

CELL ELECTROPHYSIOLOGY

BRAIN SLICE ELECTROPHYSIOLOGY

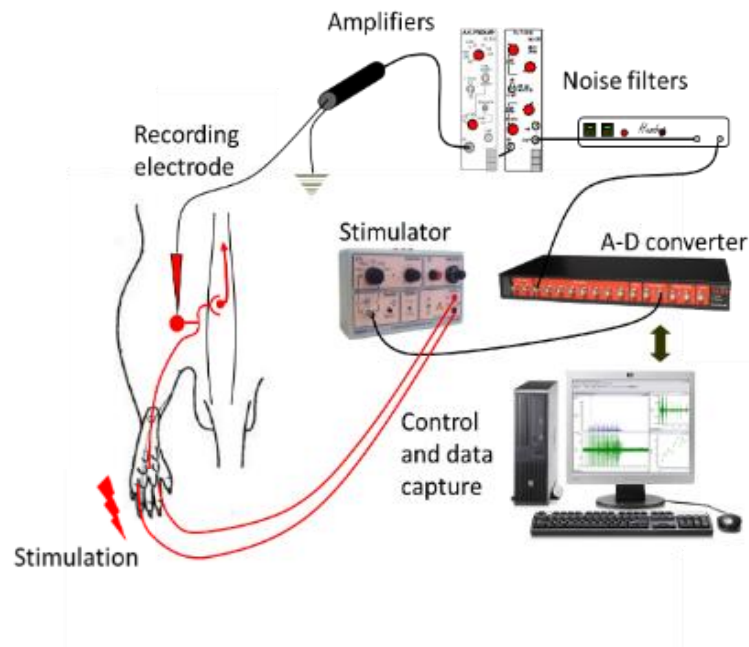
IN VIVO BRAIN ELECTROPHYSIOLOGY

IN VIVO SC & DRG ELECTROPHYSIOLOGY

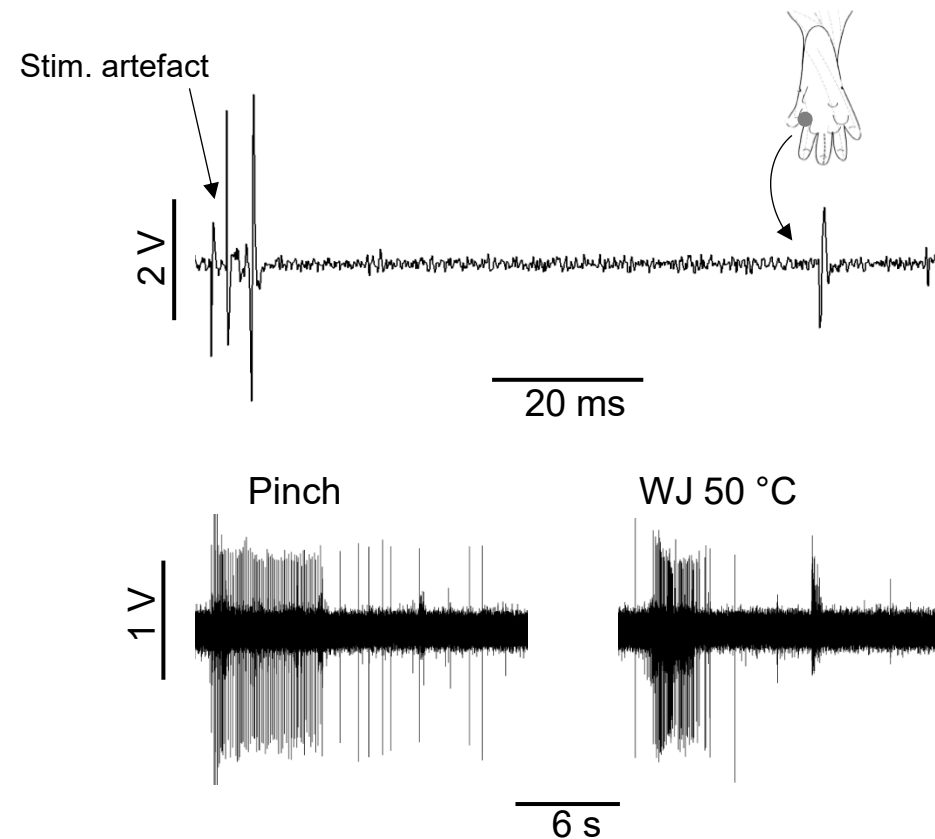
In vivo recordings of DRG neurons



Recording of DRG neurons

