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Review

The kynurenine pathway and neurodegenerative disease

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ABSTRACT

Neuroactive metabolites of the kynurenine pathway (KP) of tryptophan degradation have been closely linked to the pathogenesis of several neurodegenerative diseases. Tryptophan is an essential amino acid required for protein synthesis, and in higher eukaryotes is also converted into the key neurotransmitters serotonin and tryptamine. However, in mammals >95% of tryptophan is metabolized through the KP, ultimately leading to the production of nicotinamide adenosine dinucleotide (NAD^+). A number of the pathway metabolites are neuroactive; *e.g.* can modulate activity of several glutamate receptors and generate/scavenge free radicals. Imbalances in absolute and relative levels of KP metabolites have been strongly associated with neurodegenerative disorders including Huntington's, Alzheimer's, and Parkinson's diseases. The KP has also been implicated in the pathogenesis of other brain disorders (*e.g.* schizophrenia, bipolar disorder), as well as several cancers and autoimmune disorders such as HIV. Pharmacological and genetic manipulation of the KP has been shown to ameliorate neurodegenerative phenotypes in a number of model organisms, suggesting that it could prove to be a viable target for the treatment of such diseases. Here, we provide an overview of the KP, its role in neurodegeneration and the current strategies for therapeutic targeting of the pathway.

Contents

Abbreviations: 3-HANA, 3-hydroxyanthranilic acid; 3-HAO, hydroxyanthranilate 3,4-dioxygenase; 3-HK, 3-hydroxykynurenine; α7nACh, α7-nicotinic acetylcholine; Aβ, β-amyloid peptide; ACMS, 2-amino-3-carboxymuconic 6-semialdehyde; AD, Alzheimer's disease; aSyn, α-synuclein; BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; FAD, flavin adenine dinucleotide; GAS, INF-γ activated site; GST, glutathione S-transferase; HD, Huntington's disease; HDAC, histone deacetylase; *HTT*, huntingtin gene; HTT, huntingtin protein; IDO, indoleamine-2,3-dioxygenase; INF-γ, interferon-γ; IL, interleukin; IL-1β, interleukin-1 beta; iNOS, inducible nitric oxide synthase; KAT, kynurenine aminotransferase; KMO, kynurenine monooxygenase; KP, kynurenine pathway; KYNA, kynurenic acid; KYNU, kynureninase; L-KYN, L-kynurenine; LPS, lipopolysaccharide; L-TRP, L-tryptophan; mHTT, mutant HTT; NAD^+, nicotinamide adenosine dinucleotide; NMDA, N-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; OGT, oren-gedoku-to; PD, Parkinson's disease; QUIN, quinolinic acid; QPRT, quinolinate phosphoribosyltransferase; TDO, tryptophan 2,3-dioxygenase; TNFα, tumor necrosis factor α; ROS, reactive oxygen species; SOD, superoxide dismutase.

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1. Introduction

In mammals, the kynurenine pathway (KP) is initiated by the oxidative cleavage of the indole-ring of L-tryptophan (L-TRP) by either one of two indoleamine-2,3-dioxygenases (IDO1 and IDO2) or tryptophan 2,3-dioxygenase (TDO2) to produce *N*-formylkynurenine (see Fig. 1). This is followed by the synthesis of the first stable molecule of the pathway, L-kynurenine (L-KYN). The subsequent metabolism of L-KYN occurs *via* one of three mechanisms: (1) deamination of L-KYN by the kynurenine aminotransferase (KAT) family of enzymes results in the production of kynurenic acid (KYNA); (2) degradation of L-KYN by kynureninase results in the production of anthranilic acid; or (3) hydroxylation of L-KYN by kynurenine monooxygenase (KMO) produces 3-hydroxykynurenine (3-HK). 3-HK is subsequently converted into 3-hydroxyanthranilic acid (3-HANA) by kynureninase (KYNU), and then oxidized by 3-hydroxyanthranilate 3,4-dioxygenase (3-HAO) into 2-amino-3-carboxymuconic 6-semialdehyde (ACMS). Under physiological conditions, this intermediate spontaneously reassembles to form quinolinic acid (QUIN), which is subsequently transaminated by quinolinate phosphoribosyltransferase (QPRT) to generate nicotinic acid, and ultimately NAD^+. QPRT levels in the brain are low [1], thereby limiting the rate of NAD^+ production. The metabolite ACMS can also be metabolized to produce picolinic acid *via* the activity of 2-amino-3-carboxymuconic-6-semialdehyde decarboxylase [2].

2. Neuroactive kynurenine metabolites

KP metabolites show diverse properties that can cause contrasting effects in neurons. The arm of L-KYN metabolism catalyzed by KMO produces the metabolites 3-HK, 3-HANA and QUIN, all of which are neurotoxic. QUIN selectively activates N-methyl-D-aspartate (NMDA) receptors [3] and was first identified as a potential neurotoxin when intracerebroventricular injection in mice caused strong convulsions [4]. Subsequent work found that striatal injection of QUIN into rodent brains was excitotoxic, causing axon-sparing lesions of dose-dependent size, proximal to the site of injection [5], which could be rescued by co-administration of a selective NMDA receptor antagonist [6]. QUIN levels marginally above physiological levels are also sufficient to cause rapid neurodegeneration in rat corticostriatal cell culture [7]. The highly efficacious nature of QUIN is likely due to the number of mechanisms through which this neurotoxin can cause neuronal insult. Not only does QUIN stimulate neuronal release of glutamate, it also inhibits the astroglial reuptake of this neurotransmitter [8] and reduces the activity of glutamine synthetase [9] – which facilitates glutamine production from glutamate and ammonia. High concentrations of extracellular glutamate and persistent activation of excitatory neurons causes excitotoxicity due to augmented Ca^{2+} influx through the ion-channel complex, leading to mitochondrial dysfunction, cytochrome C release, the activation of proteases and caspases, as well as NOS activation [10].

