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IONIC MECHANISMS OF THE EFFECT OF PHENIBUT AND GABA NOT ASSOCIATED WITH A CHANGE IN THE FUNCTION OF THE CHLORIDE CHANNELS

I. V. Komissarov and I. I. Abramets

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In experiments on isolated spinal cord of young rats 7-14 days old under conditions of takeoff of the electrical activity of the spinal roots with a sugar bridge, it was established that the GABA-mimetic phenibut induces direct depolarization of the motoneurons. In the same concentration range (10^{-5}-10^{-4} M), GABA has a dual effect. The depolarizing component of the action of GABA in part of the experiments and the depolarizing effect of phenibut in all the experiments are preserved in the presence of picrotoxin (10^{-5} M) and under conditions of superfusion of the brain with a solution with a reduced chloride concentration. This depolarizing effect of phenibut, not associated with the activation of $GABA_A$ receptors and chloride channels coupled with them, is unchanged in a medium with Na^+ deficiency, is enhanced during depolarization of the motoneurons due to an increased concentration of K^+ (10 mM) and in the presence of imidazole, but is entirely eliminated in a medium with Ca^{2+} deficiency, containing 2 mM Mn^{2+}, or in the presence of theophylline (10^{-4} M). It is suggested that phenibut, and to some degree, GABA lower the intracellular concentration of cAMP by means of activation of the $GABA_B$ receptors, which leads to blocking of the functional activity of the potential-dependent calcium channels and a decrease in the calcium-activated outflowing potassium currents. The ability to weaken the inflowing calcium currents may also be the basis of the presynaptic inhibiting effect of GABA and GABA-mimetics (phenibut, baclofen, etc.) on the pulsed release of mediators by the axon terminals of catecholaminergic, glutamatergic, and GABA-ergic neurons.

INTRODUCTION

Changes in the functioning of nerve cells induced by γ-aminobutyric acid (GABA) are usually due to an increase in the chloride conductivity of the neuron membranes as a result of activation by the neuromediator of $GABA_A$ receptors, coupled with the chloride channels. The effects of GABA mediated by these receptors are potentiated by benzodiazepines and are eliminated by bicuculline or picrotoxin [17, 22]. However, the inhibiting effect of GABA on the pulsed release of catecholamines (CA) by the terminals of postganglionic sympathetic nerves and the axons of the CA-containing neurons of the brain [11] is unchanged under the action of bicuculline (picrotoxin) and occurs through the bicuculline-insensitive $GABA_B$-receptors [11].

A specific activator of the presynaptic $GABA_B$-receptors is β-(p-chlorophenyl)-GABA (baclofen). In concentrations close to or equal to the concentrations of GABA it inhibits the pulsed release of CA by the axon

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terminals of the CA-ergic neurons [10, 12, 23], as well as amino acid mediators from the terminals of glutamatergic and GABA-ergic neurons [16], but does not reproduce the effects of GABA that are the result of an increase in the chloride conductivity of the neuron membranes [10]. In the course of radioligand investigations it was established that [^{3}H]baclofen exhibits high-affinity binding to the membrane fragments of the brain, while baclofen displaces [^{3}H]GABA from the bond to the membranes only in the presence of Ca^{2+} [13]. Analogous properties in radioligand investigations are exhibited by β-phenyl-GABA (phenibut) [6].

Since a study of the properties and functions of the $GABA_B$-receptors of the neurons has been carried out exclusively on models of the presynaptic release of mediators, the ionic dependence of the action of baclofen or phenibut has received little investigation. Virtually nothing is known about the mechanisms of the coupling of the activation of the $GABA_B$-receptors with the change in the permeability of the neuron membranes. On the other hand, it is unclear whether the $GABA_B$-receptors are exclusively an attribute of the presynaptic terminals [10, 12] or whether they may have a postsynaptic localization [14, 21].

This communication presents data on the postsynaptic localization of phenibut-sensitive $GABA_B$-receptors of the motoneurons of the rat spinal cord and the results of an investigation of the ionic mechanisms of the action of phenibut.

