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Lowering of kynurenic acid formation – anti-dementia drugs

Kynurenic acid (KYNA) is an endogenous metabolite of the kynurenine pathway of tryptophan degradation and is an antagonist of the glutamate ionotropic excitatory amino acid and of the nicotine cholinergic receptors and its involvement in memory impairment has been suggested. The therapeutic effect of Cerebrolysin treatment of dementia and of brain injury has been proposed because of neurotrophic properties of this compound. Since an increased kynurenine metabolism has been shown in several brain pathologies including dementia we investigated the biochemical properties of Cerebrolysin with respect to KYNA formation in an *in vitro* study. The activities of the KYNA synthesising enzymes kynurenine aminotransferase I, II and III (KAT I, KAT II, KAT III) in rat liver, and rat and human brain homogenates were analysed in the presence of Cerebrolysin. Data revealed demonstrate the ability of Cerebrolysin to lower KYNA formation in homogenates. We suggest that the anti-dementia effect of Cerebrolysin observed in Alzheimer patients could be due to Cerebrolysin induced reduction of KYNA levels, thus enhancing the cholinergic and glutamatergic neurotransmissions. D-Cycloserine, anti- mycobacterial drug, known as a partial agonist at the glycine modulatory site of the glutamatergic NMDA receptor, exerts anticonvulsive activities and improves cognitive function. We evaluated the action of D-cycloserine with respect to the biosynthetic machinery of KYNA synthesis. Interestingly, we found that D-cycloserine blockes significantly KATs activities in rat liver and brain homogenates and in the frontal cortex homogenate of human post mortem tissue, as well. These results allowed us to propose that lowering of KYNA content likely due to D- cycloserine inhibition of KATs activities might be involved in the postulated mechanism for D- cycloserine to act as a partial agonist at the glycine site of the NMDA receptor. It is reasonable to believe that this mechanism(s) is in part responsible for the improvement of symptoms like dementia, cognition and/or delusion in schizophrenia patients, Alzheimer's, HIV-1 infected patients or Parkinson's patients. Finally we evaluated the action of Jerusalem balsam with respect to the biosynthetic machinery of KYNA synthesis. Jerusalem balsam is widely used because of good reputation as a natural remedy. It is a mixture of certain plants, which supposes to have antibacterial and anti-oxidative properties. Jerusalem balsam is used to improve liver and lung diseases, as for example bronchopneumonia. Interestingly, we found that Jerusalem balsam blocks significantly KATs activities, too. Lowering of KYNA synthesis by Jerusalem balsam represents notable biochemical effect since it might influence KYNA levels. Therefore increased KYNA levels observed in stroke patient, in patient with respiration and cardiovascular problem, in neuropsychiatric disorders, in patient infected with HIV-1 and patients with bronchopneumonia could be treating by Jerusalem balsam. We speculate the possible therapeutic application and advantage of the remedy Jerusalem balsam, i.e. mixture of plants and discuss comparing to effect of anti-dementia drugs D-cycloserine and Cerebrolysine.

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