QUIN promotes lipid peroxidation [11] in an NMDA receptor [12] and iron (II) [13] dependent manner. Furthermore, QUIN–iron complexes produce reactive oxygen species (ROS) upon auto-oxidation [14]. In cultured human neurons and astrocytes, treatment with QUIN results in a dose-dependent increase in the activity of inducible and neuronal nitric oxide synthase (iNOS and nNOS respectively), leading to increased cellular toxicity, depletion of NAD^+ and activation of the NAD^+ dependent nuclear DNA repair enzyme PARP-1 [15]. Inhibition of iNOS and nNOS is sufficient to rescue all of these effects, indicating that nitric oxide production likely plays a causative role in QUIN excitotoxicity. QUIN-induced increases in both iNOS and nNOS are accompanied by lipid peroxidation and neuronal excitotoxicity in rat brains, both of which are prevented by inhibiting both forms of NOS [16] Furthermore the antioxidants melatonin [17], alpha-phenyl-t-butyl nitrone and U-83826E [18] are able to reduce QUIN-induced cell death in rat striatal neurons *in vivo* and *in vitro*.

The neuroactive KP metabolite 3-HK is synthesized by KMO and generates free-radicals by oxidizing interacting molecules [19,20]. Indeed, 3-HK treatment of cultured striatal and cortical neurons results in reduced viability, shrunken, irregular somata and reduced neuritic outgrowths, which is prevented by the antioxidant catalase, but not superoxide dismutase (SOD) [21–23]. Notably, intrastriatal co-injection of 3-HK with QUIN potentiates excitotoxic neuronal lesions [24]. The formation of these lesions can be blocked *via* either NMDA receptor inhibition or scavenging of free radicals using N-tert-butyl-a-(2-sulphophenyl)-nitrone. Synthesized further downstream in the pathway, the metabolite 3-HANA readily auto-oxidizes and consequently generates highly reactive species such as hydrogen peroxide and hydroxyl radicals [25,26], which is enhanced by SOD but abolished by catalase [26,23]. These data suggest that 3-HK and 3-HANA mediated neurotoxicity is caused by ROS, which can be specifically counteracted by catalase activity. It has also been reported, however, that both 3-HK and 3-HANA are also capable of antioxidant activity [27,28]. Notably, 3-HK dependent toxicity is observed in neuronal cell cultures [22,23], but not in cultured glioma cells [28]. As the KP takes place predominantly in microglia and astrocytes in the central nervous system (CNS), these data may indicate that glial cells are more likely to tolerate the presence of 3-HK than neurons, where 3-HK is not endogenously produced [29]. Interestingly, it has been observed *via* both *in vitro* and *in vivo* approaches that at high concentrations (50–100 μM), 3-HK was in fact protective against known neurotoxins in the rat striatum, likely due stimulation of the antioxidant enzymes glutathione S-transferase (GST) and SOD [29].

KYNA, on the other hand, possesses antioxidant properties due to its ability to scavenge free radicals such as hydroxyls and superoxide anions [30]. At physiological levels, it also acts as a non-competitive antagonist of α7-nicotinic acetylcholine (α7nACh) receptors, subsequently reducing acetylcholine, dopamine and glutamate signalling [31]. At high micromolar concentrations, KYNA is a non-selective antagonist of NMDA receptors [32]. Through this modulation of glutamate signalling and antioxidant activity, KYNA is likely able to counteract the neurotoxicity conveyed by QUIN, 3-HK, and 3-HANA. During normal physiological conditions, the relative flux through the two arms of L-KYN metabolism must therefore be tightly regulated to ensure the ratio of these metabolites is maintained at a level that prevents cellular toxicity.

3. Regulation of the kynurenine pathway in the CNS and periphery

The initial rate-determining step of the KP is controlled by TDO/IDO activity, enzymes which show low sequence similarity, different affinities for specific tryptophan isoforms and are regulated by separate mechanisms [33,34]. TDO is a heme-containing dioxygenase that can be induced by the binding of corticosteroids to their receptors [35]. Reduction of the TDO heme group from heme-Fe^{3+} to heme-Fe^{2+} allows it to oxidize L-TRP, therefore its activity is modulated by reducing agents and ROS [36]. TDO activation can also be induced by proinflammatory cytokines, although this is thought to occur indirectly through the activation of glucocorticoid receptors [37]. IDO1 is induced directly by proinflammatory cytokines which are released during immune response. Interferon-γ (INF-γ) is one of the key mediators of *IDO1* transcription, binding to one of two INF-γ activated sites (GAS) in the 5′ flanking region of the *IDO1*

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