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Quinine-Induced Hypothermia in Cold-Exposed Rats

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SATINOFF, EVELYN. *Quinine-induced hypothermia in cold-exposed rats.* PHARMAC. BIOCHEM. BEHAV. 6(5) 539–543, 1977. – Quinine HCl in doses from 10–50 mg/kg lowered the body temperatures of nonfebrile rats in the cold, primarily by suppressing shivering. However, if given an opportunity to turn on a heat lamp the rats worked much more than normal after a quinine injection and were thereby able to counteract the hypothermia to some extent. The effect of quinine is interpreted as an action on effector mechanisms rather than as an alteration of the thermal setpoint.

Quinine Behavioral thermoregulation Shivering Body temperature

THE CHARACTERISTIC fever of malaria is caused by the growth of a protozoan parasite in human red blood corpuscles. The parasite grows larger than the erythrocyte, which eventually bursts. The fever is due to the liberated foreign protein and cell products traveling through the blood stream and affecting the firing rate of central neural thermosensitive cells. Quinine is effective as an antimalarial agent because it prevents the growth of the parasite and the erythrocyte does not burst [1]. Thus, quinine lowers malarial fever in humans by its specific action on the cause of the disease and is otherwise ineffective as an antipyretic agent.

However, quinine does lower body temperature in cold-exposed rats. Ten Cate and Knoppers [6] reported that quinine and other cinchona alkaloids, in doses from 35–150 mg/kg, lowered the body temperatures of rats kept at an ambient temperature of 18°C. Satinoff and Shan [4] found that, at 5°C, quinine lowered the body temperature and increased the rate of bar-pressing for heat in rats with lateral hypothalamic lesions. It was of interest, therefore, to study more closely the effects of quinine on reflexive and behavioral thermoregulation. In this paper I report that quinine HCl, in doses as low as 10 mg/kg, lowers the body temperature of rats in the cold, mainly by suppressing shivering. At the same time, the drug increases operant responding to obtain heat.

METHOD

Effect of Quinine on Body Temperature

Forty female albino rats weighing between 250–340 g were placed, in groups of five at a time (4 drug and one control), in individual metal cages in a cold chamber maintained at 5°C ± 1°. The fur of half of the rats was shaved on the day preceding the test. After 15 min in the cold the rats received an intraperitoneal injection of quinine HCl (5, 10, 25, or 50 mg/kg) dissolved in 2 ml isotonic saline, or two ml of saline alone. Each rat was tested only once. The rats remained in the cold chamber for one hour and then were returned to an environmental temperature of 23°C ± 1°. Their rectal temperatures were taken before they were placed in the cold and every 15 min thereafter until they had returned to within 0.5°C of their preinjection temperature. Temperatures were taken with a thermistor probe inserted 5 cm into the anus. The probe was connected to a telethermometer (Yellow Springs Instrument Co.). Tests were similarly conducted on unshaved rats in environments of 23°C and 36°C [four rats each given quinine (10 or 25 mg/kg) and 4 rats given saline at each ambient temperature for a total of 24 rats].

Physiological Thermoregulation

Measures were obtained on 6 naive rats to determine the effect of quinine (50 mg/kg) on physiological mechanisms of heat production and heat loss at 5°C. The rats were restrained in a Plexiglas cage and leads were attached to gold-plated safety pins in the appropriate places on the rat's body to measure EMG, EKG, and respiration rate. Tail and rectal temperatures were measured with thermistors. A rat, with leads attached, was placed in a Collins small animal chamber connected to a spirometer for determining oxygen consumption, and the leads were connected to the appropriate preamplifiers of a Grass Model 7 polygraph (for details of this procedure see [5]). On the first test, three rats were individually placed in the cold for 30 min for baseline measures, and then were injected with 2 ml isotonic saline, after which measurements were continued

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for one hr further. One week later, the procedure was repeated with an injection of quinine HCl (50 mg/kg in a 2 ml volume). On the following week the rats were again tested after a saline injection. Since the measurements of all saline tests were extremely similar, we tested three more rats that were injected with quinine only.

