ORIGINAL ARTICLE

Effects of Tryptophan Depletion vs Catecholamine Depletion in Patients With Seasonal Affective Disorder in Remission With Light Therapy

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Background: Although hypotheses about the therapeutic mechanism of action of light therapy have focused on serotonergic mechanisms, the potential role, if any, of catecholaminergic pathways has not been fully explored.

Methods: Sixteen patients with seasonal affective disorder who had responded to a standard regimen of daily 10 000-lux light therapy were enrolled in a double-blind, placebo-controlled, randomized crossover study. We compared the effects of tryptophan depletion with catecholamine depletion and sham depletion. Ingestion of a tryptophan-free amino acid beverage plus amino acid capsules was used to deplete tryptophan. Administration of the tyrosine hydroxylase inhibitor α-methyl-paratyrosine was used to deplete catecholamines. Diphenhydramine hydrochloride was used as an active placebo during sham depletion. The effects of these interventions were evaluated with measures of depression, plasma tryptophan levels, and plasma catecholamine metabolites.

Results: Tryptophan depletion significantly decreased plasma total and free tryptophan levels. Catecholamine depletion significantly decreased plasma 3-methoxy-4-hydroxyphenylethyleneglycol and homovanillic acid levels. Both tryptophan depletion and catecholamine depletion, compared with sham depletion, induced a robust increase ($P<.001$, repeated-measures analysis of variance) in depressive symptoms as measured with the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version.

Conclusions: The beneficial effects of light therapy in the treatment of seasonal affective disorder are reversed by both tryptophan depletion and catecholamine depletion. These findings confirm previous work showing that serotonin plays an important role in the mechanism of action of light therapy and provide new evidence that brain catecholaminergic systems may also be involved.

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SEASONAL AFFECTIVE disorder, winter type (SAD), is a condition characterized by regularly occurring depressions in fall and winter, alternating with nondepressed periods in spring and summer.[1] Light therapy with bright, fluorescent white light has been shown to be an effective antidepressant.[1-3] Evidence suggests that brain monoaminergic systems may be involved in the pathogenesis of SAD and in the mechanism of action of light therapy.

Hypothalamic serotonin (5-HT) concentrations in human brain specimens decrease in the winter and peak in the fall.[4] Similar seasonal patterns have been shown in platelet 5-HT uptake[5] and tritiated imipramine binding,[6,7] in levels of 5-HT and its metabolites in the cerebrospinal fluid,[8] and in plasma tryptophan levels.[9] The 5-HT_2C receptor agonist meta-chlorophenylpiperazine has been shown to induce abnormal activation-euphoria responses in untreated, depressed patients with SAD,[10-12] but not after light therapy[10,11] or during summer.[12] Further evidence of dysfunctional serotonergic systems in depressed patients with SAD can be inferred from their abnormal hormonal responses to meta-chlorophenylpiperazine[13] and sumatriptan succinate.[14] Additionally, patients with SAD, but not controls, have been reported to feel energized after ingestion of carbohydrates,[15] suggesting a behavioral-biochemical feedback loop to increase brain 5-HT concentrations.[16] Finally, serotonergic agents have been found to be effective in the treatment of SAD.[17-19]

One study supporting the importance of noradrenergic mechanisms in the pathogenesis of SAD showed resting plasma norepinephrine levels to be inversely correlated with the level of depression in untreated patients with SAD.[20] Light

PATIENTS AND METHODS

PATIENTS

The protocol of the study was approved by the National Institute of Mental Health Intramural Program Review Board. Patients gave written informed consent to participate. The consent stated that in 1 or more of the depletion procedures, a transient return of depressive symptoms might occur.

Depressed outpatients, who were recruited through advertisements, met the Rosenthal et al criteria for SAD[1] and the criteria for a major depressive episode according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[29] based on a direct interview with the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. All subjects were screened for alcohol and drug use and for smoking. No other current Axis I diagnosis, including substance abuse, or smoking was allowed. Complete medical and neurological examinations, including standard laboratory tests and electrocardiograms, ensured that all patients were medically healthy. Patients had been free of drugs affecting the central nervous system for at least 6 months before being studied. During the whole study period, no alcohol or drug use was allowed. Female patients received a urine pregnancy test at the initial screening as well as on the morning of each depletion procedure.

