If after receiving CRG the rats were subjected to stress, their adrenocortical activity did not increase by the same degree as that of animals not receiving CRG. Changes in the PGE_2 concentration were similar.

The causes of the "cytoprotective" action of CRG, which we observed previously, must also be noted; the PGE_2 level in the rats' blood plasma fell sharply during stress (this may also have given rise to ulcers in the stomach), and injection of CRG prevented this change [2]. The writers showed previously that CRG inhibits arachidonic acid release and leukotriene biosynthesis [4]. The results of the present investigation indicate that CRG can also affect activity of PGG_2-PGE_2-isomerase.

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EFFECT OF ISOLATION STRESS ON BLOOD ETHANOL PHARMACOKINETICS DURING ALCOHOL MOTIVATION FORMATION AND PHYSICAL DEPENDENCE ON ALCOHOL IN RATS

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Isolation stress has been shown to be one factor conditioning the induction of ethanol-oxidizing enzyme systems [1]. Activity of these systems, induced by isolation of animals, may lead to a marked increase in their ethanol consumption, for there is evidence [2] that alcohol can abolish the consequences or prevent the development of emotional stress in rats associated with painful electrical stimulation of the limbs, in a similar way to what happens under the influence of tranquilizers, such as diazepam.

Considering the facts described above and the conditions for production of models of experimental alcoholism (keeping animals in individual cages), in the investigation described below the effect of isolation stress on the pharmacokinetics of the blood ethanol level were studied in rats with different levels of alcohol motivation and in rats with physical dependence on alcohol.

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TABLE 1. Pharmacokinetic Parameters of Blood Ethanol in Rats with Different Levels of Alcohol Motivation, against the Background of Alcohol Consumption and during the Withdrawal Period, under Conditions of Isolation Stress (M ± m)

Experimental conditions	Predisposition of animals to ethanol consumption	Elimination constant (K_e), g^{-1}	Absorption constant (K_a), g^{-1}	Maximal time (T_{max}), h	Maximal concentration (C_{max}), μmoles/ml	Partition volume (V_p), ml/kg	Clearance (CLT), ml/kg/h
Isolation + ethanol consumption	Predisposed (n = 6)	0,36±0,04	3,0±0,2	0,88±0,15	5,4±0,7*	3036±360	967±83
	Not predisposed (n = 6)	0,35±0,11	5,7±0,46	0,8±0,1	7,6±1,3	2450±701	888±201
Isolation + ethanol withdrawal	Predisposed (n = 6)	0,38±0,02	5,2±0,6	0,58±0,09	3,5±0,5	5100±98	1089±70
	Not predisposed (n = 6)	0,34±0,04	6,3±1,8	0,52±0,1	5,8±0,3	3160±132	673±116

Legend. *$p < 0.05$ compared with predisposed rats during ethanol withdrawal.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats. In series I 12 rats weighing 200 g were used; these animals had been tested beforehand for the level of their alcohol motivation, with freedom of choice between 15% ethanol solution and water, and kept in individual cages for 10 days [3].

After testing 6 rats, voluntarily choosing ethanol and consuming on average 17.3 ± 1.4 ml (group 1) and 6 rats not consuming ethanol solution under these conditions (group 2) were chosen. After the study of the pharmacokinetics of ethanol, rats of both groups were returned to their previous conditions for a further 10 days, but with no possibility of drinking ethanol. After 10 days the pharmacokinetics of ethanol was again studied.

In the experiments of series II the pharmacokinetics of ethanol were tested on 12 rats weighing 500-600 g, in stage III of experimental alcoholism, namely physical dependence on alcohol (8 months of voluntary consumption of ethanol in a dose of 38.2 ± 3.8 ml daily) [2]. The animals were divided into two groups with 6 rats in each group: the rats of group 1 were kept for 10 days before the experiment in individual cages, with freedom of choice between ethanol and water; the rats of group 2 were kept in a common cage, and also were able to drink ethanol and water.

