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Effects of the GABA Receptor Agonist Phenibut on Spike Activity and Interactions between Neocortex and Hippocampus Neurons in Emotionally Negative Situations

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The nature of the spike activity of single neurons and interactions of neighboring cells in the hippocampus (field CA1) and parietal-temporal areas of the neocortex were compared in rabbits in emotionally negative situations in normal conditions and with decreased anxiety levels produced by systemic administration of the GABA receptor agonist phenibut. Analysis of the shapes of neuron spike activity autocorrelograms showed that phenibut increased the grouping of discharges in both structures, decreased interspike intervals within trains, increased the numbers of neurons with oscillations in the delta frequency range, and decreased the numbers of neurons with oscillations in the theta-1 range; in the hippocampus there was also an increase in frequencies in the theta-2 range. After phenibut, stimuli induced smaller rearrangements in neuron spike activity than in normal conditions. Analysis of cross-correlation histogram shapes showed that phenibut increased the numbers of common inputs to the neuron pairs being recorded and decreased the numbers of excitatory connections between cells in both structures; the hippocampus also showed an increase in the number of inhibitory connections. These changes provide evidence of a reduced level of activation of the hippocampus and neocortex after phenibut, with increases in neuron synchronization and decreases in the propagation of excitation between cells within structures, which correlated with decreases in the animals' behavioral reactivity and anxiety.

KEY WORDS: GABA receptor agonists, phenibut, hippocampus, neocortex, neurons.

Among the brain structures involved in selecting behavioral strategies in emotionally negative situations, there is much interest in the hippocampus and the parietal-temporal areas of the neocortex, which are tightly associated with it. These structures play a significant role in mediating freezing [1], which is one of the most widespread forms of passive defensive behavior in aversive contexts. The nature of the spike activity of individual neurons in the hippocampus and parietal-temporal areas of the neocortex has been shown to change during freezing as compared with calm waking and active orientational-investigative responses to stimuli [7]. Animals of different typological groups (with active and passive strategies) showed differences in the nature of neuron spike activity in these structures [6].

With the aim of identifying the role of the characteristics of information processing in the neural networks of the hippocampus and neocortex in mediating passive and active behavioral strategies, there is interest in comparing neuron interactions in normal conditions and in conditions of decreased anxiety and fear. GABA receptor agonists are known to decrease anxiety, emotional tension, and fear both after systemic administration at particular doses [2, 3, 5, 10] and after local administration into the emotiogenic structures of the brain [9, 16, 25, 26]. Thus, for example, microinjection of benzodiazepine receptor agonists into the hippocampus led to increased investigative behavior in an open field and disinhibition of rats in a conflict test [25]. Microinjection of the $GABA_A$ receptor agonist muscimol into the hippocampus decreased contextual fear in a classi-

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cal defensive conditioned reflex [16]. Administration of muscimol into the basolateral amygdala decreased the startle reflex [26]. Phenibut is a nonspecific GABA receptor agonist, acting mainly on $GABA_B$ receptors; this agent is quite widely used in clinical practice [20] and animal experiments [3, 9, 10, 13, 14]. Systemic administration of phenibut has been shown to lead to decreases in motor activity and orientational-investigative responses in mice [10] and rabbits [3], along with decreases in the probability and duration of freezing in rabbits exposed to emotionally significant contact stimuli [3] and in isolated mice when presented with an intruder [2]. Microinjection of phenibut into the central nucleus of the amygdala in rats has been shown to reduce anxiety in an illuminated area avoidance test and in a threatening situation test [9]. The aim of the present work was to compare the nature of spike activity and interactions of neighboring cells in the hippocampus (field CA1) and parietal-temporal areas of the neocortex in normal conditions and after systemic administration of the GABA receptor agonist phenibut in emotionally negative situations.

