Tryptophan Depletion and Depressive Vulnerability

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Background: *Rapid and transient depletion of tryptophan (TRP) causes a brief depressive relapse in most patients successfully treated with and taking selective serotonin reuptake inhibitors, but little change in drug-free, symptomatic depressed patients. This study investigates the effects of TRP depletion in drug-free subjects in clinical remission from a prior major depressive episode (MDE).*

Methods: *Twelve subjects with a prior MDE, currently in clinical remission and drug-free for at least 3 months (patients), and 12 healthy subjects without personal or family history of Axis I disorder (controls), received TRP depletion. The study was conducted in a double-blind, controlled [full (102-g) and quarter-strength (25 g) 15-amino acid drinks], crossover fashion. Behavioral ratings and plasma TRP levels were obtained prior to, during, and after testing.*

Results: *All subjects experienced significant depletion of plasma TRP on both test-drinks, showing a significant dose–response relation. Healthy control subjects had minimal mood changes, but patients had a depressive response of greater magnitude.*

Conclusions: *In the context of prior TRP depletion studies with antidepressant-treated, and drug-free symptomatic depressed patients, these results suggest that depression may be caused not by an abnormality of 5-HT function, but by dysfunction of other systems or brain regions modulated by 5-HT.* Biol Psychiatry 1999;46:498–505
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Key Words: Tryptophan, depletion, serotonin, prediction, depression, vulnerability

Introduction

A large body of experimental data supports a central role for enhanced serotonin (5-HT) neurotransmission in the therapeutic mechanism of action of some antidepressant drugs (Blier et al 1990), although the primary role of diminished 5-HT neurotransmission in the pathophysiology of depression is less clear (Delgado et al 1994a; Murphy et al 1978). Some of the most provocative data in this regard come from studies utilizing the tryptophan (TRP) depletion paradigm (Delgado et al 1990, 1991, 1994a, 1999). Plasma TRP levels are dependent on dietary intake of TRP (Rose et al 1954), and brain 5-HT levels are, in turn, dependent on plasma levels of TRP (Curzon 1979, 1981; Fernstrom 1977; Moja et al 1989). A rapid but transient depletion of 80% to 90% of TRP plasma levels can be accomplished in less than 5 hours by oral administration of a 15-amino acid, TRP-free drink (Young et al 1989). This drink induces hepatic protein synthesis and causes rapid depletion of plasma TRP in the anabolic process (Moja et al 1991), which causes a significant decrease in the rate of 5-HT synthesis (Nishizawa et al 1997). A drink proportionally identical in composition to that used in humans attenuates the release of 5-HT by about 50% in the frontal cortexes of rats treated with fluvoxamine for 2 weeks (Bell and Artigas et al 1996).

TRP depletion causes a rapid but transient relapse of clinical depression in 50% to 70% of recently remitted depressed patients treated with selective 5-HT reuptake inhibitors (SSRIs), but in only 20% of those treated with the norepinephrine reuptake inhibitor desipramine (Delgado et al 1998). Similarly, TRP depletion transiently reverses the antidepressant effect of a standard course of bright light therapy in 80% of patients with seasonal affective disorder (Lam et al 1996).

Benkelfat and co-workers (1994) found that TRP depletion induced mild depressive symptoms in 30% of young male subjects with family histories of mood disorder but did not affect healthy male control subjects without personal or family histories of mood disorder. The authors suggest that the mood response to TRP depletion might be a marker for genetic vulnerability for major affective disorders. If this is true, then TRP depletion could be used to identify these individuals before they become ill, ensuring early intervention, decreasing suffering, minimizing social and occupational dysfunction, and lowering health care expenditures (Wells et al 1989).

