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Serotonin and Thermoregulation

Physiologic and Pharmacologic Aspects of Control Revealed by Intravenous m-CPP in Normal Human Subjects

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Meta-chlorophenylpiperazine (m-CPP), a probe of central serotonergic function, elevates core temperature in rodents, nonhuman primates, and humans via serotonin receptor–mediated mechanisms. To further characterize the thermoregulatory aspects of this response, we studied 16 healthy volunteers using multiple core and skin temperature recording sites. Compared to placebo, intravenous m-CPP (0.08 mg/kg) produced statistically significant biphasic changes in rectal temperature, characterized by initial hypothermia (−0.04°C at 12 minutes) followed by progressive hyperthermia (+0.17°C at 90 minutes). m-CPP also produced significant increases in plasma norepinephrine concentrations. Analysis of the skin temperature recordings suggests that the effector mechanism primarily responsible for m-CPP–induced core hyperthermia is increased metabolic thermogenesis. Individual differences in the magnitude of the hyperthermia were independent of m-CPP plasma concentrations but were found to be linearly correlated with the level of the previous night's core rectal temperature minimum and mean. It appears that m-CPP activates a mode of metabolic thermogenesis governed by a nocturnally sensitive proportional control mechanism. The operation of such a proportional controller is characterized by a set point and a gain, and has been implicated in the general economy of mammalian energy balance. ***[Neuropsychopharmacology 13:105–115, 1995]***

KEY WORDS: *Temperature; Meta-chlorophenylpiperazine; Serotonin; Norepinphrine*

Serotonin (5-HT) is a major neurotransmitter involved in both central and peripheral aspects of thermoregulation (Simon et al. 1986; Bruck and Hinckel 1990; Hori 1991). While the anterior hypothalamus has been conclusively identified as a primary central site for the thermoregulatory action of serotonin (Bligh 1979), 5-HT receptors are also located throughout the peripheral vasomotor and peripheral nervous systems (Fozard 1984), indicating that the serotonergic regulation of body temperature is complex. Elevated core body temperature, especially at night, has been a reproducible finding in depressed patients, as has been the reduction of nocturnal core temperature following successful antidepressant treatment (Avery et al. 1982; Lund et al. 1983; Smallwood et al. 1983; von Zerssen et al. 1985; Souetre et al. 1988; Rosenthal et al. 1990). Given this association between abnormal thermoregulation and depression (Avery et al. 1982; Elsenga and van den Hoofdakker 1988; Wehr 1989), and given that serotonin is clearly an important neurotransmitter in both mood (Meltzer and Lowy 1987; Coppen and Boogan 1988; Murphy 1990) and temperature regulation, dis-

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entangling the interactions between the various components of the serotonergic and thermoregulatory systems remains an important challenge for depression research.

In clinical studies, serotonergic pharmacological probes have been used to perturb mood, plasma hormones, and temperature to provide possible indices of the status of brain serotonergic neurotransmission. One such probe, meta-chlorophenylpiperazine (m-CPP), has been consistently found to induce hyperthermia in rodents (Maj and Lewandowska 1980; Mazzola-Pomietto et al. 1995), nonhuman primates (Aloi et al. 1984), and humans (Mueller et al. 1985, 1986; Zohar et al. 1987; Lawlor et al. 1989; Murphy et al. 1989; Kahn et al. 1992). In addition, the hyperthermic response to m-CPP is modified by antidepressant medication in animals (Wozniak et al. 1989; Volterra et al. 1991) and humans (Zohar et al. 1988), making m-CPP's thermoregulatory mechanism of action of potential clinical interest.

In binding studies, m-CPP has affinity for 5-HT_{2C} > 5-HT_3 > 5-HT_{2A} > 5-HT_{1B} > 5-HT_{1A} receptors (Invernizzi et al. 1981; Martin and Sanders-Bush 1982; Kilpatrick et al. 1987; Hoyer 1988) as well as for α_2-adrenergic receptors (Smith and Suckow 1985). In rats, the hyperthermic response to m-CPP seems selectively mediated by the 5-HT_{2C} receptor, as it is attenuated by metergoline (5-HT_1/5-HT_2 antagonist), mesulergine, and ritanserin (5-HT_{2C}/5-HT_{2A} antagonists), but not by propranolol or pindolol (5-HT_{1A}, 5-HT_{1B}, and β-adrenergic receptor antagonists), prazosin (α_1-adrenergic antagonist), or MDL 72222, ondansetron, or tropisetron (5-HT_3 antagonists) (Wozniak et al. 1989a; Klodzinska and Chojnacka-Wojcik 1992; Mazzola-Pomietto et al. 1995). In humans, the hyperthermia is attenuated by metergoline (Mueller et al. 1986) but not by ondansetron (a 5-HT_3 antagonist) (Broocks et al. 1992), leaving several receptor subtypes as potential mediators of the hyperthermic response in humans.

