EFFECT OF MUSCARINIC AND NICOTINIC ANTICHOLINERGIC DRUGS ON EXCITABILITY OF THE DORSAL HIPPOCAMPUS IN ACUTE ALCOHOL INTOXICATION

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KEY WORDS: alcohol intoxication; hippocampus; rabbit; anticholinergic drugs.

In alcohol intoxication the functional state of brain structures is modified [1, 4] in association with disturbances of neurotransmitter systems [1, 7]. The effect of alcohol on the cholinergic system has been studied least, but it has been shown that ethanol disturbs acetylcholine synthesis and delays its release in the brain [8, 12]. The latter effect coincides with an increase in the number of muscarinic (M) acetylcholine receptors in the hippocampus and cortex [14]. Substances which can be used to modify activity of the cholinergic system in ethanol intoxication are limited to M anticholinergic drugs and acetylcholinesterase inhibitors [5, 8, 9].

The aims of this investigation were to study excitability of the dorsal hippocampus (a structure linked with emotions and behavior and responsible for the paroxysmal syndrome during ethanol withdrawal) under conditions of acute alcohol intoxication and the possibility of pharmacotherapy of the induced pathological state by means of M and nicotinic (N) anticholinergic agents with a central type of action.

EXPERIMENTAL METHODS

Experiments were carried out on 12 rabbits with chronically implanted electrodes in the sensometer cortex, dorsal hippocampus (areas CA-1 and CA-2), and the mesencephalic reticular formation.

Acute alcohol intoxication was induced by administration of ethanol in doses of 1 g/kg (intravenously) and 3 g/kg (by the intragastric route). A 30% solution of ethanol made up in physiological saline was used.

The indicator of excitability of the dorsal hippocampus was the minimal threshold of after-discharges (AD) evoked by electrical stimulation of this structure by square pulses of current, with a frequency of 50 Hz and a duration of 5 msec; the duration of stimulation was 5 sec.

The M cholinolytic metamizil* (1 mg/kg) and the Soviet N cholinolytic éterofen (IÉM-506), in a dose of 20 mg/kg, were injected intraperitoneally. Both compounds were synthesized in the Department of Pharmacology of the Institute. The compounds were injected 20 min before ethanol. Each experiment lasted 6 h and the intervals between stimulations were 10-20 min. The experimental results were analyzed visually and statistically by Student's test ($p = 0.05$, $n = 6$). After the end of the experiments the location of the electrodes was verified histologically.

EXPERIMENTAL RESULTS

After injection of ethanol changes in the EEG consisted of the development of dominance of stable slow waves in all brain structures recorded for 25-30 min after a transient activa-

*Methylbenactyzine.

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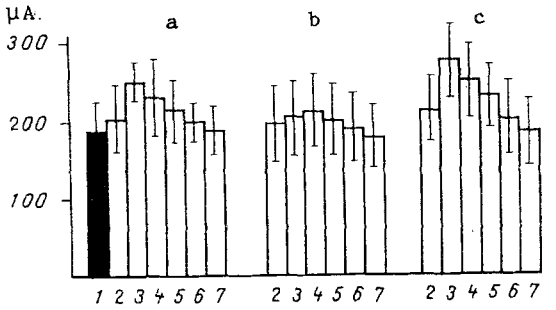

Fig. 1. Time course of thresholds of afterdischarges in dorsal hippocampus: a) under the influence of ethanol (3 g/kg, by the intragastric route); b) after prophylactic injection of eterofen 20 min before ethanol; c) under the influence of eterofen alone.

tion reaction. This was followed by alternation of slow-wave activity and the activation reaction. With slowing of the rhythm of brain electrical activity, gradual disturbance of coordination, relaxation of the muscles, and assumption of the side position were observed in the animals.

