synaptic receptors, sensitive to glutamate, and characterized by properties of the qusiqualate subtype, are also present there. The similar effects of DALA and baclofen, an agonist of type B GABA receptors, cannot be classed as receptor-determined because of the absence of a generally accepted specific antagonist of receptors of this type. Meanwhile antagonism of these analogs with blockers of the GABA transport systems suggests the existence of a connection between this system and labeled DA release. The coexistence of functional systems of two neurotransmitters, and in particular, of DA and GABA, demonstrated for the first time in the study, may be confirmed by [10], in which this possibility was demonstrated on the example of discovery of glutamate decarboxylase and tyrosine hydroxylase immunoreactivity in neurons of the olfactory bulbs. It was noted recently that DA is taken up by serotoninergic neurons of the neostriatum [13].

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EFFECT OF SOME DRUGS ON ETHANOL-INDUCED CHANGES IN BLLOD-BRAIN BARRIER PERMEABILITY FOR ^{14}C-TYROSINE

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In the modern view [1] the blood-brain barrier (BBB) is a complex membrane which functions in accordance with general principles that are similar for all membranes, whereas on the other hand, it is complex structural-functional formation that is under various kinds of physiological control and, in particular, under the influence of neurotransmitter systems. It has been shown that ethanol, with its marked membranotropic action [9] and with the ability to interfere with neurotransmitter processes in the brain [2, 3, 5], increases the permeability of the BBB for physiologically active substances, including amino acids, and among them, tryptophan [13] and dopa [8], which are precursors of neurotransmitters. This suggests that changes in permeability of BBB induced by ethanol may evidently be linked with its membranotropic effect and (or) its effect on neurotransmitter processes. This hypothesis is confirmed by data on the ability of chlorpromazine (CP), used as a membrane stabilizer, to reduce the permeability of BBB for albumin following microtraumatic brain damage in rats exposed to ethanol [14], and also on the ability of haloperidol (HP), as dopaminergic antogonist, to prevent the amphetamine-induced increase in permeability of BBB for albumin [15].

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The aim of this investigation was to compare the effects of membrane stabilizers CP and α-tocopherol (TP) and also the dopaminergic antagonist HP, on changes in permeability of BBB for ^{14}C-tyrosine.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 300-350 g. In acute experiments the animals were given ethanol in doses of 1, 2, and 4 g/kg body weight intraperitoneally 60 min before determination of the permeability of BBB. In chronic experiments a 25% solution of ethanol was given by the intragastric route three times a day for 10 days in increasing doses: from 8 to 11 g/kg daily during the period of administration. Permeability of BBB was determined 24 h after the last intragastric dose of ethanol, i.e., in a state of abstinence, without intragastric administration of ethanol, and 60 min after a single intragastric injection of ethanol in a dose of 4 g/kg. HP and CP were injected intraperitoneally 30 min before ethanol, each in a dose of 2 mg/kg, in which they can reduce the permeability of BBB, or prevent its increase, for high-molecular-weight compounds and, in particular, for albumin [14, 15]. Considering that the effect of TP develops while it accumulates in the tissues [12], it was injected intraperitoneally in a dose of 50 mg/kg once a day for 2 weeks. ^{14}C-tyrosine (specific radioactivity 492 mCi/mmole) was injected in a dose of 5 μCi, dissolved in 0.5 ml of physiological saline, into the animals' femoral vein. Immediately after injection of the indicator the cerebral blood vessels were washed out to remove blood with 60 ml of physiological saline, heated to 36°C, through the left ventricle of the heart, after preliminary excision of the right atrium. Pieces of brain tissue weighing 100 mg, taken from the cortex, cerebellum, hypothalamus, and medulla, were homogenized in 0.3 ml of 0.6M $HClO_4$ solution. The homogenate was centrifuged for 20 min at 10,000 g and 0.3 ml of 1.5M $KHCO_3$ was added to 10 ml of "Aquasol" universal cocktail and the number of disintegrations recorded on an LKB liquid scintillation counter (Sweden). The numerical results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

In a dose of 1 g/kg ethanol did not affect permeability of the BBB, but in a dose of 2 g/kg, and even more, in a dose of 4 g/kg, it increased its permeability in the cortex, hypothalamus, medulla, and cerebellum (Table 1). CP did not affect the increase in permeability of BBB induced by ethanol in a dose of 2 g/kg, and TP did not change the permeability of BBB induced by ethanol in doses of 2 and 4 g/kg. HP prevented the increase in permeability of BBB for ^{14}C-tyrosine induced by ethanol in a dose of 2 g/kg but, like TP, it did not affect penetration of the indicator into the brain induced by ethanol in a dose of 4 g/kg. Data in the literature indicate that the membrane-stabilizing effect of CP and TP is realized through different mechanisms. CP exerts its effect through its inhibitory effect on adenylate cyclase [6], which controls the synthesis of cyclic AMP, whose level, in turn, determines the intensity of membrane macro- and micropinocytosis [11]. The membrane-protective effect of TP is connected with its action on the level of free radicals formed during peroxidation of membrane lipids [7]. Considering this, and also the ability of HP, by contrast with CP and

