Pharmacology Biochemistry & Behavior, Vol. 18, pp. 935–942, 1983. © Ankho International. Printed in the U.S.A.

Temperature Responses in Rats After Acute and Chronic Administrations of Caffeine[1]

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Received 22 November 1982

SCHLOSBERG, A. J. *Temperature responses in rats after acute and chronic administrations of caffeine.* PHARMACOL BIOCHEM BEHAV **18**(6) 935–942, 1983.—Acute administrations (IP) of caffeine produced dose-dependent changes in the body temperature of rats. Low doses (12.5 and 25 mg/kg) induced hyperthermia soon after drug administration, while high doses (50 and 100 mg/kg) produced maximal hypothermia approximately 2 hr later. The acute effects of caffeine were also dependent on ambient temperature. The hyperthermic and hypothermic responses were attenuated and blocked, respectively, in rats maintained at 32°C. At 4°C, the hypothermic response was exacerbated, and the hyperthermic response was absent. Tolerance rapidly developed to the hypothermic actions of caffeine when rats were administered the drug over 28 days. Following the emergence of tolerance, hyperthermia was observed in rats given 50 mg/kg of caffeine. The hyperthermic responses to the low doses of caffeine were not altered by the frequency of drug administration. Both the acute and chronic effects of caffeine on thermoregulation are not unlike those found for morphine. Possible mechanisms of action underlying the thermoregulatory effects of caffeine are discussed.

Caffeine Body temperature Tolerance Ambient temperature

SUCCESSFUL body temperature regulation in mammals is the product of complex processes involving both central nervous system and peripheral autonomic mechanisms. Brain monoamines appear to play important roles in the central nervous control and regulation of body temperature. In general, serotonin and the catecholamines, norepinephrine and dopamine, have been associated with heat production and heat loss, respectively (for reviews, see [9, 13, 22, 36]). A number of sympathetically- and hormonally-mediated responses also play essential roles in the regulation of body temperature. Some of these include lipolysis in brown adipose tissue and the metabolism of non-esterified fatty acids (NEFA), glycolysis and carbohydrate metabolism, as well as hepatic and muscle glycogenolysis [17, 20, 25, 33, 45].

Methylxanthines (i.e., caffeine, theophylline and theobromine) have numerous actions on a variety of physiological systems, some of which have already been shown to be involved in thermoregulation. The brain levels of serotonin and/or 5-hydroxyindoleacetic acid (the major breakdown product of serotonin) in rodents are significantly elevated following the administration of caffeine, theophylline or aminophylline (the ethylenediamide salt of theophylline) [6, 14, 37, 43]. While these agents do not appear to alter the brain levels of norepinephrine and dopamine [12, 43, 51, 52], evidence suggests that the methylxanthines increase the turnover of norepinephrine [8, 12, 51]; whether the alkaloids increase or decrease the turnover of dopamine may be related to drug dose [12, 37, 51].

Caffeine, theophylline and aminophylline also increase the serum concentrations of glucose and NEFA [5, 14, 43, 47]. These effects may be due to both the indirect result of xanthine-induced increases in sympatho-adrenal activity and the release of catecholamines [3, 26, 40, 46, 47], and the direct result of the xanthines' actions on the liver [48] and adipose tissue [4, 21, 39]. Besides increasing serum glucose levels, methylxanthines stimulate the pancreatic release of insulin [2, 11, 28] and elevate the levels of insulin in blood [14,43].

Since a number of central and peripheral sites of action of methylxanthines include some of the underlying mechanisms concerned with body temperature regulation, one would expect these alkaloids to have specific effects on thermoregulation. However, little work has been performed in this area, and reports on the effects of methylxanthines on body temperature are not in total agreement. Doses of 20 and 50 mg/kg of both caffeine and theophylline, delivered intraperitoneally (IP) to rats, have been shown to produce slight, but nonsignificant increases in body temperature of approximately 0.5–0.9°C [49]. On the other hand, mice similarly administered 50 mg/kg of caffeine have displayed small, but significant, decreases in body temperature of about 0.8°C [15].

[1]This research was supported in part by a University of Alabama in Birmingham Faculty Research Grant and the International Life Sciences Institute.