METHODS

Studies were performed in chronic experimental conditions using eight male Chinchilla rabbits. Experiments were performed in accordance with the Regulations for Laboratory Practice in the Russian Federation, ratified by decree of the Russian Federation Ministry of Health No. 267 of Jyne 19, 2003. During experiments, animals were kept in conditions of free behavior in a comfortable chamber, which was a cylinder of base diameter of 45 cm and height 32 cm. Animals were presented with sound stimuli (rustling at 30–40 dB and loud noises at 60–80 dB for 7 sec), contact stimuli (pressing on the nape of the neck for 7 sec, lifting by the nape for up to 30 sec), and vibroacoustic stimulation of the pinnae. Rustling generally evoked an orientational-investigative response, while the loud noise induced panic running followed by freezing (passive defensive behavior). Pressing on the nape could initially induce active defensive reactions, which were followed by freezing. Lifting by the nape initially produced freezing, which was in some cases followed by active defensive activity. Vibroacoustic stimulation of the pinnae provoked shaking reactions and, less commonly, freezing. Animals received one or two identical stimuli per experiment, with the total number not exceeding 3–7; intervals between stimuli were at least 60 sec.

Emotionally significant stimuli were used on the background of phenibut in five of the eight rabbits. Phenibut was given subcutaneously 2 h before the experiment at a dose of 40 mg/kg, dissolved in 3 ml of physiological saline. As demonstrated previously [3], this dose at this time decreases freezing duration in response to emotionally negative stimuli. In some experiments, stimuli were initially presented without treatment (controls), and phenibut was then given, stimulus presentation being repeated 2 h later. In other experiments, animals were given phenibut 2 h before beginning the experiments without any other procedures.

Neuron activity was recorded from symmetrical leads in the sensorimotor and parietal areas of the cortex of the right and left hemispheres and from hippocampal field CA1 on the right and left sides. Coordinates: parietal area: $P = 2$, $L = 9–10$ (representation areas of the ears and head); sensorimotor cortex: $P = 3$, $L = 4–5$ (representation area of the hind paws); hippocampus: $P = 3–4$, $L = 4–5$, $H = 4$. Neuron spike activity was recorded using chronically implanted Nichrome semimicroelectrodes of diameter 50 μm, glued to plates in bundles of eight. Recordings were bipolar. The rabbits were scalped under local anesthesia (2% novocaine) several days before electrode implantation. Neuron activity was recorded using an eight-channel miniature preamplifier with a differential input which was attached to the rabbit's head. Neuron activity was inputted into a computer using an L-783 analog-to-digital converter (L-Card, Russia) with a sampling interval of 10 μsec in each channel. The experimental methods and analysis of neuron spike activity have been described in more detail previously [6, 7].

Neuron spike activity was analyzed in three states: in calmly sitting rabbits in baseline conditions or in the absence of responses to stimuli, during freezing, and during and immediately after active orientational-investigative or defensive reactions. Segments of 15–30 sec were analyzed.

Neuron spike activity was analyzed statistically using the Neuron program (by Yu. V. Pavlov). Spike shape was used to extract the activity of individual neurons (from three to six neurons) from traces of multineuron activity; mean discharge frequencies were calculated and autocorrelation (ACH) and cross-correlation (CCH) histograms were plotted. Single segments were used to plot histograms with bin widths of 1, 2, 5, 10, 20, and 30 msec and analysis epochs of 50, 100, 250, 500, 1000, and 1500 msec, respectively. Significant intervals were determined with significance levels of 0.99 both for narrow (single-bin) and wide (two- and five-bin) peaks and troughs.

The shapes of the ACH identified and analyzed in these experiments have been described previously [6, 7]. Discharge periodicity frequencies were analyzed on ACH by determining mean intervals between peaks (T_{mean}) and peak frequencies ($1000/T_{mean}$). Histograms of the distributions of neurons by frequency of discharge oscillations were plotted using the same limits for frequency ranges as used for EEG analyses: delta – up to 3.9 Hz; theta – 4.0–9.0 Hz; alpha – 9.1–13.0 Hz; beta – 13.1–30 Hz; gamma – 30.1–100 Hz. Secondary processing of results and construction of plots were performed using the standard program bundles Statistica 5.5. and 6.0. Percentage ratios were compared using 2×2 linkage tables; the χ^2 test was used, differences being regarded as significant at $p < 0.05$, with tendencies identified at $0.05 \leq p < 0.15$. Mean neuron discharge frequencies were compared in different states using Student's t test.

