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Locomotor Responses and Neuron Excitability in Conditions of Haloperidol Blockade of Dopamine in Invertebrates and Vertebrates

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Levels of movement activity were used to identify two groups of rats: those with high- and low-activity levels. Blockade of dopamine receptors with haloperidol led to suppression of locomotor activity in both groups of rats; in common snails, haloperidol decreased the rate of locomotion. The excitability of spinal centers in rats decreased 5 min after single i.v. injections, with gradual recovery seen by 30 min. Chronic administration of haloperidol suppressed post-tetanic potentiation of the H response in the gastrocnemius muscle of spinal rats. Prolonged use of haloperidol induced significant hyperpolarization of the membrane potential of command neurons in common snails and increased the action potential generation threshold. Selective pharmacological exclusion of the brain dopamine system was found to lead to decreases in the excitability of defined neurons in snails and the spinal motor centers in rats, also producing impairments in locomotor responses in these animals.

KEY WORDS: haloperidol, dopamine, locomotor activity, neuron excitability, membrane potential, threshold potential, gastrocnemius muscle reflex H response.

The brain dopaminergic system is known to be involved in the execution of a variety of functions, including motor functions [4, 5, 9, 14, 17, 18, 21, 24, 31]. The brain dopaminergic system has also been shown to have modulatory functions in the integrative activity of the body, including emotions, motivation, learning, memory, etc. ([6, 8, 28, 29] and others). The dopaminergic mechanisms underlying motor functions have been shown to have different pharmacological properties. The question of the role of the dopaminergic system in motor activity mediated by spinal centers can be addressed in studies involving both inhibited synthesis and accumulation of dopamine and blockade of dopamine receptors [1, 18]. Depletion of dopamine or blockade of its receptors leads to abnormalities in brain activity and particularly to defects in the motor systems. Thus, experiments on mammals have demonstrated that alterations in monoamine metabolism in the brain and in the activity of monoaminergic receptors in animals leads to the formation of pathological behaviors [20]. Overactivity of dopaminergic mechanisms may be the basis of a number of nervous system diseases. The unwanted appearance of this type of activity can be eliminated by blocking dopamine receptors with neuroleptic agents. Haloperidol [30] is an agent with calming actions on all types of mental activity and is widely used in the treatment of a variety of neurotic states, particularly those with severe impairments of nervous system activity. The effects of haloperidol result from a decrease in the level of excitation of dopamine neurons and blockade of postsynaptic receptors, as it is an antagonist of dopaminergic neurons [2, 3, 11, 12, 15, 16, 18, 25–27]. Thus, the actions of haloperidol are pharmacologically suitable for studying the role of the

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dopaminergic system. The aim of the present work was to investigate the mechanism of action of haloperidol on the state of nerve centers and motor responses on the basis of comparative studies of the effects of this agent on behavior and the electrical activity of nerve centers in vertebrates and invertebrates.

METHODS

Experiments addressing locomotor responses were performed using 82 adult white mongrel rats weighing 200–250 g. The classical Holl method [22] was used in the open field to study orientational-investigative activity in the rats. The open field was a platform of size 100 × 100 cm, divided into 25 squares of size 10 × 10 cm and surrounded by a barrier of height 40 cm; the nine central squares were regarded arbitrarily as the center of the field, where the animal was placed at the start of the experiment. The field was illuminated with two 150-W lamps. Observations were continued for 5 min. Counts were made of the numbers of squares crossed (horizontal orientational activity), the numbers of rearings on the hindlimbs (vertical investigative activity), and the numbers of grooming episodes in control and experimental animals. Haloperidol was given i.p. at doses of 0.1 and 0.5 mg/kg 1 h before testing the animals' behavioral responses, or daily for seven days at the same doses, when testing was performed on the third and seventh post-injection days. Control animals received the same volumes of physiological saline at the same times.

