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Seasonal Variation in Neuroendocrine and Mood Responses to IV L-Tryptophan in Depressed Patients and Healthy Subjects

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Seasonality of mood disorders might involve alterations in the rhythmicity of serotonin [5-HT] function. We examined seasonal effects on the neuroendocrine and mood responses to L-tryptophan (L-TRP) in depressed patients and healthy subjects. In this study, 126 drug-free patients with DSM-III-R major depression and 58 healthy subjects received in IV infusion of L-TRP. Serum prolactin (PRL) and plasma tryptophan levels were measured. Mood was assessed with visual analogue scales. Cosinor analysis revealed seasonal variation in peak change (Δ) PRL and baseline tryptophan levels in the combined depressed and in unipolar, nonmelancholic, and nonpsychotic patients. Peak Δ PRL and tryptophan levels were inversely correlated in combined depressed and unipolar patients. Seasonality was more evident in female than in male patients. These data support previous evidence that 5-HT function is abnormal in depression and further suggest a seasonal variability of such abnormalities that is absent in healthy subjects.
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Seasonal variation has been described in several psychiatric conditions (Wirz-Justice 1995) including mood disorders, seasonal affective disorders (SAD) (Rosenthal et al. 1984), alcoholism (Poikolainen 1982), aggressive disorders (Michael and Zumpe 1983), and bulimia (Rosenthal et al. 1987). Moreover, seasonality has been reported in the severity of depression and in the occurrence of violent suicide (Maes et al. 1993a,b). Epidemiologic studies show that depression peaks in the spring and fall (Eastwood and Stiasny 1978), whereas mania occurs more often in summer (Carney et al. 1988). A peak incidence of suicide in May and October has been reported in over 20 studies (Goodwin and Jamison 1990). Recent data suggest that the seasonality of some conditions, such as major depression, violent suicide, and SAD, might be related to alterations in the rhythmicity of serotonin (5-hydroxytryptamine [5-HT]) function (Brewerton 1989).

Studies of 5-HT function in humans can be grouped according to whether measures are static (e.g., biochemical levels in body fluids or blood elements) or dynamic (e.g., neuroendocrine responses to pharmacologic provocation) (Price et al. 1990a,b). Several lines of evidence based on static measures support the hypothesis of 5-HT seasonal variation in humans: (1) hypothalamic 5-HT levels in post-mortem brain specimens are decreased in winter after values peak in the fall (Carlsson

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et al. 1980); (2) platelet 5-HT uptake and ^{3}[H]-imipramine (IMI) binding show a seasonal pattern (albeit with some differences in seasonal peaks and troughs) (Whitaker et al. 1984; Tang and Morris 1985; DeMet et al. 1989); (3) serum levels of melatonin, a hormone derived from 5-HT, demonstrate summer and winter peaks in healthy males (Arendt et al. 1977); (4) plasma levels of the 5-HT precursor tryptophan show a spring trough in healthy subjects (Maes et al. 1995); and (5) levels of 5-HT and its metabolites in cerebrospinal fluid (CSF) show seasonal fluctuation, varying with the latitude and the population studied (Åsberg et al. 1980). The variability in the specific seasonal peaks and nadirs reported by different investigators reflects the use of different research designs, methods, sample sizes, and measures of 5-HT function. Furthermore, the statistical methods used have varied from those more accurate in detecting biological rhythms (e.g., cosinor analysis, spectral analysis) to those less sensitive (e.g., *t*-tests, analysis of variance).

In depression, evaluation of 5-HT seasonality is complicated by abnormalities in 5-HT function intrinsic to the disorder (Heninger et al. 1984; Meltzer and Lowy 1987; Van de Kar 1989; Charney et al. 1991; Delgado et al. 1992). Among studies utilizing static measures, some have detected a parallel 5-HT rhythm in depressed compared with healthy subjects (Arora et al. 1984; Chicz-De Met et al. 1991; DeMet et al. 1991), but others have observed no differences between the two groups (Whitaker et al. 1984; Egrise et al. 1986; Kanof et al. 1987).

