

Group 2 Metabotropic Glutamate Receptor Activation after Pilocarpine Administration Inhibits Status Epilepticus

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Status epilepticus (SE) in humans is often resistant to first-line therapies, such as diazepam, thus establishing the need for novel interventions. Pilocarpine-induced SE is a model of human temporal lobe epilepsy and epileptogenesis. SE is characterized by clonic/tonic seizures and electroencephalographic (EEG) activity, with accompanying increased power in the delta and theta bandwidths that lasts for several hours. We have previously demonstrated Group 2 metabotropic glutamate receptor (mGluRs) agonists reduce seizures in an absence model and that pretreatment with Group 2 mGluR compounds could inhibit the behavioral and EEG consequences of SE. Here, we tested whether the Group 2 mGluR agonist LY379268 could interrupt or arrest seizures in C57Bl/6 mice that underwent pilocarpine-induced SE. C57Bl/6 mice (8 weeks) were injected with the muscarinic antagonist scopolamine (1 mg/kg, i.p.) followed by pilocarpine (330 mg/kg, i.p.) 30 min later to induce SE. Mice were visually monitored for Stage 3 Racine seizure, consisting of forelimb clonus. It was at this point that drugs were administered to the following groups: vehicle (10% 1 N NaOH, 10% Tween 80, i.p.) or saline (0.25 ml, i.p.) controls (n = 8), or LY379268 (20 mg/kg, i.p.). Animals were observed to record the latency to the first Stage 5 seizure, bouts of Stage 5 seizures during SE, and the Racine score. No mouse treated after a Stage 3 seizure with LY379268 exhibited a Stage 5 seizure. LY379268 treated mice had a lower Racine score (mean = 3.5) than control mice (mean = 5.875, one-way ANOVA, p = 0.0003). Significantly fewer animals that received LY379268 reached a Stage 5 seizure (0 of 6 mice) compared to the control group (7 of 8, one-way ANOVA, p=0.0002). We are currently seeking to determine if post-treatment with this drug inhibits the EEG correlate of acute SE by reducing power increases in the delta and theta bandwidths.