Ion channels and neurologic disorders

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Historical note and nomenclature

Ion channels are protein pores in the cell membrane that allow the passage of ions down their respective electrochemical gradients. Ion channels are classified according to the ion passing through them (eg, sodium, potassium, calcium, or chloride), and the mechanisms by which they are opened or closed. Acetylcholine, for example, opens chloride channels. Channel blockers are molecules that can enter the pores and physically plug them.

The importance of ion channels in the generation and transmission of signals in the nervous system has been well recognized for over 50 years, since the classical work of Hodgkin and Huxley, in measurement of ion currents and conductance in sodium and potassium channels by classical voltage clamp techniques (Hodgkin and Huxley 1952). These authors were awarded the Nobel Prize in 1963 for their concept of ion channels. Introduction of electrophysiological methods for the study of ion channels led to an explosion of research on ion channels in many different systems. Thirty years ago Bernard Katz showed that calcium was indispensable for the release of acetylcholine from the neuromuscular junction and, based on this work, shared the Nobel Prize for physiology and medicine with von Euler and Axelrod (Katz 1969). In 1976 Neher and Sakmann demonstrated single channel current recording from ion channels (Neher and Sakmann 1976). The Nobel Prize was awarded in 1991 to these authors for discovery of the patch clamp technique, which enabled the study of currents passing through single ion channels. Molecular techniques have been applied to the study of ion channels during the past 15 years. In 1986 a complete sequence of cDNA coding of a sodium channel was published (Noda et al 1986). The genes encoding several classes of ion channels have been cloned and sequenced during the past decade. Parallel to this, the number of human diseases resulting from mutations in the genes encoding ion channels has also increased.

Ion channels are essential for a wide range of cellular functions, including neuronal signaling, muscle contraction, sensory conduction, and endocrine secretions. Ion channels have a critical role in neurons because they enable the neurons to signal. It is to be expected that disturbances of ion channels and transporters would lead to disease. The first ion channel disorders were recognized in the skeletal muscle. Evidence for a defective chloride channel in myotonia congenita was presented in the 1970s, but it was not until 1994 that a mutation in the gene encoding the human skeletal muscle chloride channel was identified (Lorenz et al 1994). These diseases are often called channelopathies, whereas those involving the nervous system are called neuronal channelopathies. This term does not include disturbances in ion channels seen in a large range of neurologic disorders, including trauma and cerebrovascular ischemia.

There are 2 basic types of ion channels, (1) voltage-gated and (2) ligand- or transmitter-gated, but some channels exhibit dual gating mechanisms. This clinical summary deals with the role of voltage-gated ion channels in the pathophysiology of neurologic diseases, and also with their role as targets for therapy. With the recent recognition of active glial participation in information processing, a physiological role for

some of the glial channels and receptors is gradually emerging. Ion channels are expressed by astrocytes and oligodendrocytes as well as by Schwann cells.

Top

Description

Voltage-gated channels. The stimulus for gating is the change of voltage across the membrane in which the channels are embedded. Obvious candidates for voltage sensors are charged residues in the membrane-embedded domain of the channel protein. Voltage-gated potassium (K+), sodium (Na+), and calcium (Ca2+) channels are members of a related gene family, and are fractionally autonomous in voltage-dependent activation. Purification, molecular cloning, and determination of primary structures of primary subunits of voltage-gated channels have provided a molecular template for probing the relationship between their structure and function.

Potassium channels. Potassium channels act like electrical switches to regulate cellular excitability. They can be compared to electrical rectifiers that conduct potassium better in one direction than in another. Potassium channels have an important role to play in the physiology and pharmacology of the cardiovascular and nervous systems. The molecular diversity of potassium-selective channels is mirrored by the broad spectrum of physiological functions subserved by these proteins. There are more subtypes of potassium channels than any other ion channel. Studies from the *Caenorhabditis elegans* genome project indicate that more than 70 distinct potassium channel genes exist. The best characterized potassium channels are members of 1 of the 2 so-called super families. Superfamily 1 includes the A-channel (KA), the delayed rectifier (Kv), and the large conductance Ca-sensitive channel (KCa). Superfamily 2 includes the inward rectifier (KIR) and ATP-sensitive channels.

Sodium channels. Open sodium channels in biological membranes are selective for Na+ ions, and have only minor permeability for other anions and cations. They are classified into types 1, 2, 3, μ1, H1, and PN3. Of these types, 1, 2, and 3 are predominantly expressed in the nervous system, and type μ1 is expressed in the skeletal muscle. The voltage-gated sodium channels play an essential role in nerve tissue, where they are responsible for the rapidly conducting nerve impulse. A single gene on human chromosome 19 encodes the b-subunit expressed in the brain, heart, and skeletal muscle. Although the a-subunit, alone, forms the functional channel, the muscle b-subunit binds to the perimeter, perhaps by interaction of its transmembrane helix with 1 or more of the repeat domains. There are multiple types of sodium channels in the skeletal muscle, based on sensitivity to toxins and antibodies.

Calcium channels. Voltage-dependent calcium channels open in response to membrane depolarization, and allow the passage of calcium through the channel's pore without significant flux of any other ion. The resulting entry of calcium into a cell triggers a variety of intracellular processes, including muscle contraction and secretion of neurotransmitters. Although the sodium and potassium pump is mainly involved in the action potential, calcium channels also play an important part in the nerve impulse. These channels are normally closed at the resting membrane potential, and opened reversibly by depolarization to more positive potentials. The opening and closing occurs within a few milliseconds, in most instances. Calcium channels are also subject to inactivation during prolonged depolarizations. Some instances of calcium channel inactivation are secondary to intracellular calcium accumulation; others are a direct effect of membrane depolarization. Calcium channel subtypes with different electrophysiological and pharmacological properties are related to differences in alpha1-subunit structure. A classification of calcium channels is shown in Table 1.

