This Week in The Journal

Short-Term Facilitation Differs for P/Q- and N-Type Channels

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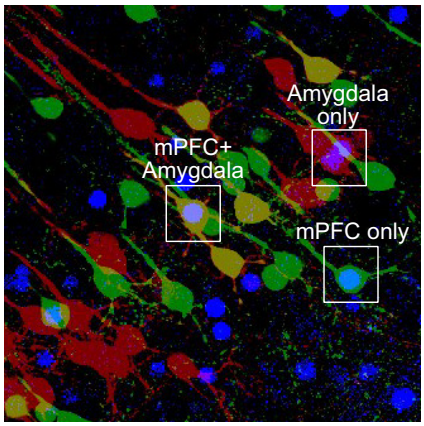
(see pages 4913–4927)

When an action potential enters a synaptic terminal, voltage-gated calcium channels open, allowing calcium ions to enter and promote synaptic vesicle release. How many vesicles are released depends on the number of release sites and the density and location of calcium channels. If channels are close to release sites, incoming ions quickly bind to vesicle-associated calcium sensors, and relatively few channels must open to trigger release. If channels are farther away, calcium ions have to diffuse farther to reach the sensors, and many ions instead bind to other proteins; thus, more channels must open to trigger vesicle release. In either case, the probability of release may increase during spike trains, when calcium accumulates in the synaptic terminal. This phenomenon, called short-term facilitation, causes neurons to exert greater influence during bursts than during single spikes.

Prominent short-term facilitation occurs at synapses between dentate granule cells and CA3 pyramidal cells. Previous work by Chamberland et al. (2014 J Neurosci 34: 11032) indicated that both an increase in the number of release sites and an increase in multivesicular release contribute to this facilitation. They now report that when P/Q-type calcium channels were blocked in mouse hippocampal slices, spike trains no longer increased the number of release sites; trains continued to stimulate multivesicular release, however. Conversely, when N-type channels were blocked, spike trains increased the number of release sites, but did not promote multivesicular release. Imaging revealed that blocking P/Q-type channels made spike-evoked calcium elevation less spatially homogeneous within the presynaptic terminal, whereas blocking N-type channels did not. Finally, comparing the effects of channel blockers and a calcium buffer on short-term facilitation suggested that while N-type channels activate release only at nearby sites, P/Q-type channels activate release at both nearby and more distant sites.

These results suggest that N- and P/Q-type channels produce different patterns of calcium elevation in mossy fiber terminals and make distinct contributions to short-term facilitation. Specifically, N-type channels cause calcium elevation at discrete locations and trigger multivesicular release during spike trains, whereas P/Q-type channels cause more widespread calcium elevation and allow more release sites to be activated during trains. This distinction may allow the two types of facilitation to be independently regulated by selectively modulating N- or P/Q-channel function.



Double-projecting vCA1 neurons are more likely than single-projecting neurons (red or green) to be activated (as indicated by c-fos labeling, blue) when mice are exposed to a novel environment. See Kim and Cho for details.

Double-Projecting CA1 Neurons Convey Contextual Information

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(see pages 4868–4882)

Some stimuli, such as loud noises, signal danger only in particular situations. Responding appropriately to such stimuli requires interactions between the hippocampus, which encodes context cues; the amygdala, which stores associations between conditioned and unconditioned stimuli; and the medial prefrontal cortex (mPFC), which signals whether a defensive response is appropriate in the present context. These three areas communicate through direct and indirect pathways, the roles of which are still being elucidated. Kim and Cho have advanced this endeavor by investigating the function of CA1 pyramidal neurons in the ventral hippocampus that project to both the amygdala and the mPFC (double-projecting vCA1 neurons).

Retrograde labeling of projection neurons revealed that ~17% of vCA1 neurons that projected to the amygdala or the mPFC were in fact double-projecting neurons. These neurons were more likely than single-projecting neurons to be activated when mice were exposed to a novel context, whether or not foot shocks were delivered in that context. These neurons likely contribute to fear responses, because acutely inhibiting archeorhodopsin-expressing vCA1 neurons in a shock-associated context reduced freezing behavior.

Photostimulation of channelrhodopsin-expressing double-projecting vCA1 neurons elicited glutamatergic EPSCs and longer-latency GABAergic IPSCs in principal neurons of the amygdala and in pyramidal neurons of prelimbic and infralimbic regions of mPFC. Notably, the stimulation evoked spiking in mPFC neurons that projected to the amygdala. In addition, EPSCs elicited in the prelimbic region of mPFC, which is thought to promote fear responses, were much larger than those elicited in the infralimbic region, which is thought to inhibit fear responses after extinction training (Izquierdo et al. 2016 Physiol Rev 96:695).

These results show that activity in CA1 pyramidal neurons of ventral hippocampus are required for the expression of learned fear responses. This role likely depends on the activation of neurons that project to both the amygdala and the mPFC when a mouse encounters a new environment. These double-projecting neurons not only directly excite principal neurons in the amygdala and mPFC, but also indirectly excite amygdala neurons by inducing spiking in amygdala-projecting mPFC neurons. This connectivity may facilitate both the formation of context–fear associations and their retrieval when the context is encountered again.

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