If a depressive response to TRP depletion is primarily seen in those individuals at risk for depression, then TRP

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Table 1. Demographic Information

Patient/Gender/Age	Subject category	Age at onset of MDE	Time in remission before study (in weeks)	Episodes	Number of previous drug treatments
1/F/39	Control	N/A	N/A	N/A	N/A
2/F/63	Control	N/A	N/A	N/A	N/A
3/F/68	Control	N/A	N/A	N/A	N/A
4/F/23	Control	N/A	N/A	N/A	N/A
5/F/45	Control	N/A	N/A	N/A	N/A
6/F/24	Control	N/A	N/A	N/A	N/A
7/F/26	Control	N/A	N/A	N/A	N/A
8/M/65	Control	N/A	N/A	N/A	N/A
9/M/75	Control	N/A	N/A	N/A	N/A
10/M/46	Control	N/A	N/A	N/A	N/A
11/M/49	Control	N/A	N/A	N/A	N/A
12/F/35	Control	N/A	N/A	N/A	N/A
13/F/34	History (+)	22	39	3	Fluoxetine
14/F/29	History (+)	22	24	3	No response to medication (spontaneous remission)
15/F/61	History (+)	41	18	2	Amitriptyline, then sertraline (both help)
16/F/26	History (+)	22	34	1	Unknown medication from primary care physician
17/M/48	History (+)	21	150	3	None
18/M/80	History (+)	79	18	1	Nefazodone
19/F/45	History (+)	36	54	1	None
20/F/44	History (+)	15	24	5	Amitriptyline, then bupropion, then buspirone
21/M/68	History (+)	34	26	2	Fluoxetine
22/M/49	History (+)	44	48	1	Alprazolam along with psychotherapy
23/F/72	History (+)	52	1040	1	None
24/F/24	History (+)	23	12	1	Sertraline

F, female; M, male; Control, healthy subject without personal or family history of mental disorder; History (+), subject with prior history of major depression; MDE, major depressive episode; and N/A, not applicable.

depletion should lead to clinically meaningful depressive symptoms in clinically remitted subjects with an established past history of a major depressive episode (history-positive subjects). The present study was designed to test this hypothesis by comparing the mood response to TRP depletion of 12 history-positive subjects with that of 12 age- and gender-matched control subjects with no personal or family history of mental disorders.

Methods and Materials

Subjects

Twenty-eight subjects were recruited through local newspaper advertisements and word of mouth, and they provided written informed consent to participate in this study. Twenty-four subjects completed the entire protocol; 4 dropped out prior to completion. One history-positive subject was discontinued for using prescription opiates prior to testing. Another history-positive subject and 1 control subject discontinued the study due to nausea and vomiting during the first TRP depletion test. The second control subject dropped out prior to testing due to scheduling difficulties.

Of the 24 subjects completing the study, there were 12 [8 women, 4 men; aged 24 to 80 years; mean age, 48 ± 19 (SD)] who had past histories of a major depressive episode (MDE) but were currently in remission (history-positive subjects) and 12 age- and gender-matched subjects [8 women, 4 men; aged 23 to 75 years; mean age, 47 ± 18 (SD)] with no personal or family history of any mental disorder (control subjects). The clinical and demographic characteristics of the subjects are listed in Table 1.

All subjects were free of general medical or neurologic conditions based on a clinical history and review of systems, physical examination, electrocardiogram, routine blood tests, pregnancy test, and urine drug screen. History-positive subjects were selected if, after completing the Structured Clinical Interview for DSM-III-R (SCID)-patient version (Spitzer 1987), they: 1) met DSM-III-R (American Psychiatric Association 1987) criteria for past MDE; 2) did not meet DSM-III-R criteria for any other current or lifetime Axis I condition; 3) had been in clinical remission for at least 3 months [mean, 29 ± 54 (SD) months] prior to screening; 4) had been medication-free for at least 3 months prior to screening; and 5) had a score of <10 in the 25-item Hamilton Depression Rating Scale (HAM-D) (Mazure et al 1986). Control subjects were selected if, after psychiatric interview using the SCID-nonpatient version (Spitzer 1987), they: 1) did not meet DSM-III-R criteria for any current or lifetime Axis I condition; and 2) did not report during the clinical interview any DSM-III-R Axis I conditions in any first-degree relative.