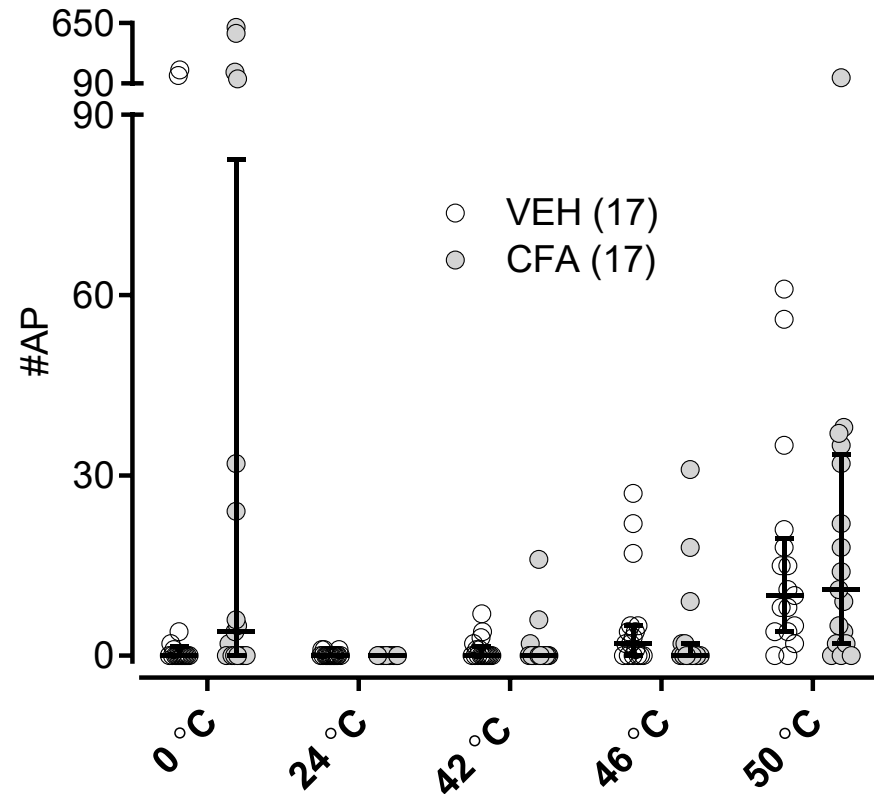


Response to electrical stimulation



- The essential challenge is to obtain a sufficient signal-to-noise ratio when recording from unmyelinated nociceptor.

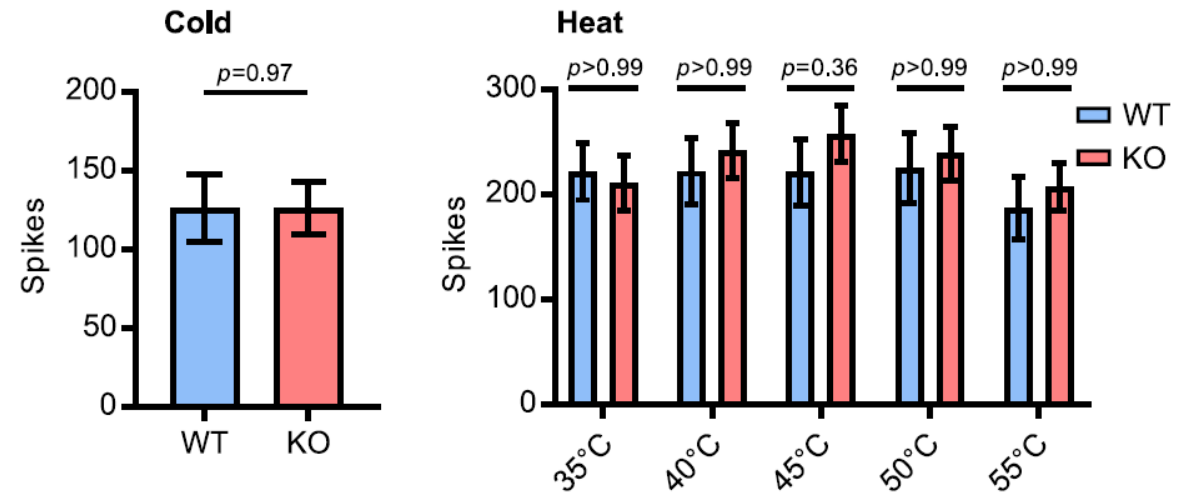
Don't get them mixed up...



