ORIGINAL ARTICLE

Hormonal and Subjective Responses to Intravenous *m*-Chlorophenylpiperazine in Women With Seasonal Affective Disorder

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Background: There is emerging evidence of serotonergic dysfunction in patients with seasonal affective disorder (SAD). We examined central serotonergic function in female patients with SAD (fall-winter pattern) by means of neuroendocrine and subjective responses to the postsynaptic serotonin receptor agonist *m*-chlorophenylpiperazine.

Methods: Using a double-blind, randomized, placebo-controlled design, we assessed neuroendocrine and subjective responses to *m*-chlorophenylpiperazine (0.1 mg/kg intravenously) and placebo in 14 unmedicated female patients with SAD in the depressed state and 15 female normal controls. All testing was done in the fall-winter months and during the follicular phase of the menstrual cycle. Plasma prolactin and cortisol levels were used as neuroendocrine measures, while subjective responses were assessed by means of visual analog scales of 10 mood states.

Results: On the basis of net responses to *m*-chlorophenylpiperazine (placebo effects subtracted from drug effects), patients with SAD exhibited blunted prolactin responses and less sadness than normal controls in response to the drug. When order of presentation of drug and placebo was taken into consideration, altered "calm" and "high" responses were also found in the patient group.

Conclusion: Evidence of dysfunction at or downstream to central serotonergic receptors in female patients with SAD confirms and extends findings from previous research.

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WINTER SEASONAL affective disorder (SAD) is a relatively poorly understood illness characterized by recurrent onset of depression in the fall-winter months, with spontaneous recovery in the spring-summer period.[1] The typical patient with SAD is a premenopausal woman who experiences subjective dysphoria with hypersomnia, profound fatigue, hyperphagia, and carbohydrate craving while depressed.[1] Much initial work on the cause and pathophysiological features of SAD focused on the possible role of altered melatonin secretion and/or circadian rhythms in this disorder.[2-6] While these factors may be important in individual patients, work in this area has not conclusively demonstrated a primary role for these mechanisms in SAD, establishing a need for other etiological models of this disorder.

Emerging evidence suggests a possible role for the neurotransmitter serotonin in the cause and pathophysiological features of SAD. Several studies have demonstrated clear seasonal changes in serotonin metabolism,[7-10] with most measures pointing to decreased serotonin metabolism in the winter. Serotonin has been implicated in mood regulation,[11-21] satiety mechanisms,[22-26] and sleep,[27,28] all of which are abnormal in the SAD population.[29-31] A variety of serotonergic agents, including D-fenfluramine,[32] tryptophan,[33] and fluoxetine,[34,35] have been found effective in SAD. On the other hand, rapid depletion of the serotonin precursor tryptophan has been shown to reverse the antidepressant effect of light therapy in SAD.[36] Patients with SAD report increased activation after high-carbohydrate meals, while normal controls feel more sedated,[37] which may be consistent with altered tryptophan and serotonin metabolism in the SAD population; dietary carbohydrates are believed to enhance serotonin synthesis and transmission via increased tryptophan uptake into the brain.[38,39]

There is preliminary evidence of abnormal neuroendocrine responses to both presynaptic and postsynaptic serotonergic agents in SAD. Abnormal responses to

PATIENTS AND METHODS

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

The SAD group consisted of 14 consecutive female outpatients who came to the Mood Disorders Clinic of the Clarke Institute of Psychiatry, Toronto, Ontario. They ranged in age from 20 to 45 years, met *DSM-III-R*[53] criteria for major depression with a seasonal pattern based on the mood disorders section of the Structured Clinical Interview for *DSM-III*,[54] and scored 20 or greater on the 29-item Hamilton Depression Rating Scale (HDRS)[55]; this version of the HDRS includes an 8-item addendum designed to assess the "atypical" symptoms of depression commonly seen in SAD.[56]

Patients were excluded from the study if they were acutely suicidal or currently involved in substance abuse. All subjects with SAD were untreated for at least 8 weeks at the time of entry to the study.

The normal control group consisted of 15 healthy volunteer female subjects, aged 20 to 45 years, with no history of psychiatric illness or substance abuse based on a modified version of the Schedule for Affective Disorders and Schizophrenia[57] administered by a psychiatrist (R.D.L.). Controls were recruited through posters and announcements distributed at the University of Toronto.

