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Effects of the GABA Receptor Agonist Phenibut on Behavior and Respiration in Rabbits in Emotionally Negative Situations

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Three groups of rabbits differing in terms of movement activity in an open field (active, passive, and intermediate animals) were used to study the effects of systemic administration of the GABA receptor agonist phenibut (40 mg/kg, s.c.) on behavior in the open field, behavioral reactivity, and changes in measures of respiration during exposure to emotionally negative stimuli. Phenibut administration led to decreases in horizontal movement activity and some elements of investigative behavior in rabbits in the open field, along with decreases in the reactivity of the animals to emotionally significant stimuli. There were reductions in the probabilities of both active (orientational-investigative, active defensive) and passive defensive (freezing) reactions. The effects of phenibut depended on the typological characteristics of the rabbits: its actions on behavior were most marked in active rabbits and were less marked in passive animals; phenibut had virtually no effect on the behavior of intermediate rabbits. The duration of inhalation by the rabbits on exposure to emotionally significant stimuli increased after phenibut, which contrasted with a reduction seen in normal animals; this is evidence for changes in the autonomic reactivity of the animals.

KEY WORDS: open field, behavior, GABA receptor agonist, external respiration.

The behavior of animals in emotionally negative situations is known to be determined to a significant extent by the levels of anxiety, fear, and tension, the extents of which differ between animals of different typological groups. According to published data [6], GABAergic receptor agonists and benzodiazepine tranquilizers, which activate $GABA_A$ receptors [11], decrease fear and anxiety; this has been demonstrated in a variety of behavioral models in animals [1, 9, 16–18, 21, 24, 25, 27, 28, 30]. According to the concepts of Grey [3], increases in GABAergic inhibition lead to both a reduction in the activity of the "fight-or-flight" system and to blockade of the "behavioral inhibition" system, which determines the state of anxiety in humans and animals and organizes responses to notional aversive stimuli.

One agonist of GABA receptors acting predominantly on $GABA_B$ receptors is the Russian preparation phenibut, whose tranquilizing effect was first demonstrated in the studies of Khaunina [12]. Phenibut is now widely used in psychiatry and neurology [13], and it has been noted that its anxiolytic effect is weaker than that of the benzodiazepine tranquilizers. Previous studies have shown that on acquisition of classical defensive conditioned reflexes, prolonged systemic administration of phenibut before experiments accelerated the acquisition of conditioned inhibition [4], while single doses improved the discrimination of positive and inhibitory stimuli [14]. These data provided significant support for the hypothesis developed in Livanov's laboratory regarding the role of inhibitory hyperpolarizing processes for the development of internal inhibition [14].

This led naturally to the question of whether phenibut, given at the doses and time intervals at which it was seen to have a positive effect on internal inhibition, changes the free behavior of rabbits, as well as their behavioral and autonomic reactivity in emotionally negative situations. Judging from published data, the effects of systemic administration of GABA agonists may be different and may show a significant dependence on the dose given [17, 27], while the

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TABLE 1. Numbers of Rabbits of Different Typological Groups whose Behavior was Analyzed in the Open Field and on Exposure to Emotionally Significant Stimuli With and Without (Controls) Phenibut

Group of rabbits	Open field			Stimuli	
	First setting	Second setting (control)	Second setting (phenibut)	Control	Phenibut
I	11	7	4	9	5
II	10	3	5	9	8
III	7	3	3	4	3
Total	28	13	12	22	16

Note. I) passive, II) intermediate-activity, III) active rabbits.

influence of phenibut in emotionally negative situations has not received adequate study [1, 9, 12]. It is unclear whether animals of different typological groups differ in their sensitivity to phenibut. The literature contains data on differences in individual sensitivity to benzodiazepine tranquilizers, morphines, and alcohol [2, 5, 20]. The aim of the present work was to study the effects of systemic administration of phenibut on behavior in the open field, behavioral reactivity, and the reactivity of external respiration during exposure to emotionally negative stimuli in rabbits of different typological groups (active, passive, and intermediate in the open field). The pattern of external respiration, as previously demonstrated [7, 8], is a measure of the functional state of the animal and can serve as a prognostic sign for the passive defensive reaction (freezing).