The excitability of nerve centers was assessed in terms of electrical processes recorded in the gastrocnemius muscles in chordotomized rats immobilized on their backs. As a preliminary procedure, animals anesthetized with ether underwent spinal cord section at the level of the first and second thoracic vertebrae and the sciatic nerve was prepared. Spinal nerve center excitability was assessed in terms of the H reflex 1.5 h after spinalization. The sciatic nerve was stimulated via inserted bipolar electrodes using square-wave stimuli of duration 0.3 msec from an ÉSL-2 stimulator; gastrocnemius muscle reflex and motor responses were recorded with bipolar needle electrodes. Muscle electrical activity was recorded using a Medikor myograph. The threshold, latent period, and dynamics of responses to stimuli of increasing intensity were assessed before and after treatment with agents. The post-tetanic potentiation effect was induced by conditioning stimulation of the sciatic nerve at a frequency of 200 Hz for 5 sec, with single tests performed every 10 sec for 2 min. Paired-pulse stimuli applied to the sciatic nerve with intervals ranging from 1 to 200 msec were used to study inhibitory processes in the spinal cord. In this series of experiments, haloperidol was given into the tail vein at a dose of 0.05 mg/kg; chronic dosage was given over seven days at an i.p. dose of 0.1 mg/kg; changes in the state of spinal centers were studied on days 3 and 7 in acute conditions. Control animals received injections of physiological saline by the same protocol. Data were analyzed statistically using Origin and assessed using Student's *t* test.

The second part of the study was performed on the terrestrial gastropod pulmonate mollusk *Helix lucorum*. Before experiments, animals were kept for at least two weeks in the active state in a glass terrarium in a humid atmosphere at room temperature (18–22°C) and an excess of food. Experiments were performed using animals of similar body weight (about 20 g). Aqueous haloperidol (1 mg/kg) was given with a syringe daily for seven days in the area of the sinus node. Active controls received injections of the same volume of physiological saline for common snails at the same times as in the experimental series. Studies were performed on 20 snails, with 10 in each series of experiments. Experiments assessed the animals' defensive responses (the time of pneumostoma closing, i.e., the duration of its closed state was recorded) after application of tactile stimuli with a bundle of fibers in the area of the mantle ridge, and the rate of locomotion was measured in terms of the distance traveled by the mollusk per minute on the vertical wall of the glass terrarium.

In the next series of experiments, injections were followed by use of a standard microelectrode method to study the electrical characteristics of defensive behavior command neurons LPa3, RPa3, LPa2, and RPa2 [10] in isolated snail central nervous systems. This series of experiments also used 20 snails, with measurements made on 30 neurons, 15 after injection of physiological saline and 15 after chronic administration of haloperidol. Before preparation of nervous systems, animals were cooled in iced water for 15–30 min for anesthesia. Recordings were made of the membrane resting potential (V_m) and the threshold potential (V_t). The threshold potential was measured from the cell resting potential to the evoked response. Biopotentials were recorded using an ADC directly into the computer. All data were analyzed statistically on Origin and assessed using Student's *t* test.

RESULTS

In studies of motor responses in the open field test, control rats were divided into two groups in terms of the level of activity: group I were animals with high levels of activity and group II were those with low activity. During the 5-min test period, animals of group I crossed an average of 40.5 ± 0.6 squares, reared onto the hindlimbs 14.6 ± 0.7 times, and performed 4.1 ± 0.4 episodes of grooming. In group II, horizontal activity averaged 15.3 ± 0.5 squares, vertical activity averaged 8.4 ± 0.3 rearings, and grooming averaged 2.1 ± 0.5 episodes. Rats previously adapted to and tested in the open field were given i.p. haloperidol and locomotor responses were retested after 1 h. This revealed significant suppression of all components of orientational-

