

Metabotropic glutamate receptor 5 antagonist, two-methyl-6-phenylethynyl-pyridine (MPEP), with low doses of MK801 and diazepam: A novel approach for controlling status epilepticus

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Background and Objective: Status epilepticus (SE) is the most severe and feared form of epilepsy. The overall incidence of SE varies from 10 to 60 per 100,000 person-years, and the mortality is approximately 20% with 15 to 20% for adults and 3 to 15% for children. Chronic epilepsy often MTLE (20-40%), permanent neurologic deficits (9 to 11%) and encephalopathy (6 to 15%) are probably caused by SE. Although many of current anti-status epilepticus drugs have been reported to be neuroprotective, this effect is not consistently with all these drugs and in all models of SE. Furthermore, most of these drugs targets on GABA_A receptor, Na⁺, Ca⁺⁺, K⁺ channels, not on glutamate and its receptors, the most common neurotransmitter and receptor in the central nervous system. This study aimed to assess anti-status epilepticus and neuroprotective effects of different antagonists of group I metabotropic glutamate receptor (mGluR) including mGluR1 and mGluR5. The pharmacokinetic profile and long-term side effect of the promising candidate drug MPEP were also evaluated.

Methods: Candidate drugs including mGluR1 antagonists AIDA or LY367385, mGluR5 antagonists SIB1757, SIB1893, MPEP were administered intravenously at 1 or 2hrs during pilocarpine induced status epilepticus (PISE), their anticonvulsive effect was evaluated by either behavioral monitoring, or both EEG and behavioral monitoring. The neuroprotective effect of candidate drugs was studied by histochemical staining of hilar neurons 1 day after PISE. Furthermore, pharmacokinetic profile of the effective candidate drug was analyzed by high-performance liquid chromatography (HPLC).

Results: We showed that mGluR1 antagonists AIDA or LY367385 (at dosages ranging from 25 to 400mg/kg for AIDA or to 200mg/kg for LY367385), mGluR5 antagonists SIB1757 (at dosages ranging from 25 to 200mg/kg), SIB1893 (from 25 to 100mg/kg), MPEP (from 25 to 100mg/kg) injected at 1 or 2 hrs during PISE were ineffective in controlling SE. However, when administered at 1 hr during PISE, MPEP at 200mg/kg, combination of MPEP (200mg/kg) with MK801 (0.1mg/kg) or with MK801 (0.1mg/kg) and diazepam (0.5mg/kg), combination of SIB1893 (200mg/kg) with MK801 (0.1mg/kg) could effectively control behavioral SE, and was neuroprotective. In particular, the combination of MPEP with MK801 and diazepam could stop both behavioral SE and electrographic discharges (under EEG monitoring) within a few minutes after administration. HPLC study showed that high level of MPEP was maintained in the blood and its metabolism rate was slow in experimental mice with PISE.

Conclusion: Combination of MPEP (200mg/kg) with MK801 (0.1mg/kg) and diazepam (0.5mg/kg) could effectively stop SE and its subsequent neuronal loss when administered 1 hr during PISE. It may provide a new approach to effectively control intractable SE.