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► **To cite this version:**

Guillaume Sandoz, Pablo Ávalos Prado. TREK for High-Speed and High-Frequency Conduction through the Axon. *Neuron*, 2019, 104 (5), pp.831-833. 10.1016/j.neuron.2019.11.015 . hal-03002213

HAL Id: hal-03002213

<https://hal.science/hal-03002213>

Submitted on 21 Dec 2021

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TREK for high speed and high frequency conduction through the axon

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Abstract

In this issue of Neuron, Kanda et al. (2019) find that the two-pore domain potassium channels TRAAK and TREK1 drive axonal action potential repolarization for high-speed and high-frequency nervous impulses in mammalian myelinated nerves.

An action potential (AP) corresponds to a fast modification of the membrane potential, which rapidly rises and then falls, driven, in the soma, by the sequential activation of the voltage-dependent Na⁺ and the voltage-dependent K⁺ channels. In neurons, the main function of the AP is cell-to-cell communication by its propagation along the axon toward synaptic boutons. In non-myelinated axon, the AP travels by regenerating itself (Hodgkin in 1937). The AP induces a sufficient depolarization of the neighbor region inducing the activation of the voltage-dependent Na⁺ channels allowing AP regeneration. This AP propagation has a maximum speed of ~1 m/s. Fast AP propagation requires myelin sheaths. Myelin is a multilamellar membrane that enwraps the axon in segments separated by intervals known as nodes of Ranvier (NRs). Myelin presents a high electrical resistance that prevents the AP conduction along the myelinated segments. However, the current carried at near distance, through the axon cable properties, generates a sufficient depolarization at subsequent NRs allowing AP regeneration. This propagation, known as saltatory conduction, allows a propagation of the AP over 100 m/s.

Since Hodgkin and Huxley established the first ionic conductances of the AP in giant squid axon, AP generation and transmission in the nervous system has been a subject of continuous study. Nevertheless, 80 years after their experiments, the molecular identity of the

channels underlying AP propagation and regeneration at the NRs in mammals is still a matter of conjecture. Whereas some research suggests that AP depolarization and repolarization in both soma and NRs are carried by Na⁺ and K⁺ voltage-dependent channels, respectively (Bean, 2007), others suggest that there is no K⁺ channel implication in AP in intact NRs (Chiu and Ritchie, 1980). One important issue concerning this debate has been the lack of reliable tools to address the molecular identity of ion currents of APs at NRs. Standard patch-clamp pipettes often fail to access this region due to the presence of myelinating cells and tiny perineural tissue surrounding the nodes. In this issue of *Neuron*, Kanda and co-workers have developed an “in situ” pressure-patch-clamp technique which overcomes this problem and allows one to directly patch-clamp intact NRs (Kanda et al., 2019). This novel system finely controls the internal pressure of the patch-clamp pipette, enabling to clean the surface areas around nodes of Ranvier of intact rat trigeminal axons and make proper seals.

Once sealed, the application of different ion channel blockers on trigeminal A β -afferent nerves showed two interesting findings. Firstly, as expected, when the voltage-gated Na⁺ channel inhibitor TTX was applied, the inward-depolarizing currents were completely abolished, matching with previous works showing that voltage-dependent Na⁺ channels are required for saltatory conduction (Caldwell et al., 2000). Secondly, addition of TEA and intracellular Cs⁺, two typical blockers of voltage-gated K⁺ channel, elongated AP repolarization in soma but not in NRs. This last result confirmed that molecular actors involved in AP propagation at mammal myelinated axons differ from those which are used at the soma.

When Kanda et al. looked in more detail into the ionic current kinetics at A β -afferent nerves, they noticed the presence of a fast non-inactivating outward current following depolarizing which was not inhibited by classical voltage-gated K⁺ or Cl⁻ channel blockers. However, the changes in extracellular K⁺ concentration altered the reversal potential. These properties made two-pore domain K⁺ (K2P) channels good candidates for carrying this outward current. In fact, K2P channels create non-inactivating K⁺ currents which are nearly instantaneous and are strongly expressed within the nervous system. In neurons, K2P channels serve as a hub for the generation and regulation of the negative resting membrane potential (Noël et al., 2011). Their importance is reflected by the large number of neurological diseases related with dysfunction of these channels such as depression (Heurteaux et al., 2006) and migraine (Royal et al., 2019).

