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The role of kynurenines in disorders of the central nervous system: Possibilities for neuroprotection

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ABSTRACT

The metabolism of tryptophan mostly proceeds through the kynurenine pathway. The biochemical reaction includes both an agonist (quinolinic acid) at the N-methyl-D-aspartate receptor and an antagonist (kynurenic acid). Besides the N-methyl-D-aspartate antagonism, an important feature of kynurenic acid is the blockade of the alpha7-nicotinic acetylcholine receptor and its influence on the alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid receptor.
Kynurenic acid has proven to be neuroprotective in several experimental settings. On the other hand, quinolinic acid is a potent neurotoxin with an additional and marked free radical-producing property.
In consequence of these various receptor activities, the possible roles of these substances in various neurological disorders have been proposed. Moreover, the possibility of influencing the kynurenine pathway to reduce quinolinic acid and increase the level of kynurenic acid in the brain offers a new target for drug action designed to change the balance, decreasing excitotoxins and enhancing neuroprotectants. This review surveys both the early and the current research in this field, focusing on the possible therapeutic effects of kynurenines.

1. Introduction

The kynurenine pathway (KP) (Fig. 1) is a central route in the tryptophan (TRP) metabolism in most mammalian tissues, including the brain [1]. This main metabolic cascade is known to be responsible for the formation of nicotine adenine dinucleotide (NAD) and NAD phosphate (NADP); accordingly, it acts on basic cellular processes. The KP has been shown to be followed in the macrophages and microglial cells [2] and in part in the astrocytes [3].

L-Kynurenine (L-KYN) serves as a source for the synthesis of all the other metabolites ('kynurenines') of the KP. It is readily transported across the blood-brain barrier (BBB) by a neutral amino acid carrier [4] which is thought to be modulated by L-valine in metabolic disorders [5]. Certain kynurenines have been demonstrated to have neuroactive properties [6]. In the brain, L-KYN can be converted to four metabolites of the neuroactive components of the KP: 3-hydroxykynurenine (3-HK), anthranilic acid (ANA), quinolinic acid (QUIN) and kynurenic acid (KYNA). The intracerebroventricular administration of these metabolites induces significant behavioural effects in mice [6].

The experimental data suggest that peripheral treatment with L-KYN dose-dependently increases the concentration of the neuroprotective KYNA in the brain, offering an opportunity for the treatment of stroke and neurodegenerative disorders [7–9].

KYNA, a neuroactive metabolite of the KP produced by astrocytes and neurones [10], behaves as an endogenous neuroprotective agent able to prevent neuronal loss following excitotoxic, ischaemia-induced, and infectious neuronal injuries [11–13]. It is synthesized from L-KYN in the enzymatic reactions mediated by kynurenine aminotransferases (KATs) [14].

In the human cerebrospinal fluid (CSF), the concentration of KYNA is in the nanomolar range [15]. It is known that the level of KYNA changes in various human neurodegenerative disorders: it decreases in epilepsy, infantile spasm and Huntington's disease (HD), and increases in Alzheimer's disease (AD) and viral infections, among others [16,17].

KYNA is one of the few known endogenous excitatory amino acid (EAA) receptor inhibitors with a broad spectrum of antagonistic properties. KYNA could potentially have therapeutic effects in neurological disorders [17,18], but its use as a neuroprotective agent is rather restricted because it has only a very limited ability to cross the BBB [4].

Abbreviations: 3-HA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; AD, Alzheimer's disease; AMPA, alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid; ANA, anthranilic acid; BBB, blood-brain barrier; CSD, cortical spreading depression; EAA, excitatory amino acid; HD, Huntington's disease; HIV, human immunodeficiency virus; IDO, indoleamine 2,3-dioxygenase; KAT, kynurenine aminotransferase; KP, kynurenine pathway; KYNA, kynurenic acid; L-KYN, L-Kynurenine; NAD, nicotine adenine dinucleotide; NADP, NAD phosphate; NMDA, N-methyl-D-aspartate; PD, Parkinson's disease; QUIN, quinolinic acid; TRP, tryptophan; α7-nACh, alpha7-nicotinic acetylcholine; α-MTRP, alpha-[^{11}C]me-L-TRP.