Procedure

After completing the initial screening and giving informed consent, all subjects underwent two 2-day test sessions, separated

by 1 week. Each session included an amino acid drink day and a follow-up day. The experiment was conducted in a double-blind, controlled, crossover fashion. Full TRP depletion was achieved by subjects ingesting a 102-g, TRP-free, 15-amino acid drink as described in prior studies (Delgado et al 1990; Young et al 1985). Previous studies used a control drink consisting of an identical amino acid mixture supplemented with 2.3 g of L-tryptophan. For this study, however, we selected an alternative control preparation consisting of a proportionally identical 25-g, TRP-free, 15-amino acid drink (quarter-strength drink), because the FDA had banned the use of L-tryptophan following an outbreak of eosynophilia-myalgia syndrome associated with its use. In previous studies, this quarter-strength drink led to significantly less depletion of plasma TRP but was similar in nonspecific effects (Krahn et al 1996). The sequence of full- and quarter-strength tests was randomly assigned. Because of the unpleasant taste of methionine, cysteine, and arginine, these amino acids were encapsulated into 25 capsules. (For the control test, these consisted of 9 amino acid capsules and 16 lactose placebo capsules.) Subjects took the capsules 15 min before drinking the remaining amino acids suspended in water (300 mL) and flavored with 30 mL of chocolate syrup.

Testing was performed in the outpatient Psychopharmacology Research Program of the Department of Psychiatry at the University of Arizona Health Sciences Center. On Day 1 of each test session, the subjects arrived at approximately 8:30 AM after an overnight fast. At that time, plasma (10 mL) for free- and total-TRP levels was obtained and behavioral ratings were conducted. Fifteen min later, subjects ingested the 25 amino acid-containing capsules. The amino acid drink was administered approximately 15 min after the capsules by a research assistant not involved in the behavioral ratings. Behavioral ratings and plasma for free- and total-TRP levels were obtained 5 hours after the drink (approximately 2 PM) and between 11 AM and noon on Day 2. Behavioral ratings were also performed 7 hours after the drink (approximately 4 PM). During Day 1, subjects were asked to stay in a specialized procedure room that allowed for constant observation. They were allowed to move about freely, go to the bathroom, and drink water or fruit juice, but they could not eat until after 4 PM. Subjects were encouraged to read or listen to the radio, but they were not allowed to sleep, watch television, or engage in extensive interactions. There were no dietary or activity restrictions after 4 PM on Day 1.

Measurements

Behavioral ratings at each time point included the 25-item HAM-D, the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959), the self-rated Inventory of Depressive Symptoms (IDS) (Rush et al 1986), the Symptom Checklist (Woods et al 1988), and the Profile of Mood States (POMS) (McNair et al 1988). Ratings were performed by experienced research assistants with established reliability on these scales. During depletion testing, ratings of the items of the HAM-A, HAM-D, and IDS were restricted to symptoms experienced since the previous rating. The only exception to this was that ratings on the sleep-items at 2 and 4 PM of Day 1 were left unchanged from the Day 1 morning ratings. Repeated ratings on each patient were performed by the same clinician. Subjects and raters remained blinded to the sequence of testing.

Total plasma TRP was assayed by high-performance liquid chromatography with fluorometric detection (HPLC-F) (Anderson et al 1981). Free plasma TRP was measured by obtaining the ultrafiltrate of plasma from commercially available membrane filters, centrifuging (1000 *g*) at room temperature, and subjecting the ultrafiltrate to the HPLC-F method.

Data Analysis

Changes in TRP levels and in behavioral ratings (HAM-D, HAM-A, POMS, IDS) were assessed by analysis of variance (ANOVA) in a repeated measures design. This allowed for an assessment of the main effect of test dose (102 g versus 25 g drink), time (9 AM, 2 PM Day 1 and 11 AM Day 2), and group (history positive versus control), as well as the dose × time, and group × dose × time interactions. Tukey's test was used to assess the significant interactions revealed by ANOVA.

Pearsons' correlation coefficients were calculated to evaluate the relationship between change in plasma TRP levels and behavioral changes. Results were considered significant when $p = .05$. Trends are also reported when $p = .10$. All tests were two-tailed. Post-hoc analysis of changes in mood was performed with ANOVA comparing baseline and peak scores in behavioral ratings. Data analysis and graphic presentation utilized SPSS (Marija J. Norusis, SPSS Inc., Chicago, IL), Cricket Graph (Cricket Graph Users Guide, 1986, Malvern, PA.), and Statview 512 (Brain Power, Inc. 1986, Calabasas, CA) computer programs.

