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24-Hour Control of Body Temperature in the Rat: II. Diisopropyl Fluorophosphate-Induced Hypothermia and Hyperthermia

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GORDON, C. J. *24-Hour control of body temperature in the rat: II. Diisopropyl fluorophosphate-induced hypothermia and hyperthermia.* PHARMACOL BIOCHEM BEHAV **49**(3) 747–754, 1994.—Diisopropyl fluorophosphate (DFP) and other anticholinesterase (antiChE) agents have been found to induce marked hypothermic responses in laboratory rodents. To characterize the effects of DFP on autonomic and behavioral thermoregulation, rats of the Long-Evans strain were injected with DFP while housed in a temperature gradient. The gradient allowed for the measurement of selected ambient temperature (T_a) and motor activity (MA) over a 6- to 7-day period. Core temperature (T_c) and heart rate (HR) were also monitored simultaneously using radiotelemetry. Injection of the peanut oil vehicle led to transient elevations in T_c, HR, and MA, but no change in selected T_a. The next day animals were injected with 0.25, 1.0, or 1.5 mg/kg DFP. DFP (1.0 AND 1.5 mg/kg) led to a marked reduction in T_c. The decrease in T_c was accompanied by reductions in HR, MA, and selected T_a. During the first night after DFP, selected T_a remained elevated as T_c recovered to its preinjection level. The second 24-h period after 1.0 and 1.5 mg/kg DFP was associated with a significant elevation in the daytime T_c. In conclusion, with the option of using behavioral thermoregulatory responses, the hypothermic effects of acute DFP treatment are mediated by a selection for cooler T_as. An elevation in T_c during recovery from acute DFP corroborates the many incidents of fever in humans exposed to anti-ChE agents.

Behavioral thermoregulation Heart rate Motor activity Core temperature Telemetry
Organophosphate Stress Fever

ANTICHOLINESTERASE (anti-ChE) agents including organophosphate (OP) and carbamate (CB)-based pesticides have been found to exert profound effects on the body temperature of rodents and other species of mammals (5,6,12,20–23,26). OPs such as diisopropyl fluorophosphate (DFP) irreversibly bind to the active site of cholinesterase enzymes, causing a marked elevation in acetylcholine levels resulting in a variety of behavioral and autonomic effects (1). Generally, the acute response to anti-ChE exposure in laboratory rodents is characterized by a marked reduction in body temperature followed with a gradual recovery over the next 24 h (6, 12,18,21). On the other hand, there are reports suggesting that anti-ChEs cause an elevation in core temperature (i.e., a fever) in humans and some experimental species (12,15,16,25).

The mechanism of the thermoregulatory effects of anti-ChEs has been assessed by several investigators (11,20–22). The hypothermic effects of exposure to OPs appears to be mediated predominantly through central thermoregulatory processes because administration of peripherally acting cholinergic antagonists does not block OP- or CB-induced hypothermia (14,20,23). Most work has focussed on the effects of anti-ChEs on the autonomic thermoregulatory processes of the laboratory rodent, and little attention has been given to the possible changes in behavioral thermoregulation. Yet, it is well known that behavioral processes play a critical role in the regulation of body temperature, especially in times of a thermal stress where homeostatic processes must respond to modulate heat exchange. For example, when given a choice between using autonomic or behavioral effectors, behavioral thermoregulation is preferentially utilized to maintain thermal homeostasis (11,27). If an animal is exposed to an anti-ChE agent and given the option of using behavioral and autonomic

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effectors, its thermoregulatory response may differ from that of animals that are maintained under typical housing environments (i.e., with no behavioral options).

A temperature gradient provides an ideal environment for studying behavioral thermoregulatory responses to neurotoxicants such as anti-ChE agents. A gradient represents an innate environment for the unconditioned animal. It can sleep, eat, and exhibit other behaviors while maintaining an optimal selected T_a. Anti-ChE agents lead to skeletal muscle dysfunction including tremor, weakness, and reduced motor activity (1). Hence, a temperature gradient system is preferred for these studies because selected T_a can be controlled with relatively little motor activity compared to that of operant systems (11). A gradient system recently described in detail (9,10) has been incorporated with a radiotelemetry system which permits continuous monitoring of core temperature, heart rate, motor activity, and selected T_a in unrestrained animals over periods of days or weeks. Radiotelemetry is an ideal method for measuring body temperature while avoiding the impact of handling-induced changes in thermoregulation (5,12). Hence, to further understand anti-ChE-induced changes in body temperature, the present study was designed to simultaneously measure behavioral and autonomic thermoregulatory processes over an extended period of time when treated with the anti-ChE agent, DFP.

METHOD

Ten male rats of the Long-Evans strain were obtained from Charles River Laboratories (Raleigh, NC) at an age of 60 days. The rats were housed in groups of two in cages lined with wood shavings at a T_a of 22°C, 50% relative humidity, and a 12 L : 12 D photoperiod (lights on at 0600 h). The rats were approximately 3 months of age when studied and had a mean ± SE body weight of 452 ± 13.2 g.