TABLE 1. Distributions of Neurons in Terms of the Shapes of ACH of Their Spike Activity during Active Motor Responses to Stimuli in Normal Conditions and after Phenibut

Brain area	State	Number of neurons	P, %	G, %	G + Pe, %	Pe, %
Hippocampus	Normal	805 (100 %)	33	9	40	18
	Phenibut	219 (100 %)	35	22 ↑ $p = 0.000$	28 ↓ $p = 0.001$	15
Neocortex	Normal	709 (100 %)	33	9	32	26
	Phenibut	311 (100 %)	44 ↑ $p = 0.001$	15 ↑ $p = 0.001$	16 ↓ $p = 0.000$	25

Notes. P identifies equal-probability distributions of discharges on ACH; G is discharge grouping; G + Pe is discharge grouping and periodicity; Pe is discharge periodicity. Arrows show significant changes in numbers of ACH of a particular shape after phenibut compared with normal conditions (χ^2 test); p is the level of significance.

TABLE 2. Changes in Mean Interspike Intervals (msec) within Trains of Neuron Discharges after Phenibut in Different Experimental Situations

Brain area	State	Baseline	Active responses	Freezing
Hippocampus	Normal	25.40 ± 2.95 $n = 243$	26.16 ± 2.16 $n = 398$	32.95 ± 3.71 $n = 285$
	Phenibut	13.60 ± 2.33 ↓$p = 0.0002$, $n = 58$	15.43 ± 1.79 ↓$p = 0.000$, $n = 108$	16.08 ± 2.37 ↓$p = 0.0002$, $n = 53$
Neocortex	Normal	36.09 ± 4.95 $n = 144$	30.89 ± 3.18 $n = 291$	43.38 ± 6.25 $n = 166$
	Phenibut	15.29 ± 6.03 ↓$p = 0.000$, $n = 104$	18.72 ± 3.27 ↓$p = 0.000$, $n = 97$	19.32 ± 3.87 ↓$p = 0.000$, $n = 49$

Note. Arrows show significant changes (Student's test) in mean latencies of the first peaks on ACH in the presence of discharge grouping after phenibut as compared with normal conditions. p is the level of significance, n is the number of neurons analyzed. 95% confidence intervals are shown by ± signs.

Behavioral measures in normal conditions and after phenibut were compared using the Mann–Whitney test.

After experiments, morphological monitoring of correct electrode positioning in the hippocampus was performed. Brain sections were cut on a cryomicrotome and were stained by the Nissl method. Data obtained in rabbits in which the electrodes were positioned in the upper layers of field CA1 of the dorsal hippocampus are reported here.

RESULTS

In the study rabbits, as previously [3], administration of phenibut led to decreases in the proportion of orientational-investigative reactions to sound stimuli to 50% ($p = 0.015$) as compared with normal conditions (76%). Freezing times to contact stimuli decreased from 12 to 6 sec ($p = 0.019$), and there was a tendency to a decrease in the number of freezing episodes on pressure from 56% to 31% ($p = 0.055$). Thus, administration of phenibut led to decreases in the behavioral reactivity of the animals to emotionally significant stimuli.

Administration of phenibut decreased mean neuron spike activity frequency both in the hippocampus and in the neocortex. While mean neuron discharge frequency in baseline conditions in calmly sitting animals was 14.60 ± 1.87 spikes/sec ($n = 499$) in the hippocampus, the frequency decreased after phenibut to 8.38 ± 1.24 spikes/sec ($n = 131$, $p = 0.0008$). In the neocortex, the mean discharge frequency decreased from 10.14 ± 0.92 spikes/sec ($n = 439$) in normal conditions to 7.72 ± 0.75 spikes/sec ($n = 272$, $p = 0.0004$) after phenibut.

Changes in the shape of ACH of neuron spike activity depending on the type of behavioral response to stimuli in normal conditions without any pharmacological substances have been described previously [7]. Administration of phenibut led to rearrangements in the nature of neuron spike activity, these changes being in the same direction when the animals were in different states. As an example, Table 1 shows the distribution of neurons in terms of the shape of the ACH of their spike activity in normal conditions and after phenibut after stimulation accompanied by active orientational-investigative reactions. As compared with nor-

