Channels active in the excitability of nerves and skeletal muscles across the neuromuscular junction: basic function and pathophysiology

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Goodman BE. Channels active in the excitability of nerves and skeletal muscles across the neuromuscular junction: basic function and pathophysiology. Adv Physiol Educ 32: 127–135, 2008; doi: 10.1152/advan.00091.2007.—Ion channels are essential for the basic physiological function of excitable cells such as nerve, skeletal, cardiac, and smooth muscle cells. Mutations in genes that encode ion channels have been identified to cause various diseases and disorders known as channelopathies. An understanding of how individual ion channels are involved in the activation of motoneurons and their corresponding muscle cells is essential for interpreting basic neurophysiology in nerves, the heart, and skeletal and smooth muscle. This review article is intended to clarify how channels work in nerves, neuromuscular junctions, and muscle function and what happens when these channels are defective. Highlighting the human diseases that result from defective ion channels is likely to be interesting to students in helping them choose to study about channel physiology.

action potential; synaptic transmission; muscle function; channelopathies; muscle function; teaching

TEACHERS OF PHYSIOLOGY spend significant amounts of time explaining to their students how nerves and muscles generate and carry electrical signals and use their excitability to perform their basic functions. Excitable cells (nerve, heart, skeletal, and smooth muscle cells) are characterized by having a high number of voltage-gated ion channels and using propagating action potentials to initiate their responses. In contrast, nonexcitable cells (epithelial, skin, liver, and salivary gland cells) have few voltage-gated ion channels and generally use only small changes in membrane potential (generator potentials) to initiate their responses. For an in-depth understanding of neuromuscular excitable cell functions, necessary knowledge includes ion fluxes involved in standard neuronal action potentials, in excitation-secretion coupling at the axon terminal, and in the stimulation of the skeletal muscle fiber after ACh for excitation-contraction coupling. While these channel activities may be fascinating to cell physiologists, the relevance of these cellular events for students may be strengthened by involving students in figuring out how various mutations and autoantibodies will directly result in serious pathological situations for the affected individuals. This Staying Current article seeks to clarify which ion fluxes through which channels are involved in the generation of action potentials in neurons, synaptic transmission, and stimulation of contraction in skeletal muscles and how defects in certain channels (channelopathies) can lead to further understanding of channel functions and dysfunctions.

Primer on Neuronal Action Potentials

As described in numerous physiology textbooks (4), the resting membrane potential of mammalian neurons is about −70 mV. When an input signal occurs, mechanically, chemically, or voltage-gated channels (usually Na⁺, Cl⁻, or Ca²⁺) open to lead to a graded potential at the dendrites or the cell body. If the graded potential is sufficient (when it arrives at the trigger zone of the axon hillock) to depolarize the membrane to threshold (−55 mV), voltage-gated Na⁺ channels rapidly open, and Na⁺ rushes into the cell (Fig. 1). Rapid Na⁺ entry depolarizes the cell, and the membrane potential approaches the Nernst equilibrium potential for Na⁺ (E_{Na}) of +67 mV (9). This causes the depolarizing or rising phase of the action potential. The positive membrane potential (above 0 mV) is sometimes called the overshoot. Voltage-gated Na⁺ channels are both fast activating and fast inactivating and thus close quickly (at about +30 mV) before E_{Na} is reached (9). Voltage-gated K⁺ channels, which take slightly longer than voltage-gated Na⁺ channels to open, begin to open and allow K⁺ to move out of the cell. As K⁺ leaves the cell, the membrane potential rapidly becomes more negative. This causes the repolarizing or falling phase of the action potential and sends the membrane potential back toward the resting membrane potential. Voltage-gated K⁺ channels and other K⁺ channels remain open, and the membrane potential undershoots the resting value, approaching the Nernst equilibrium potential for K⁺ (E_{K}) of −98 mV (9). This phase is called the afterhyperpolarization (AHP). Finally, voltage-gated K⁺ channels close, and small ion fluxes return the membrane potential to its resting value. Macroscopic ion fluxes depend on the number of individual ion-selective channels present in the cell, the probability that those channels are open at any time, and the conductance of individual channels, all of which may vary and depend on the potential difference across the membrane.

The stars of the basic description of the ion fluxes responsible for the neuronal action potential are voltage-gated Na⁺ and K⁺ channels; however, other K⁺ channels and small ion fluxes are known to be involved in the return of the membrane potential to resting during the AHP phase from either single action potentials or after a series of action potentials. The maintenance of resting membrane potentials in the steady state for neurons also depends primarily on small fluxes of Na⁺, K⁺, and Cl⁻ through their channels. At resting membrane potential, axonal ion channels tend to be closed, thus minimizing fluxes. Resting membrane potential is best estimated using the Goldman-Hodgkin-Katz equation, which incorporates the differential permeabilities and concentration differences across cell membranes for Na⁺, K⁺, and Cl⁻. Mutations in genes for channel proteins may lead to changes in the resting membrane potentials of neurons or muscle cells and result in

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pathophysiology, leading to neuromuscular diseases and disorders. Thus, an understanding of the actions of various types of channels involved in the physiology of excitable cells is helpful for interpreting how certain channelopathies affect neuromuscular function.

