Rapid Tryptophan Depletion in Drug-Free Depressed Patients With Seasonal Affective Disorder

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Objective: *Brain serotonin systems might be involved in the pathophysiology of seasonal affective disorder. The authors tested whether tryptophan depletion alters the mood of depressed patients with seasonal affective disorder.* *Method:* *Eleven drug-free depressed patients with seasonal affective disorder underwent tryptophan depletion in a placebo-controlled, double-blind crossover study. Tryptophan depletion was induced by a 24-hour low-tryptophan diet and by ingestion of a tryptophan-free amino acid beverage. During control testing the diet and the beverage were supplemented with tryptophan. Behavioral ratings and plasma total and free tryptophan levels were obtained before the diet started and several times after administration of the beverages.* *Results:* *The diet and the tryptophan-free amino acid drink reduced plasma total and free tryptophan levels by 79.0% and 87.5%, respectively. Both levels increased during control testing. No significant behavioral changes were induced by tryptophan depletion or control testing.* *Conclusions:* *The failure of tryptophan depletion to exacerbate the depressive syndrome suggests that dysfunctional serotonergic activity does not play a primary, direct role in the pathogenesis of winter depression.*

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Recurrent winter depression, also termed seasonal affective disorder, has been systematically investigated during recent years. There is evidence that the neurotransmitter serotonin (5-hydroxytryptophan, 5-HT) might be involved in the pathophysiology of seasonal affective disorder and also in the mechanism of action of light therapy.

Tryptophan depletion provides a tool for studying 5-HT mechanisms in the pathophysiology and treatment of depression (1). Tryptophan depletion causes depressive symptoms in healthy subjects at genetic risk for major affective disorder and a depressive relapse in most patients with nonseasonal depression during remission induced by selective serotonin reuptake inhibitors or in drug-free patients who have recovered from a prior depressive episode. Bimodal changes of mood are observed on the day after tryptophan depletion in untreated depressed patients with nonseasonal depression. The antidepressant effects of light therapy are disrupted by tryptophan depletion in patients with seasonal affective disorder (2, 3).

Testing the hypothesis that the pathophysiology of seasonal affective disorder is associated with a deficiency in serotonergic neurotransmission, we predicted that tryptophan depletion would exacerbate depression in symptomatic depressed patients with seasonal affective disorder.

METHOD

Patients who met DSM-IV criteria for seasonal affective disorder, as determined by a semistructured interview, were recruited in our seasonal affective disorder clinic. After a complete description of the study, written informed consent was obtained. The study had the approval of the Ethics Committee of Vienna University. Before patients entered the study protocol, complete medical, ophthalmological, and neurological examinations, including laboratory tests, guaranteed that they were free of medical and neurological illnesses. Behavioral ratings included a modified version of the 21-item version of the Hamilton Depression Rating Scale (4) and seven supplementary items (seasonal affective disorder addendum) that are of particular rele-

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TABLE 1. Characteristics of Drug-Free Depressed Patients With Seasonal Affective Disorder in Placebo-Controlled Crossover Study of

Patient	Sex	Age (years)	DSM-IV Diagnosis[c]	Order of Treatment[d]	Level of Plasma Total Tryptophan or Plasma Free Tryptophan (μmol/liter)							
					Tryptophan Depletion				Control Testing			
					Before Diet		5 Hours After Amino Acid Drink		Before Diet		5 Hours After Amino Acid Drink	
					Total	Free	Total	Free	Total	Free	Total	Free
1	F	35	MDD	TD-CT	29.7	4.4	2.7	0.2	47.8	5.7	68.3	10.1
2	M	23	MDD	CT-TD	54.3	4.6	6.9	0.4	43.3	4.5	43.5	7.1
3	F	46	MDD	TD-CT	37.8	6.6	4.0	0.4	44.5	10.4	78.6	17.6
4	F	39	MDD	CT-TD	53.1	5.6	8.7	0.9	44.1	6.3	56.1	12.4
5	F	49	BPII	TD-CT	41.8	4.7	5.4	0.4	55.4	4.6	160.7	18.8
6	F	32	BPII	CT-TD	43.6	4.2	28.2	2.3	50.2	8.0	174.9	40.4
7	F	24	MDD	TD-CT	35.5	7.5	14.6	0.5	45.0	4.9	59.0	12.9
8	F	26	BPII	CT-TD	42.6	4.7	15.2	1.3	34.1	5.6	56.9	10.1
9	F	55	MDD	TD-CT	59.5	4.5	5.8	0.4	49.5	2.9	45.4	9.1
10	F	35	MDD	CT-TD	27.9	6.8	5.1	0.4	45.8	6.0	111.0	15.2
11	F	23	BPII	TD-CT	54.3	7.8	4.4	0.7	43.3	6.4	79.7	11.6
Total												
Mean					43.6	5.6	9.2	0.7	44.9	5.9	84.9	15.0
SD					10.6	1.4	7.5	0.6	6.3	2.0	45.2	9.1

[a]Tryptophan depletion was induced by a 24-hour low-tryptophan diet followed by ingestion of a tryptophan-free amino acid beverage. During control testing the diet and beverage were supplemented with tryptophan.
[b]See text for description of modifications.

vance to seasonal affective disorder (5). The items concerning sleep, diurnal variation, eating, and weight were excluded, since they cannot be meaningfully assessed during the test situation. Entry criteria were a score greater than 14 on the Hamilton depression scale and drug-free status during the current episode. Behavioral ratings were obtained by an experienced psychiatrist (N.P.-R.) who was blind to challenge type.

