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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TABLE 1. Activity of Various Forms of MAO (in nmoles ammonia/mg protein/min) in Parts of Brain of Control Rats and Rats Exposed Antenatally to Ethanol (M ± m)

Exptl. conditions	Time after birth, days	MAO		MAO-MT		MAO-MD	
		cortex	brain stem	cortex	brain stem	cortex	brain stem
Control	30	2,11±0,10	2,53±0,06	1,63±0,20	1,93±0,20	1,60±0,16	1,77±0,10
Exposed to alcohol	30	1,05±0,20	0,80±0,06	1,18±0,01	0,88±0,05	1,46±0,06	1,52±0,04
Control	60	1,55±0,09	1,52±0,18	1,57±0,10	1,75±0,20	2,15±0,14	1,60±0,06
Exposed to alcohol	60	2,05±0,20	0,70±0,20	0,90±0,08	0,95±0,06	2,07±0,10	1,80±0,10

The object of the investigation described below was accordingly to study activity of different forms of MAO, namely type A MAO (MAO-A) and two forms of MAO of mixed type (MAO-M), using dopamine (MAO-MD) and tyramine (MAO-MT) as substrates, in different parts of the brain of young rats at different stages of postnatal development and exposed in utero to the action of alcohol. The preliminary results of this investigation were published previously [4].

EXPERIMENTAL METHODS

Experiments were carried out on two groups of animals: group 1) control female rats kept on the standard animal house diet during pregnancy, group 2) female rats allowed to drink only 10% ethanol solution as the sole source of fluid throughout pregnancy. Each rat received about 6 g/kg of ethanol daily. The progenies of the rats of both groups were decapitated 30 and 60 days after birth, the brain was removed, and the cerebral cortex and brain stem (the mesencephalon and diencephalon together) were isolated. All procedures with the brain were carried out at 0°C. In each group tissue from the corresponding parts of the brain of two or three young rats was pooled and the mitochondrial fraction was isolated by differential centrifugation [10]. Activity of different forms of MAO was determined in this fraction spectrophotometrically: MAO-A – substrate serotonin; MAO-MD – substrate dopamine; MAO-MT – substrate tyramine. Activity was expressed in nanomoles of ammonia formed per milligrams protein per minute at 37°C [2, 5]. Protein was determined by Lowry's method [9]. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that each form of MAO studied differed in the course of its ontogenetic development. For instance, MAO-A activity in the cortex and brain stem fell between the 30th and 60th days, activity of MAO-MT remained constant during this period, whereas MAO-MD activity rose significantly in the cortex between the 30th and 60th days, and remained unchanged in the brain stem. Incidentally, the patterns of development of MAO-A activity thus revealed also were confirmed by a more localized regional investigation: MAO-A activity also fell in the visual and motor cortex and in the lateral geniculate body after the 30th day of postnatal life. These findings are confirmed by data in [7], showing that, first, depending on the oxidation substrate, MAO follows a different course of ontogenetic development, and second, MAO-A activity in homogenates of rat cerebral cortex and brain stem fell after the 30th day of postnatal life.

Exposure of the pregnant rats to alcohol led to inhibition of MAO-A activity in the brain of the young rats aged 30 days – by 50 and 68% in the cortex and brain stem, respectively ($p < 0.01$) compared with the control (Table 1). When the experimental rats were 60 days old, MAO-A activity in their brain stem still remained significantly lower than in control animals of the same age, and was the same as in the experimental rats at the age of 30 days. Meanwhile MAO-A activity in the cortex was significantly higher than in control rats of the same age, and its level of activity was that characteristic of the control rats at the age of 30 days.

MAO-MT activity was significantly lowered in the brain of the 30-day-old progeny of rats exposed to alcohol: by 28% in the cortex and by 54% in the brain stem compared with the control (Table 1). MAO-MT activity in the 60-day-old rats remained significantly lower than that in the control animals of both age groups. Moreover, activity of this type of MAO in the cortex of 60-day-old rats exposed to alcohol before birth continued to fall significantly compared with this parameter in the 30-day-old progeny of the rats of group 2.

MAO-MD activity in the progeny of rats receiving alcohol was reduced (significantly) by 15% on the 30th day after birth in the mitochondrial fraction of the brain stem only (Table 1). Only a tendency for activity to fall was observed in the cortex. On the 60th day after birth MAO-MD activity in the cortex and brain stem now was virtually identical with the control.

The results thus show that not only is the activity of different forms of MAO disturbed in the brain of animals exposed antenatally to alcohol, but the trend of their development in postnatal life also is distorted. The damaging effect of alcohol also exhibits marked regional differences.

Much clinical evidence of the teratogenic effect of ethanol on the developing brain has now been collected. Elucidation of the mechanism of the damaging action of ethanol on the fetal brain and the development of appropriate preventive and corrective measures are therefore urgent tasks at the present time. Previously the writers suggested that antenatal exposure to alcohol intensifies free radical production and activates free-radical processes [4]. This hypothesis is based on the following facts. First, tissue hypoxia, accompanying antenatal exposure to alcohol [6], leads to an increase in the level of reduction of respiratory chain carriers, causing excessive production of free radicals [8]. Second, we previously found a sharp increase in the dopamine concentration in the brain of young rats with antenatal exposure to alcohol [3]. Catecholamines facilitate reduction of molecular oxygen into the superoxide radicals [8], which leads both to further activation of free-radical processes and to worsening of tissue anoxia. Our preliminary data confirmed this hypothesis. For instance, reduced glutathione, the most powerful natural antioxidant, had a protective action on biogenic amine metabolism when administered to animals exposed antenatally to alcohol [4].

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