Voltage-Gated Na\(^+\) Channels and the Neuronal Action Potential

Voltage-gated Na\(^+\) channels are responsible for the rapid depolarization of a neuron causing an action potential (4) (Fig. 1). Voltage-gated Na\(^+\) channels are very voltage sensitive, and their open probability is very low at the resting membrane potential. Thus, few Na\(^+\) ions move across neuronal cell membranes during resting. A depolarizing stimulus increases the probability of individual Na\(^+\) channels opening, and the open probability of the channel is strongly time dependent. Thus, Na\(^+\) channels open briefly after a short delay and then rapidly close again (4). Greater than 95% of the individual Na\(^+\) channels are closed by the time the membrane is depolarized to 0 mV or above (9). Voltage-gated Na\(^+\) channels are relatively selective for the flux of Na\(^+\) over K\(^+\) and other monovalent cations and are essentially impermeable to Ca\(^{2+}\) and other divalent cations. Their protein structure includes a pore-forming \(\alpha\)-subunit and two membrane-spanning \(\beta\)-subunits, which are likely to be involved in modulating channel gating or channel expression (4) (Fig. 2). Mutations in any of the eight homologous genes that encode for \(\alpha\)-subunits in various excitable cells are known to lead to genetic defects in Na\(^+\) channels.

Voltage-gated Na\(^+\) channels are composed of activation and inactivation gates that alternate between keeping the channel open and closed. A common model of the gating activity in an individual voltage-gated Na\(^+\) channel during the action potential has the activation gate (internal to the pore) closed at the

![Fig. 1. Neuronal action potential showing channels involved in ion fluxes that contribute to the membrane potential changes.](image1)

![Fig. 2. Hydropathy plot of a voltage-gated Na\(^+\) channel showing predicted folding of the \(\alpha\)-subunit from skeletal muscle channels. Mutations known to cause hyperkalemic periodic paralysis are in round-edged boxes; mutations known to cause paramyotonia congenita are in circles; mutations known to cause K\(^+\)-aggravated myotonia are in sharp-edged boxes. [From Ref. 12.]](image2)
resting membrane potential and then opened by a depolarizing stimulus. When the activation gate is open, Na\(^+\) flows into the neuron. As the cell is depolarized toward \(E_{Na}\), the inactivation gate closes, and Na\(^+\) entry rapidly stops. Voltage-gated Na\(^+\) channels display two modes of inactivation: fast and slow. Fast inactivation is likely due to a structure similar to a rigid hinged lid on the cytoplasmic side of the protein that controls access to the pore and is latched closed during inactivation (1). Slow inactivation likely results from rearrangement of the pore (7).

Delayed Rectifier Voltage-Gated K\(^+\) Channels and the Neuronal Action Potential

These voltage-gated K\(^+\) channels are responsible for the repolarization (falling phase) of an action potential in a neuron (4) (Fig. 1). Also known as \(K_v\) class (or Shaker-related) K\(^+\) channels, they have strong selectivity for K\(^+\) over other cations (9). Mammalian neuronal voltage-gated K\(^+\) channels are made up of four \(\alpha\)-subunits and one cytoplasmic \(\beta\)-subunit (Fig. 3).

Their primary role in excitable cells is inhibitory because when they are open, K\(^+\) tends to leave the cell, making the inside less positive (more negative) and approach \(E_K\). Thus, they stabilize the membrane potential by bringing the membrane potential closer to \(E_K\) and farther away from firing threshold (9). Therefore, voltage-gated K\(^+\) channels in excitable cells determine the resting membrane potential, decrease the time duration of action potential spikes, time the interspike intervals during repetitive firing, and make it more difficult to bring neurons to threshold when they are open (9).

These channels are known as delayed (outward) rectifier K\(^+\) channels because they change membrane conductance with a delay after a depolarizing voltage (even though most other channels also have a delay) and K\(^+\) passes in an outward direction toward the extracellular fluid (4). Various K\(^+\) channels have different degrees of delayed rectification when their voltage-sensing segment detects that the neuron is depolarized. They open after short depolarization but eventually close with long depolarization. It is likely that cytoplasmic ball-and-chain portions of these protein channels from either \(\alpha\)-subunits alone or from adjacent \(\beta\)-subunits block the pore to stop K\(^+\) fluxes and inactivate individual channels (Fig. 3). Three different families of seventeen distinct genes are known to be involved in encoding excitable cell K\(^+\) channels, and their mutations cause several identified channelopathies (4). Different types of delayed rectifier K\(^+\) channels are found in vertebrate nervous, the heart, and skeletal muscle, and they are encoded by different genes (9). Loss of function mutations (mutations that cause channels to conduct fewer ions) in voltage-gated K\(^+\) channels prolong the duration of the action potential (2).

