Health Benefits of Tryptophan in Children and Adults

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Abstract

This mini-review provides a brief overview of the role of L-tryptophan in the synthesis of serotonin, quinolinic acid, and kynurenic acid, which are critically important for neuronal development and synaptogenesis, neuroimmune activity, and mitochondrial function. Tryptophan is not synthesised in the human body and it is only available in the diet. As an essential amino acid, it is required for protein synthesis and as a precursor of key biomolecules such as serotonin, melatonin, tryptamine, niacin, quinolinic acid and kynurenic acid, nicotinamide adenine dinucleotide etc. Adequate intake of this amino acid is crucial for growth and development in children and adults. Excessive dietary restriction and malnutrition decreases brain serotonin stores and leads to behavioral changes such as hyperactivity, depression, anxiety, suppression of appetite, anorexia nervosa, and behavioral impulsivity. Dietary supplementation of tryptophan may improve these disorders. Our studies showed that tryptophan isolated from human milk depicted profoundly higher antioxidant activity compared with whole human milk. Tryptophan's powerful antioxidant activity assists in reducing oxidative stress and exerts anti-inflammatory effects. Bioactive factors in human milk are crucial to the health of newborns. Some mothers may not be able to breastfeed their babies. Addition of L-tryptophan to infant formula, equivalent to concentration in breast milk, may significantly improve infant growth and increase antioxidant properties of the formula.

Keywords: Tryptophan, Serotonin, Melatonin, Human Milk, Antioxidant potential of tryptophan

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Introduction

Tryptophan is an essential amino acid necessary for normal development and growth in children and for nitrogen balance in adults. The principal role of tryptophan in the human body is synthesis of proteins, and muscle tissues. Dietary sources of tryptophan in adult humans are dairy products, meats, fish, eggs, bananas, oats, pumpkin and sesame seeds, chocolate, dried dates, soy, tofu, tree nuts, including peanuts and peanut butter. Breast milk is the primary source of tryptophan in nursing infants.

Tryptophan occurs in L- and D-isomeric forms with an indole ring and aromatic side chain. The L-form occurs most commonly in the biological systems particularly in the higher organisms, including humans. The D-form is confined to some bacterial cell wall proteins and certain peptide antibiotics [1]. Figure 1 shows the tetrahedral arrangement of the binding orbitals around the α-carbon atom by four different groups, viz, $H3N^-$, H, R, and COO^-.

As illustrated in Figure 1, tryptophan is the precursor of several biologically active compounds such as serotonin (5-hydroxy tryptamine, 5-HT), quinolinic acid, and kynurenic acid, which are important for neuronal development and synaptogenesis, neuroimmune activity, and mitochondrial function. Tryptophan is also the precursor of melatonin and niacin. Serotonin is a monoamine neurotransmitter and is involved in mood and cognition function. As the sole precursor of brain serotonin, tryptophan plays an important role in induction of sleep, appetite, mood and sensory perception. Evidence indicates that the enterochromaffin cells in the gastrointestinal (GI) tract also produce serotonin which maintains GI contractibility, motility, permeability, and secretions. It's now becoming clear that serotonin plays an important role in the brain-gut axis and such serotonergic neurotransmission is influenced by gut microbiota. The developing serotonergic system in child's GI tract may be vulnerable to differential microbial colonisation patterns prior to the emergence of stable microbiota that exists in the adult GI tract [2]. Melatonin either produced by tryptophan metabolism or by the pineal gland not only acts as a neurohormone, but is also a powerful free-radical scavenger [3]. It plays an important physiological role in circadian rhythms involved in sleep timing and blood pressure regulation [4]. Decreased availability of tryptophan or its disturbed metabolism may alter brain development in children. Recently, it was reported that abnormal metabolic pathways of tryptophan or perturbed metabolism of tryptophan may be involved in patients with autism [5]. The pathophysiological relevance of genetically altered tryptophan pathways in autism patients remains to be defined. Some emerging evidence from clinical trials suggest that L-tryptophan supplementation may be beneficial in treating psychiatric disorders, especially when used in combination with antipsychotic medications [6].