While these effects can be considered marginal at best, significant elevations in body temperature of 1.1–1.4°C have been observed in rats following the IP or intraventricular administration of caffeine (10 mg/kg and 100 μg, respectively) and theophylline (20 mg/kg and 200 μg, respectively) [30]. Lastly, high doses of caffeine (100 mg/kg, IP) and theophylline (200 mg/kg, IP) induce significant hypothermic responses in rats with body temperatures being lowered by at least 1°C [7]. It is unclear whether the thermoregulatory properties of methylxanthines are essentially dose-dependent since the above-mentioned studies differ with regards to experimental methodologies; more importantly, only one or two doses of drug were employed per experiment. In the present study, three experiments were performed in order to (1) characterize both the dose-response and time-course effects of caffeine on the body temperature of rats; (2) assess the thermoregulatory actions of caffeine in rats exposed to either warm or cold ambient temperatures; and (3) determine the dose effects of caffeine on the body temperature of rats given daily injections of the drug.

METHOD

Subjects

Adult, male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were caged in groups of 3–5 with food (Charles River Rat, Mouse, and Hamster Maintenance Formula, Charles River Laboratories, Wilmington, MA) and water provided ad lib. The rats were acclimated for a 1–2 week period to the animal quarters which were on a 12:12 hr light-dark schedule (lights on at 0700 hr) and maintained at an ambient temperature of 22°C. In Experiments 1 and 2, the rats were caged individually during testing and were randomly assigned to the various drug treatment groups. In Experiment 3, the rats were caged in groups of 3 upon arrival at the animal quarters and remained as such throughout the duration of the experiment.

Drug Injections

Caffeine, obtained from the National Soft Drink Association, Washington, D.C. (Experiment 1) and Sigma Chemical Corp., St. Louis, MO (Experiments 2 and 3), was prepared daily in distilled water and adjusted to pH 6.9–7.1 with NaOH. Control animals received distilled water (vehicle) at the same pH. Caffeine (12.5, 25, 50 and 100 mg/kg) and vehicle were delivered IP in a volume of 5 ml/kg.

Body Temperature Measurements

Body temperatures were taken 2–3 days preceeding the various drug treatments to accustom the rats to this procedure. Core body temperatures were recorded with a Yellow Springs Instrument Co. (Yellow Springs, OH) rectal thermistor (No. 423), inserted 6 cm, and a tele-thermometer (Model 43). On drug treatment days, body temperatures were measured immediately prior to the injection of vehicle or caffeine and at times specified in each experiment. Food was withdrawn from the rats 60–90 min before the administration of drugs; water remained freely available. Experiments 1 and 3 were conducted with the ambient room temperature maintained between 21–23°C. In Experiment 2, groups of rats were tested in an environmental chamber with the ambient temperature maintained at either 4 or 32°C.

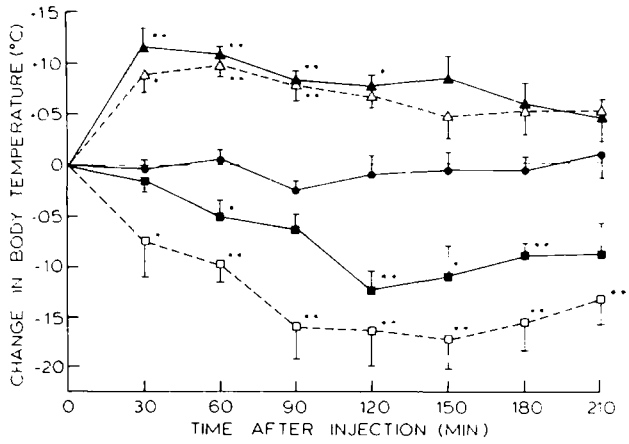

FIG. 1. Dose-response and time-course effects of a single injection of caffeine on body temperature (Experiment 1). Groups of rats (n=5 per dose), weighing 200±2 g (mean±S.E.M.), were administered vehicle (●) or 1 dose of caffeine, 12.5 (▲), 25 (△), 50 (■) or 100 (□) mg/kg, IP. Beginning at 1100 hr, body temperatures were measured every 30 min after drug administration over a 3.5 hr period. The plotted values represent mean change in body temperature±S.E.M. (vertical lines), and were calculated from the differences between the body temperatures of rats after drug administration and their predrug (time 0) body temperatures. The baseline body temperatures of rats assigned to each treatment were not statistically different from each other, and the group (n=25) mean was 37.7±0.06°C. *$p<0.05$, **$p<0.01$, significantly different from vehicle as calculated by Dunnett's test.

Statistics

Multifactorial analyses of variance with appropriate follow-up tests for simple main effects and interactions were employed to analyze the data for significance; in experiments in which repeated measures were taken on each rat, multifactorial treatments-by-subjects analyses were performed [24]. Changes in the body temperature of individual rats after drug administration were expressed as the difference between baseline (time 0) and post-drug temperatures, and tests of significance were made on these difference values.

