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Effects of Serotonin Receptor Antagonist Methiothepin on Membrane Potential of Premotor Interneurons of Naïve and Learned Snails

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Abstract
It was shown that the application of methiothepin, the antagonist of serotonin (5-HT) receptors, caused a decrease in the membrane potential of the high-threshold premotor interneurons LPa3 and RPa3 of the intact snails and its increase to the previous level after the subsequent application of 5-HT in vitro. The application of methiothepin also led to a decrease in the membrane potential of these neurons, but the subsequent application of 5-HT did not lead to the return of the membrane potential to the previous level in animals trained in defensive reflex. It can be assumed that conditioning of the defensive reflex causes a state change of the 5-HT receptor system of premotor interneurons of defensive behavior.

Keywords Serotonin · Methiothepin · Identified neurons · Membrane and threshold potentials · Learning · Snail

1 Introduction

There are a large number of studies that demonstrate the necessity of serotonin (5-HT) for the elaboration of the defensive reflexes conditioning in mollusks [1–3]. The concept about the important role of extrasynaptic transmission of 5-HT in the mechanisms of memory in mollusks is recently developing [4, 5]. The modulatory neurons of the pedal ganglion of the terrestrial snails are responsible for those modulations [6, 7]. It has been shown that the electrophysiological correlates of plasticity can be reproduced by the application of 5-HT in the solution, washing the central nervous system [8–14]. One of the sites for 5-HT action may be the 5-HT receptors. So, it was shown that the methiothepin (MET), an antagonist of the 5-HT receptors, prevented posttetanic potentiation caused by acetylcholine-evoked current in premotor interneurons and behavioral sensitization in snails [15]. It was also found that the mianserin, another antagonist of the 5-HT receptors, blocked two forms of the defensive behavior of *Lymnaea*, caused by unconditioned stimulus (extract of the cray-fish tissue). The methysergide, also antagonist of 5-HT receptors, disrupted the formation of long-term memory after training [16]. On the soma of snails, premotor interneurons, which are the object of our study, were found only the 5-HT receptors, inhibited by MET (possibly of first type 5-HT receptors) [15, 17]. The aim of present work was the study of the changes of excitability of premotor interneurons in response to sequential applications of MET (antagonist of serotonin receptors) and 5-HT in preparations of naive and trained snails.

2 Methods

The terrestrial snails *Helix lucorum* were used in experiments. The animals were kept in active state in a glass terrarium, in a humid atmosphere, at room temperature, with an excess of

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food for at least 2 weeks before experiments. The defensive conditioned reflex to tap on the shell was developed in a half of the snails [18, 19]. Tapping on the shell (two times) was used as a conditioned stimulus, which does not produce any defensive reaction in a snail in normal conditions. The blowing of the air into pneumostome which usually produces the defensive reaction of pneumostome closure in animals was used as an unconditioned stimulus. The pairings of stimuli were presented with a random interval that ranged from 2 to 4 min. The defensive reflex was elaborated over a 3-day period, as a result of presentation of 150 pairs of the conditioned and unconditioned stimuli. The result of this training is the complete closure of the pneumostome in response to the conditioned stimuli that were observed as positive reaction. Evidence of animals learning is active control, as which served using of nonpaired presentation of conditioned and unconditioned stimuli, in the same amount and in the same time intervals, that under the paired presentation of these stimuli. This method described by us earlier [19].

