Review Article

Neuropsychobiology

Neuropsychobiology 2020;79:89–99
DOI: 10.1159/000496293

Received: October 5, 2018
Accepted after revision: December 18, 2018
Published online: February 26, 2019

Tryptophan Metabolism and Related Pathways in Psychoneuroimmunology: The Impact of Nutrition and Lifestyle

Johanna M. Gostner[a] Simon Geisler[b] Marlies Stonig[a] Lisa Mair[a]
Barbara Sperner-Unterweger[c] Dietmar Fuchs[b]

[a]Division of Medical Biochemistry, Medical University of Innsbruck, Innsbruck, Austria; [b]Division of Biological Chemistry, Biocenter, Medical University of Innsbruck, Innsbruck, Austria; [c]Department of Psychiatry and Psychotherapy, Medical University of Innsbruck, Innsbruck, Austria

Keywords
Tryptophan · Neopterin · Nutrition · Exercise · Microbiome · Psychoneuroimmunology

Abstract
In the past, accelerated tryptophan breakdown was considered to be a feature of clinical conditions, such as infection, inflammation, and malignant disease. More recently, however, the focus has changed to include the additional modulation of tryptophan metabolism by changes in nutrition and microbiota composition. The regulation of tryptophan concentration is critical for the maintenance of systemic homeostasis because it integrates essential pathways involved in nutrient sensing, metabolic stress response, and immunity. In addition to tryptophan being important as a precursor for the synthesis of the neurotransmitter serotonin, several catabolites along the kynurenine axis are neuroactive. This emphasizes the importance of the immunometabolic fate of this amino acid for processes relevant to neuropsychiatric symptoms. In humans, besides hepatic catabolism, there is usually a strong relationship between immune activation-associated tryptophan breakdown and increased levels of biomarkers, such as neopterin, which has particular relevance for both acute and chronic diseases. A shift towards neopterin synthesis during oxidative stress may indicate a corresponding decrease in tetrahydrobiopterin, a cofactor of several mono-oxygenases, providing a further link between tryptophan metabolism and serotonergic and catecholaminergic neurotransmission. The psychoneuroimmunological consequences of tryptophan metabolism and the susceptibility of this pathway to modulation by a variety of nutritional and lifestyle-related factors have important implications for the development of both diagnostic and treatment options.

Introduction

In recent years, tryptophan metabolism emerged as a central hub for the metabolic control of immunological and neuropsychological processes. Several kynurenine downstream metabolites are neuroactive, and some are even able to cross the blood-brain barrier (BBB) [1]. A deeper insight into the relationship between tryptophan

E-Mail karger@karger.com
www.karger.com/nps

Dietmar Fuchs
Division of Biological Chemistry, Biocenter
Innsbruck Medical University, Innrain 80
AT–6020 Innsbruck (Austria)
E-Mail dietmar.fuchs@i-med.ac.at

availability and systemic responses may not only be helpful for disease monitoring or therapeutic interventions, but also for the better understanding of the "immune-brain" loop, and thus how immunological status impacts behavior, stress, mood and thought, cognition, and, moreover, the development of psychiatric illness.

The breakdown of tryptophan along the kynurenine axis is accelerated in a variety of inflammation-associated disorders. Chronic inflammatory disorders, in particular, are frequently accompanied by a decreased quality of life, mood-lowering, and depression, but also neurocognitive symptoms [2, 3]. In addition, proinflammatory mechanisms contribute to the pathophysiology of major depression, including cell-mediated responses. Alterations of the serotonergic, noradrenergic, and glutamatergic neurotransmission may be provoked by the direct effects of cytokines on neurotransmitter storage and/or release, but also by indirect mechanisms such as changes of metabolite concentrations as reported, e.g. for several tryptophan catabolites [4, 5]. Changes in kynurenine and downstream metabolites have also been observed in a variety of central nervous system (CNS) disorders, including AIDS-dementia complex, Huntington's disease, Alzheimer's disease (AD), and CNS infections [6–8].

Moreover, the modulation of the tryptophan-kynurenine pathway by immunological activation and stress is recognized as a mediator of environmental factors on cognition and behavior [9]. It becomes more and more evident that several lifestyle parameters influence these metabolic circuits. Importantly, the enzyme indoleamine 2,3-dioxygenase-1 (IDO-1), which catalyzes the first and rate-limiting step in tryptophan breakdown along the kynurenine axis, has been shown to be susceptible to modulation by dietary components, microbiome composition, and physical exercise [10–13].

Tryptophan Metabolism

Tryptophan and Immunity

The aromatic amino acid tryptophan is 1 of 9 essential amino acids, and is the least available of all proteinogenic amino acids. As such, tryptophan availability is an important factor in the control of protein biosynthesis. This may be one important reason why the immune system utilizes tryptophan starvation to restrict the unwanted proliferation of pathogens and malignant cells [14]. Activation of the tryptophan-degrading enzyme IDO-1 is an integral defense mechanism in the cell-mediated immune response, whereby the T helper type 1 (Th1) cytokine, interferon (IFN)-γ, is the main activating factor [15, 16]. IDO catalyzes the first and rate-limiting step of tryptophan breakdown to kynurenine, and the kynurenine-to-tryptophan ratio (Kyn/Trp) was proposed as an estimate of IDO enzyme activity in the early 1990s [17].

In addition to its function as a defense strategy, tryptophan metabolism plays a pivotal role in the regulation of the immune response, by slowing down T cell proliferation. Moreover, kynurenine triggers regulatory T cell (Treg) development, and some of the tryptophan catabolites such as 3-hydroxyanthranilic and quinolinic acid have been shown to selectively drive Th1 cells (but not Th2 cells) into apoptosis [18]. In this way, a negative feedback loop is established that prevents overwhelming immune reactions, and a status of immunotolerance can be achieved. Accordingly, in patients with an activated immune system, IDO activity can contribute to immunosuppression, especially in chronic conditions. Indeed, enhanced IDO-1 activity has been observed in the blood of patients suffering from infections like HIV-1, autoimmune pathologies like systemic lupus erythematosus, several malignancies, and cardiovascular (CV) and neurodegenerative disorders [2]. Furthermore, low tryptophan concentrations together with high levels of neopterin, a biomarker of oxidative stress and immune activation, were associated with shorter survival in patients suffering from cancer (e.g., colorectal cancer and malignant melanoma) [19, 20], and enhanced overall and disease-specific mortality in CV disease [21, 22].

Tryptophan Kynurenine Pathway

Despite being so important for protein synthesis, most dietary tryptophan (>95%) is fed into the kynurenine pathway [23], giving rise to a number of downstream metabolites, the absolute and relative concentrations of which vary among cell types due to different enzymatic repertoires [16]. Further changes occur in disease conditions [7, 24]. The importance of tryptophan in depressive disorders was already being promoted in the 1960s and treatment possibilities were explored [25, 26]. Further studies accumulated, reporting on the correlation of accelerated tryptophan breakdown with neurologic/neuropsychiatric symptoms in conditions of activated cellular immunity, e.g., in HIV-1-infected patients [27].

