Voltage-gated Sodium Channel

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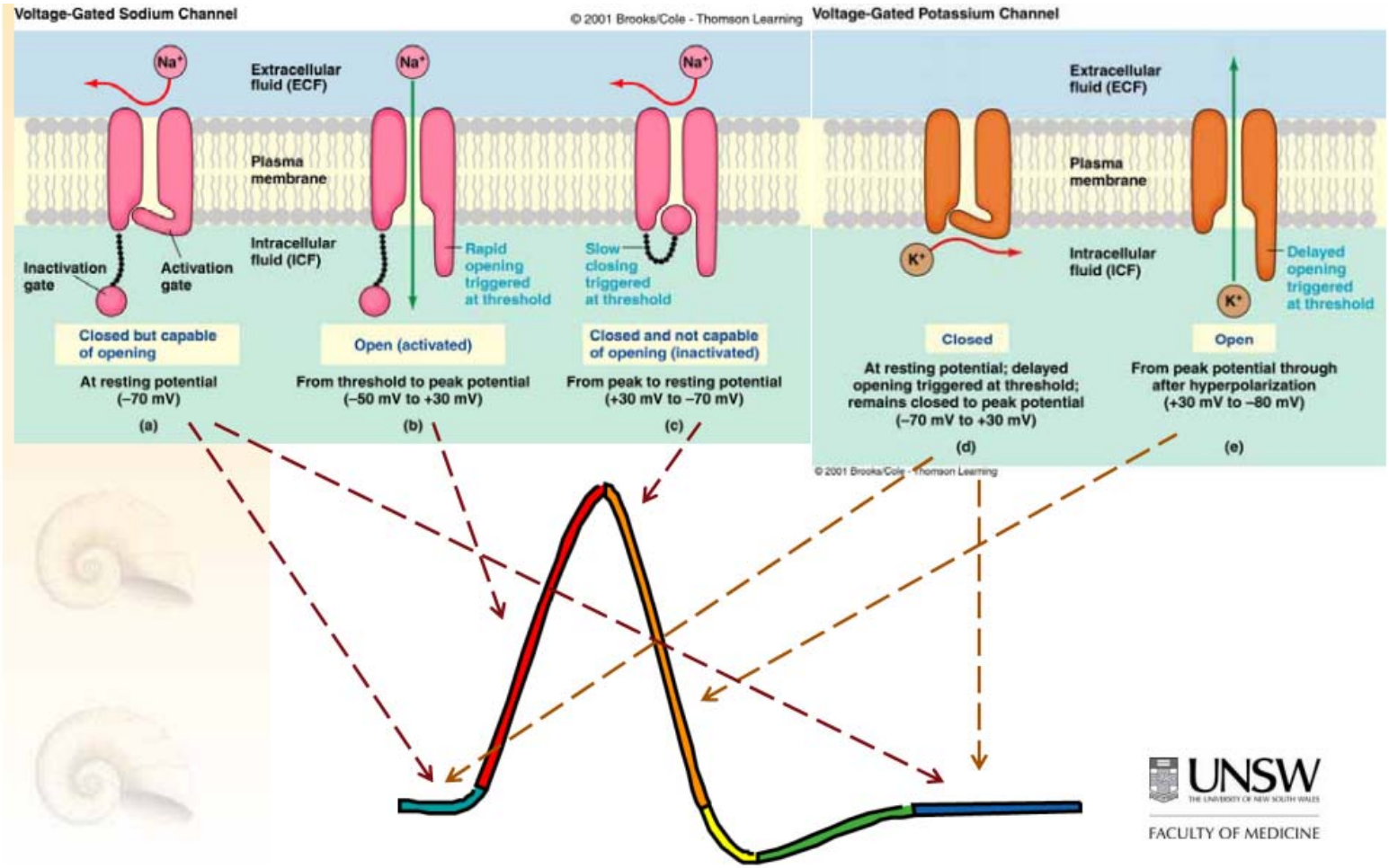
Membrane Biophysics

Introduction

1. Function
2. Structure
   - Subunit structure
   - Transmembrane core
   - Voltage-dependent activation
3. pharmacology

Function: initiating action potential



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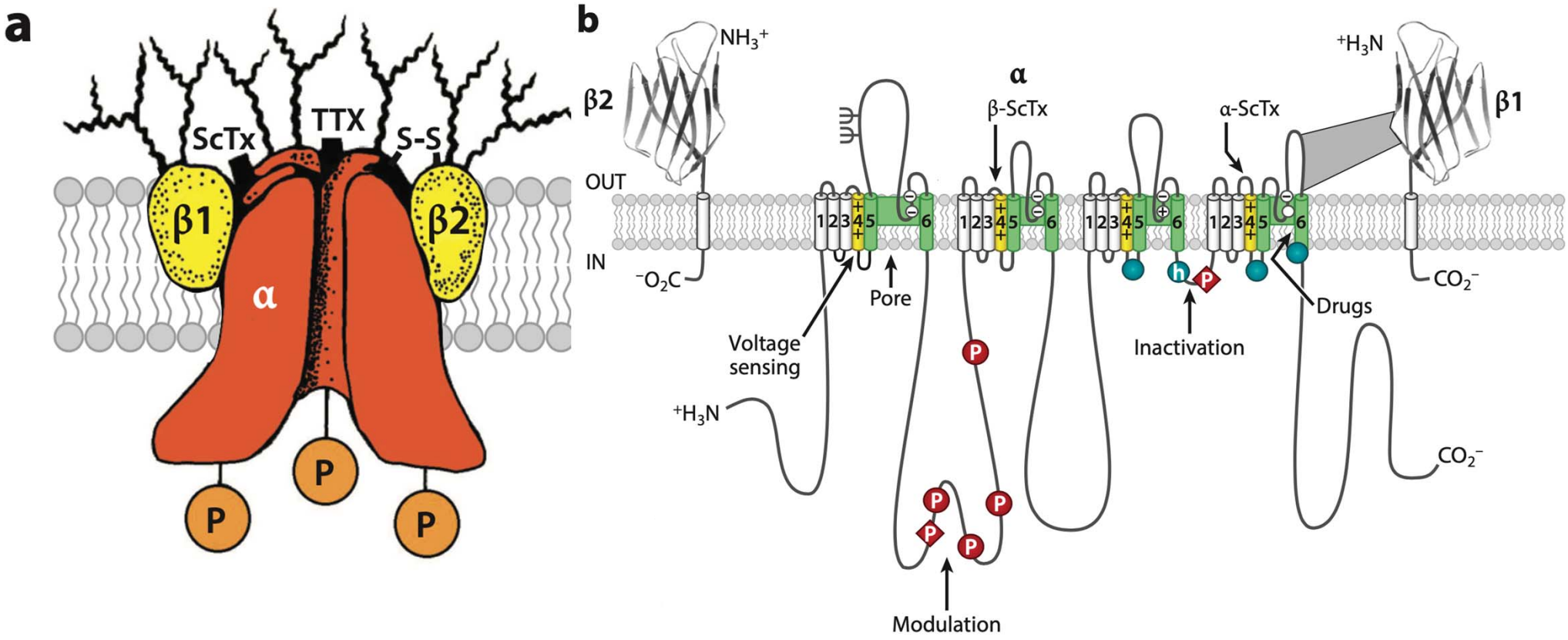
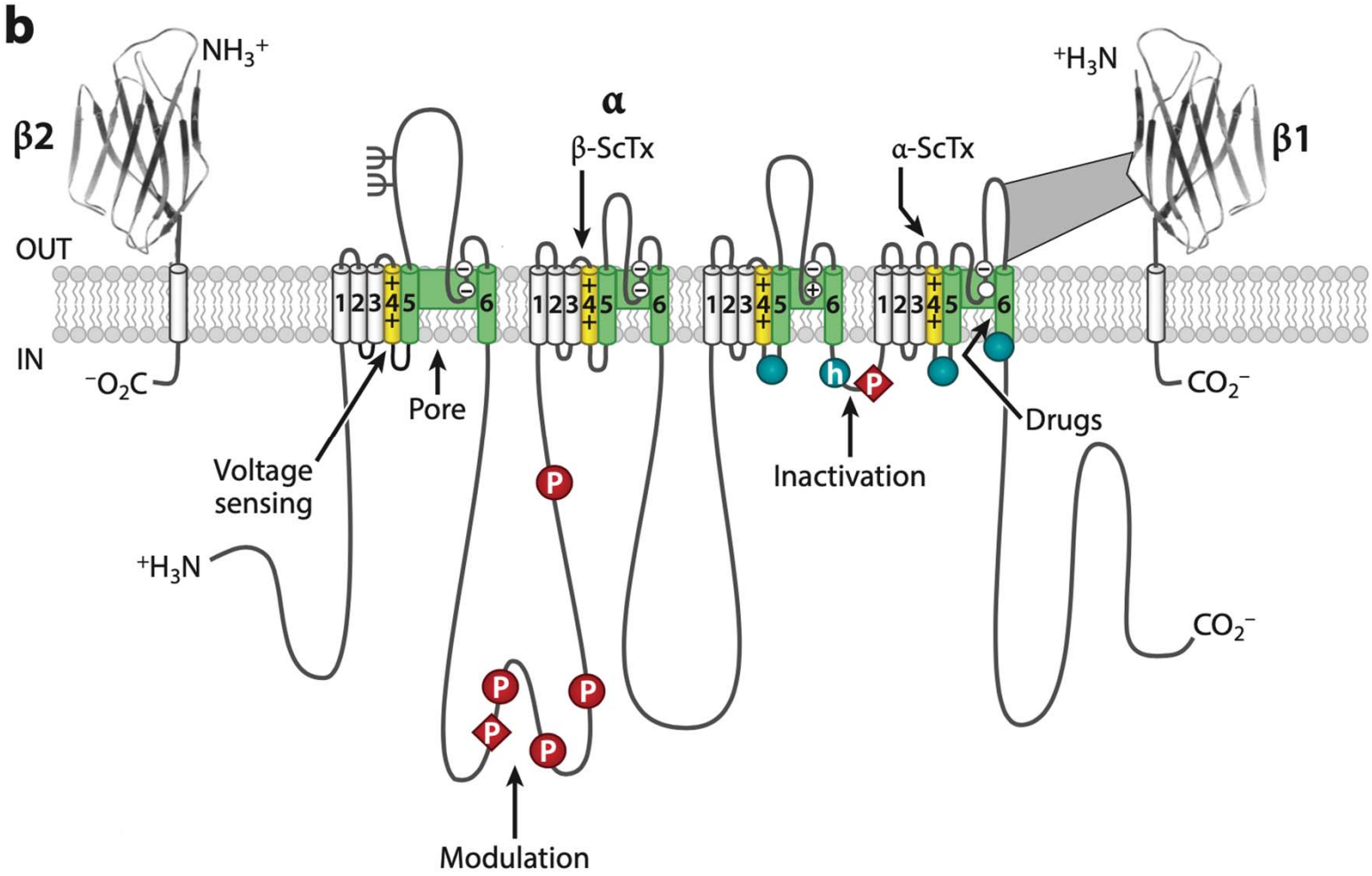
Structure: α subunit and β subunit

