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Induced Hypersensitivity to Barbital in the Female Rat

Abstract. *Female rats, treated with two daily anesthetic doses of barbital, exhibit 1 month later a significant increase in sleeping time over that of control animals. Hypersensitive animals, as compared to controls, show no alteration in liver weight (as percentage of body weight), but they manifest a significant shortening of time for induction of anesthesia. Induced hypersensitivity to barbiturates is apparently not the result of alterations in the metabolism of these agents, but it may be related to enhanced susceptibility of the central nervous system to these drugs.*

The induction of delayed hypersensitivity to the depressant effects of pentobarbital on the central nervous system of the rat, after induction of acute tolerance to the drug (*1*), might be related to a decrease in the rate of metabolism of the barbiturate, an alteration in the distribution of the drug in vivo, or enhancement of the sensitivity of central neuronal systems to the agent. We now report on the use of barbital (which is not normally metabolized to any significant extent in the rat) to determine whether hypersensitivity could be developed to this agent. In addition, liver weights were determined, as an index of the activity of hepatic enzyme, and times of induction of anesthesia were recorded on the premise that an increase in central nervous responsiveness to the drug should be reflected in a reduced time of induction of sleep with the drug.

Table 1. Mean sleeping times (± standard error) of female rats receiving sodium barbital (200 mg/kg) intraperitoneally. The figures in parentheses refer to numbers of animals. Group A, animals not previously treated; group B, those treated 24 hours in advance; and group C, those treated 28 and 29 days previously.

Group	Mean sleeping times (min)			
	Day 1	Day 2	Day 29	Day 30
Control	Saline	Saline	Saline	Saline (18)
A	Saline	Saline	Saline	261 ± 15.8 (19)
B	Saline	Saline	221 ± 10.8 (25)	224 ± 12.7 (22)
C	234 ± 12.0 (23)	214 ± 10.2 (21)	Saline	323 ± 14.6 (18)

Four groups of female rats of the Holtzman strain were used. All groups were held in separate quarters for 20 days prior to the initiation of the study to insure acclimation to the laboratory environment. All animals weighed from 134 to 174 g on day 1 of the study and from 176 to 220 g (mean = 196 g) on days 29 and 30. These rats received either 0.9-percent saline (6.67 ml/kg) or sodium barbital (200 mg/kg), prepared as a 3-percent aqueous solution, on days 1, 2, 29, and 30 of the study (Table 1). All injections were intraperitoneal. Induction times and sleeping times for those animals receiving the barbiturate were measured as reported previously (*1*). Any animal with an induction time greater than its group mean plus 4 standard deviations was omitted from the reported data. All error estimates refer to standard error (S.E.).

Table 1 gives the mean sleeping times on day 30 for animals not previously treated (group A), for those treated 24 hours in advance (group B), and for those treated 28 and 29 days previously (group C). Application of the Student *t*-test failed to reveal a significant reduction in sleeping time in group B as compared to group A. This failure to demonstrate significant tolerance to barbital, with a two-dose schedule, is in accord with other reports that stress the difficulty of inducing acute tolerance to barbital in the rat (*2*). The mean sleeping time of group C, however, was 23.8 percent greater than that of group A. This proved to be a statistically significant increase ($P = .01$). These results are similar to those previously obtained with pentobarbital (*1*). Such delayed barbital hypersensitivity is probably not due to alterations in the metabolism of the drug, because, in nontolerant animals, only 3.7 percent of a dose of barbital undergoes biotransformation (*2*). Therefore, even complete inhibition of metabolism could not readily account for the observed increase of sleeping time in hypersensitive animals. Similar conclusions may be made on the basis of observations of liver weight. The mean liver weight (as percentage of body weight) ± S.E. on day 30 for the control group, and groups A, B, and C was 3.70 ± 0.05, 3.63 ± 0.07, 3.89 ± 0.07, and 3.60 ± 0.05, respectively. These estimates are based on the same number of animals as in the day-30 column of Table 1. Only in the case of the tolerant group is liver weight significantly changed from that of the control group ($P = .05$). This increased liver weight indicates that accelerated protein synthesis and enhanced activity of hepatic metabolizing enzyme occurred. This is corroborated by the observation (made by other workers) that acute barbital treatment fails to produce autotolerance, but does cause tolerance to other barbiturates to be manifested (*3*). Also, since the mean liver weight was the same in groups A and C, it is unlikely that depletion of protein precursors, during the phase of enzyme induction, with a resultant decrease in activity of hepatic metabolizing enzyme, could account for a postulated reduction in biotransformation rate, even if the latter could be held responsible for the development of hypersensitivity. This lack of effect on liver weight corroborates similar observations in which significant hypersensitivity to pentobarbital was induced in female rats (*4*).

The mean anesthetic induction time for barbital in 44 rats receiving a first injection of the drug (group B on day 29 and group A on day 30) was found to be 51.0 ± 2.6 minutes. For groups B and C on day 30, the mean induction time was 49.3 ± 4.1 and 38.1 ± 3.5, respectively. The induction time of the rats in group C was significantly shorter than that of both the group receiving a first injection of barbital

($P = .01$) and the tolerant group ($P = .05$). This observation is consistent with the concept of an enhanced responsiveness of the central nervous system to the drug as an explanation of hypersensitivity.