The study used a double-blind, balanced, placebo-controlled crossover design. Tryptophan depletion and control testing were separated by 7 to 9 days. The experimental session consisted of a 24-hour, low (160 mg/day)-tryptophan diet with placebo capsules (tryptophan depletion) or 500-mg tryptophan capsules (control testing) taken three times daily (day 1). The following morning the participants were given a tryptophan-free 15-amino acid beverage, which was supplemented with 2.3 g of tryptophan in the control session (day 2). Blood samples to determine plasma total and free tryptophan levels, together with psychopathological ratings, were obtained at 8:30 a.m. on day 1, before the start of the diet, as well as 5, 7, and 24 hours after ingestion of the beverages.

Behavioral ratings and changes in plasma total and free tryptophan levels were analyzed by a three-way repeated measures analysis of variance (ANOVA), with order of sessions as grouping variable and two intrasubject factors: treatment and time. Deviations from sphericity were adjusted by using Greenhouse-Geisser's eta. Post hoc analyses used Bonferroni-corrected t tests (two-tailed). Analyses were performed by using the SPSS for the personal computer, version 7.0.

RESULTS

The study group (table 1) consisted of 11 drug-free, symptomatic depressed patients with seasonal affective disorder (mean age=35.2 years, SD=11.1).

Tryptophan depletion significantly lowered the levels of plasma total and free tryptophan by means of 79.0% and 87.5%, respectively. The ANOVA disclosed a statistically significant treatment-by-time interaction for plasma total tryptophan ($F=26.11$, $df=3, 27$, $eta=0.55$, $p<0.001$) and free tryptophan ($F=28.37$, $df=3, 27$, $eta=0.41$, $p<0.001$). To meet a global alpha level of 0.05, the adjusted alpha level for the conducted paired t tests is 0.006. Post hoc comparisons showed significantly decreased plasma tryptophan concentrations 5 hours (total tryptophan: $t=8.86$, $df=10$, $p<0.001$; free tryptophan: $t=9.78$, $df=10$, $p<0.001$) and 7 hours (total tryptophan: $t=5.17$, $df=10$, $p<0.001$; free tryptophan: $t=6.58$, $df=10$, $p<0.001$) after intake of the beverage compared with the baseline level before the diet started. Control testing resulted in significantly increased plasma free tryptophan levels 5 hours ($t=3.63$, $df=10$, $p<0.005$) after ingestion of the beverage. No further tryptophan measurements during control testing reached statistical significance.

No significant behavioral changes occurred during tryptophan depletion and control testing (treatment-by-time interaction, Hamilton depression scale: $F=0.70$, $df=3, 27$, $eta=0.80$, $p=0.53$, and seasonal affective disorder addendum: $F=0.56$, $df=3, 27$, $eta=0.71$, $p=0.59$). There were no significant sequence of condition effects (order by treatment by time) in any of the plasma tryptophan level or behavioral change analyses.

DISCUSSION

Depressive symptoms did not worsen in drug-free, symptomatic depressed patients with seasonal affective disorder, although there was a significant decrease in 5-HT precursor levels and, by implication, brain 5-HT. Our findings support hypotheses (1) suggesting that the magnitude of depression during a depressive episode is not closely related to short-term 5-HT availability.

Tryptophan Depletion[a]

Score on Modified Hamilton Depression Rating Scale or Modified Seasonal Affective Disorder Addendum of Hamilton Scale[b]							
Tryptophan Depletion				Control Testing			
Before Diet		5 Hours After Amino Acid Drink		Before Diet		5 Hours After Amino Acid Drink	
Scale	Addendum	Scale	Addendum	Scale	Addendum	Scale	Addendum
16	7	15	5	18	5	15	5
15	9	13	9	16	10	16	12
15	11	16	9	12	8	10	8
15	13	16	11	13	10	17	12
17	13	17	13	15	13	15	12
16	11	14	10	19	11	19	10
18	10	17	8	24	7	23	10
13	9	13	8	14	8	16	8
12	7	12	9	13	6	13	9
16	14	16	15	17	14	16	11
17	4	17	5	14	7	15	6
15.5	9.8	15.1	9.3	15.9	9.0	15.9	9.4
1.8	3.0	1.8	3.0	3.5	2.9	3.3	2.4

[c]MDD indicates major depressive disorder; BPII indicates bipolar II disorder.
[d]Indicates whether tryptophan depletion (TD) or control testing (CT) was given first.

Tryptophan depletion failed to exacerbate depressive symptoms in patients with seasonal affective disorder; thus, it can be hypothesized that other brain neurobiologic systems have more direct effects on regulating mood. It would have been interesting to determine whether a catecholaminergic depletion would have resulted in a worsening of the depressive symptoms; such a finding would have given additional support to the theory that the progression of the severity of untreated depression is influenced by factors other than a serotonergic one alone.

Since tryptophan depletion induced a transient reoccurrence of depressive symptoms in patients with remitted seasonal affective disorder induced by light therapy (2, 3), it can be hypothesized that light therapy compensates for the underlying deficit of seasonal affective disorder, possibly involving serotonergic mechanisms. Findings from previous studies in the literature suggest that disturbances of brain 5-HT function might be one etiological factor in the pathophysiology of seasonal affective disorder, but our data indicate that brain 5-HT systems do not have a primary direct role in the pathogenesis of depression with seasonal mood cycles.

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