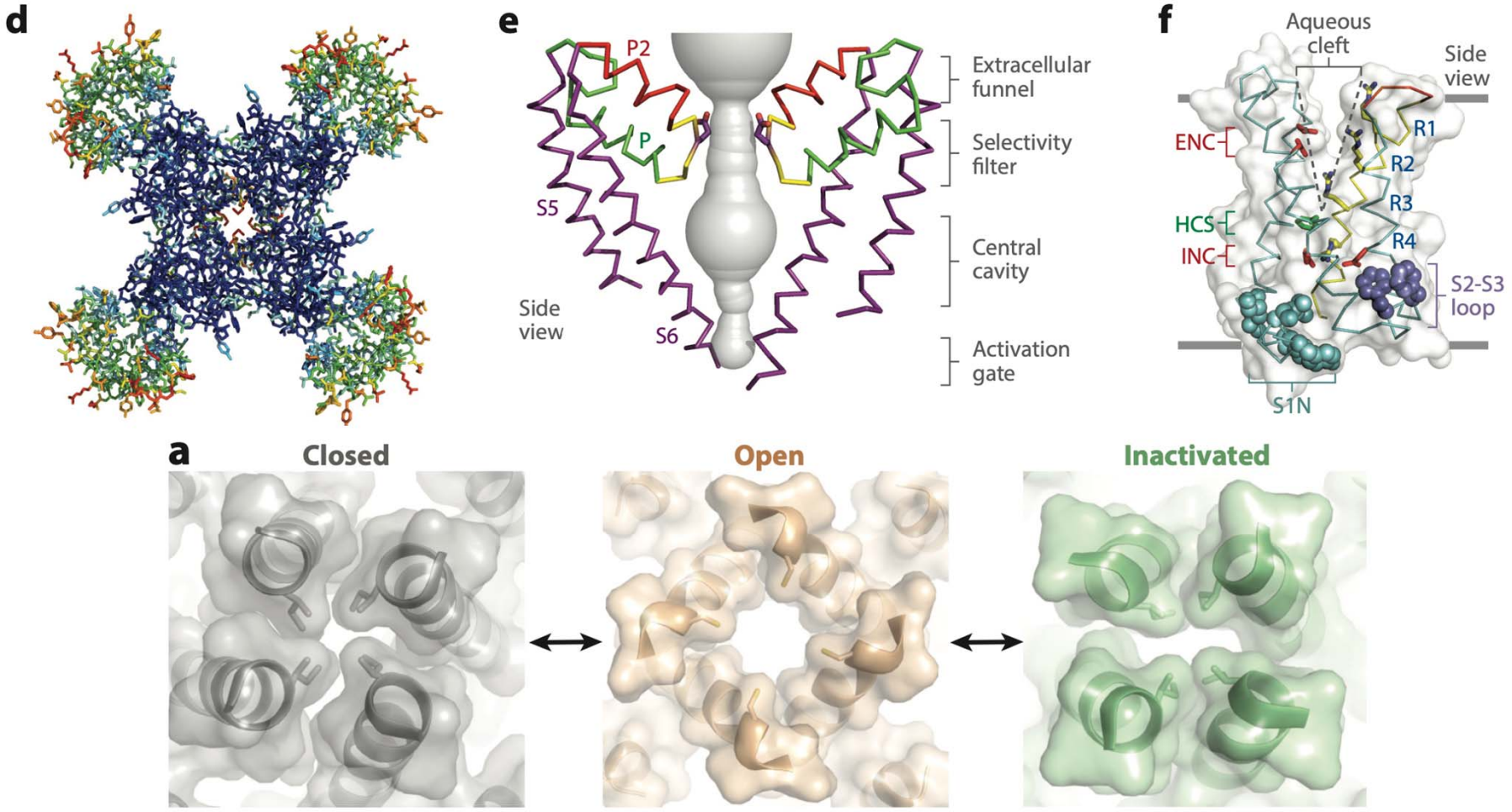


Structure: The transmembrane Core



https://www.youtube.com/watch?v=dDVh25TtihA

Structural basis for Voltage-dependent Activation



Pharmacology: State-Dependent Drug Block

Voltage-dependent Block

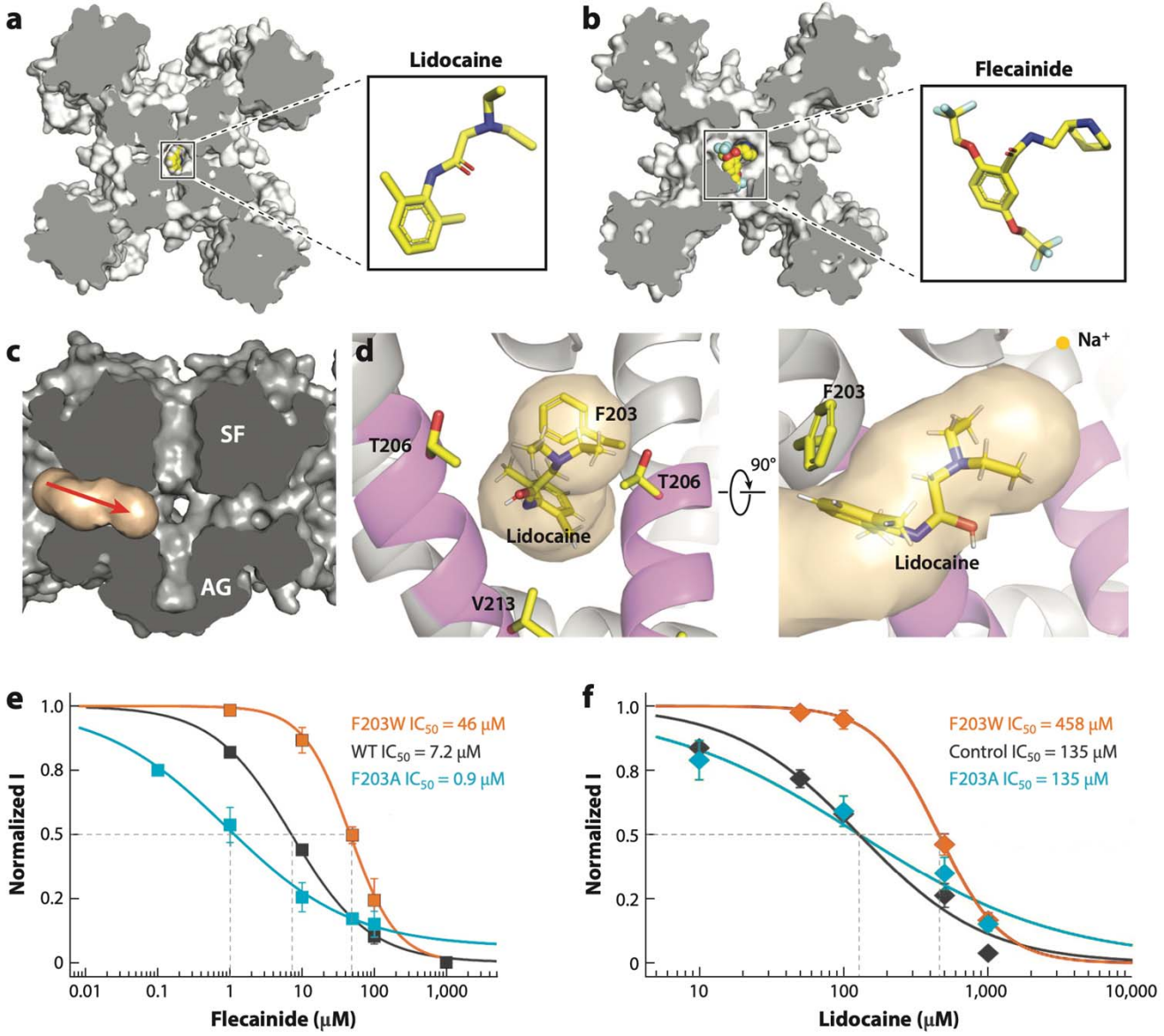
- Denpends on the resting membrane potential
- Inhibit the sodium currents in depolarized cells that are damaged and driving inappropriate AP generation.
- Bind to inactivated state of sodium channels with high affinity.

Frequency-dependent Block

- Denpends on the frequency of AP generation