Table 1. Classification of Calcium Ion Channels

Type: L

Properties: High-voltage activated; slow inactivation
Location: Smooth muscles, endocrine cells
Principal function: Smooth muscle contraction; endocrine secretion
Blockers: Dihydropyridines

Type: N

Properties: High-voltage activated; moderate rate of inactivation
Location: Only in neurons
Principal function: Neurotransmitter disease
Blockers: Omega-conotoxins

Type: P/Q

Properties: Moderately high-voltage activated; nonactivating
Location: Some CNS neurons (Purkinje cells)
Principal function: Unknown
Blockers: Omega-agatoxin and omega-conotoxins

Type: T

Properties: Low-voltage activated; inactivation slower than L or N types
Location: Heart neurons
Principal function: Influences pacemaker activity in the heart
Blockers: Mibefradil

Intracellular calcium concentration in neurons can be transiently increased by 2 mechanisms: (1) calcium influx through calcium-permeable channels in the plasma membrane or (2) the mobilization of calcium from intracellular calcium stores. Neurotransmitters can trigger both mechanisms. Glutamate activates ionotropic glutamate-receptor channels, which induce cell depolarization and, hence, calcium influx through voltage-sensitive calcium channels. A close functional interaction thus exists between glutamate receptors, intracellular calcium stores, and calcium-sensitive ion channels in the cell membrane.

Chloride channels. Chloride channels belong to the group of anion channels, which contribute to the regulation of membrane potential and cell signaling. Chloride channels mediate passive transport of chloride ions across the lipid bilayer by forming an aqueous diffusion pore. They are present in plasma membranes, as well as in intracellular organelles. In the intracellular compartment, chloride channels are often found in conjunction with cation transport systems, where chloride serves as a counter ion to the transported cation. There is no satisfactory classification of chloride channels. Many different types of chloride channels have been found by electrophysiological studies and are subject to various types of regulation. Most chloride channels, like other ion channels, show some dependence of open-probability on the membrane voltage. Three well-defined, structural classes of plasma membrane chloride channels exist. Voltage-gated (swelling-activated, volume-dependent) chloride channels are activated by an increase in cell volume, but it is likely that other mediators are also involved. Physiological concentrations of Ca^{2+} and Mg^{2+} can modulate volume-regulated Cl^- currents in epithelial tissues. ClC-1 is the major skeletal muscle chloride channel that is essential for muscle excitability.

Aquaporins. These are transmembrane proteins that selectively allow the passage of water through the plasma membrane. In the brain, they are involved in the production of cerebrospinal fluid and the control of water movement at the blood-brain barrier. They have been implicated in the formation of brain edema (Griesdale and Honey 2004). Further research on aquaporins may lead to targeted therapies for cerebral edema. In intractable epilepsy, expression of aquaporin ion channels increased in astrocytes, but

not in neurons or oligodendrocytes (Zhou et al 2008). Whether this is the cause or an effect of seizures remains to be determined.

Gap junctions. These are connections that allow molecules and ions to flow between cells. Junctions are composed of 2 hemichannels that bridge the intercellular space.

Ligand-gated and transmitter-gated ion channels. Ligand-gated and transmitter-gated ion channels form a class of multisubunit membrane-spanning receptors that are essential for rapid signal transduction. The property that defines this class is that the transmitter molecule itself operates the opening and closing of the channel by binding to a site on the receptor. Gating refers to conformational change in ion channels that is triggered by ligand binding. In the nervous system, voltage-gated ion channels mediate action potentials and trigger transmitter release, whereas ligand-gated channels are responsible for chemical signaling mediated by classical fast-acting neurotransmitters. Neurotransmitters also trigger slower transmitter responses that are mediated by G protein-coupled receptors. Ligand-activated ion channels are preferably termed transmitter-gated ion channels and divided into 2 categories: (1) extracellularly-activated and (2) intracellularly-activated. A simplified and brief list is shown in Table 2.

Table 2. Ligand- and Transmitter-Gated Ion Channels

Ligand	Ion selectivity
Extracellularly activated:	
GABAA	Cl-, HCO3-
Glycine	Cl-, HCO3-
Acetylcholine (nicotinic, muscle type)	Na+, K+, Ca2+
Acetylcholine (nicotinic, neuronal)	Na+, K+, Ca2+
5-HT3	Na+, K+
Glutamate: non-NMDA	Na+, K+, (Ca2+)a
Glutamate: NMDA	Na+, K+, Ca2+
ATP	Ca2+, Na+, K+
Intracellularly activated:	
cGMP (photoreceptors)	Na+, K+
cAMP (olfactory neurons)	Na+, K+
IP3 Ca2+ (ryanodine receptor)	Ca2+

Structure of ion channels. Ion channels are macromolecular proteins that span the cell membrane. The cell membrane is generally considered to have 2 essential components: (1) a lipid bilayer and (2) a protein; it also has 3 general functions:

(1) Controlled maintenance of water and electrolytes, as well as nonelectrolytes between 2 separate aqueous compartments. This is accomplished by a series of solute leaks, ion transporters, and ion pumps.

(2) Signal transduction

(3) Surface for molecular interactions

The lipid bilayer is an effective barrier for ion permeation; hydrophilic solutes permeate bilayers poorly, but their flux across the membrane can be dramatically increased by ion channel proteins.

Recent studies of the cell membrane indicate that in the liquid crystalline state (fluid), the cell membrane is approximately 50 angstrom thick and is composed of a wide variety of different phospholipids and cholesterol. The ionic channels originally proposed as a result of studies of excitable membranes have now been detected in virtually all membranes in the cell, including the endoplasmic reticulum, liposomes, and vacuoles.

