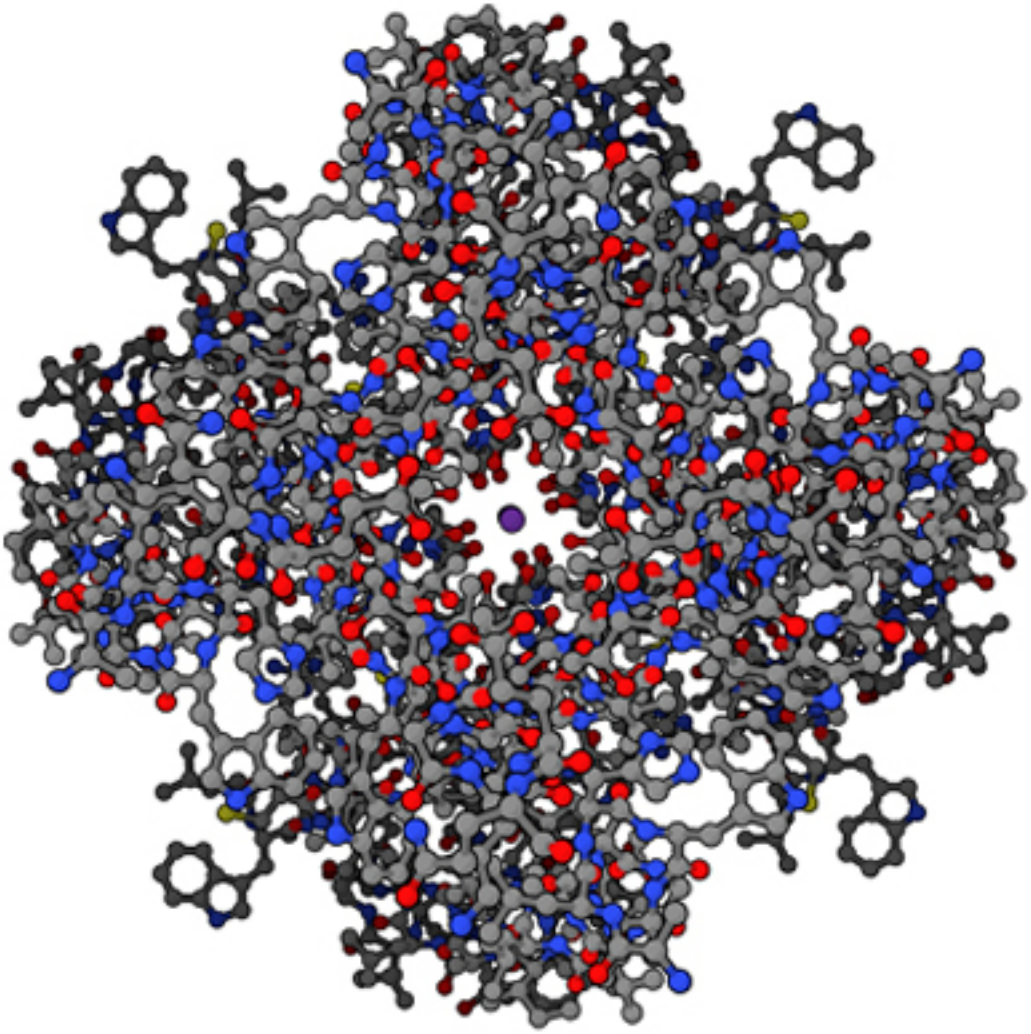
Potassium and Sodium Channels



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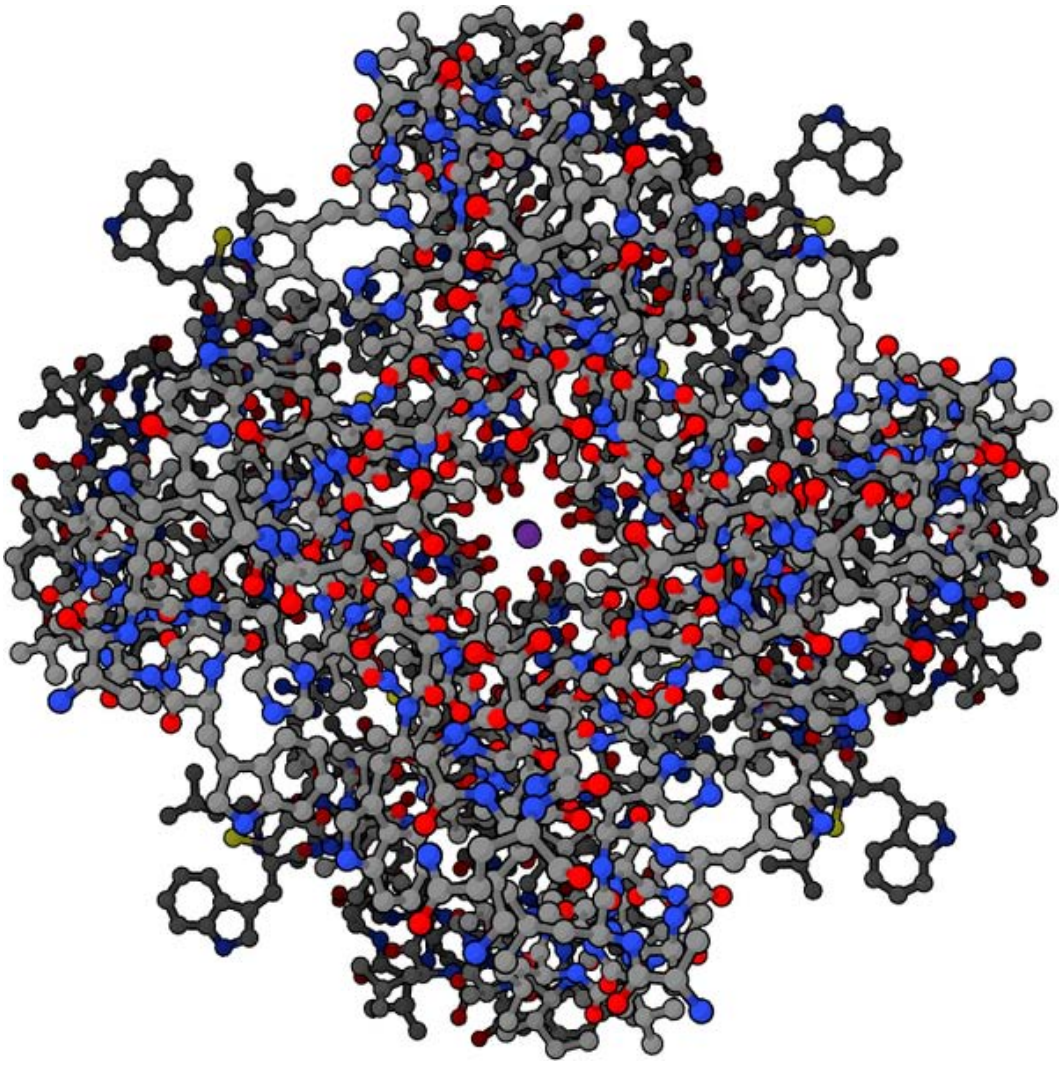
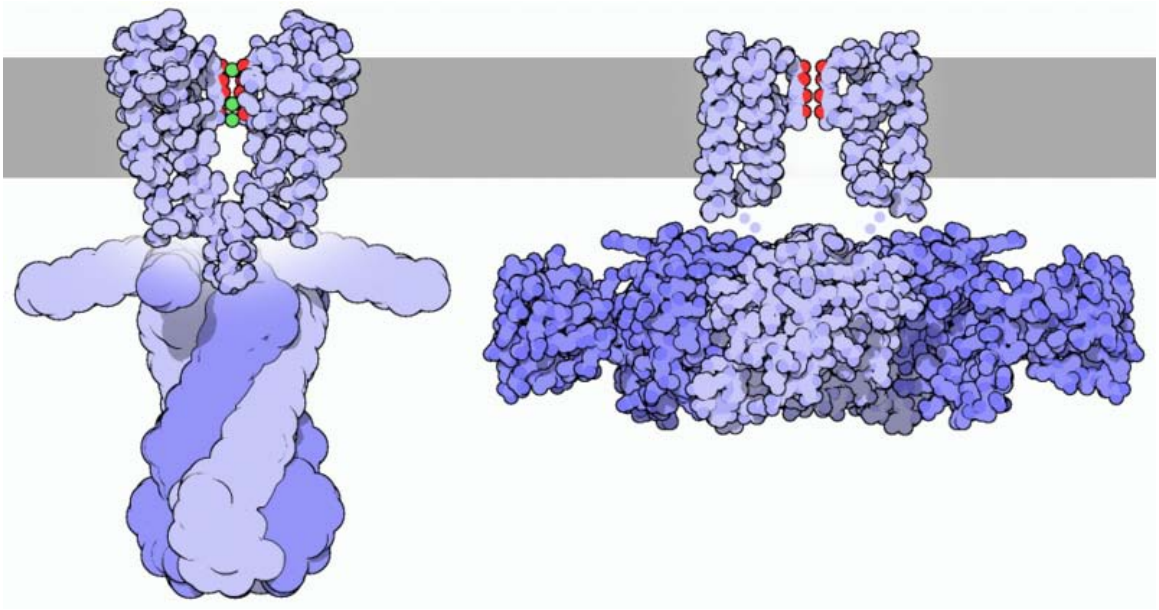
Potassium Channel



Top view of purple potassium ions moving through potassium channel (PDB 1BL8)



Bacterial potassium channels shut (left, PDB 1k4c) and open (right, 1lnq). They can sense voltage differences across membrane, and then change conformation.

In the field of cell biology, **potassium channels** are the most widely distributed type of ion channel and are found in virtually all living organisms. They form potassium-selective pores that span cell membranes. Furthermore potassium channels are found in most cell types and control a wide variety of cell functions.

Function

In excitable cells such as neurons, they shape action potentials and set the resting membrane potential.

By contributing to the regulation of the action potential duration in cardiac muscle, malfunction of potassium channels may cause life-threatening arrhythmias.

They also regulate cellular processes such as the secretion of hormones (*e.g.*, insulin release from beta-cells in the pancreas) so their malfunction can lead to diseases (such as diabetes).

Types

There are four major classes of potassium channels:

- Calcium-activated potassium channel - open in response to the presence of calcium ions or other signalling molecules.
- Inwardly rectifying potassium channel - passes current (positive charge) more easily in the inward direction (into the cell).

- Tandem pore domain potassium channel - are constitutively open or possess high basal activation, such as the "resting potassium channels" or "leak channels" that set the negative membrane potential of neurons. When open, they allow potassium ions to cross the membrane at a rate which is nearly as fast as their diffusion through bulk water.
- Voltage-gated potassium channel - are voltage-gated ion channels that open or close in response to changes in the transmembrane voltage.

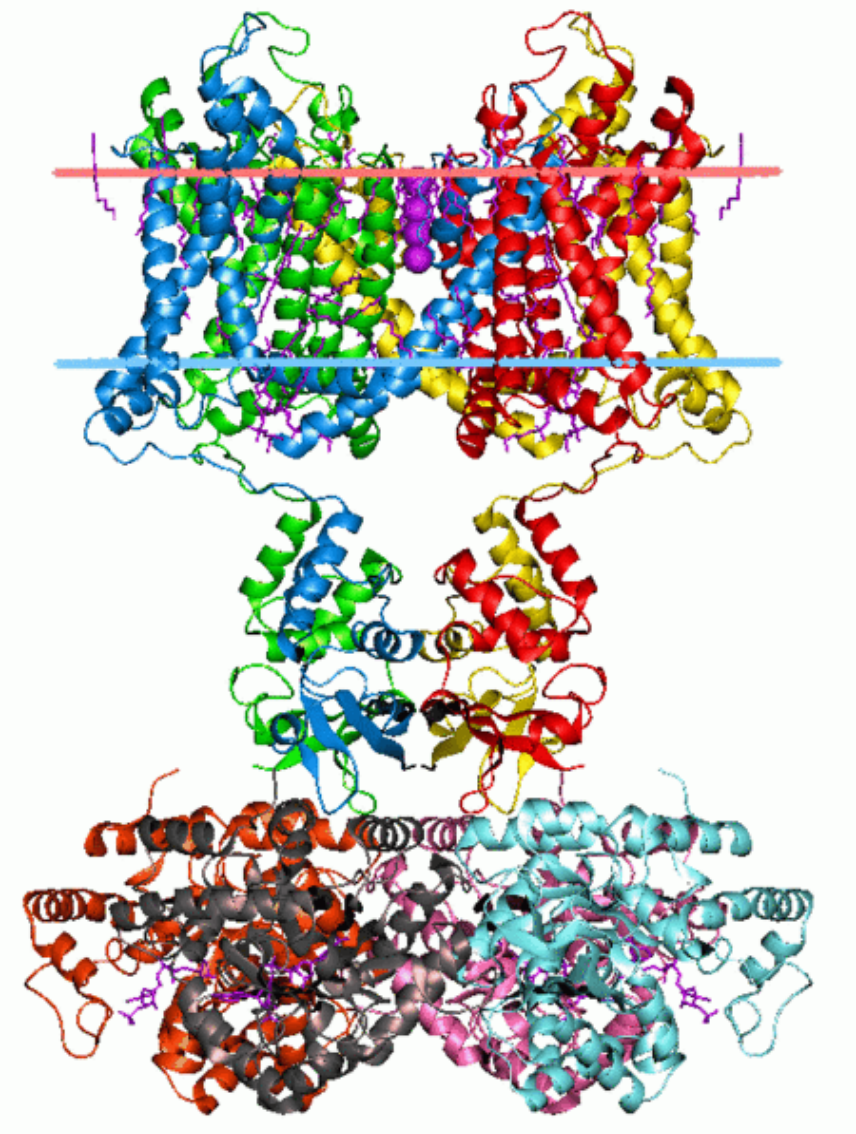
The following table contains a comparison of the major classes of potassium channels with representative examples.

Potassium channel classes, function, and pharmacology.

Class	Subclasses	Function	Blockers	Activators
Calcium-activated 6T & 1P	BK channel	inhibition following stimuli increasing intracellular calcium	charybdotoxin, iberiotoxin	1-EBIO NS309
	SK channel		apamin	CyPPA
Inwardly rectifying 2T & 1P	ROMK ($K_{ir}1.1$)	recycling and secretion of potassium in nephrons	Nonselective: Ba^{2+}, Cs^{+}	none
	GPCR regulated ($K_{ir}3.x$)	mediate the inhibitory effect of many GPCRs	GPCR antagonists ifenprodil	GPCR agonists
	ATP-sensitive ($K_{ir}6.x$)	close when ATP is high to promote insulin secretion	glibenclamide tolbutamide	diazoxide pinacidil
Tandem pore domain 4T & 2P	TWIK (TWIK-1, TWIK-2, KCNK7)	Contribute to resting potential	bupivacaine quinidine	halothane
	TREK (TREK-1, TREK-2, TRAAK)			
	TASK (TASK-1, TASK-3, TASK-5)			
	TALK (TASK-2, TALK-1, TALK-2)			
	THIK (THIK-1,			

	THIK-2)			
	TRESK			
		action potential repolarization	tetraethylammonium	
Voltage-gated 6T & 1P	hERG (K_v11.1)	limits frequency of action potentials (disturbances cause dysrhythmia)	4-aminopyridine	retigabine (K_v7)
	KvLQT1 (K_v7.1)		dendrotoxins (some types)	

Structure

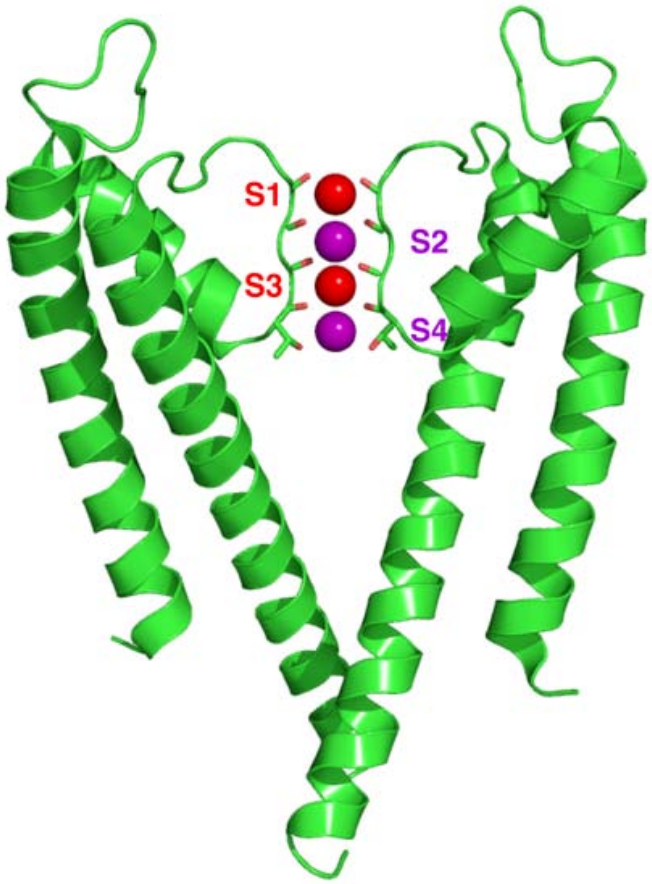


Potassium channel KvAP, structure in a membrane-like environment. Calculated hydrocarbon boundaries of the lipid bilayer are indicated by red and blue dots.

Potassium channels have a tetrameric structure in which four identical protein subunits associate to form a fourfold symmetric (C_4) complex arranged around a central ion conducting pore (i.e., a homotetramer). Alternatively four related but not identical protein subunits may associate to form heterotetrameric complexes with pseudo C_4 symmetry. All potassium channel subunits have a distinctive pore-loop structure that lines the top of the pore and is responsible for potassium selective permeability.

There are over 80 mammalian genes that encode potassium channel subunits. However potassium channels found in bacteria are amongst the most studied of ion channels, in terms of their molecular structure. Using X-ray crystallography, profound insights have been gained into how potassium ions pass through these channels and why (smaller) sodium ions do not. The 2003 Nobel Prize for Chemistry was awarded to Rod MacKinnon for his pioneering work in this area.

Selectivity filter



Crystallographic structure of the bacterial KcsA potassium channel (PDB 1K4C). In this figure, only two of the four subunits of the tetramer are displayed for the sake of clarity. The protein is displayed as a green cartoon diagram. In addition backbone

carbonyl groups and threonine sidechain protein atoms (oxygen = red, carbon = green) are displayed. Finally potassium ions (occupying the S2 and S4 sites) and the oxygen atoms of water molecules (S1 and S3) are depicted as purple and red spheres respectively.

Potassium ion channels remove the hydration shell from the ion when it enters the selectivity filter. The selectivity filter is formed by five residues (TVGYG-in prokaryotic species) in the P loop from each subunit which have their electro-negative carbonyl oxygen atoms aligned towards the centre of the filter pore and form an anti-prism similar to a water solvating shell around each potassium binding site. The distance between the carbonyl oxygens and potassium ions in the binding sites of the selectivity filter is the same as between water oxygens in the first hydration shell and a potassium ion in water solution. Passage of sodium ions would be energetically unfavorable since the strong interactions between the filter and pore helix would prevent the channel from collapsing to the smaller sodium ion size. The selectivity filter opens towards the extracellular solution, exposing four carbonyl oxygens in a glycine residue (Gly79 in KcsA). The next residue towards the extracellular side of the protein is the negatively charged Asp80 (KcsA). This residue together with the five filter residues form the pore that connects the water filled cavity in the centre of the protein with the extracellular solution.

The carbonyl oxygens are strongly electro-negative and cation attractive. The filter can accommodate potassium ions at 4 sites usually labelled S1 to S4 starting at the extracellular side. In addition one ion can bind in the cavity at a site called SC or one or more ions at the extracellular side at more or less well defined sites called S0 or Sext. Several different occupancies of these sites are possible. Since the X-ray structures are averages over many molecules, it is, however, not possible to deduce the actual occupancies directly from such a structure. In general, there is some disadvantage due to electrostatic repulsion to have two neighbouring sites occupied by ions. The mechanism for ion translocation in KcsA has been studied extensively by simulation techniques. A complete map of the free energies of the 2^4=16 states (characterised by the occupancy of the S1, S2, S3 and S4 sites) has been calculated with molecular dynamics simulations resulting in the prediction of an ion conduction mechanism in which the two doubly occupied states (S1, S3) and (S2, S4) play an essential role. The two extracellular states, S_{ext} and S_0, were found in a better resolved structure of KcsA at high potassium concentration. In free energy calculations the entire ionic pathway from the cavity, through the four filter sites out to S_0 and S_{ext} was covered in MD simulations. The amino acids sequence of the selectivity filter of potassium ion channels is conserved with the exception that an isoleucine residue in eukaryotic potassium ion channels often is substituted with a valine residue in prokaryotic channels.

Central Cavity

A 10 Å wide central pore is located near the center of the transmembrane channel where the energy barrier is highest for the transversing ion due to the hydrophobity of the channel wall. The water-filled cavity and the polar C-terminus of the pore helices ease the energetic barrier for the ion. Repulsion by preceding multiple potassium ions is

thought to aid the throughput of the ions. The presence of the cavity can be understood intuitively as one of the channel's mechanisms for overcoming the dielectric barrier, or repulsion by the low-dielectric membrane, by keeping the K^+ ion in a watery, high-dielectric environment.

Blockers

Potassium channel blockers, such as 4-aminopyridine and 3,4-diaminopyridine, have been investigated for the treatment of conditions such as multiple sclerosis.

Muscarinic potassium channel

Some types of potassium channels are activated by muscarinic receptors and these are called *muscarinic potassium channels* (I_{KACh}). These channels are a heterotetramer composed of two GIRK1 and two GIRK4 subunits. Examples are potassium channels in the heart, which, when activated by parasympathetic signals through M2 muscarinic receptors, causes an outward current of potassium which slows down the heart rate.

Chapter 2

Voltage-gated Potassium Channel and Tandem Pore Domain Potassium Channel

Voltage-gated potassium channel

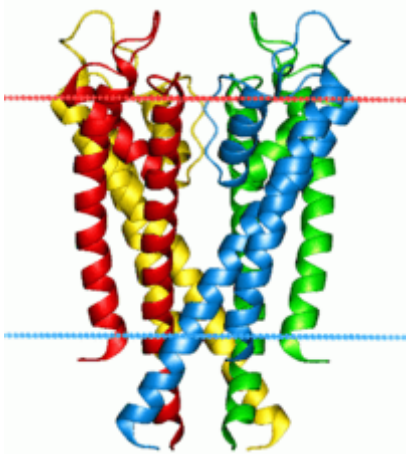
Ion channel (eukariotic)

Potassium channel, structure in a membrane-like environment. Calculated hydrocarbon boundaries of the lipid bilayer are indicated by red and blue dots.

Identifiers	
Symbol	Ion_trans
Pfam	PF00520
InterPro	IPR005821
SCOP	1bl8
TCDB	1.A.1

OPM family	8
OPM protein	2a79

Ion channel (bacterial)



Potassium channel KcsA. Calculated hydrocarbon boundaries of the lipid bilayer are indicated by red and blue dots.

Identifiers	
Symbol	Ion_trans_2
Pfam	PF07885
InterPro	IPR013099
SCOP	1bl8
OPM protein	1r3j

Voltage-gated potassium channels are transmembrane channels specific for potassium and sensitive to voltage changes in the cell's membrane potential. During action potentials, they play a crucial role in returning the depolarized cell to a resting state.

Classification

Alpha subunits

Alpha subunits form the actual conductance pore. Based on sequence homology of the hydrophobic transmembrane cores, the alpha subunits of voltage-gated potassium channels are grouped into 12 classes, labeled $K_v\alpha$1-12. The following is a list of the 40 known human voltage-gated potassium channel alpha subunits grouped first according to function and then subgrouped according to the K_v sequence homology classification scheme:

Delayed rectifier

slowly inactivating or non-inactivating

- K_vα1.x - Shaker-related: K_v1.1 (KCNA1), K_v1.2 (KCNA2), K_v1.3 (KCNA3), K_v1.5 (KCNA5), K_v1.6 (KCNA6), K_v1.7 (KCNA7), K_v1.8 (KCNA10)
- K_vα2.x - Shab-related: K_v2.1 (KCNB1), K_v2.2 (KCNB2)
- K_vα3.x - Shaw-related: K_v3.1 (KCNC1), K_v3.2 (KCNC2)
- K_vα7.x: K_v7.1 (KCNQ1) - KvLQT1, K_v7.2 (KCNQ2), K_v7.3 (KCNQ3), K_v7.4 (KCNQ4), K_v7.5 (KCNQ5)
- K_vα10.x: K_v10.1 (KCNH1)

A-type potassium channel

rapidly inactivating

- K_vα1.x - Shaker-related: K_v1.4 (KCNA4)
- K_vα3.x - Shaw-related: K_v3.3 (KCNC3), K_v3.4 (KCNC4)
- K_vα4.x - Shal-related: K_v4.1 (KCND1), K_v4.2 (KCND2), K_v4.3 (KCND3)

Outward-rectifying

- K_vα10.x: K_v10.2 (KCNH5)

Inward-rectifying

Passes current more easily into the inwards direction (Into the cell).

- K_vα11.x - ether-a-go-go potassium channels: K_v11.1 (KCNH2) - hERG, K_v11.2 (KCNH6), K_v11.3 (KCNH7)

Slowly activating

- K_vα12.x: K_v12.1 (KCNH8), K_v12.2 (KCNH3), K_v12.3 (KCNH4)

Modifier/silencer

Unable to form functional channels as homotetramers but instead heterotetramerize with K_vα2 family members to form conductive channels.

- K_vα5.x: K_v5.1 (KCNF1)
- K_vα6.x: K_v6.1 (KCNG1), K_v6.2 (KCNG2), K_v6.3 (KCNG3), K_v6.4 (KCNG4)
- K_vα8.x: K_v8.1 (KCNV1), K_v8.2 (KCNV2)
- K_vα9.x: K_v9.1 (KCNS1), K_v9.2 (KCNS2), K_v9.3 (KCNS3)

Beta subunits

Beta subunits are auxiliary proteins which associate with alpha subunits, sometimes in a $\alpha_4\beta_4$ stoichiometry. These subunits do not conduct current on their own but rather modulate the activity of K_v channels.

- $K_v\beta1$ (KCNAB1)
- $K_v\beta2$ (KCNAB2)
- $K_v\beta3$ (KCNAB3)
- minK (KCNE1)
- MiRP1 (KCNE2)
- MiRP2 (KCNE3)
- MiRP3 (KCNE4)
- KCNE1-like (KCNE1L)
- KCNIP1 (KCNIP1)
- KCNIP2 (KCNIP2)
- KCNIP3 (KCNIP3)
- KCNIP4 (KCNIP4)

Proteins minK and MiRP1 are putative hERG beta subunits.

Animal research

The voltage-gated K^+ channels that provide the outward currents of action potentials have similarities to bacterial K^+ channels.

These channels have been studied by X-ray diffraction, allowing determination of structural features at atomic resolution.

The function of these channels is explored by electrophysiological studies.

Genetic approaches include screening for behavioral changes in animals with mutations in K^+ channel genes. Such genetic methods allowed the genetic identification of the "Shaker" K^+ channel gene in *Drosophila* before ion channel gene sequences were well known.

Study of the altered properties of voltage-gated K^+ channel proteins produced by mutated genes has helped reveal the functional roles of K^+ channel protein domains and even individual amino acids within their structures.

Structure

Voltage-gated K^+ channels of vertebrates typically are tetramers of four identical subunits arranged as a ring, each contributing to the wall of the trans-membrane K^+ pore. Each subunit is composed of six membrane spanning hydrophobic α-helical sequences. A high resolution crystallographic structure of the rat $K_v\alpha1.2/\beta2$ channel has recently been

solved (Protein Databank Accession Number 2A79), and then refined in a lipid membrane-like environment (PDB 2r9r).

Selectivity

Voltage-gated K^+ channels are selective for K^+ over other cations such as Na^+. There is a selectivity filter at the narrowest part of the transmembrane pore.

Channel mutation studies revealed the parts of the subunits that are essential for ion selectivity. They include the amino acid sequence (Thr-Val-Gly-Tyr-Gly) or (Thr-Val-Gly-Phe-Gly) typical to the selectivity filter of voltage-gated K^+ channels. As K^+ passes through the pore, interactions between potassium ions and water molecules are prevented and the K^+ interacts with specific atomic components of the Thr-Val-Gly-X-Gly sequences from the four channel subunits.

It seems illogical at first that a channel should be able to allow potassium ions but not the smaller sodium ions through. However in an aqueous environment, potassium and sodium cations are solvated by water molecules. When moving through the selectivity filter of the potassium channel, these solvated water molecules are replaced by backbone carbonyl groups of the channel protein. The diameter of the selectivity filter is ideal for the potassium cation, but too big for the smaller sodium cation. Hence the potassium cations are well "solvated" by the protein carbonyl groups, but these same carbonyl groups are too far apart to adequately solvate the sodium cation. Hence the passage of potassium cations through this selectivity filter is strongly favored over sodium cations.

Open and closed conformations

Attempts continue to relate the structure of the mammalian voltage-gated K^+ channel to its ability to respond to the voltage that exists across the membrane. Specific domains of the channel subunits have been identified that are important for voltage-sensing and converting between the open conformation of the channel and closed conformations. There are at least two closed conformations; in one, the channel can open if the membrane potential becomes positive inside. Voltage-gated K^+ channels inactivate after opening, entering a distinctive, second closed conformation. In the inactivated conformation, the channel cannot open, even if the transmembrane voltage is favorable. The amino terminal domain of the K^+ channel or an auxiliary protein can mediate "N-type" inactivation. The former has been described as a "ball and chain" model where the N-terminus of the protein forms a ball which is tethered to the rest of the protein through a loop (the chain). The tethered ball is transiently sucked into the inner porehole, preventing ion movement through the channel.

