCK-4 affected dopaminergic system. Hence, it was interesting to examine the possibility of enhancement of the anxiogenic effect during simultaneous introduction of the two peptides related to different systems.

Effects of the combined action of CCK-4 and 5-HT-moduline. In the experiments with mutual single parenteral introduction of CCK-4 and 5-HT-moduline, we used both peptides in their most effective dose of 100 μg per rat. Testing was performed within 24 h after this introduction. This time was determined by the fact that the strongest anxiogenic effect was observed at this time after introduction of 5-HT-moduline, as was described above. We have previously described the delayed anxiogenic effects of CCK-4 [18–20]. The results of these experiments were rather unexpected.

Table 2. Content of biogenic amines (ng/mg of tissue) in the rat striatum

	Control	Immunization against 5-HT-moduline	
			% of the control
DA	4.89	4.6	94.0
DOPAK	0.54	0.58	107.4
HVA	0.39	0.4	102.6
5-HT	0.79	0.55*	69.6
HIAA	0.47	0.49	104.2
HIAA/5-HT	0.59	0.9*	138.5
DOPAK/DA	0.11	0.12	109.0
HVA/DA	0.8	0.8	100.0

Note: * $p < 0.05$ according to the Wilcoxon–Mann–Whitney test.

Thus, we demonstrated in the dark–light test that introduction of 5-HT-moduline or CCK-4 alone increased the anxiety level of rats, which was indicated by a decreased number of entries to the light part of the chamber and a decreased time of stay in this compartment. At the same time, the group treated with both peptides did not show behavior of increased anxiety. Moreover, these characteristics of the rats of this group were practically the same as those in the control (Fig. 5), i.e., the anxiogenic effect after the introduction of two anxiogenic agents was eliminated. Similar elimination of the anxiogenic effect was also observed during testing of rats in the elevated cross maze. The characteristics of the group simultaneously treated with both peptides either did not differ or even exceeded the control values (Figs. 6 and 7). The behavior of rats following treatment with both peptides in the forced swimming test was also similar to that in the control and distinct from the depressive behavior of the rats treated with 5-HT-moduline or CCK-4 alone.

Thus, we demonstrated the anxiogenic effects of 5-HT-moduline and its elimination during introduction of the two anxiogenic drugs (Table 3).

The elimination of anxiogenic effects during the combined introduction of two anxiogenic peptides (5-HT-moduline and CCK-4), which are modulators of the serotonergic and CCK-ergic systems, respectively, is of interest due to the interaction of these systems and, possibly, the dopaminergic system in the development of anxious behavior. There is data which suggest a functional interaction between the serotonergic and CCK-ergic systems [24–26]. 5-HT-moduline is also known to specifically interact with both 5HT-1B-auto-

Table 3. Comparative effects of the parenteral introduction of 5-HT-moduline and CCK-4 and immunization

Tests		Effects			
		5-HT-moduline	5-HT-moduline + CCK-4	CCK-4	
Anxiogenic/anxiolytic effect	Dark–light chamber	anxiogenic ▼▼ ($p < 0.01$)	~ = control		
	ECM	anxiogenic	tendency to anxiolytic	anxiogenic	according to [18–20, 22, 23]
Depressiveness	ECM $T_{freez.}$	depressive ▲ ($p < 0.05$)	tendency to anxiolytic		
	Porsolt forced swimming $T_{immob.}$ $T_{act.\ swim.}$	depressive ▲▲▲ ($p < 0.005$) ▼▼ ($p < 0.01$)	= control	depressive	
Active immunization	ECM	anxiolytic ▲ ($p < 0.05$)		anxiolytic	
	Porsolt forced swimming	antidepressive ▲ ($p < 0.05$)		antidepressive	

