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Review Article

CELL COMMUNICATION AND ION CHANNELS: A REVIEW

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ABSTRACT

Cell Communication plays a pivotal role in transmitting information from one cell to another. Cells may receive a variety of signals like chemical signals, electromagnetic signals, and mechanical signals. Connexons of two cells come together to form a channel, only 1.5 nm wide i.e too small for proteins, but wide enough for signaling molecules. Communication process involves Reception and transduction. Response occur when transduced signal triggers a specific cellular activity. Ion channels are pore-forming proteins that help establish and control the small voltage gradient across the plasma membrane of cells by allowing the flow of ions down their electrochemical gradient. Ion channels are key components in a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal, and smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation and pancreatic beta-cell insulin release. Also in new drug discovery, ion channels are a frequent target.

Keywords: Connexon, Second messenger, Transient receptor potential channel, Channelopathies.

INTRODUCTION

- Cell-to-cell communication is absolutely essential for multicellular organisms and is also important for many unicellular organisms. Cells may communicate by direct contact and cells must communicate to coordinate their activities. Biologists have discovered some universal mechanisms of cellular regulation, involving the same small set of cell-signaling mechanisms. Cells may receive a variety of signals, chemical signals, electromagnetic signals, and mechanical signals.
- Signal-transduction pathway is a process by which a signal on a cell's surface is converted into a specific cellular response. Multicellular organisms can also release signaling molecules that target other cells. Some transmitting cells release local regulators that influence cells in the local vicinity. In synaptic signaling, a nerve cell produces a neurotransmitter that diffuses to a single cell that is almost touching the sender. Plants and animals use hormones to signal at greater distances.
- Multicellular organisms have cell junctions that allow communication: Animals readily communicate through Gap junctions but plants make use of Plasmodesmata to communicate.

Gap junctions are channels present between adjacent cells traversed by proteins called **connexons.** Connexons of two cells come together to form a channel, only 1.5 nm wide. too small for proteins, but wide enough for signaling molecules. Gap junctions permit metabolic cooperation by sharing ATP, amino acids, and coenzymes. Ensures concentrations of ions are similar in linked cells. Lens cells of mammalian eyes have abundant gap junctions. Only cells at periphery are close to blood vessels. Second messengers such as cAMP may be able to pass through gap junctions. Only a few cells would need to have signal receptors—signal could spread through entire tissue for a coordinated response.

Communication Process

- The process involves three stages. Reception involves a chemical signal binds to a cellular protein, typically at the cell's surface. Transduction involving of signal molecule leading to a change in the receptor that triggers a series of changes along a signal-transduction *pathway.* Response occur when transduced signal triggers a specific cellular activity.

Communication plays a pivotal role in transmitting information from one cell to another. The behavior of a cell can be attained depending upon type of signal it receives. All cells process information from the environment. The information can be a physical stimulus, such as light or chemical. Signals can come from outside the organism or from neighboring cells as in fig 1. To respond to a signal, a cell must have a specific *receptor* that can detect it. A signal transduction pathway is the series of steps involved in a cell's response to a signal. In a large multicellular organism, signals reach target cells by diffusion or by circulation in the blood as in fig 2. Autocrine signals affect the cells that made them and Paracrine signals affect nearby cells. *Hormones* travel to distant cells, usually via the circulatory system.

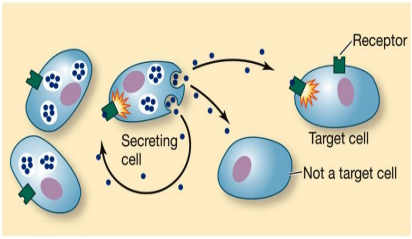


Fig. 1

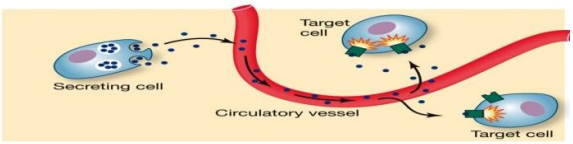


Fig. 2

Signal transduction pathway is the entire signaling process, including the cell's response. The pathway has two major components a receptor and a responder. The signal causes receptor protein to change its conformation and this change causes the activation of protein kinase. Phosphorylation alters function of a responder protein, then signal is amplified and transcription factor is activated. Synthesis of a specific protein is turned on and the action of the protein alters cell activity.

