ORIGINAL ARTICLE

Serotonin 1A Receptors, Melatonin, and the Proportional Control Thermostat in Patients With Winter Depression

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Background: In patients with seasonal affective disorder, light treatment lowers core temperature during sleep in proportion to its antidepressant efficacy. The regulation of the level of core temperature during sleep is linked with a proportional control thermostat in the central nervous system whose operation appears abnormal in patients with seasonal affective disorder. Because both melatonin and serotonin 1A receptor activation also lower core temperature, we investigated the relationship between (1) endogenous melatonin and core temperature profiles, (2) the proportional control thermostat, and (3) the core hypothermic response to the serotonin 1A receptor partial agonist ipsapirone hydrochloride in patients with seasonal affective disorder and healthy controls.

Methods: Eighteen patients with seasonal affective disorder and 18 controls first completed a 24-hour study in which their melatonin profiles were characterized. Subjects then returned 3 to 5 days later for the first of 2 drug challenges (ipsapirone hydrochloride, 0.3 mg/kg, or placebo), each separated by 3 to 5 days. Overnight rectal and facial temperatures were recorded before and after each drug challenge.

Results: The magnitudes of the core hypothermic responses to ipsapirone were (1) not different between groups and (2) independently correlated with both the levels of the previous nights' core temperature minima ($P = .002$) and the amounts of nocturnal melatonin secreted ($P < .001$).

Conclusion: The daytime regulation of core temperature by serotonin 1A receptors appears normal in seasonal affective disorder. The magnitude of serotonin 1A receptor–activated hypothermia is governed by a central nervous system proportional control thermostat whose operation appears modulated by both melatonin and the level of the core temperature minimum.

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WE AND OTHERS have investigated the hypothesis that many of the symptoms of winter depression[1,2] are associated with central serotonergic (5-HT) dysfunction. In related lines of investigation, we have also examined the role of photoperiodic[3,4] and thermoregulatory[5,6] mechanisms in seasonal affective disorder (SAD). With regard to photoperiodism, endogenous nocturnal melatonin secretion, which is regulated by the amount of exogenous light exposure,[7,8] lowers the level of core temperature during sleep.[9,10] With regard to thermoregulation, bright-light treatment, like melatonin and like other effective antidepressants,[11,12] also lowers the level of core body temperature during sleep,[5,6,13] and the magnitude of this temperature reduction is proportional to the degree of mood improvement in patients with winter depression.[6]

We recently described the existence of a central nervous system proportional control thermostat in humans that links the mechanisms that govern the level of core temperature during sleep with mechanisms that govern several other homeostatic responses to stress (in addition to mood).[6,14] The existence of such a thermostat was suggested after the observation that the magnitude of hyperthermia induced by meta-chlorophenylpiperazine (m-CPP) was directly proportional (by a factor known as the gain) to the difference between the core temperature minimum during sleep (T_{min}) and a threshold temperature (the set point, or T_{set}). In addition, it was observed that the light treatment–induced changes in the amount of somatotropin secreted were also proportional to the corresponding light treatment–induced changes in the level of T_{min}, suggesting that somatotropin secretion was also governed in part by this proportional control thermostat. In patients with

SUBJECTS AND METHODS

SUBJECTS

Patients with SAD and healthy controls were recruited through the local media and were studied between November 17, 1993, and March 15, 1994. Patients were required to (1) meet the diagnostic criteria of Rosenthal et al[1] for SAD and (2) be medically healthy, as determined by physical examination and routine laboratory tests. Patients with a lifetime history of a second Axis I comorbid condition (n = 3; 2 with past substance abuse, 1 with past panic disorder) were accepted into the program provided this condition had been in remission for more than a year before the study. Exclusion criteria were (1) the ingestion of any mood-regulating medications within 3 months before the study, (2) a history of migraine headaches,[29] (3) pregnancy, and (4) smoking.

Healthy controls, matched to patients by sex and age, were required to (1) have had no personal or family history (first-degree relatives) of any Axis I psychiatric condition, as determined by the Structured Clinical Interview for *DSM-IV*,[30] and (2) be medically healthy (as above).

Each group contained 13 women and 5 men. There were no group differences in age (patients with SAD, 38.9 ± 9.2 years; controls, 38.6 ± 9.8 years; $P>.70$), weight (patients with SAD, 68.5 ± 12.9 kg; controls, 74.5 ± 17.9 kg; $P>.25$), or body mass index (patients with SAD, 24.5 ± 3.6 kg/m^2; controls, 25.1 ± 4.4 kg/m^2; $P>.67$).

