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RESEARCH NEWS

BK channels promote neuromuscular transmission

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Mice lacking BK channels are weak because of reduced vesicle release at neuromuscular junctions.

Large-conductance voltage- and Ca^{2+}-activated K^+ channels, known as BK channels, are widely expressed throughout the nervous system and, among many other defects, mice lacking these channels suffer a variety of motor deficits, including impaired coordination (ataxia) and muscle weakness. In this issue of *JGP*, Wang et al. reveal that weakness in BK-deficient mice is due to reduced vesicle release at neuromuscular junctions (NMJs; 1).

The coordination defects in BK-null mice are caused by deficits in cerebellar function (2), but the mechanisms underlying the animals' weakness are unknown. Mark Rich and Andrew Voss at Wright State University initially suspected that the problem might lie in the skeletal muscle itself, where BK channels are also highly expressed. But when the researchers, including first author Xueyong Wang and co-author Steven Burke, directly stimulated the plantar flexor muscles of $BK^{-/-}$ mice, they found that they produced the same amount of force as wild type muscle. When the muscles were stimulated via the sciatic nerve, however, force production was reduced by ∼50% in $BK^{-/-}$ mice. "That suggested a problem with either the neurons or the NMJ," Rich says.

Voltage-clamp recordings showed that action potentials are normal in $BK^{-/-}$ motor axons but that the number of vesicles released at NMJs is reduced by over 50%. Repetitive stimulation indicated that the probability of vesicle release is decreased at $BK^{-/-}$ NMJs, suggesting a reduction in either the entry or effectiveness of Ca^{2+} at the presynaptic terminal. Accordingly, the Rich and Voss laboratories found that increasing Ca^{2+} entry by using the K_v channel-blocker 3,4-diaminopyridine to prolong the presynaptic action potential was sufficient to rescue evoked vesicle release at $BK^{-/-}$ NMJs. Moreover, systemic administration of 3,4-diaminopyridine to mutant mice normalized force production in vivo, indicating that reduced vesicle release is the cause of muscle weakness in $BK^{-/-}$ mice.

Xueyong Wang (left), Andrew Voss (middle), Mark Rich (right), and colleagues show that mice lacking BK channels are weak due to a reduction in neuromuscular transmission. Compared with wild type animals, muscles from $BK^{-/-}$ mice generate similar force upon direct muscle stimulation but reduced force in response to nervous stimulation. The researchers trace this defect to reduced vesicle release at mutant NMJs, a phenotype that appears to be independent of BK-mediated K^+ currents.

Knocking out BK channels in *Drosophila melanogaster* has similar effects (3), but previous studies in mice have suggested that blocking BK channels can increase vesicle release at NMJs (4,5). The authors tested several BK channel-blocking toxins and saw no effect with any of them, suggesting that the reduced vesicle release at $BK^{-/-}$ NMJs might not be due to the absence of BK-mediated currents in adulthood.

"Our data suggest BK channels play an important role in neuromuscular transmission and muscle force production, and, interestingly, this role is independent of their ion channel function." Rich says. "One possibility is that BK channels have a developmental role in NMJ assembly and have no function at all in adults, which would explain why we don't see any effect with the toxins. However, there are now some hints in the literature that BK channels have structural functions and can act as scaffolding proteins at presynaptic active zones." In the absence of BK channels, the authors suggest, NMJ active zones might contain fewer voltage-gated Ca^{2+} channels, reducing Ca^{2+} entry in response to nervous stimulation, or synaptic vesicles might be tethered further away from Ca^{2+} channels, reducing the ability of Ca^{2+} to trigger their release.

Elucidating the role of BK channels at NMJs could have important clinical implications (6). "Andrea Meredith and colleagues have recently identified patients with BK channel mutations and one of their clinical phenotypes is hypotonia," Rich says. "Our paper suggests that NMJ dysfunction and muscle weakness may contribute to this aspect of their symptoms."

References

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