Surgical implantation of the radiotelemetry transmitters has been described in detail (12). Briefly, rats were anesthetized (sodium pentobarbital, ~50 mg/kg; IP) and a small incision was made along the midline of the abdomen for implantation of the radiotransmitter for monitoring the electrocardiogram (ECG), core temperature, and motor activity (Data Sciences Int., St. Paul, MN; model TA10ETA-F20-L20). The body of the transmitter containing the thermistor to measure core temperature was sutured inside the abdominal cavity. The transmitter's ECG leads were tunneled under the skin and positioned around the chest to optimize the strength of the ECG signal. After surgery, the rat was given 30,000 units of penicillin and allowed at least 7 days' recovery prior to being tested in the gradient.

Selected T_a and motor activity were measured in a temperature gradient (9,10). The system was modified to allow the placement of four telemetry receivers (RLA 3000; Data Sciences) inside the gradient, which served to pick up the telemetry signal. A wire-mesh runway (12.7 × 12.7 × 183 cm) was placed in the gradient, which had a T_a range of 8 to 37°C. Thermocouples and photosensors placed at 10 cm intervals along the length of the gradient served to monitor position and selected T_a of the rat in the gradient at 60-s intervals. A food cup and water source were positioned in the middle of the gradient corresponding to a T_a of ~26°C. A series of low voltage, miniature lamps spaced at 20 cm intervals along the top of the gradient provided ambient light levels inside the wire-mesh cage of 0.1 to 0.45 lx. The gradient was set on a 12 L : 12 D cycle (lights on at 0600 h).

Protocol

Prior to placement in the gradient the transmitter was turned on by activating a magnetic field-sensitive switch inside the device. The rat was weighed and placed into the runway which was then inserted inside the gradient. This laboratory has found that a normal circadian rhythm of selected T_a and core temperature of the Long-Evans rat placed in a temperature gradient requires at least 24 h to be established (10). Thus, to assure complete adaptation to this novel system, the animals were allotted approximately 72 h in the gradient prior to experimental manipulation. At 1045 h on the third day after placement in the gradient, the rat was removed from the system, weighed, and then administered a control injection of peanut oil (0.1 ml/100 g, SC). The food dispenser was refilled and the rat was returned to the gradient. The entire injection procedure required less than 5 min to complete. Twenty-four hours after the vehicle injection, the rat was removed from the gradient and injected with DFP (Sigma) in a peanut oil vehicle at a dose of 0.25 or 1.0 mg/kg (0.1 ml/100 g b.wt.). The animal was returned to the gradient and monitored without interruption for another 48 h. At the end of the experiment the rat was killed by CO_2 asphyxiation and the transmitter was removed and checked for temperature calibration.

Data Analysis

Data collected at 60-s intervals were averaged into hourly bins for statistical analysis. The effect of peanut oil and DFP administration on each of the four variables recorded in the temperature gradient was analyzed for significance using a repeated measures analysis of variance (ANOVA) (GB-Stat, Bethesda, MD). With this method each animal's baseline response (i.e., prior to any injection) was used as a control period which included data measured between 01100 to 0959 h. The period between 1000 to 1059 was excluded because it was during this time that the injections occurred. The 23-h period following the injection of peanut oil and the subsequent 23-h period following the injection of DFP were compared to the control data. Two-way ANOVAs were performed using a probability of $p < 0.05$ to detect significant effects of DFP treatment, time, and treatment × time interactions.

Analysis of the hyperthermic effects of the DFP treatments was done in a slightly different manner. The change in body temperature averaged over a 24-h period prior to injection of peanut oil was first calculated. Each animal was then used as its own control as described above. Post hoc analysis of the time course data revealed a trend for body temperature to increase above basal levels during the second day after DFP administration. Using a two-way repeated measures ANOVA, the change in average core temperature during the second day after DFP was compared to the equivalent time period during injection of peanut oil as well as during the equivalent period prior to injection. Significant treatment effects detected with the ANOVA were further analyzed using a Tukey's protected *t*-test.

In the initial study, 10 rats were injected with peanut oil, 4 rats with 0.25 mg/kg DFP, and 6 rats with 1.0 mg/kg DFP. Two of the six rats given the 1.0 mg/kg DFP treatment failed to show any hypothermic response or any reduction in motor activity and heart rate as is typically observed. It appears that the 1.0 mg/kg dose of DFP is borderline for activating a cholinergic response in some rats, as has been found in an earlier study from this laboratory (12). On the other hand, increasing the dose by just 0.5 mg/kg elicits consistent cholin-

ergic responses in the Long-Evans rat, but the responses are quite severe and occasionally may lead to death. It was decided to exclude the two nonresponding animals from the general analysis of the thermoregulatory effects of the 1.0 mg/kg treatment group. It was originally intended to keep the dose of DFP at 1.0 mg/kg to avoid the severe toxicity. However, in view of the inconsistent response to the 1.0 mg/kg dose of DFP, it was decided to add to the data base by testing three additional rats in the gradient at a dose of 1.5 mg/kg. Two of the animals in this group were to be used in another study and had been implanted with subcutaneous osmotic pumps filled with 0.9% saline; however, this procedure had no bearing on their response in the gradient to DFP. These data were statistically analyzed using a repeated measures ANOVA as described earlier.