METHODS

Experiments were performed in chronic experimental conditions on 28 Chinchilla rabbits weighing 2.6–3.4 kg. At the first stage, all animals were tested in the open field, which was a round arena of diameter 131 cm with walls 37 cm high. The floor of the arena was divided into 32 squares (sides were of length 21 cm), among which four were central, 12 were intermediate, and 16 were side squares. At the beginning of the experiment, the animal was placed in the center of the open field. The observation time was 10 min. The following parameters were measured every minute and overall for the whole observation period: 1) horizontal investigative movement activity (numbers of jumps, runs, squares crossed); 2) vertical activity (number of rearings, and also the number of attempts to gnaw the walls or floor of the chamber); 3) grooming (number of episodes of washing, shaking, and scratching); 4) motor asymmetry (numbers of right and left turns); 5) social behavior (number of episodes of marking the chamber – the rabbits rubbed their snouts against the floor and walls of the chamber); 6) aggressive behavior (number of strong blows with the hindpaws against the floor and walls of the chamber); 7) emotional tension (number of boluses); and 8) passive-defensive behavior (latency of excursion from the central squares after animals were set in the chamber, and also freezing time). Analysis of the rabbits' behavior in the open field on the first setting allowed three groups of animals to be identified, differing in terms of the numbers of squares crossed – passive (11 rabbits, less than 50 squares), intermediate (10 animals, 50–100 squares), and active (seven rabbits, more than 100 squares). More detailed differences between groups of rabbits have been described previously [7]. Table 1 shows data on the numbers of rabbits assigned to the different groups.

Most of the animals were retested in the open field at 7–14 days. Twelve animals received s.c. phenibut (40 mg/kg) dissolved in 3 ml of physiological saline 2 h before the experiment (the experimental group), while 13 (the control group) either received physiological saline (3 ml, nine animals) or were intact (four rabbits). The experimental and control groups of rabbits included both passive, active, and intermediate animals (see Table 1). Data processing included assessment of the influences of the parameters ("phenibut administration" and "setting No." by dispersion analysis (ANOVA–MANOVA) using the F test run on the standard Statistica 5.5 program; the behavior of animals of different groups was compared using the least significant difference criterion.

In the second part of the study, the behavior of 22 rabbits was studied in a small, comfortable, cylindrical chamber with a round bottom of diameter 45 cm and walls of height 32 cm. Various emotionally significant stimuli were used; these evoked orientational-investigative, active defensive, and passive defensive (freezing) reactions in the rabbits. Sound stimuli (rustling at 30–40 dB, or loud white noise at 60–80 dB) were presented for 7–10 sec and evoked predominantly orientational-investigative reactions and, more rarely, freezing. Pressure on the nape of the neck for 7 sec led to the appearance of active attempts to escape, which was followed by freezing of different durations. Suspension by the nape of the neck initially induced freezing, when the rabbit dangled without moving, and then active defensive actions, when the animal was lowered to the floor. Vibroacoustic stimulation of the pinna at threshold intensity