- Inhibit the sodium currents in rapidly firing cells that transmit pain information and drive hyperexcitability in epilepsy.
- The receptor site is located in the pore.

Pharmacology: Drug Receptor Sites

- Amino acid residues in the S6 segments converge to form the drug receptor site.
- The fenestrations in the side of the pore control block of voltage-gate sodium channel in the resting state.



Cellular/Molecular

Cannabidiol Inhibition of Murine Primary Nociceptors: Tight Binding to Slow Inactivated States of $Na_v1.8$ Channels

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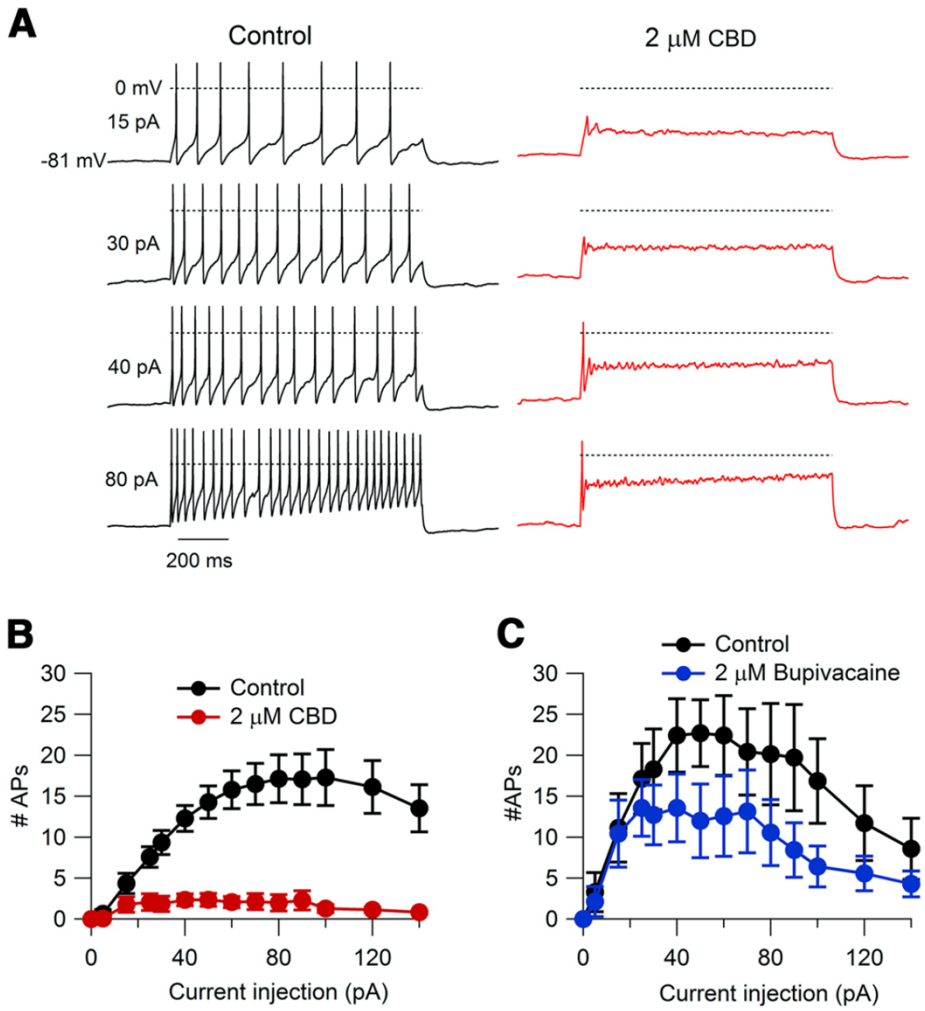
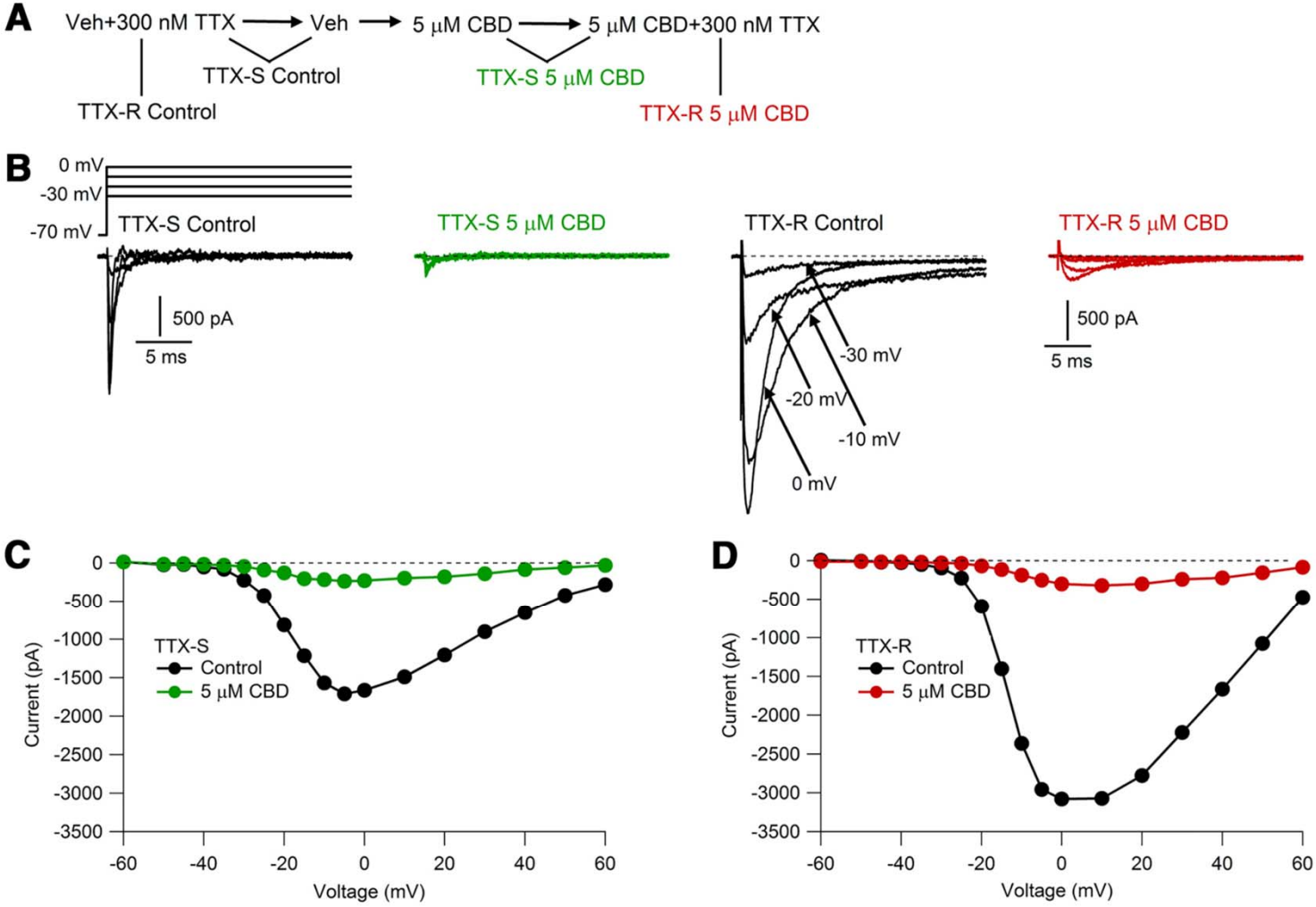
Significance Statement