RESULTS

After 3 days in the temperature gradient, all variables were relatively stable during the light phase and showed clear 24-h oscillations (Figs. 1-3). The average value of each parameter during the light phase between 0900 and 1759 h were: core temperature, 37.1°C; selected T_a, 29.1°C; heart rate, 312.1 beats/min; and motor activity, 1.47 m/h. During the dark phase, core temperature, heart rate, and motor activity increased, whereas selected T_a decreased. The analysis of the 24-h rhythms of these responses in untreated rats is reported in a another article (13).

Following the injection of peanut oil there were transient elevations in core temperature, heart rate, and motor activity, whereas selected T_a exhibited an insignificant decrease (Figs. 1-3). The transient elevations in core temperature and heart rate were highly significant relative to the preinjection baseline values. Recovery to baseline required approximately 2 h for all variables (Fig. 4). Although there were significant elevations in the variables shortly after peanut oil injection, analysis of the 23-h period following peanut oil was not significantly different compared to the 23-h baseline period for any of the variables.

Administration of 0.25 mg/kg DFP had no effects on any of the variables measured in the gradient (Fig. 1). This treatment led to transient elevations in core temperature, heart

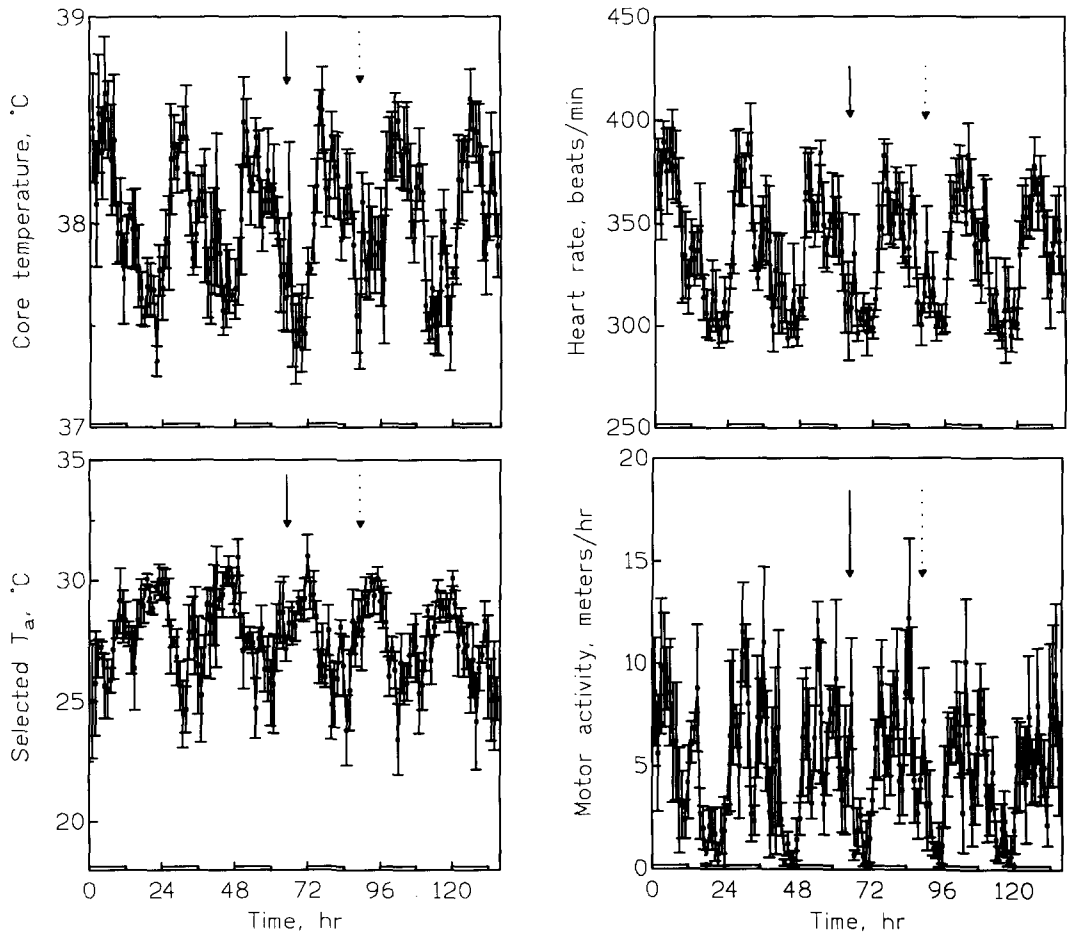

FIG. 1. Time course of the mean ± SE of core temperature, selected T_a, heart rate, and motor activity before and after the administration (SC) of peanut oil (solid arrow) and 0.25 mg/kg DFP (dotted arrow) (n = 4). Blocks on abscissa indicate periods of darkness. There were no treatment effects of DFP on any of the variables. All time effects were highly significant ($p < 0.0001$).

