

Sodium Channels

Key References

- Akopian, A.N. et al. "A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons." *Nature* **379**, 257-262 (1996).
- Catterall, W.A. "Structure and function of voltage-gated ion channels." *Annu. Rev. Biochem.* **64**, 493-531 (1995).
- Catterall, W.A. "From ionic currents to molecular mechanisms: The structure and function of voltage-gated sodium channels." *Neuron* **26**, 13-25 (2000).
- Cummins, T.R. et al. "A novel persistent tetrodotoxin-resistant sodium current in SNS-null and wild type small primary sensory neurons." *J. Neurosci.* **19**, RC43, 1-6 (1999).
- Dib-Hajj, S.D. et al. "NaN, a novel voltage-gated Na channel, is expressed preferentially in peripheral sensory neurons and down-regulated after axotomy." *Proc. Natl. Acad. Sci. USA* **95**, 8963-8968 (1998).
- Goldin, A.L. "Resurgence of sodium channel research." *Annu. Rev. Physiol.* **63**, 871-894 (2001).
- Narahashi, T. "Mechanism of tetrodotoxin and saxitoxin action." in *Handbook of Natural Toxins* Vol. 3, Marine Toxins and Venoms. A.T. Tu, Ed., pp. 185-210, Marcell Dekker, Inc., New York (1988).
- Sangameswaran, L. et al. "A novel tetrodotoxin-sensitive, voltage-gated sodium channel expressed in rat and human dorsal root ganglia." *J. Biol. Chem.* **272**, 14805-14809 (1997).
- Schaller, K.L. et al. "A novel, abundant sodium channel expressed in neurons and glia." *J. Neurosci.* **15**, 3231-3242 (1995).
- Song, J.H., Narahashi, T. "Differential effects of the pyrethroid tetramethrin on tetrodotoxin-sensitive and tetrodotoxin-resistant single sodium channels." *Brain Res.* **712**, 258-264 (1996).
- Tate, S. et al. "Two sodium channels contribute to the TTX-R sodium current in primary sensory neurons." *Nature Neurosci.* **1**, 653-655 (1998).
- Toledo-Aral, J.J. et al. "Identification of PN1, a predominant voltage-dependent sodium channel expressed principally in peripheral neurons." *Proc. Natl. Acad. Sci. USA* **94**, 1527-1532 (1997).

Overview

Voltage-gated sodium channels are present in most excitable cell membranes and play an important role in generating action potentials. A variety of toxins and chemicals are known to either block or modulate sodium channels and have proven invaluable in investigating the physiological characteristics of these channels. Most notably, tetrodotoxin (TTX), isolated from puffer fish, is a potent and selective blocker of sodium channels. Saxitoxin (STX), a toxin isolated from dinoflagellates, was also found to have the same blocking action as TTX. The sodium channels present in brain, along with those found in peripheral nerves and skeletal muscle, are highly sensitive to TTX/STX at nanomolar concentrations, whereas those of heart are much less sensitive being blocked at concentrations in the micromolar range. TTX-resistant sodium channels have also been reported in dorsal root ganglion neurons.

Structurally, the sodium channels of brain comprise one α subunit of 260 kDa, one $\beta 1$ subunit of 36 kDa, and one $\beta 2$ subunit of 33 kDa, forming a heterotrimeric structure. The α subunit is the major constituent comprising four domains that form a channel, and each domain consists of six transmembrane segments. The TTX resistant sodium channels in the dorsal root ganglia comprise an α and $\beta 3$ subunit. The sodium channels of skeletal muscle consist of one α and one $\beta 1$ -like subunit, whereas those of the heart appear to be composed of only one α subunit.

A variety of toxins and chemicals that modulate the function of sodium channels have been discovered and many of these are now being used as chemical tools to study these ion channels. These may be

classified into several groups based on the mechanisms of modification of channel gating kinetics and on the binding sites. TTX, STX and μ -conotoxins bind to site 1 to block sodium channels. Batrachotoxin, grayanotoxins, veratridine and aconitine alter the channel activation kinetics and inhibit the sodium channel inactivation through binding to site 2. Sea anemone toxins and α -scorpion toxins (class 1) block the sodium channel inactivation by binding to site 3. Pronase, N-bromo-acetamide and chloramine-T also block the channel inactivation, but their exact binding site is unknown. Class 2 β -scorpion toxins alter the voltage dependence of channel activation, and class 3 β -scorpion toxins alter the voltage dependence of both activation and inactivation; toxins of both classes bind to site 4. Brevetoxins are similar to batrachotoxin and grayanotoxins in their alteration of activation kinetics and inhibition of inactivation, but unlike the latter group, brevetoxins bind to site 5. The pyrethroid insecticides alter the voltage dependence and kinetics of both activation and inactivation of sodium channels and appear to bind to a putative site 6.

