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Review article

Improving therapeutics in anorexia nervosa with tryptophan

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Chemical compound studied in this article:
Tryptophan (2-amino-3-(1H-indol-3-yl) propanoic acid)
Serotonin (5-hydroxytryptamine)
Dopamine (3,4-dihydroxyphenyl ethylamine)
Kynurenic acid (4-hydroxyquinoline-2-carboxylic acid)
Quinolinic acid (pyridine-2,3-dicarboxylic acid)
5-HIAA (5-hydroxyindole acetic acid)
5-HTP (5-hydroxytryptophan)
Valine (2-amino-3-methylbutyric acid)
Fluoxetine (*N*-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine
GABA (gamma-aminobutyric acid)

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ABSTRACT

A growing body of evidence suggests that our diet is an important contributing factor in the development, management and prevention of a number of psychiatric illnesses. Tryptophan, an essential amino acid, is the sole precursor of neurotransmitter 5-hydroxytryptamine (5-HT; serotonin). Administration of tryptophan can boost serotonin neurotransmission to produce therapeutically important effects in serotonin deficiency disorders. Anorexia nervosa (AN) an eating disorder associated with high levels of psychiatric comorbidity including psychosis, hyperactivity, depression and anxiety has highest lethality of all psychiatric illnesses. Evidence suggests that excessive dieting and food restriction can decrease brain tryptophan and serotonin in AN patients to precipitate depression, psychosis and hyperactivity. There are currently no FDA approved pharmacological treatments available for AN patients; antidepressants and antipsychotics, largely used to treat associated psychiatric comorbidities are also not very effective. The aim of this non-systematic review article is to evaluate and document a potential importance of tryptophan supplementation in improving therapeutics in AN patients.

Contents

Abbreviations: AN, Anorexia nervosa; 5-HIAA, 5-hydroxyindole acetic acid; 5-HT, 5-hydroxytryptamine; 5-HTP, 5-hydroxytryptophan; LNAAs, Large neutral amino acids; LAADC, L-Aromatic amino acid decarboxylase; MAO, Monoamine oxidase; SSRIs, Selective serotonin reuptake inhibitors.

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1. Introduction

It is now becoming increasingly recognized that our diet play an important role in mental health and behavior. A number of dietary nutrients are important contributing factors in the development, management and treatment of psychiatric illnesses such as depression, schizophrenia, attention deficit hyperactivity and eating disorders [1]. The present article addresses role of tryptophan in improving therapeutics in anorexia nervosa (AN) patients. Tryptophan, an essential amino acid, is the sole precursor of neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) and administration of tryptophan has been shown to increase tryptophan as well as serotonin levels in the brain [2–3]. The neurotransmitter serotonin is implicated in a number of cerebral functions including mood, anxiety, appetite and cognition. It is also involved in responses to stress and can modulate dopamine mediated behaviors such as motor activity, and addiction [4–6]. Therefore, it is worth suggesting that tryptophan administration can facilitate serotonin neurotransmission and may be useful in treating 5-HT deficiency in various brain diseases.

AN is a behavioral disorder characterized by body image distortion, self-imposed starvation and refusal to eat. Though underweight and malnourished, AN patients have an intense fear of weight gain [7]. The disease is associated with high levels of psychiatric comorbidity including psychosis, hyperactivity, depression and anxiety; resulting in significant functional impairment [8]. Relapse after treatment is very common and AN has the highest lethality of all psychiatric illnesses. The disease starts harmlessly with an intense and uncontrollable desire of becoming thin and some cultural pressures resulting in self-imposed starvation and loss of weight. The turning point at which dieting becomes unnecessary is missed by AN patients and with continued dietary restriction, a false perception of body image, addiction to excessive exercise and hyperactivity appear as the hallmark symptoms of the disease. Because AN is an eating disorder and increasing serotonin neurotransmission via arcuate nucleus of the hypothalamus is known to elicit satiety signal and inhibit feeding [9]; serotonin neurotransmission seems important in the etiology as well pharmacotherapy of AN. Moreover, serotonin is also implicated in other behavioral dysregulations such as depression, anxiety and psychosis, which occur frequently in AN patients [4,6,9].