There are several physiological mechanisms through which m-CPP might induce hyperthermia. Thus, m-CPP–induced hyperthermia could result from (1) a change in the characteristics of the central temperature controller, (2) a change in thermoeffector outputs (e.g., metabolic heat production or vasomotor heat dissipation), (3) a change in the processing of afferent thermal information, or (4) some combination of these, to name but a few possibilities. Conceivably, m-CPP acts via several different mechanisms, including direct or indirect effects at central or peripheral serotonergic or adrenergic receptors (Cohen and Fuller 1983; Bagdy et al. 1989a; Murphy et al. 1991). Indeed, direct serotonergic activation of peripheral effectors alone (e.g., peripheral vasomotor heat exchange) can be sufficient to induce changes in core temperature in animals at room temperature (Sugimoto et al. 1991; Key and Wigfield 1992).

To investigate further the integration of the component parts of the thermoregulatory response to m-CPP and the potential relevance of this response to mood disorders, we measured m-CPP–induced changes in core and skin temperature in healthy volunteers and in patients with winter-seasonal affective disorder (SAD). A condition of recurrent fall/winter depressions, SAD (Rosenthal et al. 1984) may involve pathology of central serotonin function (Rosenthal and Wehr 1992), which may vary seasonally even in normals (Carlsson et al. 1980). Herein we describe a detailed investigation of the temperature responses to m-CPP in healthy volunteers.

METHODS

Subjects

Sixteen subjects (13 women, 3 men; mean age 37.1 ± 10.2 years) were recruited as age- and sex-matched healthy volunteers for the SAD patients. Subjects were screened using the Structured Clinical Interview from the DSM III-R (SCID; Spitzer et al. 1989) and were judged free of any current or past Axis I psychiatric disorders. In addition, none had any first-degree family members with a history of psychiatric illness. All subjects had a complete physical exam and laboratory evaluation, including thyroid function studies. Individuals with any history of significant medical illness (including migraine headaches [Brewerton et al. 1988]) were excluded. Subjects were free of all medications throughout the study and were specifically instructed to avoid all temperature-altering medications, such as aspirin and acetaminophen. No alcohol was permitted during the study. All subjects had normal sleep-wake schedules, with sleep onset routinely occurring between 10:00 P.M. and midnight. All subjects gave written consent prior to their participation in the study.

Procedures

Subjects were outpatients for the six-week protocol, except when they were admitted to the NIH Clinical Center the night before the infusions. The study was conducted between December 15, 1991, and March 21, 1992. All subjects underwent a pair of infusions (one m-CPP and one placebo, separated by at least 2 days, order randomized) after completing 2 weeks in each of two respective lighting conditions (off lights vs. on lights, order also randomized). Subjects went directly from the first to the second lighting condition, with no intervening days in between. In the off-light condition, subjects wore dark, wraparound goggles (3% transmittance) when outdoors in bright sunlight, in order to maximize the contrast between the off- and on-light conditions. In the on-light condition, subjects sat in front

of a 10,000-lux bright white light for 45 minutes twice a day between 6:00 and 9:00 A.M. and 6:00 and 9:00 P.M., in a manner previously described (Terman et al. 1990), and did not wear goggles while outdoors. We did not control for or systematically track menstrual phase.

The evening prior to their infusions, subjects were admitted to the research ward. Subjects were allowed to sleep from 11:00 P.M. to 7:00 A.M. in hospital pajamas (light cotton, short sleeves, and long pants). Overnight rectal temperatures were recorded by a rectal thermocouple (Malinckrodt Anesthesia, St. Louis, MO), connected to a high-resolution electronic thermometer (Isothermex, Columbus Instruments, Columbus, OH; accuracy = 0.1°C, resolution = 0.015°C). Upon awakening at 7:00 A.M., subjects arose only to void, returning immediately to bed, where they remained without covers and with their torsos inclined at 45° throughout the morning study. Subjects wore standard styrofoam slippers which left their insteps exposed. Between 7:00 and 7:30 A.M., two intravenous catheters were inserted, and skin temperature probes were (Malinckrodt Anesthesia) attached. Skin sites used were forehead (1 cm superior to the midpoint of one eyebrow), hand (just distal to the first metacarpal-carpal joint on the dorsum of the hand), trunk (mid-axillary line at level of xiphoid process), and foot (instep).

At 9:30 A.M., over the course of 90 seconds, 20 ml of m-CPP (0.08 mg/kg) or saline placebo was administered intravenously. Temperatures were recorded every minute for the next 90 minutes. Subjects were observed for, and were asked to note, any shivering. Pulse and blood pressure were monitored every 10 minutes. Blood samples for norepinephrine (NE) concentrations and m-CPP levels were obtained immediately before the infusion, and at 10, 30, and 60 minutes after the infusion for NE, and at 10, 30, and 90 minutes for m-CPP. Plasma for m-CPP assays was obtained through the intravenous line not previously used for the infusion, in order to avoid contamination of blood samples with any m-CPP that might have adhered to the tubing.

Inpatient Environmental Conditions

Room temperature was maintained at 22.75 ± 0.75°C. Ambient lighting conditions were maintained at <1 lux overnight and at 30 lux after awakening. Humidity was not controlled. In the on-lights condition only, subjects received their usual 10,000-lux light treatment from 8:00 to 9:00 P.M. the nights before, and from 8:00 to 9:00 A.M. the mornings of their infusions.