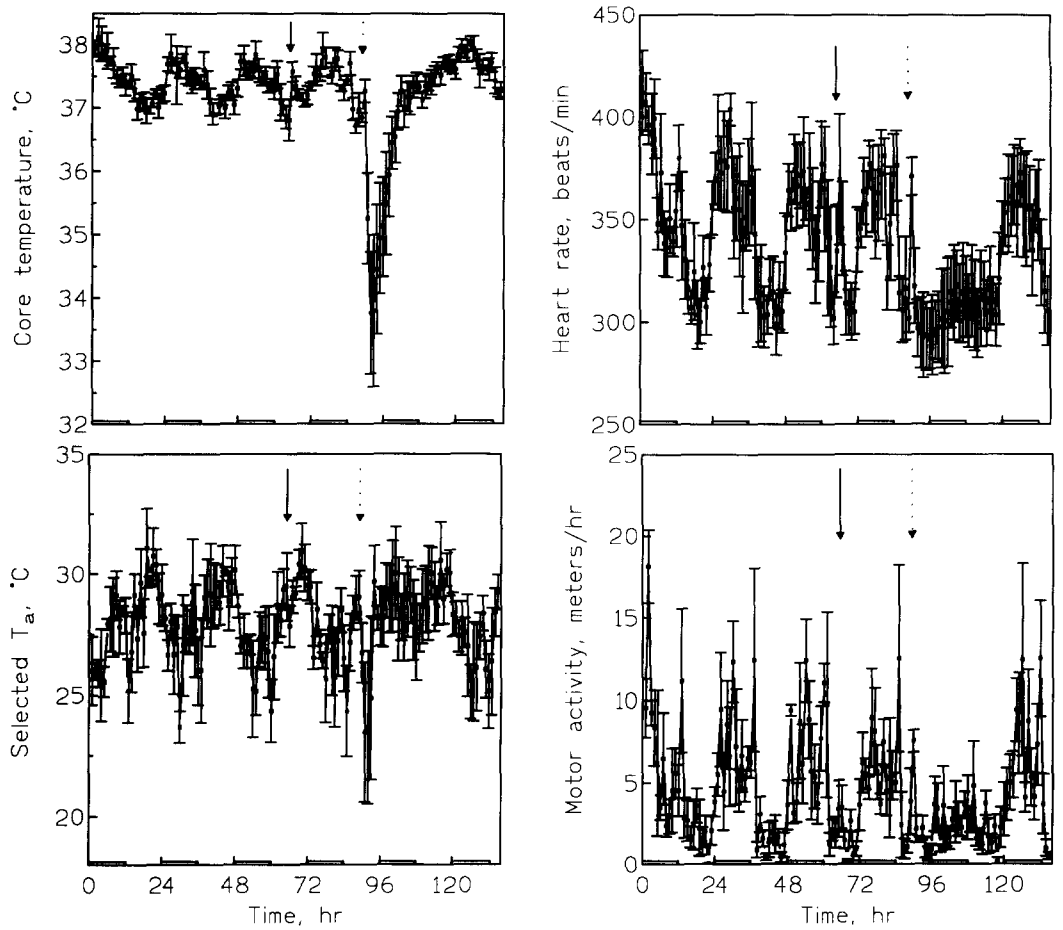

FIG. 2. Time course of core temperature, selected T_a, heart rate, and motor activity before and after the administration of peanut oil and 1.0 mg/kg DFP (n = 4). Abbreviations same as in Fig. 1. Repeated ANOVA results: core temperature [treatment, $F(2, 22) = 5.8$, $p = 0.023$]; selected T_a [treatment, not significant (NS); treatment × time, $F(44, 198) = 2.11$, $p = 0.0003$]; heart rate [treatment, NS; treatment × time, $F(44, 198) = 2.5$, $p < 0.0001$]; motor activity [treatment, $F(2, 9) = 10.3$, $p = 0.004$; treatment × time, $F(44, 198) = 1.6$, $p = 0.008$]. Note that all time effects were highly significant ($p < 0.0001$).

rate, and motor activity, and a decrease in selected T_a; however, these responses paralleled that following the administration of peanut oil (Fig. 4). The repeated measures ANOVA indicated no significant treatment effect over the 23-h period following 0.25 mg/kg DFP. There were highly significant time effects ($p < 0.0001$) for all variables that reflects the circadian variation as described earlier.

