This Week in The Journal

MAP1B Limits Endocytosis of $Na_v1.6$ at Axon Initial Segment

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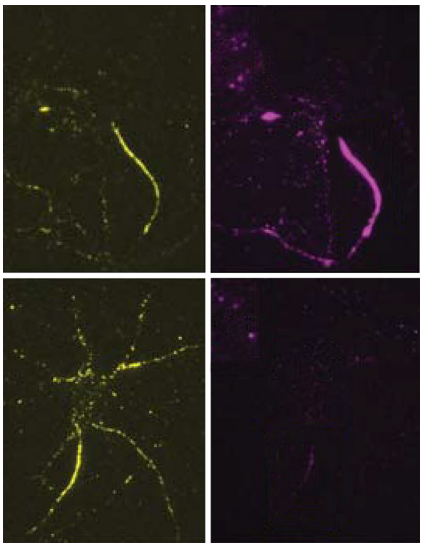
(see pages 4238 – 4251)

Action potential generation is made possible by a dense concentration of voltage-sensitive sodium channels near the base of axons, in a specialized structure called the axon initial segment (AIS). In mature neurons, $Na_v1.6$ is the predominant sodium channel in the AIS, and its expression level determines the threshold for action potential generation. Although $Na_v1.6$ expression is not restricted to the axon—it is present in patches on the soma, for example—it is highly enriched at the AIS. This enrichment results partly from $Na_v1.6$ binding to ankyrin G, a scaffolding protein instrumental in the formation and maintenance of the AIS, and partly from the channel's resistance to endocytosis when anchored at this site (Leterrier, 2018, J Neurosci 38:2135).

Solé et al. now report that the microtubule-associated protein MAP1B also helps to concentrate $Na_v1.6$ in the AIS. Previous work showed that $Na_v1.6$ binds to MAP1B via a four-amino-acid sequence in its N terminus. Coexpression of $Na_v1.6$ and MAP1B increased sodium currents in a neuronal cell line, and these currents were eliminated by mutating the MAP1B-binding site of $Na_v1.6$. The authors therefore concluded that MAP1B is required for trafficking of $Na_v1.6$ to the plasma membrane (O'Brien et al., 2012, J Biol Chem 287:18459).

Consistent with this hypothesis, Solé et al. found that eliminating the MAP1B-binding site reduced levels of $Na_v1.6$ in the AIS of cultured rat hippocampal neurons. Surprisingly, however, clusters of mutant $Na_v1.6$ still formed on neuronal somata. Moreover, fluorescence recovery after photobleaching and labeling of channels as they appeared on the cell surface indicated that mutant $Na_v1.6$ was appropriately delivered to the AIS. The authors therefore investigated other explanations for the reduced steady-state levels of $Na_v1.6$ in the AIS. Single-particle tracking experiments indicated that anchoring of mutant $Na_v1.6$ was similar to that of wild-type channels. But blocking endocytosis increased AIS levels of mutant channels without affecting wild-type levels, suggesting that loss of MAP1B binding led to increased $Na_v1.6$ endocytosis.

These results suggest that MAP1B promotes the accumulation of $Na_v1.6$ at the AIS by inhibiting its endocytosis at this site. How MAP1B prevents $Na_v1.6$ endocytosis is unclear, but it might prevent interactions between $Na_v1.6$ and the endocytic machinery. Future work should address this question and determine whether MAP1B binding also disrupts accumulation of $Na_v1.6$ at nodes of Ranvier.



Wild-type $Na_v1.6$ (top right) is concentrated with Neurofascin-186 (left panels) at the AIS. $Na_v1.6$ lacking the MAP1B interaction sequence (bottom right) does not concentrate at the AIS. See Solé et al. for details.

Dural CGRP Induces Pain Hypersensitivity Only in Females

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(see pages 4323– 4331)

Calcitonin gene-related peptide (CGRP) is a signaling molecule released by the central and peripheral terminals of most peptidergic nociceptors. It is thought to contribute to inflammatory and neuropathic pain by stimulating the release of proinflammatory molecules in the periphery and by sensitizing pain pathways centrally. Notably, drugs and antibodies that interfere with CGRP release or its binding to receptors can prevent migraines. Moreover, several of these treatments do not cross the blood–brain barrier, suggesting that peripheral actions of CGRP contribute to migraine. Given that CGRP is a potent vasodilator, that meningeal vessels are dilated during migraine, and that CGRP-expressing nociceptors of the trigeminal nerve innervate meningeal and cerebral vessels, the meninges are a likely site of CGRP action in the genesis of migraine.

Avona et al. tested this hypothesis by applying CGRP to the dura in rats. Consistent with previous work, CGRP did not directly activate meningeal nociceptors. Nonetheless, it reduced mechanical nociceptive thresholds in the periorbital region of the face for up to 72 h. Surprisingly, however, this effect was only seen in females. In addition, CGRP primed nociceptive responses in females, but not in males. Specifically, after recovery from CGRP-induced hypersensitivity, substances that did not normally induce such hypersensitivity—including subthreshold doses of a nitric oxide donor that induces migraines in people—reduced mechanical pain thresholds in the periorbital region. Similar female-specific responses to dural application of CGRP occurred in mice.

These results indicate that release of CGRP onto the dura can increase pain sensitivity in female rodents. If such female-specific effects occur in humans, this might explain why migraines are more than twice as common in women as in men. It should be noted, however, that in previous studies, higher concentrations of CGRP applied to other peripheral tissues sensitized nociceptive responses in males. Therefore, more work is needed to clarify the sex- and concentration-dependent effects of CGRP, the molecular pathways underlying sex differences, and the implications for such differences in migraine treatment.

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