Key Words: tryptophan, serotonin, depression, genetics, pathophysiology

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,[1] and the catecholamines norepinephrine,[2,3] and dopamine[4] 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.[5] Altered serotonin system indices including lower plasma tryptophan levels[6,7] reduced cerebrospinal fluid 5-hydroxyindolacetic (5-HIAA) levels,[8] decreased platelet serotonin

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uptake,[9] and blunted neuroendocrine responses in challenge studies of different serotonin receptors suggesting decreased brain serotonin responsiveness,[10-13] have been reported in depressed patients relative to healthy controls. Brain imaging studies suggest widespread impairment of serotonergic function in depression with[14] and without suicidality.[15,16] Finally, cognitive deficits have been reported in patients with major depression during an acute episode of depression[17,18] and cognitive performance, particularly impairments in memory and learning have been found to be associated with serotonin dysfunction.[19,20]

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.[21] 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.[22] Animal studies have shown that the synthesis and content of serotonin in rat brain vary in parallel with brain tryptophan concentrations.[23] Moreover, it has been shown that an increase in brain tryptophan concentration raises serotonin release *in vitro*[24,25] and *in vivo*,[26,27] although some studies disagree with these findings.[28,29] 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.[30] Studies in

humans show profound decreases of plasma tryptophan levels,[31,32] and cerebrospinal fluid levels of 5-HIAA[33-35] 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.[35] Notably, the cerebrospinalfluid 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.[36] 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 without tryptophan 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.[37-40] Particularly, studies in monkeys[41] and humans[42] 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.

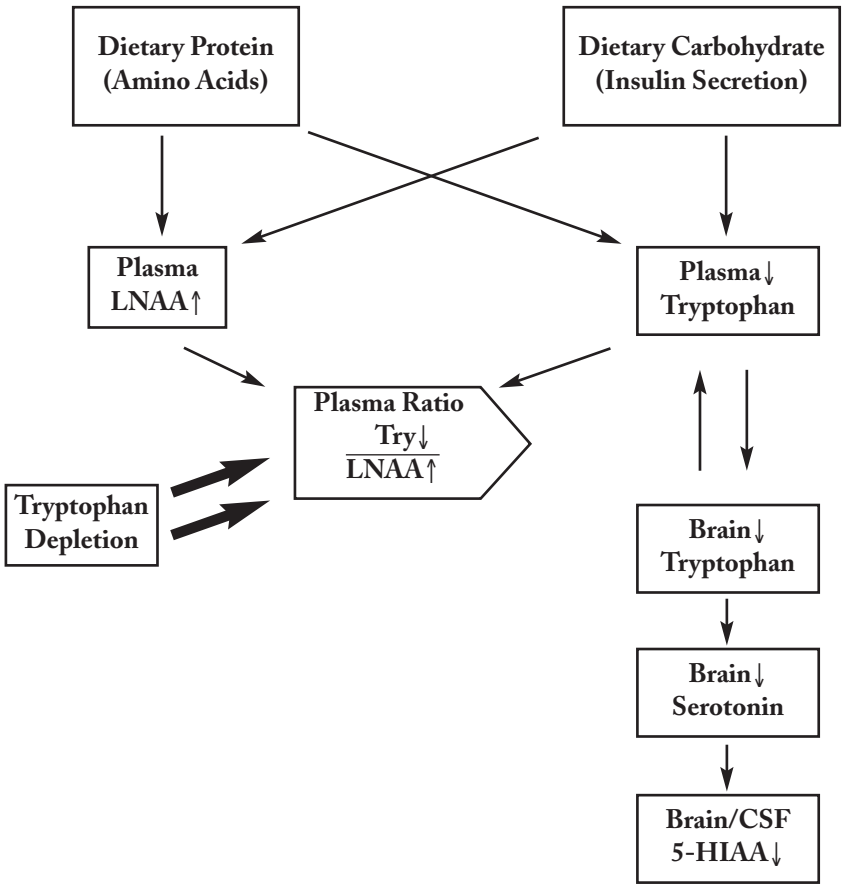
TRYPTOPHAN DEPLETION STUDIES IN HEALTHY SUBJECTS WITHOUT GENETIC RISK FOR DEPRESSION

