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NEUROLOGICAL DISEASE

Unsticking for seizure prevention

Most anti-epileptic drugs (AEDs) target ion channels with the aim of decreasing neuronal excitability and, thus, the potential for epileptic seizures. However, approximately one-third of patients with epilepsy are refractory to existing treatments, highlighting the need for new therapeutic approaches. Recent new insights into the pathogenesis of epilepsy reported in *Nature Medicine* open a whole new avenue for the development of novel and improved AEDs.

Using a mouse model of epilepsy, Fabene and colleagues have found that epileptic seizures increase the interaction of leukocytes with blood-vessel walls, leading to inflammation and damage to the blood–brain barrier. Although previous data have suggested a role for brain inflammation in epilepsy, none of the current epilepsy treatments addresses the inflammatory component of the disease.

The authors show that pilocarpine-induced acute seizure activity in mice increases the expression of leukocyte adhesion molecules — such as mucin P-selectin glycoprotein ligand 1 (PSGL1), α4β1 and αLβ2 integrins, and vascular cell adhesion molecule 1 (VCAM1) — in the vasculature. Prior administration of the CNS depressant diazepam — which suppresses the induced seizures — prevented the increase in expression of VCAM1 in brain blood vessels, indicating that neuronal hyperactivity contributes to this upregulation.

In agreement with these findings, intravital microscopy showed that the induction of seizures increased leukocyte and T helper type 1 cell rolling (that is, movement along the endothelial surface of the microvasculature) and arrest. Inhibiting adhesion with blocking antibodies or by genetically interfering with PSGL1 not only decreased these rolling interactions and 'sticking' behaviour, but also markedly reduced the seizures when administered before injection of pilocarpine. Moreover, treatment after the seizures had been induced (starting immediately and continuing every other day for 20 days) prevented the recurrence of spontaneous seizures that are characteristic of chronic epilepsy. In both cases, blocking the contribution of immune-cell adhesion to epileptogenesis prevented leakage of the blood–brain barrier and correlated with a reduction in neuronal cell loss and prevention of delayed cognitive impairment.

Interestingly, the authors found more leukocytes in the brains of patients with epilepsy than in controls, suggesting that anti-adhesion therapies with humanized antibodies could hold promise for the treatment of this condition.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPER Fabene, P. F. *et al.* A role for leukocyte–endothelial adhesion mechanisms in epilepsy. *Nature Med.* 23 Nov 2008 (doi:10.1038/nm.1878)