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What is the tryptophan kynurenine pathway and why is it important to neurotherapy?

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Abstract

The kynurenine pathway has received increasing attention as its connection to inflammation, the immune system, and neurological conditions became more apparent. It is the primary route for tryptophan catabolism in the liver and the starting point for the synthesis of nicotinamide adenine dinucleotide in mammals. Dysregulation or overactivation of this pathway can lead to immune system activation and accumulation of potentially neurotoxic compounds. These aspects make the kynurenine pathway a promising target for therapeutic development to treat inflammation and some diseases with neurological aspects, especially in cancer patients undergoing chemotherapy.

Keywords

Excitotoxicity; melatonin; inflammation; quinolinic acid; serotonin

Tryptophan is an essential amino acid which is used to build protein and is a biosynthetic precursor to numerous neurologically active compounds. It is probably most well known as the starting point for the biosynthesis of serotonin and melatonin. While the generation of these two compounds may have garnered the most attention in the past, a less well known pathway for tryptophan metabolism, the kynurenine pathway, has recently seen steadily increasing research activity. The importance of the kynurenine pathway, which accounts for the catabolism of ~99% of ingested tryptophan not used for protein synthesis [1], was originally ascribed to its role in the biogenesis of nicotinamide adenine dinucleotide (NAD), however apparent links with neurodegenerative diseases, tumor proliferation, inflammation, and depression are currently driving the study of the kynurenine pathway.

The kynurenine pathway was first discovered in 1853 through the detection excreted products from animals fed tryptophan. In the ensuing century, much work was performed to establish the chemical transformations, enzymes involved, and possible disease relations of the kynurenine pathway. In the 1960s, the component enzymes of the kynurenine pathway

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were fully elucidated through the laborious work of extracting each component enzyme from mammalian tissue, respectively, and determining their corresponding activities [2].

As the link between the kynurenine pathway and major depressive disorder became more apparent, the serotonin hypothesis was proposed stating that upon activation, the kynurenine pathway would divert available tryptophan away from serotonin production towards further catabolism [3]. Though the correlation between kynurenine pathway activity and inflammation has been confirmed in many instances, the serotonin hypothesis has not survived in its original form. It was shown that kynurenine pathway activation by interferon-α (IFN-α) did not significantly lower the tryptophan concentration in cerebral spinal fluid, though it did lead to inflammation by increasing the amounts of kynurenine pathway metabolites, namely kynurenine, kynurenic acid, and quinolinic acid (QUIN), concentrations in cerebrospinal fluid [4]. Inflammation caused by kynurenine pathway activation has also been implicated in the treatment resistance of some patients suffering from depression as well as with patients undergoing chemotherapy [5].

Thanks to modern molecular biological methods, as well as the discovery of analogous kynurenine pathways in bacterial species [6], the individual enzymes of the kynurenine pathway have recently been able to be studied at the molecular level. The first and rate-limiting step of the kynurenine pathway is made by tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO). These heme-dependent enzymes insert molecular oxygen across the 2–3 bond of the indole moiety of tryptophan [7] and were formerly known as tryptophan pyrrolase. TDO is a homotetramer with rigid substrate selectivity which is found mostly in hepatic tissue, while IDO is a monomer with much more relaxed specificity that is found in most tissues. Notably, IDO is increasingly recognized as a link between the immune system and the kynurenine pathway, as it is activated by cytokines and appears to have some anti-inflammatory effects. It is also implicated in the tumor-suppressive abilities of interferon-γ [8]. From a mechanistic enzymology viewpoint, these enzymes are unique, as they are the only known dioxygenases which employ a heme prosthetic group as a cofactor. Furthermore, IDO is the only enzyme, other than superoxide dismutase, which can utilize superoxide as a substrate, implicating it in oxidative stress response.

The product of the TDO/IDO-catalyzed reaction, *N*-formylkynurenine, is then hydrolyzed to kynurenine. Depending on the tissue type, kynurenine either continues down its pathway towards the tricarboxylic acid cycle or is transformed to kynurenic acid in microglial cells or astrocytes, respectively [9]. Kynurenine and its immediate metabolites do not appear to any direct effects on neurons; however they do possess various pro- and anti-oxidant activities. Alternatively, kynurenic acid competitively antagonizes glutamate receptors and non-competitively inhibits the α7 nicotinic acetylcholine receptor [9].