- Cannabidiol (CBD) has been shown to inhibit pain in various rodent models.
- CBD interacts with TTX-resistant sodium channels in a state-dependent manner: it tightly bind to slow inactivated state of Nav1.8 channels.
- CBD can exert analgesic effects in part by directly inhibiting repetitive firing of primary nociceptors.

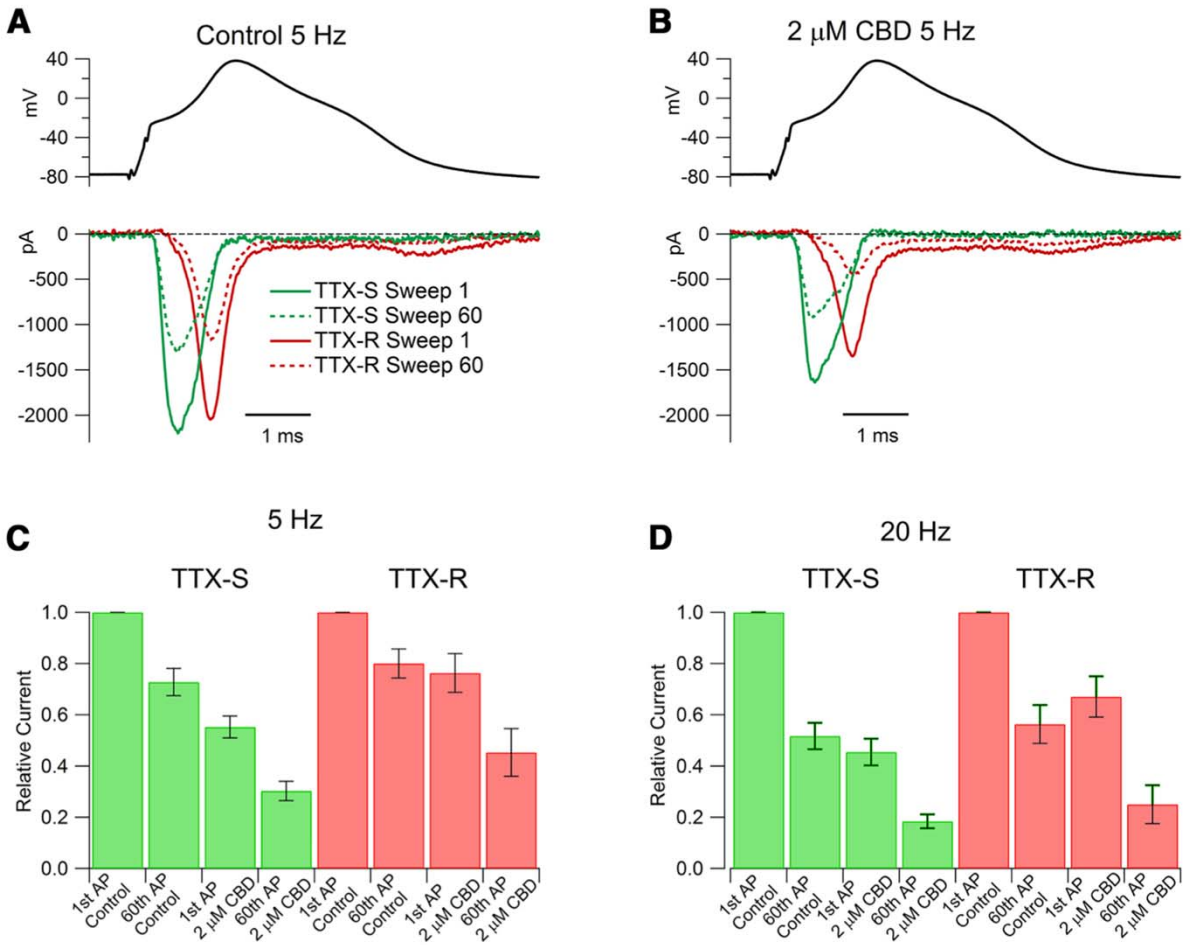
CBD reduces the excitability of nociceptors



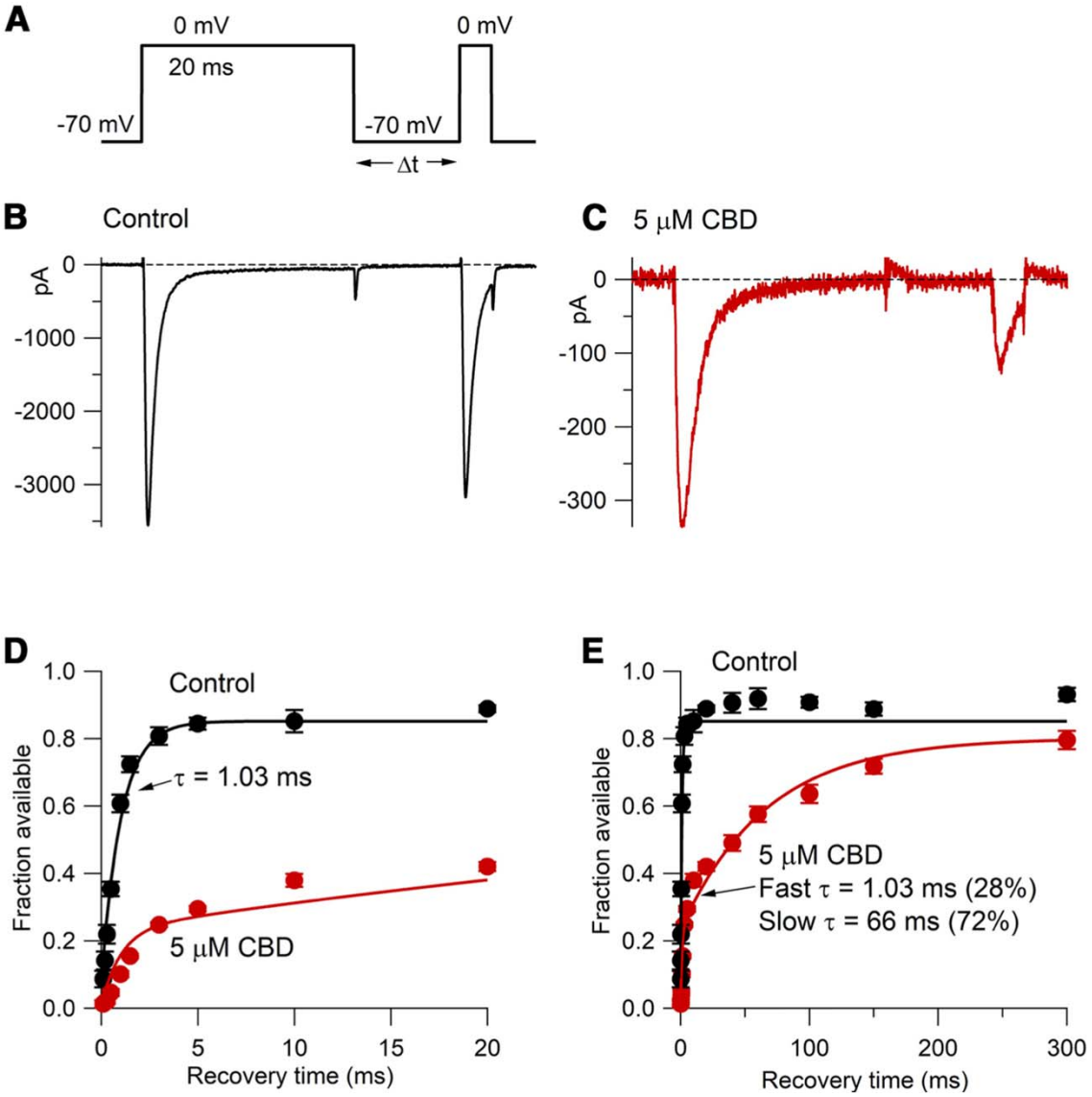
CBD inhibits TTX-S and TTX-R sodium currents



