Migraine meets membrane trafficking

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Having a drug that works clinically, but without a clear mechanism, is like having a key that can be tried on many doors—eventually one will open, but what will be found? The paper by Burstein and colleagues (1) in this issue of *Cephalalgia* describes an unexpected connection between migraine and membrane trafficking associated with mechanical pain. In an elegant series of experiments, they show that onabotulinumtoxinA (BoNT-A) inhibits mechanical hyperalgesia, and proposed that it may act by preventing the insertion of mechanoreceptors at the plasma membrane. The authors used their well-established rat model of inflammatory agent-induced cranial pain to test the effect of BoNT-A on electrophysiological responses to mechanical stimulation. As an added bonus, they examined both intracranial and extracranial nociceptive branches of meningeal nociceptors, which was logical given that BoNT-A is injected extracranially. BoNT-A inhibited C-fiber responses to suprathreshold stimuli that could produce mechanical pain, but not responses to threshold non-pain stimuli. The remarkably long latency of hours for BoNT-A action is consistent with inhibition of mechanoreceptor translocation to the plasma membrane.

This study is the first to test BoNT-A effects on nociceptive neurons believed to mediate migraine headache. As such, it takes us a step closer to understanding how this therapy may benefit migraine patients. While clinically proven effective for chronic migraine, the mechanism of action has been a mystery. Dogma predicted that BoNT-A would inhibit neurotransmission similar to its known action at the neuromuscular junction by inhibiting soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-mediated vesicle fusion to the plasma membrane. Indeed, BoNT-A was shown to inhibit peripheral glutamate release from sensory neurons in vivo (2) and CGRP release from cultured trigeminal neurons (3). A similar inhibitory mechanism at the central terminals of trigeminal neurons has also been proposed (4). Those mechanisms may still contribute to BoNT-A action, but there had to be more to the story. As cell biologists know, vesicles do not just carry neurotransmitters, but their cargo also includes transmembrane proteins for delivery to the plasma membrane. So a regulated membrane trafficking role fits well with the known actions of BoNT-A. To further underscore the importance of this process, this past year’s Nobel Prize for Physiology or Medicine was awarded for discoveries of the proteins regulating vesicle trafficking.

This finding begins, but does not end, the story. Like any good experiment, it has left more questions. What is the molecular identity of the suprathreshold mechanoreceptor? The sensitivity to BoNT-A should help with this pursuit. Is induced translocation a common theme of chronic pain? As discussed in Burstein et al. (1), SNAREs are involved in cell surface delivery of TRPV1, TRPA1, and P2X3 receptors in neurons, TRPV1 channels are trafficked to the cell surface in response to inflammation and contribute to inflammatory hyperalgesia, and nociceptive signals induce TRPA1 translocation (5–7). In addition, regulated translocation has been observed for other pain-associated receptors, including the 5-HT1D triptan receptor (8), delta-opioid receptor (9), and the CGRP receptor, which is normally localized only on central, not peripheral, terminals of trigeminal neurons (10). Since many of these molecules are involved in peripheral nociceptor sensitization, it is tempting to speculate that Burstein and colleagues may have uncovered a broader target of BoNT-A action at peripheral terminals. Perhaps regulation of receptor trafficking to the cell surface may be an emerging mechanism underlying chronic pain.

Conflict of interest
None declared.

References

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