KYNURENINE SYSTEM, THE NEGLECTED PLAYER IN NEUROLOGICAL DISORDERS

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Several lines of evidence support that excitotoxicity plays a key role in the pathogenesis of both acute and chronic neurological disorders. Kynurenine (KYN) has been identified as a constituent of the human and rodent brain, where it occurs at a concentration of approximately 1uM. It became clear that two of its metabolic products quinolinic acid (QA) and kynurenic acid (KYNA), act as agonist and antagonist, respectively, at receptors for excitatory amino acids. Furthermore, 3-hydroxy-kynurenine (3-OH-KYN), a biological precursor of QUIN present in the brain in nanomolar concentrations, and has neurodestructive properties. The role of kynurenine system in many disorders of the central nervous system (infections, dementia, epilepsy, ischemia, traumatic brain injury, multipe sclerosis, Parkinson's disease, Huntington's disease and other neurodegenerative disorders) has been hypothesized. As the glutamate receptors are involved in many neurological disorders neuroprotective abilities of the KYNA has been tested. KYNA itself poorly penetrated the blood-brain barrier (BBB), so the protective effects of KYNA is limited by its low central nervous system (CNS) availability. Chemically related drugs with better penetration and higher potency have been developed. These drugs do not have serious side-effects associated with NMDA receptor blockers. To improve the BBB penetration pro-drugs of KYNA can be used, which enter the brain, and are hydrolyzed in the CNS to active compounds. Manipulating the pathway by inhibiting the activity of different enzymes is another therapeutic possibility. With this strategy, one can divert KYN metabolism to the KYNA or QUIN branch. Furthermore, magnetic resonance spectroscopy (MRS) revealed a significantly higher glutamate/glutamine ratio in the occipital cortex in women with migraine during interictal state as compared to healthy controls. This suggest neuronal hyperexcitability of the CNS during migraine attacks. Several recent results clearly confirmed that KYNA and its derivatives exert effects on the functional anatomical sturctures of the nervous system participating in the leading hypothesis of migraine.

Reference:
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