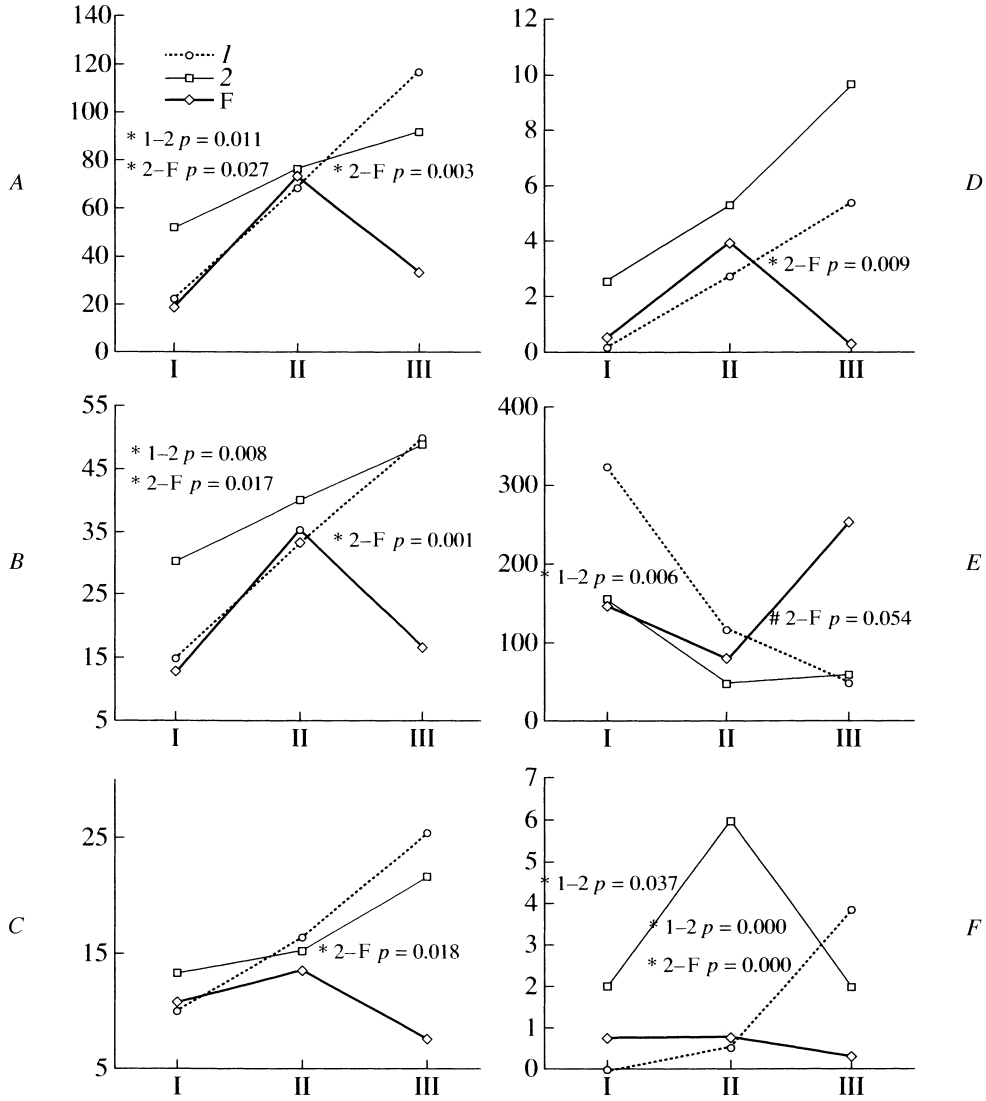

Fig. 1. Comparison of various measures of the activity of rabbits in the open field on the first setting (*1*), the second setting without treatment (*2*), and the second setting with phenibut (F) in different groups of rabbits. The vertical axes show: *A*) number of squares crossed; *B*) number of runs; *C*) total number of turns; *D*) number of grooming acts (washing, shaking, scratching); *E*) total freezing time (sec); *F*) number of cases of gnawing. I) Passive; II) intermediate-activity; III) active rabbits. *Significant within-group differences in data for first and second settings (1–2), on the second setting without treatment and with phenibut (2–F); #tendency to changes; *p* = level of significance.

led to the appearance of active shaking movements and, more rarely, freezing. Stimulation parameters and the orders in which stimuli were used have been described in more detail elsewhere [8]. Behavior on exposure to emotionally significant stimuli on the background of phenibut was studied in 16 of the 22 rabbits (Table 1). In some experiments, stimuli were initially presented without any treatment (control); phenibut was then given (40 mg/kg, s.c.) and stimulus application was repeated 2 h later. In other experiments, phenibut was given 2 h before the start of the experiment. Each rabbit took part in 20 experiments without phenibut and the same number with phenibut, during which a total of up to 50 applications of the same stimulus were made. The mean proportions (%) of active and passive (freezing) reactions were calculated for each stimulus for each animal before and after administration of phenibut. Statistical processing of data involved comparison of different groups of rabbits before and after administration of phenibut by dispersion analysis (ANOVA–MANOVA) run on Statistica 5.5.