Behavioral Thermoregulation

Four rats were kept shaved and maintained at 85% normal body weight. Behavioral thermoregulation was measured in a cylindrical Plexiglas cage which had a Plexiglas lever protruding from the side of the cage and a 250 W red bulb infrared heat lamp mounted 30 cm above the floor. This apparatus is described more fully elsewhere [2]. It was housed in a refrigerated chamber kept at 5° C ± 1°. To insure that any changes in rate of bar-pressing for heat after quinine administration were not due to a general, nonspecific action of the drug, a food-motivated bar-pressing task was required of the animals immediately after their stay in the heat reinforcement apparatus. Thus, any decrease in both tasks might reflect debilitating effects of the drug, whereas an increase in both might reflect a general excitation rather than a specific response to cold stress. Bar-pressing for food was tested in a rectangular metal cage with a lever and foodwell (Lehigh Valley Co.). This cage was kept at an ambient temperature of 23° C ± 2°.

The rats were trained and tested in both heat and food reinforcement situations on a 15 sec variable interval schedule of reinforcement with a range of one to 30 sec. This means that a bar-press was reinforced with food or heat, on the average, once every 15 sec regardless of how often the rat actually pressed the bar. This schedule generates a high steady work output. When the reinforcement was heat, the infrared lamp above the cage went on and remained on for 2 sec. When it was food, a 45 mgm Noyes pellet was delivered to the foodwell.

After the rats had been in the cold for 15 min they were given an injection of either quinine or saline and remained in the cold for one hr. Immediately afterward they were put in the food reinforcement apparatus for one hr. After steady responding had been achieved, each rat was tested twice at three dose levels of quinine (40, 50, and 60 mg/kg) and twice with isotonic saline. The tests were conducted one week apart and the solutions administered in random order.

RESULTS

Body Temperature

Figure 1 illustrates the effects of quinine on the body temperature of unshaved rats in the cold. There is a progressive dose-dependent decrease in body temperature. According to Dunnett's test for comparisons involving a control mean [7], 10 mg/kg was significantly different from saline (t = 3.66; df = 5/30; $p<0.005$). The body temperatures of the shaved rats also decreased with increasing quinine doses (Fig. 2), and again, 10 mg/kg was significantly different from saline ($p<0.005$). An analysis of variance of the body temperatures for one hr after injection revealed: (1) in all rats, a significant effect of the drug, $F(4,30) = 23.93$, $p<0.01$; (2) a significant effect of shaving $F(1,30) = 26.96$, $p<0.01$; (3) the absence of an interaction effect between shaving and the drug $F(4,30) = 1.54$, $p>0.10$.

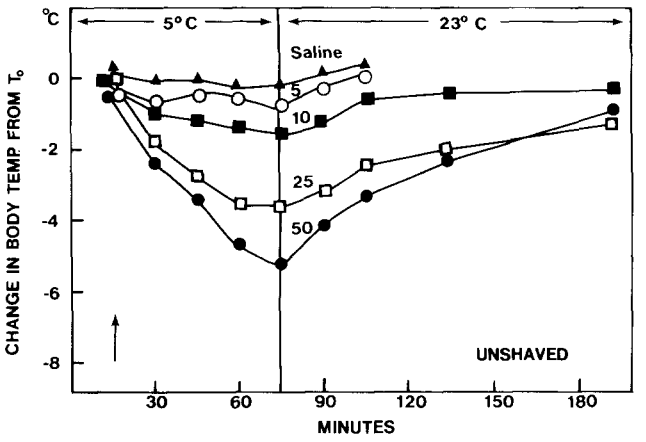

FIG. 1. Change in body temperature of unshaved rats in the cold. (Body temperature at 23°C immediately before being placed at 5°C = T_0.) The numbers at each curve indicate doses of quinine HCl in mg/kg. The time of injection of quinine or saline is indicated by the arrow. Each point represents the mean of four rats.

