Mood, food, and cognition: role of tryptophan and serotonin

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Purpose of review
Food is not only necessary as a metabolic fuel for the body, it becomes more and more evident that there exists an association between food and brain functions like mood and cognition. Tryptophan represents a key element for brain functioning, because of its role as a precursor for production of neurotransmitter serotonin (5-hydroxytryptamine). In clinical conditions, which involve chronic immune system activation or under cytokine therapy, lower tryptophan levels because of high catabolism of tryptophan as indicated by the kynurenine to tryptophan ratio are common and often associate with depressive mood.

Recent findings
Studies in the in vitro model of mitogen-stimulated peripheral blood mononuclear cells revealed that several phytocompounds, mainly antioxidants like polyphenols and vitamins, can interfere with inflammatory signaling cascades including tryptophan breakdown. If extrapolated to the in vivo situation, such compounds could increase blood and brain tryptophan availability for serotonin production. Although there is some in vivo evidence for the effect of such compounds, outcomes are hardly predictable and most likely depend on the individual’s immunological state.

Summary
Not only a diet rich in tryptophan but also a diet rich in antioxidants can have a positive impact on mood and cognition. This could be of special relevance for individuals who present with low grade inflammation conditions.

Keywords
brain, cognition, food compounds, immunity, mood

INTRODUCTION
The food we eat is not only necessary as a metabolic fuel for the body, it also influences brain functions including mind and cognition. Food can increase well-being, both physically and emotionally. It becomes more and more accepted that food intake affects mood and even more, mood seems to influence on the decision, which kind of food we prefer. Availability of tryptophan can represent a key element for both, mood and cognitive functioning, because of its role as a precursor for production of neurotransmitter serotonin (5-hydroxytryptamine, 5-HT).

TRYPTOPHAN AND SEROTONIN METABOLISM
Tryptophan is an essential amino acid for humans and only less than 1% of tryptophan is utilized for protein biosynthesis. The vast majority of tryptophan is converted to biomolecules of great relevance for neuroimmunological signaling processes and they are generated by two important biochemical pathways [1]: the production of 5-hydroxytryptophan by tryptophan 5-hydroxylase, which requires 5,6,7,8-tetrahydrobiopterin (BH\textsubscript{4}) as cofactor and the kynurenine pathway with the end product nicotinamide adenine dinucleotide (NAD), which is initiated by enzymes tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenases-1 and -2 (IDO). 5-Hydroxytryptophan is further converted to 5-hydroxytryptamine (SHT, serotonin), which...
is mainly found in the brain, in platelets, and in the gastrointestinal tract. Notably, IDO also binds and metabolizes serotonin, although with lower affinity than tryptophan.

TDO and IDO convert tryptophan to N-formylkynurenine, which is rapidly deformylated to kynurenine by formamidase [1]. Kynurenine can be utilized in the liver and in certain other cells for biosynthesis of downstream metabolites like kynurenic acid, picolinic acid, and quinolinic acid, the latter representing a source for the metabolic end products NAD/NADH. However, outside liver there are only a few cell types identified thus far, which possess the necessary enzymatic machinery to carry out these further conversion steps, among them are monocyte-derived macrophages, glial cells, astrocytes, and probably dendritic cells [2].

FOODS HIGH IN TRYPTOPHAN

It is generally recommended that healthy adults consume around 5 mg/kg body weight per day of L-tryptophan. Foods known to be high in tryptophan comprise nuts such as cashews, walnuts, peanuts, and almonds; seeds such as sesame, pumpkin, and sunflower seeds and soybeans and grains such as wheat, rice, and corn. Intake of such food can increase tryptophan availability in the body and induces the enzymatic machinery in the liver and the blood such as TDO, which is activated when blood tryptophan goes up. As a consequence, concentrations of tryptophan metabolites like serotonin but also kynurenine and its downstream catabolites increase. However, this does not necessarily lead to an increase of serotonin availability in brain tissue, because serotonin cannot efficiently pass the BBB and for the transport of tryptophan into the brain the leucine-preferring L1 transporter system is utilized in competition with the so-called large neutral amino acids (LNAA). The ratio of tryptophan: LNAA determines the flux of tryptophan into the brain and thus serotonin biosynthesis [1]. Nutrients rich in tryptophan usually also contain other amino acids in high concentrations. Then the net effect of the high tryptophan is widely lost when it must compete with LNAA for the brain transport (Fig. 1).