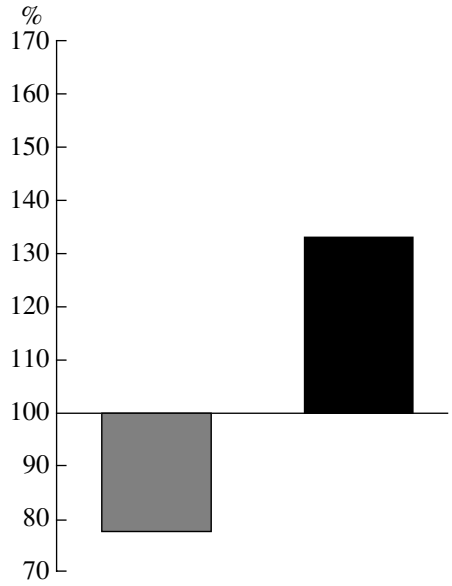

Fig. 6. Risk behavior of rats in the elevated cross maze (% of control). Grey bars and black bars correspond to 5-HT-moduline (100 μg/rat) and the combined treatment with 5-HT-moduline and CCK-4, respectively.

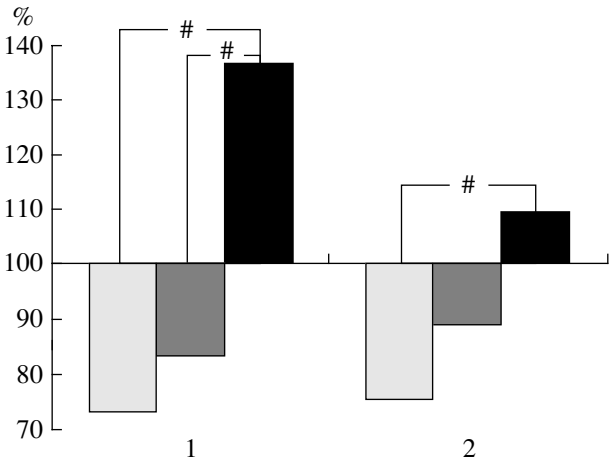

Fig. 7. Characteristics of locomotor activity of rats in the elevated cross maze (% of control). Bright bars, gray bars, and black bars correspond to CCK-4 (100 μg/rat), 5HT-moduline (100 μg/rat), and their combined introduction. 1, number of transitions in the closed arms; 2, number of rearings. #$p < 0.05$ according to the Fisher criterion (between experimental groups).

and hetero-receptors located in the dopaminergic terminals, and to be involved in the control of both serotonergic and dopaminergic transmission [4]. It has been shown that 5-HT-moduline introduced directly to the striatum of the rat brain increases the release of dopamine in this area. The authors associated this increase with desensitization of 5-HT-1B receptors located on the dopaminergic terminals [27, 28]. On the other hand, the anxiogenic effect of CCK-4 is mediated by stimulation of some parts of the dopaminergic system through the CCK-B receptors. However, all these premises and the experimental data are quite ambiguous. They point to the complex interaction of these systems and are a subject for further studies on the interaction of CCK-B and 5-HTIB receptors in the modulation of anxious behavior.

On the basis of the obtained data showing a decrease in the components of anxiety and depression during the induction of antibodies against 5-HT-moduline by immunization of rats with conjugates of 5-HT-moduline, we performed experiments (together with the Research Center for Mental Health of the Russian Academy of Medical Sciences) on the possible role of antibodies against 5-HT-moduline in the pathogenesis and course of schizophrenia. These studies showed that autoantibodies against 5-HT-moduline were present in the blood sera of patients with schizophrenia prior to treatment and that the titers of the autoantibodies increased after combined treatment with haloperidol and clozapine. It was hypothesized that autoantibodies to 5-HT-moduline are among the factors that are generated in the body of a schizophrenic for compensation of the pathological process, because they are already present in untreated patients and because treatment enhances their generation. Keeping in mind the role of serotonergic transmission in the pathogenesis of schizophrenia and the identification of 5-HT-moduline as its important regulator at the level of 5-HT-1B receptors, it may be hypothesized that the autoantibodies bind 5-HT-moduline, an internal inductor of anxiety and depressive behavior, decrease the components of pathological behavior of the patient, and suppress affective and depressive manifestations of schizophrenia, especially during its successful treatment [30].

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