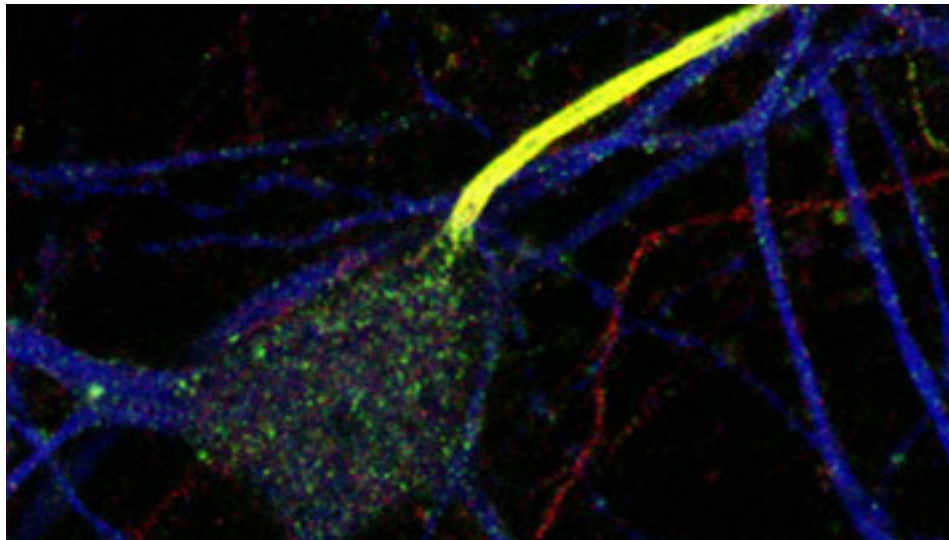
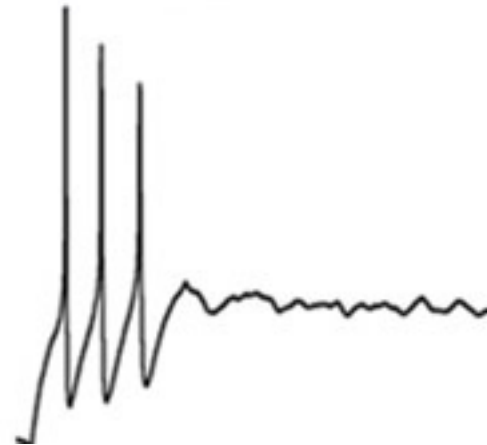




Firing Blocked by



Action potential generation is governed by the opening, inactivation, and recovery of voltage-gated sodium channels. A channel's fast inactivation particle mediates both onset of inactivation upon membrane depolarization and rapid recovery upon repolarization.

The cover-featured Journal of Physiology article from Mitch Goldfarb's lab describes a novel inactivation particle housed within an accessory channel subunit (A-type FHF protein) mediating rapid-onset, long-term inactivation of several sodium channels.

The channel-intrinsic and tethered FHF-derived particles compete for induction of inactivation, causing channels to progressively accumulate into the long-term refractory state during multiple depolarization cycles. A short peptide corresponding to the FHF particle can reproduce channel long-term inactivation and inhibit repetitive firing of cerebellar granule neurons. A-type FHFs may therefore serve to modulate action potential generation, and small molecules that mimic the FHF peptide particle may have utility in managing clinical disorders of cellular hyperexcitability.