The electrical characteristics of the withdrawal interneurons LPa3 and RPa3 of the defensive withdrawal reflex circuit were analyzed [20]. The measurements were performed by using glass intracellular microelectrodes, filled with 2.5 M KCl with resistance 4–15 MΩ. The recordings of the electrical characteristics were carried out from the control (naive) snails and snails on the day after training. The changes of membrane (Vm) and threshold (Vt) potentials of premotor interneurons in response to application of MET (at a concentration of 4×10^{-5} M/l) and after 30 min subsequent replacement washing solution with MET on solution of 5-HT (at a concentration of 4×10^{-5} M/l) were studied on naive and trained snails. The analysis of premotor interneurons response to application of MET and subsequent application of 5-HT were carried out on preparations from 4 (four) naive and 5 (five) learned snails. The analysis of premotor interneurons response to application only of 5-HT was carried out on preparations from 11 (eleven) naive and 13 (thirteen) learned snails. The electrical activity was measured only in one premotor interneuron (beginning from LPa3) in each preparation to avoid the background influence of the previous substances. In a separate series of experiments, the comparative analysis of membrane and threshold potentials of neurons LPa3 and RPa3 were conducted; the measurements were carried out on both neurons on each preparation of intact ($n = 5$) and trained snails ($n = 5$). These experiments are control and are repetitive from our previous results [21].

The results are shown as mean ± SEM. The unpaired Student's t test and non-parametric Mann–Whitney test were used for comparison between two groups.

3 Results and Discussion

In the first series of experiments, it was demonstrated that Vm and Vt of premotor interneurons LPa3 of intact snails do not differ significantly from those in neurons RPa3. This allowed us to combine the results of the measurements for the two interneurons: LPa3 and RPa3 Vm = − 60.1 ± 0.8 mV ($n = 8$) and Vt = 19.3 ± 0.5 mV ($n = 8$). For interneurons LPa3 and RPa3 of trained snails, the values were, respectively, Vm = − 56.1 ± 0.8 mV ($n = 8$) and Vt = 16.0 ± 0.5 mV ($n = 8$). These results are similar to the ones obtained by us earlier [21].

In the next series of experiments, we found that application of MET during 30 min caused a reliable decrease in Vm of premotor interneurons LPa3 and RPa3 of naive snails (from − 60.5 ± 1.7 to − 54.8 ± 0.5 mV) and its increase under subsequent changing of the washing solution on solution with 5-HT (under − 60.0 ± 1.5 mV, reliable difference from the value of the membrane potential after application of MET, $p < 0.01$; unreliable difference from control initial level) (Fig. 1). The change of Vm continued for the first 15–20 min, and then the value of Vm was stabilized for 30 min, we chose this value as the final effect. Similarly, in the trained snails after application of MET, the value of the Vm reliably decreased from − 56.2 ± 0.9 to −51.2 ± 2.5 mV. Here, also the change of Vm continued for the first 15–20 min, and then the value of Vm was stabilized for 30 min, we chose this value as the final effect. The increase in Vm after changing the washing solution to the solution containing 5-HT was not reliable; its value was equal

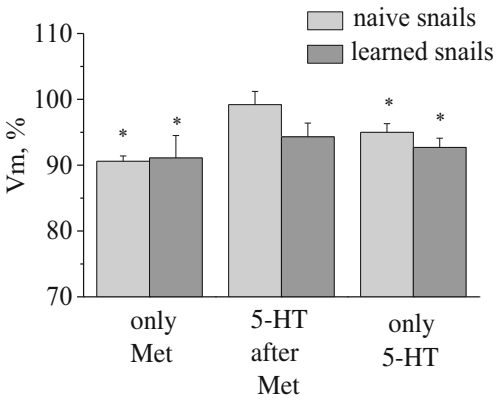

Fig. 1 The effect of the consecutively application of methiothepin (Met) and serotonin (5-HT) into the washing solution on the membrane potential (-Vm) of the premotor interneurons of the defensive reflex LPa3 and PPa3 in intact and trained snails (changes of Vm in %). Met (only)—application of methiothepin ($n = 4$ for intact snails, $n = 5$ for learned snails), 5-HT (after Met)—consecutively application of serotonin after methiothepin ($n = 4$ for intact snails, $n = 5$ for learned snails), 5-HT (only)—application of serotonin without Met ($n = 11$ for intact snails, $n = 13$ for learned snails). Vertical axis shows value of membrane potential, in %, where 100% is equal for Vm before application of substances: Vm = − 59.5 mV for naïve snails and Vm = − 55.5 mV for learned snails. Asterisks (*) indicate significant difference ($p < 0.05$, independent t test and one-way ANOVA) from the level of Vm before application of substances