After the first and rate-limiting step of tryptophan conversion to kynurenine, the downstream catabolism may divide into different branches, leading to the formation of 3-hydroxykynurenine, anthranilic acid, or kynurenic acid (Fig. 1). Catabolism of 3-hydroxykynurenine

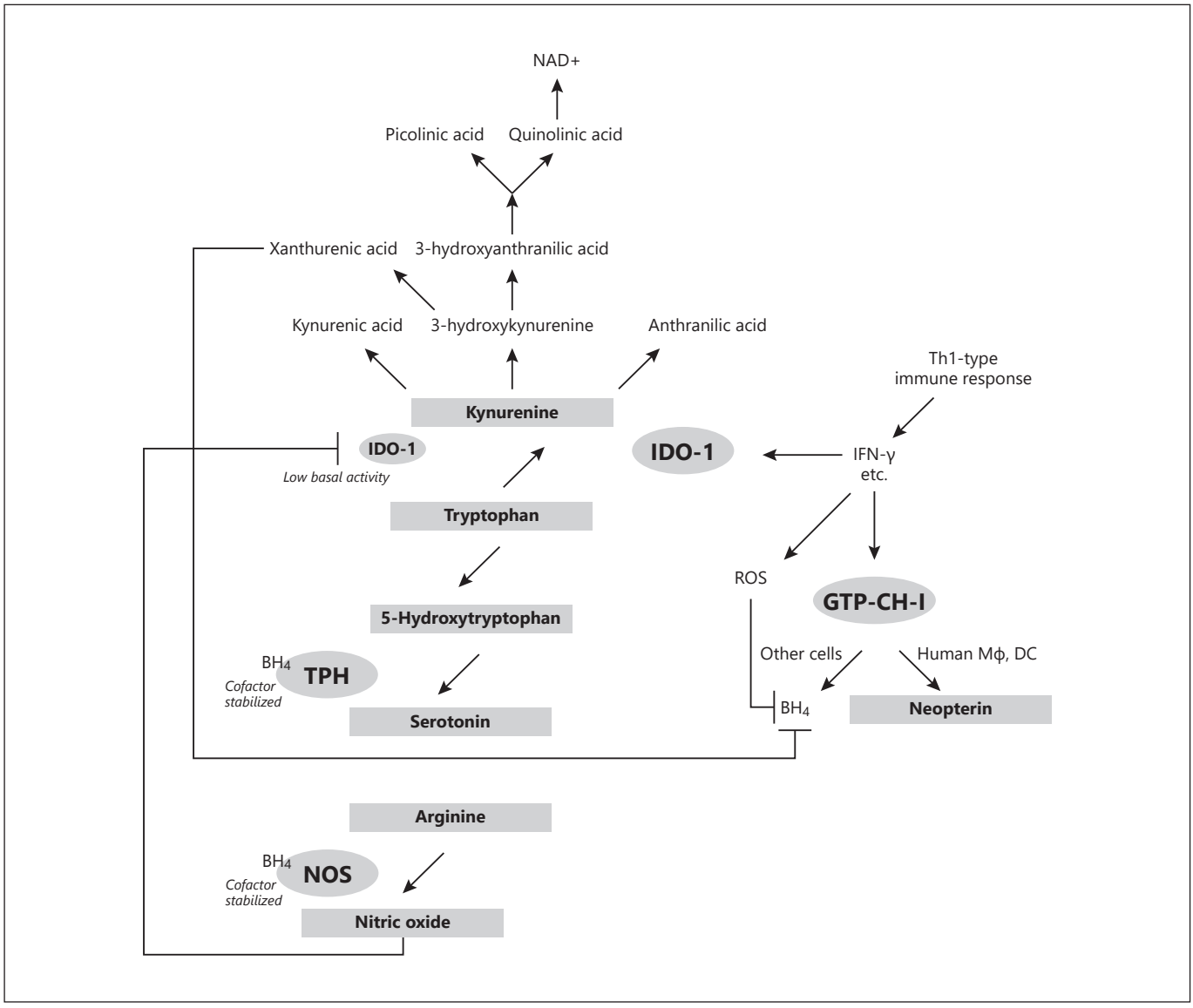

Fig. 1. Tryptophan catabolism and related pathways. Proinflammatory stimuli such as the major T helper type 1 (Th1) cytokine, interferon (IFN)-γ, stimulate the breakdown of tryptophan along the kynurenine axis via the activation of indoleamine 2,3-dioxygenase (IDO-1), which is responsible for the first and rate-limiting step in this pathway. IFN-γ also stimulates the NADPH oxidase-mediated formation of reactive oxygen species (ROS), and the activity of GTP-cyclohydrolase 1 (GTP-CH-I) which synthesizes 7,8-dihydroneopterin, the precursor of tetrahydrobiopterin (BH_4), and neopterin. While most cell types preferentially produce BH_4, this pathway is directed towards neopterin synthesis in human monocyte-derived cells such as macrophages (MΦ) and dendritic cells (DC), due to the deficiency of a downstream processing enzyme. Under inflammatory conditions, levels of the oxidation-sensitive cofactor BH_4 are diminished further, resulting in reduced tryptophan 5-hydroxylase (TPH) and nitric oxide synthase (NOS) activity, and thus in decreased levels of serotonin and nitric oxide levels. In addition, xanthurenic acid may interfere with BH_4 synthesis. As nitric oxide is an IDO-1 inhibitor, the tryptophan catabolism is directed towards kynurenine, enhancing the synthesis of several neuroactive catabolites.

can lead to the generation of picolinic acid, quinolinic acid, and nicotinamide.

Several of these metabolites are neuroactive. Kynurenic acid is able to block ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA) and kainate glutamate receptors [28]. Quinolinic acid is excitotoxic due to its NMDA receptor agonistic effects [29, 30]. While the neuroprotec-

tive kynurenic acid is present mainly in astrocytes, neurotoxic 3-hydroxykynurenine and excitotoxic quinolinic acid are found in microglial cells [31]. Besides directly targeting neurotransmitter receptors, the tryptophan metabolites, in particular 3-hydroxykynurenine and 3-hydroxyanthranilic acid, are redox active, leading to further effects that impact brain physiology [31, 32]. Not surprisingly, several enzymes are considered as important druggable targets, also for CNS-related disorders (comprehensively reviewed elsewhere [7]).

Besides the manifold biological activities of tryptophan catabolites, activation of this pathway contributes to a nicotinamide nucleotide pool which is considered important in situations of dietary shortage, as under normal conditions food is the main source of this metabolite in mammals. Furthermore, kynurenine metabolites are interlinked with other metabolic pathways, e.g., picolinic acid is involved in the intestinal absorption of zinc and quinolinic acid regulates gluconeogenesis by blocking phosphoenolpyruvate [33]. Thus, the modulation of the tryptophan-kynurenine pathway can be suggested as an indicator for a coherent metabolic shift.