Injection of 1.0 mg/kg of DFP led to changes in all variables (Fig. 2). During the first hour there was a transient elevation in core temperature, heart rate, and motor activity. This was soon followed by a marked reduction in all variables. Core temperature decreased by ~3°C, reaching its nadir by 3 h after DFP administration. Selected T_a decreased by ~5°C during the initial onset of DFP-induced hypothermia but then rebounded to basal levels and remained elevated throughout the dark phase. Heart rate and motor activity remained depressed throughout the first 24-h period after 1.0 mg/kg DFP.

A recovery of selected T_a, motor activity, and heart rate was apparent during the 24- to 48-h period after 1.0 mg/kg DFP administration. That is, the typical decrease in selected T_a and increase in motor activity and heart rate were observed during the dark phase of the second day after DFP treatment. Repeated measures ANOVA between the preinjection period and the 24- to 48-h period after 1.0 mg/kg DFP indicated no significant change in selected T_a and heart rate, but a significant treatment effect on core temperature, $F(1, 6) = 4.1$, $p = 0.042$, and a significant treatment × time effect on motor activity, $F(22, 132) = 2.08$, $p = 0.0005$.

The 1.5 mg/kg dose of DFP had even more profound effects on all variables recorded in the temperature gradient (Fig. 3). The responses were similar to that seen in the 1.0 mg/kg dose group (Fig. 2) except that the decrease in core temperature and selected T_a was more pronounced. Core temperature decreased by ~5°C and reached its nadir 7 h after DFP treatment. During this hypothermic period selected T_a was reduced at times by over 10°C. Motor activity and heart rate were reduced in a similar pattern as seen in the 1.0 mg/kg treatment group. However, recovery was not observed until the third day following DFP treatment. Selected T_a also recovered more slowly with the rats displaying a continued preference for warmer T_as during the first and second nights after DFP treatment.

The recovery of core temperature 24 h after 1.0 and 1.5 mg/kg DFP indicates a persistent elevation that is most promi-