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.[32,39]

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.[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 animals[55-57] and in humans.[36,58] 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,[63] 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,[64,65] and two common polymorphisms have been described: a Variable-Number-Tandem-Repeat (VNTR) located in intron 2 (5-HTT-VNTR),[65] and a deletion/insertion in the transcriptional control region approximately 1 kilobase (kb) upstream of the transcription initiation site (5-HTTLPR).[66] 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'.[66-70] 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.[71] 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,

TABLE

TRYPTOPHAN DEPLETION STUDIES IN PATIENTS WITH DEPRESSION

Structure	Study Design	Reference	N of Subjects	Intervention	Outcome
A. Untreated depressed patients					
Untreated, symptomatic depressed patients	Double blind, placebo-controlled, balanced crossover study	Delgado et al.[75]	43	TD vs SD	Bimodal mood response one day after TD: 37% of patients show decrease of HDRS total score, 23% increase of HDRS score
Untreated, symptomatic depressed patients	Double blind, placebo-controlled, balanced crossover study	Neumeister et al.[31]	11	TD vs SD	No exacerbation of depressive syndrome
Untreated, symptomatic depressed patients, mCPP Infusion during depletion	Double blind, placebo-controlled, balanced crossover study	Price et al.[73]	22	TD vs SD	Cortisol response to i.v. mCPP greater during TD than SD
Untreated, symptomatic depressed patients TRP-Infusion at maximum point of depletion	Double blind, placebo-controlled, balanced crossover study	Price et al.[72]	38	TD vs SD	Depressive Symptoms decreased after i.v. TRP following TD, not SD
B. Remitted depressed patients on antidepressant medications					
Remitted depressed patients on SSRI citalopram	Double-blind, placebo controlled, parallel-group design	Aberg-Wistedt et al.[79]	20	TD vs SD	Transient depressive relapse on 5/12 patients after TD, not SD
Remitted depressed patients on SSRIs	Double blind, placebo-controlled, balanced crossover study	Bremner et al.[80]	21	TD vs SD	Transient depressive relapse on 7 patients after TD, not SD
Remitted depressed patients in antidepressant-induced remission	Double blind, placebo-controlled, balanced crossover study	Delgado et al.[38]	21	TD vs SD	Transient depressive relapse on 14 of 21 after TD
Fluoxetine- or Desipramine-Responders	Double blind, placebo-controlled, balanced crossover study	Delgado et al.[81]	30	TD vs SD	8/15 fluoxetine responders relapsed, 1/15 desipramine responders relapsed after TD, not SD

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symptomatic depressed patients prior to initiation of an antidepressant treatment.[72-75] 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[72,75] 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.[76] 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.)

TRYPTOPHAN DEPLETION STUDIES IN PATIENTS WITH DEPRESSION *(Continued)*

Structure	Study Design	Reference	N of Subjects	Intervention	Outcome
C. Remitted depressed patients off treatment					
Remitted drug free patients	Double blind, controlled, balanced crossover study	Moreno et al.[54]	24 (including 12 healthy controls)	TD vs SD	Transient depressive relapse in patients
Remitted drug free patients	Double blind, placebo-controlled, balanced crossover study	Smith et al.[85]	15 Women	TD vs SD	Transient depressive relapse after TD, not SD
Patients fully remitted, off therapy	Double blind, placebo-controlled, balanced crossover study	Leyton et al.[84]	14	TD	No exacerbation of depressive syndrome

TD=tryptophan depletion; SD=sham depletion; SSRI=selective serotonin reuptake inhibitor.

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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[77] 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[38,78-81] but not of catecholaminergic antidepressants.[81,82] This finding, and the finding that catecholamine depletion predominantly induces a depressive relapse in subjects treated with noradrenergic antidepressants,[81,83] 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.[54,84,85] The two studies[54,85] 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.[80] 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 $[^{15}O]H_2O$ 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.[86-88] These areas have also been implicated in depressive subjects during an acute episode of depression[89] 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[80,90] and a critical threshold effect with mood changes occurring when tryptophan is depleted beyond a certain level.[33] Patients who were recently remitted (at least 2 weeks[90]) 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.