Research focused on the microbiome suggests an important role for the gut microbiota in influencing brain development, behavior, and mood in humans [3**]. Recently, it was observed in patients with Alzheimer’s dementia that disturbed intestinal barrier function, as indicated by increased concentrations of fecal calprotectin, could be of relevance for lowering of essential aromatic amino acids concentrations in the blood [4]. Thus, not surprisingly the composition of the microbiome may also have an impact on the availability of tryptophan.

FIGURE 1. Antioxidants increase brain serotonin availability. Large neutral amino acids (LNAA) compete with tryptophan for its transport across the blood–brain barrier (BBB) via the leucine-preferring L1 transporter system (L1). A diet rich in tryptophan will increase the availability of tryptophan in the brain for biosynthesis of 5-hydroxytryptamine (5HT, serotonin). However, such a diet often contains also other amino acids in high concentrations, so the change of the tryptophan to LNAA ratio is small. Dietary antioxidants can have two positive effects on serotonin production rates: they protect tetrahydrobiopterin (BH4), cofactor of enzyme tryptophan 5-hydroxylase (T5H), from oxidation and thus support serotonin biosynthesis (+), and they slow down (−) production of Th1-type cytokine interferon-γ (IFN-γ) and thus activity of indoleamine 2,3-dioxygenase (IDO), which rescues tryptophan and its transport into the brain will increase.

KEY POINTS

- Serotonin and tryptophan metabolism play an important role in mood and cognition.
- Antioxidants dampen cell-mediated immunity and tryptophan breakdown via indoleamine 2,3-dioxygenase (IDO).
- Nutrients rich in tryptophan and antioxidants exert a positive impact on mood and cognition.
of growth of infectious agents and malignant cells. For this reason during cell-mediated immune response, IDO is activated, mainly via Th1-type cytokine interferon-γ (IFN-γ) representing the most powerful stimulus in humans. Also other proinflammatory cytokines exert a stimulatory effect, although less prominent, for example, IFN-α and IFN-β [5]. Significant tryptophan decrease because of IDO-mediated breakdown was reported in patients with hepatitis C virus infection and with malignant melanoma undergoing IFN-α therapy [6,7]. Other cytokines and also other proinflammatory stimuli like tumor necrosis factor α (TNF-α) and lipopolysaccharide (LPS) can induce IDO and potentiate the action of IFN-γ. Thus, it is not just the amount of dietary tryptophan, which determines tryptophan availability, the immune system status can have a drastic influence to lower tryptophan levels in case of continuous activation.

As IDO converts tryptophan to kynurenine, in clinical conditions which involve acute or chronic immune system activation or under cytokine therapy, lower tryptophan levels and higher kynurenine to tryptophan ratios (Kyn/Trp) are common and often coincide with increased risk of neuropsychiatric abnormalities such as depressive mood [1,8]. This is preferentially true in patients with HIV-1 infection and with various forms of cancer but also in patients treated with proinflammatory cytokines [7,9,10]. Also in older adults poor mental health status was associated with lower tryptophan levels [11]. Because of the association of high Kyn/Trp with adverse neuropsychiatric conditions, the kynurenine pathway came into focus as a therapeutic target [1].

In these clinical conditions, higher rates of tryptophan breakdown, leading to higher Kyn/Trp and lower tryptophan levels, correlate with higher concentrations of immune activation biomarkers indicating higher IDO activity [12] and predict poor prognosis such as shorter survival. For example, low tryptophan was found to be associated with higher risk of depression and weight loss [13].

Certainly, tryptophan metabolism is not the only determinant of mood changes in patients suffering from chronic inflammatory diseases. More recently, phenylalanine metabolism was also found to be disturbed in such diseases [10], for example in the healthy older adults several significant relationships between ongoing immune activation and inflammation, disturbed tryptophan and phenylalanine metabolism, and signs of depression and neurovegetative complaints were observed [13]. In addition, in a recent cross-sectional study it was noted that lower serum tryptophan levels in patients undergoing coronary angiography was predictive for higher total, cardiovascular and for noncardiovascular mortalities [14]. Thus, the increased risk in patients with major depression for developing cardiovascular disease, and the poor response to treatment and the increased morbidity and mortality could relate to greater disturbances of tryptophan metabolism [15].