Transport across Membranes

CNS concentrations of tryptophan derivatives are not isolated but linked to peripheral metabolite concentrations. For the transport of tryptophan into the brain, the leucine-preferring system L1 large amino acid transporter (LAT1) is utilized in competition with the large neutral amino acids (LNAAs) [34]. Fukui et al. [1] reported on the uptake of several tryptophan metabolites in rat brains: L-kynurenine is also transported by the L-system, and the same carrier mediates the uptake of 3-hydroxykynurenine, both competing with the brain transfer of L-leucine. Anthranilic acid is taken up by passive diffusion; this has also been shown for 3-hydroxykynurenine, kynurenic acid, and quinolinic acid, though less pronounced. While plasma protein-binding plays a role for several of the metabolites, this is not the case for quinolinic acid.

Tryptophan, L-kynurenine, and 3-hydroxykynurenine efficiently cross the BBB whereas serum concentrations of the more polar compounds quinolinic acid, kynurenic acid, and 3-hydroxyanthranilic acid are less relevant for brain pools in conditions with an intact BBB [1, 31]. A LAT1 independent efflux transport for kynurenine has only recently been described, although the transporter responsible here is not yet known [35]. Thus, kynurenine concentrations are not only controlled by influencing the metabolic rate (which is limited because the downstream processing machinery may be saturated, or the accumulating catabolites can become too toxic), but also through clearance mechanisms. The origin of tryptophan metabolites in a compartment may change in the presence of inflammatory stimuli, as was observed in gerbils with systemic or CNS inflammation by using labeled metabolites and comparing local formation and transport [36]. In addition to cytokine-mediated induction of enzymatic activity, it is hypothesized that there is a major impact of systemic inflammation on the function of the BBB.

Tryptophan Serotonin Pathway

Tryptophan is also the precursor of 5-hydroxytryptamine (serotonin), which is involved in the physiological regulation of several behavioral and neuroendocrine functions. In this way, enhanced IDO-1 activity may contribute to mood-lowering when tryptophan availability becomes low during periods of immune activation [37]. In addition, serotonin is accepted as a substrate by IDO-1. In conditions that provoke prolonged high IDO-1 activity, not only brain tryptophan but also serotonin may become destroyed. Unlike tryptophan, serotonin itself cannot pass the BBB. If the immune activation process takes place primarily outside the brain, decreased tryptophan availability due to the accelerated breakdown may contribute to serotonin deficiency in the brain. The effects on serotonergic neurotransmission may be somewhat retarded when compared to the decrease of plasma tryptophan, and then become more severe when the pool of stored serotonin is exhausted. However, special attention must be paid to immune activation processes that develop directly in the brain, e.g., viral infections with encephalitis, Guillain-Barré syndrome [38], and neuroborreliosis, or brain tumors.

The pineal gland-derived hormone melatonin is an end-product of the serotonin pathway, and it is important for the regulation of the circadian rhythm. Circadian malfunction is associated with seasonal affective disorder and mood disturbances, and treatment options based on the modulation of melatonin concentrations have been a topic of discussion [39]. Melatonin itself can promote IDO-1 activity [40], which may represent a negative-feedback loop probably involved in the regulation of the circadian rhythm.

Of note, serotonin was first discovered in the gut which is the major source for this neurotransmitter in the periphery. About 95% of serotonin is synthesized and stored in the gastrointestinal tract, where it acts as a paracrine messenger to modulate sensation, secretion, and motility, and is also involved in appetite control [41, 42].

Plasma Concentrations of Tryptophan and Kynurenine

Physiological concentrations of tryptophan and kynurenine are usually kept in a relatively narrow range by hepatic tryptophan dioxygenase (TDO). So far, little is known about the TDO regulation, besides its substrate activation and stabilization by tryptophan, hormonal induction by glucocorticoids, cofactor activation by heme, and feedback inhibition by NADPH [43]. Serum concentrations of tryptophan are in the range of 70 ± 10 μmol/L for males and 65 ± 10 μmol/L for females, as reported for a cohort of human healthy blood donors [44]. Gender-specific differences of about 15% are in agreement with earlier reports [45]. Kynurenine concentrations are around 1.8 ± 0.4 μM and do not differ between genders, most likely due to the hepatic responses which stabilize the circulating concentrations of the metabolites. Ageing, which is associated with an increase of immune activation, also in otherwise-healthy individuals, affects tryptophan metabolism, giving rise to higher kynurenine and lower tryptophan concentrations that are often associated with neuropsychiatric symptoms [46].

Neopterin and Tetrahydrobiopterin

Neopterin Metabolism

During cellular immune activation with IFN-γ as the major stimulus, enzyme GTP-cyclohydrolase (GTP-CH-I) is induced, which synthesizes 7,8-dihydroneopterin triphosphate from GTP. Further enzymatic conversion by 6-pyruvoyl-tetrahydropterin synthase leads to the formation of 5,6,7,8-tetrahydrobiopterin (BH_4), a cofactor for several mono-oxygenases [47].

While most cell types produce BH_4 when GTP-CH-I is activated, in human monocytes/macrophages, the metabolic route is directed towards the formation of neopterin and 7,8-dihydroneopterin [48] (Fig. 1). Neopterin and 7,8-dihydroneopterin interfere with a variety of redox-regulated intracellular signaling pathways. Moreover, neopterin has emerged as an important diagnostic marker of cellular immune activation in a variety of disorders associated with oxidative stress including CV, neurodegenerative, and tumor diseases, viral infections, and during allograft rejection [48]. In the course of a Th1-type immune reaction, neopterin formation parallels IDO-1 activity [27, 49].

Serum concentrations of neopterin are in the range of 5.9 ± 1.6 nmol/L in human healthy blood donors [44]. Like kynurenine and tryptophan concentrations, neopterin levels increase in the elderly [46].

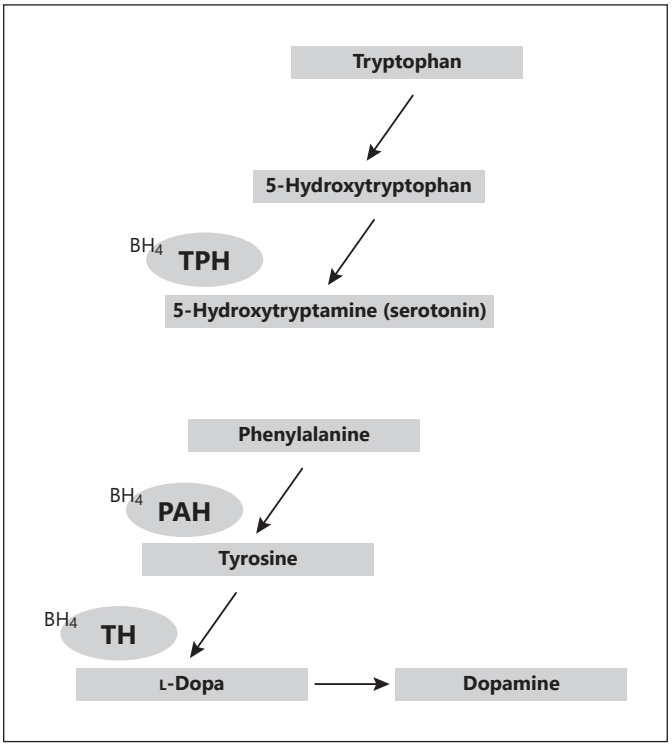

Fig. 2. Tetrahydrobiopterin (BH_4)-dependent enzymes are involved in serotonergic and dopaminergic neurotransmitter synthesis. TPH, tryptophan 5-hydroxylase; PAH, phenylalanine 4-hydroxylase; TH, tyrosine 3-mono-oxygenase.