METHODS

The experiments were conducted on parasagittal sections of isolated spinal cord of young rats 7-10 days old. The procedure was outlined in detail earlier [1]. The electrotonic potentials of the ventral roots of the fourth lumbar segment (L_4) and the postsynaptic reflex discharges of the motoneurons in the same root in the case of electrical stimulation of the dorsal root of L_3 by single rectangular current pulses with duration 0.3 msec and intensity 6-8 thresholds, were taken off with the aid of a sucrose bridge.

In the first series of experiments we investigated the influence of various concentrations of GABA and the $GABA_B$-mimetic phenibut at the level of polarization of the ventral roots and the amplitude of the polysynaptic reflex discharges of the motoneurons in the case of superfusion of spinal cord preparations with standard salt solution of the following composition (in millimoles per liter): sodium chloride 118, potassium chloride 1, monosubstituted potassium phosphate 1, sodium hydrocarbonate 24, calcium chloride 2.5, glucose 10; pH 7.4. The experiments were conducted at the temperature 22-24°C.

In the second series of experiments we investigated the dependence of the effects of phenibut ($2 \cdot 10^{-5}$ M) on the changes in the ionic composition of the solution with which superfusion of the isolated rat spinal cord was performed. The concentrations of Na^+, Cl^-, Ca^{2+}, and K^+ were measured: the Na^+ concentration was decreased from 142 to 14 mM by replacement of sodium chloride and 10 mM sodium hydrocarbonate with an equivalent amount of choline chloride; the Cl^- concentration was decreased from 124 to 41 mM by replacement of 83 mM sodium chloride with the corresponding amount of sodium sulfate; the Ca^{2+} concentration was decreased from 2.5 to 0.5 mM, and an additional 2 mM manganese chloride was added to this solution; the K^+ concentration was increased to 10 mM. In the case of all ionic substitutions, the pH of the medium was monitored, and when necessary adjusted to 7.4. The influence of phenibut on the spinal cord was begun 15-45 min after the beginning of superfusion of the spinal cord with a solution with changed ionic composition.

In the third series of experiments we investigated the influence of cyclic adenosine monophosphate (cAMP), theophylline, and imidazole on the effects of phenibut. In the work we used GABA, the sodium salt of adenosine-3',5'-cyclophosphoric acid, imidazole (Reanal, Hungary), phenibut, and theophylline (official preparations of the Riga Industry, USSR).

The influence of each concentration of the investigated substances was studied on four to six preparations of isolated rat spinal cord.

RESULTS

Superfusion of an isolated rat spinal cord with a salt solution containing phenibut in concentrations of 10^{-5}-10^{-4} M was accompanied by a concentration-dependent depression of polysynaptic discharges of the motoneurons, recordable in the ventral roots (Fig. 1a). GABA had an analogous effect in the same concentrations. However, in the presence of GABA the reaction of the motoneurons to the action of exciting amino acids, for example, L-glutamate, was reduced; in the presence of phenibut, on the other hand, the responses of the motoneurons to L-glutamate, on the contrary, increased. This is indicated by the increase in the depolarization electrotonic potentials (ETP) in the ventral roots, induced by the action of L-glutamic acid ($3 \cdot 10^{-4}$ M) on the spinal cord in the presence of $2 \cdot 10^{-5}$ M phenibut (Fig. 1b).