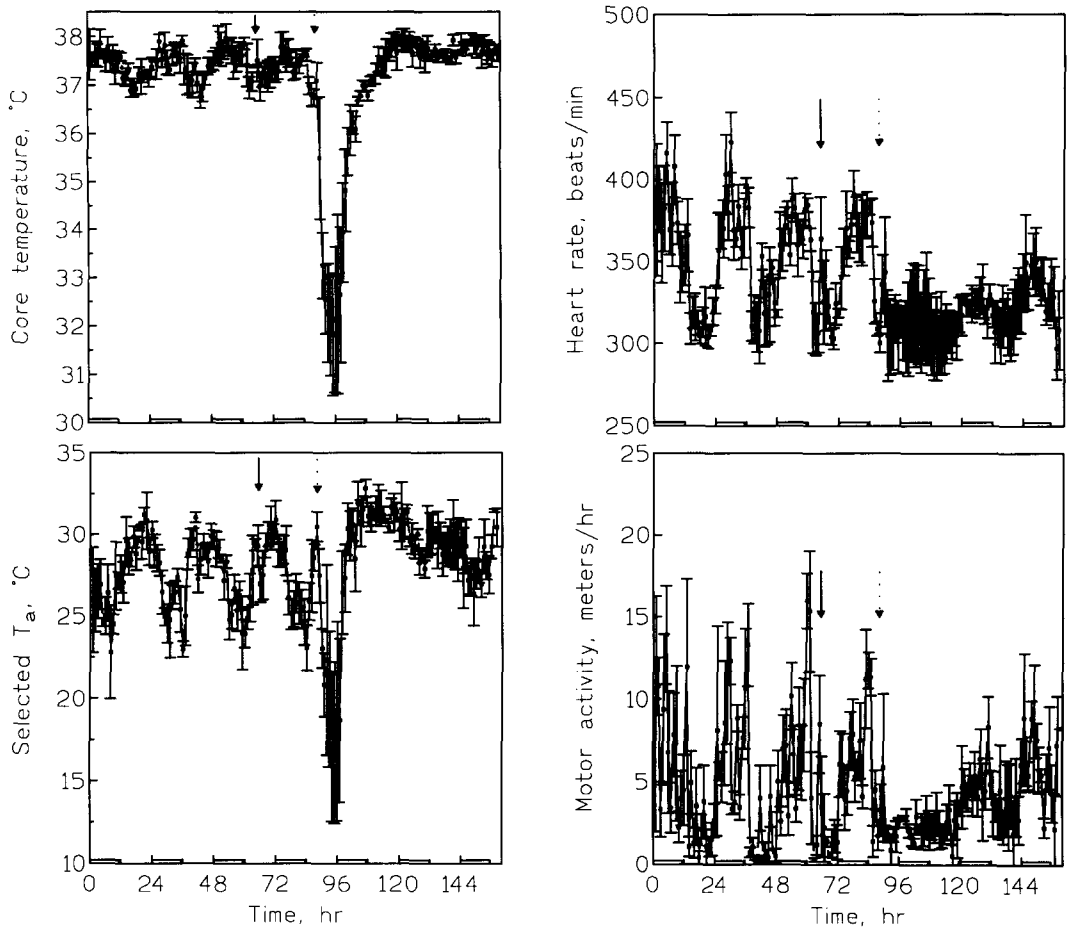

FIG. 3. Time course of core temperature, selected T_a, heart rate, and motor activity before and after the administration of peanut oil and 1.5 mg/kg DFP (n = 3). Abbreviations same as in Fig. 1. Repeated ANOVA results: core temperature [treatment, $F(2, 6) = 17.7, p = 0.003$; treatment × time, $F(44, 132) = 7.8, p < 0.0001$]; selected T_a [treatment, NS; treatment × time, $F(44, 132) = 7.0, p < 0.0001$]; heart rate [treatment, NS; treatment × time, $F(44, 132) = 2.3, p = 0.0001$]; motor activity [treatment, $F(2, 6) = 15.2, p = 0.004$; treatment × time, $F(44, 132) = 2.7, p < 0.0001$]. Note that all time effects were highly significant ($p < 0.0001$).

nent during the light phase (Figs. 2 and 3). Calculating the change in average body temperature provides a clearer view of the DFP-induced decrease and increase in core temperature (Fig. 5). The 0.25 mg/kg treatment had no effect on core temperature throughout the experimental period. However, after recovery to the hypothermic effects of 1.0 and 1.5 mg/kg DFP, there was an elevation in the daytime core temperature, lasting for up to 3 days in the 1.5 mg/kg treatment group. Averaging of the time periods 25 to 48 h after DFP indicates a significant elevation in average body temperature in the 1.0 and 1.5 mg/kg treatment groups when compared to the equivalent time periods prior to any injection and following the administration of peanut oil (Fig. 6).

DISCUSSION

In this study the rats were provided with an environment that permitted both behavioral and autonomic effectors to be continuously operative. Following administration of a relatively high dose of the anti-ChE agent, DFP, a thermoregulatory pattern was elicited that can be divided into a short-term and recovery response. The short-term hypothermic effect of 1.0 and 1.5 mg/kg DFP was facilitated behaviorally, meaning that the rats preferred cooler T_as during the period of DFP-induced hypothermia. During recovery from the DFP-induced hypothermia the rats preferred relatively warm T_as at night. Throughout the next day there was a gradual elevation in core temperature. There was no appreciable change in the nocturnal core temperature during this recovery, but the daytime temperature remained elevated into the third day after the 1.5 mg/kg DFP treatment. Heart rate and motor activity were also severely inhibited during the first 24 h after 1.0 and 1.5 mg/kg DFP. These variables recovered by the second and third night after 1.0 mg/kg and 1.5 mg/kg DFP, respectively.

The preference for cooler T_as concomitant with hypothermia is indicative of a reduction in the set point for the control of body temperature (11). Meeter (22) first proposed a reduction in set point to be operative in the rat exposed to the anti-ChE OP, soman. This conclusions was based primarily on the increase in tail blood flow of the rat following soman treatment, a response resulting in increased heat loss and decrease in body temperature. The results showing a decrease in

