Tryptophan Depletion, Serotonin, and Depression: Where Do We Stand?

By Alexander Neumeister, MD

ABSTRACT - Tryptophan depletion is a widely used paradigm to study serotonin system-related mechanisms in the pathophysiology and treatment of depression. There is convincing evidence that tryptophan depletion primarily and selectively affects serotonergic transmission. The behavioral data in healthy controls with and without genetic risk for depression, and in patient populations during the symptomatic phase of depression and when being remitted, suggest a trait abnormality of serotonin function in depression and that antidepressants may compensate for the underlying deficit. Tryptophan depletion may be a useful tool to create more integrative models for the pathophysiology of depression that take into account neurobiological systems beyond monoamines. More recent studies combining tryptophan depletion with genetic variables may provide an important approach for studying gene/environment interactions using candidate genes to define endophenotypes, which ultimately will improve currently used diagnostic categories and help to generate more advanced models to understand the neurobiology of depression. This may lead to the development of truly novel treatment approaches for depression. Psychopharmacology Bulletin. 2003;37(4):99-115.

INTRODUCTION

There is considerable evidence available in the literature supporting the idea that brain monoamine systems play a key role in the pathogenesis of affective disorders, particularly major depression. These hypotheses have primarily taken the form of proposing abnormal regulation in serotonin, and the catecholamines norepinephrine and dopamine in the disorder. The involvement of serotonergic pathways in the pathogenesis of unipolar depression has been the subject of intensive research for many years. There is now substantial evidence available suggesting that altered brain serotonergic transmission plays a key role in the development of depression. Altered serotonin system indices including lower plasma tryptophan levels, reduced cerebrospinal fluid 5-hydroxyindolacetic (5-HIAA) levels, decreased platelet serotonin

Dr. Neumeister is a psychiatrist at the National Institute for Mental Health's Mood and Anxiety Disorders Program in Bethesda, MD.

To whom correspondence should be addressed: Alexander Neumeister, MD, NIMH, Mood and Anxiety Disorders Program, 15 K, North Drive, Room 200, Bethesda, MD 20892-2670; Tel: (301) 594-1430; Fax: (301) 594-9959; E-mail: neumeira@intra.nimh.nih.gov.
uptake, and blunted neuroendocrine responses in challenge studies of different serotonin receptors suggesting decreased brain serotonin responsiveness have been reported in depressed patients relative to healthy controls. Brain imaging studies suggest widespread impairment of serotonergic function in depression with and without suicidality. Finally, cognitive deficits have been reported in patients with major depression during an acute episode of depression and cognitive performance, particularly impairments in memory and learning have been found to be associated with serotonin dysfunction.

The situation regarding how to evaluate the potential role of serotonin in depression has been hampered by the fact that, until recently it has not been possible to measure brain serotonin directly, which means that researchers had to rely on indirect evidence. Over the past years, tryptophan depletion has provided another means of examining serotonin systems in depression and has become an important tool to investigate the role of serotonin in depression and its treatment modalities. The purpose of this review is to present the tryptophan depletion paradigm, its biochemical background, and observe how this paradigm inspired research about the pathophysiology of depression.

**BIOCHEMICAL BACKGROUND**

The aim of tryptophan depletion is to lower brain serotonin by depleting its precursor tryptophan. Most of the tryptophan in plasma is protein-bound, with only about 5% being left free and available for being transported into the brain across the blood-brain barrier by an active protein shuttle for which five other large amino acids (valine, leucine, isoleucine, phenylalanine, and tyrosine) also compete. Once in the brain, the initial step in the biosynthesis of serotonin is the conversion of L-tryptophan to 5-hydroxytryptophan, a reaction catalyzed by the rate-limiting enzyme tryptophan hydroxylase. The Michaelis constant for tryptophan hydroxylase is higher than tryptophan concentration in the brain, suggesting that under physiological conditions the activity of this enzyme is limited by the availability of the substrate. Animal studies have shown that the synthesis and content of serotonin in rat brain vary in parallel with brain tryptophan concentrations. Moreover, it has been shown that an increase in brain tryptophan concentration raises serotonin release in vitro and in vivo, although some studies disagree with these findings. In summary, the concentration of brain serotonin appears to depend upon the availability of its precursor tryptophan.