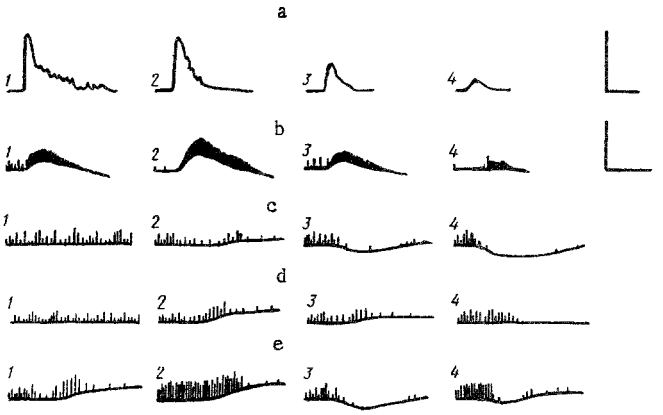

Fig. 1. Influence of GABA and phenibut on the polysynaptic reflex discharges of motoneurons and the level of polarization of the ventral roots of the rat spinal cord. a) Polysynaptic reflex discharges of motoneurons in the absence (1) and in the presence of phenibut in concentrations of 10^{-5} (2), $3 \cdot 10^{-5}$ (3), and 10^{-3} (4) M; b) electrotonic potentials (ETP) of the ventral root under the influence of L-glutamic acid ($3 \cdot 10^{-4}$ M) on the spinal cord before (1, 3) and after a 3 min influence of $2 \cdot 10^{-5}$ M phenibut (2) or $5 \cdot 10^{-5}$ M GABA (4); ETP of ventral roots before (1) and during the influence of GABA on the spinal cord in concentrations of $2 \cdot 10^{-5}$ (2), $5 \cdot 10^{-5}$ (3), and 10^{-4} (4) M; d) ETP before (1) and during the influence of phenibut in concentrations of 10^{-5} (2), $3 \cdot 10^{-5}$ (3), and 10^{-5} M (4); e) ETP of ventral roots under the influence on the spinal cord of $2 \cdot 10^{-5}$ M phenibut (1) and $5 \cdot 10^{-5}$ M GABA (3) before (1, 3) and after (2, 4) 20 min superfusion of the spinal cord with picrotoxin solution (10^{-5} M). On oscillograms b-e the beginning and end of the oscillographic recording coincide with the period of superfusion of the spinal cord with a solution containing the investigated substance. Calibration: 0.5 mV, 100 msec (for a) and 1 mV, 30 sec (for b-e).

Phenomenologically the influence of phenibut on the spinal motoneurons is only partly similar to the influence of GABA. The latter in superthreshold concentrations ($1-5 \cdot 10^{-5}$ M) induced hyper- and depolarization ETP in the ventral roots, while in higher concentrations ($1 \cdot 10^{-4}$ M) it induced primarily hyperpolarization of the motoneurons (Fig. 1c). Phenibut in the entire range of investigated concentrations (10^{-5}–10^{-4} M) led to the appearance only of depolarization ETP of the ventral roots. It is characteristic that with increasing concentration of phenibut acting on the spinal cord, the amplitude of the depolarization ETP decreased, but the inhibition of the background activity recordable in the ventral roots was enhanced (Fig. 1d).

Preliminary (for 20 min) superfusion of the spinal cord with a solution containing picrotoxin ($1 \cdot 10^{-5}$ M) not only did not decrease but even enhanced the depolarizing influences of phenibut on the motoneurons. Under the same conditions, hyperpolarization ETP of the ventral roots, due to GABA, were suppressed, while the depolarization ETP induced by it were preserved in most cases and were even enhanced in certain cases (Fig. 1e).

The depolarization ETP of the ventral roots were induced by phenibut after 30-45 min of superfusion of the isolated spinal cord with a solution with Na^+ deficiency (Fig. 2a), when the background activity (Fig. 2a) and the reflex discharges in the ventral roots were not reproduced. The depolarizing influence of phenibut on the motoneurons not only was not decreased but even was somewhat enhanced in the case of superfusion of the spinal cord for 20-30 min with a solution with Cl^- content decreased to 1/3 (Fig. 2b). The amplitude of the depolarization ETP induced in the ventral roots by phenibut increased extremely substantially after preliminary superfusion of the spinal cord with a solution with K^+ concentration increased to 10 mM as well (Fig. 2C). And yet, superfusion of isolated spinal cord with a solution containing 2 mM Mn^{2+}, while the Ca^{2+} concentration was lowered to 0.5 mM, prevented the development of depolarization ETP of the ventral roots under the influence of phenibut concentrations effective in the usual salt solution (Fig. 2d).