All subjects were nonpregnant, had no notable medical illnesses, and had regular mentrual cycles during the 3 months before their study date. Menstrual phase was documented by self-report, defined as follows: days 0 to 5, menstrual; days 5 to 14, follicular; and days 14 to menses, luteal. All subjects were tested during the follicular phase to control for possible effects of menstrual cycle on serotonergic function. Each subject underwent a routine physical examination and laboratory tests, including an electrocardiogram and blood work. Each subject was given an oral and written summary of the purposes, procedures, and potential risks of the project and gave informed consent. Testing was first done from October 1, 1994, through March 31, 1995, and then from October 1, 1995, through March 31, 1996.

PREPARATION OF *m*-CHLOROPHENYLPIPERAZINE

Dry *m*-chlorophenylpiperazine–dihydrochloride powder (1500 mg) (Research Biochemicals, Natick, Mass) was diluted with 500 mL of normal saline solution to create a 3-mg/mL solution (based on the salt with molecular weight of 269.7). Sodium hydroxide solution was added to bring the final pH to 5.15. Under sterile conditions, the solution was passed through a 0.22-µm polymer filter. A portion was obtained for pyrogen and sterility testing and the remainder packaged in sterile 10-mL vials in 5-mL aliquots.

m-CHLOROPHENYLPIPERAZINE TEST PROCEDURE

All subjects were admitted to the clinical investigation unit of The Toronto Hospital in the evening before the first challenge and were given nothing orally (except for clear fluids) after 8 PM. On the evening of admission, patients completed the Beck Depression Inventory[58] and were administered the 29-item HDRS by one of the study investigators (R.D.L.).

At 7 the next morning, an indwelling venous catheter was inserted in a forearm vein and kept patent with normal saline solution. At 8 AM, vital signs were taken and, by means of a double-blind procedure, an injection of either *m*-chlorophenylpiperazine, 0.1 mg/kg, or normal saline was administered over 10 minutes. On each day, the test solution was diluted in 50 mL of normal saline for intravenous administration. Blood samples were taken at –15, 0, 30, 60, 90,

Continued on next page

the nonselective serotonergic agonists 5-hydroxytryptophan (HT) and D,L-fenfluramine have been reported.[40,41] The postsynaptic agent *m*-chlorophenylpiperazine has been found to produce elevated subjective reports of activation-euphoria[42,43] and blunted corticotropin responses[43] in patients with SAD compared with controls. Blunted growth hormone responses to the 5-HT-1D receptor agonist sumatriptan also have been reported.[44]

Interpretation of neuroendocrine challenge tests in SAD to date has been problematic because of the lack of double-blind, placebo-controlled designs in most studies, inclusion of both male and female subjects, and failure to control for menstrual status in female subjects. Given these limitations of previous research, we examined central serotonergic function in depressed female patients with SAD during the follicular phase of the menstrual cycle, using neuroendocrine and subjective responses to intravenous *m*-chlorophenylpiperazine and placebo. *m*-Chlorophenylpiperazine is a postsynaptic serotonin receptor agonist known to reliably stimulate release of prolactin and cortisol in normal human subjects in a safe manner.[45] *m*-Chlorophenylpiperazine binds with highest affinity to 5-HT-2c receptors, but also binds to 5-HT-1a, 5-HT-2, and moderately to α_2-noradrenergic receptors.[46,47] Studies with *m*-chlorophenylpiperazine in humans indicate that its hormonal and behavioral effects (eg, anxiety production) are serotonergically mediated.[45,48,49]

The decision to use *m*-chlorophenylpiperazine was based on the working hypothesis that, because of postsynaptic serotonin dysfunction in SAD, altered hormonal and subjective responses to serotonergic challenge would occur in this group. Intravenous *m*-chlorophenylpiperazine was chosen because previous work indicated less variability in blood levels in comparison with oral administration.[50,51] A 0.1-mg/kg dose was used because a previous study showed robust hormonal and subjective responses in normal controls in this dose range.[52]

RESULTS

DEMOGRAPHICS

All error terms are SDs. There were no significant differences between the groups (patients with SAD vs controls) in age (32.2±9.1 vs 27.4±7.5 years) or weight (61.3±14.0 vs 65.5±9.5 kg). The SAD group had a mean HDRS-29 score of 33.3±8.0 (range, 20-49), a mean HDRS-8 score of 13.1±4.4 (range, 7-21), and a mean Beck Depression Inventory score of 21.4±10.8 (range, 10-47).