Before undergoing the first depletion procedure, patients had to (1) become symptomatically depressed; (2) receive a standard regimen of 10 000-lux cool-white fluorescent light therapy for 45 minutes twice daily between 6 AM and 9 AM and again between 6 PM and 9 PM; (3) attain remission criteria as defined by a total score less than 12 on the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD)[30]; and (4) fulfill the remission criteria for at least 2 weeks.

Of the 16 patients initially enrolled, 3 did not complete the study. Two of the 3 refused to continue the study after completing the first depletion procedure and 1 patient became nauseated and vomited shortly after ingesting the beverage. Their data were not included in the statistical analysis. The clinical and demographic data of the remaining 13 patients are reported in the **Table**.

DEPLETION PROCEDURES

After patients had remained in clinical remission for 20.4±10.2 (mean±SD) days, they entered the double-blind, 3-period, 3-treatment crossover study comparing 2 active depletions (tryptophan depletion and catecholamine depletion) with a control (sham depletion). To avoid carryover effects, a period of at least 6 days between each depletion procedure was established. The basic 3×3 Latin square was replicated 6 times to accommodate the total sample of 16 patients, and the rows and treatment numbers in each square were separately and independently randomized.

Tryptophan depletion was induced on day 1 at 8:45 AM by administration of 23 white capsules containing methionine, cysteine, and arginine, as well as 4 pink placebo capsules, containing lactose, followed at 9 AM by administration of a tryptophan-free amino acid beverage. The total amount of amino acids was 100 g, and the specifications of the amino acid mixtures are described elsewhere.[31] Placebo capsules containing lactose were also administered at midnight and 3 PM on day 1, as well as at 8:45 AM on day 2.

Catecholamine depletion was induced with 1 g of α-methylparatyrosine (AMPT), administered in 4 pink capsules 3 times on day 1 (at the capsule administration times noted above) and in the morning (8:45 AM) on day 2. During sham depletion, the pink capsules contained 25 mg of diphenhydramine hydrochloride. To make all 3 depletion procedures appear similar, 23 white placebo capsules containing lactose and placebo beverages consisting of water and crushed ice, as well as chocolate syrup and mint extract as flavorings, were given in the catecholamine depletion and sham depletion procedures. We also used the same flavorings in the tryptophan-depleting beverage.

Four raters, blind to the condition, used the SIGH-SAD to assess mood. The intraclass correlation coeffi-

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therapy has been shown to decrease the urinary output of norepinephrine and its metabolites.[21] However, plasma concentrations of 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), a major metabolite of norepinephrine, did not distinguish depressed patients with SAD from either light-treated patients with SAD or controls.[20] Also, cerebrospinal fluid levels did not differentiate patients from controls in relation to either MHPG or the 5-HT metabolite 5-hydroxyindoleacetic acid.[20]

To investigate dopaminergic mechanisms in SAD, studies report increased[22] but also decreased[23,24] basal prolactin levels in patients with SAD compared with controls. One study,[23] but not another,[25] showed that patients with SAD have an increased eyeblink rate. Initial findings of an abnormal thermoregulatory response to a thermal challenge in patients with SAD compared with controls[26] were not replicated. Also, the combination of levodopa plus carbidopa was not superior to placebo in the treatment of SAD.[27]

Tryptophan depletion and catecholamine depletion have been shown to be useful research paradigms to evaluate the role of serotonergic and catecholaminergic neurotransmitter systems, respectively, in the pathogenesis of depression and the mechanisms of antidepressant treatment modalities.[28] Thus far, only tryptophan depletion studies have been conducted in patients with SAD.