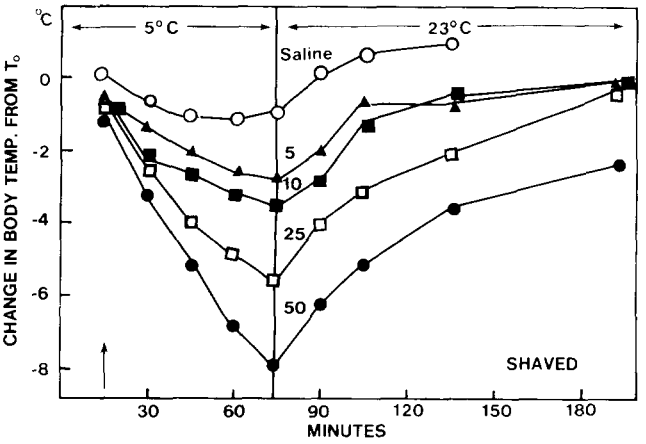

FIG. 2. Same as Fig. 1 for shaved rats.

There were no significant differences between the body temperatures of the rats given saline and those of rats given quinine (10 or 25 mg/kg) and tested at ambient temperatures of 23° or 36°.

Physiological Thermoregulation

Within 3 min of the quinine injection, all shivering was eliminated in all six rats tested. Figure 3 illustrates EMG activity in a typical rat. After an injection of saline (left side) there is no interruption of shivering, which continues with great regularity for the remainder of the hour. In contrast, shivering is markedly lessened within 2 min after an injection of quinine (50 mg/kg). By 3 min it is completely absent. Bursts of muscle activity did not appear on the polygraph until about 20 min postinjection. By the end of the hour, shivering was still not quite back to normal in any quinine-treated rat and mean core temperature had declined to 32.9°C, whereas 1 hr after a saline injection it had declined to only 36.3°C (Table 1).