Molecular structure of ion channels. Most ion channel proteins are composed of individual subunits or groups of subunits, with each subunit containing 6 hydrophobic transmembrane regions S1 to S6. Sodium and calcium channels consist of a single alpha subunit, containing 4 repeats of the 6 transmembrane-spanning motifs. Potassium channels consist of 4 subunits, each containing the 6 transmembrane-spanning motifs.

Physiology of ion channels. Membrane potentials are the voltages that occur across cell membranes. These are conventionally expressed as the voltage of the inside of the cell relative to the extracellular fluid and are measured in millivolts. In the resting stage, most animal cells have negative membrane potentials that range from negative 30 mV to negative 90 mV. The term "depolarization" indicates a reduction in the membrane potential values so that the inside of the cell becomes less negative, as occurs in the upward stroke of the action potential, eg, during flow of positively charged sodium from the extracellular space to the inside of the cell. The downstroke, or the return of the membrane potential to its resting value, is called "repolarization," which can occur during outflow of positively charged ions such as potassium through potassium channels. Outflow of negatively charged ions such as chloride will depolarize the cell.

The knowledge of equilibrium potential for an ion in a particular cell is important for determining the way in which a channel permeable to that ion will affect the membrane potential of the cell. The direction and magnitude of the electrochemical gradient can be calculated for the ion, and the direction, as well as the rate of ion flow through an open channel, can be predicted. The current carried by an ion flow through a single channel is depicted by the symbol "i." The average current flowing through a channel depends on the open probability of the channel and the amount of current flowing through it during the open state.

Voltage-gated ion channels are responsible for generation of electrical signals in neurons and other excitable cells. The basic principle of channel conformation is that the channel conformation, closed or open, is regulated by the membrane potential. This implies that the voltage sensor must link the voltage to these conformational changes. The obvious candidates are electrical charges embedded in the cell membrane. All channels studied so far display discrete open and closed states with transition between these states attributable to the conformational changes of the channel proteins. The ion channels open only during excitation of nerve and muscle cells, implying that they are closed in the nonexcitable state.

Acetylcholine carries chemical messages across all human nerve-muscle synapses. The acetylcholine receptor channel is a molecule-sized valve that opens and closes to regulate the flow of electricity in nerve and muscle cells (Purohit et al 2007). More than 40 different channelopathies have been identified, with representative disorders from every major class of ion channel and affecting all electrically excitable tissues, including the nervous system, muscles, and the heart (Cannon 2007).

Role of ion channels in the nervous system. Classical roles of ion channels in the nervous and neuromuscular systems are signal propagation along a cell surface and signal translation (by release of transmitters) into the cytoplasm of the cell. Ion channels discriminate between calcium, potassium, and sodium, although these ions are similar in size. It is generally accepted that ions bind selectively to the channels. Neurotransmitter-gated channels are of fundamental importance in cell signaling but are less ion-selective than voltage-gated channels.

The membrane of the myelinated axon of the nervous system contains the following physiologically active molecules:

- Voltage-sensitive Na+ channels.
- The K+IR channels modulate axonal excitability.
- Na+/K+-ATPase and Ca2+-ATPase maintain transmembrane gradients of Na+, K+, and Ca2+.

Disturbances of the fluid and electrolytes are associated with pathologic processes in the brain. Glial cells have a capacity to sense transmitter-mediated activity in the CNS. Voltage-gated ionic channels in astrocytes may have a possible role in ionic homeostasis. Swelling of astrocytes leads to marked changes in the membrane transport properties, which would seriously affect astrocyte regulation of the ionic environments of the nervous tissue.

Transient receptor potential ion channels transduce thermal, chemical, and mechanical stimuli into inward currents as the first step for eliciting thermal and pain sensations (Wang and Woolf 2005).

Hyperpolarization-activated cation channels (h-channels) are key regulators of neuronal excitation and inhibition, and are affected by seizures.

Nicotinic acetylcholine receptors (nAChRs), widely expressed throughout the central and peripheral nervous systems, form ligand-gated ion channels involved in fast synaptic transmission. Various subunits of nAChRs play crucial roles in modulating a wide range of higher cognitive functions by mediating presynaptic, postsynaptic, and extrasynaptic signaling (Yang et al 2009).

Genomics and ion channels. Genomics is in the center stage of molecular biology and will have a tremendous impact on the practice of medicine. Vertebrate genomes encode several hundred ion channel subtypes, each of which has evolved to perform a highly-selective electrical "task" within specific cells. These "tasks" can be discerned by examining those cellular conditions that gate (open and close) the channel. Each phase of an "excitability cycle" is associated with specific channel subtypes, and recruitment of the "appropriate" components (from the possibilities encoded by the genome) is precisely specified by the gene expression program for that developmental cell-type. The cell-specific excitability cycle model enables the building-up of a logical hierarchy for cell function from the ionic or molecular level to the cell-type and organism levels. Thus, it may form a useful "frameworking" tool for correlating different descriptions of genome structure, gene expression pattern, and molecular or cell function (phenotype).

All these activities are gathering momentum, as the sequencing of the human genome project has been completed. Molecular cloning and functional expression studies have revealed that many genes underlie ion channels. New ion channels are also being discovered. It is expected that mutations of several genes will be correlated with several diseases and will form the basis of rational drug discovery for these diseases.

Role of ion channels in pathophysiology of neurologic disorders. Channelopathies may be acquired as well as inherited. Maternal antibodies can cross the placenta and cause neonatal disease, and some neurodevelopmental conditions can be caused by maternal antibodies to specific neuronal and muscle ion channels (Vincent et al 2003).

Inherited neurologic channelopathies. Several channelopathies involving the nervous system have been described. Descriptions of the individual diseases are given in more detail in their respective *MedLink Neurology* clinical summaries. Non-neurologic diseases such as cystic fibrosis are related to ion channel defects. Cardiac ion channel disorders, such as the congenital long Q-T syndrome, may cause syncope, seizures, or sudden death due to cardiac arrhythmia.