During experiments, a needle probe was used to record the pneumogram and mechanogram from the rabbits. The nature of the animals' responses was assessed visually and

TABLE 2. Comparison of Averaged Measures of the Behavioral Reactions of Rabbits on Exposure to Different Stimuli in Controls and after Phenibut

Behavioral reactivity	Control (n = 22)	Phenibut (n = 16)	p
Proportion of orientational-investigative movements to sound stimuli, %	73.2	48.1	0.005
Proportion of freezing to sound stimuli, %	11.2	1.0	0.027
Proportion of active defensive reactions during pressing, %	50.8	14.7	0.014
Proportion of freezing after pressing, %	70.0	24.9	0.000
Duration of freezing after pressing, sec	21.9	10.2	0.001
Duration of immobility on suspension by the nape of the neck, sec	23.0	28.0	0.046
Proportion of shaking in response to vibroacoustic stimulation of the ears, %	64.9	69.8	0.8
Proportion of freezing in response to vibroacoustic stimulation of the ears, %	9.5	3.7	0.37

Notes. p is the level of significance on comparison using the F test (ANOVA); n is the total number of rabbits used for calculation of the mean.

in terms of changes on the mechanogram and pneumogram, which were recorded on a pen recorder. According to previous data [8], reductions in respiratory rate and increases in the duration of exhalation were taken as measures of freezing.

More detailed analysis of rabbit pneumograms was performed in some experiments, using traces of duration 10–15 sec with the rabbit not moving, before and after different treatments. Traces were scanned and digitized using the Paint program. The durations of the respiratory cycle and inhalation and exhalation were measured. The methods for analyzing respiration have been described in detail elsewhere [7, 8]. Each trace fragment contained 20–40 respiratory cycles. Comparison of different respiratory parameters before and after treatments was performed using the Mann–Whitney test run on Statistica 5.5, differences being taken as significant at $p < 0.05$. The percentages of cases with increases and decreases in different respiratory parameters were compared in rabbits after emotionally significant stimuli before and after phenibut administration. Comparison of percentage ratios used 2×2 linkage tables and the χ^2 test, differences being taken as significant at $p < 0.05$; tendencies to change were recorded at $p > 0.05$.

RESULTS

1. Effects of phenibut on the behavior of rabbits in the open field. On repeat setting in the open field, the behavior of control rabbits changed mainly in passive animals (Fig. 1): as compared with the first setting, passive rabbits crossed a larger number of squares (p = 0.011), made more runs (p = 0.008), and froze for a smaller amount of time (p = 0.006); passive and intermediate rabbits more often gnawed the walls and floor of the chamber (p = 0.037 and 0.000, respectively).

The data from these experiments showed that the effects of phenibut was evident on comparison of the second setting in the control and experimental groups of rabbits. On comparison of all rabbits, experimental animals on the second setting crossed fewer squares (p = 0.029), made fewer runs (p = 0.005), and gnawed the walls and floor of the chamber less (p = 0.001) after phenibut treatment as compared with the control group. Comparison by individual groups of animals showed (Fig. 1) that changes in the behavior of rabbits after phenibut were seen in a large number of measures and were most marked in active animals; passive animals showed smaller changes in behavior, while intermediate rabbits showed virtually no change in behavior. In active animals, phenibut significantly decreased the number of squares crossed, the number of runs, the total number of turns, and the number of grooming acts; there was a tendency to an increase in the immobility time. In passive animals, there were changes in the number of squares crossed and the number of runs. The only change in intermediate rabbits was a reduction in the number of attempts to gnaw the chamber. Phenibut had no effect on the latent period of excursion from the central squares after setting, on the number of rearings, the number of marking episodes, the number of forceful blows with the hindlimbs against the floor, and the number of boluses. Thus, phenibut decreased the horizontal investigative movement activity of the rabbits in the open field and produced behavioral impoverishment. The most phenibut-sensitive were active rabbits; passive rabbits were less sensitive, and intermediate rabbits showed virtually no changes in behavior.

