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Introduction: Ion Channels in Plasma Membrane Signal Transduction

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Ion channels are a major class of membrane signaling proteins which produce changes in transmembrane electrical potential in response to many different stimuli. They initiate electrical signals in response to extracellular ligands, propagate changes in membrane potential for long distances along the cell surface, and respond to changes in intracellular second messengers and regulatory proteins with changes in ion conductance and membrane potential. Ion channels which respond primarily to extracellular ligands are termed "ligand-gated ion channels." They include the receptors for many neurotransmitters such as acetylcholine, gamma butyric acid, glycine, and glutamate. They are tetramers or pentamers of membrane-spanning subunits of two families whose founding members are the acetylcholine receptors at the neuromuscular junction and glutamate receptors in the brain (Hille, 1992). These families of ligand-gated ion channels are not included in this volume. The reviews in this series focus on ion channels that are involved in generation and conduction of propagated electrical signals and are regulated by a wide range of intracellular second messengers and regulatory proteins.

The voltage-gated sodium, calcium, and potassium channels are responsible for the generation of propagated electrical signals in neurons and other excitable cells (Hille, 1992). These ion channels respond to changes in transmembrane potential, often produced by binding of neurotransmitters to ligand-gated ion channels, and activate to generate action potentials and propagate the membrane potential change over the surface of the cell or along a nerve axon or muscle fiber. Activation of the ion channels opens a selective transmembrane pore through which specific ions may diffuse down their electrochemical gradient into or out of the cell. Thus, in most cases, activation of sodium or calcium channels leads to inward movement of these ions and depolarization of the cell while activation of potassium channels leads to outward movement of potassium ions and repolarization or hyperpolarization of the cell. During action potentials, small changes in membrane potential activate voltage-gated sodium channels for a few milliseconds. The large depolarization produced by the activation of sodium channels activates voltage-gated calcium channels which allow calcium entry into the cell and prolong the depolarizing phase of the action potential. The prolonged depolarization caused by activation of sodium and calcium channels is terminated by activation of voltage-gated and calcium-activated potassium channels which repolarize and hyperpolarize the cell. The potassium channels are also primarily responsible for maintaining the resting membrane potential of the cell at a negative value and regulating it in response to intracellular second messengers.

The permeability increase resulting from activation of the voltage-gated ion channels is biphasic. Upon depolarization, permeability to sodium, calcium, or potassium increases dramatically over a period of 0.5 to hundreds of msec and then decreases to the baseline level over a period of 2 msec to seconds. This biphasic behavior results from two experimentally separable gating processes that control ion channel function: activation, which controls the rate and voltage dependence of the permeability increase following depolarization, and inactivation, which controls the rate and voltage dependence of the subsequent return of the ion permeability to the resting level during a maintained depolarization. The voltage-gated ion channels can therefore exist in three functionally distinct states or groups of

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states: resting, active, and inactivated. Both resting and inactivated states are nonconducting, but channels that have been inactivated by prolonged depolarization are refractory unless the cell is repolarized to allow them to return to the resting state. The ion conductance of the activated ion channels is both highly selective and remarkably efficient. Selectivity among the physiological ions ranges from 12-fold for sodium channels to over 1000-fold for calcium channels, and all three classes of ion channels conduct ions across biological membranes at rates approaching their rates of diffusion through free solution. Understanding the molecular bases for voltage-dependent activation, rapid inactivation, and selective and efficient ion conductance is a major goal of current research on these critical signaling proteins.

The voltage-gated sodium, calcium, and potassium channels are also regulated by intracellular second-messenger pathways including protein phosphorylation and G proteins (Hille, 1992). In addition, some closely related potassium channels are primarily regulated by intracellular messengers including calcium and cyclic nucleotides. The newer members of this superfamily are distant relatives of the voltage-gated K^+ channels whose ion conductance activity is regulated by intracellular cyclic nucleotides and cations. The Ca^{2+}-activated potassium channels are both voltage-gated and Ca^{2+}-activated and thereby serve to couple changes in intracellular Ca^{2+} to changes in membrane excitability. The cyclic nucleotide-gated ion channels couple changes in the intracellular concentrations of cAMP and/or cGMP to activation of a Na^+ and K^+ selective ion conductance pathway in response to sensory stimuli in the visual and olfactory systems. Like the voltage-gated ion channels, these distant relatives are all rapidly gated, highly selective for cations, and remarkably efficient in ion conductance. All of these K^+ channels have a core structural motif containing six transmembrane segments that is thought to be the central building block upon which other ion channel structures are based (cover figure). Understanding the molecular basis for gating, selective and efficient ion conductance, and physiological regulation of this core structural motif is a major goal of current research on these critical signaling proteins and is the main focus of this minireview series.

Recent experiments focusing on cloning a wider range of K^+ channels have yielded even more diversity of channel structure (Jan and Jan, 1994). The inwardly rectifying K^+ channels conduct K^+ into cells but are blocked by intracellular Mg^{2+} ions and cannot conduct outward K^+ movement efficiently. They are regulated by other intracellular effectors including G proteins and ATP and are important in setting the resting membrane potential in excitable cells and in ion transport pathways in the kidney and other epithelial tissues. Remarkably, their structure contains only two transmembrane segments and an intervening hydrophobic segment which are distantly related to the fifth and sixth transmembrane segments of voltage-gated K^+ channels and are thought to comprise the pore region. Ion channels from yeast and nematodes combine these structural motifs in pairs (reviewed in Salkoff and Jegla, 1995). The TOK1 channel from yeast contains a six-membrane-spanning motif like a voltage-gated K^+ channel fused to a two-membrane-spanning motif like an inward rectifying K^+ channel, and the CeK channels from nematodes contain a pair of fused two-membrane-spanning motifs like inward rectifying K^+ channels. The structures of these ion channels illustrate the flexibility and diversity that can be derived from the core ion channel motif which forms the basis for the structures of the voltage-, calcium-, and cyclic nucleotide-gated ion channels reviewed here.

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