Assay Procedures

Venous blood samples were collected with EDTA as the anticoagulant, and plasma samples obtained by centrifugation were stored at −70°C until analysis. High-performance liquid chromatography (HPLC) with electrochemical detection procedures was used to assay plasma m-CPP levels (Murphy et al. 1989) and plasma NE concentrations (Mefford et al. 1987). For the NE assays, the internal standard, dihydroxybenzylamine (1 μm), was added to 0.8 ml plasma, and the free amines were extracted in a two-stage procedure using aluminum oxide/Tris (pH 8.5) and 1% acetic acid elution. The HPLC system consisted of an LKB (Pharmacia, Piscataway, NJ) 2150-010 pump, a Gilson (Thomson Instrument Co., Springfield, VA) 231 autosampler/401 diluter fitted with a 50 μl sample loop, a BAS (Bioanalytical Systems, Inc., W. Lafayette, IN) LK-4B amperometric detector at an applied potential of 0.6V vs. Ag/AgCl reference electrode, and a 3 μm C-18 Axxion (Thomson Instrument Co., Springfield, VA) ODS column (4.6 × 150 mm length). The mobile phase was sodium phosphate monobasic with sodium dodecyl sulfate as the ion pairing agent and methanol, 10% to 12%.

Statistical Analysis

Core rectal temperature data were smoothed using a low-pass filter (fast Fourier transform filtering, Passage Software) to eliminate occasional spike noise distortions. Overnight (11:00 P.M. to 7:00 A.M.) rectal temperature minimum (T_{min}) and mean (T_{mean}) were extracted for the preinfusion nights. Morning temperatures were analyzed by repeated measures ANOVA, with three within-factors, namely, light condition (off vs. on lights), drug (m-CPP vs. placebo), and time. Greenhouse-Geisser corrections were used for all repeated measures analyses. Data were also baseline corrected at $t = 0$ (time of infusion) for additional analyses. When significant drug × time interactions occurred, post hoc Bonferroni t tests, comparing average (off lights and on lights) responses to m-CPP and placebo at each time point, were used to determine the specific time points at which the m-CPP–induced temperature response differed from that of placebo. Plasma NE concentrations were similarly analyzed by repeated measures ANOVA. Temperature and NE responses were also analyzed by calculating the total area under the curve (AUC after baseline corrections, trapezoidal rule) over the 90-minute postinfusion sampling period (negative deflections resulted in negative contributions to the AUC). Maximum temperature rise from baseline (Max $\Delta = T_{maximum} - T_{base}$) following the infusion (before and after bright-light exposure) was also analyzed by repeated measures ANOVA. Data are presented as mean ± SD unless otherwise specified. Data were analyzed with SuperAnova (Abacus Concepts, Berkeley, CA).

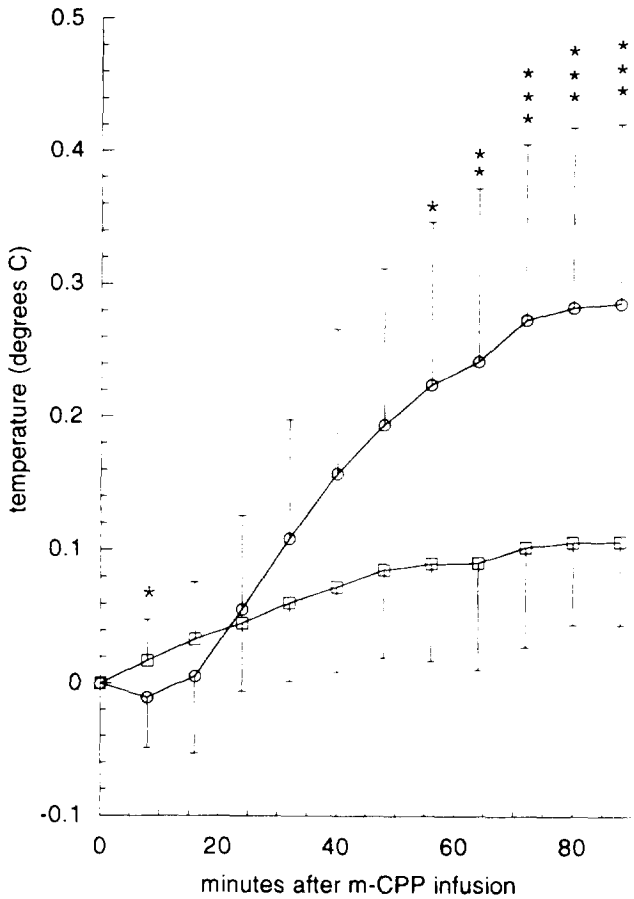

Figure 1. m-CPP (0.08 mg/kg) induces a biphasic response in core rectal temperature. Data are smoothed and corrected to baseline; mean ± SD are shown. Post hoc Bonferroni *t* tests comparing m-CPP to placebo change from baseline: * $p < .05$, ** $p < .01$, *** $p < .001$, o, m-CPP; · · ·, placebo.