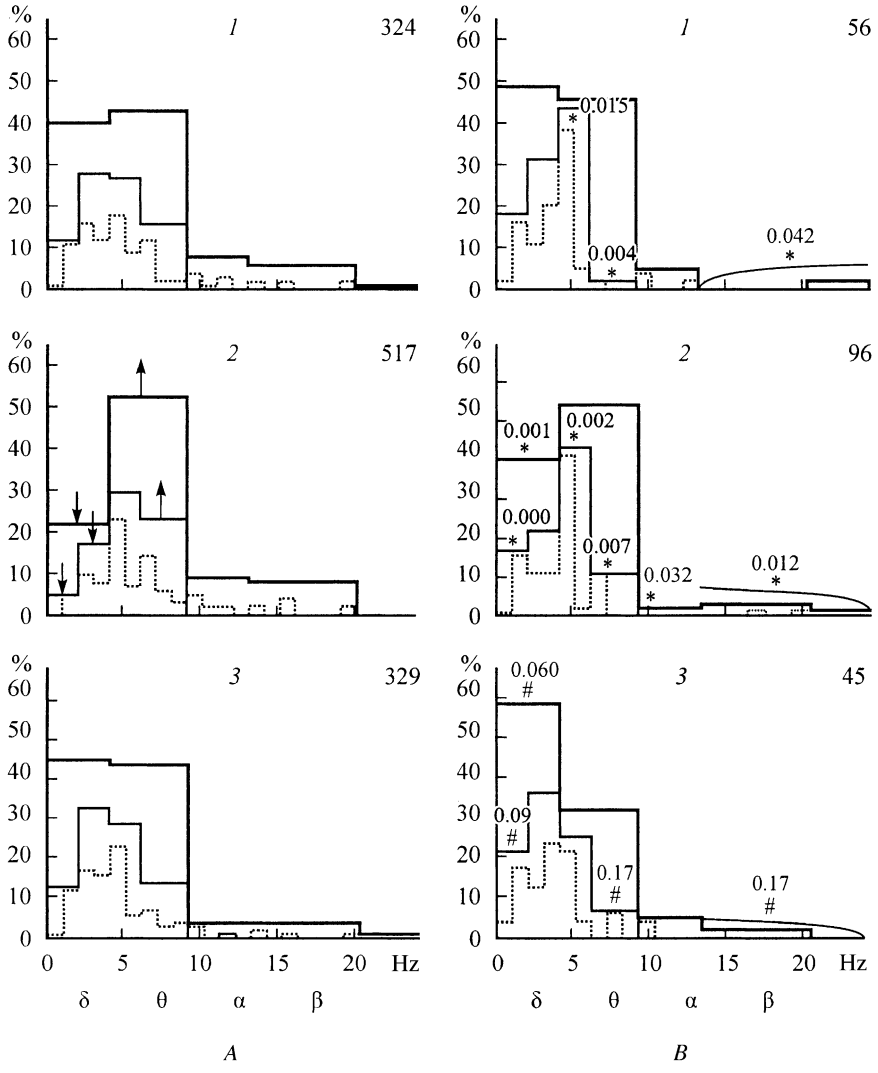

Fig. 1. Distributions of hippocampal neurons depending on their oscillation frequencies in different states in normal conditions (*A*) and after phenibut (*B*). *1*) Calm waking; *2*) active orientational-investigative responses or shaking; *3*) freezing. The abscissa shows frequency, Hz, range of frequencies; the ordinate shows the proportion of neurons with oscillations at the frequency concerned. Thick continuous lines show distributions by range; thin continuous lines show distributions by subrange; dotted lines show distributions by frequency. Arrows show significant changes (χ^2 test) in different states compared with baseline; down arrows show decreases in the number, up arrows shows increases. *Significant differences (χ^2 test) between normal conditions and after phenibut; #tendencies. Numbers beside asterisks show significance levels (*p*). Numbers at upper right of each histogram show numbers of neurons analyzed.

mal conditions, phenibut increased the number of neurons with grouped discharges and decreased the number of neurons with grouped and periodic discharges. Furthermore, phenibut decreased mean interspike intervals in trains, as evidenced by the decrease in the latency of the first short-latency peak on ACH (Table 2), i.e., the density of trains of neuron discharges increased.

Administration of phenibut led to significant rearrangements in neuron discharge oscillation frequencies both in the hippocampus (Fig. 1) and the neocortex (Fig. 2). As in the previous study [7], the neocortex and hippocampus in rabbits in normal conditions making active orientational-investigative responses as compared with baseline, showed reductions in the numbers of neurons with oscillations in the delta frequency range (Fig. 1, *A*, *1*, *2* and Fig. 2, *A*, *1*, *2*) and increases in the numbers of cells with oscillations in the theta range, the extent of low-frequency oscillations in the theta-2 range increasing in the neocortex and the extent of high-frequency theta-1 oscillations increasing in the hippocampus. On freezing, as compared with baseline, the neocortex showed increases in the number of neurons with oscillations in the delta frequency range (Fig. 2, *A*, *3*), while no significant changes occurred in the hippocampus (Fig. 1, *A*, *3*).