Metabolic degradation of tryptophan yields both glucogenic (alanine) and ketogenic (glutaryl Co A precursors through kynurenine pathway. The major metabolites of tryptophan include serotonin, melatonin, kynurenine, 3-hydroxy-DL-kynurenine, 3-hydroxy anthranilic acid, and xanthuneric acid. Tryptophan also provides the starting material for the vitamin niacin which is needed in energy metabolism. The metabolic fate of tryptophan by the kynurenine pathway is important to the pathogenesis of inflammatory and degenerative diseases. The 3-hydroxy kynurenine branch of the kynurenine pathway is activated in macrophages by infection and inflammation. 3-Hydroxy anthranilic acid, a product of 3-hydroxy kynurenine plays anti-inflammatory and neuroprotective roles during inflammation [7]. According to Krause et al. [7], the kynurenine pathway depicts an aerobic L-tryptophan degradation route of catabolism in mammals, and is involved in the pathogenesis of inflammatory, infectious, and degenerative diseases, including Huntington’s disease and stroke-induced brain disease [8]. The 3-hydroxykynurenine (3-HK) branch of the kynurenine pathway is activated in macrophages and microglia, leading to the generation of 3-HK, 3-hydroxyanthranilic acid (3-HAA), and quinolinic acid, which are considered neurotoxic owing to their free radical-generating action and N-methyl-d-aspartic acid receptor agonist activities. The antioxidant potential of L-tryptophan isolated from human milk was analyzed for oxygen radical absorption capacity

(ORAC) and its ability to mitigate bacterial lipopolysaccharide-induced pro-inflammatory cytokines (IL-6, TNF α) using an *in vitro* cell-based assay. Our unpublished findings indicate that tryptophan isolated from human milk possesses nearly 99-fold higher ORAC capacity than that of whole human milk (7,986 ± 468 µm Trolox equivalent (TE)/g *versus* 80.4± 13.3 µm TE/g). These results suggest that tryptophan isolated from human milk is a powerful antioxidant as depicted by ORAC values (Table 1). The high antioxidant and free radical scavenging capacity of tryptophan may be due to its aromatic side chain and the indole ring [9]. As mentioned earlier, the primary source of tryptophan in nursing infants is breast milk [10]. Tryptophan released from mother's milk has high antioxidant properties and free radical scavenging activity. The antioxidant and anti-inflammatory properties of breast milk may not only help in the normal development of CNS, GI tract but also other organ systems in the newborns, especially preterm infants. Tryptophan supplements are recommended to relieve pain, depression and insomnia. Tryptophan supplementation may improve pharmacotherapy in patients with anorexia nervosa by increasing serotonin content in brain [11]. Daily adult dietary intake of tryptophan should not exceed 220 mg. Whey protein concentrate or isolates are good source of tryptophan. As an antioxidant, tryptophan supplementation is recommended in infant foods. To determine the free and total tryptophan levels in breast milk and plasma, a group of 30 healthy breastfeeding women either received 2-4 grams of L-tryptophan, or 20 - 40 grams of alpha-lactalbumin, or no supplement. Total tryptophan concentration in breast milk remained unaffected by oral administration of L-tryptophan or alpha-lactalbumin, whereas the levels of free L-tryptophan and alpha-lactalbumin were found to be significantly greater in breast milk (representing about 2% of total tryptophan). Free tryptophan levels were also measured in 12 different infant formulas marketed in North America. Two infant formulas showed free tryptophan contents below the detection limit (< 0.5 µ mol/L), while in other ten the free tryptophan ranged from 31.34 to 24,994.29 µmol/L. All study groups had significantly lower amounts of free tryptophan in breast milk compare to free tryptophan in extensively hydrolysed formulas. The results of this study show that even though single oral doses of L-tryptophan or alpha-lactalbumin had increased the free tryptophan levels in breast milk, these levels were within the range of concentrations found in marketed infant formulas. Maternal supplementation of diet containing tryptophan or proteins rich in tryptophan is unlikely to provide high levels of tryptophan to breastfed infants. Further, diets rich in tryptophan or alpha-lactalbumin do not seem to have the therapeutic potential to improve sleep disturbances commonly observed during early post-partum as well as reduce the risk of post-partum depression [12].

