EFFECT OF AMBIENT TEMPERATURE ON THERMAL RESPONSES TO DRUGS[1]

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Abstract

Thermal responses to a variety of drugs have been investigated at various ambient temperatures, using unanesthetized rats, either lightly restrained or paralyzed with tubocurarine. The results indicate that ambient temperature is a major factor determining thermal responses to many drugs. Experiments on lightly restrained rats demonstrated that the *critical ambient temperature*, the temperature above which hyperthermia is evoked and below which hypothermia is produced, is about 30° C (in the thermoneutral range) for Hydergine, ergotamine, LSD-25, and serotonin. The critical ambient temperature for chlorpromazine is approximately 36° C, and that for 2,4-dinitrophenol, 20° C. Reserpine produced a consistent hypothermia at 23° C, but somewhat inconsistent effects at ambient temperatures above this up to 39° C. Complete curarization abolished the hypothermic effects of all the above agents except chlorpromazine. The production of both hyperthermia and hypothermia by most of the drugs studied suggests that they influence temperature-regulating centers of the central nervous system.

Most reports dealing with the effects of drugs on body temperature fail to include information about environmental temperature at the time of the experiment or do not attach significance to it. Failure to recognize this variable has led to considerable confusion, well exemplified by the literature on the ergot alkaloids. Every possible type of body temperature response has been attributed to these agents, including no change (1), hypothermia (2,3), and hyperthermia (4,5). Differences in species and dosage have been suggested as possible explanations of these conflicting results (6). However, these factors cannot be responsible for the variable results obtained by the same dose and in the same species. More recently it has been reported that ergotoxine may evoke any one of these responses, the type depending on the ambient temperature (7). A few other reports also have noted modification of thermal responses to various drugs by changes in ambient temperature (8,9,10,11,12).

The present studies were undertaken to assess the role of ambient temperature in determining thermal responses to a variety of drugs. Six agents with some known action on the central nervous system were investigated. These were chlorpromazine (Thorazine, Largactil), ergotamine, Hydergine, lysergic acid diethylamide (LSD-25), serotonin (5-hydroxytryptamine), and reserpine.[3] 2,4-Dinitrophenol, an agent presumed to have a predominantly peripheral action on body temperature, also was included in the study.

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Methods

Unanesthetized female albino rats (150 to 200 g body weight) were placed in individual wire mesh holders in a constant temperature room ($\pm 0.5°$ C) and their colonic temperatures recorded with copper–constantan thermocouples inserted five to six centimeters beyond the anal sphincter. The thermocouples were calibrated before and after each experiment; maximal drift during this period was 0.08° C. After a 2-hour equilibration period, the agent under study was injected subcutaneously and colonic temperatures recorded hourly for an additional 3 hours. Each rat was used as its own control during a separate equal period at the same ambient temperature. The drug-induced effect was calculated for each animal as the difference between the maximal temperature change after a drug and the corresponding temperature in the control experiment. Body temperature just prior to drug injection was taken as the basal temperature. The significance of drug-induced changes was calculated by the method of individual (paired) comparison (13).

In another series of experiments, the thermal effects of the above agents on curarized rats were investigated at a room temperature of $16 \pm 1°$ C. Female albino rats (150 to 200 g) were paralyzed with a minimal curarizing dose of tubocurarine chloride (0.75 mg/kg intramuscularly). Tracheotomy was quickly accomplished under local procaine anesthesia, a tracheal cannula inserted, and artificial respiration started. Complete skeletal muscle flaccidity was maintained throughout the experiment with small supplements of tubocurarine. Colonic temperatures were recorded as described above. After a half-hour equilibration period, the agent under study was injected subcutaneously and the colonic temperature recorded every half-hour for an additional 2 hours. Control experiments were carried out on another group of animals under identical conditions. In the calculation of responses, the body temperature just prior to drug injection was taken as the basal temperature, and the maximal change in body temperature in the ensuing 2 hours, noted. The significance of drug-induced changes was calculated using the method of group comparison (13).

All drugs except reserpine were administered as salts; chlorpromazine hydrochloride, ergotamine and lysergic acid diethylamide tartrates, Hydergine methanesulphonate, serotonin creatinine sulphate, and sodium 2,4-dinitrophenol. Dosages are expressed as the free base or acid, and were selected as adequate to produce readily measurable changes in body temperature. They do not necessarily represent minimal effective doses. Drugs were dissolved in the following vehicles: chlorpromazine, serotonin, and dinitrophenol in 0.9% sodium chloride; ergotamine and LSD-25 in 0.5% tartaric acid; and reserpine in a vehicle consisting of benzyl alcohol, citric acid, polyethylene glycol 300, and water. Controls were injected with the appropriate vehicle in volumes equivalent to those administered to treated animals.