How Do Signal Receptors Initiate a Cellular Response?

Receptor proteins have very specific binding sites for chemical signal molecules, or ligands. Binding of ligand causes receptor protein to change shape which is a reversible process. Inhibitors that can bind to the receptor proteins include natural and artificial inhibitors.

***Ligands with cytoplasmic receptors*:** Small or nonpolar ligands can diffuse across plasma membrane (e.g., estrogen).

***Ligands with plasma membrane receptors*:** Large or polar ligands bind to plasma membrane receptors (e.g., insulin).

Plasma membrane receptors are of three types they are:

- Ion channels
- Protein kinases
- G protein-linked receptors

Ion channel receptors are proteins that allow ions to enter or leave a cell. Signals can be chemical ligands such as hormones or sensory stimuli such as light.

Example: acetylcholine

Protein kinase receptors (Fig 3):

- Some receptors catalyze the transfer of a phosphate group from ATP to a target protein. Then the conformation and activity of target protein is altered two molecules of insulin bind to receptor, changing the conformation. The receptor autophosphorylates, then catalyzes phosphorylation of the target proteins leading to a release of insulin response substrates.

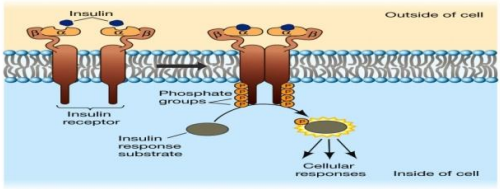


Fig. 3

G protein-linked receptors (Fig 4): These are seven-transmembrane-spanning G protein-linked receptors. G proteins are the mobile membrane proteins with three subunits that bind G protein-linked receptors, and GDP + GTP. GTP-subunit separates from G protein and moves through plasma membrane until it encounters an effector protein. Binding activates the effector which causes a change in cell function leading to the hydrolysis of GDP. G proteins can either activate or inhibit an effector for example, Epinephrine (adrenalin) binds to G protein-linked receptor in heart muscle and activates an enzyme to produce cyclic AMP. In the smooth muscle, G protein mediated inhibition can occur due to inhibition of enzyme that produces cAMP.

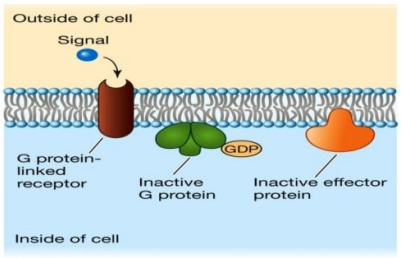


Fig. 4

Cytoplasmic receptors (Fig 5) can bind to signals that can cross plasma membrane. Binding to ligand causes receptor to change shape—allows it to enter nucleus, where it acts as a transcription factor. Receptor may be bound to a chaperonin and binding to ligand releases the chaperonin.

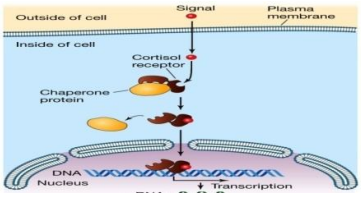


Fig. 5

How Is a Response to a Signal Transduced through the Cell?

Direct signal transduction occurs at plasma membrane and is a function of the receptor itself, Where as Indirect signal transduction means a second messenger mediates interaction between receptor and cell's response. In both, signal initiates a **cascade** of events. A weak signal can be *amplified*, and *distributed* to cause several different responses in the target cell. Protein kinase receptors cause a direct signal transduction that means signal binds to protein kinase receptor, changes conformation, leading to the exposition of an active site to phosphorylate a target protein.

Second messengers were discovered in research on the liver enzyme *glycogen phosphorylase*, and how it is activated by epinephrine. Binding of the hormone to the membrane receptor caused production of a small molecule (cyclic AMP, or cAMP) that diffused into the cytoplasm to activate the enzyme. The signal is the first messenger and the second messenger is released into the cytoplasm, after signal binds to receptor. Second messengers affect many processes in the cell and also amplify the signal. A single epinephrine molecule can induce the production of many cAMP moieties. Second messengers act as cofactors or allosteric regulators of target enzymes. cAMP is a common second messenger and the enzyme that catalyzes formation of cAMP from ATP is located on cytoplasmic side of plasma membrane. cAMP, binds to ion channels in many kinds of sensory cells and opens the channel or binds to protein kinases in cytoplasm and exposes the active site.

