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ESSENTIALS Ion channels are membrane proteins that act as gated pathways for the movement of ions across cell membranes. They are found in both surface and intracellular membranes and play essential roles in the physiology of all cell types. An ever-increasing number of human diseases are now known to be caused by defects in ion channel func- tion. Ion channel diseases may arise in several different ways: Mutations in the coding region of the gene, or its control elements, leading to the gain, or loss, of channel function—Such diseases are often known as channelopathies and their frequency in the gen- eral population is usually very low. Many channelopathies are gen- etically heterogeneous and the same clinical phenotype may be caused by mutations in different genes, as is the case for long-QT syndrome. Conversely, mutations in the same gene may produce different phenotypes. For example, gain-of-function mutations in the epithelial Na+ channel produce Liddle's syndrome, whereas loss-of-function mutations cause pseudohypoaldosteronism type 1. Disease severity may vary with different mutations in the same gene, as is seen with gain-of-function mutations in KATP channel subunits: all cause neonatal diabetes, but the most functionally se- vere also cause neurological problems. Defects in expression levels and trafficking, leading to the gain, or loss, of channel density may also cause disease. Defective regulation of channel activity by intracellular or extra- cellular ligands, or by channel modulators—This can be due to mu- tations in the genes encoding the regulatory molecules themselves, or defects in the pathways leading to their production. For instance, glucokinase mutations cause one type of maturity-onset diabetes of the young (MODY2) by impairing the metabolic regulation of ATP-sensitive K+ channels in pancreatic β cells. Autoantibodies to ion channel proteins—which may either down regulate or enhance channel function. Ion channels that act as lethal agents—These are secreted by cells and insert into the membrane of the target cell to form large non- selective pores that cause cell lysis and death. Examples include bac- terial toxins such as staphylococcal α-toxin and the amoebapore of Entamoeba histolytica. The membrane-attack complex of comple-ment, perforin, and the defensins also acts in this way. Properties of ion channels To understand how ion channel defects give rise to disease, it is helpful to understand how ion channel proteins work. This chapter therefore considers what is known of ion channel structure, ex- plains the properties of the single ion channel, and shows how single-channel currents give rise to action

potentials and synaptic potentials. Ion channel structure Some ion channels consist of a single subunit, as in the case of the Ca2+-release channel of the sarcoplasmic reticulum. In other cases, the channel pore is formed from a single (α) subunit but associ- ated regulatory subunits may modify the ion channel properties, as in the case of voltage-gated Na+ and Ca2+ channels. Yet other ion channels are multimeric and several subunits are involved in pore formation—the nicotinic acetylcholine receptor comprises five sub- units (2α, β, δ and either γ or ε), while the voltage-gated K+ channels are composed of four subunits (which are sometimes, but not in- variably, identical). Mutations in both pore-forming and regulatory subunits can cause disease. The multimeric nature of an ion channel may influence whether a channelopathy is inherited in a dominant or recessive fashion. Individuals who are heterozygous for voltage-gated K+ channel muta tions will express both mutant and wild-type subunits in the same cell. If the mutant subunits coassemble with wild-type subunits to form hetero-oligomeric channels that are nonfunctional, the resulting K+ current will be much smaller than if hetero-multimerization does not occur. This is known as the ‘dominant-negative’ effect and may give rise to a disease that is dominantly inherited. Single-channel properties An ion channel can either be open or closed. When it is open, per- meant ions are able to move through the channel pore. The cur- rent flowing through the open pore is known as the single-channel current. Its magnitude is determined by the ion concentrations on either side of the membrane (the chemical gradient), by the mem- brane potential (the electrical gradient), and by the ease with which the ion can move through the channel pore (its permeability). At the 3.4 Ion channels and disease Frances Ashcroft and Paolo Tammaro

3.4 Ion channels and disease 247 equilibrium potential of an ion, the electrical and chemical gradients are equal in magnitude but opposite in direction, and thus there is no net ion flux. The single-channel conductance (γ) is a measure of the permeability of the ion and can be approximated by the single- channel current (i) divided by the membrane potential ($\gamma = i/V$). Ion channels are often highly selective in the ions they conduct. K+ channels, for example, are far more permeable to K+ than to Na+, while Na+ channels conduct Na+ but discriminate against K+. Ion selectivity takes place within a narrow region of the pore known as the selectivity filter. While some ions are excluded on the basis of their size or their charge, hydrophobic interactions and the en- ergy required to remove the waters of hydration can also important. Different types of ion channel may utilize different mechanisms to achieve selectivity. The fraction of time the channel spends in the open state is known as the open probability. Some channels open and close at random, but in other channels gating is regulated. In voltage-gated chan- nels the open probability is determined by the membrane potential, whereas in ligand-gated channels it is regulated by the binding of extracellular or intracellular ligands. Gating may also be subject to modulation, a process in which channel opening or closing is modi- fied, usually by one of several factors, such as ion or lipid binding, G- protein interactions, or post-translational modifications like protein phosphorylation and sumoylation (covalent attachment of a small ubiquitin-related modifier, SUMO, to a protein). Gating is believed to involve conformational changes in the channel structure that re- sult in the opening or closing of the pore. Ion channels are also influenced by the potential difference across the cell membrane, which usually lies between –60 and –100 mV at rest. A change in the membrane potential to a more positive value is known as depolarization; hyperpolarization is a change to more negative potentials. At the resting potential of the cell, most voltage-gated channels are closed. In response to a membrane de- polarization, the open probability of the channel is increased. This voltage-dependent activation may be followed by a further con- formational transition (inactivation) to an inactivated state in which the channel no

