

# Tryptophan Supplementation in the Pharmacotherapy of Anorexia Nervosa

**Opinion****Abstract**

The significance of diet in human health, behavior and therapeutics is becoming increasingly recognized. All amino acids, being building blocks to the synthesis of proteins, are critical for life, but scientific interest on the role of tryptophan, an essential amino acid, in the modulation of behavior and treatment of brain disorders emerged because tryptophan is the precursor of neurotransmitter 5-hydroxytryptamine (5-HT; serotonin). Tryptophan hydroxylase, the rate limiting enzyme of serotonin biosynthesis exists unsaturated with its substrate under normal physiological conditions. It can be speculated that tryptophan supplementation could boost serotonin synthesis and neurotransmission and may be effective in the treatment of serotonin deficiency disorder. Anorexia nervosa, an eating disorder, characterized by false body perception, intense fear of weight gain, hyperactivity and amenorrhea is associated with high risk of mortality. Excessive starvation and exercise in anorexia nervosa, despite its negative consequences, parallels some features of addiction. Evidence suggests that the efficacy of pharmacotherapy in anorexia nervosa is not satisfactory. This article draws attention towards improving pharmacotherapy in anorexia nervosa by tryptophan supplementation. Studies performed in our laboratory on rat models show that excessive dietary restriction and starvation decreases serotonin neurotransmission, firstly by decreasing the nutritional availability of the essential amino acid tryptophan, the precursor of serotonin and secondarily by an increase in the effectiveness of feedback control over the synthesis and release of serotonin. A deficiency of serotonin produces depression like effects while the release of dopamine neurotransmission from the inhibitory effects of serotonin may lead to hyperactivity and addiction like behavior observed in anorexia nervosa patients. It is suggested that tryptophan supplementation can improve efficacy of pharmacotherapy in anorexia nervosa by increasing availability of precursor for serotonin synthesis and normalizing feedback control over serotonin synthesis and release.

**Keywords:** Tryptophan; Essential amino acid; Anorexia nervosa; Serotonin; Appetite; Depression; Hyperactivity; SSRIs; Antipsychotics

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**Abbreviations:** 5-HT: 5-hydroxytryptamine; SSRIs: Selective Serotonin Reuptake Inhibitors; AN: Anorexia Nervosa

**Introduction**

The significance of diet in human behavior and brain functions is becoming increasingly recognized. A range of dietary factors can alter the chemistry of developing as well as an adult brain to produce therapeutically important effects on mental functions. On the other hand, there is a growing need of side effect free treatments to boost mood and cognition and help coping daily life stresses. The importance of tryptophan supplementation in the treatment of anorexia nervosa is the focus of this article. All amino acids, being building blocks to the synthesis of proteins, are critical for life, but scientific interest on the role of tryptophan as a dietary factor in the modulation of behavior and treatment of brain disorders emerged because tryptophan is the precursor of neurotransmitter serotonin and the availability of tryptophan is known to have important role in the synthesis of serotonin [1-6]. It can be speculated that tryptophan supplementation could boost serotonin neurotransmission and may be effective in the treatment of serotonin deficiency disorder.

**Anorexia nervosa and its pharmacotherapy**

Anorexia nervosa (AN) is a severe eating disorder which is much prevalent in women than men. The AN patients have an intense fear of weight gain, even when they are underweight. The eating disorder is thought to be caused by cultural pressures for thinness. It is characterized by false body perception, intense fear of weight gain and amenorrhea and is associated with high risk of mortality [7-11]. The disease usually starts quite harmlessly and may begin as a simple attempt to lose weight to look more beautiful and attractive. Sociocultural pressure for thinness triggers self-imposed starvation and excessive exercise to precipitate AN [12].

**Starvation and diet restriction: effects on tryptophan and brain serotonin**

Although starvation and excessive dietary restriction can affect a number of metabolic pathways, its effects on circulating tryptophan and brain serotonin are focused in this article. In an early study<sup>13</sup> we found that male rats fed on a restricted feeding schedule of 4h/day for 5 days exhibited 16% reduction in the body weight. Serotonin levels and synthesis rate in the hypothalamus

also decreased. Long term diet restriction (4h/ day for 4 weeks) produced 25 % reduction in the body weights of male rats and 20% reduction in the body weights of female rats [14]. Plasma and brain tryptophan levels decreased and the decreases were greater in female than male rats, suggesting that female sex is more vulnerable to food restriction-induced deficiency of tryptophan.

In later investigations on the mechanism involved in diet restriction-induced decreases of brain serotonin we found that diet restriction produces a marked increase in the effectiveness of serotonin receptors located on cell body and dendrites of serotonergic neurons [15]. These somatodendritic receptors provide a feedback control over synthesis and release of serotonin. An increase in the effectiveness of these receptors is expected to decrease synthesis of serotonin as well as its release at the functional postsynaptic sites. A similar mechanism impairs adaptation to stress to produce depression like behavior in rat models. Conversely adaptation to stress is associated with a decrease in the effectiveness of these receptors [16]. Therapeutic effects of selective serotonin reuptake inhibitors (SSRIs) and other antidepressants are also mediated via a decrease in the effectiveness of feedback regulation over serotonin synthesis and release. These studies tend to suggest that excessive dieting and starvation can decrease serotonin neurotransmission to produce depressive symptoms by decreasing the availability of serotonin precursor tryptophan as well as by increasing the effectiveness of somatodendritic serotonin receptors. Diet restriction-induced decreases of serotonin neurotransmission also produce hyperactivity<sup>15</sup> because dopamine neurotransmission is released from the inhibitory influence of serotonin.

That a restricted diet lowers plasma tryptophan levels in healthy humans has been also shown (for review [11]). A decrease in plasma tryptophan and a decrease in the availability of tryptophan, represented as the ratio of tryptophan to other large neutral amino acids in plasma [17] associated with reduced serotonin neurotransmission [11-12] is also reported in underweight anorexia nervosa patients. However, these deficits of tryptophan and serotonin as well as anxiety and depressive symptoms of anorexia nervosa are not always reversed after weight recovery.

## Conclusion

The pharmacological options for anorexia nervosa include antipsychotics and antidepressants<sup>12, 18</sup>. The rationale for the use of antipsychotics is based upon psychomotor hyperactivity and obsessions with weight and body shape, while treatment with antidepressants is thought to alleviate stress effects on mood. Available information [12,18] suggest that efficacy of pharmacotherapy in anorexia nervosa is not satisfactory. Although low doses of olanzapine and haloperidol produce some clinically useful effects; treatment with most antipsychotic drugs is associated with moderate to severe side effects. SSRIs, the most commonly prescribed antidepressant, are not very effective in treating depressive symptoms in anorexia nervosa patients. Because therapeutic effects of SSRIs heavily depend upon the availability of tryptophan and serotonin synthesis, a nutritional deficiency of tryptophan can limit therapeutic effects of SSRIs. Increasing serotonin neurotransmission by tryptophan

supplementation can also reduce hyperactivity [19] and improve therapeutic use of antipsychotic drugs [20].

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