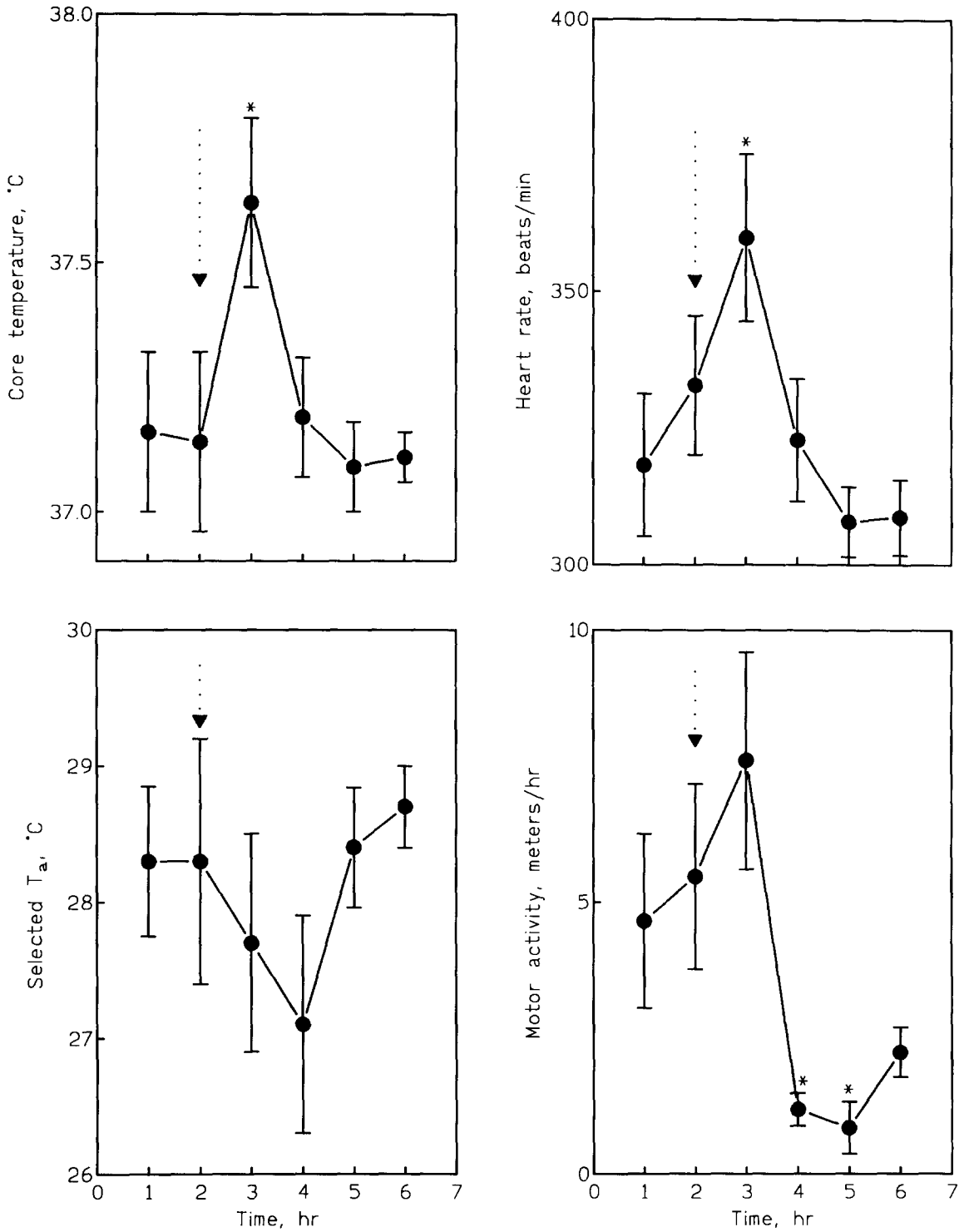

FIG. 4. Time course of core temperature, selected T_a, heart rate, and motor activity before and after the administration of peanut oil (arrow). n = 10. Repeated ANOVAs were all highly significant. Asterisks indicate significant difference when compared to baseline responses at 1 h time point using a Tukey's protected t-test.

selected T_a at the same time that core temperature is reduced provides additional support for a decrease in set point. That is, a chemical agent could lower body temperature without affecting the CNS by stimulating vasodilation and/or inhibiting heat production. It is possible that an increase in skin temperature following exposure to an OP is responsible for causing a reduction in selected T_a. However, if a change in set point was not involved in this response, the marked reduction

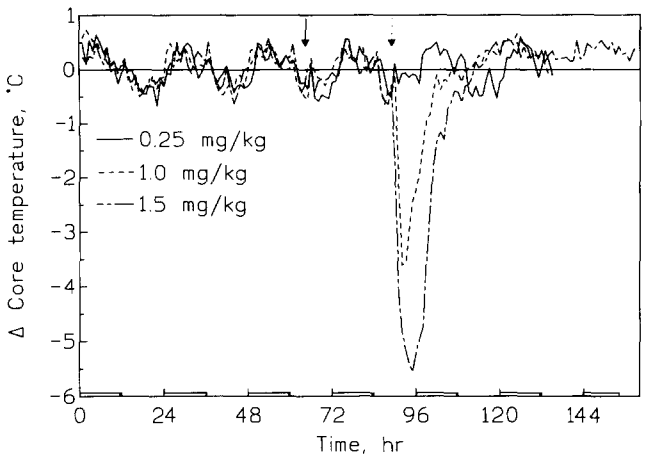

FIG. 5. Time course of change in mean body temperature before and after administration of peanut oil (solid arrow) and DFP (dotted arrow).

in core temperature during this period would be a factor causing the selection of a warmer T_a.

An earlier study from this laboratory measured thermoregulatory behavior in rats treated with DFP and placed in a temperature gradient for 60 min (8). In that study, rats given 1.0 and 1.5 mg/kg DFP were significantly hypothermic and remained in the cool end of the gradient; however, the control rats also stayed at the cooler side of the gradient. It has been discovered that the Long-Evans rat requires about 6 h of adaptation in a temperature gradient before its thermoregulatory behavior will stabilize (9). Hence, in the present study the rats were allowed adequate time to adapt to the temperature gradient. In this way, the behavior to initially select cool T_as then warm T_as during DFP treatment illustrates the marked effect of DFP on thermoregulatory behavior.

