FORMATION OF EXPERIMENTAL ALCOHOLISM IN A POPULATION OF NONINBRED ALBINO RATS

Yu. V. Burov, A. B. Kampov-Polevoi, and O. P. Kashevskaya

UDC 616.89-008.441.13-092.9

KEY WORDS: alcohol narcosis; alcohol motivation; rats.

It can be concluded from clinical data that there are at least two categories of patients with chronic alcoholism [1-3]. The most characteristic feature of patients of one category is what may be called their "ready-made high tolerance" to ethanol. They also have a marked primary alcohol motivation, and cases of chronic alcoholism have usually been noted in the family history. In patients of the other category, as a rule an initially high tolerance to ethanol was not observed. There was no primary attraction to alcohol in these patients, but consumption of alcohol was usually due to situational factors (an attempt to reduce emotional stress, to overcome inhibitions, etc.). Such patients were much more sensitive to the toxic action of ethanol, and as a rule the disease followed a more malignant course in this group.

In experiments on animals similar data have been obtained on correlation between the duration of alcohol narcosis and the level of alcohol consumption. For instance, in mice of line B10.R107, a genetically determined increased inclination toward alcohol was accompanied by an initially high tolerance to ethanol [5].

With the above facts in mind it was decided to study the course of experimental alcoholism in a population of noninbred rats differing in their metabolic tolerance to ethanol.

EXPERIMENTAL METHOD

Experiments were carried out on 84 noninbred male albino rats weighing 180-200 g at the beginning of the experiment. The duration of the side position for all animals after intraperitoneal injection of 25% ethanol solution in a dose of 4.5 g/kg was tested. The short-sleeping animals were then chosen, in which the duration of ethanol anesthesia was under 90 min, and long-sleeping animals with a duration of anesthesia of more than 175 min were placed in cages measuring 32 × 47 × 16 cm, with four rats to a cage. The cages were equipped with feeding bowls and two graduated drinking vessels: one containing water and the other containing 15% ethanol solution. The quantity of ethanol solution consumed by the animals of each group was recorded daily for 10 days.

All the rats were then returned from communal cages into individual cages measuring 40 × 12 × 15 cm, also equipped with a feeding bowl and two graduated drinking vessels (water and 15% ethanol solution). For 10 days the animals' ethanol consumption was recorded daily. A burette containing 0.13% saccharine solution was then placed in the cage with the rats and consumption of the three fluids was recorded for the next 10 days. On the 21st day the drinking vessel with saccharine was removed and for 8 months the character of ethanol consumption of all the experimental animals was studied in individual cages.

The animals were then placed in communal cages three at a time (because of the increase in body weight of the rats to 320-460 g) for 10 days, after which they were transferred to individual cages for 10-day testing of their alcohol consumption. At the end of testing the burette containing saccharine solution also was placed in these same cages. Ethanol consumption was recorded daily.

The results were subjected to statistical analysis by Student's t test [14].

Laboratory for the Search for and Study of Substances for the Prevention and Treatment of Drug Addictions, Institute of Pharmacology, Academy of Medical Sciences of the USSR, 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. 96, No. 8, pp. 67-68, August, 1983. Original article submitted January 31, 1983.

 0007/4888/83/9608-1110$07.50

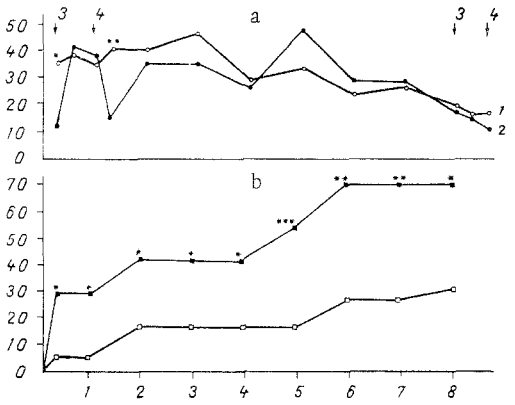

Fig. 1. Time course of alcohol consumption (15% solution) and mortality of rats with free access to alcohol and water. Abscissa: a) alcohol consumption (in ml/kg), b) mortality (in %); ordinate, duration of contact of animals with alcohol (in months). 1) Short-sleeping, 2) long-sleeping rats, 3) communal cages, 4) additional presentation of saccharine solution.

EXPERIMENTAL RESULTS

To determine the duration of alcohol anesthesia 18 short-sleeping rats (mean duration of side position 67 ± 4.5 min) and 24 long-sleeping (mean duration of side position 222 ± 11.6 min) rats were chosen from the total of 84 animals. Differences in the development of experimental alcoholism were subsequently observed in the animals of the two groups. For instance, placing all the rats in more comfortable situations (in communal groups), for instance, revealed a significant difference in their alcohol consumption (Fig. 1a): the mean daily volume of ethanol solution consumed by the short-sleeping rats was 36.6 ± 5.79 ml/kg per animal, compared with 10.8 ± 6.48 ml/kg for the long-sleepers ($P < 0.05$). Under the influence of stress factors (transfer to individual cages, keeping in isolation) an increase in alcohol consumption by the long-sleeping rats was observed to 38.0 ± 5.3 ml/kg, whereas the level of alcohol consumption by the short-sleeping animals remained virtually unchanged (Fig. 1a). The additional presentation to the animals of saccharine solution, without the pharmacological effects of ethanol and with no calorific value, and to which the rats were inclined to show preference [6, 7], again proved effective only for the long-sleeping rats: their alcohol consumption fell to 17.0 ± 6.7 ml/kg (41.0 ± 8.1 ml/kg for the short-sleeping rats, $P > 0.05$). The results evidently indicate that the primary alcohol motivation of the long-sleeping animals was less stable in character than that of the short-sleeping animals and it was depressed by the action of positive emotional factors (saccharine and keeping the animals in groups).