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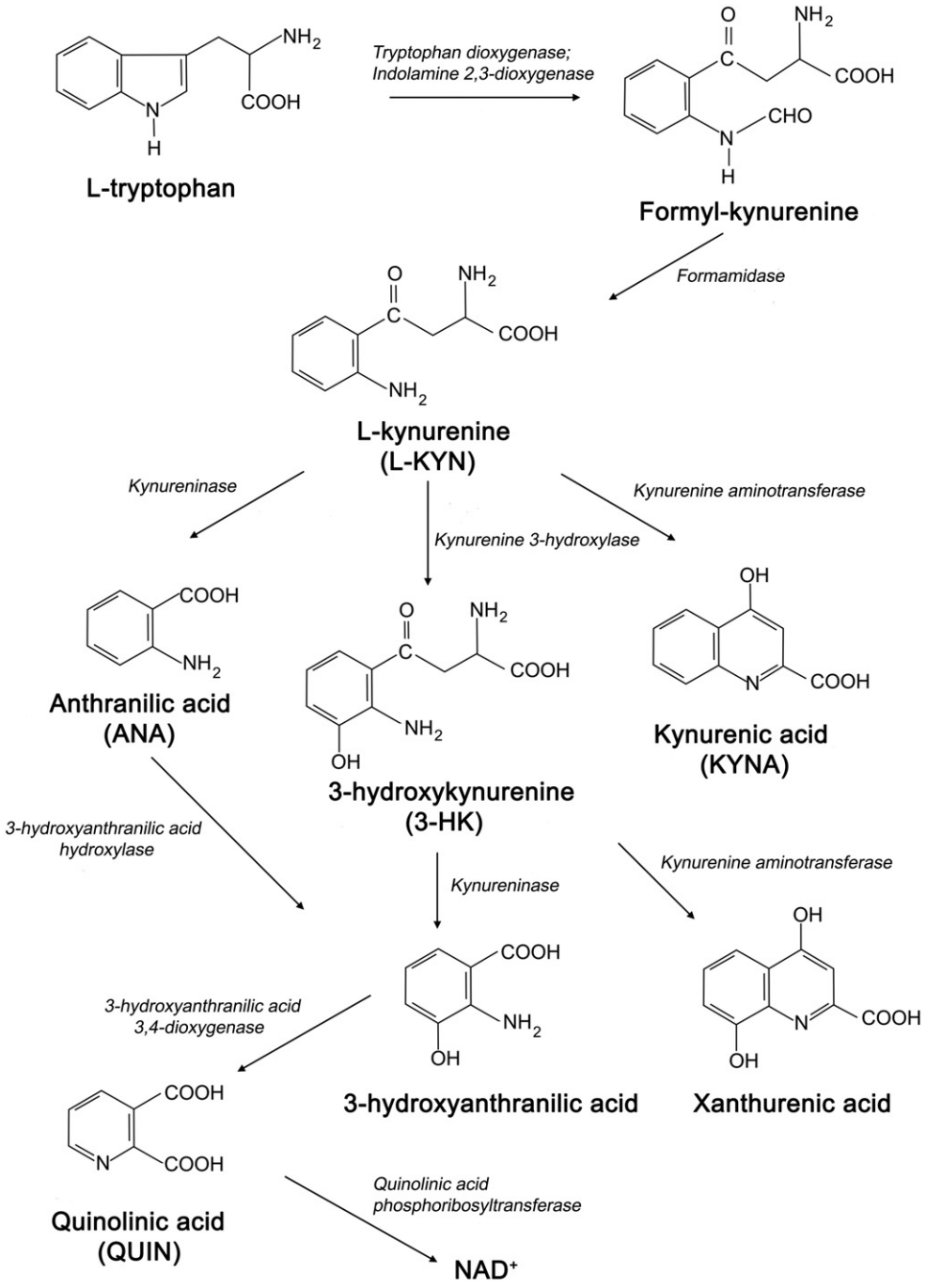

Fig. 1. The kynurenine pathway.

QUIN, produced by L-KYN, is present in the CSF in concentrations similar to those of KYNA (50–100 nM) [19] or in low micromolar concentrations [20]. It has been reported to be associated with the pathogenesis of certain neurodegenerative diseases since it acts as an excitotoxic agonist of the N-methyl-D-aspartate (NMDA) receptor [21–24]. Intrastriatal injection of QUIN induces a substantial neuronal loss [25].

3-HK and ANA, produced directly from L-KYN, can generate free radicals and elevate the oxidative stress level, causing neuronal damage.

In the mammalian brain, the concentration of 3-HK is in the nanomolar range, but under pathological conditions it can rise to the micromolar level [26].

3-hydroxyanthranilic acid (3-HA), synthesised from 3-HK and/or ANA exhibits an increased level in patients affected by neurological disorders such as HD [27,28], Parkinson's disease (PD) [29,30], and human immunodeficiency virus (HIV)-1-associated dementia [31]. Furthermore, it has been demonstrated that 3-HK and 3-HA cause the death of cultured neuronal cells with apoptotic features, condensed and fragmented nuclear morphology and DNA fragmentation [32,33,26]. The cortical and striatal neurones have been shown to be particularly vulnerable to the toxic effects of 3-HK [34].

Although some enzymes show differences between different brain regions, and activities may vary depending on species, age, no consistent patterns have emerged so far to identify specific functions of the cerebral KP. Qualitatively the enzyme characteristics of the QUIN branch of the pathway do not appear to differ between brain and periphery, showing the same high substrate specificity and high substrate affinity (low Km values). Moreover, cerebral and peripheral kynurenine 3-hydroxylase, kynureninase, 3-hydroxyanthranilic acid