Differential Effect of Hypobaric Hypoxia on Potency of CNS Depressants in Rats and Mice (34275)

IRWIN BAUMEL, JOHN J. DEFEO, AND HARBANS LAL
(Introduced by H. W. Youngken, Jr.)
Department of Pharmacology and Institute of Environmental Biology, University of Rhode Island, Kingston, Rhode Island 02881

Acute exposure of mice to hypobaric hypoxia alters their sensitivity to drugs considerably. Toxicity of amphetamine and strychnine is enhanced (1, 2), hexobarbital-sleep is prolonged (3), and semicarbazide (4) or *m*-fluorotyrosine convulsions are reduced (5). During our recent studies on the mechanisms responsible for these effects we noticed that rats were far less sensitive to hypobaric environments than mice. In the studies reported here actions of selected CNS depressants in the rat were compared with those in the mouse exposed to hypobaric hypoxia. Barbital, which is excreted unmetabolized (6–8), was chosen to indicate any alteration in CNS sensitivity. Pentobarbital, which is metabolized by hepatic microsomal enzymes (9), and chloral hydrate which is metabolized by soluble alcohol dehydrogenase (10) were employed to test drug metabolizing mechanisms. Since drug-induced CNS depression is sensitive to body temperature (11, 12) and hypoxia induces hypothermia (13), concurrent measurement of rectal temperature was included in this study.

Methods. The hypobaric chambers (14) consisted of four plexiglass dessicators (internal diameter, 10 in. height, 14 in.) connected in series to a pump through a manifold. They were installed in a constant temperature environmental chamber and utilized room air. All measurements were made at 22°.

Swiss albino, random bred male mice, weighing 25–35g, and Sprague-Dawley albino, random bred male rats (Charles River Farms), weighing 150–250 g were used. They were housed in animal quarters maintained at 21–23° with room lights alternated on a 12-hr light–dark cycle. Food and water were available *ad libitum* except in the environmental chamber where they were brought 1 hr before the experiment.

Drug solutions were freshly prepared just before intraperitoneal injection. The animals were injected with drug and immediately placed, in pairs, in each of the four altitude chambers which were then decompressed in a 10-min period to 364 mm Hg (10% O_2). Controls were run concurrently in identical chambers open to room air (760 mm Hg, 21% O_2). Animals were continually exposed to hypobaric hypoxia throughout the determination of sleeping time.

Sleeping time was taken as the interval between the loss and the gain of righting reflex. The chambers were tilted gently to determine if the animals righted themselves and maintained balance by extension of the front paw outward on the chamber floor.

Body temperature under hypobaric hypoxia was recorded at appropriate intervals by a rectal probe (Yellow Springs Instrument, No. 402) connected to a telethermometer (Yellow Springs Instrument, No. 42SC) placed outside the chamber. For the temperature studies, the animals were confined in plastic animal holders (Arthur H. Thomas Co.) placed inside the chambers. Mean sleeping times were compared using the *t* test as described by Snedecor and Cochran (15).

Results. The effect of acute exposure to hypobaric hypoxia on drug induced sleep is summarized in Table I. Sleeping times were prolonged under the hypobaric environment in both mice and rats. The effect was significant in all cases except in rats in which prolongation of pentobarbital sleep did not reach statistical significance. The magnitude of the effect produced by hypobaric hypoxia

TABLE I. Effect of Hypobaric Exposure on Drug-Induced Hypnosis.

Drug	Dose (mg/kg)	Sleeping time (min ± SE) (N) Control	Hypobaric	% Increase
Mice				
Barbital	300	91 ± 9.2 (10)	584 ± 44[a] (11)	540
Pentobarbital	50	90 ± 8.4 (12)	148 ± 13.7[b] (11)	65
Chloral hydrate	350	105 ± 6.6 (13)	206 ± 16.6[a] (13)	96
Rats				
Barbital	200	244 ±10.5 (23)	304 ± 23.5[c] (19)	25
Pentobarbital	35	56 ± 2.7 (12)	62 ± 3.7[d] (11)	11
Chloral hydrate	300	75 ± 3.0 (10)	91 ± 3.9[b] (11)	21

[a] $p < .001$, control vs. hypobaric; [b] $p < .01$; [c] $p < .05$; and [d] $p > .05$.

differed greatly in mice and rats. The comparison illustrated in Table I shows that in the case of barbital, increase in the sleeping time was nearly 20-fold greater in mice; the effect on pentobarbital or chloral hydrate was 5-fold greater.

The rectal temperature of mice exposed to the hypobaric environment dropped at a rate of 0.1°/min reaching a maximum drop of 5.8° at 90 min of exposure. The rate of temperature drop was only half this in the rats and reached a maximum of only 2.5° (Fig. 1). The rectal temperature of 2 mice and 2 rats restrained in the hypobaric chamber under room atmosphere declined less than 1° in 6 hr.

Discussion. Recent interest in space exploration, as well as the problems of life at high altitudes, stimulated a search for protective mechanisms against hypobaric environments. The biological mechanisms which enable rats to resist potentiation of CNS depressants and hypothermia under acute hypobaric hypoxia may provide a useful research approach in this regard. Rats are also less sensitive than mice to the convulsive effects of hyperbaric oxygen (16) and the lethal effects of hypoxia (17).