Movement disorders due to mutations of the ion channel genes. Examples of these are:

- Some epilepsy and paroxysmal movement disorders are channelopathies that may overlap and share some common pathophysiology (Huang and Hwang 2009).
- A gene for familial paroxysmal choreoathetosis has been mapped to a region of chromosome 1p, where a cluster of potassium genes is located.

Idiopathic epilepsies as disorders of ion channels. Several paroxysmal disorders, including epilepsy, have been considered to be due to ion channel abnormalities or channelopathies. Both familial and de novo mutations in neuronal voltage-gated and ligand-gated ion channel subunit genes have been identified in autosomal dominant

epilepsies (Heron et al 2007a). Functional studies characterizing the molecular defects of the mutant channels point to a central role of GABAergic synaptic inhibition in the pathophysiology of idiopathic generalized epilepsies (Lerche et al 2005).

Generalized epilepsies with Mendelian inheritance pattern are associated with the mutations in genes encoding ion channel proteins (Chang and Lowenstein 2003). Two human epilepsy syndromes, benign familial neonatal convulsions and generalized epilepsy with febrile seizures, represent K+ and Na+ channelopathies. KCNQ2/KCNQ3 K+ channels that are mutated in benign familial neonatal convulsions represent an important new target for antiepileptic drugs. Further work has revealed the sequences of 3 related brain channel genes KCNQ3, KCNQ4, and KCNQ5. Mutations in KCNQ3 and KCNQ5 were shown to cause benign familial neonatal convulsions whereas KCNQ4 was associated with hereditary deafness (Cooper and Jan 2003). Some epilepsies, previously classified as idiopathic, have been shown to be channelopathies on the basis of gene analysis in animal models of epilepsy and human familial epilepsies. This knowledge will provide a better understanding of epilepsy and enable the design of novel therapies.

Examples of epilepsy syndromes as channelopathies are as follows:

(1) Autosomal dominant frontal nocturnal epilepsy, an ACh receptor channelopathy due to mutation of CHRNA4, CHRNB2, and ENFL2 genes.

(2) Familial generalized epilepsy with febrile seizures, plus a GABA(A) receptor channelopathy, due to mutation of the GABRG2 gene.

(3) Genetic variations in the T-type calcium channel gene CACNA1H are found in patients with various generalized epilepsy syndromes; they contribute to susceptibility to epilepsy but are not the cause of epilepsy on their own (Heron et al 2007b).

(4) Mutations in nAChR genes are found in nocturnal frontal lobe epilepsy.

Hereditary muscle channelopathies. Release of intracellular calcium triggers generation and propagation of action potentials for mechanical contraction of skeletal muscle, which depends on the proper functioning of ion channels. Several muscle channelopathies caused by mutations in muscle ion channel genes have been identified (Meola et al 2009).

Acquired or secondary neurologic channelopathies. Ion channels may be involved in several acquired disorders. Recognized causes include toxins and autoimmune phenomena. Some examples are:

Marine ciguatoxin toxin. This contaminant of fish is a potent sodium channel blocker that causes a rapid onset of numbness, intense paresthesias, and muscle weakness.

Toxic effects of drugs. The effect of toxins at the neuromuscular junction can be mediated by a rise of intracellular-free calcium within the presynaptic motor nerve terminals. This is due to the decreased efficiency of the organelles within the terminal to sequestrate calcium using an ATP-dependent pump. This mechanism has been offered as an explanation for distal motor axonopathy caused by cycloleucine, an inhibitor of adenosyltransferase. The resulting abnormalities in phospholipid composition of the axolemma impair the efficiency of the ion channels and pumps that are responsible for maintaining electrochemical gradients essential for the maintenance of the structural and functional integrity of the neuromuscular junction.

Drug-induced disturbances of sensory receptors may involve ion channel disturbances. Some examples of this are as follows:

- Drug action involving sodium channels: amiloride, spironolactone, lithium.
- Drug action involving calcium channels: calcium channel blockers.

Drug addiction. Nicotinic AChR belongs to a family of proteins that form ligand-gated transmembrane ion channels. Several therapeutic agents and drugs of abuse, such as cocaine, inhibit the AChR and interfere with nervous system function. Some ligands bind to a regulatory site on the closed-channel conformation of the AChR with higher affinity than to the site on the open-channel form, resulting in inhibition of the receptor. Such AChR ion channel inhibitors have a potential as therapeutic agents for drug abuse.

Autoimmune channelopathies. Several other antibody-mediated neuromuscular disorders have been identified, each associated with an antibody against a ligand- or voltage-gated ion channel (Vernino 2007). Examples are myasthenia gravis, Lambert-Eaton syndrome, autoimmune autonomic ganglionopathy, and acquired neuromyotonia (Isaac syndrome), which is a type of neuromyotonia caused by antibodies to peripheral nerve potassium channels.

Lambert-Eaton myasthenic syndrome (muscle weakness). This is due to reduced release of acetylcholine from motor nerve terminals. This syndrome has a presynaptic origin, whereas myasthenia gravis (another form of neuromuscular weakness) has a postsynaptic origin. The pathomechanism is a reduction of voltage-activated calcium channels by autoimmune-generated antibodies. The reduction involves N-type functional calcium channels that are sensitive to w-conotoxin and are involved in the control of neurotransmitter (such as acetylcholine) release from neurons. These patients have an exaggerated response to neuromuscular blocking agents, and the disease may be first recognized when there is prolonged apnea after use of neuromuscular blocking agents during surgery. Lambert-Eaton syndrome may also occur as an autoimmune paraneoplastic syndrome in patients with lung carcinoma. A high frequency of P/Q-type calcium-channel antibodies are found in these patients, indicating that voltage-gated calcium channels have a role in the pathogenesis of this disorder. In 1 case, myasthenic syndrome was reported to be caused by V1442E mutation of the SCN4A sodium channel (Tsujino et al 2003).