RESULTS

Acute Effects of Caffine on Body Temperature (Experiment 1, Fig. 1)

Caffeine given acutely, produced dose-dependent increases and decreases in body temperature which followed different time-courses. These actions of caffeine were evidenced by the significant main effects of dose, $F(4,20)=30.75$, $p<0.001$, and time, $F(6,120)=11.18$, $p<0.001$, and the dose × time interaction, $F(24,120)=1.67$, $p<0.05$. The hyperthermic responses to the low doses of caffeine, 12.5 and 25 mg/kg, were observed soon after drug administration. Peak increases in body temperature of approximately 1°C occurred between 30 and 60 min after the injection of caffeine. The latter responses to such doses were also of short duration; the body temperatures of the caffeinated rats approached baseline levels by 2–25. hr and were no longer significantly different from the body temperatures of

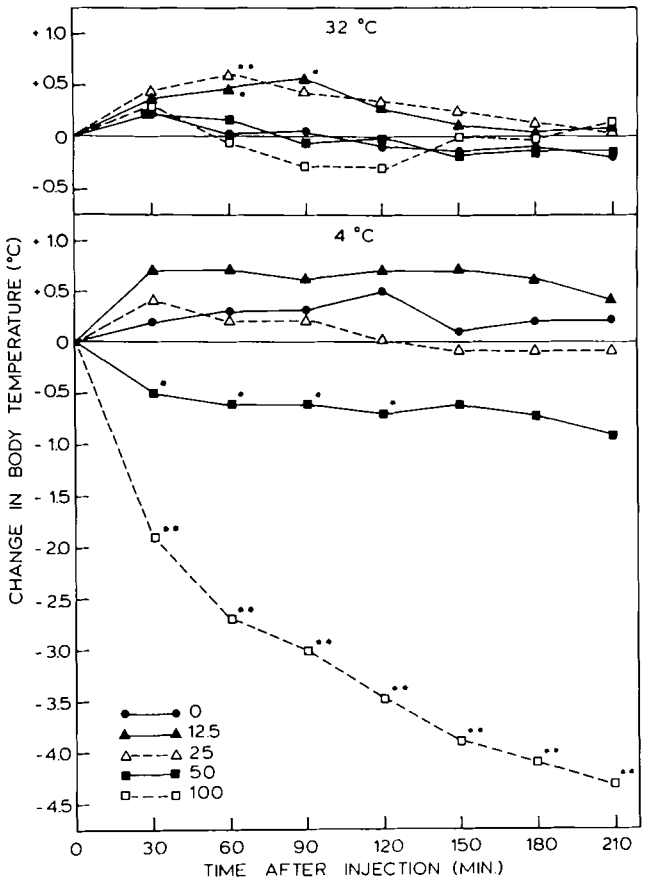

FIG. 2. Alterations of the dose-response effects of a single injection of caffeine on body temperature by changes in ambient room temperature (Experiment 2). Separate groups of rats, weighing 192±3 and 201±2 g, respectively, were tested at an ambient temperature of 32°C (upper panel) or 4°C (lower panel). Rats (n=9 per dose) were placed in an environmental chamber 90 min prior to drug administration. The measurement and expression of changes in body temperature are the same as described in Fig. 1. Mean values are plotted without S.E.M. for clarity. The baseline body temperatures of rats assigned to each drug treatment and exposed to 32 or 4°C were not statistically different from each other, and the group (n=45) means were 38.5±0.06°C and 37.8±0.08°C, respectively. *$p<0.05$, **$p<0.01$, significantly different from 0 dose (vehicle) as calculated by Dunnett's test.

the vehicle-treated rats. Both the high doses of caffeine, 50 and 100 mg/kg, on the other hand, induced hypothermia with maximal decreases of between 1–1.5°C appearing about 2 hr after injection of the alkaloid. The alterations in body temperature produced by the 100 mg/kg dose at each time point were greater than those found for 50 mg/kg, but these differences were not statistically significant. The duration of the hypothermic response to the high doses of caffeine was longer than the hyperthermic response to the low doses. Although there was some indication of the body temperatures returning toward pre-drug levels, the rats given 50 and 100 mg/kg of caffeine continued to be hypothermic by at least 1°C at the end of the 3.5 hr test session.

The caffeine from the National Soft Drink Association and Sigma Chemical Corp. was chemically the same and of equal purity as determined by melting point and spectrophotometric analyses. In a direct comparison, caffeine from both sources produced identical dose-dependent effect on body temperature which followed similar time-courses. These results were in close agreement with the data presented in Fig. 1.