The effects of quinine on other physiological responses

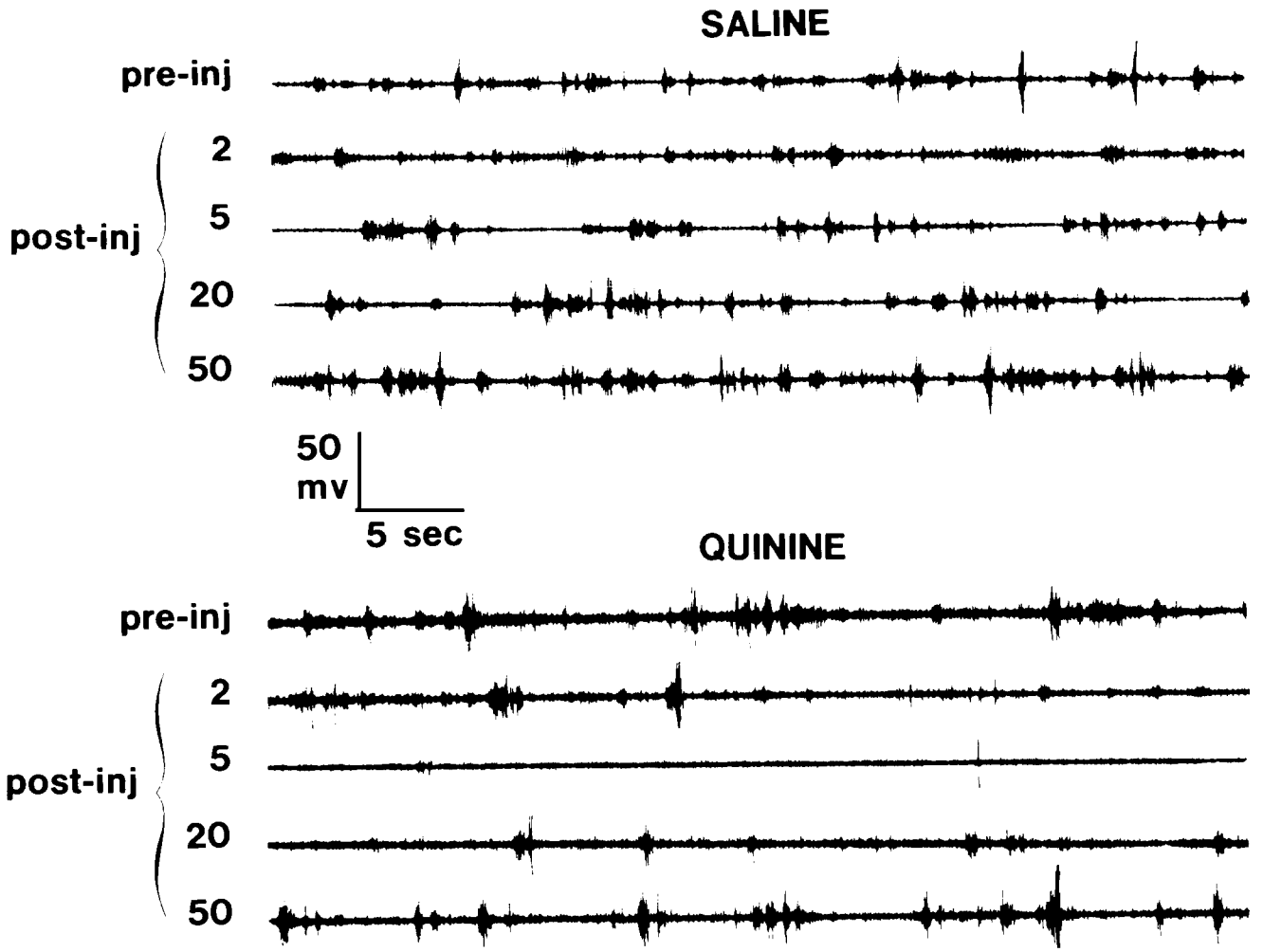

FIG. 3. Effects of injections of saline or quinine HCl (50 mg/kg) on EMG activity in a representative rat. The top records were taken one min before the injections, after the rat had spent 30 min in the cold. The next four records illustrate the course of shivering at 2, 5, 20, and 50 min postinjections.

TABLE 1

MEAN (± SE) CHANGES IN BODY TEMPERATURE AND REFLEXIVE RESPONSES AFTER INJECTION OF QUININE HCl (50 mg/kg) OR SALINE IN UNSHAVED RATS AT 5°C

	1 min Presaline (30 min at 5°C)	min Postsaline 30	60	1 min Prequinine (30 min at 5°C)	min Postquinine 30	60
T_{body} (°C)	37.1 ± 0.3	36.5 ± 0.2	36.3 ± 0.2	37.5 ± 0.3	34.5 ± 0.5	32.9 ± 0.5
T_{tail} (°C)	10.2 ± 0.4	9.3 ± 0.15	9.2 ± 0.15	10.6 ± 0.55	10.4 ± 0.6	9.6 ± 0.45
O_2 Consumption (ml/kg/hr)	2387 ± 80	2348 ± 165	2628 ± 81	2496 ± 83	1699 ± 168	1760 ± 187
Heart rate (beats/min)	462 ± 13	475 ± 11	482 ± 8	484 ± 6	392 ± 9	372 ± 13
Respiration (breaths/min)	107 ± 4	108 ± 6	100 ± 6	127 ± 6	103 ± 6	99 ± 4

are shown in Table 1. Oxygen consumption dropped to 68% of the rate it had been 30 min previously, just prior to the injection. By 60 min it had recovered to only 71% of preinjection levels. This fall was most probably due to the lack of shivering, although a direct effect on nonshivering thermogenesis cannot be discounted. Since all normal rats maintain or continuously increase their metabolic rate in the cold, the percent decrease of the treated rats is actually greater than it appears.

Quinine may also interfere somewhat with vasoconstriction. The mean tail temperature of the treated rats was slightly higher than that of the rats given saline, even though body temperatures were much lower in the former group. However, this effect was small, and needs to be investigated more thoroughly.