In order to narrow down what members of the K2P channel family are responsible of the K⁺ leak currents at NRs, Kanda and co-workers performed whole-cell and single-channel experiments to show that this current is mechano- and thermosensitive. This regulation is consistent with the poly-modal gating of the TWIK-Related K⁺ (TREK) channel subfamily, which includes TREK1, TREK2 and TRAAK (Noël et al., 2011). Moreover, immunocytochemistry data revealed the presence of TREK1 and TRAAK, but not of TREK2, in NRs. Since TREK1 and TRAAK subunits tend to combine and generate heterodimers with intermediate functional properties when they are co-expressed in heterologous systems (Levitz et al., 2016), the authors wondered whether this mechanism could be also present in myelinated nerves. As the single-channel K⁺ conductance in trigeminal A β -afferent axons was similar to the one observed in TREK1-TRAAK heterodimers in heterologous system, Kanda and co-workers concluded that the K⁺ leak currents in NRs is mostly carried by TREK1-TRAAK heterodimers, with a minor participation of TRAAK and TREK1 homodimers.

Henceforth, the role of TREK1 and TRAAK K2P channels in AP propagation at NRs is nicely demonstrated genetically by injecting specific shRNA and pharmacologically using TREK channel blockers and activators. The inhibition of TREK1-TRAAK led to an increase of the AP duration, a depolarization of the resting membrane potential and a decrease of the nodal membrane input resistance, demonstrating that TREK1 and TRAAK channels are also important regulators of intrinsic membrane properties.

Furthermore, as myelinated A β -afferent nerves constitute one of the fastest carriers of sensory information in the nervous system (Djoughri and Lawson, 2004), Kanda and co-workers also searched to elucidate whether TREK1-TRAAK nodal rapid repolarization was consistent with high-frequency and high-speed impulses of these fibers. Patch-clamp recordings showed AP broadening, in a frequency-dependent manner in soma but not in axon of trigeminal A β -afferent. Also, in contrast with soma, high-frequency stimulation did not alter the rate of success to generate AP. This superiority of the axon for high-fidelity reproduction in the shape of the AP underlying the high AP success rate was strongly reduced in axons of neurons in which TREK1-TRAAK were genetically and pharmacologically inhibited. Finally, to challenge *in vivo* the functional role of TREK1-TRAAK channel in velocity and fidelity of firing, Kanda and co-workers performed whisker tactile behavioral tests in rats in which TREK1-TRAAK were genetically depleted using shRNA in D2 whisker hair follicles. As tactile stimuli are conducted by myelinated A β -afferent nerves (Djoughri and Lawson, 2004), they expected that invalidation of TREK1 and/or TRAAK would impair

sensory responses. Indeed, rats injected with specific shRNAs showed a strong decrease of tactile response in comparison with the scrambled shRNA control group. This *in vivo* test reinforced the strong *in vitro* evidence, proving that mechanosensitive and thermosensitive K2P channels are crucial for nervous conduction.

To conclude, Kanda and co-workers have demonstrated by genetic and pharmacological invalidation approaches that fast AP repolarization in mammal NRs is mediated by TREK1-TRAAK heterodimeric channels. Furthermore, by setting the resting membrane potential at very negative values, they increased the number of responsive voltage-gated Na⁺ channels by enabling fast recovery from their inactivated state. This mechanism explains the high-frequency fidelity and high-speed conduction through the NRs of myelinated afferent nerves. *In vivo*, behavioral experiments confirmed this observation, as tactile stimuli are mainly conducted by trigeminal A β -afferent myelinated nerves at high-frequency and high-speed (Djoughri and Lawson, 2004). This work ends the old debate about whether AP in nervous system is carried by the same ion channels in soma and NRs, where the AP is regenerated and conducted, pointing out the importance of K2P channels in neuronal transmission. Nevertheless, whether this repolarization mechanism in myelinated axons is shared by other classes in the animal kingdom is still uncertain since in amphibian it involves voltage-gated K⁺ channels. This question and the elucidation of additional contributors to the AP propagation at NRs may be solved with the novel pressure-patch-clamp technique.

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Figure 1. TREK1-TRAAK channels mediate rapid action potential repolarization enabling fast saltatory action potential conduction in mammal myelinated axons.

Recordings of action potentials (APs) in different regions of a pseudounipolar trigeminal neuron of mammal. At the soma, during high frequency stimulation, APs are long due to the slow repolarization phase mediated by voltage-gated K⁺ channels. At the nodes of Ranvier, this process is faster because it is mainly driven by background K₂P channels that rapidly set the resting potential to very negative values. Rapid regeneration of APs and very hyperpolarized membrane potential allow high-frequency and high-speed saltatory conduction of nervous impulses through myelinated axons.