Effects of Changes in Ambient Temperature on the Thermoregulatory Actions of Caffeine (Experiment 2, Fig. 2)

Changes in ambient temperature significantly altered the thermoregulatory actions of caffeine. With the temperature at 32°C, the hypothermic responses to 50 and 100 mg/kg of caffeine were completely abolished, and the body temperatures of rats receiving these doses were not unlike those found in vehicle-treated rats. At the higher room temperature, the hyperthermic responses to 12.5 and 25 mg/kg of caffeine were attenuated, but significant effects were found when comparisons were made with the vehicle-treated group both 60 and 90 min following drug administration.

With the ambient temperature at 4°C, caffeine produced significant dose, $F(4,35)=47.47$, $p<0.001$, time, $F(6,210)=10.75$, $p<0.001$, and dose × time, $F(24,210)=4.17$, $p<0.001$, effects. These effects were due solely to the high doses of caffeine. The significant decreases in body temperature following the administration of 50 mg/kg of caffeine were, for the most part, in the range found previously at normal ambient temperatures (see Fig. 1), and these changes remained essentially constant throughout the test session. The reductions in body temperature induced by 100 mg/kg of caffeine, on the other hand, were considerably greater in magnitude than those observed in rats given the same dose but with the ambient temperature at 21–23°C. By the end of the 3.5 hr test session, the mean body temperature of these caffeinated rats was reduced by almost 4.5°C. In Experiment 1, the decreases in the body temperature of rats administered the high doses of caffeine had attained asymptotic levels well within the test session. This was not the case at 4°C with the largest dose of caffeine. Consistent reductions in body temperature were observed following the injection of 100 mg/kg of caffeine over the entire duration of the experiment. In contrast to the results of Experiment 1, these decreases in body temperature were significantly different ($p<0.01$ for each comparison, Tukey's Honestly Significant Difference test) from those produced by 50 mg/kg at each time point. At 4°C, the changes in body temperature following the administration of the low doses of caffeine were not statistically different from those of vehicle-treated rats; in the case of 12.5 mg/kg, the lack of effect was probably due to the somewhat elevated body temperatures of the control animals (compare Fig. 2 with Fig. 1).

Effects of Daily Caffeine Administation on Body Temperature Over a 28-Day Period (Experiment 3, Fig. 3)

Caffeine produced alterations in body temperature which were dependent on not only dose, but also on the degree of exposure to the xanthine. The importance of these factors was confirmed by the results of a repeated measures analysis of variance for each of the two daily post-drug time intervals. At 45 min, significant effects were found for dose, $F(4,25)=30.26$, $p<0.001$, days, $F(9,225)=13.17$, $p<0.001$, and dose × days, $F(36,225)=3.80$, $p<0.001$. At 2 hr, similar results were obtained for dose, $F(4,25)=65.72$, $p<0.001$, days, $F(9,225)=19.29$, $p<0.001$, and dose × days,

