This Week in The Journal

Perineuronal Nets in the Prelimbic Cortex

Hector Carceller, Ramon Guirado, Edna Ripolles-Campos, Vicent Teruel-Marti, and Juan Nacher
(see pages 5008–5018)

Perineuronal nets (PNNs) are condensed extracellular matrix structures that form around the cell body and proximal dendrites of a subset of neurons throughout the CNS. In the cerebral cortex, PNNs form primarily around fast-spiking, parvalbumin-expressing (PV⁺) interneurons. PNN composition and functions vary somewhat between regions, but they generally limit plasticity, stabilize perisomatic synapses, and protect neurons from oxidative stress. Notably, the formation or maintenance of PNNs is impaired in several brain areas, including the prefrontal cortex, in people with schizophrenia (Fawcett et al., 2019, *Nat Rev Neurosci* 20:451).

To learn how the loss of PNNs might affect prefrontal cortical function, Carceller et al. compared PV⁺ interneurons having PNNs with those lacking PNNs in the prefrontal cortex. Staining for parvalbumin was stronger in neurons with PNNs than in those without. In addition, PV⁺ neurons with PNNs had more perisomatic puncta labeled with the vesicular GABA transporter (VGAT), and more with the vesicular glutamate transporter 1 (VGLUT1), than PNN-lacking PV⁺ neurons. The balance of excitatory and inhibitory input was similar in neurons having and lacking PNNs, however. Finally, PV⁺ neurons with PNNs had longer axon initial segments than those without PNNs.

To determine whether the differences between PNN-enwrapped and PNN-lacking PV⁺ neurons depend on the continued presence of the PNN, the authors enzymatically degraded these structures. This did not affect PV expression levels or the density of VGLUT1, but it reduced perisomatic VGAT labeling, and thus increased the VGLUT1/VGAT ratio. Nevertheless, PNN digestion reduced the expression of FosB, a marker of basal neural activity, in both PV⁺ and pyramidal neurons. Finally, PNN degradation led to a reduction in gamma-

frequency, but not theta-frequency oscillations after tail-pinch stimulation.

These results suggest that PNNs preferentially surround more mature PV⁺ neurons (those with relatively high parvalbumin expression and synaptic input) in the prefrontal cortex, and that PNNs help to maintain perisomatic inhibitory input. Consequently, the disruption of PNNs leads to an imbalance of excitatory and inhibitory input and disrupts gamma oscillations. Whether these effects underlie symptoms of schizophrenia should be examined in future work.

PNNs (green) surround a subset of neurons in the prefrontal cortex, including interneurons that express parvalbumin (blue). PV⁺ neurons with PNNs have longer axon initial segments (magenta) than those without. See Carceller et al. for details.

Changes in PV-Expressing Basket Cells in Alzheimer's Model

Adam Caccavano, P. Lorenzo Bozzelli, Patrick A. Forcelli, Daniel T. S. Pak, Jian-Young Wu, et al.

(see pages 5116–5136)

Alzheimer's disease (AD) is characterized by the accumulation of β -amyloid (A β) peptides and tau protein, accompanied by synaptic loss, neurodegeneration, and cognitive decline; but changes in brain activity, including hippocampal hyperactivity and abnormal interactions between the hippocampus and prefrontal cortex, may occur before other symptoms are noticeable. These early changes might stem from deficits in inhibitory transmission, which not only prevents hyperactivity, but also generates synchronous oscillations that are thought to mediate

communication between brain areas (Varela et al., 2019, *Neurobiol Dis* 127:605).

To investigate early deficits in AD, Caccavano et al. examined synaptic function and network activity in the hippocampus of 3-month-old mice harboring five AD-linked mutations (5xFAD mice). These mice had some extracellular A β plaques in CA1 and showed mild deficits in a spatial memory task, but they did not yet show synaptic or neuronal degeneration. Because spatial memory formation relies on hippocampal sharp-wave ripples, the authors focused on these events in CA1 of hippocampal slices.

The frequency and amplitude of sharp-wave ripples were greater, but the duration was shorter and the number of incomplete ripples was larger in 3-month-old 5xFAD mice than in controls. To investigate the cellular basis for these changes, the authors assessed the activity of pyramidal cells and three types of parvalbumin-expressing (PV⁺) interneurons. The largest effects were on PV⁺ basket cells. These neurons had a significantly lower spike rate during sharp-wave ripples in 5xFAD slices, likely because the excitatory input was lower than in controls. Furthermore, basket-cell spiking during sharp-wave ripples was confined to a narrower window in 5xFAD mice. In contrast, spike rates were similar in 5xFAD and control pyramidal cells. The number of active pyramidal cells was higher in 5xFAD slices than in controls, however, possibly because of reduced inhibitory input and increases in excitatory input, particularly during sharp-wave ripples. Spiking and synaptic input to bistratified and axo-axonic PV⁺ interneurons of 5xFAD mice were similar to those of controls.

These results suggest that decreased excitatory input to CA1 PV⁺ basket cells leads to reduced spiking during sharp-wave ripples, possibly shortening ripple duration. Increased excitation of pyramidal cells, along with reduced inhibition during sharp-wave ripples, may explain the increased number of pyramidal cells active during sharp-wave ripples. These larger ensemble sizes might make memory consolidation less precise, thus contributing to impaired spatial memory.

This Week in The Journal was written by Teresa Esch, Ph.D.
<https://doi.org/10.1523/JNEUROSCI.twij.40.26.2020>