STUDY DESIGN

The patient-control pairs were scheduled for the melatonin study when the patient scored either (1) at least 14 on the 21-item Hamilton Depression Rating Scale[31] or (2) at least 12 on the Hamilton Depression Rating Scale and a total of 20 on the Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder Version (SIGH-SAD,[32] a scale combining the Hamilton Depression Rating Scale and a supplementary 8-item atypical symptom scale). On the day of the melatonin study, 11 patients met *DSM-IV* criteria[33] for current major depression, and 7 met *DSM-IV* criteria for current minor depression. All participants were instructed to abstain from alcohol consumption and over-the-counter medications for at least 2 weeks before all study procedures.

During the inpatient melatonin study (which lasted from 4 PM to 4 PM and was performed under continuous dim light,<1 lux), subjects sat upright in a lounge chair during their habitual waking hours, and slept reclining in bed during their habitual sleep hours (sleep-wake schedules determined by sleep logs), while having their blood drawn via an indwelling intravenous catheter every 30 minutes (see Schwartz et al[34] for complete methodological details). Subjects returned to the hospital 3 to 5 days later for the first of 2 drug challenges, each of which was separated by 3 to 5 days. For these 2 procedures, subjects slept overnight (11 PM to 6:45 AM,<1 lux) with cheek, forehead, and rectal temperature recordings (see Schwartz et al[34] for methodological details). At 6:45 AM, dim lights (30 lux) were turned on. Subjects then went to the bathroom, returned to bed (head now elevated to 45°), and read quietly. By 9 AM, a SIGH-SAD rating (covering the previous 2 days) was obtained by an experienced rater who was blind to drug condition. At 9 AM, either ipsapirone hydrochloride (0.3 mg/kg, rounded to the nearest 5 mg) (Miles Pharmaceutical Division, West Haven, Conn) or placebo (in identical capsules) was administered orally according to a balanced, randomized, double-blind design (mean dosages: patients with SAD, 20.8 ± 4.6 mg; controls, 21.9 ± 5.2 mg; $P>.52$). Exactly half the patients and half the controls received ipsapirone first.

For menstruating women, all 3 procedures were confined to 1 phase of the menstrual cycle. Six of the SAD-control women pairs were studied in the follicular phase, 4 pairs were studied in the luteal phase, and in 3 pairs the phase was indeterminate (1 pair continuing their use of birth control pills).

Before all studies, participants were briefed fully about the nature and purpose of the research, and written informed consent was obtained. The protocol was approved by the National Institute of Mental Health institutional review board.

HORMONAL ASSAYS

Melatonin specimens were assayed by radioimmunoassay (StockGrand; Guildford, Surrey, England). Details of the blood-drawing procedures and assay are available on request. The limit of detection of the assay was 5 pg/mL.

STATISTICS

Comparisons between groups on the melatonin profiles (ie, timing of onsets and offsets, durations, and areas under curves [AUCs]) were analyzed with 1-factor analyses of variance (ANOVAs). *Melatonin onsets (offsets)* were defined as the time 15 minutes before (after) the first (last) sample that was above the detection threshold. The analyses of the overnight temperature profiles from the 2 nights before the drug challenges have been reported previously.[34] Since forehead and cheek temperatures behaved essentially similarly both overnight and after drug administration in the morning, only the cheek temperature results are reported here. The levels of the overnight T_{min} on the nights before the drug challenges were extracted from the raw data to assess correlations between T_{min} and other variables.

The morning baseline temperature values were analyzed by means of ANOVAs with 2 grouping factors (diagnosis, order of drug condition) and 1 repeated measure (drug condition). The induced effects of ipsapirone vs placebo on these measures were assessed with baseline-corrected, full-interaction ANOVAs, with 2 grouping factors (diagnosis, order of drug condition) and 2 repeated measures (drug condition, time). These baseline corrected data were also used to calculate AUCs (trapezoid rule), which were then used to generate correlations between variables. Melatonin samples below the detection threshold were treated as zero (baseline). Henceforth, all AUCs reported are baseline-corrected AUCs.

