Voltage-Gated Sodium Channel

1. Catterall WA, Lenaeus MJ, Gamal El-Din TM. Structure and Pharmacology of Voltage-Gated Sodium and Calcium Channels. Annu Rev Pharmacol Toxicol. 2020 Jan 6;60:133-154. doi: 10.1146/annurev-pharmtox-010818-021757. Epub 2019 Sep 19. PMID: 31537174.

Catterall et al.’s paper briefly introduces the functions and structures of voltage-gated sodium and calcium channels, and also reviews the molecular basis for their complex pharmacology. Willliam Albert Catterall is a well-known pharmacologist and neurobiologist who first discovered the voltage-gated sodium and calcium ion channels. This review will serve as the lead article for my topic, as it contains multiple significant discoveries and breakthroughs in the field of the structure of voltage-gated sodium channels in recent decades. It can better help us understand the following research articles.

1. Catterall WA, Wisedchaisri G, Zheng N. The conformational cycle of a prototypical voltage-gated sodium channel. Nat Chem Biol. 2020 Dec;16(12):1314-1320. doi: 10.1038/s41589-020-0644-4. Epub 2020 Nov 16. PMID: 33199904; PMCID: PMC7678813.

This review, also from Willliam Albert Catterall, serves as supplementary material to the first review as it can help us learn the structure of voltage-gated sodium channels in more detail. The review thoroughly describes the dynamic conformational changes of voltage-gated sodium channels from resting state to activation to inactivation. The videos posted at the end of the review show this dynamic change visually and It is well worth watching.

1. MacDonald DI, Sikandar S, Weiss J, Pyrski M, Luiz AP, Millet Q, Emery EC, Mancini F, Iannetti GD, Alles SRA, Arcangeletti M, Zhao J, Cox JJ, Brownstone RM, Zufall F, Wood JN. A central mechanism of analgesia in mice and humans lacking the sodium channel NaV1.7. Neuron. 2021 May 5;109(9):1497-1512.e6. doi: 10.1016/j.neuron.2021.03.012. Epub 2021 Apr 5. PMID: 33823138; PMCID: PMC8110947.

MacDonald and their team are looking for the roles of sodium channels in nociceptive sensitization, and this paper focuses on the voltage-gated sodium channel Nav1.7. They found out that Nav1.7 knockout mice still have regular nociceptor activity, even though they are pain insensitive. Thus, the correlation or causation between pain insensitivity and the voltage-gated sodium channels in Nav1.7-null animals was further revealed in this paper.

1. Zhang HB, Bean BP. Cannabidiol Inhibition of Murine Primary Nociceptors: Tight Binding to Slow Inactivated States of Nav1.8 Channels. J Neurosci. 2021 Jul 28;41(30):6371-6387. doi: 10.1523/JNEUROSCI.3216-20.2021. Epub 2021 Jun 15. PMID: 34131037; PMCID: PMC8318087.

Zhang et al.’s paper takes an in-depth look at the blocking steps of the voltage-gated sodium channel Nav1.8 in the primary pain-sensing neurons by the nonpsychoactive phytocannabinoid cannabidiol (CBD). This article reveals the mechanism by which CBD inhibits the repetitive action potential of primary nociceptive neurons: CBD has a greater affinity for sodium channels in the slow inactivated states. In my view, their studies also help us better understand the experimental design of two pulse voltage-clamps and the state-dependence of ion channel blockers.

1. Nunes D, Kuner T. Axonal sodium channel NaV1.2 drives granule cell dendritic GABA release and rapid odor discrimination. PLoS Biol. 2018 Aug 20;16(8):e2003816. doi: 10.1371/journal.pbio.2003816. PMID: 30125271; PMCID: PMC6117082.

The research object of this article is the olfactory nervous system in mice, and it mainly focuses on the dendrodendritic inhibition between mitral cells and granule cells in the olfactory bulbs. They abolished Na+ current in granule cells by knockdown of the Nav1.2 subunit, and then detected a prominently reduced inhibition of synaptically connected mitral cells. It uncovers the important role of the voltage-gated sodium channel in dendrodendritic synaptic interactions.

1. Sait LG, Sula A, Ghovanloo MR, Hollingworth D, Ruben PC, Wallace BA. Cannabidiol interactions with voltage-gated sodium channels. Elife. 2020 Oct 22;9:e58593. doi: 10.7554/eLife.58593. PMID: 33089780; PMCID: PMC7641581.

Based on Catterall et al.'s review paper, this research provides us with a more detailed explanation of the atomic structural basis of the interactions between the ion channel blockers and the voltage-gated sodium channel. They discovered a novel binding site for Cannabidiol (CBD) in the voltage-gated sodium channels by high-resolution X-ray crystallography. It may provide new ideas for studying the way CBD combines with sodium channels.

1. Bouza AA, Edokobi N, Hodges SL, Pinsky AM, Offord J, Piao L, Zhao YT, Lopatin AN, Lopez-Santiago LF, Isom LL. Sodium channel β1 subunits participate in regulated intramembrane proteolysis-excitation coupling. JCI Insight. 2021 Feb 8;6(3):e141776. doi: 10.1172/jci.insight.141776. PMID: 33411695; PMCID: PMC7934843.

In class, we initially learned the two subunits of the sodium channel: α subunit and β subunit, and we mainly focused on the structure and functions of α subunit. While this research focuses on β subunit and gives us a deeper understanding of the important roles of β subunit in intracellular signal transduction and cell morphological regulation. It also provides novel insights into the mechanism of some channelopathies.

