



Published in final edited form as:

Trends Pharmacol Sci. 2019 October ; 40(10): 718–720. doi:10.1016/j.tips.2019.08.009.

The Sodium Channel Voltage Sensor Slides to Rest

Vladimir Yarov-Yarovoy¹, Paul DeCaen²

¹Department of Physiology and Membrane Biology, University of California at Davis, Davis, CA, USA.

²Department of Pharmacology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.

Abstract

Voltage-gated sodium channels (Na_vs) initiate the action potential waveforms in excitable cells. The molecular mechanisms controlling this process have been actively debated. New prokaryotic Na_v structures by Wisedchaisri *et al.* have completed our understanding of the molecular conformations required for cellular electrical signaling, and provide key templates for research to examine eukaryotic Na_vs.

Keywords

sodium channel; voltage-gated ion channel; voltage-dependent channel gating; membrane protein; resting state; gating charge

Hodgkin, Huxley, and Katz, 67 years ago, measured the current–voltage relationship in the membrane of the giant axon and concluded that an influx of sodium ions across the membrane was responsible for generating the ‘action potential’ – the means by which fast electrical signaling occurs in excitable cells such as neurons and myocytes [1]. Hodgkin and Huxley ultimately won the 1963 Nobel Prize in Physiology or Medicine ‘for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane’ and inspired generations of scientists to study the molecular mechanism of electrical signaling [2].

It is well-understood that transmembrane proteins called voltage gated sodium channels (Na_vs) are responsible for selectively conducting sodium ions that drive the first phase of the action potential. Na_vs open their ion-conducting pore or ‘gate’ in response to membrane depolarization. The steep voltage-dependence of sodium channel opening is preceded by outward movement of positively charged amino acids (arginines or lysines), called ‘gating charges’ found in the voltage sensor domain (VSD) (Figure 1) [2]. The VSD transitions from the resting to the activated state when the membrane potentials shift from negative to depolarized voltages. Here, the state of the VSD is physically linked to the opening of the sodium ion-conducting pore domain [3]. The molecular mechanism responsible for how the VSD changes structure in response to voltage has been extensively studied using

experimental, structural, and computational modeling approaches. Most results support a sliding helix model in which gating charges sequentially form ion pairs with anionic residues within the VSD as it transitions from the resting to the activated state 4, 5. However, a complete view of the VSD activation cycle has remained elusive. Although several crystallographic and cryo-electron microscopic (cryo-EM) Na_v structures have been captured in activated states, the resting state has escaped determination 3, 6. This is partly because the resting state is a high-energy conformation that depends on a negative membrane potential to hold the VSD in the deactivated position and the ion-conducting pore in the closed state. Because current methodologies can only capture ion channel structures at zero millivolts, the resting state has remained the missing first step.

However, recent work published by Wisedchaisri and colleagues tackles this challenge head-on. They solved the structure of a Na_v from the bacteria *Arcobacter butzleri* (Na_vAb), in the resting/closed state at 4 Å overall resolution using a clever approach [7]. The authors introduced several mutations into Na_vAb (called the KAV mutant channel) that shifted its voltage-dependence by several hundred millivolts, and trapped the VSD in the deactivated position, by creating a disulfide bond between G94C (in S3–S4) and Q150C (in S5). Although efforts to crystallize this channel were unsuccessful, the authors linked the N-terminus of Na_vAb to the C-terminal helix of maltose-binding protein and solved the channel structure using cryo-EM. The VSD of the resulting channel was stabilized in a resting state, without the need for a membrane potential [7]. Notably, the structure of the Na_vAb VSD in the resting state is reminiscent of the Rosetta-modeled resting-state VSD structure of a bacterial Na_v from *Bacillus halodurans* (NaChBac), and is validated by the electrophysiology results presented by Wisedchaisri *et al.* as well as by previous work to capture disulfide bridge interactions from functional channels in real-time [8].

Further, the work also captured the Na_vAb channel structure in an activated state using a disulfide bridge between V100C (in S4) and Q150C (in S5) [7]. Comparison of the Na_vAb channel structures in the resting (G94C–Q150C) and activated (V100C–Q150C) states revealed that S4 has a ₃₁₀ helix conformation that orients all gating charges on the same face of the helix toward S2 during the gating cycle. From the resting to the activated states, the VSD transfers three gating charges across the hydrophobic constriction site (HCS) while moving S4 ~11.5 Å in the plane of the membrane – features that are most consistent with the sliding helix model proposed more two decades ago (Figure 1) [4].

Since the discoveries of Hodgkin, Huxley, and Katz, this epic story continues – the end is really the beginning. Given that structural determination of most of the prokaryotic Na_v gating-cycle steps is now complete, new questions loom for the more complex gating mechanism of eukaryotic Na_vs [9]. Although some of this work has already begun, the findings from the homotetrameric prokaryotic Na_vs still need to be compared with heterotetrameric eukaryotic Na_vs [10]. More specifically, what are the precise conformational changes in each of the four homologous VSDs and the pore in eukaryotic Na_vs during channel opening, and during fast and slow inactivation? Ultimately, these research pursuits will bring a greater understanding of the molecular dysregulation caused by Na_v mutations, and will facilitate the rational design of novel therapeutics for the control of pain, epilepsy, arrhythmia, and other Na_v related diseases.