Few studies of seasonal variation in humans have used dynamic measures of 5-HT function. Brewerton (1989) described higher prolactin (PRL) responses to the 5-HT receptor agonist *m*-chloro-phenylpiperazine (mCPP) during winter in 36 bulimic patients and 15 healthy controls. Using the 5-HT releaser d,l-fenfluramine, Coiro et al. (1993) observed blunted PRL and cortisol responses in seven seasonal affective disorder (SAD) patients compared with eight healthy subjects, but no seasonal differences were detected. In contrast, Joseph-Vanderpool et al. (1993) described seasonal variation in the behavioral response (activation/euphoria) to mCPP in 10 winter SAD patients compared with eight summer SAD patients. To our knowledge, seasonal variation of dynamic 5-HT function has not been assessed in depressed patients not specifically selected for seasonality.

This study examines seasonal effects on the neuroendocrine and mood responses to IV infusion of the 5-HT precursor L-tryptophan (L-TRP) in 126 depressed patients and 58 healthy subjects. We (Heninger et al. 1984; Price et al. 1991) and others (Koyama and Meltzer 1986; Cowen and Charig 1987; Deakin et al. 1990) have previously observed blunted neuroendocrine responses to L-TRP in depressed patients when seasonality was not taken into account.

SUBJECTS AND PROCEDURES

Subjects

As previously described (Price et al. 1991), 126 depressed patients and 58 healthy controls gave voluntary written informed consent to participate in this study, conducted at the Clinical Neuroscience Research Unit of the Connecticut Mental Health Center, New Haven, CT. The geographical coordinates for the study site were 41.1° N and 72.5° W. The study span extended from January 26, 1983 until June 26, 1987. All subjects were free of serious medical conditions, based on complete physical and neurologic examinations, electrocardiogram, and screening laboratory tests.

All patients met DSM-III-R criteria for a principal diagnosis of major depression and had a score ≥18 on a 25-item version of the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960). Substance abuse or dependence, schizophrenic or other psychoses, organic mental disorders, and obsessive compulsive disorder (OCD) were exclusionary criteria. Comorbidity with anxiety disorders other than OCD was not an exclusionary criterion. Diagnoses were made by consensus of the authors based on residents' and nurses' assessments, family evaluation, medical records, interview with the Yale Depressory Inventory (Mazure et al. 1986), and direct interview. Healthy controls were obtained by newspaper advertisements and by referral from other healthy volunteers. In addition to the medical screening described above, they were also screened for a personal or family history of mental disorder by a research psychiatrist using a semi-structured interview. Controls were paid to participate.

Demographic and clinical characteristics for the entire sample, including DSM-III-R depressive subtype, age, gender, weight, and HDRS score, are provided in Table 1.

Study Procedures

Patients were studied during a placebo period preceding a single-blind antidepressant drug trial. At the time of testing, patients had been receiving placebo for at least 2 weeks and had been free of psychotropic drugs (except for low-dose benzodiazepines for severe agitation and insomnia) for at least 3 weeks. Healthy controls were unmedicated and additionally agreed to refrain from alcohol use for at least 2 weeks and other psychoactive drug use for at least 4 weeks before testing.

Subjects fasted overnight and throughout the 3-hour test, which began at 9:00 A.M. in a specially designated challenge room. The test dose consisted of L-TRP 7 g IV infused over a 20-minute period. Subjects remained awake in a supine position with head elevated during the procedure. Blood sampling for PRL was performed

Table 1. Demographic and Clinical Characteristics of Depressed Patients and Healthy Subjects

	Age (years)		Sex		Hamilton Depression Score (25 items)	
Group	Mean	SD	M	F	Mean	SD
Healthy subjects (n = 58)	38	13	17	41	—	—
All depressed (n = 126)	43[a]	14	38	88	33	10
Unipolar (n = 109)	44[b]	14	31	78	34	11
Bipolar (n = 17)	40	15	7	10	30	7
Melancholic (n = 68)	47[c]	15	21	47	36	10
Nonmelancholic (n = 58)	38	10	17	41	30	10
Psychotic (n = 28)	45[d]	15	6	22	40	10
Nonpsychotic (n = 98)	43[e]	13	32	66	31	10