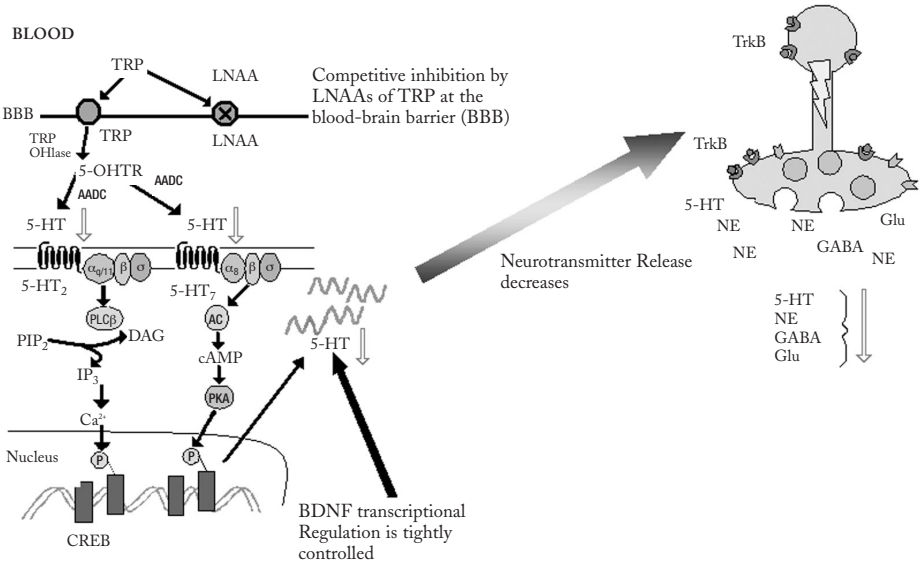
The findings that depressive symptom exacerbation during antidepressant treatment is specific to the type of treatment and type of antidepressant (which tryptophan depletion failed to exacerbate depressive symptoms in untreated, symptomatic depressed patients and healthy controls without genetic risk 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.[91-94] BDNF may have antidepressant effects,[92,95] possibly enhancing serotonin synthesis[94] and promoting the survival and sprouting of serotonergic fibers.[96,97] 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.[98] 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.[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

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 PHOSPHATIDYL-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; IP=inositolmonophosphate; 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.

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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