Preclinical data show that the acute administration of a tryptophan-free amino acid mixture of essential amino acids produces a rapid and substantial decrease in plasma tryptophan levels, associated with a decrease in brain tryptophan, brain serotonin, and 5-HIAA levels in rats. Studies in
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Humans show profound decreases of plasma tryptophan levels, and cerebrospinal fluid levels of 5-HIAA after oral administration of an amino acid mixture without tryptophan. Nadir values of plasma tryptophan concentration are found between 5 and 7 hours after ingestion of the amino acid load, whereas reductions in cerebrospinal fluid tryptophan and 5-HIAA are found around 2.5 hours and 4 hours after tryptophan depletion, respectively. Notably, the cerebrospinal fluid 5-HIAA continues to decrease 14 hours after the tryptophan depleting amino acid mixture was given. A positron emission tomography (PET) study of humans showing a marked lowering of brain serotonin synthesis and release induced by tryptophan depletion confirms the assumption that brain serotonin activity is transiently reduced during tryptophan depletion. However, it has to be acknowledged that uptake of alpha-methyl L-tryptophan is not clearly established as a reliable indicator of serotonin synthesis.

Two mechanisms are responsible for the transient decrease in brain serotonin activity during tryptophan depletion: 1) the amino acid mixture given to the subjects during tryptophan depletion stimulates protein synthesis in the liver, which uses up endogenous tryptophan reserves; and 2) the amino acid mixture contains large amounts of the other large neutral amino acids, which compete with tryptophan for the transport across the blood-brain barrier and thus restrict uptake of tryptophan into the brain. Both mechanisms lead to the rapid and substantial, albeit transient reduced synaptic availability of serotonin in the brain (Figure 1).

The value of a depletion paradigm depends on whether the method is reliable, reversible, and specific for the neurotransmitter system in question. All three requirements have been addressed in several studies and it has been shown that the tryptophan depletion paradigm fulfills all three requirements to be considered an important research tool to study brain serotonin function. Particularly, studies in monkeys and humans have shown that tryptophan depletion does not change the metabolism of other neurotransmitters, whereas levels of tryptophan and 5-HIAA in plasma and cerebrospinal fluid, respectively, were lowered. Thus, if the effects of tryptophan depletion can be attributed to changes in a monoaminergic transmitter system in the brain, it is most likely the serotonin system.

TRYPTOPHAN DEPLETION STUDIES IN HEALTHY SUBJECTS WITHOUT GENETIC RISK FOR DEPRESSION

Studies of tryptophan depletion in healthy subjects have shown inconsistent results. Healthy male subjects with baseline ratings of depression in the upper normal range exhibit a transient worsening of mood during tryptophan depletion, although this never amounts to clinical depression.
In contrast, healthy male subjects who were euthymic at baseline and who were rigorously screened for any psychiatric or somatic illness remained unaffected by tryptophan depletion.\textsuperscript{34,43-45} The discrepancy between these studies may be explained by differences in baseline mood states of the subjects enrolled in these studies: subjects with mean baseline depression and aggression scores at the upper end of the normal range were shown to be more susceptible to the mood-lowering effects of tryptophan depletion, whereas negative findings have been obtained in subjects who were fully

**FIGURE 1**

TRYPTOPHAN DEPLETION INDUCES A REDUCTION IN BRAIN SEROTONIN INVOLVING 2 KEY MECHANISMS: 1) THE ADMINISTRATION OF LARGE NEUTRAL AMINO ACIDS (LNAA) LACKING TRYPTOPHAN INDUCES PROTEIN SYNTHESIS IN THE LIVER WHICH LOWERS PERIPHERAL TRYPTOPHAN LEVELS; AND 2) PREDOMINANTLY THE LNAA, BUT NOT TRYPTOPHAN ARE TRANSPORTED ACROSS THE BLOOD BRAIN BARRIER WHICH LEADS TO A TRANSIENT REDUCTION IN BRAIN SEROTONIN SYNTHESIS AND RELEASE.

