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The Effects of Agonists of Ionotropic $GABA_A$ and Metabotropic $GABA_B$ Receptors on Learning

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The research described here investigates the role played by inhibitory processes in the discriminations made by the nervous system of humans and animals between familiar and unfamiliar and significant and nonsignificant events. This research compared the effects of two inhibitory mediators of gamma-aminobutyric acid (GABA): 1) phenibut, a nonselective agonist of ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors and 2) gaboxadol a selective agonist of ionotropic $GABA_A$ receptors on the process of developing active defensive and inhibitory conditioned reflexes in alert non-immobilized rabbits. It was found that phenibut, but not gaboxadol, accelerates the development of defensive reflexes at an early stage of conditioning. Both phenibut and gaboxadol facilitate the development of conditioned inhibition, but the effect of gaboxadol occurs at later stages of conditioning and is less stable than that of phenibut. The earlier and more stable effects of phenibut, as compared to gaboxadol, on storage in memory of the inhibitory significance of a stimulus may occur because $GABA_B$ receptors play the dominant role in the development of internal inhibition during an early stage of conditioning. On the other hand this may occur because the participation of both $GABA_A$ and $GABA_B$ receptors are essential to the process. We discuss the polyfunctionality of GABA receptors as a function of their structure and the positions of the relevant neurons in the brain as this factor can affect regulation of various types of psychological processes.
Keywords: learning, defensive reflex, internal inhibition, discrimination, GABA, $GABA_A$ and $GABA_B$ receptors, phenibut, gaboxadol

Este trabajo investiga el papel de los procesos inhibitorios en la discriminación realizada por el sistema nervioso de los humanos y los animales entre sucesos familiares y no familiares y significativos y no significativos. Se comparó los efectos de dos mediadores inhibitorios del ácido gamma-aminobutírico (GABA): 1) Phenibut, un agonista no selectivo de los receptores del $GABA_A$ ionotrópico y del $GABA_B$ metabotrópico y 2) gaboxadol, un agonista selectivo de los receptores del $GABA_A$ ionotrópico, sobre el desarrollo de reflejos condicionados de defensa activa e inhibitorios en conejos en alerta y no inmovilizados. Se encontró que el phenibut, pero no el gaboxadol, acelera el desarrollo de reflejos defensivos en una etapa temprana del condicionamiento. Tanto el phenibut como el Gaboxadol facilitaron el desarrollo de la inhibición condicionada, pero el efecto del gaboxadol ocurre en etapas tardías del condicionamiento y es menos estable que el del phenibut. Los efectos más estables y más tempranos del phenibut, en comparación con el gaboxadol, sobre el almacenaje en la memoria de la significación inhibitoria de un estímulo pueden deberse a que los receptores del $GABA_B$ tienen el papel dominante en el dearrollo de la inhibición interna durante la fase inicial del condicionamiento. Por otro lado esto puede deberse a que la participación de los receptores tanto del $GABA_A$ como del $GABA_B$ son esenciales para el proceso. Comentamos la multifuncionalidad de los receptores del GABA como función de su estructura y de las posiciones de las neuronas relevantes en el cerebro, dado que este factor puede afectar la regulación de varios tipos de procesos psicológicos.
Palabras clave: aprendizaje, reflejo defensivo, inhibición interna, discriminación, GABA, receptores del $GABA_A$ y $GABA_B$, phenibut, gaboxadol