1. Coppen A. The biochemistry of affective disorders. *Br J Psychiatry*. 1967;113(504):1237-64.
2. Schatzberg AF, Schildkraut JJ. Recent studies on norepinephrine systems in mood disorders. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press; 1995:911-920.
3. Bunney WE, Jr., Davis JM. Norepinephrine in depressive reactions. A review. *Arch Gen Psychiatry*. 1965;13(6):483-94.
4. Kapur S, Mann JJ. Role of the dopaminergic system in depression. *Biol Psychiatry*. 1992;32(1):1-17.
5. Heninger GR, Charney DS, Sternberg DE. Serotonergic function in depression. Prolactin response to intravenous tryptophan in depressed patients and healthy subjects. *Arch Gen Psychiatry*. 1984;41(4):398-402.
6. Coppen A, Eccleston EG, Peet M. Total and free tryptophan concentration in the plasma of depressive patients. *Lancet*. 1973;2(7820):60-3.
7. Cowen PJ, Parry-Billings M, Newsholme EA. Decreased plasma tryptophan levels in major depression. *J Affect Disord*. 1989;16(1):27-31.
8. Asberg M, Thoren P, Traskman L, Bertilsson L, Ringberger V. "Serotonin depression"-a biochemical subgroup within the affective disorders? *Science*. 1976;191(4226):478-80.
9. Healy D, Leonard BE. Monoamine transport in depression: kinetics and dynamics. *J Affect Disord*. 1987;12(2):91-103.
10. Cowen PJ, Charig EM. Neuroendocrine responses to intravenous tryptophan in major depression. *Arch Gen Psychiatry*. 1987;44(11):958-66.
11. Mann JJ, McBride PA, Malone KM, DeMeo M, Keilp J. Blunted serotonergic responsivity in depressed inpatients. *Neuropsychopharmacol*. 1995;13(1):53-64.
12. Meltzer HY, Maes M. Effects of ipsapirone on plasma cortisol and body temperature in major depression. *Biol Psychiatry*. 1995;38(7):450-7.
13. Siever LJ, Murphy DL, Slater S, de la Vega E, Lipper S. Plasma prolactin changes following fenfluramine in depressed patients compared to controls: an evaluation of central serotonergic responsivity in depression. *Life Sci*. 1984;34(11):1029-39.
14. Oquendo MA, Placidi GP, Malone KM, Campbell C, Keilp J, Brodsky B, Kegeles LS, Cooper TB, Parsey RV, Van Heertum RL, Mann JJ. Positron emission tomography of regional brain metabolic responses to a serotonergic challenge and lethality of suicide attempts in major depression. *Arch Gen Psychiatry*. 2003;60(1):14-22.
15. Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, Sanacora G, Owens MJ, Nemeroff CB, Rajeevan N, Baldwin RM, Seibyl JP, Innis RB, Charney DS. Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. *Biol Psychiatry*. 1998;44(11):1090-8.
16. Mann JJ, Malone KM, Diehl DJ, Perel J, Cooper TB, Mintun MA. Demonstration in vivo of reduced serotonin responsivity in the brain of untreated depressed patients. *Am J Psychiatry*. 1996;153(2):174-82.
17. Sweeney JA, Kmiec JA, Kupfer DJ. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biol Psychiatry*. 2000;48(7):674-84.
18. Grant MM, Thase ME, Sweeney JA. Cognitive disturbance in outpatient depressed younger adults: evidence of modest impairment. *Biol Psychiatry*. 2001;50(1):35-43.
19. Riedel WJ, Klaassen T, Deutz NE, van Someren A, van Praag HM. Tryptophan depletion in normal volunteers produces selective impairment in memory consolidation. *Psychopharmacol (Berl)*. 1999;141(4):362-9.

