This Week in The Journal

Strong Dendritic Role in Tonic Spiking of Dopamine Neurons

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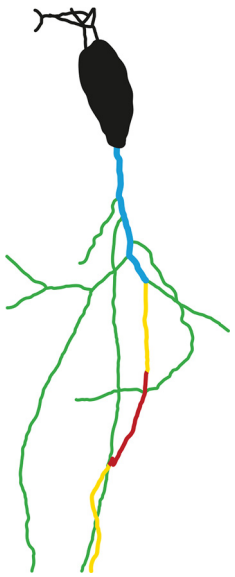
(see pages 5044–5063)

The axon initial segment (AIS) is the site of action potential generation in most cells. The AIS length, ion-channel density, and distance from the soma vary across neurons and influence neuronal excitability, spike shape, and firing frequency. For example, previous work (Meza et al., 2018 J Neurosci 38:733) suggested that variation in AIS geometry underlies variation in the rate of tonic spontaneous spiking of dopaminergic neurons in mouse substantia nigra (SN). But Moubarak et al. report that in rats, the influence of AIS parameters is small compared to that of the morphology and sodium-channel density of certain dendrites.

Unlike in most neurons, axons of SN dopaminergic neurons typically arise from a dendrite rather than the soma. The dendrites have a high concentration of voltage-sensitive sodium channels that support back-propagation of spikes from the AIS. Moubarak et al. found that the length, branching complexity, and sodium-channel density of the dendritic stem proximal to the axon varied greatly across neurons. The tonic spike rate and the amplitude and half-width of spikes measured in the soma also varied considerably across cells. None of these parameters was correlated with variations in AIS length or soma–AIS distance; but the density of dendritic sodium channels greatly influenced the spike waveform measured at the soma.

The authors used experimentally derived morphological and channel-density properties to build a computational model that reproduced the characteristic electrophysiological properties of dopaminergic neurons. This model allowed them to investigate the effects of AIS and dendrites on spike shape and frequency. Varying sodium-channel density in the somatodendritic compartment had a much greater effect on spontaneous spike rate than varying the channel density in the AIS. Changing the length of the AIS or the proximal stem of the axon-bearing dendrite had intermediate effects on spike rate. But the largest effect on spike rate resulted from adding proximal branches to the axon-bearing dendrite.

Altogether, the results suggest that the spike rate of rat SN dopaminergic neurons is strongly influenced by the morphological complexity and concentration of sodium channels in the axon-bearing dendrite. These factors appear to far outweigh the influence of AIS length and sodium-channel density.



The axon (yellow) of SN dopaminergic neurons typically arises from a dendrite (blue), which may have branches (green) proximal to the axon initiation site. Properties of this axon-bearing dendrite have a greater impact on spontaneous spike rate and shape than the geometry of the AIS (red). See Moubarak et al. for details.

Controlling Endoplasmic Reticulum Movement in Growth Cones

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(see pages 5095–5114)

Axon extension is guided by extracellular molecules that bind to receptors on axonal growth cones. Localized activation of these receptors produces gradients of intracellular signaling molecules that regulate cytoskeletal organization and vesicle trafficking, thus influencing the direction of axon growth. Brain-derived neurotrophic factor (BDNF) induces localized release of calcium from endoplasmic reticulum (ER) stores in the growth cone. Depletion of these stores activates an ER membrane protein, STIM1, that interacts with plasma membrane calcium channels to induce store-activated calcium entry. This greatly increases the local calcium concentration, leading to microtubule extension and growth-cone turning toward the cue (Sutherland et al., 2014 Trends Neurosci 37:424). Knocking down STIM1 inhibits growth cone turning toward BDNF. But STIM1 knockdown also blunts the repellant effects of semaphorin-3, which does not depend on store-activated calcium entry, suggesting that STIM1 has additional roles in growth cone guidance.

In other cell types, STIM1 interacts with end-binding proteins (EBs) that bind to the plus ends of microtubules to facilitate elongation. Pavez, Thompson, et al. therefore asked whether STIM1–EB interactions are involved in growth-cone guidance. STIM1 and the ER were colocalized with EB3 in the microtubule-rich central region of growth cones of cultured rat sensory neurons, as well as near the tips of filopodia. Furthermore, ER calcium concentration was elevated near EB3 puncta in filopodia. Importantly, the ability of localized activation of STIM1 to induce growth-cone turning depended on binding between STIM1 and EB3.

Knocking down STIM1 did not affect the number of filopodia, but it reduced both the number of EB3-tipped microtubules extending into filopoda and the rate of microtubule extension. STIM1 knockdown also slowed entry of ER into filopodia and eliminated localized ER calcium elevation. Moreover, STIM1 knockdown reduced extension of EB3-tipped microtubules toward BDNF and away from semaphorin-3. Finally, knocking down STIM1 in zebrafish embryos impaired guidance of motor axons *in vivo*.

These results suggest that STIM1 contributes to axon guidance by promoting extension of microtubules into the growth-cone periphery, including filopodia. This role occurs independently of the role of STIM1 in store-operated calcium entry. How STIM1 affects calcium-independent turning is unclear, but by promoting microtubule extension, it might facilitate the delivery of the proteins and vesicles required for growth.

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