Results

The type of data obtained is illustrated in Fig. 1, which shows the results of representative experiments in which chlorpromazine (22 mg/kg) was administered to two different rats exposed to room temperatures of 30 and 39° C. Each animal was used as its own control during a separate equal period at the same ambient temperature. Chlorpromazine evoked a hyperthermia at 39° C and a hypothermia at 30° C.

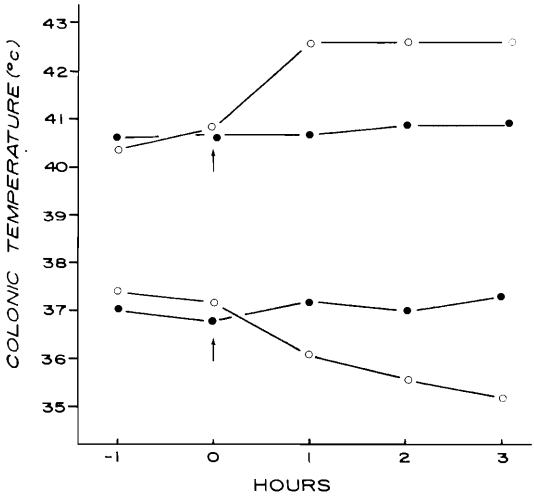

FIG. 1. Effects of chlorpromazine on body temperature of lightly restrained rats at ambient temperatures of 30° C (lower) and 39° C (upper). Drug (22 mg/kg) injected subcutaneously at zero time. Drug response (○–○) and control values (●–●) at each temperature determined in the same animal. Maximal drug-induced effects at 1 and 3 hours, upper and lower records respectively.

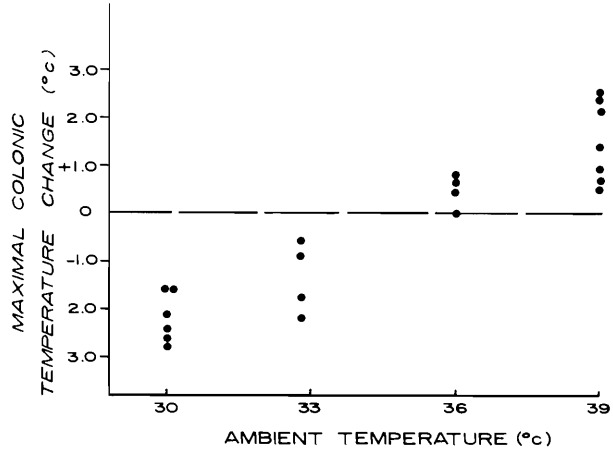

FIG. 2. Relation of ambient temperature to thermal responses of lightly restrained rats to chlorpromazine (22 mg/kg subcutaneously). Each point represents the maximal drug-induced change in body temperature in a single animal.

The maximal drug-induced changes in body temperature for all rats treated with chlorpromazine are presented in Fig. 2. The drug produced hypothermia at ambient temperatures of 30 and 33° C; no significant effect at 36° C; and significant hyperthermia at 39° C.

The average maximal changes in body temperature produced by each of the agents studied at ambient temperatures ranging from 18 to 39° C are shown in Table I. Dinitrophenol evoked a significant hypothermia at an

TABLE I

THERMAL RESPONSES OF LIGHTLY RESTRAINED RATS AT VARIOUS AMBIENT TEMPERATURES

Agent	Dose, mg/kg	Mean drug-induced changes in colonic temperature, ° C						
		18°	20°	23°	25°	30°	33°	39°
Dinitrophenol	20	−1.6 <.01* (6)†	−0.8 >.05 (7)	+2.3 <.01 (4)		+1.6 <.01 (7)		
Chlorpromazine	22					−2.2 <.01 (6)	1.4 <.05 (4)	+1.5 <.01 (7)
Hydergine	0.9	−0.9 <.02 (5)			−1.1 <.01 (5)	−0.2 >0.3 (10)	+0.6 <.02 (10)	
Ergotamine	4.0	−1.2 >.05 (5)			−1.9 <.01 (8)	+0.8 >.05 (12)	+2.0 <.01 (4)	
Serotonin	3.0				−2.2 <.01 (8)	+0.4 >.05(13)	+1.5 <.01 (7)	
LSD-25	0.5				−1.0 <.01 (8)	+0.2 >.05 (9)	+0.8 <.05 (9)	
Reserpine	1.0			−1.4 <.05 (5)	0.0 (10)	+0.6 <.01 (10)	+0.5 >0.2 (10)	+0.3 >0.2 (9)

*P value of significance of drug-induced change.
†Figures in parentheses indicate the number of animals used.

ambient temperature of 18° C, no significant change at 20° C, and a significant hyperthermia at 23 and 30° C. Hydergine, ergotamine, serotonin, and LSD-25 all produced a significant hypothermia at 25° C, no consistent effect at 30° C, and a significant hyperthermia at 33° C. Reserpine caused a significant hypothermia at 23° C, but produced somewhat inconsistent effects at higher temperatures (up to 39° C).