20. Schmitt JA, Jorissen BL, Sobczak S, van Boxtel MP, Hogervorst E, Deutz NE, Riedel WJ. Tryptophan depletion impairs memory consolidation but improves focussed attention in healthy young volunteers. *J Psychopharmacol*. 2000;14(1):21-9.
21. Fernstrom JD. Role of precursor availability in control of monoamine biosynthesis in brain. *Physiol Rev*. 1983;63(2):484-546.
22. Friedman PA, Kappelman AH, Kaufman S. Partial purification and characterization of tryptophan hydroxylase from rabbit hindbrain. *J Biol Chem*. 1972;247(13):4165-73.
23. Fernstrom JD, Wurtman RJ. Brain serotonin content: physiological dependence on plasma tryptophan levels. *Science*. 1971;173(992):149-52.
24. Schaechter JD, Wurtman RJ. Tryptophan availability modulates serotonin release from rat hypothalamic slices. *J Neurochem*. 1989;53(6):1925-33.
25. Auerbach S, Lipton P. Regulation of serotonin release from the in vitro rat hippocampus: effects of alterations in levels of depolarization and in rates of serotonin metabolism. *J Neurochem*. 1985;44(4):1116-30.
26. Sharp T, Bramwell SR, Grahame-Smith DG. Effect of acute administration of L-tryptophan on the release of 5-HT in rat hippocampus in relation to serotoninergic neuronal activity: an in vivo microdialysis study. *Life Sci*. 1992;50(17):1215-23.
27. Carboni E, Cadoni C, Tanda GL, Di Chiara G. Calcium-dependent, tetrodotoxin-sensitive stimulation of cortical serotonin release after a tryptophan load. *J Neurochem*. 1989;53(3):976-8.
28. Marsden CA, Conti J, Strope E, Curzon G, Adams RN. Monitoring 5-hydroxytryptamine release in the brain of the freely moving unanaesthetized rat using in vivo voltammetry. *Brain Res*. 1979;171(1):85-99.
29. Elks ML, Youngblood WW, Kizer JS. Serotonin synthesis and release in brain slices: independence of tryptophan. *Brain Res*. 1979;172(3):471-86.
30. Gessa GL, Biggio G, Fadda F, Corsini GU, Tagliamonte A. Effect of the oral administration of tryptophan-free amino acid mixtures on serum tryptophan, brain tryptophan and serotonin metabolism. *J Neurochem*. 1974;22(5):869-70.
31. Neumeister A, Praschak-Rieder N, Hesselmann B, Tauscher J, Kasper S. [The tryptophan depletion test. Basic principles and clinical relevance.] *Nervenarzt*. 1997;68(7):556-62.
32. Young SN, Smith SE, Pihl RO, Ervin FR. Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacol*. 1985;87(2):173-7.
33. Salomon RM, Kennedy JS, Johnson BW, Schmidt DE, Kwentus J, Gwirtsman HE, Ebert MH. Association of a critical CSF tryptophan threshold level with depressive relapse. *Neuropsychopharmacol*. 2003;28(5):956-60.
34. Carpenter LL, Anderson GM, Pelton GH, Gudin JA, Kirwin PD, Price LH, Heninger GR, McDougle CJ. Tryptophan depletion during continuous CSF sampling in healthy human subjects. *Neuropsychopharmacol*. 1998;19(1):26-35.
35. Williams WA, Shoaf SE, Hommer D, Rawlings R, Linnoila M. Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. *J Neurochem*. 1999;72(4):1641-7.
36. Nishizawa S, Benkelfat C, Young SN, Leyton M, Mzengeza S, de Montigny C, Blier P, Diksic M. Differences between males and females in rates of serotonin synthesis in human brain. *Proc Natl Acad Sci USA*. 1997;94(10):5308-13.
37. Ellenbogen MA, Young SN, Dean P, Palmour RM, Benkelfat C. Mood response to acute tryptophan depletion in healthy volunteers: sex differences and temporal stability. *Neuropsychopharmacol*. 1996;15(5):465-74.
38. Delgado PL, Charney DS, Price LH, Aghajanian GK, Landis H, Heninger GR. Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch Gen Psychiatry*. 1990;47(5):411-8.
39. Smith SE, Pihl RO, Young SN, Ervin FR. A test of possible cognitive and environmental influences on the mood lowering effect of tryptophan depletion in normal males. *Psychopharmacol*. 1987;91(4):451-7.
40. Moja EA, Cipolla P, Castoldi D, Tofanetti O. Dose-response decrease in plasma tryptophan and in brain tryptophan and serotonin after tryptophan-free amino acid mixtures in rats. *Life Sci*. 1989;44(14):971-6.
41. Young SN, Ervin FR, Pihl RO, Finn P. Biochemical aspects of tryptophan depletion in primates. *Psychopharmacol*. 1989;98(4):508-11.