Tandem pore domain potassium channel

The **two-pore-domain potassium channel** is a family of 15 members form what is known as "leak channels" which possess Goldman-Hodgkin-Katz (open) rectification. These channels are regulated by several mechanisms including oxygen tension, pH, mechanical stretch, and G-proteins. Their name is derived from the fact that the α subunits consist of four transmembrane segments, each containing two pore loops. As such, they structurally correspond to two inward-rectifier α subunits and thus form dimers in the membrane.

Below is a list of the 15 known two-pore-domain human potassium channels:

Gene	Channel	Family	Aliases
KCNK1	$K_{2p}1.1$	TWIK	TWIK-1
KCNK2	$K_{2p}2.1$	TREK	TREK-1
KCNK3	$K_{2p}3.1$	TASK	TASK-1
KCNK4	$K_{2p}4.1$	TREK	TRAAK
KCNK5	$K_{2p}5.1$	TASK	TASK-2
KCNK6	$K_{2p}6.1$	TWIK	TWIK-2
KCNK7	$K_{2p}7.1$	TWIK	
KCNK9	$K_{2p}9.1$	TASK	TASK-3
KCNK10	$K_{2p}10.1$	TREK	TREK-2
KCNK12	$K_{2p}12.1$	THIK	THIK-2
KCNK13	$K_{2p}13.1$	THIK	THIK-1
KCNK15	$K_{2p}15.1$	TASK	TASK-5
KCNK16	$K_{2p}16.1$	TALK	TALK-1
KCNK17	$K_{2p}17.1$	TALK	TALK-2, TASK-4
KCNK18	$K_{2p}18.1$		TRIK, TRESK

Chapter 3

Inward-rectifier Potassium Ion Channel and Calcium-activated Potassium Channel

Inward-rectifier potassium ion channel

Inwardly rectifying potassium channels (**K_{ir}**, **IRK**) are a specific subset of potassium selective ion channels. To date, seven subfamilies have been identified in various mammalian cell types. They are the targets of multiple toxins, and malfunction of the channels has been implicated in several diseases.

Overview of inward rectification

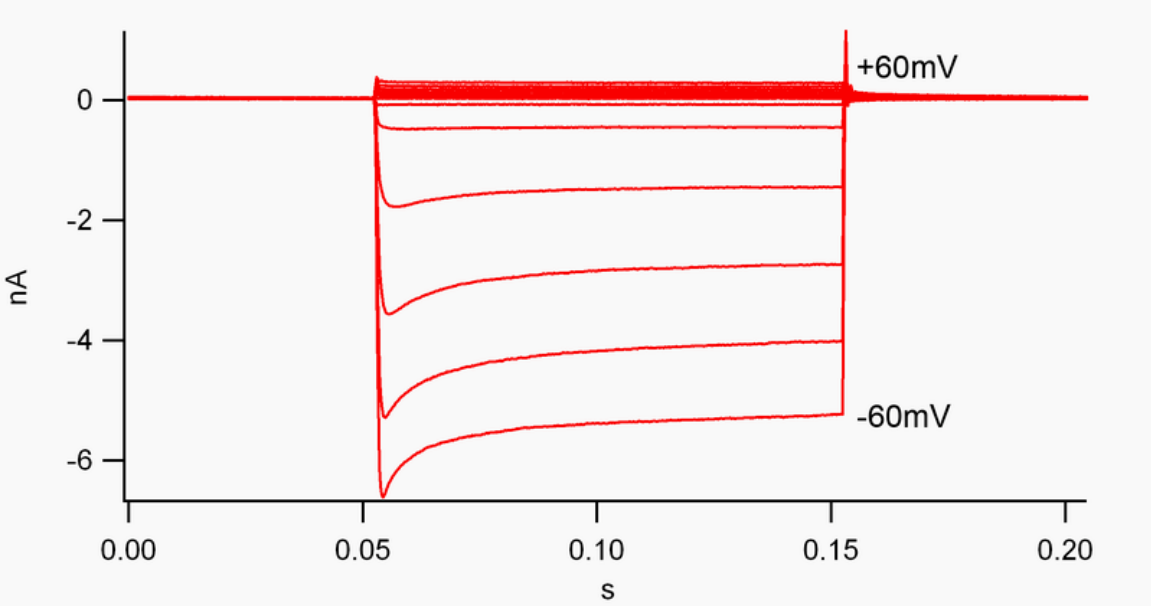


Figure 1. Whole-cell current recordings of $K_{ir}2$ inwardly-rectifying potassium channels expressed in an HEK293 cell. (This is a strongly inwardly rectifying current. Downward deflections are inward currents, upward deflections outward currents, and the x-axis is time in seconds.) There are 13 responses superimposed in this image. The bottom-most

trace is current elicited by a voltage step to negative 60mV, and the top-most to positive 60mV, relative to the resting potential, which is close to the K^+ reversal potential in this experimental system. Other traces are in 10mV increments between the two.

A channel that is "inwardly-rectifying" is one that passes current (positive charge) more easily in the inward direction (into the cell). It is thought that this current may play an important role in regulating neuronal activity, by helping to establish the resting membrane potential of the cell.

By convention, inward current is displayed in voltage clamp as a downward deflection, while an outward current (positive charge moving out of the cell) is shown as an upward deflection. At membrane potentials negative to the potassium's reversal potential, inwardly rectifying K^+ channels support the flow of positively charged K^+ ions into the cell, pushing the membrane potential back to the resting potential. This can be seen in figure 1: when the membrane potential is clamped negative to the channel's resting potential (e.g. -60 mV), inward current flows (i.e. positive charge flows into the cell). However, when the membrane potential is set positive to the channel's resting potential (e.g. +60 mV), these channels pass very little charge out of the cell. Simply put, this channel passes much more current in the inward direction than the outward one. Note that these channels are not perfect rectifiers, as they can pass some outward current in the voltage range up to about 30 mV above resting potential.

These channels differ from the potassium channels that are typically responsible for repolarizing a cell following an action potential, such as the delayed rectifier and A-type potassium channels. Those more "typical" potassium channels preferentially carry outward (rather than inward) potassium currents at depolarized membrane potentials, and may be thought of as "outwardly rectifying." When first discovered, inward rectification was named "anomalous rectification" to distinguish it from outward potassium currents.

Inward rectifiers also differ from tandem pore domain potassium channels, which are largely responsible for "leak" K^+ currents. Some inward rectifiers, termed "weak inward rectifiers," carry measurable outward K^+ currents at voltages positive to the K^+ reversal potential (corresponding to, but larger than, the small currents above the 0 nA line in figure 1). They, along with the "leak" channels, establish the resting membrane potential of the cell. Other inwardly rectifying channels, termed "strong inward rectifiers," carry very little outward current at all, and are mainly active at voltages negative to the reversal potential, where they carry inward current (the much larger currents below the 0 nA line in figure 1).

Mechanism of inward rectification

The phenomenon of inward rectification of K_{ir} channels is the result of high-affinity block by endogenous polyamines, namely spermine, as well as magnesium ions, that plug the channel pore at positive potentials, resulting in a decrease in outward currents. This voltage-dependent block by polyamines causes currents to be conducted well only in the

inward direction. While the principal idea of polyamine block is understood, the specific mechanisms are still controversial.

Role of K_{ir} channels

K_{ir} channels are found in multiple cell types, including macrophages, cardiac and kidney cells, leukocytes, neurons, and endothelial cells. By mediating a small hyperpolarizing K^+ current at negative membrane potentials, they help establish resting membrane potential, and in the case of the $K_{ir}3$ group, they help mediate inhibitory neurotransmitter responses, but their roles in cellular physiology vary across cell types:

Location	Function
cardiac myocytes	K_{ir} channels close upon depolarization, slowing membrane repolarization and helping maintain a more prolonged cardiac action potential. This type of inward-rectifier channel is distinct from delayed rectifier K^+ channels, which help repolarize nerve and muscle cells after action potentials; and potassium leak channels, which provide much of the basis for the resting membrane potential.
endothelial cells	K_{ir} channels are involved in regulation of nitric oxide synthase.
kidneys	K_{ir} export surplus potassium into collecting tubules for removal in the urine, or alternatively may be involved in the reuptake of potassium back into the body.
neurons and in heart cells	G-protein activated IRKs ($K_{ir}3$) are important regulators, modulated by neurotransmitters. A mutation in the GIRK2 channel leads to the weaver mouse mutation. "Weaver" mutant mice are ataxic and display a neuroinflammation-mediated degeneration of their dopaminergic neurons. Weaver mice have been examined in labs interested in neural development and disease for over 30 years.
pancreatic beta cells	K_{ATP} channels (composed of $K_{ir}6.2$ and SUR1 subunits) control insulin release.

Biochemistry of K_{ir} channels

There are seven subfamilies of K_{ir} channels, denoted as $K_{ir}1$ - $K_{ir}7$. Each subfamily has multiple members (i.e. $K_{ir}2.1$, $K_{ir}2.2$, $K_{ir}2.3$, etc) that have nearly identical amino acid sequences across known mammalian species.

K_{ir} channels are formed from as homotetrameric membrane proteins. Each of the four identical protein subunits is composed of two membrane-spanning alpha helices (M1 and M2). Heterotetramers can form between members of the same subfamily (ie $K_{ir}2.1$ and $K_{ir}2.3$) when the channels are overexpressed.

Diversity

Gene	Protein	Aliases	Associated subunits
KCNJ1	$K_{ir}1.1$	ROMK1	NHERF2
KCNJ2	$K_{ir}2.1$	IRK1	$K_{ir}2.2$, $K_{ir}4.1$, PSD-95, SAP97, AKAP79
KCNJ12	$K_{ir}2.2$	IRK2	$K_{ir}2.1$ and $K_{ir}2.3$ to form heteromeric channel, auxiliary subunit: SAP97, Veli-1, Veli-3, PSD-95
KCNJ4	$K_{ir}2.3$	IRK3	$K_{ir}2.1$ and $K_{ir}2.3$ to form heteromeric channel, PSD-95, Chapsyn-110/PSD-93
KCNJ14	$K_{ir}2.4$	IRK4	$K_{ir}2.1$ to form heteromeric channel
KCNJ3	$K_{ir}3.1$	GIRK1, KGA	$K_{ir}3.2$, $K_{ir}3.4$, $K_{ir}3.5$, $K_{ir}3.1$ is not functional by itself
KCNJ6	$K_{ir}3.2$	GIRK2	$K_{ir}3.1$, $K_{ir}3.3$, $K_{ir}3.4$ to form heteromeric channel
KCNJ9	$K_{ir}3.3$	GIRK3	$K_{ir}3.1$, $K_{ir}3.2$ to form heteromeric channel
KCNJ5	$K_{ir}3.4$	GIRK4	$K_{ir}3.1$, $K_{ir}3.2$, $K_{ir}3.3$
KCNJ10	$K_{ir}4.1$	$K_{ir}1.2$	$K_{ir}4.2$, $K_{ir}5.1$, and $K_{ir}2.1$ to form heteromeric channels
KCNJ15	$K_{ir}4.2$	$K_{ir}1.3$	
KCNJ16	$K_{ir}5.1$	BIR 9	
KCNJ8	$K_{ir}6.1$	K_{ATP}	SUR2B
KCNJ11	$K_{ir}6.2$	K_{ATP}	SUR1, SUR2A, and SUR2B
KCNJ13	$K_{ir}7.1$	$K_{ir}1.4$	

Diseases related to K_{ir} channels

- *Persistent hyperinsulinemic hypoglycemia of infancy* is related to autosomal recessive mutations in $K_{ir}6.2$. Certain mutations of this gene diminish the channel's ability to regulate insulin secretion, leading to hypoglycemia.
- *Bartter's syndrome* can be caused by mutations in K_{ir} channels. This condition is characterized by the inability of kidneys to recycle potassium, causing low levels of potassium in the body.
- *Andersen's syndrome* is a rare condition caused by multiple mutations of $K_{ir}2.1$. Depending on the mutation, it can be dominant or recessive. It is characterized by periodic paralysis, cardiac arrhythmias and dysmorphic features.
- *Barium poisoning* is likely due to its ability to block K_{ir} channels.
- *Atherosclerosis (heart disease)* may be related to K_{ir} channels. The loss of K_{ir} currents in endothelial cells is one of the first known indicators of atherogenesis (the beginning of heart disease).

Calcium-activated potassium channel

Calcium-activated potassium channels are divided into BK channels, IK channels, and SK channels based on their conductance (big, intermediate, and small conductance).

This family of ion channels is, for the most part, activated by intracellular Ca^{2+} and contains 8 members. However, some of these channels (the $K_{Ca}4$ and $K_{Ca}5$ channels) are responsive instead to intracellular Na^{+} and Cl^{-}. Furthermore, the $K_{Ca}1$ family is both Ca^{2+} and voltage activated, further complicating the description of this family. The K_{Ca} channel α subunits have six transmembrane segments similar to the K_Vs, except $K_{Ca}1$, in which the N-terminus makes a seventh pass across the membrane to end up outside the cell. The α subunits make homo- and hetero-tetrameric complexes.

Homology classification

Below is a list of the 8 known calcium-activated potassium channel grouped according to sequence homology of transmembrane hydrophobic cores:

BK channel

- $K_{Ca}1.x$: $K_{Ca}1.1$ (*KCNMA1*)

SK channel

- $K_{Ca}2.x$: $K_{Ca}2.1$ (*KCNN1*), $K_{Ca}2.2$ (*KCNN2*), $K_{Ca}2.3$ (*KCNN3*)
- $K_{Ca}3.x$: $K_{Ca}3.1$ (*KCNN4*)
- $K_{Ca}4.x$: $K_{Ca}4.1$ (*KCNT1*), $K_{Ca}4.2$ (*KCNT2*)

IK channel

- $K_{Ca}5.x$: $K_{Ca}5.1$ (*KCNU1*)

Chapter 4

Potassium Channel Opener

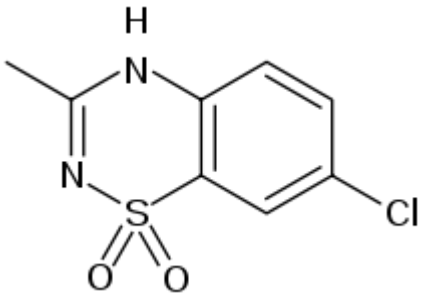
A **potassium channel opener** is a type of drug which facilitates ion transmission through potassium channels.

Some examples include:

- Diazoxide vasodilator used for hypertension, smooth muscle relaxing activity
- Minoxidil vasodilator used for hypertension, also used to treat hair loss
- Nicorandil vasodilator used to treat angina
- Pinacidil
- Retigabine, an anticonvulsant
- Flupirtine, analgesic with muscle relaxant and anticonvulsant properties

Diazoxide

Diazoxide



Systematic (IUPAC) name
7-chloro-3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide
Identifiers
CAS number 364-98-7

ATC code	C02DA01 V03AH01
PubChem	CID 3019
IUPHAR ligand	2409
DrugBank	APRD00914
ChemSpider	2911 ✓
UNII	O5CB12L4FN ✓
KEGG	D00294
ChEMBL	CHEMBL181 ✓
Chemical data	
Formula	$C_8H_7ClN_2O_2S$
Mol. mass	230.672 g/mol
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Protein binding	90%
Metabolism	Hepatic oxidation and sulfate conjugation
Half-life	21-45 hours
Excretion	Renal
Therapeutic considerations	
Pregnancy cat.	C(AU) C(US)
Legal status	POM (UK) ℞-only (US)
Routes	Oral, intravenous

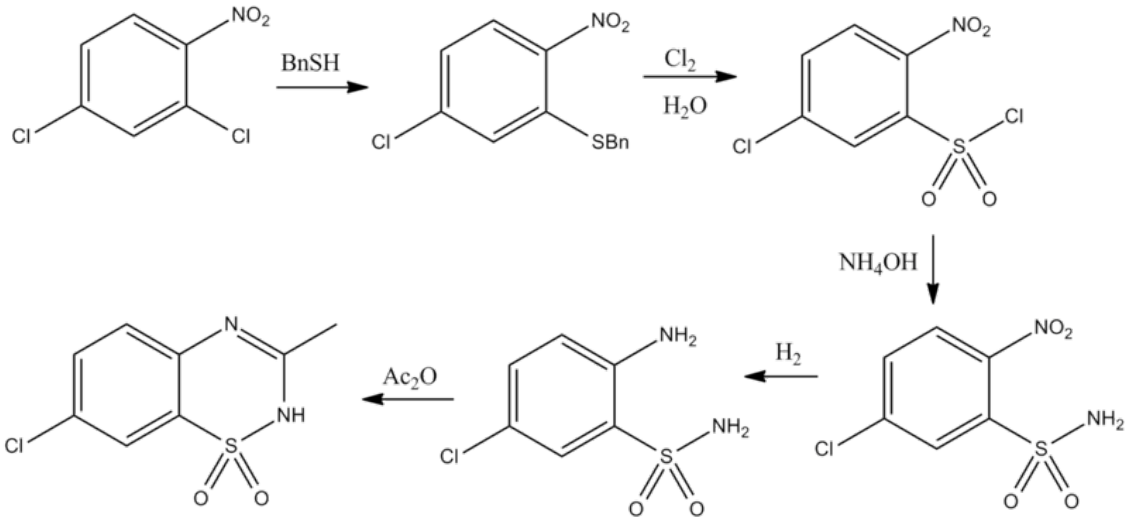
Diazoxide is a potassium channel activator, which causes local relaxation in smooth muscle by increasing membrane permeability to potassium ions. This switches off voltage-gated calcium ion channels which inhibits the generation of an action potential.

Uses

It is used as a vasodilator in the treatment of acute hypertension or malignant hypertension.

It is also used to decrease hypoglycemia due to the secretion of insulin in disease states such as insulinoma (a tumor producing insulin) or congenital hyperinsulinism.

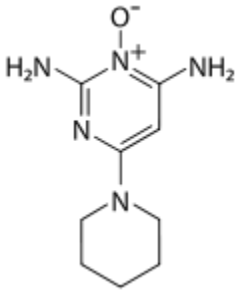
Chemistry

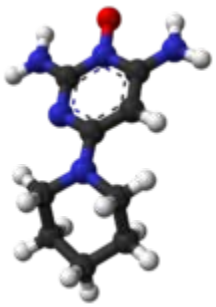


Rubin, A. A.; Roth, F. E.; Winbury, M. M.; Topliss, J. G.; Sherlock, M. H.; Sperber, N.; Black, J. (1961). "New Class of Antihypertensive Agents".

Minoxidil

Minoxidil





Systematic (IUPAC) name

6-piperidin-1-ylpyrimidine-2,4-diamine 3-oxide

Identifiers	
CAS number	38304-91-5
ATC code	C02DC01 D11AX01
PubChem	CID 4201
ChemSpider	10438564 ✓
KEGG	D00418 ✗
Chemical data	
Formula	$C_9H_{15}N_5O$
Mol. mass	209.251 g/mol
Pharmacokinetic data	
Metabolism	Primarily hepatic
Half-life	4.2 hours
Excretion	renal
Therapeutic considerations	
Pregnancy cat.	C
Legal status	P(UK) for topical use, otherwise POM. Cannot be prescribed on the NHS.
Routes	Oral / topical

Minoxidil (trade names **Rogaine**, **Regaine**, **Avacor**, **Loniten** (orally), and **Mintop** among others-- now that Minoxidil is off patent) is an antihypertensive vasodilator medication also known for its ability to slow or stop hair loss and promote hair regrowth. It is available over the counter for treatment of androgenic alopecia, among other baldness treatments, but measurable changes disappear within months after discontinuation of treatment.

History

Minoxidil was first used exclusively as an oral drug (trade name **Loniten**) to treat high blood pressure. However, it was discovered to have an interesting side-effect: *Minoxidil may cause increased growth or darkening of fine body hairs. When the medication is discontinued, the hair will return to normal within 30 to 60 days.* Upjohn Corporation produced a topical solution that contained 2% minoxidil to be used to treat baldness and hair loss, under the brand name Rogaine in the United States and Canada, and Regaine in

Europe and the Asia-Pacific. Treatments usually include a 5% concentration solution that is designed for men, whereas the 2% concentration solutions are designed for women. The patent on minoxidil expired on February 11, 1996.

In 2007 a new foam-based formulation of 5% minoxidil was shown to be as effective as the liquid-based treatment for male pattern baldness.

While the drug is available in the United Kingdom, it cannot be prescribed on the NHS, so patients must either buy it over-the-counter or have a private prescription for it.

Results

One study in healthy males aged 18–50 years with androgenic alopecia (male pattern baldness) found that compared to a baseline of 103 to 106 hairs/cm^2, those who applied a 5% solution of minoxidil for 32 weeks increased their non-vellus hair counts by an average of 39 hairs/cm^2, in contrast to 5 hairs/cm^2 in subjects who received a placebo.

Mechanism

The mechanism by which minoxidil promotes hair growth is not fully understood. Minoxidil contains the nitric oxide chemical moeity and may act as a nitric oxide agonist. Similarly, Minoxidil is a potassium channel opener, causing hyperpolarization of cell membranes. Minoxidil is less effective when there is a large area of hair loss. In addition, its effectiveness has largely been demonstrated in younger men (18 to 41 years of age). Minoxidil use is indicated for central (vertex), or top of head, balding only.

Minoxidil is also a vasodilator. It is speculated that by widening blood vessels and opening potassium channels, it allows more oxygen, blood, and nutrients to the follicle. This can also cause follicles in the telogen phase to shed, usually soon to be replaced by new, thicker hairs (in a new anagen phase).

Side effects

Common side effects of minoxidil include burning or irritation of the eye; itching; redness or irritation at the treated area; unwanted hair growth elsewhere on the body. Users should seek medical attention right away if they experience the severe side effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); chest pain; dizziness; fainting; fast heartbeat; sudden, unexplained weight gain; swollen hands or feet.

Alcohol present in topical preparations may dry the scalp, resulting in dandruff. Side effects of *oral* minoxidil may include swelling of the face and extremities, rapid and irregular heartbeat, lightheadedness, cardiac lesions, and focal necrosis of the papillary muscle and subendocardial areas of the left ventricle. There have been cases of allergic reactions to minoxidil or the non-active ingredient propylene glycol, which is found in some forms of topical Rogaine.

Pseudoacromegaly is an extremely rarely reported side effect of large doses of oral minoxidil.

Ironically, hair loss is a common side effect of minoxidil treatment. Manufacturers note that minoxidil-induced hair loss is a common side effect and describe the process as 'shedding'. Although this phenomenon demonstrates that minoxidil is indeed affecting hair follicles, manufacturers offer no guarantee that the new hair loss will be replaced with hair growth.

The speculated reason for this "shedding" is the encouragement of hairs already in the telogen phase to shed early, before often beginning a fresh, healthier anagen phase.

Toxic effects

Minoxidil is highly toxic to, and may cause death in, cats and rats.

Application

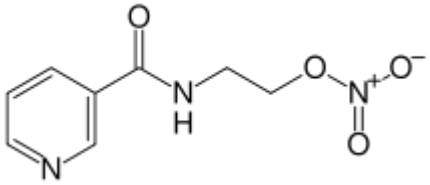
Minoxidil needs to be applied once or twice daily for hair gained to be maintained. For maximum effect, the solution should be in contact with the scalp for four hours before being washed out. It does not seem capable of reducing DHT or the enzyme responsible for its accumulation around the hair follicle, 5-alpha reductase, which are the main causes of male pattern baldness in genetically susceptible individuals. Therefore, when treatment is stopped, the DHT already accumulated around the follicle has its expected effect, and the follicle usually shrinks again and eventually dies.

Minoxidil solutions are sold under many brand names. Many high priced as well as generic brands of minoxidil regrowth solutions exist and do not differ in their active ingredient or concentration (except differing versions within each brand).

Minoxidil products involve contact with hair strands, which may cause problems with hair styling since minoxidil must be in an alcohol solution. If the solution is not a problem, hair styling devices can be used as soon as the minoxidil solution has dried.

Nicorandil

Nicorandil



Systematic (IUPAC) name	
2-[(pyridin-3-ylcarbonyl)amino]ethyl nitrate	
Identifiers	
CAS number	65141-46-0
ATC code	C01DX16
PubChem	CID 47528
IUPHAR ligand	2411
ChemSpider	43240 ✓
UNII	260456HAM0 ✓
KEGG	D01810 ✓
ChEMBL	CHEMBL284906 ✓
Chemical data	
Formula	$C_8H_9N_3O_4$
Mol. mass	211.175 g/mol
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Bioavailability	75 to 80%
Protein binding	25%
Metabolism	Hepatic
Half-life	1 hour
Excretion	Renal (21%)
Therapeutic considerations	
Pregnancy cat.	B3(AU)
Legal status	POM (UK)

Routes	Oral

Nicorandil is a vasodilatory drug used to treat angina. It is marketed under the trade names **Ikorel** (in the United Kingdom, Australia and most of Europe), **Dancor** (in Switzerland), **Nikoran** (in India), **Aprior** (in the Philippines), **Nitorubin** (in Japan) and **Sigmart** (in Japan, South Korea and Taiwan). Nicorandil is not available in the United States.

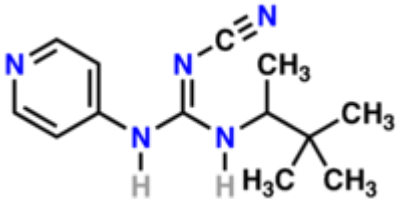
It works by opening K_{ATP} potassium channels.

Side effects

Common side effects include flushing, palpitation, weakness, headache, mouth ulcers, nausea and vomiting. More recently peri-anal, ileal and peri-stomal ulceration has been reported as a side effect. Anal ulceration is now included in the British National Formulary as a reported side effect.

Can also give the feeling of severe toothache, and nasal congestion

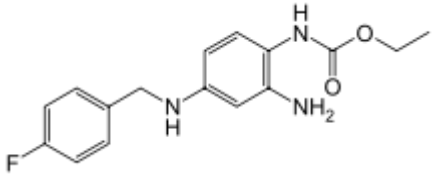
Pinacidil

Pinacidil	
	
IUPAC name	
N-cyano-*N*′-pyridin-4-yl-*N*″-(1,2,2-trimethylpropyl)guanidine	
Identifiers	
CAS number	85371-64-8
PubChem	4826
ChEMBL	CHEMBL1159 ✓
IUPHAR ligand	2412
Properties	
Molecular formula	$C_{13}H_{19}N_5$
Molar mass	245.32346

Pinacidil is a cyanoguanidine drug that opens ATP-sensitive potassium channels producing peripheral vasodilatation of arterioles. It reduces blood pressure and peripheral resistance and produces fluid retention.

Retigabine

Retigabine



Systematic (IUPAC) name	
ethyl *N*-[2-amino-4-[(4-fluorophenyl)methylamino]phenyl]carbamate	
Identifiers	
CAS number	150812-12-7
ATC code	N03AX21
PubChem	CID 121892
ChemSpider	108740
Chemical data	
Formula	$C_{16}H_{18}FN_3O_2$
Mol. mass	303.331 g/mol
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Bioavailability	60%
Protein binding	60–80%
Metabolism	Hepatic glucuronidation and acetylation. CYP not involved
Half-life	8 hours (mean)
Excretion	Renal (84%)
Therapeutic considerations	
Pregnancy cat.	N/A
Legal status	Investigational (phase III trials ongoing)
Routes	Oral

Retigabine (INN) or **ezogabine** (USAN), codenamed **D-23129**, is an anticonvulsant being investigated as a possible treatment for partial epilepsies. As of July 2010, several Phase III clinical trials are underway for this indication, and retigabine is being reviewed for approval by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The drug is being developed by Valeant Pharmaceuticals and GlaxoSmithKline, with the proposed trade name **Potiga**.

Retigabine works primarily as a potassium channel opener—that is, by activating a certain family of voltage-gated potassium channels in the brain. This mechanism of action is unique among antiepileptic drugs, and may hold promise for the treatment of other neurologic conditions, including migraine and neuropathic pain; a Phase II trial to assess the safety and efficacy of retigabine for treating postherpetic neuralgia is ongoing.

History

Among the newer anticonvulsants, retigabine was one of the most widely studied in the preclinical setting: it was the subject of over 100 published studies before clinical trials began. In preclinical tests, it was found to have a very broad spectrum of activity—being effective in nearly all the animal models of seizures and epilepsy used: retigabine suppresses seizures induced by electroshock, electrical kindling of the amygdala, pentylenetetrazol, kainate, NMDA, and picrotoxin. Researchers hoped this wide-ranging activity would translate to studies in humans as well.

Clinical trials and regulatory affairs

In a double-blind, randomized, placebo-controlled Phase II clinical trial, retigabine was added to the treatment regimen of 399 participants with partial seizures that were refractory to therapy with other antiepileptic drugs. The frequency with which seizures occurred was significantly reduced (by 23 to 35%) in participants receiving retigabine, and approximately one fourth to one third of participants had their seizure frequency reduced by more than 50%. Higher doses were associated with a greater response to treatment.

The U.S. Food and Drug Administration accepted Valeant's New Drug Application for retigabine on December 30, 2009, and the drug has been under review since. The FDA Peripheral and Central Nervous System Drugs Advisory Committee met on August 11, 2010 to discuss the process and unanimously recommended approval of Potiga. However, the possibility of urinary retention as an adverse effect was considered a significant concern, and the panel's members recommended that some sort of monitoring strategy be used to identify patients at risk of bladder dysfunction.

Adverse effects

The adverse effects found in the Phase II trial mainly affected the central nervous system, and appeared to be dose-related. The most common adverse effects were drowsiness,

dizziness and vertigo, confusion, and slurred speech. Less common side effects included tremor, memory loss, gait disturbances, and double vision.

Pharmacokinetics

Retigabine is quickly absorbed, and reaches maximum plasma concentrations in 1.5 hours after a single oral dose. It has a moderately high oral bioavailability (50–60%), a high volume of distribution (6.2 L/kg), and a terminal half-life of 8 to 11 hours. Retigabine appears to require thrice-daily dosing due to its short half-life.