BH_4 and Its Role in Neurotransmitter Synthesis

BH_4-dependent enzymes include tryptophan 5-hydroxylase (TPH), phenylalanine 4-hydroxylase (PAH), tyrosine 3-mono-oxygenase (alternative name: tyrosine 3-hydroxylase; TH), nitric oxide synthase (NOS), and alkylglycerol mono-oxygenase [47, 50, 51] (Fig. 1, 2). BH_4 is sensitive to the oxidative condition that arises during immune activation and inflammation, and the activity of dependent enzymes is therefore reduced under oxidative stress (Fig. 1). Furthermore, xanthurenic acid, a metabolite formed from 3-hydroxykynurenine [52], has been shown to inhibit sepiapterin reductase, the final enzyme in de novo BH_4 synthesis [53].

Such interactions have important consequences for the generation of serotonergic neurotransmitters and catecholamines. Dopamine, noradrenaline, and adrenaline are synthesized from tyrosine-derived L-DOPA. Both the conversion of phenylalanine to tyrosine and the following reaction to L-DOPA are BH_4-dependent steps. The direct measurement of BH_4 in clinical samples is somewhat hampered due to the oxidation-sensitive nature of this molecule. The phenylalanine-to-tyrosine ratio (Phe/Tyr)

has been proposed as an estimate of BH_4 levels [54], because phenylalanine and tyrosine can be regarded as more stable analytes than BH_4. Serum concentrations of phenylalanine and tyrosine are in the range of 53–79 and 61–116 μmol/L, respectively [44]. Of note, Phe/Tyr is also often increased in the elderly [55].

The cross-talk involving the different isoforms of NOS present in different cell types, the activating nature of IFN-γ signaling, and the suppressing nature of reactive oxygen species (ROS) provide a variety of interactions that are important for the temporal and spatial regulation of NO concentrations. NO is a gaseous signaling molecule implicated in a broad range of processes, endothelial, neuronal, and immunological (reviewed elsewhere [56]). Importantly, it is able to inhibit IDO activity by reversibly binding to heme at the active site [57].

Impact of Nutrition and Lifestyle

In light of the above-described consequences of altered tryptophan and neopterin metabolism, it becomes obvious that the treatments or conditions which affect these metabolic routes may result in altered CNS function with mood-related, behavioral, and/or cognitive effects. Moreover, several in vitro and in vivo studies involving human primary cells and cell lines show that these pathways are highly susceptible to modulation by dietary constituents including phytochemicals, preservatives, colorants, and probiotics as well as by other lifestyle-related factors [11, 58–60]. Both direct interfering activities as well as upstream regulatory events may be relevant. Already in 2013, tryptophan metabolism was discussed due to its role as a mediator of environmental factors on cognition and behavior [9]. In line with this, the following summary on the modulation of the abovementioned pathway by a variety of nutritional and lifestyle-related factors further underlines the role of IDO-mediated tryptophan catabolism as a pathway that is particular sensitive to environmental influences [61].

Nutrition

As mentioned, for the transport of tryptophan into the brain, the leucine-preferring L1-system is important, in competition with LNAAs. In addition, there is evidence that eating carbohydrates along with protein can increase the tryptophan available to the brain [62]. When carbohydrates are consumed, the body produces insulin which directs other amino acids to muscle tissue, but tryptophan remains in the bloodstream. Thus, competing amino acids in the circulation decline and tryptophan more freely enters the brain. Taking pure tryptophan works in a qualitatively different way than when it is obtained from a food source [63].

Under inflammatory conditions, where peripheral tryptophan concentrations are low anyway, the kynurenine transport via LAT1 becomes even more relevant. L-leucine was shown to efficiently interfere with kynurenine transport into the brain of lipopolysaccharide-challenged mice, which could efficiently counteract depressive-like behavior [35]. Another possibility is that the tryptophan concentration in the blood stream may increase when the breakdown of the amino acid is counteracted. This can take place when the intake of compounds slows down inflammation and IDO-1 activity [59].

Food rich in antioxidant compounds could improve both serotonin and tryptophan status in the brain. These compounds counteract immune response and tryptophan breakdown by IDO, e.g., compounds like vitamin C and E, and also stilbene resveratrol and coffee flavonoids, were observed to slow down T cell activation and IFN-γ production in vitro in mitogen-stimulated human peripheral blood mononuclear cells (PBMC) from healthy donors, followed by lower activity of the downstream biochemical pathways (like tryptophan breakdown) by IDO-1 or neopterin production [64]. In CV disease, elevated neopterin concentrations were found to correlate with a decrease of the plasma antioxidants lycopene, lutein, and zeaxanthin, and the vitamins ascorbic acid and α-tocopherol [65], so several metabolites could benefit from decreasing oxidative stress. An antioxidative milieu stabilizes the oxidation-sensitive molecule BH_4, thus affecting the activity of BH_4-dependent enzymes.

Though the prediction of the net effects of dietary components of phytochemicals in humans based on in vitro data only is somewhat limited due to sometimes missing ADME (absorption, distribution, metabolism, and excretion) data, individual susceptibility, interferences with the microbiome, or interactions with other food components, some of the effects on tryptophan metabolism and related pathways have been reported. In a pilot study with healthy volunteers who received a single dose of resveratrol administered orally after overnight fasting, the Kyn/Trp was found to be slightly but significantly elevated, and tryptophan concentrations were decreased up to 5 h after the intervention [66]. Of note, resveratrol treatment in PBMC in vitro suppressed IDO-1 activity dose-dependently under inflammatory conditions; at low concentrations, a nonmonotonic response provoked an increased activity in otherwise-untreated

PBMC [67]. Similar results were obtained when investigating the effect of the intake of regular black tea over a 6-month period: plasma Kyn/Trp and kynurenine concentrations increased in volunteers compared to the placebo group, while tryptophan and neopterin concentrations were not affected [68]. The tea-drinkers were healthy individuals, with no major illnesses and normal-to-mildly elevated systolic blood pressure. In vitro, the stimulating effects of black tea were also shown on otherwise-unstimulated PBMC, reflected by the elevation of neopterin concentrations [69].

Though polyphenol-rich food/beverages and phytochemicals such as resveratrol are generally considered to act as antioxidants, the data suggest that the net effect depends on an individual's immune status, being immunostimulatory in healthy individuals while a dampening of responses may occur on an inflammatory background.