42. Neumeister A, Turner EH, Matthews JR, Postolache TT, Barnett RL, Rauh M, Vetticad RG, Kasper S, Rosenthal NE. Effects of tryptophan depletion vs catecholamine depletion in patients with seasonal affective disorder in remission with light therapy. *Arch Gen Psychiatry*. 1998;55(6):524-30.
43. Abbott FV, Etienne P, Franklin KB, Morgan MJ, Sewitch MJ, Young SN. Acute tryptophan depletion blocks morphine analgesia in the cold-pressor test in humans. *Psychopharmacol*. 1992;108(1-2):60-6.
44. Benkelfat C, Ellenbogen MA, Dean P, Palmour RM, Young SN. Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. *Arch Gen Psychiatry*. 1994;51(9):687-97.
45. Knott VJ, Howson AL, Perugini M, Ravindran AV, Young SN. The effect of acute tryptophan depletion and fenfluramine on quantitative EEG and mood in healthy male subjects. *Biol Psychiatry*. 1999;46(2):229-38.
46. Keller MB. Long-term treatment strategies in affective disorders. *Psychopharmacol Bull*. 2002;36 Suppl 2:36-48.
47. Ellenbogen MA, Young SN, Dean P, Palmour RM, Benkelfat C. Acute tryptophan depletion in healthy young women with a family history of major affective disorder. *Psychol Med*. 1999;29(1):35-46.
48. Klaassen T, Riedel WJ, van Someren A, Deutz NE, Honig A, van Praag HM. Mood effects of 24-hour tryptophan depletion in healthy first-degree relatives of patients with affective disorders. *Biol Psychiatry*. 1999;46(4):489-97.
49. Schmeck K, Sadigorsky S, Englert E, Demisch L, Dierks T, Barta S, Poustka F. Mood changes following acute tryptophan depletion in healthy adults. *Psychopathol*. 2002;35(4):234-40.
50. Murphy FC, Smith KA, Cowen PJ, Robbins TW, Sahakian BJ. The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. *Psychopharmacol (Berl)*. 2002;163(1):42-53.
51. Yatham LN, Liddle PF, Shiah IS, Lam RW, Adam MJ, Zis AP, Ruth TJ. Effects of rapid tryptophan depletion on brain 5-HT(2) receptors: a PET study. *Br J Psychiatry*. 2001;178(5):448-53.
52. Voderholzer U, Hornyak M, Thiel B, Huwig-Poppe C, Kiemen A, Konig A, Backhaus J, Riemann D, Berger M, Hohagen F. Impact of experimentally induced serotonin deficiency by tryptophan depletion on sleep EEG in healthy subjects. *Neuropsychopharmacol*. 1998;18(2):112-24.
53. Oldman A, Walsh A, Salkovskis P, Fairburn CG, Cowen PJ. Biochemical and behavioural effects of acute tryptophan depletion in abstinent bulimic subjects: a pilot study. *Psychol Med*. 1995;25(5):995-1001.
54. Moreno FA, Gelenberg AJ, Heninger GR, Potter RL, McKnight KM, Allen J, Phillips AP, Delgado PL. Tryptophan depletion and depressive vulnerability. *Biol Psychiatry*. 1999;46(4):498-505.
55. Fischette CT, Biegon A, McEwen BS. Sex differences in serotonin 1 receptor binding in rat brain. *Science*. 1983;222(4621):333-5.
56. Fischette CT, Biegon A, McEwen BS. Sex steroid modulation of the serotonin behavioral syndrome. *Life Sci*. 1984;35(11):1197-206.
57. Zhang L, Barker JL, Xing G, Giorgi O, Ma W, Chang YH, Hu Q, Choi N, Rubinow DR. 5-HT1A receptor mRNA expressions differ in the embryonic spinal cord of male and female rats. *Neurosci Lett*. 1997;237(1):41-4.
58. McBride PA, Tierney H, DeMeo M, Chen JS, Mann JJ. Effects of age and gender on CNS serotonergic responsivity in normal adults. *Biol Psychiatry*. 1990;27(10):1143-55.
59. Kornstein SG, Schatzberg AF, Thase ME, Yonkers KA, McCullough JP, Keitner GI, Gelenberg AJ, Davis SM, Harrison WM, Keller MB. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry*. 2000;157(9):1445-52.
60. Quintin P, Benkelfat C, Launay JM, Arnulf I, Pointereau-Bellenger A, Barbault S, Alvarez JC, Varoquaux O, Perez-Diaz F, Jouvent R, Leboyer M. Clinical and neurochemical effect of acute tryptophan depletion in unaffected relatives of patients with bipolar affective disorder. *Biol Psychiatry*. 2001;50(3):184-90.
61. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem*. 1994;40(2):288-95.
62. Tylee A. Depression in Europe: experience from the DEPRES II survey. Depression Research in European Society. *Eur Neuropsychopharmacol*. 2000;10 Suppl 4:S445-8.
63. Suhara T, Takano A, Sudo Y, Ichimiya T, Inoue M, Yasuno F, Ikoma Y, Okubo Y. High levels of serotonin transporter occupancy with low-dose clomipramine in comparative occupancy study with fluvoxamine using positron emission tomography. *Arch Gen Psychiatry*. 2003;60(4):386-91.