The data for the all variables appeared normally distributed, and all data points were within 3 SDs of their respective means. Values reported are means ± SDs unless otherwise specified. All tests were 2 tailed, and significance level was set at $P<.05$. Greenhouse-Geisser corrections were included in all ANOVAs. Statistical analyses were performed with SuperANOVA and StatView 4.01 (Abacus Concepts, Berkeley, Calif).

There were no differences between groups or drug conditions in ambient room temperatures during either the overnight recordings (23.62°C ± 0.95°C) or the morning experiments (23.97°C ± 0.90°C).

SAD, this proportional influence of T_{min} on somatotropin secretion was significantly abnormal, further suggesting that disturbances of this thermostat play a role in the pathogenesis of SAD.

For these and the following reasons, we decided to investigate further the potential involvement of both serotonin 1A ($5\text{-}HT_{1A}$) receptors and endogenous melatonin in the operation of this thermostat in patients with SAD. First, $5\text{-}HT_{1A}$ receptors are located on neurons that regulate overall brain 5-HT metabolism[15] and modulate the organism's responsiveness to light.[16,17] Second, systemic administration of $5\text{-}HT_{1A}$ agonists is associated with dose-dependent reductions in core temperatures in healthy humans[18-21] that are blunted in some patients with nonseasonal depression.[22,23] Third, melatonin, in addition to its capacity to lower core temperature, is a major modulator of serotonin metabolism in a variety of brain regions in animals.[24,25]

Ipsapirone hydrochloride is a relatively selective partial agonist for $5\text{-}HT_{1A}$ receptors, having greater than 10 times the affinity for $5\text{-}HT_{1A}$ receptors compared with other known 5-HT, α-adrenergic, or dopamine receptors (pK_i [negative logarithm of the inhibition constant]: $5\text{-}HT_{1A}$, 7.7; α_1-adrenergic, 6.6; $dopamine_2$, 6.4; α_2-adrenergic, 5.6; $5\text{-}HT_{2A}$, 5.1; $5\text{-}HT_{1D}$, 4.9; $5\text{-}HT_{2C}$, 4.5; and $5\text{-}HT_3$, <5[26-28]). Therefore, in the present study, we administered oral ipsapirone vs placebo to 18 patients with SAD and 18 healthy controls, several days after all subjects first participated in a study in which their melatonin profiles were measured. We hoped to further characterize (1) the integrity of the mechanisms associated with $5\text{-}HT_{1A}$–mediated hypothermia in SAD, and (2) the potential relationship of this hypothermic response to both the level of core temperature during sleep and endogenous nocturnal melatonin secretion. Specifically, we hypothesized that, like m-CPP–induced hyperthermia, the magnitude of ipsapirone-induced hypothermia would be regulated proportionally, ie, would correlate with T_{min}. The behavioral and neuroendocrine measures from the present study will be reported elsewhere, as will the overall results from the multiyear melatonin study.

RESULTS

MELATONIN PROFILES

There were no differences between groups in any measure of nocturnal melatonin secretion (onset: patients with SAD, 20:04 ± 1:13 hours; controls, 20:10 ± 1:16 hours; $P>.79$; offset: patients with SAD, 9:01 ± 1:25 hours; controls, 9:07 ± 2:07 hours; $P>.89$; duration: patients with SAD, 12:59 ± 1:21 hours; controls, 12:56 ± 1:57 hours; $P>.96$; 24-hour melatonin AUC: patients with SAD, 667 ± 206 pg · h/mL; controls, 779 ± 363 pg · h/mL; $P>.26$).

OVERNIGHT TEMPERATURE PROFILES BEFORE DRUG CHALLENGES

These have been reported elsewhere.[34] Briefly, overnight mean cheek temperatures (1) were significantly lower in patients with SAD than in controls (patients with SAD, 34.35°C ± 0.82°C; controls, 34.83°C ± 0.63°C; $P<.05$) and (2) were significantly correlated with overnight mean rectal temperatures (on both nights) in controls ($r = 0.56$, $P<.05$ and $r = 0.63$, $P<.01$, respectively), but not in patients with SAD ($r = 0.37$, $P>.17$ and $r = 0.23$, $P>.34$, respectively). Overnight mean and minimum rectal temperatures were not different between groups (means: patients with SAD, 36.79°C ± 0.33°C; controls, 36.86°C ± 0.29°C; $P>.41$).