Later, when the rats of both groups were kept in individual cages, their level of ethanol consumption was found to be practically identical (Fig. 1a). By the 8th month in individual cages, incidentally, the mean daily volumes of ethanol solution consumed by the rats of both groups were much less than in the first month of alcoholization ($P < 0.05$), and this evidently reflects a decrease in tolerance to alcohol. Testing the animals for alcohol consumption when kept in groups and when provided with saccharine solution revealed no significant effect on the volume of ethanol solution consumed by the animals of the two groups ($P > 0.05$).

These experiments showed that short-sleeping animals initially possessed a stronger and more lasting alcohol motivation, whereas the alcohol motivation of the long-sleeping rats gradually became more stable in character against the background of prolonged stress and chronic alcoholization, and probably reflected the development of a secondary alcohol motivation and elements of physical dependence.

Analysis of mortality among the rats of the two groups during voluntary alcoholization showed (Fig. 1b) that during the first month of contact with alcohol about 30% of the long-sleeping animals died already. In the group of short-sleeping rats mortality during this same period of alcoholization was lower, at 5%. By the end of the 2nd month mortality in the group of long-sleeping rats reached 40% of the initial number, compared with 15% in the group of short-sleeping rats; by the 6th month the corresponding figures were 70 and 25%, and they

showed little change during the next 2 months. The lower level of mortality in the group of short-sleeping rats than in the long-sleepers evidently reflects the increased sensitivity of the latter to the toxic action of alcohol.

The great similarity between the forms of experimental alcoholism described in rats and forms of chronic alcoholism in man provides a basis for a differential approach to the simulation of this pathology in animals.

LITERATURE CITED

1. E. Bleuler, Textbook of Psychiatry [Russian translation], Berlin (1920).
2. M. E. Burno, Zh. Nevropatol. Psikhiat., No. 4, 585 (1968).
3. N. N. Ivanets, A. L. Igonin, and N. V. Ivanova, Zh. Nevropatol. Psikhiat., No. 2, 237 (1977).
4. N. A. Plokhinskii, Biometrics [in Russian], Moscow (1970).
5. S. V. Shoshina and A. I. Maiskii, Byull. Éksp. Biol. Med., No. 7, 55 (1982).
6. F. D. Sheffield and T. B. Roby, J. Comp. Physiol. Psychol., 43, 471 (1950).
7. F. D. Sheffield, T. B. Roby, and B. A. Campbell, J. Comp. Physiol. Psychol., 47, 349 (1954).

EFFECT OF NONACHLAZINE ON TRANSMEMBRANE IONIC CURRENTS OF ATRIAL TRABECULAE IN FROGS

R. Marko, S. A. Kryzhanovskii, S. Yu. Berdyaev, K. Kelemen, and N. V. Kaverina

UDC 615.224.547.869.2].015.4:612.173.1

KEY WORDS: nonachlazine; transmembrane ionic currents; ischemic heart disease.

Nonachlazine is a new antianginal drug synthesized at the Research Institute of Pharmacology, Academy of Medical Sciences of the USSR. In its chemical structure it is 1,4-diazabicyclo-(4,3,0)-nonanyl-4-propionyl-2-chlorophenothiazine, i.e., it is a 10-aminopropional-2-substituted phenothiazine, a group of compounds characterized by a marked action on the cardiovascular system. Nonachlazine is widely used in medical practice for the treatment of ischemic heart disease (IHD). The drug not only has an antianginal effect, but in some cases it also has an antiarrhythmic action. Under experimental conditions these properties are found on most models of arrhythmia, but they are less marked than those of other compounds (ethmozine, its diethylamino analog) which have a urethane group in position 2 of the phenothiazine ring [1, 2]. The antiarrhythmic properties of the latter are associated mainly with their ability to block the rapid inward sodium current, and this explains their high effectiveness in cardiac arrhythmias connected with the appearance of ectopic foci of excitation in the myocardium [3]. It was interesting to discover with what mechanisms the antiarrhythmic action of nonachlazine is connected. The investigation described below was undertaken to study this problem.

EXPERIMENTAL METHOD

The test object consisted of atrial trabeculae from the frog *Rana esculenta*, about 3 mm long and 0.1 mm in diameter. The trabeculae were placed in a double sucrose gap system to measure transmembrane ionic currents by the voltage clamp method. The apparatus described in [9] was used. Experiments were carried out in a chamber at a constant temperature of 18°C; the strip was stimulated with square pulses of direct current with a frequency of 0.6 Hz.

Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Institute of Pharmacology, Semmelweiss Medical University, Budapest, Hungary.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 8, pp. 69-70, August, 1983. Original article submitted January 31, 1983.

0007-4888/83/9608-1112$07.50