\(\text{Cl}^-\) Channels and the Neuronal Action Potential

Cells are known to have anion-selective channels that readily allow the passage of \(\text{Cl}^-\), Br\(^-\), I\(^-\), NO\(_3\), HCO\(_3\), and SCN\(^-\) (9). \(\text{Cl}^-\) is commonly distributed almost at its electrochemical equilibrium (Nernst equilibrium potential for \(\text{Cl}^- = -90\) mV) across excitable cell membranes so that the extracellular \([\text{Cl}^-]\) is higher than the intracellular \([\text{Cl}^-]\). Depolarization of an excitable cell produces an influx of \(\text{Cl}^-\) (anions tend to accompany the movement of cations across the cell membrane to maintain electroneutrality). Thus, \(\text{Cl}^-\) channels oppose excitability by limiting the depolarizing stimulus, help to return a depolarized cell to resting, and thus stabilize the membrane potential of excitable cells (Fig. 1). The characterization and cloning of \(\text{Cl}^-\) channels have not progressed as far as those of other ion channels involved in excitable cell function (voltage-gated Na\(^+\), K\(^+\), and Ca\(^{2+}\) channels); however, \(\text{Cl}^-\) fluxes are particularly important for stabilizing the
resting membrane potential in skeletal muscle (9) (Fig. 4). When mutations in Cl⁻ channels lead to an absence of this stabilizing influence of Cl⁻ fluxes, skeletal muscle is hyperexcitable, as seen in myotonia congenita.

Other K⁺ Channels and the Neuronal Action Potential

Inwardly rectifying K⁺ channels (Kir channels) have been identified in human motor axons. They are activated by hyperpolarization, leading to inward fluxes of K⁺ that depolarize the axon and bring the membrane potential back toward the resting membrane potential (15). Kir channels open after ~30 ms following an action potential and reach steady state over 100–200 ms (15). Thus, they are involved in the last phase of recovery toward resting membrane potential following an action potential or series of action potentials (Fig. 1). Their two major physiological roles are stabilizing the resting potential near E_K and assisting with transport of K⁺ across cell membranes. All Kir channels show some degree of inward rectification, which is variable due to a voltage-dependent block by intracellular cations obstructing the mouth of the channel pore (1). The normal function of inward rectifiers is likely to carry outward current because the membrane potential of animal cells is rarely more negative than E_K. Thus, inward rectifiers also carry some outward current (9). The function of inward rectifiers in fast skeletal muscle may be to accelerate the reentry of K⁺ from the t-tubular space after action potentials. At least 16 genes encode for Kir channels, which are likely found in the cell membrane as tetramers of individual subunits (9). Each Kir monomer has two transmembrane spanning domains. Mutations in Kir channels or changes in the regulation of Kir channels have been implicated in causing neuronal degeneration.

Ca²⁺-dependent K⁺ (KCa) channels are activated by both depolarization and increases in intracellular free [Ca²⁺]. KCa currents contribute to the repolarization of neurons to resting membrane potential and are involved in the AHP phase of the action potential. After the action potential spike of a motoneuron, there is an initial fast AHP that lasts 1–2 ms and a later slow AHP lasting 50 - 100 ms (9) (Fig. 1). The fast AHP is due to voltage-gated K⁺ channels that opened during the spike and then rapidly closed. The slow AHP is due to K⁺ effluxes from the cells through slow K⁺ channels activated by Ca²⁺ influxes during the action potential and lasts while intracellular Ca²⁺ is elevated. Thus, KCa channels determine the shape of the action potential and help in regulating cell excitability. To date, no human neuromuscular disease or disorder has been identified as specifically related to defects in KCa channels. KCa channels have been designated as one of three major types based on their single channel conductances. The maxi KCa channel (also known as the BKCa channel) has large single channel conductance (100–250 pS without a concentration gradient) and is activated by depolarization and micromolar [Ca²⁺]. The small (SKCa; 5–20 pS) and intermediate (20–80 pS) channels are insensitive to voltage changes and are activated by submicromolar [Ca²⁺] (1). The slow AHP in the vertebrate motoneuron involves SKCa channels that open due to Ca²⁺ entry during each action potential and remain open until intracellular Ca²⁺ is removed (9).