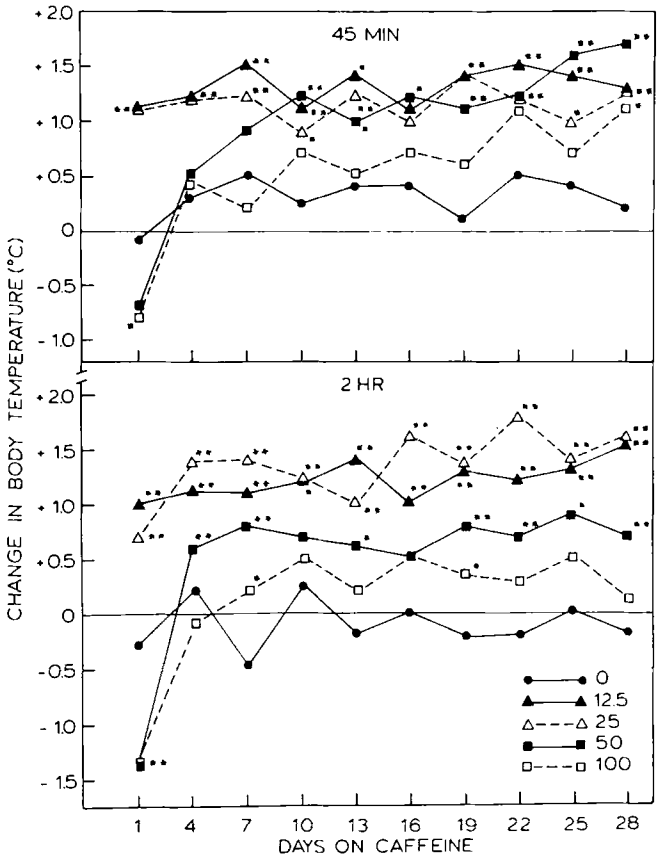

FIG. 3. Dose and time effects of chronic caffeine administration on body temperature (Experiment 3). Groups of rats (n=6 per dose) were injected with vehicle (0 dose) or caffeine for 28 consecutive days. For each dose, separate groups of rats had been tested 45 min (upper panel) and 2 hr (lower panel) following drug administration. The selection of these time intervals was based on the results of Experiment 1 and replicates in which the hyperthermic and hypothermic responses to caffeine were found to have occurred in a consistent and reliable fashion. Body temperatures were measured the same time of day beginning at 0900 hr, and were recorded every third day of the 28-day test period. Mean changes in body temperature were plotted without S.E.M. for clarity. The mean baseline body temperatures (°C) of rats given vehicle (n=12, 45 and 2 hr groups combined) at each test point (injection day in parentheses) were: 37.7±0.09 (1), 37.8±0.09 (4), 37.7±0.15 (7), 37.6±0.14 (10), 37.4±0.10 (13), 37.2±0.10 (16), 37.5±0.08 (19), 37.2±0.06 (22), 37.2±0.07 (25), 37.4±0.14 (28). The mean baseline body temperatures of rats given caffeine (n=12 per dose) were not statistically different (by Dunnett's test) from those of the vehicle-treated group, except for 12.5 mg/kg on Day 16 (+1.2% from vehicle, $p<0.05$); 25 mg/kg on Days 4 (−1.2%, $p<0.01$) and 7 (−1.5%, $p<0.01$); and 100 mg/kg on Days 7 (−1.4%, $p<0.01$) and 10 (−1.6%, $p<0.01$). $*p<0.05$, $**p<0.01$, significantly different from 0 dose as calculated by Dunnett's test.

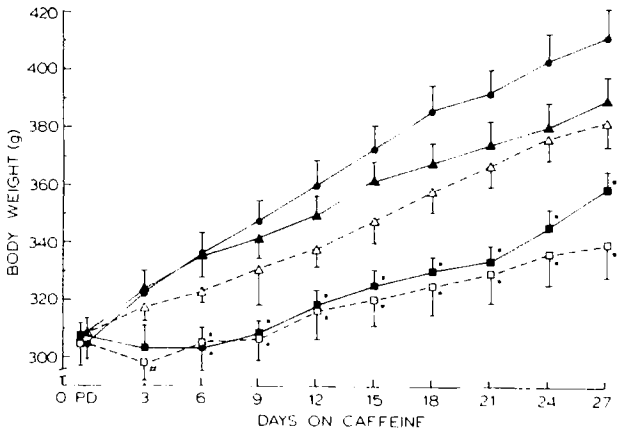

FIG. 4. Dose effects of daily caffeine injections on the body weight of rats over a 27-day period (Experiment 3). The body weights of rats were measured on the days prior to each body temperature test, presented in Fig. 3. The plotted values represent means±S.E.M. PD=Pre-drug. $\#p<0.05$, $*p<0.01$, significantly different from vehicle as calculated by Dunnett's test. See Fig. 3 for an explanation of the symbols.

$F(36,225)=4.09$, $p<0.001$. The acute, dose-dependent changes in body temperature were in agreement with the results of Experiment 1 (compare Day 1 of Fig. 3 with Fig. 1 at the appropriate time intervals). The initial hyperthermic responses 45 min and 2 hr after the injection of the two low doses of caffeine remained unaltered over the 28-day test period. Unlike the latter effect, the hypothermic responses to 50 and 100 mg/kg of caffeine were only observed on the first day of exposure to the drug with maximal decreases in body temperature occurring at 2 hr. The hypothermic responses to the high doses were no longer found in the same rats given the same doses of the alkaloid on any measurement day subsequent to the first injection. The apparent tolerance to the hypothermic actions of caffeine developed rapidly. By the fourth injection, the changes in body temperature following the administration of the high doses were not distinguishable from those of the vehicle-treated rats (except for a small, but significant, increase produced by the 50 mg/kg dose at 2 hr). With additional daily injections, 100 mg/kg of caffeine produced slight, but consistently non-significant increases in body temperature of 0.5°C or less (relative to the vehicle group) at the 45 min and 2 hr test intervals. However, after one week of caffeine injections, rats given the 50 mg/kg dose displayed significant increases in body temperature 45 min after drug administration, and this hyperthermic response was of the same magnitude as was found in rats given the low doses of caffeine. The 50 mg/kg dose continued to produce significant increases in body temperature at 2 hr (when compared to vehicle), but these changes were generally less than those observed in rats administered the 12.5 and 25 mg/kg doses, with statistical significance being attained on Days 13 and 28, and Days 16, 22 and 28, respectively (Tukey's HSD test, $p<0.01$ for each comparison).