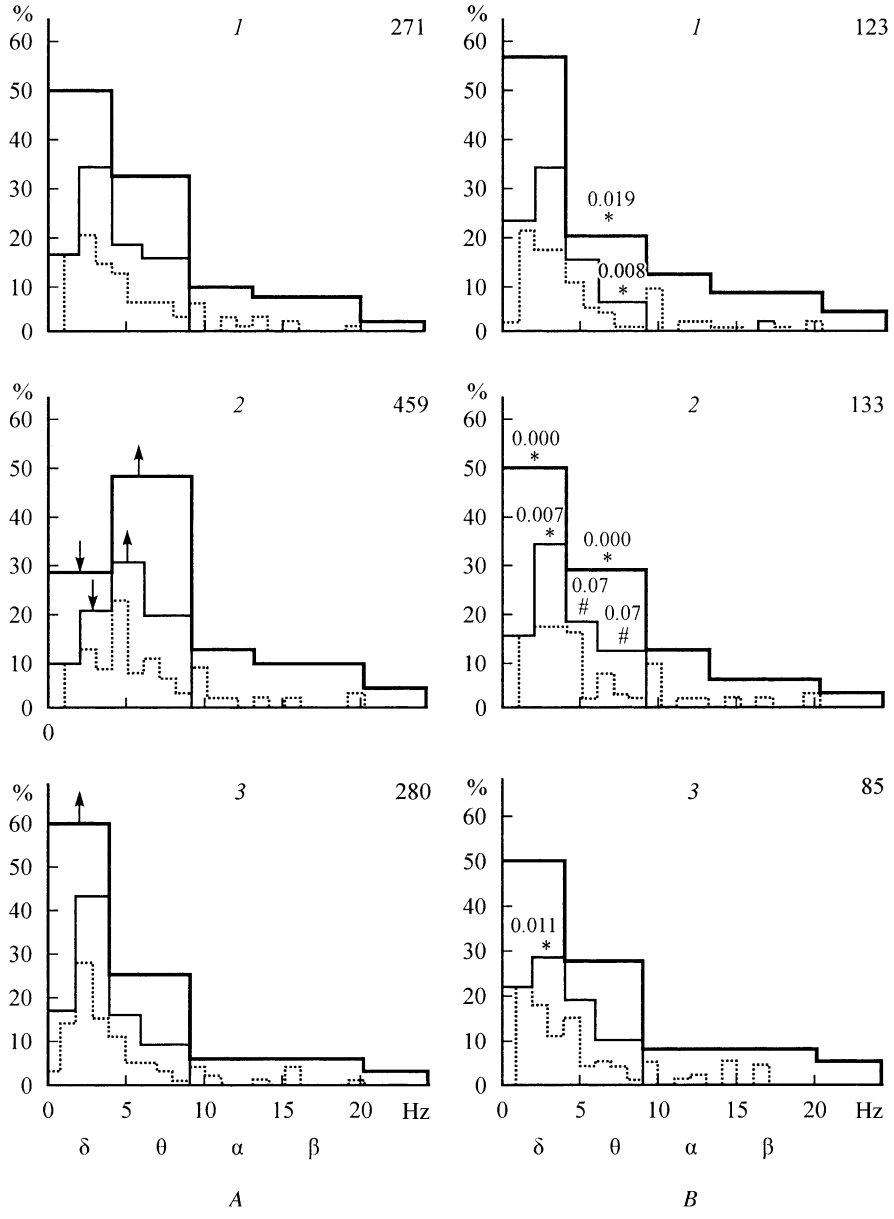

Fig. 2. Distributions of neocortical neurons depending on their oscillation frequencies in different states in normal conditions (*A*) and after phenibut (*B*). For further details see caption to Fig. 1.

