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EFFECT OF ALCOHOL ON THE SERUM TSH LEVEL IN RATS PREDISPOSED AND NOT PREDISPOSED TO ALCOHOL

S. A. Borisenko, P. T. Mannisto, and Yu. V. Burov

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An important aspect of the search for substances for the prevention and treatment of alcoholism is the discovery of the mechanisms of predisposition and nonpredisposition to alcohol. The results of investigations in this direction have shown that alcohol induces aggressiveness in unpredisposed animals and a tranquilizing effect in animals predisposed to alcohol [1], and it activates the positive reinforcement system in predisposed animals but does not change the activity of this system in animals rejecting alcohol [2]. Increased tyrosine hydroxylase activity has been found in the thalamus [3] and an increased serotonin concentration in various brain structures [5] of rats predisposed to taking alcohol.

Evidence has also been obtained of differences in the reactivity of the hypothalamic-hypophyseal neuroscretory system (HHNS) of animals predisposed to and rejecting alcohol [4], and also of changes in the activity of this system depending on the duration and stage of alcohol intoxication [7, 8, 14]. Changes in reactivity of the HHNS may be the cause of the different modulating effects on regulation of production and secretion of thyroid hormones in animals predisposed and not predisposed to taking alcohol.

This paper describes a study of the effect of chronic administration of alcohol on the blood serum levels of thyroid-stimulating hormone (TSH) in rats predisposed and not predisposed to alcohol, kept in a state of physical dependence on and abstinence from alcohol.

EXPERIMENTAL METHOD

Experiments were carried out on 156 female Wistar rats weighing 150-220 g. In the course of the experiment the rats were kept on a standard diet and were allowed water *ad lib*.

In previous investigations negative correlation was found between the length of sleep of the rats following administration of alcohol in a narcotic dose and the quantity of alcohol consumed under conditions of free choice between alcohol and water. Accordingly, in the present investigation the animals were divided into those predisposed and not predisposed to alcohol, by determining the duration of sleep after intraperitoneal injection of a narcotic dose (4.5 ml/kg body weight) of 25% ethanol solution. Rats sleeping a short time (less than 60 min) were described as predisposed, and those sleeping a long time (over 2 h) as not pre-

Laboratory for the Search and Study of Methods of Prevention and Treatment of Drug Addictions, Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Department of Pharmacology, University of Helsinki, Finland. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 92, No. 7, pp. 26-28, July, 1981. Original article submitted November 11, 1980.

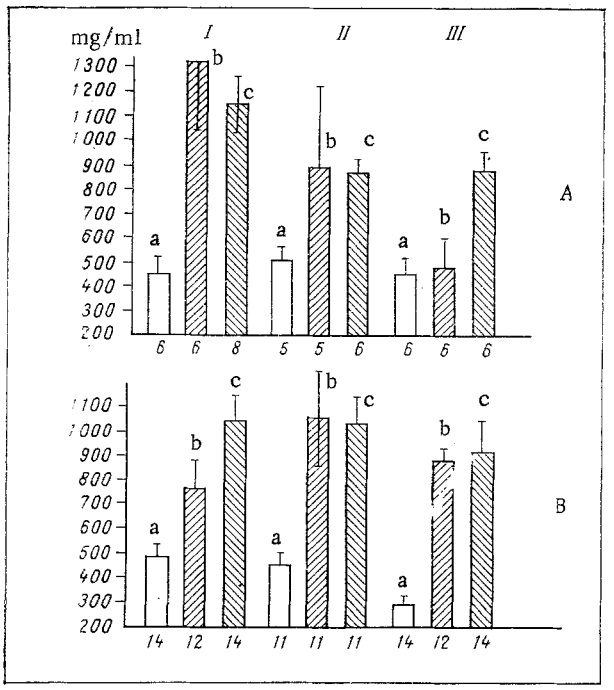

Fig. 1. Serum TSH concentration in rats predisposed (A) and not predisposed (B) to alcohol, under conditions of physical dependence (II) on and abstinence from (III) alcohol. Ordinate, serum TSH concentration (in ng/ml): A) basal; B) after injection of TSHRH; C) after cold stimulation (4°C). Numbers in columns — number of measurements. I) Control.