longer conducts ions. Recovery from inactivation occurs after a variable period following repolarization to the resting potential. Although most voltage-gated ion channels are opened by depolarization, a few types of voltage-gated channel are activated by hyperpolarization. Ligand-gated channels are opened (or more rarely closed) by binding of an appropriate ligand to a specific site on the channel protein, which induces a conformational change that allosterically opens the ion pore. The channel may open and close several times while the ligand remains bound to its receptor, but this intrinsic gating ceases on ligand dissociation. There are numerous different types of channel. For example, even among the inwardly rectifying K+ channels there are seven subfamilies, most of which have several members. In general, ion channels are named after their gating and/or selectivity properties. Single-channel currents summate to produce macroscopic currents The cell membrane contains many hundreds of ion channels. The macroscopic current (I) flowing through all ion channels of the same type is determined by the product of the number of channels in the membrane (N), the channel open probability (P), and the single-channel current (i); in other words, I = NPi. Disease-causing mutations may affect any or all of these parameters and thereby in- fluence the macroscopic current. Cell membranes also contain several different types of channel. The total current that flows across the cell membrane (the mem- brane current) represents the sum of the ion fluxes through all the different kinds of ion channel open in the membrane. If it is suffi- ciently large, the membrane current may cause a change in mem- brane potential. The size of this voltage change is given by Ohm's law (V = IR) and is therefore influenced by both the current amplitude (I) and by the membrane resistance (R) (which in turn reflects the number of open channels). Action potentials In excitable cells, a depolarizing stimulus may elicit an action potential—a transient change in membrane potential. For example, nerve axons and skeletal muscle fibres, the action potential results from the initial activation of voltage-gated Na+ channels followed shortly afterwards by activation of voltage-gated K+ channels. Because Na+ channels open rapidly on depolarization, there is an initial in- ward Na+ current. If this is greater than the outward current flowing through (voltage-independent) K+ channels which are open at the resting potential, it will produce a further depolarization. This acti- vates more Na+ channels and depolarizes the membrane even more. In this way, a regenerative increase in membrane potential is produced. The membrane is returned to its resting level by inactivation of the Na+ channels (which reduces the inward current) and the opening of K+ channels (which produces an outward, hyperpolarizing current). The potential at which the inward Na+ current exactly balances the outward current through resting K+ channels is known as the threshold potential. It is a critical potential: any increase in the Na+ current will elicit an action potential, while any reduction in the in- ward current (or increase in the outward current) will prevent ac- tion potential generation. Ion channel mutations may increase nerve or muscle excitability either by enhancing the inward current (as in hyperkalaemic periodic paralysis), or by reducing the outward cur- rent (as in some forms of long-QT syndrome). This will produce a larger depolarization, so that the threshold potential is reached more easily and a subsequent action potential is initiated. Other mutations produce a depolarizing block of action potential activity. This results from a maintained membrane depolarization of sufficient amplitude to inactivate the voltage-dependent Na+ channels. In some cells, additional types of ion channel contribute to the action potential—the ventricular action potential is mediated by voltage-dependent Na+ and Ca2+ channels, and at least four kinds of K+ channel. Several different kinds of K+ channel contribute to the repolarization of action potentials in mammalian neurons and chloride (Cl–) channels play an important role in the electrical ac- tivity of skeletal muscle. The functional importance of these different ion channels is exemplified by the fact that mutations in the genes that encode them produce a range of nerve and muscle diseases.

Synaptic potentials When a nerve impulse arrives in the presynaptic terminal it opens voltage-gated Ca2+ channels, producing a rise in the intracellular Ca2+ concentration ([Ca2+]i) that triggers the exocytosis of syn- aptic vesicles. The amount of transmitter released varies with [Ca2+]i and thus with the magnitude of the presynaptic Ca2+ current. In

 turn, this is influenced by the duration of the membrane depolar- ization and thus by the amplitude of the voltage-gated K+ current that underlies membrane repolarization. A reduction in the pre- synaptic K+ current therefore leads to excess transmitter release and postsynaptic hyperexcitability, as in episodic ataxia type 1 and ac- quired neuromyotonia. Conversely, a reduction in the presynaptic Ca2+ current is associated with reduced transmitter release, as oc- curs in Lambert–Eaton myasthenic syndrome when the density of presynaptic Ca2+ channels is decreased by receptor internalization induced by the binding of autoantibodies. Once released, the transmitter diffuses across the synaptic cleft and binds to receptors in the postsynaptic membrane. At the neuro- muscular junction, for example, acetylcholine (ACh) binds to the nicotinic acetylcholine receptor (AChR), and opens an intrinsic ion channel. The resulting synaptic current produces a depolariza- tion of the postsynaptic membrane (the endplate potential) which, if it is sufficiently large, triggers an action potential in the muscle fibre. A reduction in AChR density, as in myasthenia gravis, de- creases effective transmission, and leads to muscle weakness. Gain- of-function mutations in AChR may also induce myasthenia, by causing prolonged depolarization of the postsynaptic membrane and thereby Na+ channel inactivation. This depolarizing block is the basis of the slow-channel syndromes. Mutations in the voltage- gated Na+ channel of skeletal muscle may cause paralysis, or myotonia. In skeletal muscle, the action potential is conducted into the in- terior of the fibre via invaginations of the surface membrane known as the transverse tubules (T-tubules). Depolarization of the T-tubule membrane stimulates the opening of Ca2+-release channels (RyR) in the membrane of the sarcoplasmic reticulum (SR), the intracel- lular Ca2+ store. The T-tubule and SR membranes are not directly connected and the precise mechanism by which they interact is not fully understood. However, there is evidence that the α1-subunit of the voltage-gated Ca2+ channel in the T-tubule membrane acts as the voltage sensor for the Ca2+-release channels in the SR membrane. Mutations in the Ca2+-release channel of skeletal muscles cause ma- lignant hyperthermia and central core disease. The channelopathies This section provides brief descriptions of a selected range of channelopathies. Table 3.4.1 lists these diseases, the channels in- volved, their gene names, and chromosomal locations. The list is far from exhaustive. Additional details may be found elsewhere in the Oxford textbook of medicine or in the books and websites referenced at the end of this chapter. Neuronal channelopathies Epilepsy Many different ion channels have been implicated in the epilepsies, including both voltage-gated and ligand-gated channels. Channelopathies make up a major group of genes implicated in the epileptic encephalopathies, which are severe epilepsies typically beginning in infancy and childhood and associated with develop- mental slowing and often regression. The prototypic form of these disorders is Dravet syndrome (pre- viously known as severe myoclonic epilepsy of infancy) in which more than 80% of patients have mutations in the gene SCN1A, which encodes the α1-subunit of the voltage-gated Na+ channel. Seizures are often precipitated by fever, hot temperatures, or vac- cination. Recently, increasing numbers of patients with encephal- opathies due to other Na+ channel (SCN2A, SCN8A), K+ channel (KCNQ2, KCNT1), and Ca2+ channel (CACNA1A) genes have been identified. Ligand-gated ion channels, such as γ-aminobutyric acid (GABA) receptors and glutamate receptors, also cause epileptic en- cephalopathies. Most of these mutations arise de novo in the affected individual, but