Retigabine is metabolized in the liver, by *N*-glucuronidation and acetylation. The cytochrome P450 system is not involved. Retigabine and its metabolites are excreted by the kidneys.

Mechanism of action

Retigabine acts as a neuronal KCNQ/Kv7 potassium channel opener, a mechanism of action markedly different from than of any current anticonvulsants. This mechanism of action is similar to that of flupirtine, which is used mainly for its analgesic properties.

Interactions

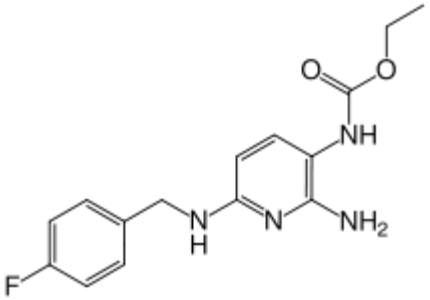
Retigabine appears to be free of drug interactions with most commonly used anticonvulsants. It may increase metabolism of lamotrigine (Lamictal), whereas phenytoin (Dilantin) and carbamazepine (CBZ, Tegretol) increase the clearance of retigabine.

Name

The International Nonproprietary Name "retigabine" was initially published as being under consideration by WHO in 1996. This was later adopted as the *recommended* International Nonproprietary Name (rINN) for the drug, and, in 2005 or 2006, the USAN Council—a program sponsored by the American Medical Association, the United States Pharmacopeial Convention, and the American Pharmacists Association that chooses nonproprietary names for drug sold in the United States—adopted the same name. In 2010, however, the USAN Council rescinded its previous decision and assigned "ezogabine" as the United States Adopted Name for the drug.

Flupirtine

Flupirtine



Systematic (IUPAC) name	
ethyl {2-amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl}carbamate	
Identifiers	
CAS number	56995-20-1
ATC code	N02BG07
PubChem	CID 53276
KEGG	D07978
Chemical data	
Formula	$C_{15}H_{17}FN_4O_2$
Mol. mass	304.32 g/mol

Flupirtine, an aminopyridine is a centrally acting nonopioid analgesic. It is available in Europe since 1984 and sold mainly under the names Katadolon, Trancolong and Metanor. It is unique as an non-opioid, non-NSAID, non-steroidal analgesic.

History

is a selective neuronal potassium channel opener that also has NMDA receptor antagonist properties. Flupirtine is a non-opioid, non-NSAID, non-steroidal, analgesic. Flupirtine was originally developed by Asta Medica and has been approved in Europe since 1984 for the treatment of pain, although it has never been introduced to the United States market for any indication. During 2008, Adeona obtained an option to license issued and pending patent applications relating to flupirtine's use in the treatment of these ophthalmic indications.

Uses

It is used as an analgesic for acute and chronic pain, mainly for moderate to severe pain. Muscle relaxant properties make it popular for back pain and other orthopaedic use but it is also used for migraine, in oncology, postoperative care and gynecology.It is a selective neuronal potassium channel opener that also has NMDA receptor antagonist properties.

It has been noted for its neuroprotective properties and possible uses for Creutzfeld-Jakob disease, Alzheimer's disease, and multiple sclerosis is being investigated.

It has been proposed as a possible treatment for Batten disease.

It is currently under a clinical trial (recruiting phase) as a treatment for multiple sclerosis. and Fibromyalgia in the US.

Clinical results in fibromyalgia

In May 2010, Adeona entered into a Sublicense Agreement (the "Agreement") pursuant to which the company granted Meda AB ("Meda") an exclusive sublicense to all of our patents covering the use of flupirtine for fibromyalgia. The Agreement provides that the Meda will assume all future development costs for the commercialization of flupirtine for fibromyalgia. As consideration for such sublicense, Adeona received an up-front payment of $2.5 million upon execution of the Agreement and are entitled to milestone payments of $5 million upon filing of a New Drug Application with the Food and Drug Administration for flupirtine for fibromyalgia and $10 million upon marketing approval.

Flupirtine shows promise for Fibromyalgia because it works differently than the three already approved FDA drugs, Lyrica,Savella, and Cymbalta.

In addition, there are case reports regarding flupirtine as a treatment for fibromyalgia. Several case reports are included in the description of the study published by Andrew L. Stoll, M.D., Belmont, MA for the use of flupirtine to treat fibromyalgia.

Case 1. Ms. S. is a 39-year-old married woman with approximately 3 years of fibromyalgia symptoms, characterized by pain in multiple joints, chronic fatigue, insomnia, and recent major depression. After numerous trials of nonsteroidal anti-inflammatory drugs, steroids, multiple antidepressant trials, opiates, and other strategies failed to relieve chronic headache and fibromyalgia symptoms, flupirtine was imported from Germany in an effort to reduce her pain. The flupirtine (up to 600 mg/day) did nothing to alter her headache pain but completely abolished her fibromyalgia pain, sleep disturbance, fatigue, and depressive symptoms within several days. Ms. S. has remained free of fibromyalgia symptoms for more than 18 months, receiving flupirtine at a dosage of 100 mg bid.

Case 4. Ms. B. is a 54-year-old woman with at least 5 years of systemic lupus erythrematosus, diffuse myofascial pain consistent with a fibromyalgia diagnosis, and

recurrent major depression. Numerous trials of corticosteroids, nonsteroidal anti-inflammatory drugs, opiate analgesics, and antidepressants failed to relieve her fibromyalgia symptoms. Flupirtine (100 mg qhs) was added to her medication regimen and increased over a 2-week period to 300 mg qhs. For the first time since the onset of her fibromyalgia, Ms. B. experienced substantial and gratifying relief from her myofascial pain. During her 5-month flupirtine trial, she also described a "miraculous" increase in energy and ability to concentrate. She has experienced no significant adverse effects.

Side effects

According to Adeona Pharmaceuticals, "substantial improvement in signs and symptoms was demonstrated in this difficult-to-treat fibromyalgia patient population."

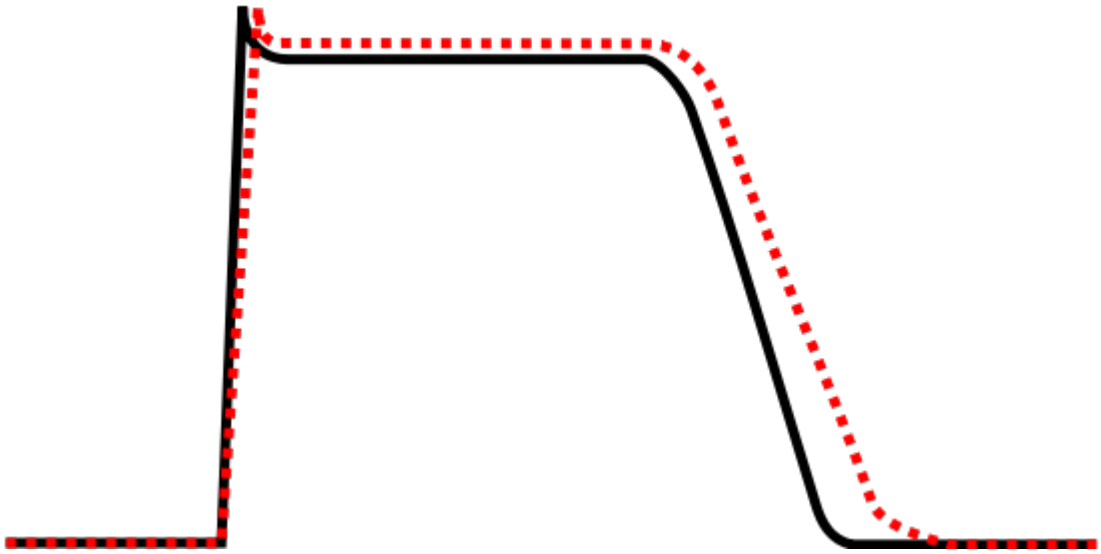
In addition, Effirma (flupirtine) was well tolerated by these patients with no untoward side effects.

Chapter 5

Potassium Channel Blocker

Potassium channel blockers are agents which interfere with conduction through potassium channels.

Arrhythmia



Effect of class III antiarrhythmic agent on cardiac action potential

Potassium channel blockers used in the treatment of cardiac arrhythmia are classified as class III antiarrhythmic agents.

Mechanism

Class III agents predominantly block the potassium channels, thereby prolonging repolarization. More specifically, their primary effect is on I_{Kr}.

Since these agents do not affect the sodium channel, conduction velocity is not decreased. The prolongation of the action potential duration and refractory period, combined with the maintenance of normal conduction velocity, prevent re-entrant arrhythmias. (The re-entrant rhythm is less likely to interact with tissue that has become refractory).

Class III antiarrhythmic agents exhibit reverse use dependent prolongation of the action potential duration (**Reverse use-dependence**). This means that the refractoriness of the ventricular myocyte increases at lower heart rates. This increases the susceptibility of the myocardium to early after-depolarizations (EADs) at low heart rates. Antiarrhythmic agents that exhibit reverse use-dependence are more efficacious at preventing a tachyarrhythmia than converting someone into normal sinus rhythm. *Because of the reverse use-dependence of class III agents, at low heart rates class III antiarrhythmic agents may paradoxically be more arrhythmogenic.*

Examples and uses

- Amiodarone is indicated for the treatment of refractory VT or VF, particularly in the setting of acute ischemia. Amiodarone is also safe to use in individuals with cardiomyopathy and atrial fibrillation, to maintain normal sinus rhythm. Amiodarone prolongation of the action potential is uniform over a wide range of heart rates so this drug does **not** have reverse use-dependent action. Amiodarone was the first agent described in this class.

- Dofetilide blocks only the rapid K channels; this means that at higher heart rates, when there is increased involvement of the slow K channels, dofetilide has less of an action potential-prolonging effect.

- Sotalol is indicated for the treatment of atrial or ventricular tachyarrhythmias, and AV re-entrant arrhythmias.

- Ibutilide is the only antiarrhythmic agent currently approved by the Food and Drug Administration for acute conversion of atrial fibrillation to sinus rhythm.

- Azimilide

- Bretylium

- Clofilium

- E-4031

- Nifekalant

- Tedisamil

- Sematilide

- Ampyra (recently approved for MS)

Side effects

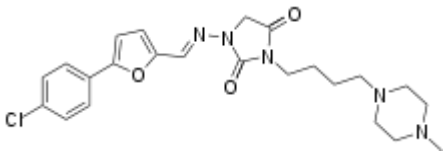
These agents include a risk of torsades de pointes.

Other uses

Potassium channel blockers have also been approved for use in the treatment of multiple sclerosis.

Azimilide

Azimilide



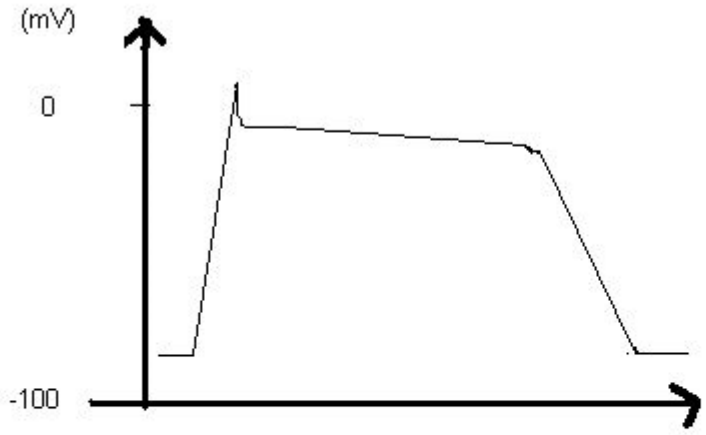
Systematic (IUPAC) name	
1-({(*E*)-[5-(4-chlorophenyl)furan-2-yl]methylidene}amino)-3-[4-(4-methylpiperazin-1-yl)butyl]imidazolidine-2,4-dione	
Identifiers	
CAS number	149908-53-2
ATC code	None
PubChem	CID 9571004
ChemSpider	7845470 ✓
Chemical data	
Formula	$C_{23}H_{28}ClN_5O_3$
Mol. mass	457.953 g·mol^{-1}
SMILES	eMolecules & PubChem

Azimilide is a class III antiarrhythmic drug (used to control abnormal heart rhythms). The agents from this heterogeneous group have an effect on the repolarization, they prolong the duration of the action potential and the refractory period. Also they slow down the spontaneous discharge frequency of automatic pacemakers by depressing the slope of diastolic depolarization. They shift the threshold towards zero or hyperpolarize

the membrane potential. Although each agent has its own properties and will have thus a different function.

Heart potential

Azimilide dihydrochloride is a chlorophenylfuranyl compound, which slows repolarization of the heart and prolongs the QT interval of the electrocardiogram. Prolongation of atrial or ventricular repolarization can provide an anti-arrhythmic benefit in patients with heart rhythm disturbances, and this has been the primary interest in the clinical development azimilide. In rare cases, excessive prolongation of ventricular repolarization by azimilide can result in predisposition towards severe ventricular arrhythmias. Most recent clinical trials have investigated the use of azimilide in reducing the frequency and severity of arrhythmias in patients with implanted cardiac pacemakers-defibrillators, where rare pro-arrhythmic events are rescued by the device.



HEART POTENTIAL

The ion currents

The action of azimilide is directed to the different currents present in atrial and ventricular cardiac myocytes. It principally blocks I_{Kr}, and I_{Ks}, with much weaker effects on I_{Na}, I_{Ca}, I_{NCX} and $I_{K.Ach}$. The I_{Kr}(rapid)and I_{Ks} (slow) are inward rectifier potassium currents, responsible for repolarizing cardiac myocytes towards the end of the cardiac action potential. A somewhat higher concentration of azimilide is needed to block the IKs current. Both blockages result in an increase of the QT interval and a prolongation of atrial and ventricular refractory periods.

Azimilide blocks hERG channels (which encode the I_{Kr} current) with an affinity comparable to that with which KvLQT1 / minK channels (which encode the I_{Ks} current) are blocked. This block exhibits reverse use-dependence, i.e. the channel blocking effect wanes at faster pulsing rates of the cell. A possible explanation is an interaction of azimilide with K^+ close to its binding site in the ion channel. However there is an agonist effect as well, which is a voltage-dependent effect. This is a dual effect, a low voltage depolarization near the activation threshold will increase the current amplitude and higher depolarizing voltages will suppress the current amplitude.The effect comes from outside of the cell membrane and does not depend on G-proteins or kinase activity inside the cell. Azimilide binds on the extracellular domain of the hERG channel, this propagates a conformational change and inhbits the current. This change makes the activation gate open more easily by low voltage depolarization. Azimilide has two separate binding sites in hERG channel,one for its antagonist function and the other for the agonist function.

Pharmacology

Azimilide has been studied for its anti-arrhythmic effects: its converts and maintains sinus rhythm in patients with atrial arrhythmias; and it reduces the frequency and severity of ventricular arrhythmias in patients with implanted cardioverter-defibrillators. Azimilide's most important adverse effect is torsades de pointes, which is a form of ventricular tachycardia.

Pharmacokinetics

The drug is administered orally and will be completely absorbed. It shows none or very minor interactions with other drugs and it will be eventually cleared by the kidney. A peak in concentration in the blood is observed seven hours after the administration of Azimilide. The metabolic clearance is mediated through several pathways:

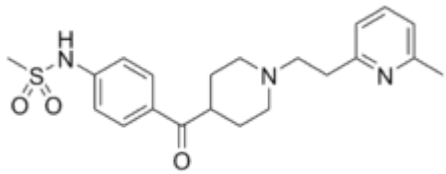
- 10% is found unchanged in the blood
- 30% will cleared by cleavage
- 25% by CYP 1A1 pathway
- 25% by CYP 3A4

F-1292 is the major metabolite of azimilide, it is formed cleavage of the aromethine bond. Unlike desmethyl azimilide, azimilide N-oxide and azimilide carboxylate F-1292 has no cardiovascular activity while the other three minor metabolites have a class III antiarrhythmic activity. They only make out 10% of azimilde in the blood, so their contribution is not measurable.

This use of azimilide is very controversial subject, but this article will give only the plain scientific information about this drug.

E-4031

E-4031



Systematic (IUPAC) name
N-[4-[1-[2-(6-Methylpyridin-2-yl)ethyl]piperidine-4-carbonyl]phenyl] methanesulfonamide

Identifiers	
CAS number	113558-89-7 113559-13-0 (dihydrochloride)
ATC code	?
PubChem	CID 3185
Synonyms	(1-[2-(6-methyl-2-pyridyl)ethyl]-4-(4-methylsulfonyl-aminobenzoyl)piperidine)

Chemical data	
Formula	$C_{21}H_{27}N_3O_3S$
Mol. mass	401.52 g/mol

E-4031 is an experimental class III antiarrhythmic drug that blocks potassium channels of the hERG-type.

Chemistry

E-4031 is a synthetized toxin that is a methanesulfonanilide class III antiarrhythmic drug.

Target

E-4031 acts on a specific class of voltage-gated potassium channels mainly found in the heart, the hERG channels. hERG channels (Kv11.1) mediate the I_{Kr} current, which repolarizes the myocardial cells. The hERG channel is encoded by ether-a-go-go related gene (hERG).

Mode of action

E-4031 blocks hERG-type potassium channels by binding to the open channels. Its structural target within the hERG-channel is unclear, but some other methanesulfonanilide class III antiarrhythmic drugs are known to bind to the S6 domain or C-terminal of the hERG-channel.

Reducing I_{Kr} in myocardial cells prolongs the cardiac action potential and thus prolongs the QT-interval. In non-cardiac cells, blocking I_{kr} has a different effect: it increases the frequency of action potentials.

Toxicity

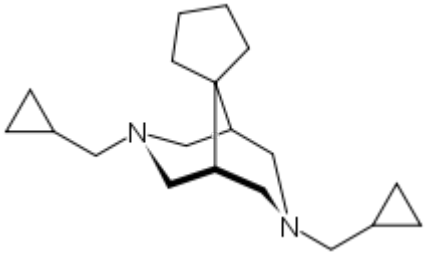
As E-4031 can prolong the QT-interval, it can cause lethal arrhythmias.

Therapeutic use

As of yet, E-4031 is solely used for research purposes. So far, one clinical trial has been conducted to test the effect of E-4031 on prolongation of the QT-interval.

Tedisamil

Tedisamil



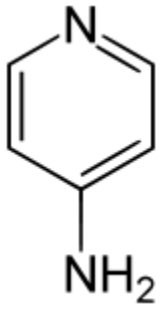
Systematic (IUPAC) name	
3,7-bis(cyclopropylmethyl)-3,7-diazaspiro[bicyclo[3.3.1]nonane-9,1'-cyclopentane]	
Identifiers	
CAS number	90961-53-8
ATC code	C01BD06
PubChem	CID 65825

KEGG	D06652 ✓
Chemical data	
Formula	$C_{19}H_{32}N_2$
Mol. mass	288.470 g/mol
SMILES	eMolecules & PubChem

Tedisamil (planned trade name **Pulzium**) is an investigational class III antiarrhythmic for atrial fibrillation and atrial flutter. It is currently being developed by Solvay and is currently under regulatory review by the United States Food and Drug Administration.

On April 25, 2007, Solvay submitted a New Drug Application for tedisamil, and on December 12, 2007, the Cardio-Renal Advisory Committee of the FDA voted against approval of tedisamil, at this time, requesting that Solvay Pharmaceuticals provides additional information to the FDA.

4-Aminopyridine

4-Aminopyridine	
	
IUPAC name pyridin-4-amine	
Other names 4-pyridinamine, 4-Pyridylamine, Fampridine	
Identifiers	
CAS number	504-24-5 ✓
PubChem	1727
ChemSpider	1664 ✓
UNII	BH3B64OKL9 ✓
KEGG	D04127 ✓
MeSH	4-Aminopyridine
ChEMBL	CHEMBL284348 ✓
IUPHAR ligand	2416
ATC code	N07XX07

Properties	
Molecular formula	$C_5H_6N_2$
Molar mass	94.1146
Appearance	colourless solid
Melting point	155-158 °C
Boiling point	273 °C, 546 K, 523 °F
Solubility in water	polar organic solvents
Pharmacology	
Bioavailability	96%
Routes of administration	Oral
Legal status	℞-only(US)
Pregnancy category	C(US)

4-Aminopyridine (dalfampridine) is an organic compound with the chemical formula $H_2NC_5H_4N$. The molecule is one of the three isomeric amines of pyridine. It is used primarily as a research tool, in characterizing subtypes of potassium channel, and has also been used to manage some of the symptoms of multiple sclerosis, for which it has orphan drug status in the United States under the INN **fampridine** (trade name **Neurelan**). It was undergoing Phase III clinical trials as of 2008, and the U.S. Food and Drug Administration (FDA) approved the compound on January 22, 2010. Dalfampridine is marketed as **Ampyra** (pronounced "am-PEER-ah," according to the maker's website) in the United States by Acorda Therapeutics and will be available in March 2010.

Production

4-Aminopyridine (4-AP) is prepared by the decarbonylation of pyridine-4-carboxamide using sodium hypochlorite via the Hofmann rearrangement. The pyridine carboxamide is generated from the corresponding nitrile, which in turn is obtained from ammoxidation of 4-methylpyridine.

Applications

The largest scale industrial application of 4-aminopyridine is as a precursor to the drug pinacidil, which affects potassium ion channels.

In the laboratory, 4-AP is a useful pharmacological tool in studying various potassium conductances in physiology and biophysics. It is a relatively selective blocker of members of Kv1 (Shaker, KCNA) family of voltage-activated K+ channels. At concentration of 1 mM it selectively and reversibly inhibits Shaker channels without significant effect on other sodium, calcium, and potassium conductances.

Vertebrate pesticide

4-Aminopyridine is also used as a bird control agent, under the trade name Avitrol; it causes convulsions and typically death, depending on dosage. The use of 4-aminopyridine in bird control has been criticized by the Humane Society of the United States.

Medical use

Fampridine has been used clinically in Lambert-Eaton myasthenic syndrome and multiple sclerosis. It acts by blocking potassium channels, prolonging action potentials and thereby increasing neurotransmitter release at the neuromuscular junction. The drug has been shown to reverse tetrodotoxin toxicity in animal experiments.

Multiple sclerosis

Fampridine has been shown to improve visual function and motor skills and relieve fatigue in patients with Multiple Sclerosis (MS). 4-AP is most effective in patients with the chronic progressive form of MS, in patients who are temperature sensitive, and in patients who have had MS for longer than three years. Common side effects include dizziness, nervousness and nausea, and the incidence of adverse effects was shown to be less than 5% in all studies.

4-AP works as a potassium channel blocker. Electrophysiologic studies of demyelinated axons show that augmented potassium currents increase extracellular potassium ion concentration which decreases action potential duration and amplitude which may cause conduction failure. Potassium channel blockade reverses this effect. However, a recent study has shown that 4-AP is a potent calcium channel activator and can improve synaptic and neuromuscular function by directly acting on the calcium channel beta subunit (J Biol Chem. 2009 Dec 25;284(52):36453-61).

MS patients treated with 4-AP exhibited a response rate of 29.5% to 80%. A long-term study (32 months) indicated that 80-90% of patients who initially responded to 4-AP exhibited long-term benefits. Although improving symptoms, 4-AP does not inhibit progression of MS.

Spinal cord injury patients have also seen improvement with 4-AP therapy. These improvements include sensory, motor and pulmonary function, with a decrease in spasticity and pain.

Overdose

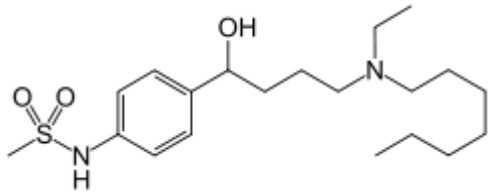
Case reports have shown that overdoses with 4-AP can lead to paresthesias, seizures, and atrial fibrillation.

Branding

The drug was originally intended, by Acorda Therapeutics, to have the brand name *Amaya*, however the name was changed to *Ampyra* to avoid potential confusion with other marketed pharmaceuticals.

Ibutilide

Ibutilide



Systematic (IUPAC) name	
N-(4-{4-[ethyl(heptyl)amino]-1-hydroxybutyl}phenyl)methanesulfonamide	
Identifiers	
CAS number	122647-32-9
ATC code	C01BD05
PubChem	CID 60753
DrugBank	APRD01025
ChemSpider	54755 ✓
UNII	9L5X4M5L6I ✓
KEGG	D00648 ✓
ChEMBL	CHEMBL533 ✓
Chemical data	
Formula	$C_{20}H_{36}N_2O_3S$
Mol. mass	384.578 g/mol
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Bioavailability	N/A

Protein binding	40%
Metabolism	Hepatic oxidation
Half-life	6 hours (2-12 hours)
Excretion	Renal (82%), fecal
Therapeutic considerations	
Pregnancy cat.	C
Routes	Intravenous

Ibutilide is a Class III antiarrhythmic agent that is indicated for acute cardioconversion of atrial fibrillation and atrial flutter of a recent onset to sinus rhythm. It exerts its antiarrhythmic effect by induction of slow inward sodium current, which prolongs action potential and refractory period (physiology) of myocardial cells. Because of its Class III antiarrhythmic activity, there should not be concomitant administration of Class Ia and Class III agents.

Ibutilide is marketed as **Corvert** by Pfizer. Administration resulted in successful heart rhythm control in 31-44% of patients within 90 minutes, with sustained polymorphic ventricular tachycardia in 0.9-2.5% of patients. It appears to show better results in atrial flutter as compared to atrial fibrillation.

Mechanism of action

Unlike most other Class III antiarrhythmic drugs, ibutilide does not produce its prolongation of action potential via blockade of cardiac delayed rectifier of potassium current, nor does it have a sodium-blocking, antiadrenergic, and calcium blocking activity that other Class III agents possess. Thus it is often referred as a “pure” Class III antiarrhythmic drug.

It does have action on the slow sodium channel and promotes the influx of sodium through these slow channels.

Although potassium current seems to play a role, their interactions are complex and not well understood. Ibutilide’s unique mechanism works by an activation of a specific inward sodium current, thus producing its therapeutic response in which a prolonged action potential increases myocytes’ cardiac refractoriness in case of atrial fibrillation and flutter.

Pharmacokinetics

Absorption

Ibutilide is intravenously administered. It has a high first-pass metabolism, which results in a poor bioavailability when taken orally. Individual pharmacokinetic properties are highly viable during the clinical trial.

Distribution

Ibutilide has a relatively large volume of distribution among individual subjects, which is about 11L/kg. Approximately 40% of the drug is bound with plasma albumin of healthy volunteers in a trial. This is also approximately close to patients with atrial fibrillation and flutter.

Metabolism

Ibutilide has a high systemic plasma clearance that closes to the hepatic blood flow (29mL/min/kg). Its metabolic pathway is via liver's cytochrome P450 system by isoenzymes other than CYP3A4 and CYP2D6 by which the heptyl side chain of ibutilide is oxidized. With eight metabolites are detected in the urine, however, only one is an active metabolite that shares the similar electrophysiologic property of the Class III antiarrhythmic agents. The plasma concentration of this metabolite is only less than 10% of ibutilide.

Excretion

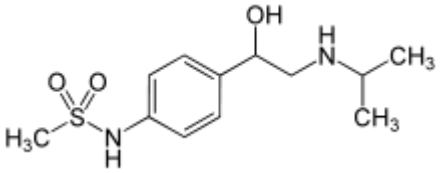
After administration of ibutilide, it is quickly excreted by renal pathway with a half-life of approximately 6 hours. Approximately 82% of a 0.01 mg/kg dose is excreted in the urine during the trial. Among those, around 7% is excreted as unchanged drug. The reminder of the drug is excreted in feces (about 19%).

Patient Information

This medication will be given intravenously for your heart disease. You will have continuously ECG monitoring during the infusion and 4 hours after your infusion. Some of the minor side effects are headache and irregular heartbeat. If you experience chest pain and respiratory difficulties, you should report to your doctors immediately.

Sotalol

Sotalol



Systematic (IUPAC) name	
(*RS*)-*N*-{4-[1-hydroxy-2-(propan-2-ylamino)ethyl]phenyl}methanesulfonamide	
Identifiers	
CAS number	3930-20-9
ATC code	C07AA07
PubChem	CID 5253
DrugBank	DB00489
ChemSpider	5063 ✓
UNII	A6D97U294I ✓
KEGG	D08525 ✓
ChEMBL	CHEMBL471 ✓
Chemical data	
Formula	$C_{12}H_{20}N_2O_3S$
Mol. mass	272.3624 g/mol
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Bioavailability	>95%
Metabolism	Not metabolized[]
Half-life	12 hours
Excretion	Renal Lactic (In lactating females)
Therapeutic considerations	
Pregnancy cat.	B(US)

Legal status	℞ Prescription only
Routes	oral

Sotalol (trade names **Betapace** and **Betapace AF**, Berlex Laboratories, **Sotalex** and **Sotacor**, Bristol-Myers Squibb) is a drug used in individuals with rhythm disturbances (cardiac arrhythmias) of the heart, and to treat hypertension in some individuals.

Sotalol is a non-selective beta blocker. It is also a potassium channel blocker and is therefore a class III anti-arrhythmic agent. Because of this dual-action, Sotalol prolongs both the PR interval and the QT interval.

Indications

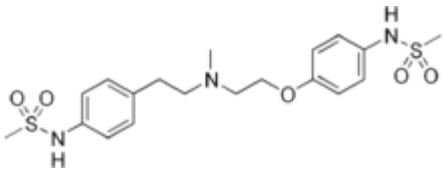
Sotalol is used to treat ventricular tachycardias as well as atrial fibrillation. Betapace AF is specifically labeled for atrial fibrillation.

Some evidence suggests that sotalol should be avoided in the setting of decreased ejection fraction due to an increased risk of death.

It has also been suggested that it be used in the prevention of atrial fibrillation.

