Neurotoxicity of tryptophan metabolites

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Abstract

The metabolism of tryptophan by the kynurenine pathway leads to the production of several neurotoxic compounds, some of which have been associated with neurological disorders. Recent investigation of some relevant compounds in this pathway has provided further evidence of their neurotoxicity.

Introduction

The kynurenine pathway is one of the metabolic routes by which the essential amino acid tryptophan can be catabolized, producing nicotinamide, a compound that is essential for normal physiological function. Metabolism through the kynurenine pathway primarily leads to formation of quinolinic acid, particularly via production of 3-HK (3-hydroxykynurenine) and 3-HAA (3-hydroxyanthranilic acid). Quinolinic acid may be metabolized further to nicotinamide or nicotinic acid. The kynurenine pathway (Figure 1) also produces kynurenic acid, picolinic acid, 5-HAA (5-hydroxyanthranilic acid) and xanthurenic acid. A number of compounds in this pathway are neurotoxic, and some are associated with central nervous system diseases.

Neurotoxic effects of tryptophan metabolites

Application of 3-HK at micromolar levels (1–100 µM) to striatal neuronal cultures causes time- and dose-dependent death which is significantly reduced by co-treatment with catalase, suggesting that neurotoxic effects of 3-HK are due to hydrogen peroxide production, with consequent excessive hydroxyl radical formation causing damage [1]. In cerebellar granule neurons, neurotoxicity induced by 3-HK involved nuclear fragmentation and chromatin condensation, suggesting involvement of apoptosis. A dose-dependent reduction in neuronal viability resulted from exposure to 3-HAA, with no observable difference in vulnerability between neurons from a number of brain regions (striatum, cerebral cortex, cerebellum and hippocampus) [2].

Quinolinic acid is an NMDA (N-methyl-D-aspartate) receptor agonist, causing increased neuronal firing, and is the only known endogenous compound with the ability to selectively activate the NMDA subtype of glutamate receptors [3]. Direct injection of quinolinic acid in the striatum in vivo produces an axon-sparing neurodegenerative lesion at concentrations of 20–60 nM, with lesion volume increasing proportionately to the quinolinic acid dose applied [4].

Associations with central nervous system diseases

Links have been shown between Huntington’s disease and several compounds in the kynurenine pathway, namely kynurenine, 3-HK, 3-HAA, quinolinic acid and kynurenic acid. Plasma kynurenine levels in Huntington’s disease patients are significantly higher, and the ratio of kynurenine to tryptophan in plasma is also significantly raised in Huntington’s disease patients compared with healthy controls. These results indicate that IDO (indolamine dioxygenase) or TDO (tryptophan dioxygenase) activity in Huntington’s disease patients is higher than normal and may be related to increased levels of superoxide ions and concomitant oxidative stress present in Huntington’s disease patients [5].

Huntington’s disease patients have significantly higher levels of 3-HK in brain tissue at post mortem, and levels of 3-HAO (3-hydroxyanthranilic acid dioxygenase), the enzyme which metabolizes 3-hydroxyanthranilic acid, in brain tissue are also significantly higher. This was found even in patients with normal CSF (cerebrospinal fluid) levels of 3-HAO, consistent with the proposal that regional differences in response to kynurenines exist, and hence differences in susceptibility to their effects [6]. There are strong associations between Huntington’s disease and quinolinic acid, with similarities between quinolinic acid effects on striatal tissue and pathological appearances of Huntington’s disease. The destruction of GABA (γ-aminobutyric acid) and substance P by quinolinic acid treatments, with concomitant sparing of somatostatin and neuropeptide Y, represents a striking parallel with Huntington’s disease [7].

Levels of plasma kynurenic acid were similar in Huntington’s disease patients and healthy controls, but, after tryptophan loading in both groups, the ratio of plasma kynurenic acid to kynurenine in Huntington’s disease patients was far lower, suggesting that KAT (kynurenine aminotransferase) activity is lower in Huntington’s disease patients than in healthy subjects, with lower levels of kynurenic acid and KAT also observed in the brain post-mortem [8].

Quinolinic acid levels in AIDS dementia complex patients are significantly higher in brain parenchyma and CSF [9].

Key words: cerebellar granule neuron, 5-hydroxyanthranilic acid, 3-hydroxykynurenine, kynurenic acid, quinolinic acid, tryptophan metabolite.

Abbreviations used: CSF, cerebrospinal fluid; 3-HAA, 3-hydroxyanthranilic acid; 3-HKA, 3-hydroxyanthranilic acid dioxygenase; 3-HK, 3-hydroxykynurenine; GABA, γ-aminobutyric acid; IDO, indolamine dioxygenase; KAT, kynurenine aminotransferase; NMDA, N-methyl-D-aspartate; TDO, tryptophan dioxygenase.

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Kynurenine pathway compounds focused on the effects of 3-HK, 3-HAA, and 5-HAA on the viability of cerebellar granule neurons in culture (for details of methods, see [14]). All three compounds caused time- and dose-dependent neurotoxicity using a concentration range of 10–1000 μM (Figure 2), with toxicity attenuated by catalase, but not by either superoxide dismutase or desferrioxamine co-application. Although 3-HK and 3-HAA have previously been demonstrated to cause neuronal cell death, this is the first demonstration of the neurotoxic effects of 5-HAA. The reductions in cell

Recent studies
Our recent investigations of the neurotoxicity of kynurenine pathway compounds focused on the effects of 3-HK, 3-HAA, and 5-HAA on the viability of cerebellar granule neurons in culture (for details of methods, see [14]). All three compounds caused time- and dose-dependent neurotoxicity using a concentration range of 10–1000 μM (Figure 2), with toxicity attenuated by catalase, but not by either superoxide dismutase or desferrioxamine co-application. Although 3-HK and 3-HAA have previously been demonstrated to cause neuronal cell death, this is the first demonstration of the neurotoxic effects of 5-HAA. The reductions in cell
viability by the three compounds were similar at equivalent concentrations. Further investigation of the neurotoxic effects of 5-HAA is ongoing, concerning the potential involvement of caspase 3 and p38 signalling in the process.

Several other kynurenine pathway compounds (kynurenine, anthranilic acid, quinolinic acid and picolinic acid) had neurotoxic effects which did not appear to be concentration-related, but did increase with prolonged exposure time.

Additionally, kynurenine, anthranilic acid, quinolinic acid and picolinic acid caused increased neurotoxicity in the presence of a higher glucose concentration in culture medium. Further investigation suggests that this was not due to the metabolism of the excess glucose during the exposure duration, as treatments in medium supplemented with a metabolically inactive form of glucose (3-O-methyl-D-glucose) rather than with D-glucose showed equivalent toxicity.

Another question that arises is whether the raised glucose concentration affects the metabolism of the compounds and we are currently carrying out HPLC studies to explore this possibility.

**Conclusion**

As tryptophan is an essential part of the diet, and since its metabolism inevitably produces neurotoxic compounds, further investigation is timely and essential, with a view to alleviating the harmful effects of these metabolites.

Additionally, the fact that the metabolic products of tryptophan may be linked with several neurological diseases warrants further investigation of these pathological effects and could provide opportunities for the development of interventions to treat these conditions.

**References**


Received 6 July 2007
doi:10.1042/BST0351287