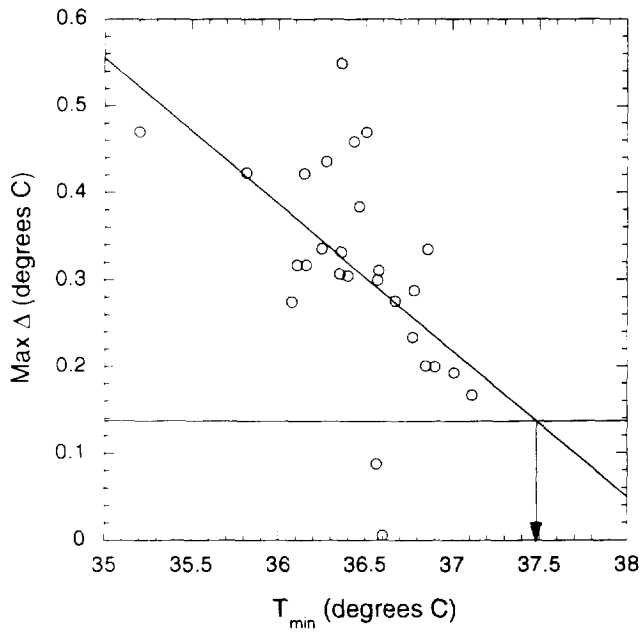

Figure 2. The maximal core hyperthermic response (Max Δ) following m-CPP is proportional to the previous night's core temperature minimum (T_{min}). The graph represents pooled data, with two m-CPP infusions for each subject. See the text for statistics and discussion.

RESULTS

Compared to placebo, m-CPP significantly altered rectal temperature in a biphasic manner (Figure 1 shows drug × time interaction: $F_{(11,132)} = 33.12$, $p < .0001$, analyzed each 8 minutes, three subjects with missing data from one of the infusions). Post hoc Bonferroni *t* tests revealed that, compared to placebo, the maximal hypothermic effect of m-CPP (−0.04°C at 12 minutes) was statistically significant, as was the later hyperthermic effect of m-CPP (+0.17°C at 90 minutes) at all time points from 56 to 90 minutes (analyzed each 8 minutes). There were no significant main or interaction effects of the bright-light exposure on the core rectal temperature response to m-CPP. Furthermore, there were no significant effects of bright-light exposure on any of the measures studied, and no significant differences first and second responses to m-CPP.

Across the individual subjects, m-CPP-induced Max Δ was correlated with the previous night's T_{min} (off lights, $r = -0.66$, $p < .05$; on lights, $r = -0.56$, $p < .05$; pooled data are depicted in Figure 2) and T_{mean} (off lights, $r = -0.55$, $p < .05$; on lights, $r = -0.61$, $p < .05$). Max Δ was also equally well correlated with T_{min} from the night prior to the placebo infusion (i.e., 2 to 4 nights either before or after the night preceding the m-CPP infusion: off lights, $r = -0.79$, $p < .001$; on lights, $r = -0.66$, $p < .01$). Max Δ was not correlated with (1) m-CPP plasma concentrations (at any time or total m-CPP AUC), (2) the baseline rectal temperature immediately preceding the m-CPP infusion, or (3) body weight, either alone as simple regressors or as second regressors when combined with T_{min} in a multiple regression model. Bright-light exposure had no significant effect on the slope of the Max Δ/T_{min} relationship (slopes: off lights, −0.17; on lights, −0.20; repeated measures multivariate test of slopes [Press 1972]: $t = 1.36$, $df = 11$, $p = .20$).

We investigated whether the Max Δ/T_{min} correlations might represent trivial correlates of the intrinsic circadian waveform. That is, subjects with the deepest overnight core temperature descent might have the steepest morning ascent, and hence a greater Max Δ, simply by having an m-CPP-induced response superimposed on a more steeply rising intrinsic temperature waveform. This was examined in two ways. First, slopes were derived for the morning rise in core temperature that occurred from 8:00 to 9:30 A.M. and from 9:00 and 9:30 A.M. There were no significant correlations between these slopes and Max Δ, indicating that the hyperthermic response to m-CPP was independent

of the rate of rise of morning rectal temperature prior to the infusion. Second, there was no correlation between the Max Δ's for the placebo days and the previous night's T_{min} or T_{mean}, indicating that the rate of rise in the intrinsic waveform from 9:30 to 11:00 A.M. was independent of the previous night's nocturnal temperature. Thus, the m-CPP–induced Max Δ/T_{min} relationships were not trivially implicit in the intrinsic circadian waveform.

