PHARMACOKINETICS OF ETHANOL IN NARCOTIC DOSES AND ENDOGENOUS ETHANOL LEVELS IN FEMALE RATS

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UDC 615.211:547.262].033:612.621.5

KEY WORDS: ethanol preference; endogenous ethanol; pharmacokinetics; estrous cycle.

The results of a previous investigation showed that female rats can be divided into three groups depending on the duration of ethanol narcosis. Group 1 includes females in which the duration of narcosis in the stage of estrus is shorter than in the stage of diestrus. Group 2 includes animals with the opposite relationship between the times of narcosis in the corresponding stages of the estrous cycle. Group 3 consists of rats in which the duration of the narcotic action of ethanol is independent of the stage of the cycle. A study of the consumption of ethanol and water by these animals under free choice conditions showed that most female rats choosing ethanol belong to group 1. This group was accordingly characterized as a "group with increased risk of subsequent formation of preference for ethanol before water in female rats" [1].

TABLE 1. Analysis of Correlation between Ratio of Duration of Ethanol Narcosis Depending on Stage of Estrous Cycle (t_D/t_θ) and Reaction of Choice of Liquid in Female Rats

Reaction of choice	t_D/t_θ				n_2
	0,34–0,43	0,5–1,0	1,1–1,4	1.5 and above	
Preference for water	2 (4) 0,29	9 (81) 5,79	2 (4) 0,29	1 (1) 0,07	14
Water + ethanol, no preference		1 (1) 0,3		2 (4) 1,33	3
Preference for ethanol		4 (16) 1,45	7 (49) 4,45		11
n_1	2	14	9	3	28
$\Sigma\,(f_2{:}n_2)$	0,29	7,54	4,74	1,4	
$\sum\left(\frac{f_2{:}n_2}{n_1}\right)$	0,15	0,54	0,53	0,47	1,69
General results	Coefficient of contingency $\varphi^2 = 0.69$ Polychoric index of correlation $K = 0.68$ When $\lambda = 6$, $\chi^2_K = 19.4$. $\begin{pmatrix}12.6\\16.8\\22.5\end{pmatrix}$ χ^2 statist.				

Laboratory of Pharmacology of Narcotics, V. P. Serbskii All-Union Research Institute of General Forensic Psychiatry, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 94, No. 12, pp. 60-62, December, 1982. Original article submitted June 1, 1982.

0007-4888/82/9412-1689$07.50

TABLE 2. Analysis of Correlation between Ratio of Duration of Ethanol Narcosis Depending on Stage of Estrous Cycle (t_D/t_θ) and Ethanol Consumption in Female Rats

Dose of ethanol, g/kg	t_D/t_θ				n_2
	0,34—0,48	0,5—1,0	1,1—1,4	1.5 and above	
0—0,9	2 (4) 1,0	2 (4) 1,0			4
1—1,9		1 (1) 0,3	2 (4) 1,3		3
2—3,9		7 (9) 0,44	2 (4) 0,44		9
4—12		4 (16) 1,33	4 (16) 1,33	4 (16) 1,33	12
n_1	2	14	8	4	28
$\Sigma (f_2:n_2)$	1,0	8,07	3,07	1,33	
$\sum\left(\frac{f_2:n_2}{n_1}\right)$	0,5	0,58	0,38	0,33	1,79
General results	Coefficient of contingency $\varphi^2 = 0.79$ Polychloric index of correlation $K = 0.72$ When $\lambda = 6$, $\chi^2_K = 22.12$. (χ^2 statist. $\begin{pmatrix}16.9\\21.7\\27.9\end{pmatrix}$				