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Euthymic at baseline. This is in line with the literature suggesting that even low levels of depression may increase the risk to develop an episode of depression in the future.46

Tryptophan depletion studies in healthy females also yielded inconsistent results with some studies,47-49 but not others,50-54 reporting an increased risk for women to develop depressive symptoms during tryptophan depletion relative to men. This is noteworthy particularly in view of the evidence on gender-related differences in serotonin system functioning in animals55-57 and in humans.56,58 Moreover, further evidence for differential modulation of serotonergic transmission between males and females is inferred by their differing responsivity and tolerability to selective serotonin reuptake inhibitors and tricyclic antidepressants in the treatment of depression.59

TRYPTOPHAN DEPLETION STUDIES IN HEALTHY SUBJECTS AT GENETIC RISK FOR DEPRESSION

During the past decade multiple lines of evidence have supported the importance of genetic factors in the pathophysiology of major depression. Recently, there is increasing interest in whether family history, specific genes, or gene variants affect the behavioral and biochemical effects of tryptophan depletion. Several studies addressed the question of whether family history may explain the highly variable mood responses to tryptophan depletion in healthy controls. Subjects with no personal history of depression but with a positive family history of affective disorders have been shown to be at increased risk to develop depressive symptoms during tryptophan depletion relative to subjects with a negative family history of depression,44,48,60 but one study disagrees.47 Although the reasons for this discrepancy are unknown, the reported elevated drop-out rate in that study may explain the differing results. Thirty-four percent of participants did not complete the study because of increased fatigue, loss of interest in completing the study, and due to having started an antidepressant treatment during the study. It can be speculated that at least some of these subjects have developed depressive symptoms. In conclusion, a positive family history for affective disorders appears to increase the risk to develop depressive symptoms during tryptophan depletion, which further substantiates the role of genetic factors in the pathophysiology of depression.

Based on the consistent biochemical results obtained with tryptophan depletion, the paradigm appears to be a useful tool to study serotonin-system related genes and gene variants and their potential implication in the pathophysiology of depression. Given the reported serotonergic abnormalities in major depression related to the serotonin transporter (5-HTT)61 and the fact that serotonergic antidepressants, which are mainstays in the pharmacological treatment of depression,62 target the
5-HTT, genetic research explored the potential role of that gene in depression. The human 5-HTT gene has been cloned and maps to chromosome 17q11.1-q12, and two common polymorphisms have been described: a Variable-Number-Tandem-Repeat (VNTR) located in intron 2 (5-HTT-VNTR), and a deletion/insertion in the transcriptional control region approximately 1 kilobase (kb) upstream of the transcription initiation site (5-HTTLPR). The promotor polymorphism has been shown to influence transcription activity and 5-HTT function. The short form of this variant, designated ‘s’, is associated with lower basal and induced transcriptional efficiency of the 5-HTT gene promotor, resulting in lower serotonin uptake activity when compared to the long form, designated ‘l’. The l/l genotype yielded higher levels of 5-HTT function and expression than did the s/l and s/s genotypes, which did not differ significantly from each other. Altogether, both in vitro and in vivo studies showed that the s-allele leads to reduced transcription and expression.