Examination of the average skin temperature responses at the different body locations (Figure 3) revealed that they were essentially independent of the core temperature response. The progressive increase in average core temperature from 20 to 90 minutes was not accompanied by a progressive decrease in skin temperature (i.e., heat conservation) at any of the sites over the same period of time, and, except for the forehead temperature, there were no statistically significant changes in skin temperature after infusion of m-CPP. In three cases, progressive core hyperthermia was observed despite a progressive increase in temperature (increased heat loss) at all skin sites. Comparison of the Max Δ's following m-CPP in these three experiments with the Max Δ's following placebo revealed a significantly greater Max Δ response for the m-CPP infusions compared with the placebo infusions (0.21 vs. 0.10, $p < .01$).

Nonetheless, we investigated whether some of the interindividual variability in core hyperthermic responses might have been attributable to individual differences in the degree of heat exchange at the peripheral skin sites (taking the component lead baseline-corrected AUCs to represent an approximation of the cumulative heat exchange at each site). We found no significant correlations between peripheral (AUC_{hand}) and core (AUC_{rectal}) responses to m-CPP (off lights: $r = 0.41$, $p = .13$; on lights: $r = 0.39$, $p = .15$), even after T_{min} was included as a regressor for AUC_{rectal} in a multiple regression model. Similar analyses were performed for the temperature responses at the remaining skin sites (including an unweighted mean skin temperature), and no significant correlations were found. Thus, the magnitude of the hyperthermia was only significantly correlated with T_{min} and T_{mean} from the previous night.

m-CPP administration elevated circulating NE plasma concentrations (Figure 4: baseline corrected ANOVA, main effect of drug, $F_{(1,10)} = 10.44$, $p < .01$; five subjects with missing data). We found no correlation between rectal temperature Max Δ and AUC_{NE}, either alone or with T_{min} included in a multiple regression model.

Mean plasma concentrations of m-CPP were maximal at 10 minutes (43.0 ± 33.9 ng/ml), declining fairly

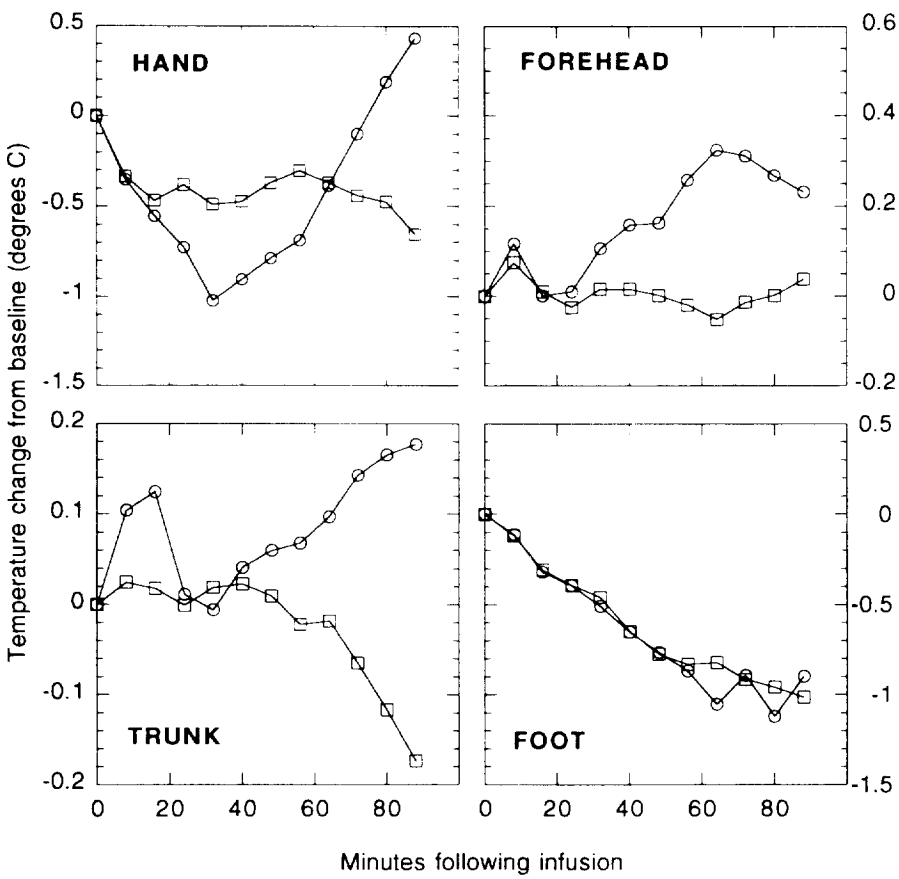

Figure 3. Peripheral skin temperature responses to m-CPP. Drug × time interactions: hand, $F_{(11,132)} = 3.25$, $p = .07$; trunk, $F_{(11,132)} = 0.88$, $p = .59$; foot, $F_{(11,143)} = 0.51$, $p = .60$; forehead, $F_{(11,110)} = 3.46$, $p = .02$. ⊖, m-CPP; ⊟, placebo.

