This Week in The Journal

TRPV1 Microdomains Underlie Spontaneous Vesicle Release

Jessica A. Fawley, Mackenzie E. Hofmann, and Michael C. Andresen

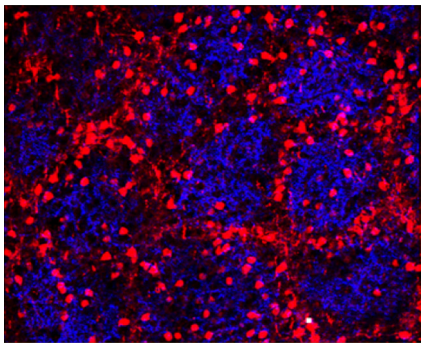
(see pages 8957–8966)

The nucleus of the solitary tract (NTS) integrates sensory inputs from the heart, lungs, and gastrointestinal organs, and it coordinates the activity of these organs across behavioral states. Sensory information is carried to the NTS by two classes of visceral afferents: low-threshold, myelinated A-fibers and high-threshold, unmyelinated C-fibers. A-fibers fire at high, regular frequencies and each spike triggers a burst of synchronous synaptic vesicle release. In contrast, C-fibers—which comprise ~90% of visceral afferents—fire irregularly, and synchronous vesicle release is often followed by a prolonged period of asynchronous release. C-fibers also exhibit high levels of spike-independent, spontaneous vesicle release that provides tonic excitatory drive to NTS neurons (Andresen et al. 2012 Am J Physiol Regul Integr Comp Physiol 303: R1207).

Like in other neurons, synchronous release in visceral A- and C-fibers is triggered by Ca^{2+} influx through voltage-sensitive Ca^{2+} channels (CaVs) that are positioned in microdomains near docked vesicles. Spontaneous release in C-fibers is mediated by Ca^{2+} influx through temperature-sensitive TRPV1 channels, which are located on C-fiber terminals in the NTS. In general, asynchronous release requires widespread Ca^{2+} increases resulting from prolonged activation of CaVs or other Ca^{2+} channels. Because asynchronous release occurs in TRPV1-expressing C-fibers, but not in TRPV1-lacking A-fibers, Fawley et al. hypothesized that TRPV1 channels are the Ca^{2+} source for asynchronous release in C-fibers. They found evidence against this hypothesis, however.

In whole-cell recordings of NTS neurons in rat brainstem slices, a TRPV1 agonist more than doubled the frequency of spontaneous EPSCs without affecting stimulation-induced synchronous EPSCs or the rate of subsequent asynchronous EPSCs. Similarly, raising the temperature (which activates TRPV1 channels) increased spontaneous release without affecting synchronous or asynchronous release. Finally, Ca^{2+} buffers greatly reduced asynchronous release without affecting thermally evoked release.

These data suggest that spontaneous vesicle release—like synchronous release—is mediated by Ca^{2+} channels clustered in microdomains near synaptic vesicle pools. Spike-induced opening of CaVs triggers synchronous release of vesicles in CaV microdomains, whereas activating TRPV1 channels triggers spike-independent ("spontaneous") release of a separate set of vesicles clustered in TRPV1 microdomains. Although asynchronous release, by definition, only occurs after spikes, whether it can be influenced by Ca^{2+} influx through TRPV1 channels remains unclear.



Stellate cells lacking mGluR5 (red) often fail to migrate into barrel walls surrounding thalamocortical axons (blue) in layer IV of mouse somatosensory cortex. See Ballester-Rosado, et al. for details.

mGluR5 Guides Stellate Cell Migration and Dendritic Pruning

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(see pages 8802–8814)

In layer IV of rodent somatosensory cortex, bundles of thalamocortical afferents, each representing a single whisker, are encircled by "barrels" of spiny stellate neurons. These neurons project dendrites into the center of the barrel where they receive glutamatergic input from thalamocortical axons. The development of barrel structures requires activation of type 5 metabotropic glutamate receptors (mGluR5) on stellate neurons. Knocking out mGluR5 in cortical glutamatergic neurons reduces the length and branching of thalamocortical axons, increases the length and branching of stellate cell dendrites, prevents formation of barrel walls, and disrupts the preferential orientation of stellate cell dendrites toward barrel centers (Ballester-Rosado, et al. 2010).

Because some of the effects of mGluR5 depletion on stellate cells could be secondary to disruption of thalamocortical axon arborization, Ballester-Rosado et al. now asked how knocking out mGluR5 in just a subset of layer IV stellate cells affected barrel development. They used *in utero* electroporation of Cre recombinase to excise mGluR5 in excitatory cortical neurons born on embryonic day 14, when neurons destined for layer IV are generated. They then examined layer IV during the second postnatal week.

Although thalamocortical axon bundles and barrel walls appeared normal in these mice, neurons that lacked mGluR5 were more likely to be located in the septa between barrels and less likely to be found in barrel walls than wild-type neurons. In addition, the dendritic arbors of mGluR5-deficient neurons were less likely to be oriented toward barrel centers. Instead, mGluR5-deficient neurons were more likely than controls to have an apical dendrite oriented toward the pial surface—a morphology characteristic of pyramidal neurons. Furthermore, dendrites were longer, more branched, and had a higher density of immature-looking spines in mGluR5-deficient than in control neurons. Finally, the frequency of spontaneous EPSCs in mGluR5-deficient neurons was significantly higher than in their wild-type neighbors, suggesting they received more synaptic inputs.

These results demonstrate unequivocally that mGluR5 signaling within individual cells is required for positioning stellate neuron somata and pruning dendritic arbors to produce normal barrel architecture. How mGluR5 mediates these effects should be explored in future work. This, and identifying the source of mEPSCs in misplaced mGluR5-deficient cells, will further elucidate the complex mechanisms guiding cortical circuit development.

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