TABLE 1. Effect of CP, TP, and HP on Permeability of BBB after a Single Dose of Ethanol

Experimental conditions	Radioactivity in brain structures (in cpm in supernatant/100 mg tissue)			
	cortex	hypothalamus	medulla	cerebellum
Control	591±33 (6)	515±19 (6)	510±29 (6)	562±34 (6)
Physiological saline with ethanol:				
1 g/kg	622±26 (6)	544±32 (6)	493±27 (6)	540±41 (6)
2 »	724±30* (6)	666±38*** (6)	650±29* (6)	744±37** (6)
4 »	926±50 (6)	862±71*4 (6)	875±74** (6)	880±59*** (6)
CP, 2 mg/kg	707±40 (5)	660±50 (5)	682±52 (5)	711±61 (5)
TP, 50 mg/kg				
Ethanol 2 g/kg	678±22 (5)	652±31 (5)	596±18 (5)	698±36 (5)
" 4 g/kg	976±57 (6)	882±52 (6)	920±77 (6)	970±68 (6)
HP, 2 mg/kg				
Ethanol 2 g/kg	604±42* (6)	551±39* (6)	538±28* (6)	673±48* (6)
" 4 g/kg	974±54 (4)	876±46 (4)	850±60 (4)	949±52 (4)

Legend. *P < 0.02, **P < 0.01, ***P < 0.002, ****P < 0.001 compared with corresponding control. Number of animals shown in parentheses here and in Table 2.

TABLE 2. Effect of HP on Permeability of BBB in Rats in a State of Abstenence after Alcoholization for 10 Days

Experimental conditions	Radioactivity in brain structures (in cpm in supernatant/100 mg tissue)			
	cortex	hypothalamus	medulla	cerebellum
Control before alcoholization	566±48 (12)	489±31 (12)	495±22 (12)	528±44 (12)
State of abstinence:				
physiological saline intraperitoneally	829±73 (9)	729±60 (9)	692±52 (9)	771±64 (9)
ethanol (4 g/kg) intraperitoneally	1296±104 (12)	1039±82 (12)	1086±74 (12)	1148±94 (12)
HP, 2 mg/kg (state of abstinence):				
physiological saline intraperitoneally	567±32*** (5)	537±28** (5)	532±40* (5)	723±54**** (5)
ethanol (4 g/kg) intraperitoneally	886±61*** (6)	734±42** (6)	817±59* (6)	872±51** (6)

Legend. *P < 0.02, **P < 0.01, ***P < 0.001 compared with corresponding control; ****) result not statistically significant.

TP, to reduce the ethanol-induced increase in BBB permeability, it can be tentatively suggested that the mechanism of stabilization of the membrane structures of BBB, linked with changes in cAMP synthesis and with influences directed toward peroxidation of membrane lipids is evidently less important in the regulation of permeability for tyrosine than the level of activity of the dopaminergic and also, perhaps, other neurotransmitter systems. This view, in our opinion, is confirmed by the complexity of the functional organization of BBB and the impossibility of regarding it purely as a membrane, even if the complex organization of this membrane due to the morphological and functional features of the cerebral microcapillaries is accepted. In experiments with chronic administration of ethanol increased permeability of BBB for ^{14}C-tyrosone was found in all the structures tested in animals in a state of abstinence (Table 2). A single intraperitoneal injection of ethanol in a dose of 4 g/kg caused an even greater increase in permeability of the BBB, HP, injected into animals in a state of abstinence, significantly reduced the increased permeability of the BBB in the cortex, hypothalamus, and medulla, accompanied by a tendency for it to be decreased in the cerebellum. After intraperitoneal injection of ethanol against the background of HP a significant decrease in permeability for ^{14}C-tyrosine also was found in all the structures studied.

The results, when compared with data showing marked activation of the dopaminergic system during abstinence from alcohol [10], confirm the role of the dopaminergic system in the mechanisms of regulation of BBB permeability for tyrosine. Further evidence in support of this view is given by data on the ability of HP, because of its ability, as dopaminergic antagonist, to prevent the increase in permeability of BBB for high-molecular-weight compounds such as albumin [15] which, without any specific mechanisms of transport into the brain, can nevertheless pass through the BBB with the aid of mechanisms of nonspecific transport during exposure to stress factors [4]. Increased activity of the dopaminergic system evidently correlates directly with the degree of permeability of BBB. A theoretical suggestion which stems logically from this argument is the possibility that a certain neurotransmitter system or systems, whose activity may correlate with permeability of the BBB for physiologically active substances, may also exert a regulating influence.

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