Results

Demographic Characteristics

The clinical characteristics of history-positive subjects and relevant demographic characteristics of control subjects are listed in Table 1. While the two groups differ in clinical history relevant to a prior MDE, there are no significant differences in age or gender distribution.

Somatic Effects

The amino acid drinks and capsules were generally well tolerated. No serious adverse effects were reported. Based on the symptom checklist scores, the most common side effects of the amino acid drink were nausea (80%) and vomiting (29% of subjects; 6/16 women and 1/8 men, 4/12 history-positive and 3/12 control subjects). All cases of vomiting occurred with the 102-g amino acid drink. The presence of vomiting did not affect the change in plasma (free or total) TRP levels after ingestion of the amino acid drink ($F = .191$; df = 1, 21; $p = .667$; and $F = .015$; df = 1,22; $p = .903$, respectively), and there was not any difference in the mood response of subjects who vomited. There were no group (history positive versus control subjects) × time interactions on ANOVA with repeated

Table 2. Tryptophan Plasma Levels During Depletion Testing[a]

		Blood sampling			
		Free TRP plasma levels		Total TRP plasma levels	
Test Dose	Time	History-positive	Control	History-positive	Control
25-g Drink	Baseline	16.67 ± 3.85	16.29 ± 3.71	54.16 ± 17.73	61.09 ± 10.84
	5 hours	7.52 ± 3.90	6.50 ± 2.41	25.63 ± 11.23	23.99 ± 9.20
	Next day	16.96 ± 4.34	17.83 ± 3.37	59.12 ± 10.74	64.13 ± 12.53
102-g Drink	Baseline	17.59 ± 3.18	16.29 ± 3.85	55.55 ± 12.29	54.73 ± 11.76
	5 hours	3.04 ± 2.02	2.31 ± 1.59	9.35 ± 6.31	8.00 ± 3.90
	Next day	15.90 ± 3.23	15.85 ± 3.66	57.53 ± 12.05	56.18 ± 15.08

[a]Units: μmol/L.
TRP, tryptophan.

measures of symptom checklist scores. Neither amino acid drink had significant effects on pulse and blood pressure.

Effects on TRP Levels

Both the 102-g and the 25-g amino acid drinks significantly lowered plasma levels of free and total TRP in all subjects. ANOVA for free TRP revealed significant main effects of dose ($F = 13.7$; df = 1,19; $p = .002$), and time ($F = 343.8$; df = 2,38; $p = .0001$), as well as a significant interaction between dose × time ($F = 12.7$; df = 2,38; $p = .0001$), but no significant main effect of group ($F = 0.385$; df = 1; $p = .542$). Similar effects were seen for the total TRP levels with ANOVA showing significant main effects of dose ($F = 20.3$; df = 1,22; $p = .0002$), time ($F = 293.11$; df = 2, 40; $p = .0001$), and a significant dose × time interaction ($F = 9.93$; df = 2,40; $p = .0003$), but no significant main effect of group ($F = .051$, df = 1, $p = .823$).

When measured at 5 hours after ingestion, the 25-g drink caused on average a 50% depletion of free and 57% depletion of total TRP, while the 102-g drink caused, on average, an 85% depletion of free and 84% depletion of total TRP. There was full recovery to baseline levels by the next morning (see Table 2).

Effects on Behavioral Measurements

Behavioral changes varied markedly in latency of onset. For this reason, the peak behavioral scores obtained during testing were considered for post-hoc analysis. TRP depletion caused significant increases in depressive symptoms as reflected by the HAM-D score in history-positive subjects but not in control subjects. This is demonstrated by the highly significant main effects of diagnosis ($F = 37.6$, df = 1,22; $p = .0001$), time ($F = 39.9$; df = 1,22; $p = .0001$), and the diagnosis × time interaction ($F = 16.1$; df = 1,22, $p = .0006$) in ANOVA of change between baseline and peak HAM-D score. HAM-D scores for history-positive and control subjects at all time points during full strength (102 g) depletion test are illustrated in Figure 1. Those observed during quarter strength (25 g) depletion test are illustrated in Figure 2.

There was a trend towards a greater depressive response in the history-positive subjects after the 102-g drink than after the 25-g drink: mean peak HAM-D scores for the 102-g drink were 14 ± 6 (SD), compared with 10 ± 7 (SD) for the 25-g drink ($t = 2.0$, $p = .057$).