The recovery of core temperature from 1.0 and 1.5 mg/kg DFP also involves the utilization of behavioral thermoregulation. During the first night after 1.5 mg/kg DFP and 2 nights after 1.5 mg/kg DFP, selected T_a remained at an elevated level compared to that following the vehicle injection. It is interesting to note that in the temperature gradient the rats could select T_as as warm as 37°C, yet such behaviors were not seen in spite of the fact that the DFP-treated rats were hypothermic for over 12 h after injection. That the rats did not use behavior to raise their core temperature as quickly as possible would indicate a change in the regulation of core temperature mediated by DFP (i.e., change in set point).

The short-term effects of DFP on core temperature and selected T_a are likely a result of cholinergic stimulation of muscarinic receptors in the CNS. A 1.0 mg/kg dose of DFP in the rat results in a > 70% reduction in ChE activity in the hypothalamic area within 60 min, a response that should lead to a marked elevation in acetylcholine levels (18). Several studies have shown that injections of cholinomimetic agents into either the cerebral ventricles or directly into the hypothalamic area leads to a hypothermic response in the rat (7, 26). In one study, the hypothermic response occurred concomitantly with an operant thermoregulatory response to reduce heat intake, indicating a decrease in the set point (2). These results parallel that of the behavioral response of the rats during the first several hours after treatment with 1.0 and 1.5 mg/kg DFP.

The hyperthermic response may also be cholinergically related. Some studies show that small doses of cholinomimetic substances can lead to an elevation in core temperature in the rat and other species (24). It is possible that a rebound type effect could be operative, meaning that the rise in core temperature is an autonomic overcompensation from the depressed core temperature. The mechanism of core temperature overshoots are not well studied, but an overshoot lasting several days as seen in the present study would not be expected. It should be noted that a few experimental animal studies have reported anti-ChE-induced elevations in core temperature including: (a) daily malathion exposures (15); relatively small doses of DFP (9,12); soman at a relatively warm T_a (23); and recovery from relatively high doses of DFP (12). Furthermore, analysis of the clinical data base of thermoregulatory effects in humans has shown that a fever, lasting for several days in many cases, is frequently reported following acute exposer to OP anti-ChE agents (16,25).

It is noteworthy to discuss the behavioral thermoregulatory response following administration of the peanut oil vehicle (Fig. 1). The injection procedure led to a transient elevation in heart rate and core temperature but an insignificant drop in the selected T_a. The rise in core temperature is undoubtedly a stress reaction in response to the handling and injection procedure. Interestingly, recent studies have found that various pyschological stresses in the rat lead to a fever-like elevation in core temperature (3,17,19). Because the hyperthermia can be attenuated by the preadministration of antipyretic agents, it is thought that stress-induced hyperthermia involves a regulated elevation in temperature, akin to that of a fever (17). Based on earlier discussions of set point, the stress from the peanut oil injection would be expected to lead to an increase in the selected T_a provided that the hyperthermia was regulated. Similar to the results of this study is the recent work by Briese (4) showing that stress from handling led to an elevation in core temperature but a decrease in selected T_a in the rat. Hence, it appears that stress from handling or injection procedures resulting in significant elevations in core tem-

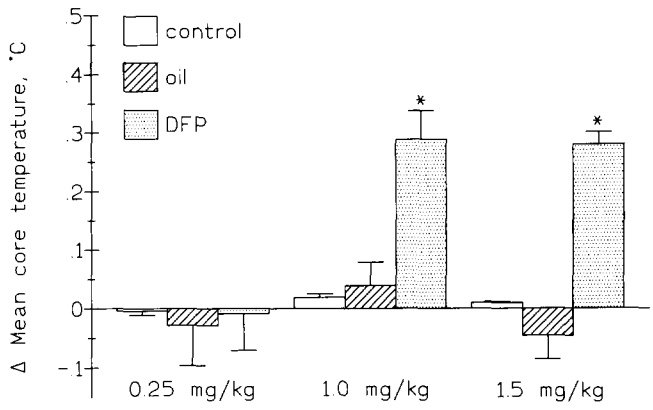

FIG. 6. Comparison of change in mean body temperature during the control period (i.e., prior to injection) and after peanut oil injection, and 25 to 49 h after injection of DFP. Asterisks denote significant difference when compared to preinjection and peanut oil time periods. Calculations for control period and peanut oil injection were made over same clock time as used in calculation of DFP response.

perature is not mediated by behavioral thermoregulatory responses. On the other hand, some of the reported behavioral patterns (4) indicate a response to attenuate the stress-induced hyperthermia.

In conclusion, this study provides evidence for a behaviorally mediated reduction in core temperature in the rat following acute exposure to the anti-ChE agent, DFP. Behavioral thermoregulation is also important during the recovery from DFP-induced hypothermia, as is evident from the selection of warmer T_as during the dark phase. During recovery from acute DFP there is a persistent elevation in core temperature lasting for several days. These results are important from the standpoint that human exposures to anti-ChE agents is reported to cause a fever. It will be of interest to elucidate the possible neural mechanisms of hypothermia and hyperthermia following OP exposure.

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