A recent tryptophan depletion (TD) in healthy women provides preliminary evidence that the mood lowering effect of tryptophan depletion depends upon the genotype for the 5-HTTLPR, as well as upon family history. In healthy females the s/s allele of the 5-HTTLPR was associated with an increased risk of developing depressive symptoms during TD, irrespective of family history for mood disorders. In contrast, individuals with the l/l genotype did not develop depressive symptoms in response to TD, irrespective of the family history of mood disorders, implying this genotype exerted a protective effect on mood in the TD paradigm. Finally, l/s subjects without MDD relatives showed a mood response to TD that was intermediate between the s/s and l/l subjects, while l/s subjects with MDD relatives showed the same depressiogenic effect of TD as was seen in the s/s subjects. Thus, the s-allele and a positive family history for mood disorders appeared to be additive risk factors for the development of depression during TD in healthy women.

Altogether, behavioral responses to tryptophan depletion in healthy subjects show a high variability. In contrast, the biochemical effects of tryptophan depletion are highly consistent across studies. Subgroups of control subjects without a personal history of depression appear to be at a greater risk to develop depressive symptoms during tryptophan depletion. Possible explanations include a positive family history of depression, specific gene variants, female gender, and possibly high baseline ratings of depression, albeit not reaching the levels of clinical depression.

**TRYPTOPHAN DEPLETION STUDIES IN SUBJECTS WITH MAJOR DEPRESSION**

To test the hypothesis that decreased serotonin function is associated with depression, several studies were performed, including untreated,
### Tryptophan Depletion Studies in Patients with Depression

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<td>Untreated, symptomatic depressed patients</td>
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<td>Depressive Symptoms decreased after i.v. TRP infusion during depletion</td>
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<td><strong>B. Remitted depressed patients on antidepressant medications</strong></td>
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<td>Remitted depressed patients on SSRIs citalopram</td>
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symptomatic depressed patients prior to initiation of an antidepressant treatment. It was hypothesized that tryptophan depletion would lead to an exacerbation of the depressive syndrome. However, it was shown consistently that tryptophan depletion did not exacerbate depressive symptoms in these subjects. Of note, in two studies some patients showed an improvement on the day after tryptophan depletion. Also, tryptophan depletion failed to disrupt the antidepressant effects of sleep deprivation in unmedicated depressed patients and extended the beneficial effects beyond a night of recovery sleep. The failure to aggravate depression by depleting brain serotonin was explained via brain serotonin function, which is already maximally dysfunctional in depressed patients and thus further lowering of serotonin activity has no additional effects on depressive symptoms. Alternatively, it can be hypothesized that disturbed serotonin function does not explain the biological basis of depression, and there is no apparent relationship between severity of the depressive syndrome and brain serotonin function. A possible explanation for the improvement in symptoms the day after tryptophan depletion is an increased sensitivity of serotonin receptors on the postsynaptic neuron after tryptophan depletion. Typically, serotonin levels are restored the day after tryptophan depletion and the net effect may be an enhancement of brain serotonin function, resulting in an improvement of the patient’s condition.

### Table (Cont.)

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<td>C. Remitted depressed patients off treatment</td>
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<td>No exacerbation of depressive syndrome</td>
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TD = tryptophan depletion; SD = sham depletion; SSRI = selective serotonin reuptake inhibitor.

Tryptophan depletion has been used extensively to explain the mechanisms of action of antidepressants. There have been a number of studies published involving depressed patients who had responded to antidepressant medications with putative different mechanisms of action. The hypothesis for these studies was that administration of antidepressant leads to a time-dependent process of neuronal adaptation with an enhancement of serotonergic transmission that mediates the antidepressant effects. Thus, it was expected that tryptophan depletion would disrupt the antidepressant effects of medications with a predominantly serotonergic mode of action but would leave patients on catecholaminergic antidepressants unaffected. Overall, tryptophan depletion was shown to induce a transient return of depressive symptoms with peak behavioral effects about 4-6 hours after ingestion of the amino acid mixture at the time when the plasma tryptophan levels are lowest. Notably, the content of the depressive symptomatology during the depressive symptom exacerbation is remarkable similar to the original presentation of the depressive syndrome.

