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PHARMACOKINETICS OF ETHANOL WHEN INJECTED INTRAPERITONEALLY AND INTRAVENOUSLY INTO RATS DIFFERING IN INITIAL ALCOHOL MOTIVATION

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KEY WORDS: ethanol; predisposition; pharmacokinetics

It was shown previously that animals differing in their initial level of alcohol motivation differ in their rate of elimination of ethanol when injected intraperitoneally [2, 3]. A distinguishing feature of these groups of animals was found to be differences in their ethanol absorption constant [3].

To determine the importance of absorption of ethanol for its elimination, the pharmacokinetics of ethanol was studied in the blood of rats differing in their initial predisposition to the formation of alcohol motivation.

EXPERIMENTAL METHOD

Experiments were carried out on 40 male laboratory albino rats weighing 180-200 g, divided initially into two groups depending on the duration of ethanol narcosis (dose of ethanol 4.5 g/kg of a 25% solution, intraperitoneally), and possessing different levels of initial alcohol addiction [1]. Two groups of rats were selected for the experiments: short sleepers — predisposed to alcohol consumption with a mean duration of ethanol narcosis of 72.8 ± 13.8 min (group 1) and long-sleepers — not predisposed to alcohol consumption, with a mean duration of ethanol narcosis of 141 ± 7.5 min (group 2). After the study of the duration of ethanol narcosis, the animals were kept for 3 days in communal animal house cages so that their metabolism could become normalized, after which the pharmacokinetics of their blood ethanol was determined. The kinetics of ethanol was studied 15 and 30 min and

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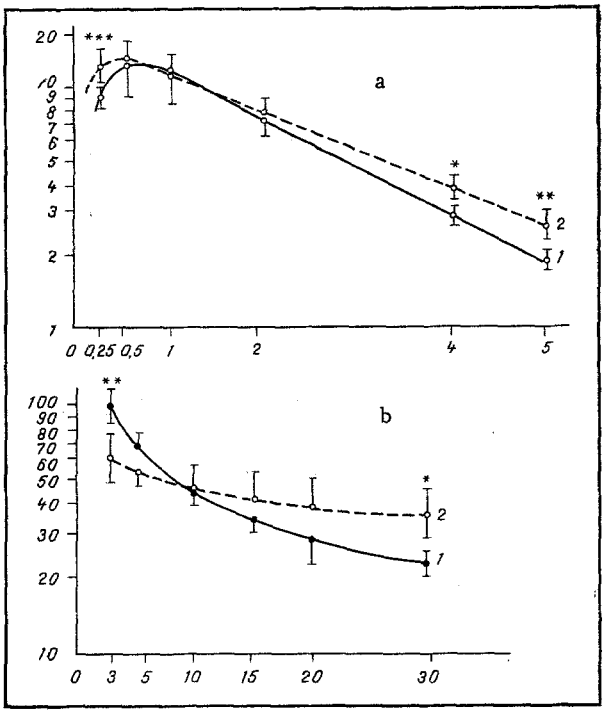

Fig. 1. Kinetics of blood ethanol level in rats differing in predisposition to the development of alcoholism, after intraperitoneal (a) and intravenous (b) injection. Abscissa, time after injection of ethanol (in h); ordinate, logarithm of ethanol concentration (in μmoles/ml). 1) Animals of group 1; 2) animals of group 2. *p < 0.05, **p < 0.01, ***p < 0.001. Ethanol was injected in a dose of 1 g/kg in the form of a 25% solution.

1, 2, 4, and 5 h after its intraperitoneal injection and 3, 5, 10, 15, 20, and 30 min after its intravenous injection. Ethanol was injected in a dose of 1 g/kg in the form of a 25% solution. The time intervals for taking blood samples after intravenous injection were chosen on the grounds that ethanol absorption takes place in the course of 30 min after intraperitoneal injection. Ethanol was determined quantitatively by gas-liquid vapor-phase analysis [3, 7]. The pharmacokinetic parameters of ethanol were calculated by computer, using an equation of first-order kinetics, and allowing for the process of absorption for intraperitoneal injection, but disregarding absorption for intravenous injection [6]. The results were subjected to statistical analysis by Student's method [5].

EXPERIMENTAL RESULTS

Experiments to study the pharmacokinetics of ethanol in the blood of rats differing in their predisposition to alcohol consumption, when injected intraperitoneally, showed that the ethanol concentration after 15 min in rats predisposed to develop experimental alcoholism was 12.8 μmoles/ml, compared with 18.2 μmoles/ml in the case of rats not so predisposed. By the 5th hour of the experiment the blood ethanol concentration in the animals of group 1 was only half (1.6 μmoles/ml) of that in the rats of group 2 (3.4 μmoles/ml; Fig. 1a). Values of the pharmacokinetic parameters K_a, K_e, and T_{max} (Tables 1 and 2) differed significantly in the animals of these groups. In rats predisposed to alcohol consumption K_e was 1.6 times higher but K_a was 2.5 times lower than in rats rejecting alcohol. The value of T_{max} was reduced by half in animals not predisposed to alcohol consumption, evidence of differences in the processes of ethanol resorption and elimination in the animals of the two groups. Differences were present also in the values of V_p: in rats predisposed to develop alcoholism this parameter was only two-thirds of its value in the other group. Differences in the animals of the two groups were less marked with respect to such parameters as CIT and C_{max}.