All comparisons are between depressive subtype group and healthy subjects.
[a] $t = 2.6$, $df = 182$, $p < .02$.
[b] $t = 2.8$, $df = 165$, $p < .007$.
[c] $t = 3.8$, $df = 124$, $p < .0002$.
[d] $t = 2.2$, $df = 84$, $p < .03$.
[e] $t = 2.3$, $df = 154$, $p < .03$.

through an indwelling intravenous cathether kept patent by a slow saline drip. Sampling began at least 1 hour after catheter insertion, and 15 minutes before ("baseline") and 30, 40, 50, 60, 70, and 90 minutes after the start of the L-TRP infusion. Visual analog scales (0 mm = "not at all," 100 mm = "most ever") on 13 different mood states (talkative, happy, drowsy, nervous, sad, calm, depressed, anxious, energetic, fearful, mellow, high, angry) were scored by the patients at these times (omitting the 70-minute time point). At the same times, sitting pulse and blood pressure were measured with a sphygmomanometer in the usual clinical fashion. Blood samples for basal plasma trptophan were obtained 15 minutes before the infusion.

Biochemical Methods

The L-TRP infusions were prepared by dissolving 8.4 g of L-TRP in 600 ml of 0.45% saline solution, with 50% NaOH added to bring the solution to pH 7.4. Each 600-ml aliquot was sterilized by passage though a 0.22-mm filter (Millipore) and was tested for pyrogenicity and sterility before use. Serum samples were assayed for PRL levels using a radioimmunoassay kit from Serono Diagnostics, Inc., with intraassay and interassay coefficients of variation (CV) of 3% and 7%, respectively. Total plasma tryptophan concentration was measured in 35 patients and 28 controls by high performance liquid chromatography, with intraassay and interassay CVs of 2.1% and 6.8%, respectively. Each assay was carried out in duplicate.

Data Analysis

Dates of sampling were evaluated for uniform distribution over the course of a calendar year. Analysis of seasonal variation was conducted separately for depressed and healthy subjects on baseline and peak change (Δ) plasma PRL, baseline plasma TRP, and peak Δ mood responses using the cosinor method. Peak Δ was calculated by subtracting the baseline score from the highest value after L-TRP administration. Because peak Δ PRL responses and baseline plasma tryptophan were inversely correlated (Price et al. 1991), peak Δ PRL levels were evaluated using baseline tryptophan levels as a covariate. These residualized values were then used in the cosinor analysis. Because depressed and healthy subjects differed significantly in age (cf. Table 1) and because previous studies suggest that age may be a factor in seasonality (LaCoste and Wirz-Justice 1989), age was also used as a covariate in all analyses. Seasonal best fits of the variables were determined by multiple linear regression, using $X1 = \text{Cos}(2\pi \times \text{DAY}/365)$, $X2 = \text{Sin}(2\pi \times \text{DAY}/365)$, and age as independent variables. The estimated seasonal peak (acrophase) and seasonal trough were determined from the regression equation for those seasonal best fits that were statistically significant. The mesor (expected average of individual levels if these values were over 1 year) and the amplitude (maximum ordinate value of the sinusoidal curve) were determined by linear regression, with $X = \text{Cos}[2\pi \times (\text{DAY}-\text{ACROPHASE})/365]$ as the independent variable (Bingham et al. 1982; De Meyer and Vogelaere 1991; DeMet et al. 1991).

Biochemical and mood variables were also analyzed for seasonal differences within and between diagnostic groups (patients vs. controls) by analysis of covariance (ANCOVA), using age as the covariate. The cosinor method and ANCOVAs were then used to examine seasonal variation by gender and specific depressive subgroups (unipolar/bipolar; melancholic/nonmelancholic; psychotic/nonpsychotic) for each variable when the initial analysis of that variable was significant. Pearson correlations were used to evaulate the relationships between the PRL response to IV L-TRP and baseline tryptophan levels during each season.

All statistical tests were two-tailed, with significance at $p < .05$. Data were analyzed using SPSS version 4.0 (SPSS 1990).