Effects of Repeated Caffeine Administration on Body Weight, and Food and Water Intake (Experiment 3, Fig. 4 and 5)

Reductions in body weight produced by the high doses of caffeine were observed from the outset of the daily drug regime (Fig. 4). After one week on caffeine, the mean body weights of rats administered the 50 and 100 mg/kg doses were

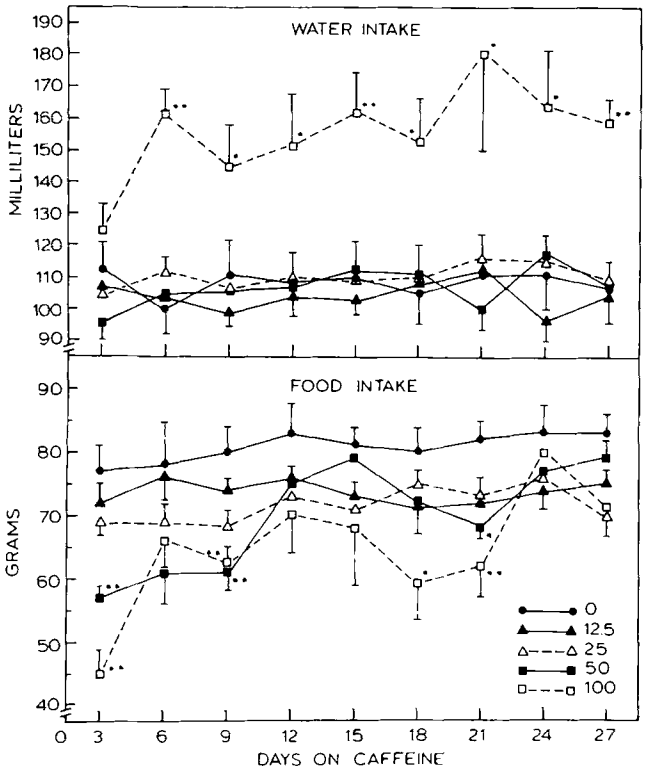

FIG. 5. Dose effects of daily caffeine injections on the water (upper panel) and food (lower panel) intake of rats over a 27-day period (Experiment 3). Food and water intake were measured on the days prior to each body temperature test, presented in Fig. 3, and represent 24-hr determinations. Mean values±S.E.M. are plotted and were calculated from 4 groups (n=3 per group) given each of the drug treatments. *$p<0.05$, **$p<0.01$, significantly different from vehicle as calculated by Dunnett's test.

approximately 10% below that of vehicle-treated rats. The 12.5 and 25 mg/kg doses produced only 0.3 and 4% reductions, respectively, in body weight after the same number of injections. By the end of the experiment, the body weights of rats given 12.5, 25, 50 and 100 mg/kg of caffeine were 5, 7, 13 and 17%, respectively, below that of the control animals. These differential effects of caffeine were supported by a repeated measures analysis of variance which revealed a significant dose × days interaction, $F(36,495)=12.70$, $p<0.001$. While the reductions in body weight appeared to be dose-related, only the two high doses of caffeine produced significant decreases in body weight on each of the measurement days (with the exception of 50 mg/kg on Day 3). Rats given each drug treatment exhibited significant gains in body weight over the total duration of the experiment (treatment-by-subjects analyses of variance, $p<0.001$ per dose). The body weights of rats administered vehicle and the two low doses of caffeine were significantly above pre-drug levels beginning on Day 3 of the drug regime (Dunnett's test, $p<0.01$ for each dose). It was not, however, until Days 12 and 15 that rats given 50 and 100 mg/kg, respectively, displayed significant increases in body weight over pre-drug levels (Dunnett's test, $p<0.01$ for each dose).

Rats given 100 mg/kg of caffeine displayed significant increases in the consumption of water (Fig. 5). These increases were relatively constant beginning on Day 6 and attained levels which were about 1.5 times greater than those of the vehicle-treated rats. Chronic caffeine appeared to have produced two different effects on food intake which were related to dose (Fig. 5). Rats administered the two low doses of caffeine exhibited small and constant reductions in food intake over the duration of the experiment; however, these effects failed to attain significance. The two high doses of caffeine produced maximal reduction in food consumption at the outset of testing. The levels of food intake of these caffeinated rats gradually returned to the levels displayed by the vehicle-treated rats, such that by the end of the repeated series of injections (Days 24 and 27), no statistical significance was found among all the experimental treatments.