Microbiome and Probiotics

The importance of tryptophan metabolism in the cross-talk of gut and microbiome was addressed in a recent study by Laurans et al. [70], who reported ameliorating effects on obesity, liver steatosis, and insulin sensitivity in the absence of IDO-1 activity in mice, which were mediated by microbiota-dependent production of interleukin 22. In addition, microbiota can be a source of tryptophan and tryptophan-derived metabolites, some of which can be transported across membranes [71], and of neurotransmitters and precursors such as noradrenalin, γ-aminobutyric acid (GABA), and other neuroactive substances [72]. Thus, interferences with the microbiome are likely to influence the gut-brain axis.

No major effects regarding exercise-induced Kyn/Trp and neopterin concentrations were reported in a study with trained athletes receiving probiotics compared to those receiving placebo [73]. Though tryptophan degradation rates were somewhat lower in subjects supplemented with probiotics, this effect was not significant; however, there was a reduced incidence of upper respiratory tract infections compared to the placebo group [73]. However, probiotic supplementation provoked an increase in neopterin concentrations and a subclinical increase in neutrophil resting burst compared to treatment with placebo in patients with liver cirrhosis who suffered from intestinal dysbiosis and pro-inflammatory conditions [74]. Serum kynurenine concentrations increased slightly but significantly in AD patients treated with probiotics [75]. The influence of gut microbiome composition on neuropsychiatric conditions like anxiety, depression, cognition, and autism spectrum disorder is largely accepted, likewise that there is a link between gut-derived signals and healthy brain development but also with the progression of neurological disorders [76]. The leaky gut syndrome, an increase of the intestinal barrier permeability allowing the entry of microbes and metabolites into the bloodstream, is associated with AD pathogenesis and provides a mechanistic explanation for this connection [77].

Though the abovementioned studies are limited due to small samples, these preliminary data indicates that, particularly in patients likely suffering from leaky gut syndrome on probiotic treatments, personalized monitoring is required, as the consequences of the observed immunostimulatory effects have not yet been fully clarified. Like with phytochemicals, the effects seem to be highly dependent on an individual's immune status and epithelial barrier function. The type of probiotic and the treatment duration also play a role here.

Exercise

In line with an augmentation of oxidative metabolism, an increase of tryptophan catabolism and neopterin formation has been observed with different types of exercise [11, 78]. Trying to explain the beneficial effects of physical exercise on a metabolic level, Lewis et al. [79] generated a metabolic signature of exercise detectable in the plasma, which indicated an exercise-induced metabolic shift towards glycogenolyis, lipolysis, effects on tricarboxylic acid, insulin sensitivity, and fatty acid oxidation. In addition to the expected catabolic consequences seen with a decreased tryptophan concentration, marathon running resulted in an increased kynurenate concentration [79]. Exercise-induced increased expression of kynurenine aminotransferase, which is mediated by the peroxisome proliferator-activated receptor (PPAR)-γ coactivator (PGC)-1α (a key transcriptional coactivator in energy metabolism), was shown to contribute to the lowering of the plasma kynurenine concentration in mice [80].

Phenylalanine catabolism may also be driven by exercise, and increased substrate availability for dopaminergic neurotransmission could counteract negative consequences on mood resulting from accelerated tryptophan breakdown, though such effects may depend on the type and duration of the training [11]. It is well established that prolonged exhaustive/endurance exercise can be associated with immunosuppression as well as low mood and depression, which may be explained that the short time lowering of neurotransmitter precursors can

be counterregulated, while the exercise-driven continuous catabolic reaction will negatively impact psychoneuroimmunological circuits.

Interpreting Metabolic Changes

It is important to take into account that, under certain conditions, the interpretation of changes in Kyn/Trp and neopterin concentrations may differ. For example, in children with persistent IgE-mediated food allergy, tryptophan concentration was higher and Kyn/Trp lower than in healthy, age-matched controls, but kynurenine concentrations were not different [81]. This may relate to the loss of tolerance due to lowered IDO-1 activity. Furthermore, cultures of PBMC from patients with different phenotypes of cow's milk allergy showed distinct cytokine responses after treatment with casein and β-lactoglobulin [81].

A higher tryptophan concentration despite a minor affected Kyn/Trp has also been reported in patients suffering from allergic rhinitis [82]. An increased concentration of NO, as observed in asthma and allergic rhinitis patients, may be responsible here and is due to the specific blockage of IDO-1 activity [83]. Interestingly, an elevated serotonin concentration, associated with behavioral symptoms, has been reported in pollinosis patients [84].

In a study on obese/overweight juveniles and a normal-weight, age-matched control population, it was observed that in the obese juveniles, early vascular burden and chronic low-grade inflammation were already present and concentrations of C-reactive protein were increased, but there was a decrease of neopterin compared to in the healthy population [85]. In addition, a lower Kyn/Trp has been reported in overweight/obese juvenile males but not in females aged ≤18 years. This is a major difference when compared to overweight adults and adult patients with metabolic syndrome who show elevated Kyn/Trp [86], or adults at a risk of CV disease in whom Kyn/Trp and neopterin concentrations are elevated [65, 87]. The reason for the lower neopterin and Kyn/Trp levels in obese (male) juveniles has not yet been determined on the molecular level, although the potential implications of an excessive uptake of food antioxidants has been discussed. An influence of elevated nitrite concentrations might also provide a reasonable explanation in such patients because it is well known that NO is increased in certain allergies and inhibits IDO-1 [88].

These examples further highlight that individual immune status varies substantially in the general population, which adds another degree of complexity when trying to interpret personalized tryptophan metabolite concentrations in clinical settings.

Therapeutic and Diagnostic Options

Dietary interventions to increase tryptophan have been used to study the metabolism for a long time, and nutritional interventions to modulate these pathways hold great therapeutic potential, particularly for long-term treatment. Supplementation of tryptophan is suggested to be less effective as the net effect of the high tryptophan is widely lost when it must compete with LNAAs for BBB transport. However, as discussed above, the modulation of serum tryptophan breakdown rates by nutritional constituents or probiotics may be a feasible way to attain long-term changes.

Moreover, specific interventions can also be used for diagnostic purposes, e.g., for acute tryptophan depletion (ADT), a neurodietary, short-term, physiological serotonin precursor-related challenge test, consisting of the administration of a cocktail of LNAAs and a lack of tryptophan, results in a decreased tryptophan concentration in the circulation and brain a few hours after treatment. The antidepressant action of ADT was the aim of studies in the 1980s and 1990s and is currently again in focus [89–91].