RESULTS

Subject Characteristics

The distribution of the sampling dates was evaluated (Table 2). A normal probability plot of the sampling dates showed a pattern consistent with a uniform distribution ($p < .002$ for lack of normality, Kolmogorov-

Table 2. Seasonal Distribution of Sampling Dates for Healthy Subjects and Depressive Subgroups

	Winter	Spring	Summer	Autumn
Healthy subjects	14	14	10	20
All depressed	32	27	31	36
Unipolar	30	26	22	31
Bipolar	2	1	9	5
Nonmelancholic	17	11	14	16
Melancholic	15	16	17	20
Nonpsychotic	22	21	27	28
Psychotic	10	6	4	8

Smirnov test), with median, 25th percentile, and 75th percentile sampling points on days 181, 81, and 276, respectively.

Table 1 shows that the combined depressed group was significantly older than the healthy group. Age difference was also significant for the unipolar, melancholic, nonpsychotic, and psychotic groups, whereas there was no significant age difference between bipolar and healthy subjects. Neither combined nor subtyped depressed groups differed significantly from healthy controls in sex ratio.

Prolactin

Baseline PRL did not fit to a sinusoidal function in either healthy controls or depressed patients, nor were significant findings evident by ANCOVA.

Residualized peak ΔPRL response after L-TRP infusion in the combined depressed group showed a significant seasonal variation, which fitted to a 12-month sinusoidal function ($F = 10.7$, $df = 1,107$, $p < .001$), with a seasonal peak on February 15, seasonal trough on July 24, mesor = 10.1 ng/ml, and amplitude = ± 0.9 ng/ml (Figure 1). Peak Δ PRL in the depressed patients also fitted to a 4-month sinusoidal model ($F = 4.7$, $df = 3,105$, $p < .003$; acrophase, April 10; trough, February 4; mesor = 1.1 ng/ml; amplitude = ±10.2 ng/ml). Peak Δ PRL in the healthy controls did not fit to a 12-month sinusoidal curve, nor to 1-, 3-, 4-, or 6-month sinusoidal models. Significant 12-month seasonal variation in peak Δ PRL was present in unipolar ($F = 3.9$, $df = 3,91$, $p < .01$; seasonal peak, February 15; seasonal trough, July 24; mesor = 10.1 ng/ml; amplitude = ± 1.1 ng/ml), nonmelancholic ($F = 3$, $df = 3,43$, $p < .03$; peak, February 18; trough, June 27; mesor = 9.4 ng/ml; amplitude = ±1.2 ng/ml), and nonpsychotic ($F = 2.9$, $df = 3,82$, $p < .03$; peak; December 28; trough, June 4; mesor = 9.9 ng/ml; amplitude = ±0.7 ng/ml) depressed patients (Figure 1). Seasonality was not detected in bipolar, melancholic, or psychotic patients. No gender differences were detected in either healthy subjects or depressed patients. ANCOVAs of peak Δ PRL responses revealed no significant findings either within or between the main diagnostic groups.

Plasma Tryptophan

Baseline plasma tryptophan levels fitted to a 12-month sinusoidal function in depressed patients ($F = 3.5$, $p < .01$), but not in healthy subjects, with a seasonal peak on July 24, trough on January 24, mesor = 7.6 μg/ml, and amplitude = ±0.7 μg/ml (Figure 2). Significant seasonal variation in plasma tryptophan was also detected in unipolar ($F = 4.0$, $p < .009$; peak, July 24; trough, February 18; mesor = 7.6 μg/ml; amplitude = ±0.8 ng/ml), nonmelancholic ($F = 3.3$, $p < .02$; peak, June 27; trough, February 18; mesor = 8.2 μg/ml; amplitude = ±1.0 μg/ml, and nonpsychotic ($F = 2.9$, $p < .03$; peak, June 4; trough, December 6; mesor = 7.8 μg/ml; amplitude = ±0.6 μg/ml) patients (Figure 2). Bipolar, melancholic, and psychotic patients did not fit to a sinusoidal function. A trend toward significance for gender-specific seasonal pattern was detected only in the combined depressed females ($F = 2.6$, $p < .054$). ANCOVA of plasma tryptophan was significant in the combined de-

