GENE THERAPY

Suppressing seizures

> gene therapy can not only successfully prevent the generation of seizures but also treat established epilepsy

Epilepsia partialis continua is a severe, drug-resistant form of focal neocortical epilepsy that is characterized by almost continuous motor seizure activity. Surgical removal of the epileptogenic zone is not feasible in most patients, and alternative treatments are largely ineffective. Now, a study led by Walker, Schorge and Kullmann and reported in *Science Translational Medicine* indicates that gene therapy might be a viable approach to control this debilitating condition.

The authors used a rat model of refractory focal neocortical epilepsy induced by tetanus toxin injection into the motor cortex, which results in neuronal alterations resembling those observed in human focal neocortical epilepsy. They then assessed the ability of three gene therapy strategies to reduce seizure activity acutely, prevent the evolution of seizure activity and treat established epilepsy.

First, they injected a lentivirus expressing halorhodopsin (a chloride pump) into the motor cortex of the rats, which was followed by laser illumination after 7–10 days. Photoactivation of halorhodopsin suppresses neuronal firing; consistent with this, laser illumination decreased tetanus toxin-induced epileptic activity and resulted in acute attenuation of seizures specifically within this targeted region of the brain — something that cannot be achieved using conventional antiepileptic drugs. Furthermore, there were no visible behavioural side effects.

Next, the authors investigated whether overexpression of the voltage-gated potassium channel Kv1.1 could be an effective approach for decreasing neuronal excitability *in vivo*, as Kv1.1 deletion has been shown to result in neuronal alterations resembling epileptic seizures, such as increased firing of pyramidal neurons and increased neuronal excitability. They injected a Kv1.1-expressing lentivirus into the motor cortex of rats and detected seizures by measuring electroencephalographic (EEG) activity. Kv1.1-overexpressing neurons generated fewer action potentials, and no behavioural deficits were detected after 4 weeks of observation. Co-injection of Kv1.1 with tetanus toxin completely blocked the increase in neuronal excitability observed in rats injected with the toxin alone.

Finally, to assess the potential of the approach in treating established focal epilepsy, the authors also injected Kv1.1 into rats 1 week after tetanus toxin injection. EEG activity was significantly decreased in Kv1.1-treated rats and returned to the baseline after 4 weeks, but it remained high in untreated rats.

Together, these findings demonstrate that gene therapy can not only successfully prevent the generation of seizures but also treat established epilepsy. Although optogenetic inhibition is invasive because of the need to deliver laser light to the halorhodopsin-transduced neurons, it could be effective for spontaneous seizure suppression without requiring permanent excision of brain regions. Importantly, Kv1.1 overexpression represents an effective and well-tolerated long-term approach that is likely to last longer than 4 weeks and may even be effective in other forms of epilepsy or other disorders characterized by excessive neuronal firing.

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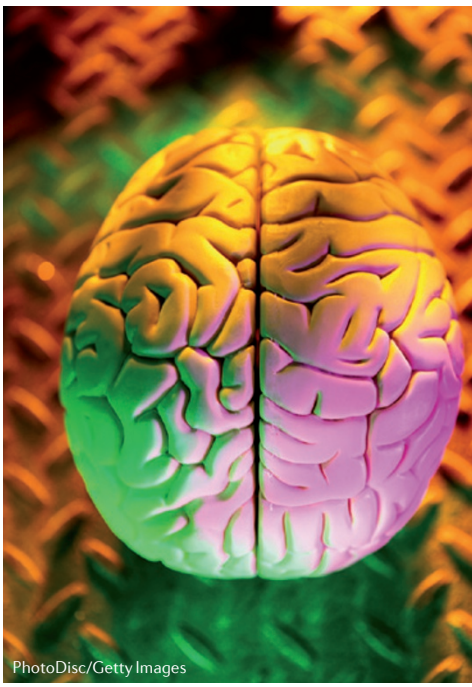

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ORIGINAL RESEARCH PAPER Wykes, R. C. *et al.* Optogenetic and potassium channel gene therapy in a rodent model of focal neocortical epilepsy. *Sci. Transl. Med.* **4**, 161ra152 (2012)