Heart rate had declined to 77% of control values by the end of an hour postquinine, and respiration rate declined to 78% of control. However, these effects could very likely have been associated with the low body temperatures of the quinine treated animals (which had decreased an average of 4.6°C). After lesions in the preoptic/anterior hypothalamic area, rats do not shiver in the cold and their body temperatures fall. In such a group of lesioned, restrained rats, whose body temperature also declined an average of 4.6°C after one hour at 5°C, heart rate fell to 81% and respiration rate to 87% of initial values [5].

Behavioral Thermoregulation

Figure 4 illustrates the effect of quinine on bar-pressing for heat in the cold. The rats worked at least twice as much for heat after a quinine injection as after saline. This is not a general excitatory effect of the drug, because the rate of working for food decreased progressively as the quinine dosages increased. The dose of quinine that produced a 300% increase in response rate for heat, 50 mg/kg, caused a decrease of 150% in response rate for food. Above 50 mg/kg, quinine appears to have debilitating effects; the rate of working for heat declined significantly after injections of 60 mg/kg, as did the rate of working for food. Figure 5 is a cumulative record showing the rate of working for heat and food of a typical animal before and after injections of either quinine (50 mg/kg, top record) or saline (bottom record). The rate of working for heat increases greatly over the prequinine rate (top) and there is no increase after a saline injection (bottom). The rates are reversed in the food reinforcement situation, where the rat works much harder for food after saline than after quinine.

The average decline in body temperature for all 4 rats 1 hr postinjection at doses of saline and quinine (40, 50, and 60 mg/kg) were, respectively, 0.2, 1.4, 2.4, and 3.1°C. Although on this reinforcement schedule the rats were not able to obtain enough heat to maintain normal body temperature, they were able to maintain a much higher body temperature than rats given comparable doses but without access to the heat lamp (see Fig. 2 for comparison). On two occasions, after injections of quinine (40 and 50 mg/kg), the heat lamp failed to go on when the bar was pressed. At the end of the hour the body temperatures of the rats had fallen 5.4 and 6.5°C below preinjection temperatures. The largest decrease in body temperature seen in these rats at those dosage levels when the heat lamp was operating was 1.8 and 3.1°C respectively.

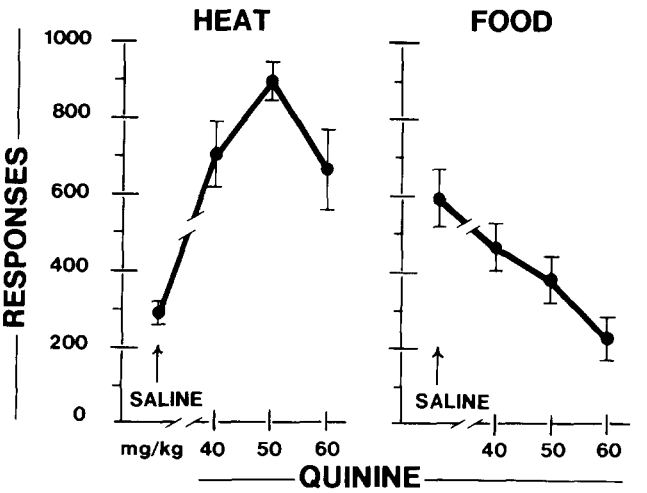

FIG. 4. Response rates for heat and food reinforcement after administration of saline or quinine. Each point is the mean of 8 measures, 4 rats given each dosage twice. Vertical lines indicate standard error of the mean.

DISCUSSION

The question we would like answered about any drug that alters body temperature is whether it does so by altering the setpoint around which the animal regulates or whether it acts on effector mechanisms important for maintaining thermal balance. If quinine had lowered the setpoint, behavior should have supported it and the rats should have worked less for heat. In fact, they worked more, indicating that thermodetector and integrative mechanisms maintaining the setpoint were unaltered.

This interpretation is supported by the fact that quinine had no effect on body temperature when the animals were in thermoneutral or warm environments. It lowered body temperature in the cold primarily by drastically suppressing shivering so that heat production was impaired. There was some indication that the rats did not vasoconstrict as well after quinine injections, although this aspect of the problem warrants more careful study.