ANTIOXIDANTS AND tryptophan METABOLISM

Antioxidants are reducing agents or chemicals that can terminate radical chain reactions. However, nowadays and especially in food and natural compound-related discussions, the term ‘antioxidant’ is also used for compounds that can indirectly prevent the oxidation of other biomolecules, for example because of chelation of transition metal ions or because of activating transcription or activity of cytoprotective antioxidant enzymes such as hemoxgenase, superoxide dismutase, glutathione peroxidase, or catalase [16].

Among the most discussed food-contained antioxidants are vitamins, flavonoids, and polyphenols. High concentrations of antioxidant compounds are contained in fruits, vegetables, and nuts, but also grains and especially in berries such as cranberry or strawberry. Regarding fish, fruits and vegetables, nuts, and seeds, the list overlaps to some extent with foods that are rich in tryptophan. Such foods are considered to bring special health benefit, because antioxidant compounds help to improve blood circulation, enhance memory and lower cholesterol and thus can improve overall health [17,18].

Studies in various in vitro models including human peripheral blood mononuclear cells (PBMC) revealed that there are several plant extracts and phytochemicals, mainly antioxidants like polyphenols, flavonoids, vitamins with one or more unsaturated double bonds in their chemical structure that potently suppress Th1-type immune responses [17]. Upon exposure to these compounds, mitogen-stimulated IDO activity becomes diminished. This was also true for, for example, tea and coffee extracts and specific compounds such as stilbene resveratrol [16]. Among coffee compounds, gallic acid and less strongly also caffeic acid had a consistent suppressive influence on Th1-type immune activation in vitro, whereas pure caffeine and chlorogenic acid had not [19]. Similar observations were made with cacao extracts [16]. If these findings could be extrapolated in vivo, this background could explain why diet rich in antioxidants is of certain benefit to improve mood, cognition, and also immune system function. Indeed, inverse associations were detected.
between blood concentrations of inflammation biomarkers and concentrations of antioxidative compounds such as vitamins C (ascorbic acid) and E (α-tocopherol), and lycopene, lutein, and zeaxanthin [20].

Still there is only limited information available from in vivo and whether the intake of such nutrients and compounds may interfere with tryptophan breakdown and thus increase blood and brain tryptophan availability for serotonin production. Because merely based on in vitro only, the relationship between antioxidants and tryptophan must still remain widely speculative until in-vivo data become available. Moreover, there is only robust data showing that tryptophan concentrations influence serotonin biosynthesis, but not necessarily that intracellular serotonin is released from the cell. This is particularly true in the absence of a physiological/pathological stimulus.

Higher dietary intake of foods rich in antioxidants in older aged healthy individuals was associated with reduced inflammation [11] and with lower tryptophan breakdown rates and production of immune biomarker neopterin [21]. However, although the anti-inflammatory nature of black tea extracts is well established, in a randomized controlled trial, black tea consumption increased blood kynurenine concentrations in healthy individuals [22]. This could be explained if the benefit of a healthy diet would exist preferentially in individuals with an ongoing low-level inflammatory condition, which can be suppressed by the antioxidants, whereas in healthy, inflammation-free individuals antioxidants could trigger the same pathways.

There are in vitro data available that show the activation of IDO in unstimulated PBMC treated with low dose of resveratrol [23]. A similar behavior, being inhibitory in an IFN-γ driven proinflammatory situation, while activating certain inflammatory pathways in unstimulated immune cells in vitro, has been observed with complex extracts of plants like Hypericum perforatum [23]. However, which pathways are activated varied, probably because of different bioactivities of the contained phytochemicals. In vivo, stimulation of inflammatory pathways could be of relevance especially with high doses of antioxidant supplements that in consequence could even increase risks.

Better than a protein-rich diet, food rich in antioxidants is able to increase flux of tryptophan into the brain, when antioxidants diminish tryptophan breakdown (Fig. 1). Then tryptophan levels rise without a concomitant increase of other amino acids, and LNAA would not change. Thus, the ratio of tryptophan to LNAA goes up and brain transport via the L1 system [1] follows in parallel and tryptophan becomes available for serotonin biosynthesis in the brain.