In an oxygen-deprived cell where intracellular ATP levels fall, ATP-sensitive K⁺ (KATP) channels open to hyperpolarize the cell, suppress firing of action potentials, and reduce the use of cellular energy (1). KATP channels open to allow K⁺ effluxes when there is no cytoplasmic ATP, some are closed when there are moderate levels of ATP, and most are closed when there are high levels of ATP. KATP channels have been identified in nerves, the heart, and skeletal muscle, but their physiological functions are unclear. However, recent evidence has indicated that the inhibition of KATP channels in high-altitude hypoxia may be involved in causing high altitude pulmonary edema (11). KATP channels are most commonly studied for their role in pancreatic β-cells, where at low nutrient levels they inhibit the release of insulin into the bloodstream (9).

Slow delayed rectifiers of the slowly gating KCNQ class of K⁺ channels are expressed in neurons and regulated by neurotransmitters (1). They appear to gate too slowly to be activated by individual action potentials; however, tonically open KCNQ channels leading to K⁺ effluxes would help to decrease

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Fig. 4. Hydropathy plot of a voltage-gated Cl⁻ channel in skeletal muscle. Mutations shown in rectangles are known to underlie Becker’s myotonia congenita, and those shown in circles are known to cause Thomsen’s myotonia congenita. [From Ref. 12.]
excitability by keeping the resting membrane potential away from threshold (9).

Primer on Neuronal Action Potential Arriving at Neuromuscular Junction

Following repetitive changes in ion fluxes across the axonal cell membrane through the various types of channels described above, a series of all-or-nothing action potentials reaches the axon terminal at the synapse of the neuromuscular junction (1). The arrival of the action potentials depolarizes the membrane at the axon terminal, opens voltage-gated Ca^{2+} channels located there, and allows Ca^{2+} to enter the neuron. Voltage-gated Ca^{2+} channels have been classified as L, N, P, Q, R, and T types and are normally distinguished by their sensitivity to pharmacological blockers, their characteristic single channel conductances, their kinetics, and their degree of voltage dependence (1). For example, T-type voltage-gated Ca^{2+} channels have low thresholds of activation, allowing them to open with small levels of depolarization. They inactivate rapidly and completely when the membrane potential becomes positive. In contrast, the L-, N-, P-, Q-, and R-type channels require much stronger levels of depolarization to open. Pharmacologically, L-type channels are blocked by dihydropyridines, and N-type channels are blocked by toxins from fish-hunting cone snails. A toxin from a funnel web spider blocks both P- and Q-type channels but with different affinities. P/Q types of voltage-gated Ca^{2+} channels are present at presynaptic nerve terminals and appear to be the most important channels for the excitation-secretion coupling of ACh release at the neuromuscular junction. Ca^{2+} channels are functionally similar to Na^{+} channels except that high-affinity binding of Ca^{2+} inside the pore makes them extremely selective for Ca^{2+} over monovalent cations (4). At least seven different genes coding for \( \alpha_1 \)-subunits of voltage-gated Ca^{2+} channels have been identified (1).

Primer on How the Neurotransmitter ACh Activates Muscle

ACh is released from the presynaptic motor neuron into the synapse based on excitation-secretion coupling facilitated by P/Q-type voltage-gated Ca^{2+} channels (1). These neurotransmitter molecules diffuse across the 20- to 30-nm synaptic cleft and interact with nicotinic ACh receptor (AChR) channels clustered in junctional folds across from the axon terminal on the muscle cell membrane (also known as the end plate). The AChR is known to be a pentamer of homologous subunits arranged in a ring around a central ion pore (1). When two ACh molecules bind to an AChR, a conformational change in the receptor opens the central pore and allows cations to flow into or out of the muscle cell. Since generally (due to electrochemical gradients) more Na^{+} flows in than K^{+} leaves, the muscle cell is depolarized. If enough ACh is released, then sufficient AChR channels are activated and the muscle cell membrane is depolarized to threshold for opening the voltage-gated Na^{+} channels nearby and initiating a muscle action potential. Generally, stimulation of a motoneuron automatically releases enough ACh into the cleft to stimulate the adjacent muscle cell to threshold. Thus, an action potential (with similar ion fluxes to the neuronal action potential) is initiated at the postsynaptic site on the muscle cell membrane.

Primer on Muscle Action Potentials Spreading Down t-Tubules and Activating Ca^{2+} Channels

Action potentials originating after a muscle cell is depolarized to threshold propagate along the skeletal muscle membrane and down t-tubules (4). The action potential membrane depolarization opens L-type voltage-gated Ca^{2+} channels in the t-tubule membrane. These L-type Ca^{2+} channels are also known as dihydropyridine receptors because they are inhibited by the class of antihypertensives known as dihydropyridines. Conformational changes in L-type Ca^{2+} channels following depolarization allow Ca^{2+} to enter the skeletal muscle sarcoplasm. The conformational change in L-type Ca^{2+} channels induces a conformational change in an adjacent Ca^{2+}-release channel located in the membrane of the sarcoplasmatic reticulum (SR) of the muscle cell. The Ca^{2+}-release channel is also known as the ryanodine receptor because it is inhibited by the plant alkaloid ryanodine. When the L-type Ca^{2+} channel on the t-tubule membrane mechanically opens the Ca^{2+}-release channel in the SR, Ca^{2+} sequestered in the SR rapidly leaves via Ca^{2+}-release channels, binds to troponin C on the actin myofilament, and leads to the initiation of cross-bridge cycling of the muscle in the process known as excitation-contraction coupling (34).