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The Pavlovian school's approach to studying the principles underlying the working of the brain is based on observation of behavior phenomenology and features detailed analysis of the interaction among excitation, inhibition and disinhibition in the perception, storage and retrieval of information in the central nervous system (CNS) (Pavlov 1954, 1973). Between the 1960s and the present, much information has been amassed relating to the neurophysiology of the CNS at the cellular, intracellular and molecular levels. It is noteworthy that, despite the high technological level of the methodology used in contemporary research, some issues that remained unclear during Pavlov's lifetime have still not been resolved. A detailed analysis of the neurophysiological and neuromediatory underpinnings of basic neural processes is essential not only for resolution of theoretical issues, but also for attainment of extremely practical goals. The Pavlovian ideas of the decisive importance of the properties (strength, plasticity, equilibrium) of the excitatory and inhibitory processes in determining human personality trains have allowed psychologists to develop successful recommendations for education, training and psychotherapy. Pavlov also laid the foundation for understanding various types of disorders of brain function resulting from disrupted interactions among these basic neural processes. At the present time it has been shown that such common neurological diseases as epilepsy, schizophrenia, and various types of psychosis, as well as the effects of narcotics result from disruption of the normal interactions between excitation and inhibition in the CNS (see: Enomoto & Ajmone-Marsan, 1959; Soriano & Frotscher, 1989; Lubow, 1989; Lubow & Gewirtz, 1995; Avoli, 1996; Luscher, 2002; Vaitl, Bauer & Schaler 2002; Kaluev & Natt, 2003; Kalkman & Loetscher, 2003; Costa, Davis & Dong, 2004 and others). Thus, to an astonishing extent, Pavlov managed to pose the most essential problems of contemporary neurophysiology on the sole basis of his observations of behavioral phenomenology. Some of these problems may already be resolvable on the basis of discoveries that have been made in contemporary neurophysiology, cytochemistry and molecular biology. A significant number of them still require specially designed experiments.

Our past research has shown that the development of all the types of internal inhibition Pavlov identified, as well as the extinction of the orienting reflex to a new stimulus, are accompanied by increased amplitude of total slow wave potentials, of background and secondary evoked potentials and of the corresponding phasic activity of neurons (alternation of activation and inhibition of impulses) either locally in the projection areas of the conditioned stimuli, or, as extinguishing inhibition gets stronger, throughout the entire cerebral cortex. Consideration of these results in light of contemporary ideas about general neurophysiology suggests that when the orienting reflex is being extinguished and when internal inhibition is being developed inhibitory hyperpolarizing processes are intensified in the cerebral cortex. (Shulgina, 1976, 2005). Thus, a stimulus that is becoming familiar, but is not biologically significant, induces an intensification of inhibitory hyperpolarizing processes in the CNS. This is probably a consequence of the increased reactivity of inhibitory systems, localized as well as throughout the brain, in response to the nonreinforced stimulus, which prevents excitation of the peripheral areas of the nervous system. One of the main symptoms exhibited by schizophrenia patients is inability to distinguish between significant and insignificant events in their lives and inability to inhibit ideas and images that do not exist in reality.

One of the most widespread functional symptoms experienced in our time is sleep deficit or insomnia. According to the U.S. National Institutes of Health, more than 40 million Americans suffer from chronic sleep disturbances and 20 million more have occasional sleep problems. Insomnia and other sleep disturbances have a negative impact on labor productivity, driving and social activity. According to Pavlovian ideas, the processes underlying internal inhibition and sleep are identical (Pavlov, 1973, p. 265; Voronin, Sokolov, 1962). The need to correct sleep abnormalities has led to an intensive search for drugs that can normalize the excitation-inhibition interaction without inducing side effects in CNS function and without exhibiting a tendency to create tolerance and/or dependence on the part of those who use them.

It can be said that the neurophysiological conditions required to create conditioned inhibition by activating inhibitory interneurons in local areas of the CNS (either by direct afferent fiber or via recurrent collaterals from active nerve cells) exist in all the brain structures that have been studied [see: Eccles, 1964, 1969; Clemente, 1968; Sukhov A. G. 1968 and others]. Brain-wide inhibitory systems include the orbitofrontal cortex, the basal forebrain, certain nuclei of the hypothalamus and thalamus, a subthalamic nucleus—the *zona incerta*, the reticular formation of the ventromedial *medulla oblongata*. (Clemente, 1968; Eccles, 1969; Lin, Nicolelis & Schneider 1990; Onodera & Hicks, 1998; Steriade, Gloor & Llinas, 1990; Steriade, 2005; Trageser & Keller, 2004; Lavalée, Urbain & Dufresne, 2005; Shehab, McGonigle & Hughes, 2005 and others).