1. Wang Z, Vermij SH, Sottas V, Shestak A, Ross-Kaschitza D, Zaklyazminskaya EV, Hudmon A, Pitt GS, Rougier JS, Abriel H. Calmodulin binds to the N-terminal domain of the cardiac sodium channel Nav1.5. Channels (Austin). 2020 Dec;14(1):268-286. doi: 10.1080/19336950.2020.1805999. PMID: 32815768; PMCID: PMC7515574.

Mutations in sodium channels are known to be associated with many cardiac diseases, but the mechanisms behind them are still being explored by many researchers. This article focuses on the role of the voltage-gated sodium channel Nav1.5 N-terminal domain (NTD) in cardiac arrhythmias and explores the dominant-negative effect from several mutant types of Nav1.5 NTD on wild-type channel function. They also discovered first evidence for the interaction of calmodulin with the Nav1.5 NTD.

1. Qiu J, Zhang L, Hong J, Ni X, Li J, Li G, Zhang G. Magnolol inhibits sodium currents in freshly isolated mouse dorsal root ganglion neurons. Clin Exp Pharmacol Physiol. 2021 Mar;48(3):347-354. doi: 10.1111/1440-1681.13422. Epub 2020 Oct 27. PMID: 33064853.

This article investigated another drug that exhibits analgesic effects: magnolol, through a similar line of research to Zhang et al.'s article. They found that compared to TTX-sensitive sodium currents, magnolol inhibits TTX-resistant Na+ currents more strongly. Moreover, magnolol significantly delayed the recovery time of sodium channels from the inactivated state. Learning the different characteristics of variant ion channel blockers can help us better understand various mechanisms of the interaction between blockers and ion channels.

1. Sowers JR, Habibi J, Jia G, Bostick B, Manrique-Acevedo C, Lastra G, Yang Y, Chen D, Sun Z, Domeier TL, Durante W, Whaley-Connell AT, Hill MA, Jaisser F, DeMarco VG, Aroor AR. Endothelial sodium channel activation promotes cardiac stiffness and diastolic dysfunction in Western diet fed female mice. Metabolism. 2020 Aug;109:154223. doi: 10.1016/j.metabol.2020.154223. Epub 2020 Apr 7. PMID: 32275972; PMCID: PMC7676474.

Currently, obesity has become a global epidemic. This article attempts to uncover the mechanisms behind the effects of obesity on the diastolic relaxation function of heart by studying the endothelial sodium channels (EnNaC). Firstly they created s new transgenetic mouse line in which α subunit of the EnNaC was knocked out, then they discovered that the impairment of diastolic relaxation induced by high-fat diet was significantly rescued in these mice. Their finding indicates that high-fat diet can activate the sodium channel in the vasculature.

1. <https://www.sciencedirect.com/topics/neuroscience/sodium-channel>

This website provides a very comprehensive overview of sodium channels, including their atomical structure, pharmacological applications, and the molecular regulatory mechanisms involved. It not only summarizes important previous findings but also includes the latest discoveries in the field.

1. <https://www.ibiology.org/neuroscience/sodium-channels/>

This website is a source of lectures from Dr. Catterall, who is best known for his discovery of voltage-gated ion channels. His lectures provide a clear overview of voltage-gated sodium channels and are more accessible than review papers. Combining the video lectures with the previous review paper will help us to understand the complex structure of sodium channels more clearly.

1. <http://pittmedneuro.com/actionpotentials.html>

This website is a video-based tutorial that explains the fundamental knowledge about the voltage-gated sodium channels. It helps beginners to quickly understand the generation of action potentials and the role of voltage-gated ion channels during this process.

1. <https://www.rcsb.org>

The Protein Data Bank (PDB) is a database that stores three-dimensional structural data of large biological molecules which include proteins such as voltage-gated sodium channels. Searching for a particular sodium channel of our interest in the database can give us plenty of information about it, such as its 3D model, protein sequences, and gene names, etc.

1. <https://case.edu/groups/ANCL/pages/01/01_10.htm>

The website introduces, mainly in the form of animations, the structure of the voltage-gated sodium channels and the conformational changes of sodium channels in different states, as well as a basic introduction to some physiological experiments, such as voltage clamp.

1. <https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=82>

This website is designed to provide a concise overview of all pharmacological targets, including the voltage-gated sodium channels. The physiological functions, disease models of different types of sodium channels, and their inhibitors, activators, and blockers are all available on this website.

1. <https://go.drugbank.com/categories/DBCAT000615>

The DrugBank database is a comprehensive database of drugs and drug targets. Searching voltage-gated sodium channel blockers in it will give us the name, background, structure, etc. of these drugs. Applying these ion channel blockers can help us to better study the structure and function of sodium channels in more depth.

1. <https://sites.tufts.edu/tetrodotoxin/mechanism/>

This website provides a detailed description of tetrodotoxin (TTX), a well-known voltage-gated sodium channel blocker. It presents the pharmacological applications of TTX, the mechanism of TTX’s interaction with sodium channels, and the atomic structure of TTX. The study of TTX can provide a new insight for learning the structure and function of voltage-gated sodium channels.

1. <https://blog.eyewire.org/the-nervous-system-action-potential-crash-course-2/>

This website describes the generation of action potentials and the role of ion channels in this process in an easy-to-understand manner. Simplified ion channel structural graphics make it much easier to distinguish between the different types of ion channels and their different roles.

1. <https://doctorlib.info/ophthalmology/vaughan-asbury-general-ophthalmology/3.html>

This website presents the way or mechanism of interaction between sodium channels and their blockers in a witty and easy-to-understand manner. It also explains the interactions between sodium channels and other ion channels during signal propagation.