Conclusion

Maintenance of the tryptophan-kynurenine balance seems to be critical for the physiological homeostasis. The same is true for neopterin concentration. Both are indicators of individual immunological status. However, a variety of physiological, lifestyle, nutritional, and environmental factors affects tryptophan metabolism and the related metabolic pathways. Though the organism can balance slight and temporarily limited increases or decreases in these metabolites, long-term perturbation may be associated with more severe symptoms. The observations reported in this review are limited because the main focus was the effect of metabolic changes, observable in the plasma or urine. However, the connection of peripheral and brain metabolite concentrations has been explained. Other drug-induced changes were not included in the discussion. Indeed, several enzymes in the tryptophan-kynurenine pathway are under investigation as promising drug targets with potential application for the treatment of metabolic, neurodegenerative, and psychiatric disorders as well as cancer. Susceptibility to the modulation of tryptophan breakdown and the related pathways, due to a variety of different factors, is a further challenge for these drug-targeting approaches as, most likely, such interventions require a profound

knowledge of disease development combined with a strict personalized monitoring so as not to risk a complete blocking of activities that are potentially necessary to reobtain homeostasis. However, this high susceptibility also holds great potential for less specific interventions, such as dietary and physical (exercise-based) interventions.

Acknowledgements

This work was supported by the Austrian Science Funds (FWF T703).

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Fukui S, Schwarcz R, Rapoport SI, Takada Y, Smith QR. Blood-brain barrier transport of kynurenines: implications for brain synthesis and metabolism. J Neurochem. 1991 Jun; 56(6):2007–17.
2 Schröcksnadel K, Wirleitner B, Winkler C, Fuchs D. Monitoring tryptophan metabolism in chronic immune activation. Clin Chim Acta. 2006 Feb;364(1-2):82–90.
3 Dantzer R. Role of the kynurenine metabolism pathway in inflammation-induced depression: preclinical approaches. Curr Top Behav Neurosci. 2017;31:117–38.
4 Myint AM, Schwarz MJ, Müller N. The role of the kynurenine metabolism in major depression. J Neural Transm (Vienna). 2012 Feb; 119(2):245–51.
5 Müller N. Immunology of major depression. Neuroimmunomodulation. 2014; 21(2-3): 123–30.
6 Stone TW, Mackay GM, Forrest CM, Clark CJ, Darlington LG. Tryptophan metabolites and brain disorders. Clin Chem Lab Med. 2003 Jul;41(7):852–9.
7 Stone TW, Darlington LG. Endogenous kynurenines as targets for drug discovery and development. Nat Rev Drug Discov. 2002 Aug; 1(8):609–20.
8 Widner B, Ledochowski M, Fuchs D. Interferon-gamma-induced tryptophan degradation: neuropsychiatric and immunological consequences. Curr Drug Metab. 2000 Sep;1(2): 193–204.
9 Stone TW, Darlington LG. The kynurenine pathway as a therapeutic target in cognitive and neurodegenerative disorders. Br J Pharmacol. 2013 Jul;169(6):1211–27.
10 Gostner J, Ciardi C, Becker K, Fuchs D, Sucher R. Immunoregulatory impact of food antioxidants. Curr Pharm Des. 2014;20(6):840–9.
11 Strasser B, Fuchs D. Diet versus exercise in weight loss and maintenance: focus on tryptophan. Int J Tryptophan Res. 2016 May;9: 9–16.
12 Notarangelo FM, Pocivavsek A, Schwarcz R. Exercise your kynurenines to fight depression. Trends Neurosci. 2018 Aug;41(8):491–3.
13 Gao J, Xu K, Liu H, Liu G, Bai M, Peng C, et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. Front Cell Infect Microbiol. 2018 Feb;8: 13.
14 Pfefferkorn ER. Interferon gamma blocks the growth of Toxoplasma gondii in human fibroblasts by inducing the host cells to degrade tryptophan. Proc Natl Acad Sci USA. 1984 Feb;81(3):908–12.
15 Yoshida R, Imanishi J, Oku T, Kishida T, Hayaishi O. Induction of pulmonary indoleamine 2,3-dioxygenase by interferon. Proc Natl Acad Sci USA. 1981 Jan;78(1):129–32.
16 Werner ER, Hirsch-Kauffmann M, Fuchs D, Hausen A, Reibnegger G, Schweiger M, et al. Interferon-gamma-induced degradation of tryptophan by human cells in vitro. Biol Chem Hoppe Seyler. 1987 Oct;368(10):1407–12.
17 Fuchs D, Möller AA, Reibnegger G, Werner ER, Werner-Felmayer G, Dierich MP, et al. Increased endogenous interferon-gamma and neopterin correlate with increased degradation of tryptophan in human immunodeficiency virus type 1 infection. Immunol Lett. 1991;28):207-211.
18 Fallarino F, Grohmann U, Vacca C, Bianchi R, Orabona C, Spreca A, et al. T cell apoptosis by tryptophan catabolism. Cell Death Differ. 2002 Oct;9(10):1069–77.
19 Brandacher G, Perathoner A, Ladurner R, Schneeberger S, Obrist P, Winkler C, et al. Prognostic value of indoleamine 2,3-dioxygenase expression in colorectal cancer: effect on tumor-infiltrating T cells. Clin Cancer Res. 2006 Feb;12(4):1144–51.
20 Weinlich G, Murr C, Richardsen L, Winkler C, Fuchs D. Decreased serum tryptophan concentration predicts poor prognosis in malignant melanoma patients. Dermatology. 2007;214(1):8–14.
21 Pedersen ER, Midttun Ø, Ueland PM, Schartum-Hansen H, Seifert R, Igland J, et al. Systemic markers of interferon-γ-mediated immune activation and long-term prognosis in patients with stable coronary artery disease. Arterioscler Thromb Vasc Biol. 2011 Mar; 31(3):698–704.
22 Murr C, Grammer TB, Kleber ME, Meinitzer A, Böhm BO, März W, et al. Low serum free tryptophan is associated with immune activation, inflammation and predicts mortality in patients with cardiovascular disease, the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Eur J Clin Invest. 2015;45: 247–54.
23 Peters JC. Tryptophan nutrition and metabolism: an overview. Adv Exp Med Biol. 1991; 294:345–58.
24 Chen Y, Guillemin GJ. Kynurenine pathway metabolites in humans: disease and healthy States. Int J Tryptophan Res. 2009;2:1–19.
25 Coppen A, Shaw DM, Herzberg B, Maggs R. Tryptophan in the treatment of depression. Lancet. 1967 Dec;2(7527):1178–80.
26 Hertz D, Sulman FG. Preventing depression with tryptophan. Lancet. 1968 Mar;1(7541): 531–2.
27 Fuchs D, Möller AA, Reibnegger G, Stöckle E, Werner ER, Wachter H. Decreased serum tryptophan in patients with HIV-1 infection correlates with increased serum neopterin and with neurologic/psychiatric symptoms. J Acquir Immune Defic Syndr. 1990;3(9):873–6.
28 Perkins MN, Stone TW. An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid. Brain Res. 1982 Sep;247(1):184–7.
29 Stone TW, Perkins MN. Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS. Eur J Pharmacol. 1981 Jul; 72(4):411–2.
30 Schwarcz R, Whetsell WO Jr, Mangano RM. Quinolinic acid: an endogenous metabolite that produces axon-sparing lesions in rat brain. Science. 1983 Jan;219(4582):316–8.
31 Schwarcz R, Bruno JP, Muchowski PJ, Wu HQ. Kynurenines in the mammalian brain: when physiology meets pathology. Nat Rev Neurosci. 2012 Jul;13(7):465–77.
32 Weiss G, Diez-Ruiz A, Murr C, Terul I, Fuchs D. Tryptophan metabolites as scavengers of reactive oxygen and chlorine species. Pteridines. 2002;13(4):140–4.
33 Lardy HA. The role of tryptophan metabolites in regulating gluconeogenesis. Am J Clin Nutr. 1971 Jul;24(7):764–5.
34 Fernstrom JD, Wurtman RJ. Brain serotonin content: physiological regulation by plasma neutral amino acids. Science. 1972 Oct; 178(4059):414–6.
35 Walker AK, Wing EE, Banks WA, Dantzer R. Leucine competes with kynurenine for blood-to-brain transport and prevents lipopolysaccharide-induced depression-like behavior in mice. Mol Psychiatry. 2018 Jul. DOI: 10.1038/s41380-018-0076-7.