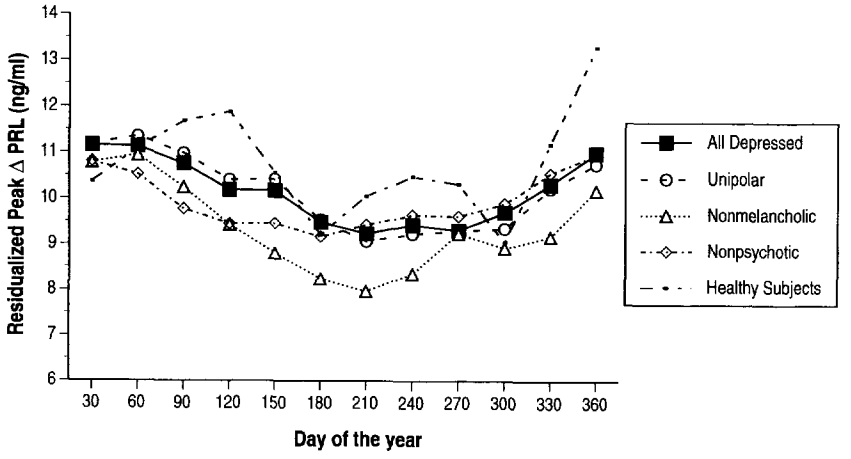

Figure 1. Seasonal variation of residualized peak Δ PRL response to L-TRP in healthy subjects and all depressed, unipolar, nonmelancholic, and nonpsychotic subgroups (cosinor analysis with baseline plasma tryptophan and age as covariates; to simplify presentation, monthly means are plotted).

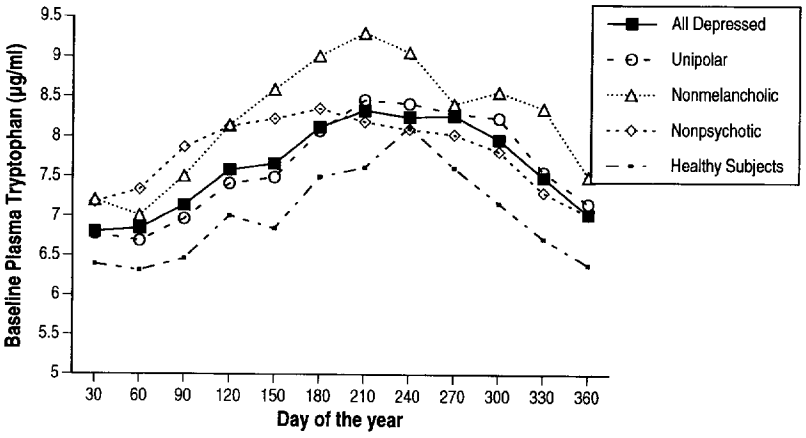

Figure 2. Seasonal variation of baseline plasma tryptophan in all depressed, unipolar, nonmelancholic, and nonpsychotic subgroups (cosinor analysis with age as a covariate; to simplify presentation, monthly means are plotted).

pressed group ($F = 2.7$, $df = 3,105$, $p < .04$), but not in healthy controls. Subsequent ANCOVAs showed significant seasonal variation only in the psychotic subgroup ($F = 3.3$, $df = 3,68$, $p < .02$), and there were no significant gender differences. A significant negative correlation was found between peak Δ PRL and plasma tryptophan levels during winter ($r = -0.47$, $p < .02$) and summer ($r = -0.49$, $p < .008$) in the combined depressed patients. The same negative correlation was maintained in unipolar depressed patients in winter ($r = -0.53$, $p < .01$) and summer ($r = 0.45$, $p < .04$), but not in nonmelancholic and nonpsychotic patients.

Mood Responses

Subjective mood responses to L-TRP did not fit to sinusoidal functions in either depressed patients or healthy controls, nor were ANCOVAs of mood responses significant.