Alternatively, the hypersusceptibility observed in the animals in group C might result from damage to the central nervous system caused by cerebral hypoxia during the periods of anesthesia on days 1 and 2. However, it has been shown that significant hypersensitivity is induced on day 30 in rats exposed to an atmosphere of 100 percent oxygen during anesthesia on days 1 and 2 (*5*). In addition, it was found that the oxygen content of venous blood, measured 75 minutes after the administration of barbital (200 mg/kg) to untreated rats, did not differ significantly from that in animals previously treated with saline. These findings indicate that induced hypersensitivity to barbiturates does not result from lack of oxygen in the brain.

We find that barbiturate-induced hypersusceptibility is probably not the result of a reduction in the activity of hepatic barbiturate-metabolizing enzyme. In view of the suggestion by Remmer (*6*) that long-acting barbiturates produce tolerance by an alteration of the responsiveness of the central nervous system to the drug, it is reasonable to expect that induced hypersensitivity may be based on a similar mechanism. These considerations do not, of course, obviate the possibility of alterations in the distribution of the drug across the blood-brain barrier or within the brain, particularly in view of the fact that it has been reported that barbital is differentially localized within the central nervous system (*7*).

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Traffic Signals and Depth Perception

Abstract. *Automobiles approaching red traffic signals at night appear to go beyond them when viewed from some distance to the rear. The phenomenon is doubly illusory because the higher of two objects has been presumed to appear more distant. The illusion is probably limited to small visual angles (about 2 degrees).*

An amusing illusion can be experienced by any motorist driving at night in city traffic whenever he finds himself following an automobile that is approaching a traffic signal. From a viewing distance of about a city block away, the taillights of the lead car will appear to "go through" a red stoplight and the car will appear to stop someplace beyond the intersection. As the follower closes the gap he sees the lead vehicle standing discretely well in front of the signal light. What the observation amounts to is this: at a certain low angle of elevation, a stimulus will look closer to the observer than a stimulus at or below eye level. In the traffic signal illusion the lower lights (taillights) appear to be beyond the upper (traffic signal) light. To make the lower lights appear to be just under the signal the automobile would have to be backed up, closer to the observer.

This illusion, which is readily experienced by anyone looking for it, does not appear to have been reported hitherto. The closest reference to such a phenomenon is a casual remark by Adelbert Ames (in *1*) in his description of unusual perceptual experiences to the effect that in an otherwise dark room a light on a wall below another light will appear more distant if both are above eye level and that the reverse effect appears if the lights are below eye level. Kilpatrick (*2*) cites the same perceptual effects.

In a laboratory study by Epstein (*3*) subjects judged two lights vertically separated by from 3½ to 7½ deg of visual angle and reported no differences in depth between the lights when no textural cues were present. It may be that the visual angles employed by Epstein were too large for the illusory or any other effect to appear in the absence of texture. He did find that when texture was supplied the upper light appeared more distant.

The illusion reported here is then doubly illusory in that, as Epstein reports, "the higher of two objects will generally appear more distant." The latter statement stems from Gibson's (*4*) descriptions of depth perception as a function of optical gradients of texture. It should be noted that in the illusion described here, textural cues are at a minimum, as the illusion is experienced best at night.

Because of the contradiction of reality and presumed common phenomenal experience, the illusion appeared worthy of some study, and the traffic situation was brought into the laboratory via a procedure that lends itself to numerous parametric investigations.

To reproduce the street situation, a box 8 by 2 by 1 foot (2.4 by 0.6 by 0.3 m) was constructed, open at the front end. The inside of the box was painted flat black. Ten inches (25 cm) above the floor of the box a small (½ inch) radio unfaceted ruby-light was mounted in a fixed position. On the floor of the box a small wooden block was arranged with strings leading from the front end and rear over pulleys so that a continuous loop of string could be manipulated to draw the block back and forth. On the block a duplicate ruby light was mounted. Both lights were powered by a 6-volt transformer. A stylus fitted to the block projected through a slit in the side of the box and ran along a meter stick mounted on the side. The box was fitted so that it could be placed on one side to provide a horizontal displacement. In principle, except for substituting lights for dowels, the box resembles the rather unreliable Howard-Dolman apparatus as discussed by Weymouth and Hirsch (*5*).

College student subjects ($N = 23$) from an elementary psychology class were seated so that the lower light was at eye level, 20 feet away. The upper light was seen at an angle of approximately 2 deg (head position was not fixed). In a darkened hallway the subjects could see nothing of importance but the two lights. The experimenter gave the endless loop of string to the subject and asked him to pull one way or another to bring the lower light precisely under the upper light (vertical condition) or to bring the right light next to the left light (horizontal condition). Half the subjects went through the vertical condition first; the other subjects began with the horizontal condition. The experimenter moved the comparison stimulus well ahead or well beyond the standard before each trial. Each sub-