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Chapter VI

The kynurenine pathway of tryptophan degradation as a target for neuroprotective therapies

Introduction

In the kynurenine pathway, oxidative cleavage of the indole ring of tryptophan by tryptophan 2,3-dioxygenase or indoleamine 2,3-dioxygenase initiates the formation of a series of compounds of which nicotinic acid and nicotinamide adenine dinucleotide (NAD^+) constitute essential products. Although the kynurenine pathway appears to be quantitatively less important in extra-hepatic tissues, certain intermediates may play a role in the brain (see Stone, 1993). The interest in the role of neuroactive kynurenines was stimulated by the finding that certain kynurenines may act on cerebral excitatory amino acid (EAA) receptors. In particular, the kynurenines quinolinic acid (QUIN) and kynurenic acid (KYNA) have been found to act as agonist and antagonist, respectively, at the N-methyl-D-asparate (NMDA) EAA receptor. When injected into the brain QUIN causes convulsions (Lapin, 1978) as well as neurodegeneration (Schwarcz et al., 1983). At the same time, it has been recognized that the nature of QUIN toxicity is difficult to explain solely on a NMDA receptor mediated action, while there are evidence of a free radical component. This topic is addressed in the contribution by Trevor Stone and coworkers, in which lesions induced by intrahippocampal QUIN injections is shown to be prevented by administration of the established antioxidants melatonin and deprenyl. This finding not only provides further support for the notion that free radicals are implicated in QUIN neurotoxicity, but also presents an avenue to develop therapeutics for neurological conditions in which major increases in cerebral QUIN levels have been described.

Still, a major question concerning neuroactive kynurenines remains to be resolved; can endogenous kynurenines reach levels that exert relevant pharmacological or pathological effects in the brain? Helen Scharfman and colleagues describe a set of studies trying to pin-point the relevance of KYNA as a glycine site NMDA antagonist. In vivo, stimulation-induced population spike amplitudes were inhibited in the CA1 after systemic KYNA infusion, while CA3 and dentate gyrus regions appeared to be less sensitive. In hippocampal slices, inhibition of evoked CA1 responses was seen only at relatively high concentrations of KYNA, while addition of its precursor L-kynurenine (KYN) was without effect. However, under conditions of epileptiform activity KYN-induced de novo synthesis of KYNA was found to have a distinct anticonvulsant effects. The potential to affect seizures by

modulating the kynurenine pathway is also described by Johan Luthman. Protective effects were found against both chemically- and sound-induced seizures after systemic treatment with the an inhibitor (NCR-631) of the kynurenine pathway enzyme 3-hydroxyanthranilic acid dioxygenase (3-HAO). Although the pharmacological effect of the 3-HAO inhibitor remains to be characterized in detail, this provides further evidence for a role of kynurenines in excitatory events.

In the work by Tiho Obrenovitch and Jutta Urenjak, the importance of accumulation of endogenous QUIN or KYNA is challenged. The authors have used a combination of microdialysis with built-in eletrophysiology to study the effects of local kynurenine infusion in rats. It was found that infusions of very high concentrations of QUIN or KYNA were required to elicit depolarization or inhibition of NMDA-induced depolarization, respectively, in rat frontal cortex. Moreover, extracellular increases in KYNA after systemic administration of a kynurenine-3-hydroxylase inhibitor (Ro-61-8048) did not reach levels needed for inhibition of NMDA responses. While these findings may cast doubt on the role of KYNA as a direct acting NMDA modulator, it may suggest that other mechanisms are involved in its anti-convulsant actions.

At the same time, there are important developmental aspects on kynurenine pharmacology. Indeed, as shown in the work by Robert Schwarcz and collaborators, levels of KYN, KYNA and 3-OH-KYN are much higher in rats pre-term than postnatally, whereas the activity of KAT-II, but not KAT-I, critical enzymes of the kynurenine pathway, rises during the later postnatal period. Moreover, KYNA may originate from the maternal circulation in the perinatal period. These findings raises the interesting perspective that KYNA may serve as an important neuroprotectant during the perinatal period. This hypothesis is further supported by their finding that levels of KYNA remain high even after exposure to perinatal asphyxia.

The different contributions underline the roles various kynurenines may play in brain function. Most importantly, however, novel therapeutic approaches can be identified in the presented work that may lead to the development of refined treatments for neurodegenerative and convulsive disorders.

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