pression of monoaminergic and GABA transmission, according to the data described above, was probably due to a decrease in the content of transmitters in the presynaptic zone of the synaptic junctions on account of increased activity of the transmitter reuptake systems and, possibly, inhibition of the released transmitters, leading to a decrease in the content of the latter in the synaptic space.

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ACTION OF β-CARBOLINE DERIVATIVES ON EVOKED HIPPOCAMPAL UNIT ACTIVITY

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Specific benzodiazepine receptors (BDR), mediating their pharmacologic activity, have been found in the CNS of higher vertebrates, including man [8]. Originally it was considered that only pharmacologically active benzodiazepines (BD) interact with high affinity with BDR. More recently, however, several compounds with high affinity for BDR, but not exhibiting anticonvulsant or anxiolytic effects characteristic of BD at the clinical level, have been found. A special place among these compounds is occupied by β-carboline derivatives, which interact with high affinity with BDR, thereby giving rise to biochemical and behavioral changes opposite to the effects of BD [4]. It has been shown, for instance, that β-carboline derivatives such as 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) and methyl-β-carboline-3-carboxylate possess marked ability to induce seizures in experimental animals. It has also been shown that the intensity of the convulsant activity of these derivatives correlates with the degree of occupancy of BDR by them *in vivo* [4].

The writers previously described the effect of BD on the evoked potential (EP) arising in area CA1 of the hippocampus in response to stimulation of Schaffer's collaterals [1]. The aim of the present investigation was to study the action of β-carboline derivatives in the same experimental system and to compare it with the effect of BD.

EXPERIMENTAL METHOD

Experiments were carried out on surviving hippocampal slices from Wistar rats aged 2-3 weeks, by the method described previously [1]. The synthesis of methyl ester of tetrahydro-β-carboline also was described previously [6]. The methyl ester of 1-phenyl-tetrahydro-β-carboline was synthesized as follows: 10 g tryptophan was dissolved in 50 ml of 1 M H_2SO_4,

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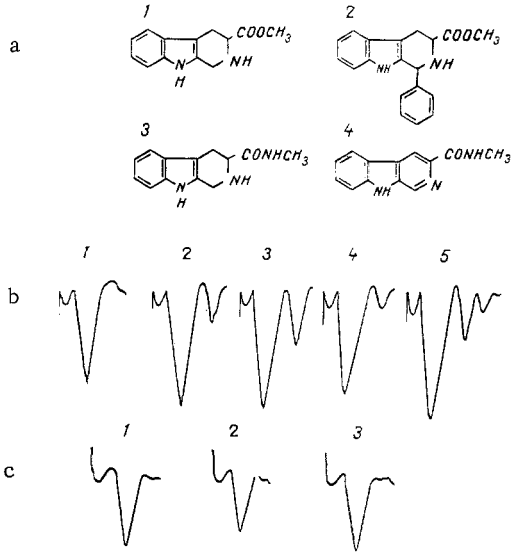

Fig. 1. Effects of β-carboline derivatives on EP: a) structural formulas of substances tested; 1) methyl ester of tetrahydro-β-carboline; 2) methyl ester of 1-phenyl-tetrahydro-β-carboline; 3) tetrahydro-β-carboline methylamide; 4) β-carboline methylamide (FG7142); b) excitatory action of FG7142 (4 μM) on EP (separate case): 1) control EP; 2) EP after application of GR7142 for 10 min; 3) elution for 3 min; 4) elution for 15 min; 5) elution for 35 min; c) inhibitory action of methyl ester of tetrahydro-β-carboline (4 μM) on EP (separate case): 1) control EP; 2) EP after application of substance for 10 min; 3) elution for 15 min.