Dofetilide

Dofetilide



Systematic (IUPAC) name
N-[4-(2-{[2-(4-methane sulfonamidophenoxy)ethyl](methyl)amino}ethyl)phenyl]methanesulfonamide

Identifiers	
CAS number	115256-11-6
ATC code	C01BD04
PubChem	CID 71329
DrugBank	APRD00367

ChemSpider	64435 ✓
UNII	R4Z9X1N2ND ✓
KEGG	D00647 ✓
ChEMBL	CHEMBL473 ✓
Chemical data	
Formula	$C_{19}H_{27}N_3O_5S_2$
Mol. mass	441.567 g/mol
SMILES	eMolecules & PubChem
Pharmacokinetic data	
Bioavailability	96% (oral)
Protein binding	60% -70%
Half-life	10 hours

Dofetilide is a class III antiarrhythmic agent.

It is marketed under the trade name **Tikosyn** by Pfizer, and is available in the United States in capsules containing 125, 250, and 500 μg of dofetilide.

Due to the pro-arrhythmic potential of dofetilide, it is only available by prescription by physicians who have undergone specific training in the risks of treatment with dofetilide. In addition, it is only available by mail order or through specially trained local pharmacies to individuals who are prescribed dofetilide by a physician who is registered as being able to prescribe the pharmaceutical.

Uses

It is used for the maintenance of sinus rhythm in individuals prone to the formation of atrial fibrillation and flutter, and for the chemical cardioversion to sinus rhythm from atrial fibrillation and flutter.

Pharmacokinetics

The elimination half-life of dofetilide is roughly 10 hours, however this is variable based on many physiologic factors (most significantly creatinine clearance), and ranges from 4.8 to 13.5 hours.

Mechanism of action

Dofetilide works by selectively blocking the rapid component of the delayed rectifier outward potassium current (I_{Kr}).

This causes the refractory period of atrial tissue to increase, hence its effectiveness in the treatment of atrial fibrillation and atrial flutter.

Dofetilide does not effect V_{max} (The slope of the upstroke of phase 0 depolarization), conduction velocity, or the resting membrane potential.

There is a dose-dependent increase in the QT interval and the corrected QT interval (QTc). Because of this, many practitioners will initiate dofetilide therapy only on individuals under telemetry monitoring or if serial EKG measurements of QT and QTc can be performed.

Metabolism

A steady-state plasma level of dofetilide is achieved in 2–3 days.

80% of dofetilide is excreted by the kidneys, so the dose of dofetilide should be adjusted in individuals with renal insufficiency, based on creatinine clearance.

In the kidneys, dofetilide is eliminated via cation exchange (secretion). Agents that interfere with the renal cation exchange system, such as verapamil, cimetidine, hydrochlorothiazide, itraconazole, ketoconazole, prochlorperazine, and trimethoprim should not be administered to individuals taking dofetilide.

About 20 percent of dofetilide is metabolized in the liver via the CYP3A4 isoenzyme of the cytochrome P450 enzyme system. Drugs that interfere with the activity of the CYP3A4 isoenzyme can increase serum dofetilide levels. If the renal cation exchange system is interfered with (as with the medications listed above), a larger percentage of dofetilide is cleared via the CYP3A4 isoenzyme system.

Side effects

Torsades de pointes is the most serious side effect of dofetilide therapy. The incidence of torsades de pointes is dose-related, and is 0.3-10.5%. The risk appears to be dose-dependent, with an increased incidence of torsades de pointes associated with higher doses of dofetilide administered.

The risk of inducing torsades de pointes can be decreased by taking precautions when initiating therapy, such as hospitalizing individuals for a minimum of three days for serial creatinine measurement, continuous telemetry monitoring and availability of cardiac resuscitation.

Clinical use

Based on the results of the Danish Investigations of Arrhythmias and Mortality on Dofetilide (DIAMOND) study, dofetilide does not affect mortality in the treatment of patients post-myocardial infarction with left ventricular dysfunction. Because of the

results of the DIAMOND study, many physicians use dofetilide in the suppression of atrial fibrillation in individuals with LV dysfunction.

Chapter 6

Sodium Channel

Sodium channels are integral membrane proteins that form ion channels, conducting sodium ions (Na^+) through a cell's plasma membrane. They are classified according to the trigger that opens the channel for such ions, i.e. either a voltage-change (voltage-gated sodium channels) or binding of a substance (a ligand) to the channel (ligand-gated sodium channels).

In excitable cells such as neurons, myocytes, and certain types of glia, sodium channels are responsible for the rising phase of action potentials.

Voltage-gated

Structure

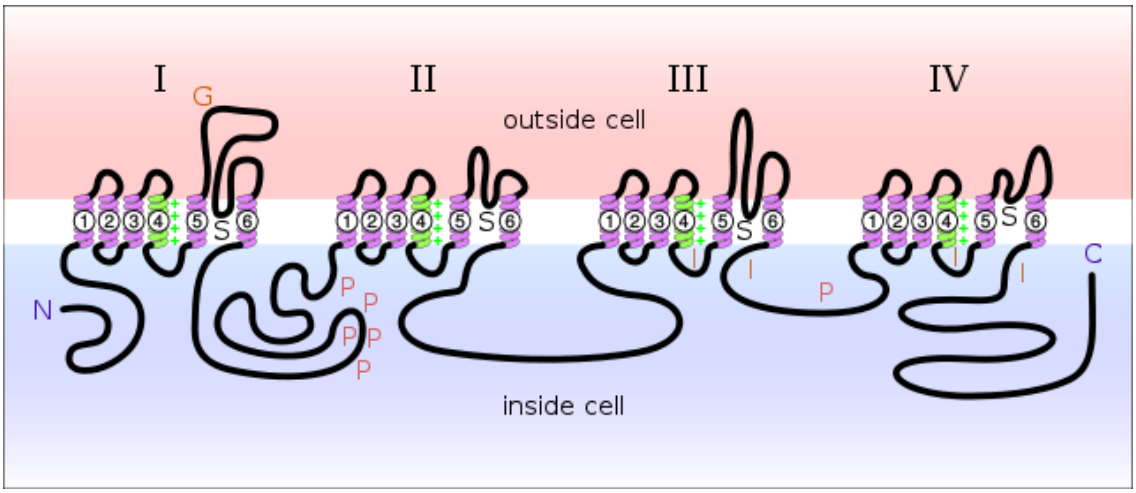


Diagram of a voltage-sensitive sodium channel α-subunit. G - glycosylation, P - phosphorylation, S - ion selectivity, I - inactivation, positive (+) charges in S4 are important for transmembrane voltage sensing.

Sodium channels consist of a large α subunit that associates with other proteins, such as β subunits. An α subunit forms the core of the channel and is functional on its own. When the α subunit protein is expressed by a cell, it is able to form channels that conduct Na^+ in a voltage-gated way, even if β subunits or other known modulating proteins are not

expressed. When accessory proteins assemble with α subunits, the resulting complex can display altered voltage dependence and cellular localization.

The α-subunit has four repeat domains, labeled I through IV, each containing six membrane-spanning regions, labeled S1 through S6. The highly conserved S4 region acts as the channel's voltage sensor. The voltage sensitivity of this channel is due to positive amino acids located at every third position. When stimulated by a change in transmembrane voltage, this region moves toward the extracellular side of the cell membrane, allowing the channel to become permeable to ions. The ions are conducted through a pore, which can be broken into two regions. The more external (i.e., more extracellular) portion of the pore is formed by the "P-loops" (the region between S5 and S6) of the four domains. This region is the most narrow part of the pore and is responsible for its ion selectivity. The inner portion (i.e., more cytoplasmic) of the pore is formed by the combined S5 and S6 regions of the four domains. The region linking domains III and IV is also important for channel function. This region plugs the channel after prolonged activation, inactivating it.

Gating

Voltage-gated sodium channels have three types of states: deactivated (closed), activated (open), and inactivated (closed). Channels in the deactivated state are thought to be blocked on their intracellular side by an "activation gate", which is removed in response to stimulation that opens the channel. The ability to inactivate is thought to be due to a tethered plug (formed by domains III and IV of the alpha subunit), called an inactivation gate, that blocks the inside of the channel shortly after it has been activated. During an action potential the channel remains inactivated for a few milliseconds after depolarization. The inactivation is removed when the membrane potential of the cell repolarizes following the falling phase of the action potential. This allows the channels to be activated again during the next action potential. Genetic diseases that alter sodium channel inactivation can cause muscle stiffness or epileptic seizures because of the introduction of a so-called window current, during which sodium channels are tonically active, causing muscle and/or nerve cells to become over-excited.

The temporal behaviour of sodium channels can be modeled by a Markovian scheme or by the Hodgkin-Huxley-type formalism. In the former scheme, each channel occupies a distinct state with differential equations describing transitions between states; in the latter, the channels are treated as a population that are affected by three independent gating variables. Each of these variables can attain a value between 1 (fully permeant to ions) and 0 (fully non-permeant), the product of these variables yielding the percentage of conducting channels.

Impermeability to other ions

The pore of sodium channels contains a selectivity filter made of negatively charged amino acid residues, which attract the positive Na^+ ion and keep out negatively charged ions such as chloride. The cations flow into a more constricted part of the pore that is 0.3

by 0.5 nm wide, which is just large enough to allow a single Na^+ ion with a water molecule associated to pass through. The larger K^+ ion cannot fit through this area. Differently sized ions also cannot interact as well with the negatively charged glutamic acid residues that line the pore.

Diversity

Voltage-gated sodium channels normally consist of an alpha subunit that forms the ion conduction pore and one to two beta subunits that have several functions including modulation of channel gating. Expression of the alpha subunit alone is sufficient to produce a functional channel.

Alpha subunits

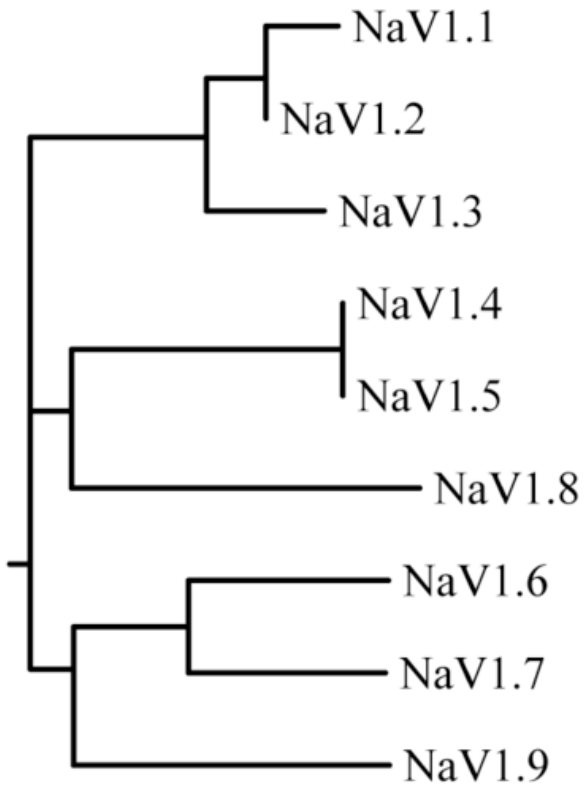


Figure 1. Likely evolutionary relationship of the nine known human sodium channels

The family of sodium channels has nine known members, with amino acid identity >50% in the transmembrane and extracellular loop regions. A standardized nomenclature for sodium channels is currently used and is maintained by the IUPHAR.

The proteins of these channels are named $Na_v1.1$ through $Na_v1.9$. The gene names are referred to as SCN1A through SCN11A (the SCN6/7A gene is part of the Na_x sub-family and has uncertain function). The likely evolutionary relationship between these channels, based on the similarity of their amino acid sequences, is shown in figure 1. The individual sodium channels are distinguished not only by differences in their sequence but also by their kinetics and expression profiles. Some of this data is summarized in table 1, below.

Table 1. Nomenclature and some functions of voltage-gated sodium channel alpha subunits

Protein name	Gene	Expression profile	Associated human channelopathies
$Na_v1.1$	*SCN1A*	Central neurons, [peripheral neurons] and cardiac myocytes	febrile epilepsy, GEFS+, Dravet syndrome (also known as *severe myclonic epilepsy of infancy* or SMEI), borderline SMEI (SMEB), West syndrome (also known as *infantile spasms*), Doose syndrome (also known as *myoclonic astatic epilepsy*), intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTC), Panayiotopoulos syndrome, familial hemiplegic migraine (FHM), familial autism, Rasmussens's encephalitis and Lennox-Gastaut syndrome
$Na_v1.2$	*SCN2A*	Central neurons, peripheral neurons	inherited febrile seizures and epilepsy
$Na_v1.3$	*SCN3A*	Central neurons, peripheral neurons and cardiac myocytes	none known
$Na_v1.4$	*SCN4A*	Skeletal muscle	hyperkalemic periodic paralysis, paramyotonia congenita, and potassium-aggravated myotonia
$Na_v1.5$	*SCN5A*	Cardiac myocytes, uninnervated skeletal muscle, central neurons	Long QT syndrome, Brugada syndrome, and idiopathic ventricular fibrillation
$Na_v1.6$	*SCN8A*	Central neurons, dorsal root ganglia, peripheral neurons, heart, glia cells	none known
$Na_v1.7$	*SCN9A*	Dorsal root ganglia, sympathetic neurons, Schwann cells, and neuroendocrine cells	erythromelalgia, PEPD and channelopathy-associated insensitivity to pain
$Na_v1.8$	*SCN10A*	Dorsal root ganglia	none known
$Na_v1.9$	*SCN11A*	Dorsal root ganglia	none known

Na_x	*SCN7A*	heart, uterus, skeletal muscle, astrocytes, dorsal root ganglion cells	none known

Beta subunits

Sodium channel beta subunits are type 1 transmembrane glycoproteins with an extracellular N-terminus and a cytoplasmic C-terminus. As a member of the Ig superfamily, beta subunits contain a prototypic V-set Ig loop in their extracellular domain. Interestingly, beta subunits share no homology with their counterparts of calcium and potassium channels. Instead, they are homologous to neural cell adhesion molecules (CAMs) and the large family of L1 CAMs. There are four distinct betas named in order of discovery: SCN1B, SCN2B, SCN3B, SCN4B (table 2). Beta 1 and beta 3 interact with the alpha subunit non-covalently while beta 2 and beta 4 associate with alpha via disulfide bond.

Role of beta subunits as cell adhesion molecules

In addition to regulating channel gating, sodium channel beta subunits also modulate channel expression and form links to the intracelluar cytoskeleton via ankyrin and spectrin. Voltage-gated sodium channels also assemble with a variety of other proteins, such as FHF proteins (*F*ibroblast growth factor *H*omologous *F*actor), calmodulin, cytoskeleton or regulatory kinases, which form a complex with sodium channels, influencing its expression and/or function. Several beta subunits interact with one or more extracellular matrix (ECM) molecules. Contactin, also known as F3 or F11, associates with beta 1 as shown via co-immunoprecipitation. Fibronectin-like (FN-like) repeats of Tenascin-C and Tenascin-R bind with beta 2 in contrast to the Epidermal growth factor-like (EGF-like) repeats that repel beta2. A disintegrin and metalloproteinase (ADAM) 10 sheds beta 2's ectodomain possibly inducing neurite outgrowth. Beta 3 and beta 1 bind to neurofascin at Nodes of Ranvier in developing neurons.

Table 2. Nomenclature and some functions of voltage-gated sodium channel beta subunits

Protein name	Gene link	Assembles with	Expression profile	Associated human channelopathies
$Na_v\beta1$	*SCN1B*	$Na_v1.1$ to $Na_v1.7$	Central Neurons, Peripheral Neurons, skeletal muscle, heart, glia	epilepsy (GEFS+)
$Na_v\beta2$	*SCN2B*	$Na_v1.1$, $Na_v1.2$, $Na_v1.5$ to $Na_v1.7$	Central Neurons, peripheral neurons, heart, glia	none known
$Na_v\beta3$	*SCN3B*	$Na_v1.1$ to $Na_v1.3$, $Na_v1.5$	central neurons, adrenal gland, kidney, peripheral neurons	none known

$Na_v\beta4$	*SCN4B*	$Na_v1.1$, $Na_v1.2$, $Na_v1.5$	heart, skeletal muscle, central and peripheral neurons	none known

Ligand-gated

Ligand-gated sodium channels are activated by binding of a ligand instead of a change in membrane potential.

They are found e.g. in the neuromuscular junction as nicotinic receptors, where the ligands are acetylcholine molecules. Most channels of this type are permeable to potassium to some degree as well as to sodium.

Role in action potential

Voltage-gated sodium channels play an important role in action potentials. If enough channels open when there is a change in the cell's membrane potential, a small but significant number of Na^+ ions will move into the cell down their electrochemical gradient, further depolarizing the cell. Thus, the more Na^+ channels localized in a region of a cell's membrane, the faster the action potential will propagate, and the more **excitable** that area of the cell will be. This is an example of a positive feedback loop. The ability of these channels to assume a closed-inactivated state causes the refractory period and is critical for the propagation of action potentials down an axon.

Na^+ channels both open and close more quickly than K^+ channels, producing an influx of positive charge (Na^+) toward the beginning of the action potential and an efflux (K^+) toward the end.

Ligand-gated sodium channels, on the other hand, create the change in the membrane potential in the first place, in response to the binding of a ligand to it.

Pharmacologic modulation

Activators

The following naturally produced substances persistently activate (open) sodium channels:

- Alkaloid based toxins
  - aconitine
  - batrachotoxin
  - brevetoxin
  - ciguatoxin
  - delphinine
  - grayanotoxin
  - veratridine

Gating modifiers

The following toxins modify the gating of sodium channels:

- Peptide based toxins
  - μ-conotoxin
  - δ-atracotoxin
  - Scorpion venom toxins, such as Birtoxin

Chapter 7

Action Potential

An **action potential** is a short-lasting event in which the electrical membrane potential of a cell rapidly rises and falls, following a consistent trajectory. Action potentials occur in several types of animal cells, called excitable cells, which include neurons, muscle cells, and endocrine cells, as well as in some plant cells. In neurons, they play a central role in cell-to-cell communication. In other types of cells, their main function is to activate intracellular processes. In muscle cells, for example, an action potential is the first step in the chain of events leading to contraction. In beta cells of the pancreas, they provoke release of insulin. Action potentials in neurons are also known as "nerve impulses" or "spikes", and the temporal sequence of action potentials generated by a neuron is called its "spike train". A neuron that emits an action potential is often said to "fire".

Action potentials are generated by special types of voltage-gated ion channels embedded in a cell's plasma membrane. These channels are shut when the membrane potential is near the resting potential of the cell, but they rapidly begin to open if the membrane potential increases to a precisely defined threshold value. When the channels open, they allow an inward flow of sodium ions, which changes the electrochemical gradient, which in turn produces a further rise in the membrane potential. This then causes more channels to open, producing a greater electric current, and so on. The process proceeds explosively until all of the available ion channels are open, resulting in a large upswing in the membrane potential. The rapid influx of sodium ions causes the polarity of the plasma membrane to reverse, and the ion channels then rapidly inactivate. As the sodium channels close, sodium ions can no longer enter the neuron, and they are actively transported out of the plasma membrane. Potassium channels are then activated, and there is an outward current of potassium ions, returning the electrochemical gradient to the resting state. After an action potential has occurred, there is a transient negative shift, called the afterhyperpolarization or refractory period, due to additional potassium currents. This is the mechanism which prevents an action potential traveling back the way it just came.

In animal cells, there are two primary types of action potentials, one type generated by voltage-gated sodium channels, the other by voltage-gated calcium channels. Sodium-based action potentials usually last for less than one millisecond, whereas calcium-based action potentials may last for 100 milliseconds or longer. In some types of neurons, slow calcium spikes provide the driving force for a long burst of rapidly-emitted sodium spikes. In cardiac muscle cells, on the other hand, an initial fast sodium spike provides a

"primer" to provoke the rapid onset of a calcium spike, which then produces muscle contraction.

Overview for a typical neuron

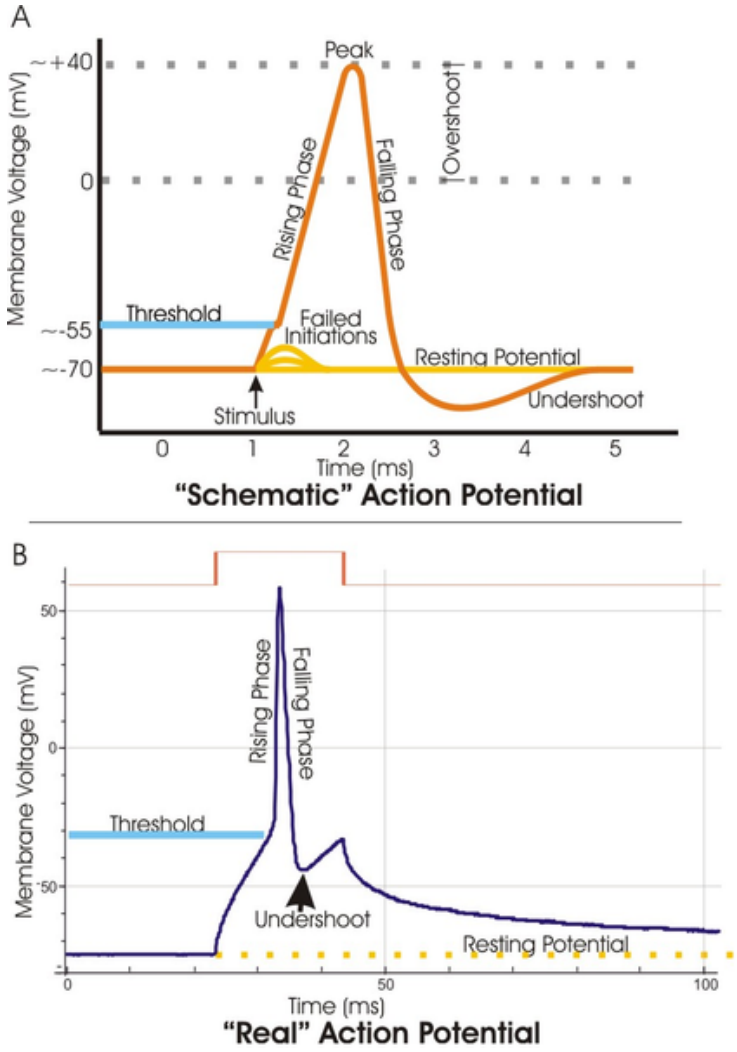


Figure 1. **A.** view of an idealized action potential shows its various phases as the action potential passes a point on a cell membrane. **B.** Recordings of action potentials are often distorted compared to the schematic view because of variations in electrophysiological techniques used to make the recording.

All cells in animal body tissues are electrically polarized—in other words, they maintain a voltage difference across the cell's plasma membrane, known as the membrane potential. This electrical polarization results from a complex interplay between protein structures embedded in the membrane called ion pumps and ion channels. In neurons, the types of ion channels in the membrane usually vary across different parts of the cell, giving the dendrites, axon, and cell body different electrical properties. As a result, some parts of the membrane of a neuron may be excitable (capable of generating action potentials) while others are not. The most excitable part of a neuron is usually the axon

hillock (the point where the axon leaves the cell body), but the axon and cell body are also excitable in most cases.

Each excitable patch of membrane has two important levels of membrane potential: the resting potential, which is the value the membrane potential maintains as long as nothing perturbs the cell, and a higher value called the threshold potential. At the axon hillock of a typical neuron, the resting potential is around -70 millivolts (mV) and the threshold potential is around -55 mV. Synaptic inputs to a neuron cause the membrane to depolarize or hyperpolarize; that is, they cause the membrane potential to rise or fall. Action potentials are triggered when enough depolarization accumulates to bring the membrane potential up to threshold. When an action potential is triggered, the membrane potential abruptly shoots upward, often reaching as high as +100 mV, then equally abruptly shoots back downward, often ending below the resting level, where it remains for some period of time. The shape of the action potential is stereotyped; that is, the rise and fall usually have approximately the same amplitude and time course for all action potentials in a given cell. In most neurons, the entire process takes place in less than a thousandth of a second. Many types of neurons emit action potentials constantly at rates of up to 10-100 per second; some types, however, are much quieter, and may go for minutes or longer without emitting any action potentials.

At the biophysical level, action potentials result from special types of voltage-gated ion channels. As the membrane potential is increased, sodium ion channels open, allowing the entry of sodium ions into the cell. This is followed by the opening of potassium ion channels that permit the exit of potassium ions from the cell. The inward flow of sodium ions increases the concentration of positively-charged cations in the cell and causes depolarization, where the potential of the cell is higher than the cell's resting potential. The sodium channels close at the peak of the action potential, while potassium continues to leave the cell. The efflux of potassium ions decreases the membrane potential or hyperpolarizes the cell. For small voltage increases from rest, the potassium current exceeds the sodium current and the voltage returns to its normal resting value, typically −70 mV. However, if the voltage increases past a critical threshold, typically 15 mV higher than the resting value, the sodium current dominates. This results in a runaway condition whereby the positive feedback from the sodium current activates even more sodium channels. Thus, the cell "fires," producing an action potential.

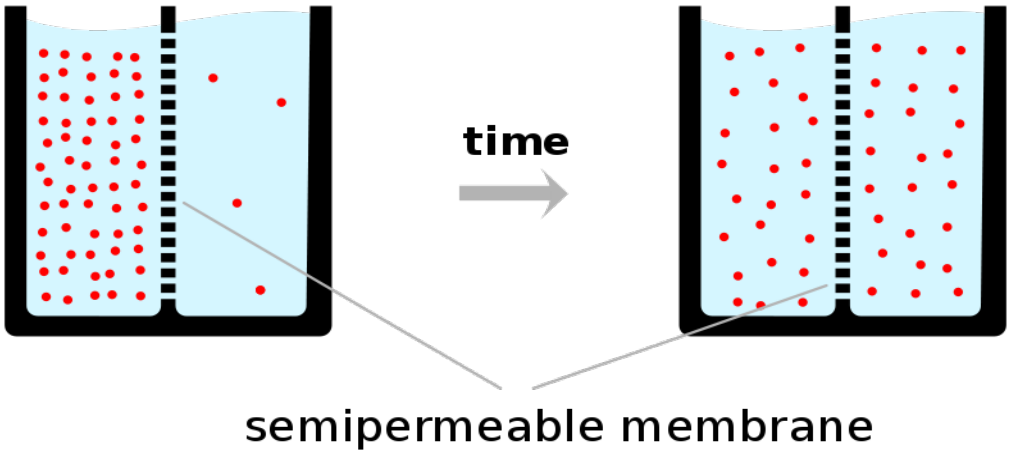
Currents produced by the opening of voltage-gated channels in the course of an action potential are typically significantly larger than the initial stimulating current. Thus the amplitude, duration, and shape of the action potential are largely determined by the properties of the excitable membrane and not the amplitude or duration of the stimulus. This all-or-nothing property of the action potential sets it apart from graded potentials such as receptor potentials, electrotonic potentials, and synaptic potentials, which scale with the magnitude of the stimulus. A variety of action potential types exist in many cell types and cell compartments as determined by the types of voltage-gated channels, leak channels, channel distributions, ionic concentrations, membrane capacitance, temperature, and other factors.

The principal ions involved in an action potential are sodium and potassium cations; sodium ions enter the cell, and potassium ions leave, restoring equilibrium. Relatively few ions need to cross the membrane for the membrane voltage to change drastically. The ions exchanged during an action potential, therefore, make a negligible change in the interior and exterior ionic concentrations. The few ions that do cross are pumped out again by the continual action of the sodium–potassium pump, which, with other ion transporters, maintains the normal ratio of ion concentrations across the membrane. Calcium cations and chloride anions are involved in a few types of action potentials, such as the cardiac action potential and the action potential in the single-celled alga *Acetabularia*, respectively.

Although action potentials are generated locally on patches of excitable membrane, the resulting currents can trigger action potentials on neighboring stretches of membrane, precipitating a domino-like propagation. In contrast to passive spread of electric potentials (electrotonic potential), action potentials are generated anew along excitable stretches of membrane and propagate without decay. Myelinated sections of axons are not excitable and do not produce action potentials and the signal is propagated passively as electrotonic potential. Regularly spaced unmyelinated patches, called the nodes of Ranvier, generate action potentials to boost the signal. Known as saltatory conduction, this type of signal propagation provides a favorable tradeoff of signal velocity and axon diameter. Depolarization of axon terminals, in general, triggers the release of neurotransmitter into the synaptic cleft. In addition, backpropagating action potentials have been recorded in the dendrites of pyramidal neurons, which are ubiquitous in the neocortex. These are thought to have a role in spike-timing-dependent plasticity.

Biophysical and cellular context

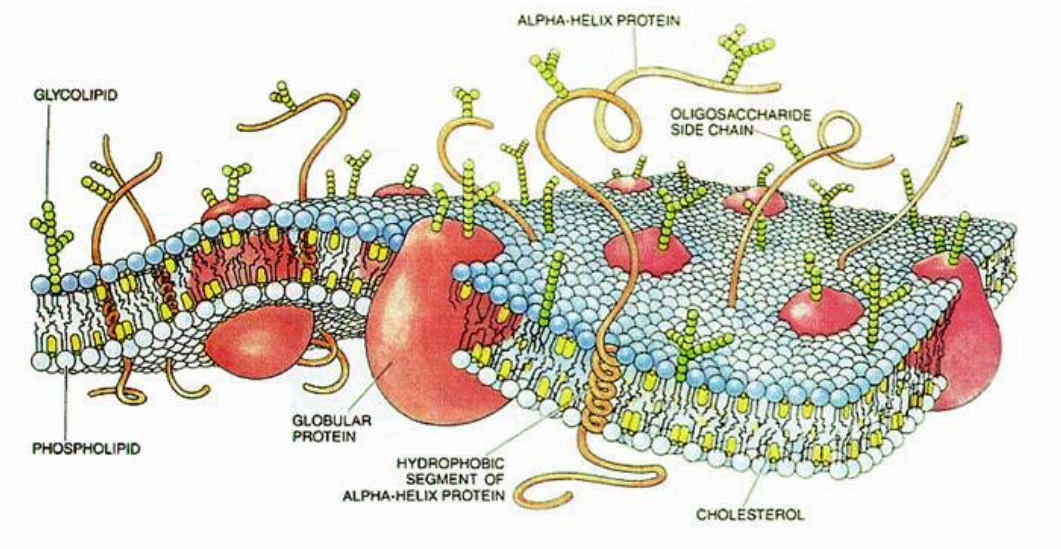
Ions and the forces driving their motion



Ions (pink circles) will flow across a membrane from the higher concentration to the lower concentration (down a concentration gradient), causing a current. However, this creates a voltage across the membrane that opposes the ions' motion. When this voltage reaches the equilibrium value, the two balance and the flow of ions stops.

