

Sodium Channels

Key References

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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 some sodium channels in the heart are blocked at concentrations in the micromolar range, and TTX-resistant sodium channels in dorsal root ganglion neurons are only blocked at concentrations approaching 100 μ M.

Structurally, the sodium channels of brain comprise one α subunit of 260 kDa, one β 1 subunit of 36 kDa, and one β 2 subunit of 33 kDa, forming a heterotrimeric structure. β 3 may substitute for β 1 and β 4 for β 2 in these brain sodium channel complexes. The sodium channels of skeletal muscle consist of one α and one β 1-like subunit, whereas those of the heart and peripheral neurons are likely to be complexes of α , β and possibly other proteins/subunits, in unknown stoichiometry.

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 chan-

nel gating kinetics and on the binding sites. TTX, STX and μ -conotoxins bind to neurotoxin receptor site 1 to block sodium channels. Batrachotoxin, grayanotoxins, veratridine and aconitine alter the kinetics and voltage dependence of sodium channel activation and inhibit sodium channel inactivation through binding to neurotoxin receptor site 2. The combination of effects of these toxins causes persistent activation of sodium channels at the resting membrane potential. Sea anemone toxins and α -scorpion toxins block the sodium channel inactivation by binding to neurotoxin receptor site 3. The protease pronase and the chemical reagents N-bromo-acetamide and chloramine-T also block inactivation, but their exact sites of action are unknown. β -scorpion toxins shift the voltage dependence of activation negatively by binding to neurotoxin receptor site 4. Brevetoxins and ciguatoxins are similar to batrachotoxin and other site 1 toxins in their alteration of the kinetics and voltage dependence of activation and inhibition of inactivation, but brevetoxins and ciguatoxins bind to neurotoxin receptor site 5. The pyrethroid insecticides alter the voltage dependence and kinetics of both activation and inactivation of sodium channels and appear to bind to neurotoxin receptor site 6.

Sensory ganglion neurons (e.g. dorsal root and nodose ganglia), particularly those associated with small-diameter afferent fibers, express sodium channels that are highly resistant to TTX and play an important role in nociceptive mechanisms. Recent research efforts have focused on the development of agents selective for the TTX-resistant sodium channels of dorsal root ganglia, in anticipation that these might prove to be novel analgesic drugs.

Numerous clinically used drugs block sodium channels. Local anesthetics used in control of acute pain, antiarrhythmic drugs used in therapy of cardiac arrhythmias, and some antiepileptics used in control of seizures all bind to a common local anesthetic receptor site on sodium channels. Many of these drugs exhibit use-dependent block, a characteristic crucial for their therapeutic effects, as the channel block becomes more potent during rapid firing in arrhythmic or epileptic conditions.

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NOMENCLATURE ^a	NaV1.1	NaV1.2	NaV1.2a	NaV1.3	NaV1.4	NaV1.5	NaV1.6	NaV1.7	NaV1.8	NaV1.9		
PREVIOUS NAMES	I	II	IIA	III	μ1	h1	VI	PN1	PN3/SNS	SNS2		
PRIMARY SOURCE	CNS	CNS (neonatal)	CNS (adult)	CNS (embryonic)	Skeletal muscle	Heart	CNS	Sympathetic and dorsal root ganglia	Dorsal root ganglia	Dorsal root ganglia		
STRUCTURAL INFORMATION	2009 aa (rat)	2005 aa (rat)	2005 aa (rat)	1951 aa (rat)	1840 aa (rat)	2019 aa (rat)	1976 aa (rat)	1984 aa (rat)	1957 aa (rat)	1765 aa (rat)		
SUBUNITS	α, β1-β4	α, β1-β4	α, β1-β4	α, β1-β4	α, β1	α, β1-β4	α, β	α, β	α, β	α, β		
CONDUCTANCE	--	20-25 pS	20-25 pS	--	20-25 pS	20-25 pS	—	--	--	--		
IONIC SELECTIVITY BLOCKERS	Na ⁺ > K ⁺ > Ca ²⁺	→										
NEUROTOXIN RECEPTOR SITE 1												
TTX (T5651)	10 nM	10 nM	10 nM	10 nM	10 nM	1 μM	10 nM	10 nM	≥ 50 μM	≥ 50 μM		
STX (S1417)	2 nM	2 nM	2 nM	2 nM	2 nM	Active	Active	Active	Not known	Not known		
μ-Conotoxin	—	—	—	—	Active	—	—	—	—	—		
LOCAL ANESTHETIC RECEPTOR SITE	Local Anesthetics (L5647, P9879) ^b Class I Antiarrhythmic Drugs Phenytoin (D4505) Carbamazepine (C4024) Lamotrigine (L3791)									→	—	—
MODULATORS												
NEUROTOXIN RECEPTOR SITE 2 (ENHANCE ACTIVATION AND BLOCK INACTIVATION)	Batrachotoxin Grayanotoxin (G2786) Veratridine (V5754) Aconitine (A8001)									→	—	—
NEUROTOXIN RECEPTOR SITE 3 (SLOW INACTIVATION)	α-Scorpion toxins Sea anemone toxins (A7475, C4488)									→	—	—
NEUROTOXIN RECEPTOR SITE 4 (ENHANCE ACTIVATION)	β-Scorpion toxins									→	—	—

FOOTNOTES

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NEUROTOXIN RECEPTOR SITE 5 (ENHANCE ACTIVATION AND BLOCK INACTIVATION)	Brevetoxins (B0912 , B1162)	→									—	—
	Ciguatoxin	→									—	—
	Versutoxin	→									—	—
NEUROTOXIN RECEPTOR SITE 6 (ENHANCE ACTIVATION AND BLOCK INACTIVATION)	Pyrethroid insecticides	→									—	—
RADIOLIGANDS	[³ H]-Brevetoxin	→									—	—
	[³ H]-Batrachotoxinin A 20 α -benzoate	→									—	—
	[³ H]-Saxitoxin	→									—	—
PRIMARY TISSUE EXPRESSION	CNS	CNS	CNS	CNS	Skeletal muscle	Heart	CNS	PNS	DRG	DRG		
PHYSIOLOGICAL FUNCTION	Action potential initiation and conduction →											
	Synaptic integration →						←→					
DISEASE RELEVANCE	Epilepsy	Epilepsy	Epilepsy	Chronic pain epilepsy	Periodic paralysis paralysis	Arrhythmia	Pain	Chronic pain	Chronic pain	Chronic pain		

Abbreviations

CNS: Central nervous system
DRG: Dorsal root ganglion
PNS: Peripheral nervous system
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 Commonly used local anesthetics include Lidocaine (**L5647**), Mexiletine (**M2727**), Procainamide (**P9391**), Procaine (**P9879**), Flecainide (**F6777**) and Tetracaine (**T7508**). Typically, these local anesthetic, antiarrhythmic, and antiepileptic drugs have similar affinity for Na_v1.1-1.7 and reduced affinity for Na_v1.8 and Na_v1.9.