and 160 ml water, 40 ml dioxane, and 5.4 g benzaldehyde were added. The mixture was heated with a reflux condenser for 2 h, then cooled and extracted with 3 × 100 ml of ether. The aqueous solution was neutralized with ammonia and the precipitate of 1-phenyl-tetrahydro-β-carboline was filtered and dried under a vacuum. The methyl ester of 1-phenyl-tetrahydro-β-carboline was obtained by boiling for 2 h in absolute methanol saturated with HCl, followed by purification by recrystallization from aqueous ethanol. Methylamides of tetrahydro-β-carboline and β-carboline were obtained by heating the corresponding methyl esters for 4 h in dioxane, saturated with methylamine at 100°C, and purification by recrystallization from ethanol. All the compounds synthesized were chromatographically pure and their structures were confirmed by mass-spectrometry. Their formulas are given in Fig. 1a. The β-carboline derivatives were dissolved in ethanol to $2 \cdot 10^{-2}$ M, and then diluted to a working concentration of 4 μM with Hanks' solution. In the control, the corresponding volume of ethanol, which caused no changes in EP, was added to the flow.

EXPERIMENTAL RESULTS

Each compound was tested on five slices. The general features of the action of all β-carboline derivatives were an increase in the amplitude of the population spike (PS) by 10-20% of the control level after application for 10-15 min, an increase in the number of PS, potentiation of the effect of the substance after the beginning of elution, and poor elutability (incomplete recovery of EP after elution for 40-60 min).

No significant differences were found in the ability of the compounds tested to increase the amplitude of PS. In virtually all cases an increase in the effect of the substance took place after the beginning of elution. In some cases changes in EP during and after elution were periodic in character: at first the effect was potentiated, and this was followed by almost complete recovery of EP to the initial level, whereupon a new increase in the response began (Fig. 1b). In one of five slices methyl ester of 1-phenyl-tetrahydro-β-carboline caused a decrease in PS by 15% (Fig. 1c). A similar effect also was observed in one of five experiments during application of the methyl ester of tetrahydro-β-carboline.

β-Carboline derivatives are high-affinity ligands of BDR. In this respect their activity is opposite to the activity of BD, and, in particular, they behave as convulsants [4]. It has also been shown that the affinity of BD-agonists for BDR is increased in the presence of GABA, whereas the affinity of β-carbolines is reduced [4].

The writers showed previously that the effect of BD on evoked hippocampal unit activity is manifested as a reversible decrease in PS [1]. This effect was partially abolished by the specific BF-antagonist RO15-1788 [2], which suggested that the action of BD in this system is mediated through BDR. In the present investigation the action of β-carboline derivatives was studied to compare their activity with the action of BD on models of hippocampal slices. In this system β-carboline derivatives in most cases had an excitatory action. whereas BD inhibit hippocampal unit activity [1, 2]. This is in good agreement with data in the literature on the opposite effects of β-carbolines compared with the action of BD in behavioral and biochemical experiments [4-7]. Changes evoked by β-carbolines in the present experiments can

be explained from the standpoint of their interaction with BDR subpopulations specific for BD antagonists [3, 5]. It was shown previously [2] that the specific BD antagonist RO15-1788 in some cases exhibited an excitatory action on neurons in hippocampal slices. It can accordingly be postulated that in the given experimental system there exists BDR which mediate the facilitatory action of certain ligands, including β-carbolines, in EP. Such receptors can perhaps be represented as what have been called the BDR conformation with a closed chloride channel [4]. Interaction of BD antagonists with this receptor would fix it in that particular state and would thereby reduce GABA-neurotransmission, by reducing the probability of opening of the chloride channel during occupation of the GABA receptor. This hypothesis is confirmed by the fact that DMCM reduced the electrophysiological effect of GABA in a culture of spinal neurons [4], and also by the results of our earlier observations, in which GABA antagonists bicuculline and picrotoxin gave rise to changes outwardly similar to the effect of β-carbolines [1].

Enhancement of the effect of β-carbolines at the beginning of elution and also the need to elute the preparations for a long time remain difficult to explain. The reason may perhaps be that the conformation of BDR with a closed chloride channel is fixed and persists for some time in the absence of the ligand. Another possibility is that β-carbolines trigger more prolonged physiological processes than in the case of action of BD.

The results of this investigation suggest the existence of mechanisms in the hippocampal formation for realization of the opposite effects connected with occupation of BDR.

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