120, and 180 minutes for prolactin and cortisol levels. Samples were kept on ice and centrifuged, and plasma was aliquoted and frozen until subsequent analysis by radioimmunoassay. At the same time that blood samples were drawn, each subject completed subjective mood ratings with the use of visual analog scales consisting of 10 parallel 100-mm lines. Each line had a left border marked "not at all" and a right border marked "most ever." Ten mood variables were assessed, including *happy, sad, anxious, drowsy, nervous, energetic, calm, fearful, high,* and *mellow*.[59]

After completion of the first challenge, subjects were given a day pass and returned to the unit in the evening. Following the same protocol as described above, subjects completed a second challenge the next morning with the agent not used in the first test. The investigator (R.D.L.) who administered the challenge tests was blind to which substance was injected; however, a coinvestigator (A.S.K.) was nonblind to the placebo or *m*-chlorophenylpiperazine condition.

DATA ANALYSIS

Baseline Measures

For both hormonal and mood variables, for a given test day, baseline was defined as the average of the 2 prechallenge values (ie, times –15 and 0 minutes) on that day. Mean overall baseline ratings were also calculated for each variable by averaging the baseline levels for the 2 study days.

Responses to *m*-Chlorophenylpiperazine and Placebo

All data were tested for normal distribution. The hormonal data met criteria for normality, and comparisons between subject groups were analyzed with repeated-measures analysis of variance, with the corresponding mean baseline hormonal value, age, and weight as covariates. Post hoc analysis of group differences was done with simple effects. To test for possible order effects, a second repeated-measures analysis of variance was done for each of the hormonal variables with both group and drug day (*m*-chlorophenylpiperazine on day 1 or day 2) as between-subject factors.

For mood ratings, to capture subjective responses most likely to be attributable to the placebo or drug, only baseline values and the first 3 postchallenge time points (ie, 30, 60, and 90 minutes) were included in the analysis. Insufficient *df* were available for a single multivariate analysis of variance. To limit the number of analyses, net change scores were used to assess possible group differences in response to the drug and placebo. Net change scores were calculated by first subtracting baseline values from each postchallenge data point, then subtracting placebo day results from *m*-chlorophenylpiperazine day results. For normally distributed variables, a repeated-measures analysis of variance was done on these net change scores with group and drug day (*m*-chlorophenylpiperazine on day 1 or day 2) as between-subject factors and the corresponding mean overall baseline mood rating as a covariate. For the nonnormally distributed variables *high* and *calm*, net change scores were calculated as above. For each postchallenge time point, the groups were then compared by means of Mann-Whitney tests corrected for ties. To assess possible order effects, subjects were further grouped on the basis of which day they received *m*-chlorophenylpiperazine (day 1, 9 patients with SAD and 8 controls; day 2, 6 patients with SAD and 6 controls), and the above procedure was repeated for each day separately.

Pearson correlation coefficients were used to evaluate relationships between neuroendocrine responses, subjective responses, and key clinical variables. For all results, the α level of significance was set at the 0.05 level.

NEUROENDOCRINE MEASURES

Prolactin

Baseline Measures. Mean baseline prolactin levels did not differ significantly between the 2 groups (14.2±6.6 vs 17.6±5.4 µg/L, SAD vs controls, respectively; $P>.10$, unpaired *t* test). The correlation between mean baseline prolactin level and body weight was insignificant within each group and for the total group of subjects. There was a trend for a negative correlation between mean baseline prolactin level and age across all subjects ($r=-0.35$, $P=.06$). Further analysis showed a significant negative correlation between baseline prolactin level and age in the control group ($r=-0.57$, $P=.03$) but not in the SAD group. There was no significant correlation between mean baseline prolactin level and any of the depression scores in the SAD group.

Response to *m*-Chlorophenylpiperazine and Placebo. Repeated-measures analysis of variance indicated significant group × time ($F=3.92$, $df=5,23$, $P=.01$) and drug×time ($F=15.64$, $df=5,23$, $P<.001$) interactions and a trend for a group×drug×time interaction ($F=2.39$, $df=5,23$, $P=.07$) (**Figure 1**). The main effects of drug ($F=76.1$, $df=1,27$, $P<.001$) and of time ($F=9.27$, $df=5,23$, $P<.001$) were significant. The main effect of group was not significant.

To further investigate the effect of *m*-chlorophenylpiperazine relative to placebo, prolactin change scores were calculated by subtracting baseline prolactin values from each postchallenge data point. Net change scores, defined as the difference in prolactin change scores on the *m*-chlorophenylpiperazine and placebo days, were then calculated. A repeated-measures analysis of variance using these net change scores showed a significant main effect of group ($F=5.95$, $df=1,26$, $P=.02$). Results of simple effects tests showed significant differences between patients and controls at 90 minutes ($F=7.86$, $df=1,25$, $P=.01$) and 120 minutes ($F=4.73$, $df=1,25$, $P=.04$).