Chronic inflammatory demyelinating myelopathy. The neurophysiological abnormalities associated with demyelination can be explained by sodium channel dysfunction mediated by antibodies. Acute paralysis in Guillain-Barré syndrome may be related to a sodium channel-blocking factor in the cerebrospinal fluid.

Multiple sclerosis. This is a demyelinating disease in which axon block due to loss of myelin produces clinical deficits. In addition to demyelination, dysregulation of ion channel expression can further interfere with the neuronal signaling process. Although much work needs to done to understand the pathophysiology of multiple sclerosis at the molecular level, there is the suggestion that dysregulated sodium channels can trigger calcium-mediated axonal injury via reverse sodium-calcium exchange and can explain cerebellar deficits in patients with multiple sclerosis (Waxman 2002). Pharmacological blockade of these channels might ameliorate the loss of axons. The voltage-gated potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain and provides the rationale for the use of specific Kv1.3 antagonists in management of this disease (Rus et al 2005). Only 2 broad-spectrum potassium channel blockers, 4-aminopyridine and 3,4-diaminopyridine, have been tested in multiple sclerosis patients, and even though both produce clear neurologic benefits, their use has been limited by toxicity (Judge and Bever 2006). 4-aminopyridine is currently in phase 3 clinical trials.

Stroke. In cerebral ischemia, oxygen/glucose deprivation opens hemichannels, or half gap junctions, in neurons (Thompson et al 2006). This disrupts levels of calcium and potassium in brain cells and is associated with ischemic neuronal death. It is possible that stroke therapies may be developed to block brain cell hemichannels from opening.

Pathomechanism of disease due to mutated proteins. There are several ways in which changes occur in the properties or regulation of ion channels:

- Genetic mutations of the ion channel gene.
- Abnormalities in the regulatory mechanism of the channels, such as phosphorylation.
- Presence of toxic materials that block channels or prevent their resynthesis.
- Development of autoimmune disease directed at the channel protein or its regulator, resulting in down-regulation or dysfunction of the channel, as in Lambert-Eaton syndrome.

Genetic mutations of the ion channels gene. Defective and malfunctioning proteins may be expressed as a result of improper coding. It is possible for a defect to occur in a subunit or a regulator shared by several types of channels. This explains the malfunction of more than 1 type of channel in a disease. Three mechanisms explain how mutated proteins give rise to diseases:

- Gain of function in which the altered protein due to an ion channel defect augments a function, eg, hypokalemic periodic paralysis, familial hemiplegic migraine, and malignant hyperthermia.
- Loss of function due to quantitative insufficiency of the protein to support normal cell function, eg, episodic ataxia type 2. The ataxic attacks are remarkably sensitive to acetazolamide, a carbonic anhydrase inhibitor that is considered to ameliorate ion channel function.
- Dominant negative effects in which the mutant protein interferes with the activity of the normal protein. An example is spinocerebellar ataxia, in which abnormal alpha 1A subunits may interfere with the assembly of P/Q channels.

Channelopathies according to channel involved. More than 1 gene may regulate a function in a channel, thus, different genetic mutations may manifest with the same disorder. Episodic neurologic disorders range from episodic weakness to paroxysmal movement disorders, and several of these are caused by mutations in ion channels and transporters (Ptacek and Fu 2004). Disorders involving sodium, potassium, calcium, and chloride channels are listed here.

Potassium channelopathies. Potassium channel dysfunction has been implicated in a variety of genetic and acquired neurologic disorders that are collectively referred to as the potassium channelopathies. These include the following:

- Acquired neuromyotonia
- Episodic ataxia type-1
- Hereditary deafness syndromes
- Benign familial neonatal convulsions
- Hypokalemic periodic paralysis

Calcium channelopathies. These include the following:

- Hypokalemic periodic paralysis
- Malignant hyperthermia
- Congenital myopathy with susceptibility to malignant hyperthermia
- Familial hemiplegic migraine. The CACNA1A gene encoding the brain-specific P/Q type calcium channel has been cloned and mutations in this gene, located on chromosome 19p13, have been shown to be involved in familial hemiplegic migraine (Carrera et al 2001).
- Episodic ataxia type 2
- Spinocerebellar ataxia (SCA-6). This is due to triple repeat of the CACNA1A gene, coding for the voltage-gated calcium channels type P/Q, expressed in the cerebellar Purkinje and granule cells.
- Absence epilepsy can be associated with dysfunction of the brain P/Q-type voltage-gated calcium channel.

Sodium channelopathies. Reductions in the expression of some previously active sodium channel genes have been found in peripheral neuropathies. A sodium channel gene that is normally silent in spinal sensory neurons is induced by nerve injury. These changes are thought to lead to hyperexcitability and might contribute to the hyperalgesia and allodynia that are observed in cases of neuropathic pain. Nav1.3 and Nax are the only 2 subtypes of tetrodotoxin sodium channels that are upregulated, suggesting their potentially important role in neuropathic pain generation (Chung and Chung 2004).

Mutations of the SNC4A gene are associated with the following:

- Hyperkalemic periodic paralysis
- Paramyotonia congenita

• Potassium-aggravated myotonia
• Genetic defects in genes encoding 2 pore-forming alpha subunits (SCN1A and SCN2A) and the accessory beta1 subunit (SCN1B) are responsible for a group of epilepsy syndromes with overlapping clinical characteristics but divergent clinical severity.
• Familial hemiplegic migraine type 3 is caused by mutations in the sodium channel NaV1.1, which are also associated with generalized epilepsy, indicating that both disorders may share common molecular mechanisms (Kahlig et al 2008).
• Painful inherited neuropathy is associated with mutations in the SCN9A gene.