Pathologies of Ion Channel Function in Nerves and Skeletal Muscles

Over 340 human genes are thought to encode ion channels, and mutations in over 60 ion channel genes are known to cause human diseases (2). Ion channels are a large family of >400 related proteins and make up ~1% of the human genome (6). Ion channel diseases were first recognized in 1989 with the discovery of the contribution of CFTR to the symptoms of cystic fibrosis. Ion channel diseases have come to be known as channelopathies and may arise in a number of different ways (1):

1. Mutations in the promoter region of an ion channel gene may lead to an underexpression or overexpression of channel proteins.
2. Mutations in the coding region of an ion channel gene may lead to gain or loss of channel function.
3. Mutations in genes encoding for regulatory molecules or for pathways leading to regulatory molecules may lead to defective regulation of channel activity by its intracellular or extracellular ligands or modulators.
4. Autoantibodies to channel proteins are made that may lead to downregulation or upregulation of channel function.
5. Ion channels may act as lethal agents to form large nonselective pores in the target cells leading to target cell lysis or death.”

In the future, healthcare providers will be able to use diagnostic tests for genetic screening and prenatal diagnosis of various channelopathies. In addition, a clear understanding of the defect at the cellular level can facilitate design of selective drugs and treatment for affected individuals. Specific gene therapy by introducing normal genes or upregulating fetal genes to substitute for the genetic defect may help cure the defects. Translational research studying how various individuals with channelopathies exhibit symptoms and react to treatments have led to major breakthroughs in understanding the basic physiology of various ion channels and how they contribute to homeostasis. Interpreting at the cellular level what
problems will be caused by a specific ion channel defect in a nerve or muscle can help to establish relevance for learning for students. Thus, the next section of this review will describe some ion channel mutations and changes for the channels already described and correlate the defects with changes in normal physiological function in nerve and muscle cells (Fig. 5 and Table 1). The APPENDIX at the end of the article helps to clarify some of the clinical definitions of the terms. To facilitate the learning process, think, pair, share questions to be used with students have been designed for a number of defects that lead to human diseases. Case studies or simulated drug design projects would also be interesting ways to introduce the channelopathies so that students can learn the relevance of these changes in channel function (3, 5, 13).

Table 1. Channelopathies linked to neuromuscular diseases and disorders

<table>
<thead>
<tr>
<th>Channel</th>
<th>Channelopathy</th>
<th>Change of Ion Fluxes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle voltage-gated Na⁺ channels</td>
<td>Hyperkalemic periodic paralysis</td>
<td>Sustained inward Na⁺ fluxes</td>
</tr>
<tr>
<td>Muscle Cl⁻ channels</td>
<td>Paramyotonia congenita</td>
<td>Sustained inward Na⁺ fluxes</td>
</tr>
<tr>
<td>Muscle AChRs</td>
<td>K⁺-aggravated myotonia</td>
<td>Sustained inward Na⁺ fluxes</td>
</tr>
<tr>
<td>Muscle voltage-gated Ca²⁺ channels</td>
<td>Hypokalemic periodic paralysis</td>
<td>Reduced Cl⁻ fluxes</td>
</tr>
<tr>
<td>Muscle ryanodine receptor Ca²⁺ channels of the SR</td>
<td>Thomsen or Becker myotonia congenita</td>
<td>Loss of Cl⁻ channels</td>
</tr>
<tr>
<td>Neuronal voltage-gated K⁺ channels</td>
<td>Myotonic dystrophy</td>
<td>Prolonged depolarization of the muscle membrane</td>
</tr>
<tr>
<td>Neuronal inward rectifying K⁺ channels</td>
<td>Slow channel syndrome</td>
<td>Decreased rate of opening of channels</td>
</tr>
<tr>
<td>Neuronal voltage-gated K⁺ channels</td>
<td>Fast channel syndrome</td>
<td>Unknown; cell may be depolarized</td>
</tr>
<tr>
<td>Neuronal inward rectifying K⁺ channels</td>
<td>Episodic ataxia type 1</td>
<td>Increased cytoplasmic Ca²⁺ leaking out of the SR</td>
</tr>
<tr>
<td>Neuronal inward rectifying K⁺ channels</td>
<td>Andersen’s syndrome</td>
<td>Reduced K⁺ effluxes</td>
</tr>
</tbody>
</table>

Channelopathies caused by the formation of autoantibodies

| Muscle AChRs                  | Myasthenia gravis                   | Loss of AChRs                           |
| Neuronal P/Q-type voltage-gated Ca²⁺ channels | Lambert-Eaton myasthenic syndrome | Loss of Ca²⁺ channels for excitation-secretion coupling |
| Neuronal voltage-gated K⁺ channels | Acquired neuromyotonia              | Loss of K⁺ channels                     |

AChRs, ACh receptors; SR, sarcoplasmic reticulum.