BASELINE MEASURES BEFORE DRUG CHALLENGES

Mean SIGH-SAD scores were greater for patients than for controls (patients with SAD, 21.8 ± 8.5; controls, 3.0 ± 2.9; $F_{1,32} = 88.51$, $P<.001$). There were no significant group differences in either rectal (patients with SAD, 36.98°C ± 0.31°C; controls, 37.06°C ± 0.28°C; $F_{1,27} = 1.07$, $P>.44$; 5 subjects with missing data) or cheek (patients with SAD, 34.42°C ± 0.48°C; controls, 34.54°C ± 0.59°C; $F_{1,29} = 0.43$, $P>.51$; 3 subjects with missing data) temperatures.

BASELINE-CORRECTED MEASURES AFTER DRUG ADMINISTRATION

Compared with placebo, ipsapirone was associated with significant reductions in both rectal temperatures (main effect of drug: $F_{1,27} = 48.74$, $P<.001$; 5 subjects with missing data; data analyzed every 12 minutes) and cheek temperatures ($F_{1,29} = 30.84$, $P<.001$; 3 subjects with missing data), with no differences between groups (**Figure 1**).

There were no differences between groups in ipsapirone concentrations (mean peak levels: patients with SAD, 106 ± 89 µg/L; controls, 101 ± 58 µg/L; $F_{1,31} = 0.04$, $P>.83$; 3 subjects with missing data).

CORRELATIONS BETWEEN THE VARIABLES

Ipsapirone level AUCs correlated with ipsapirone-induced cheek temperature AUCs in both patients and controls ($r = 0.66$, $P<.001$), but not with ipsapirone-induced rectal temperature AUCs ($r = 0.08$, $P>.67$). There was no correlation between the ipsapirone-induced cheek and rectal temperature AUCs ($r = 0.19$, $P>.29$).

To test our hypotheses about the potential involvement of the proportional control thermostat and of melatonin secretion in the regulation of $5\text{-}HT_{1A}$–mediated hypothermia, we generated correlations between T_{min}, melatonin, and the rectal temperature AUCs after ipsapirone administration. There was a significant linear correlation between the level of the overnight T_{min} and the rectal temperature AUCs after ipsapirone administration ($r = -0.38$, $P<.05$; **Figure 2**, top). Rectal temperature AUCs after ipsapirone administration were also linearly correlated with the melatonin AUCs ($r = 0.52$, $P<.005$), but not with the duration of nocturnal melatonin secretion ($r = 0.24$, $P>.18$). In a multiple regression model, the rectal temperature AUCs after ipsapirone administration were significantly and independently correlated with both the level of the overnight T_{min} and the melatonin AUCs (T_{min}, $F_{1,30} = 11.63$,

