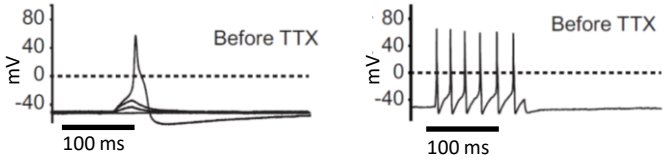
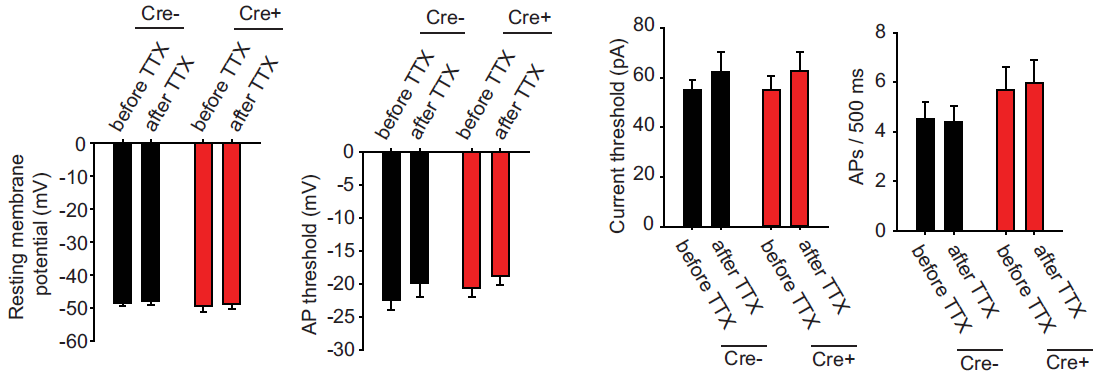
Whereas results from primary cultures point to a complete lack of function of Nav1.7 in sensory neurons, results obtained in vivo conclude to an essential role of Nav1.7 in the generation of action potential in unmyelinated nociceptors.

Analgesic efficacy cannot be inferred from data obtained in isolated DRG neurons.

- ## In vitro DRG data from Shields et al, J Neuroscience, 2018

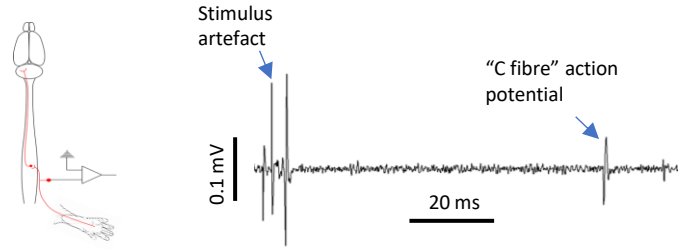


Current-clamp recordings were performed on acutely isolated small-diameter DRG neurons (presumably unmyelinated nociceptors). Cells were stimulated with short 10 ms depolarizing current pulses of increasing amplitude until the cell fired an action potential (AP, left) or with long 500 ms depolarizing current pulses to examine AP firing frequency (right) with and without 500 nM TTX.



Membrane resting potentials, membrane AP threshold, current threshold to trigger AP and number of AP induced by suprathreshold current were similar in control mice (Cre-, black) or Nav1.7 conditional knock out mice (Cre+, red) after complete decay of Nav1.7 protein, in presence or absence of TTX.

- ## In vivo DRG data from Deng et al, Neuron, 2022



Extracellular recordings were performed from unmyelinated DRG nociceptors in vivo in anesthetized mice. The latency of the AP in response to electrical stimulation of the receptive field at 1.2 x threshold intensity was measured.

Infusion of a specific Nav1.7 channel blocker (GNE-3565) resulted in increased latency and AP generation failure in WT mice. An identical infusion had no effect in mice with a modification of the Nav1.7 channel preventing the binding of the compound (Nav1.7 MBS), the channel being fully functional otherwise.