2. Effects of phenibut on Behavioral Reactivity of Rabbits on Exposure to Emotionally Significant Stimuli. Phenibut decreased behavioral reactivity when results were summed for all rabbits (Table 2). The number of orientational-investigative reactions to sound stimuli decreased from 73.2% to 48.1% and the number of episodes of freezing in response to these signals decreased from 11.2% to 1.0%. During pressing on the nape of the neck, the number of active defensive reactions decreased from 50.8% to 14.7%, and the number of episodes of freezing and their mean duration also decreased (from 70.0 to 24.9 and from 21.9 to 10.2 sec, respectively). The latent period of appear-

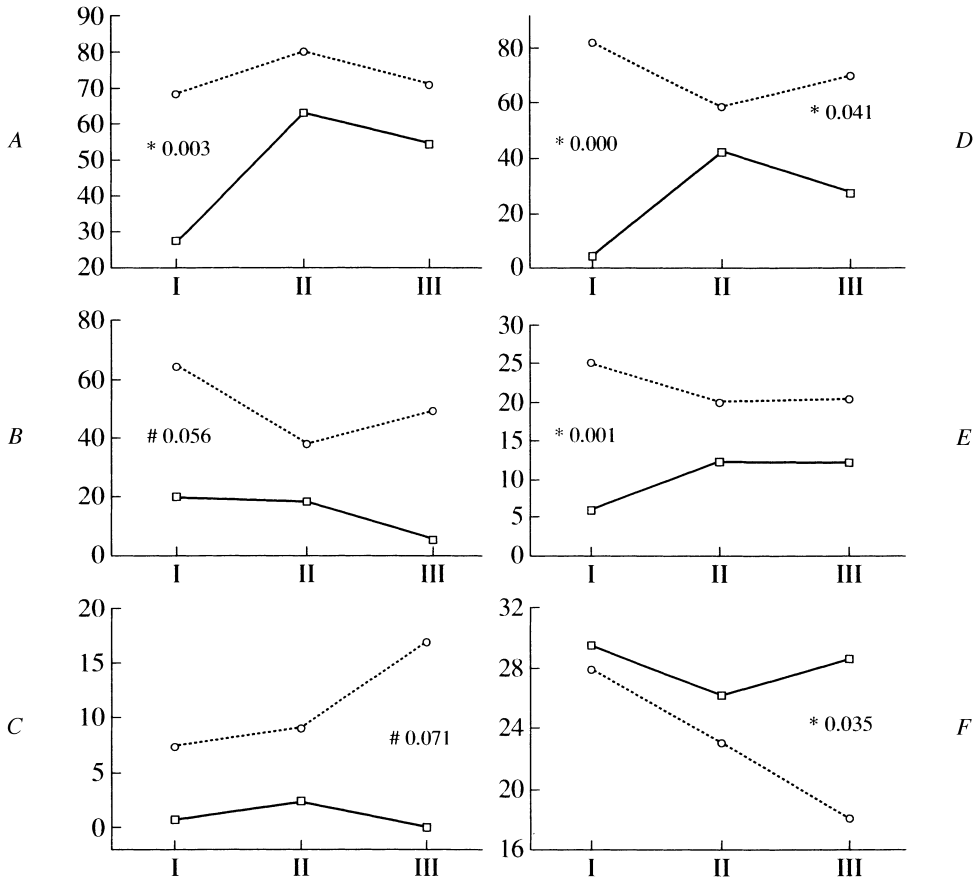

Fig. 2. Comparison of the behavioral reactivities of rabbits on presentation of emotionally significant stimuli in normal conditions (dotted line) and after phenibut (continuous line) in different groups of rabbits. *A*) Proportion of orientional-investigative movements in response to sound stimuli, %; *B*) proportion of active defensive responses during pressing on the nape of the neck, %; *C*) proportion of freezing in response to sound stimulation, %; *D*) proportion of freezing after pressing on the nape of the neck, %; *E*) freezing time after pressing, sec; *F*) immobility time on suspension by the nape of the neck, sec. *Significant within-group differences between rabbits in normal conditions and after phenibut. For further details see caption to Fig. 1.

ance of active defensive reactions when animals were suspended by the nape of the neck increased from 23.0 to 28.0 sec. phenibut had no effect on the number of shaking reactions in response to vibroacoustic stimulation of the ears. Thus, phenibut decreased the behavioral reactivity of the rabbits, such that it became more difficult to elicit active (orientational-investigative, defensive) and passive (freezing) reactions in the animals.