Electrical signals within biological organisms are, in general, driven by ions. The most important cations for the action potential are sodium (Na^+) and potassium (K^+). Both of these are *monovalent* cations that carry a single positive charge. Action potentials can also involve calcium (Ca^{2+}), which is a *divalent* cation that carries a double positive charge. The chloride anion (Cl^-) plays a major role in the action potentials of some algae, but plays a negligible role in the action potentials of most animals.

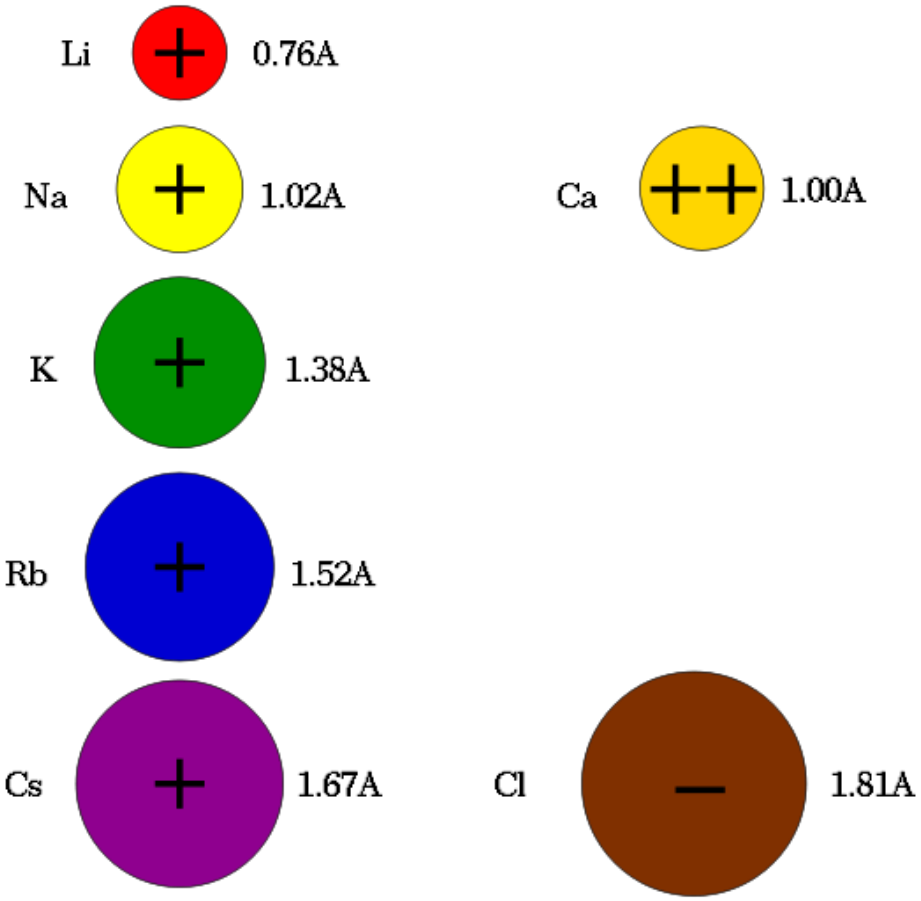
Ions cross the cell membrane under two influences: diffusion and electric fields. A simple example wherein two solutions—A and B—are separated by a porous barrier illustrates that diffusion will ensure that they will eventually mix into equal solutions. This mixing occurs because of the difference in their concentrations. The region with high concentration will diffuse out toward the region with low concentration. To extend the example, let solution A have 30 sodium ions and 30 chloride ions. Also, let solution B have only 20 sodium ions and 20 chloride ions. Assuming the barrier allows both types of ions to travel through it, then a steady state will be reached whereby both solutions have 25 sodium ions and 25 chloride ions. If, however, the porous barrier is selective to which ions are let through, then diffusion alone will not determine the resulting solution. Returning to the previous example, let's now construct a barrier that is permeable only to sodium ions. Since solution B has a lower concentration of both sodium and chloride, the barrier will attract both ions from solution A. However, only sodium will travel through the barrier. This will result in an accumulation of sodium in solution B. Since sodium has a positive charge, this accumulation will make solution B more positive relative to solution A. Positive sodium ions will be less likely to travel to the now-more-positive B solution. This constitutes the second factor controlling ion flow, namely electric fields. The point at which this electric field completely counteracts the force due to diffusion is called the equilibrium potential. At this point, the net flow of this specific ion (in this case sodium) is zero.



The hydrophobic cell membrane prevents charged molecules from easily diffusing through it, permitting a potential difference to exist across the membrane

Cell membrane

Each neuron is encased in a cell membrane, made of a phospholipid bilayer. This membrane is nearly impermeable to ions. To transfer ions into and out of the neuron, the membrane provides two structures. Ion pumps use the cell's energy to continuously move ions in and out. They create concentration differences (between the inside and outside of the neuron) by transporting ions against their concentration gradients (from regions of low concentration to regions of high concentration). The ion channels then use this concentration difference to transport ions down their concentration gradients (from regions of high concentration to regions of low concentration). However, unlike the continuous transport by the ion pumps, the transport by the ion channels is noncontinuous. They open and close in response to signals only from their environment. This transport of ions through the ion channels then changes the voltage of the cell membrane. These changes are what bring about an action potential. As an analogy, ion pumps play the role of the battery that allows a radio circuit (the ion channels) to transmit a signal (action potential).



Despite the small differences in their radii, ions rarely go through the "wrong" channel. For example, sodium or calcium ions rarely pass through a potassium channel.

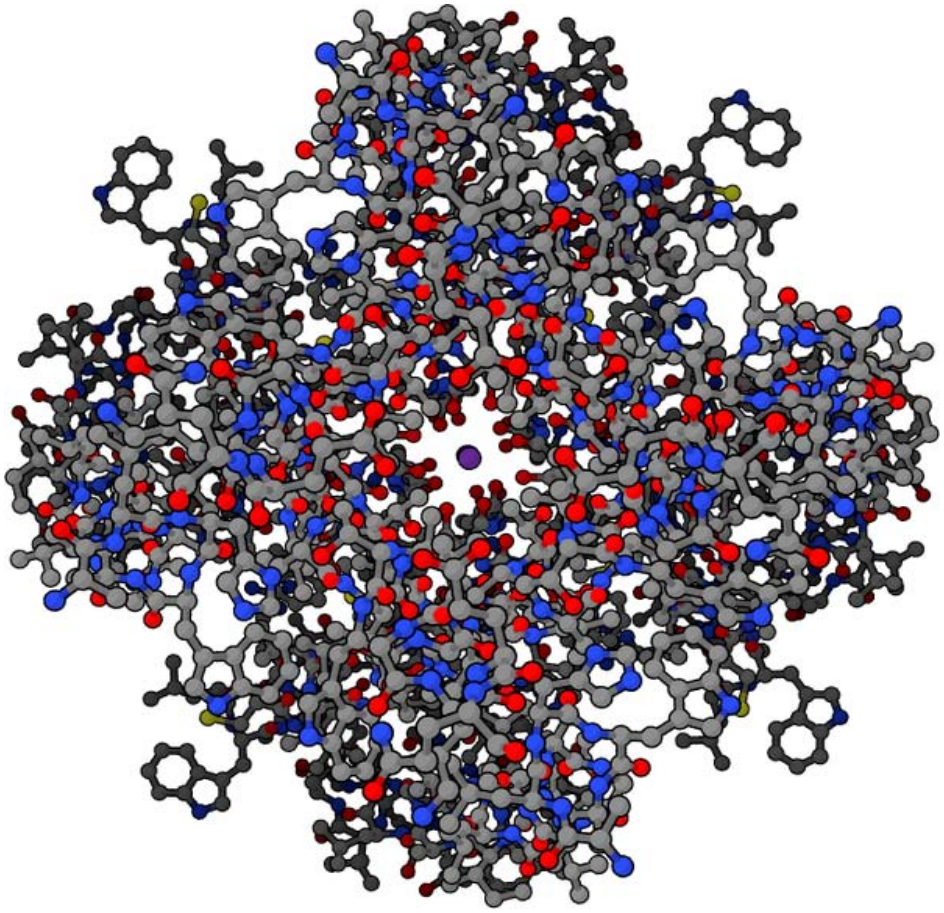
Membrane potential

The cell membrane acts as a barrier that prevents the inside solution (intracellular fluid) from mixing with the outside solution (extracellular fluid). These two solutions have different concentrations of their ions. Furthermore, this difference in concentrations leads to a difference in charge of the solutions. This creates a situation whereby one solution is more positive than the other. Therefore, positive ions will tend to gravitate towards the negative solution. Likewise, negative ions will tend to gravitate towards the positive solution. To quantify this property, one would like to somehow capture this relative positivity (or negativity). To do this, the outside solution is set as the zero voltage. Then the difference between the inside voltage and the zero voltage is determined. For example, if the outside voltage is 100 mV, and the inside voltage is 30 mV, then the difference is –70 mV. This difference is what is commonly referred to as the membrane potential.

Ion channels

Ion channels are integral membrane proteins with a pore through which ions can travel between extracellular space and cell interior. Most channels are specific (selective) for one ion; for example, most potassium channels are characterized by 1000:1 selectivity ratio for potassium over sodium, though potassium and sodium ions have the same charge and differ only slightly in their radius. The channel pore is typically so small that ions must pass through it in single-file order. Channel pore can be either open or closed for ion passage, although a number of channels demonstrate various sub-conductance levels. When a channel is open, ions permeate through the channel pore down the transmembrane concentration gradient for that particular ion. Rate of ionic flow through the channel, i.e. single-channel current amplitude, is determined by the maximum channel conductance and electrochemical driving force for that ion, which is the difference between instantaneous value of the membrane potential and the value of the reversal potential.

The action potential is a manifestation of different ion channels opening and closing at different times.



Depiction of the open potassium channel, with the potassium ion shown in purple in the middle, and hydrogen atoms omitted. When the channel is closed, the passage is blocked.

A channel may have several different states (corresponding to different conformations of the protein), but each such state is either open or closed. In general, closed states correspond either to a contraction of the pore—making it impassable to the ion—or to a separate part of the protein, stoppering the pore. For example, the voltage-dependent sodium channel undergoes *inactivation*, in which a portion of the protein swings into the pore, sealing it. This inactivation shuts off the sodium current and plays a critical role in the action potential.

Ion channels can be classified by how they respond to their environment. For example, the ion channels involved in the action potential are *voltage-sensitive channels*; they open and close in response to the voltage across the membrane. *Ligand-gated channels* form another important class; these ion channels open and close in response to the binding of a ligand molecule, such as a neurotransmitter. Other ion channels open and close with mechanical forces. Still other ion channels—such as those of sensory neurons—open and close in response to other stimuli, such as light, temperature or pressure.

Ion pumps

The ionic currents of the action potential flow in response to concentration differences of the ions across the cell membrane. These concentration differences are established by ion pumps, which are integral membrane proteins that carry out active transport, i.e., use cellular energy (ATP) to "pump" the ions against their concentration gradient. Such ion pumps take in ions from one side of the membrane (decreasing its concentration there) and release them on the other side (increasing its concentration there). The ion pump most relevant to the action potential is the sodium–potassium pump, which transports three sodium ions out of the cell and two potassium ions in. As a consequence, the concentration of potassium ions K^+ inside the neuron is roughly 20-fold larger than the outside concentration, whereas the sodium concentration outside is roughly ninefold larger than inside. In a similar manner, other ions have different concentrations inside and outside the neuron, such as calcium, chloride and magnesium.

Ion pumps influence the action potential only by establishing the relative ratio of intracellular and extracellular ion concentrations. The action potential involves mainly the opening and closing of ion channels, not ion pumps. If the ion pumps are turned off by removing their energy source, or by adding an inhibitor such as ouabain, the axon can still fire hundreds of thousands of action potentials before their amplitudes begin to decay significantly. In particular, ion pumps play no significant role in the repolarization of the membrane after an action potential.

Resting potential

As described in the section Ions and the forces driving their motion, equilibrium or reversal potential of an ion is the value of transmembrane voltage at which the electric force generated by diffusional movement of the ion down its concentration gradient becomes equal to the molecular force of that diffusion. The equilibrium potential for any ion can be calculated using the Nernst equation. For example, reversal potential for potassium ions will be as follows

$$E_{eq,K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i},$$

where

- E_{eq,K^+} is the equilibrium potential for potassium, measured in volts
- R is the universal gas constant, equal to 8.314 $J \cdot K^{-1} \cdot mol^{-1}$
- T is the absolute temperature, measured in kelvins (temperature in kelvins equals degrees Celsius + 273.15)
- z is the number of elementary charges of the ion in question involved in the reaction
- F is the Faraday constant, equal to 96,485 $C \cdot mol^{-1}$ or $J \cdot V^{-1} \cdot mol^{-1}$

- $[K^+]_o$ is the extracellular concentration of potassium, measured in $mol \cdot m^{-3}$ or $mmol \cdot l^{-1}$
- $[K^+]_i$ is the intracellular concentration of potassium.

Even if two different ions have the same charge (i.e. K^+ and Na^+), they can still have very different equilibrium potentials, provided their outside and/or inside concentrations differ. Take, for example, the equilibrium potentials of potassium and sodium in neurons. The potassium equilibrium potential E_K is –84 mV with 5 mmol/L potassium outside and 140 mmol/L inside. The sodium equilibrium potential, on the other hand, E_{Na} is approximately +40 mV with 1–2 mmol/L sodium inside and 120 mmol/L outside.

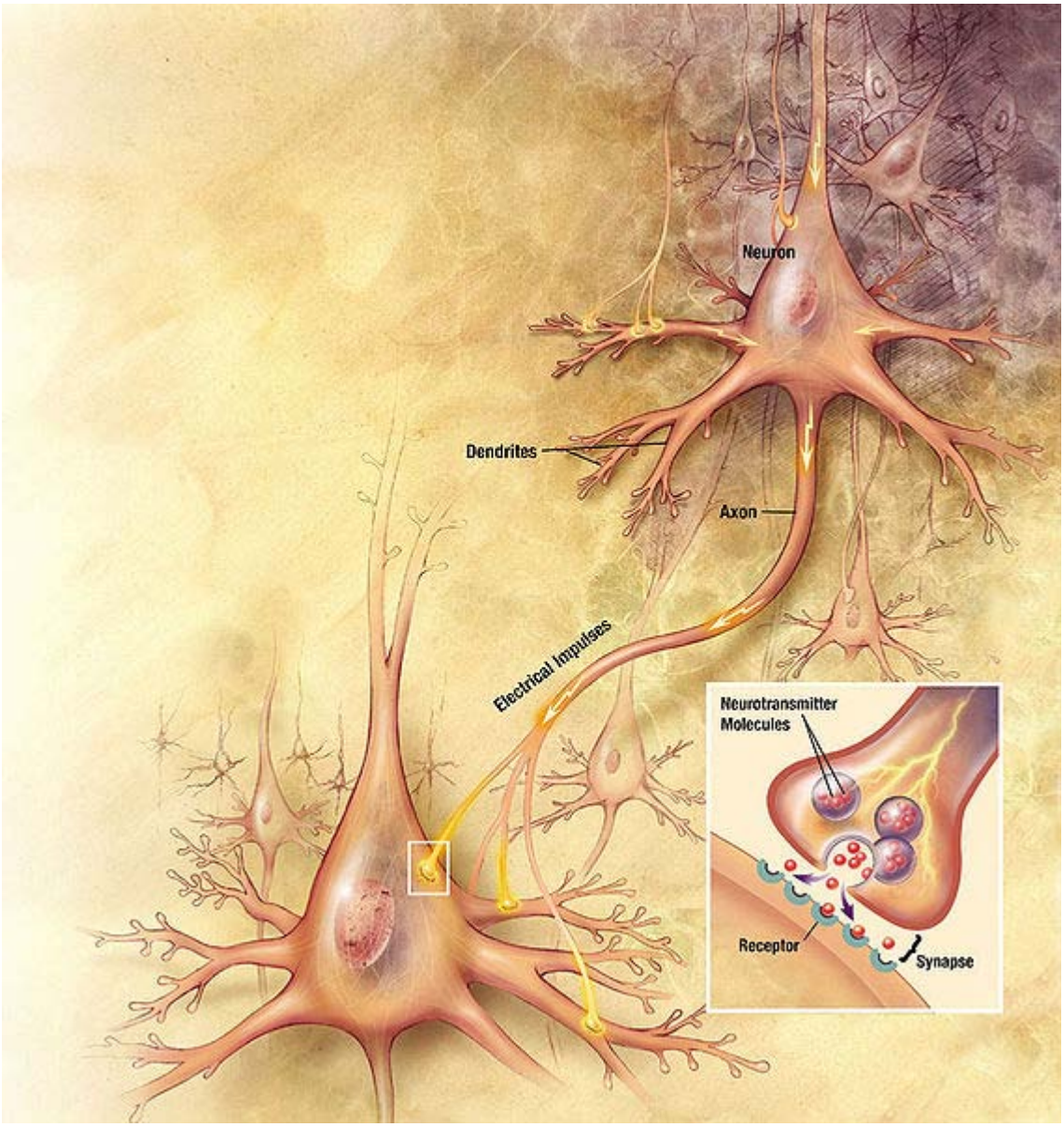
However, there is an equilibrium membrane potential E_m at which the *net* flow of all ions across the membrane is zero. This potential is calculated by the Goldman equation In essence, it is the Nernst equation, in that it is based on the charges of the ions in question, as well as the difference between their inside and outside concentrations. However, it also takes into consideration the relative permeability of the plasma membrane to each ion in question.

$$E_m = \frac{RT}{F} \ln \left(\frac{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathrm{out}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathrm{out}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathrm{in}}}{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathrm{in}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathrm{in}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathrm{out}}} \right)$$

for the three monovalent ions most important to action potentials: potassium (K^+), sodium (Na^+), and chloride (Cl^-). Being an anion, the chloride terms are treated differently than the cation terms; the inside concentration is in the numerator, and the outside concentration is in the denominator, which is reversed from the cation terms. P_i stands for the permeability of the ion type *i*. If calcium ions are also considered, which are critically important for action potentials in muscles, the formula for the equilibrium potential becomes more complicated.

Generation of resting membrane potential is explicitly explained by the Goldman equation. The resting plasma membrane of most animal cells is much more permeable to K^+, which results in the resting potential V_{rest} to be close to the potassium equilibrium potential.

It is important to realize that ionic and water permeability of a pure lipid bilayer is very small, and it is, in a similar manner, negligible for ions of comparable size, such as Na^+ and K^+. The cell membranes, however, contain a large number of ion channels, water channels (aquaporins), and various ionic pumps, exchangers, and transporters, which dramatically and selectively increase permeability of the membrane for different ions. The relatively high membrane permeability for potassium ions at resting potential results from inward-rectifier potassium ion channels, which are open at negative voltages, and so-called leak potassium conductances such as the open rectifier K^+ channel (ORK^+), which are locked in the open state. These potassium channels should not be confused with voltage-activated K^+ channels responsible for membrane repolarization during action potential.



Action potentials arriving at the synapses of the upper right neuron stimulate currents in its dendrites; these currents depolarize the membrane at its axon hillock, provoking an action potential that propagates down the axon to its synaptic knobs, releasing neurotransmitter and stimulating the post-synaptic neuron (lower left).

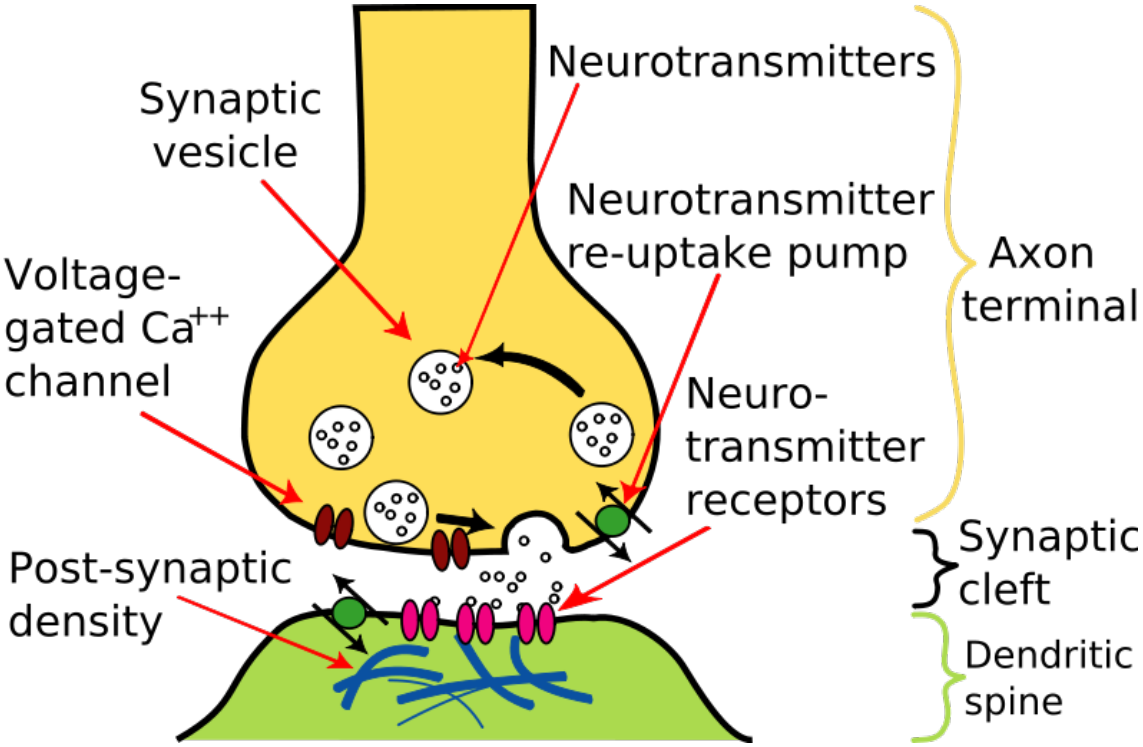
Anatomy of a neuron

Several types of cells support an action potential, such as plant cells, muscle cells, and the specialized cells of the heart (in which occurs the cardiac action potential). However, the main excitable cell is the neuron, which also has the simplest mechanism for the action potential.

Neurons are electrically excitable cells composed, in general, of one or more dendrites, a single soma, a single axon and one or more axon terminals. The dendrite is one of the two types of synapses, the other being the axon terminal boutons. Dendrites form protrusions in response to the axon terminal boutons. These protrusions, or spines, are designed to capture the neurotransmitters released by the presynaptic neuron. They have a high concentration of ligand activated channels. It is, therefore, here where synapses from two neurons communicate with one another. These spines have a thin neck connecting a bulbous protrusion to the main dendrite. This ensures that changes occurring inside the spine are less likely to affect the neighbouring spines. The dendritic spine can, therefore, with rare exception, act as an independent unit. The dendrites then connect onto the soma. The soma houses the nucleus, which acts as the regulator for the neuron. Unlike the spines, the surface of the soma is populated by voltage activated ion channels. These channels help transmit the signals generated by the dendrites. Emerging out from the soma is the axon hillock. This region is characterized by having an incredibly high concentration of voltage activated sodium channels. In general, it is considered to be the spike initiation zone for action potentials. Multiple signals generated at the spines, and transmitted by the soma all converge here. Immediately after the axon hillock is the axon. This is a thin tubular protrusion traveling away from the soma. The axon is insulated by a myelin sheath. Myelin is composed of Schwann cells that wrap themselves multiple times around the axonal segment. This forms a thick fatty layer that prevents ions from entering or escaping the axon. This insulation both prevents significant signal decay as well as ensuring faster signal speed. This insulation, however, has the restriction that no channels can be present on the surface of the axon. There are, therefore, regularly spaced patches of membrane, which have no insulation. These nodes of ranvier can be considered to be 'mini axon hillocks' as their purpose is to boost the signal in order to prevent significant signal decay. At the furthest end, the axon loses its insulation and begins to branch into several axon terminals. These axon terminals then end in the form the second class of synapses, axon terminal buttons. These buttons have voltage-activated calcium channels, which come into play when signaling other neurons.

Initiation

Before considering the propagation of action potentials along axons and their termination at the synaptic knobs, it is helpful to consider the methods by which action potentials can be initiated at the axon hillock. The basic requirement is that the membrane voltage at the hillock be raised above the threshold for firing. There are several ways in which this depolarization can occur.



When an action potential arrives at the end of the pre-synaptic axon (yellow), it causes the release of neurotransmitter molecules that open ion channels in the post-synaptic neuron (green). The combined excitatory and inhibitory postsynaptic potentials of such inputs can begin a new action potential in the post-synaptic neuron.

Neurotransmission

Action potentials are most commonly initiated by excitatory postsynaptic potentials from a presynaptic neuron. Typically, neurotransmitter molecules are released by the presynaptic neuron. These neurotransmitters then bind to receptors on the postsynaptic cell. This binding opens various types of ion channels. This opening has the further effect of changing the local permeability of the cell membrane and thus the membrane potential. If the binding increases the voltage (depolarizes the membrane), the synapse is excitatory. If, however, the binding decreases the voltage (hyperpolarizes the membrane), it is inhibitory. Whether the voltage is decreased or increased, the change propagates passively to nearby regions of the membrane (as described by the cable equation and its refinements). Typically, the voltage stimulus decays exponentially with the distance from the synapse and with time from the binding of the neurotransmitter. Some fraction of an excitatory voltage may reach the axon hillock and may (in rare cases) depolarize the membrane enough to provoke a new action potential. More typically, the excitatory potentials from several synapses must work together at nearly the same time to provoke a new action potential. Their joint efforts can be thwarted, however, by the counter-acting inhibitory postsynaptic potentials.

Neurotransmission can also occur through electrical synapses. Due to the direct connection between excitable cells in the form of gap junctions, an action potential can be transmitted directly from one cell to the next. The free flow of ions between cells enables rapid non-chemical mediated transmission. Rectifying channels ensure that action potentials move only in one direction through an electrical synapse. In the human nervous system this type of synapse is uncommon however.

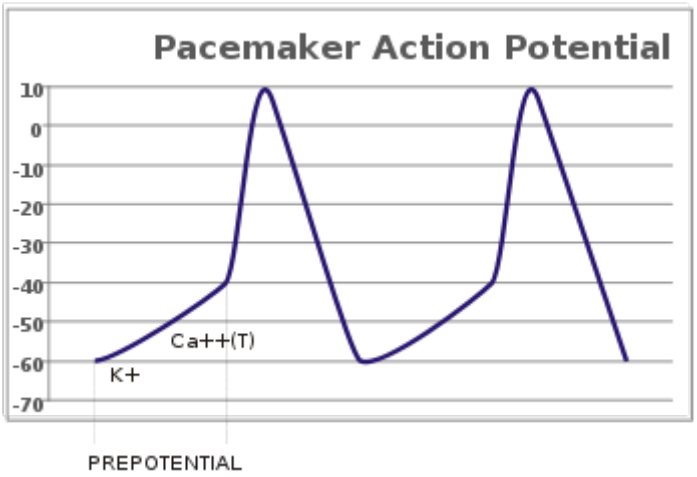
"All-or-none" principle

The amplitude of an action potential is independent of the amount of current that produced it. In other words, larger currents do not create larger action potentials. Therefore action potentials are said to be *all-or-none* (or boolean), since they either occur fully or they do not occur at all. Instead, the frequency of action potentials is what encodes for the intensity of a stimulus. This is in contrast to receptor potentials, whose amplitudes are dependent on the intensity of a stimulus.

Sensory neurons

In sensory neurons, an external signal such as pressure, temperature, light, or sound is coupled with the opening and closing of ion channels, which in turn alter the ionic permeabilities of the membrane and its voltage. These voltage changes can again be excitatory (depolarizing) or inhibitory (hyperpolarizing) and, in some sensory neurons, their combined effects can depolarize the axon hillock enough to provoke action potentials. Examples in humans include the olfactory receptor neuron and Meissner's corpuscle, which are critical for the sense of smell and touch, respectively. However, not all sensory neurons convert their external signals into action potentials; some do not even have an axon! Instead, they may convert the signal into the release of a neurotransmitter, or into continuous graded potentials, either of which may stimulate subsequent neuron(s) into firing an action potential. For illustration, in the human ear, hair cells convert the incoming sound into the opening and closing of mechanically gated ion channels, which may cause neurotransmitter molecules to be released. In similar manner, in the human retina, the initial photoreceptor cells and the next two layers of cells (bipolar cells and horizontal cells) do not produce action potentials; only some amacrine cells and the third layer, the ganglion cells, produce action potentials, which then travel up the optic nerve.

Pacemaker potentials



In pacemaker potentials, the cell spontaneously depolarizes (straight line with upward slope) until it fires an action potential

In sensory neurons, action potentials result from an external stimulus. However, some excitable cells require no such stimulus to fire: They spontaneously depolarize their axon hillock and fire action potentials at a regular rate, like an internal clock. The voltage traces of such cells are known as pacemaker potentials. The cardiac pacemaker cells of the sinoatrial node in the heart provide a good example. Although such pacemaker potentials have a natural rhythm, it can be adjusted by external stimuli; for instance, heart rate can be altered by pharmaceuticals as well as signals from the sympathetic and parasympathetic nerves. The external stimuli do not cause the cell's repetitive firing, but merely alter its timing. In some cases, the regulation of frequency can be more complex, leading to patterns of action potentials, such as bursting.