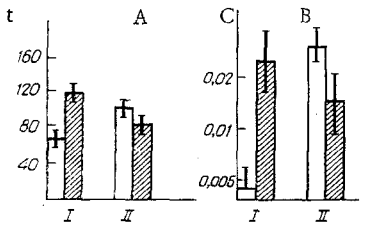

Fig. 1

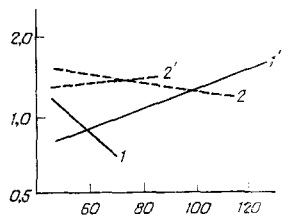

Fig. 2

Fig. 1. Duration of ethanol narcosis (A) and endogenous ethanol level (B) in female rats of groups 1 and 2 depending on stage of estrous cycle. Vertical axis: t duration of anesthesia (in min); C) log of blood ethanol concentration (in %). Unshaded column — stage of diestrus.

Fig. 2. Pharmacokinetics of ethanol after administration of narcotic dose to female rats of groups 1 and 2. 1, 1') group 1, stages of estrus and diestrus respectively; 2, 2') group 2, stages of estrus and diestrus respectively. Abscissa, time (in min); ordinate, log of blood ethanol concentration (in %).

The aims of the present investigation were as follows: 1) to analyze correlation between the ratio of the duration of ethanol narcosis in the stages of diestrus and estrus and two parameters characterizing preference of ethanol to water: the response of choice of water or ethanol and the quantity of ethanol consumed; 2) to study the endogenous levels and pharmacokinetics of ethanol in the blood of female rats with different durations of narcosis depending on the stage of the estrous cycle.

EXPERIMENTAL METHOD

Experiments were carried out on 28 noninbred female albino rats weighing 250-300 g. The duration of the narcotic action of ethanol in a dose of 4.5 g/kg, injected intraperitoneally in a 25% aqueous solution, was determined in all the female rats in the stages of estrus and diestrus by the side position test. The stages of the cycle were determined by examination of vaginal films. The results of this part of the investigation were expressed as the ratio of the duration (t) of narcosis in the stages of diestrus (D) and estrus (θ), i.e., t_D/t_θ. If the duration of narcosis was independent of the stage of the cycle, the ratio had the value of 1.

The endogenous level and also the concentration of ethanol in the blood were measured in 20 rats (in 11 with a longer and 9 with a shorter duration of narcosis in the stage of estrus) 30 min after injection of a narcotic dose and when the animal was coming round from a state of narcosis. Blood was taken in a volume of 0.1 ml by capillary tube after amputation of the tip of the tail. Ethanol in the blood was determined quantitatively by gas chromatography (GC) [2].

When 24 h had elapsed after the narcotic test the animals were placed in individual cages where they had access for 24 h daily for 15 days to bowls of drinking water and of 15% ethanol solution. The criterion of preference for one liquid or the other was that its consumption was more than twice that of the other liquid. For each female the mean daily ethanol consumption in g/kg body weight was calculated for the 15 days.

The experimental data were analysed by Student's test at the 0.05 level of significance. Polychoric indices of correlation were determined between the relevant factors [3]. Correlation matrices were constructed for the number of animals grouped in accordance with one feature at a time. The elimination constant (K_{el}) and the half-elimination time of ethanol from the blood ($T_{1/2}$) were calculated by graphic analysis of a one-part model [4].

EXPERIMENTAL RESULTS

Data on correlation between the duration of narcosis and subsequent choice of liquid are given in Table 1. Positive correlation will be noted between the ratio of the duration of narcosis in the different stages of the estrous cycle (t_D/t_θ) and preference of ethanol to water. The polychoric index is 0.68, corresponding to average closeness of correlation between the factors studied.

The results of analysis of correlation between the duration of narcosis and ethanol consumption under free choice conditions are given in Table 2. Correlation between the ratio of the duration of narcosis in the different stages of the estrous cycle (t_D/t_θ) and the dose of ethanol consumed by the rats can be seen to be positive. The polychoric index of correlation was 0.72, corresponding to close correlation. Differences in the closeness of correlations thus revealed are probably attributable to the fact that the duration of narcosis and the quantity of ethanol consumed are determined largely by the character of ethanol metabolism, whereas the reaction of choice of ethanol and its preference to water is a complex behavioral act, which is only partially dependent on the character of ethanol metabolism.