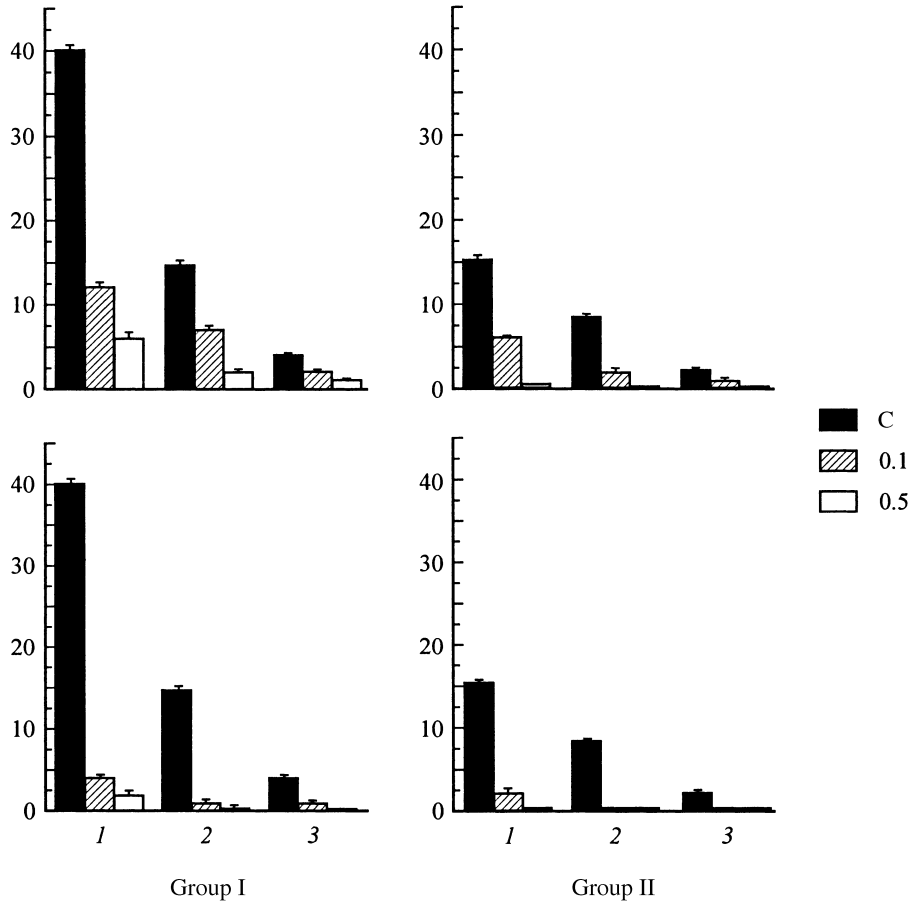

Fig. 1. Locomotor activity in rats after single (above) and chronic (below) doses of haloperidol. The horizontal axes show types of movement activity: *1*) horizontal; *2*) vertical; *3*) grooming; the vertical axes show the numbers of actions. C = control group; 0.1 and 0.5 identify series of experiments with haloperidol at these doses (mg/kg).

TABLE 1. Effects of Haloperidol on Locomotor Responses in Rats of Groups I and II

Types of activity and groups of animals	Number of rats, *n*	Controls	Haloperidol					
			One hour		Chronic injections			
			0.1 mg/kg	0.5 mg/kg	0.1 mg/kg		0.5 mg/kg	
					day 3	day 7	day 3	day 7
Group I	18							
Horizontal		40.1 ± 0.6	12.2 ± 0.8*	6.4 ± 0.8*	10.4 ± 0.5*	4.3 ± 0.4*	4.3 ± 0.8*	1.8 ± 0.6*
Vertical		14.6 ± 0.7	7.3 ± 0.3*	2.3 ± 0.3*	3.2 ± 0.3*	1.0 ± 0.4*	1.2 ± 0.6*	0.3 ± 0.5*
Grooming		4.1 ± 0.4	2.1 ± 0.3*	1.3 ± 0.1*	1.1 ± 0.6*	1.3 ± 0.3*	0.7 ± 0.5*	–
Group II	18							
Horizontal		15.3 ± 0.5	6.3 ± 0.1*	0.4 ± 0.1*	5.3 ± 0.1*	2.2 ± 0.1*	0.1 ± 0.05*	–
Vertical		8.4 ± 0.3	2.0 ± 0.1*	–	1.0 ± 0.1*	–	–	–
Grooming		2.1 ± 0.5	1.0 ± 0.1	–	1.0 ± 0.1*	–	–	–

Note. * Significant differences from control, $p < 0.05$.

