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Post-status epilepticus treatment with the cannabinoid agonist WIN55,212-2 prevents chronic epileptic hippocampal damage in rats

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Repeated seizures are often associated with development of refractory chronic epilepsy, the most common form of which is temporal lobe epilepsy. G-protein-coupled cannabinoid receptors (CB1 and CB2 receptors) regulate neuronal excitability and have been shown to mediate acute anticonvulsant effects of cannabinoids in animal models. However, the potential of cannabinoids to prevent chronic neuronal damage and development of epilepsy remains unexplored. We hypothesized that treatment with a CB receptor agonist after an episode of status epilepticus – but before development of spontaneous recurrent seizures – might prevent the development of functional changes that lead to chronic epilepsy. Using the rat pilocarpine model, a therapeutic approach was simulated by administering the CB agonist, WIN55,212-2 after an episode of status epilepticus. Epileptic behavior was monitored during development of spontaneous recurrent seizures for up to 6 months. Histology, neurochemistry, redox status and NMDA receptor subunit expression were assessed at 6 months after pilocarpine-induced seizures. Sub-acute treatment with WIN 55,212-2 (for 15 days starting 24 h after PILO injection) dramatically attenuated the severity, duration and frequency of spontaneous recurrent seizures.

Further, in contrast to vehicle-treated animals, hippocampi from WIN 55,212-2-treated animals showed: normal thiol redox state, normal NR2A and NR2B subunit expression, preservation of GABAergic neurons and prevention of abnormal proliferation of GABAergic progenitors. This study shows for the first time that, after a known triggering event, treatment with a compound targeting CB receptors has the potential to prevent the epileptogenic events that result in chronic epileptic damage.

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