The objective of the present investigation was to compare the effects of tryptophan depletion and catecholamine depletion in the same group of patients with SAD who responded well to light therapy. Given the strong evidence implicating serotonergic mechanisms in the antidepressant effects of light therapy, and the relatively preliminary nature of the evidence favoring a role for noradrenergic and dopaminergic systems, we predicted that tryptophan depletion, but not catecholamine depletion or sham depletion, would reverse the antidepressant effects of light therapy.

cient[32] among raters was 0.95. All ratings were performed whenever possible by the same rater for the same patient throughout the study. The SIGH-SAD items assessing sleep, diurnal variation, eating, and weight change were omitted. For simplicity, only total scores of the modified version of the SIGH-SAD are presented.

The SIGH-SAD ratings and blood samples for determinations of plasma concentrations of total and free tryptophan and the catecholamine metabolites MHPG and homovanillic acid (HVA) were obtained within each depletion procedure on day 1 at 8:30 AM, 2 PM, and 4:30 PM, and on day 2 at 8:30 AM and 2 PM.

Patients did not eat on day 1 of each depletion procedure until about 5 PM. Thereafter, patients were given a low-monoamine diet and they returned to unrestricted food intake after 2 PM on day 2. The patients continued their light therapy throughout the study, including days between the 3 depletion procedures.

All patients were medically cleared by a physician who was unaware of their treatment before returning home at the end of each depletion procedure. Thereafter, patients were able to contact their physician if needed.

BIOCHEMICAL ASSAYS

Patients were asked to rest for 30 minutes before each blood draw. Collected blood was immediately centrifuged for 17 minutes at 4°C and 3000 rpm. Serum was frozen at –70°C until analyzed. Plasma total tryptophan concentrations were assessed by means of high-performance liquid chromatography with fluorometric detection.[33] For determination of plasma free tryptophan levels, an ultrafiltrate was obtained by centrifuging 1 mL of plasma through an anisotropic, hydrophilic ultrafiltration membrane (Amicon Centrifee Filter; Amicon, Witten, Germany). Tryptophan in the ultrafiltrate was measured by high-performance liquid chromatography with fluorometric detection.[33] Plasma free levels of HVA[34] and MHPG[35] were measured by gas chromatography and mass spectrometry, with the use of carbon 13–labeled internal standards.

DATA ANALYSIS

The SIGH-SAD ratings as well as plasma total and free tryptophan, MHPG, and HVA levels were analyzed by repeated-measures 1-way analysis of variance (ANOVA) of the baseline values to determine whether any baseline differences existed between the 3 test periods.

To assess the main effects of depletion (tryptophan depletion vs catecholamine depletion vs sham depletion) and time (changes over the 5 time points sampled), SIGH-SAD ratings were evaluated by a 2-way ANOVA with repeated measures. The interaction of depletion×time reflects the effects of the interventions in the sample as a whole. When significant effects on SIGH-SAD total scores were identified in the ANOVA, repeated-measures 2-way ANOVAs on the individual items were performed to identify which symptoms were responsible for the change in total score.

To compare the maximum behavioral effects induced by the 3 depletion procedures, we subtracted each patient's baseline SIGH-SAD value from his or her peak value during the specific depletion procedure. These change values were analyzed by repeated-measures 1-way ANOVAs. Post hoc analyses used paired *t* tests.

Exacerbation of depressive symptoms during each depletion procedure was defined as at least a 50% increase of the SIGH-SAD total score from baseline and a SIGH-SAD score of 14 or more.

Changes in plasma total and free tryptophan levels, as well as plasma MHPG and HVA concentrations, were assessed with a 2-way ANOVA with repeated measures. Post hoc analyses used paired *t* tests.

Pearson correlation coefficients were calculated to evaluate the relationship between plasma tryptophan, MHPG, and HVA levels and behavioral changes. The reported *P* values of all ANOVAs used the Huynh-Feldt correction factor when the sphericity assumption was not met. For clarity, uncorrected *df* are reported. Significant interactions in the ANOVAs were further examined with paired *t* tests. Since all tests were hypothesis-driven, no multiple comparison correction was made in the individual *t* tests. Results were considered significant at $P < .05$. All tests were 2 tailed.