Phospholipids in the plasma membrane can be hydrolyzed by phospholipases forming second messengers. Second messengers from phosphatidyl inositol-bisphosphate (PIP_2) has a hydrophobic portion which is diacylglycerol (DAG) embedded in plasma membrane and a hydrophylic portion which is inositol triphosphate (IP_3) projecting into cytoplasm. These receptors are G protein-linked. G protein subunit activates phospholipase C, which cleaves off IP3 from PIP2, leaving **diacylglycerol (** DAG) in the membrane. IP_3 and DAG are both second messengers**.** **Diacylglycerol (**DAG) activates membrane-bound protein kinase C(PKC) and is dependent on Ca^{2+}. IP_3 diffuses to the smooth

endoplasmic reticulum, where it opens an ion channel, releasing Ca^{2+} to the cytoplasm. The Ca^{2+} with DAG activates PKC which then phosphorylates a variety of proteins. An overactive IP_3/DAG signal transduction pathway in the brain leads to excessive brain activity in bipolar disorder. Liithium ion (Li+) inhibit G protein activation of phospholipase C, and inhibits synthesis of IP_3. Low Ca^{2+} concentrations in the cytoplasm are maintained by active transport proteins at plasma and endoplasmic reticulum membranes. Many signals can cause Ca^{2+} channels to open leading to increase. Ca^{2+} concentrations in cytoplasm.

Ca^{2+} acts as a second messenger

Activates protein kinase C, controls other channels and stimulates secretion by exocytosis.

Nitric oxide (NO)

This was discovered in studies of acetylcholine effects on smooth muscle tissue. Acetylcholine stimulates the IP_3/DAG signal transduction pathway to cause influx of Ca^{2+} which leads to another second messenger cyclic GMP (cGMP). Acetylcholine stimulates IP_3/DAG pathway of *endothelial cells* that line blood vessels.The influx of Ca^{2+} activates an enzyme NO synthase that catalyzes production of NO from arginine. NO diffuses to nearby smooth muscle cells where it stimulates synthesis of cGMP. Concentration of Ca^{2+} depends on activity of membrane pumps and ion channels.

Protein kinases, G proteins, and cAMP are regulated by enzymes that convert activated form back to inactive form. Cells alter the balance by synthesis or breakdown of the enzymes or by activation or inhibition of the enzymes by other molecules

A signal can cause the Opening ion channels, Change enzyme activity, affect gene transcription

Opening ion channels

It is a key step in response of nervous system cells.

Example: the sense of smell.

Changing enzyme activities

Addition of a phosphate group by a protein kinase changes enzyme conformation. cAMP binds to enzymes allosterically leading to changed conformation. In both, an active site is exposed and enzyme catalyzes new reactions. In the G protein-stimulated protein kinase cascade in liver cells by epinephrine can produce phospharilation two enzymes are phosphorylated, for example Glycogen synthase preventing glucose being stored as glycogen phosphorylase kinase stimulates a protein kinase cascade that leads to inhibition activated glycogen phosphorylase which catalyzes glycogen to glucose transformation. Both events lead to more glucose available for "flight or fight" response.