The major mediator of inhibitory hyperpolarizing processes in the higher nervous system is gamma-aminobutyric acid (GABA) (Krnjevic & Schwartz, 1967; Krnjevic, 1974; Tebecis, 1974; Johnston, 2005 and others). Detailed study of the processes of information processing in the CNS involving inhibitory mediators, has identified the following types of GABA receptors: $GABA_A$, $GABA_B$ and $GABA_C$ receptors. $GABA_A$ receptors are sensitive to bicuculline and insensitive to baclofen, $GABA_B$ receptors are insensitive to bicuculline and sensitive to baclofen, $GABA_C$ receptors are insensitive to both bicuculline and baclofen (Hill & Bowery, 1981, Drew, Johnston, & Weatherby, 1984; Krogsgaard-Larsen P., Frølund, B. et al. 1997).

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The purpose of the present work is to analyze participation of GABA receptors in learning and in the structure of psychological processes of various types. The main goal of the experiments we performed was to compare the effect of phenibut – a nonselective agonist of $GABA_A$ and $GABA_B$ receptors and gaboxadol, a selective agonist of $GABA_A$ receptors on learning so as to generate data on the possible difference in the contributions made by $GABA_A$ and $GABA_B$ receptors to the learning process. It should be noted that gaboxadol is not only an agonist of $GABA_A$ receptors, but also an antagonist of $GABA_C$ receptors. However, $GABA_C$ receptors are not as extensively represented in the CNS as $GABA_A$ and $GABA_B$ receptors. They have been found mainly in the membrane of retinal cells (Johnston, 2005). Thus, it may be hypothesized that this aspect of gaboxadol's action will not have a significant effect on the results of this study of the role of GABA receptors in learning.

Phenibut — β-phenyl-λ-aminobutyric acid — a derivative of GABA ($C_{10}H_{13}NO_2$) is currently more and more frequently used in Russian neuropathology and psychiatry as a drug to normalize the functioning of the nervous system in patients with a deficiency in inhibition (schizophrenics, hyperactive children, etc.). In clinical practice phenibut is prescribed to decrease stress, panic, anxiety, and to improve sleep in psychosomatic and neurological patients in the practice of pre- and postherapeutic medicine (Khaunina & Lapin, 1989; Lapin, 2001; Mashkovsky, 2002). Symptoms of anxious-depressive excitement and stress, and stuttering in children are considered indications for the use of phenibut (Shmuyilovich & Kudrin, 1987). Phenibut improves the quality of sleep (Mashkovsky, 2002; Lapin, 2001) and has the capacity to potentiate the effects of concomitantly used soporifics (Shmuyilovich & Kudrin, 1987).

Gaboxadol or THIP (4,5,6,7-tetrahydroisoxsolo[4,5-c]pyridin-3-ol), is an analog of muscimol. Its molecular formula is $C_6H_8N_2O_2$ (Huckle, 2004). Gaboxadol is currently being studied in detail and actively advocated for use in clinical practice by Merck (USA) and H. Lundbeck A/S (Denmark). Clinical studies have shown that gaboxadol is capable of inducing sleep, as well as maintaining it, and it is thus anticipated that it will become the first representative of a new class of drugs for treating sleep disorders.

Phenibut and gaboxadol are similar in a number of their neurophysiological effects. When injected systemically both pass through the blood-brain barrier (Perecalin & Zobacheva, 1959; Moroni, Forchetti & Krogssgaard-Larsen, 1982). They have a similar effect on EEGs, intensifying slow, high-amplitude waves. (Shulgina, Petritcheva, Kusnetzova, 1985; Faulhaber, Steiger, Lancel, 1997; Huckle, 2004; Lancal & Langebartels, 2000)). Gaboxadol, like phenibut, improves the quality of sleep (Krogsgaard–Larsen, Frølund & Liljefars, 2004) and increases the duration of slow wave sleep in rats (Lancal & Langebartels, 2000; Huckle, 2004) and humans (Mathias, Zihi & Steiger, 2005). Thus, both gaboxadol and phenibut have a soporific component in their pharmacological action profile. This shows that the GABAergic neuromediator system participates in the sleep process.

An analgesic effect has been noted after systemic injection of both phenibut (Talalaenko, 1989; Mechilane, Rjago, Allikmets, 1990) and gaboxadol (in rats (Cheng & Brunnet, 1985; Zorn & Enna, 1987; Rode, Jensen & Blackburn-Munro, 2005) and in humans (Krogsgaard–Larsen, Frølund & Liljefars, 2004)).

