The results of this investigation confirm the conclusions of studies with procaine, benzocaine [11], and quinidine [8], showing that a decrease in the flow of Na^+ ions into the myocardial cell under the influence of antiarrhythmic agents of the first group may be accompanied by a negative inotropic effect. The mechanism of this negative inotropic effect is evidently linked with depression of sodium-calcium exchange.

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EFFECT OF THE CENTRAL α-ADRENOBLOCKER IEM-611 ON ALCOHOL AND ALDEHYDE DEHYDROGENASES IN RAT LIVER

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During the formation of an attachment to alcohol an important role is played by the activity of neurotransmitter systems [2, 4, 5] and the enzymes of ethanol and acetaldehyde metabolism [11]. Depending on whether animals have a predisposition for drinking water or ethanol, significant differences are found in the functioning of their corresponding enzyme systems [1, 3]. Pharmacological intervention directed toward the functional state of either of these systems (neurotransmitter or enzyme) may affect ethanol consumption and the development of addiction to it [7, 9].

The aim of the present investigation was to study the effect of the central α-adrenoblocker IEM-611 (p-di-isopropylaminophenylacetic acid β-phenylisopropylamide) on ethanol consumption and to estimate the activity of alcohol dehydrogenase (AlDH – E.C. 1.1.1.1) and aldehyde dehydrogenase (AdDH – E.C. 1.2.1.3) in the liver of animals preferring water or ethanol, and receiving or not receiving the drug.

EXPERIMENTAL METHOD

Experiments were carried out on 150 noninbred male albino rats weighing 200-250 g and divided into three groups: 1) animals preferring water (19% of the total number of rats), 2) intermediate group (56%), 3) rats preferring ethanol (13% of the total number of animals). Selection was carried out in the course of 10 days when the animals were allowed free choice between 15% ethanol solution and water. The rats were kept in individual cages measuring

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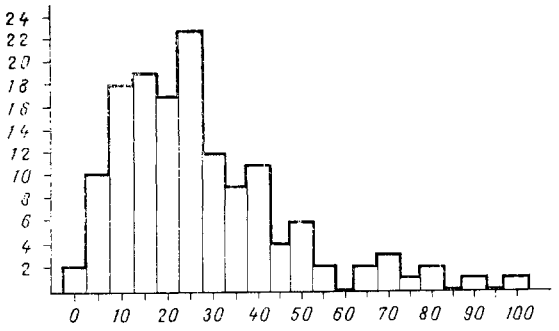

Fig. 1. Distribution of rats by predisposition for drinking water or 15% ethanol solution. Abscissa, consumption of 15% ethanol solution (6% of total volume of fluid drunk); ordinate, number of animals.

TABLE 1. AlDH and AdDH Activity in Liver of Rats Preferring Water or Ethanol

Group of animals	Number of animals	Protein, mg/g liver	Dehydrogenase activity, μmoles /min/g liver				AlDH/AdDH
			AlDH	total AdDH	AdDH1	AdDH2	
1	6	127,0±5,1	4,81±0,03*	0,083±0,007‡	0,030±0,002*	0,053±0,006*	58±4,5*
2	7	146,4±10,9	4,65±0,19*	0,094±0,007	0,047±0,005	0,051±0,007	49±1,7
3	6	128,7±7,9	5,19±0,13	0,132±0,015	0,058±0,11	0,073±0,008	39±3,5

Legend. *P < 0.05, ‡P < 0.02 compared with rats of group 3.

TABLE 2. Effect of IEM-611 on AlDH and AdDH Activity in Liver of Intermediate Group of Rats

Time of administration, days	Number of experiments		Protein, mg/g liver		AlDH, μmoles /min/g liver		Total AdDH, μmoles / min/g liver		AlDH/AdDH	
	control	IEM-611	control	IEM-611	control	IEM-611	control	IEM-611	control	IEM-611
6	6	6	117,1±6,1	129,7±5,2	4,69±0,65	4,43±0,63	0,078±0,019	0,058±0,009	60,0±6,3	76±1,0
12	3	3	127,7±20,5	124,5±15,9	4,56±0,13	5,11±0,11*	0,105±0,020	0,058±0,010*	43±5,7	88±13,3*

Legend. *P < 0.05 compared with control.

40 × 15 × 20 cm, supplied with two bowls (one containing water, the other ethanol solution), and with dry food ad lib. The volume of fluid drunk was recorded daily at the same time. Consumption of 15% ethanol solution was 0-8% for the rats of group 1, 16-35% for those of group 2, and over 50% for those of group 3. The distribution of the animals according to predisposition for water or ethanol is shown in Fig. 1.

The animals were used in the experiments 2 months after the end of selection. The central α-adrenoblocker IEM-611 was injected subcutaneously into animals of the intermediate group once a day in a dose of 30 mg/kg body weight, or the animals were given an equal volume of physiological saline (0.4-0.5 ml; control); rats of the first subgroup received the injections for 6 days, those of the second subgroup for 12 days. Consumption of 15% ethanol solution and of water was recorded daily.

Mitochondria were isolated from the liver and activity of total AdDH, AdDH1 with low K_m for acetaldehyde, and AdDH2, with high K_m for acetaldehyde, was measured by the method in [12]. AlDH activity in the postmitochondrial supernatant was measured by a modified method in [6]. The reaction mixture for determination of AlDH activity contained 0.1 M phosphate buffer, pH 7.4, 0.19 mM NADH, and 3.3 mM acetaldehyde. The reaction was started by adding acetaldehyde. Activity of both enzymes was recorded on the SF-26 spectrophotometer and expressed in micromoles/min/g wet weight of liver. The protein concentration was determined by Lowry's method [10].