Fig. 5. Schematic diagram of a neuromuscular junction and the diseases and disorders known to be associated with the motor neuron or skeletal muscle fiber.
**Na⁺ Channelopathies**

Think, pair, share. What electrophysiological changes in skeletal muscle and their resultant symptoms are likely to be seen if a mutation causing defective voltage-gated Na⁺ channels leads to failure of the channels to inactivate and stop ion fluxes?

Diseases related to mutations in voltage-gated Na⁺ channels include hyperkalemic periodic paralysis, paramyotonia congenita, and K⁺-aggravated myotonia (1). Mutations in voltage-gated Na⁺ channels cause diseases of skeletal muscle, and most are mutations that alter some aspect of channel inactivation. Na⁺ channels with these gain of function mutations fail to inactivate and conduct sustained inward Na⁺ fluxes (Fig. 2). Such diseases are characterized by skeletal muscle hyperexcitability or muscle weakness that is exacerbated by an increase in extracellular [K⁺] or exposure to cold temperatures. The variability of the symptoms of the defect from hyperexcitability to weakness is due to the characteristic of Na⁺ channels whereby small membrane depolarizations lead to more excitable cells (as the membrane potential is closer to the threshold potential) and larger membrane depolarizations (above threshold) can lead to depolarization block, which results in one contraction followed by paralysis. Depolarization block likely occurs because individual voltage-gated Na⁺ channels never return to resting membrane potential to be reset for the opening of activation gates after the next depolarizing stimulus. Increased plasma K⁺ may precipitate an attack because the depolarization it causes keeps the defective Na⁺ channels open longer (1). Cells that are more excitable generate repetitive action potentials that lead to myotonia (an inability to relax and thereby muscle stiffness) (10). Myotonia can also result in fasciculations or visible rippling contractions of the muscles. One of these voltage-gated Na⁺ channel diseases known as hyperkalemic (elevated plasma K⁺ levels) periodic paralysis is characterized by short, mild, frequent attacks of profound muscle weakness, beginning in infancy, that can be provoked by rest after exercise or stress and often demonstrates myotonia between attacks (6). Both myotonia and paralysis can occur in the same patient within a few minutes of each other (1). Attacks are either spontaneous or precipitated by exercise, stress, fasting, or eating K⁺-rich food (bananas). Periodic paralyses and myotonias are generally painless and not life threatening, although they can be very inconvenient. They are unlikely to affect the respiratory muscles and cause difficulty in breathing (1). Paramyotonia congenita is characterized by a cold-exacerbated myotonia (1) and results in very unpleasant stiffening of muscles that happens when working in the cold. The muscle stiffness results from continued firing of action potentials in muscles after the cessation of voluntary effort or stimulation (1). Patients may also have muscle hypertrophy (overdevelopment) as a consequence of the continuous muscle activity. K⁺-aggravated myotonia is characterized by muscle stiffness mostly when muscles are used after a period of rest (1).

**K⁺ Channelopathies**

Think, pair, share. What electrophysiological changes in neurons and their resultant symptoms are likely to be seen if a mutation causing defective voltage-gated K⁺ channels leads to decreased outward K⁺ fluxes?

Three diseases that have been identified to be due to mutations in neuromuscular K⁺ channels include episodic ataxia type 1, Andersen’s syndrome, and acquired neuromyotonia (see Autoantibodies Affecting Neuromuscular Transmission) (1). Episodic ataxia type 1 affects peripheral and central nervous, causing attacks of imbalance and uncoordinated movements often with nausea, vertigo, and headaches. K⁺ effluxes are reduced, prolonging the falling or repolarization phase of the action potential (Fig. 3). This loss of function mutation induces repetitive nerve firing, causing excessive and unregulated neurotransmitter release at the neuromuscular junction (1). Neurotransmitters stimulate the skeletal muscle to produce ataxia and myokymia. In contrast, Andersen’s syndrome is caused by a loss of function mutation reducing the K⁺ current that is involved in returning the membrane potential from hyperpolarization to resting (8). These defects in K⁺ channels lead to difficulty in restimulating the muscle and episodic muscle weakness.

