This Week in The Journal

Potassium Channel Types at Motor-Axon Nodes of Ranvier

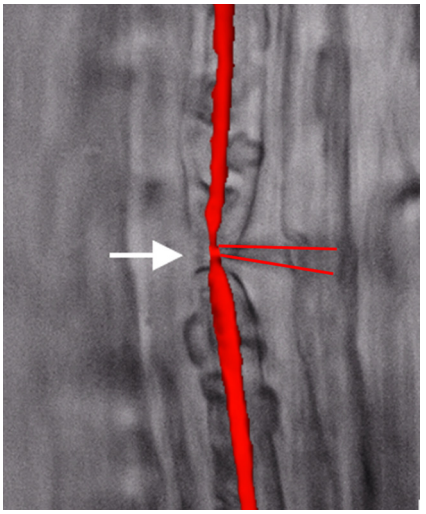
Sotatsu Tonomura and Jianguo G. Gu

(see pages 4980–4994)

In myelinated axons, ion channels involved in action potential propagation are located exclusively at nodes of Ranvier. In neuronal somata and unmyelinated axons, voltage-gated potassium channels (VGKCs) open during action potentials and speed repolarization, thus shortening action potential duration. Whether VGKCs are also present at nodes of Ranvier in myelinated axons was long debated, largely because the small size of nodes and the presence of perineural tissue precluded patch-clamp recording. Tonomura and Gu recently overcame these obstacles by developing the pressure patch-clamp technique, in which positive pressure applied through the recording electrode clears access to nodes, which are visualized by filling axons with fluorescent dye. Using this technique, Kanda et al. (2019, Neuron 104:960) discovered that VGKCs are not, in fact, present at nodes of Ranvier in rat sensory axons. Instead, an unusually high concentration of two-pore domain potassium (K2P) channels—often referred to as leak channels—is present at nodes. These channels help set the resting membrane potential, influence action potential shape and conduction velocity, and help maintain high-frequency spiking. Tonomura and Gu now report that both K2P and VGKCs contribute to these properties at nodes of Ranvier in rat motor axons.

The authors recorded from nodes in freshly dissected ventral spinal nerves. Depolarizing voltage steps evoked inward currents followed by large noninactivating outward currents in these fibers. As in sensory axons, the outward current was substantially reduced by inhibitors of K2P channels. But blockers of VGKCs also reduced outward currents, albeit modestly. Blocking either channel type depolarized the resting membrane potential, increased input resistance, increased action potential width, and increased (depolarized) spike threshold. Blocking VGKCs also reduced the ability of nodes to propagate spikes at high frequency, but it did not affect conduction velocity. In contrast, multiple K2P channel inhibitors slowed conduction velocity, but only one inhibitor affected the fidelity of high-frequency transmission.

These data suggest that, like in sensory axons, K2P channels are expressed at high levels at nodes of Ranvier in motor axons, influencing resting membrane potential, action potential duration, and conduction velocity. Unlike in sensory axons, however, nodes in motor axons also contain VGKCs, which also influence electrical properties and spike propagation. Future work should explore the functional consequences of these differences.



A pressure-patch-clamp electrode approaches a node of Ranvier in a dye-filled motor axon. See Tonomura and Gu for details.

Effects of Striatal Targets on Engrafted Dopamine Neurons

Niamh Moriarty, Jessica A. Kauhausen, Chiara Pavan, Cameron P. J. Hunt, Isabelle R. de Luzy, et al.

(see pages 4995–5006)

Parkinson's disease (PD) is characterized by motor impairment resulting from loss of dopaminergic projections from the substantia nigra to the dorsal striatum. One potential strategy for restoring motor function in PD is to graft fetal midbrain tissue or dopamine neurons derived from induced pluripotent stem cells (iPSCs) into the striatum. Indeed, this strategy improves motor function in animal models. Unfortunately, however, results of clinical trials have been less successful (Barbuti et al., 2021, Mov Disord 36:1772). Notably, restoring motor function in animal models of PD requires replacement specifically of the A9 subtype of dopamine neurons, which normally innervate the striatum, rather than the A10 subtype, which innervate cortex and limbic structures. Therefore, identifying factors that boost survival, integration, and maturation of A9 neurons in grafts may improve clinical outcomes. Moriarty et al. suggest that such factors might be produced by striatal medium spiny neurons (MSNs).

The authors grafted ventral midbrain progenitors derived from fetal mice or from human iPSCs into mice in which dopamine neurons alone or dopamine neurons along with MSNs had been killed. Killing MSNs did not affect the survival of engrafted dopamine neurons derived from fetal tissue, but it reduced survival of iPSC-derived neurons. Regardless of graft origin, killing MSNs significantly reduced growth of dopaminergic axons into the striatum, increased axonal growth into the cortex, and reduced the proportion of grafted dopamine neurons that acquired the A9 phenotype (e.g., expressing GIRK2 potassium channels). When iPSC-derived neurons were implanted, killing MSNs increased the proportion of dopamine neurons with a calbindin-positive A10 phenotype; when fetal cells were implanted, however, killing MSNs increased the proportion of unspecified dopamine neurons.

These results suggest that contact with striatal targets is required for grafted ventral midbrain progenitors to acquire the A9 phenotype and thus to restore motor function after loss of nigrostriatal dopamine neurons. Discovering how MSNs promote the A9 phenotype might therefore lead to increases in the therapeutic value of tissue grafts in people with PD.

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

https://doi.org/10.1523/JNEUROSCI.twij.42.25.2022