RESULTS

BIOCHEMICAL CHANGES

Changes in Plasma Tryptophan Levels

Baseline levels of plasma free ($F_{2,24} = 0.37$, $P = .61$) and total ($F_{2,24} = 0.93$, $P = .41$) tryptophan were not significantly different between the 3 depletion procedures. Tryptophan depletion decreased plasma free tryptophan levels (depletion×time interaction: $F_{8,96} = 36.25$, $P < .001$), with minimal values occurring 5 hours after ingestion of the amino acid beverage (88.3% decrease; $t = 16.43$, $df = 12$, $P < .001$). No significant changes in plasma free tryptophan levels occurred during catecholamine depletion and sham depletion (**Figure 1**, top).

Total tryptophan levels (Figure 1, bottom) also decreased during tryptophan depletion, with lowest levels 5 hours after ingestion of the amino acid beverage (88.2% decrease; $t = 20.84$, $df = 12$, $P < .001$). Modest decreases of plasma total tryptophan levels were also found during catecholamine depletion (16.1% decrease; $t = 8.12$, $df = 12$, $P < .001$) and sham depletion (9.7% decrease; $t = 2.58$, $df = 12$, $P = .02$). The depletion×time interaction was highly significant ($F_{8,96} = 76.99$, $P < .001$).

Changes in Plasma Catecholamine Metabolite Levels

Baseline levels of plasma HVA ($F_{2,24} = 0.79$, $P = .46$) and MHPG ($F_{2,24} = 0.60$, $P = .56$) were not statistically different between the 3 depletion procedures. Catecholamine depletion produced statistically significant decreases in plasma MHPG (depletion×time interaction: $F_{8,96} = 11.88$, $P < .001$) and HVA (depletion×time interaction: $F_{8,96} = 6.33$, $P < .001$) levels. Nadir values of plasma MHPG were found on day 2, at 8:30 AM (63% decrease; $t = 13.28$, $df = 12$, $P < .001$; **Figure 2**, top). Lowest HVA

Clinical and Demographic Characteristics*

Patient No./ Sex/Age, y	Diagnosis *DSM-IV*/Specifier	Sequence of Depletion Procedures	SIGH-SAD (Modified Version) Total Score				
			Before Light Therapy	After Light Therapy	Peak TD	Peak CD	Peak SD
1/F/47	BPII/atypical	SD/CD/TD	23	4	19	22	8
2/F/28	MDD/atypical	CD/TD/SD	24	2	22	30	2
3/F/57	BPII/atypical	TD/SD/CD	15	2	23	10	13
4/M/50	BPII/atypical	CD/SD/TD	13	1	19	14	2
5/M/51	MDD/atypical	TD/CD/SD	17	3	18	17	2
6/F/44	MDD	CD/SD/TD	26	10	16	10	14
7/M/64	MDD/atypical	TD/CD/SD	21	2	11	15	10
8/F/45	MDD/atypical	SD/CD/TD	18	2	22	12	10
9/F/22	MDD/atypical	SD/TD/CD	14	5	15	11	10
10/F/43	MDD/atypical	CD/TD/SD	22	7	28	15	6
11/F/31	MDD/atypical	CD/SD/TD	20	2	11	7	3
12/F/49	MDD/atypical	TD/CD/SD	24	2	20	21	11
13/M/55	BPII/melancholic	TD/SD/CD	24	3	13	9	14
Mean±SD							
45.2 ± 12.0 y	. . .	. . .	20.1 ± 4.3	3.5 ± 2.5	18.2 ± 5.0	14.8 ± 6.4	8.1 ± 4.6

*DSM-IV *indicates* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; *SIGH-SAD, Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version; TD, tryptophan depletion; CD, catecholamine depletion; SD, sham depletion; BPII, bipolar II disorder; atypical, current episode meets criteria for atypical features specifier* (DSM-IV)*; MDD, major depressive disorder; melancholic, current episode meets criteria for melancholic features specifier* (DSM-IV)*; and ellipses, not applicable.*

levels were found on day 2, at 2 PM (61% decrease; $t = 5.13$, $df = 12$, $P < .001$; Figure 2, bottom). Modest increases of plasma HVA levels were found during tryptophan depletion on day 1, at 4:30 PM ($t = -2.86$, $df = 12$, $P = .01$). No further measurements of plasma catecholamine metabolite concentrations reached statistical significance during tryptophan depletion or sham depletion.