Chloride channelopathies. Myotonia congenita (dominant and recessive forms) is associated with mutations of the CLCN1 sarcolemmal rectifying chloride channel. Impaired chloride transport can lead to disorders such as epilepsy, hyperekplexia, lysosomal storage disease, and deafness.

Pathomechanism of disease due to mutated proteins. There are several ways in which changes occur in the properties or regulation of ion channels:
• Genetic mutations of the ion channel's gene.
• Abnormalities in the regulatory mechanism of the channels, such as phosphorylation.
• Presence of toxic materials that block channels or prevent their resynthesis.
• Development of autoimmune disease directed at the channel protein or its regulator, resulting in down-regulation or dysfunction of the channel, as in Lambert-Eaton syndrome.

Genetic mutations of the ion channels gene. These occur in genetic neurologic channelopathies such as epilepsy syndromes that show a Mendelian pattern of inheritance, certain forms of migraine and disorders of cerebellar function, as well as periodic paralysis. The diversity of these disorders is due partly to the tissue-specific expression of the dysfunctional channel, but is likely influenced by other, as yet unidentified, genetic and nongenetic factors (Hanna 2006). Defective and malfunctioning proteins may be expressed as a result of improper coding. It is possible for a defect to occur in a subunit or a regulator shared by several types of channels. This explains the malfunction of more than 1 type of channel in a disease. Three mechanisms explain how mutated proteins give rise to diseases:
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• Dominant negative effects in which the mutant protein interferes with the activity of the normal protein. An example is spinocerebellar ataxia, in which abnormal alpha 1A subunits may interfere with the assembly of P/Q channels.

Ion channels and pain. Multiple sodium channels, with distinct electrophysiological properties, are encoded by distinct mRNAs within small dorsal root ganglion neurons, which include nociceptive cells. Several of these neuron-specific sodium channels now have been cloned and sequenced. Sodium channel expression in dorsal root ganglia neurons is dynamic, changing significantly after injury. Sodium channels within primary sensory neurons may play an important role in the pathophysiology of pain. The voltage-gated sodium channels may play a crucial role in neuropathic pain, but their role is mostly documented for mechanical static and dynamic allodynia, and either peripheral or central sodium channels may be involved (Attal and Bouhassira 2006). Familial pain syndromes may be due to mutations in the Na(V)1.7 channel. Gain-of-function mutations cause paroxysmal pain disorders as a result of hyperexcitability of sensory neurons, whereas loss-of-function mutations cause congenital indifference to pain due to attenuation of action potential firing (Catterall et al 2008).

Sodium and calcium channels, along with central glutamate mechanisms, are the main targets for anticonvulsant drugs in neuropathic pain. A number of receptors and ion

channels present in sensory neurons are now under investigation as potential new analgesic drug targets. These include the following:

- Voltage-gated sodium channels that are specific for sensory neurons
- Novel sodium channels
- Adenosine triphosphate-gated channels
- Capsaicin-gated channels, such as vanilloid receptor 1
- Proton-gated channels, such as acid-sensing ion channel

The use of antisense oligonucleotides to target specific channel subtypes shows that the functional localization of the channel subtype sodium V1.8 after nerve injury is essential for persistent pain states (Lai et al 2003). As sodium V1.8 expression is restricted to sensory neurons, this channel offers a highly specific and effective molecular target for the treatment of neuropathic pain.

The acid-sensing ion channels are able to induce action potential triggering on sensory neurons after a moderate extracellular pH decrease. They participate in the hypersensitization of the nociceptive system in inflammatory pain. Inhibition of their expression is the mechanism of action of nonsteroidal anti-inflammatory drugs (Voilley 2004).

Top

Clinical applications

Knowledge about the role of ion channels in neurologic disorders would be of practical use in the management of neurologic disorders. This could be both preventive and therapeutic. For example, if individual predisposition to malignant hyperthermia can be detected by genetic testing, exposure to anesthetics precipitating the disease can be avoided. Channelopathies due to gain of function might respond to drugs blocking the action of those channels, eg, calcium channel blockers. Molecular studies of mutated ion channels or channel subunits will also help to develop effective drug treatments for channelopathies.

Ion channels as targets for drug action. The voltage-gated potassium, sodium, and calcium channels control nerve impulse conduction and frequency; because of this, they are common targets for anesthetics. Neurotransmitter-gated ion channels, particularly receptors for GABA and glutamate, are modulated by most anesthetics at both synaptic and extrasynaptic sites (Hemmings et al 2005). Ion channels are considered to be pharmacologic receptors with specific drug binding sites and are regulated by chronic drug action. The binding sites are usually multiple. Examples of drugs targeted to ion channels for the treatment of neurologic disorders are shown in Table 3.

Table 3. Ion Channels as Targets for Drugs Used in the Treatment of Neurologic Disorders

Sodium channel blocking

Drugs in clinical use:

- Carbamazepine, phenytoin, valproic acid
  - Category/ indication: anticonvulsant
  - Investigational applications: phenytoin has been tested as a neuroprotective in phase 3 trials, but was found to be not effective.
- Bupivacaine, lidocaine, mepivacaine
  - Category/ indication: local anesthetics
  - Investigational applications: none

Chloride channel blocking

Drugs in clinical use:

- Clonazepam, phenobarbital
  - Category/ indication: anticonvulsants

- Investigational applications: none

- Lorazepam
  - Category/ indication: hypnotics
  - Investigational applications: none
- Diazepam
  - Category/ indication: muscle relaxants
  - Investigational applicants: none

Calcium channel blocking

Drugs in clinical use:

- Nimodipine: L-type calcium channel antagonists
  - Category/ indication: inhibition of calcium-dependent vasospasm associated with aneurysmal subarachnoid hemorrhage.
  - Investigational applications: reduces infarct size after experimental cerebral ischemia. Clinical trials in stroke patients did not prove efficacy.
- Flunarizine: T-type calcium channel antagonist
  - Category/ indication: prophylaxis of migraine
  - Investigational applications: neuroprotective effect. Reduces infarct size after experimental cerebral ischemia. Clinical trials in stroke patients did not prove efficacy.
- Ziconotide: N-type calcium channel antagonist
  - Category/ indication: intrathecal ziconotide used for management of chronic pain (Jain 2000).
  - Investigational applications: in phase 3 clinical trials for cerebral ischemia.