ANOVA results of the total score on the self-rated scale IDS were similar to those reported for the HAM-D revealing significant diagnosis × time interactions ($F = 15.91$; df = 1, 22; $p = .001$). Alternatively, ANOVA of total HAM-A, total POMS, and depression subscale of POMS scores showed no significant effects.

All subjects experiencing depressive symptoms during depletion returned to baseline mood within 12 to 24 hours

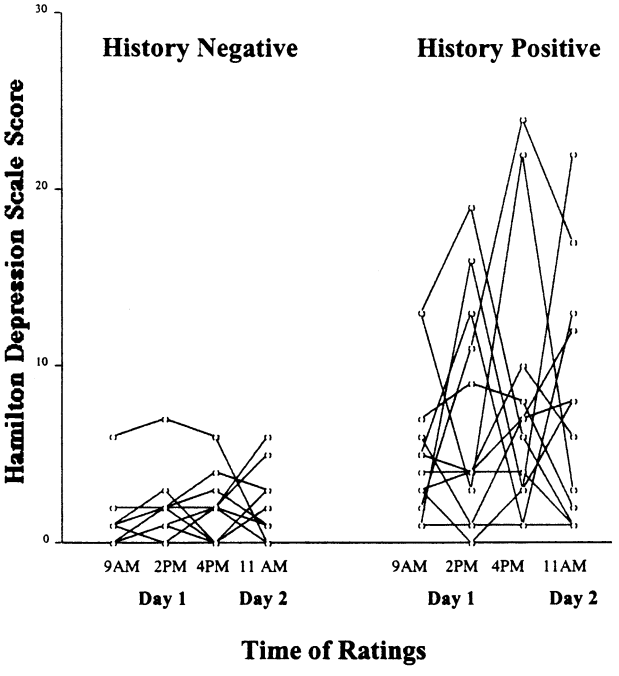

Figure 1. Depressive symptoms during full-strength tryptophan depletion.

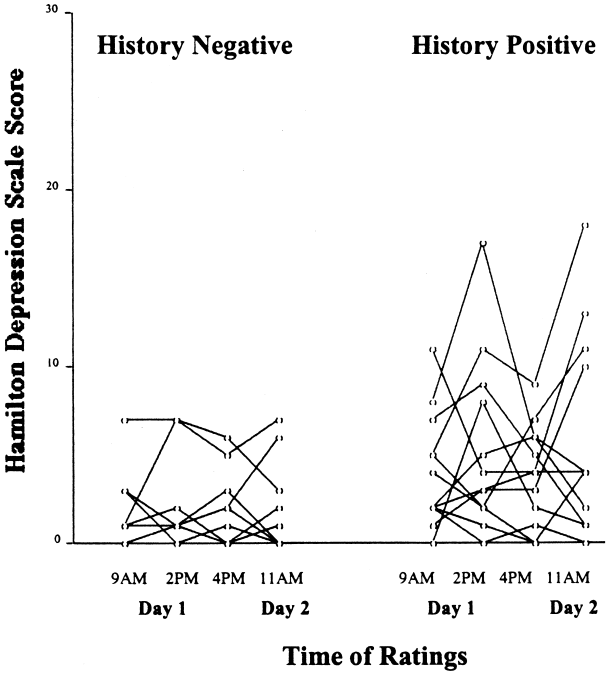

Figure 2. Depressive symptoms during quarter-strength tryptophan depletion.

of testing. Follow-up of subjects participating in this study is ongoing, and the relationship of behavioral responses to TRP depletion and future depressive episodes is being examined.

Relationships between Mood Response and Other Variables

Plasma levels of TRP during depletion did not correlate with behavioral scores. There was no effect of test sequence on behavioral response. Changes from baseline to peak HAM-D in history-positive subjects did not correlate significantly with gender, age, prior treatment form, length of remission, or number of prior episodes. However, the small sample size limits the ability to detect possible relationships.