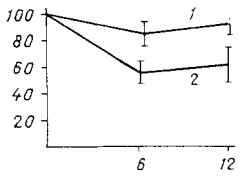

Fig. 2. Effect of IEM-611 on consumption of 15% ethanol solution by rats of intermediate group during period of formation of attachment to alcohol. Abscissa, time of administration of preparations (in days); ordinate, alcohol consumption (in %). 1) Physiological saline; 2) IEM-611 (30 mg/kg).

EXPERIMENTAL RESULTS

In rats preferring ethanol AlDH activity in the postmitochondrial supernatant was significantly higher (by 8 and 12%; $P < 0.05$) than in animals preferring water and rats of the intermediate group (Table 1). Other workers observed higher (with a difference of 23%) AlDH activity in the liver of rats which preferred ethanol compared with animals which preferred water [3].

Much greater differences were found in AdDH activity in the three groups of rats (Table 1). Total AdDH activity in the liver mitochondria of rats of group 3 was 37% higher than in rats of group 1. The high level of total AdDH in the animals of group 3 was due to the high content of AdDH1 and AdDH2 in their liver (Table 1). In the rats of group 2, AdDH activity occupied an intermediate position between its values in the rats of groups 1 and 3. Very probably preference for water or ethanol is associated with the level of AlDH and AdDH activity in the rat liver.

The primary oxidation product of ethanol in the liver is acetaldehyde, which is converted into acetate by the action of AdDH. The ratio between AlDH/AdDH activities in the liver, on which depends the quantity of acetaldehyde entering the blood stream and brain cells from the liver, may perhaps play an important role [8]. This ratio was highest in rats preferring ethanol (Table 1). Consequently, the high general level of activity of enzymes of ethanol metabolism, coupled with a relatively low AlDH/AdDH ratio in the liver of these animals, ensure favorable conditions for the oxidation of ethanol to acetate.

The action of IEM-611 was studied on animals of the intermediate group. IEM-611, when given for 6 and 12 days, reduced ethanol consumption in rats kept under conditions of free choice between water and 15% ethanol solution by 29 and 30% respectively (Fig. 2) compared with control (Table 2).

AlDH activity in the liver during administration of IEM-611 for 6 days remained virtually unchanged, but was significantly higher than the control after its administration for 12 days. However, mitochondrial AdDH activity after 6 days of treatment was reduced by 26% below the control, and after 12 days by 45%. The AlDH/AdDH ratio was 88 ± 13.3, much higher than the control figure (43 ± 5.7) and than its initial value for the intermediate group (49 ± 1.7).

The action of IEM-611, reducing ethanol consumption, may be associated to a certain degree with reduction of AdDH activity and an increase in the AlDH/AdDH ratio, i.e., the drug modifies activity of the enzymes of ethanol metabolism toward the level characteristic of animals preferring water.

Changes in the ratio of AlDH/AdDH activity may thus perhaps be one of the mechanisms responsible for reduction of ethanol consumption in the experimental animals.

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EFFECT OF HEPARIN ON PROSTACYCLIN ACTIVITY IN THE AORTIC WALL

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KEY WORDS: heparin; platelets; aggregation; prostacyclin.

The mechanism of the anticoagulant activity of heparin is explained chiefly by its ability to block thrombin and fibrin formation. However, although heparin delays blood clotting, at the same time it induces intravascular platelet aggregation [1, 4]. The platelet-aggregating action of heparin is a substantial obstacle in the way of its use in an artificial circulation and in thrombophilic states due to activation of the adhesive and aggregating function of the platelets. The mechanism of intravascular platelet aggregation after injection of heparin has not been finally studied. The important role of prostacyclin (prostaglandin I_2), synthesized by the endothelium of the vascular wall, in regulation of aggregating activity of platelets has recently been established [13]. The inhibition of prostacyclin synthesis observed in diabetes, ischemic heart disease, and other diseases is accompanied by increased platelet aggregation [2, 9, 10, 15].

The object of this investigation was to study the effect of heparin on prostacyclin activity in the aortic wall.

EXPERIMENTAL METHOD

Experiments were carried out on 25 Wistar rats weighing 200 g. A solution of heparin (from Richter, Hungary) was injected into the caudal vein of the animals in a dose of 750 Units/kg. Prostacyclin activity was determined in the aortic wall by the method in [11] 15 and 60 min after injection of heparin. Segments of the abdominal aorta were removed under pentobarbital anesthesia (50 mg/kg). Platelet-enriched plasma was obtained from blood of donor rats taken from the abdominal aorta and stabilized with 3.14% sodium citrate solution in the ratio of 9:1. Aggregation was studied by the method in [3]. The disodium salt of ADP (from Serva, West Germany), in a final concentration of 10^{-5} M, was used as inducer of aggregation. The statistical analysis was carried out by Student's t test.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that ADP-induced platelet aggregation in healthy animals averaged 90 ± 2.1%, its lag period was short (30-50 sec), the mean value of the angle α was 66 ± 2.8°, and as a rule deaggregation did not develop. After incubation of platelet-enriched plasma with aortic wall taken from intact control animals, platelet aggregation was reduced on average to 20 ± 1.7%, the lag period was lengthened to 100-120 sec, and the angle

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