Potassium channel opening

Drugs in clinical use: none

- Category/ indication: none
- Investigational applications: BMS-204352 has a neuroprotective effect. Phase 3 clinical trials in acute stroke are in progress.
- Retigabine opens neuronal KCNQ voltage activated K+ channels. Phase 3 trials in refractory epilepsy with partial onset seizures.

Potassium channel blocking

Drugs in clinical use: none

- Category/ indication: none
- Investigational applications: 4-aminopyridine in episodic ataxia type 2, phase 3 trials in multiple sclerosis and spinal cord injury.

Sodium channel blockers. The best known sodium channel blockers are established antiepileptic drugs: carbamazepine and phenytoin. Carbamazepine reduces currents through sodium channels. Phenytoin enhances active sodium extrusion and inhibits passive sodium entry leading to normalization of the sodium gradient and stabilization of the membrane. It may also inhibit transmitter release by reducing calcium-dependent phosphorylation of membrane proteins. It may also modulate GABA receptors. The antiepileptic effect of valproic acid may be mediated via multiple mechanisms, which include inhibition of glutamate and aspartate and reduction of excitability of neuronal membranes, through its influence on sodium and potassium channels. Lamotrigine acts on voltage-sensitive sodium channels to stabilize the neuronal membrane and inhibit the release of glutamate and aspartate. The exact mechanism of action of gabapentin is not understood. Experimental evidence indicates that gabapentin inhibits voltage-gated

calcium channels. One explanation of its efficacy in relieving neuropathic pain is that it affects a calcium channel in the pain-transmitting nerve cells of the spinal cord.

A functional link has been shown between sodium V1.3 expression and neuronal hyperexcitability associated with central neuropathic pain (Hains et al 2003). In this study, antisense oligonucleotide injection targeting the sodium V1.3 channel resulted in decreased production of the sodium V1.3 sodium channels, less hypersensitivity of the pain-signaling nerve cells within the spinal cord, and reduced pain-related behaviors.

Calcium channel antagonists (blockers). Calcium channels have been implicated indirectly in some neurologic disorders by the therapeutic effect of calcium antagonists. For example, calcium entry blockers bind to the L-type calcium channels and reduce the transport of calcium through these channels. The resulting effect is relaxation of smooth muscle in cerebral arterial vasospasm following subarachnoid hemorrhage.

Potassium channel openers. Potassium channel openers or activators have aroused considerable pharmaceutical interest during the last decade as smooth muscle relaxants. This characteristic property can be predicted from knowledge of their site and mechanism of action. Effects of K-openers on tissues can be antagonized by inhibitors of KATP-like glyburide. Patch clamp studies have shown that K-channel openers open KATP. Besides ATP, other factors that modify KATP channels include adenosine and neurotransmitters. The effect of K-channel openers on the skeletal muscle has been investigated in relatively fewer studies. Cromakalim increases channel opening probability in the presence of an inhibitory concentration of ATP. Most of the K-channel openers are in development for non-neurologic indications.

Potassium channel blockers. Potassium channel blocker, 4-aminopyridine, has been used for the treatment of episodic ataxia type 2 due to mutations in the CACNA1A gene (Strupp et al 2004). Attacks recurred after treatment was stopped; subsequent treatment alleviated the symptoms.

Chloride channel modulators. GABA antagonists are chloride channel blockers. This is the likely mechanism of action of barbiturates and benzodiazepines. As a benzodiazepine, the binding site for diazepam is linked to the GABA receptor, which has a major role in inhibitory functions in the CNS. Benzodiazepine binding sites are contained within the GABA receptor complex in CNS neurons. Activation and inhibition of GABA receptors by several pharmacological agents has been employed in the treatment of several neurologic and neuromuscular disorders.

Future prospects. Advances in genomic technologies will enable personalized medicines, including those for patients with neurologic disorders. Demonstration of heterogeneity in diseases such as migraine may facilitate a rational individualized treatment with currently available drugs. Ion channels will provide targets for medicines to treat neurologic disorders for which no cure is available. Ion channels associated with more than 1 disorder might provide a clue to common factors in pathogenesis, as well as treatment, of more than 1 disorder with a single drug. Examples of epilepsy and neurodegenerative disorders are given to provide a glimpse into the impact of knowledge of ion channels on the future management of neurologic disorders.

There are specific alterations in the structure or function of ion channels in the epileptic brain. If these properties cannot be found in control (nonepileptic) neurons, these channels might be called "epileptic" ion channels. These may yield important clues for future therapeutic approaches aimed at preventing epileptogenesis.

Multiple neurotransmitter systems can be modulated via gated ion channels to produce therapies for enhancing cognition and memory in patients with neurodegenerative disorders. These efforts include the following:

- Gamma-aminobutyric acid subtype A receptor and benzodiazepine inverse agonists
- Nicotinic acetylcholine receptor agonists
- Serotonin subtype 3 receptor (5-HT3R) antagonists
- Potassium (K+) M-channel inhibitors

Top

Associated disorders

None identified

Top

Related summaries

Ciguatera
Epilepsy
Hyperekplexia
Lambert-Eaton myasthenic syndrome
Migraine
Myasthenia gravis
Neuropharmacology
Pharmacological treatment of epilepsy in adolescents and adults

Top

References cited

Attal N, Bouhassira D. Translating basic research on sodium channels in human neuropathic pain. J Pain 2006;7(1 Suppl 1):S31-7.