Currently, there is no proven effective pharmacotherapy for patients affected by AN. Antidepressants and antipsychotics are largely used to treat psychiatric comorbidities in AN patients; however, the efficacy of these treatments is also not adequate [10]. Studies on the mechanism of action of antidepressants and antipsychotics suggest that deficits in serotonin neurotransmission can reduce efficacy of the treatment [4,6,9]. This article is a non-systematic review on the role of tryptophan in improving therapeutics in AN patients. The first part of the article describes the mechanism of a tryptophan-induced increase of brain serotonin and its effectiveness in facilitating serotonin mediated functions. Next, preclinical and clinical studies on long term starvation-induced changes of circulating tryptophan and serotonin neurotransmission are presented to understand the pathophysiology of AN. Finally, a potential role of tryptophan supplementation in improving efficacy of pharmacotherapy in anorexia nervosa is evaluated.

2. Tryptophan, an essential amino acid

Tryptophan is a non-polar, hydrophobic amino acid. In humans and many other organisms, it is an essential amino acid and cannot be synthesized endogenously. Plants and micro-organisms can, however, produce tryptophan. The English chemists Frederick Hopkins and Sydney Cole [11] isolated it from casein and soon thereafter its molecular structure determined.

Very small amount of tryptophan is stored in the body. Therefore, compared to other amino acids it is present in very low concentration in the body and a daily intake is essential to meet the need. The recommended daily intake is between 250 mg and 425 mg per day [12]. A protein rich diet is a good source of tryptophan, but compared to other amino acids little tryptophan is there in a protein rich diet and ingestion of a protein rich diet produces little effect on brain tryptophan concentration [13].

3. The metabolic role of tryptophan

Once ingested with the food, all amino acids, including tryptophan are absorbed into the blood circulation. These are taken up by cells to be part of the amino acid pool used for the synthesis and turnover of proteins. Tryptophan is required for a number of metabolic pathways, shown in Fig. 1. As a constituent of protein, tryptophan is critical for protein synthesis, but unlike a non-essential amino acid, for which, de novo synthesis can regulate homeostatic balance; the plasma concentration of tryptophan is related directly to its dietary availability. The synthesis of protein therefore depends upon the availability of tryptophan. However, the extent to which part of absorbed tryptophan is utilized for protein synthesis remains not clear.

Quantitatively the most important route of tryptophan metabolism is the synthesis of kynurenine. About 90% of the tryptophan is metabolized via the kynurenine pathway [14]. Kynurenic acid and quinolinic acid, the two metabolites of kynurenine have the potential to modulate glutamate neurotransmission. Kynurenic acid acts as an antagonist at glutamate receptors while quinolinic acid is an agonist at these receptors [14]. Acting via the quinolinic acid pathway, tryptophan may be utilized as a precursor of niacin. A large amount of tryptophan is however required to produce one mg of niacin, while adequate amount of niacin is usually available from food. Tryptophan supplementation for niacin synthesis is therefore less important.

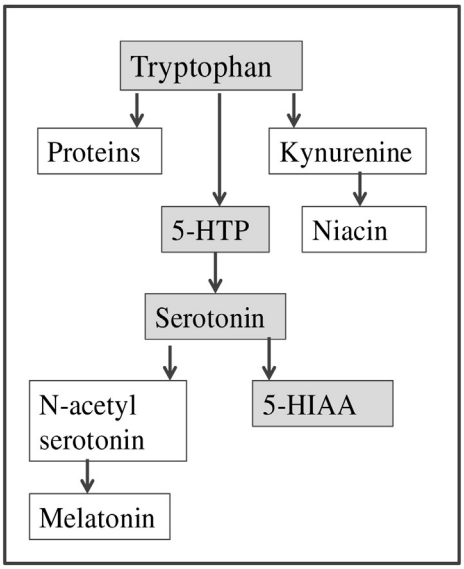

Fig. 1. Schematic representation of metabolic role of tryptophan.