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Reserpine, Chlorpromazine, and Physiological Functions of Mammals That Hibernate[1]

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Abstract. Since two of the tranquilizing drugs, chlorpromazine and reserpine, are believed to act upon the hypothalamus, and since mammals that hibernate are presumed to have a different hypothalamus from non-hibernating laboratory animals, a logical design was to study the effects of these two drugs on bats, hamsters, mice, and white rats. The bats were more resistant than mice to reserpine. Hamsters did not show hypothermic effects with either drug at room temperature, except as reflected in the heart rate under reserpine. In a cold environment when rats and hamsters were compared, effects were opposite in respect to both core temperature and heart rate. Rats were consistently more sensitive to chlorpromazine in the cold (perhaps a peripheral effect), whereas hamsters were consistently more sensitive to reserpine (perhaps a central effect).

Biologists are continuing to search actively for the explanation of mammalian hibernation. Mammals that hibernate, such as the golden hamster and the North American migratory cave bat, show a completely different response to the cold environment from that shown by the white rat. The present theory of hibernation which is proving the most useful is that described by Morrison (1960). This theory can be explained by considering the example of white rats exposed to cold as the only environmental change. Their cold-response will be an increase in metabolism over resting level, and the usual body temperature is maintained. Morrison's theory states that under some circumstances some mammals may draw upon the mechanism of hibernation by "turning off" the cold-response just described for combating this extreme environment. If the animal is the size of a marmot or smaller, and if it remains resting in a cold environment, then its body temperature will drop steadily. If the animal is the size of a raccoon or bear, the circumstances may be the same but the drop in body temperature will not occur. It is apparent that the regulation of body temperature is different in the mammalian hibernators, and presumably this difference must be a function of the hypothalamus. This means that the physiological architectures of the rat, hamster, and bat are quite different even at room temperature.

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Since differences in these three experimental animals are especially noticeable in the central nervous system and hypothalamus, it was reasonable to design experiments using two of the tranquilizing drugs which are believed to act on the central nervous system in the area of the hypothalamus. It was presumed that two questions could be posed: (1) would mammals which show striking differences in central nervous control over temperature regulations respond in a markedly different manner to drugs with specific central nervous effects; (2) since the differences between the two tranquilizers to be used, chlorpromazine and reserpine, have not shown easily distinguished effects, would the use of rodents of approximately the same size but with different homeostatic mechanisms help to separate the characteristics of the two drugs.

The physiological effects of reserpine and chlorpromazine are similar (Miner, 1955; Whitelock, 1957). With moderate doses the following effects are noted: hypotension, closing of the pupils, slowing of heart rate, augmentation of secretory and motor activity in the gastrointestinal tract, partial suppression of sympathetic predominates (in particular, suppression of the sympathetic activity in the hypothalamus), stimulation of the reticular formation, and a drop in body temperature. These drugs also depress oxygen consumption in rodents apparently via the mechanism of an anti-thyroid activity. Thus they antagonize the effect of thyroid hormone on oxygen consumption. There are few species which have exceptions within the list of the above generalizations.

Although these two agents appear to have approximately the same influences on the mammal, there is some evidence that they act by different mechanisms. Reserpine is usually assumed to act upon medullary centers, while chlorpromazine alters autonomic function by acting upon the peripheral autonomic structures. However, both agents are considered to have a direct effect upon the thermo-regulatory center. After due consideration of this background information, experiments were designed to test the effects of high dosages of tranquilizing drugs on mammals that hibernate.

Methods

Dosage of drugs. The dosage of tranquilizing drugs administered in experimental work has changed markedly over a period of years. In the case of reserpine, it is because of an unusual characteristic: when a massive dose of this drug is used, increasing the dose by a factor of four produces no change in effects but merely a tendency to prolong them. Because of this effect the usefulness of very low dosages of reserpine was not at first recognized. In early experiments the dose for rodents for both chlorpromazine and reserpine was apt to be five mg/kg in a single intraperitoneal injection. In

experiments today one would be apt to use a dose of 0.1 mg/kg or 0.2 mg/kg in the case of reserpine. In the present experiments dosages of 5 mg and 10 mg/kg were used. These will be called massive doses, in spite of the fact that 25 and 50 mg/kg have been used in rodent work.