Comparison of the behavioral reactivities of the three groups of animals (Fig. 2) showed that the greatest changes in reactivity on administration of phenibut in comparison with controls were seen in passive and active rabbits; rabbits with intermediate activity showed no significant changes in any of the measures.

3. Effects of phenibut on Respiration in Rabbits Before and After Emotionally Significant Stimuli. Comparison of the durations of respiratory cycles, inhalations, and exhalations without stimuli showed no significant differences (Mann–Whitney test) on the background of phenibut compared with control conditions (Table 3). At the same time, changes in respiratory measures on exposure to emotionally significant stimuli differed in normal conditions and after phenibut. Previous analysis of respiration in intact rabbits exposed to emotionally significant stimuli showed that the direction of changes in the duration of exhalation and whole respiratory cycle depended on the type of behavioral reaction: in active movement reactions, values predominantly decreased, while in freezing, values increased [8]. The duration of inhalation almost always decreased regardless of the type of reaction. These results are presented in Fig. 3. Phenibut produced changes in respiratory reactivity. Regardless of the type of behavioral reaction, the duration of inhalations predominantly increased after stimuli presented on the background of phenibut. Changes in the duration of exhalation, as in normal conditions, correlated with the type of behavioral reaction – increases in freezing

TABLE 3. Comparison of Mean Durations of the Respiratory Cycle (T_{cycle}), Inhalation (T_{inh}), and Exhalation (T_{exh}), in Baseline Conditions Without Stimuli in Normal Conditions and on Administration of Phenibut

State	T_{cycle}, sec	T_{inh}, sec	T_{exh}, sec
Normal (n = 16)	0.326 ± 0.071	0.156 ± 0.030	0.170 ± 0.063
Phenibut (n = 6)	0.256 ± 0.112	0.112 ± 0.043	0.145 ± 0.087

Note. n is the number of rabbits used for averaging ± 95% confidence limits.

and decreases in active movement. The overall proportions by which various respiratory parameters changed was the same in normal animals and those given phenibut.

DISCUSSION

The data reported here provide evidence of a reduction in horizontal movement activity in the open field in rabbits given phenibut (number of squares crossed, runs) and various elements of investigative behavior (attempts to gnaw the floor and wall of the chamber). Most reported studies have also described decreases in movement activity in the open field in rats and mice given systemic doses of $GABA_B$ receptor agonist baclofen [19], the $GABA_A$ receptor agonist muscimol [23, 29], or agonists of the benzodiazepine site of $GABA_A$ receptors [17], as well as decreases in the total kinetic energy recorded by the electronic integrator and investigative activity after administration of phenibut [12]. In the elevated plus maze, muscimol also decreased total movement activity [23]. Only a few studies in which small doses of agents were used and the study system was generally mice showed increases in horizontal movement activity in the open field [16] and investigative activity [17], the number of excursions, and the time spent in the open arms of the elevated plus maze [15, 25, 27]. Thus, judging from published data, sedative and anxiolytic effects can appear in behavior after systemic administration of GABA agonists, though these cannot always be separated. At the phenibut dose of 40 mg/kg used in the present experiments, there was a clear sedative influence on the behavior of the rabbits in the open field, as shown by the decrease in horizontal movement activity.