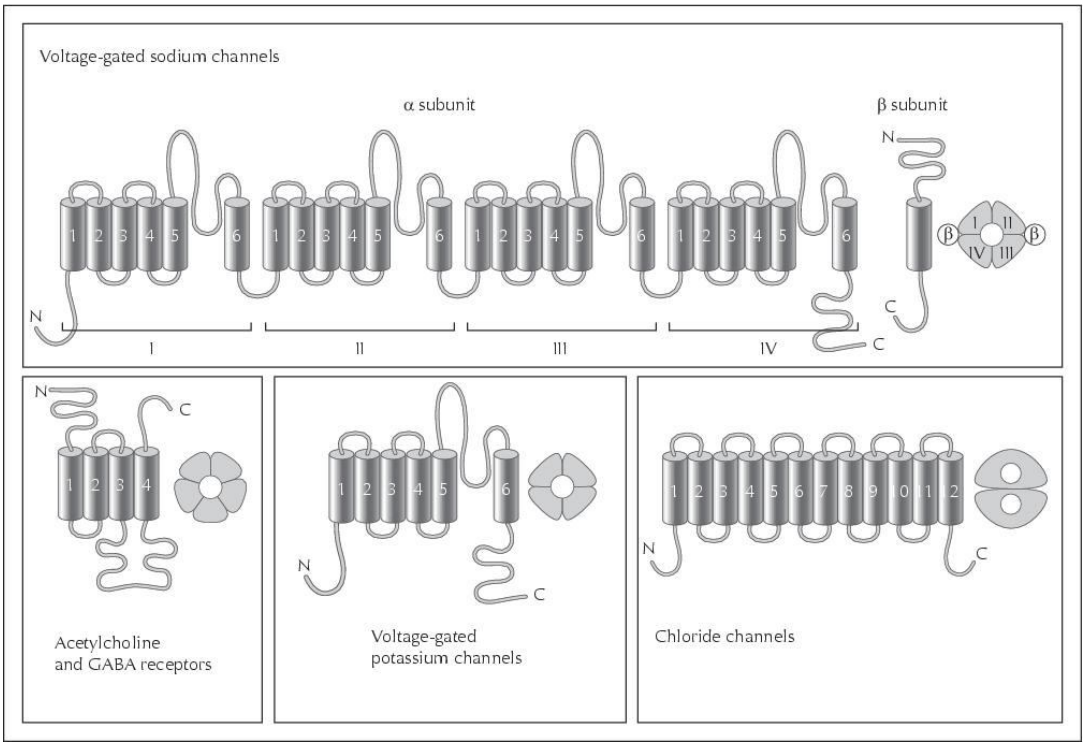
Differential gene transcription

Signals can initiate gene transcription, e.g., in the Ras (abnormal form of a G protein in human bladder) signaling pathway. Final protein kinase, MAPk enters nucleus and stimulates transcription of genes for cell division.

Lipid soluble hormones bind to receptors in cytoplasm and enter nucleus to bind to gene promoters. In plants, light can be a signal to form chloroplasts. Red wavelengths are absorbed by *phytochromes*. Activated phytochrome binds to proteins in the cytoplasm, they enter nucleus and bind to promoters of genes for chloroplast proteins.

Ion channels

These are pore-forming proteins that help establish and control the small voltage gradient across the plasma membrane of cells by allowing the flow of ions down their electrochemical gradient. They are present in the membranes that surround all biological cells.



Types of ion channels

There are over 300 types of ion channels in a living cell. Ion channels may be classified by the nature of their gating, the species of ions passing through those gates, the number of gates (pores) and localization of proteins. Further heterogeneity of ion channels arises when channels with different constitutive subunits give rise to a specific kind of current. Absence or mutation of one or more of the contributing types of channel subunits can result in loss of function and, potentially, underly neurologic diseases.

By gating

Ion channels may be classified by gating, depending upon what opens and closes the channels. Voltage-gated ion channels open or close depending on the voltage gradient across the plasma membrane, while ligand-gated ion channels open or close depending on binding of ligands to the channel.

Voltage-gated

Voltage-gated ion channels open and close in response to membrane potential.

Voltage-gated sodium channels: This family contains at least 9 members and is largely responsible for action potential creation and propagation. The pore-forming α subunits are very large (up to 4,000 amino acids) and consist of four homologous repeat domains (I-IV) each comprising six transmembrane segments (S1-S6) for a total of 24 transmembrane segments. The members of this family also coassemble with auxiliary β subunits, each spanning the membrane once. Both α and β subunits are extensively glycosylated.

Voltage-gated calcium channels: This family contains 10 members, though these members are known to coassemble with $\alpha_2\delta$, β, and γ subunits. These channels play an important role in both linking muscle excitation with contraction as well as neuronal excitation with transmitter release. The α subunits have an overall structural resemblance to those of the sodium channels and are equally large.