Procedure. In separate series the body temperatures of white rats, golden hamsters, and bats (*Eptesicus fuscus*) were studied under the influence of the two drugs. Measurements were made at room temperature (26°C.±1°) and in a cold box (4°C.±1°). Body weights were recorded at noon for a period from two days preceding injection to approximately 8 days after injection of the single dose of tranquilizer. Saline was injected into the control animals at the same time that the drugs were administered. The colonic or rectal temperatures were taken with a thermocouple at the time of injection and at one, two, four, twenty-four, and forty-eight hours following injection.

Heart rate was also studied as an index to the activity of a key autonomic structure. The effectiveness of the two drugs to depress the heart rate of the rat, hamster, and bat (*Eptesicus fuscus*) was studied. Each species received each drug both at room temperature and while maintained at 4°C.±1°. The heart rates of restrained animals were measured by Burdick electrocardiograph, with the readings taken for 6 hours post-injection and then at 24 hours. Surgical-clip electrodes placed on the thorax were used. Dosages of 10 mg/kg for the rats and bats and 5 mg/kg for hamsters were administered intraperitoneally. A final experiment with reserpine alone was designed because the bats appeared to be very resistant to this agent. In this case they were compared with white mice of similar weight (range of both species, 11.3 gm-22.4 gm). Dosages of 10 mg/kg to 50 mg/kg were used. In this series no restraint was used and only weight loss was recorded.

Results

In most experiments reserpine was tolerated poorly, compared to chlorpromazine. Under reserpine, unless the experimental animals died within 6 hours (except the bats and mice), they usually lasted at least 72 hours.

Effects on body temperature and body weight. Only white rats and hamsters were tested in this series. The effects of the drugs upon body temperatures of rats and hamsters (10 mg/kg, room temperature) showed the hamsters to be the most tolerant to both agents and showed a greater hypothermic response with reserpine. In the cold there was a faster drop in body temperature in the hamsters than in the rats, presumably due to the small size of the hamsters (Figures 1 and 2).

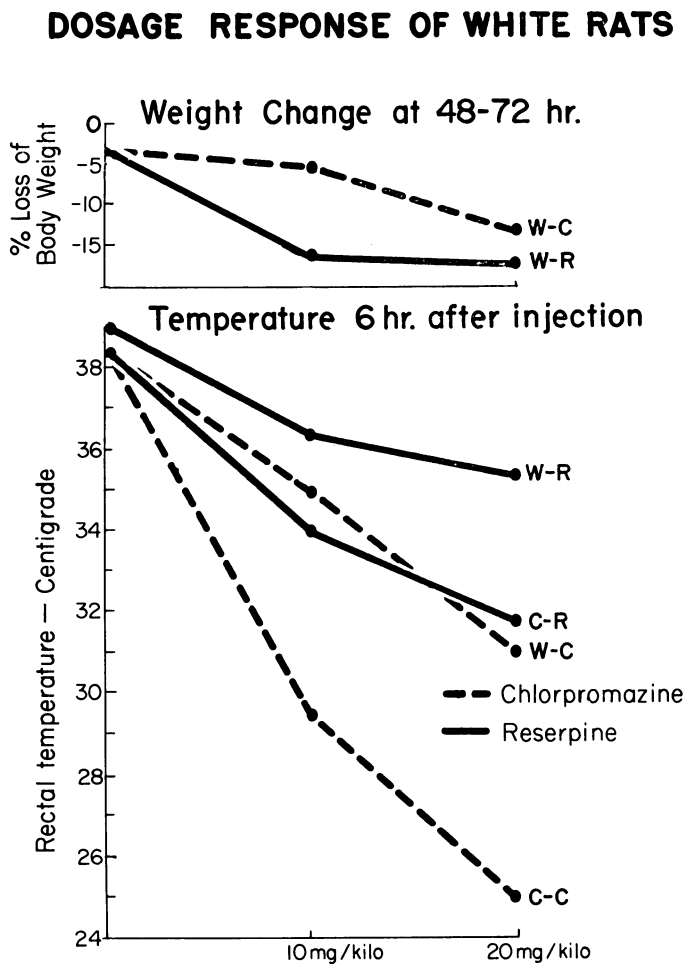

Figure 1. Effects of chlorpromazine and reserpine upon body weight and core temperature of rats. Each temperature represents a mean of three different rats. The experiment was done in both warm (w) and cold (c) rooms.

Body weight responses differed. There was a drop in body weight in the hamsters at low doses of chlorpromazine, but this effect required higher doses with the white rats.