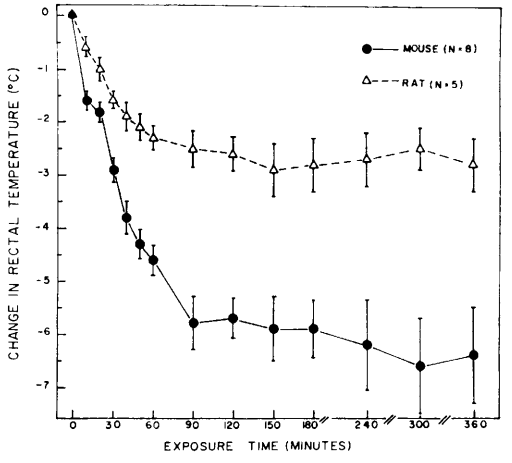

FIG. 1. Rectal temperature of mice and rats exposed to hypobaric environment.

Since both CNS stimulants as well as CNS depressants are potentiated under acute hypobaric hypoxia, it is likely that oxidative *in vivo* metabolism of drugs is impaired. However, marked potentiation of barbital hypnosis suggests that the CNS sensitivity to drugs may be enhanced due to central biochemical effects. In the absence of biochemical measurements the pharmacodynamic effects (sleeping time) of barbital, pentobarbital, and chloral hydrate failed to delineate the exact mechanism.

Hypobaric hypoxia causes respiratory alkalosis (18) which could alter drug binding with plasma proteins (19) that could affect availability of the drugs to the site of action and subsequent interaction with receptors. Hypoxia has been observed to cause an increase in brain gamma-aminobutyric acid (17) which could sensitize the nerve cell to drug-induced depression.

Potentiation of CNS depressants may be expected by the hypothermia that accompanies exposure to hypobaric environments. However, amphetamine which is generally less toxic in hypothermic animals (20)

showed greater toxicity in an hypoxic environment (1).

Although it is too early to speculate on a precise mechanism by which acute hypobaric hypoxia enhances the potencies of CNS depressants, it seems that depressed hepatic drug metabolism due to hypothermia (21) and enhanced sensitivity of nerve cells may play important roles. In this experiment, the effect of decreased oxygen tension cannot be separated from that of low barometric pressure as room air was employed under hypobaric conditions.

Summary. Acute exposure of mice and rats to hypobaric hypoxia (364 mm Hg, 10% O_2) enhanced the depressant effects of sodium barbital, sodium pentobarbital, and chloral hydrate. Mice were far more sensitive than rats, barbital hypnosis being affected to the greatest extent. In addition, hypothermia observed under the hypobaric environment was greater in mice than in rats.

This investigation was supported by PHS Training Grant No. 1T01ES 00104 from the Division of Environmental Health Sciences.

1. Robinson, S. M., Baumel, I. P., and Blatt, W. F., Toxicol. Appl. Pharmacol. **15**, 304 (1969).

2. Moore, A. W. and Ward, J. C. J. Am. Pharm. Assoc. Sci. Ed. **24**, 460 (1935).

3. Robinson, S., Blatt, W., Schatz, R., and Joy, R., Federation Proc. **27**, 283 (1968).

4. Baumel, I. P., Schatz, R., DeFeo, J. J., and Lal, H., J. Pharm. Pharmacol. **21**, 119 (1969).

5. Baumel, I. P., Schatz, R., DeFeo, J. J., and Lal, H., J. Pharm. Pharmacol. **21**, 475 (1969).

6. Dorfman, A. and Goldbaum, L. R., J. Pharmacol. Exptl. Therap. **90**, 330 (1947).

7. Ebert, A. G., Yim, G. K., and Miya, T. S., Biochem. Pharmacol. **13**, 1267 (1964).

8. Maynert, E. W. and VanDyke, H. B., J. Pharmacol. Exptl. Therap. **98**, 184 (1950).

9. Cooper, J. R. and Brodie, B. B., J. Pharmacol. Exptl. Therap. **120**, 75 (1957).

10. Friedman, P. J. and Cooper, J. R., J. Pharmacol. Exptl. Therap. **129**, 373 (1960).

11. Fuhrman, F. A., Science **105**, 387 (1947).

12. Setnikar, I. and Temelcou, O., J. Pharmacol. Exptl. Therap. **135**, 222 (1962).

13. Gellhorn, E., Am. J. Physiol. **120**, 190 (1937).

14. Baumel, I. P., Robinson, S. M., and Blatt, W. F., J. Pharm. Sci. **56**, 918 (1967).

15. Snedecor, G. W. and Cochran, W. G., "Statistical Methods." Iowa State Univ. Press, Ames, Iowa (1957).

16. Wood, J. D., Watson, W. J., and Ducker, A. J., J. Neurochem. **14**, 1067 (1967).

17. Wood, J. D., Watson, W. J., and Ducker, A. J., J. Neurochem. **15**, 603 (1968).

18. Henderson, Y. and Radloff, E. M., Am. J. Physiol. **101**, 647 (1932).

19. Newbould, B. B. and Kilpatrick, R., Lancet **1**, 887 (1960).

20. Menon, M. K. and Dandiya, P. C., J. Pharm. Pharmacol. **19**, 596 (1967).

21. Kalser, S. C., Kelvington, E. J., and Randolph, M. M., J. Pharmacol. Exptl. Therap. **159**, 389 (1968).

Received May 16, 1969. P.S.E.B.M., 1969, Vol. 132.