BEHAVIORAL CHANGES

The ANOVA assessing the baseline SIGH-SAD values between the 3 test conditions did not approach statistical significance ($F[2,24] = 0.73$, $P = .47$), suggesting no effect of order on mood. Evaluation of the behavioral effects of the 3 depletion procedures showed a significant depletion×time interaction ($F_{8,96} = 5.08$, $P < .001$). The highest depression ratings during tryptophan depletion occurred for most patients on day 1, at 4:30 PM ($t = -5.61$, $df = 12$, $P < .001$), during catecholamine depletion on day 2, at 2 PM ($t = -7.33$, $df = 12$, $P < .001$), and during sham depletion on day 1, at 2 PM ($t = -3.39$, $df = 12$, $P = .005$), all compared with baseline on day 1, at 8:30 AM (**Figure 3**). The single-item analysis showed significant depletion×time interactions for depressed mood ($F_{8,96} = 3.17$, $P = .009$), fatigability ($F_{8,96} = 8.08$, $P < .001$), retardation of speech ($F_{8,96} = 3.86$, $P = .002$), decreased activity ($F_{8,96} = 3.77$, $P = .003$), social withdrawal ($F_{8,96} = 2.67$, $P = .01$), and somatic anxiety ($F_{8,96} = 2.71$, $P = .04$).

The assessment of the maximum effects of the 3 depletion procedures showed a statistically significant effect of condition ($F_{2,24} = 7.51$, $P = .004$). Both tryptophan ($t = -3.68$, $df = 12$, $P = .003$) and catecholamine ($t = -2.23$, $df = 12$, $P = .05$) depletion caused significantly higher change scores than sham depletion, and no difference was found between the maximum effects of tryptophan and catecholamine depletion ($t = -1.56$, $df = 12$, $P = .14$). Ten patients experienced a depressive relapse during tryptophan depletion, 7 patients during catecholamine depletion, and 2 patients during sham depletion.

There were no significant correlations between the effects of the depletion procedures on plasma tryptophan, MHPG, or HVA levels and changes in SIGH-SAD scores. Behavioral ratings obtained after each of the depletion procedures showed that all patients gradually recovered from the effects of the procedures within 4 days after discharge from the unit.

COMMENT

This placebo-controlled study compared the effects of tryptophan depletion, catecholamine depletion, and sham depletion within the same set of depressed patients. Moreover, it examined the biochemical and behavioral effects of catecholamine depletion in SAD. The primary finding of our investigation is that both tryptophan depletion and catecholamine depletion, but not sham depletion, reversed the therapeutic effects of light therapy. Diphenhydramine proved to be a plausible control, since it produced a degree of drowsiness and fatigue similar to that of AMPT but did not lead to an increase of depressive mood in these patients.

The biochemical changes induced by the depletion procedures were comparable with those in previous studies that used tryptophan depletion and catecholamine depletion paradigms. The transient decrease of plasma tryptophan levels after ingestion of the tryptophan-free amino acid beverage was expected to cause a reduction in brain 5-HT function.[36-38] This assumption is supported by a positron emission tomographic study of humans showing a marked lowering of brain 5-HT synthesis after tryptophan depletion.[39] However, animal studies suggest that the peripheral biochemical correlates of tryptophan depletion do not necessarily reflect the degree of central impairment of se-

