This Week in The Journal

The Role of α-Synuclein in Endocytosis

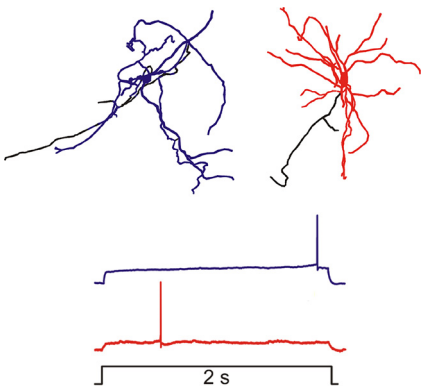
Jianhua Xu, Xinsheng Wu, Jiansong Sheng, Zhen Zhang, Hai-Yuan Yue, et al.

(see pages 4408 – 4414)

Intracellular inclusions containing aggregated α-synuclein are a prominent pathological feature of Parkinson's disease (PD), and mutations in α-synuclein cause inherited forms of the disease. In healthy neurons, α-synuclein is concentrated in presynaptic terminals, where it associates with vesicles. Some studies have suggested that α-synuclein facilitates synaptic vesicle release by promoting assembly of the SNARE complex, but overexpressing α-synuclein inhibits neurotransmitter release. Other studies suggest that α-synuclein regulates synaptic vesicle pools, possibly by promoting endocytosis. Indeed, knocking out α-synuclein slows endocytosis and reduces vesicle stores (Vargas et al. 2014 J Neurosci 34:9364).

Xu, Wu et al. now report that the PD-linked A53T mutation in α-synuclein also impairs endocytosis. Mutant α-synuclein was overexpressed selectively in mouse cochlear neurons that form calyx-of-Held synapses. The large size of these synapses allows vesicle release and recycling to be measured by recording directly from the synaptic terminal. Depolarizing cochlear neurons caused an increase in capacitance in the calyx of Held as vesicles fused with the plasma membrane. This was followed by a slow decrease in capacitance as vesicles were endocytosed. The rate of decay of the capacitance was altered by expression of A53T α-synuclein, suggesting that the mutation selectively impaired endocytosis. Likely as a consequence of this impairment, replenishment of the readily releasable vesicle pool was impaired. In addition, A53T α-synuclein overexpression decreased the amplitude of evoked EPSCs in postsynaptic cells, indicating synaptic release was reduced. Importantly, similar effects were produced by acute infusion of mutant α-synuclein into synaptic terminals, indicating the effects did not result from long-term overexpression.

These results suggest that defects in endocytosis resulting from mutations in α-synuclein impair synaptic function before neurodegeneration in PD. Besides this scientific advance, this study introduces a mutant mouse that can be used to express proteins selectively in neurons that form calices of Held. Use of these mice should facilitate investigation of the roles of other proteins in synaptic vesicle release and recycling.



Nearly all neurons in the CeL can be classified as early spiking (red) or late spiking (blue). Cell reconstructions (top) show no obvious morphological differences between these classes. See Hou et al. for details.

Characterizing Neurons in the Lateral Central Amygdala

Wen-Hsien Hou, Ning Kuo, Ge-Wei Fang, Hsien-Sung Huang, Kun-Pin Wu, et al.

(see pages 4549 – 4563)

Neural circuits in the amygdala are essential for fear learning and the generation of defensive responses to frightening stimuli. Afferents conveying sensory information primarily target the lateral nucleus of the amygdala, and behavioral responses to sensory stimuli are triggered primarily by neurons in the medial subdivision of the central nucleus (CeM). The lateral subdivision of the amygdala's central nucleus (CeL) was long considered a simple relay station between the lateral nucleus and the CeM; but recent studies have indicated that synaptic plasticity in the CeL contributes to fear learning and that CeL neurons can elicit fear responses independently of the CeM.

To advance our understanding of the CeL, Hou et al. investigated physiological properties and synaptic connectivity of CeL neurons. Based on the delay between current injection and action-potential generation, they classified ~95% of neurons as early or late spiking. Besides the longer spike delay, a more hyperpolarized resting membrane potential, greater rheobase, and the presence of a pronounced depolarizing ramp distinguished late-spiking neurons from early-spiking cells. These differences were attributable to the presence of a slowly inactivating D-type K^+ current mediated by K_V1 channels in late-spiking neurons.

Early- and late-spiking neurons formed synapses with each other and with neurons of the same class. Synapses between neurons of different classes were more common, stronger, and showed stronger short-term depression during spike trains than synapses between neurons of the same class, however. Notably, only synapses in which the presynaptic cell was early-spiking exhibited depolarization-induced suppression of inhibition, which results from activation of presynaptic cannabinoid receptors. Some neurons in each class also formed autaptic synapses, but those in early-spiking neurons were stronger and more strongly depressing during spike trains than those in late-spiking neurons.

What distinct roles might early- and late-spiking neurons have? CeL neurons that express somatostatin play a key role in fear conditioning (Li et al. 2013 Nat Neurosci 16: 332), but Hou et al. found that similar proportions of somatostatin-expressing and somatostatin-negative neurons were early-spiking cells, providing no clues about the role of these neurons in conditioning. Future work might take advantage of the differential expression of cannabinoid receptors and/or K_V1 channels to selectively target early- or late-spiking neurons and thus reveal their contributions to amygdala function.

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