The group×drug day and group×drug day×drug interactions, and the main effect of drug day, were all nonsignificant.

Cortisol

Baseline Measures. There was no statistical difference in mean baseline cortisol level between normal controls and patients with SAD (180.7±58.3 vs 170.9±69.0 nmol/L, respectively). The correlation between mean baseline cortisol level and body weight was insignificant within each

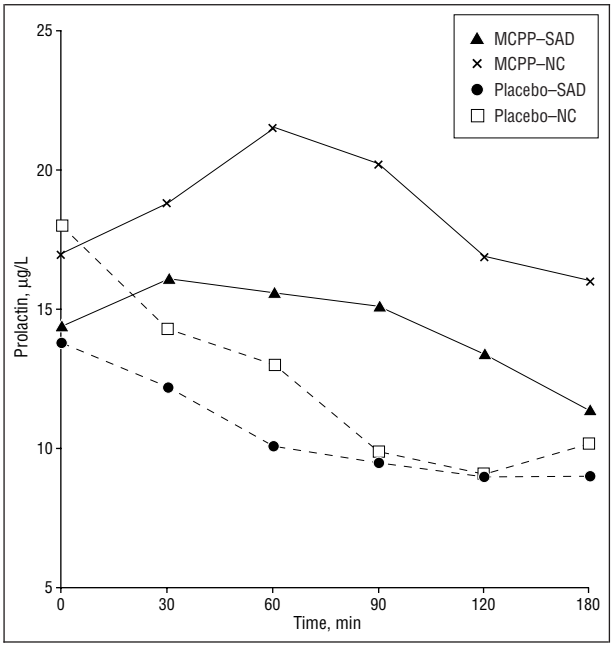

Figure 1. *Prolactin responses to* m*-chlorophenylpiperazine (MCPP) and placebo in 14 patients with seasonal affective disorder (SAD) and 15 normal controls (NC).*

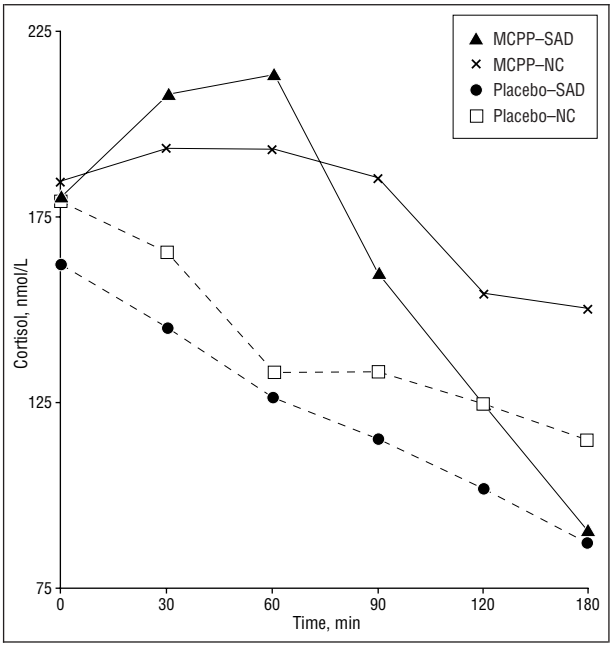

Figure 2. *Cortisol responses to* m*-chlorophenylpiperazine (MCPP) and placebo in 14 patients with seasonal affective disorder (SAD) and 15 normal controls (NC).*

group and for the total group of subjects. There was a trend for a positive correlation between baseline cortisol level and age across all subjects (r=0.32, P=.09). Within the SAD group, there was a positive correlation between HDRS-8 scores and plasma cortisol levels (r=0.61, P=.02); no significant correlation between baseline cortisol levels and other depression scores was found.

Response to *m*-Chlorophenylpiperazine and Placebo. Repeated-measures analysis of variance indicated no significant interaction or main effect related to group. There were significant main effects of drug (F=10.10, df=1,27, P=.004) and of time (F=19.47, df=5,23, P<.001) and a significant drug×time interaction (F=4.40, df=5,23, P=.006) (**Figure 2**).

