NMDA ANTAGONISTS ARE USEFUL IN PD: YES

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N-methyl-D-aspartate (NMDA) receptors have been implicated as a mediator of neuronal injury associated with many neurological disorders including, ischemia, epilepsy, brain trauma, dementia and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (PD). It has become increasingly evident that the NMDA receptor complex is intimately involved in the regulation of corticostriatal long-term potentiation, which altered in experimental PD. Patients with PD receiving dopamine replacement therapy in the form of levodopa develop dyskinesia that becomes a major complicating factor in treatment. Dykinesia can only be effectively influenced by a reduction in drug dose, which limits efficacy, by co-administration of the weak NMDA antagonist amantadine or by surgical treatment. Recently it was reported short term beneficts of amantadine therapy in the treatment of dyskinesia. Therefore, the effects of other NMDA receptor antagonists need to be evaluated further in preclinical studies and clinical trials.

In various animal models, memantine has been reported to be a neuroprotective agent that positively impacts both neurodegenerative and vascular processes. While excessive levels of glutamate result in neurotoxicity, in part through the overactivation of NMDARs, memantine –as a partial NMDAR antagonist- blocks the NMDA glutamate receptors to normalize the glutamatergic system and ameliorate cognitive and memory deficits. The key memantine's therapeutic action lies in its uncompetitive binding to the NMDAR. Therefore, memantine may be useful in PD treatment with possibly fewer side effects. Prolonged memantine treatment of patients with PD complicated by dementia leads to improvements in cognitive functions, stabilizing of motor impairments, and decreases in the severity of mental disorders, especially in patients with hyperhomocysteinemia. Furthermore, patients with Dementia with Lewy Body (DLB) or Parkinson's disease dementia (PDD) might benefit from treatment with memantine, which was well tolerated. Large-scale studies are now required to confirm these preliminary findings.

Furthermore, kynurenic acid (KYNAC) is an endogenous product of the tryptophan metabolism. Studies on the mechanism of its action have revealed that KYNAC at high concentrations is a compatitive antagonist of the NMDA receptor and acts as a neuroprotectant in different neurological disorders including PD (1). It is interesting that in nanomolar concentrations, KYNAC does not give rise to inhibition, but in fact facilitates the field excitatory postsynaptic potentials. This „Janus-face" effect of KYNAC is a good basis for drug development in PD.

In conclusion, selected antagonists of glutamate (and adenosine receptors) have been proposed as anti-dyskinetic agents. Promising results have been obtained in preclinical investigations and in initial clinical trials, but long-term safety, tolerability and efficacy studies in patients are still required.

Reference

(1) Vécsei, L., Szalárdy, L., Fülöp, F., Toldi, J.: Kynurenines in the CNS: recent advances and new questions. Nat. Rev. Drug Discover. in press, 2013 January