These results to some extent contradict those of other investigations [3], which show that naloxone can abolish analgesia induced by SSR. This difference may perhaps be explained by the different neurochemical mechanisms forming the nociceptive response to stimuli of different modalities [6].

According to Borisenko [2], morphine has a facilitory action on SSR in rats only in a dose corresponding to ED_{50} of the analgesic effect (3 mg/kg). Trimeperidine (4.5 mg/kg) did not affect it, fentanyl (40 mg/kg) reduced the intensity of self-stimulation, whereas pentazocine (20 mg/kg) completely suppressed it.

It can thus be concluded that the euphoria-inducing component is not essential for manifestation of the analgesic effect of narcotic analgesics.

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CORRELATION BETWEEN THE RATE OF ETHANOL ELIMINATION AND PSYCHOPHYSIOLOGICAL DIFFERENCES IN RATS

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KEY WORDS: ethanol; rats; pharmacokinetics

The development of alcoholism as a multifactorial disease can be attributed to a number of environmental and genetically determined features [5, 13]. In particular, one feature of the genetic predisposition to alcohol addiction from the beginning is the high rate of its elimination [4]. It has also been shown that primary predisposition to alcohol consumption may be due to individual differences in higher nervous activity in a population of laboratory albino rats.

For the above reasons it was decided to study the rate of ethanol elimination (an indirect parameter of activity of ethanol-oxidizing enzyme systems) from the blood of rats distinguished *ab initio* with respect to their psychophysiological features, in order to discover if the general principles mentioned above can be identified in the complex system of predisposition to alcohol consumption in a model of experimental alcoholism.

EXPERIMENTAL METHOD

Experiments were carried out on 12 laboratory male albino rats weighing 180-200 g, divided beforehand into two groups, by a method based on differences in behavioral activity

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TABLE 1. Pharmocological Parameters of Blood Ethanol in Rats with Differing Behavioral Activity in the Compulsory Swimming Test

Group of animals	K_e	K_a	C_{max}, μmoles/ml	Ethanol clearance, ml/kg/g	$T_{1/2}$, h^{-1}
Highly active ($n = 6$)	0,3±0,03	10±0	8,2±0,4	790±64	2,3±0,2
Inactive ($n = 6$)	0,4±0,03*	5,2±0,5***	7,0±0,5	933±68	1,8±0,1*

Legend. *p < 0.05, **p < 0.01, ***p < 0.001. n) Number of animals.

in a stress situation (unavoidable swimming), described in [2] and modified. The rats were placed for 10 min in a tank of water (20°C). The total time spent by the animal in a posture of immobilization, when it swam passively in a slightly inclined forward vertical position, with its head only just above the surface of the water, was recorded, i.e., the time of refusing energetic activity. Rats staying a short and long time in a posture of immobilization were selected, i.e., those considered to be highly active, or uninclined to develop a depression-like state, could be distinguished from those considered to be inactive, or inclined to develop a depression-like state [4]. Next day, the pharmacokinetics of ethanol in the blood was studied in animals of both groups after interperitoneal injection of ethanol in a dose of 1 g/kg body weight as a 25% solution. The ethanol concentration was determined by headspace gas chromatographic analysis [1, 10]. The pharmacokinetic parameters were calculated by computer, using a first-order kinetics equation and allowing for absorption [8]. The results were subjected to statistical analysis by Student's test [6].

EXPERIMENTAL RESULTS

Comparison of the parameters of pharmacokinetics of ethanol in the blood in rats with high and low activity revealed differences in the rate of resorption and elimination of alcohol (Table 1). In highly active animals the maximal ethanol concentration (C_{max}) was established after 15 min (8.1 μmole/ml), whereas in inactive animals it was established after 30 min (8.3 μmole/ml) of the experiment. These data indicate differences in ethanol absorption, and these are confirmed by the value of the absorption constant (K_a): this was twice as high for highly active animals as for inactive ($p < 0.01$). Rats of the groups studied also differed in the value of their ethanol elimination constant (K_e), which was 1.3 times higher in inactive animals, and was associated with high ethanol clearance in these rats. These results are confirmed by values obtained for the half-elimination time ($T_{1/2}$) of ethanol, which was almost twice as long in the highly active animals (2.3 h^{-1}) as in those with low activity (1.8 h^{-1}).