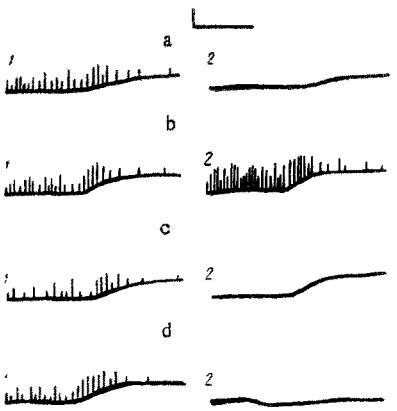

Fig. 2. Phenibut-induced electrotonic potentials (ETP) of ventral roots in the case of superfusion of isolated spinal cord with salt solutions of various ionic compositions. Phenibut ($2 \cdot 10^{-5}$ M)-induced ETP of ventral roots under conditions of superfusion of the spinal cord with a solution containing 14 mM Na^+ (a), 41 mM Cl^- (b), 10 mM K^+ (c), and 0.5 mM Ca^{2+} and 2 mM Mn^{2+} (d). 1) Superfusion with the usual salt solution; 2) with a solution with a change in the ionic composition. The EPT were recorded after 45 (a), 30 (b, d), and 15 (c) min of superfusion of the spinal cord with solutions with changed ionic composition. Calibration: 1 mV, 30 sec.

Using theophylline as an inhibitor of cyclic 3',5'-adenosine monophosphate (cAMP) phosphodiesterase, and imidazole as an activator of this enzyme, we attempted to determine to what degree the depolarizing influence of phenibut on the motoneurons may depend on the intracellular concentration of cAMP. The threshold concentration at which theophylline increased the background activity and somewhat increased the amplitude and duration of the evoked postsynaptic potentials of the ventral roots proved to be 10^{-4} M. Against a background of preliminary 15 min superfusion of the brain with a solution of theophylline in the indicated concentration, the depolarization ETP of the ventral roots induced by phenibut ($2 \cdot 10^{-5}$ M) decreased, while the inhibition of the background activity in the ventral roots, usually observed under the action of phenibut, was not detected under these conditions (Fig. 3a). Depression of the polysynaptic reflex discharges in the ventral root, caused by phenibut, against a background of the action of theophylline, was substantially less pronounced than in its absence (Fig. 3c). In one of the four experiments, preliminary superfusion of the spinal cord with a solution of cAMP (10^{-3} M), like theophylline, eliminated the depolarizing effect of phenibut ($2 \cdot 10^{-5}$ M) on the motoneurons. Superfusion of the spinal cord with a solution of imidazole ($5 \cdot 10^{-4}$ M) somewhat enhanced the background activity of the motoneurons, while the depolarizing effect of phenibut increased against this background (Fig. 3b). The inhibition of the polysynaptic reflex responses by phenibut in the presence of imidazole was more pronounced (Fig. 3d).

DISCUSSION

In the course of our experiments it was established that β-phenyl-GABA (phenibut) inhibits the polysynaptic discharges of the motoneurons (Fig. 1a) and their background pulse activity (Fig. 1d), but in addition, it induces a depolarization of the motoneurons (Fig. 1d). Both effects cannot be the result of the influence of phenibut on the same neuron structures, since against a background of the phenibut-induced depolarization of the motoneurons and their increased sensitivity to the influence of exciting factors, for example, to L-glutamate (Fig. 1b), we should expect a facilitation by phenibut of the polysynaptic reflex responses.

The influences of phenibut on the synaptic conduction in the spinal cord is analogous to the influence of β-(p-chlorophenyl)-GABA (baclofen). The inhibiting action of this compound on the evoked potentials in the spinal cord [8] or the olfactory cortex of the brain [16] of rats is associated with inhibition of the release of mediators by the terminals of the corresponding afferents. An analogous presynaptic mechanism, consisting of inhibition of the release of mediators by the terminals of the primary afferents, evidently lies at the basis of the inhibiting effect of phenibut on the polysynaptic reflex discharges of the spinal motoneurons and their background activity.

