to decipher the mechanisms regulating secretion of insular hormones. To solve the problem of whether PMAP and peptides similar to it may be used to correct diabetes, further investigations in vivo are necessary.

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EFFECT OF 5-HT_{1A} RECEPTOR AGONISTS ON AMINO ACID- AND DOPAMINERGIC RESPONSES OF NEURONS

I. I. Abramets, I. V. Komissarov, and I. M. Samoilovich

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The anxiolytic action of buspirone and its structural analogs (gepirone, ipsapirone, campirone, etc.) is due to their activating effect on 5-HT_{1A} receptors of brain nerve cells [10]. The result of activation of 5-HT_{1A} receptors in somatodendritic synapses of neurons of the mesencephalic nuclei raphe and neurons of the limbic system of the brain is depression of their functional activity [6, 7, 11]. Depression of the function of these cells may be the result of changes in the passive properties of the cell membranes arising during hyperpolarization or the result of modulation of the response to the action of nervous influences converging on the neurons. It has been shown that despite the weakness [3] or absence [8] of a hyperpolarizing influence on the hippocampal pyramidal cells, buspirone, if given by the systemic or intrahippocampal routes [9], and also in brain slices [8], suppresses excitatory postsynaptic potentials (EPSP) evoked in pyramidal neurons by stimulation of hippocampal afferent fibers. However, it is not clear whether this effect is the result of the pre- or postsynaptic action of buspirone.

The present investigation showed that agonists of 5-HT_{1A} receptors, acting postsynaptically, potentiate the effects of gamma-aminobutyric acid (GABA), but significantly reduce the inhibitory effects of dopamine and the excitatory effect of aspartate on nerve cells.

EXPERIMENTAL METHOD

The effect of buspirone and campirone (10 μmoles/liter) on responses of motoneurons of the isolated sagitally divided spinal cord of Central Asiatic frogs, evoked by GABA or aspartate, and on GABA- or dopamine (DA)-induced neuronal responses of spinal sensory ganglia of adult rats, were studied. The test objects were superfused with salt solutions

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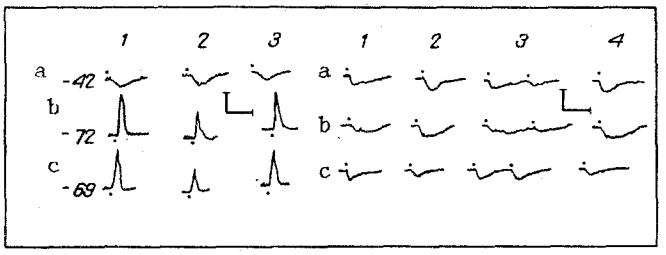

Fig. 3 Fig. 4

Fig. 1. Modulating effect of campirone and 5-HT on responses of spinal motoneurons of frogs evoked by GABA and aspartate. Changes in membrane potential of motoneurons during microapplication of GABA (a) and aspartate (b, c) before (1) and 5 min after superfusion of brain with solution of campirone (2a, b) or 5-HT, in the presence of methysergide (2c), and 15 min after their rinsing out (3). Moments of application indicated by dots. Numbers on left show initial MP of motoneurons. Calibration: 5 mV, 1 min.

Fig. 2. Effect of 5-HT and its 1A-agonists on neuronal responses of rat sensory ganglia to dopamine. Changes of MP of neurons during microapplication of buspirone (1a), campirone (1b), 5-HT (1c), and dopamine (2a-c, 4a-c), or dopamine applied immediately after the end of the effects of preliminary application of buspirone (3a), campirone (3b), or 5-HT (3c). Ganglion was superfused between traces 1 and 2, 2 and 3, and 3 and 4 with salt solution for 5, 10, and 15 min respectively. Calibration: 5 mV, 1 min.