Both the reaction of choice of ethanol and, in particular, the quantity of ethanol consumed can thus be predetermined to some extent by measuring the ratio between the duration of anesthesia in different stages of the estrous cycle.

During subsequent analysis of the experimental data the duration of narcosis, the endogenous level of ethanol, and the pharmacokinetics of ethanol after injection of a narcotic dose in two groups of female rats in the stages of estrus and diestrus were compared. Figure 1 shows that the animals of group 1, with a longer duration of narcosis in diestrus and a shorter duration in estrus (i.e., the ratio t_D/t_θ had a mean value of 1.6) had a high level of endogenous ethanol in diestrus and a low level in the stage of estrus. The rats of group 2, on the other hand, had a somewhat longer duration of narcotic action of ethanol in estrus ($t_D/t_\theta = 0.67$) and a higher blood endogenous ethanol level in this same stage of the estrous cycle.

The study of the pharmacokinetics of ethanol in narcotic doses showed that when the animal was coming round from narcosis an appreciable fall in the blood ethanol concentration occurred only in the rats of group 1 in the stages of estrus ($K_{el} = 1.99\ g \cdot min^{-1}$, $T_{1/2} = 28$ min). In the same rats in the stage of diestrus and in the rats of group 2 in both stages

of the estrous cycle, the blood ethanol levels in animals coming round from narcosis were about equal but no fall in ethanol concentration was observed under these circumstances (Fig. 2).

The short duration of ethanol narcosis in the stage of estrus and its longer duration in the stage of diestrus ($t_D/t_\theta > 1$), the low endogenous ethanol level in the stage of estrus, and the rapid fall in the blood ethanol concentration after administration of a narcotic dose during estrus are thus characteristic of female rats which choose ethanol in preference to water under free choice conditions and consume it in larger doses.

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NEUROPHARMACOLOGIC PROPERTIES OF PYRACETAM DERIVATIVES

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UDC 615.214.311:547.745].015.4

KEY WORDS: neurotropic agents; pyracetam; GABA; hypoxia; amnesia.

The high clinical efficacy of pyracetam justifies the study of the mechanism of its action and the search for new compounds with neurotropic activity. The aim of the investigation described below was to study some derivatives and analogs of pyracetam, with neurotropic activity, synthesized at the Institute of Pharmacology, Academy of Medical Sciences of the USSR.*

EXPERIMENTAL METHOD

In stage I the compounds were tested on male mice by the basic tests of neurotropic screening: general action, motor activity, action on the effect of amphetamine, pentobarbital, ethanol, chlorpromazine, various convulsants (Table 1), and thiopental sodium. To discover potential neurotropic drugs models of oxygen insufficiency [2, 3] were used: normobaric hypoxia (length of survival in an airtight chamber) and hypobaric hypoxia (pressure chamber, experiments under two conditions: survival after 15-min exposure at an "altitude" of 11,000 m or determination of the tolerated altitude ceiling). The most active substances according to these tests were studied in electrophysiological experiments. Their effect on the recovery cycle of evoked potentials (RCEP) recorded in the somatosensory cortex during paired stimulation of the sciatic nerve, and averaged by means of an LP-4840 analyzer, was investigated in acute experiments on 20 rats (details of the method were described previously [4]). The threshold dose in which pentobarbital induces particular phases of ECoG depression in animals after preliminary injection of physiological saline (control) or of the test substance were determined in experiments on twelve rabbits. Potential neurotropic drugs were studied on

*Most of these compounds are mentioned in the patent literature [9, 10], but no data have been published on the spectrum of their pharmacologic activity.

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(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 94, No. 12, pp. 62-65, December, 1982. Original article submitted June 29, 1982.

0007-4888/82/9412-1692$07.50