Hyperpolarization-Activated Currents in a Partial Sciatic Nerve Ligation (pSNL) Mouse Model of Chronic Pain

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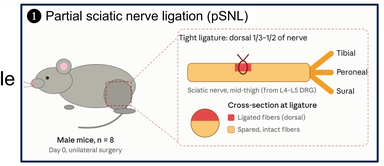
Introduction and background

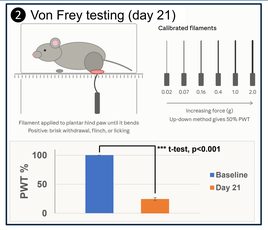
- Chronic pain affected an estimated 24.3% of US adults in 2023, the highest prevalence ever recorded in the National Health Interview Survey.
- Chronic pain, defined as pain persisting beyond 3 months, often has a neuropathic origin, arising from a lesion or disease of the somatosensory nervous system.
- Peripheral nerve injury can lead to neuropathic pain, driven in part by increased sensory neuron excitability.
- HCN channels are hyperpolarization-activated cation channels that pass both Na^+ and K^+, producing a net inward, depolarizing current at negative physiological potentials.
- HCN channels can also be gated by intracellular cyclic nucleotides (cAMP and cGMP), which adds complexity to the regulation of neuronal excitability by these channels.
- Multiple independent studies suggest HCN channel function is upregulated after peripheral nerve injury, implicating HCN channels in pain signaling.
- Functional data on HCN activity across a broad range of resting membrane potentials is still lacking.

In vivo and *in vitro* Methods

In vivo: experimental chronic pain in mice

❶ Chronic neuropathic pain was induced in male mice (n = 8 mice) by partial sciatic nerve ligation (pSNL) technique.





In vivo: validation of pSNL with von Frey testing

❷ Mechanical allodynia was assessed before (Baseline) and 21 days after pSNL surgery (Day 21) using von Frey filaments applied to the plantar hind paw. The 50% paw withdrawal threshold was determined by the up-down method in the ipsilateral (injured, see graph) and contralateral (intact, data not shown) paws.

In vitro: Electrophysiological analysis on isolated neurons

❸ DRG neurons were isolated 21 days post-pSNL from the ipsilateral (injured) and contralateral (control) sides and kept in an incubator.

❹ Whole-cell patch clamp recordings were performed in current-clamp mode to monitor membrane potential and test action potential firing frequency.

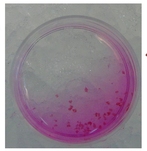
❺ Neurons were held at a wide range of resting membrane potentials (RMP, −90 to −55 mV).

❻ A family of 500-ms current injections (−50 to +150 pA) was applied to each neuron, and the membrane potential response was analyzed.

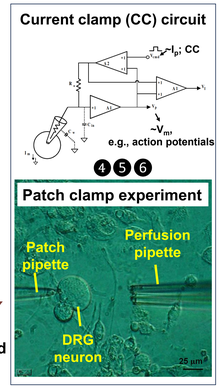
❸ Isoflurane anesthesia
Cervical dislocation



❸ DRG harvesting

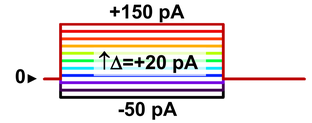


Monodispersed neurons

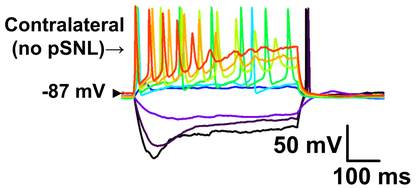


Results (electrophysiology on isolated neurons)