TABLE 1. Pharmacokinetic Parameters of Blood Ethanol in Rats Differing in Initial Level of Motivation for Intraperitoneally Injected Alcohol (M ± m)

Group of animals	Elimination constant (K_e)	Absorption constant (K_a)	Maximal time (T_{max}), h	Maximal concentration (C_{max}), μmoles/ml	Partition volume V_p, ml/kg	Clearance (CIT), ml/kg/h
1 (10)	0,48±0,03	3,5±0,2	0,65±0,02	15,5±2,1	886±30	425±30
2 (10)	0,34±0,02**	9,1±0,4***	0,37±0,01*	16,2±2,2	1176±29*	402±19

Legend. Here and in Table 2: *p < 0.05, **p < 0.01, ***p < 0.001; number of animals given in parentheses.

TABLE 2. Pharmacokinetic Parameters of Blood Ethanol in Rats Differing in Initial Level of Motivation for Intravenously Injected Alcohol (M ± m)

Group of animals	K_e	C_{max}, μmoles/ml	V_p, ml/kg	CIT, ml/kg/h
1 (10)	3,14±0,3	91,5±7,3	234±48	722±47
2 (10)	0,8±0,19***	54,5±6,18**	400±43*	355±85*

Analysis of the pharmacokinetics of ethanol after its intravenous injection enabled its distribution and elimination to be differentiated, whereas after intraperitoneal injection these processes were insufficiently clear, and it was found that the distribution of ethanol in the rats of group 2 took place much faster (by 1.5 times in a concentration of 54.5 μmoles/ml). In the animals of group 1 this process was observed when the concentration was 91.5 μmoles/ml (Fig. 1b; Tables 1 and 2). This state of affairs was confirmed by the high value of V_p (400 ml/kg) in the rats of group 2, compared with its value (234 ml/kg) in the animals of group 1. Moreover, the value of V_p gives additional information on the distribution of ethanol by volume among the organs and tissues [4]. In the rats of group 1, for instance, the value of this parameter relative to the blood volume was 23%, evidence of its distribution in the extracellular fluid, whereas in group 2 it was 40%, indicating its distribution in the aqueous phase of the body [4]. The rate of ethanol elimination was much higher in the rats of group 1: the value of K_e was 3.5 times higher than in the animals of group 2, whereas the value of CIT was twice as high.

The results of the studies of the pharmacokinetics of ethanol after intraperitoneal injection in the blood of rats differing in their initial level of alcohol motivation confirm previous experiments [2, 3] and show that a test dose of ethanol enters the blood stream more slowly in rats predisposed to alcohol consumption, but is eliminated much faster; in animals not predisposed to alcohol consumption these processes bear the opposite relationship.

The differences found in the pharmacokinetic parameters of ethanol absorption after intraperitoneal injection in the animals of the two groups can be attributed to differences in the distribution of ethanol by volume and, correspondingly, differences in the rate of this process, for after intraperitoneal injection ethanol is distributed simultaneously with its absorption (Fig. 1a). Intravenous injection excludes the absorption process, whereas elimination activates the distribution, metabolism, and excretion of alcohol. Analysis of the values of V_p for ethanol obtained after injection by both routes is evidence that in animals predisposed to the development of alcoholism, besides the high rate of elimination of ethanol, it is distributed more slowly, whereas in animals not predisposed to ethanol consumption the rate of its elimination is 3.5 times slower, although it is distributed much more rapidly.

It can be concluded from these experiments that the rate of elimination of ethanol, including the whole range of processes leading to a decrease in the concentration of the drug, in the general picture of the pharamacokinetics of ethanol studied after intraperitoneal and intravenous injection, with allowance for processes of absorption and (or) distribution, may be one of the most important parameters for the selection of animals differing in their initial level of alcohol motivation.

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INDIVIDUAL DIFFERENCES IN PAIN SENSITIVITY AND THE ANALGESIC EFFECT OF MORPHINE IN NONINBRED MICE

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KEY WORDS: nociceptive stimulation; pain threshold; morphine analgesia

Clinical observations show that during the relief of pain by neuroleptanalgesia, the analgesic properties of the narcotic analgesics are manifested only weakly in 10% of patients [2]. This state of affairs is evidence that patients differ in their sensitivity to substances of this group.

The aim of the investigation described below was accordingly to study individual differences in levels of sensitivity to pain and in the analgesic effect of opiates (with morphine as the example) in a population of noninbred mice, during nociceptive stimulation of varied modality (thermal, mechanical, electrical), in order to discover individual predictors of the degree of the pain-relieving action of narcotic analgesics.

EXPERIMENTAL METHOD

Experiments were carried out on 197 noninbred male mice weighing 21-26 g. The animals were divided into three groups (for thermal, mechanical, and electrical stimulation respectively) and were kept during the testing period in individual transparent plastic cages measuring 2.5 × 2.5 × 8 cm.

For thermal stimulation the animal's tail was immersed in a glass of hot water (55°C) [4]. The latent period of tail withdrawal in response to thermal stimulation was determined in each mouse before and after administration of morphine. Mechanical stimulation was effected by means of an analgesimeter (No. 21025, Ugo Basile Biological Research Apparatus, Italy). The animal's tail was subjected, at a distance of 1 cm from its base, to gradually increasing mechanical compression by means of a weight of 350 g moving along a lever. The threshold of pain sensation was recorded in conventional units in accordance with the reading on the analgesimeter scale when the animal gave a motor response. Electrical pain stimulation was applied through two needle electrodes 0.3 mm in diameter, made of stainless steel and arranged parallel to each other at a distance of 20 mm apart. The electrode nearest to the animal's trunk was located 7 mm from the base of the tail. Stimulation was given by

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