DISCUSSION

Using the cosinor method, this study detected seasonal variation (Table 3) (winter peak, summer trough) in the peak Δ PRL response to IV L-TRP in depressed patients, but not in healthy subjects. Baseline plasma tryptophan levels also displayed seasonal variation (summer peaks, winter troughs) in depressed, but not in healthy, subjects. Furthermore, a significant negative correlation between peak Δ PRL and baseline plasma tryptophan was found during winter and summer in depressed patients. Previous studies have demonstrated blunting of both the PRL response to IV L-TRP in depressed patients compared with controls (Heninger et al. 1984; Koyama and Meltzer 1986; Cowen and Charig 1987; Deakin et al. 1990; Price et al. 1991). Our data suggest that there are qualitative differences in the seasonality of these responses within these groups. However, such differences do not seem to account for the magnitude of blunted responses in depression (Brewerton 1992; Price et al. 1992), because no season x diagnosis interactions were detected by ANCOVA.

Significant seasonal variation was evident only in specific depressive subgroups. For example, unipolar, nonmelancholic, and nonpsychotic patients showed winter peaks and summer troughs in the peak Δ PRL response, while simultaneously showing summer peaks and winter troughs in baseline plasma tryptophan.

The present data suggest a possible relationship between seasonal changes in neuroendocrine and biochemical measures of 5-HT function and the seasonal recurrence of mood disorders. One of our major findings was a winter peak and summer trough in the PRL response to L-TRP in depressed patients. Interestingly, Wehr et al. (1993) found that sleep time and blood levels of melatonin and PRL were increased in simulated winter photoperiods in healthy volunteers. It would be reasonable to hypothesize that the winter peak in the PRL response to L-TRP relates to other biological rhythms (e.g., sleep, light-dark cycle, weight, appetite, gonadotropins) that can be altered in depression. However, it is difficult to interpret how the timing of the most blunted PRL responses (summer) or the greatest PRL response (winter) relate to the occurrence of such

Table 3. Seasonal Peaks/Troughs in Measures of 5-HT Function in Depressed Patients and Healthy Subjects (12-month model)

Group	Baseline PRL	Peak Δ PRL (peak/trough)	Mesor (ng/ml)	Amplitude (ng/ml)
Healthy subjects	NS	NS		
All depressed	NS	Feb 15/Jul 24	10.1	0.9
Unipolar	NS	Feb 15/Jul 24	10.1	1.1
Bipolar	NS	NS		
Melancholic	NS	NS		
Nonmelancholic	NS	Feb 18/Jun 27	9.4	1.2
Psychotic	NS	NS		
Nonpsychotic	NS	Dec 28/Jun 4	9.9	0.7

clinical phenomena as the peak incidences of depression and suicide (spring and fall).

The summer peak and winter trough of plasma tryptophan levels detected in depressed patients must be considered in light of the dependence of central 5-HT synthesis on such levels (Young and Teff 1989). Numerous studies have found decreased plasma tryptophan levels in depressed patients (Joseph et al. 1984; Maes et al. 1987; Cowen et al. 1989; Russ et al. 1990), although others have failed to confirm this (Riley and Shaw 1976; Møller et al. 1979). In the only previous study of seasonal variation, Swade and Coppen (1980) also observed that free tryptophan levels in depressed patients showed a summer peak, although they found that this pattern was the reverse of that seen in healthy controls. Cowen and Charig (1987) reported that baseline tryptophan levels were lower in depressed patients with significant weight loss and with PRL response to IV L-TRP greater than controls. Consistent with this is our finding in depressed patients that lower tryptophan levels correlated with higher PRL responses to L-TRP during summer and winter, the seasons in which PRL responses troughed and peaked while plasma tryptophan levels peaked and troughed. This suggests that seasonal variation in central 5-HT function in depression may be related to seasonal changes in tryptophan availability or metabolism.