The major difference between gaboxadol and phenibut is that phenibut is a nonselective agonist of GABA and acts on both ionotropic ($GABA_A$) and metabotropic ($GABA_B$) receptors (Allikmets, Rjago, 1983; Mechilane, Rjago, Allikmets, 1990), while gaboxadol is a selective agonist of ionotropic $GABA_A$ receptors (Brown, Kerby & Bonnert, 2002; Mortensen, Wafford & Wingrove, 2003).

The division of receptors of various types of mediators into ionotropic and metabotropic was first introduced in works by (McGreer, Eccles, & McGreer, 1978; Eccles, McGreer, 1979). Ionotropic GABA receptors are associated with chlorine ion channels (Bormann, Hamill & Sakmann, 1987; Semyanov, 2002). They activate the rapid component of the synaptic current. When GABA binds with these receptors, the chlorine channels open, which leads to a mass entry of chlorine ions into the cells, hyperpolarization and generation of inhibitory postsynaptic potential. Metabotropic effects are slower than ionotropic transmission. Metabotropic receptors do not have channels. The interaction of the mediator with metabotropic receptors does not lead to the development of postsynaptic potentials. When exposed to the appropriate mediator, metabotropic receptors alter the state of the neuron. This is achieved by activating secondary mediator molecules, primarily cAMP. The secondary mediators process information inside the cells and change the state of potassium and calcium channels by means of G protein. This changes the sensitivity of the neuron membranes to mediators acting on ionotropic receptors (McGreer, Eccles & McGreer, 1978; Eccles, McGreer, 1979.).

Thus, our analysis of results in the literature has shown that some of the physiological effects of phenibut and gaboxadol are similar. These include improvement in the quality and duration of sleep and an analgesic effect. However, the question of whether they have similar effects on the process of learning remains unresolved. We have previously shown that phenibut has a positive effect on discrimination between excitatory and inhibitory conditioned stimuli in conditioning situations (Shulgina, Petritcheva, Kusnetzova, 1985) and a facilitative effect on the process of developing defensive and inhibitory conditioned reflexes (Shulgina & Zyablitseva, 2005; Zyablitseva & Shulgina, 2006). Despite a rather careful study of the data in the literature concerning gaboxadol, we have not been able to find any information on the effect of this substance on learning and conditioning.

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Method

We conducted two experiments on alert, non-immobilized rabbits. In the first experiment (10 subjects, 5 each in the control and experimental groups) we investigated the effect of phenibut (in a subcutaneous dose of 40 mg/kg in three ml normal saline). The second experiment (4 subjects, 2 each in the control and experimental groups) investigated the effect of gaboxadol (in a subcutaneous dose of 3 mg/kg in 3 ml normal saline). In both experiments, each control subject was paired with an experimental subject. In the conditioning process, the rabbits developed a conditioned defensive reflex to light flashes (two flashes separated by a one second interval) reinforced by cutaneous shocks delivered by electrodes applied to the hind leg. The negative reinforcement consisted of two shocks separated by a one second interval, sufficient to induce motion of the leg. The first shock coincided in time with the second flash. The procedure was that of classical conditioning in that the reinforcement was delivered regardless of presence of absence of response (consisting general movement of the rabbit or movement of the paw to which the electrode was attached) to the conditioned stimulus (light flash). The inhibitory stimulus was an identical pair of flashes but against a background of continuous illumination (conditioned inhibition stimulus) and was not followed by shock reinforcement. Continuous illumination began one second before presentation of the non-reinforced light flashes. In this procedure the discrimination between excitatory and inhibitory stimuli is difficult.

Selection of doses for comparing the effects of phenibut and gaboxadol was based on similarity of EEG changes involving intensified slow high amplitude waves in response to various doses of the two drugs (Shulgina, Petricheva, Kusnetzova, 1985; Huckle, 2004). Experimental sessions took place at one-day intervals. Drugs were injected two hours before each session. In both experiments, the control animals were injected with 3 ml of normal saline. In the course of a session, each rabbit was exposed to six series of light flashes combined with shock and 6 series of light flashes against a background of continuous illumination (the inhibitory conditioned stimulus) without shocks as reinforcement. According to data in the literature, neither phenibut nor gaboxadol have a cumulative effect (Machkovsky, 2002; Huckle, 2004). During each session, a pneumogram, electrocardiogram and myogram of the gastrocnemius muscle to which the shock was delivered were recorded for each rabbit.