References

1. Hodgkin AL, et al. Measurement of current–voltage relations in the membrane of the giant axon of *Loligo*, *J. Physiol*, 116 (1952), pp. 424–448 [PubMed: 14946712]
2. Armstrong CM, Bezanilla F Charge movement associated with the opening and closing of the activation gates of the Na channels *J. Gen. Physiol*, 63 (1974), pp. 533–552 [PubMed: 4824995]
3. Sula A, et al. The complete structure of an activated open sodium channel, *Nat. Commun*, 8 (2017), Article 14205
4. Catterall WA Molecular properties of voltage-sensitive sodium channels *Annu. Rev. Biochem*, 55 (1986), pp. 953–985 [PubMed: 2427018]
5. Guy HR, Seetharamulu P Molecular model of the action potential sodium channel, *Proc. Natl. Acad. Sci. U. S. A.*, 83 (1986), pp. 508–512 [PubMed: 2417247]
6. Payandeh J, et al. The crystal structure of a voltage-gated sodium channel, *Nature*, 475 (2011), pp. 353–358 [PubMed: 21743477]
7. Wisedchaisri G, et al. Resting-state structure and gating mechanism of a voltage-gated sodium channel *Cell*, 178 (2019), pp. 993–1003 [PubMed: 31353218]
8. Yarov-Yarovoy V, et al. Structural basis for gating charge movement in the voltage sensor of a sodium channel, *Proc. Natl. Acad. Sci. U. S. A.*, 109 (2012), pp. E93–E102 [PubMed: 22160714]
9. Chanda B, Bezanilla F Tracking voltage-dependent conformational changes in skeletal muscle sodium channel during activation, *J. Gen. Physiol*, 120 (2002), pp. 629–645 [PubMed: 12407076]
10. Shen H, et al. Structure of a eukaryotic voltage-gated sodium channel at near-atomic resolution *Science*, 355 (2017)

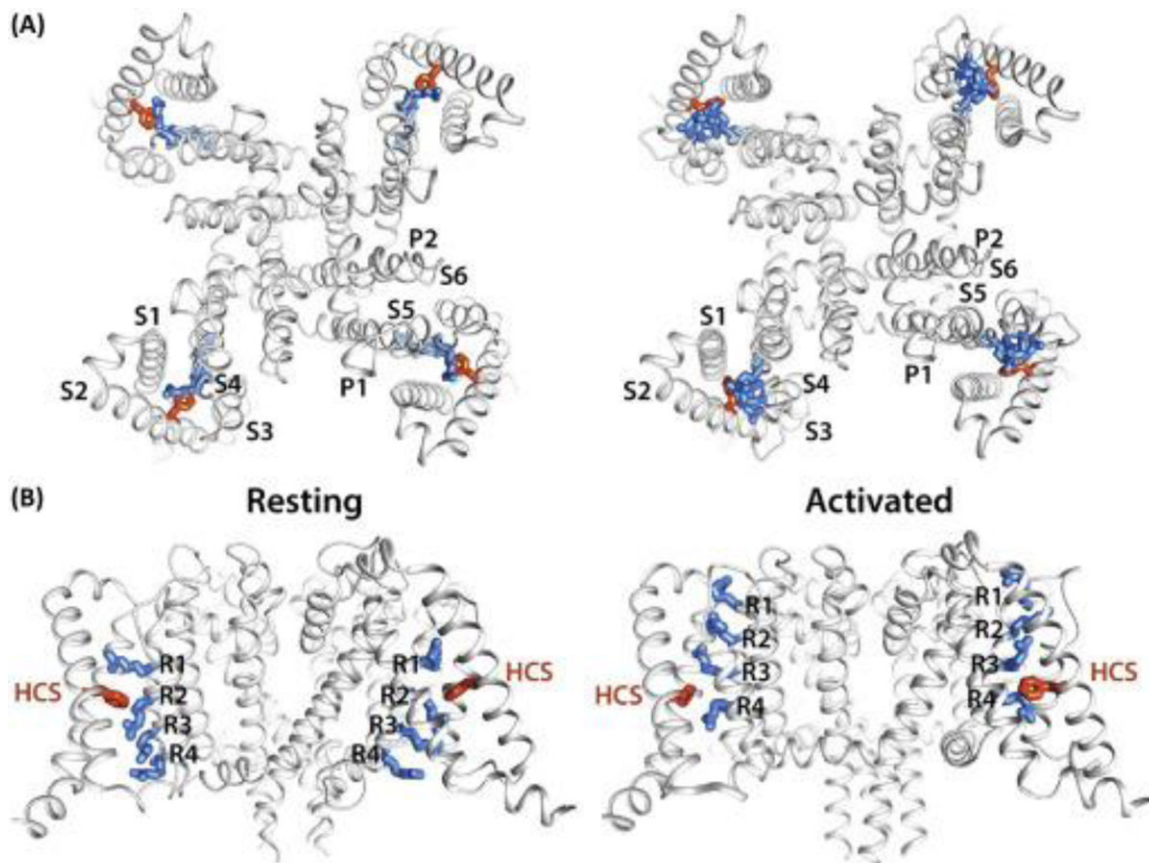


Figure 1. Comparison of Bacterial Na_vAb Channel Structures in the Resting and Activated States.

(A) Extracellular view of the resting and activated states. Bacterial voltage-gated sodium channels (Na_vs) consist of four identical subunits, each containing six transmembrane segments (S1 through S6). The voltage-sensing domain (VSD) is formed by S1–S4, where S4 contains the four arginines that carry the gating charges (shown as blue sticks). The hydrophobic constriction site (HCS) residue F56 (in S2) is shown in stick representation and is colored in orange. The pore domain (PD) is formed by S5 and S6, and the membrane-reentrant P1 and P2 helices containing loop that forms the selectivity filter. (B) Transmembrane view of the resting and activated states. The gating charge-carrying arginines (R1–R4) in transmembrane segment S4 and HCS residue F56 are shown in stick representation and are colored blue and orange, respectively. Structures were rendered using the CHIMERA program at the University of California San Francisco (www.cgl.ucsf.edu/chimera/).