in the mechanism of development of cardiovascular diseases [7]. Inhibition of TXA_2 biosynthesis in the platelets by trapidil and simultaneous activation of PGI_2 formation in the coronary arteries and also, possibly, in the heart tissue, are thus two mutually complementary processes whereby trapidil exerts its antiaggregating, coronary-dilating, and positive inotropic and chronotropic effects on the myocardium.

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TIME COURSE OF BLOOD ETHANOL IN RATS DURING ALCOHOL DEPENDENCE AND WITHDRAWAL

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KEY WORDS: pharmacokinetics; alcohol; alcohol abstinence.

During chronic alcohol intake both in animals and man, a considerable increase is observed in the activity of ethanol-oxidizing enzyme systems [5, 7]. The rapid disappearance of ethanol from the blood eliminates many of its toxic effects, and thus causes the development of metabolic tolerance, which in turn is the precursor of physical dependence on alcohol. Alcohol deprivation in the stage of dependence leads to a state of alcohol abstinence. According to one view [1], one of the mechanisms of formation of the abstinence syndrome is increased activity of ethanol-oxidizing enzyme systems in the period of alcohol deprivation.

The investigation described below accordingly was undertaken with the aim of studying the kinetics of ethanol as a parameter of the rate of its elimination in the stage of alcohol dependence and also during its withdrawal.

EXPERIMENTAL METHOD

Experiments were carried out on 25 noninbred male albino rats weighing 500-600 g, separated into four groups with six rats in each group. Animals of the first three groups were kept in individual cages with free choice between 15% ethanol solution and water for 8 months, the time required to form physical dependence on alcohol [2]. Animals of group 4, of the same age but with no contact with alcohol, served as the control. The time course of the blood alcohol of the animals of group 1 was studied 15 h after withdrawal, and in rats of groups 2 and 3, 2 and 7 days, respectively, after withdrawal.

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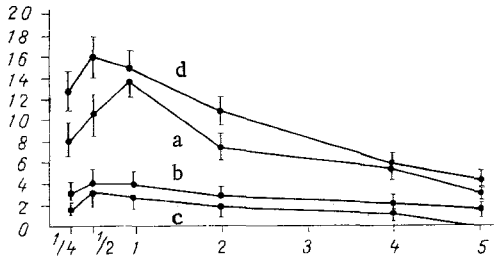

Fig. 1. Time course of blood ethanol in stage of alcohol dependence and withdrawal. a) During alcohol consumption; b) 2 days, c) 7 days after alcohol withdrawal; d) control. Abscissa, time after alcohol withdrawal (in h); ordinate, ethanol concentration (in μM).

The ethanol concentration was determined by gas-liquid chromatography on a "Tsvet-152" chromatograph, with flame-ionization detector, on a steel column containing 15% polyethyleneglycol on Chromaton NAW-DMCS 0.200-0.250 mm in diameter and 3 m long. The conditions of analysis were: temperature of column 100°C of vaporizer 170°C. Rate of flow of carrier gas 25 ml/min. Blood in a volume of 50 μl was taken from the caudal vein, transferred into a 15-ml receiver containing 50 μl of sodium citrate solution (2 g/liter), and a solution of the internal standard, containing 8.6×10^{-4} μM propanol, was added. The vessel was then hermetically sealed and incubated for 15 min at 65°C. Next, 2 ml of the gas phase was analyzed [4] and a 25% solution of ethanol was injected intraperitoneally in a test dose of 1 g/kg. Blood was collected after 15 and 30 min and 1, 2, 4, and 5 h. The calculations were done on a computer and the pharmacokinetic parameters calculated by a first-order kinetic equation, allowing for absorption [3].