For purposes of statistical analysis the dependent variable used for the excitatory stimulus was probability of motor reactions in response to the first light flash. In the inhibitory condition the dependent variables were the probability of motor reactions to both the first and the second light flash after the discriminative stimulus for inhibition—continuous illumination—had been presented. During interstimulus intervals we recorded mean respiratory and heart rates at the early, middle and late stages of the experiment. The statistical significance of differences in indicators of brain function in the control and experimental drug conditions were evaluated using the STATISTICA 5.5. computer program. Intra-group differences (i.e., differences in the response probability to the excitatory and inhibitory conditioned stimuli in the same animals measured for groups given phenibut or gaboxadol) were tested using the Wilcoxon signed rank test for repeated measures. Between group differences between the control group and each of the drug groups (with respect to response likelihood in the excitatory and inhibitory conditions, as well as heart and respiration rates during interstimulus intervals) were tested using the Mann-Whitney test for independent samples.

Results

Comparison of the effects of phenibut and gaboxadol on development of a conditioned defensive reflex. During the early stage of conditioning experimental rabbits receiving phenibut developed active defensive behavior faster than did the controls. The experimental rabbits began to move more frequently in response to the light flashes serving as the conditioned stimulus for the defensive reflex than a total did controls during the first 10 sessions (60 trials, i.e. combinations of flashes and shock, $p<0.05$) Figure 1, 1A). Administration of gaboxadol did not lead to an analogous early facilitation of conditioning of the defensive reflex (Figure 1, 2 A).

*Comparison of the effects of phenibut and gaboxadol on development of conditioned inhibition***.** After administration of both phenibut and gaboxadol probabilities of motor reactions to the light flashes acting as the conditioned inhibitory stimulus were significantly different for experimental and control animals. Both drugs facilitated development of conditioned inhibition. However, effects associated with the two drugs occurred at different stages of inhibitory conditioning. Rabbits in the experimental condition receiving phenibut differed significantly from the controls, with respect to diminished likelihood of the motor response to the flash under inhibition conditions, starting during the second 10 sessions (60th-120th combinations of light flash with shock, $p<0.01$) (Figure 1, 1B). Experimental rabbits receiving gaboxadol differed significantly from controls, with respect to diminished likelihood of the motor response to unreinforced light flashes, only during the third 10 sessions (120th-180th combinations, $p<0.05$) (Figure 1, 2B).

Thus, the facilitating effects of gaboxadol—a selective agonist of ionotropic $GABA_A$ receptors — on development of conditioned inhibition occurred during later stages of conditioning than did the effects of phenibut—a nonselective agonist of ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors. It is noteworthy that the group receiving phenibut

