Gacyclidine: A New Neuroprotective Agent Acting at the N-Methyl-D-Aspartate Receptor

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ABSTRACT

Gacyclidine is a new phencyclidine derivative with neuroprotective properties. Tritiated gacyclidine and its enantiomers bind to NMDA receptors with binding parameters similar to those of other non-competitive NMDA receptor antagonists. The (−)-enantiomer, (−)GK11, exhibits an affinity (2.5 nM) similar to that of dizocilpine (MK-801), while the (+)-enantiomer, (+)GK11, has a 10 times lower affinity. When its interaction with NMDA receptors is prevented, gacyclidine binds also to “non-NMDA” binding sites which are mainly located in the molecular layer of the cerebellum on the dendritic tree of Purkinje cells. These binding sites do not appear to be related to any known neurotransmitters.

In primary cortical cultures, gacyclidine and its enantiomers, at 0.1 to 5.0 μM, prevent glutamate-induced neuronal death. In rats, in vivo neurotoxicity of gacyclidine is far lower than that of MK-801. No necrotic neurons were detected in animals sacrificed at 18 or 96 h after treatment with gacyclidine (1, 5, 10 or 20 mg/kg i.v.). At the highest (20 mg/kg) but not the lower doses (1–100 mg/kg) electron microscopy revealed the presence of few cytoplasmic or intramitochondrial vacuoles. In soman-treated monkeys gacyclidine enhanced neuroprotective activity of “three drugs cocktail” (atropine + diazepam + pralidoxime). Moreover, in rats, gacyclidine exerts a dose- and time-dependent neuroprotection in three models of spinal cord lesion. Beneficial effects of gacyclidine include reduction of lesion size and improvement of functional parameters after injury. In traumatic brain injury models gacyclidine improves also behavioral parameters and neuronal survival. Optimal protection is obtained when gacyclidine is administered at 0 to 30 min after injury.

It is, therefore, concluded that gacyclidine exhibits neuroprotective effects similar to those of other NMDA receptor antagonists, with the advantage of being substantially less neurotoxic maybe due to its interaction with “non-NMDA” binding sites.