Dorsal root ganglion neurons associated with C-fibers express sodium channels that are highly resistant to TTX and play an important role in nociceptive mechanisms. The TTX-resistant sodium channels, PN3/SNS and SNS2, comprise 1,957 and 1,765 amino acids, respectively. Recent research efforts have focused on the development of analgesic agents selective for the TTX-resistant sodium channels of dorsal root ganglion.

Finally certain drugs block sodium channels thereby causing therapeutic effects, including local anesthetics, anti-arrhythmics and

anti-epileptics. Many of these drugs exhibit use-dependent block, a characteristic crucial for their therapeutic effects as the channel block becomes more potent in arrhythmic or epileptic conditions.

Sodium Channels

	Tetrodotoxin Sensitive							Tetrodotoxin Resistant			
CURRENTLY RECOGNIZED NAME	I	II	IIA	III	μ1	PN1	VI	h1	PN3/SNS	SNS2	
RECENTLY ACCEPTED NOMENCLATURE ^a	Na _v 1.1	Na _v 1.2	Na _v 1.2a	Na _v 1.3	Na _v 1.4	Na _v 1.7	Na _v 1.6	Na _v 1.5	Na _v 1.8	Na _v 1.9	
SOURCES	Brain	Brain (young)	Brain (adult)	Brain	Skeletal muscle	Sympathetic ganglia	Brain	Heart	Dorsal root ganglion	Dorsal root ganglion	
STRUCTURAL INFORMATION	2009 aa (rat)	2005 aa (rat)	2005 aa (rat)	1951 aa (rat)	1840 aa (rat)	1984 aa (rat)	1976 aa (rat)	2019 aa (rat)	1957 aa (rat)	1765 aa (rat)	
SUBUNITS	α, β1, β2				α, β	α	α	α	α, β3	α	
CONDUCTANCE	2.5 – 25 pS					6.3 – 10.7 pS		—	2.5 – 25 pS	3.4 – 6.3 pS	16 pS
IONIC SELECTIVITY	Na ⁺ = Li ⁺ > K ⁺ > Rb ⁺ > Cs ⁺						—	—	Na ⁺ = Li ⁺ > K ⁺ > Rb ⁺ > Cs ⁺	—	
BLOCKERS	TTX (T 5651) ^b STX (S 1417) ^e Local Anesthetics (L 5647, P 9879) ^h Phenytoin (D 4505)							TTX (T 5651) ^c STX (S 1417) ^f			
		Phenytoin (D 4505)	Phenytoin (D 4505)	Phenytoin (D 4505)	μ-Conotoxin	Phenytoin (D 4505)		Cd ²⁺ Zn ²⁺	Phenytoin (D 4505) Cd ²⁺ Pb ²⁺	TTX (T 5651) ^c —	
MODULATORS	Batrachotoxin Grayanotoxins (G 2786) Veratridine (V 5754) Aconitine (A 8001) α-Scorpion toxins β-Scorpion toxins Sea anemone toxins Brevetoxins (B 0912, B 1162) Versutoxin Chloramine-T (C 9887) Pyrethroids Pronase (P 6911) N-Bromoacetamide (B 2377) Ciguatoxin-1										
RADIOLIGANDS OF CHOICE	[³ H]-Brevetoxin [³ H]-Batrachotoxin A 20 α-benzoate [³ H]-Saxitoxin							—	—	—	

ABBREVIATIONS
STX: Saxitoxin
TTX: Tetrodotoxin

FOOTNOTES

- a** This nomenclature, proposed by Goldin et al. in *Neuron*, **28**, 365-368 (2000) has been reviewed and accepted by the Nomenclature Committee of IUPHAR.
b,e Tetrodotoxin and saxitoxin inhibit with IC₅₀ values of ~ 1 nM.
c,f Tetrodotoxin and saxitoxin inhibit with IC₅₀ values of ~ 1 μM.
d,g Tetrodotoxin and saxitoxin inhibit with IC₅₀ values of ~ 100 μM.
h Commonly used local anesthetics include Lidocaine ([L 5647](#)), Mexiletine ([M 2727](#)), Procainamide ([P 9391](#)), Procaine ([P 9879](#)), Flecainide ([F 6777](#)) and Tetracaine ([T 7508](#)).