The rates of symptom exacerbation from these studies as determined by an increase in depressive symptoms on the Hamilton Depression Rating Scale vary across studies and clearly showed an association with the antidepressant medication. Apparently, tryptophan depletion is capable of disrupting the antidepressant effects of serotonergic antidepressants but not of catecholaminergic antidepressants. This finding, and the finding that catecholamine depletion predominantly induces a depressive relapse in subjects treated with noradrenergic antidepressants, suggests that intact serotonergic or noradrenergic transmission is necessary to maintain the antidepressant responses to serotonergic or catecholaminergic agents, respectively.

The effects of tryptophan depletion in formerly depressed, fully remitted patients off medication is of particular interest in understanding the role of serotonin in the pathophysiology of depression. Several studies have tested the hypothesis that deficient serotonin function plays a key role in the pathophysiology of depression and may trigger a depressive episode and consequently expected remitted subjects to experience a transient depressive symptom exacerbation during tryptophan depletion. The two studies showing that tryptophan depletion can induce acute temporary depressive symptom exacerbation in untreated, euthymic patients suggest that serotonin dysfunction represents a trait marker for depression.

**DISCUSSION**

The serotonin hypothesis of depression and the involvement of serotonin in antidepressant treatments have received strong support from the tryptophan depletion studies. Given that animal studies and later studies...
in humans have proven that the paradigm is specific for the serotonin system, tryptophan depletion is a useful tool to study serotonin-related mechanisms in depression. Findings that tryptophan depletion induces depressive symptom exacerbation in healthy controls at genetic risk for depression, and in untreated, remitted patients with a history of depression—but not in control subjects without genetic risk for depression—suggest that serotonin dysfunction is a trait abnormality in depression. However, it must be acknowledged that we do not fully understand the neural correlate of the depressive symptom exacerbation and increased vulnerability for depression because the published neuroimaging studies have a number of limitations, such as small sample size. In addition, most of the subjects were on antidepressant medications that most likely interacted with the neurochemical effects of tryptophan depletion. These limitations notwithstanding, the functional imaging studies using PET of tryptophan depletion-induced depressive relapse in remitted depressed subjects showed that glucose metabolism decreased in the orbitofrontal, ventrolateral prefrontal cortex, the frontal polar cortex, the pregenual cingulate cortex, and thalamus in patients who relapsed during tryptophan depletion, but not in subjects who did not relapse during tryptophan depletion. In addition, at baseline (prior to tryptophan depletion), relapsers had a more increased metabolism in the amygdala than nonrelapsers. These data were largely consistent with other PET studies of remitted subjects with MDD (most of whom were on medication) conducted using $[^15O]H_2O$ which found that decreased tryptophan levels and exacerbation of depressive symptoms were associated with diminished cerebral blood flow in the ventral anterior cingulate, orbitofrontal cortex and caudate nucleus. These areas have also been implicated in depressive subjects during an acute episode of depression and thus may represent an important circuitry in depression. However, to identify the key circuitry in depression and the direction of changes in metabolism and blood flow underlying the syndrome of depression, functional imaging studies during tryptophan depletion in unmedicated remitted depressed patients are needed.

The time course of the effects of tryptophan depletion needs to be addressed. Most remitted depressed patients experience a transient depressive symptom exacerbation during tryptophan depletion with peak effects occurring between 4-6 hours after intake of the amino acid mixture, irrespective of the medication status. As of yet, there is no explanation for individual vulnerability to relapse. The likelihood of depressive symptom exacerbation is obviously affected by the length of remission and a critical threshold effect with mood changes occurring when tryptophan is depleted beyond a certain level. Patients who were recently remitted (at least 2 weeks) were at higher risk to develop
depressive symptoms during tryptophan depletion than those being remitted for a longer period (an average of 45 weeks in Bremner et al.80). This suggests maintenance of the antidepressant effects depends on the synaptic availability of serotonin in the early phase of the treatment and that long-term administration of antidepressants may induce biological changes in neurons that make the subjects less vulnerable to acute changes in synaptic serotonin availability.