parental mosaicism is becoming increasingly ap- preciated and is important for reproductive counselling regarding recurrence risk. An important, emerging picture is that many of the channelopathies are associated with a spectrum of epilepsies from self-limited (pre- viously called benign) epilepsies to severe phenotypes such as the encephalopathies. SCN1A mutations are found in 10–20% of large families with genetic epilepsy with febrile seizures plus (GEFS+). These families have marked phenotypic heterogeneity, ranging from febrile seizures in some individuals to more severe focal and gener- alized epilepsies in others. GEFS+ has also been linked to mutations in the β1-subunit of the voltage-gated Na+ channel (SCN1B). The presence of the β-subunit accelerates both the rate of inactivation, and the rate of recovery from inactivation, of the voltage-gated Na+ channel. Precisely how SCN1A and SCN1B mutations lead to GEFS+ remains unclear. Similarly, SCN2A is associated with the syndrome of benign familial neonatal-infantile epilepsy, while KCNQ2 and KCNQ3 are linked with benign familial neonatal epilepsy; both are mild self-limited disorders occurring in individuals of normal intel- lect (see next). Identification of a causative mutation is important as it may carry treatment implications. For example, in Dravet syndrome, in which loss-of-function SCN1A mutations are usual, Na+ channel blockers such as carbamazepine are contraindicated as they bring out and/ or exacerbate myoclonic seizures. In contrast, clinical observations suggest that Na+ channel blockers such as phenytoin and carbamaze- pine are effective in SCN2A and SCN8A encephalopathies in which gain-of-function mutations are seen. Benign familial neonatal convulsions Benign familial neonatal convulsions (BFNC) is characterized by neonatal convulsions within the first 7 days after birth that nor- mally show spontaneous remission by the third month of life. There is an increased risk of epilepsy in later life in 10 to 15% of individ- uals. Mutations in the voltage-gated K+ channel genes KCNQ2 and KCNQ3 are associated with BFNC. KCNQ2 and KCNQ3 associate in a heteromeric complex to form the M-channel. This channel plays a critical role in determining the electrical excitability of many neurons. It is slowly activated when the membrane is depolarized to around the threshold level for action potential firing, thereby hyperpolarizing the membrane back towards its resting level. This reduces neuronal excitability by limiting the spiking frequency and decreasing the responsiveness of the neuron to synaptic inputs. Some benign familial neonatal epi- lepsy (BNFC) mutations result in reduced channel density. Others alter the channel kinetics. Both are expected to lead to neuronal hyperexcitability, accounting for the epileptic seizures. Because the M-channel is a heteromer of KCNQ2 or KCNQ3, mutations in ei- ther gene will disrupt channel function and cause BNFC.

3.4 Ion channels and disease 249 Table 3.4.1 Examples of ion channel genes associated with disease Gene Chromosome location Protein Disease Neuronal diseases SCN1A 2q24 Voltage-gated Na+-channel α-subunit, Nav1.1 Dravet syndrome, epilepsy (GEFS+ type-2) SCN2A 2q23–q24.3 Voltage-gated Na+-channel α-subunit, Nav1.2 Benign familial infantile seizures SCN8A 12q13.3 Voltage-gated Na+-channel α-subunit, Nav1.6 Infantile epileptic encephalopathy SCN9A 2q24 Voltage-gated Na+-channel α-subunit, Nav1.7 Erythermalgia, paroxysmal extreme pain disorder, congenital indifference to pain SCN1B 19q13.1 Voltage-gated Na+-channel β-subunit Epilepsy (GEFS+ type-1) KCNA1 12p13 Voltage-gated K+ channel, Kv1.1 Episodic ataxia type-1 KCNQ2 20q13.3 Voltage-gated K+ channel Epilepsy (BNFS) KCNQ3 8q24 Voltage-gated K+ channel Epilepsy (BNFS) CACNA1A 19p13.1 Voltage-gated Ca2+ channel α-subunit (P/Q type) Episodic ataxia type-2, familial hemiplegic migraine, and spinocerebellar ataxia type-6 CACNB4 2q22–q23 Voltage-gated Ca2+ channel β4-subunit Juvenile myoclonic epilepsy Generalized epilepsy and praxis seizures CHRNA4 20q13.2–13.3 nACh-receptor α4-subunit Epilepsy (nocturnal frontal lobe epilepsy type-1) CHRNB2 1q21 nACh-receptor β-subunit Epilepsy (nocturnal frontal lobe epilepsy

