The ATP-gated P2X7 receptor contributes to the development of drug-resistant status epilepticus in mice

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Abstract

Background and Purpose Refractory status epilepticus is a clinical emergency associated with high mortality and morbidity. Increasing evidence suggests neuroinflammatory pathways contribute to the development of drug-refractoriness during status epilepticus. The ATP-gated P2X7 receptor (P2X7R) has been described as potential link between inflammation and increased hyperexcitability. The aim of the present study was to determine the contribution of the P2X7R to drug-refractory status epilepticus and its therapeutic potential. Experimental Approach Status epilepticus was induced via a unilateral microinjection of kainic acid into the amygdala in adult mice. Severity of status epilepticus was compared in animals overexpressing or knock-out in the P2X7R, after inflammatory priming by the pre-injection of bacterial lipopolysaccharide (LPS) and in mice treated with P2X7R-targeting and anti-inflammatory drugs. Key Results P2X7R overexpressing mice were unresponsive to several anti-convulsants (lorazepam, midazolam, phenytoin and carbamazepine) during status epilepticus. P2X7R expression was increased in microglia during drug-refractory status epilepticus, P2X7R overexpression led to a pro-inflammatory phenotype in microglia during status epilepticus and the anti-inflammatory drug minocycline restored normal responsiveness to anticonvulsants in P2X7R overexpressing mice. Pre-treatment of wildtype mice with LPS increased P2X7R levels in the brain and promoted the development of pharmaco-resistant status epilepticus, which was overcome by either a genetic deletion of the P2X7R or the administration of the P2X7R antagonists AFC-5128 or ITH15004. Conclusion and Implications Our results demonstrate that P2X7R-induced pro-inflammatory effects contribute to resistance to pharmacotherapy during status epilepticus and suggest therapies targeting the P2X7R as novel adjunctive treatments for drug-refractory status epilepticus.

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