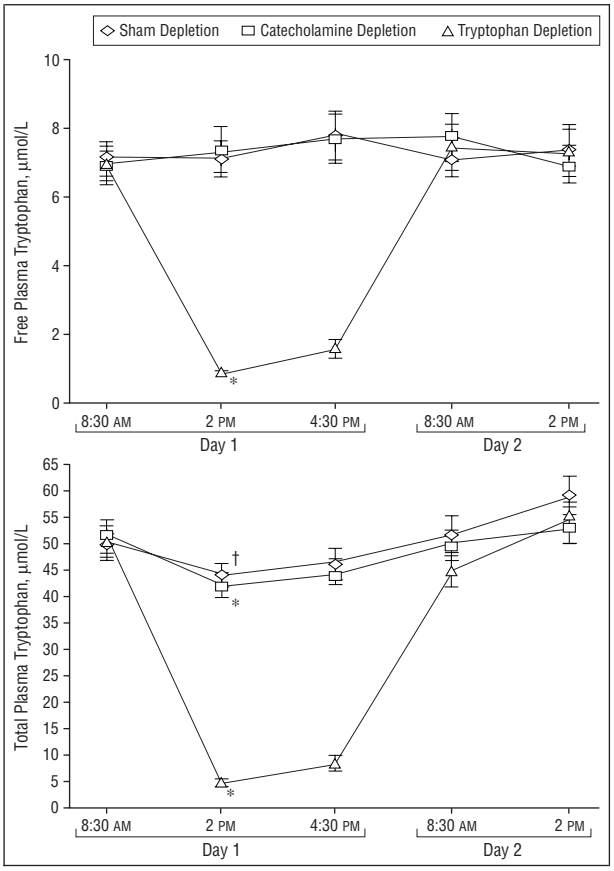

Figure 1. *The effects of tryptophan depletion, catecholamine depletion, and sham depletion on plasma free (top) and total (bottom) tryptophan levels (mean±SE). Asterisk indicates* P <*.001; dagger,* P <*.05 (paired* t *tests, 2 tailed, compared with day 1, at 8:30* AM*).*

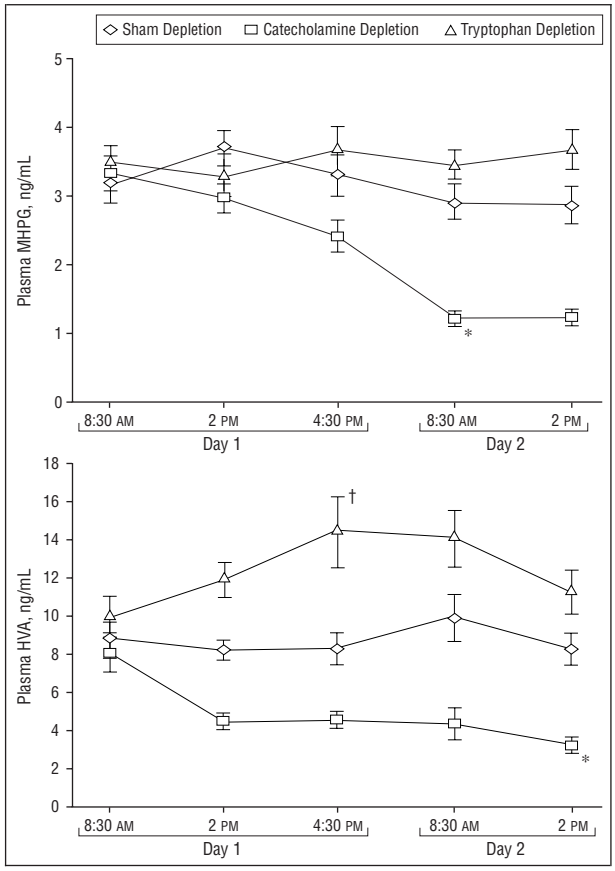

Figure 2. *The effects of tryptophan depletion, catecholamine depletion, and sham depletion on plasma 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG; top) and homovanillic acid (HVA; bottom) levels (mean±SE). Asterisk indicates* P <*.001; dagger,* P <*.05 (paired* t *tests, 2 tailed, compared with day 1, at 8:30* AM*).*

rotonergic transmission.[40] During catecholamine depletion and sham depletion, we found modest decreases of plasma total tryptophan levels but no changes of plasma free tryptophan concentrations. The most likely explanation for this is that the patients were not allowed to eat during day 1 of the study. Previous data indicate that plasma free tryptophan levels are a better predictor of brain tryptophan concentrations than are plasma total tryptophan concentrations.[41] Thus, we conclude that no decrease in brain 5-HT concentrations occurred during either catecholamine depletion or sham depletion.