Evidence of diagnostic subtype specificity for nonmelancholic patients in the seasonality of PRL responses is notable given that our previous analysis of these data found blunting of the PRL response to be clearest in the same group (Price et al. 1991). Although we did not evaluate our patients for a diagnosis of SAD, it must be considered that the typical symptom profile of this syndrome (increased appetite, weight gain, hypersomnia, fatigue, decreased physical activity, depressed mood, irritability) (Rosenthal et al. 1984; Blehar and Lowy 1990) is most consistent with patients in our nonmelancholic group. This raises the possibility that SAD patients in our sample may have contributed to our finding of seasonal variation in the PRL response. Abnormal 5-HT function in SAD has been hypothesized by others, with reports of increased neuroendocrine responses to mCPP (Jacobsen et al. 1987; Garcia-Borreguero et al. 1995) and blunted responses to to fenfluramine (Coiro et al. 1993), but normal responses to the 5-HT precursor 5-hydroxytryptophan (Jacobsen et al. 1989). As noted previously, seasonal variation in 5-HT–mediated responses in SAD has been inconsistent (Coiro et al. 1993).

There has been only one previous report using IV L-TRP as a dynamic probe of 5-HT function seasonality in humans. Brewerton (1989) found significant seasonal differences between a subgroup of nonanorectic bulimic patients and heathly controls in response to L-TRP. In the same report, a winter peak for the PRL response to oral mCPP was observed in both patients and controls. In addition to the obvious diagnostic differences between studies, Brewerton (1989) evaluated seasonality using analysis of variance but not the cosinor method.

Static measures of 5-HT function, such as platelet 5-HT uptake and ^{3}[H]-IMI binding, have been reported to show seasonal variation, although with some inconsistency in the timing of peaks and troughs. Egrise et al. (1986) described a peak B_{max} of ^{3}[H]-IMI binding and V_{max} of 5-HT uptake in September and October, respectively, in seven depressed patients. DeMet et al. (1991), assessing ^{3}[H]-IMI binding in 49 depressed patients and 20 controls, reported lower than normal B_{max} in the depressed group, with an acrophase on January 19. Acrophase values of V_{max} were observed by Arora et al. (1984) in fall and winter in 82 depressed and 104 normal subjects, with lower V_{max} in depressed patients throughout the year. Swade and Coppen (1980) described seasonal variation in V_{max} in 26 depressed patients, with troughs in May-June and peaks in January-February. Malmgren (1989) reported abnormally low platelet 5-HT uptake in 64 depressed patients compared with 120 controls, with V_{max} peak values in October-November.

Some limitations of the present study deserve comment. First, data came from different subjects throughout the year rather than repeated measures on the same subjects. However, the large sample (n = 184) balances this weakness. A year-long longitudinal study of 5-HT function in acutely depressed subjects would not be methodologically or ethically feasible. Furthermore, several studies have shown the same outcome when cross-sectional and longitudinal methods were compared (Wirz-Justice and Richter 1979; Reinberg 1974). However, Maes et al. (1995) were recently able to detect seasonal variation of plasma tryptophan in a year-long study of 26 healthy subjects.

Second, the cosinor method tends to minimize patterns with greater fluctuations that might have occurred on a semiannual, quarterly, or monthly basis. Secondary analyses using cosinor fits to 1-, 3-, 4-, or 6-month models generally failed to identify significant patterns in the present data. The sole exception to this was the fit of peak Δ PRL response to a 4-month model in the depressed patients, although the neurobiological significance of this isolated finding is unclear. However, the cosinor method allowed us to evaluate variability and magnitude of seasonal rhythms (Wirz-Justice and Richter 1979), which we could not have detected using analysis of variance; it also minimized the influence of individual outliers that could have significantly altered monthly means (DeMet et al. 1990).

Third, our database did not enable us to identify patients with SAD. This would have been particularly useful in further elucidating the seasonal variations observed in our nonmelancholic subgroup.

Our data are consistent with previous evidence that

central 5-HT function is abnormal in depressed patients and further suggest a seasonal variability of such abnormalities that is absent in healthy subjects. Concentration of these findings in unipolar and nonmelancholic patients raises the possibility that both 5-HT dysfunction and seasonal variation may be of particular relevance to the pathophysiology of depression in these groups. Additional studies will be important to assess the clinical significance of these findings.

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