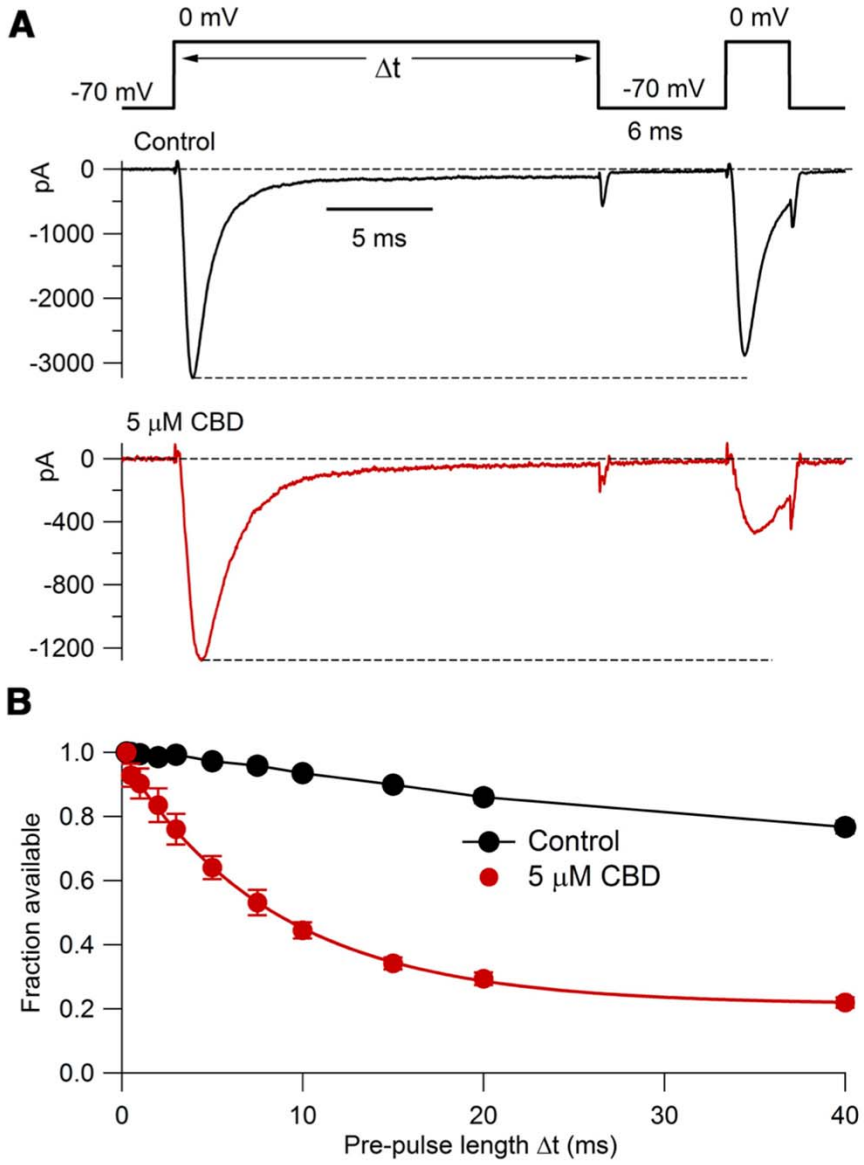
Use-dependent inhibition of action potential-evoked sodium currents



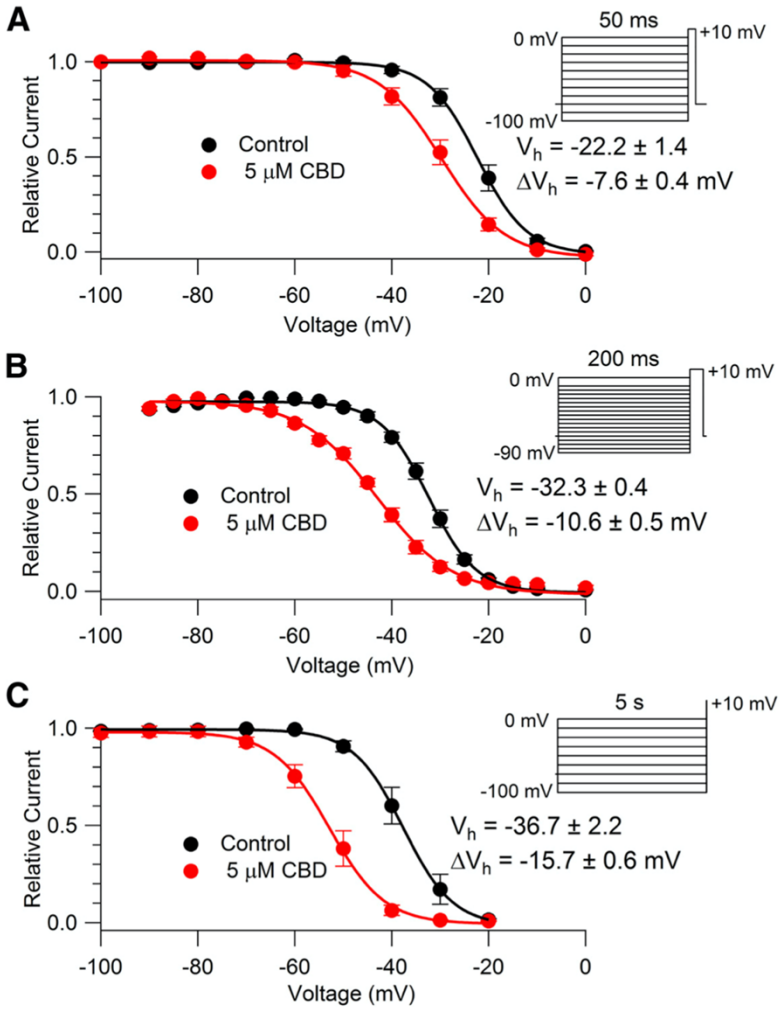
CBD slowing of recovery of availability of TTX-R channels



