This Week in The Journal

Cannabinoid-Mediated LTD of O-LM Interneuron Excitability

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(see pages 9521–9538)

Oriens-lacunosum-moleculare interneurons (OLMs) in hippocampal area CA1 provide feedforward inhibition at the distal dendrites of pyramidal cells and thus reduce the effects of entorhinal input to these cells. At the same time, OLMs inhibit interneurons that inhibit the proximal dendrites of pyramidal cells, which may enhance the effects of input from CA3. These functions may be modulated by endocannabinoid-dependent long-term depression (LTD) of both excitatory input and the intrinsic excitability of OLMs.

Consistent with previous results, Incontro et al. found that the amplitude of evoked EPSPs in OLMs exhibited LTD when activation of OLMs was repeatedly followed by activation of afferent input. This synaptic LTD was attributed to a decrease in presynaptic glutamate release, and it was blocked by a cannabinoid CB1-receptor antagonist. More importantly, the pairing protocol produced a long-lasting reduction in the intrinsic excitability of OLMs, so more input current was needed to evoke a spike. The authors traced this decrease in excitability to an increase in M currents mediated by K_v7 voltage-dependent potassium channels. The decrease in excitability was prevented by inhibiting endocannabinoid synthesis, and it was occluded by application of an endocannabinoid, which increased M currents on its own. But blocking CB1 receptors had no effect on the decrease in excitability. Molecular modeling indicated that endocannabinoids might instead enhance M currents and thus decrease excitability by binding directly to K_v7 channels.

These results suggest that when OLMs spike immediately before receiving excitatory input, they synthesize endocannabinoids, which bind both to presynaptic CB1 receptors, to reduce glutamate release, and

to postsynaptic K_v7 channels, to enhance M current. The consequential decrease in OLM output may alter information processing in CA1 by allowing cortical input to exert greater influence on pyramidal cell spiking.

An O-LM interneuron with dendrites (purple) in stratum oriens, and axon (red) arborizing in stratum lacunosum-moleculare. See Incontro et al. for details.

Impaired Pattern Separation in Epilepsy

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(see pages 9669–9686)

Much information about ongoing experience enters the hippocampus through the dentate gyrus, whose dentate granule cells project to CA3. The intrinsic properties of granule cells, along with strong inhibition, make the cells relatively resistant to spiking. This property is thought to have two important functions. First, it reduces overall activity levels in the hippocampus, thus preventing the development of seizures. Second, it allows granule cells to transform similar inputs into distinct output. The latter function, called neural pattern separation, is thought to be essential

for behavioral pattern separation: the ability to determine whether a given object or environment has been encountered before. These functions may be disrupted in people with temporal lobe epilepsy. Indeed, repeated spontaneous seizures in humans and rodent models are associated with memory deficits, as well as axon sprouting and circuit reorganization in the dentate gyrus. Whether the memory deficits result from deficient pattern separation at either the behavioral or the cellular level has not been determined, but work by Madar et al. suggests it might be.

When asked to distinguish previously seen images from similar novel images, people with temporal lobe epilepsy performed significantly worse than control subjects. Similarly, mice with a kainate-induced epilepsy-like condition were less able than controls to detect when a previously encountered object was moved a small distance. Recordings of dentate granule cells in brain slices revealed deficits in pattern separation at the cellular level in these mice. Specifically, compared with granule cells from control mice, those from kainate-treated mice were less able to convert similar input spike trains into less similar output spike trains. This deficit was associated with increases in the probability that a granule cell would spike in response to a single input spike and that it would fire a burst of action potentials. Notably, these changes in spike pattern occurred in only a subset of granule cells, and they were not associated with a measurable increase in excitatory drive.

These results indicate that pattern separation at both behavioral and cellular levels is disrupted in temporal lobe epilepsy. At the cellular level, the disruption likely results from an increase in overall spike rates and bursting in dentate granule cells. Future experiments should determine whether loss of inhibition leads to these cellular changes and whether preventing such changes can improve performance on tasks requiring pattern separation.

This Week in The Journal was written by Teresa Esch, Ph.D.
<https://doi.org/10.1523/JNEUROSCI.twij.41.46.2021>