EFFECT OF DESTRUCTION OF THE BRAIN SEROTONINERGIC SYSTEM ON ALCOHOL INTAKE BY RATS IN THE EARLY STAGES OF EXPERIMENTAL ALCOHOLISM

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The study of the role of the serotoninergic system (SES) in the formation of alcohol addiction has not yet yielded unambiguous results [8, 9], the reason evidently being that different species and strains of animals have been used for these purposes without regard to their different initial predisposition toward alcohol consumption [2]. Investigations conducted on rats predisposed and not predisposed to alcohol have revealed differences in the serotonin (5-HT) content and response of the SES of the brain to administration of a single dose of alcohol to animals of opposite groups [6, 7]. These results shed some light on the problem but do not reveal the mechanisms of participation of the SES in the development of alcohol motivation.

The aim of this investigation was to study the effect of destruction of the brain SES by means of 5,6-dihydroxytryptamine (DHT) and by electrocoagulation of the dorsal or medial nucleus raphe on alcohol intake in rats predisposed and not predisposed to its consumption.

EXPERIMENTAL METHOD

Two series of experiments were conducted on noninbred male albino rats weighing 180-200 g. In series I the rats were divided, according to their alcohol intake, into predisposed (6.15 g/kg) and not predisposed (2.62 g/kg), when kept in individual cages with free access to a 15% solution of alcohol and water for 21 days. The experimental animals then received an injection of DHT in a dose of 75 μg into the lateral cerebral ventricle in a volume of 10 μl, whereas the control animals received an injection of the same volume of physiological saline; all the animals were then replaced in individual cages for 18 days.

In series II the experiments were conducted on rats previously divided, on the basis of the duration of ethanol anesthesia test (4.5 g/kg body weight, intraperitoneally) into predisposed (69.1 min) and not predisposed (195.6 min) to alcohol consumption [4]. All the animals were then divided into four groups: In the rats of group 1 the medial group of nuclei raphe was destroyed electrolytically (A 0.7; L 0; H 3), in rats of group 2 the dorsal nucleus raphe was destroyed (A 0.7; L 0; H 2.5) [10], on the rats of group 3, a mock operation without electrocoagulation was performed, and group 4 served as the control. Immediately after the operation all the animals were placed in individual cages for 10 days, and their intake of 15% alcohol solution and water was recorded daily; the mean intake of absolute alcohol in grams/kg/24 h was then calculated for a definite period and the results were compared between the groups. Numerical results were subjected to statistical analysis by Student's test [1]. After the end of the experiment the rats were killed and the zone of coagulation verified histologically.

EXPERIMENTAL RESULTS

The alcohol intake of animals not predisposed to alcohol was sharply increased after injection of DHT, compared both with the background and with the control. Predisposed animals reduced their alcohol intake a little, but compared with the control these changes were not statistically significant (Table 1). In the experiments of series II animals undergoing the mock operation consumed significantly more alcohol in the first five days of the experiment than later. This was probably connected with the effect of stress [2] due to the operation. To distinguish between the effect of operative stress and actual destruction of the nuclei raphe,

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TABLE 1. Effect of DHT on Alcohol Consumption (in g/kg/24 h) by Rats (M±m)

Experimental conditions	Experiment		Control	
	predisposed rats	rats not predisposed	predisposed rats	rats not predisposed
Before injection of DHT (background, 21st day)	6,64±0,48	2,06±0,54	5,39±0,38	2,34±0,18
After injection of DHT				
1—6-th day	5,64±1,07	3,21±0,73[a]	4,36±1,05	1,15±0,62
7—12-th day	5,74±0,93	4,9±0,62[b]	5,4±1,08	1,5±0,68
13—18-th day	4,06±0,5[c]	4,84±0,44[a]	5,1±1,15	0,88±0,28[b]

Legend. a) $P < 0.001$ compared with control; b, c) $P < 0.01$ and $P < 0.05$ compared with background, respectively.

