A novel anticonvulsant mechanism via inhibition of complement receptor C5ar1 in murine epilepsy model

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Objective – Currently used anti-epileptic drugs act through only a few known mechanisms and can be associated with refractoriness (failure of medication to decrease seizures) and side-effects. Hence, one area of epilepsy research is identification of new therapies for epilepsy. Since seizures can be associated with activation of the immune system leading to inflammation, targeting mechanisms that cause inflammation are currently being studied in the lab. One component of the immune system is called complement peptide C5a; in the current study, the authors studied the role of C5a in experimental seizures in mice. In the lab, investigators can study both acute seizures and chronic seizures (epilepsy is defined as spontaneous, chronic, recurrent seizures).

Results – The complement C5a acts through a receptor called C5ar1. Mice were given drugs called chemoconvulsants to cause seizures experimentally, and the levels of C5ar1 were checked. The levels of C5ar1 were increased in the brains of mice that had seizures. The researchers then asked if (or how) decreasing C5a would affect seizures. A decrease in function of C5a was found to decrease seizures. In general, seizures cause injury to cells (called neurodegeneration), but inhibiting or decreasing C5a reduced injury to neurons. The next question was how exactly inhibition of C5a decrease seizures in mice? The researchers found that blocking C5a reduces excitability and inflammation, explaining how blockade of C5ar1 receptor could be beneficial in acute seizures and chronic seizures (epilepsy).

Interpretation - This study was done in experimental animals in the lab, and whether or not it applies to people with epilepsy in the clinic still remains to be seen. However, the authors define the role of the complement system C5a in epilepsy – eventually, this may prove to be a novel mechanism that could be targeted by drugs to help people with refractory epilepsy.

Short summary for scientists – Studying inflammation could give us insights into novel drugs for seizure disorders. In this study, the researchers examined a certain pro-inflammatory complement peptide C5a and its receptor C5ar1 in experimental epilepsy. C5ar1 was found to be increased in experimental models of epilepsy; blockade of C5ar1 with an antagonist had anticonvulsant effects. Inhibition of C5ar1 decreased seizure-induced mortality and neurodegeneration. The anticonvulsant effects of C5ar1 inhibition were explained by a decrease in activation of the inflammatory mediator TNFα.

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