in small chambers (0.5-3 ml) accompanied by aeration with oxygen at a temperature of 18-22°C (for details of the method, see in [1, 2]). Changes of membrane potential (MP) and input resistance of the nerve cell membranes were recorded by the standard microelectrode technique. Motoneurons were identified by their antidromic action potentials in response to electrical stimulation of the ventral root. Motoneurons which responded to application of aspartate (in the absence of Mg^{2+}) by depolarization and by reduction of membrane resistance, abolished by ketamine (10 μmoles/liter), were used. They could accordingly be regarded as NMDA-sensitive neurons. Neurons in which GABA modified MP through the intermediary of $GABA_A$-receptors were identified with the aid of picrotoxin (2 μmoles/liter). Among neurons of the spinal ganglion, those which reacted to dopamine by hyperpolarization, abolished by sulpiride (Eglonil, 10 μmoles/liter), were chosen for investigation. Solutions of GABA and L-aspartate (Reakhim, USSR), dopamine (Orion, Finland), and 5-HT (Reanal, Hungary) in 0.05 M concentration were applied to the neurons under pressure through a micropipet whose tip was as close as possible to the recording microelectrode. Solutions of other substances (0.1 ml) were injected into the antechamber in dilutions sufficient to create the specified final concentrations in the chamber itself.

EXPERIMENTAL RESULTS

Motoneurons whose initial MP did not exceed −50 mV responded to GABA by hyperpolarization amounting to 3-6 mV. Preliminary superfusion of the brain for 5 min with solutions of buspirone or campirone potentiated the hyperpolarization responses of the motoneurons to GABA (Fig. 1a). Under the influence of campirone (10 μmoles/liter) hyperpolarization responses evoked by GABA were increased on average by 27 ± 4%. Conversely, application of aspartic acid to the motoneurons evoked their rapid depolarization with mean amplitude of 11.2 ± 1.3 mV (n = 32) and a temporary increase of membrane conduction. After superfusion of the brain with a solution containing 10 μmoles/liter of buspirone or campirone, the amplitudes of the depolarization responses to aspartate decreased (Fig. 1b) by 30-50 (38 ± 7) percent. Subsequent rinsing of the spinal cord restored the original effects of both GABA and aspartate (Fig. 1a, b).

Responses of motoneurons to GABA and aspartate were modified even though preliminary application of buspirone or campirone caused no significant changes in MP of the nerve cells (Fig. 1). Moreover, buspirone and campirone potentiated the effect of GABA on the sensory ganglionic neurons of the rats (not shown in Figs. 1 and 2), which were depolarized on application of GABA, just as in neurons of the sensory ganglia of other mammals [4].

Changes in the effects of aspartate described above are specific, for 5-HT_{1A}-agonists did not change aspartate-induced depolarization responses of motoneurons if they were resistant to ketamine, i.e., were mediated through the kainate/quisqualate type of receptors of dicarboxylic amino acids. The significant fact is that analogous changes in motoneuronal responses to aspartate were observed after superfusion of the brain with salt solution containing 5-HT (3 μmoles/liter) and methysergide in a concentration (1 μmole/liter) sufficient to block R_2-5-HT (Fig. 1c). This suggests that the modulating effect of 1A-agonists, like that of 5-HT itself, is realized through R_{1A}-5-HT. It is probably due to a change in the degree of phosphorylation of substrates of internal ionic channels of $GABA_A$- and NMDA-receptors. Activation of R_{1A}-5-HT by 5-HT and its 1A-agonists is known to be accompanied by lowering of the intracellular concentration of cAMP in nerve cells [1, 5].

Effects of dopamine mediated by R_2-DA also were modified by buspirone and campirone (Fig. 2a, b). However, weakening of the effects of DA after preliminary exposure of sensory ganglionic neurons to buspirone or campirone is not the result of their modulating effect, for serotonin, which causes hyperpolarization of sensory ganglionic neurons also through the intermediary of R_{1A}-5-HT [1], does not possess an analogous action, but actually potentiates the effect of DA (Fig. 2a). Weakening of the D_2-effects of dopamine is evidently due to specific buspirone- and campirone-induced blockade of R_2-DA. In radioligand investigations buspirone exhibits quite high affinity for them, counteracting binding of ^{3}H-sulpiride with membranes in the striatum (EC_{50} = 235 nmoles/liter). At the same time it potentiates the metabolic turnover of DA in the corpus striatum [12].

The modulating effect of 1A-agonists of 5-HT on $GABA_A$- and NMDA-reception of nerve cells, as a result of which buspirone and its structural analogs can potentiate GABA-ergic inhibition, while simultaneously reducing the efficacy of the excitatory effects of dicarboxylic amino acids, may play a significant role in the anxiety-relieving effects of the buspironelike anxiolytics.

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