Phases

The course of the action potential can be divided into five parts: the rising phase, the peak phase, the falling phase, the undershoot phase, and finally the refractory period. During the rising phase the membrane potential depolarizes (becomes more positive). The point at which depolarization stops is called the peak phase. At this stage, the membrane potential reaches a maximum. Subsequent to this, there is a falling phase. During this stage the membrane potential hyperpolarizes (becomes more negative). The undershoot phase is the point during which the membrane potential becomes temporarily more negatively charged than when at rest. Finally, the time during which a subsequent action potential is impossible or difficult to fire is called the refractory period, which may overlap with the other phases.

The course of the action potential is determined by two coupled effects. First, voltage-sensitive ion channels open and close in response to changes in the membrane voltage V_m.

This changes the membrane's permeability to those ions. Second, according to the Goldman equation, this change in permeability changes in the equilibrium potential E_m, and, thus, the membrane voltage V_m. Thus, the membrane potential affects the permeability, which then further affects the membrane potential. This sets up the possibility for positive feedback, which is a key part of the rising phase of the action potential. A complicating factor is that a single ion channel may have multiple internal "gates" that respond to changes in V_m in opposite ways, or at different rates. For example, although raising V_m *opens* most gates in the voltage-sensitive sodium channel, it also *closes* the channel's "inactivation gate", albeit more slowly. Hence, when V_m is raised suddenly, the sodium channels open initially, but then close due to the slower inactivation.

The voltages and currents of the action potential in all of its phases were modeled accurately by Alan Lloyd Hodgkin and Andrew Huxley in 1952, for which they were awarded the Nobel Prize in Physiology or Medicine in 1963. However, their model considers only two types of voltage-sensitive ion channels, and makes several assumptions about them, e.g., that their internal gates open and close independently of one another. In reality, there are many types of ion channels, and they do not always open and close independently.

Stimulation and rising phase

A typical action potential begins at the axon hillock with a sufficiently strong depolarization, e.g., a stimulus that increases V_m. This depolarization is often caused by the injection of extra sodium cations into the cell; these cations can come from a wide variety of sources, such as chemical synapses, sensory neurons or pacemaker potentials.

The initial membrane permeability to potassium is low, but much higher than that of other ions, making the resting potential close to $E_K \approx -75$ mV. The depolarization opens both the sodium and potassium channels in the membrane, allowing the ions to flow into and out of the axon, respectively. If the depolarization is small (say, increasing V_m from −70 mV to −60 mV), the outward potassium current overwhelms the inward sodium current and the membrane repolarizes back to its normal resting potential around −70 mV. However, if the depolarization is large enough, the inward sodium current increases more than the outward potassium current and a runaway condition (positive feedback) results: the more inward current there is, the more V_m increases, which in turn further increases the inward current. A sufficiently strong depolarization (increase in V_m) causes the voltage-sensitive sodium channels to open; the increasing permeability to sodium drives V_m closer to the sodium equilibrium voltage $E_{Na} \approx +55$ mV. The increasing voltage in turn causes even more sodium channels to open, which pushes V_m still further towards E_{Na}. This positive feedback continues until the sodium channels are fully open and V_m is close to E_{Na}. The sharp rise in V_m and sodium permeability correspond to the *rising phase* of the action potential.

The critical threshold voltage for this runaway condition is usually around −45 mV, but it depends on the recent activity of the axon. A membrane that has just fired an action

potential cannot fire another one immediately, since the ion channels have not returned to their usual state. The period during which no new action potential can be fired is called the *absolute refractory period*. At longer times, after some but not all of the ion channels have recovered, the axon can be stimulated to produce another action potential, but only with a much stronger depolarization, e.g., −30 mV. The period during which action potentials are unusually difficult to provoke is called the *relative refractory period*.

Peak and falling phase

The positive feedback of the rising phase slows and comes to a halt as the sodium ion channels become maximally open. At the peak of the action potential, the sodium permeability is maximized and the membrane voltage V_m is nearly equal to the sodium equilibrium voltage E_{Na}. However, the same raised voltage that opened the sodium channels initially also slowly shuts them off, by closing their pores; the sodium channels become *inactivated*. This lowers the membrane's permeability to sodium relative to potassium, driving the membrane voltage back towards the resting value. At the same time, the raised voltage opens voltage-sensitive potassium channels; the increase in the membrane's potassium permeability drives V_m towards E_{K}. Combined, these changes in sodium and potassium permeability cause V_m to drop quickly, repolarizing the membrane and producing the "falling phase" of the action potential.

Afterhyperpolarization

The raised voltage opened many more potassium channels than usual, and some of these do not close right away when the membrane returns to its normal resting voltage. In addition, further potassium channels open in response to the influx of calcium ions during the action potential. The potassium permeability of the membrane is transiently unusually high, driving the membrane voltage V_m even closer to the potassium equilibrium voltage E_{K}. Hence, there is an undershoot or hyperpolarization, termed an afterhyperpolarization in technical language, that persists until the membrane potassium permeability returns to its usual value.

Refractory period

Each action potential is followed by a refractory period, which can be divided into an *absolute refractory period*, during which it is impossible to evoke another action potential, and then a *relative refractory period*, during which a stronger-than-usual stimulus is required. These two refractory periods are caused by changes in the state of sodium and potassium channel molecules. When closing after an action potential, sodium channels enter an "inactivated" state, in which they cannot be made to open regardless of the membrane potential—this gives rise to the absolute refractory period. Even after a sufficient number of sodium channels have transitioned back to their resting state, it frequently happens that a fraction of potassium channels remains open, making it difficult for the membrane potential to depolarize, and thereby giving rise to the relative refractory period. Because the density and subtypes of potassium channels may differ greatly

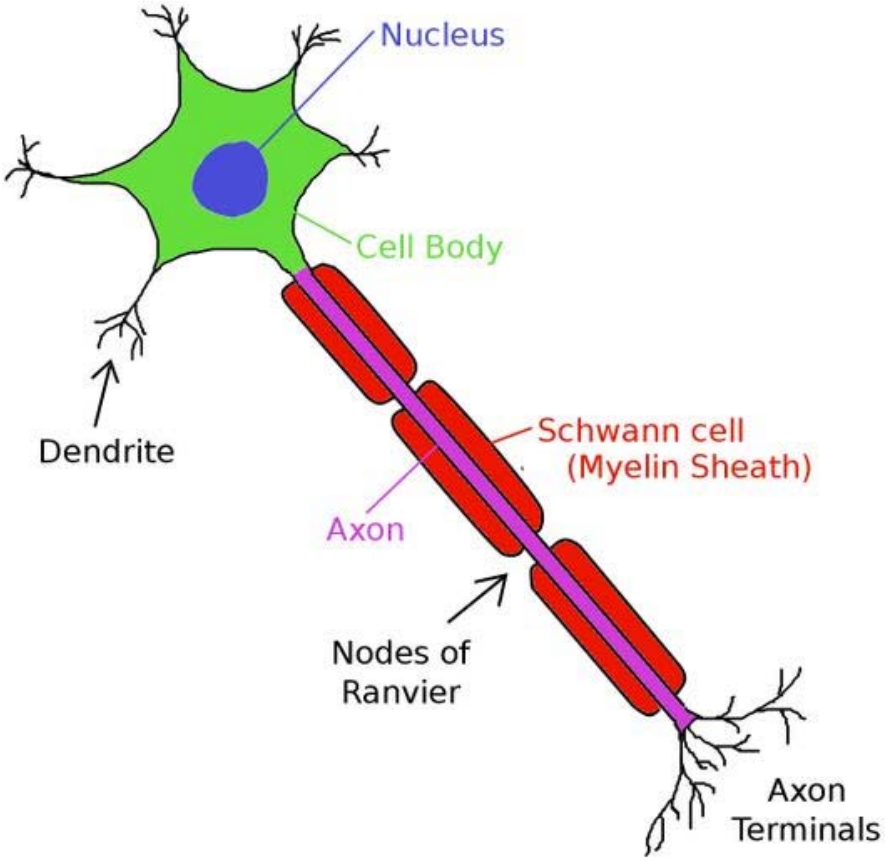
between different types of neurons, the duration of the relative refractory period is highly variable.

The absolute refractory period is largely responsible for the unidirectional propagation of action potentials along axons. At any given moment, the patch of axon behind the actively spiking part is refractory, but the patch in front, not having been activated recently, is capable of being stimulated by the depolarization from the action potential.

Propagation

The action potential generated at the axon hillock propagates as a wave along the axon. The currents flowing inwards at a point on the axon during an action potential spread out along the axon, and depolarize the adjacent sections of its membrane. If sufficiently strong, this depolarization provokes a similar action potential at the neighboring membrane patches. This basic mechanism was demonstrated by Alan Lloyd Hodgkin in 1937. After crushing or cooling nerve segments and thus blocking the action potentials, he showed that an action potential arriving on one side of the block could provoke another action potential on the other, provided that the blocked segment was sufficiently short.

Once an action potential has occurred at a patch of membrane, the membrane patch needs time to recover before it can fire again. At the molecular level, this *absolute refractory period* corresponds to the time required for the voltage-activated sodium channels to recover from inactivation, i.e., to return to their closed state. There are many types of voltage-activated potassium channels in neurons, some of them inactivate fast (A-type currents) and some of them inactivate slowly or not inactivate at all; this variability guarantees that there will be always an available source of current for repolarization, even if some of the potassium channels are inactivated because of preceding depolarization. On the other hand, all neuronal voltage-activated sodium channels inactivate within several millisecond during strong depolarization, thus making following depolarization impossible until a substantial fraction of sodium channels is not returned to their closed state. Although it limits the frequency of firing, the absolute refractory period ensures that the action potential moves in only one direction along an axon. The currents flowing in due to an action potential spread out in both directions along the axon. However, only the unfired part of the axon can respond with an action potential; the part that has just fired is unresponsive until the action potential is safely out of range and cannot restimulate that part. In the usual orthodromic conduction, the action potential propagates from the axon hillock towards the synaptic knobs (the axonal termini); propagation in the opposite direction—known as antidromic conduction—is very rare. However, if a laboratory axon is stimulated in its middle, both halves of the axon are "fresh", i.e., unfired; then two action potentials will be generated, one traveling towards the axon hillock and the other traveling towards the synaptic knobs.



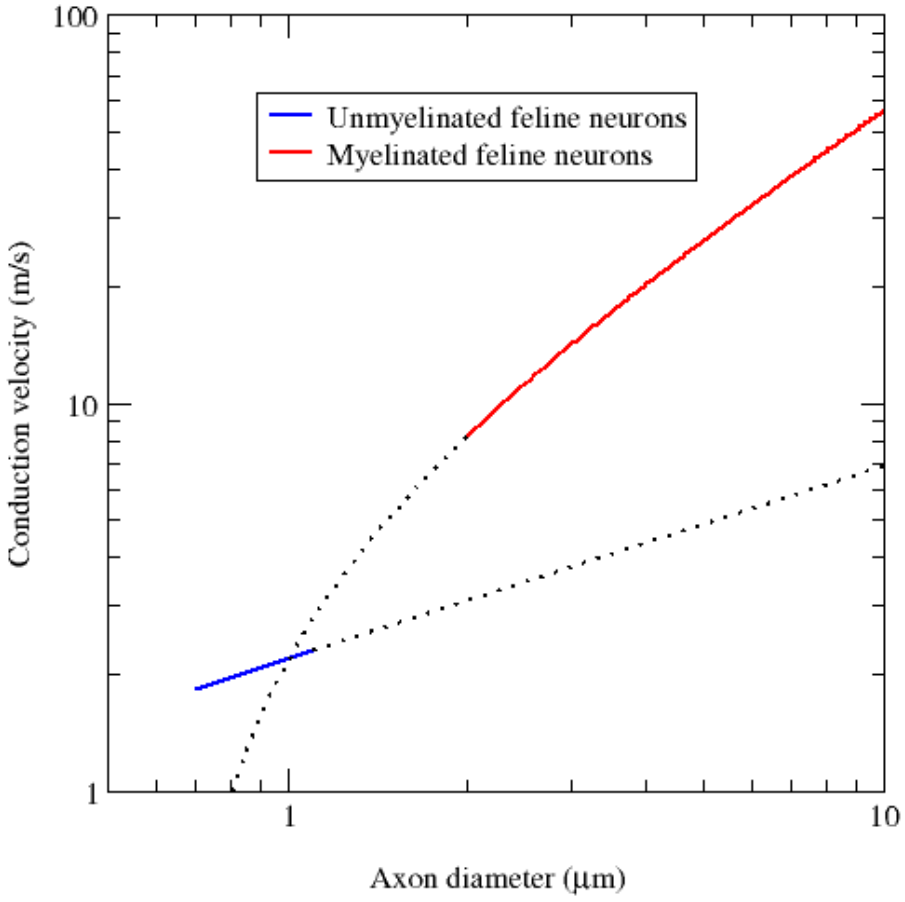
In saltatory conduction, an action potential at one node of Ranvier causes inwards currents that depolarize the membrane at the next node, provoking a new action potential there; the action potential appears to "hop" from node to node.

Myelin and saltatory conduction

In order to enable fast and efficient transduction of electrical signals in the nervous system, certain neuronal axons are covered with myelin sheaths. Myelin is a multilamellar membrane that enwraps the axon in segments separated by intervals known as nodes of Ranvier, is produced by specialized cells, Schwann cells exclusively in the peripheral nervous system, and by oligodendrocytes exclusively in the central nervous system. Myelin sheath reduces membrane capacitance and increases membrane resistance in the inter-node intervals, thus allowing a fast, saltatory movement of action potentials from node to node. Myelination is found mainly in vertebrates, but an analogous system has been discovered in a few invertebrates, such as some species of shrimp. Not all neurons in vertebrates are myelinated; for example, axons of the neurons comprising autonomous (vegetative) nervous system are not myelinated in general.

Myelin prevents ions from entering or leaving the axon along myelinated segments. As a general rule, myelination increases the conduction velocity of action potentials and makes them more energy-efficient. Whether saltatory or not, the mean conduction velocity of an action potential ranges from 1 m/s to over 100 m/s, and, in general, increases with axonal diameter.

Action potentials cannot propagate through the membrane in myelinated segments of the axon. However, the current is carried by the cytoplasm, which is sufficient to depolarize the next 1 or 2 node of Ranvier. Instead, the ionic current from an action potential at one node of Ranvier provokes another action potential at the next node; this apparent "hopping" of the action potential from node to node is known as saltatory conduction. Although the mechanism of saltatory conduction was suggested in 1925 by Ralph Lillie, the first experimental evidence for saltatory conduction came from Ichiji Tasaki and Taiji Takeuchi and from Andrew Huxley and Robert Stämpfli. By contrast, in unmyelinated axons, the action potential provokes another in the membrane immediately adjacent, and moves continuously down the axon like a wave.



Comparison of the conduction velocities of myelinated and unmyelinated axons in the cat. The conduction velocity v of myelinated neurons varies roughly linearly with axon diameter d (that is, $v \propto d$), whereas the speed of unmyelinated neurons varies roughly as

the square root ($v \propto \sqrt{d}$). The red and blue curves are fits of experimental data, whereas the dotted lines are their theoretical extrapolations.

Myelin has two important advantages: fast conduction speed and energy efficiency. For axons larger than a minimum diameter (roughly 1 micrometre), myelination increases the conduction velocity of an action potential, typically tenfold. Conversely, for a given conduction velocity, myelinated fibers are smaller than their unmyelinated counterparts. For example, action potentials move at roughly the same speed (25 m/s) in a myelinated frog axon and an unmyelinated squid giant axon, but the frog axon has a roughly 30-fold smaller diameter and 1000-fold smaller cross-sectional area. Also, since the ionic currents are confined to the nodes of Ranvier, far fewer ions "leak" across the membrane, saving metabolic energy. This saving is a significant selective advantage, since the human nervous system uses approximately 20% of the body's metabolic energy.

The length of axons' myelinated segments is important to the success of saltatory conduction. They should be as long as possible to maximize the speed of conduction, but not so long that the arriving signal is too weak to provoke an action potential at the next node of Ranvier. In nature, myelinated segments are generally long enough for the passively propagated signal to travel for at least two nodes while retaining enough amplitude to fire an action potential at the second or third node. Thus, the safety factor of saltatory conduction is high, allowing transmission to bypass nodes in case of injury. However, action potentials may end prematurely in certain places where the safety factor is low, even in unmyelinated neurons; a common example is the branch point of an axon, where it divides into two axons.

Some diseases degrade myelin and impair saltatory conduction, reducing the conduction velocity of action potentials. The most well-known of these is multiple sclerosis, in which the breakdown of myelin impairs coordinated movement.

Cable theory

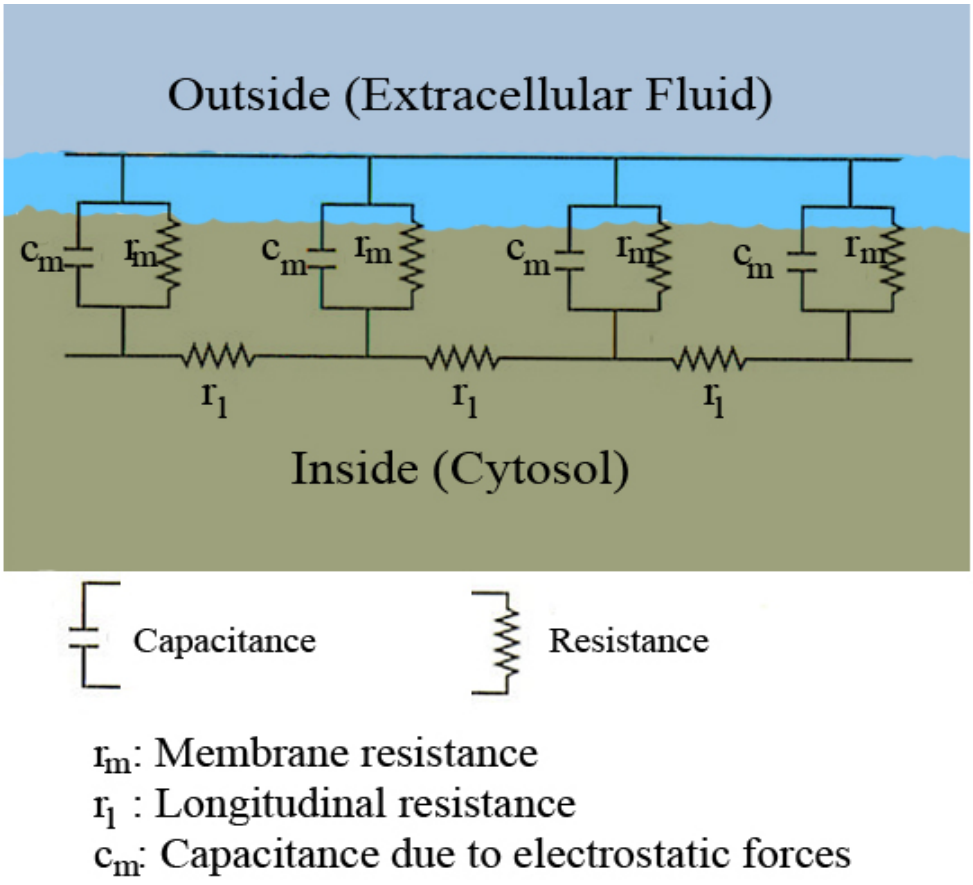


Figure.1: Cable theory's simplified view of a neuronal fiber. The connected RC circuits correspond to adjacent segments of a passive neurite. The extracellular resistances r_e (the counterparts of the intracellular resistances r_i) are not shown, since they are usually negligibly small; the extracellular medium may be assumed to have the same voltage everywhere.

The flow of currents within an axon can be described quantitatively by cable theory and its elaborations, such as the compartmental model. Cable theory was developed in 1855 by Lord Kelvin to model the transatlantic telegraph cable and was shown to be relevant to neurons by Hodgkin and Rushton in 1946. In simple cable theory, the neuron is treated as an electrically passive, perfectly cylindrical transmission cable, which can be described by a partial differential equation

$$\tau \frac{\partial V}{\partial t} = \lambda^2 \frac{\partial^2 V}{\partial x^2} - V$$

where *V(x, t)* is the voltage across the membrane at a time *t* and a position *x* along the length of the neuron, and where λ and τ are the characteristic length and time scales on which those voltages decay in response to a stimulus. Referring to the circuit diagram above, these scales can be determined from the resistances and capacitances per unit length

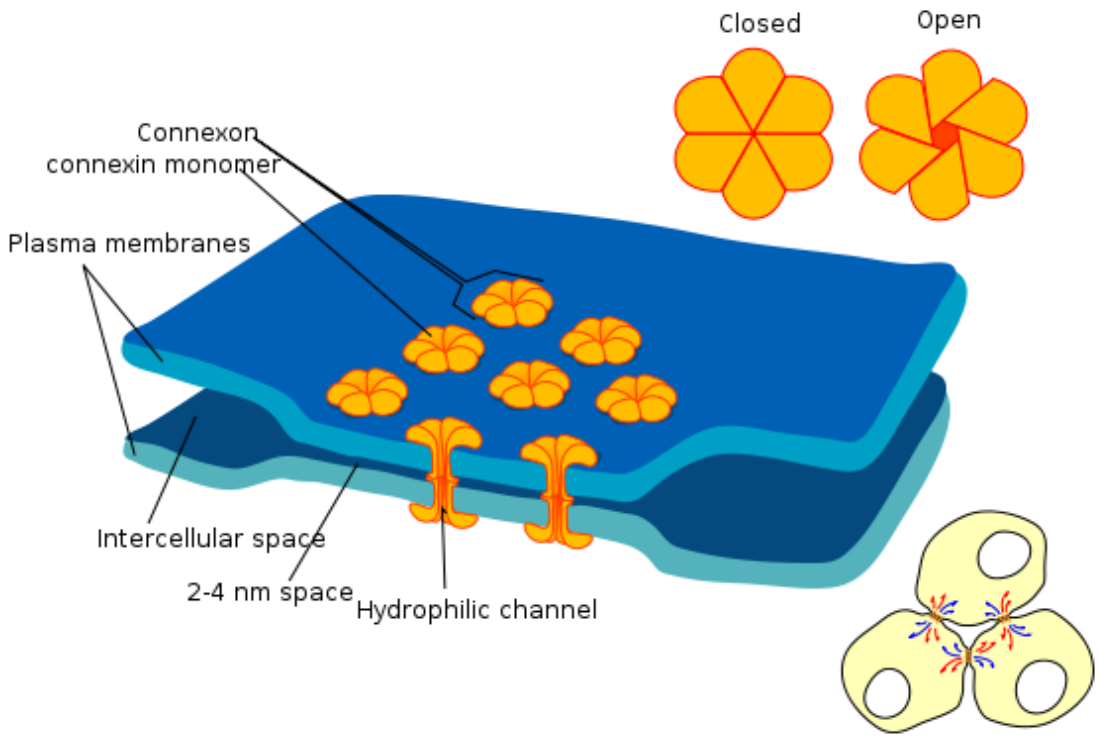
$$\tau = r_m c_m$$
$$\lambda = \sqrt{\frac{r_m}{r_l}}$$

These time and length-scales can be used to understand the dependence of the conduction velocity on the diameter of the neuron in unmyelinated fibers. For example, the time-scale τ increases with both the membrane resistance r_m and capacitance c_m. As the capacitance increases, more charge must be transferred to produce a given transmembrane voltage (by the equation $Q=CV$); as the resistance increases, less charge is transferred per unit time, making the equilibration slower. In similar manner, if the internal resistance per unit length r_i is lower in one axon than in another (e.g., because the radius of the former is larger), the spatial decay length λ becomes longer and the conduction velocity of an action potential should increase. If the transmembrane resistance r_m is increased, that lowers the average "leakage" current across the membrane, likewise causing λ to become longer, increasing the conduction velocity.

Termination

Chemical synapses

In general, action potentials that reach the synaptic knobs cause a neurotransmitter to be released into the synaptic cleft. Neurotransmitters are small molecules that may open ion channels in the postsynaptic cell; most axons have the same neurotransmitter at all of their termini. The arrival of the action potential opens voltage-sensitive calcium channels in the presynaptic membrane; the influx of calcium causes vesicles filled with neurotransmitter to migrate to the cell's surface and release their contents into the synaptic cleft. This complex process is inhibited by the neurotoxins tetanospasmin and botulinum toxin, which are responsible for tetanus and botulism, respectively.



Electrical synapses between excitable cells allow ions to pass directly from one cell to another, and are much faster than chemical synapses.

Electrical synapses

Some synapses dispense with the "middleman" of the neurotransmitter, and connect the presynaptic and postsynaptic cells together. When an action potential reaches such a synapse, the ionic currents flowing into the presynaptic cell can cross the barrier of the two cell membranes and enter the postsynaptic cell through pores known as connexins. Thus, the ionic currents of the presynaptic action potential can directly stimulate the postsynaptic cell. Electrical synapses allow for faster transmission because they do not require the slow diffusion of neurotransmitters across the synaptic cleft. Hence, electrical synapses are used whenever fast response and coordination of timing are crucial, as in escape reflexes, the retina of vertebrates, and the heart.

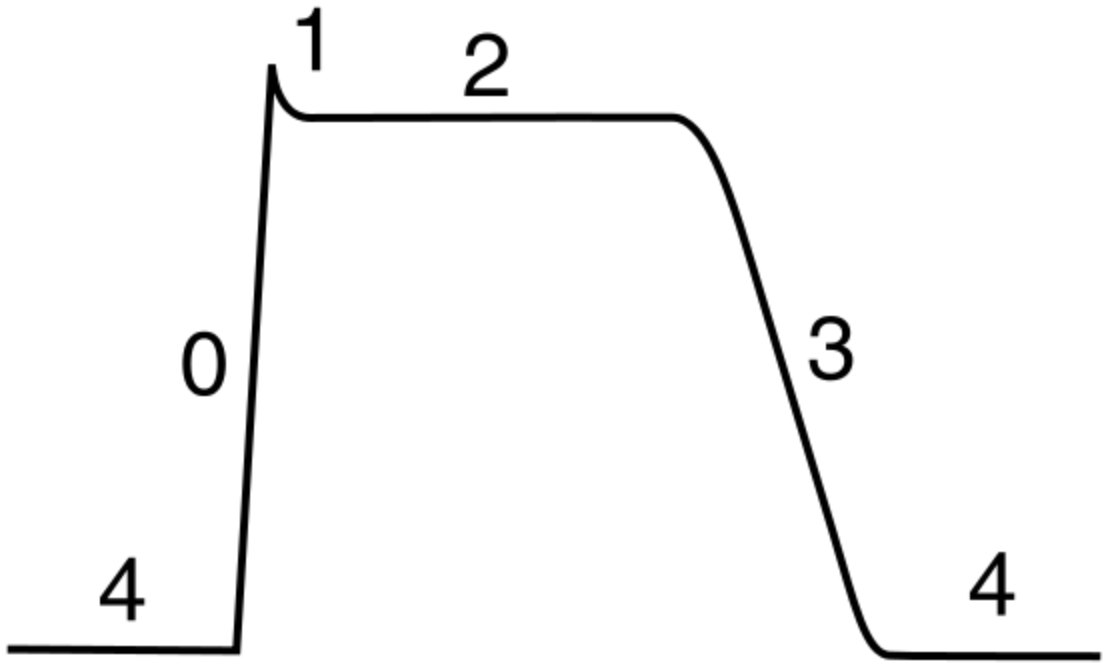
Neuromuscular junctions

A special case of a chemical synapse is the neuromuscular junction, in which the axon of a motor neuron terminates on a muscle fiber. In such cases, the released neurotransmitter is acetylcholine, which binds to the acetylcholine receptor, an integral membrane protein in the membrane (the *sarcolemma*) of the muscle fiber. However, the acetylcholine does not remain bound; rather, it dissociates and is hydrolyzed by the enzyme, acetylcholinesterase, located in the synapse. This enzyme quickly reduces the stimulus to

the muscle, which allows the degree and timing of muscular contraction to be regulated delicately. Some poisons inactivate acetylcholinesterase to prevent this control, such as the nerve agents sarin and tabun, and the insecticides diazinon and malathion.

Other cell types

Cardiac action potentials



Phases of a cardiac action potential. The sharp rise in voltage ("0") corresponds to the influx of sodium ions, whereas the two decays ("1" and "3", respectively) correspond to the sodium-channel inactivation and the repolarizing eflux of potassium ions. The characteristic plateau ("2") results from the opening of voltage-sensitive calcium channels.

The cardiac action potential differs from the neuronal action potential by having an extended plateau, in which the membrane is held at a high voltage for a few hundred milliseconds prior to being repolarized by the potassium current as usual. This plateau is due to the action of slower calcium channels opening and holding the membrane voltage near their equilibrium potential even after the sodium channels have inactivated.

The cardiac action potential plays an important role in coordinating the contraction of the heart. The cardiac cells of the sinoatrial node provide the pacemaker potential that synchronizes the heart. The action potentials of those cells propagate to and through the atrioventricular node (AV node), which is normally the only conduction pathway between the atria and the ventricles. Action potentials from the AV node travel through the bundle of His and thence to the Purkinje fibers. Conversely, anomalies in the cardiac action potential—whether due to a congenital mutation or injury—can lead to human

pathologies, especially arrhythmias. Several anti-arrhythmia drugs act on the cardiac action potential, such as quinidine, lidocaine, beta blockers, and verapamil.

Muscular action potentials

The action potential in a normal skeletal muscle cell is similar to the action potential in neurons. Action potentials result from the depolarization of the cell membrane (the sarcolemma), which opens voltage-sensitive sodium channels; these become inactivated and the membrane is repolarized through the outward current of potassium ions. The resting potential prior to the action potential is typically −90mV, somewhat more negative than typical neurons. The muscle action potential lasts roughly 2–4 ms, the absolute refractory period is roughly 1–3 ms, and the conduction velocity along the muscle is roughly 5 m/s. The action potential releases calcium ions that free up the tropomyosin and allow the muscle to contract. Muscle action potentials are provoked by the arrival of a pre-synaptic neuronal action potential at the neuromuscular junction, which is a common target for neurotoxins.

