The channelopathies: an overview

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What at first glance appears to be a random selection of widely differing clinical presentations and syndromes, has recently been found to have as their common underlying factor an inherited abnormality of the mechanism in the cell wall, the ion channel, which is responsible for the transmembrane passage of various ions. Included in this diverse array of diseases are malignant hyperthermia, long QT syndrome, myotonia congenita, Eaton Lambert syndrome, certain forms of migraine and epilepsy, as well as cystic fibrosis.[1] The common pathophysiology in all these diseases is an inherited abnormality of the amino acid sequence of the complex protein structure from which the ion channel is composed. These ion channels are ubiquitous in the body, their expression is not restricted only to excitable cells such as neurons or myocytes, and they may be found in the external membrane as well as internal organelles of cells such as pancreatic and renal cells. Because each of these diseases is caused by a discrete abnormality of an ion channel protein, this diverse variety of clinical manifestations is grouped together and described as the channelopathies.[2]

In order to better understand the pathophysiology involved in each of the channelopathies, it is necessary to review the normal physiology of the individual ion channels themselves.

Key words:
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Ion channel physiology

In a system as complex as the human body, maintenance of homeostasis depends upon efficient short and long distance intercellular communication. While many methods of intercellular communication exist, the cell membrane is specialised to take advantage of electrical signalling via intercellular signals in the form of action potentials. These action potentials can be propagated substantial distances along a cell membrane, and from cell to cell by anions and cations such as sodium, potassium, chloride and calcium.[3] Such propagation depends upon the movement of these ions across cellular membranes which are specifically designed not to permit ions to penetrate the normal bilipid layers. Discrete channels have evolved within the cell membrane for each ion. These ion channels are a class of proteins, which, by their physi-

Figure 1: Surface veiw of channel proteins surrounding an ion-selective pore.

cal and chemical characteristics, when incorporated into the cell membrane, permit the controlled passage of a specific ion that results in the generation or propagation of an action potential. The ion channels are therefore responsible for controlling the myriad of electrical signals passing through the brain, heart, muscle and other tissues each second throughout life.[3]

The action potentials that propagate along the plasma membranes of excitable cells are generated by sequential changes in electrical potential between the cytoplasm and the surrounding extracellular space.[4] Depolarisation (a reduction in the electronegativity of the cytoplasm) occurs when cations (sodium and calcium) move into the cell and generate an inward ionic current. Repolarisation of the cell involves a return to resting potential and occurs when outward ionic currents restore the resting electronegativity of the cell. Repolarisation is usually due to potassium moving out of the cell but an inward movement of chloride ions may augment this.[4]

The hydrophobic lipid cell membranes are inherently impermeable to the ions normally responsible for the modulation, generation and propagation of the action potentials. This barrier to ionic passage has been overcome by the evolution of specialised portals formed by the ion channel proteins and embedded within the cell membranes. These ion channels are macromolecular protein tunnels that span the lipid bilayer of the cell membranes.[4] The direction of ionic movement through these channels is governed by electrical and chemical gradients. Ion channels are usually classified according to the type of ion they permit to pass (sodium, chloride, potassium or calcium), although some channels are less selective. Channels may be gated by extracellular ligands, changes in transmembrane voltage or intracellular second messengers.[3] As is common to all proteins, various genes code for the amino acids of which the proteins making up the ion channel are constructed. Mutations in these genes results in an abnormality of the ion channel protein. Channel proteins are not solid struc-
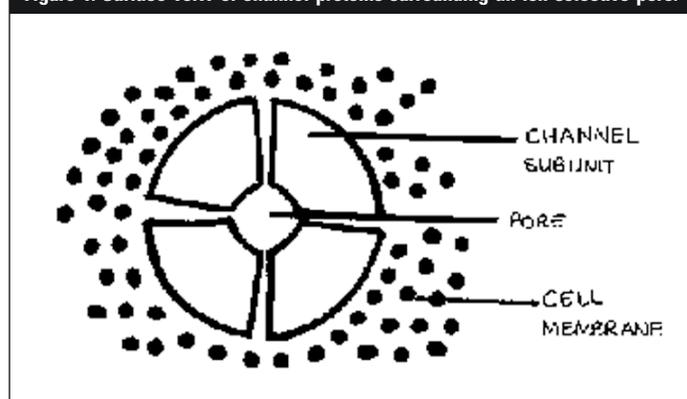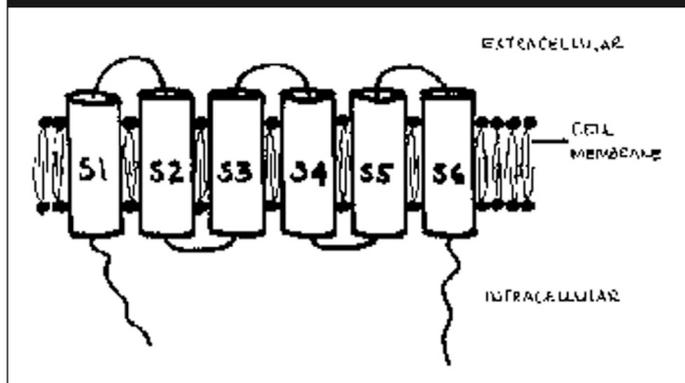
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Figure 2. Two-dimensional depiction of a domain comprising six trans-membrane subunits.