Cortisol net change scores, defined as the difference in cortisol change scores on the *m*-chlorophenylpiperazine and placebo days, were then calculated for each time point. A repeated-measures analysis of variance on these net change scores showed no significant main effect of group.

The group×drug day and group×drug day×drug interactions, and the main effect of drug day, were all nonsignificant.

SUBJECTIVE RESPONSES

Baseline Scores

Unpaired t tests demonstrated significant differences in mean overall baseline scores between patients with SAD and controls on ratings of *anxious* (35.0±24.0 vs 17.0±15.4, P=.02), *nervous* (32.1±24.6 vs 16.1±14.9, P=.04), *happy* (35.1±14.1 vs 44.8±9.6, P=.04), and *sad* (37.7±16.4 vs 15.1±15.5; P=.001) (SAD vs controls); Mann-Whitney tests showed no differences between groups on baseline ratings of *calm* or *high*.

Response to *m*-Chlorophenylpiperazine and Placebo

Repeated-measures analysis of variance on net change scores showed a significant main effect of group only for *sad* ratings (F=4.23, df=1,24; P=.05). Simple effects testing at each time point indicated a significant difference between patients and controls at 30 minutes (F=7.31, df=1,24; P=.01); the raw data suggest that *m*-chlorophenylpiperazine produced a net *decrease* in sadness in the SAD group, while controls had a net *increase* in sadness in response to the drug (**Table**).

No significant drug day or group×drug day effects were found for the normally distributed variables.

For the variables *high* and *calm*, there were no differences between groups before order effects were taken into account. Patients with SAD were found to have significantly decreased net *calm* ratings at 60 minutes when *m*-chlorophenylpiperazine was administered on day 2 (mean rank, 4.0 vs 9.0, SAD vs controls, Mann-Whitney Z=–2.40, P=.02). There was also a trend for patients with SAD to report increased net *high* ratings at 30 minutes when *m*-chlorophenylpiperazine was administered on day 1 (mean rank, 11.4 vs 6.9, SAD vs controls, Mann-Whitney Z=–2.21, P=.07).

COMMENT

The present investigation was a double-blind, placebo-controlled challenge study to assess postsynaptic serotonergic function in SAD. The homogeneity of the SAD group studied, ie, depressed female subjects in the follicular phase of the menstrual cycle, is unique in SAD research of this type. The results demonstrate significantly blunted net prolactin responses to *m*-chlorophenylpiperazine in the SAD group. While the subjective responses did not differ markedly between groups, there were statistical differences on items related to sadness, calmness, and euphoria (ie, *high* ratings). Taken as a whole, these results point to altered

Acute Subjective Responses to *m*-Chlorophenylpiperazine and Placebo in Normal Controls (n=15) and Patients With SAD (n=14)*