TABLE II

THERMAL RESPONSES OF CURARIZED RATS AT AN AMBIENT TEMPERATURE OF 16° C

Agent	Dose, mg/kg	No. of animals	Mean change in colonic temperature*	
			° C	±S.E.
Control	—	6	−6.5	±0.5
Dinitrophenol	20	6	−6.7	±0.5
Chlorpromazine	22	7	−8.5	±0.4
Hydergine	0.9	8	−6.0	±0.3
Ergotamine	4.0	6	−6.7	±0.2
Serotonin	3.0	6	−6.4	±0.3
LSD-25	0.5	6	−6.8	±0.3
Reserpine	1.0	6	−6.1	±0.3

*Measured over 2-hour period following drug injection.

The effects of various agents on the body temperature of curarized rats under artificial respiration in a room maintained at $16 \pm 1°$ C are shown in Table II. The average fall in body temperature over a 2-hour period following drug injection is recorded. Chlorpromazine was the only agent that elicited a significantly greater hypothermia than that observed in the control animals. The body temperature of the chlorpromazine-treated group decreased an average of 8.5° C, whereas that of the control group fell 6.5° C ($P < 0.01$).

Discussion

The results of this study show that ambient temperature is a critical factor determining thermal responses to many drugs. Investigation of a variety of agents has demonstrated the existence for each drug of a *critical ambient temperature*, above which hyperthermia occurred and below which hypothermia was evoked. One possible exception was reserpine, which produced a consistent hypothermia at an ambient temperature of 23° C, but somewhat inconsistent effects at higher temperatures. Bein (8) reported reserpine-induced hyperthermia in rabbits at higher room temperatures, but his limited data did not reveal the consistency of this effect. It is possible that the slow onset of the effects of reserpine may have been a factor in the inconstant results obtained. However, the effects at an ambient temperature of 23° C were consistent, and the relatively large dose employed should have been effective within the 3-hour test period.

Because changes in body temperature depend on an imbalance of heat production and heat loss, ambient temperature may influence the net thermal response to a drug via several mechanisms. Both heat loss and heat production depend to a large degree on environmental temperature. For example, drug-induced enhancement of heat loss is minimized by high ambient temperatures, because of the reduced gradient between skin and external environment. This effect would be a continuous function of ambient temperature. On the other hand, a drug which suppresses the thermogenetic response to cold would affect body temperature only in the range of ambient temperatures in which this response is elicited. It is obvious that ambient temperature also will affect responses to any agent inducing poikilothermia.

The effect of ambient temperature on thermal responses to drugs noted in the present investigation suggests that these agents interfere with central body temperature regulation. It is only within the central nervous system that the various factors involved in temperature regulation are integrated, and it is in this area that defenses against both hyperthermia and hypothermia can be impaired by a single drug action. Even the response to dinitrophenol, an agent which has been assumed to have a predominantly peripheral effect of increasing heat production, is modified qualitatively by changes in ambient temperature. (A more detailed analysis of the action of dinitrophenol will be published separately.)

It is interesting that the critical ambient temperatures for four of the drugs included in the present investigation lie in the range of thermal neutrality

for the rat. In this range of environmental temperature the homothermic animal maintains a constant body temperature with minimal physiological control. A critical ambient temperature of 30° C for Hydergine, ergotamine, serotonin, and LSD-25 suggests that these drugs induce poikilothermia, probably by an action on areas in the hypothalamus. The fact that these agents all appear to produce hypothermia by an effect on skeletal muscle tone or activity, as evidenced by their failure to act in curarized rats, is consistent with this interpretation. The thermogenetic effect of increased skeletal muscle activity is the most important defense against cold in homothermic animals, and is under central nervous system control (14).

In contrast to the other drugs studied, chlorpromazine induced hypothermia in curarized animals. This action and the production of hypothermia at ambient temperatures above thermoneutrality suggest that factors other than central suppression of skeletal muscle thermogenesis are involved in its hypothermic action. Chlorpromazine does not depress basal metabolism (15,16,17) but has been shown to produce cutaneous vasodilatation (18,19) and it appears probable that enhanced heat loss is a major component of its hypothermic effect. The high critical ambient temperature for chlorpromazine (about 36° C) may be the resultant of enhanced heat loss superimposed on impairment of central temperature regulation. Similarly, it appears probable that the low critical temperature for dinitrophenol is determined by the combined effects of impaired temperature regulation and increased peripheral heat production.

Deming *et al.* (20) claimed that the hypothermic action of reserpine is mediated through serotonin and it has been implied by Brodie *et al.* (21) that the central effects of LSD-25 are a result of serotonin antagonism. The present studies offer no conclusive evidence concerning the relationship of reserpine and serotonin in their effects on body temperature, although it is clear that responses to the two agents are not identical. However, the finding that LSD-25 and injected serotonin produce qualitatively identical effects on body temperature at various ambient temperatures indicates that serotonin antagonism cannot be invoked as the mechanism of the thermal responses of rats to LSD-25.

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