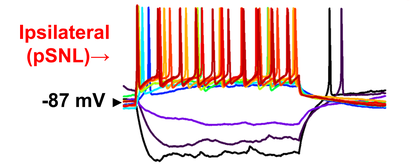
♦ **Current clamp protocol (stimulus)**

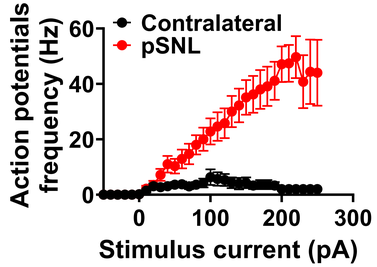


♦ **Membrane potential recordings**



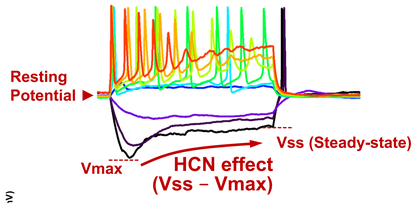
More action potentials; higher excitability

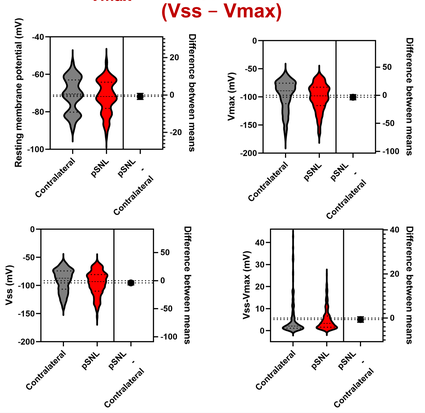


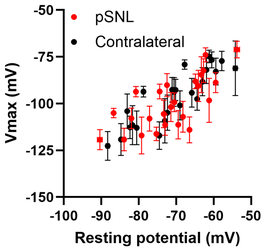


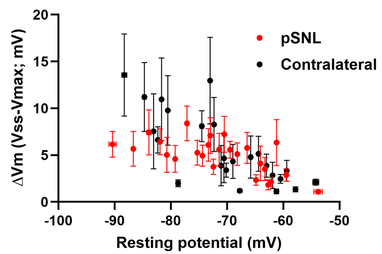
- *More action potentials*
- *Higher excitability*
- *More neuronal activity*

♦ **Membrane potential recordings**

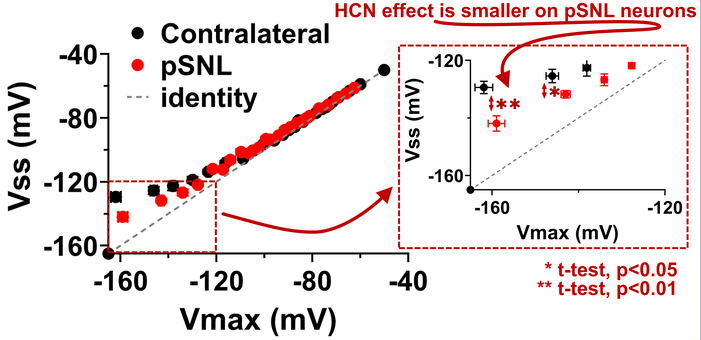






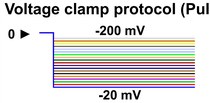


HCN effect is smaller on pSNL neurons

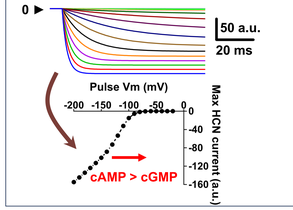


HCN is activated by more negative membrane potentials

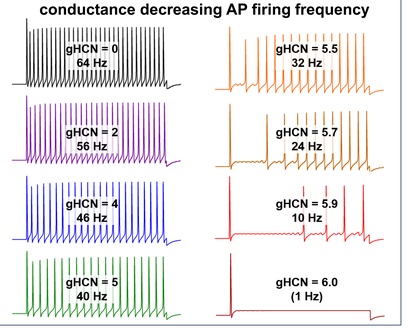
Voltage clamp protocol (Pulse)



Simulated HCN currents recordings



Simulated action potentials show HCN conductance decreasing AP firing frequency



Conclusions

- Chronic neuropathic pain is associated with decreased HCN channel function in DRG neurons, in contrast to the increase reported in the literature. This difference may reflect the pain model used and our analysis across a broad range of resting membrane potentials.
- We propose that the role of HCN channels in chronic pain be revisited, and our results may inform new therapeutic strategies for chronic pain.

References: