#P1–D–112

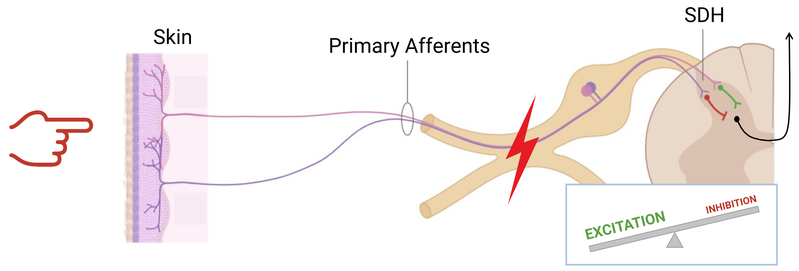
Multiscale computer model of the spinal dorsal horn reveals changes in network processing associated with chronic pain

Laura Medlock[1,2], K Sekiguchi[3], S Hong[5], S Dura-Bernal[4], WW Lytton[4], Steven A. Prescott[1,2]

[1]The Hospital for Sick Children, Canada; [2]University of Toronto, Canada; [3]Shionogi Pharmaceutical Research Center, Japan; [4]SUNY Downstate Health Sciences University, United States; [5]Okinawa Institute of Science and Technology, Japan

Background

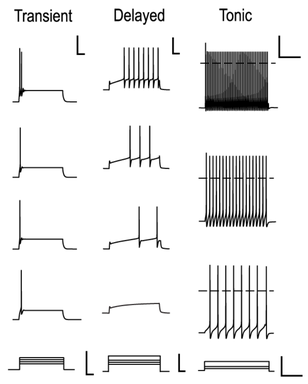
- The spinal dorsal horn (SDH) is an important site for the integration of touch and pain signals.
- Input is processed by excitatory (e) and inhibitory (i) spinal interneurons before being relayed to the brain by spinal projection (p) neurons.
- Despite recent progress, it remains unclear how the SDH processes sensory input or how that processing is disrupted under pathological conditions.



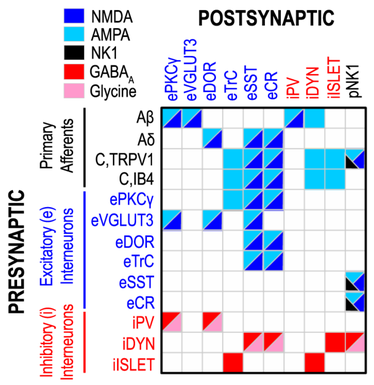
- Following nerve injury there is **disinhibition** in the SDH and this disruption of excitatory-inhibitory balance in the spinal cord leads to chronic pain.
- We sought to investigate the effects of disinhibition on the cellular- and network-level properties underlying somatosensory processing.

Methods

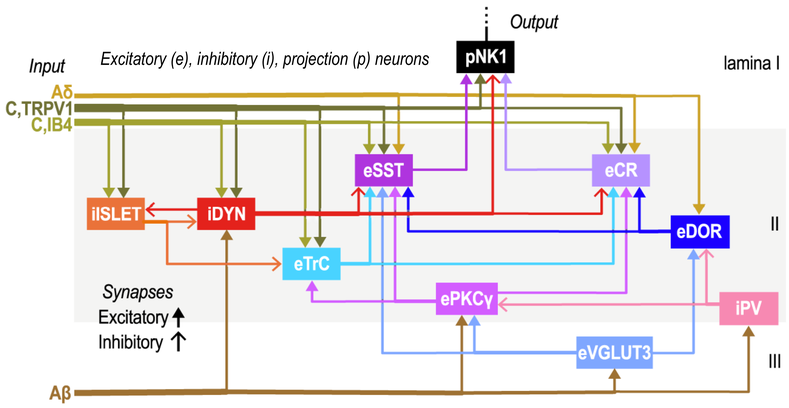
A. Spinal neuron models



B. Synapse models



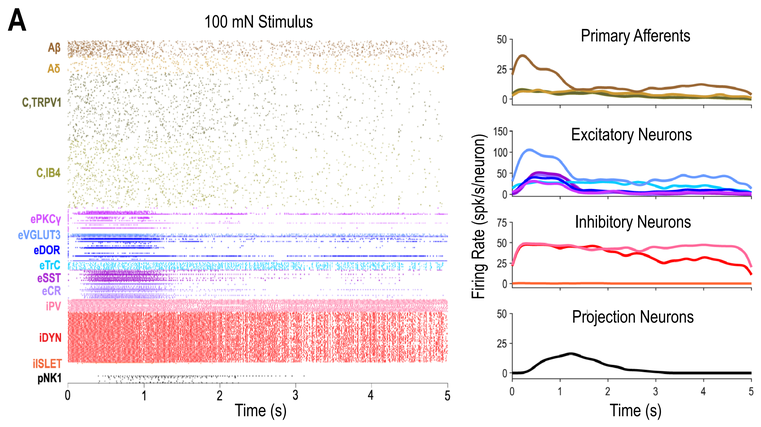
C. Synaptic connectivity



- Using NetPyNE, we developed the SDH model which includes conductance based neuron models (A) and various synapse models (B).
- We used a genetic algorithm to tune synaptic weights such that the circuit model (C) reproduced experimental projection neuron firing rates (output) in response to primary afferent firing rates (input) across a range of mechanical stimulus intensities (10–200 mN).

