Why myelinated mammalian nerves are fast and allow high frequency

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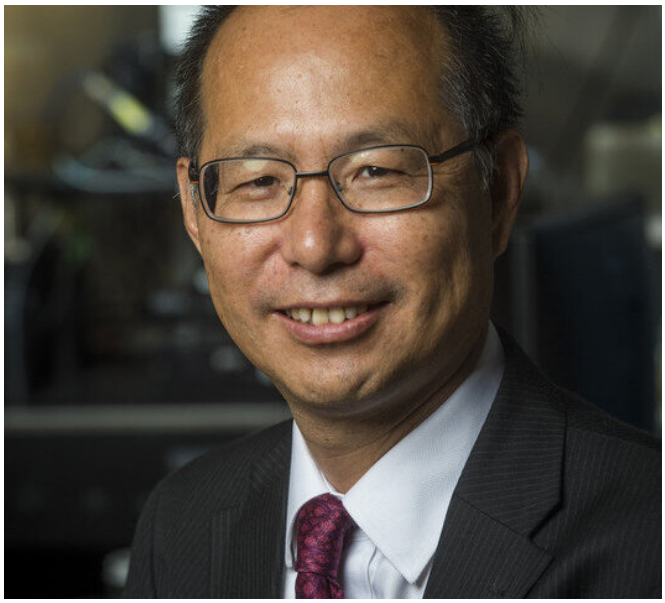

Jianguo Gu. Credit: UAB

University of Alabama at Birmingham researchers, for the first time ever, have achieved patch-clamp studies of an elusive part of mammalian myelinated nerves called the Nodes of Ranvier. At the nodes, they found unexpected potassium channels that give the myelinated nerve the ability to propagate nerve impulses at very high frequencies and with high conduction speeds along the nerve. Both qualities are necessary for fast conduction of sensations and rapid muscle control in mammals—keys to an animal's survival in a predator-prey world.

Discovered by French scientist Louis-Antoine Ranvier in 1878, these tiny nodes have been known since 1939 to act like relay stations placed about 1 millimeter apart along the myelinated nerve to conduct mammalian nerve impulses at rates of 50 to 200 meters per second. Between each bare node, the nerve is wrapped with insulating sheaths of myelin. When the nerve fires, the electrical impulse hops from one node to the next, moving 100-times faster than the nerve impulse of an unmyelinated nerve. Neuroscientists have long known that release and uptake of ions at the nerve cell membrane is the mechanism of electrical nerve impulses. But whether any potassium ion channels were present in the Nodes of Ranvier—and if so, what type—has been a matter of debate for decades because no one had been able to successfully apply patch clamps to the 1 to 2 micron-wide nodes of intact nerves in mammals.

In a study published in the Cell Press journal *Neuron*, Jianguo Gu, Ph.D., his postdoctoral fellow Hirosato Kanda, Ph.D., and other colleagues at UAB report that two ion channels called TREK-1 and TRAAK act as the principal potassium channels in the Nodes of Ranvier of a rat myelinated nerve. More importantly, they showed that those two channels at the Nodes of Ranvier were required for high-speed and high-frequency saltatory, or "hopping," conduction along myelinated afferent nerves. Knockdown of the channels reduced nerve conduction speed by 50 percent, and behavioral experiments showed that knockdown in the nerve reduced a rat's aversive reaction to a flick of its whisker.

In the classic experiments that led to a Nobel Prize in 1963 for the nerve impulse mechanism, nerves used a voltage-gated potassium channel (meaning a change in voltage makes it fire) to release potassium ions from an unmyelinated squid giant nerve. Gu and his colleagues initially expected to find such channels at the Nodes of Ranvier.

However, their earliest experiments confounded that expectation—so much so that they dropped the study for a year. When they added known inhibitors of voltage-gated potassium channels, they saw no significant decrease in the electrical spikes at the Node of Ranvier. That finding challenged dogma, and it meant some other unidentified potassium

channel or channels instead were serving as the workhorses at each node.

Possible candidates included three members of a family of 15 proteins known as "leak" potassium channels, which are constitutively open rather than voltage-gated and were known to have large conductance, says Gu, the Edward A. Ernst, M.D., Endowed Professor and director for pain research in the UAB Department of Anesthesiology and Perioperative Medicine's Division of Molecular and Translational Biomedicine. Gu's lab found that two of them, TREK-1 and TRAAK, are the active channels in the Nodes of Ranvier. Their tests to show this included the pressure-patch-clamp recording technique the researchers developed for the nodes, along with immunohistochemical, genetic and pharmacological approaches.

Furthermore, the UAB team found that TREK-1 and TRAAK—which are thermosensitive and mechanosensitive two-pore-domain potassium channels—are highly clustered at the nodes of the rat trigeminal A-beta nerve, with a current density that is 3,000-fold higher than that of the cell body.

Leak potassium channels and voltage-gated potassium channels act to repolarize the nerve membrane after a nerve impulse, known as an action potential. TREK-1 and TRAAK in the Nodes of Ranvier acted quite differently from the voltage-gated potassium channels that are found in the cell body, or soma, of the rat nerve. During a stimulation of the soma at 50-times per second, the action potentials that use the voltage-gated potassium channels typically failed. But Gu and colleagues found that action potentials at the Nodes of Ranvier with the "leak" channels showed no significant failures at stimulation frequencies up to 200-times per second.

In other words, the two leak potassium channels allowed very rapid repolarization at the Nodes of Ranvier, and high frequency as well as rapid conductance of the myelinated rat nerves. Interestingly, the TREK-1 and TRAAK two-pore-domain potassium channels appeared to form heterodimers in the Nodes of Ranvier.

Gu says these new fundamental findings have implications in neurological diseases or conditions where nodal dysfunctions affect action potential conduction. These include carpal tunnel syndrome, Guillain-Barré syndrome, multiple sclerosis, spinal cord injuries and amyotrophic lateral sclerosis.

More information: Hirosato Kanda et al, TREK-1 and TRAAK Are Principal K+ Channels at the Nodes of Ranvier for Rapid Action Potential Conduction on Mammalian Myelinated Afferent Nerves, *Neuron* (2019). DOI: 10.1016/j.neuron.2019.08.042

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