Effects on heart rates. The effectiveness of the two drugs to depress the heart rates of the rat, hamster, and bat was studied. Dosages of 10 mg/kg for the rats and bats and 5 mg/kg for hamsters were administered intraperitoneally. Control values were 300 to 650 beats/minute for bats (N=4); 316 to 424 beats/minute for hamsters (N=4); and 408 to 470 beats/minute for rats (N=4). Heart rates of control bats dropped about 13 percent in 30 minutes

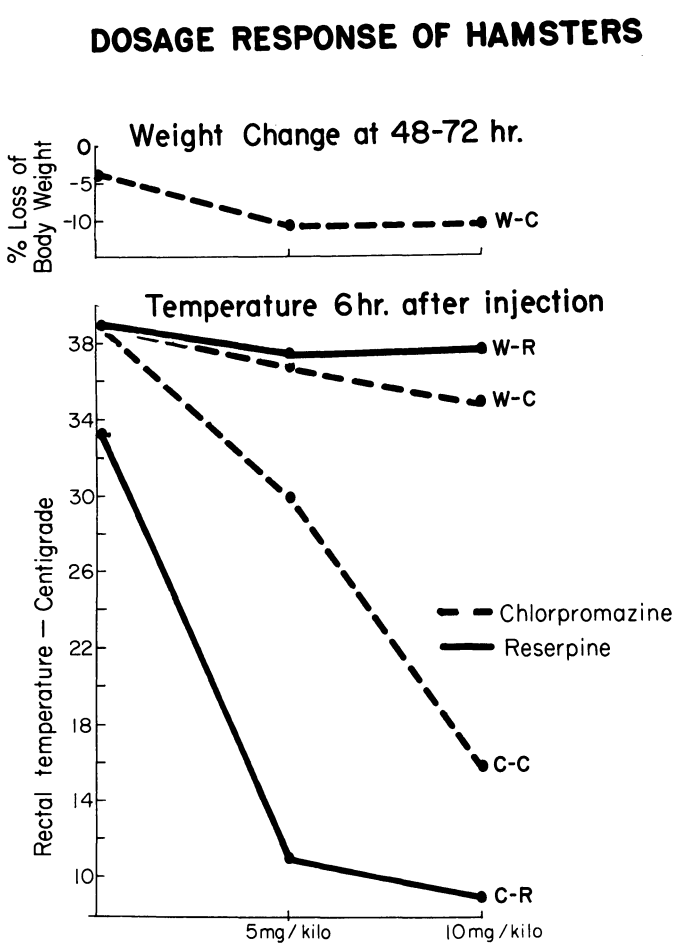

Figure 2. Effects of chlorpromazine and reserpine upon body weight and core temperature of hamsters. Each temperature represents a mean of three different hamsters. The experiment was done in both warm (w) and cold (c) rooms.

and 16 percent more in 150 minutes; body temperatures dropped correspondingly to room temperature. Heart rate is a function of room temperature in this resting mammal (compare Hock, 1951). The drugs produced no clear-cut influence on this control response described.

In the hamster, chlorpromazine in the dosage employed did not lower the heart rate (Figures 3 and 4). In all other cases the heart rate was lowered, with the amount of depression being uniformly greater in the cold than at room temperature. The responses of rats under chlorpromazine simulated that of the control bats, but only in cold. Here heart rates dropped 29 percent in 150 minutes. The