The findings that depressive symptom exacerbation during antidepressant treatment is specific to the type of treatment and type of antidepressant (which tryptophan depletion failed to exacerbate depressive symptoms in untreated, symptomatic depressed patients and healthy controls without genetic risk for depression), and that remitted patients off medication have a return of symptoms during tryptophan depletion, suggest that serotonin systems are modulating other neurobiological systems, which may play a more primary role in the pathophysiology of depression. There is a growing body of evidence for the role of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) in the pathophysiology and treatment of depression. BDNF may have antidepressant effects, possibly enhancing serotonin synthesis and promoting the survival and sprouting of serotonergic fibers. Antidepressants which increase synaptic levels of monoamines, (eg, serotonin) by either blocking their reuptake or metabolism of these monoamines, induce activation of intracellular signal transduction cascades that target neurotrophins (eg, BDNF) which maintain homeostatic plasticity in the central nervous system. Thus, tryptophan depletion which is expected to reduce synaptic serotonin levels, which will result in decreased BDNF levels, will not undo the trophic effects, but the chemical signal which would use the circuitry re-instated by the neurotrophic factors is gone temporarily. Moreover, in a positive feedback-loop, the reduction in levels of neurotrophins will ultimately lead to a transient decrease of a number of neurotransmitters, including serotonin (Figure 2). However, it is unlikely that any long-lasting effects on neurotrophin function are induced by tryptophan depletion leading to any chronic major effects on brain structure or function. This can explain why recently remitted patients on medication have a greater likelihood to relapse during tryptophan depletion than patients who are in a more stable remission. It can be assumed that recently remitted patients depend primarily upon availability of serotonin to maintain the antidepressant response whereas in patients with a more stable remission the primary antidepressant effects are primarily maintained by neurotrophic factors which allows the chemical signal (serotonin) to restore the affective circuitry. However, this model does not fully explain why untreated remitted patients relapse during tryptophan depletion. It can be
speculated, and preliminary data support this hypothesis, that specific serotonin-related genes and gene variants modify the risk to experience depressive symptoms during tryptophan depletion.\textsuperscript{71,99} Although, the noted studies have a number of methodological limitations that need to be addressed in more conclusive studies.

In conclusion, the data obtained from tryptophan depletion studies provide insight into the neurobiological mechanisms involved in the pathophysiology of depression, and also into the mechanisms of action of antidepressant treatments. Future research should try to further increase our knowledge about the changes in transmitter function and its

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**FIGURE 2**

Tryptophan depletion induces a transient reduction in serotonin (5-HT) synthesis and release via reduced uptake of tryptophan across the blood brain barrier (BBB). Reduction of the 5-HT signal leads to a reduced activation of intracellular signal transduction cascades, including the cAMP-CREB cascade and the phosphatidylinositol-inositol pathway, which results in a reduction of BDNF levels. This reduction is believed to acutely decrease a number of neurotransmitters, but should not induce a long-lasting disruption of the neurotrophic support. Consequently, no major effects of tryptophan depletion on brain structure can be expected but the affective circuitry will be transiently dysfunctional.

TRP=tryptophan; LNAA=large neutral amino acids; 5-OHTR=5-hydroxytryptophan; TRY Ohlase=tryptophan-hydroxylase; AADC=aromatic amino acid decarboxylase; PLC=phospholipase; PIP2=phosphoinositide 4,5-biphosphate; DAG=diacylglycerol; IP3=inositol monophosphate; cAMP=cyclic adenosine monophosphate; CREB=cAMP response element-binding protein; BDNF=brain-derived neurotrophic factor; PKA=cAMP-dependent protein kinase; TrkB=specific tyrosine kinases receptor; NE=norepinephrine; GABA=γ-aminobutyric acid; Glu=Glutamate.

implications on other neurobiological systems downstream of the serotonin system. This may become of clinical relevance considering the growing body of evidence suggesting plasticity regulators as targets for the next generation of agents for the treatment of depression.

REFERENCES


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