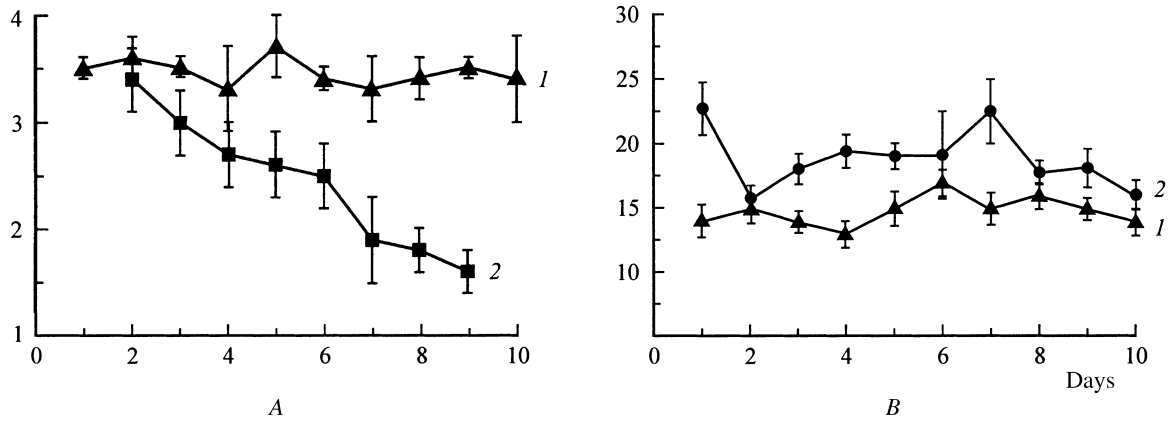

Fig. 2. Effects of haloperidol on locomotion and defensive responses in snails given chronic haloperidol (1 mg/kg) for seven days. *A*) Dynamics of changes in the speed of locomotion in intact snails and snails treated with haloperidol; *B*) dynamics of changes in pneumostoma responses in intact snails and snails given haloperidol. The abscissa shows time, days; the ordinate in *A* shows the speed of movement, cm/min; the ordinate in *B* shows changes in the pneumostoma response, sec. *1*) Intact snails; *2*) snails given haloperidol.

TABLE 2. Parameters of M and H Responses in the Gastrocnemius Muscle in Spinal Rats in Conditions of Stimulation of the Sciatic Nerve

Series of experiments	Number of rats, *n*	M response			H response			$H_{max}/M_{max} \times 100\%$
		Threshold, V	LP, msec	Amplitude, mV	Threshold, V	LP, msec	Amplitude, mV	
Controls	16	0.6 ± 0.1	1.7 ± 0.1	1.9 ± 0.1	1.3 ± 0.1	3.5 ± 0.1	0.3 ± 0.1	15.7 ± 0.1
HAL, 5 min	15	0.8 ± 0.1*	1.7 ± 0.1	1.5 ± 0.1*	–	–	–	–
HAL, 30 min	15	1.0 ± 0.1*	1.7 ± 0.1	1.3 ± 0.1*	2.3 ± 0.1*	3.8 ± 0.1	0.2 ± 0.1*	15.3 ± 0.1
HAL, 7 days	15	1.0 ± 0.2*	1.7 ± 0.2	1.4 ± 0.1*	1.7 ± 0.1*	3.7 ± 0.2	0.2 ± 0.1*	14.2 ± 0.1*

Notes. * Significant difference from controls, $p < 0.05$. LP = latent period.

investigative responses in animals of both groups (Fig. 1, Table 1). In group I, horizontal movement activity decreased by averages of 70% and 85% after doses of 0.1 and 0.5 mg/kg respectively. In group II, these decreases were by 60% and 97% (for more detail see Table 1 and Fig. 1). Chronic haloperidol also led to progressive decreases in the rats' movement activity from the third to the seventh observation days. On day 7, changes were more marked: horizontal movement activity decreased by an average of 90% to the level of complete disappearance of some responses in rats of group II (Fig. 1, Table 1).