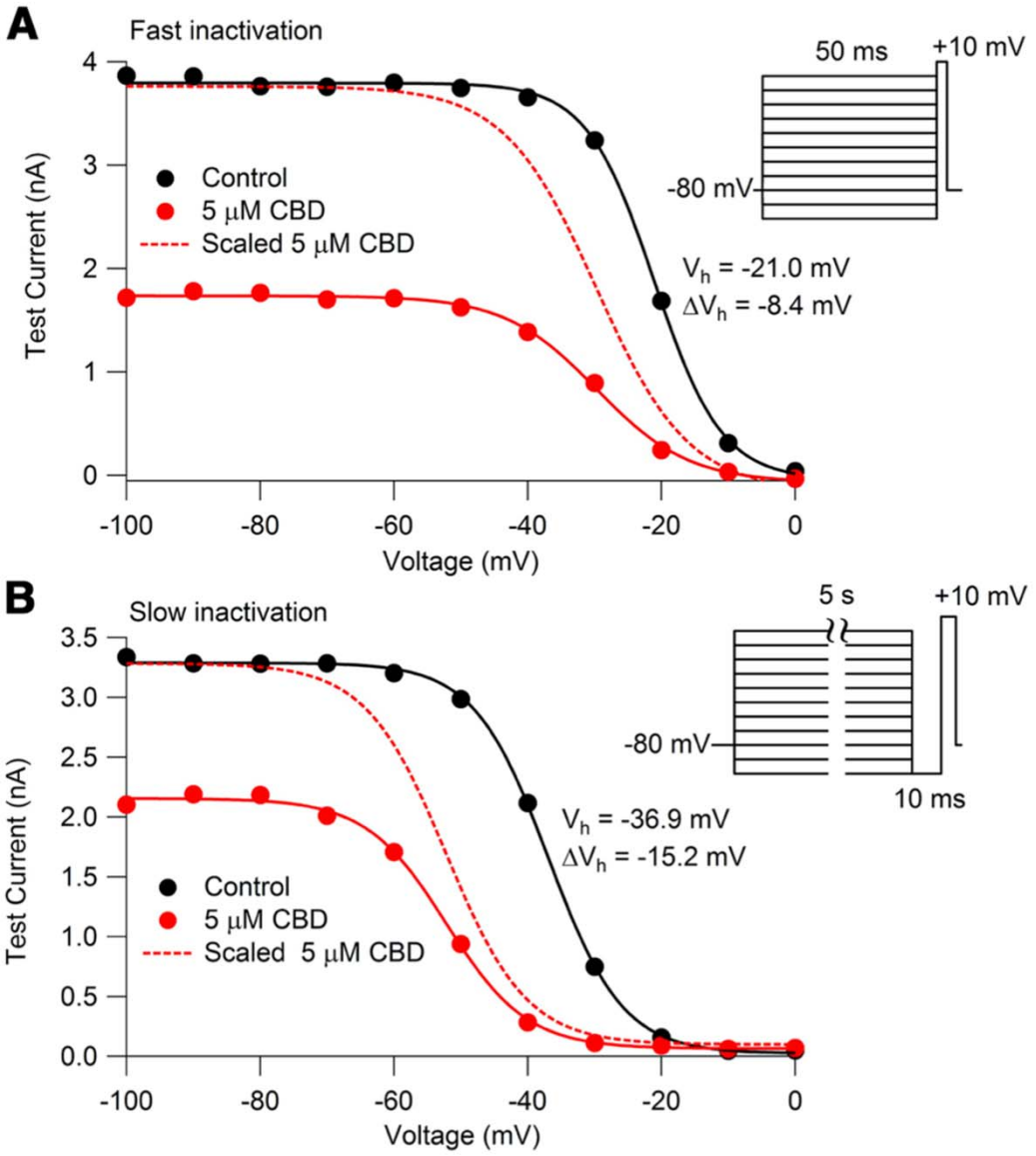
Time course of CBD-induced entry into slowly recovering states of TTX-R channels



Altered availability of TTX-R sodium channels with CBD



CBD binding to slow versus fast inactivated states



Neuron

Article

A central mechanism of analgesia in mice and humans lacking the sodium channel $Na_V1.7$

Highlights

- Loss of sodium channel $Na_V1.7$ abolishes pain without silencing peripheral nociceptors
- Synaptic input to dorsal horn is compromised by an opioid-dependent mechanism
- Impaired neurotransmission from olfactory sensory neurons is opioid independent
- Blocking opioid receptors reverses analgesia in mice and humans lacking $Na_V1.7$

