J Neural Transm (2006) [Suppl] 70: 285–304

Page 2, L-dopa depletes serotonin

Kynurenines, Parkinson's disease and other neurodegenerative disorders: preclinical and clinical studies

H. Németh[1,2], **J. Toldi**[2], and **L. Vécsei**[1,3]

[1] Department of Neurology, and
[2] Department of Comparative Physiology, University of Szeged, and
[3] Neurology Research Group of the Hungarian Academy of Sciences and University of Szeged, Szeged, Hungary

Summary. The kynurenine pathway is the main pathway of tryptophan metabolism. L-kynurenine is a central compound of this pathway since it can change to the neuroprotective agent kynurenic acid or to the neurotoxic agent quinolinic acid. The break-up of these endogenous compounds' balance can be observable in many disorders. It can be occur in neurodegenerative disorders, such as Parkinson's disease, Huntington's and Alzheimer's disease, in stroke, in epilepsy, in multiple sclerosis, in amyotrophic lateral sclerosis, and in mental failures, such as schizophrenia and depression. The increase of QUIN concentration or decrease of KYNA concentration could enhance the symptoms of several diseases. According to numerous studies, lowered KYNA level was found in patients with Parkinson's disease. It can be also noticeable that KYNA-treatment prevents against the QUIN-induced lesion of rat striatum in animal experiments. Administrating of KYNA can be appear a promising therapeutic approach, but its use is limited because of its poorly transport across the blood–brain barrier. The solution may be the development of KYNA analogues (e.g. glucoseamine-kynurenic acid) which can pass across this barrier and disengaging in the brain, then KYNA can exert its neuroprotective effects binding at the excitatory glutamate receptors, in particular the NMDA receptors. Furthermore, it seems hopeful to use kynurenine derivatives (e.g. 4-chloro-kynurenine) or enzyme inhibitors (e.g. Ro-61-8048) to ensure an increased kynurenic acid concentration in the central nervous system.

Introduction

Kynurenine (KYN) is an intermediate in the pathway of the tryptophan (TRP) metabolism. This pathway is known to be responsible for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) (Fig. 1). KYN is formed in the mammalian brain (40%) and is taken up from the periphery (60%). The rate of cerebral KYN synthesis was 0.29 nmol/g/h (Gal and Sherman, 1978). In the brain, KYN can be converted to other components of the pathway: the neurotoxic 3-hydroxy-kynurenine (3-HK) or quinolinic acid (QUIN) and the neuroprotective kynurenic acid (KYNA).

Some 25 years ago it was found that intermediates of the kynurenine pathway (KP) have neuroactive properties: convulsions were appeared after mice received QUIN (Lapin, 1978). QUIN is a selective ligand of N-methyl-D-aspartate (NMDA) receptor (Stone and

substantia nigra may be implicated in this masking of this disease. Reversible pharmacological blockage of this input effect the appearance of motor disturbances. This blockade could lead to presymptomatic diagnosis of Parkinson's disease (Bezard et al., 1997a, b).

Ogawa et al. (1992) investigated the concentration of the tyrosine and tryptophan metabolites in the frontal cortex, putamen and substantia nigra pars compacta in Parkinson's diseased and control brain tissue. Dopamine concentration was significantly decreased in the putamen and substantia nigra of diseased tissue, regardless of L-DOPA therapy. KYN and KYNA concentrations were lowered in each region of the diseased groups (with or without L-DOPA-treatment) than in the control group, but the molar ratios of TRP to KYN and KYN to KYNA were unchanged among three groups. In contrast, 3-hydroxykynurenine concentration was increased in the putamen in the Parkinson's disease without L-DOPA-group and in the three regions of the brain tissue with Parkinson's disease with L-DOPA therapy (Ogawa et al., 1992). However, the concentration of total serotonin, 3-hydroxytryptophan, KYN and 3-hydroxykynurenine decreased significantly in diseased patient according to the study of Tohgi. 3-Hydroxykynurenine concentration had significant positive correlations with L-DOPA doses (Tohgi et al., 1993a, b). Neopterin concentration and KYN/TRP ratios were increased both in serum and cerebrospinal fluid of patients as compared to controls. Furthermore, significant correlations existed between the neopterin level and KYN/TRP ratio. This suggests the activated cell-mediated immune response in subgroup of patients with advanced Parkinson's disease (Widner et al., 2002b).

Catalepsy-akinesia with rigor- and reduced locomotion show similarities with symptoms of Parkinson's disease. 7-chloro-KYNA dose-dependently counteracts dopamine D2 receptor-mediated catalepsy, induced by haloperidol, but it has not influence on locomotion and on dopamine D1 receptor-mediated catalepsy. These findings are surprising since NMDA receptor antagonists counteract both dopamine D1 and D2 receptor-mediated catalepsy. D1 and D2 receptors are located on different populations of neurons, so it may be supposed that these different neuronal populations have different sensitivity for ligands binding at the glycine site of the NMDA receptors (Kretschmer et al., 1994; Ossowska et al., 1998).

The subthalamic nucleus has been implicated in movement disorders in Parkinson's disease because of its pathological mixed burst firing mode and hyperactivity. In physiological conditions the bursty pattern of this nucleus has been shown to be dependent on slow wave cortical activity, thus glutamate afferents might be involved in this bursting activity. But according to a recent study glutamatergic-receptors blockade does not regularize the slow wave sleep bursty pattern of subthalamic nucleus (Urbain et al., 2004).

QUIN and Parkinson's disease

Excitotoxins constitute a group of agents are capable of activating excitatory amino acid receptors and producing axon-sparing neuronal lesions. QUIN is a pyridine-dicarboxylic acid which is localized to glia and immune cells, and its content increases with ages. Focal injections of QUIN into the nucleus basalis magnocellularis produced sustained loss of cholinergic neuron markers in the neocortex and amygdala. This resulted in an impairment of performance of memory-related tests. In the striatum focal QUIN injections have been found to largely replicate the neurotransmitter deficits prevailing in Huntington's disease. QUIN is also highly damaging to the striatopallidal encephalinergic neurons (Jhamandas et al., 1994). Autoradiographic techniques were used to study distribution of histamine H2-receptors in the brains of patients affected by human neurodegenerative pathologies compared with control cases. The highest level of