64. Ramamoorthy S, Bauman AL, Moore KR, Han H, Yang-Feng T, Chang AS, Ganapathy V, Blakely RD. Antidepressant- and cocaine-sensitive human serotonin transporter: molecular cloning, expression, and chromosomal localization. *Proc Natl Acad Sci U S A*. 1993;90(6):2542-6.
65. Lesch KP, Balling U, Gross J, Strauss K, Wolozin BL, Murphy DL, Riederer P. Organization of the human serotonin transporter gene. *J Neural Transm Gen Sect*. 1994;95(2):157-62.
66. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, Lesch KP. Allelic variation of human serotonin transporter gene expression. *J Neurochem*. 1996;66(6):2621-4.
67. Heils A, Mossner R, Lesch KP. The human serotonin transporter gene polymorphism—basic research and clinical implications. *J Neural Transm*. 1997;104(10):1005-14.
68. Little KY, McLaughlin DP, Zhang L, Livermore CS, Dalack GW, McFinton PR, DelProposto ZS, Hill E, Cassin BJ, Watson SJ, Cook EH. Cocaine, ethanol, and genotype effects on human midbrain serotonin transporter binding sites and mRNA levels. *Am J Psychiatry*. 1998;155(2):207-13.
69. Collier DA, Stober G, Li T, Heils A, Catalano M, Di Bella D, Arranz MJ, Murray RM, Vallada HP, Bengel D, Muller CR, Roberts GW, Smeraldi E, Kirov G, Sham P, Lesch KP. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol Psychiatry*. 1996;1(6):453-60.
70. Greenberg BD, Tolliver TJ, Huang SJ, Li Q, Bengel D, Murphy DL. Genetic variation in the serotonin transporter promoter region affects serotonin uptake in human blood platelets. *Am J Med Genet*. 1999;88(1):83-7.
71. Neumeister A, Konstantinidis A, Stastny J, Schwarz MJ, Vitouch O, Willeit M, Praschak-Rieder N, Zach J, De Zwaan M, Bondy B, Ackenheil M, Kasper S. Association Between Serotonin Transporter Gene Promoter Polymorphism (5HTTLPR) and Behavioral Responses to Tryptophan Depletion in Healthy Women With and Without Family History of Depression. *Arch Gen Psychiatry*. 2002;59(7):613-20.
72. Price LH, Malison RT, McDougle CJ, Pelton GH, Heninger GR. The neurobiology of tryptophan depletion in depression: effects of intravenous tryptophan infusion. *Biol Psychiatry*. 1998;43(5):339-47.
73. Price LH, Malison RT, McDougle CJ, McCance-Katz EF, Owen KR, Heninger GR. Neurobiology of tryptophan depletion in depression: effects of m- chlorophenylpiperazine (mCPP). *Neuropsychopharmacol*. 1997;17(5):342-50.
74. Neumeister A, Praschak-Rieder N, Hesselmann B, Vitouch O, Rauh M, Barocka A, Kasper S. Rapid tryptophan depletion in drug-free depressed patients with seasonal affective disorder. *Am J Psychiatry*. 1997;154(8):1153-5.
75. Delgado PL, Price LH, Miller HL, Salomon RM, Aghajanian GK, Heninger GR, Charney DS. Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. *Arch Gen Psychiatry*. 1994;51(11):865-74.
76. Neumeister A, Praschak-Rieder N, Hesselmann B, Vitouch O, Rauh M, Barocka A, Tauscher J, Kasper S. Effects of tryptophan depletion in drug-free depressed patients who responded to total sleep deprivation. *Arch Gen Psychiatry*. 1998;55(2):167-72.
77. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
78. Spillmann MK, Van der Does AJ, Rankin MA, Vuolo RD, Alpert JE, Nierenberg AA, Rosenbaum JF, Hayden D, Schoenfeld D, Fava M. Tryptophan depletion in SSRI-recovered depressed outpatients. *Psychopharmacol (Berl)*. 2001;155(2):123-7.
79. Aberg-Wistedt A, Hasselmark L, Stain-Malmgren R, Aperia B, Kjellman BF, Mathe AA. Serotonergic 'vulnerability' in affective disorder: a study of the tryptophan depletion test and relationships between peripheral and central serotonin indexes in citalopram-responders. *Acta Psychiatr Scand*. 1998;97(5):374-80.
80. Bremner JD, Innis RB, Salomon RM, Staib LH, Ng CK, Miller HL, Bronen RA, Krystal JH, Duncan J, Rich D, Price LH, Malison R, Dey H, Soufer R, Charney DS. Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. *Arch Gen Psychiatry*. 1997;54(4):364-74.
81. Delgado PL, Miller HL, Salomon RM, Licinio J, Krystal JH, Moreno FA, Heninger GR, Charney DS. Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. *Biol Psychiatry*. 1999;46(2):212-20.