These pharmacokinetic parameters are evidence that rats refusing energetic activity in a stress situation have a high rate of elimination of ethanol from the blood.

These results confirm the principle discovered previously in mice of an inbred line (C56BL/6), characterized by a high rate of ethanol elimination, and predisposed to the development of alcoholism [3, 5, 9, 11, 12], which were distinguished by the shortest duration of immobilization [7], whereas CBA mice, with a lower rate of elimination of ethanol from the blood, had low alcohol motivation from the beginning [3, 4, 9, 11, 12], and were distinguished by a long period of immobilization [8].

It can thus be concluded from these results that the observations made on noninbred rats confirm the conclusion established previously on inbred mice, namely that the level of an inborn tendency to develop a depression-like state correlates with a high rate of ethanol elimination, and it may probably be one of the genetic features that contribute to the formation of the primary alcohol motivation and predisposition to the development of experimental alcoholism.

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BIOTRANSFORMATION OF A ^{14}C-HYDROGENATED PHENAZEPAM ANALOG IN INBRED MICE *IN VIVO*

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KEY WORDS: hydrogenated phenazepam analog; metabolism; kinetics; excretion; differences

It was shown previously that the pharmacological activation of some psychotropic drugs depends on some genetically controlled features of their metabolism [4, 5].

The aim of this investigation was to study excretion of a ^{14}C-hydrogenated analog of phenazepam (5-o-chlorophenyl-7-bromo-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one) (I), synthesized by ourselves [6], and which, compared with phenazepam itself, induces a much weaker degree of muscle relaxation and ataxia [5], and excretion of its metabolites, from inbred lines of mice with different oxidation phenotypes [4, 5].

TABLE 1. Content (in % of injected dose) of ^{14}C-I and Its Metabolites (total quantities) in Excreta of Inbred Lines of Mice, Excreted over a Period of 1-4 Days (M ± m)

Interval, days	Line of mice	Urine			Feces			
		total radioactive material	free metabolites lites	residual radioactivity (aqueous)	total radioactive material	free metabolites	glucuronides	residual radioactivity (aqueous)
1	B6	7,75±1,86	3,91±0,74	3,38±0,59	35,71±3,68	8,62±0,25	4,60±0,55	7,65±0,78
	C	3,95±0,63	0,96±0,01	2,09±0,09	43,14±4,35	9,56±0,94	5,92±0,57	5,12±0,14
	CBA	4,17±0,62	1,28±0,10	2,00±0,34	46,19±3,99	8,95±0,62	7,40±0,62	5,25±0,34
2	B6	2,06±0,33	0,75±0,11	1,15±0,09	11,39±1,04	2,46±0,09	2,09±0,19	2,17±0,23
	C	1,42±0,62	0,31±0,03	0,92±0,09	13,39±1,72	3,35±0,47	2,19±0,31	1,49±0,16
	CBA	1,29±0,10	0,25±0,05	0,90±0,08	13,29±1,97	2,67±0,19	2,30±0,14	1,74±0,21
3	B6	0,92±0,15	0,29±0,07	0,36±0,06	7,59±0,55	1,54±0,31	1,12±0,13	1,34±0,17
	C	0,71±0,08	0,18±0,02	0,43±0,05	7,10±0,74	1,48±0,07	0,94±0,08	0,75±0,09
	CBA	0,68±0,09	0,20±0,03	0,39±0,04	8,01±0,97	1,39±0,09	1,10±0,10	0,80±0,06
4	B6	0,39±0,08	0,12±0,03	0,14±0,02	4,64±0,82	0,97±0,14	0,65±0,12	0,70±0,13
	C	0,35±0,05	0,09±0,01	0,19±0,03	4,11±0,39	0,91±0,01	0,36±0,04	0,36±0,05
	CBA	0,32±0,05	0,11±0,01	0,19±0,02	5,25±0,44	0,50±0,04	0,42±0,04	0,36±0,04

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