type-3) GLRA1 5p32 Glycine receptor α1-subunit Hyperekplexia (startle disease) GJB1 Xq13.1 Connexin 32 Charcot–Marie–Tooth disease Cardiac muscle diseases SCN5A 3p21–24 Voltage-gated Na+-channel α-subunit Long-QT syndrome (LQT3), Brugada syndrome, congenital conduction defects, atrial fibrillation KCNQ1 11p15.5 Voltage-gated K+ channel α-subunit Long-QT syndrome (LQT1), short QT syndrome, atrial fibrillation (Romano–Ward syndrome, Jervall–Lange–Nielsen syndrome) KCNH2 7q35–36 Voltage-gated K+ channel α-subunit (HERG) Long-QT syndrome (LQT2), short QT syndrome KCNE1 21q22.1–q22.1 Voltage-gated K+-channel β-subunit (MinK) Long-QT syndrome (LQT5) Jervall–Lange–Nielsen syndrome KCNE2 21q22.1 Voltage-gated K+-channel β-subunit (MiRP1) Long-QT syndrome (LQT6), atrial fibrillation KCNJ2 17q24.3 Inwardly rectifying K+ channel (Kir2.1) Anderson syndrome, atrial fibrillation HCN4 15q24.1 Hyperpolarization-activated K+ channel Sick sinus syndrome CACNA1C 12p13.33 Voltage-gated ion channel Timothy syndrome RYR2 1q42.1–q43 Ca2+ release channel of cardiac SR Ventricular tachycardia Skeletal muscle diseases SCN4A 17q23–q25 Voltage-gated Na+-channel α-subunit HyperPP, PAM, paramyotonia congenita CACNA1S 1q32 Voltage-gated Ca2+ channel α-subunit (L-type) Hypokalaemic periodic paralysis Malignant hyperthermia KCNE3 11q13–14 Voltage-gated K+-channel β-subunit (MiRP2) Hypokalaemic periodic paralysis KCNJ2 17q23 Inward rectifier K+ channel, Kir2.1 Andersen syndrome CLCN1 7q35 Voltage-gated Cl– channel, ClC-1 Myotonia congenita, generalized myotonia RYR1 19q13.1 Ca2+-release channel of SR Malignant hyperthermia, central core disease CHRNA1 2q24–q32 nACh-receptor α1-subunit Slow-channel syndrome (SCS), fast-channel syndrome (FCS) CHRNB1 17p12–p11 nACh-receptor β-subunit SCS, nAChR deficiency syndrome CHRND 2q33–q34 nACh-receptor δ-subunit SCS, FCS CHRNE 17p13.1 nACh-receptor ε-subunit SCS, nAChR deficiency syndrome Kidney diseases KCNJ1 11q24 Inward rectifier K+ channel, Kir1.1 Bartter’s syndrome (type II) KCNJ10 1q23.2 Inward rectifier K+ channel, Kir4.1 SeSAME syndrome CLCNKB 1p36 Voltage-gated Cl– channel Bartter’s syndrome (type III) (continued)

250 SECTION 3 Cell biology Episodic ataxia type 1 Episodic ataxia type 1 (familial periodic cerebellar ataxia with myokymia) is an autosomal dominant disorder that causes ataxia accompanied by myokymia, nausea, vertigo, and headache. It re- sults from mutations in the voltage-gated K+ channel KV1.1, which is expressed in the synaptic terminals and dendrites of many brain neurons. These mutations either prevent the formation of functional channels or result in a reduced K+ current. This is expected to pro- long the neuronal action potential, inducing repetitive firing and excessive and unregulated transmitter release, and thereby produce the clinical symptoms of ataxia and myokymia. Familial hemiplegic migraine, episodic ataxia type 2, and spinocerebellar ataxia type 6 There are three human diseases with different phenotypes that are as- sociated with mutations in the same Ca2+-channel gene, CACNA1A. These are familial hemiplegic migraine (FHM), episodic ataxia type 2 (EA-2), and spinocerebellar ataxia type 6 (SCA-6). All three diseases result in progressive cerebellar atrophy, but they differ in the extent and rate of progression of neuronal degeneration, with SCA-6 showing the greatest atrophy, and FHM the least. Migraine-like symptoms also occur in all three diseases and are most severe in patients with FHM, who suffer transient hemiparesis. EA-2 and SCA-6 are also character- ized by ataxia and nystagmus. FHM is associated with missense muta- tions. In mice, these lead to an increase in the P/Q type Ca2+ current of cerebellar and cortical neurons and an enhanced tendency to cortical spreading depression, which may underlie the migraine. Startle disease (hyperekplexia) Glycine is the major inhibitory transmitter in the brainstem and spinal cord. It binds to a ligand-gated Cl– channel, producing an in- crease in Cl– permeability that reduces the membrane depolariza- tion and neuronal firing induced by excitatory neurotransmitters. The glycine receptor is a pentamer of