After phenibut, there were no significant rearrangements in neuron oscillation frequencies in response to changes in the animals' state, though tendencies were seen in the same directions as in normal conditions (Fig. 1, *B* and 2, *B*). Comparison of the frequencies in similar states in normal conditions and after phenibut showed that phenibut increased the number of neurons with oscillations in the delta range in active movement responses and freezing in the hippocampus (Fig. 1, *B*, *2*, *3*), decreased the number of neurons with frequencies in the theta-1 range, though there was, conversely, an increase in the theta-2 range (in baseline conditions and active motor responses), and decreased the level of expression of frequencies in the beta range (Fig. 1, *B*, *1*, *2*, *3*). In the neocortex, phenibut increased the number of neurons with frequencies in the delta range in active motor responses (Fig. 2, *B*, *2*). Furthermore, there were reductions in the expression of frequencies in the theta range (mainly in the theta-1 range) in baseline conditions and in active motor responses.

Thus, judging from the nature of spike activity in individual neurons, phenibut decreased the level of activation of the hippocampus and neocortex, changes in the oscillation

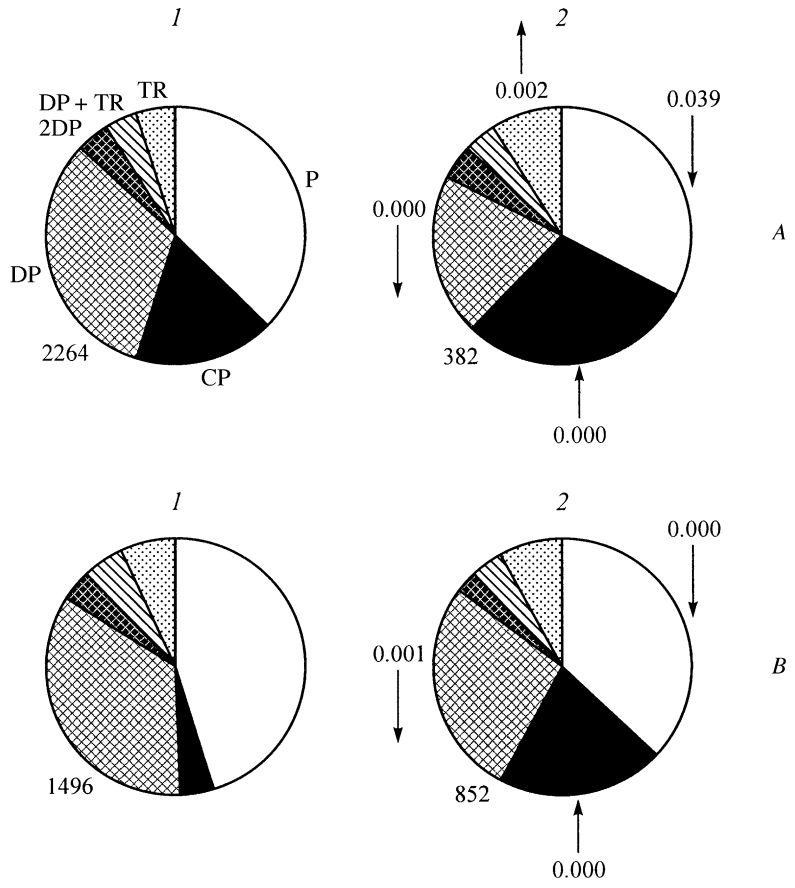

Fig. 3. Plots of the distributions of neuron pairs in the hippocampus (*A*) and neocortex (*B*) depending on the shapes of their cross-correlation histograms in normal conditions (*1*) and after phenibut (*2*). P identifies equal-probability distributions on CCH; CP identifies wide central peaks on CCH; DP identifies peaks displaced from the null point; 2DP identifies two peaks displaced from the null point; DP + TR identifies displaced peaks and troughs; TR identifies troughs on CCH. Arrows show significant changes after phenibut compared with normal conditions; numbers beside arrows show levels of significance (*p*). Numbers at below left of each plot show numbers of cross-correlation histograms analyzed.