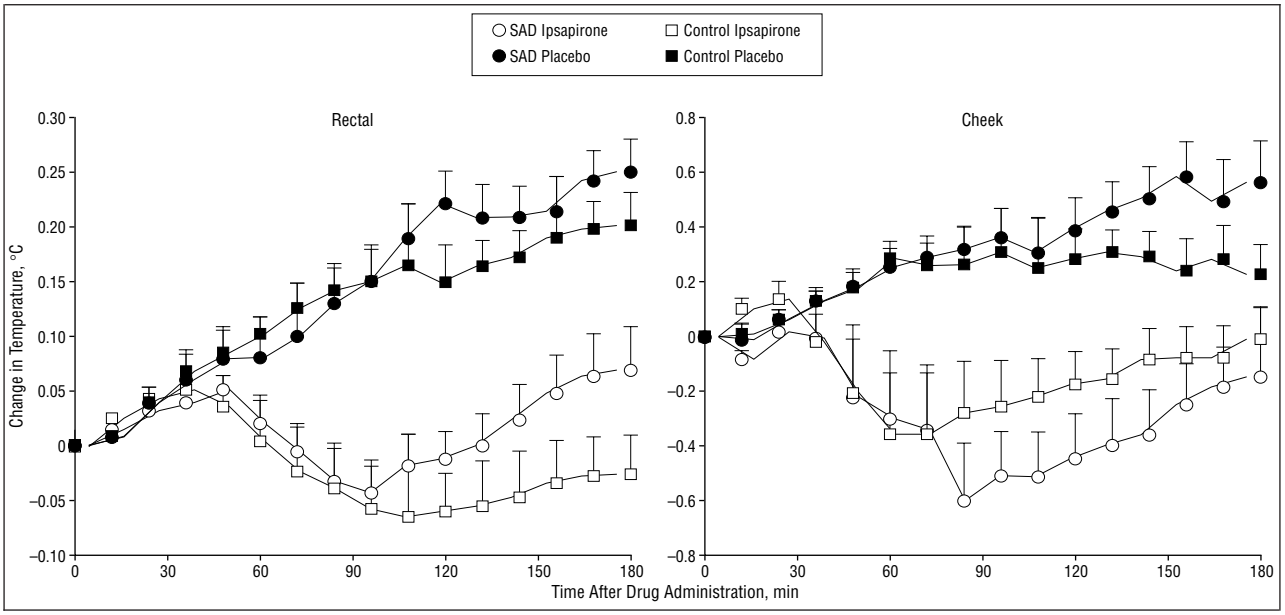

Figure 1. *Rectal and facial temperature responses to ipsapirone hydrochloride and placebo. Error bars represent SEMs. See "Results" for statistics. SAD indicates seasonal affective disorder.*

$P = .002$; melatonin AUC, $F_{1,30} = 18.32$, $P < .001$; correlation coefficient between T_{min} and melatonin AUCs, –0.13; overall model, $r = 0.69$, $P < .001$). There were no differences between groups in this model.

In an exploratory expansion of the above multiple regression model, habitual sleep length was found to be a third significant orthogonal regressor of the rectal temperature AUCs after ipsapirone administration ($P < .05$).

Rectal temperature AUCs after placebo administration were independent of both the previous night's T_{min} ($r = 0.15$, $P > .42$) and the melatonin AUCs ($r = 0.13$, $P > .40$) when considered either separately, or together in a multiple regression model. Cheek AUCs after ipsapirone adminstration were independent of both T_{min} ($r = 0.02$, $P > .91$) and the melatonin AUCs ($r = 0.06$, $P > .73$).

We found no significant effects of either sex or menstrual cycle. In the above multiple regression model, both T_{min} and melatonin AUCs were significant regressors of the rectal temperature AUCs in women who were studied during the follicular phase ($P < .05$ and .01, respectively) as well as in women who were studied during the luteal phase ($P < .05$ and .05, respectively).

COMMENT

The main findings of this investigation are that (1) the rectal and facial temperature responses to ipsapirone were similar between groups, (2) the levels of the overnight T_{min} and the nocturnal melatonin profiles (AUCs) were similar between groups, and both were significantly and independently correlated with the rectal temperature AUCs after ipsapirone administration, and (3) overnight facial temperatures were regulated abnormally in patients with SAD compared with controls.

Since the hypothermic effect of 5-HT_{1A} agonists is generally blocked by 5-HT_{1A} receptor antagonists in both animals[35-37] and humans,[20,21,38] but not by antagonists at other 5-HT receptor subtypes, this hypothermia is likely directly mediated by 5-HT_{1A} receptors (however, see Durcan et al[39] and Patel and Hutson[40]). Therefore, insofar as the rectal temperature responses to ipsapirone were similar between groups, the core body temperature–regulating function of 5-HT_{1A} receptors in patients with SAD would appear to be normal (at least during the morning hours, when the ipsapirone was administered). A power analysis lends further support to this conclusion, as it would have been necessary to study 178 subjects to detect a significant difference between groups with a power of 0.8 and an α of .05. Blunted oral hypothermic responses to 5-HT_{1A} agonists have been found in some[22,23] (but not all[41]) previous studies of patients with nonseasonal depression. Conceivably, the lack of hypercortisolemia in our patients with SAD (data not presented) accounts for their normal core temperature responses to ipsapirone.[42-44]

Although we also found no differences between groups in the cheek temperature responses to ipsapirone, patients with SAD did exhibit several abnormalities in the regulation of their cheek temperatures during sleep on the nights before the drug challenges. These cheek temperature abnormalities during sleep have subsequently been completely replicated in a separate group of 23 patients with SAD and 23 healthy controls (P.J.S., E. H. Turner, MD, N. Kajimura, MD, N.E.R., and T.A.W., unpublished data, 1996). In the present context, we simply note that (1) such differences in overnight facial temperatures may reflect differences in the degree of underlying facial blood flow, which in turn may reflect differences in the degree of overnight brain cooling activity,[34] and (2) facial blood flow is regulated by several brainstem nuclei, including the 5-HT_{1A} receptor–rich dorsal raphe nucleus.[45,46] Therefore, while the overnight cheek temperature abnormalities in patients with SAD bear an uncertain relationship to 5-HT_{1A} receptors (as well as to the endogenous melatonin profile and the proportional