Authors

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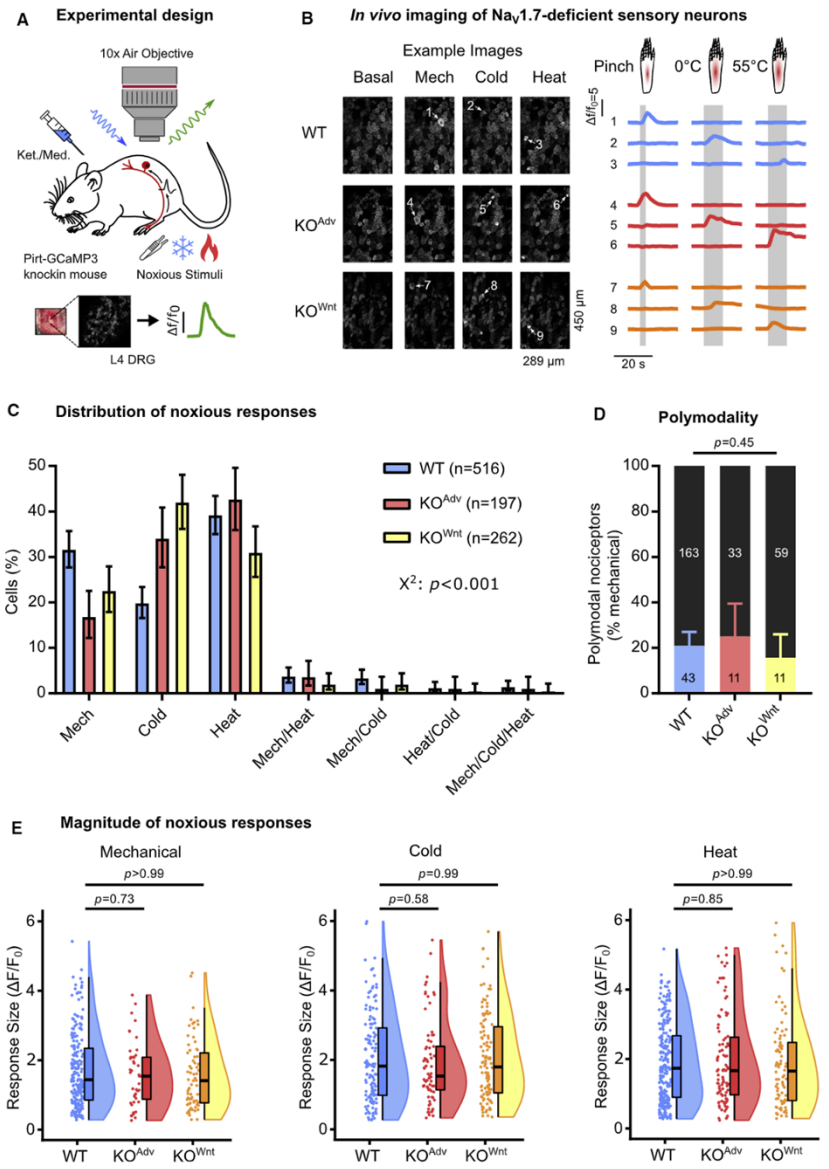
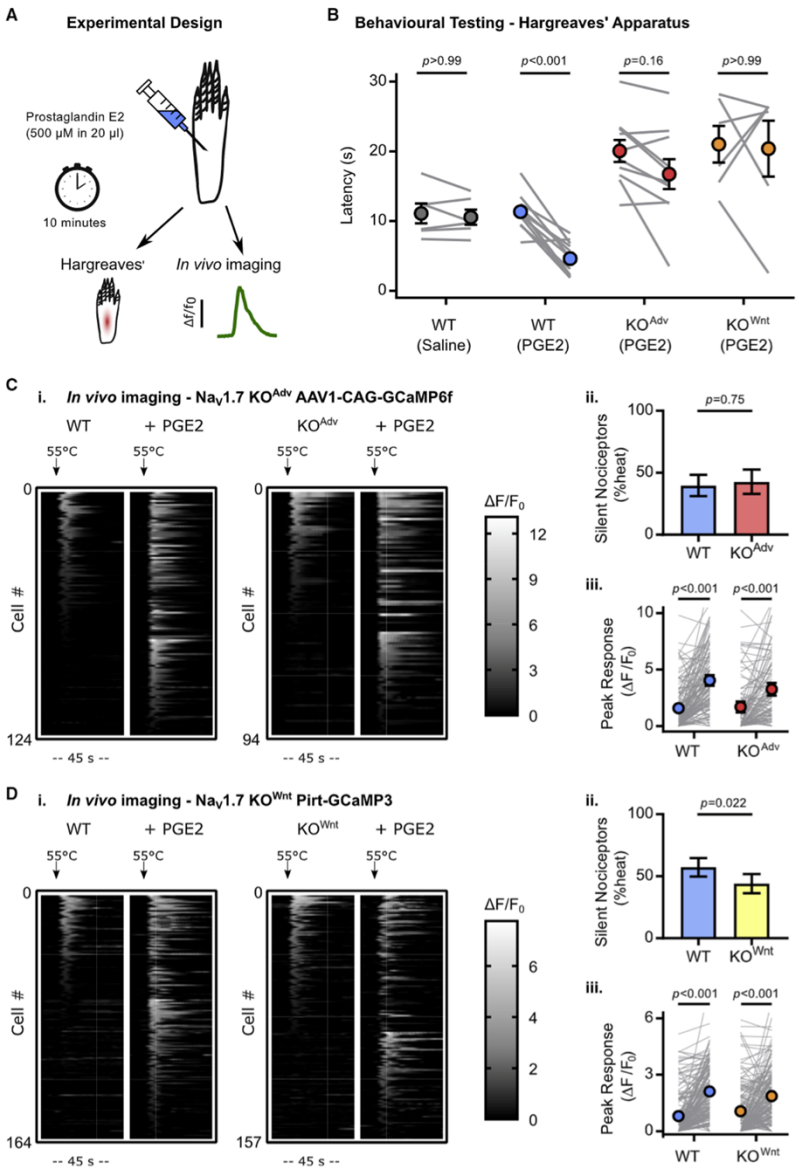
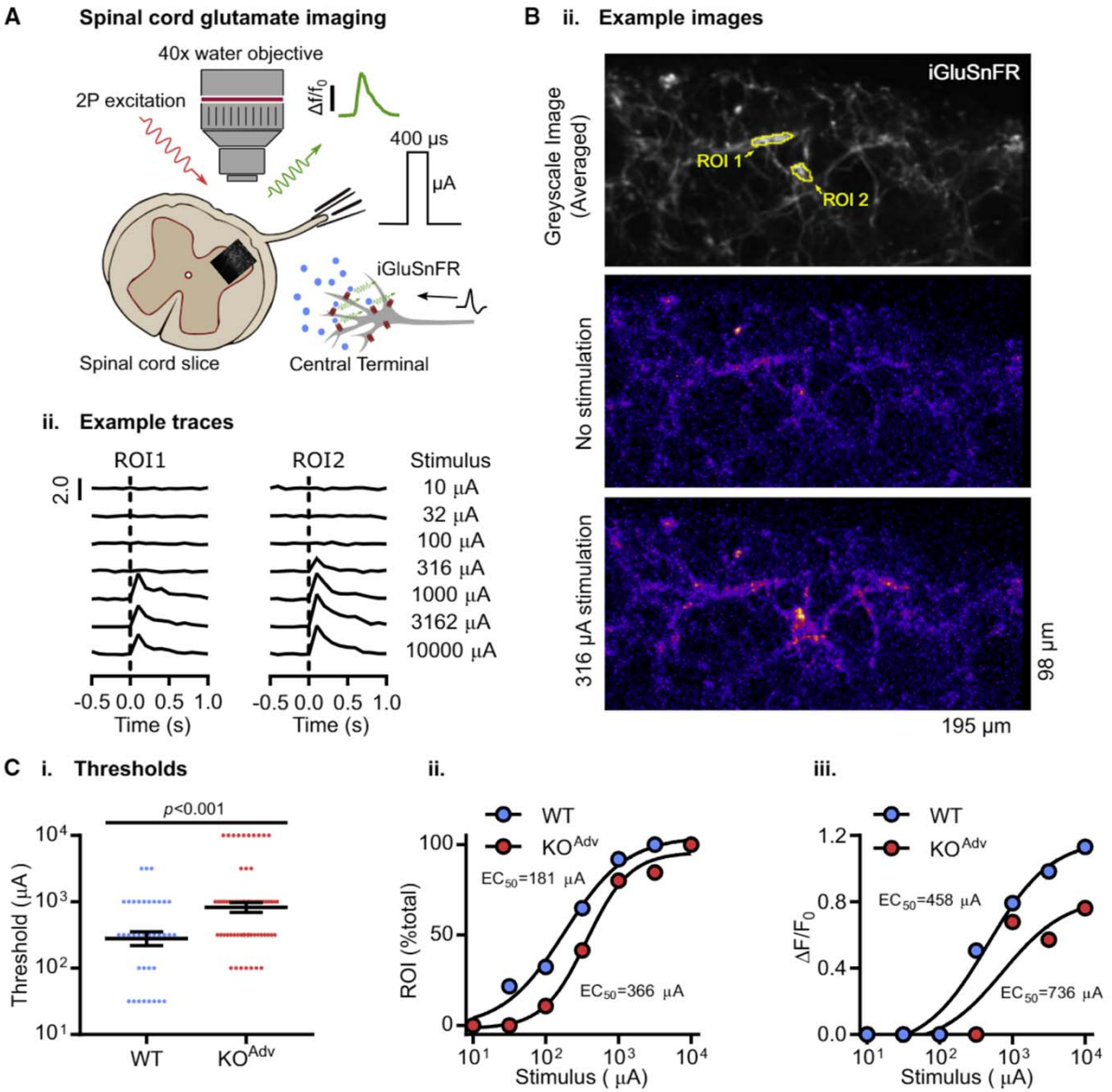
Deletion of $Na_V1.7$ in sensory neurons does not silence peripheral nociceptors



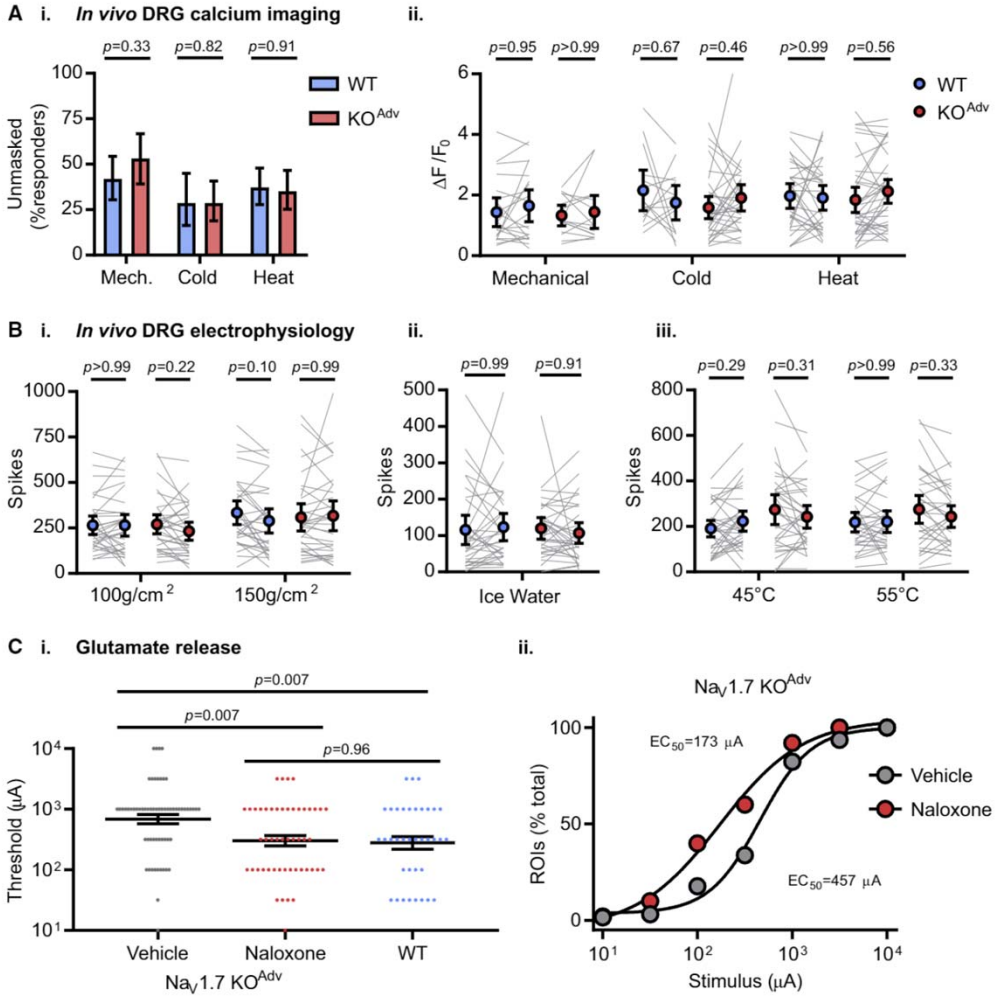
$Na_v1.7$ deletion impairs thermal hyperalgesia but doesn't abolish peripheral sensitization