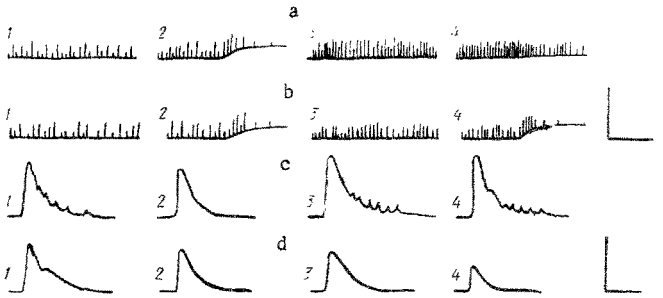

Fig. 3. Influence of theophylline and imidazole on the effects of phenibut. a, b) Electrotonic; c, d) induced polysynaptic potentials of the ventral roots before (1) and 15 min after (3) superfusion of the spinal cord with a solution containing 10^{-4} theophylline (a, c) or $5 \cdot 10^{-4}$ M imidazole (b, d). 2) Changes in the potentials in superfusion of the spinal cord with phenibut solution ($2 \cdot 10^{-5}$ M) before superfusion and (4) after preliminary (15 min) superfusion of the spinal cord with a theophylline solution (a, c) or imidazole (b, d). Remaining notations the same as in Fig. 1.

The depolarization of the motoneurons due to the influence of phenibut, on the contrary, is of postsynaptic origin, since the depolarization ETP of the ventral roots are induced by phenibut under conditions of superfusion of the brain not only by the usual salt solution but also by a solution in which 90% of the Na^+ is replaced by choline, and, consequently, the interneuronal transmission in the rat spinal cord is entirely eliminated. The direct depolarizing action of phenibut is resistant to the action of picrotoxin in a concentration in which it inhibits the hyperpolarizing influence of GABA on the motoneurons (Fig. 1e). The depolarizing action of phenibut is also preserved under conditions of superfusion of the brain with a solution with a two thirds reduced content of chloride (Fig. 2b). These facts permit us to assert that the direct depolarizing influence of phenibut on the spinal motoneurons is exerted not through the $GABA_A$-receptors, coupled with the chloride channels, since, as is well known, picrotoxin blocks the chloride channels [24], while the chloride-dependent depolarization responses of the neurons of vertebrates in hypochloride or chloride-free media, mediated by activation of the $GABA_A$-receptors, are substantially decreased [2, 19]. Evidently this effect of phenibut is exerted by means of the $GABA_B$-receptors, insensitive to bicuculline and picrotoxin. It is not associated with a change in the chloride conductivity of the membranes of the motoneurons and is of a different ionic nature. Probably an analogous effect is also characteristic of GABA to a definite degree. Although GABA primarily hyperpolarizes the spinal cord, under definite conditions it induces depolarization ETP in the ventral roots (Fig. 1c), which in most experiments are preserved and even increased somewhat in the presence of picrotoxin (Fig. 1e).

The preservation of the depolarizing effects under conditions of superfusion of the isolated spinal cord with a sodium-deficient salt solution is evidence that the influence of phenibut is not associated with a change in the sodium conductivity of the membranes of the motoneurons, On the other hand, the phenibut-induced depolarization of the spinal motoneurons proved to be a calcium-dependent phenomenon: Under conditions of superfusion of the brain with a salt solution with a reduced content of Ca^{2+} and in the presence of Mn^{2+}, phenibut does not lead to the appearance of depolarization ETP in the ventral roots (Fig. 2d).