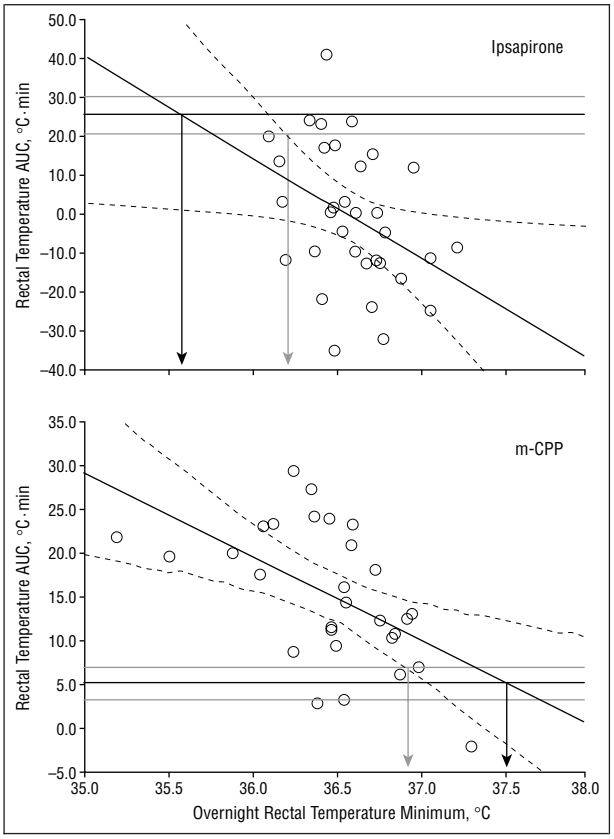

Figure 2. *Thermoregulatory responses to ipsapirone hydrochloride (top) and meta-chlorophenylpiperazine (*m*-CPP) (bottom). Top, The hypothermic responses to ipsapirone are negatively correlated with the levels of the core temperature minima during sleep (T_{min}) from the previous night. The thick regression line is bounded by 2 thin curves that demarcate the 95% confidence interval (CI) for the means of the ipsapirone-induced rectal temperature areas under the curve (AUCs). The thick horizontal line represents the mean for the placebo-induced rectal temperature AUCs, which were independent of T_{min} (data points not presented for clarity). The thin horizontal lines demarcate the 95% CI for the mean of the placebo-induced rectal temperature AUCs. The intersection of the 2 thick lines marks the location of the set point for the activation of ipsapirone-induced hypothermia (thick arrow). The thin arrow, located at the intersections of the boundaries of the respective 95% CIs, represents our "uppermost estimate" for this set point. The likelihood that the actual set point (ie, the projection onto the T_{min} axis of the intersection of the 2 thick lines of means) falls below this uppermost estimate is 97.5% × 97.5% = 95.1% (17 depressed patients with seasonal affective disorder and 16 controls). Bottom, Same as top, except that the data are from the "off-lights" condition of our previous* m*-CPP experiment (14 depressed patients with seasonal affective disorder and 15 controls). The thin arrow represents our lowermost limit for the set point for the activation of* m*-CPP–induced hyperthermia. The likelihood that the actual set point falls above this lowermost limit is 95.1%. Therefore, the likelihood that the set points for the activation of ipsapirone-induced hypothermia and* m*-CPP–induced hyperthermia both fall between the interval defined by the 2 thin arrows is less than 2.5%.*