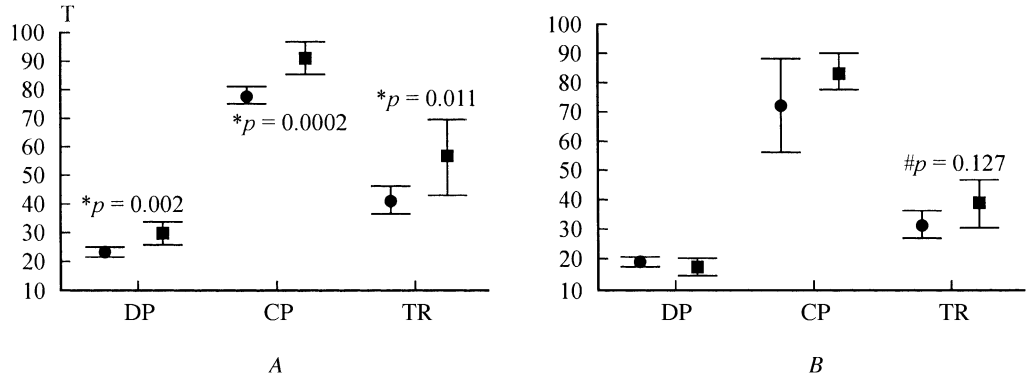

Fig. 4. Mean widths of displaced peaks (DP), central peaks (CP), and troughs (TR) on CCH of the spike activity of pairs of neurons in the hippocampus (*A*) and neocortex (*B*) in normal conditions (circles) and after phenibut (squares). The ordinate shows widths of peaks and troughs, msec. *Significant differences (Student's test) between normal conditions and after phenibut; #tendencies; *p* – significance level; 95% confidence intervals.

frequency mainly affecting the delta and theta frequency ranges, evidently creating conditions preventing active motor reactions.

Administration of phenibut affected the interaction of neighboring neurons. Figure 3 shows the effects of phenibut on the nature of the interaction of neighboring neurons in the hippocampus (*A*) and neocortex (*B*), which was assessed in terms of the shapes of CCH of their spike activity. The effects of phenibut administration were similar in the neocortex and hippocampus (Fig. 3, *A*, *2*, *B*, *2*): there were increases in the numbers of neuron pairs with correlated functioning, increases in the numbers of CCH with central peaks (common inputs to the pair of cells being recorded [23]), and decreases in the numbers of CCH with displaced peaks (excitatory connections between cells). In the hippocampus, there was also a significant increase in the number of troughs on CCH (inhibitory connections between cells).

Phenibut led to increases in the widths of both central peaks (Fig. 4, *A*) and displaced peaks on CCH of the spike activity of pairs of neurons in the hippocampus; there was also an increase in the width of troughs (Fig. 4, *B*).

DISCUSSION

Systemic administration of phenibut had effects on many brain structures, such that we appear to be dealing not only with its direct effects on the structures being investigated, but also with secondary effects. As a result of these influences, phenibut produced changes in the functioning of the septohippocampal system in the present experiments, which were reflected in changes in the frequency on oscillations in the theta rhythm in both the hippocampus and the neocortex. Alterations in the functioning of the hippocampus and neocortex mediate the anxiolytic actions of phenibut, which is evidence for the role of these structures in freezing. Possible points of action of phenibut in the septohippocampal system and neocortex consist of increases in the effects of GABAergic interneurons in the septum, hippocampus, and neocortex, and of septohippocampal neurons [18]. The literature contains data on the functioning of both $GABA_A$ and $GABA_B$ receptors in the hippocampus and neocortex [8, 21, 24, 27, 28, 32].

Administration of phenibut in baseline conditions led to significant changes in neuron oscillation frequencies in the hippocampus and neocortex. The proportions of neurons with oscillation frequencies in the theta-1 frequency range in both structures decreased. The hippocampus showed an increase in the proportion of neurons with frequencies in the theta-2 range, which compensated for the decrease in the high-frequency subrange; there was no overall decrease in the frequency of the theta range, in contrast to the neocortex. Considering the fact that the neuron discharge oscillation frequency is linked with variations in cell membrane potential, which is reflected in total brain potentials, it is interesting to compare our data with results obtained from EEG frequency analysis. The literature contains descriptions of decreases in the proportions of frequencies in the theta-1 range in the neocortex and hippocampus EEG on exposure to benzodiazepine tranquillizers [4, 12, 19], which is taken to be the main EEG correlate of the anxiolytic action of these agents. Blockade of $GABA_B$ receptors is known, conversely, to increase the theta rhythm in rats [21]. It can be suggested that the significant decrease in the high-frequency theta-1 rhythm in the hippocampus on exposure to phenibut leads to the decrease in active orientational-investigative and active defensive responses to stimuli [3], as the theta rhythm reflects the level of activation of the motor system and its role in sensorimotor integration is known [29]. Administration of phenibut led to decreases in the reactivities of individual neurons to the stimuli used; after phenibut, no significant changes in oscillation frequencies depending on the type of behavioral response to stimuli were seen. Decreases in hippocampal and neocortical neuron reactivity may be associated with decreases in the probability of responding to stimuli [3].