to − 53.0 ± 1.2 mV (Fig. 1). In the separate groups of naïve and trained animals, the experiments with application in the washing solution of 5-HT alone without the preliminary application of MET were performed. It was shown that the decrease in Vm of premotor interneurons in response to the application of 5-HT was statistically reliable both in naive animals (from − 60.6 ± 0.3 to − 57.6 ± 0.8 mV) and trained animals (from − 56.2 ± 0.7 to − 52.1 ± 0.8 mV) (Fig. 1).

The changes of Vt of premotor interneurons LPa3 and RPa3 in the group of naïve snails as in response to application of MET (from 19.3 ± 0.5 to 19.8 ± 0.8 mV) and after the subsequent replacement, the solution with MET to the solution containing 5-HT (up to 18.5 ± 05 mV) were not reliable (Fig. 2). The change of Vt continued for the first 15–20 min, and then the value of Vt was stabilized for 30 min, we chose this value as the final effect. The reliable changes of the Vt in response to the application of MET (from 16 ± 0.8 to 17.4 ± 0.4 mV) and after the subsequent replacement, the solution with MET to the solution containing 5-HT (up to 17.4 ± 0.4 mV) in the group of trained snails were also not observed (Fig. 2). Here, also the change of Vt continued for the first 15–20 min, and then the value of Vt was stabilized for 30 min, we chose this value as the final effect. In the case of application of 5-HT alone, the reliable changes of the Vt (from 19.7 ± 0.5 to 20.8 ± 0.6 mV) in naive snails were not observed (Fig. 2). However, in the group of trained animals, after application of 5-HT alone, a reliable increase in Vt (from 16.4 ± 0.7 to 19.0 ± 0.9 mV) was observed (Fig. 2).

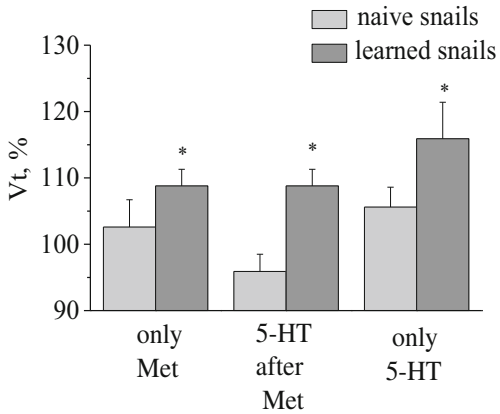

Fig. 2 The effect of the consecutively application of methiothepin (Met) and serotonin (5-HT) into the washing solution on the threshold potential (Vt) of the premotor interneurons of the defensive reflex LPa3 and PPa3 in intact and trained snails (changes of Vt in %). Met (only)—application of methiothepin ($n = 4$ for intact snails, $n = 5$ for learned snails), 5-HT (after Met)—consecutively application of serotonin after methiothepin ($n = 4$ for intact snails, $n = 5$ for learned snails), 5-HT (only)—application of serotonin without Met ($n = 11$ for intact snails, $n = 13$ for learned snails). Vertical axis shows value of threshold potential, in %, where 100% is equal for Vt before application of substances: Vt = 19.3 mV for naïve snails and Vt = 16.0 mV for learned snails. Asterisks (*) indicate significant difference ($p < 0.05$, independent t test and one-way ANOVA) from the level of Vt before application of substances