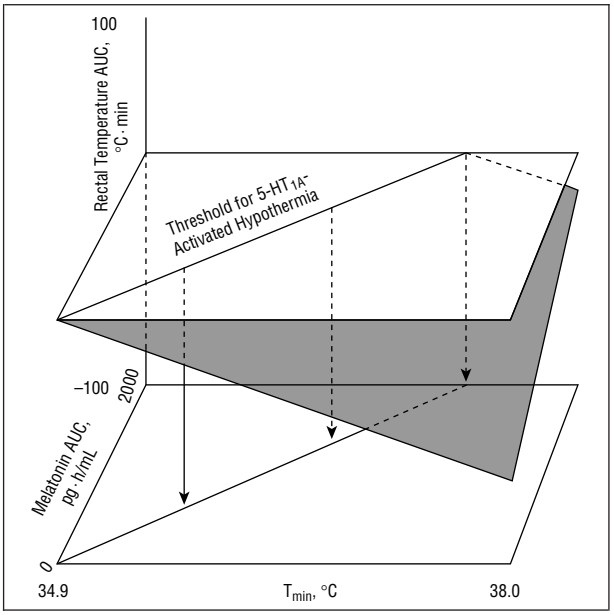

Figure 3. *Schematic representation of the multiple regression model of the proportional control thermostat. The data for the placebo-induced rectal temperature areas under the curve (AUCs), which were independent of both core temperature minima during sleep (T_{min}) and the melatonin AUCs, are represented by the upper, white horizontal plane. The data for the ipsapirone hydrochloride–induced rectal temperature AUCs are represented by the tilted, shaded plane. The line of intersection of these 2 planes represents the threshold for the activation of ipsapirone-induced hypothermia. This threshold (the orthogonal projection of which is depicted on the lower, white horizontal plane) depends on both T_{min} and the melatonin AUCs. 5-HT_{1A} indicates serotonin 1A. See "Comment" for further explanation.*

control thermostat[47]), we cannot rule out the possibility that there are regulatory processes involving 5-HT_{1A} receptors that are specifically and manifestly nocturnal and that are dysfunctional in SAD.[14]

The significant linear correlation between the rectal temperature AUCs after ipsapirone administration and T_{min} (Figure 2, top) supports our hypothesis that a proportional control mechanism regulates this hypothermic response. Together with our previous experiments using m-CPP (Figure 2, bottom), the results indicate that the absolute level of T_{min} during sleep reflects an important determinant of the magnitude of several serotonergically activated homeostatic metabolic processes. Note that the temperature set point (T_{set}) for the activation of ipsapirone-induced hypothermia (ie, the "melatonin-independent" T_{set}, derived without regard to the additional significant correlation between T_{min} and the melatonin AUCs) appears to be lower than the T_{set} for the activation of m-CPP–induced hyperthermia. These upper and lower temperature set points may be related to the operating parameters that influence the thermoneutral zone,[48,49] basal metabolism,[14,50] sleep length,[51] and/or the circadian amplitude of core body temperature.[52-54] Given that changes in the level of T_{min}, sleep length, and body weight are not only frequent, but variable manifestations of the different subtypes of depression,[55] these thermostat parameters are of some interest.

In the multiple regression model (**Figure 3**), the additional significant correlation between the rectal temperature AUCs after ipsapirone administration and the overnight melatonin AUCs ($P<.001$) suggests that melatonin directly[56,57] or indirectly[58] modulates the expression of this centrally mediated, 5-HT_{1A} receptor–activated core hypothermic response. The model further suggests that the threshold for the activation of 5-HT_{1A}–mediated hypothermia depends on both T_{min} and the endogenous melatonin profile. Such a thermomodulatory role for the action of endogenous melatonin (1) is consistent with several other studies indicating that endogenous melatonin secretion is associated with reductions in core temperature in humans,[9,10] (2) is consistent with an array of observations regarding the thermoregulatory role of melatonin in animals,[59] and (3)

may help to explain the observation that melatonin-induced hypothermia appears to be a threshold event in humans.[60]

There are several limitations to this study. First, the correlations involving the melatonin AUCs are based on data from the melatonin study obtained 3 to 10 days before the data from the ipsapirone study. Second, our estimation of the T_{set} for ipsapirone-induced hypothermia depends on a linear extrapolation that extends somewhat beyond the actual range of the observed T_{min}. As such, one cannot be certain either that a linear relationship still holds in this region, or that the estimate of T_{set} is entirely accurate. Third, several patients with SAD experienced partial remissions in their depressions after the melatonin study and were only mildly depressed at the time of the ipsapirone study. However, removing these less-depressed patients from the analyses did not lead to any changes in our results or power analyses.

CONCLUSIONS

We have further characterized several of the operating parameters of the proportional control thermostat, namely (1) the set point for 5-HT_{1A}–mediated hypothermia and (2) the dependence of this set point on both the level of core temperature during sleep and on the AUC of the endogenous melatonin profile. Although abnormalities of this thermostat have been implicated previously in SAD, the present study suggests that such thermostat abnormalities do not include 5-HT_{1A} receptor-mediated heat loss.

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