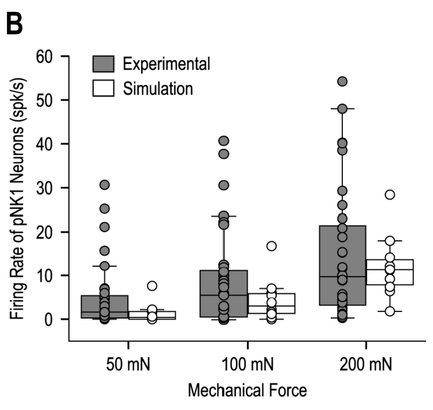
Results

Result 1: The SDH model reproduces experimental responses to mechanical stimulation across multiple intensities

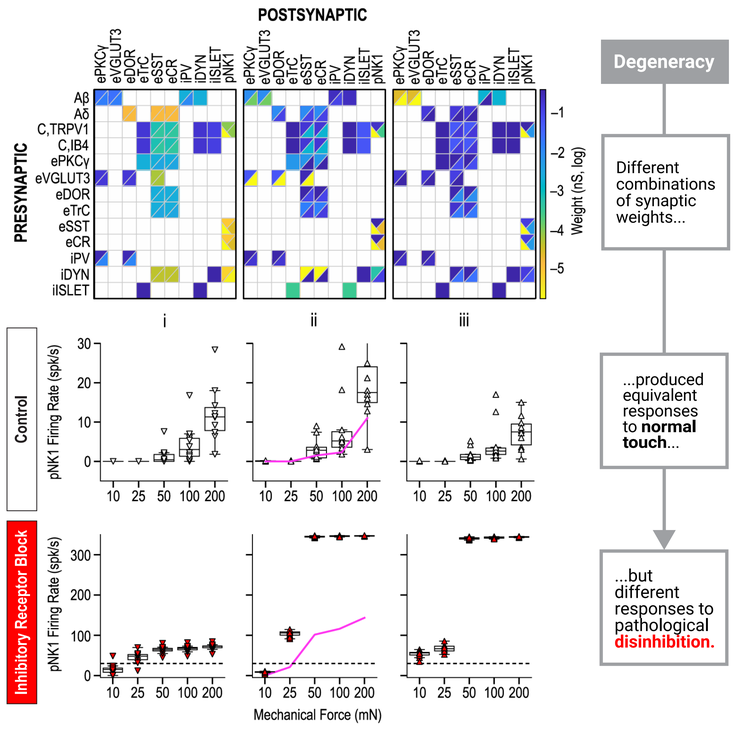


A. Sample raster plot (left) and firing rate histograms (right) of a model response to 100 mN mechanical stimulation.

B. The SDH model reproduces experimental pNK1 firing rates across various mechanical stimulus intensities (10–200 mN).



Result 2: Disparate synaptic weight combinations produce equivalent circuit function, revealing degeneracy in the SDH

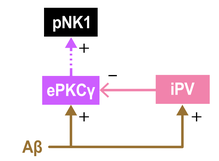


This degeneracy in spinal circuit wiring may underlie heterogeneous responses of different circuits (i.e. different individuals) to pathological insult or therapeutic intervention.

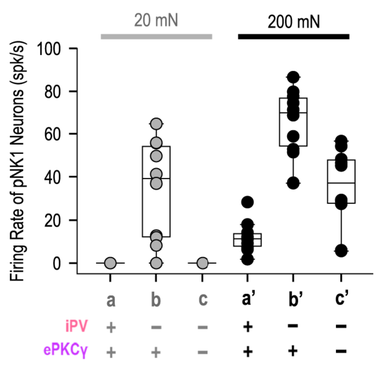
Result 3: The SDH model qualitatively reproduces experimental responses to spinal neuron ablation

A. iPV & ePKCγ Ablation:

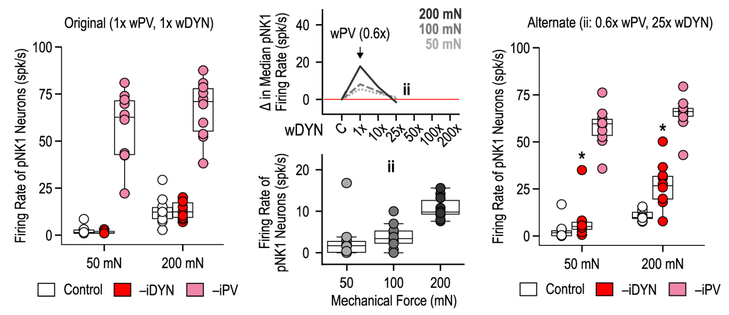
Experimental PV ablation leads to mechanical allodynia. This is mitigated by simultaneous PKCγ ablation.



In our model, iPV ablation increases pNK1 firing (a proxy for increased pain), which is mitigated by ePKCγ ablation.



B. iPV & iDYN Ablation:



- Increasing iDYN-mediated inhibition can compensate for reduced iPV-mediated inhibition.
- This trade-off between iPV- and iDYN-mediated inhibition did not disrupt the functional integrity of the circuit and therefore, further demonstrates degeneracy in the SDH.

Conclusions

- We built a data-driven network model of the SDH that reliably reproduces experimental data under normal and chronic pain conditions.
- Model optimization via a genetic algorithm revealed degeneracy in the SDH that may help explain why different individuals respond differently to pathological insult or therapeutic intervention.
- Ablation simulations highlight the importance of inhibitory and excitatory spinal interneurons for relaying low-threshold input.
- Our model provides a new tool for making testable predictions about therapeutic targets for combating the effects of disinhibition.

This work is now published in *The Journal of Neuroscience*

Freely available here!

SCAN ME

laura.medlock@mail.utoronto.ca

@laurmedlock

CIHR IRSC

This work was supported by SickKids and CIHR