The clearest decrease in anxiety and fear were seen after microinjections of GABA receptor agonists into emotiogenic structures. Thus, microinjections of phenibut into the central nucleus of the amygdala in rats led to decreases in anxiety in the illuminated platform avoidance test and the threatening situation test [9]. Injection of muscimol into the septum [18, 24] or medial prefrontal cortex [30] increased movement activity in the open field and the time spent investigating the open arms of the plus maze. The same behavioral changes in the plus maze were produced by injections of midazolam, an agonist of the benzodiazepine site of the $GABA_A$ receptor, into the periaqueductal gray matter [28]. Injection of midazolam into the hippocampus increased investigative behavior in rats in the open field and disinhibited movement activity in the Vogel test [21].

In our experiments, phenibut decreased the behavioral reactivity of rabbits on exposure to various emotionally significant stimuli. There were reductions in the probabilities that an orientational-investigative reaction would appear in response to sound stimuli and an active defensive reaction in response to pressing on the nape of the neck; the latent period of the active phase increased on suspension, and the probability of passive defensive reactions (freezing in response to sound stimuli and pressing on the nape of the neck) decreased, as did the durations of these reactions. The single exclusion to this general rule was the phenibut-induced increase in the duration of immobility on suspension, which was seen predominantly in active rabbits. These data indicate that immobility on suspension is a special type of passive defensive reaction, resembling a cataleptic state.

In previous studies, systemic phenibut also decreased orientational-investigative reactions in mice [12]. Weakening of conditioned reflex fear was seen on systemic administration of GABA receptor agonists, with weakening of startle reactions and restoration of drinking in rats in the Vogel test [15, 26]. Weakening of the startle reaction to sound was also seen after microinjection of muscimol into the basolateral amygdala [22]. Systemic administration of phenibut and muscimol were found to decrease various elements of anxious-protective behavior in a model of a depressive-like behavior in isolated mice [1], this being associated with a reduction in freezing duration and inappropriate defensive rearings in response to addition of an intruder, as well as an increase sociability.

It is interesting to compare data on the effects of phenibut in a classical defensive conditioned reflex [4, 14] with the data on its actions on motor activity in the open field and reactivity to emotionally negative stimuli obtained in the present study. In the conditioned reflex, the number and duration of intersignal movements in the presence of phenibut could decrease [4, 14], while the probability of movement responses to conditioned stimuli did not change [14] or could even increase at the initial stages of training [4]. The increase in the probability of movements can be explained by the fact that phenibut, as shown in the present study, decreased the freezing in rabbits which could be present in

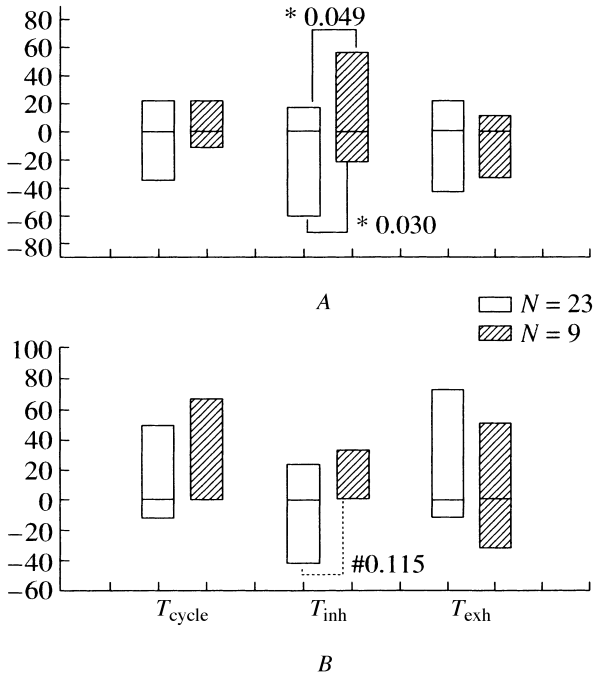

Fig. 3. Changes in respiratory parameters after emotionally significant stimuli with increases in movement activity (*A*) and freezing (*B*). White columns show normal conditions; shaded columns show results with phenibut. T_{cycle} shows changes in the duration of the respiratory cycle, T_{inh} in the duration of inhalation, and T_{exh} in the duration of exhalation. The vertical axis shows the number of cases (%) with significant increases (positive values) or decreases (negative values) of respiratory measures, Mann–Whitney test. *N* is the number of experiments analyzed. Significance is as in Fig. 1.

an unformed conditioned reflex. The fact that phenibut had no effect on conditioned reflex movement at the later stages of reflex acquisition may, evidently, be associated with decreases in emotional tension in the animals and the absence of any influence of phenibut on the fixed conditioned reflex skill. Phenibut, as demonstrated previously [12], does not affect pain sensitivity in mice. The decrease in the behavioral reactivity of animals on treatment with phenibut is probably manifest as the reduction in movements in response to inhibitory conditioned stimuli [4, 14].