three α-subunits, which con- tain the glycine-binding site, and two β-subunits. In humans, two types of the α-subunit have been identified. Mutations in the gene encoding the α1-subunit of the glycine receptor give rise to startle disease (hyperekplexia). This is an autosomal dominant neuro- logical disorder characterized by muscle spasm in response to an un- expected stimulus. It manifests as facial grimacing, hunching of the shoulders, clenching of the fists, exaggerated jerks of the limbs and sudden falls. Startle disease mutations produce a dramatic decrease Gene Chromosome location Protein Disease CLCN5 Xp11.22 Voltage-gated Cl– channel, ClC-5 Nephrolithiasis (Dent's diseasea) SCNN1A 12p13 Epithelial Na+-channel α-subunit Pseudohypoaldosteronism (PHA-1) SCNN1B 16p13–p12 Epithelial Na+-channel β-subunit Liddle's syndrome, PHA-1, bronchiectasis (BESC) SCNN1G 16p13–p12 Epithelial Na+-channel γ-subunit Liddle's syndrome, PHA-1, BESC AQP2 12q13 Aquaporin 2 (water channel) Nephrogenic diabetes insipidus PDK1 16p13.3 Polycystin 1 (associates with PDK2) Polycystic kidney disease PDK2 4q22.1 TRPP2 channel (polycystin 2) Polycystic kidney disease Other diseases KCNJ11 11p15.1 ATP-sensitive K+ channel subunit, Kir6.2 Neonatal diabetes, congenital hyperinsulinaemia of infancy ABCC9 11p15.1 ATP-sensitive K+ channel subunit, SUR1 Neonatal diabetes, congenital hyperinsulinaemia of infancy KCNJ8 12p12.1 ATP-sensitive K+ channel subunit, Kir6.1 Cantu syndrome ABCC9 12p12.1 ATP-sensitive K+ channel subunit, SUR2 Cantu syndrome CFTR 7q31 CFTR Cl– channel Cystic fibrosis CLCN7 16p13 Voltage-gated Cl– channel, ClC-7 Osteopetrosis CNGA1 4p12–cen Cyclic nucleotide-gated channel α-subunit Retinitis pigmentosa STIM1 11p15.5 CRAC channel subunit Immunodeficiency and autoimmunity syndrome ORAI1 12q24 CRAC channel subunit Immunodeficiency and autoimmunity syndrome GJB2 13q11–q12 Connexin 26 Deafness (DFNA3 and DFNB1) Vohwinkel's syndrome GJB3 1p35.1 Connexin 31 Nonsyndromal sensineural deafness (DFNA2) Erythrokeratodermia variabilis GJB6 13q12 Connexin 30 Deafness (DFNA3) Ectodermal dysplasia GJA3 13q11 Connexin 46 Cataract (zonular pulverulent type-3) GJA8 1q21.1 Connexin 50 Cataract (zonular pulverulent type-1) BNFC, benign familial neonatal seizures; GEFS+, generalized epilepsy with febrile seizures plus; HyperPP, hyperkalaemic periodic paralysis; PAM, potassium-aggravated myotonia; PHA-1, pseudohypoaldosteronism type 1, BESC, bronchiectasis with or without elevated sweat chloride. a Dent's disease is now recognized to include X-linked recessive nephrolithiasis, X-linked hypophosphataemic rickets, and a renal tubular defect in Japanese children Table 3.4.1 Continued

 in glycine-activated currents. Because glycinergic interneurons are important for normal spinal cord reflexes, muscle tone, and the pat- tern of motor neuron firing during movement, this leads to excessive and uncontrolled movements.

Charcot–Marie–Tooth disease Charcot–Marie–Tooth disease type 1 (CMT1) causes progressive de- generation and demyelination of the peripheral nerves. It is genetic- ally heterogeneous, but the X-linked form of the disease results from mutations in the gap junction channel connexin 32 (Cx32). It shows incomplete dominant inheritance, with heterozygous females being affected less severely than hemizygous males. The phenotype may vary from mild, in which the patient has a normal gait, to a severe form which may necessitate the use of a walking stick or wheelchair. More than 100 mutations in CX32 have been identified. They fall into two main groups—those in which the protein never reaches the plasma membrane, and those where the protein reaches the membrane but forms channels with altered functional properties. The former give rise to a severe phenotype, whereas the latter may be associated with either mild or severe phenotypes, according to whether they partially or completely disrupt channel function. The Cx32 protein is primarily expressed in the Schwann cells of peripheral myelinated nerves, at the nodes of Ranvier and at Schmidt–Lanterman

incisures. In these regions, the myelin is not complete and there is a thin layer of cytoplasm between each of the enveloping turns of the Schwann cell. This suggests that Cx32 may serve as a short-cut pathway for nutrients and other substances moving to the innermost layers of the Schwann cell, and perhaps also to the axon itself. This might explain why loss of Cx32 function causes axonal degeneration and demyelination. Familial pain syndromes Mutations in the peripheral nerve voltage-gated Na+ channel Nav1.7 (SCN9A) cause familial pain disorders. Gain-of-function mutations produce inherited erythermalgia, paroxysmal extreme pain disorder (PEPD), and idiopathic small fibre neuropathy. Erythermalgia is characterized by episodes of erythema and burning pain of the lower legs and feet that usually are provoked by warmth or exercise. The pain can be extreme. PEPD is associated with severe pain triggered by bowel movements: it may be accompanied by nonepileptic seiz- ures and cardiac problems. These symptoms arise because Nav1.7 is expressed in nociceptive neurons and activating mutations enhance their excitability. By contrast, loss-of-function mutations in Nav1.7 lead to im- paired action potential transmission and a reduced ability to sense pain. Patients may not recognize they have hurt themselves as they feel no pain from bone fractures or walking on hot coals. A drug that inhibits Nav1.7 might be an effective therapy for chronic pain and is the subject of much current pharmaceutical research effort. Cardiac muscle channelopathies The ion channels that underlie the cardiac action potential differ in different regions of the heart (ventricle, atria, Purkinje cell, SA node, and so on), accounting for the fact that the action potentials in these regions have a different time course and duration. Mutations in the genes encoding these channels can cause a range of cardiac arrhythmias. Long-QT syndrome Long-QT syndrome is a congenital cardiac disorder associated with an abrupt loss of consciousness and sudden death from ventricular arrhythmia in children and young adults. It is characterized by an abnormally long-QT interval in the electrocardiogram, which re- flects the delayed repolarization of the ventricular action potential. This predisposes to torsade de pointes and ventricular fibrillation. The duration of the cardiac action potential is determined by the balance between the inward and outward currents flowing during the plateau phase. Prolongation of the action potential can therefore be caused by a persistent inward current or by a reduction in outward K+ currents. Several different cardiac ion channels are associated with long-QT syndrome, the most common being KCNQ1, KCNH2 (HERG), and SCN5A (Table 3.4.1). The IKs channel is a complex of two different proteins, KCNQ1 and minK. Likewise, IKr is a complex of HERG and Mirp1. Mutations in these four genes either abolish or mark- edly decrease the repolarizing K+ currents IKs and IKr, and are there- fore expected to prolong the cardiac action potential and increase the QT interval. Mutations in the cardiac muscle Na+ channel gene (SCN5A) also cause long-QT. These mutations affect Na+ channel inactivation, producing a sustained inward current that results in an increased action potential duration. The larger the component of non-inactivating current, the more severe the phenotype. In many cases, long-QT syndrome is not inherited but acquired. For example, drugs that block IKr or IKs currents prolong the cardiac action potential and induce long-QT syndrome. Among these are the antibiotic erythromycin, the class III antiarrhythmic agents such as sotalol, dofetilide, and quinidine (which selectively block IKr) and the antihistamine H1-receptor antagonists terfenadine and astemizole (which block HERG). In most people, terfenadine does not produce cardiac problems as it is rapidly broken down in the liver and its me- tabolite, terfenadine carboxylate, does not block IKr. However, if the activity of the P450 enzymes that break down terfenadine is impaired (due to liver disease or drugs such as ketoconazole and the macrolide antibiotics), there is a risk of torsade de pointes. Other cardiac arrhythmias Many other cardiac arrhythmias result from ion channel mutations. These include short QT syndrome, Brugada syndrome, Lev-Lenegré syndrome, Timothy syndrome, and atrial fibrillation. Short QT

