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Tryptophan Metabolism: Implications for Biological Processes, Health and Disease

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Preface

Tryptophan Metabolism: Implications for Biological Processes, Health and Disease

In many organs and tissues, the major route for the metabolism of tryptophan is the kynurenine pathway. One of the initial enzymes for this pathway is indoleamine-2,3-dioxygenase, present in most organs and tissues except the liver. The second enzyme, tryptophan-2,3-dioxygenase, is almost exclusively found in the mammalian liver and is responsible for tryptophan catabolism. A small portion of tryptophan is used for the synthesis of serotonin. Serotonin is a key neurotransmitter that modulates a wide variety of functions in both peripheral organs and the central nervous system. In response to signals from the circadian clock, N-acetylserotonin is converted to melatonin, which is synthesized not only in the pineal gland but also in many other parts of the body. Melatonin shows a strong antitumor activity by decreasing tumor cell viability and reactive oxygen species generation.

Most of the endogenous metabolites of tryptophan particularly derived from kynurenine pathway are implicated in cell damage in a wide range of psychiatric, neurological, and systemic disorders such as osteoporosis, neurodegenerative diseases, allergic and infectious diseases, brain injury, ischemic stroke injury, depression, immune response modulation, and immune tolerance. Additionally disrupted circadian rhythm, sleep restriction, and sleep deprivation-associated metabolic disorders are the subject of current research; however, extremely limited data has been obtained concerning the immune modulation, immune escape mechanisms, spontaneous immune tolerance, and the biosynthesis of quorum-sensing molecules.

Extensive screening of the tryptophan degradation pathway components aimed to clarify and update the selected topics within the scope of recent opinions. However, reappraisal of conceptualized definitions of tryptophan-related disorders within the current perspectives surprisingly revealed that several details of tryptophan metabolism still remain unknown. Last of all, complementary investigations

are required to comprehend the complex interaction between tryptophan-derived metabolites among themselves and within the central nervous system and in the periphery. Overall this publication focuses on the critical and controversial points of tryptophan metabolism. We believe that the reassessment of tryptophan metabolism may lead to new perceptions.

Ankara, Turkey

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Atilla Engin, M.D., Ph.D., was formerly Professor of General Surgery at Gazi University. He is currently professor emeritus. He earned Ph.D. in Biochemistry from Hacettepe University in 1971. His doctoral research led to the discovery of the relationship between the cancer growth rate and tissue glutathione concentrations, and these works have been cited for several times and won the "Science Award in Surgery." He is a pioneer scientist in experimental surgery. His nationally and internationally funded research projects' findings have been cited in numerous international journals and books. While some of these outcomes won national and international awards, some of them were registered and included into scientific databases. His works are mainly focused on oxidative stress and antioxidants and endocrine and metabolic response to trauma.

Ayse Basak Engin, Ph.D., is Associate Professor of Toxicology and currently working in Gazi University, Faculty of Pharmacy, Department of Toxicology, in Ankara, Turkey. Dr. Engin has several publications related to pteridine and tryptophan metabolism, immunological alterations in biological systems, application of these biomarkers in cancer diagnosis and prognosis, oxidative stress, nanotoxicology-nanomedicine, and mycotoxins. She has participated as principal investigator or researcher, in many research projects funded by national and international organizations and her findings have been cited in numerous international journals. While some of these were registered and included into scientific databases, some of them won national and international awards. She edited and wrote two chapters in a book related to endothelium. Dr. Engin is currently the Secretary General of Turkish Society of Toxicology.