Chronic administration of haloperidol to common snails resulted in decreased locomotion. This decreased two-fold over seven days, as compared with controls (Fig. 2, *A*). The linear relationship between speed and leg length in snails did not change after injections of haloperidol. Measures of defensive responses were not significantly different before and after treatment (Fig. 2, *B*).

Studies of the electrical characteristics of command neurons in common snails were performed by applying square-wave current impulses of duration 1 sec, inducing action potentials. Stimulus intensity was selected to be minimal for generation of action potentials and varied from 1.7 to 3.5 nA. Measurements of the electrical characteristics of defensive behavior command neurons showed that administration of haloperidol led to membrane hyperpolarization in neurons LPa3, RPa3, LPa2, and RPa2. The resting potential showed hyperpolarization changes by 9 mV after seven days of haloperidol injections; the threshold potential (V_t) increased by some 3 mV (Fig. 3).

The excitability of spinal centers in rats was studied by the H response method. Application of single stimuli to the sciatic nerve induced two responses in the gastrocnemius muscle of rats: a motor M response with a short latent period (1.7 ± 0.1 msec) and an H response with a longer latent period (3.5 ± 0.1 msec). Increases in stimulation intensity led to characteristic changes in the amplitude dynamics of these responses. As shown in Table 2, the threshold for M responses in controls averaged 0.6 ± 0.1 V; increases in the stimulus intensity led to increases in the response amplitude, to a maximum of 1.9 ± 0.1 mV. I.v. injections of haloperidol were followed 5 and 30 min later by 25% and 56% increases in the threshold of the M response compared with controls. The amplitude of this response did not reach

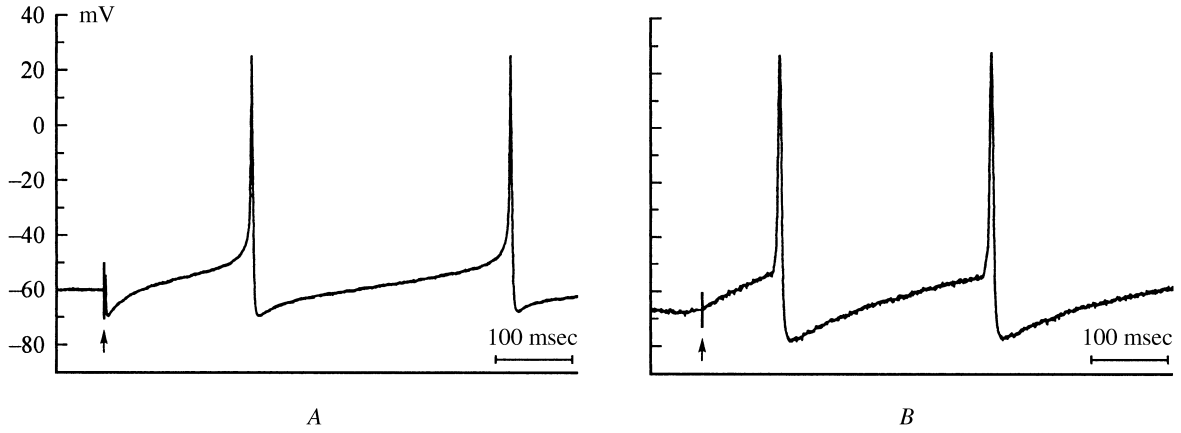

Fig. 3. Membrane potential (V_m) and action potential generation threshold (V_f) in defensive behavior command neurons (LPa3, RPa3, LPa2, and RPa2) in snails given physiological saline (*A*) and snails given haloperidol (1 mg/kg) for seven days (*B*).

