This Week in The Journal

K_V4.1 Channels Limit Spiking in Mature Granule Cells

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(see pages 2200–2214)

New granule cells are generated in the rodent dentate gyrus throughout life. These cells become incorporated into dentate circuitry within 3–4 weeks, but they remain distinguishable from embryonically born cells for >2 months. Recently born granule cells are more excitable and receive less feedback inhibition than older granule cells, and therefore they are more active and undergo synaptic plasticity more readily. These properties are thought to allow young granule cells to perform unique functions. For example, they appear to be essential for pattern separation—the creation of distinct neural representations to distinguish similar places or things. Ablating young adult-born granule cells disrupts performance on pattern-separation tasks, whereas increasing the number of young cells improves performance. In contrast, blocking the output of old granule cells does not affect pattern separation, but instead impairs pattern completion—the activation of previously stored representations by similar stimuli (Nakashiba et al., 2012, *Cell*, 149:188). But Kim, Lee, et al. report that increasing the activity of old granule cells impairs pattern separation.

The authors first established that K_V4.1 potassium channels contribute to the low excitability of mature granule cells. K_V4.1 expression in the dentate gyrus was highest in the outer granule cell layer, where older cells reside, and it was rarely detected in doublecortin-expressing immature granule cells. Furthermore, a K_V4.1 antibody reduced outward currents and increased spike frequency in neurons that resembled old granule cells (cells with low spike frequency, low input resistance, and relatively hyperpolarized resting membrane potential). The antibody also increased the slope of the input output curve (i.e., how much spiking increased with increasing current), but it did not alter the resting membrane potential, input resistance, or amount of current required

to elicit spikes. Importantly, the antibody did not affect outward currents or spike frequency in granule cells that had immature characteristics (high frequency, high input resistance, and more depolarized resting potential) or in GABAergic interneurons. Finally, knocking down K_V4.1 impaired learning in context- and object-discrimination tasks.

These data suggest that K_V4.1 expression increases as adult-born granule cells mature and that this expression limits spiking. This effect appears to be important for pattern separation, possibly because it shifts dentate function toward pattern completion.

A mature dentate granule cell. K_V4.1 channels limit the excitability of these cells, and they are required for normal pattern separation. See Kim, Lee, et al. for details.

CCK-Expressing Interneurons Aid Working-Memory Recall

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(see pages 2314–2331)

Cortical GABAergic interneurons can be divided into several subtypes based on morphology, laminar position, electrophysiological properties, and protein expression profile. Each subtype likely has distinct roles in shaping cortical output. The best studied subtype is fast-spiking, parvalbumin (PV)-expressing basket cells, which innervate pyramidal-cell somata. Relatively little is known about the other major class of basket cells—those that express cholecystokinin (CCK)—largely because CCK is also expressed in pyramidal cells, complicating efforts to selectively target CCK⁺ interneurons. Nguyen,

Venkatesan, et al. met this challenge by using a combination of Flp-FRT and Cre-Lox recombination to restrict the expression of fluorescent and light-activated proteins to forebrain GABAergic neurons that express CCK⁺. They then compared the properties and functions of CCK⁺ neurons with those of PV⁺ interneurons in the medial prefrontal cortex (mPFC).

CCK⁺ and PV⁺ interneurons formed partially overlapping populations: 20–25% of CCK⁺ interneurons also expressed PV and/or exhibited a fast-spiking phenotype. The remaining CCK⁺ interneurons were classified as non-fast spiking. Like PV⁺ neurons, CCK⁺ interneurons were abundant in layer 5; but only CCK⁺ interneurons were abundant in layers 2/3 and 6. Unlike PV⁺ neurons, CCK⁺ neurons evoked IPSCs in most other surrounding cells, including pyramidal cells and regular-spiking, low-threshold, and some fast-spiking interneurons. Notably, activation of CCK⁺ neurons evoked glutamatergic EPSCs in ~14% of nearby cells (mostly regular-spiking interneurons), consistent with previous findings that some CCK⁺ interneurons express a vesicular glutamate transporter.

To investigate interneuron function, the authors silenced neurons during the sampling, delay, or response phases of an olfactory working-memory task. Silencing CCK⁺ interneurons during the response (memory retrieval) phase increased errors, whereas silencing them during the sample or delay phases had no effect. In contrast, silencing PV⁺ neurons during the delay phase increased errors, whereas silencing them during the response phase reduced errors.

These results suggest that CCK⁺ GABAergic interneurons in the mPFC are important for the retrieval of working memories. Because silencing PV⁺ neurons during the retrieval phase improved performance on the working memory task, CCK⁺ interneurons lacking PV⁺ are likely to be the ones that promote retrieval. Future work should determine whether and how the properties and functions of PV⁺/CCK⁺ interneurons differ from those of neurons that express PV⁺ or CCK⁺ alone.

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