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SERUM AND LIVER ALCOHOL DEHYDROGENASE LEVELS IN RATS DIFFERING IN ALCOHOL MOTIVATION

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KEY WORDS: alcohol dehydrogenase; chronic alcohol poisoning.

Research in the last decade in the field of enzyme diagnosis of alcoholism has led to the use of enzyme tests as additional diagnostic and prognostic criteria in patients with alcohol-induced lesions of organs and tissues, especially the liver [2]. Research in this direction also encourages the hope that specific biochemical markers of alcoholism will be discovered; enzymes of ethanol and acetaldehyde metabolism and their numerous molecular forms are of great interest from this point of view [6]. With the appearance of new and highly sensitive methods of determining activity of ethanol-metabolizing enzymes in material so readily available as blood [3, 7], on the one hand our ideas on the role of these enzymes in the pathogenesis of alcoholism have been widened and, on the other hand, the need has arisen for the place of these tests in clinical practice to be assessed.

The aim of this investigation was to study alcohol dehydrogenase (ADH; EC 1.1.1.1.) in the blood serum and liver of rats with a preference for drinking ethanol or water, and also in animals during chronic ethanol poisoning and after withholding ethanol.

EXPERIMENTAL METHOD

Noninbred male albino rats weighing 200-250 g, with free choice between water and 15% ethanol solution, were divided into three groups: those preferring water (PW), an intermediate group (IG), and those preferring ethanol (PE), by the method described previously [4]. The IG rats were subjected to chronic alcoholization, with an initial consumption of ethanol solution equivalent to 16-35% of the total quantity of liquid drunk. For 4 months the animals received only 15% ethanol solution to drink, and for the next 11 months the animals were given the choice between water and 15% ethanol solution. At the end of alcoholization, animals whose ethanol consumption had increased to not less than 50% of the total volume of fluid drunk, evidence of the formation of addiction to alcohol, were used in the experiments. Control animals were given water for 15 months.

ADH activity was determined in the blood serum by the method in [7] and in the postmitochondrial supernatant of the liver by the method in [5], and expressed in μ moles NAD/min/liter of serum and μ moles NADH/min/g of liver tissue (subsequently described as activity units), respectively. The histological investigations were carried out in the Department of Biochemistry, Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, by Professor V. A. Nagornev.

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TABLE 1. ADH Activity in Serum and Liver of Rats Preferring Water or Ethanol

Group of animals	ADH activity, activity units	
	liver	blood
PW	4,8±0,1	4,2±0,8
IG	4,7±0,2	4,3±0,9
PE	5,2±0,1*	4,2±0,9

*P < 0.05. In each series the number of experiments was not less than 6.

TABLE 2. Effect of Chronic Alcohol Poisoning and Withdrawal of Ethanol on ADH Activity in Blood and Liver of Rats

Experimental conditions	Number of animals	ADH activity, activity units	
		liver	blood
Control	13	6,4±0,4	12,6±0,9
Chronic alcohol poisoning (15 months)	11	5,2±0,4*	22,9±3,6 †
Ethanol withdrawal (7 days)	12	6,2±0,4	9,4±1,5

*P < 0.05, †P < 0.02.

EXPERIMENTAL RESULTS

Experiments on animals differing in alcohol motivation (PW, IG, PE) showed that ADH activity in the liver of PE rats was significantly higher than in that of PW rats. However, ADH activity in the serum of PW, IG, and PE rats was the same (Table 1), i.e., serum ADH activity did not correlate with activity of ethanol-metabolizing enzymes of the liver in PW and PE rats.

In rats of all three groups, in some cases the serum ADH activity was sharply increased. To determine the causes of this phenomenon a histological investigation of the liver was carried out on animals with normal ADH activity (4.3 ± 0.7 activity units), observed in most rats, and animals with high ADH activity (34.1 ± 1.6 activity units) in their blood (each group contained PW and PE rats). The histological picture of the liver was found to be normal in rats with low serum ADH activity, whereas in all animals with high ADH activity signs of fatty and cloudy-swelling degeneration of the liver were observed. Such marked deviations from the normal blood ADH level in individual animals were evidently not connected with any predisposition of the animals to ethanol consumption, but reflect disturbance of the structural integrity of the liver cells.

ADH activity in the rat liver after 15 months of alcoholization was significantly reduced, but in the blood serum it was almost twice as high as in the control (Table 2). ADH activity in the liver 7 days after withdrawal of ethanol was raised, whereas in the blood it was lowered, and was close to the control level (Table 2). These results are in agreement with data obtained by other workers who found lowering of ADH activity in the liver in chronic ethanol poisoning [8], and they are evidence that prolonged alcoholization does not induce ADH synthesis in the hepatocytes. The opposite direction of the changes in ADH activity in the liver and blood suggests that in chronic alcohol poisoning serum ADH activity rises on account of intensification of ADH transport from the liver into the blood stream. The main cause of this process is evidently the heptotoxic action of ethanol and its metabolites.

We also observed a raised blood level of ADH activity in patients with alcoholism, and in this case it correlated with the duration of alcohol consumption [3]. This indicated that determination of blood ADH activity can be used as an additional biochemical test for the diagnosis of alcoholism.

We have also shown that the blood ADH cannot play an essential role in the elimination of exogenous ethanol in man, but activity of the enzyme is high enough to regulate the endogenous ethanol level [3].

In the last few years attempts have been made to associate differences in predisposition to alcohol consumption with the endogenous ethanol level [1]. According to data in [1], PW, IG, and PE animals have identical blood ADH activity. Consequently, the lower endogenous ethanol level in the tissues of PE animals than of PW rats [1] is due entirely to increased ADH activity in the liver. The blood ADH evidently does not participate in mechanisms responsible for the preference phenomenon in animals.

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EFFECT OF IMMUNOSTIMULANTS ON TUBULAR SECRETION OF XENOBIOTICS IN THE KIDNEY

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KEY WORDS: prodigiosan; levamisole; renal tubular secretion.

Secretion of organic substances by cells of the proximal portion of the renal tubules plays an essential role in the removal of foreign substances, including drugs, from the body and it is one of the important factors in pharmacokinetics. Features of similarity between tubular secretion and immune processes were observed in 1970 [1]. It was shown later that tubular secretion is subject to substrate induction [4, 8], which is linked with neogenesis of transport proteins. The secretory-transport system has been shown to recognize what is "its own" and what is "foreign," as a result of which endogenous substances are not secreted under ordinary conditions [2]. It has been shown in the writers' laboratory that immunosuppressants selectively inhibit tubular secretion [5, 11], even in the absence of any marked catabolic action. Meanwhile tubular secretion is enhanced by agents which stimulate protein biosynthesis: potassium orotate [6], retabolil (nandrolone) [10], and testosterone [9].

In the investigation described below the effect of immunostimulants with no anabolic action was studied on secretory transport; the bacterial lipopolysaccharide prodigiosan and the synthetic compound levamisole were used.

EXPERIMENTAL METHOD

Experiments were carried out on 45 noninbred albino rats weighing 180-220 g. Renal tubular secretion was determined as diodone excretion [7] several times in each animal: before the experiment began, on the day after each injection of the test substance, and 3 and

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