DISCUSSION

Earlier reports of caffeine increasing [30,49] and decreasing [7,15] the body temperature of rodents under various experimental conditions were confirmed as being dose-dependent by the results of the present experiment. Under the same testing procedures, rats given single low and high doses of caffeine displayed hyperthermia and hypothermia, respectively. In most cases, the hyperthermic response was of short duration and magnitude, occurring soon after drug administration. In contrast, the hypothermic response developed over a longer period of time and was greater in magnitude. The acute, dose-dependent thermoregulatory actions of caffeine do not appear to be unique, and closely resemble the effects of acute morphone on the body temperature of both freely moving and restrained rats [16, 19, 31].

The thermoregulatory properties of caffeine were also found to be dependent on ambient temperature. The most noticeable effects of warm and cold temperatures were observed in rats given high doses of caffeine. The hypothermic responses to 50 and 100 mg/kg of caffeine found at 21–23°C were absent when rats were exposed to 32°C. However, rats given 100 mg/kg of caffeine and maintained at 4°C exhibited decreases in body temperature which were greater than those found at normal ambient temperatures. The hypothermic response to 50 mg/kg, on the other hand, was not appreciably altered by this change in ambient temperature. Thermal responses to morphine are also known to be dependent on ambient temperature, and are not unlike those found for caffeine. At normal ambient temperatures, animals undergo decreases or no change in body temperature following the administration of a given dose of morphine; however, by lowering the ambient temperature, the hypothermic response is either exacerbated [29,42] or induced for the first time [38]. Conversely, increasing the ambient temperature above normal may abolish the hypothermic response [29] or produce hyperthermia in animals which previously displayed either no change [38] or a biphasic response (hypothermia followed by hyperthermia) [42] to morphine at normal ambient temperatures.

One study was found which examined the effects of different ambient temperatures on the thermoregulatory actions of caffeine, but only one dose of the drug was tested [30]. In agreement with the results of the present experiment, 10 mg/kg of caffeine administered IP to minimally restrained rats produced hyperthermia (+1.4°C) with the ambient temperature at 22°C; however, this response was unaltered in rats exposed to either 8 or 30°C. At 32°C, rats in the present study given 12.5 and 25 mg/kg of caffeine displayed signifi-

cant increases in body temperature, but these responses were not as large as those found at 21–23°C. Furthermore, the alterations in body temperature produced by the latter doses of caffeine at 4°C were not distinguishable from those observed in rats given vehicle. In a previous report, 10 mg/kg of morphine induced hyperthermia of equal magnitude in restrained mice which were exposed to ambient temperatures of 25 and 32°C; with the temperature lowered to only 30°C, a biphasic response (hypothermia-hyperthermia) was found in mice given the same dose of morphine [42]. Due to differences in experimental methodologies, it is difficult to resolve the discrepencies in these findings, especially pertaining to the actions of these agents at low ambient temperatures. Dose, ambient temperature, species of animal [18], along with the conditions under which animals are tested (freely moving vs. restraint) [23] undoubtedly contribute in a complex fashion to the magnitude and direction of effect of drugs on body temperature. It is known, for example, that restraint can alter the thermal responses to morphine. At normal ambient temperatures (21–24°C), the hypothermic response to threshold doses of morphine (30–60 mg/kg) is observed in restrained rats, but in freely moving rats, no change or increases in body temperature are found [34,35]. However, with high doses of morphine, hypothermia may also be observed in freely moving animals [16]. The hyperthermic response to low doses of morphine (5–15 mg/kg), on the other hand, is most pronounced in freely moving rats; with restraint, the response may be attenuated or absent [34,35].

Caffeine appears to share a third characteristic with morphine, that being the rapid development of tolerance to the hypothermic responses to high doses of the drug and the subsequent emergence of hyperthermia. The hypothermic responses to 50 and 100 mg/kg of caffeine were no longer observed during the second body temperature measurement session (Day 4). That the appearance of tolerance could have occurred earlier was demonstrated in more recent studies (to be published): Within 24 hr of the first injection of 100 mg/kg of caffine, the body temperatures of rats given a second injection of the same dose were no different from those of vehicle-treated rats. This time-course is similar to the development of tolerance to the hypothermic actions of morphine [16, 32, 41]. Following the appearance of tolerance, rats given 50 mg/kg of caffeine on a chronic basis developed hyperthermia, which was comparable to that produced by low doses of the drug, and it was consistently observed throughout the remainder of the experiment (Days 7–28). This change in direction of the body temperature response to repeated drug administrations is also similar to that produced by chronic morphine treatments [16,32]. There is evidence indicating that tolerance may likewise occur to the acute hyperthermic effects of morphine [16,44]. However, under the conditions of the present study, hyperthermia was repeatedly produced by the low doses of caffeine irrespective of the frequency of administration, and this response remained unaltered over the 28-day test period.