	Time, min							
	m-Chlorophenylpiperazine Responses				Placebo Responses			
Response	Baseline	30	60	90	Baseline	30	60	90
High								
Controls	14.3±16.6	28.5±25.4	19.7±21.3	18.5±22.1	15.8±17.3	13.4±15.7	13.0±17.0	13.3±16.1
SAD	24.1±20.0	47.3±27.2	40.7±22.8	37.2±22.5	18.3±17.7	19.6±21.2	20.7±21.4	20.4±21.5
Happy								
Controls	44.8±13.5	43.1±12.7	44.8±8.7	46.1±17.4	44.9±12.2	45.5±9.9	44.9±11.6	46.0±10.2
SAD	33.4±15.9	32.4±16.1	37.7±16.9	40.1±19.5	36.8±14.5	39.4±20.9	36.1±16.5	35.0±15.6
Sad								
Controls	14.6±17.1	16.3±18.4	15.5±15.6	13.6±15.6	15.5±18.1	11.2±12.0	11.6±15.1	11.4±13.9
SAD	37.0±21.7	35.4±23.0	36.4±21.0	36.8±26.9	38.3±20.2	38.5±23.2	37.6±21.7	43.5±22.0
Drowsy								
Controls	27.1±25.1	32.5±27.4	14.7±14.0	11.8±14.8	25.9±20.4	16.6±22.0	17.1±20.6	18.5±22.7
SAD	42.8±26.3	47.3±26.4	42.9±25.3	46.5±28.4	45.6±29.2	37.6±30.8	49.4±28.8	44.4±28.1
Energetic								
Controls	30.4±18.3	36.1±20.1	31.1±19.0	40.7±20.0	24.4±15.6	26.1±15.9	29.9±15.4	33.5±17.4
SAD	28.2±15.8	35.4±15.8	33.4±19.8	31.6±23.3	23.7±19.1	33.5±23.2	24.9±14.2	22.6±12.4
Anxious								
Controls	18.2±17.8	29.4±27.3	20.5±17.7	10.6±11.2	15.8±15.9	13.3±18.3	11.4±16.2	12.5±17.1
SAD	35.9±26.6	49.9±26.0	39.7±25.7	25.4±20.1	34.1±25.8	31.3±28.6	32.5±26.7	28.4±26.5
Nervous								
Controls	16.7±17.2	23.8±26.1	17.1±16.9	9.6±9.9	15.4±15.9	13.2±18.4	11.5±15.9	12.8±17.2
SAD	31.9±27.5	42.8±29.4	35.6±28.0	24.5±21.5	32.2±26.1	30.6±27.8	29.6±27.5	27.5±25.4
Fearful								
Controls	15.5±17.6	20.9±20.4	14.5±15.0	11.4±13.9	19.0±19.4	14.9±18.0	15.5±19.2	17.9±21.9
SAD	26.0±22.9	34.6±30.7	28.9±28.1	21.2±21.8	28.3±25.9	28.1±27.6	24.3±26.1	25.4±27.1
Calm								
Controls	51.6±20.5	43.3±23.0	47.3±18.3	53.9±22.5	51.1±18.6	49.1±20.7	49.5±20.2	55.1±22.6
SAD	46.0±17.5	40.9±29.2	43.9±29.9	55.7±23.1	46.8±21.4	48.3±21.7	50.0±14.0	50.6±50.6
Mellow								
Controls	40.4±24.9	32.2±25.9	40.6±25.0	37.5±30.1	35.4±23.5	33.4±25.6	31.4±24.4	40.0±28.7
SAD	52.4±20.4	35.4±23.2	44.9±26.0	49.6±26.0	42.7±21.1	46.0±17.3	49.6±18.6	45.9±22.3

**SAD indicates seasonal affective disorder. Each measure is based on a visual analog scale rated from 0 to 100.*

activity at or downstream to central serotonin receptors in female patients with SAD in the depressed state.

Although previous research has also pointed to abnormal postsynaptic serotonergic activity in SAD, the direction of change of the hormonal data in particular has been inconsistent. In 1 study, patients with SAD tested during the winter months exhibited exaggerated prolactin and cortisol responses to *m*-chlorophenylpiperazine.[60] A double-blind follow-up study with *m*-chlorophenylpiperazine failed to replicate this, finding blunted corticotropin responses in untreated patients with SAD compared with controls.[43] A placebo-controlled study using D,L-fenfluramine found blunted prolactin responses in patients with SAD,[41] similar to the current findings. Blunted hormonal responses to the 5-HT-1D agonist sumatriptan also have been found in SAD in a non–placebo-controlled study.[44] Overall, the lack of a placebo control in many of these studies, and failure to control for menstrual cycle in female subjects, greatly limits their interpretation. Notwithstanding, taken together with the current results, most of the hormonal evidence to date points to down-regulation at or downstream to central serotonin receptors in SAD.

A moderately different pattern of subjective responses to *m*-chlorophenylpiperazine and placebo were found in patients with SAD relative to controls in the present study. While these differences were not marked, the overall direction of change is consistent with previous reports of increased activation or euphoria in patients with SAD in response to *m*-chlorophenylpiperazine.[42,43] These previous studies found normal subjective responses to *m*-chlorophenylpiperazine in patients with SAD after light therapy, suggesting that activation or euphoria in response to this drug may be a state marker of winter depression.[42,43]

Because of the preponderance of women in populations with SAD[1] and the difficulty in recruiting large samples for invasive studies of this type, we chose to include only female subjects and to carefully control for menstrual status. While intended to limit intersubject variability given the relatively small sample sizes anticipated, these strategies also limit the generalizability of our findings to men. A previous study of SAD with a preponderance of male subjects found blunted prolactin responses to the serotonergic agent D,L-fenfluramine in patients compared with controls,[41] similar to the current findings; this would suggest that serotonergic abnormalities in SAD are not limited to women.

The relative lack of specificity of *m*-chlorophenylpiperazine makes it difficult to ascertain which particular serotonin receptor systems might be abnormal in SAD. The development of more specific serotonin agonists and antagonists, suitable for use in the human population, would be helpful in this regard. Notwithstanding this limitation, the current results are consistent with a model of central sero-

tonergic dysfunction in female patients with SAD in the depressed state.

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