Phenibut increased the expression of delta frequencies in both structures. These changes appeared to reflect the sedative effect of phenibut. In previous studies, administration of phenibut was followed by the appearance of slow waves in the neocortex EEG, along with increases in early negative and late positive and negative components of evoked potentials to visual stimuli [14]. The appearance of high-amplitude slow waves and low-frequency rhythms in the delta range in the cortical EEG was seen after systemic administration of the specific $GABA_A$ receptor agonists muscimol and gaboxadol [30, 31].

Administration of phenibut affected the interaction of neighboring neurons both in the hippocampus and the neocortex. There were increases in the numbers of common inputs to the neurons being recorded, with decreases in the numbers of excitatory connections; in the hippocampus, there was also an increase in the number of inhibitory connections. It can be suggested that the increase in inhibitory influences from interneurons on exposure to the GABA receptor agonist had a synchronizing influence on neighboring cells, which led to an increase in the number of common inputs and an increase in the number of neurons showing correlated functioning. The hypothesis that inhibitory interneurons have a synchronizing role was first put forward by Andersen and Eccles [15]. It should be noted that common excitatory and inhibitory inputs to the neurons recorded here were similar in their appearances on CCH – as broad central peaks [23]. Studies using a neural network model showed that increases in hyperpolarization processes, leading to phasic neuron activity with alternating activation and inhibition, limit the conduction of excitation through brain structures [13]. Judging from our experimental data, the transmission of excitation through neural net-

works within structures decreased after phenibut, i.e., information within structures was processed to a lesser extent. It can be suggested that after phenibut, as compared with normal conditions, there was a characteristic "swing" in the network, when more long-lasting and synchronous inhibitory postsynaptic potentials in neighboring neurons were replaced by long-lasting and large depolarization potentials, which was reflected as increases in the grouping of discharges and decreases in the intervals between spikes within trains and as increases in the durations of peaks on CCH.

It is important to note that the CCH method has previously been regarded as having low sensitivity for detecting inhibitory connections. However, plotting of CCH with wide bins and calculation of significant intervals for wide (2–5 bins) peaks in our studies nonetheless allowed us to detect 12–13% of neuron pairs with inhibitory connections, and troughs were wider than the displaced peaks.

The similarity in the effects of GABA receptor agonists and M-cholinoreceptor blockers [11] on the network properties of neurons in the neocortex cannot be missed: in both cases, there were increases in the grouping of the discharges of individual neurons, with increases in the numbers of common inputs and decreases in excitatory connections. These data support the existence of M-cholinergic modulation of GABAergic transmission. Acetylcholine has been shown to elicit long-term depolarization of pyramidal neurons in the neocortex and hippocampus following transient hyperpolarization, which was associated with activation of GABAergic interneurons [17, 22]. Comparison of these data suggests that decreases in neuron excitation on exposure to anticholinergic substances somehow lead to increases in the functioning of inhibitory GABAergic neurons and the appearance of changes in the network properties of cells, which is similar to the effects of GABA receptor agonists.

CONCLUSIONS

Systemic administration of the nonspecific GABA receptor agonist phenibut at a dose of 40 mg/kg led to changes in the pattern of neuron discharges in the parietal-temporal areas of the neocortex and hippocampal field CA1. There were increases in the grouping of discharges, with decreases in interspike intervals within trains, increases in the numbers of neurons with oscillations in the delta frequency range, and decreases in the numbers of neurons with oscillations in the theta-1 range; in the hippocampus, this was compensated for by an increase in neurons with oscillations in the theta-2 range. After phenibut, emotionally significant stimuli evoked smaller rearrangements in neuron spike activity than in normal conditions.

Analysis of the shapes of cross-correlation histograms of the spike activity of pairs of neighboring neurons showed that phenibut increased the numbers of common inputs to the pairs of cells being recorded and decreases the numbers of excitatory connections between cells in both structures; in the hippocampus, there was also an increase in the number of inhibitory connections.

By enhancing the GABAergic inhibitory system, phenibut decreased the propagation of excitation in the hippocampus and neocortex and information was transmitted without being processed.

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