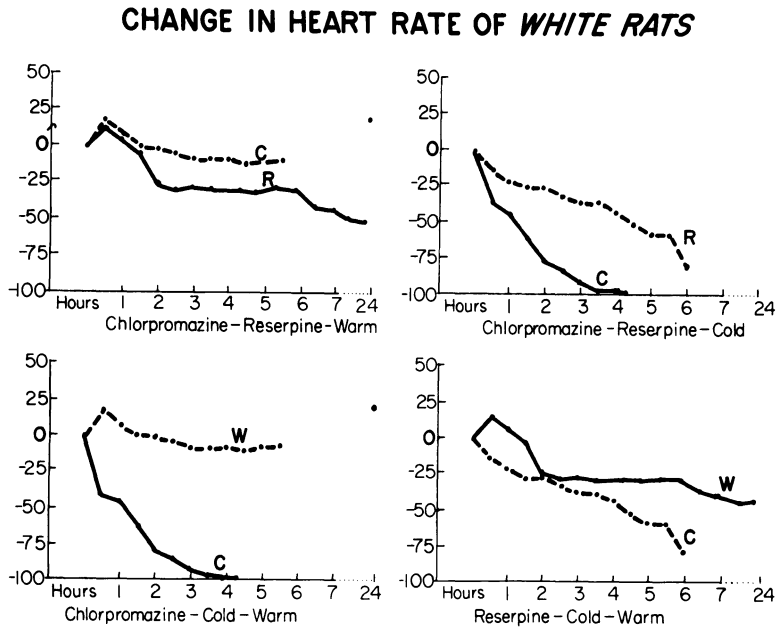

Figure 3. Change in heart rate from control level in beats per minute under four conditions. Results presented are a mean of four different rats.

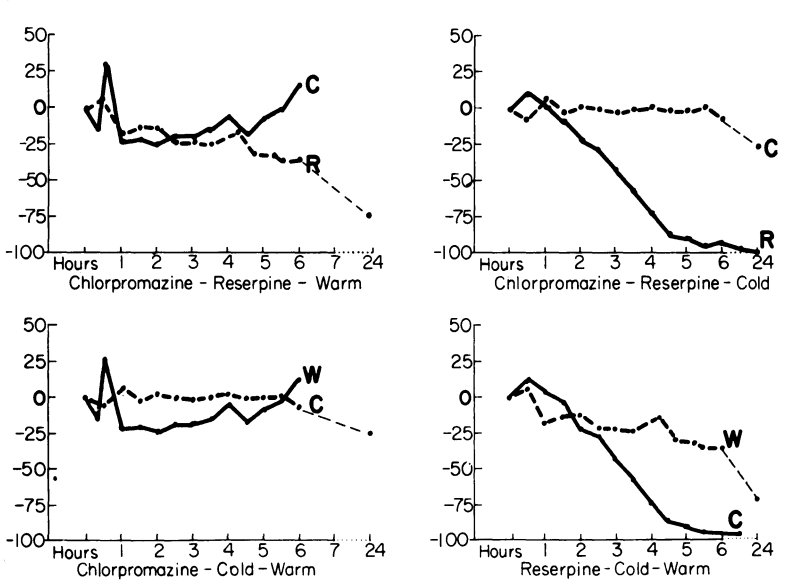

Figure 4. Change in heart rate from control level in beats per minute under four conditions. Results presented are a mean of four different hamsters.

results from animals without drugs (controls), but exposed to cold, have been reported elsewhere (Lipp and Folk, 1960). The fundamental question asked here is merely whether tranquilized rats and hamsters show similar physiological responses in the cold. The bats appear to represent a special case.

Tolerance of bats and mice. Since the effects of neither drug could be detected in the first series on bats, it was necessary to try a larger range of doses with the more powerful of the two drugs (reserpine) in order to determine whether bats are particularly resistant to this drug. The effects on six bats were compared with those on white mice. The bats did not live longer than mice under the influence of reserpine (Table 1), but they were very much more active and normal-appearing than the mice were. Furthermore, at the 20 mg/kg dose, bats could eat, whereas mice could not. Bats do indeed appear to be slightly more tolerant than mice, but mice recover from higher doses more readily than do rats or hamsters.

Table 1

Survival After Injection of Reserpine (0.7 ml. Intraperitoneal Injection)

DOSAGE mg/kg	SURVIVAL TIME BATS (N=1)	MICE (N=3 ea. dose) 1st	2nd	3rd
2.5	—	Normal	Normal	Normal
5.0	Normal	Normal	Normal	Normal
10.0	Normal	Normal	Normal	Normal
20.0	6 days	6 days	6 days	9 days
30.0	5 hours	4 days	6 days	7 days
40.0	0 hours	2 days	8 days	8 days
50.0	24 hours	—	—	—

Discussion

The hamsters and rats showed similar cardiac responses at room temperature, with less effect from chlorpromazine. This is probably because the doses of reserpine used were relatively large. In the cold the reduced effect of chlorpromazine on hamsters and the marked response to reserpine is of interest: it is as if the hamster heart is resistant to a local effect (due to chlorpromazine), but not to a central nervous effect (due to reserpine). With the white rat the situation is reversed. The body temperature data for both species were obtained in a separate series and of course with different animals, but the data fit the same explanation, i.e., that the hamster has a different physiological design in both the hypothalamus and the heart, compared to the white rat.

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