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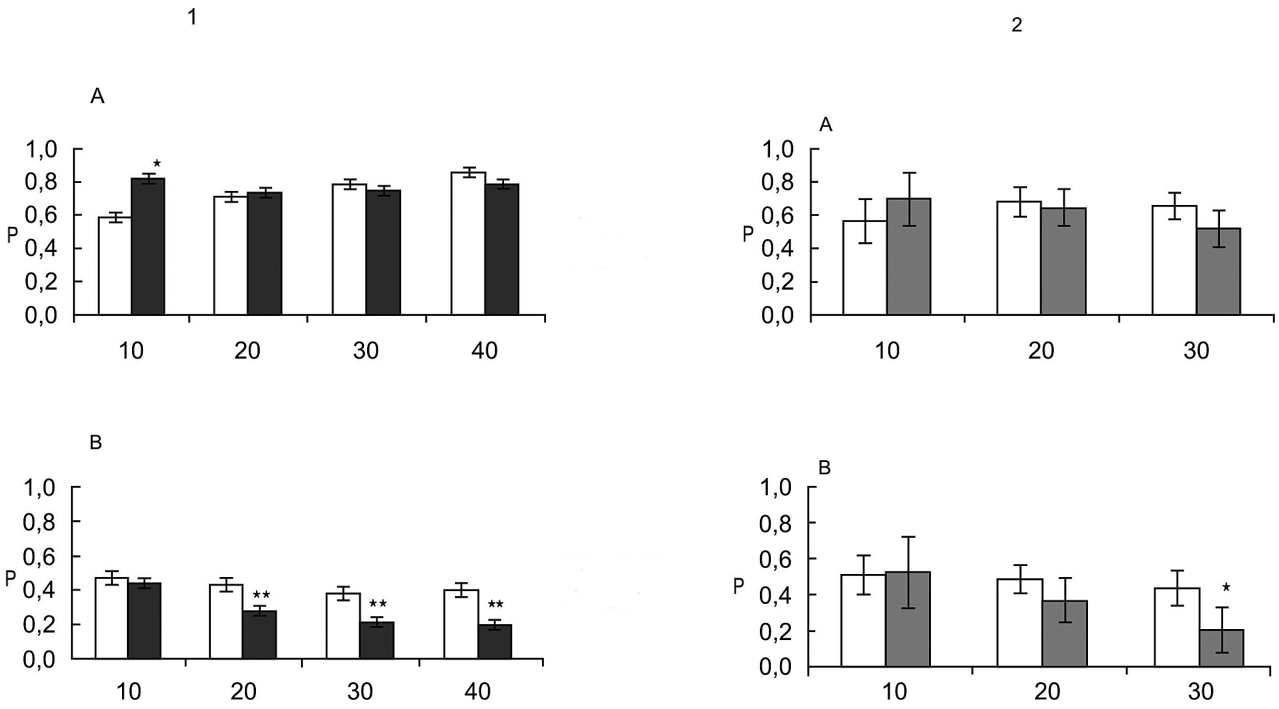

Figure 1. Probability of motor reactions in rabbits in response to the first light flash, the conditioned stimulus for the defensive reflex (A); and in response to the unreinforced flashes in the conditioned inhibition condition (signaled by continuous illumination) (B): 1 – in the control group (white columns) and the group given phenibut (black columns) or 2- in the control group (white columns) and the group given gaboxadol (gray columns). Vertical axis shows probability of motor response to a flash, horizontal axis is—ordinal number of session. *p<0.05, **p<0.01 (Mann-Whitney test for independent samples).