Loss of $Na_v1.7$ impairs synaptic transmission from nociceptors



Opioid receptor blockade rescues impaired neurotransmission after Nav1.7 deletion but does not affect peripheral excitability



RESEARCH ARTICLE

Axonal sodium channel $Na_V1.2$ drives granule cell dendritic GABA release and rapid odor discrimination

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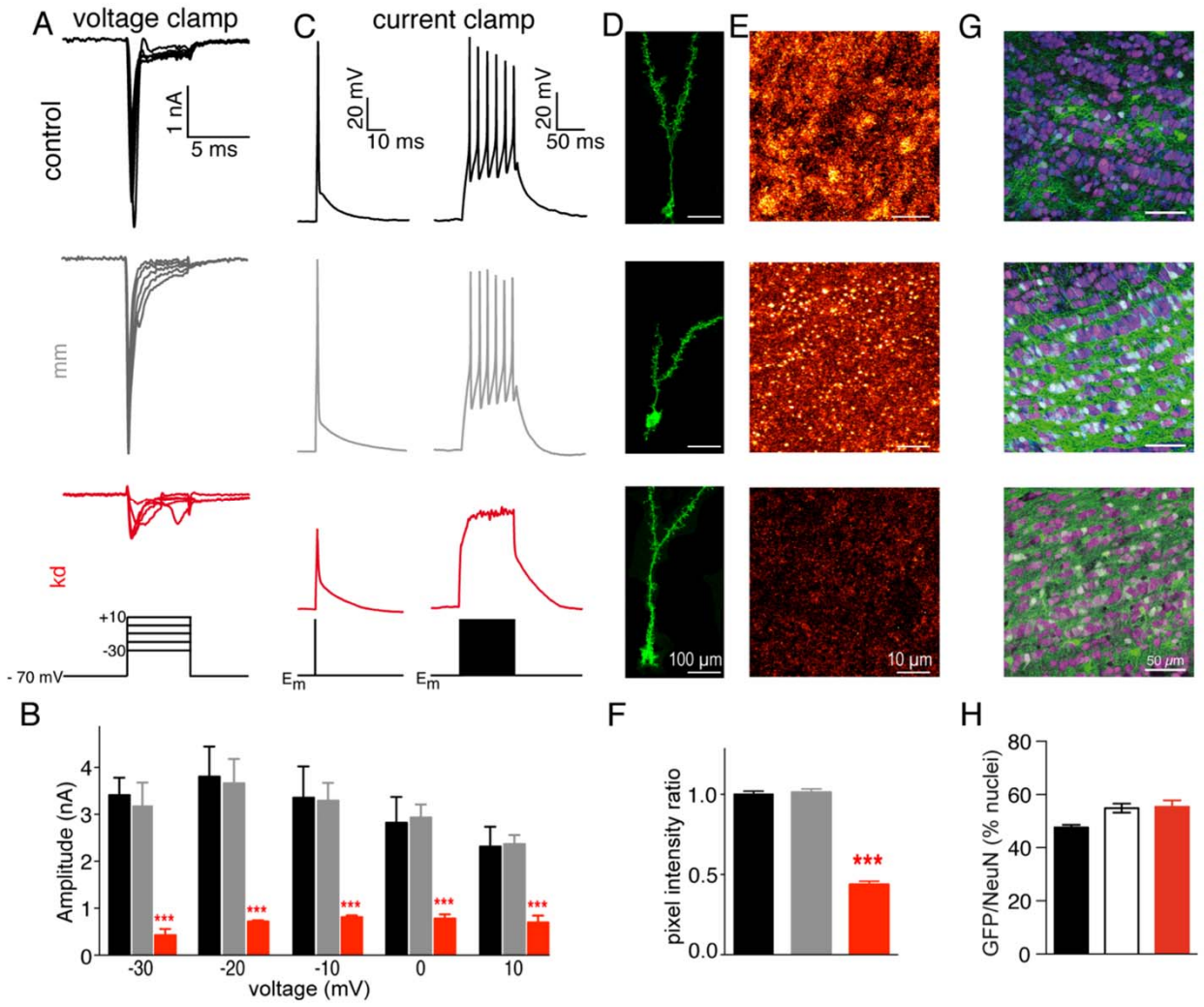
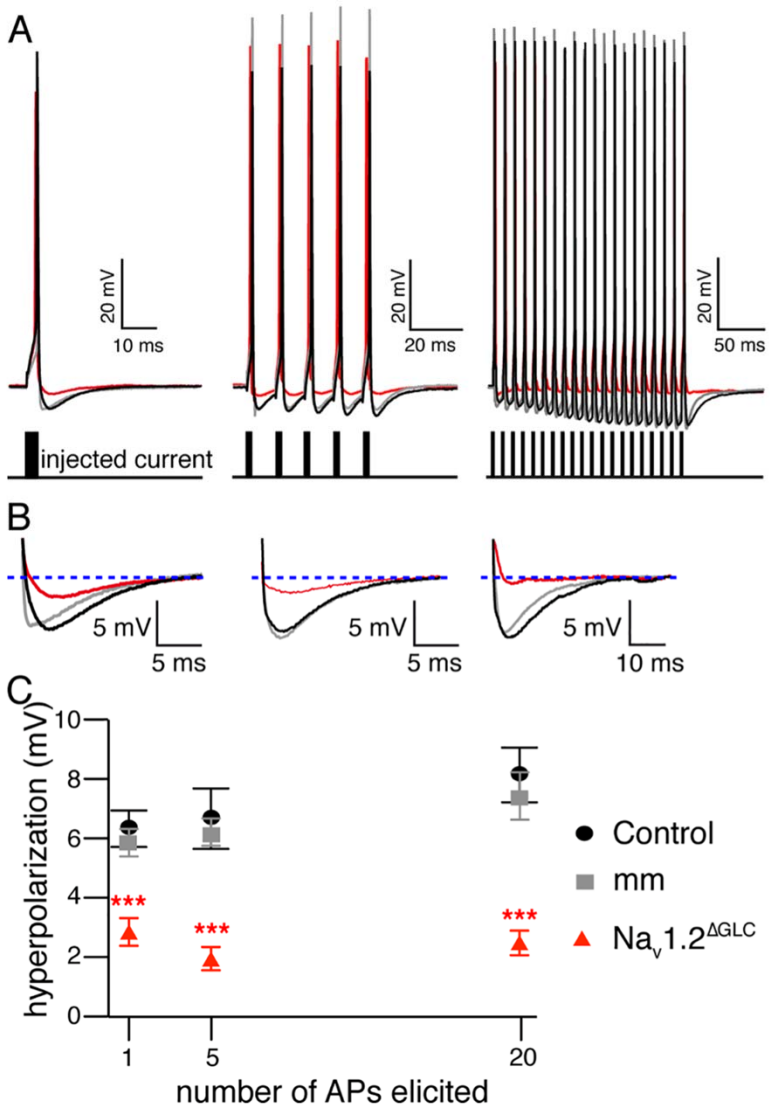
Knockdown of the Nav1.2 subunit abolishes AP firing in granule cells



Voltage-gated sodium channels are essential for GABA release from granule cells and inhibition of mitral cells



Significance Statement: Model of dendrodendritic inhibition