syndrome is associated with a reduced QT interval and is caused by mutations in the K+ channels KCNH2, KCNJ2, and KCNQ1 that are believed that these lead to a gain of function. Brugada syndrome was initially identified as being due to mutations in the Na+ channel SCN5A: other channels have subsequently been implicated, although the most recent work has cast doubt on many such reports. It leads to right ventricular conduction abnormalities, ventricular fibrillation, and sudden cardiac death in young people. Lev-Lenegré syndrome is a progressive conduction disorder also caused by loss-of-function mutations in SCN5A. Timothy syndrome is characterized by multiorgan dysfunction, including severe arrhythmias, and is associated with high mor- tality. It is due to gain-of-function mutations in the Ca2+ channel CACNA1C, which lead a longer QT interval. Catecholaminergic ventricular tachycardia is a cardiac arrhythmia triggered by physical or emotional stress that can lead to syncope or sudden cardiac death. About half of cases are due to mutations in the

252 SECTION 3 Cell biology sarcoplasmic Ca2+ channel RYR2 which lead to increased intracel- lular Ca2+ release and thereby arrhythmia. Anderson syndrome is associated with mutations in the inwardly rectifying K+ channel KCNJ2. It is a complex multisystem disorder characterized by ventricular arrhythmia, periodic paralysis, and dysmorphic features of both the skeleton and face. Atrial channelopathies Atrial fibrillation is one of the most common arrhythmias, occurring in about 1% in the general population and increasing with age. However, it can also be caused by mutations in Na+ (SCN5A, SCN1B, SCN2B) and K+ channels (KCNQ1, KCNE2, KCNA5, KCNJ2, and KCNH2). These mutations generally cause loss of Na+ current or gain of K+ current and may result in shortening of action poten- tial duration and effective refractory period, which can precipitate atrial fibrillation. Of note is the case of a mutation in KCNQ1 (R14C) which causes a reduced K+ current only when the cell is exposed to stretch (experimentally achieved with exposure to a hypotonic solu- tion). This finding emphasizes the importance of genetic and envir- onmental interactions in the development of the disease. Rare mutations in the hyperpolarization-activated cyclic nucleotide-gated channel HCN4, which underlies the pacemaker current in sinoatrial node cells, lead to sick sinus syndrome. This is characterized by idiopathic sinus bradycardia and chronotropic in- competence. In some families, long-QT and torsade de pointes have also been seen. In addition, increased HCN4 expression may occur during cardiac hypertrophy and congestive heart failure, and con- tribute to the increased risk of arrhythmia. In addition to mutations in ion channel genes themselves, an increasing number of disorders have been found to associate with mutations in genes that dictate the density of ion channels in the membrane or regulate their function. For example, muta- tions in caveolin-3 or a1-syntrophin enhance SCN5A currents, so causing long-QT syndrome, and mutations in calsequestrin affect the extent of Ca2+ release through RYR2 function and give rise to catecholaminergic ventricular tachycardia. Skeletal muscle channelopathies Myasthenia gravis, slow-channel, fast-channel, and
AChR deficiency syndromes Myasthenia gravis is usually produced by autoantibodies directed against the nicotinic acetylcholine receptor (nAChR), as discussed elsewhere. These antibodies lead to loss of nAChR due to internal- ization and thus to a smaller endplate potential that fails to reach the threshold for action potential initiation. At least three different congenital myasthenic syndromes are pro- duced by mutations in the muscle nAChR channel. Slow-channel syndrome (SCS) mutations are found in all four subunits of the adult channel (α, β, δ, ε) and result in protracted channel activa- tion by acetylcholine. The increase in channel open probability pro- duces a prolonged synaptic current and endplate potential. Impaired neuromuscular transmission is thought to result from a combin- ation of three pathogenic mechanisms. First, temporal