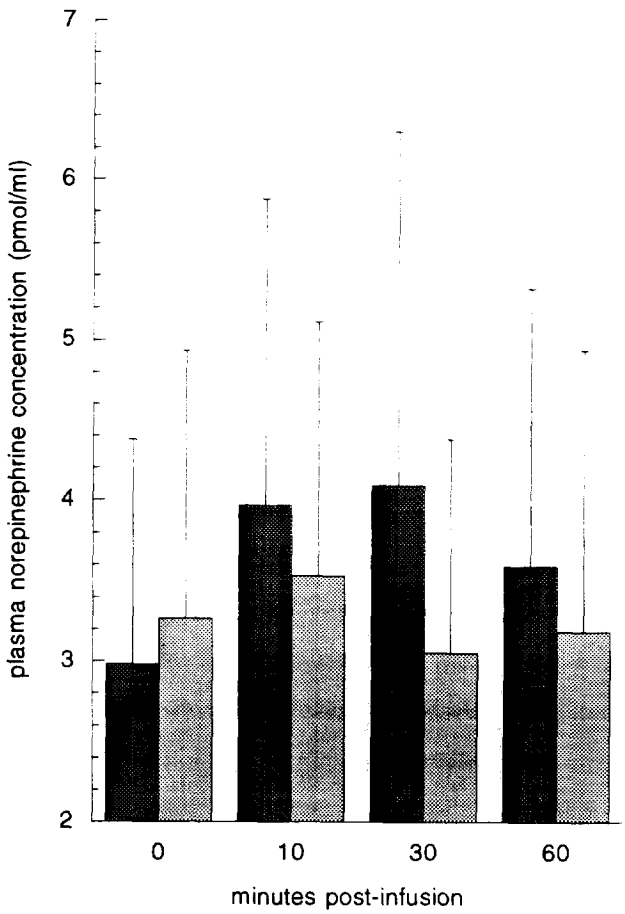

Figure 4. m-CPP (■) induces a significant increase in average plasma NE concentration compared with placebo (□). Mean ± SD are shown.

rapidly by 30 minutes (29.9 ± 10.1 ng/ml), and reaching a relative plateau subsequently (22.4 ± 6.2 ng/ml at 90 minutes). The mean plateau-phase (30 to 90 minutes) m-CPP level was 26.3 ± 6.3 ng/ml. These m-CPP concentrations at the 10-, 30-, and 90-minute time points were slightly lower than those in our prior study (48, 33, and 25 ng/ml, respectively), which used a dose of 0.1 mg/kg intravenous m-CPP (Murphy et al. 1989).

No subjects reported or were observed shivering in any of the experiments. Although the subjective responses to m-CPP were varied, most subjects reported a marked and distinctive "hot flushing" sensation that started minutes after the infusion and spread gradually over the face and torso. This flushing was sometimes accompanied by a burning sensation down the neck and upper back and by truncal sweating.

DISCUSSION

The results of the present experiment are consistent with earlier observations that m-CPP induces oral hyperthermia (0.3 to 0.6°C) in human subjects (Mueller et al. 1985, 1986; Zohar et al. 1987; Lawlor et al. 1989; Murphy et al. 1989; Kahn et al. 1992). This is the first human study in which (1) continuous temperature measurements were obtained, (2) core rectal temperature was documented, (3) skin temperatures were measured, and (4) overnight, pre-m-CPP/placebo baseline core temperatures were measured. These features permitted a more careful dissection of the factors that contributed to the hyperthermic response.

The biphasic, "signoidal" shape (Figure 1) of the average hyperthermic response was characteristic of the individual responses as well, with interindividual variations in response mainly a function of the final temperature attained. Therefore, the lack of a relationship between m-CPP plasma concentrations and the magnitude of these hyperthermic responses suggests that (1) the former is not a significant source of this interindividual variability in the latter, and (2) the latter is probably regulated by a graded response mechanism. Although a dose-response relationship for temperature has yet to be demonstrated in humans (Kahn et al. 1990), m-CPP-induced hyperthermia has been found dose dependent in rats (Wozniak et al. 1989). Further dose-response studies in humans using lower dosages of m-CPP may reveal whether m-CPP's activation of this graded response is dose dependent.

The physiological basis of the hyperthermic response to m-CPP can be inferred from the results of this study. As hyperthermia was observed in three cases despite instances of widespread peripheral vasomotor dilatation (increased heat loss) at all skin sites, heat production must have (1) exceeded the increased heat loss, and (2) contributed significantly to the increase in core temperature. In the absence of overt shivering, the necessary conclusion is that hyperthermia primarily resulted from increased metabolic heat production. This conclusion is further supported by the fact that the skin temperature (vasomotor) responses were inconsistent in direction and magnitude, and quantitatively insignificant in the overall determination of the much more statistically robust core hyperthermia. Although, without EMG recordings, we cannot rule out the possibility of a small increase in asynchronous muscle fiber activity as a cause for some of the heat production, it is improbable that this degree of hyperthermia could be caused by such a mechanism (Kleinebeckel and Klussmann 1990). We also had no quantitative measure of the skin surface/boundary characteristics of heat exchange in response to m-CPP (e.g., sweating). However, our observation that sweating generally increased following m-CPP infusions reinforces the inference that a significant increase in heat production occurred, since hyperthermia was observed despite an apparent increase in evaporative heat loss from sweating.