**MOOD FOOD AND BRAIN FOODS**

Mood foods and brain foods are usually summarized as foods that possess the property of protecting brain tissue from insults because of oxidative stress and to support synthesis of neurotransmitters serotonin, adrenaline (epinephrine), and noradrenaline (nor-epinephrine), which derive from precursor amino acids tryptophan, phenylalanine, and tyrosine [24]. Both aspects rely on the protection from reactive oxygen species (ROS), which may become overwhelming when antioxidant pools are depleted. ROS generation is a biochemical reaction mainly in mitochondria which is required for normal cell metabolism [16**]. However, in states of inflammation and immune activation the amount of such compounds formed is drastically enhanced. Thereby, cytokine IFN-γ that is released during the Th1-type immune response is probably the strongest stimulator of ROS production in target cells like macrophages. In turn, antioxidant pools become depleted in states of prolonged Th1-type immune activation. This presumably explains why in patient groups very often an inverse relationship between antioxidant concentrations in the blood and biomarkers of inflammation is observed [20]. At the same time tryptophan breakdown is increased. As a consequence, patients present with lower tryptophan concentrations than those with less expressed inflammation and low ROS production [16**].

The biosynthesis of the most important neurotransmitters such as serotonin, dopamine, epinephrine, norepinephrine but also of nitric oxide (NO) is achieved by enzymes tryptophan 5-hydroxylase, phenylalanine 4-hydroxylase, tyrosine 3-hydroxylase, and nitric oxide synthase, and all these enzymes require BH4 as a cofactor [25]. BH4 is a strong reductant and therefore undergoes oxidation easily [26]. Consequently, an antioxidant rich environment can prolong lifespan of BH4 and contribute to increase activity of the BH4-dependent enzymes [9,16**], and the biosynthesis of the mentioned neurotransmitters increases. This relationship may explain why foods rich in antioxidants are considered as mood enhancers and to improve cognitive abilities.

**ROLE OF SEROTONIN IN DISTURBED MOOD AND COGNITIVE IMPAIRMENT**

Mood and cognition in older persons are closely related [27] and linked to the biochemistry of
serotonin [28*,29]. Classical antidepressant drugs such as fluoxetine and sertraline belong to the so-called selective serotonin reuptake inhibitors (SSRIs) and work by increasing serotonin levels in the brain. Serotonin was suggested as key in depression pathogenesis. However, recent findings weaken this hypothesis. It was observed very soon that only a subgroup of patients with depressive symptoms responds well to treatments with SSRI [30]. SSRIs block the reuptake of serotonin increasing the concentrations of the neurotransmitter in the synaptic cleft and leading to an enhanced postsynaptic neuronal activity. Inhibitors of monoamine oxidase (MAO), the key enzyme for serotonin, dopamine, and norepinephrine inactivation, prevent inactivation of monoamines in the neurons, causing excess neurotransmitter to diffuse into the synaptic space. Thereby, it is not exclusively the insufficient supply with the neurotransmitter itself which is of relevance; its release and the distribution of serotonin receptors also play a major role. There are seven main receptor subtypes (5-HT) and of major pharmacotherapeutic importance are the G-protein-coupled receptors #1, #2, #4 and #7.

The fact that SSRIs take several weeks to effectively work indicates that availability of serotonin is only one step of cellular changes in depression. More recently developed selective serotonin/norepinephrine reuptake inhibitors (SNRIs) involve blockade of 5-HT and norepinephrine reuptake in a concentration-dependent manner. This class of agents may be effective for the treatment of depression in patients in whom SSRIs are ineffective [30]. Notably, overdose of a combination of serotonergic agents, SSRI, or serotonin receptor agonists can occasionally lead to the appearance of adverse symptoms which were summarized as the so-called serotonin syndrome [31*].

In older aged people, cognitive decline is often accompanied by the development of signs of depression. A meta-analysis of several clinical trials observed a procognitive effect of antidepressants in patients with major depressive disorder. Accordingly, antidepressants have a significant positive effect on psychomotor speed and delayed recall [28*]. Most recent data suggest that serotonergic 5-HT\(_7\) receptors play a major role in cognition [32].