summation of endplate potentials can occur at physiological rates of stimu- lation, leading to prolonged depolarization of the muscle mem- brane, inactivation of voltage-gated Na+ channels, and failure of muscle excitability. A similar ‘depolarization block’ is observed with acetylcholinesterase (AChE) inhibitors or with nAChR agonists like suxamethonium. Second, the prolonged endplate potential causes excess Ca2+ entry and activation of proteolytic enzymes, which may account for the progressive destruction of the postsynaptic neuro- muscular junction observed in SCS—loss of junctional nAChRs and destruction of the junctional folds has been reported. Abnormal channel openings in the absence of acetylcholine may also contribute to the ‘endplate myopathy’. Third, the slow-channel mutations give an increased propensity for the nAChR to enter a desensitized state in which it is unable to respond to acetylcholine. Fast-channel syndrome (FCS) is the converse of SCS: nAChR mu- tations shorten channel openings thereby reducing the endplate po- tential amplitude below that required to trigger action potentials. nAChR deficiency, the most common congenital myasthenic syn- drome, results from mutations (often in the ε subunit) that impair channel assembly and insertion into the plasma membrane. Mutations in genes that affect the clustering and/or density of nAChR at the synapse, such as AGRN, LRP4, MuSK, and DOK7, are another cause of congenital myasthenic syndromes, and mutations in the early steps of the N-glycosylation pathway may affect both channel assembly and insertion into the plasma membrane as well as AChR clustering. Acetylcholinesterase inhibitors ameliorate the symptoms of nAChR deficiency and FCS but exacerbate those of SCS. Patients with DOK7 and MuSK mutations show a dramatic response to sal- butamol whereas AChE inhibitors are detrimental, although the mechanism is unclear. Recently it has been found that patients with severe nAChR deficiency on treatment with cholinergic inhibitors respond very well to the addition of oral salbutamol or ephedrine. SCS often benefits from treatment with open channel blockers of nAChR, such as fluoxetine or quinidine. As expected, nAChR gen- etic disorders are unresponsive to immunotherapies. The periodic paralyses Hyperkalaemic periodic paralysis, paramyotonia congenita, and the potassium-aggravated myotonias result from mutations in the α- subunit of the human skeletal muscle Na+ channel. All are inherited as dominant traits and usually present within the first or second decade of life. Hyperkalaemic periodic paralysis (HyperPP) may occur spon- taneously, but attacks are commonly precipitated by exercise, stress, fasting, or eating potassium-rich foods. Paralysis is often preceded by signs of muscle hyperexcitability such as myotonia or fasciculations. The duration is variable (minutes to hours) and may be so severe that the patient is unable to remain standing. It is associated with a raised blood K+ concentration (5–7 mM). Paramyotonia congenita is pre- cipitated by cold and (in contrast to most classical myotonias) aggra- vated by exercise. In some patients, the myotonia may be followed by prolonged paralysis. Potassium-aggravated myotonia is charac- terized by myotonia without muscle weakness or paralysis. It can be distinguished from classical myotonias by the fact that the myotonia is exacerbated by a mild elevation of the plasma K+ concentration. All three types of disorder result from mutations in the α- subunit of the skeletal muscle Na+ channel (SCN4A), which dis- rupt Na+ channel inactivation. As a consequence, they produce a persistent inward current that causes a tonic depolarization of the muscle membrane (the larger the current, the greater the depolar- ization). The magnitude of the depolarization determines whether

 myotonia or paralysis occurs. A small depolarization causes mem- brane hyperexcitability by lowering the action potential threshold, whereas a large depolarization can lead to Na+ channel inactivation and thereby paralysis. It is still not understood how cold or an ele- vated plasma K+ level precipitate attacks. Myotonia Loss-of-function mutations

in the gene CLCN1 encoding the skel- etal muscle Cl– channel produce two forms of myotonia—autosomal dominant myotonia congenita (Thomsen's disease) and autosomal recessive generalized myotonia (Becker's disease). Clinical descrip- tions of the disease can be found in Chapter 24.19.3. In normal skeletal muscle, the Cl– conductance accounts for be- tween 70 and 80% of the resting membrane conductance. Mutations in CLCN1 that result in a loss of functional Cl– channels will therefore produce a marked increase in the input resistance of the muscle fibre. Consequently, muscle excitability will be enhanced (because a smaller Na+ current will be sufficient to trigger an action potential). The ele- vated input resistance also produces a reduced rate of action potential repolarization, which enhances muscle excitability. An important role of the muscle Cl– conductance is to counteract the depolarizing effect of K+ accumulation in the transverse tubular system that accompanies muscle activity. During an action potential, K+ ions leave the muscle fibre. In normal muscle, the amount of K+ entering the transverse tubular system during a single action potential is not sufficient to alter the membrane potential, because the tubular Cl– conductance is very high. But in myotonic muscle, the Cl– conductance is very low and a small rise in tubular K+ produces a significant depolarization fol- lowing an action potential. If several action potentials occur in rapid succession, summation of the after-depolarizations may be sufficient to trigger spontaneous action potentials and thereby myotonia. Mutations in CLCN1 give rise to both recessive and dominant forms of myotonia. This may be because the muscle Cl– channel is a dimer. In heterozygotes, mutant subunits might combine with wild-type sub- units to form heteromeric channels. The extent to which the mutant subunit reduced the function of the heteromeric channel would thus dictate the severity of myotonia. Total inactivation of the channel by a single mutant subunit (the dominant-negative effect) would produce dominant myotonia, whereas recessive myotonia might occur if the heteromeric channel was unaffected by the mutant subunit. Malignant hypothermia and central core disease Mutations in the ligand-gated Ca2+ channel of skeletal muscle cause malignant hyperthermia and central core disease. This channel me- diates Ca2+ release from the sarcoplasmic reticulum, allowing Ca2+ to enter the cytoplasm and activate the contractile proteins. It is also known as the ryanodine receptor (or RYR1) because it binds the al- kaloid ryanodine with high affinity. Malignant hyperthermia (MH) is one of the main causes of death due to anaesthesia. In susceptible individuals, common inhalation anaesthetics or depolarizing muscle relaxants trigger accelerated skeletal muscle metabolism, muscle contractures, hyperkalaemia, arrhythmias, respiratory and metabolic acidosis, and a rapid rise in body temperature (as much as 1°C every 5 min). It is thought that this is due to stimulation of Ca2+ release from the SR, which pro- duces a sustained increase in intracellular Ca2+. This activates both metabolic and contractile activity; the former results in respiratory and metabolic acidosis and the latter produces the elevation in body temperature. The syndrome can be treated with dantrolene sodium, which blocks Ca2+ release from the SR. Malignant hyperthermia is genetically heterogeneous and is not linked to RYR1 in all families. Central core disease (CCD) is an autosomal dominant, non- progressive myopathy that presents in infancy as proximal muscle weakness and hypertonia. Diagnosis is by muscle biopsy, which re- veals that regions of type 1 skeletal muscle fibres (known as 'central cores') are depleted of mitochondria and oxidative enzymes. The disease is often associated with a predisposition to malignant hyper- thermia and results from mutations in RYR1. Thus CCD and MH are allelic disorders of the same gene. It is not clear how the different phenotypes arise, especially because the same mutation can give rise to MH in some individuals and CCD in others. Because all CCD patients are MH-susceptible, it is possible that additional factors are necessary for the development of central core disease. Kidney channelopathies Liddle's syndrome Liddle's syndrome is a congenital form of salt-sensitive