**Cl⁻ Channelopathies**

Think, pair, share. What electrophysiological changes in skeletal muscle and their resultant symptoms are likely to be seen if a mutation causing defective Cl⁻ channels leads to decreased Cl⁻ fluxes?

Diseases associated with defects in Cl⁻ channels include both Thomsen and Becker myotonia congenita and myotonic dystrophy (1). Decreased Cl⁻ conductance also leads to myotonia. In normal skeletal muscle, Cl⁻ fluxes account for 70–80% of the resting membrane conductance. With defective Cl⁻ channels and smaller Cl⁻ influxes, smaller influxes of Na⁺ are needed to reach threshold and trigger action potentials, and thus muscle excitability is enhanced (1) (Fig. 4). There are two types of loss of function mutations of Cl⁻ channels that cause myotonia. The dominant form of myotonia congenita is also known as Thomsen’s disease, and the recessive form of generalized myotonia is known as Becker’s disease. Myotonia congenita usually has low Cl⁻ conductances and hyperexcitability exhibited as muscle cramping with exercise. Patients with myotonic dystrophy exhibit increased excitability of the muscle membrane due to loss (underexpression) of Cl⁻ channels (1).

**Mutations in AChRs**

Think, pair, share. What electrophysiological changes in skeletal muscle and their resultant symptoms are likely to be seen if a mutation causing prolonged AChR channel activation or reduced AChR channel activation?

Congenital myasthenic syndromes are related to defects in neuromuscular transmission. Mutations in genes that encode the various subunits of nicotinic AChRs in skeletal muscle are known to cause either slow channel syndrome or fast channel syndrome. Slow channel syndrome is caused by a gain of function mutation in the AChR. Symptoms of slow channel syndrome include muscle weakness, rapid muscle fatigue, progressive muscle atrophy, and repetitive muscle action potentials from a single nerve stimulus (1). Mutations in the AChR appear to result in prolonged channel activation by ACh. The increased duration of channel opening of the AChR leads to prolonged excitatory postsynaptic potentials and prolonged depolarization of the muscle membrane. Prolonged
depolarization inactivates voltage-gated Na\(^+\) channels (depolarization block) and leads to failure of muscle excitability, thus resulting in muscle weakness and rapid fatigue. Fast channel syndrome with clinical features similar to slow channel syndrome is due to a reduction in ACh affinity and decreased rate of channel opening (1). Thus, fast channel syndrome is due to a loss of function change in the AChR. Fewer receptors are activated, and those activated are open for shorter periods, leading to reduced excitatory postsynaptic current and potential changes and a failure to elicit an action potential in the muscle cell.

\(\text{Ca}^{2+}\) Channelopathies

Skeletal muscle channelopathies due to defects in \(\text{Ca}^{2+}\) channels include hypokalemic periodic paralysis (HypoPP) (Fig. 6) and malignant hyperthermia (1). While understanding how defects in \(\text{SR Ca}^{2+}\)-release channels cause malignant hyperthermia is logical and interesting, the explanation for how defects in \(\text{L-type voltage-gated Ca}^{2+}\) channels with low levels of extracellular K\(^-\) cause periodic paralysis is not yet clear (1). No functional effects on \(\text{Ca}^{2+}\) fluxes in skeletal muscles have been found in HypoPP patients. Patients with HypoPP have episodes of skeletal muscle weakness when serum [K\(^-\)] is low. This paralysis can be triggered by a high-carbohydrate meal, insulin, or exercise and may last from hours to days. Fortunately, the muscles controlling speech, swallowing, and respiration are not usually affected. However, there are electrophysiological changes in skeletal muscle that have been identified in patients with HypoPP. Muscle biopsies from patients with HypoPP are depolarized by \(-5\)–\(-15\) mV (compared with muscle fibers from normal individuals) between attacks and exhibit reduced excitability. It is not clear how hypokalemia causes periodic paralysis in individuals with this \(\text{Ca}^{2+}\) channel mutation; however, during an episode, plasma K\(^+\) levels drop as K\(^+\) rushes into the muscle cells. Thus, the best explanation so far is that the muscle weakness and paralysis is due to membrane depolarization that inactivates the voltage-gated Na\(^+\) channel (as in depolarization block with the Na\(^+\) channel not being able to be activated at all) (1).

Think, pair, share. What changes in skeletal muscle and their resultant symptoms are likely to be seen if a mutation causes prolonged increased free cytoplasmic \(\text{Ca}^{2+}\)?

