EFFECTS OF SUBNARCOTIC DOSES OF ETHYLURETHANE ON RESISTANCE TO SEVERE ANOXIA IN RATS

KATSUO KAMAKURA, WATARU KAIJO AND AKIRA MORIKAWA

Department of Physiology, Nara Medical College, Unebi-cho Nara Prefecture

About a decade ago Emerson et al. (1) reported the effect of narcotic agents, ethyl alcohol, amytal and pentobarbital on resistance to severe acute anoxic anoxia in mice. During our study (2) of adaptation of rats to a simulated high altitude of about 12 km., it was observed that the rats administered with subnarcotic doses of ethylurethane (U) considerably tolerated to the same high altitude than control animals did. The present paper deals essentially with the action of U against severe acute anoxia, and also with that of other narcotics some of which have been employed by previous investigators (1, 3).

METHOD

Albino rats, of both sexes, weighing between 150 g. and 300 g. were used. The diet of wheat, vegetable, dry fish and water was allowed ad libitum except about three hrs. prior to the test. All of experimental animals were employed only once and no or little attention was paid to other factors such as sex, age, and weight, because no significant influences upon experimental results were observed. A desiccator possessing a capacity of about 5 l. was used as a decompression chamber, provided with a vacuum pump. At a rate simulating an increase in altitude of about 375 m. per min., the pressure in animal chamber was reduced to 145 mm Hg within 32 min., corresponding with an altitude of about 12 km., and it was then maintained within a fluctuation of ±2 mm Hg. Survival times of rats were determined from the time when the simulated altitude of about 12 km. was attained to the last gasp of the animals; the respiration rate of the rats was measured simultaneously.

As narcotic agents, besides U, sodium phenobarbiturate (B), chloralose (C), and morphine hydrochloride (M) were employed. All agents were administered intraperitoneally, sometimes subcutaneously, with various doses. Thirty minutes after the injections, the decompression in the animal chamber was started.

RESULTS AND DISCUSSION

Survival times of normal rats in the pressure of 145 mm Hg. By reducing the chamber pressure at the aforesaid rate (375 m/min.), more than 40% of control
rats (67 cases) succumbed at the pressure of approximately 170 to 150 mm Hg before the simulated altitude of about 12 km was attained. As is well known, the resistance of animal to anoxia is augmented at low environmental temperatures, and in these experiments the rats also tended to prolong survival below 8°C, and tended to shorten above 22°C (fig. 1). Experiments below 8°C and above 21°C being therefore omitted, the mean value of survival times in control animals and the confidence limit of the mean was calculated as 1.9 ± 1.6 min. (P = 0.001). However, survival times over 10 min. were taken as the significant level as their individual and occasional variations were large in the experiments.

**Experiments with ethylurethane.** Survival times of rats administered with U of from 0.05 to 1.0 g per kg. of body weight were considerably longer. In this and the following experiments, observations were made at 145 mm Hg. In these experiments, the prolongation of survival time was noticed in 106 out of 115 cases, namely: 75 cases (65%) survived above 60 min., 18 cases above 30 min. and 13 cases above 10 min. (fig. 2). It will be noted that 48 out of the 75 rats survived beyond 90 min. and that one-third of them maintained respiration so rhythmically over 120 min. or longer so that the experiments had to be stopped. With regard to U-doses resisting anoxia, 0.5 g/kg. was most effective, i.e. in the majority of the rats given this dose (89%), survival times of 60 min. or longer were observed, though the rats were ataxic during about 20 min. after U-injection and subsequently somewhat more quiet than the control animals during decompression. It is worthy of note that about half of the animals with lower doses such as from 0.05 to 0.2 g/kg. which showed no abnormal behaviour, survived above 60 min. (fig. 2). This is in contrast to Emerson et al.'s finding that the effect could be found after a full narcotic dose of ethyl alcohol.

**Experiments with phenobarbital.** Rats injected with B of various doses within a range of 0.05 to 0.2 g/kg. of body weight also survived a long time
FIG. 2. Effects of ethylurethane on survival times of rats in 145 mm Hg. The cases in the hatched area are statistically insignificant.

In 85 (88%) out of 97 cases a prolongation was recorded, the details of which can be seen from the figure. A distinct inhibition of respiration occurred occasionally, particularly in animals administered with higher dosages. The most effective dosage on the rat survival was about 0.13 g/kg, which was far more than half of narcotic doses (0.16-0.2 g/kg.).
It appears certain that the B-effect on increasing the tolerance to low pressure is 10% or more less than the U-effect. The depth of narcosis seemed to be deeper in animals with B than those with U, both in the optimal respective doses. The effect of B against anoxia seemed, however, more specific compared with that of C, as follows:

**Experiments with chloralose and morphine.** Survival time of rats injected with C intraperitoneally within a range of 0.04 to 0.1 g/kg. was significantly longer in 14 out of 20 cases than that of control rats (fig. 4), although the extent of effects was obviously less than that of U or B, viz. only 2 animals surviving above 60 min. with a dose of 0.1 g/kg. in which the rats fell into a coma-tose state and their respiration was inhibited strongly (fig. 5). Since the survival times in C-tests were lengthened proportionally to the doses, it seems likely that the C-effects on survival are closely related with narcosis.

By administration of M within a range of 0.007 to 0.2 g/kg., most of the rats could not survive above 10 min., although there was a slight tendency of prolongation with lower dosages like 0.009 g/kg.

**Changes in the respiration of urethanized and barbitalized rats.** Changes in the respiratory rate of rats with U, B, or C during the survival period are shown in fig. 5, in which the optimal doses of the respective drugs were given. The respiration rate was highest in the U-test, among others, from the beginning of experimentation and the initial rate was maintained throughout the whole survival period. In the B-test the rate was not only lower in general, but also fell considerably with the progress of the experiments. The drop of the rate was more pronounced when C was used.

The correlation of the rate of respiration to the doses of drugs was observed with U and B. The respiratory rates at the 60 min. survival were used as indices, and they were plotted against the doses, as illustrated in fig. 6. With B, the respiratory rate fell linearly with increased dosage, while, with U, it re-
mained almost unchanged until the dose reached 0.8 g. per kg. U appears therefore to be capable of increasing the tolerance of the rat to the high altitude before there is any narcotic effect on the respiratory movements, possibly as a result of a specific action on the cell metabolism. On the contrary, in B, the effect of increasing the tolerance is associated with its narcotic action.

Fig. 6. Relation between respiration rate and narcotic doses.

SUMMARY

Effects of ethylurethane, phenobarbital, chloralose and morphine on the survival of rats in 145 mm Hg (altitude of about 12 km.) were studied at 8° to 20° C.

1. The mean survival time of control rats and the confidence limit was 1.9 ± 1.6 min. (P = 0.001).
2. The survival time of rats administered with ethylurethane, 0.05 to 1.0 g/kg., was prolonged; over 60 min. in the majority of cases.
3. The survival time of rats administered with phenobarbital, 0.05 to 0.2 g/kg, was similarly prolonged, though accompanied with a certain inhibition of respiration.
4. With chloralose (0.1 g/kg.), half of the rats survived over 30 min. Respiration was strongly inhibited.
5. With morphine, no increased survival was observed.

REFERENCES