A potential role of tryptophan depletion in the cognitive ability has already been suggested and is further strengthened by the fact that in patients with Alzheimer’s dementia and with Huntington’s disease [7**], a significant relationship was found between the mini-mental test scores and tryptophan levels. Of note, lavender oil and some of its constituents were shown to be potent inhibitors of IDO-mediated tryptophan breakdown in vitro [33], and the orally admitted lavender oil preparation Silexan was shown to improve anxiety and sleep in a randomized double-blind placebo controlled study [34].

**CALORIE INTAKE AND WEIGHT GAIN**

**BECAUSE OF FOOD COMPOSITION**

Food intake is a complex process that initiates a number of physiological and biochemical processes, including the activation of activate reward and pleasure centers in the brain. An individual will repeatedly eat a particular food to experience these positive feelings. The experienced gratification through consumption of a favorable food may lead to overeating and in its extreme form to morbid obesity. Altered mood can alter food choice, and tryptophan catabolism may provide the biochemical link of mood, food, and obesity [35]. Importantly, low tryptophan levels have been observed in obese individuals [36] and this was preferentially true in females [37]. Disturbed serotonin availability can lead to carbohydrate craving, because carbohydrate-rich diet triggers insulin response to enhance bioavailability of tryptophan in the central nervous system [38]. Moreover, the combination of carbohydrate-rich foods with antioxidants can potentiate this effect, because antioxidants can promote serotonin production, when the immunobiological cascades behind the activation of IDO are counteracted [23]. Also the hunger regulatory impact of leptin production can be influenced by antioxidant food supplements such as preservatives sodium sulfite and benzoate [39]. Thus, the marketing strategy of combining sweet foods and drinks with extra vitamin supplements and other antioxidants like food preservatives and colorants could be a reasonable contributing factor in the increase of obesity during recent years [40].

Under certain clinical situations, supplementation of food with tryptophan or even better with 5-hydroxytryptophan could be useful, for example in a controlled calorie-reduced diet for obese patients [41*]. Here, tryptophan supplementation could have similar mood enhancing effects such as in depressive patients, although effectiveness still needs to be further clarified.

**AGEING, EXERCISE, AND NUTRITION**

Ageing is typically associated with a progressive loss of skeletal muscle mass and strength, which has been linked to increased morbidity and mortality of older people [42]. Recent findings from the KORA-Age study demonstrate higher concentrations of interleukin-6 and high sensitivity C-reactive protein
(hsCRP) in older individuals with lower levels of muscular function, independent of disease state, suggesting that the muscular system per se is effective in reducing low-grade inflammation [43]. However, only muscle function but not muscle mass was measured in the KORA-age study. Therefore, not only the decline of muscle mass could per se have an inflammatory activity, but also inflammation may increase muscle loss and thus reduce muscle strength [44,45]. With increasing age there is also an increase of inflammation and immune activation, which manifests in increasing neopterin concentrations and higher IDO activity, leading to significant lowering of tryptophan concentrations in the blood [7**]. Lower serum tryptophan levels are predictive for higher cardiovascular and overall mortality [14*].

Accumulating evidence suggests that diet and lifestyle can play an important role in delaying the onset of age-related health disorders and can improve or maintain cognitive functioning in older people at risk [46]. A higher level, total daily physical activity is associated with a reduced risk for neurodegenerative diseases [47]. Regular exercise may play an important role in the production of brain-derived neurotrophic factor and upregulates the production of several neurotransmitters, which like serotonin, are associated with mood enhancement and reduced depressive symptoms [31*]. Furthermore, exercise can stimulate BH₄ production via GTP-GCH-I and the BH₄-dependent enzymes and thus the production of several neurotransmitters like serotonin and dopamine [25]. However, prolonged exercise and overtraining could have the opposite effect [48*].

**CONCLUSION**

Tryptophan is an essential amino acid and its dietary intake is important for its proper supply, but also a diet rich in antioxidants can contribute to keep the tryptophan level high. This may relate to the positive impact of a healthy diet on mood and cognition. This could be of special relevance for individuals who present with low-grade inflammation conditions.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

16. Gostner JM, Becker K, Ueberall F, Fuchs D. The good and bad of antioxidant foods: an immunological perspective. Food Chem Toxicol 2015; 80:72–79. This review article discusses the role of antioxidative dietary supplements do exert not only beneficial influence in humans, they can also increase specific disease risks including obesity and allergic disorders.
This review highlights how exercise and training exerts influence on neuropsychiatric performance.

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