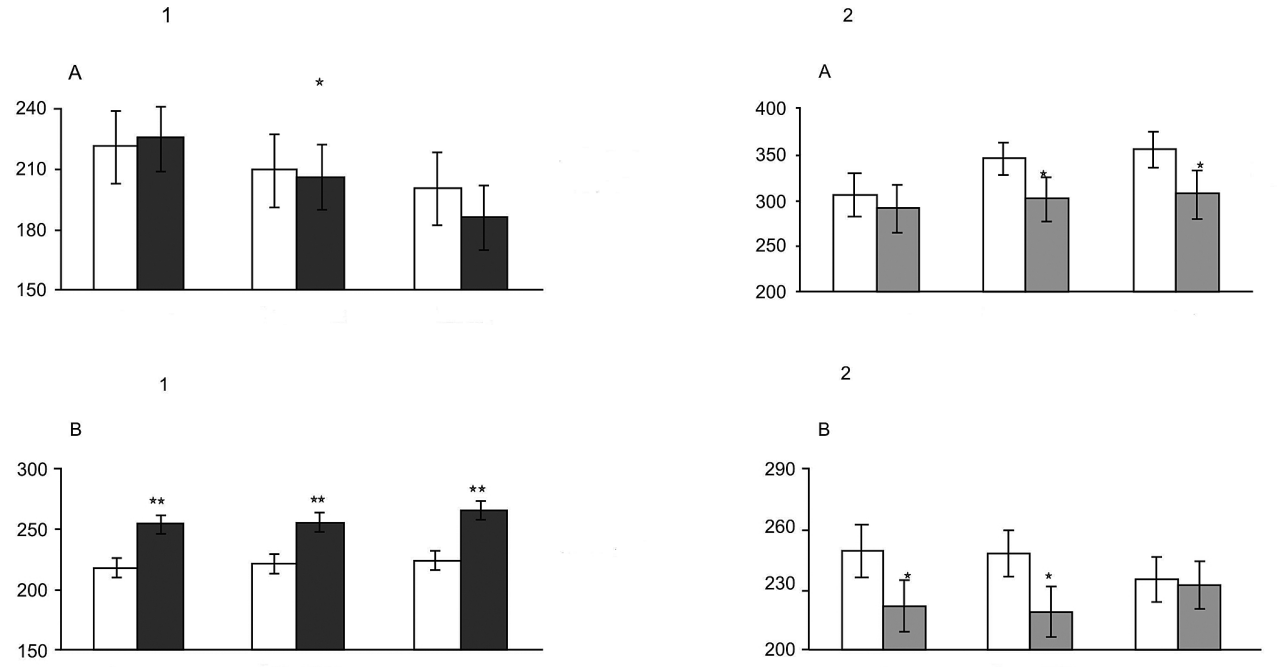

Figure 2. Respiration rate (A) and heart rate (B) during interstimulus intervals: 1 – in the control condition (white columns) and after subcutaneous injection of phenibut (40 mg/kg) (black columns); 2 – in the control condition (white columns) and after subcutaneous injection of gaboxadol (3 mg/kg) (gray columns). Horizontal axis designates period during the course of the experiment – early, middle, late. *p<0.05, **p<0.01 (Mann-Whitney test for independent samples)

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showed more stable session-to-session discrimination between reinforced and nonreinforced light flashes than did those receiving gaboxadol.

Comparison of the effects of phenibut and gaboxadol on respiration and heart rate. In the condition using phenibut both the experimental and the control rabbits showed a decrease in respiration rate toward the end of the experiment. However, only in the experimental group was this decrease significant compared to rate at the beginning of the experiment ($p<0.05$, Figure 2, 1A). The control group in the gaboxadol condition showed an increase in respiration rate over the course of the experiment. (Evidently because it was conducted during a period of hot summer weather). In the experimental group receiving gaboxadol there was no increase in respiration rate over the course of the experiment (Figure 2, 2A). Thus, both phenibut and gaboxadol, as evidenced by respiration rate, tranquilized the rabbits in comparison to the control group.

In the experimental group of animals receiving phenibut heart rate was significantly higher throughout the experiment than in controls ($p<0.01$), (Figure 2 1B). In contrast, animals receiving gaboxadol had significantly lower heart rates than control counterparts during the early and middle phases of the experiment ($p<0.05$). At the end of the experiment there was no difference in heart rates of control animals and those receiving gaboxadol (Figure2, 2B). Thus, animals receiving phenibut showed an increase in heart rate, while those receiving gaboxadol showed a decrease.

Discussion

Results of this experiment have demonstrated significant differences in the effects of the nonselective agonist of ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors, phenibut, and the selective agonist of ionotropic $GABA_A$ receptors, gaboxadol, on the process of learning. Unlike gaboxadol, phenibut accelerated the development of active defensive reflexes. Phenibut also had an earlier and more marked facilitating effect on development of conditioned inhibition reflexes than did gaboxadol. We can advance two hypotheses to explain these differences.

1) The facilitative effect of phenibut on development of conditioned defensive reflexes and its earlier and more stable facilitating effect on development of conditioned inhibition compared to that of gaboxadol could result from the fact that, during the early stages of conditioning, the leading role is played by metabotropic $GABA_B$-receptors. The hypothesis that metabotropic receptors make a greater contribution to the process of learning is compatible with the idea of the more essential role of this type of receptor, compared to ionotropic ones, in the dynamics of nerve component plasticity (Eccles & McGreer, 1979).
2) Phenibut's facilitation of conditioned inhibition at earlier stages of conditioning than occurs with gaboxadol may also be explained by the fact that phenibut is a nonselective agonist of both $GABA_A$ and $GABA_B$ receptors. In experimental modeling using animals it was found that anti-epileptic drugs acting on both $GABA_A$ and $GABA_B$ receptors are more effective than selective agonists of either one of these receptors (Lloyd, 1986). It is possible that in our experiments too the earlier and more stable facilitation of conditioned inhibition attributable to phenibut, as opposed to gaboxadol, results from the simultaneous effect of phenibut on $GABA_A$ and $GABA_B$ receptors. Both of these hypotheses could be tested in targeted experiments. However, regardless of their results, it is already clear that, despite the great importance of the participation of $GABA_B$ receptors in the process of learning, ultimately their significance results from their facilitating effect on the functions of the $GABA_A$ receptors (CM. Johnston, 2005).