Further down the kynurenine pathway, a second dioxygenase, 3-hydroxyanthranilic acid dioxygenase (HAO), is utilized to open the remaining aromatic ring which once belonged to tryptophan. HAO is a type III, non-heme, iron-dependent, extradiol dioxygenase [10]. Though not as unique as TDO/IDO, HAO still has interesting features. Notably, HAOs from bacterial sources often contain an extra, rubredoxin-like metal binding domain which is not necessary for catalysis. This domain is not found in HAOs from animal sources, leaving the

question as to the function and significance of such an extra metal binding domain. HAO cleaves the ring of 3-hydroxyanthranilic acid, a known free radical generator, to create α-amino-β-carboxymuconate-ε-semialdehyde, a compound that decays non-enzymatically to the NAD precursor, quinolinic acid (QUIN). The renewed interest in the kynurenine pathway is due in large part to the discovery that QUIN can selectively activate *N*-methyl-D-aspartate (NMDA) receptors [11, 12]. Though the basal levels of QUIN are not such that they can significantly excite NMDA receptors, activation of the kynurenine pathway can lead to dangerous QUIN levels, which are associated with numerous neurological diseases: Alzheimer's disease, anxiety, depression, epilepsy, human immunodeficiency virus-associated neurocognitive disorders, and Huntington's disease [11, 13–17]. The generation of QUIN is thought to be the major link between the kynurenine pathway and inflammatory response [18].

The next enzyme in the kynurenine pathway not only exhibits unique chemistry, but it is also the major branching point between a non-enzymatic formation of the excitotoxic NAD precursor, QUIN, and further metabolism. This enzyme is α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD), the only known metal-dependent, oxygen-independent, decarboxylase. The X-ray crystal structure of this enzyme was recently solved, and biochemical work has shown a potential mechanism for regulating the activity of this enzyme. It was shown that only the homo-dimer form of ACMSD is able to catalyze the decarboxylation of the substrate, opening the door to the possibility that modulation of the quaternary structure of ACMSD may be the dominant regulatory mechanism for this enzyme [19, 20]. Another interesting feature of ACMSD is that both its substrate and its product are unstable and will undergo electrocyclizations to QUIN and picolinic acid, respectively. Though there are a wealth of studies which show the deleterious effects of quinolinic acid, the literature on picolinic acid is much more sparse, and no consensus has yet been reached as to its physiological roles and effects [21]. It seems to represent a metabolic dead-end for the kynurenine pathway, as it is excreted.

At least in the *in vitro* studies, the substrate of ACMSD is an order of magnitude more stable than its product [22], which brings up the natural question of how the rates of these two non-enzymatic decay reactions are controlled in the cell. Answering this question will require detailed knowledge of the enzymatic mechanism of HAO, ACMSD, and the next enzyme in the pathway, α-aminomuconate-ε-semialdehyde dehydrogenase (AMSDH). The structure and mechanism of ACMSD are relatively well studied [19, 20], and the structure of HAO is defined [23]. However, little was known about this third enzyme, which presumably controls the partitioning between further metabolism and picolinic acid formation, until very recently, when the crystal structure was solved, and catalytic mechanism proposed [22]. AMSDH is a member of the aldehyde dehydrogenase superfamily and the first energy harvesting step of the kynurenine pathway, oxidizing its semialdehyde substrate while reducing NAD.

To summarize, the primary metabolic route for tryptophan catabolism in mammals produces neuroactive compounds, one of which, quinolinic acid, is both the biosynthetic precursor to NAD production and an agonist of NMDA receptors. Elevation of quinolinic acid concentrations in cerebrospinal fluids has been seen in several neurodegenerative diseases,

and injection of exogenous quinolinic acid can cause neurodegeneration in mice. The kynurenine pathway can be stimulated in the brain by treatment with IFN-α. These findings point to the production of quinolinic acid by the kynurenine pathway as a contributing factor to neurodegenerative diseases which are associated with inflammation.

In conclusion, the kynurenine pathway is the major route for tryptophan catabolism in mammalian cells, and many of the intermediates and products of this pathway are implicated in numerous neurological diseases. As such, the kynurenine pathway is a ripe target for drug discovery, especially since so little is known regarding its regulation. The kynurenine pathway also has some connection to tumor growth and proliferation through one of its initiating enzymes, IDO, and there are IDO inhibitors currently in phase II clinical trials [24]. In recent years, the kynurenine pathway has received increased attention from clinicians, biologists, and biochemists as its medical relevance became more apparent. Even with the renewed effort, there is still a lack of understanding of how the production of arguably the most detrimental metabolite, QUIN, is controlled and work must be done to target its production therapeutically. There is a current need for investigations into the mechanisms by which the kynurenine pathway is regulated, especially the enzymes involved in QUIN formation.

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