Chapter 1
Tryptophan-Related Signaling Molecules: Targets and Functions

Atilla Engin

Abstract Most of the daily dietary tryptophan (Trp) is oxidatively degraded through the kynurenine (Kyn) pathway, and the remaining may be consumed either in serotonin synthesis or in conversion into melatonin through the methoxyindole pathway. Trp degradation products along the Kyn pathway include three neuroactive metabolites: the neuroinhibitory agent kynurenic acid (KA), the free radical generator 3-hydroxykynurenine (3HK), and the excitotoxin quinolinic acid (QA). Kyn is the major metabolite of Trp and is readily transported across the blood–brain barrier into the brain where it can be further metabolized in perivascular macrophages, microglia, and astrocytes, also to generate neuroactive intermediates. In contrast to Kyn, QA, KA, and 3-hydroxyanthranilic acid (3HAA) penetrate through the blood–brain barrier only poorly due to its polar nature. Although the cytokines do not pass through the blood–brain barrier, their signals reach the brain through humoral, neural, and cellular pathways and stimulate Trp degradation by interacting with a cytokine network in the brain. The induction of Kyn pathway by indoleamine 2,3-dioxygenase (IDO) activity exhausts L-Trp in the medium and produces toxic metabolites. While Kyn to Trp ratio reflects IDO activity, Kyn to KA ratio indicates the neurotoxic challenge. Alpha7 nicotinic acetylcholine receptor (alpha7nAChR) constitutes a crucial link between excessive KA formation and reduction in glutamate. KA-induced reduction in prefrontal glutamate levels emerges as a result of alpha7nAChR inhibition. Changes in the endogenous concentrations of KA, as a potent alpha7nAChR and N-methyl-D-aspartate (NMDA) receptor antagonist, affect extracellular dopamine levels in the brain. The entire monoaminergic neurotransmission involves functional interactions between serotonin, norepinephrine, and dopamine systems (Fig. 1.1). Serotonin transporter (SERT) reuptakes biogenic amine neurotransmitters following release in the nervous systems and terminates the action of serotonin. SERT can be regulated by a membrane-bound G-protein-coupled receptor, and this occurs via nitric oxide (NO) and cyclic guanosine monophosphate (cGMP). Desensitization and re-sensitization of G-protein-coupled

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receptors (GPCRs) can modulate receptor responsiveness in regulation of many cellular functions. Diet restriction-induced exaggerated feedback control over serotonin synthesis decreases serotonin neurotransmission at postsynaptic sites by reducing availability of Trp. Enterochromaffin (EC) cells of the intestinal mucosa respond to chemical and mechanical stimuli by releasing serotonin. The enteric serotonin transporter plays a critical role in serotonergic neurotransmission and in the initiation of peristaltic and secretory reflexes.

Keywords Tryptophan • Kynurenine • Kynurenic acid • Quinolinic acid • Indoleamine 2,3-dioxygenase • N-Methyl-D-aspartate receptor • Serotonin • Serotonin transporter • Serotonin receptors

1.1 Introduction

Amino acids are not only regulators of gene expression and the protein phosphorylation cascade but are also cell signaling molecules. Carbon skeletons of essential amino acids cannot be synthesized by animal cells and, therefore, must be provided from the diet (Wu 2010). The average daily nutritional requirement of L-tryptophan (Trp) as an essential amino acid is 5 mg/kg. In order to improve mood or sleep, many adults may consume Trp much more, up to 4–5 g/day (60–70 mg/kg) (Fernstrom 2012). Ninety-five percent of dietary Trp is oxidatively degraded in the liver through the kynurenine (Kyn) pathway. Actually there are two rate-limiting enzymes of Kyn formation: first, tryptophan 2,3-dioxygenase (TDO) and, the second, indoleamine 2,3-dioxygenase (IDO) (Marazziti et al. 2013). TDO reaction generates nicotinamide adenine dinucleotide [NAD^+] following Trp oxidation. A small amount of Trp degradation can also occur extrahepatically by the enzyme IDO. IDO is expressed by a large variety of cells and can be directly activated by proinflammatory cytokines such as interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha, whereas TDO is only located in the liver cells and is activated by stress hormones (Wirleitner et al. 2003). Degradation of Trp mainly occurs along the Kyn pathway. Eventually Kyn is metabolized along one of two catabolic branches, leading to the formation of either hydroxykynurenine (3HK) and quinolinic acid (QA) or kynurenic acid (KA). The cerebral Kyn pathway is driven mainly by blood-borne L-Kyn, which enters from the circulation to the brain using the large neutral amino acid transporter, whereas QA, KA, and 3-hydroxyanthranilic acid (3HAA) cannot pass the blood–brain barrier easily (Fig. 1.1) (Fukui et al. 1991). In the brain, L-Kyn is then rapidly taken up by astrocytes and, presumably, by microglial cells. Almost all enzymes of the Kyn pathway are primarily contained in astrocytes and microglial cells (Schwarcz 2004). However, astrocytes do not contain kynurenine 3-hydroxylase and therefore favor KA synthesis, whereas microglial cells have very little kynurenine aminotransferase (KAT) activity which catalyzes the irreversible transamination of L-Kyn to KA and preferentially forms intermediates of the QA (Guillemin et al. 2001). KA can antagonize the neuronal degeneration mediated by excessive stimulation of N-methyl-D-aspartate (NMDA) receptors in vivo (Lekieffre et al. 1990). During the stress response

