This Week in The Journal

Activity-Driven Myelination Parallels Increased Branching

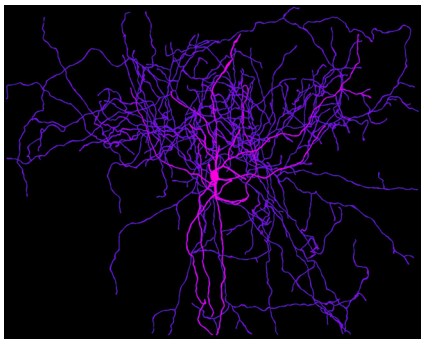
Jeffrey Stedehouder, Demi Brizee, Guy Shpak, and Steven A. Kushner

(see pages 3631–3642)

Myelination speeds action potential conduction and provides trophic and metabolic support for axons; therefore, demyelination impairs nervous system function and leads to axonal degeneration. But not all axons are myelinated, even within long axon tracts such as the corpus callosum. Moreover, the length of internodes—the stretch of myelinated axon between two nodes of Ranvier—varies across axons, and single axons can have both myelinated and unmyelinated segments. The factors that regulate myelination patterns are only partially understood, but one important factor is neuronal activity. Indeed, axonal myelination increases on neurons that are experimentally activated, whereas myelination decreases when activity is reduced (Mitew et al. 2018 Nat Comm 9: 306).

Most studies of myelination focus on long-range projection neurons, which are thought to be especially dependent on myelin. But recent work revealed that the axons of parvalbumin-expressing interneurons in mouse cerebral cortex are also myelinated. Like in some other types of neurons, the axons of these cells are incompletely myelinated: some segments have myelin, while others do not. Stedehouder, Brizee, et al. therefore asked how activity affected myelination in these neurons. They found that increasing spiking of parvalbumin-expressing neurons (using designer receptors exclusively activated by designer drugs) increased the total length of myelinated segments in the axons of these neurons. The overall length and branching of axons also increased, however, and the increased myelination appeared to occur primarily on new, higher-order branches.

These results suggest that activity-induced increases in myelination in cortical interneurons does not occur on previously unmyelinated axonal segments, but rather on newly formed segments. This is consistent with previous work in zebrafish, which showed that after demyelination, the original pattern of myelination was restored (Auer et al. 2018 Curr Biol 28:549). Such findings reinforce the idea that factors present in or surrounding axons determine their myelination pattern. Future work should determine whether activity-dependent changes in myelination of projection neurons also results from increases in branching, as well as determining how increased myelination of cortical interneurons affects circuit function.



Chemogenetic activation of cortical parvalbumin-expressing interneurons increases axonal branching and myelination. See Stedehouder, Brizee, et al. for details.

Corticostriatal Projections Regulate Itch-Related Scratching

Yu-Chen Lu, Yu-Jun Wang, Bin Lu, Ming Chen, Ping Zheng, et al.

(see pages 3823–3839)

Itch and pain are closely related yet easily distinguishable somatosensory experiences that evoke distinct behavioral responses. Whereas itch is defined by its ability to drive and be relieved by scratching, pain evokes protective responses, such as withdrawal or licking. The two main classes of itch-inducing stimuli—histaminergic and nonhistaminergic—activate multiple populations of primary afferent and spinal neurons, nearly all of which also respond to painful stimuli. After local processing in the spinal cord, itch information is sent to the brain, where it activates many of the same regions as nociceptive inputs, including areas involved in somatosensation, emotion, and motivation. Thus, from the periphery to higher brain structures, itch-inducing and painful stimuli activate highly overlapping populations of neurons. How itch is differentiated from pain to drive a unique behavioral response remains poorly understood.

One site for discriminating pain and itch is the dorsal horn of the spinal cord, where transmission of itch signals is inhibited by B5-I interneurons that release the κ-opioid receptor (KOR) ligand dynorphin. B5-I interneurons are activated by itch-insensitive nociceptive neurons, as well as by descending inputs from the brain. Lu et al. now report that regulation of itch circuitry in the spinal cord depends partly on communication between the anterior cingulate cortex (ACC) and the dorsomedial striatum (DMS).

The authors showed that neurons projecting from ACC to DMS were activated when histamine was injected subcutaneously. Furthermore, light-mediated inhibition of archaerhodopsin-expressing ACC terminals in DMS reduced scratching in response to histamine and reduced histamine-induced expression of c-fos (a marker of neural activation) in the dorsal horn. In contrast, photoactivation of ACC–DMS projections evoked scratching and increased c-fos expression in the dorsal horn. Notably, this scratching was attenuated by administration of antagonists of either histamine receptors or gastrin-releasing peptide receptors (which are expressed in spinal interneurons), suggesting that it required activation of peripheral and spinal itch pathways. Finally, inhibiting B5-I interneurons potentiated scratching evoked by ACC–DMS activation, whereas a KOR agonist reduced photoactivation-induced scratching.

These results suggest that projections from ACC to DMS modulate scratching in response to histamine. In some ways, this is not surprising, because ACC and DMS have previously been shown to be involved in motivated behaviors. But how and why activation of this pathway leads to activation of itch-sensitive spinal neurons is unclear. These questions should be addressed in future research.

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