Discussion

TRP depletion caused clinically significant depressive symptoms in history-positive but not in age- and gender-matched control subjects. The differences between the two groups of subjects in mood response to TRP depletion cannot be accounted for by differences in demographic characteristics or TRP levels before or during depletion, but appear to be related to the presence of a past history of depression. As will be discussed, these findings are most consistent with the hypothesis that mood may be more vulnerable to alterations in 5-HT neurotransmission in individuals having had an episode of major depression than in healthy control subjects. The implications of this for the pathophysiology of depression are discussed in the context of prior studies with TRP depletion in other patient groups.

Before drawing conclusions from these results, it is important to acknowledge the limitations of this study. First, and most importantly, the sample size for the study was relatively small, restricting the generalizability of our results. Second, the control-drink (25-g amino acid mixture) had a larger than anticipated effect on TRP plasma levels and, consequently, on behavioral ratings in patients with history of depression. These findings differ from a previous report in which the 25-g drink had negligible effects on plasma levels of TRP (Krahn et al 1996). Methodological differences, including the time of day in which the drink was administered (evening versus morning) and the use of a TRP-lowering diet, may contribute to such variations. Third, the latency of onset for behavioral effects was highly variable. Some subjects experienced increases in HAM-D and IDS at 5 hours, others at 7 hours after testing, and others not until the following day. A possible explanation is the fact that the brain biochemical effects of TRP depletion may be achieved later than peripheral TRP changes occur (5 to 7 hours). Carpenter and co-workers (1998) observed that significant lowering in the levels of CSF TRP and the 5-HT metabolite 5-hydoxyindoleacetic acid (5-HIAA) occur 8 to 12 hours after ingestion of the TRP depletion drink. Therefore, for analysis of data, we selected the highest behavioral score during testing, regardless of the timing (peak score).

In contrast to prior studies in healthy, as well as in genetically predisposed, subjects (Benkelfat et al 1994; Ellenbogen et al 1996; Young et al 1985), the depression subscale of the POMS was less sensitive in this study to changes in depressive symptoms during TRP depletion compared with the HAM-D and IDS. A possible explanation may be that the HAM-D and IDS rely on an averaging of symptoms over a period of time, rather than on the assessment of feelings at one point in time. Another explanation may be that patients are commonly unaware of mood changes. Furthermore, the POMS asks different questions. The HAM-D has been consistently used in our prior work as well in the work by Smith and co-workers (1997).

With these cautions in mind, there are considerable data supporting the interpretation of our results in the context of effects of TRP depletion on brain 5-HT turnover. The preclinical literature on this topic is extensive and highly consistent. All studies investigating the effects of plasma TRP depletion on brain neurochemistry in laboratory animals have shown that brain levels of TRP, 5-HIAA, and 5-HT are rapidly decreased by plasma TRP depletion (Biggio et al 1974; Gessa et al 1974).

Data from human studies using this paradigm are also highly consistent. PET imaging utilizing the radio tracer alpha (C11)-methyl TRP was performed during TRP depletion in 15 young adults without personal or family history of mental disorders. The authors reported observing a significant decrease in unidirectional trapping of alpha (C11)-methyl TRP in brain during TRP depletion when compared to baseline rates. This finding is at least indicative of a decrease of TRP availability in brain during TRP depletion, and suggestive of a decrease in the rate of brain 5-HT synthesis during the same procedure (Nishizawa et al 1997).

Rapid TRP depletion causes transient, mild, nonclinical increases in negative mood in healthy young men (Benkelfat et al 1994; Carpenter et al 1998; Moreno et al 1997; Nishizawa et al 1997; Young et al 1985). Healthy women may have greater mood responses than men (Ellenbogen et al 1996). The possibility of gender differences during TRP depletion is also supported by the greater brain biochemical effects observed in female subjects during PET imaging studies (Nishizawa et al 1997).