It has to be considered that the tryptophan-depleting beverage includes large amounts of the other large neutral amino acids competing with tryptophan at the same carrier system across the blood-brain barrier. In the present study, measurements of catecholaminergic metabolites during tryptophan depletion showed modest increases in plasma HVA but not MHPG concentrations. Lowering plasma tryptophan levels and increasing large neutral amino acid levels may induce changes in the metabolism of insulin/glucagon[42] that may affect tryptophan uptake into the brain or possibly has behavioral and metabolic effects of its own.[43] Previous studies in primates, however, suggest that brain catecholamine metabolism is not affected by tryptophan depletion.[38]

As in previous studies of patients with nonseasonal depression,[44-46] AMPT administration significantly reduced plasma levels of MHPG and HVA, the metabolites of norepinephrine and dopamine. Animal studies have shown that AMPT easily passes through the blood-brain barrier and lowers brain catecholamine concentrations by inhibiting tyrosine hydroxylase.[47] Altogether, it

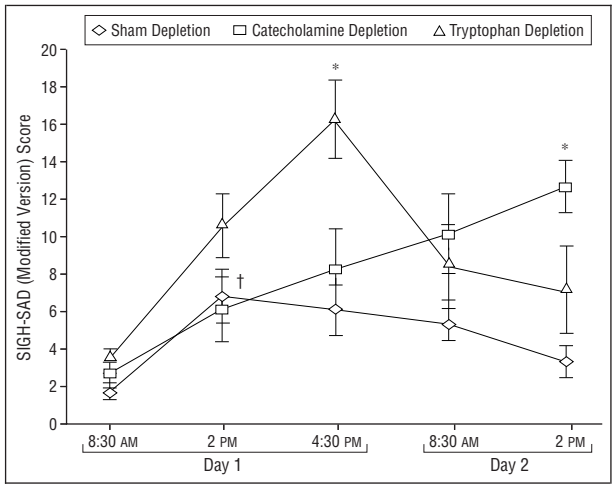

Figure 3. *Scores (mean±SE) on a modified version (see text) of the Structured Clinical Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD). Asterisk indicates* P <*.001; dagger,* P <*.01 (paired* t *tests, 2 tailed, compared with day 1, at 8:30* AM*).*

has to be acknowledged that in the present study only the peripheral correlates of the depletion procedures were measured, and thus the degree of central 5-HT vs catecholamines is unknown.

The findings of the present study are consistent with 2 previous studies showing that tryptophan depletion reverses the antidepressant effects of light therapy.[48,49] Such studies support the hypothesis that the antidepressant effects of light are mediated via serotonergic mechanisms. Tryptophan depletion studies performed in untreated depressed patients with SAD[50] and in patients in full remission not receiving light therapy during the summer[51] suggest that deficiences in serotonergic transmission play a key role in the pathogenesis of SAD and that light probably compensates for the underlying deficit in serotonergic functioning.

The present study suggests that light therapy does not work exclusively via serotonergic pathways and that catecholaminergic pathways may be specifically implicated as well. The different time course of the depressive relapse induced by the 2 depletion paradigms may well result from the different pharmacokinetics of the 2 interventions, since behavioral and biochemical effects had a parallel time course. This provides evidence that the decreased availability of 5-HT during tryptophan depletion and of catecholamines during catecholamine depletion was responsible for the depressive relapses. It would have been of interest to know whether the AMPT-induced depressive relapse could be reversed by levodopa, as was done in a study in healthy human subjects.[52]

Brain 5-HT and catecholamine systems are known to influence one another. For example, there are anatomical and functional interconnections between serotonergic and catecholaminergic regions.[53] Electrophysiological and microdialysis studies have shown that serotonergic transmission is partially controlled by catecholaminergic systems.[54,55] Disturbed interactions between serotonergic and noradrenergic systems have been noted also in patients with SAD.[11] It is possible that light therapy works by restoring interactions between monoamine systems to normal as well as by directly affecting those systems. We recognize, however, that our study does not preclude the possibility that neurobiological systems other than those involving monoamines may be implicated as well.

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