tures but are macromolecules composed of individual subunits assembled around a central ion - selective pore (Figure 1).[4] Alpha subunits are the most important category and are primarily involved in ion transport. Each subunit is modular and contains four identical domains (I, II, III and IV). Each domain is made up of six transmembrane subunits (S1 – S6), each of which comprises an amino acid chain (Figure 2). Any alteration in the amino acid sequence of these chains will lead to a change in the permeation properties of the ion channel. This results in an alteration in the ion channel behaviour, which in turn manifests as one of this wide diversity of diseases, collectively known as the channelopathies (Table 1).

Table 1. Diseases caused by ion channel abnormalities.	
DISEASE	**ION CHANNEL INVOLVED**
Cystic fibrosis	Chloride
Episodic ataxia	Calcium
Spino-cerebellar degeneration	Calcium
Eaton Lambert syndrome	Calcium
Migraine	Calcium
X-linked congenital stationary night blindness	Calcium
Heritable hypertension (Liddle's syndrome)	Sodium
Familial persistent hyperinsulinaemic hypoglycaemia of infancy	Potassium
Hereditary nephrolithiasis (Dent's disease)	Chloride
Long QT syndrome	
LQT1	Potassium
LQT2	Potassium
LQT3	Sodium
Myopathies	
Becker's myotonia congenita	Chloride
Thomsen's myotonia congenita	Chloride
Paramyotonia congenita	Sodium
Central core disease	Calcium (RYR1)
Hyperkalaemic periodic paralysis	Sodium
Hypokalaemic periodic paralysis	Calcium
Malignant hyperthermia	Calcium (RYR1)
Masseter-muscle rigidity	Sodium

Table II. Drugs that may cause LQTS	
Quinidine	Trimethoprim
Sotalol	Procainamide
Erythromycin	Cisapride
Adrenaline	Ketoconazole
Aztemizole	Fluconazole
Diphenhydramine	Sulphamethoxazole

POTASSIUM CHANNELS

Of all the classes of ion channels, the potassium channels are the oldest or most primitive.[4] They have been isolated in unicellular organisms and are thought to have given rise to the other classes of channels. They constitute the most diverse class of ion channels and are expressed in both excitable and non-excitable tissues. More than 13 subfamilies of potassium channels have been described in vertebrates.

Of all the episodic disorders caused by defective ion channels, the long QT syndrome (LQTS) is the most severe. LQTS is a genetically heterogeneous disorder for which there are 6 loci. Three of these are associated with potassium channels; one with sodium channels (LQT3) and the last two have still to be completely identified.[5]

An elongation of the Q-T interval as a result of disturbed myocardial repolarisation characterizes LQTS.[2] There is a careful balance between inward (sodium and calcium) and outward (potassium) currents that maintains the plateau of the action potential in cardiac myocytes. Repolarisation of the cell membrane begins when the outward current exceeds the inward current. A sustained inward current or reduced outward current will prolong the action potential and thus increase the Q-T interval. LQTS may cause ventricular arrhythmias, especially Torsade de Pointes, syncope or sudden death in young and otherwise healthy individuals.[2]

Agents such as local anaesthetics and mexiletine are effective in treating LQT3 due to their ability to block sodium channels. Raising serum potassium concentration can increase outward potassium currents and may effectively shorten the Q-T interval.

LQTS may also be acquired and caused by certain drugs that block potassium channels (Table II).

SODIUM CHANNELS

Initially, localised membrane depolarisation of excitable cells results from an increase in sodium conductance of the membrane.[2] This localised phenomenon is accompanied by further depolarisation and recruitment of adjacent sodium channels leading to a more generalised membrane depolarisation. Spontaneous inactivation of the sodium channels then occurs rapidly and leads to subsequent repolarisation of the membrane.[6]

Ten different human genes have been identified each of which is known to code for one of the α-subunits of sodium channels.[2] Most of these genes are expressed in excitable tissues such as brain, peripheral nerve and skeletal muscle.

Hyperkalaemic periodic paralysis, paramyotonia congenita and long-QT syndrome (Type III) are examples of disorders associated with defective sodium channels.[2] The clinical signs and symptoms of these diseases are not present continuously, but are elicited by certain stimuli. For example, the muscle stiffness and weakness associated with hyperkalaemic periodic paralysis

is seen at rest after heavy exercise. This stiffness and weakness is caused by prolonged depolarisation of muscle fibre membranes.

