Sodium Channels – Charles Holcombe (Membrane Biophysics, Fall 2018)

1. Catterall, W. 2014. Structure and function of voltage-gated sodium channels at atomic resolution. *Exp. Physiol*. 99.1: 35-51

Review of function and structure of voltage gated sodium channels based on crystal structure of bacterial sodium channel (NavAb) and molecular modeling using ROSETTA algorithm. The author goes through the functional states of the pore (voltage sensing, pore opening, fast inactivation (1-2 ms), slow inactivation (100 ms), and Na conductance and selectivity). Attached supplemental move showing transitional states and verified conformational changes by measuring current in disulfide-locking studies (replaced amino acids with Cys residues that create disulfide bonds when they come in close proximity and no longer conduct current). Great video of Catterall reviewing this paper on YouTube - https://www.youtube.com/watch?v=hfXGsJCOC9A

1. Waxmann et al., 1999. Sodium channels and pain. *PNAS* 96: 7635-7639.

Pain pathways begin in dorsal root ganglion (DRG) and trigeminal neurons, and sodium channels are expressed there. It is accepted that hyperexcitability in these sensory neurons is associated with pain. The paper references papers that show there is hyperexcitability in DRG cells after injury and there are multiple sodium channels in primary sensory neurons (6 in DRG). The author shoes that Na channel gene expression is altered after injury (axotomy) in DRG neurons. Next, it is shown via patch clamp recording with TTX (channel blocker) that there are physiological changes accompany altered Na gene expression after DRG neuron inury. Finally, it is shown that neurotrophins can help mitigate hyperexcitability in Na channels in DRG neurons after axotomy.

1. Dab-Hajj et al., 2015. Nav1.9: A sodium channel linked to human pain. *Nature* 16: 511-519.

NaV1.9 plays an important part both in regulating sensory neuron excitability and in pain signaling, and is also a potential therapeutic target for pain. Physiology of NaV1.9 channels includes: TTX-resistant (presence of a serine residue in DI-SS2 pore region; whereas Nav1.6-7 are TTX sensitive), inactivation is unusually ultra-slow which results in persistence of Na current activation, and there is a large overlap between activation and inactivation (i.e., large window current). Table 1 of the paper is a functional characterization of mutations to the channel and the syndromes to which they are linked. The authors show that Nav1.9 acts as a threshold channel and increases the excitability in DRG neurons.

1. Patel, R.R. et al., 2016. Aberrant sodium channel activity can be targeted with cannabidiol. *Brain*. 139(8):2164-2181.

The authors show that epilepsy associated mutations in Nav1.6 increase peak resurgent current (and not in Nav1.1). Resurgent currents – atypical current predicted to enhance neuron excitability. Mechanistically, these currents arise from channel re-opening during the repolarization phase of the action potential due to unbinding of an open-channel blocker. Cannabidiol is shown to a inhibit these currents via a number of patch clamp studies with and without its presence in the patch clamp solution.

1. Yu and Catterall, Overview of the voltage-gated sodium channel family *Genome Biology* 2003, 4:207

Brief review paper the discusses the differences among 10 different sodium channels. The authors describe the structure and subunits and how those were determined thus far (NMR and crystallography). The evolutionary history and sodium channel genes (Nav1.1-9 and Nax) are discussed and a phylogenetic tree for rats and analogous human chromosomes is presented. Finally, the molecular function with regard to pore blocking neurotoxins, voltage dependence activation, and inactivation is discussed and compared with NaChBac (bacterial sodium channel with a single domain of 6 α helixes). This channel is almost identical and only lacks the voltage gate, thus inactivating on the order of 100 ms versus 1-2 ms. This is followed by a brief discussion of channelopathies that could be interesting to investigate.

1. Ahern, C. et al. The hitchhiker’s guide to the voltage-gated sodium channel galaxy *J. Gen. Physiol*. 147:1–24, 2015

The best review paper I found thus far. The authors discuss in detail the gating mechanisms (voltage, pore, fast inactivation) and also selectivity and permeation. Pharmacology is discussed in depth with reference to what toxins target sodium channels and how they influence selection and permeation. There are really nice figures throughout paper to supplement the discussed findings.

1. Frenz CT, et al.NaV1.5 sodium channel window currents contribute to spontaneous firing in olfactory sensory neurons. *J Neurophysiol* 112: 1091–1104, 2014

High level, difficult to read paper. The authors study sodium channels in olfactory sensory neurons (OSN) and the involvement of three voltage gated sodium channels (Nav1.5, 1.7 and likely 1.3) in spontaneous firing the OSN. They describe in detail a number of patch clamp experiments with neurotoxins (which can suppress spontaneous firing in OSNs). The conclude the three subtypes have different primary roles and believe the Nav1.5 contributes to the generator potential underlying the spontaneous firing.

1. Chongyang Han, Jianying Huang and Stephen G. Waxman Sodium channel Nav1.8: Emerging links to human disease *Neurology* 2016;86;473-483

Nav1.8 is prominently expressed in primary sensory neurons including DRG. This paper is a review of studies showing Nav1.8 has a more significant impact on neuronal firing than previously thought. Discussions of these impacts include the human conditions of painful neuropathy, multiple sclerosis, perturbed Purkinje neuron firing, and cardiac disorders. The discussion then shifts to therapeutic targets for Nav1.8 and pharmacogenomics.

1. Sula, A. et al. The complete structure of an activated open sodium channel. *Nat. Commun*. 8, 14205 doi: 10.1038/ncomms14205 (2017)

In depth analysis of a crystal structure of a NavMs (from Magnetococcus marinus) which has similarities to human Nav1.1. The crystal structure has an activated voltage sensor domain conformation, three sodium ions present in its open selectivity filter, and an open intracellular pore gate formed from the S6 transmembrane helices leading into a regulatory C-terminal domain. The structure is then compared with NavAb, TPC1 (related two pore channel), and others.

1. David I. Kaplan, Lori L. Isom and Steven Petrou Role of Sodium Channels in Epilepsy *Cold Spring Harb Perspect Med* published online May 3, 2016

A fairly easy to read paper that reviews the structure, subtypes and role of sodium channels in the nervous system. It’s stated that voltage gated sodium channels play a central role in epilepsy and there are over 700 known mutations among genes that encode these channels. The authors then discuss a number of the sodium channel gene mutations in detail and the importance they play in action potential generation and propagation. Experimental methods and models have been used to better understand the functional changes from these mutations and how voltage gated sodium channels contribute to neuronal excitability.