It might be argued that the higher dosages used in these experiments approached toxic levels and made the rats ill. This may indeed be true. Nevertheless, at the dosage that caused the greatest decrease in body temperature, 50 mg/kg, the rats were well enough to increase their rate of working for heat 300% over control levels. This effect was not caused by a general excitatory effect of the drug, but was specific in this case to heat, as is shown by the fact that the response rate for food decreased.

The effect of quinine on suppressing shivering may well be an action at peripheral sites, rather than an effect on central nervous effector systems. Quinine decreases neuromuscular transmission at the motor endplate region, and thus has a curare-like effect on skeletal muscle [1]. However, the fact that normal animals in the cold after quinine look very similar to rats with preoptic lesions in the cold, both in their reflexive [5] and behavioral [3] aspects, suggests that the central effects of quinine on temperature regulation would be worth investigating.

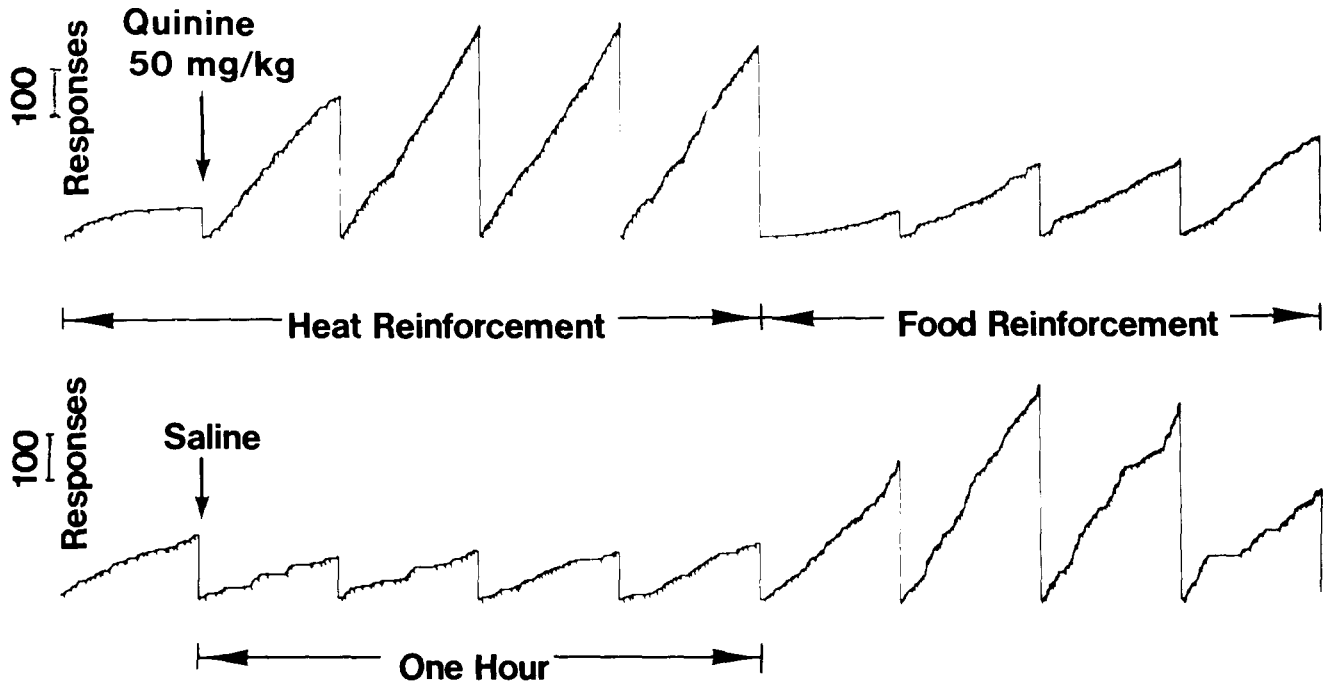

FIG. 5. Cumulative record showing response rate for heat and food of one rat before and after an injection of quinine (50 mg/kg) and saline. Each downward deflection of the pen indicates a reinforcement. The slope indicates response rate. The pen resets to baseline every 15 min.

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