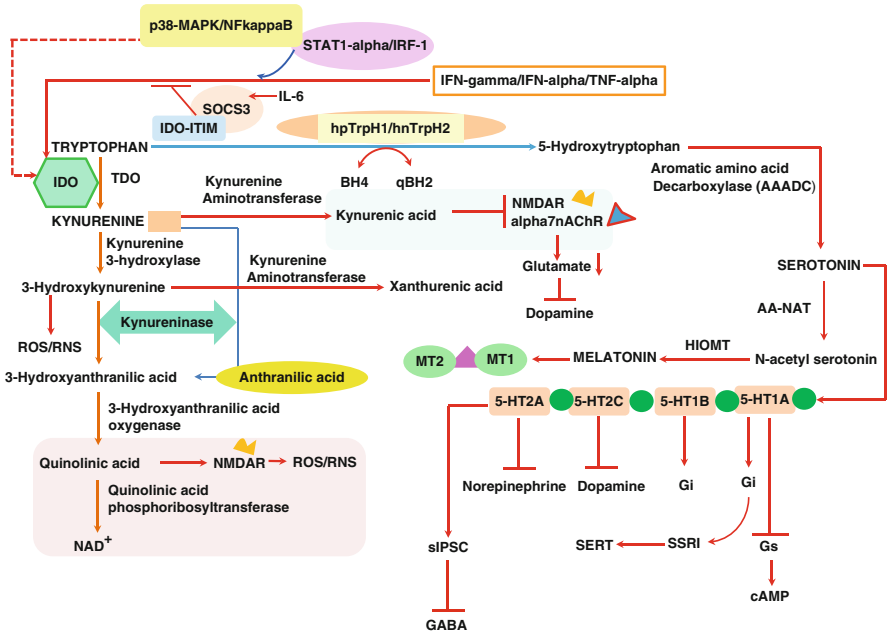

Fig. 1.1 Catabolic cascade of tryptophan metabolism. A simplified version of the kynurenine, serotonin, and methoxyindole pathways demonstrating the major enzymes, intermediates, and receptors. *TDO* tryptophan 2,3-dioxygenase, *IDO* indoleamine 2,3-dioxygenase, *SOCS* suppressor of cytokine signaling, *STAT1-alpha* signal transducer and activator of transcription 1-alpha, *IRF-1* interferon regulatory factor-1, *NF-kappaB* nuclear factor kappa B, *p38-MAPK* p38 mitogen-activated protein kinase, *IDO-ITIM* immunoreceptor tyrosine-based inhibitory motif for IDO, *IFN-gamma* interferon gamma, *IFN-alpha*, interferon alpha, *TNF-alpha* tumor necrosis factor alpha, *IL-6* interleukin-6, *ROS* reactive oxygen species, *RNS* reactive nitrogen species, *NMDAR* N-methyl-D-aspartate receptor, *NAD*$^+$ nicotinamide adenine dinucleotide, *hpTrpH1* human peripheral tryptophan hydroxylase1, *hnTrpH2* human neural tryptophan hydroxylase2, *BH4* tetrahydrobiopterin, *qBH2* quinonoid dihydrobiopterin, *alpha7nAChR* alpha7 nicotinic acetylcholine receptor, *AA-NAT* arylalkylamine-N-acetyltransferase, *HIOMT* hydroxyindole-O-methyltransferase, *5-HT2A, 5-HT2C, 5-HT1B, 5-HT1A* serotonin receptors, *Gi* inhibitory G protein, *Gs* stimulatory G protein, *SSRI* selective serotonin reuptake inhibitor, *SERT* serotonin transporter, *sIPSC* spontaneous inhibitory postsynaptic currents, *GABA* gamma-aminobutyric acid, *cAMP* cyclic adenosine monophosphate, *MT1, MT2* membrane-bound melatonin receptors

100- to 1,000-fold elevations in 3HK and QA occur upon microglial cell activation or macrophage infiltration to the brain (Schwarcz 2004). 3HK generates free radical species that can cause oxidative stress and lipid peroxidation. QA-induced excitation and neurotoxicity are mediated by N-methyl-D-aspartate receptor (NMDA) receptors. Because of the absence of effective removal mechanisms for extracellular QA (Foster et al. 1984), its ability to induce concentration-dependent increases in reactive oxidative species (ROS) formation (Santamaría et al. 2001), and its specific interaction with the NMDA receptor (De Carvalho et al. 1996), QA is particularly excitotoxin, whereas KA acts as a competitive blocker of the glycine co-agonist site of the NMDA receptor (Kessler et al. 1989) and as a noncompetitive inhibitor of the