The present studies demonstrated different sensitivities to phenibut in animals with different individual-typological behavioral characteristics in the open field. Phenibut significantly altered behavior in active rabbits, had smaller effects in passive animals, and almost no effect on intermediate-activity rabbits either in the open field or on exposure to emotionally significant stimuli. Rats with different levels of movement-investigative activity in the open field are known to have different sensitivities to morphine and alcohol [5]. Experiments in cats and rats showed that the effects of benzodiazepine tranquilizers in stress depended on the typological characteristics of the animals [2]. Agonists of the benzodiazepine site of $GABA_A$ receptors had different effects on the appearance of predatory behavior and maternal aggression in rats with initially different levels of aggression [20]. Rats with high levels of investigative activity and longer times spent in the open arms of the plus maze (low-anxiety animals) had more benzodiazepine receptors in the cerebral cortex than low-mobility (high-anxiety) rats [25]. It can be suggested that the rabbits of different groups in our experiments also had different numbers of GABA receptors, the largest deviations in different directions from the mean being in the extreme groups of rabbits, making them disequilibrated and subject to the effects of stimuli. Additional increases in the inhibitory GABAergic system produced by phenibut led to the greatest changes in behavior in these groups of animals. The results obtained here provide evidence that use of phenibut in clinical practice should take cognizance of the individual-typological characteristics of patients.

Administration of phenibut in our experiments did not lead to any changes in the time parameters of external respiration in baseline conditions without stimuli but altered reactivity to emotionally significant stimuli, which appears to be evidence of changes in the animals' autonomic reactivity. The greatest changes affected inhalation: regardless of the type of behavioral reaction, the duration of inhalation after stimuli increased, while in the absence of phenibut it decreased [8]. In anesthetized cats, systemic administration of phenibut led to periodic apneustic respiration with delays in inhalation [10]. The GABAergic system has been shown to play an important role in the functioning of the brainstem respiratory center; the delay in respiration when this transmitter system is increased occurs in inspiration, with an increase in the latent periods of discharges of inspiratory neurons and the inhibitory Hering-Breuer reflex [11]. The increase in the duration of inhalations after exposure to emotionally significant stimuli in our studies was associated with these same processes, but because of the smaller dose of phenibut and the absence of anesthesia, the effects were significantly less marked.

CONCLUSIONS

1. Systemic administration of the $GABA_B$ receptor agonist phenibut at a dose of 40 mg/kg s.c. led to decreases in horizontal movement activity of rabbits in the open field and in a number of elements of investigative activity.

2. On treatment with phenibut, data for the whole group of rabbits showed decreases in behavioral reactivity to emotionally negative stimuli (sounds of different loudnesses, pressing on the nape of the neck, suspension by the nape of the neck, vibroacoustic stimulation of the pinnas). There were reductions in the probabilities of both active (orientational-investigative, active defensive) and passive defensive (freezing) reactions.

3. The effects of phenibut depended on the individual-typological characteristics of the rabbits, which were apparent in their activity in the open field. In both the open field and on presentation of emotionally negative stimuli, phenibut had the strongest action on the behavior of active rabbits, with lesser effects in passive animals and virtually no influence on intermediate-activity rabbits.

4. Phenibut altered the reactivity of various measures of external respiration in rabbits on exposure to emotionally significant stimuli, which was evidence for changes in autonomic reactivity. Administration of phenibut led to increases in the duration of inhalations after stimuli, while phenibut decreased this duration in normal conditions.

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