In contrast, many studies have shown that TRP depletion causes clinically significant depressive symptoms in remitted depressed patients taking medication. A study by Delgado and others in 1990 found that TRP depletion caused a transient depressive relapse in 67% of depressed patients who recently had therapeutic antidepressant responses to some medications. A similar study, in which the regional cerebral blood flow was measured with PET imaging during TRP depletion, replicated these findings, although with less frequent depressive relapses (Bremner et al 1997). Patients who have recently responded to SSRIs are more likely to experience a depressive relapse during TRP depletion than those who recently responded to desipramine, a medication with primarily noradrenergic effects (Delgado et al 1999). This selectivity speaks against the possibility of indiscriminate placebo effect in recovered depressives. TRP depletion also transiently reverses antidepressant response in paroxetine-treated patients with comorbid panic disorder and depression (Delgado et al 1994b) and in light therapy-treated patients with seasonal affective disorder (Lam et al 1996; Neumeister et al 1997). It also causes an increase in depressive symptoms but not in obsessive compulsive symptoms in fluvoxamine-treated patients with obsessive compulsive disorder (Barr et al 1994).

Two studies of remitted depressed patients not on medication had contrasting results. Smith and co-workers (1997) studied 15 women with histories of recurrent depression who were in remission and no longer taking medication. The subjects underwent TRP depletion ingesting an 86-g 15-amino acid drink. A control test, consisting of an identical amino acid mixture but supplemented with 1.8 g of TRP, was also performed. HAM-D ratings were obtained at 0 and 7 hours after ingestion of the test drink. Ten of the 15 subjects, experienced transient but significant depressive symptoms during tryptophan depletion, but not during placebo testing. Five of the subjects met criteria for full recurrence, and 5 others met criteria for partial recurrence. Such findings are highly consistent with the data presented in this report.

On the other hand, Leyton and co-workers 1997 reported that tryptophan depletion did not have significant mood lowering effects on 14 remitted depressed subjects who were also medication free. Since only a nonstatistically significant portion of their subjects had depressive relapses during depletion, the authors suggested that a nonidentified subgroup of patients might be likely to experience mood changes during TRP depletion. It is possible that methodological differences may have led to a subject sample less vulnerable to the depressogenic effects of TRP depletion [i.e., the exclusion of subjects with history of suicidality, a lower female/male ratio (Ellenbogen et al 1996), and the inclusion of bipolar subjects]. Additionally, the use of different mood rating scales and the timing of ratings may have affected the ability to detect mood changes. An entirely possible explanation is that the findings of TRP depletion are inconsistent enough, that in smaller studies, the variability of results is significant. Another illustration of this variability is the fact that we did not observe a gender effect in either history-positive or control subjects in contrast to the findings by Ellenbogen and co-workers (1996). In symptomatic, medication-free patients with depression (Delgado et al 1994a), panic disorder (Goddard et al 1994), or obsessive compulsive disorder (Barr et al 1992), TRP depletion causes no significant behavioral effects. TRP depletion in nondepressed, abstinent cocaine abusers causes an increased craving for cocaine during cue exposure but does not cause depressive symptoms (Satel et al 1995).

Taken together, the response of all of the subjects who have been tested with TRP depletion suggest that individuals with a depressive illness are more sensitive than other subjects to the *transient depressogenic* effects of TRP depletion. Further, these effects are only seen in patients who have achieved a clinical remission, whether on antidepressant medications or not.

The failure of TRP depletion to cause significant depressive symptoms in healthy control subjects, drug-free depressed patients, drug-free obsessive compulsive disorder patients, and drug-free panic disorder patients contrasted with the striking effects in antidepressant-treated depressed patients, light therapy treated patients, and history-positive subjects is most consistent with a theoretical model in which 5-HT function is intimately involved but is not the primary cause of depression. If the level of

depression were linearly related to the degree of 5-HT dysfunction in most people, then healthy subjects, depressed patients, and nondepressed patients with other disorders, would be expected to demonstrate a clinically significant increase in depressive symptoms during TRP depletion. Our findings are most consistent with a model in which depression results from dysfunction in regions or circuits of the brain or neurotransmitter systems modulated by 5-HT. By transiently disrupting the modulatory influence of 5-HT, TRP depletion triggers the depressive response in those subjects who most need a stable 5-HT system. Our data, and those from Smith and colleagues (1997) and Benkelfat and co-workers (1994), support the need for a prospective follow-up study to further investigate the predictive value of the mood response to TRP depletion in identifying individuals at risk for future depression. Alternatively, the findings from Leyton and co-workers (1997); and Bremner and co-workers (1997) suggest the need for further exploration of variables that may affect the individual and varying responses to TRP depletion.

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