PHYSIOLOGY

Effects of Nootropics on Electrical Activity in Rat Hippocampal CA1 Area

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Experiments on rat hippocampal slices showed that high concentrations of nooglutil and mexidol, but not piracetam, suppressed the ortho- and antidromic population responses in the CA1 area evoked by paired stimulation, the orthodromic responses being more sensitive to the drugs. The effects of both drugs were blocked by AP7, a specific antagonist of N-methyl-D-aspartate receptors. It is suggested that N-activation of methyl-D-aspartate receptors by high concentrations of nooglutil and mexidol reduced CA1 pyramidal cell responsiveness.

Key Words: *nootropics; hippocampal slices; N-methyl-D-aspartate receptors*

The mechanisms of nootropic action are now intensely studied *in vitro* on slice preparations of the hippocampus, which plays an important role in learning and memory [5,7-10]. It was found that nootropics change electrophysiological characteristics of rat and guinea pig hippocampus. They either facilitate long-term potentiation of synaptic responses in the CA1 and CA3 areas (pitacetam, oxiracetam, aniracetam, *etc.*) [11-13], or enhance short-term potentiation of synaptic responses in CA1 pyramidal cells induced by application of N-methyl-D-aspartate (NMDA) (piracetam, etimizol, nooglutil, ambocarb) [1]. This work was aimed at investigation of the effects of nooglutil and mexidol, original nootropic preparations [2-4] on evoked electrical activity in the CA1 area.

MATERIALS AND METHODS

The experiments were carried out on hippocampal slices (350-400 μ) from 38 Wistar male rats (150-200 g) [6]. The slices were perfused with a medium containing (mM): 126 NaCl, 3 KCl, 1.2 $MgSO_4$, 1.25 NaH_2PO_4, 2 $CaCl_2$, 26 $NaHCO_3$, and 10 glucose at a rate of 2 ml/min. The medium was saturated with carbogen (95% O_2 and 5% CO_2, pH 7.4) and heated to 35±0.5°C. Electrical activity was recorded after 1-h preconditioning in the perfusion medium. CA1 population responses were recorded with glass microelectrodes filled with 0.15 M NaCl. Ortho- and antidromic stimuli were applied to the Schaffer collaterals and alveus, respectively, through bipolar platinum electrodes. Single or paired square pulses (3-8 V, 0.1 msec) were used for stimulation. Population responses were recorded with an ATAK-350 analyzer. DL-2-amino-7-phosphonoheptanoic acid (AP7, Tocris Neuramine) was used as a specific NMDA receptor antagonist.

RESULTS

Piracetam (100 μM-10 mM) did not affect the latency, amplitude, and configuration of population responses in rat hippocampal slices (n=10).

Nooglutil in concentrations from 10 μ to 5 mM (n=10) also had no effect, while in a higher concentration (10 mM, 50-min perfusion, n=5) it reversibly inhibited both the antidromic (Table 1) and, to a greater extent (p<0.002), orthodromic responses. The responses returned to the baseline after 1-h washout

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TABLE 1. Suppression of Ortho- and Antidromic Responses with Nooglutil and Mexidol (%, $M \pm m$)

Drug	Orthodromic responses		Antidromic responses	
	I	II	I	II
Nooglutil, 10 mM	86±3	81±4	50±7	43±7
Mexidol, 5 mM	91±4	87±5	53±7	52±5

(Fig. 1). No suppression was observed in the presence of NMDA receptor antagonist AP7 (20 μM) introduced into the perfusion medium 15 min prior to nooglutil (10 mM, n=5) (Fig. 1).

Mexidol in a concentration of 5 mM (n=10) caused similar suppression (Fig. 2), while in lower concentrations (10 μM-2.5 mM, n=10) it was ineffective. Orthodromic responses were also more susceptible to mexidol (p<0.001). Both ortho- and antidromic potentials returned to the baseline after 1-h washout (Fig. 2). Mexidol-induced suppression was also blocked by AP7 (n=5, Fig. 2).

Thus, both nooglutil and mexidol in high concentrations (but not piracetam) inhibited NMDA-dependent population responses in the CA1 hippocampal area induced by paired ortho- and antidromic stimulation. Synaptic transmission in the Schaffer collaterals-CA1 pyramidal cells system was very sensitive to nootropic-induced depression, because orthodromic potentials were less sensitive to the drugs.

The involvement of NMDA-receptors in this effect was not surprising. It was previously shown that specific NMDA receptors antagonist AP5 blocked the effects of oxiracetam on hippocampal CA1 field responses in rats [11]. Nootropics of different chemical structure enhance short-term potentiation of synaptic transmission in the CA1 region of hippocampal slices induced by NMDA [1].

Thus, nooglutil and mexidol in high concentrations inhibit synaptic transmission in the Schaffer collaterals-CA1 pyramidal cells system through activation of NMDA receptors.

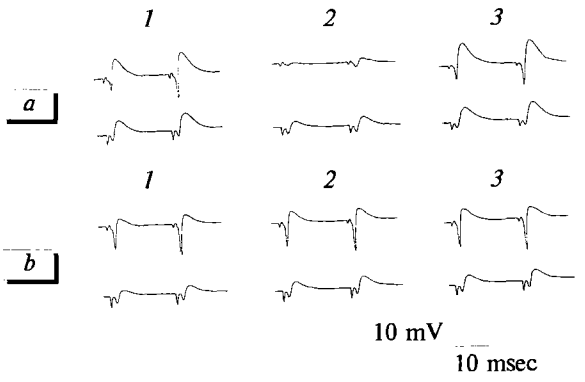

Fig. 1. Effects of nooglutil (10 mM, *a*) on orthodromic (upper curves) and antidromic (lower curves) responses in the rat hippocampal CA1 area induced by paired stimuli and their blockade with AP7 (20 μM, *b*). *1*) control; *2*) exposure; *3*) washout.

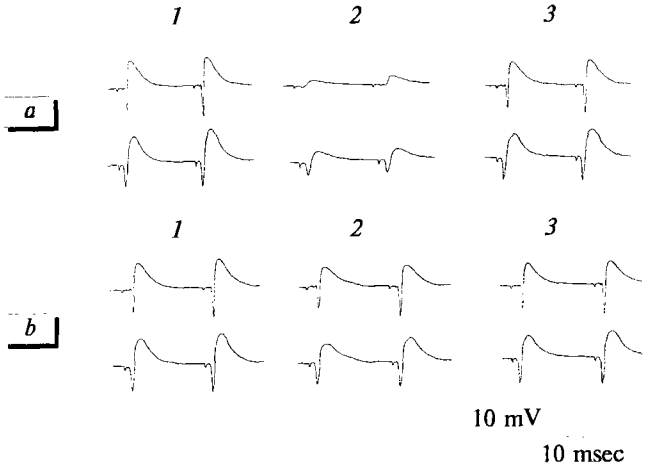

Fig. 2. Effects of mexidol (5 mM, *a*) on ortho- (upper curves) and antidromic (lower curves) responses in rat hippocampal CA1 area induced by paired stimuli and their blockade with AP7 (20 μM, *b*). *1*) control (*a*) or AP7 (*b*); *2*) exposure; 3) washout.

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