Cation channels of sperm: This small family of channels, normally referred to as Catsper channels, is related to the two-pore channels and distantly related to transient receptor potential channels.

Voltage-gated potassium channels (K_V): This family contains almost 40 members, which are

further divided into 12 subfamilies. These channels are known mainly for their role in repolarizing the cell membrane following action potentials. The α subunits have six transmembrane segments, homologous to a single domain of the sodium channels. Correspondingly, they assemble as tetramers to produce a functioning channel.

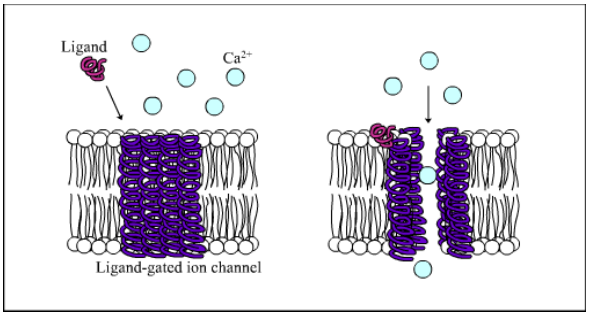
Transient receptor potential channels: This group of channels, normally referred to simply as TRP channels, is named after their role in Drosophila phototransduction. This family, containing at least 28 members, is incredibly diverse in its method of activation. Some TRP channels seem to be constitutively open, while others are gated by voltage, intracellular Ca^{2+}, pH, redox state, osmolarity, and mechanical stretch. These channels also vary according to the ion(s) they pass, some being selective for Ca^{2+} while others are less selective, acting as cation channels. This family is subdivided into 6 subfamilies based on homology: Transient Receptor Potential Classical (TRPC), Transient Receptor Potential vanilloid receptors (TRPV), Transient Receptor Potential melastatin (TRPM), Transient Receptor Potential polycystins (TRPP), Transient Receptor Potential mucolipins (TRPML), and Transient Receptor Potential ankyrin transmembrane protein 1 (TRPA).

Hyperpolarization-activated cyclic nucleotide-gated channels: The opening of these channels is due to hyperpolarization rather than the depolarization required for other cyclic nucleotide-gated channels. These channels are also sensitive to the cyclic nucleotides cAMP and cGMP, which alter the voltage sensitivity of the channel's opening. These channels are permeable to monovalent cations K^+ and Na^+. There are 4 members of this family, all of which form tetramers of six-transmembrane α subunits. As these channels open under hyperpolarizing conditions, they function as pacemaking channels in the heart, particularly the SA node.

Voltage-gated proton channels: Voltage-gated proton channels open with depolarization, but in a strongly pH-sensitive manner. The result is that these channels open only when the electrochemical gradient is outward, such that their opening will only allow protons to leave cells. Their function thus appears to be acid extrusion from cells. Another important function occurs in phagocytes (e.g. eosinophils, neutrophils, macrophages) during the "respiratory burst." When bacteria or other microbes are engulfed by phagocytes, the enzyme NADPH oxidase assembles in the membrane and begins to produce reactive oxygen species (ROS) that help kill bacteria. NADPH oxidase is electrogenic, moving electrons across the membrane, and proton channels open to allow proton flux to balance the electron movement electrically.

Ligand-gated

Also known as ionotropic receptors, this group of channels open in response to specific ligand molecules binding to the extracellular domain of the receptor protein. Ligand binding causes a conformational change in the structure of the channel protein that ultimately leads to the opening of the channel gate and subsequent ion flux across the plasma membrane. Examples of such channels include the cation-permeable "nicotinic" acetylcholine receptor, ionotropic glutamate-gated receptors and ATP-gated P2X receptors, and the anion-permeable γ-aminobutyric acid-gated $GABA_A$ receptor.Ion channels activated by second messengers may also be categorized in this group, although ligands and second messengers are otherwise distinguished from each other.



Other gating

Other gating include activation/inactivation by second messengers from the inside of the cell membrane, rather as from outside, as in the case for ligands. Ions may count to such second messengers, and then causes direct activation, rather than indirect, as in the case were the electric potential of ions cause activation/inactivation of voltage-gated ion channels.