36 Kita T, Morrison PF, Heyes MP, Markey SP. Effects of systemic and central nervous system localized inflammation on the contributions of metabolic precursors to the L-kynurenine and quinolinic acid pools in brain. J Neurochem. 2002 Jul;82(2):258–68.
37 Widner B, Laich A, Sperner-Unterweger B, Ledochowski M, Fuchs D. Neopterin production, tryptophan degradation, and mental depression—what is the link? Brain Behav Immun. 2002 Oct;16(5):590–5.
38 Rudzite V, Berzinsh J, Grivane I, Fuchs D, Baier-Bitterlich G, Wachter H. Serum tryptophan, kynurenine, and neopterin in patients with Guillain-Barre-syndrome (GBS) and multiple sclerosis (MS). Adv Exp Med Biol. 1996;398:183–7.
39 Quera Salva MA, Hartley S, Barbot F, Alvarez JC, Lofaso F, Guilleminault C. Circadian rhythms, melatonin and depression. Curr Pharm Des. 2011;17(15):1459–70.
40 Li Y, Hu N, Yang D, Oxenkrug G, Yang Q. Regulating the balance between the kynurenine and serotonin pathways of tryptophan metabolism. FEBS J. 2017 Mar;284(6):948–66.
41 Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology. 2007 Jan;132(1):397–414.
42 Wurtman RJ. Food consumption, neurotransmitter synthesis, and human behaviour. Experientia Suppl. 1983;44:356–69.
43 Badawy AA. The functions and regulation of tryptophan pyrrolase. Life Sci. 1977 Sep; 21(6):755–68.
44 Geisler S, Mayersbach P, Becker K, Schennach H, Fuchs D, Gostner J. Serum tryptophan, kynurenine, phenylalanine, tyrosine and neopterin concentrations in 100 healthy blood donors. Pteridines. 2015;26(1):31–6.
45 Widner B, Werner ER, Schennach H, Wachter H, Fuchs D. Simultaneous measurement of serum tryptophan and kynurenine by HPLC. Clin Chem. 1997 Dec;43(12):2424–6.
46 Capuron L, Geisler S, Kurz K, Leblhuber F, Sperner-Unterweger B, Fuchs D. Activated immune system and inflammation in healthy ageing: relevance for tryptophan and neopterin metabolism. Curr Pharm Des. 2014; 20(38):6048–57.
47 Werner-Felmayer G, Golderer G, Werner ER. Tetrahydrobiopterin biosynthesis, utilization and pharmacological effects. Curr Drug Metab. 2002 Apr;3(2):159–73.
48 Murr C, Widner B, Wirleitner B, Fuchs D. Neopterin as a marker for immune system activation. Curr Drug Metab. 2002 Apr;3(2): 175–87.
49 Jenny M, Klieber M, Zaknun D, Schroecksnadel S, Kurz K, Ledochowski M, et al. In vitro testing for anti-inflammatory properties of compounds employing peripheral blood mononuclear cells freshly isolated from healthy donors. Inflamm Res. 2011 Feb;60(2): 127–35.
50 Gorren AC, Mayer B. Tetrahydrobiopterin in nitric oxide synthesis: a novel biological role for pteridines. Curr Drug Metab. 2002 Apr; 3(2):133–57.
51 Watschinger K, Keller MA, Golderer G, Hermann M, Maglione M, Sarg B, et al. Identification of the gene encoding alkylglycerol monooxygenase defines a third class of tetrahydrobiopterin-dependent enzymes. Proc Natl Acad Sci USA. 2010 Aug;107(31):13672–7.
52 Sathyasaikumar KV, Tararina M, Wu HQ, Neale SA, Weisz F, Salt TE, et al. Xanthurenic Acid Formation from 3-Hydroxykynurenine in the Mammalian Brain: Neurochemical Characterization and Physiological Effects. Neuroscience. 2017 Dec;367:85–97.
53 Haruki H, Hovius R, Pedersen MG, Johnsson K. Tetrahydrobiopterin biosynthesis as a potential target of the kynurenine pathway metabolite xanthurenic acid. J Biol Chem. 2016 Jan;291(2):652–7.
54 Anderson DN, Wilkinson AM, Abou-Saleh MT, Blair JA. Recovery from depression after electroconvulsive therapy is accompanied by evidence of increased tetrahydrobiopterin-dependent hydroxylation. Acta Psychiatr Scand. 1994 Jul;90(1):10–3.
55 Capuron L, Schroecksnadel S, Féart C, Aubert A, Higueret D, Barberger-Gateau P, et al. Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. Biol Psychiatry. 2011 Jul; 70(2):175–82.
56 Wink DA, Hines HB, Cheng RY, Switzer CH, Flores-Santana W, Vitek MP, et al. Nitric oxide and redox mechanisms in the immune response. J Leukoc Biol. 2011 Jun;89(6):873–91.
57 Thomas SR, Terentis AC, Cai H, Takikawa O, Levina A, Lay PA, et al. Post-translational regulation of human indoleamine 2,3-dioxygenase activity by nitric oxide. J Biol Chem. 2007 Aug;282(33):23778–87.
58 Zaknun D, Schroecksnadel S, Kurz K, Fuchs D. Potential role of antioxidant food supplements, preservatives and colorants in the pathogenesis of allergy and asthma. Int Arch Allergy Immunol. 2012;157(2):113–24.
59 Gostner JM, Becker K, Ueberall F, Fuchs D. The good and bad of antioxidant foods: an immunological perspective. Food Chem Toxicol. 2015 Jun;80:72–9.
60 Strasser B, Geiger D, Schauer M, Gatterer H, Burtscher M, Fuchs D. Effects of exhaustive aerobic exercise on tryptophan-kynurenine metabolism in trained athletes. PLoS One. 2016 Apr;11(4):e0153617.
61 Gostner JM, Geisler S, Stonig M, Fuchs D. IDO-1 mediated tryptophan catabolism – a universal environmental sensing pathway. 15th International Society for Tryptophan Research (ISTRY) Conference, abstract P-07; 2018; Hikone, Japan.
62 Fernstrom JD, Wurtman RJ. Brain serotonin content: increase following ingestion of carbohydrate diet. Science. 1971 Dec;174(4013): 1023–5.
63 Strasser B, Gostner JM, Fuchs D. Mood, food, and cognition: role of tryptophan and serotonin. Curr Opin Clin Nutr Metab Care. 2016 Jan;19(1):55–61.
64 Jenny M, Schroecksnadel S, Fuchs D. Testing for immunomodulatory properties of nanoparticles. J Biomed Nanotechnol. 2011 Feb;7(1):11–2.
65 Murr C, Winklhofer-Roob BM, Schroecksnadel K, Maritschnegg M, Mangge H, Böhm BO, et al. Inverse association between serum concentrations of neopterin and antioxidants in patients with and without angiographic coronary artery disease. Atherosclerosis. 2009 Feb;202(2):543–9.
66 Gualdoni GA, Fuchs D, Zlabinger GJ, Gostner JM. Resveratrol intake enhances indoleamine-2,3-dioxygenase activity in humans. Pharmacol Rep. 2016 Oct;68(5):1065–8.
67 Wirleitner B, Schroecksnadel K, Winkler C, Schennach H, Fuchs D. Resveratrol suppresses interferon-gamma-induced biochemical pathways in human peripheral blood mononuclear cells in vitro. Immunol Lett. 2005 Sep; 100(2):159–63.
68 Gostner JM, Becker K, Croft KD, Woodman RJ, Puddey IB, Fuchs D, et al. Regular consumption of black tea increases circulating kynurenine concentrations: a randomized controlled trial. BBA Clin. 2014 Dec;3:31–5.
69 Zvetkova E, Wirleitner B, Tram NT, Schennach H, Fuchs D. Aqueous extracts of Crinum latifolium (L.) and Camellia sinensis show immunomodulatory properties in human peripheral blood mononuclear cells. Int Immunopharmacol. 2001 Nov;1(12):2143–50.
70 Laurans L, Venteclef N, Haddad Y, Chajadine M, Alzaid F, Metghalchi S, et al. Genetic deficiency of indoleamine 2,3-dioxygenase promotes gut microbiota-mediated metabolic health. Nat Med. 2018 Aug;24(8):1113–20.
71 Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity. 2013 Aug;39(2):372–85.
72 Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012 Oct;13(10):701–12.
73 Strasser B, Geiger D, Schauer M, Gostner JM, Gatterer H, Burtscher M, et al. Probiotic supplements beneficially affect tryptophan-kynurenine metabolism and reduce the incidence of upper respiratory tract infections in trained athletes: a randomized, double-blinded, placebo-controlled trial. Nutrients. 2016 Nov; 8(11):E752.
74 Horvath A, Leber B, Schmerboeck B, Tawdrous M, Zettel G, Hartl A, et al. Randomised clinical trial: the effects of a multispecies probiotic vs. placebo on innate immune function, bacterial translocation and gut permeability in patients with cirrhosis. Aliment Pharmacol Ther. 2016 Nov;44(9):926–35.