The pharmacokinetics of the blood ethanol in rats was studied after intraperitoneal injection in a dose of 1 g/kg, in the form of a 25% solution. The ethanol concentration was determined by vapor-phase gas chromatography [3, 7]. The pharmacokinetic parameters were calculated by computer, using a first order kinetics equation and allowing for absorption [4].

EXPERIMENTAL RESULTS

The character of the pharmacokinetic curve of ethanol in rats consuming and not consuming alcohol under conditions of free choice between a 15% alcohol solution and water, was the same, and no marked differences could be found between these groups of animals with respect to the value of pharmacokinetic parameters reflecting resorption and elimination processes (Table 1).

The study of the pharmacokinetics of ethanol in these rats, when replaced in their individual cages, but were not allowed to consume alcohol, showed that the rate of ethanol elimination was considerably increased in animals predisposed to its consumption, as shown by the pharmacokinetic parameters, K_a, T_{max}, C_{max}, and V_p. These parameters were unchanged in rats not predisposed to alcohol consumption (Table 1).

It was observed previously [1] that the rate of elimination of ethanol in intact rats, kept in individual cages (isolation stress) is three times higher than in rats kept in communal cages.

The high rate of ethanol elimination found in intact rats kept in individual cages was virtually indistinguishable for rats consuming and not consuming ethanol when kept under similar conditions, i.e., stress induced by isolation of animals facilitates induction of ethanol-oxidizing enzyme systems regardless of the level of alcohol motivation. However, prohibiting ethanol consumption by animals predisposed to it under these conditions on average

TABLE 2. Pharmacokinetic Parameters of Blood Ethanol in Rats in the Stage of Physical Dependence on Alcohol, under Different Experimental Conditions (M ± m)

Experimental conditions	K_e, g^{-1}	K_a, g^{-1}	T_{max}, h	C_{max}, μmoles/ml	V_p, ml/kg	CLT, ml/kg/h
Common cages (n = 6)	0,33±0,03	2,6±0,2	0,68±0,1	11,9±4,2	1251±112	460±73
Individual cages (n = 6)	0,34±0,02	3,3±0,4	0,8±0,04	11,4±1,2	1476±194	430±56

doubled the rate of alcohol elimination. At the same time, we know that administration of diazepam to animals kept in individual cages lowers the rate of ethanol elimination [1]. These results are in agreement with data showing that ethyl alcohol and tranquilizers act similarly in emotional stress [2].

The data described above are evidence that animals with an initially high level of alcohol motivation are more vulnerable to stress, for the value of the pharmacokinetic parameters of ethanol (indirectly characterizing activity of ethanol-oxidizing enzyme systems) were higher in these animals. Consumption of alcohol by these animals probably abolishes stress on account of its tranquilizing effect, while at the same time normalizing activity of the ethanol-oxidizing enzyme system.

In animals at the stage of physical dependence on alcohol its pharmacokinetics was independent of the conditions under which they were kept (Table 2). It has also been shown [2] that the level of ethanol consumption by these animals in communal and individual cages was virtually identical. It follows from these data that in animals in the stage of physical dependence on alcohol stress is not the leading factor determining its consumption.

Stress induced by isolation of animals is thus one factor causing them to consume alcohol. The results are in agreement with those obtained by other workers [6] who found that ethanol, given in doses of 0.5 to 2 g/kg, weakened aggressiveness evoked by isolation of mice for 28 days. Animals with a high level of alcohol motivation were more subject to stress induced by isolation. The craving for ethanol in animals under stress due to isolation, on account of its psychopharmacological effect, lasts as long as physiological readjustment takes place in the nervous system, which can function only in the presence of alcohol [5]. This stage of experimental alcoholism is characterized by physical dependence on alcohol. Under these circumstances activity of the ethanol-oxidizing enzyme system and consumption of alcohol by the animals are no longer determined by emotional stress (isolation of the animals), but, evidently, by profound biochemical and neurochemical changes.

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