The inference that m-CPP caused increased metabolic thermogenesis is consistent with a number of

studies in animals which have demonstrated increased oxygen consumption after the administration of serotonergically active compounds (Allen and Marley 1967; Bligh et al. 1974; Even and Nicolaidis 1986; Gordon et al. 1991). Direct intraventricular administration of serotonin or D-fenfluramine (both of which enhance 5-HT_{2C} receptor-mediated activity) has been shown to increase central sympathetic nervous system (SNS) outflow and peripheral NE release, resulting in increased brown adipose tissue (BAT) thermogenesis and oxygen consumption (Steiner and Evans 1976; Rothwell and Stock 1987). Corticotropin releasing hormone (CRH), when released from the paraventricular nucleus of the hypothalamus, also triggers this response (Le Feuvre et al. 1991). Thus, a central serotonergic sympathetic drive mechanism exists in animals, which, when stimulated, induces metabolic heat production. m-CPP's known action at suprahypophyseal sites resulting in increases in CRH and ACTH (Calogero et al. 1990) its consistent with the central serotonergic activation of such a drive mechanism, although the role of BAT thermogenesis in adult humans is controversial (see below). There are also animal (Levitsky et al. 1986) and human (Breum et al. 1990; Stinson et al. 1992) studies in which administration of some serotonergically active compounds (fenfluramine and fluoxetine) failed to increase resting metabolic rate. Thus, the inference that m-CPP–induced hyperthermia was secondary to a centrally mediated increase in metabolic heat production should be confirmed with studies directly measuring oxygen consumption in humans.

The m-CPP–induced elevation of plasma NE concentrations in this study is also consistent with (1) the central activation of SNS outflow, and (2) the m-CPP–induced plasma NE elevation found in rat studies (Bagdy et al. 1988, 1989a, 1989b). Both pithing and splanchnic denervation markedly reduce the NE response to systemically administered m-CPP (Bagdy et al. 1988), and this response was unaffected by pretreatment with the peripheral 5-HT_2 antagonist, xylamidine (Bagdy et al. 1989b). These findings point to a site of action of m-CPP at the brainstem or higher in the neuraxis and also indicate that the bulk of NE release following m-CPP is mainly of peripheral SNS origin. Since the increase in oxygen consumption following exogenously administered NE has been used to quantify BAT thermogenic potential in rodents (Heldmaier et al. 1981; Ellison and Skinner 1990), it is conceivable that the magnitude of m-CPP–induced hyperthermia reflects, in part, the peripheral thermogenic capacity of BAT as well as m-CPP's capacity to increase central SNS outflow.

As BAT is primarily located in the nape of the neck, interscapular area, trunk, pericardial, and perirenal areas, it is of some interest that subjects reported distinct burning sensations on their necks, upper backs, and trunks after the m-CPP infusion. While the role of BAT as an effector of facultative thermogenesis in humans remains uncertain (Himms-Hagen 1985), BAT has been estimated to account for as much as 4% to 7% of resting metabolic rate in humans (Lean et al. 1987), raising the possibility of a significant role for BAT in selected modes of human thermogenesis. Notwithstanding the uncertain role of BAT in m-CPP–induced thermogenesis, systemically administered NE can increase oxygen consumption in humans by as much as 10% to 20% (Karlberg et al. 1962; Joy 1963; Hensel et al. 1973). However, as the NE response to m-CPP was statistically less robust than the core hyperthermic response, and as there was no correlation between the amount of NE release and the core hyperthermia, the findings suggest that the NE release following m-CPP administration may not be a very reliable indicator of thermogenic activity in humans. It is conceivable that epinephrine release following m-CPP administration may be more directly related to m-CPP–induced thermogenesis in humans, although epinephrine increases following m-CPP have not yet been reported in humans. In rats, m-CPP stimulates epinephrine release to an even greater degree than NE (Bagdy et al. 1989b), and human thermogenesis appears more sensitive to epinephrine than to NE (Sjostrom et al. 1983).

We have not ruled out the possibility that m-CPP acts directly on peripheral structures (in addition to CNS sites) to effect some of the postulated increase in metabolic heat production. In rats, however, blockade of peripheral 5-HT_2 receptors by xylamidine (which does not cross the blood-brain barrier) does not alter the capacity of MK-212 (a 5-$HT_{2A/C}$ agonist) to raise core temperature (Gudelsky et al. 1986). Thus, if there are 5-HT receptors on peripheral sympathetic nerves that stimulate thermogenesis (Steiner and Evans 1976), they appear not to participate substantially in the acute hyperthermic response to 5-HT_2 agonists in rats. Since it has been shown that m-CPP–induced hyperthermia in rats is primarily mediated by 5-HT_{2C} receptors (Klodzinska and Chojnacka-Wojcik 1992; Mazzola-Pomietto et al. 1995), it appears that stimulation of central 5-HT_{2C} receptors alone accounts for the hyperthermic response in rats. Further, as m-CPP does not have important activity at β- or α_1-adrenergic receptors, the types of receptors on brown adipocytes that mediate BAT thermogenesis in most animals (Himms-Hagen 1985), direct stimulation (serotonergic or adrenergic) of BAT does not appear to account for the rat hyperthermic response to m-CPP. While m-CPP displays moderate affinity for α_2-adrenergic receptors, it has recently been shown that these receptors are not involved in sympathetically mediated thermogenesis in humans (Blaak et al. 1993). Nevertheless, further experiments are needed to rule out a role of peripheral 5-HT or adrenergic receptors in m-CPP–induced thermogenesis in humans.

