

## PERSPECTIVES

**'Leaky' neurons in the epileptic hippocampus: should we get excited?**

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The dentate gyrus (DG) is traditionally viewed as the gateway to the hippocampus. Computational theories propose that the function of the DG is pattern separation by conversion of the rich neocortical input code to a sparse representation for storage and selective recall of information in the CA areas (Leutgeb *et al.* 2005). Central to the computational functions, granule cells (GC), principal cells of the DG, show a spares discharge pattern.

The same mechanisms that maintain sparse activity of GCs are thought to be also crucial for maintaining the homeostasis of neuronal activity in and downstream of the DG. Powerful GABAergic inhibition and, importantly, specific intrinsic properties of GCs ensure that the DG can act as a filter and impede the propagation of overt excitation from the entorhinal cortex to the highly sensitive CA3 area (Heinemann *et al.* 1992; Paré *et al.* 1992). Therefore, alterations in the DG network are generally assumed to play a major role in the pathophysiology of epileptic disorders affecting the hippocampus, such as mesial temporal lobe epilepsy (mTLE).

Consistent with this hypothesis, enhanced excitability of DG has been observed in various animal models, as well as in surgical material from human patients (for a review see Williamson & Patrylo, 2007). At the network level, axons of GCs, the mossy fibres, sprout leading to an aberrant excitatory connectivity among these cells. In addition, loss of GABAergic interneurons results in reduced inhibition. At the cellular level, enhanced NMDA receptor-mediated responses and altered function of various voltage-gated channels have been observed in GCs. Despite these convergent findings, the role of the DG and GCs in the generation of interictal and ictal activities has not been

fully established (Cohen *et al.* 2002; Harvey & Sloviter, 2005; Le Duigou *et al.* 2008).

In this issue of *The Journal of Physiology*, Young *et al.* (2009) provide a new piece to this intricate puzzle. In contrast to earlier findings, they demonstrate that intrinsic excitability of GC is not increased but rather decreased in a murine model of mTLE. In this model, kainate is injected into the dorsal hippocampus and recurring seizures manifest after a 2-week latent period (Bouilleret *et al.* 1999). The seizures are associated with structural changes as observed in human patients: a progressive neuron loss and reactive gliosis (hippocampal sclerosis), scattered redistribution of GC cells (GC dispersion) with accompanied morphological alterations, and sprouting of mossy fibres.

Investigating the intrinsic properties of dispersed GCs in these mice, the authors unexpectedly find that the cells become increasingly 'leaky' and their responsiveness to current pulses strongly diminishes. Interestingly, the change in the leak conductance correlates with the degree of GC dispersion. However, morphological and computational analysis shows that structural changes, namely a larger surface area, can not account for the observed leakiness. Instead, the passive membrane conductance is increased. By dissecting the leak conductance pharmacologically, the authors further show that diverse channel types are affected, including inwardly rectifying Kir2, two-pore domain K2P channels, and tonically active GABA<sub>A</sub> receptor-channels. In good agreement with the pharmacological data, the authors detect a more intense immunostaining for subunits of Kir2 and K2P channels in the DG of the injected hippocampus. Taken together, the results point to a continued re-adjustment of GC excitability in parallel with the progression of mTLE, which could counterbalance exaggerated excitatory influences.

Findings of this study, thus, offer a new perspective on the function of GCs in mTLE, but also raise a number of questions. First, why has an increased membrane conductance not been detected previously in these cells? The observed correlation between the anatomical and physiological alterations may provide a clue:

in other animal models GC dispersion is not induced, therefore the increased leak conductance may not develop either. However, the observed change in membrane properties is not a specific feature of the murine model. In fact, in a recent study, the same research group found an increased leakiness of dispersed GCs in mTLE patients, too (Stegen *et al.* 2009). Discrepancy with previous human studies, as the authors argue, could stem from differences in seizure extent and the degree of hippocampal damage, but further experiments are required to clarify this point.

Another interesting question is the reason for the correlation of the anatomical and physiological changes. The data indicate that there is no direct causal relationship; nevertheless common mechanisms may underlie or drive the two. Are these changes indeed adaptive and take place in response to seizure activity? Or do they follow a program initiated by the noxious event of kainite injection? Systematic analysis of the events occurring in the latent period may shed light on these questions.

Finally, we need information on how synaptic and active membrane properties of GCs change in relation to the altered passive properties. How are synaptic inputs integrated in the cells with altered structure and membrane function? Can the reduced intrinsic excitability of the neurons cancel out network and cellular level pro-epileptic effects? The present results no doubt will generate some debate and initiate new experiments, but we are looking forward to further news from the DG network with its 'leaky' cells.

**References**

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