Plant action potentials

Plant and fungal cells are also electrically excitable. The fundamental difference to animal action potentials is, that the depolarization in plant cells is not accomplished by an uptake of positive sodium ions, but by release of negative *chloride* ions. Together with the following release of positive potassium ions, which is common to plant and animal action potentials, the action potential in plants infers, therefore, an osmotic loss of salt (KCl), whereas the animal action potential is osmotically neutral, when equal amounts of entering sodium and leaving potassium cancel each other osmotically. The interaction of electrical and osmotic relations in plant cells indicates an osmotic function of electrical excitability in the common, unicellular ancestors of plants and animals under changing salinity conditions, whereas the present function of rapid signal transmission is seen as a younger accomplishment of metazoan cells in a more stable osmotic environment. It must be assumed that the familiar signalling function of action potentials in some vascular plants (e.g. *Mimosa pudica*), arose independently from that in metazoan excitable cells.

Taxonomic distribution and evolutionary advantages

Action potentials are found throughout multicellular organisms, including plants, invertebrates such as insects, and vertebrates such as reptiles and mammals. Sponges seem to be the main phylum of multicellular eukaryotes that does not transmit action potentials, although some studies have suggested that these organisms have a form of electrical signaling, too. The resting potential, as well as the size and duration of the action potential, have not varied much with evolution, although the conduction velocity does vary dramatically with axonal diameter and myelination.

Comparison of action potentials (APs) from a representative cross-section of animals					
Animal	**Cell type**	**Resting potential (mV)**	**AP increase (mV)**	**AP duration (ms)**	**Conduction speed (m/s)**
Squid (*Loligo*)	Giant axon	−60	120	0.75	35
Earthworm (*Lumbricus*)	Median giant fiber	−70	100	1.0	30
Cockroach (*Periplaneta*)	Giant fiber	−70	80–104	0.4	10
Frog (*Rana*)	Sciatic nerve axon	−60 to −80	110–130	1.0	7–30
Cat (*Felis*)	Spinal motor neuron	−55 to −80	80–110	1–1.5	30–120

Given its conservation throughout evolution, the action potential seems to confer evolutionary advantages. One function of action potentials is rapid, long-range signaling within the organism; the conduction velocity can exceed 110 m/s, which is one-third the speed of sound. For comparison, a hormone molecule carried in the bloodstream moves at roughly 8 m/s in large arteries. Part of this function is the tight coordination of mechanical events, such as the contraction of the heart. A second function is the computation associated with its generation. Being an all-or-none signal that does not decay with transmission distance, the action potential has similar advantages to digital electronics. The integration of various dendritic signals at the axon hillock and its thresholding to form a complex train of action potentials is another form of computation, one that has been exploited biologically to form central pattern generators and mimicked in artificial neural networks.

Experimental methods

The giant axons of the European squid (*Loligo vulgaris*) were crucial for scientists to understand the action potential.

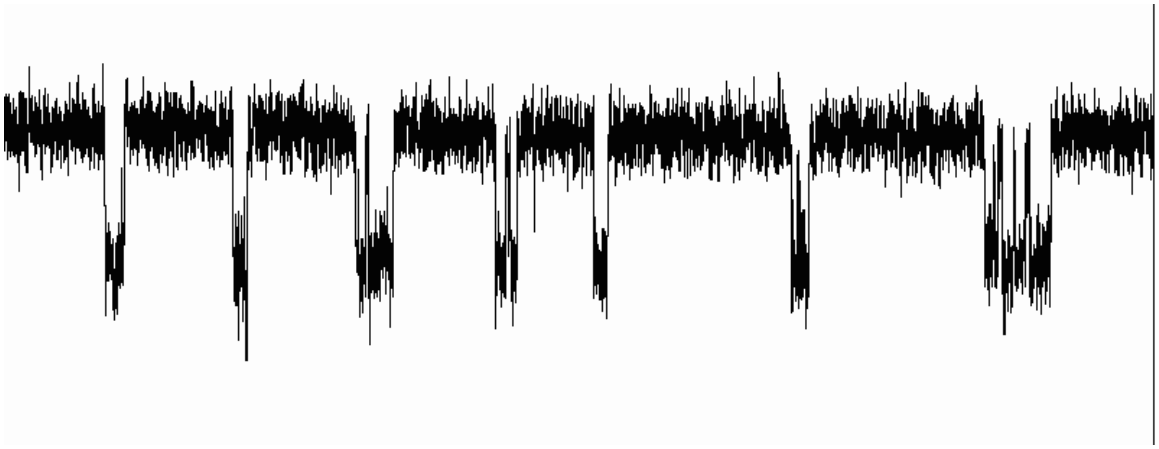
The study of action potentials has required the development of new experimental methods. The initial work, prior to 1955, focused on three goals: isolating signals from single neurons or axons, developing fast, sensitive electronics, and shrinking electrodes enough that the voltage inside a single cell could be recorded.

The first problem was solved by studying the giant axons found in the neurons of the squid genus *Loligo*. These axons are so large in diameter (roughly 1 mm, or 100-fold larger than a typical neuron) that they can be seen with the naked eye, making them easy to extract and manipulate. However, the *Loligo* axons are not representative of all excitable cells, and numerous other systems with action potentials have been studied.

The second problem was addressed with the crucial development of the voltage clamp, which permitted experimenters to study the ionic currents underlying an action potential in isolation, and eliminated a key source of electronic noise, the current I_C associated with the capacitance C of the membrane. Since the current equals C times the rate of change of the transmembrane voltage V_m, the solution was to design a circuit that kept V_m fixed (zero rate of change) regardless of the currents flowing across the membrane. Thus, the current required to keep V_m at a fixed value is a direct reflection of the current flowing

through the membrane. Other electronic advances included the use of Faraday cages and electronics with high input impedance, so that the measurement itself did not affect the voltage being measured.

The third problem, that of obtaining electrodes small enough to record voltages within a single axon without perturbing it, was solved in 1949 with the invention of the glass micropipette electrode, which was quickly adopted by other researchers. Refinements of this method are able to produce electrode tips that are as fine as 100 Å (10 nm), which also confers high input impedance. Action potentials may also be recorded with small metal electrodes placed just next to a neuron, with neurochips containing EOSFETs, or optically with dyes that are sensitive to Ca^{2+} or to voltage.

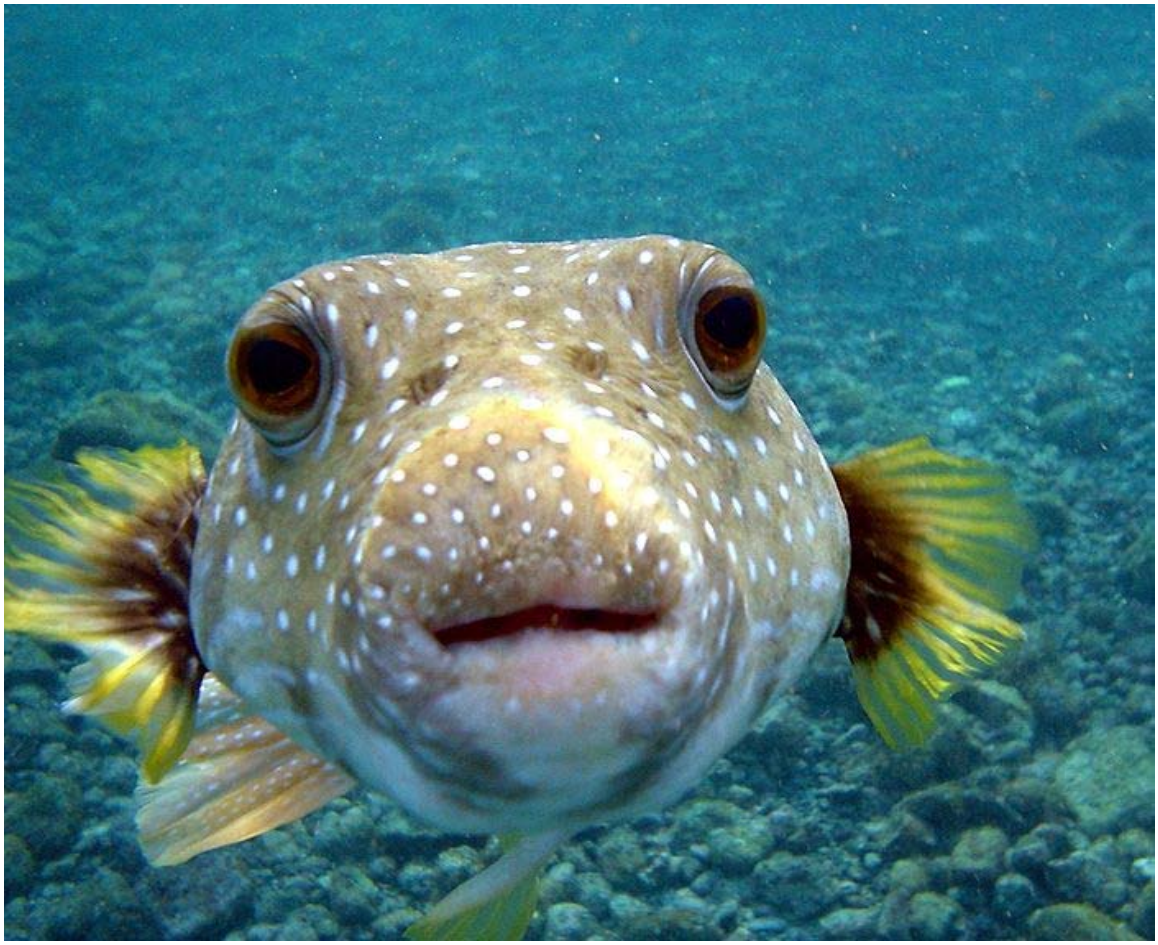


As revealed by a patch clamp electrode, an ion channel has two states: open (high conductance) and closed (low conductance).

While glass micropipette electrodes measure the sum of the currents passing through many ion channels, studying the electrical properties of a single ion channel became possible in the 1970s with the development of the patch clamp by Erwin Neher and Bert Sakmann. For this they were awarded the Nobel Prize in Physiology or Medicine in 1991. Patch-clamping verified that ionic channels have discrete states of conductance, such as open, closed and inactivated.

Optical imaging technologies have been developed in recent years to measure action potentials, either via simultaneous multisite recordings or with ultra spatial resolution. Using voltage-sensitive dyes, action potentials have been optically recorded from a tiny patch of cardiomyocyte membrane.

Neurotoxins



Tetrodotoxin is a lethal toxin found in pufferfish that inhibits the voltage-sensitive sodium channel, halting action potentials.

Several neurotoxins, both natural and synthetic, are designed to block the action potential. Tetrodotoxin from the pufferfish and saxitoxin from the *Gonyaulax* (the dinoflagellate genus responsible for "red tides") block action potentials by inhibiting the voltage-sensitive sodium channel; similarly, dendrotoxin from the black mamba snake inhibits the voltage-sensitive potassium channel. Such inhibitors of ion channels serve an important research purpose, by allowing scientists to "turn off" specific channels at will, thus isolating the other channels' contributions; they can also be useful in purifying ion channels by affinity chromatography or in assaying their concentration. However, such inhibitors also make effective neurotoxins, and have been considered for use as chemical weapons. Neurotoxins aimed at the ion channels of insects have been effective insecticides; one example is the synthetic permethrin, which prolongs the activation of the sodium channels involved in action potentials. The ion channels of insects are sufficiently different from their human counterparts that there are few side effects in humans. Many other neurotoxins interfere with the transmission of the action potential's effects at the synapses, especially at the neuromuscular junction.

History

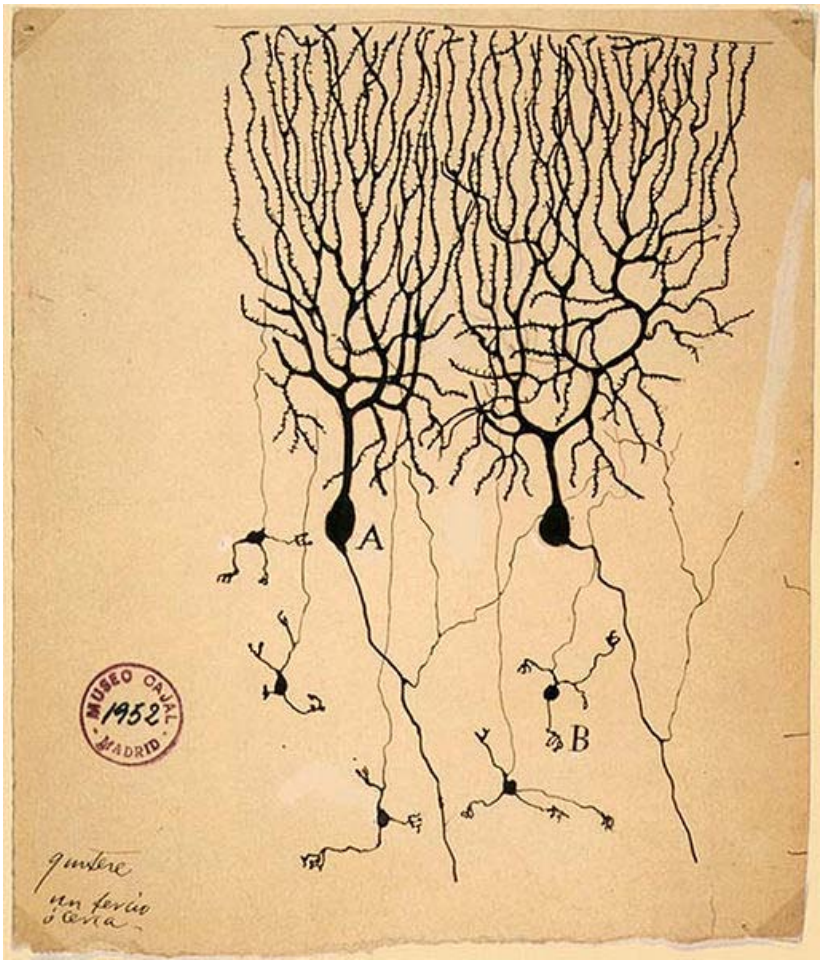
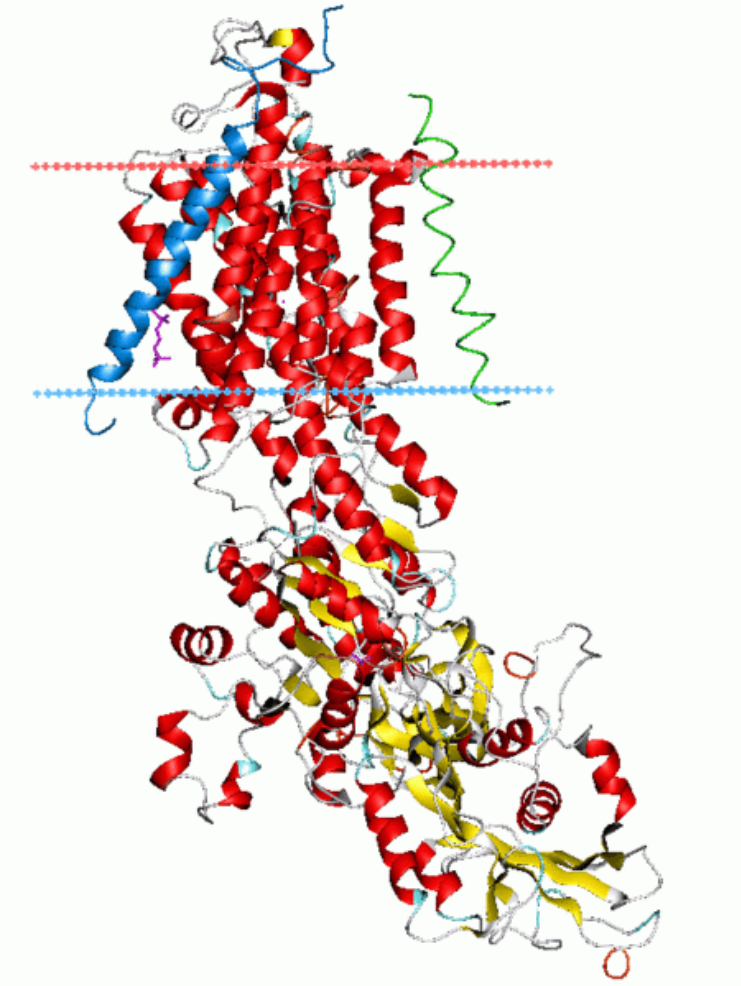


Image of two Purkinje cells (labeled as **A**) drawn by Santiago Ramón y Cajal. Large trees of dendrites feed into the soma, from which a single axon emerges and moves generally downwards with a few branch points. The smaller cells labeled **B** are granule cells.

The role of electricity in the nervous systems of animals was first observed in dissected frogs by Luigi Galvani, who studied it from 1791 to 1797. Galvani's results stimulated Alessandro Volta to develop the Voltaic pile—the earliest-known electric battery—with which he studied animal electricity (such as electric eels) and the physiological responses to applied direct-current voltages.

Scientists of the 19th century studied the propagation of electrical signals in whole nerves (i.e., bundles of neurons) and demonstrated that nervous tissue was made up of cells, instead of an interconnected network of tubes (a *reticulum*). Carlo Matteucci followed up Galvani's studies and demonstrated that cell membranes had a voltage across them and could produce direct current. Matteucci's work inspired the German physiologist, Emil du Bois-Reymond, who discovered the action potential in 1848. The conduction velocity of action potentials was first measured in 1850 by du Bois-Reymond's friend, Hermann von Helmholtz. To establish that nervous tissue is made up of discrete cells, the Spanish

physician Santiago Ramón y Cajal and his students used a stain developed by Camillo Golgi to reveal the myriad shapes of neurons, which they rendered painstakingly. For their discoveries, Golgi and Ramón y Cajal were awarded the 1906 Nobel Prize in Physiology. Their work resolved a long-standing controversy in the neuroanatomy of the 19th century; Golgi himself had argued for the network model of the nervous system.



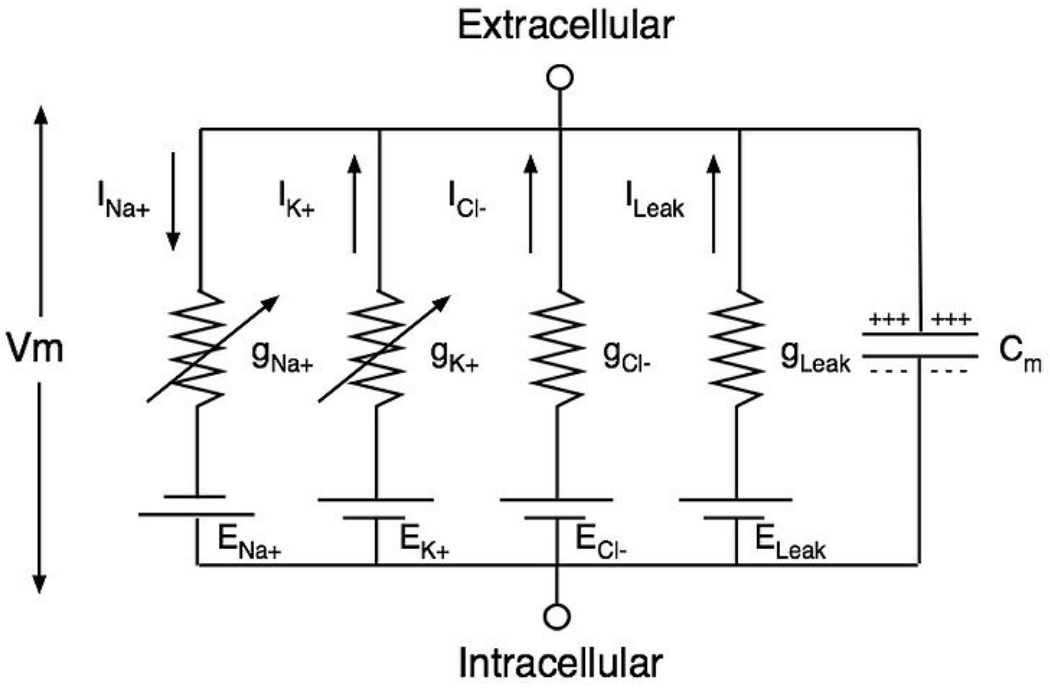
Ribbon diagram of the sodium–potassium pump in its E2-Pi state. The estimated boundaries of the lipid bilayer are shown as blue (intracellular) and red (extracellular) planes.

The 20th century was a golden era for electrophysiology. In 1902 and again in 1912, Julius Bernstein advanced the hypothesis that the action potential resulted from a change in the permeability of the axonal membrane to ions. Bernstein's hypothesis was confirmed by Ken Cole and Howard Curtis, who showed that membrane conductance increases during an action potential. In 1907, Louis Lapicque suggested that the action potential was generated as a threshold was crossed, what would be later shown as a product of the dynamical systems of ionic conductances. In 1949, Alan Hodgkin and Bernard Katz refined Bernstein's hypothesis by considering that the axonal membrane might have different permeabilities to different ions; in particular, they demonstrated the

crucial role of the sodium permeability for the action potential. This line of research culminated in the five 1952 papers of Hodgkin, Katz and Andrew Huxley, in which they applied the voltage clamp technique to determine the dependence of the axonal membrane's permeabilities to sodium and potassium ions on voltage and time, from which they were able to reconstruct the action potential quantitatively. Hodgkin and Huxley correlated the properties of their mathematical model with discrete ion channels that could exist in several different states, including "open", "closed", and "inactivated". Their hypotheses were confirmed in the mid-1970s and 1980s by Erwin Neher and Bert Sakmann, who developed the technique of patch clamping to examine the conductance states of individual ion channels. In the 21st century, researchers are beginning to understand the structural basis for these conductance states and for the selectivity of channels for their species of ion, through the atomic-resolution crystal structures, fluorescence distance measurements and cryo-electron microscopy studies.

Julius Bernstein was also the first to introduce the Nernst equation for resting potential across the membrane; this was generalized by David E. Goldman to the eponymous Goldman equation in 1943. The sodium–potassium pump was identified in 1957 and its properties gradually elucidated, culminating in the determination of its atomic-resolution structure by X-ray crystallography. The crystal structures of related ionic pumps have also been solved, giving a broader view of how these molecular machines work.

Quantitative models



Equivalent electrical circuit for the Hodgkin–Huxley model of the action potential. I_m and V_m represent the current through, and the voltage across, a small patch of membrane, respectively. The C_m represents the capacitance of the membrane patch, whereas the four

g′s represent the conductances of four types of ions. The two conductances on the left, for potassium (K) and sodium (Na), are shown with arrows to indicate that they can vary with the applied voltage, corresponding to the voltage-sensitive ion channels. The two conductances on the right help determine the resting membrane potential.

Mathematical and computational models are essential for understanding the action potential, and offer predictions that may be tested against experimental data, providing a stringent test of a theory. The most important and accurate of these models is the Hodgkin–Huxley model, which describes the action potential by a coupled set of four ordinary differential equations (ODEs). Although the Hodgkin–Huxley model may be a simplification of a realistic nervous membrane as it exists in nature, its complexity has inspired several even-more-simplified models, such as the Morris–Lecar model and the FitzHugh–Nagumo model, both of which have only two coupled ODEs. The properties of the Hodgkin–Huxley and FitzHugh–Nagumo models and their relatives, such as the Bonhoeffer–van der Pol model, have been well-studied within mathematics, computation and electronics. More modern research has focused on larger and more integrated systems; by joining action-potential models with models of other parts of the nervous system (such as dendrites and synapses), researches can study neural computation and simple reflexes, such as escape reflexes and others controlled by central pattern generators.

Chapter 8

Sodium Channel Blocker

Sodium channel blockers are agents that impair conduction of sodium ions (Na^+) through sodium channels.

Extracellular

The following naturally produced substances block sodium channels by binding to and occluding the extracellular pore opening of the channel:

- Alkaloid based toxins
  - tetrodotoxin (TTX)
  - saxitoxin (STX)

Intracellular

Drugs which block sodium channels by blocking from the intracellular side of the channel include:

- Local anesthetics
- Class I antiarrhythmic agents
- Some anticonvulsants

Unknown mechanism

- A-803467: specific blockade of $Na_v1.8$ channels (SCN10A), developed by Icagen and Abbott Laboratories

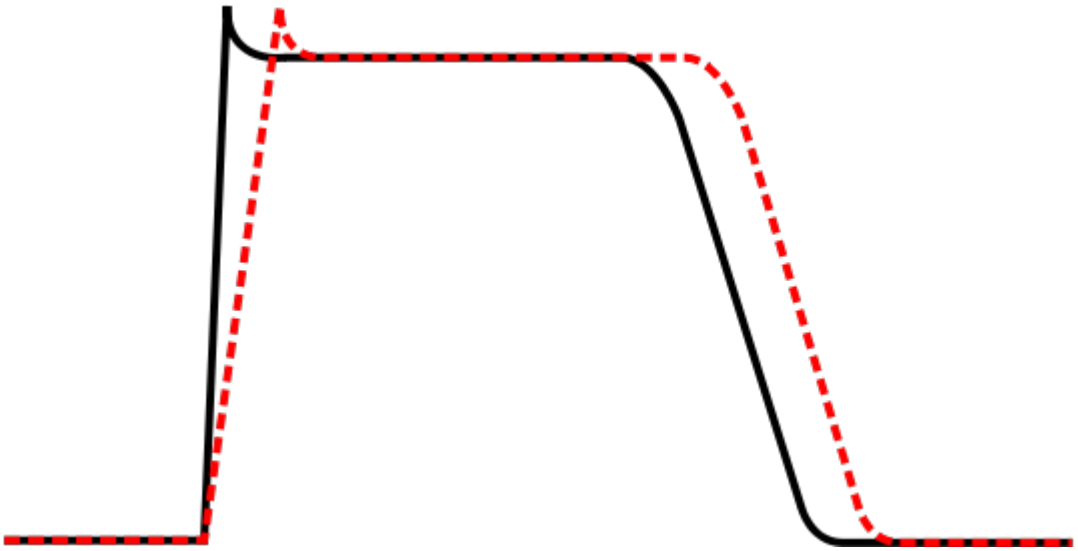
- Caffeine has been shown to inhibit Na^+ current in ventricular cells of guinea pigs.

Antiarrhythmic

Sodium channel blockers are used in the treatment of cardiac arrhythmia. They are classified as "Type I" in the Vaughan Williams classification.

Class I antiarrhythmic agents interfere with the (Na^+) channel. Class I agents are grouped by their effect on the Na^+ channel, and by their effect on cardiac action potentials. Class I agents are called Membrane Stabilizing Agents. 'Stabilizing' refers to the decrease of excitogenicity of the plasma membrane effected by these agents. A few class II agents, propranolol for example, also have a membrane stabilizing effect.

Class Ia agents



Class Ia agent decreasing V_{max}, thereby increasing action potential duration

Class Ia agents block the fast sodium channel, which depresses the phase 0 depolarization (i.e. reduces V_{max}), which prolongs the action potential duration by slowing conduction. Agents in this class also cause decreased conductivity and increased refractoriness.

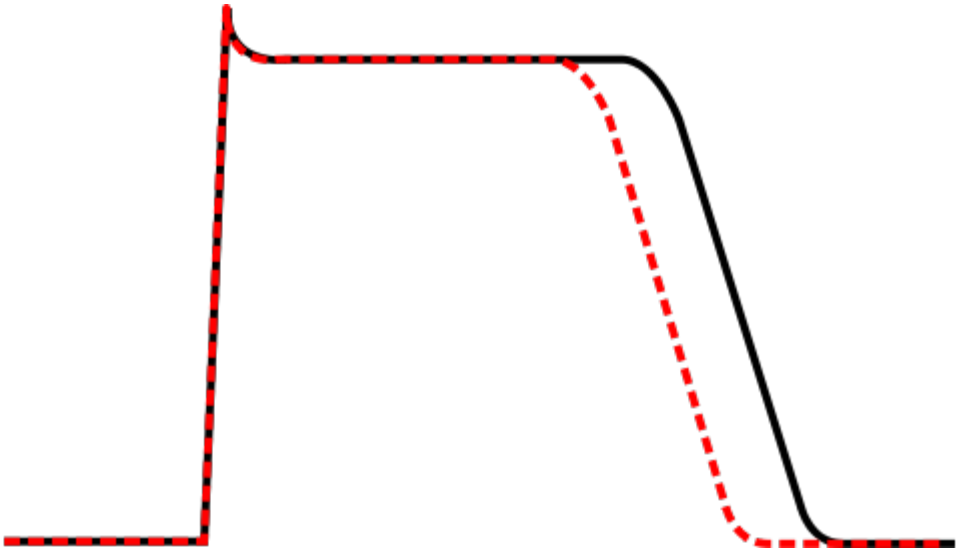
Indications for Class Ia agents are supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats, and prevention of ventricular fibrillation.

Procainamide can be used to treat atrial fibrillation in the setting of Wolff-Parkinson-White syndrome, and to treat wide complex hemodynamically stable tachycardias. Oral procainamide is no longer being manufactured in the US, but intravenous formulations are still available.

While procainamide and quinidine may be used in the conversion of atrial fibrillation to normal sinus rhythm, they should only be used in conjunction with an AV node blocking agent such as digoxin or verapamil, or a beta blocker), because procainamide and quinidine can increase the conduction through the AV node and may cause 1:1 conduction of atrial fibrillation, causing an increase in the ventricular rate.

Class Ia agents include quinidine, procainamide and disopyramide.