TABLE 2. Effect of Destruction of Medial and Dorsal Nuclei Raphe on Alcohol Consumption by Rats Predisposed (I) and Not Predisposed (II) to Alcohol (M±m)

Experimental conditions	Consumption of absolute alcohol, g/kg/24 h	
	1st-5th day	6th-10th day
Control:		
I	6,29±1,21	7,84±0,91
II	2,15±0,59	1,78±0,34
Mock operation:		
I	6,0±1,5	5,0±1,1
II	3,8±0,9	1,6±0,6
Destruction of medial nucleus raphe:		
I	5,4±1,3	5,6±2,0
II	4,4±0,9	4,0±0,7[a]
Destruction of dorsal nucleus raphe:		
I	3,7±0,93	3,84±1,6
II	6,02±0,92[c]	7,12±0,82[b]

Legend. a, b, c) $P < 0.01$, < 0.001, and < 0.05 respectively compared with rats undergoing mock operation.

alcohol intake by animals undergoing the mock operation during the second 5-day period of the experiment served as the control for results obtained on the rats after destruction of the nuclei raphe. Coagulation of the medial and, in particular, the dorsal nuclei raphe caused a sharp increase (up to 400%) in the alcohol intake of animals not predisposed, but had virtually no effect on the level of consumption of predisposed rats (Table 2).

The results thus show that destruction of SES, irrespective of the method (DHT, coagulation of the nuclei raphe) causes an increase in the alcohol intake of animals not predisposed, but has no effect on the alcohol intake of predisposed rats. Moreover, in their level of alcohol consumption the animals of the opposite groups were virtually indistinguishable after destruction of SES, i.e., this procedure, by depressing activity of SES, can be regarded as the cause of disturbance of normal brain activity causing addiction to alcohol.

It was shown previously that after a single injection of alcohol the 5-HT concentration is reduced in predisposed rats in the hypothalamus, the principal motivation zone, connected with the development of addiction to alcohol [3, 5]. During chronic alcohol consumption by these animals the reduced 5-HT concentration persisted. In rats not predisposed a single dose of alcohol, on the other hand, caused the 5-HT level to rise [6].

The fall in the 5-HT concentration in the hypothalamus of the rats was thus evidently connected with their high level of addition to alcohol. Probably, a fall in the 5-HT concentration produced by chemical or electrolytic destruction of SES must lead to the development of addiction to alcohol in rats initially not predisposed to its use. In rats predisposed to alcohol consumption, no qualitative changes evidently take place after these procedures, i.e., a lowered 5-HT concentration is present, and consequently, modification of their behavior in relation to alcohol does not arise.

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MECHANISM OF THE ANTIHYPOXIC ACTION OF ZINC COMPOUNDS

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Many compounds of metals (inorganic and complex) have an antihypoxic action [10, 13]. The protective effect of complexes of metals in carbon monoxide poisoning is of the greatest interest, because other antihypoxants are ineffective in some cases [3, 6,7]. Zinc compounds are of great practical importance in this connection because they not only have higher activity than compounds of other metals, but they also are less toxic, which encourages the hope that their clinical application may be possible [8].

The aim of this investigation was to study the mechanism of the protective action of zinc compounds in acute carbon monoxide poisoning.

EXPERIMENTAL METHOD

Hypobaric and normobaric hypoxic hypoxia and hemic hypoxia were simulated in a 10-liter exsiccator, in which the necessary conditions were created after inspiration of the animals: rarefaction of the air or gas medium of definite composition by continuous extraction ventilation. To simulate hypobaric hypoxia the mice were "lifted" to an altitude of 11 km. Normobaric hypoxia was created by inhalation of a gas mixture of 96% nitrogen and 4% oxygen. In both cases the duration of exposure was 45 min. After simulation of hemic hypoxia a mixture consisting of 7.5 or 15 mg/liter of carbon monoxide (CO) in air was supplied to the exsiccator (exposure 20 min). Histotoxic hypoxia was created by subcutaneous injection of 6 mg/kg of potassium cyanide. Male albino mice weighing 18-23 g were used. The experimental conditions were chosen so that the survival rate in the control to each model of hypoxia was 10-20%. Zinc compounds were injected intraperitoneally 1 h before the experiment in a dose of 0.15 milliatoms of zinc per kilogram body weight. Oxyhemoglobin (HbO_2) was determined by Vierordt's spectrophotometric method for 4 wavelengths. Hemolysed blood in 0.143 M phosphate buffer at 20°C and pH 6.9 was used. The experimental data were analyzed by the method of least squares, using Hill's equation $y = \frac{K \cdot x^n}{1 - K \cdot x^n}$, where y is HbO_2 as a fraction of total hemoglobin (Hb), x denotes pO_2, and K and n are empirical coefficients. The power index n is also considered to be measure of cooperative interaction between hemes – the so-called Hill's constant. For mammalian hemoglobin, its maximal value is 3 (maximal cooperativeness) and its minimal value is 1 (absence of cooperativeness). The carboxyhemoglobin (HbCO) concentration was determined by Popov's method [5]. Data for calculating the oxyhemoglobin dissociation curve were obtained by the writers' own method [9].

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