- Potassium channels
  - **Inward-rectifier potassium channels:** These channels allow potassium to flow into the cell in an inwardly rectifying manner. Potassium flows effectively into, but not out of, the cell. This family is composed of 15 official and 1 unofficial members and is further subdivided into 7 subfamilies based on homology. These channels are affected by intracellular ATP, phosphatidyl ionositol biphosphate (PIP_2), and G-protein βγ subunits. They are involved in important physiological processes such as the pacemaker activity in the heart, insulin release, and potassium uptake in glial cells. They contain only two transmembrane segments, corresponding to the core pore-forming segments of the K_V and K_{Ca} channels. Their α subunits form tetramers.
  - **Calcium-activated potassium channels:** This family of channels is, the most part, activated by intracellular Ca^{2+} and contains 8 members.
  - **Two-pore-domain potassium channels:** This family of 15 members form what is known as leak channels, and they follow Goldman-Hodgkin-Katz (open) rectification.
- **Light-gated channels** like channel rhodopsin are directly opened by the action of light.
- **Mechanosensitive ion channels** are opening under the influence of stretch, pressure, shear, displacement.
- **Cyclic nucleotide-gated channels:** This superfamily of channels contains two families: the cyclic nucleotide-gated (CNG) channels and the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. It should be noted that this grouping is functional rather than evolutionary.
  - Cyclic nucleotide-gated channels: This family of channels is characterized by activation due to the binding of intracellular cAMP or cGMP, with specificity varying by member. These channels are primarily permeable to monovalent cations such as K^+ and Na^+. They are also permeable to Ca^{2+}, though it acts to close them. There are 6 members of this family, which is divided into 2 subfamilies.
  - Hyperpolarization-activated cyclic nucleotide-gated channels.

Temperature Gated Channels: Members of the Transient Receptor Potential ion channel superfamily, such as TRPV1 or TRPM8 are opened either by hot or cold temperatures.

By ions

- **Chloride channels:** This superfamily of poorly-understood channels consists of approximately 13 members. They include Chloride channels(ClCs), Chloride ion channels (CLICs) and bestrophins . These channels are non-selective for small anions; however chloride is the most abundant anion, and hence they are known as chloride channels.
- **Potassium channels**
  - Voltage-gated potassium channels e.g., potassium voltage (Kvs), potassium ion rectifiers (Kirs).
  - Calcium-activated potassium channels e.g., BKCa or MaxiK, SK.
  - Inward-rectifier potassium channels
  - Two-pore-domain potassium channels: This family of 15 members forms what is known as leak channels, and they follow Goldman-Hodgkin-Katz (open) rectification.
- **Sodium channels**
  - voltage-gated sodium channels (NaVs)
  - epithelial sodium channels (ENaC)
- **Calcium channels (**CaVs)

- **Proton channels** Voltage-gated proton channels
- ***Non-selective cation channels***: These let many types of cations, mainly Na^+, K^+ and Ca^{2+} through the channel.
    - Most Transient receptor potential channels

Other classifications

There are other types of ion channel classifications that are based on less normal characteristics, e.g. multiple pores and transient potentials.

Almost all ion channels have one single pore. However, there are also those with two:

- **Two-pore channels:** This small family of 2 members putatively forms cation-selective ion channels. They are predicted to contain two K_V-style six-transmembrane domains, suggesting they form a dimer in the membrane. These channels are related to catsper channels channels and, more distantly, Transient receptor potential (TRP) channels.

There are channels that are classified by the duration of the response to stimuli

- **Transient receptor potential channels:** This group of channels, normally referred to simply as TRP channels, is named after their role in Drosophila phototransduction. This family, containing at least 28 members, is incredibly diverse in its method of activation. Some TRP channels seem to be constitutively open, while others are gated by voltage, intracellular Ca^{2+}, pH, redox state, osmolarity, and mechanical stretch. These channels also vary according to the ion(s) they pass, some being selective for Ca^{2+} while others are less selective, acting as cation channels. This family is subdivided into 6 subfamilies based on homology: Transient receptor potential canonical (TRPC), Transient receptor potential vanilloid receptors (TRPV), Transient receptor potential melastatin (TRPM), Transient receptor potential polycystins (TRPP), Transient receptor potential mucolipins (TRPML), and Transient receptor potential ankyrin transmembrane protein 1 (TRPA).