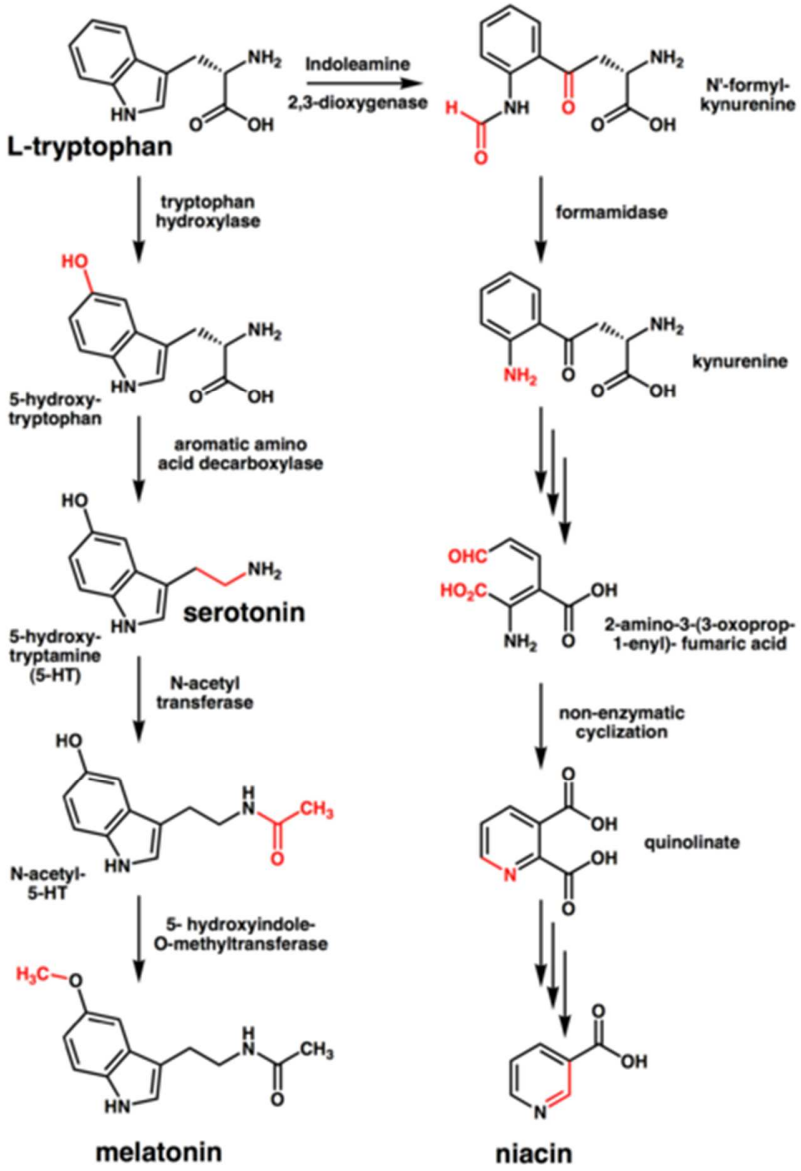

Fig. 1: Shows the enzymatic process involved in the metabolism of tryptophan and key metabolites

Table 1. Determination of anti-oxidant properties of human milk-derived tryptophan by oxygen radical absorbance capacity (ORAC).

Test material	ORAC Value (Trolox equivalent (TE))/g
Tryptophan isolated from human milk	7,986 ± 468 µm TE/g
Whole human milk	80.4± 13.3 µm TE/ g

Conclusion

Tryptophan is an essential amino acid for human health which is primarily required for protein synthesis and key biomolecules such as serotonin, melatonin, tryptamine, niacin, quinolinic acid and kynurenic acid, nicotinamide adenine dinucleotide etc. (Fig. 1). Our unpublished results of *in vitro* studies indicate that tryptophan metabolites show different growth modulating effects in human neuronal

cell line. Addition of recombinant human interferon γ in the culture medium inhibited L-tryptophan metabolism in human glial U251 cells, while L- kynurenine did not appear to be affected. The antioxidant and anti-inflammatory properties of human milk-derived peptides indicate that the peptides possess moderate degree of antioxidant and anti-inflammatory activities. In the antioxidant *in vitro* assay, the oxygen radical absorbance capacity (ORAC) values found in the presence of tryptophan isolated from human milk were 99-fold higher than that of whole human milk (Table 1).

Conflict of interest: None declared

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