Neuron

A central mechanism of analgesia in mice and humans lacking the sodium channel $\text{Na}_v1.7$

Article



- Left hand side: in house data (previous study).
- Right hand side: published data using the same technique (<https://doi.org/10.1016/j.neuron.2021.03.012>).

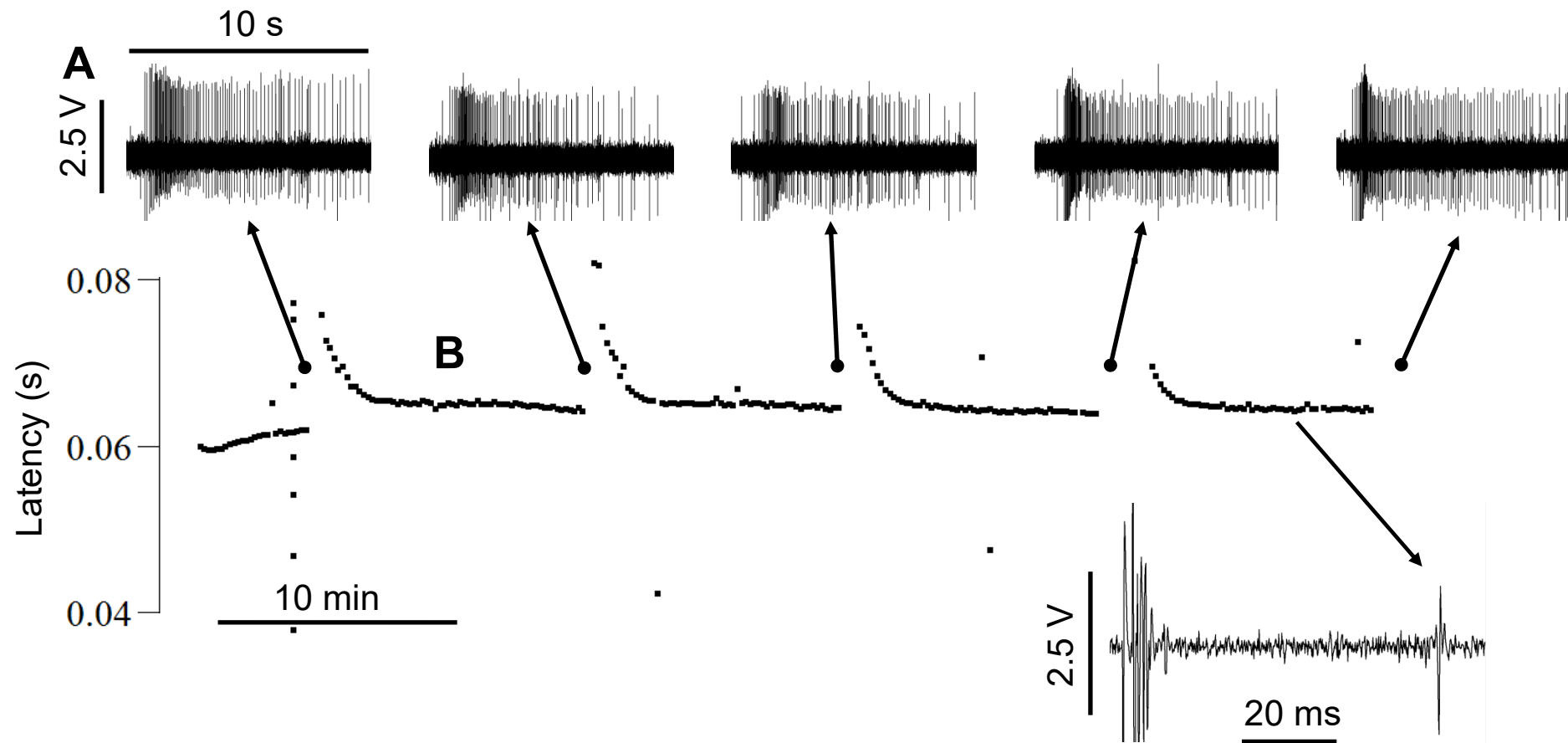


About assessing the efficacy of Nav1.7 channel blocker in vivo on electrophysiological endpoint

Nav1.7 is a challenging target prone to generate false positive:

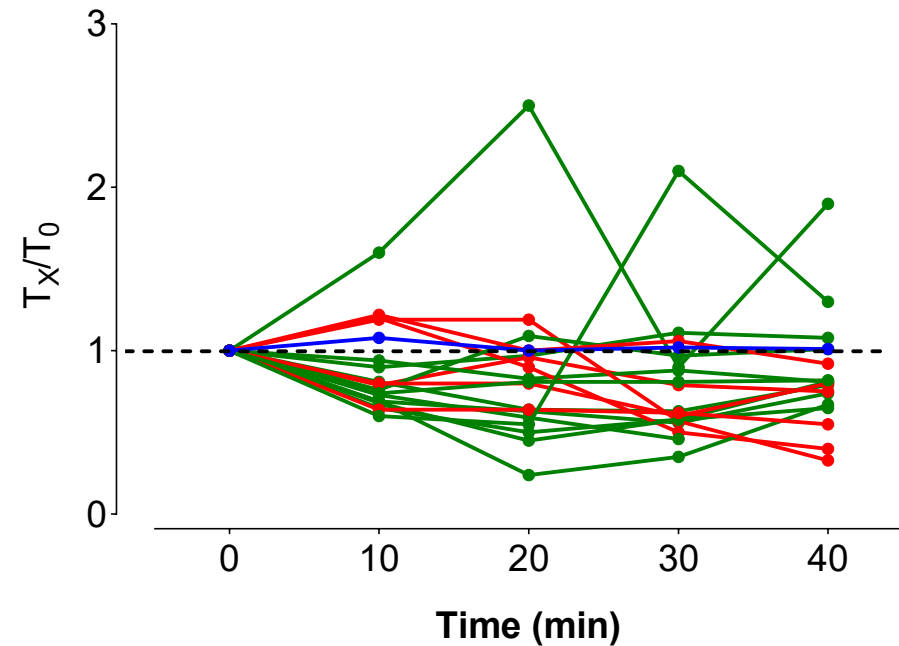
