This Week in The Journal

Role of Inhibitory Interneurons in Slow-Wave Sleep

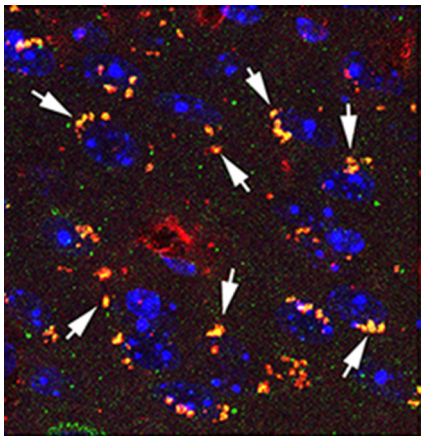
Chadd M. Funk, Kayla Peelman, Michele Bellesi, William Marshall, Chiara Cirelli, et al.

(see pages 9132–9148)

During slow-wave sleep, cortical neurons synchronously oscillate between periods of strong synaptic activity (up states) and periods of near silence (down states). The cellular mechanisms responsible for these oscillations are not entirely clear. Up states have been proposed to be initiated by pyramidal cells that are either persistently active or are activated stochastically during down states by summation of spike-independent EPSPs. Activation of inhibitory neurons might seem like a strong candidate for terminating up states, but this hypothesis was dismissed early on, because inhibitory neurons are active during up states, and their spiking decreases before down states emerge. Instead, the suppression of activity during down states has been proposed to result primarily from opening of calcium- or sodium-dependent potassium channels. Accumulating evidence suggests that inhibitory neurons do, in fact, contribute to up-state termination, however (Neske 2016 Front Neural Circuits, 9:88).

Funk et al. provide support for this hypothesis with evidence that somatostatin-expressing (SOM^+) interneurons contribute to up-state termination. In mice, brief activation of channelrhodopsin-expressing SOM^+ cortical neurons during up states silenced all neurons identified in local multiunit recordings and triggered down states similar in length to those occurring naturally during slow-wave sleep. In addition, sustained activation of SOM^+ neurons expressing the designer receptor hM3Dq during the light (inactive) period increased the amount of time spent in slow-wave sleep and increased the incidence and slope (suggesting increased synchrony) of slow-wave activity. In contrast, inhibiting SOM^+ neurons expressing hM3Di decreased slow-wave activity and increased time spent in REM sleep.

These results suggest that cortical SOM^+ interneurons promote the transition to down states during slow-wave sleep. Notably, excitatory inputs to these neurons exhibit short-term facilitation, which might promote activation of the neurons late in up states. In addition, SOM^+ neurons are connected by gap junctions and they have long-distance projections that might enable them to trigger silencing in many neurons simultaneously. Future work should examine and manipulate SOM^+ neuron activity on a cycle-to-cycle basis during slow-wave sleep or slow-wave activity in cortical slices to bolster the hypothesis that these neurons contribute to the termination of up states and the initiation of down states.



Pcdh-γC5 (green) colocalizes with vGAT (red) in mouse brain slices. See Li et al. for details.

Effects of β-Amyloid on GABAergic Synapses

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(see pages 9259–9268)

Excitatory and inhibitory neurons in the cortex are densely interconnected, and excitation and inhibition generally occur in tandem. Inhibition enhances cortical function by sharpening neural representations, adjusting gain, and regulating spike timing in excitatory neurons, as well as by driving synchronous oscillatory activity. Although inhibitory inputs to any neuron fluctuate over brief time periods, persistent and widespread elevation or reduction in inhibition can impair cortical processing and result in seizures. In fact, disruption of the balance between excitation and inhibition is thought to contribute to several neurological conditions, including epilepsy, schizophrenia, autism spectrum disorders, and Alzheimer's disease (AD).

Loss of cognitive function in AD is widely thought to result from disruption of synaptic activity and subsequent neurodegeneration stemming from accumulation of β-amyloid peptides (Aβ). But hyperactivation in the hippocampus occurs before cognitive symptoms appear in people at risk of AD, and hyperactive neurons are found near Aβ plaques in mice expressing AD-linked mutant proteins (AD-model mice). Furthermore, people with AD have an elevated risk of seizures. These findings suggest that disruption of the excitation/inhibition balance contributes to cognitive impairment in AD.

Many studies of AD have examined the effects of Aβ on excitatory neurons, but Li et al. suggest that Aβ also affects GABAergic synapses. Expression of several proteins localized to GABAergic synapses—glutamic acid decarboxylase (GAD), the vesicular GABA transporter (vGAT), and the cell adhesion molecule protocadherin-γC5 (Pcdh-γC5)—was higher in AD-model mice than in controls. Although the number of Pcdh-γC5-labeled puncta was similar in mutant and wild-type cortex, puncta were larger in mutant mice. In addition, the frequency of both spontaneous EPSCs (sEPSCs) and sIPSCs was higher in mutant mice than in controls. These effects were replicated in cultures of wild-type cortical neurons treated with Aβ. Moreover, treating wild-type mice with kainic acid to induce hyperexcitability increased the expression of Pcdh-γC5, GAD, and vGAT. Finally, knocking down Pcdh-γC5 reduced the frequency of sEPSCs and sIPSCs in cortical neurons from AD-model mice, as well as in wild-type neurons treated with Aβ.

These results are consistent with a model in which Aβ increases cortical excitability, leading to a compensatory increase in GABAergic transmission. Although this might reduce seizure risk in the short-term, it might ultimately contribute to cognitive decline in AD. Future work should investigate this possibility.

This Week in The Journal was written by Teresa Esch, Ph.D.