82. Evans L, Golshan S, Kelsoe J, Rapaport M, Resovsky K, Sutton L, Gillin JC. Effects of rapid tryptophan depletion on sleep electroencephalogram and mood in subjects with partially remitted depression on bupropion. *Neuropsychopharmacol*. 2002;27(6):1016-26.
83. Miller HL, Delgado PL, Salomon RM, Berman R, Krystal JH, Heninger GR, Charney DS. Clinical and biochemical effects of catecholamine depletion on antidepressant-induced remission of depression. *Arch Gen Psychiatry*. 1996;53(2):117-28.
84. Leyton M, Young SN, Blier P, Ellenbogen MA, Palmour RM, Ghadirian AM, Benkelfat C. The effect of tryptophan depletion on mood in medication-free, former patients with major affective disorder. *Neuropsychopharmacol*. 1997;16(4):294-7.
85. Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. *Lancet*. 1997;349(9056):915-9.
86. Rampin O, Bernabe J, Giuliano F. Spinal control of penile erection. *World J Urol*. 1997;15(1):2-13.
87. Smith KA, Morris JS, Friston KJ, Cowen PJ, Dolan RJ. Brain mechanisms associated with depressive relapse and associated cognitive impairment following acute tryptophan depletion. *Br J Psychiatry*. 1999;174:525-9.
88. Morris JS, Smith KA, Cowen PJ, Friston KJ, Dolan RJ. Covariation of activity in habenula and dorsal raphe nuclei following tryptophan depletion. *Neuroimage*. 1999;10(2):163-72.
89. Drevets WC. Neuroimaging studies of mood disorders. *Biol Psychiatry*. 2000;48(8):813-29.
90. Delgado PL, Price LH, Miller HL, Salomon RM, Licinio J, Krystal JH, Heninger GR, Charney DS. Rapid serotonin depletion as a provocative challenge test for patients with major depression: relevance to antidepressant action and the neurobiology of depression. *Psychopharmacol Bull*. 1991;27(3):321-30.
91. Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff K, N AG, Zarate CA, Jr., Charney DS. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol Psychiatry*. 2003;53(8):707-42.
92. Duman RS, Malberg J, Nakagawa S, D'Sa C. Neuronal plasticity and survival in mood disorders. *Biol Psychiatry*. 2000;48(8):732-9.
93. Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol Psychiatry*. 2001;50(4):260-5.
94. Siuciak JA, Clark MS, Rind HB, Whittemore SR, Russo AF. BDNF induction of tryptophan hydroxylase mRNA levels in the rat brain. *J Neurosci Res*. 1998;52(2):149-58.
95. Altar CA. Neurotrophins and depression. *Trends Pharmaco Sci*. 1999;20:59-61.
96. Mamounas LA, Altar CA, Blue ME, Kaplan DR, Tessarollo L, Lyons WE. BDNF promotes the regenerative sprouting, but not survival, of injured serotonergic axons in the adult rat brain. *J Neurosci*. 2000;20(2):771-82.
97. Mamounas LA, Blue ME, Siuciak JA, Altar CA. Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. *J Neurosci*. 1995;15(12):7929-39.
98. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. *Nat Med*. 2001;7(5):541-7.
99. Moreno FA, Rowe DC, Kaiser B, Chase D, Michaels T, Gelernter J, Delgado PL. Association between a serotonin transporter promoter region polymorphism and mood response during tryptophan depletion. *Mol Psychiatry*. 2002;7(2):213-6.