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Neuroactive tryptophan metabolites: focus on kynurenines

Introduction

Apart from glutamate and aspartate there are several other endogenous substances that may modulate excitatory amino acid neurotransmission and act as excitotoxins. One metabolic pathway that seems to be particularly important in that respect is the kynurenine pathway, the major route of L-tryptophan metabolism in mammalians. Several intermediates of the kynurenine pathway have been found to possess significant biological effects. The awareness of the role kynurenines may play in the central nervous system has been spurred by the finding that certain kynurenines may act on excitatory amino acid receptors. Quinolinic acid and kynurenic acid are two kynurenines that have been found to act as agonist and antagonist at excitatory amino acid receptors, respectively. When injected into the brain quinolinic acid causes convulsions and neurodegeneration. Interestingly, picolinic acid, another metabolite of the kynurenine pathway, has been found to counteract the neurotoxic effects of quinolinic acid. In the contribution by Jhmandas et al. this role of picolinic acid has been further characterized and found to be dependent on zinc. Hence, the addition of zinc augumented quinolinic acid, but not NMDA mediated toxicity, while the protective effect of picolinic acid was reduced by zinc co-administration. By the work by Schwarcz et al. a new aspect on the regulation of kynurenic acid is identified. In their work a modulatory role of cellular energy metabolism as well as dopamine system active drugs on brain levels of kynurenic acid is described. Furthermore these effects are shown to be dependent on the age of the animals. Infections and immune activation have been shown to be associated with major alterations in kynurenine pathway metabolites; effects that seem to be critically linked to activation of macrophages and microglia. In the work by Alberati-Giani et al. the regulation of the first step of the kynurenine pathway, indoleamine 2,3-dioxygenase is further characterized in different cell lines. Differences between macrophages and microglia in the expression of indoleamine 2,3-dioxygenase is found after activation with LPS or picolinic acid. In addition, NO seems to negatively modulate the expression in macrophages, but not in microglia. The potential to affect neurotoxicity by the use of an inhibitor of the kynureine pathway enzyme 3-hydroxyanthranilic acid dioxygenase is described by Luthman et al. Protective effects were found in different *in vitro* models of anoxia and neuroinflammatory-mediated neurodegeneration. The contributions by these authors underline the biological significance of the kynurenine pathway, and show the diverse role that various kynurenines may play in brain function and pathology.

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