The 5-HT receptors were described on the soma of the premotor interneurons of a terrestrial snail *Helix lucorum* [15, 17, 22]. 5-HT, applicated locally to these neurons, reversibly decreased acetylcholine-induced input current of these neurons. NAN-190 and methiothepin, the antagonists of 5-HT1 serotonin receptors, prevented the modulatory effect of 5-HT. LY-53.857, ICS-205.930, and SDZ-205.557, antagonists of 5-HT2, 5-HT3, and 5-HT4 serotonin receptors, did not change the modulatory effect of 5-HT. These results demonstrate the specific type of 5-HT receptors in premotor interneurons; however, we have applicated MET in the solution, washing the preparation, so we recorded the integrated response of these neurons, which could modified by the influence of changes in the functions of the all neural network. The possibility of participation of different types of 5-HT receptors in different ways signaling in *Helix pomatia* has also been demonstrated by T. Kiss et al. [23].

MET induces the heterologous downregulation of 5-HT receptors in humans and it does not depend on the normal signaling pathways of 5-HT receptors [24]. It was shown that MET blocks a broadening of the action potential of sensory neurons occurring after application of 5-HT in *Aplysia* [25]. It was assumed that MET-sensitive 5-HT receptors were involved in the postsynaptic mechanism of behavioral sensitization [15]. At that, it was found that the effects of MET do not depend on protein synthesis, i.e., they are caused only by membrane rearrangements [26]. It was also shown that the long-term decrease in the threshold potential caused by 5-HT was blocked by incubation of the nerve segments of *Aplysia* in MET for 30 min before application of 5-HT [27]. Application of MET on uncrushed nerves had no significant effect on the threshold of action potential generation. Induction of long-term habituation by nerve crush was blocked by MET. It is supposed that the main function of 5-HT-induced axonal long-term habituation is that it increases the sensor transmission in close proximity to damaged axons [27].

In recent years, the interest to study of neural processes that determine long-lasting plastic modifications of behavior increased [28–30]. Studies, including ours, demonstrate the important role of membrane properties of neurons and parameters of synaptic transmission in long-lasting plastic modifications of behavior [31–35]. The plasticity of neuronal networks is implemented by increasing of synaptic strength, and by increasing of inner excitability. Currently, in addition to activity-dependent long-term potentiation, it is also discovered the activity dependent changes in the internal excitability (including the activation of the sodium and potassium channels) of pyramidal neurons in hippocampus CA1 region [36].

In our work, we showed that the application of MET leads to a decrease in membrane potential of premotor interneurons LPa3 and RPa3, without affecting on threshold of the action potential generation. Despite the fact that MET is an

antagonist of 5-HT receptors, this effect is similar to the action of the 5-HT. At the same time, the substitution of washing solution for the solution with 5-HT, following after MET application, led to restore of the Vm to the previous level (the level corresponding to the level of the Vm of neurons LPa3 and RPa3 of naive snails before drugs application). By the way, there are similar results in the literature. So, MET activated ApTrkl (tropomyosin-related kinase) receptors in *Aplysia*, exactly the same way as 5-HT [37]. However, during application of MET and 5-HT together, the additive effect was not observed. Thus, during activation of ApTrkl receptors, MET acts as an agonist of 5-HT [37]. Probably, as in our study, MET linked the same site as 5-HT and caused conformational changes corresponding to an inactive state of the receptor. On the other hand, it is possible that the reason for these changes may be associated with the conduction of signals through different paths in the neural network.

During further consideration of the effects of MET, in the case of trained animals, a difference in the comparison with naive animals was found. The procedure of the replacement of the solution contained MET, for the solution with 5-HT, did not lead to the same restoration of the membrane potential to the previous level as in the preparations of naive animals. In addition, it was found that the change Vt in response to applications of only 5-HT was reliable in the case of trained animals. This suggests that training leads to a decrease of excitability of premotor interneurons of trained animals in response to the application of 5-HT. On the other hand, the excitability of these neurons increases after the learning procedure. However, the fact that a learning procedure leads to a change in the reaction to serotonin of premotor interneurons deserves attention and is another correlate of learning at the level of the neuronal network especially if you remember about the important role of 5-HT in the phenomenon of defensive reflexes conditioning.

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