EEG and behavioral changes were similar after administration of ethanol in a dose of 1 g/kg intravenously and 3 g/kg by the intragastric route. The only difference was the more rapid development of high-amplitude slow-wave activity and the more rapid subsequent return to a normal EEG and behavior in the case of intravenous injection of ethanol in a dose of 1 g/kg.

Electrical stimulation of the dorsal hippocampus with current of threshold values caused local AD in the stimulated hippocampus. Behavior was characterized by orienting reactions, adversive responses of the head and trunk to the side opposite to the stimulated hippocampus, and sometimes tonicoclonic spasms of the limbs and trunk, which occurred as a result of irradiation of paroxysmal activity in the contralateral hippocampus and mesencephalic reticular formation.

After injection of ethanol the thresholds of AD were raised (Fig. 1). They were highest in the first 30-60 min after injection of ethanol, but later, starting with the 2nd hour, they fell, and regained their initial value 4 h after injection of ethanol. The character of the behavioral responses of the animals with alcohol intoxication was virtually unchanged.

Metamizil caused no statistically significant changes in the thresholds of AD in the hippocampus. After combined administration of metamizil and ethanol the thresholds of AD rose more than when metamizil or ethanol was given along. The changes under these circumstances were more marked after prophylactic metamizil and were more clearly defined within the interval of 60-120 min. Metamizil also potentiated the behavioral effects of intoxication in the animals and delayed normalization of the EEG by 30.0 ± 2.3 min. Recovery of coordination and motor activity occurred more slowly than in the experiments with ethanol along.

Eterofen raised the thresholds of AD in the dorsal hippocampus. This effect was most marked and was statistically significant between 30 and 60 min. In acute alcohol intoxication prophylactic injection of eterofen caused virtually no change in the thresholds of AD.

After combined administration of eterofen and ethanol slow-wave activity was less abundant on the EEG than after injection of ethanol alone. Under the influence of eterofen alcohol intoxication was considerably weakened in the animals, the period of "drunkenness" was shortened, and normal behavior was restored more rapidly (by 40 ± 5 min).

The greatest rise of the AD thresholds was observed during the first 30-60 min after administration of ethanol, which coincides with the maximal blood ethanol level [13]. The hippocampus (all its layers) is a structure which is particularly sensitive to ethanol [10]. In moderate and large doses ethanol has a depressant effect on brain structures [3]. Our own investigations and also those of other workers [3, 12] have demonstrated the effect of ethanol on cholinergic systems. The M cholinolytic metamizil, which we used, which can block muscarinic acetylcholine receptors of the ascending activating reticular system [2], in acute

alcohol intoxication considerably reduced the excitability of the dorsal hippocampus, and strengthened and potentiated the EEG and behavioral effects of "drunkenness." The N cholinolytic eterofen which, according to data in [6], depressed excitability of the dorsal hippocampus and cortex and that had virtually no effect on the reticular formation, conversely weakened the effect of alcohol.

This investigation of the effects of drugs selectively blocking M or N acetylcholine receptors thus showed that those acting on N acetylcholine receptors can weaken the effects of alcohol.

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DISTURBANCE OF POSTNATAL DEVELOPMENT OF BRAIN MONOAMINE OXIDASE ACTIVITY FOLLOWING ANTENATAL EXPOSURE TO ALCOHOL

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An important role in the mechanisms of development of brain pathology which may arise as a result of the action of alcohol during intrauterine development of the human fetus is played by disturbances of biogenic amine metabolism [1]. Investigation of concentrations of monoamines and activity of the principal enzymes of their metabolism (in particular, monoamine oxidase – MAO), may help to shed light on the molecular basis of the pathogenesis of CNS disorders developing as a result of antenatal exposure to alcohol.

Current opinion is that MAO is a family of enzymes with activity mainly directed toward certain biologically active monoamines [5]. Changes in concentrations of dopamine and noradrenalin in the brain synaptosomes of the progeny of rats with antenatal exposure to alcohol were found previously in the writers' laboratory [3].

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