Diseases of ion channels

There are a number of chemicals and genetic disorders which disrupt normal functioning of ion channels and have disastrous consequences for the organism. Genetic disorders of ion channels and their modifiers are known as Channelopathies

Channelopathies are diseases caused by disturbed function of ion channel subunits or the proteins that regulate them. These diseases may be either congenital (often resulting from a mutation or mutations in the encoding genes) or acquired (often resulting from autoimmune attack on an ion channel). There are a large number of distinct dysfunctions known to be caused by ion channel mutations. The genes for the construction of ion channels are highly conserved amongst mammals and one condition, hyperkalemic periodic paralysis, was first identified in the descendants of Impressive, a registered Quarter Horse (see AQHA website).

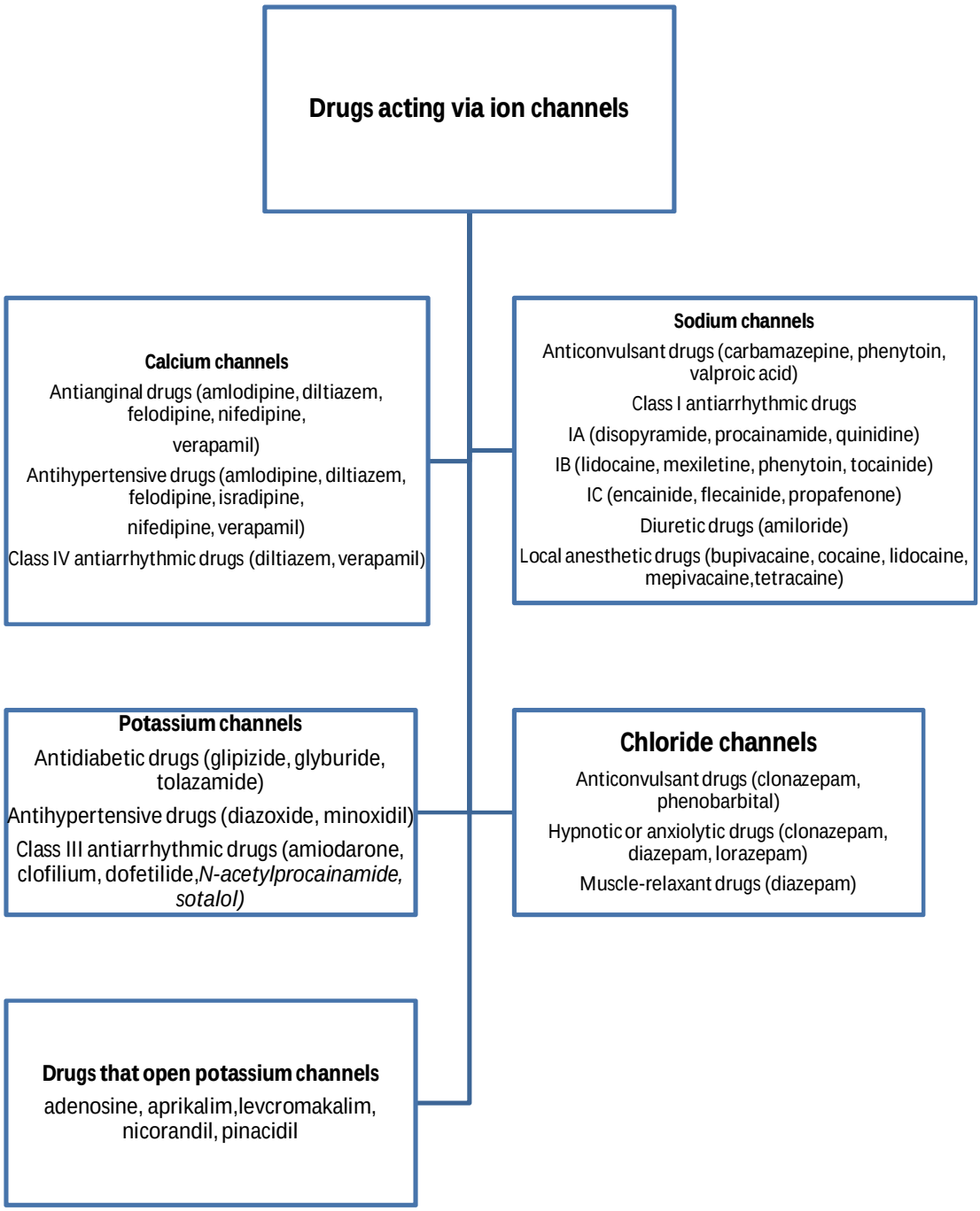
The channelopathies of human skeletal muscle include hyper-, hypo- and normokalemic (high, low and normal potassium blood concentrations) periodic paralysis, myotonia congenita and paramyotonia congenita.