EXPERIMENTAL RESULTS

A study of the pharmacokinetic curve of ethanol showed differences in the rate of absorption and excretion of alcohol into the blood in animals of all four groups (Fig. 1). A fall in the ethanol concentration in the rats of groups 2 and 3 was combined with an increase in the apparent partition volume (V_p) and the clearance (Cl). For instance, V_p in the animals of groups 2 and 3 was 2.68×10^3 and 5.7×10^3 ml/kg, respectively, compared with 1.1×10^3 ml/kg in the control animals. The substantial increase in clearance, determining the volume of test tissue freed from ethanol in unit time, in the animals of groups 3 and 2 (1.2×10^3 and 6.5×10^2 ml/kg/h, respectively) compared with clearance in the control animals (3.3×10^2 ml/kg/h) and in the rats of group 1 against a background of alcohol consumption (4.2×10^2 ml/kg/h) points to a marked increase in the rate of excretion of alcohol from the body. This is confirmed also by differences in the ethanol elimination constants (K_e). The highest values of this parameter were found in animals consuming ethanol (mean 0.3) and the lowest in rats on the 7th and 2nd days of ethanol withdrawal (corresponding mean values 0.22 and 0.25).

In the animals on the 2nd day of ethanol withdrawal after voluntary consumption for 8 months, a hyperactive state of the ethanol-metabolizing systems was observed. A study of the ethanol kinetics on the 7th day after withdrawal showed that the hyperactive state of the ethanol-oxidizing enzyme systems was preserved, although a slight return toward normal was noted. The mechanism of the abstinence state can be explained by data showing that during the period of alcohol deprivation alcohol dehydrogenase activity in the liver increased 60%, evidently on account of "liberation" of mechanisms of NAD^+ formation [8].

It can accordingly be concluded from the experiments described above that a hyperactive state of ethanol-oxidizing enzyme systems in the period of alcohol deprivation may be the leading mechanism in the formation of the abstinence state in chronic alcoholism.

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EFFECT OF POLYMETHYLENE- AND POLYHYDROXYETHYLENE-bis-(2-AMINO-1,3-DIAZEPINIUM) IODIDES ON CELL AND MODEL MEMBRANES

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The mono- and bisquaternary compounds widely used in clinical and laboratory practice have the property not only of interacting specifically with receptors of cholinergic synapses, but also of modifying the physicochemical characteristics of biomembranes and, in particular, their surface charge [1, 5]. It is also known that certain compounds of this class can enter the channels of chemically excitable membranes, blocking them partly or completely [6, 11]. Interaction with the recognition site of the receptor and its channel or modification of the surface charge near the channel leads to disturbance of the permeability of the activated postsynaptic membrane [6-8].

In the investigation described below, the role of the above-mentioned processes and the action of bisquaternary compounds on neuromuscular synapses were studied. Diazepinium derivatives were used as cationic heads. The choice of these heads was determined by the ability of certain diazepinium derivatives to block cationic channels and to modify the surface charge of biomembranes [10, 11].

EXPERIMENTAL METHOD

The effect of diazepinium derivatives on synaptic transmission was studied on the end-plate of the neuromuscular preparation of *Rana temporaria*. Resting potentials, action potentials, end-plate potentials (RP, AP, and EPP, respectively), and the membrane resistance of the muscle fibers were recorded by standard microelectrode techniques. Acetylcholine (ACh) was applied to the region of the end plate by a pulse of pressure from a microinjector. Kinetic parameters of interaction between the test substances and the acetylcholine receptor (AChR) were determined on the frog rectus abdominis muscle. The anticholinesterase activity of the substances was determined by measuring inhibition of acetylcholinesterase of human erythrocytes by an electrometric method [9]. Rat liver mitochondria were isolated by the method in [3]. Respiration of the mitochondria was determined polarographically. Bimolecular lipid membranes (BLM) were prepared from a solution of phosphatidylethanolamine (from Serva, West Germany) in decane (20 mg/ml), on holes in a Teflon jar. The surface potential of the BLM was measured potentiometrically [1].

The substances studied appear on the following page. All the compounds were synthesized in the Department of Chemistry of Macrocyclic Complexones, Physicochemical Institute, Academy of Sciences of the Ukrainian SSR.

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