Malignant hyperthermia (MH) is the main cause of death due to anesthesia (1). Patients with MH have increased [Ca\(^{2+}\)] in skeletal muscle somehow related to a mutation in the gene encoding the \(\text{SR Ca}^{2+}\)-release channels (ryanodine receptors). Ryanodine receptors are found in SR membranes of skeletal and cardiac muscles but also in organellar membranes of brain and epithelial cells (1). Individuals with MH only show evidence of the disorder when it is triggered by inhalation anesthetics or muscle relaxants. Increased cytoplasmic \(\text{Ca}^{2+}\) leads to accelerated skeletal muscle metabolism, sustained muscle contractions, hyperkalemia, cardiac arrhythmias, respiratory and metabolic acidosis, and a body temperature that rises rapidly (hyperthermia) (1). Body temperature may increase by \(1°C\) every 5 min and can exceed \(43°C\). The antidote for the MH-induced increase in body temperature is dantrolene sodium, which blocks \(\text{SR Ca}^{2+}\) release.

Autoantibodies Affecting Neuromuscular Transmission

Some common neuromuscular diseases that have been identified to be due to autoantibody formation are myasthenia gravis, Lambert-Eaton myasthenic syndrome (LEMS), and acquired neuromyotonia (1). Autoantibodies may be made to channel proteins that lead to downregulation or upregulation of channel function (1). In myasthenia gravis, there is a loss of functional AChRs in the skeletal muscle membrane due to the formation of antibodies against nicotinic AChRs in the postsynaptic membrane (1). Thus, with fewer AChR to be activated, end plate potentials are greatly reduced, and muscle weakness and fatigue result. This profound weakness of skeletal muscle generally increases with exercise. Muscle weakness of myasthenia gravis usually first appears in facial and eye muscles and later progresses to weakness in the limbs so that the patient has difficulty standing up or climbing stairs. LEMS is due to decreased ACh release from the presynaptic motoneurons caused by the production of antibodies against the P/Q-type voltage-gated \(\text{Ca}^{2+}\) channels (1). These antibodies lead to a marked reduction in ACh release and failure of neuromuscular transmission, resulting in muscle weakness. In LEMS, muscle weakness is most common in the limbs, and patients have difficulty walking. Muscle weakness does not increase with exercise; in fact, muscle strength can be briefly enhanced by maximal effort. In 60% of patients with LEMS, small cell

![Image](http://advan.physiology.org/)
carcinoma of the lung is also present. It is thought that voltage-gated Ca\(^{2+}\) channels in the tumor cause autoantibodies to be produced that block voltage-gated Ca\(^{2+}\) channels at the nerve terminal. Acquired neuromyotonia is associated with antibodies against K\(_{\text{v}}\) channels in neurons. Loss (underexpression) of K\(_{\text{v}}\) channels causes decreased K\(^{+}\) conductance and lengthens the repolarization phase of the action potential, thus enhancing neurotransmitter release. Symptoms of acquired neuromyotonia include hyperexcitability of motor nerves, leading to spontaneous muscle twitching (myokymia), muscle cramps, and muscle weakness. The myotonia is spontaneous, continuous, and not stimulated by exercise.

Summary

Resting membrane potential in neurons is determined by differences in ion conductances through voltage-gated Na\(^{+}\) channels, delayed rectifier voltage-gated K\(^{+}\) channels, and Cl\(^{-}\) channels. When a neuron is activated to threshold for opening voltage-gated Na\(^{+}\) channels, an action potential is initiated. During an action potential spike, once again, voltage-gated Na\(^{+}\) channels and delayed rectifier voltage-gated K\(^{+}\) channels are the primary channel players; however, at later times in recovery from an action potential, K\(_{\text{Ca}}\) and K\(_{\text{ir}}\) channels appear to be involved. Propagating neuronal action potentials depolarize the membrane at the axon terminal to open P/Q-type voltage-gated Ca\(^{2+}\) channels that cause the secretion of ACh from vesicles into the synaptic cleft. ACh binds to the AChR at the end plate on the skeletal muscle cell, which opens the cation-selective pores of the AChR to depolarize the muscle cell to threshold for adjacent voltage-gated Na\(^{+}\) channels that initiate an action potential spike in the muscle cell. Action potentials propagate along the sarcolemma down t-tubules and activate L-type Ca\(^{2+}\) channels there that activate Ca\(^{2+}\)-release channels in the nearby SR, causing increased levels of free sarcoplasmic Ca\(^{2+}\) and thus excitation-contraction coupling. Channelopathies (caused either by mutations or autoantibodies) involving many of these channels have been identified to lead to either diseases or disorders. Studying humans with these conditions has helped to elucidate the normal actions of ion channels in neuromuscular function (Table 1).

APPENDIX: DEFINITIONS OF TERMS

Ataxia: uncoordinated movements.
Inward rectification: current flows in the inward direction.
Myasthenia: muscle weakness.
Myokymia: spontaneous contractions (twitching) of skeletal muscle, making the muscle surface seem to ripple.
Myotonia: the inability to relax, leading to muscle tone and stiffness.
Outward rectification: current flows in the outward direction.
Paralysis: the inability to contract.
Rectification: property of membrane conductance changes with voltage.

REFERENCES