NEUROLOGICAL DISEASES

Crossing the divide

An old idea in the literature on epilepsy is that the propagation of paroxysmal activity from an affected to a naive region leads to the generation of a secondary epileptic focus. But so far, direct support for this idea is scarce. Using a bilateral *in vitro* preparation in which interhemspheric hippocampal connections are preserved, Khalilov *et al*. now provide evidence for the appearance of a secondary focus after the propagation of epileptic activity, and disclose some of the mechanisms behind its induction and expression.

The hippocampal preparation that this group had previously developed allows the selective administration of drugs in three separate places — to each of the two hippocampi or to the commissural fibres. They therefore applied kainate to one hippocampus to generate epileptic activity and tested whether this treatment led to the appearance of an epileptic focus in the naive hippocampus. They found that seizures were readily propagated across the commissures, but the formation of a secondary epileptic focus required 15–20 contralateral applications of kainate. In other words, the paroxysmal activity elicited by a single application of kainate propagated to the contralateral hippocampus, but the formation of a persistent focus required repeated treatment with the drug.

How did the secondary focus come to appear? Khalilov *et al*. focused on the involvement of glutamate receptors and found that, whereas AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-receptor antagonists blocked both seizure propagation and the formation of the secondary focus, NMDA (*N*-methyl-D-aspartate)-receptor antagonists only blocked the appearance of the focus, leaving the propagation of the epileptic activity unaffected. This result indicates that some form of NMDA receptor-dependent plasticity might be crucial for the formation of a persistent epileptic focus.

The authors also explored the mechanisms that might be involved in the maintenance of the epileptic focus and focused on the involvement of GABA (γ-aminobutyric acid), a transmitter that has long caught the attention of epilepsy researchers. In particular, they explored whether GABA, instead of having its classic inhibitory activity, acted as an excitatory transmitter. Indeed, application of a GABA-receptor antagonist suppressed epileptic activity in the secondary focus. Moreover, the authors showed that the reversal potential for Cl^- was shifted in the epileptic focus, a shift that would cause GABA receptor activation to depolarize, instead of hyperpolarize neurons.

This experimental system might help to unravel the cellular mechanisms of epileptogenesis and to identify new therapeutic targets. But as this hippocampal preparation was developed from neonatal rats, it will be important to determine whether the generation of a secondary focus and the shift in Cl^- reversal potential are also relevant to pathogenesis in mature nervous systems.

Juan Carlos López

References and links

ORIGINAL RESEARCH PAPER Khalilov, I. *et al*. *In vitro* formation of a secondary epileptogenic mirror focus by interhippocampal propagation of seizures. *Nature Neurosci.* **10**, 1079–1085 (2003)