The results of research on the effects of GABA derivatives, both phenibut and gaboxadol, corroborate the hyperpolarization theory of internal inhibition, advanced by one of the authors of the present article (Shulgina, 1987, 2005). Information about the decisive participation of the GABAergic neuromediator system in the process of inhibiting the spread of excitation to effectors during learning are very important for understanding the dynamics of psychological processes in the norm and under conditions of pathology. The capacity of the nervous system to discriminate clearly between familiar and unfamiliar and between significant and non- significant objects and phenomena depends entirely on the conditions of interaction between excitatory (depolarizing) and inhibitory (hyperpolarizing) processes at the level of the systemic organization of individual neurons. Disruption of the normal conditions for this interaction may occur as a consequence of changes in the state of the activating systems as well as of a deficit or excessive increase in the activity of inhibition systems that affect the entire brain or are local. When a human being is unable to distinguish between familiar and unfamiliar or significant and non-significant events this creates a state of ambiguity (uncertainty) and discomfort. This state is known to be one of the most psychologically difficult for animals and humans. It is precisely this state of uncertainty that induces and maintains feelings of panic, anxiety and the inability to appropriately control movement and consciousness.

Considering these facts, information about the polyfunctionality of GABA and on the significance of this polyfunctionality for regulating various aspects of mental processes is of great interest. At the present time, neurophysiologists have amassed an enormous amount of factual material concerning the way that GABA and its receptors participate in CNS functioning. Drugs affecting the functioning of GABA receptors are widely used as

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anesthetics, anticonvulsants, anxiolytics and sedatives for treating impairments of cognitive functioning, mood and sleep disorders, epilepsy and schizophrenia (see Johnston, 2005; Wassef, Baker & Kochan, 2003 and others).

The great interest in the structure and functions of GABA receptors has led to synthesis of drugs with selective effects on various aspects of mental processes that do not have side effects such as inducing tolerance or addiction. A significant breakthrough in this area was made as a result of clarification of the complex structure of GABA receptors and the development of methods to genetically modify them by means of targeted removal of the genes responsible for the formation of specific subunits of these receptors. At the present time, 16 basic subunits have been isolated: $\alpha1 - \alpha6$, $\beta1 - \beta3$, $\gamma1 - \gamma3$, δ, ε, π, θ. (see Johnston, 1996, 2005; Sperk, Schwarzer, Tsunashima & Kandhover, 1998; Rudolph, Crestani & Möhler, 2001; Farrant, 2001 and others).

It has been shown that neurons containing receptors that contain certain subunits are located in brain structures that perform certain specific functions. Thus, nerve cells whose membranes contain GABA receptors containing the $\alpha2$ subunit are primarily located in brain structures relating to reactions to emotionally significant stimuli, including painful reinforcement: the limbic system (the amygdala, the molecular layer of the dentate fascia and in field CA3 of the hippocampus), and neocortex (Sperk, Schwarzer, Tsunashima & Kandhover, 1998; Rudolph, Crestani, Möler, 2001). Neurons whose GABA receptor contains the $\alpha5$ subunit, are located primarily in the hippocampus and participate in organizing spatial memory (Caraiscos, Elliott & You-Ten, 2004). Neurons that have the $\alpha3$ subunit in their GABA receptors are located in the reticular activating system and the basal region of the forebrain (Johnston, 2005). Evidently these are noradrenergic, dopaminergic, serotinergic and cholinergic neurons. It may be hypothesized that neurons containing GABA receptors in which $\alpha3$ subunits are present participate in regulation of the alternation of sleep, rest, and alert wakefulness.

Thus, the polyfunctionality of GABA receptors of various types supports the regulation of the performance of various biological and psychological functions by brain structures. Necessary additional research should make use of parallel recording of behavior and bioelectric brain activity as well as of the discoveries of molecular biology in order to further better understanding of the participation of ionotropic and metabotropic receptors of inhibitory GABA mediators in learning.

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