Importance of ion channels

Voltage-activated channels underlie the nerve impulse and because transmitter-activated channels mediate conduction across the synapses, channels are especially prominent components of the nervous system. Indeed, most of the offensive and defensive toxins that organisms have evolved for shutting down the nervous systems of predators and prey (e.g., the venoms produced by spiders, scorpions, snakes, fish, bees, sea snails and others) work by modulating ion channel conductance and/or kinetics. In addition, ion channels are key components in a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal, and smooth muscle contraction, epithelial transport of nutrients and ions, T-cell activation and pancreatic beta-cell insulin release. In the search for new drugs, ion channels are a frequent target

Types

Condition	Channel type
Alternating hemiplegia of childhood	Na / K-ATPase
Bartter syndrome	various by type
Brugada syndrome	various, by type
Congenital hyperinsulinism	Inward-rectifier potassium ion channel
Cystic fibrosis	Chloride channel
Episodic Ataxia	Voltage-gated potassium channel
Erythromelalgia	Voltage-gated sodium channel
Generalized epilepsy with febrile seizures plus	Voltage-gated sodium channel
Familial hemiplegic migraine	Various
Hyperkalemic periodic paralysis	Voltage-gated sodium channel
Hypokalemic periodic paralysis	Voltage-gated sodium channel or voltage-dependent calcium channel (calciumopathy)
Long QT syndrome main type Romano-Ward syndrome	various, by type
Malignant hyperthermia	Ligand-gated calcium channel
Mucolipidosis type IV	Non-selective cation channel
Myasthenia Gravis	Ligand-gated sodium channel
Myotonia congenita	Voltage-dependent chloride channel
Neuromyotonia	Voltage-gated potassium channel
Nonsyndromic deafness	Various
Paramyotonia congenita (a periodic paralysis)	Voltage-gated sodium channel
Retinitis pigmentosa (some forms)	Ligand-gated non-specific ion channels
Short QT syndrome	various potassium channels suspected
Timothy syndrome	Voltage-dependent calcium channel
Seizure	Voltage-dependent potassium channel


Drugs acting via ion channels
Calcium channels
Antianginal drugs (amlodipine, diltiazem, felodipine, nifedipine,
verapamil)
Antihypertensive drugs (amlodipine, diltiazem, felodipine, isradipine,
nifedipine, verapamil)
Class IV antiarrhythmic drugs (diltiazem, verapamil)
Sodium channels
Anticonvulsant drugs (carbamazepine, phenytoin, valproic acid)
Class I antiarrhythmic drugs
IA (disopyramide, procainamide, quinidine)
IB (lidocaine, mexiletine, phenytoin, tocainide)
IC (encainide, flecainide, propafenone)
Diuretic drugs (amiloride)
Local anesthetic drugs (bupivacaine, cocaine, lidocaine, mepivacaine,tetracaine)
Potassium channels
Antidiabetic drugs (glipizide, glyburide, tolazamide)
Antihypertensive drugs (diazoxide, minoxidil)
Class III antiarrhythmic drugs (amiodarone, clofilium, dofetilide,*N-acetylprocainamide, sotalol)*
Chloride channels
Anticonvulsant drugs (clonazepam, phenobarbital)
Hypnotic or anxiolytic drugs (clonazepam, diazepam, lorazepam)
Muscle-relaxant drugs (diazepam)
Drugs that open potassium channels
adenosine, aprikalim,levcromakalim, nicorandil, pinacidil

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