Cannon SC. Physiologic principles underlying ion channelopathies. Neurotherapeutics 2007;4(2):174-83.**

Carrera P, Stenirri S, Ferrari M, et al. Familial hemiplegic migraine: a ion channel disorder. Brain Res Bull 2001;56(3-4):239-41.

Catterall WA, Dib-Hajj S, Meisler MH, Pietrobon D. Inherited neuronal ion channelopathies: new windows on complex neurological diseases. J Neurosci 2008;28(46):11768-77.

Chang BS, Lowenstein DH. Epilepsy. N Engl J Med 2003;349:1257-66.

Chung JM, Chung K. Sodium channels and neuropathic pain. Novartis Found Symp 2004;261:19-27; discussion 27-31, 47-54.

Cooper EC, Jan LY. M-channels: neurological diseases, neuromodulation, and drug development. Arch Neurol 2003;60(4):496-500.

Griesdale DE, Honey CR. Aquaporins and brain edema. Surg Neurol 2004;61(5):418-21.

Hains BC, Klein JP, Saab CY, et al. Upregulation of sodium channel Nav1.3 and functional involvement in neuronal hyperexcitability associated with central neuropathic pain after spinal cord injury. J Neurosci 2003;23:8881-92.

Hanna MG. Genetic neurological channelopathies. Nat Clin Pract Neurol 2006;2(5):252-63.

Hemmings HC Jr, Akabas MH, Goldstein PA, et al. Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci 2005;26:503-10.

Heron SE, Khosravani H, Varela D, et al. Extended spectrum of idiopathic generalized epilepsies associated with CACNA1H functional variants. Ann Neurol 2007b;62(6):560-8.

Heron SE, Scheffer IE, Berkovic SF, Dibbens LM, Mulley JC. Channelopathies in idiopathic epilepsy. Neurotherapeutics 2007a;4(2):295-304.**

Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol (London) 1952;117:500-44.

Huang CW, Hwang WJ. [The borderland between epilepsy and movement disorders.] Acta Neurol Taiwan 2009;18(1):42-55.

Jain KK. An evaluation of intrathecal ziconotide for the treatment of chronic pain. Exp Opin Invest Drugs 2000;9:2403-10.

Judge SI, Bever CT Jr. Potassium channel blockers in multiple sclerosis: neuronal Kv channels and effects of symptomatic treatment. Pharmacol Ther 2006;111(1):224-59.

Kahlig KM, Rhodes TH, Pusch M, et al. Divergent sodium channel defects in familial hemiplegic migraine. Proc Natl Acad Sci U S A 2008;105(28):9799-804.

Katz B. The release of neural transmitter substances. Liverpool: Liverpool University Press, 1969.

Lai J, Hunter JC, Porreca F. The role of voltage-gated sodium channels in neuropathic pain. Curr Opin Neurobiol 2003;13:291-7.

Lerche H, Weber YG, Jurkat-Rott K, Lehmann-Horn F. Ion channel defects in idiopathic epilepsies. Curr Pharm Des 2005;11:2737-52.

Lorenz C, Meyer-Kleine C, Steinmeyer K, Koch MC, Jentsch TJ. Genomic organization of the human muscle chloride channel CIC-1 and analysis of novel mutations leading to Becker-type myotonia. Hum Mol Genet 1994;3:941-6.

Meola G, Hanna MG, Fontaine B. Diagnosis and new treatment in muscle channelopathies. J Neurol Neurosurg Psychiatry 2009;80(4):360-5.

Neher E, Sakmann B. Single channel current recorded from membrane of denervated frog muscle fibers. Nature 1976;260:799-802.

Noda M, Ikeda T, Kayano T, et al. Existence of distinct sodium channel messenger RNAs in rat brain. Nature 1986;320:188-92.

Ptacek LJ, Fu YH. Channels and disease: past, present, and future. Arch Neurol 2004;61:1665-8.**

Purohit P, Mitra A, Auerbach A. A stepwise mechanism for acetylcholine receptor channel gating. Nature 2007;446:930-3.

Rus H, Pardo CA, Hu L, et al. The voltage-gated potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain. Proc Natl Acad Sci U S A 2005;102:11094-9.

Strupp M, Kalla R, Dichgans M, Freilinger T, Glasauer S, Brandt T. Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine. Neurology 2004;62(9):1623-5.

Thompson RJ, Zhou N, MacVicar BA. Ischemia opens neuronal gap junction hemichannels. Science 2006;312:924-7.**

Tsujino A, Maertens C, Ohno K, et al. Myasthenic syndrome caused by mutation of the SCN4A sodium channel. Proc Natl Acad Sci U S A 2003;100:7377-82.

Vernino S. Autoimmune and paraneoplastic channelopathies. Neurotherapeutics 2007;4(2):305-14.**

Vincent A, Dalton P, Clover L, Palace J, Lang B. Antibodies to neuronal targets in neurological and psychiatric diseases. Ann N Y Acad Sci 2003;992:48-55.

Voilley N. Acid-sensing ion channels (ASICs): new targets for the analgesic effects of non-steroid anti-inflammatory drugs (NSAIDs). Curr Drug Targets Inflamm Allergy 2004;3(1):71-9.

Wang H, Woolf CJ. Pain TRPs. Neuron 2005;46:9-12.

Waxman SG. Sodium channels as molecular targets in multiple sclerosis. J Rehabil Res Dev 2002;39(2):233-42.

Yang KC, Jin GZ, Wu J. Mysterious alpha6-containing nAChRs: function, pharmacology, and pathophysiology. Acta Pharmacol Sin 2009;30(6):740-51.

Zhou S, Sun X, Liu L, Wang X, Liu K. Increased expression of aquaporin-1 in the anterior temporal neocortex of patients with intractable epilepsy. Neurol Res 2008;30(4):400-5.

**References especially recommended by the author or editor for general reading.