Local anaesthetics and certain antiarrhythmic agents e.g. mexiletine are used to prevent the weakness occurring in paramyotonia with rest. The attacks of weakness observed in patients with hyperkalaemic periodic paralysis are not influenced by mexiletine, but may be treated with agents such as hydrochlorthiazide and acetazolamide.

CALCIUM CHANNELS

Specialised ion channels within the membrane of nerve cells mediate calcium influx along the electrochemical gradient. As with sodium channels, these calcium channels are activated by depolarisation of the membrane, but in contrast to sodium channels, inactivation of the channels is slower so that membrane repolarisation is consequently delayed.

There are eight different human genes that code for calcium channel proteins.[2] Calcium channels may be classified according to their inactivation properties; transient (T-type), or long lasting (L-type); or according to the tissues in which they are expressed; brain (B), nerve (N), Purkinje cell (P): or their toxin sensitivity e.g. toxin resistant (R).[2]

Of particular interest to anaesthesiologists are two distinct types of calcium channels that are expressed in skeletal muscle. These are the dihydropyridine receptor (DHPR) and the ryanodine receptor (RYR1). They are situated respectively within the t-tubules and the sarcoplasmic reticulum of skeletal muscle. RYR1 is responsible for the release of calcium ions from the sarcoplasmic reticulum or endoplasmic reticulum into the cytoplasm, an essential step for muscle contraction. RYR1 and DHPR are closely coupled.

Disease-causing mutations have been identified in the genes coding for both the DHPR and RYR channels. Point mutations of either type of gene will result in susceptibility to malignant hyperthermia (MH).

Malignant hyperthermia is not a disease per se, but a genetic predisposition of clinically inconspicuous individuals to respond abnormally when exposed to volatile anaesthetics or depolarising muscle relaxants. It is a drug-induced, potentially lethal event in carriers of calcium channel mutations.

The defect in either DHPR or RYR1 causes a massive increase in myoplasmic calcium concentration, which leads to the well-documented increases in muscle metabolism and heat production that are associated with malignant hyperthermia.

Dantrolene acts as an inhibitor of calcium release from the sarcoplasmic reticulum to abort an episode of malignant hyperthermia.

Central core disease is a less well-known, autosomal dominantly transmitted proximal myopathy that is allelic to malignant hyperthermia. It is also caused by a mutation in RYR1. Calcium channel gene mutations are also responsible for neuronal diseases such as episodic ataxia and familial hemiplegic migraine.

CHLORIDE CHANNELS

Chloride channels are found within the plasma membrane of cells involved in cell volume regulation, transepithelial transport, secretion of fluid from secretory glands, and stabilization of membrane potential.

Cystic fibrosis is a common inheritable disease associated with chloride channel abnormalities.[3] The clinical manifestations of this disease are due to a defect in a chloride channel protein called the cystic fibrosis transmembrane regulator (CFTR), situated at the apex of epithelial cells lining the ducts of organs such as the pancreas, skin and the lung.

The mutant CFTR blocks the passage of chloride ions into the lumen. In addition, this mutant CFTR increases sodium reabsorption from the lumen via sodium channels.

More than 450 mutations of CFTR have been identified. Deletion of phenylalanine at position 508 (DF508) accounts for more than 70% of cases of cystic fibrosis.[3] The DF508 CFTR channel is able to transport chloride efficiently if it is inserted into the cell membrane. However, the mutant protein becomes stuck in intracellular organelles and is therefore not inserted into the membrane properly.

As a result of loss of control of primarily chloride, but also sodium channels, thick, desiccated mucus is produced which accounts for the severe pancreatic insufficiency and pulmonary disease which are the clinical hallmarks of cystic fibrosis.

Potential Future Strategies

The completion of the human genome decoding has resulted in the potential to decode and understand the exact amino acid sequence abnormality involved in each of the channelopathies. Once this abnormality is known, the potential exists to insert corrected DNA sequences into the clinically relevant cells, thus offering a potential cure for the underlying disease. At present the major limitation to such a therapeutic strategy remains the difficulty of a suitable and lasting vector for inserting the genetic material. Currently used viruses are either self-limiting by immunity or offer the threat of a permanent viral infection. Cell culture methods imply removal and reimplantation of treated cells, with all the limitations inherent in such a technology.

One of the proposed strategies for treating cystic fibrosis in the future involves the use of theoretical "chaperonins" to ensure correct insertion of the protein within the cell membrane, but such "chaperonins" have yet to be developed.

Conclusion

The group of diseases currently classified as the channelopathies has a common entity. This is an inherited abnormality of genetic material which codes for an abnormal sequence of amino acids in one of the protein subunits of an ion channel, resulting in an abnormality of the chemical and physical behaviour of the affected ion channel protein. This abnormality may result in the failure of the protein to imbed correctly in the cell wall, or may result in excessive or deficient ion passage in response to normal stimuli, or may permit excessive or prolonged passage on ions through the channel, resulting in a failure of normal cell wall repolarisation. In each case the abnormality results in a discrete clinically recognised syndrome or disease, which are collectively known as the channelopathies.

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