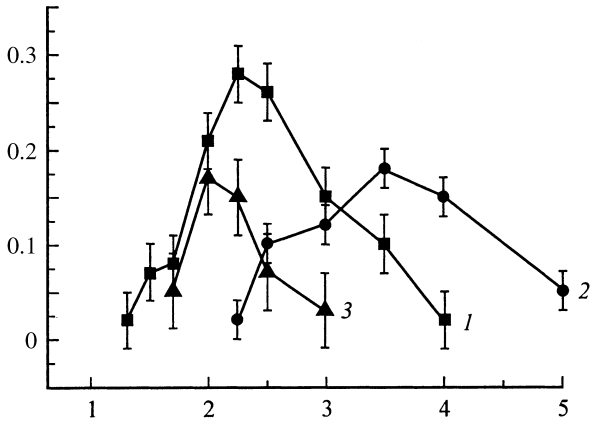

Fig. 4. Dynamics of the amplitude of reflex H responses in the gastrocnemius muscle in rats after single and chronic doses of haloperidol. The abscissa shows stimulation strength, V; the ordinate shows amplitude, mV. *1*) H response of the gastrocnemius muscle in controls; *2*) 30 min after i.v. haloperidol (0.1 mg/kg); *3*) seven days after i.p. injections of haloperidol (0.1 mg/kg).

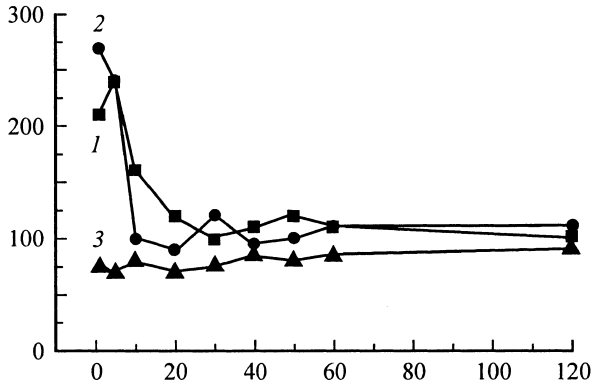

Fig. 5. Post-tetanic potentiation of the reflex H response of the gastrocnemius muscle in rats. The abscissa shows time, sec; the ordinate shows amplitude, %. *1*) Controls; *2*) single doses of haloperidol; *3*) chronic haloperidol.

the control level and values were 80% and 69% of initial at 5 and 30 min respectively. In rats given i.p. haloperidol for seven days, the parameters of the M response were similar to changes seen 30 min after i.v. doses.

The reflex H response in controls appeared at an average stimulus strength of 1.3 ± 0.1 V; its maximum amplitude was 0.3 ± 0.1 mV. Reflex activity was completely suppressed 5 min after haloperidol injections; at an average stimulus strength of 2.3 ± 0.1 V, the H response recovered at 30 min, though the maximum amplitude was 32% less than in controls. Chronic i.p. haloperidol also led to changes in reflex excitability: the threshold of the H response was 30% greater than control, the maximum amplitude was 35.8% lower, and the dynamics were significantly shorter than in controls (Fig. 4).

Studies of the effects of post-tetanic potentiation in controls showed that 5 sec after the end of conditioning tetanization of the sciatic nerve there was an increase in the amplitude of the H response of the gastrocnemius muscle in response to single test stimuli by 140% of initial. Recovery of reflex responses to the control level was seen at 20–30 sec. The maximum amplitude of the H response after i.v. injections of haloperidol was 260% at 1 sec of the test stimulus and recovery of the response to the control level was noted earlier – at 10 sec, which was twice as fast as in controls. The post-tetanic potentiation effect was not seen after

chronic i.p. administration of haloperidol. After conditioning tetanization, the response to the test stimulus in this series of experiments was followed by depression of the amplitude of the H response by an average of 12.5% of its initial value, which lasted 30–40 sec with subsequent recovery of reflex excitability to the initial level at 100–120 sec of testing (Fig. 5).

Thus, these results established that i.v. injections of haloperidol completely suppressed the excitability of spinal centers in the first minutes, with gradual recovery of reflex responses over the next 30 min, though not to the level of maximum H response amplitudes seen in controls. Chronic administration of haloperidol significantly decreased the excitability of spinal centers and blocked the post-tetanic potentiation effect.