The small, but statistically significant drop in core temperature that occurred shortly after m-CPP administration is a new finding. It could have resulted from (1) an immediate onset of sweating and increased evaporative heat loss, (2) a decrease in metabolic heat production, or (3) an increase in vasomotor (skin) heat loss. The patterns of skin temperature responses showed no initial change that could have accounted for this brief, initial hypothermia, and its mechanism remains unknown. While m-CPP has moderate affinity for 5-HT_{1A} receptors, and several 5-HT_{1A} agonists have been shown to lower temperature in humans (Lesch et al. 1989; Anderson et al. 1990) and in other species (Goodwin and Green 1985; Gudelsky et al. 1986; Murphy et al. 1991), m-CPP is an antagonist at 5-HT_{1A} sites (Raffa et al. 1992), and hence a 5-HT_{1A}-mediated effect seems unlikely.

Our finding that the magnitude of the metabolic thermogenesis (Max Δ) induced by m-CPP was proportional to the previous nocturnal (i.e., rest phase) temperature (T_{min} and T_{mean}) can now be placed in context. Considerable evidence shows that sleep or rest-phase temperature is uniquely sensitive to and reflective of the organism's metabolic state. First, Aschoff (1981; Aschoff and Pohl 1970) defined several fundamental cross-species allometric laws by relating basal metabolism to rest-phase temperature. Second, many types of animals maintain metabolic balance by selectively readjusting the level of rest phase core temperature during energetically stressful conditions such as fasting (Ketterson and King 1977; Shapiro and Weathers 1981; Berger and Phillips 1988; Daan et al. 1989), heat and cold stress (Fuller 1984), and circadian (Walker et al. 1983) and seasonal (Heller et al. 1977) torpor.

Several observations suggest that similar thermoregulatory strategies exist in humans. Nocturnal temperature normally undergoes selective readjustment during the different phases of the menstrual cycle (Lee 1988) as well as during certain psychopathological states that may involve perturbations in energy balance, such as mood disorders (Avery et al. 1982; Lund et al. 1983; Von Zerssen et al. 1985; Souetre et al. 1988; Severino et al. 1991) and anorexia nervosa (Okamoto et al. 1991). Our finding that the hyperthermic response to m-CPP in humans was proportional to the level of nocturnal temperature seems consistent with these established relationships between rest-phase temperature and metabolism.

Of particular relevance to the present study are animal studies (Hammel 1968; Heller et al. 1974) that show that the change in metabolic heat production that occurs in response to manipulations of hypothalamic temperature is proportional to the difference between hypothalamic temperature (T_{hy}) and a set-point temperature (T_{set}). In a simple proportional control model, this relationship is summarized as

$$(M - M_0 = \Delta M = \alpha(T_{hy} - T_{set})$$

where M is metabolism, M_0 is basal metabolism, and α is the gain (proportionality constant) (Hammel 1968). In the present context, our formulation becomes

$$\text{Max } \Delta = \alpha(T_{min} - T_{set}).$$

where the parameters represent population statistics rather than individual characteristics. It follows that when $T_{min} = T_{set}$, Max Δ will be zero (not different from placebo). Therefore, in Figure 2, the intersection of the regression line with the horizontal line representing the mean placebo Max Δ approximates the position on the T_{min} axis which corresponds to the location of T_{set}, while the slope corresponds to α. The unique role of the previous night's "masked" (i.e., measured during sleep) T_{min} in predicting Max Δ, as opposed to the apparent independence of Max Δ and diurnal core temperature, suggests that the mechanisms regulating this thermogenic response may be intrinsically linked with the rest phase of the circadian cycle and possibly sleep dependent.

As noted earlier, since both clinical depression and antidepressant treatment are associated with changes in the level of nocturnal temperature, it would be of interest to know whether such thermoregulatory changes result from deviations in α, T_{set}, or both. At the level of the individual neuron, the firing characteristics of thermosensitive neurons in the rodent hypothalamus are modified by both temperature (Parmeggiani et al. 1987; Hori 1991) and serotonin (Hori 1991). A recent report indicates that neuronal responsivity to serotonin is modified by temperature in hamsters (Horrigan and Horowitz 1990). In light of studies demonstrating that antidepressants, which are thought to enhance serotonin function, lower nocturnal hypothalamic temperature in hamsters (Brown and Seggie 1988; Duncan et al. 1995), it is possible that one mechanism of antidepressant action is to alter the thermoregulatory characteristics of hypothalamic neurons. Further clinical research is needed to elucidate the circuitry regulating human mood and thermoregulation.

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