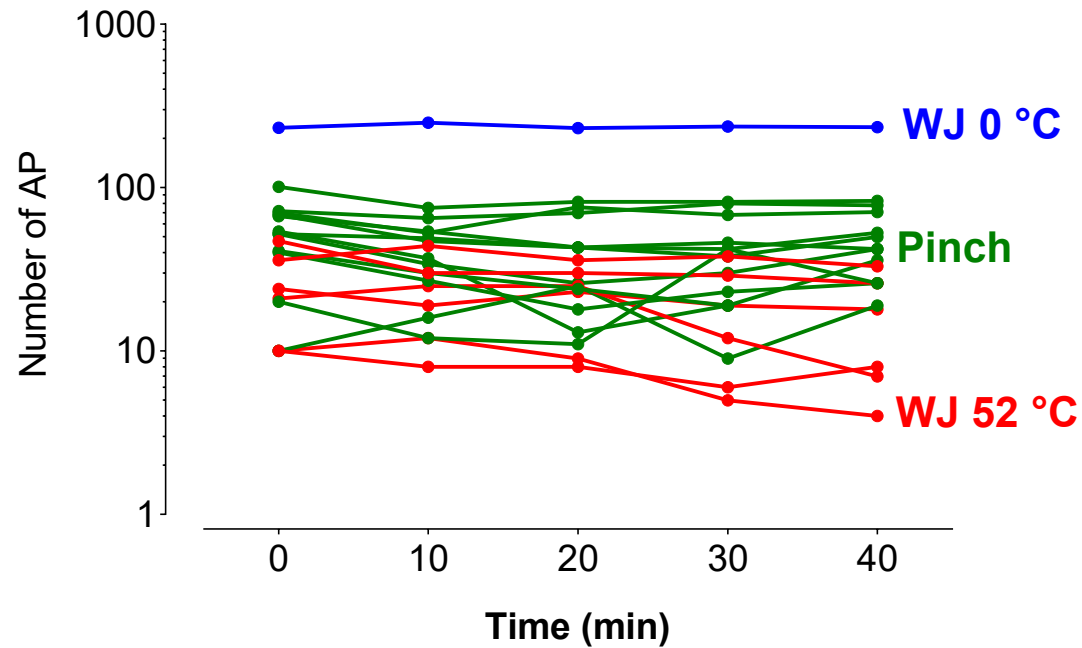
- IC50 derived from in vitro experiments is highly dependent on specific testing conditions (voltage, etc...), leading to mismatch between in vitro IC50 and actual in vivo IC50.
- The development of highly hydrophobic structure may lead to “true” Nav1.7 channel blocker with excessive protein binding fraction (Pfizer compound?).
- Lack of in vivo selectivity results in Nav1.6 channel blockade which might lead to apparent efficacy in behavioural test.