DISCUSSION

The present studies identified two groups of rats differing in terms of the nature of their movement activity: high- and low-activity rats. Published data show that the extents of motor responses can result from different levels of activity in brain neurotransmitter systems. As long ago as the 1960s, it was demonstrated that the serotoninergic and catecholaminergic brain systems are involved in the central mechanisms controlling motor activity. These systems are in a reciprocal relationship, which refers to both antagonism between these systems and mutual regulation: increases in the activity of one system are accompanied by decreases in the activity of the other and vice versa [34]. It has been suggested that the serotoninergic system is dominant in low-activity animals, while the catecholaminergic system is dominant in high-activity animals [20]. However, the present study demonstrated significant suppression of movement activity in rats with different levels of locomotor reactions in conditions of pharmacological interruption of the dopaminergic system, which leads to the conclusion that this system has the predominant role in maintaining the locomotor system. The significant role of the dopaminergic system in locomotor activity is evidenced by our results in the common snail, which demonstrate significant decreases in the rate of locomotion but not the magnitude of defensive responses in conditions of chronic administration of haloperidol.

In the open field test, rats showed suppression of the orientational-investigative responses both one hour after single i.p. injections of haloperidol and in conditions of chronic administration of haloperidol at different doses. Behavioral responses were sharply suppressed seven days after administration of this dopamine receptor blocker. The common snail also showed suppression of motor activity, evident as a two-fold decrease in the speed of locomotion after chronic (seven days) treatment with haloperidol. These results provide evidence for the involvement of the brain dopaminergic system in controlling movement activity in the vertebrate and invertebrate species studied here. There was a relationship between the degree of suppression of rat motor responses and the haloperidol dose and the duration of treatment. Changes in the behavior of rats with pharmacological lesions to the brain dopaminergic system in our studies agreed with neurochemical data obtained by a number of contemporary authors, who also reported roles for brain dopaminergic structures in organizing the whole spectrum of adaptive behaviors [7]. The literature contains reports on the ability of haloperidol to induce the state of fear [23, 32, 33]. Orlova et al. [13] showed that rats spent more time in the center of the field the day after administration of haloperidol at a dose of 2.5 mg/kg, along with display of an ethological fear posture, in the open field test in conditions of uniform daytime illumination; these manifestations were interpreted as anxiety. Dopamine release in the neostriatum has been shown to create the conditions for increases in investigative activity, while dysbalance in dopamine metabolism in the dorsal and ventral striatum may be the cause of behavioral passivity [19].

Electrophysiological studies showed that haloperidol induced changes in the state of excitability of spinal centers in rats. Reflex excitability was decreased during the first minutes after haloperidol doses and it was not possible to elicit the H reflex. There was an increase in the threshold for appearance of the H response 30 min after injections, with a decrease in its amplitude and a decrease in the duration of the reflex response as compared with controls. Chronic administration of haloperidol led to similar changes. The threshold of appearance and the dynamics of the M response amplitude were also significantly altered by haloperidol. This agent probably induced the development of inhibitory processes in the peripheral neuromuscular synapse. The ratio of the maximum amplitudes of the reflex and motor responses showed no significant change after single injections of haloperidol, demonstrating retention of the motoneuron pool involved in the response; the significant changes in the threshold values of the reflex responses provided evidence for a decrease in the excitability of spinal centers. However, the post-tetanic potentiation responses of control and experimental animals in this series showed no significant difference, demonstrating retention of the motoneuron pool involved in the response to the conditioning stimulation. Chronic administration of haloperidol led to more profound changes in the excitability of spinal centers in rats. In particular, there was no post-tetanic potentiation of the reflex response, and the ratio of the maximum values of the M and H responses decreased significantly. It is probable that destructive changes in neurons in this case were more significant and the motoneuron pool in the centers of interest was damaged. This is evidenced by our morphological studies of the state of the motoneurons in the lumbar segments of the spinal cord of rats given haloperidol [6].

We observed significant changes in the membrane potential and action potential generation threshold in identified neurons in the common snail. These results provide direct evidence for a decrease in the excitability of these cells, mainly because of a significant hyperpolarization of the membrane potential. The brain dopaminergic system probably provides one of the leading types of control of the locomotor function of nerve centers in various types of animal, and hyperpolarization changes in the membrane potential may be one of the mechanisms of this type of regulation.

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