TABLE 1. Effect of Acetaldehyde on Serum TSH Level in Rats after Cold Stimulation (M ± m)

Test	TSH concentration, ng/ml	Number of measurements	P
Control			
30 °C	920±72	4	
4 °C	3085±579	6	<0,05
4 °C + acetaldehyde:			
100 mg/kg	3156±397	6	>0,05
200 mg/kg	1526±139	7	<0,05
300 mg/kg	1310±313	6	<0,05

TABLE 2. Effect of Acetaldehyde on Serum TSH Concentration (in ng/ml) in Rats after Stimulation by TSHRH (M ± m)

Experimental conditions	Initial concentration	Dose of acetaldehyde		
		200 mg/kg	300 mg/kg	450 mg/kg
Initial concentration	510±126 (6)	—	—	—
Stimulation by TSHRH				
500 ng/kg	1423±373 (6)	1823±303 (7)	1997±470 (7)	842±182 (4)
1500 ng/kg	1622±211 (6)	2043±529 (7)	2501±354 (7)	495; 2438 (2)

Legend. LD_{50} of acetaldehyde for rats is 450 mg/kg, number of measurements shown in parentheses.

disposed to alcohol. Animals sleeping a long time under free choice conditions are known to consume small quantities of alcohol (0-3 ml of a 15% solution of ethanol per diem), whereas animals sleeping a short time consume from 10 to 40 ml. After separation of the rats into groups by duration of sleep, in order to produce states of physical dependence on and abstinence from alcohol in them, chronic alcoholization was carried out in the course of 10 days by the modified method [9], by daily peroral (3 times a day, at intervals of 8 h) administration of 10% alcohol solution in increasing doses: 8 ml/kg on the 1st-3rd days, 15 ml/kg on the 4th-6th days, and 20 ml/kg on the 7th-10th day of alcoholization. Control animals were given isotonic NaCl solution in the equivalent volume for body weight. Blood was taken from the animals after guillotine decapitation 4-6 h after the last injection (state of physical dependence) and 16-18 h thereafter (state of abstinence) and the basal blood TSH level, the TSH level after administration of TSH-releasing hormone (TSHRH) in doses of 500 and 1500 ng/kg body weight intraperitoneally, and also after cold stimulation for 30 min at 4°C, were determined by a specific radioimmunologic method [11]. The set of specific sera and other reagents for radioimmunologic assay was obtained from the NIAMDD* Rat Pitui-

*National Institute of Arthritis, Metabolism, and Digestive Diseases.

tary Program, Bethesda, Maryland, USA. The TSH concentration was expressed in ng/ml blood serum and was determined as the mean of the TSH levels in at least 6 animals. Statistical analysis of the data was carried out by Student's t-test for unpaired cases.

EXPERIMENTAL RESULTS

Starting with the 5th day of administration of alcohol to the animals, characteristic elements of the withdrawal syndrome began to appear in their behavior (contraction and tremor of the tail and body, moderate rigidity, aggressiveness), and these were observed in a distinct form 16-18 h after withdrawal of alcohol. The most marked symptom was aggressiveness in the rats receiving alcohol. Radioimmunologic assay of TSH (Fig. 1) showed significant differences between the serum hormone concentrations in predisposed and nonpredisposed rats following administration of TSHRH — 1320 and 760 ng/ml respectively ($P < 0.05$). Predisposed rats in a state of physical dependence showed a tendency for the TSH level to fall under the influence of TSHRH and a significant decrease in the concentration of the hormone after cold stimulation. By contrast to this, nonpredisposed animals did not differ from control rats in their TSH level after cold stimulation, but the TSHRH-stimulated TSH concentration showed a tendency to rise. In a state of abstinence the TSH level in the predisposed rats was lowered ($P < 0.05$) for both types of stimulation, but in nonpredisposed rats it was the same as in the control. To determine whether the decrease in the serum TSH level in rats predisposed to alcohol, in a state of abstinence was connected with the effects of the alcohol metabolite, acetaldehyde, experiments were carried out to study the effect of the latter on the TSH concentration. The results showed that acetaldehyde, in doses of 200 and 300 mg/kg (intraperitoneally 30 min before the experiment) reduced by half the increase in the TSH concentration caused by cold stimulation (Table 1), but only in a dose of LD_{50} did it reduce the increase in TSH concentration in response to administration of TSHRH (Table 2).

It can be concluded from these results that animals predisposed to alcohol, by virtue of their inborn neurophysiological and neurochemical features, have initial high reactivity of their thyroid gland function regulating system. However, chronic alcoholization leads to exhaustion of the reserve capacity of that system, and this is manifested as a state of physical dependence on alcohol and, in particular, a state of abstinence from it. This last state of affairs may evidently be connected with the increased activity of the dopaminergic system during abstinence. This hypothesis is based on data on the depriming effect of the dopaminergic system on mechanisms of regulation of TSH secretion [12], at 4°C and also on the results of experiments showing an increase in activity of dopaminergic neurons in a state of abstinence [6, 10]. Partial blockade of the mechanisms regulating TSH secretion at the hypothalamic level by acetaldehyde in doses close to LD_{50} is evidently a nonspecific action, which as has been shown previously [13], is a property of various substances with a depriming type of action.

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