Combining natural and electrical stimulations



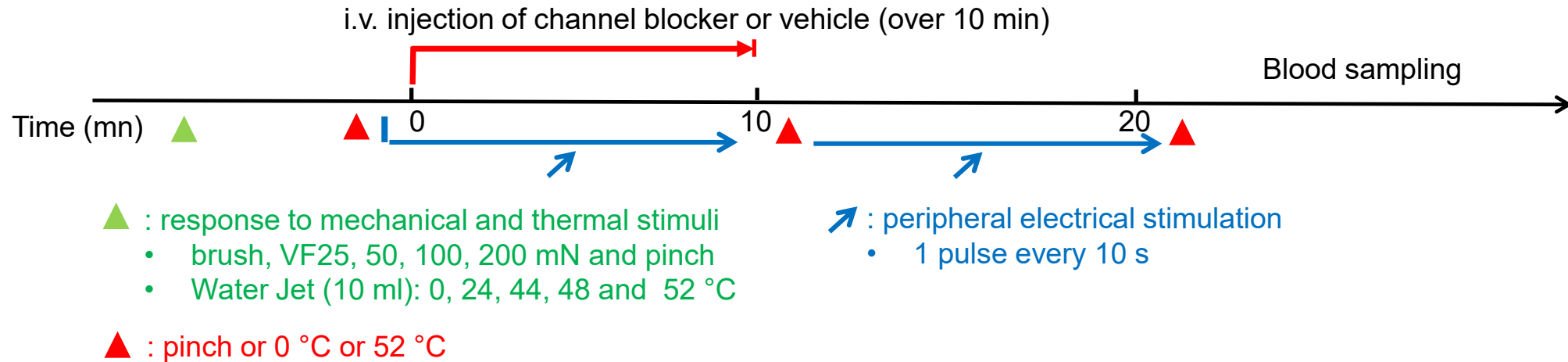
- All illustrations are extracted from one recording. Pinch was applied 5 times every 10 min (A), and electrical stimulations were applied in between to obtain a raster plot of the latency of the action potential (analogue view in C).

Desensitization might occur for some DRG neurons



- Quantification of responses in 20 experiments following the protocol illustrated on the previous slide (23 mice were experimented). There was a run down of the response for some neurons.

Protocol for assessing Nav1.7 channel blocker



Variables:

- Strain of mice (Swiss)
- Status: control
- Stimulus modalities: ad hoc noxious mechanical or thermal + noxious electrical
- Sampling: blood (+ sciatic nerve?)
- Compound: dose and formulation