Class Ib agents



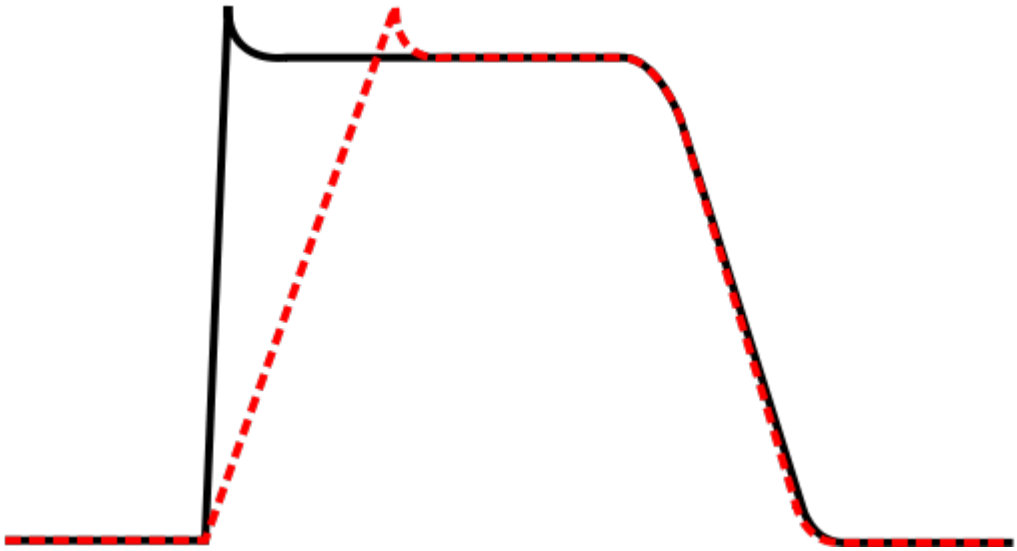
Effect of class Ib antiarrhythmic agents on the cardiac action potential

Class Ib antiarrhythmic agents are sodium channel blockers. They have fast onset and offset kinetics, meaning that they have little or no effect at slower heart rates, and more effects at faster heart rates. Class Ib agents shorten the action potential duration and reduce refractoriness. These agents will decrease V_{max} in partially depolarized cells with fast response action potentials. They either do not change the action potential duration, or they may decrease the action potential duration. Class Ib drugs tend to be more specific for voltage gated Na channels than Ia. Lidocaine in particular is highly frequency dependent, in that it has more activity with increasing heart rates. This is because lidocaine selectively blocks Na channels in their open and inactive states and has little binding capability in the resting state.

Class Ib agents are indicated for the treatment of ventricular tachycardia and symptomatic premature ventricular beats, and prevention of ventricular fibrillation.

Class Ib agents include lidocaine, mexiletine, tocainide, and phenytoin.

Class Ic agents



Effect of class Ic antiarrhythmic agent on cardiac action potential

Class Ic antiarrhythmic agents markedly depress the phase 0 depolarization (decreasing V_{max}). They decrease conductivity, but have a minimal effect on the action potential duration. Of the sodium channel blocking antiarrhythmic agents (the class I antiarrhythmic agents), the class Ic agents have the most potent sodium channel blocking effects.

Class Ic agents are indicated for life-threatening ventricular tachycardia or ventricular fibrillation, and for the treatment of refractory supraventricular tachycardia (ie: atrial fibrillation). These agents are potentially pro-arrhythmic, especially in settings of structural heart disease (e.g. post-myocardial infarction), and are contraindicated in such settings.

Class Ic agents include encainide, flecainide, moricizine, and propafenone. Encainide is not available in the US.

Other uses

Sodium channel blockers are also used as local anesthetics and epilepsy treatments.

Sodium channel blockers have been proposed for use in the treatment of cystic fibrosis, but current evidence is mixed.

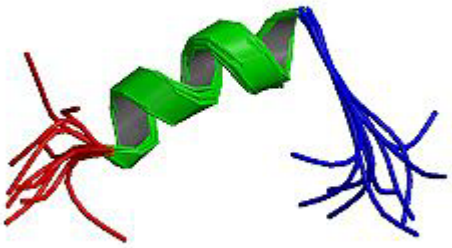
It has been suggested that the analgesic effect of some antidepressants is due to sodium channel blockade.

Chapter 9

Voltage-gated Sodium Ion Channel

$Na_v1.1$

Sodium channel, voltage-gated, type I, alpha subunit

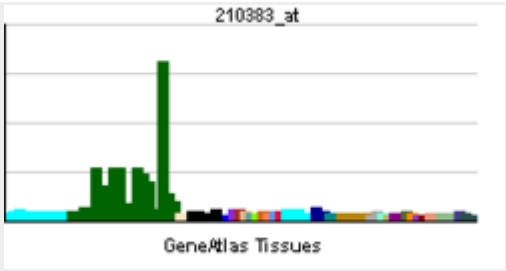


Solution structure of the rat $Na_v1.1$ sodium channel inactivation gate. This gate (25 amino acids residues in length) is a small portion of the entire sodium channel (which contains a a total of 2009 amino acids). The inactivation gate is located between repeat domains III and IV of the sodium channel protein.

Identifiers	
Symbols	SCN1A; FEB3; GEFSP2; HBSCI; NAC1; Nav1.1; SCN1; SMEI
External IDs	OMIM: 182389 MGI: 98246 HomoloGene: 21375 IUPHAR: $Na_v1.1$

	GeneCards: SCN1A Gene

RNA expression pattern



Orthologs

Species	Human	Mouse
Entrez	6323	20265
Ensembl	ENSG00000144285	ENSMUSG00000064329
UniProt	P35498	n/a
RefSeq (mRNA)	NM_006920	XM_001001733
RefSeq (protein)	NP_008851	XP_001001733
Location (UCSC)	Chr 2: 166.55 - 166.64 Mb	Chr 2: 66.07 - 66.12 Mb

$Na_v1.1$, also known as the **sodium channel, voltage-gated, type I, alpha subunit** (**SCN1A**), is a protein which in humans is encoded by the *SCN1A* gene.

Function

The vertebrate sodium channel is a voltage-gated ion channel essential for the generation and propagation of action potentials, chiefly in nerve and muscle. Voltage-sensitive sodium channels are heteromeric complexes consisting of a large central pore-forming glycosylated alpha subunit and 2 smaller auxiliary beta subunits. Functional studies have indicated that the transmembrane alpha subunit of the brain sodium channels is sufficient for expression of functional sodium channels. Brain sodium channel alpha subunits form a gene subfamily with several structurally distinct isoforms clustering on chromosome 2q24, types I, II ($Na_v1.2$), and III ($Na_v1.3$). There are also several distinct sodium channel alpha subunit isoforms in skeletal and cardiac muscle ($Na_v1.4$ and $Na_v1.5$, respectively).

Clinical significance

Mutations in the SCNA1 gene cause inherited febrile seizures and GEFS+, type 2.

Patent controversy

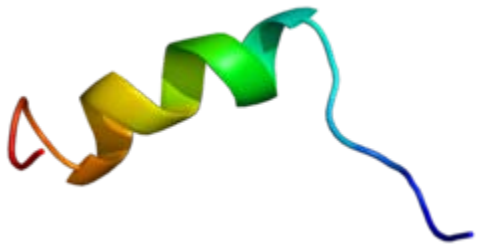
On November 29th 2008, The Sydney Morning Herald reported the first evidence of private intellectual property rights over human DNA having adversely affected medical care. The Melbourne company Genetic Technologies (GTG) controls rights to the gene, and requires royalties for tests on the gene, which can help identify Dravet syndrome. Doctors on the Children's Hospital in Westmead, Australia have told journalists that they would test 50% more infants for the gene, if they could conduct the test on site.

Interactions

$Na_v1.1$ has been shown to interact with syntrophin, alpha 1.

$Na_v1.2$

Sodium channel, voltage-gated, type II, alpha subunit

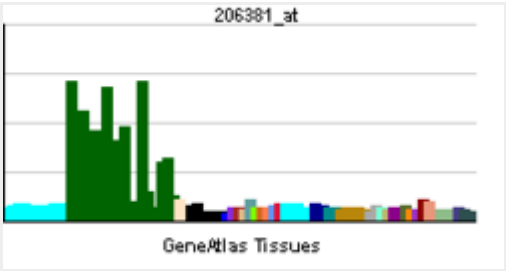


PDB rendering based on 1byy.

Identifiers	
Symbols	SCN2A; HBSCI; SCN2A1; HBA; HBSCII; Na(v)1.2; Nav1.2; SCN2A2
External IDs	OMIM: 601219 HomoloGene: 75001 IUPHAR: $Na_v1.2$

	GeneCards: SCN2A Gene

RNA expression pattern



Orthologs

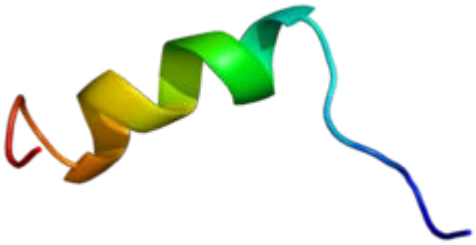
Species	Human	Mouse
Entrez	6326	n/a
Ensembl	ENSG00000136531	n/a
UniProt	Q99250	n/a
RefSeq (mRNA)	NM_001040142	n/a
RefSeq (protein)	NP_001035232	n/a
Location (UCSC)	Chr 2: 165.86 - 165.95 Mb	n/a

$Na_v\alpha 1.2$, also known as the **sodium channel, voltage-gated, type II, alpha subunit** is a protein that in humans is encoded by the **SCN2A** gene. Functional sodium channels contain an ion conductive alpha subunit and one or more regulatory beta subunits. Sodium channels which contain the $Na_v\alpha 1.2$ subunit are called **$Na_v 1.2$** channels.

Voltage-gated sodium channels are transmembrane glycoprotein complexes composed of a large alpha subunit with 24 transmembrane domains and one or more regulatory beta subunits. They are responsible for the generation and propagation of action potentials in neurons and muscle. This gene encodes one member of the sodium channel alpha subunit gene family. It is heterogeneously expressed in the brain, and mutations in this gene have been linked to several seizure disorders. Several alternatively spliced transcript variants of this gene have been described, but the full-length nature of some of these variants has not been determined.

$Na_v1.3$ (SCN3A)

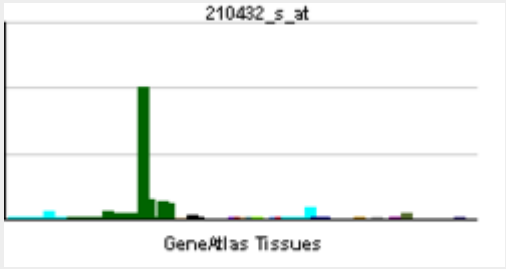
Sodium channel, voltage-gated, type III, alpha subunit



PDB rendering based on 1byy.

Identifiers	
Symbols	SCN3A; KIAA1356; NAC3; Nav1.3
External IDs	OMIM: 182391 MGI: 98249 HomoloGene: 56005 IUPHAR: $Na_v1.3$ GeneCards: SCN3A Gene

RNA expression pattern



Orthologs

Species	Human	Mouse
Entrez	6328	20269
Ensembl	ENSG00000153253	ENSMUSG00000057182
UniProt	Q9NY46	n/a
RefSeq (mRNA)	NM_001081676	XM_001001516
RefSeq (protein)	NP_001075145	XP_001001516

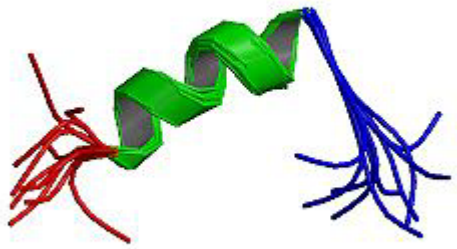
Location (UCSC)	Chr 2: 165.65 - 165.77 Mb	Chr 2: 65.3 - 65.34 Mb

Sodium channel, voltage-gated, type III, alpha subunit (**SCN3A**) is a protein that in humans is encoded by the **Nav1.3** gene.

Voltage-gated sodium channels are transmembrane glycoprotein complexes composed of a large alpha subunit with 24 transmembrane domains and one or more regulatory beta subunits. They are responsible for the generation and propagation of action potentials in neurons and muscle. This gene encodes one member of the sodium channel alpha subunit gene family, and is found in a cluster of five alpha subunit genes on chromosome 2. Multiple transcript variants encoding different isoforms have been found for this gene.

$Na_v1.4$

Sodium channel, voltage-gated, type IV, alpha subunit

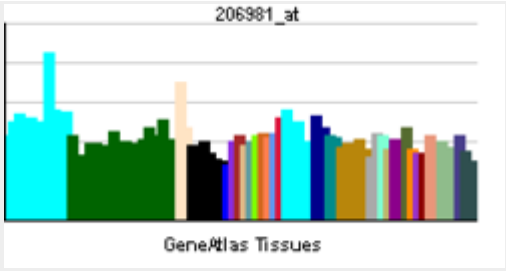


Solution NMR structure of the IFM motif/inactivation gate of the $Na_V1.4$ sodium channel (PDB 1byy).

Identifiers	
Symbols	SCN4A; HYKPP; HYPP; NAC1A; Na(V)1.4; Nav1.4; SkM1
External	OMIM: 603967 MGI: 98250

IDs	HomoloGene: 283 IUPHAR: $Na_v1.4$ GeneCards: SCN4A Gene

RNA expression pattern



Orthologs

Species	Human	Mouse
Entrez	6329	110880
Ensembl	ENSG00000007314	ENSMUSG00000001027
UniProt	P35499	n/a
RefSeq (mRNA)	NM_000334	NM_133199
RefSeq (protein)	NP_000325	NP_573462
Location (UCSC)	Chr 17: 59.37 - 59.4 Mb	Chr 11: 106.14 - 106.17 Mb

Sodium channel protein type 4 subunit alpha is a protein that in humans is encoded by the *SCN4A* gene.

The **$Na_v1.4$** voltage-gated sodium channel is encoded by the *SCN4A* gene. Mutations in the gene are associated with hypokalemic periodic paralysis, hyperkalemic periodic paralysis, paramyotonia congenita, and potassium-aggravated myotonia.

Function

Voltage-gated sodium channels are transmembrane glycoprotein complexes composed of a large alpha subunit with 24 transmembrane domains and one or more regulatory beta subunits. They are responsible for the generation and propagation of action potentials in neurons and muscle. This gene encodes one member of the sodium channel alpha subunit gene family. It is expressed in skeletal muscle, and mutations in this gene have been linked to several myotonia and periodic paralysis disorders.

Clinical significance

Periodic paralysis

In hypokalemic periodic paralysis, arginine residues making up the voltage sensor of $Na_v1.4$ are mutated. The voltage sensor comprises the S4 alpha helix of each of the four transmembrane domains (I-IV) of the protein, and contains basic residues that only allow entry of the positive sodium ions at appropriate membrane voltages by blocking or opening the channel pore. In patients with these mutations, the channel has a reduced excitability and signals from the central nervous system are unable to depolarise muscle. As a result, the muscle cannot contract efficiently, causing paralysis. The condition is hypokalemic because a low extracellular potassium ion concentration will cause the muscle to repolarise to the resting potential more quickly, so even if calcium conductance does occur it cannot be sustained. It becomes more difficult to reach the calcium threshold at which the muscle can contract, and even if this is reached then the muscle is more likely to relax. Because of this, the severity would be reduced if potassium ion concentrations are kept high.

In hypokalemic periodic paralysis, mutations occur in residues between transmembrane domains III and IV which make up the fast inactivation gate of $Na_v1.4$. Mutations have also been found on the cytoplasmic loops between the S4 and S5 helices of domains II, III and IV, which are the binding sites of the inactivation gate.

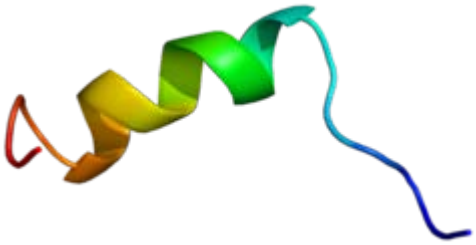
In patients with these the channel is unable to inactivate, sodium conductance is sustained and the muscle remains permanently tense. Since the motor end plate is depolarised, further signals to contract have no effect (paralysis). The condition is hyperkalemic because a high extracellular potassium ion concentration will make it even more unfavourable for potassium to leave the cell in order to repolarise it to the resting potential, and this further prolongs the sodium conductance and keeps the muscle contracted. Hence, the severity would be reduced if extracellular (serum) potassium ion concentrations are kept low.

Myotonia

The same types of mutations cause myotonia and paralysis, however the difference between these phenotypes depends on the level of sodium current that persists. If the conductance fluctuates below the voltage threshold for $Na_v1.4$, then the sodium channels will eventually be able to close, and be depolarised again. Thus, the muscle merely remains contracted for longer than normal (myotonia) but will relax and be able to contract again within a short period. If the conductance settles at a steady state with the sodium pore open and unable to inactivate, then the muscle is unable to relax at all and motor control is completely lost (paralysis).

$Na_v1.5$

Sodium channel, voltage-gated, type V, alpha subunit



Solution structure of the $Na_v1.5$ inactivation gate.

Identifiers		
Symbols	SCN5A; HB1; HB2; CDCD2; CMD1E; CMPD2; HH1; IVF; LQT3; Nav1.5; SSS1	
External IDs	OMIM: 600163 MGI: 98251 HomoloGene: 22738 IUPHAR: $Na_v1.5$ GeneCards: SCN5A Gene	
Orthologs		
Species	**Human**	**Mouse**
Entrez	6331	20271
Ensembl	ENSG00000183873	ENSMUSG00000032511
UniProt	Q14524	Q9JJV9
RefSeq (mRNA)	NM_198056	NM_021544
RefSeq (protein)	NP_932173	NP_067519
Location (UCSC)	Chr 3: 38.59 - 38.69 Mb	Chr 9: 119.33 - 119.43 Mb

The **$Na_v1.5$** sodium ion channel protein that in humans is encoded by the *SCN5A* gene. Mutations in the gene are associated with long QT syndrome type 3 (LQT3), Brugada syndrome, primary cardiac conduction disease and idiopathic ventricular fibrillation.

The protein encoded by this gene is an integral membrane protein and tetrodotoxin-resistant voltage-gated sodium channel subunit. The encoded protein is found primarily in cardiac muscle and is responsible for the initial upstroke of the action potential in an electrocardiogram. Defects in this gene are a cause of long QT syndrome type 3 (LQT3), an autosomal dominant cardiac disease. Alternative splicing results in two transcript variants encoding separate isoforms which differ by a single amino acid. Mutation nomenclature has been assigned with respect to the longer isoform.

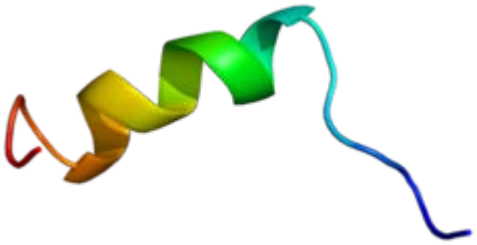
Interactions

Nav1.5 has been shown to interact with Syntrophin, alpha 1.

Nav1.5 interacts with ankyrin-G through a nine-amino acid ankyrin-G binding sequence.

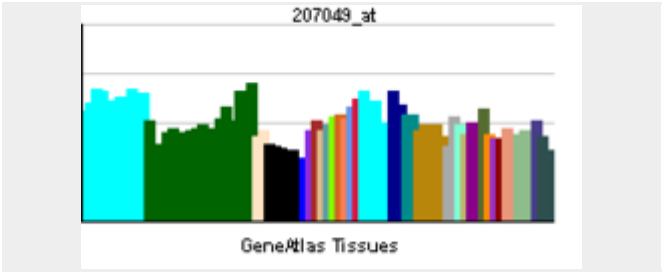
$Na_v1.6$ (SCN8A)

Sodium channel, voltage gated, type VIII, alpha subunit



PDB rendering based on 1byy.

Identifiers	
Symbols	SCN8A; MED; CerIII; NaCh6; Nav1.6; PN4
External IDs	OMIM: 600702 MGI: 103169 HomoloGene: 7927 IUPHAR: $Na_v1.6$ GeneCards: SCN8A Gene
RNA expression pattern	



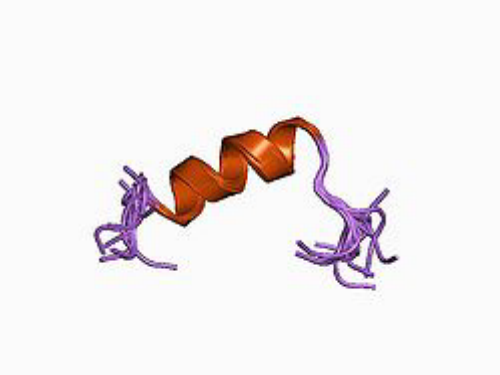
Orthologs		
Species	**Human**	**Mouse**
Entrez	6334	20273
Ensembl	ENSG00000196876	ENSMUSG00000023033
UniProt	Q9UQD0	Q9WTU3
RefSeq (mRNA)	NM_014191	NM_011323
RefSeq (protein)	NP_055006	NP_035453
Location (UCSC)	Chr 12: 50.36 - 50.49 Mb	Chr 15: 100.78 - 100.87 Mb

Sodium channel, voltage gated, type VIII, alpha subunit also known as **SCN8A** or **$Na_v1.6$** is a protein which in humans is encoded by the *SCN8A* gene. It is a voltage-gated sodium channel.

The ion channel was discovered by John Caldwell and colleagues at the University of Colorado Health Sciences Center in the rat, and by Miriam Meisler and colleagues at the University of Michigan Medical School in the mouse.

$Na_v1.7$

sodium channel



PDB rendering based on 1byy.

Identifiers		
Symbols	SCN9A; NENA; PN1; ETHA	
External IDs	OMIM: 603415 MGI: 107636 HomoloGene: 2237 IUPHAR: $Na_v1.7$ GeneCards: SCN9A Gene	
Orthologs		
Species	**Human**	**Mouse**
Entrez	6335	20274
Ensembl	ENSG00000169432	ENSMUSG00000075316
UniProt	Q15858	Q3UQV9
RefSeq (mRNA)	NM_002977	NM_018852
RefSeq (protein)	NP_002968	NP_061340
Location (UCSC)	Chr 2: 166.76 - 166.94 Mb	Chr 2: 66.32 - 66.47 Mb

$Na_v1.7$ is a sodium ion channel that in humans is encoded by the *SCN9A* gene. It is usually expressed at high levels in two types of neurons, the nociceptive dorsal root ganglion (DRG) neurons and sympathetic ganglion neurons, which are part of the autonomic (involuntary) nervous system.

Function

$Na_v1.7$ is a voltage-gated sodium channel and plays a critical role in the generation and conduction of action potentials and is thus important for electrical signaling by most excitable cells. $Na_v1.7$ is present at the endings of pain-sensing nerves, the nociceptors, close to region where the impulse is initiated. Stimulation of the nociceptor nerve endings produces "generator potentials", which is small changes in the voltage across the neuronal membranes. The $Na_v1.7$ channel amplifies these membrane depolarizations, and when the membrane potential difference reaches a specific threshold, the neuron fires. In sensory neurons, multiple voltage-dependent sodium currents can be differentiated by their voltage dependence and by sensitivity to the voltage-gated sodium-channel blocker tetrodotoxin. The $Na_v1.7$ channel produces a rapidly activating and inactivating current which is sensitive to level of tetrodotoxin. $Na_v1.7$ is important in early phases of neuronal electrogenesis. $Na_v1.7$ is described by slow transition of the channel into an inactive state when it is depolarized, even to a minor degree. This property that allows these channels to remain available for activation with even small or slowly developing depolarizations. Stimulation of the nociceptor nerve endings produces "generator potentials", which is small changes in the voltage across the neuronal membranes. This brings neurons to certain voltage that stimulate $Na_v1.8$, which has a more depolarized activation threshold that produces most of the transmembrane current responsible for the depolarizing phase of action potentials.

Clinical significance

Animal studies

Clues that $Na_v1.7$ is involved in pain is originated from the observation that DRG neurons in animal models in inflammatory pain showed increase response to $Na_v1.7$. Also knockout mice that lack $Na_v1.7$ in nociceptors showed reduced response to inflammatory pain. However, neuropathic pain(chronic pain resulting from injury to the nervous system) remained intact. These results are consistent with an important role of $Na_v1.7$ in setting the inflammatory pain threshold. To observe the role of $Na_v1.7$ in relation to other sodium channels expressed in peripheral sensory neurons, the researchers created mice deficient in both $Na_v1.7$ and $Na_v1.8$ channels. Mice deficient in $Na_v1.8$ had deficits in sensing inflammatory pain (initiated by tissue damage/inflammation) and visceral pain (initiated by damage or injury to internal organs) but not neuropathic pain. The thermal pain threshold in mice deficient in both $Na_v1.7$ and $Na_v1.8$ mice was twice that of mice lacking only $Na_v1.7$. The result clearly implicate $Na_v1.7$ as a major sodium channel in peripheral nociception and suggest a functional link to $Na_v1.8$.

Primary erythromelalgia

Mutation in $Na_v1.7$ may result in primary erythromelalgia (PE), an autosomal dominant, inherited disorder which is characterized by attacks or episodes of symmetrical burning pain of the feet, lower legs, and sometimes hands, elevated skin temperature of affected areas, and reddened extremities. The mutation causes excessive channel activity which

suggests that $Na_v1.7$ sets the gain on pain signaling in humans. It was observed that a missense mutation in the *SCN9A* gene affected conserved residues in the pore-forming α subunit of the $Na_v1.7$ channel. Many studies have found a dozen *SCN9A* mutations in multiple families as causing erythromelagia. All of the observed erythromelalgia mutations that are observed are missense mutations that change important and highly conserved amino acid residues of the $Na_v1.7$ protein. The majority of mutations that cause PE are located in cytoplasmic linkers of the $Na_v1.7$ channel, however some mutations are present in transmembrane domains of the channel. The PE mutations cause a hyperpolarizing shift in the voltage dependence of channel activation, which allows the channel to be activated by smaller than normal depolarizations, thus enhancing the activity of $Na_v1.7$. Moreover, the majority of the PE mutations also slow deactivation, thus keeping the channel open longer once it is activated. In addition, in response to a slow, depolarizing stimulus, most mutant channels will generate a larger than normal sodium current. Each of these alterations in activation and deactivation can contribute to the hyperexcitability of pain-signaling DRG neurons expressing these mutant channels, thus causing extreme sensitivity to pain hyperalgesia. While the expression of PE $Na_v1.7$ mutations produces hyperexcitability in DRG neurons, studies on cultured rat in sympathetic ganglion neurons indicate that expression of these same PE mutations results in reduction of excitability of these cells. This occurs because $Na_v1.8$ channels, which are selectively expressed in addition to $Na_v1.7$ in DRG neurons, are not present within sympathetic ganglion neurons. Thus lack of $Na_v1.7$ results in inactivation of the sodium channels results in reduced excitability. Thus physiological interaction of $Na_v1.7$ and $Na_v1.8$ can explain the reason that PE presents with pain due to hyperexcitability of nociceptors and with sympathetic dysfunction that is most likely due to hypoexcitability of sympathetic ganglion neurons. Recent studies have associated a defect in *SCN9A* with congenital insensitivity to pain.

Insensitivity to pain

Individuals with congenital insensitivity to pain have painless injuries beginning in infancy but otherwise normal sensory responses upon examination. Patients frequently have bruises and cuts, and are often only diagnosed because of limping or lack of use of a limb. Individuals have been reported to be able to walk over burning coals and to insert knives and drive spikes through their arms. It has been observed that the insensitivity to pain does not appear to be due to axonal degeneration.

A mutation that caused loss of $Na_v1.7$ function has been detected in three consanguineous families from northern Pakistan. All mutation observed were nonsense mutation with majority of affected patients having homozygous mutation in the *SCN9A* gene. Their observation linked loss of $Na_v1.7$ function with incapability to experience pain. The result was in contrast with the genetic basis of primary erythromelalgia in which the disorder results from gain-of-function mutations.

Therapeutic applications

The association of pain insensitivity with the loss of function of a certain sodium channel may have therapeutic applications. Since $Na_v1.7$ is not present in cardiac muscle or neurons in the central nervous system, blockers of $Na_v1.7$ will not have direct action on these cells and thus can have less side effects than current pain medications.

$Na_v1.8$ (SCN10A)

sodium channel

Identifiers		
Symbols	SCN10A; PN3; SNS; hPN3	
External IDs	OMIM: 604427 MGI: 108029 HomoloGene: 21300 IUPHAR: $Na_v1.8$ GeneCards: SCN10A Gene	
Orthologs		
Species	**Human**	**Mouse**
Entrez	6336	20264
Ensembl	ENSG00000185313	ENSMUSG00000034533
UniProt	n/a	n/a
RefSeq (mRNA)	NM_006514	NM_009134
RefSeq (protein)	NP_006505	NP_033160
Location (UCSC)	Chr 3: 38.71 - 38.81 Mb	Chr 9: 119.52 - 119.6 Mb

Sodium channel, voltage gated, type X, alpha subunit also known as **SCN10A** or **$Na_v1.8$** is a protein which in humans is encoded by the *SCN10A* gene.

$Na_v1.8$ is a sodium channel subunit.

Function

This subtype of voltage-gated sodium channel is expressed in nociceptors and has been proposed as a target for the development of new analgesics.

$Na_v1.9$

sodium channel, voltage-gated, type XI, alpha subunit

Identifiers		
Symbols	SCN11A; NaN; SCN12A	
External IDs	OMIM: 604385 MGI: 1345149 HomoloGene: 8041 IUPHAR: $Na_v1.9$ GeneCards: SCN11A Gene	
Orthologs		
Species	**Human**	**Mouse**
Entrez	11280	24046
Ensembl	ENSG00000168356	ENSMUSG00000034115
UniProt	Q9UI33	Q810E1
RefSeq (mRNA)	NM_014139	NM_011887
RefSeq (protein)	NP_054858	NP_036017
Location (UCSC)	Chr 3: 38.86 - 38.97 Mb	Chr 9: 119.66 - 119.73 Mb

Sodium channel, voltage-gated, type XI, alpha subunit also known as **SCN11A** or **$Na_v1.9$** is a voltage-gated sodium ion channel protein which in humans is encoded by the *SCN11A* gene.