Since Mn^{2+} effectively blocks the potential-dependent calcium channels in the membrane of the neurons, and a deficiency of Ca^{2+} in the medium but not of Na^+ is significant for a suppression of the depolarizing effect of phenibut, it can be assumed that the calcium dependence of the depolarizing effects of phenibut is provided for by electroexcitable calcium channels and not by the chemocontrolled channels, relatively unselective for cations. This, however, does not mean that phenibut induces depolarization of the motoneurons, increasing the transmembrane transport of Ca^{2+} through the potential-dependent calcium channels. It is known that the inflowing calcium current is weakened when the membrane is depolarized [5]. And yet, under conditions of artificial depolarization of the membrane of the motoneurons, created by superfusion of the isolated spinal cord with a solution containing an increased K^+ concentration (10 mM), the depolarizing effects of phenibut not only are not decreased but even increase appreciably (Fig. 2c). The enhancement of the depolarizing influence of phenibut in the case of an artificial reduction of the membrane potential of the motoneurons can be explained by a decrease in the outflowing potassium currents, keeping in mind that depolarization due to a de-

crease in the outflowing potassium currents is enhanced when the membrane potential of the neurons is lowered [7, 25]. Recalling the calcium dependence of the depolarizing effect of phenibut (Fig. 2d), it is logical to assume that phenibut suppresses the calcium-dependent outflowing potassium current of decreasing intracellular Ca^{2+} concentration.

The ability of phenibut to lower the functional activity of the electroexcitable calcium channels and decrease the calcium-dependent outflowing potassium current can occur only indirectly, probably by means of some sort of metabolic link. In recent investigations on isolated perfused neurons of mollusks and mammals, it was established that the function of the electroexcitable calcium channels is controlled by the intracellular concentration of cAMP: a decrease in it from the optimum level (on the order of 10^{-4} M) leads to a decrease in the functional activity of the potential-dependent calcium channels [3, 4]. Although GABA, mucimol, and baclofen decrease primarily the cGMP content in certain divisions of the brain (cerebellum), in other regions of the brain (anterior hypothalamus), GABA-mimetics substantially lower the cAMP level [20, 26].

The probability of the participation of cAMP in the depolarizing effects of phenibut is confirmed by the fact that the depolarization ETP of the ventral roots do not arise under the influence of phenibut if the brain was preliminarily superfused with a solution containing the phosphodiesterase blocker theophylline (Fig. 3a). And on the contrary, the phosphodiesterase activator imidazole enhances the depolarizing influence of phenibut on the motoneurons (Fig. 3b). As can be seen from Fig. 3c, d, theophylline weakens the inhibiting influence of phenibut on the polysynaptic reflex discharges, while imidazole facilitates it. If the cause of the inhibition of polysynaptic reflex responses by phenibut, as discussed above, is a suppression of the pulsed release of mediators by the terminals of the spinal afferents, then the differently directed effects of theophylline and imidazole on the reflex responses are evidence that the lowering of the intracellular concentration of cAMP by phenibut and the consequent decrease in the functional activity of the potential-dependent calcium channels of the neuron membrane also serve as a basis for the presynaptic effects of phenibut.

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NEURON ACTIVITY IN THE MOTOR CORTEX OF A CAT WITH INHIBITION OF A CONDITIONED POSTURAL CHANGE REFLEX

B. I. Busel' and M. G. Moldavan

UDC 612.825:612.822:612.821.6

A study was made of the neuron spike reactions in the primary motor cortex of the cat in the projection zone of the contralateral forelimb with external and internal inhibition of the conditioned reflex for posture change that consisted of shifting the body weight to the forelimb being studied. Spike responses of the neurons to extraneous stimuli and the conditioned signal were determined to a significant degree by the condition of the animal and its habituation to the signal used. In trained animals, the duration of responses to extraneous stimulation was shorter than in the nontrained. With external and internal inhibition, we observed simultaneous disappearance of conditioned reflex movements and the trace spike discharges connected with them. Frequently extraneous stimulations could suppress trace discharges even when learned movement was present. Extraneous stimulations of a different modality inhibited the reflex to different degrees. The change in neuron spike reaction connected with a conditioned reflex change in posture was similar to well-learned local reflex phenomena.

INTRODUCTION

It has been experimentally confirmed [8] that the coordination function of the motor area of the cortex during the realization of a conditioned reflex consists of the organization of a single integrated motor reaction that includes postural and local components. We have little information on the features of cortical regulation of postural reactions due to a conditioned reflex since in most work thus far only problems of nervous regulation of local conditioned reflex movements have been considered. In our preceding studies [4], we es-

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