75 Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic supplementation in patients with Alzheimer's dementia - an explorative intervention study. Curr Alzheimer Res. 2018;15(12):1106–13.
76 Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The central nervous system and the gut microbiome. Cell. 2016 Nov; 167(4):915–32.
77 Köhler CA, Maes M, Slyepchenko A, Berk M, Solmi M, Lanctôt KL, et al. The gut-brain axis, including the microbiome, leaky gut and bacterial translocation: mechanisms and pathophysiological role in Alzheimer's disease. Curr Pharm Des. 2016;22(40):6152–66.
78 de Lucas RD, Caputo F, Mendes de Souza K, Sigwalt AR, Ghisoni K, Lock Silveira PC, et al. Increased platelet oxidative metabolism, blood oxidative stress and neopterin levels after ultra-endurance exercise. J Sports Sci. 2014;32(1):22–30.
79 Lewis GD, Farrell L, Wood MJ, Martinovic M, Arany Z, Rowe GC, et al. Metabolic signatures of exercise in human plasma. Sci Transl Med. 2010 May;2(33):33ra37.
80 Agudelo LZ, Femenía T, Orhan F, Porsmyr-Palmertz M, Goiny M, Martinez-Redondo V, et al. Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. Cell. 2014 Sep;159(1):33–45.
81 Buyuktiryaki B, Sahiner UM, Girgin G, Birben E, Soyer OU, Cavkaytar O, et al. Low indoleamine 2,3-dioxygenase activity in persistent food allergy in children. Allergy. 2016 Feb;71(2):258–66.
82 Ciprandi G, De Amici M, Tosca M, Fuchs D. Tryptophan metabolism in allergic rhinitis: the effect of pollen allergen exposure. Hum Immunol. 2010 Sep;71(9):911–5.
83 Gostner JM, Becker K, Kofler H, Strasser B, Fuchs D. Tryptophan Metabolism in Allergic Disorders. Int Arch Allergy Immunol. 2016; 169(4):203–15.
84 Ciprandi G, De Amici M, Tosca M, Alesina R, Marseglia G, Fuchs D. Serotonin in allergic rhinitis: a possible role for behavioural symptoms. Iran J Allergy Asthma Immunol. 2011 Sep;10(3):183–8.
85 Mangge H, Freytag F, Almer G, Weghuber D, Bauer-Denk C, Fuchs D. Serum neopterin is not increased in obese juveniles. J Obes. 2011; 2011:946795.
86 Mangge H, Summers KL, Meinitzer A, Zelzer S, Almer G, Prassl R, et al. Obesity-related dysregulation of the tryptophan-kynurenine metabolism: role of age and parameters of the metabolic syndrome. Obesity (Silver Spring). 2014 Jan;22(1):195–201.
87 Murr C, Grammer TB, Meinitzer A, Kleber ME, März W, Fuchs D. Immune activation and inflammation in patients with cardiovascular disease are associated with higher phenylalanine to tyrosine ratios: the Ludwigshafen Risk and Cardiovascular Health Study. J Amino Acids. 2014;2014:783730.
88 Ciprandi G, Fuchs D. Tryptophan metabolic pathway, airway nitric oxide, and allergy. Ann Allergy Asthma Immunol. 2017 Nov;119(5): 395–6.
89 Miller HL, Delgado PL, Salomon RM, Licinio J, Barr LC, Charney DS. Acute tryptophan depletion: a method of studying antidepressant action. J Clin Psychiatry. 1992 Oct;53 Suppl: 28–35.
90 Biskup CS, Gaber T, Helmbold K, Bubenzer-Busch S, Zepf FD. Amino acid challenge and depletion techniques in human functional neuroimaging studies: an overview. Amino Acids. 2015 Apr;47(4):651–83.
91 Stewart RM, Hood SD, Rao P, Moore JK, Runions KC, Murphy SE, et al. Using acute tryptophan depletion to investigate predictors of treatment response in adolescents with major depressive disorder: study protocol for a randomised controlled trial. Trials. 2018 Aug; 19(1):434.