An extensive literature exists relating the hyperthermic and hypothermic effects of morphine to changes in the activity or levels of particular central nervous system neurotransmitters, such as serotonin, norepinephrine, dopamine and acetylcholine (for reviews, see [1,10]). Serotonin has been strongly implicated in the acute morphine-induced hypothermic response in rats. The evidence bearing on the particular involvement of catecholaminergic and cholinergic mechanisms in the thermoregulatory responses to acute and/or chronic morphine is less clear. But, there are data to suggest that acetylcholine, dopamine and norepinephrine may play roles in the hyperthermic response of morphine tolerant animals, morphine-withdrawal hypothermia, and acute morphine-induced hyperthermia or hypothermia, respectively. Since direct manipulations of neurotransmitter systems were not undertaken in the present experiment, it would be premature to conclude that particular neurotransmitters mediated one or more of the thermoregulatory responses to acute (or chronic) caffeine. However, it is known that with the destruction of central catecholaminergic neurons (via 6-hydroxydopamine delivered intraventricularly), the hyperthermic response following a single low dose of caffeine is significantly attenuated in rats [30], and high doses of caffeine which produce hypothermia [7] also significantly increase the brain levels of serotonin and 5-hydroxyindoleacetic acid [6,43]. It should be noted that most studies on the acute effects of caffeine on the levels and/or turnover of neurotransmitters (see introductory paragraphs) have been limited to measurements in whole brain or areas of the brain unrelated to sites known to be involved in the central control of body temperature. Therefore, to better understand the possible role(s) of the neurotransmitters discussed above in caffeine's actions on body temperature, it would be important to determine the dose effects of caffeine on neurotransmitter function in brain areas which include, for example, the anterior hypothalamic/preoptic nuclei. But, taking into consideration the data on the neurochemical effects of caffeine (limited as it may be), along with the similarities between caffeine's and morphine's dose effects on body temperature under acute and chronic conditions, it appears that, like morphine, brain neurotransmitters may be playing some part in caffeine-induced alterations of body temperature.

Proper body temperature regulation requires a delicate balance between heat production and heat loss. Because methylxanthines, including caffeine, have been shown to enhance peripheral autonomic function, additional sites involving sympathetic activation may mediate caffeine's disruption of body temperature. The hyperthermic response of rats given low doses of caffeine has been attributed to behavioral excitation since these animals also exhibit increases in oxygen consumption (metabolic heat production), cutaneous vasodilation, and no change in respiratory heat loss [30]. The availability of energy substrates, like glucose and NEFA, are increased in animals given acute high doses of caffeine [15,43]; while metabolic heat production is also elevated [15], body temperatures are lowered by such doses of caffeine [7,15]. Given these effects, it has been suggested that caffeine-induced hypothermia may be the result of increased heat loss via vasodilation or a preferential use of energy substrates for motor activity on account of heat production [15]. That caffeine-induced hypothermia could be the consequence of increased heat loss in the presence of normal or enhanced heat production is supported by the thermoregulatory and metabolic effects of 2-deoxy-D-glucose in humans [50].

The chronic actions of caffeine on body temperature, particularly regarding the tolerance to the hypothermic effects of the drug, may also be due to processes which are independent of or secondary to central thermoregulatory mechanisms. Caffeine and amphetamine [27] have similar effects on body weight and food intake. Upon first exposure to these drugs, both the body weights and food intake of rats are reduced. But with repeated drug administrations, food

intake recovers toward normal levels while gains in body weight are suppressed. It has been suggested that the development of tolerance to the anorectic and thermogenic actions of amphetamine is not due to pharmacological tolerance, but is the consequence of reductions in body weight and subsequent physiological and behavioral adjustments to such changes in body weight [27]. Thus, pre-drug, weight-reduced rats fail to exhibit anorexia or losses in body weight following the first administration of amphetamine. From the work on amphetamine, the following questions are raised: (1) Do the initial thermoregulatory effects of high doses of caffeine (hypothermia and increased metabolic heat production) result in the inhibition of food intake which, in turn, causes the ensuing reductions in body weight? (2) Are the effects of repeated high doses of caffeine on body temperature attenuated or abolished due to the original losses in body weight (which then restores food intake to normal levels) and possible changes in basal metabolism? (3) Despite the return of food intake to normal levels, is the continued suppression of gains in body weight by caffeine a result of incomplete recovery from the metabolic effects of the drug? Answers to these questions will require further investigation.

In brief, then, the dose-dependent effects of caffeine on body temperature may be the product of some combination of direct and indirect effects on central and/or peripheral mechanisms involved with the maintainence of thermoneutrality, or they may be secondary effects of physiological and behavioral processes which are unrelated to thermoregulation.

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