hyperten- sion characterized by a very high rate of renal Na+ uptake despite low levels of aldosterone, secondary hypokalaemia, and metabolic acidosis. It is caused by gain-of-function mutations in the epithelial Na+ channel (ENaC). This channel consists of three subunits (α, β, γ), and disease-causing mutations have been identified in both the β- and γ-subunits. All are located in the C-terminus of the protein and result in constitutive channel hyperactivity. The increase in ENaC current causes enhanced Na+ uptake. This is accompanied by increased water uptake, thereby producing a chronic increase in blood volume and ultimately hypertension. An increased Na+ uptake also has secondary consequences: in particular, K+ secretion into the tubule lumen is stimulated because the apical membrane depolarizes and so increases the driving force for K+ ef- flux. In addition, more K+ enters the cell due to the enhanced activity of the Na+/K+-ATPase. This explains why excess ENaC activity in Liddle's syndrome is associated with hypokalaemia and, conversely, why reduced ENaC activity, as in pseudohypoaldosteronism type 1, is accompanied by hyperkalaemia. Treatment is a low-salt diet and K- sparing diuretics like amiloride that directly block the ENaC channel. Pseudohypoaldosteronism type 1 While gain-of-function mutations in ENaC cause enhanced Na+ uptake and hypertension, loss-of-function mutations produce salt- wasting, hypotension, and dehydration in newborns and infants. Pseudohypoaldosteronism type 1 results from loss-of-function mutations in the α, β, or γ ENaC subunits. The marked reduction in ENaC activity leads to decreased Na+ absorption by the kidney. This stimulates renin and aldosterone secretion, but salt reabsorp- tion cannot be augmented as ENaC is not functional. The high Na+ concentration in the tubular fluid causes water to be osmotically re- tained in the tubule lumen, leading to diuresis and dehydration. Gitelman's syndrome Gitelman's syndrome is the most common genetic cause of hypo- kalaemia and is an autosomal recessive condition typically caused by biallelic inactivating mutations in the SLC12A3 gene that codes for the thiazide-sensitive Na–Cl cotransporter (NCCT). See Chapter 21.2.2 for further discussion.

 Bartter's syndrome Bartter's syndrome generally presents in childhood with features including growth failure and mental retardation, polyuria, and poly- dipsia, associated with hypokalaemia and metabolic alkalosis. The syndrome is both phenotypically and genetically heterogeneous, and several subtypes have been distinguished. Antenatal Bartter's syndrome results from loss-of-function mu- tations in the genes encoding proteins involved in salt transport in the cells of the nephron. These include the inwardly rectifying K+ channel Kir1.1 (KCNJ1; Bartter's syndrome type II), the Na-K- 2Cl cotransporter (SLC12A1, Bartter's syndrome type I), and the voltage-gated Cl– channel CLC-Kb (CLCNKB, Bartter's syndrome type III). See Chapter 21.2.2 for further discussion. SeSAME syndrome Loss-of-function mutations in the inwardly rectifying K+ channel Kir4.1 (KCNJ10) give rise to SeSAME syndrome (also called EAST syndrome). This complex disorder is characterized by seizures, sen- sorineural deafness, ataxia, mental retardation, and electrolyte im- balance (e.g. hypokalaemia, hypomagnesaemia, metabolic acidosis). Kir4.1 is expressed in the kidney, inner ear, and glial cells. It is pos- tulated that K+ recycling in the distal convoluted tubule is mediated by Kir4.1 and that in its absence the Na+/K+-ATPase is inhibited, reducing Na+ uptake. This stimulates Na+ uptake in other regions of the kidney tubule, which leads to increased K+ and H+ resorption and thereby hypokalaemia and metabolic acidosis. Dent's disease Dent's disease describes a spectrum of related inherited disorders of renal function that result from mutations in the renal chloride channel gene, CLCN5. Different mutations can produce pheno- typically distinct syndromes (Table 3.4.1), which may involve low molecular weight proteinuria, hypercalciuria, hyperphosphaturia, nephrocalcinosis, and nephrolithiasis. ClC-5 is found in apical endosomes of kidney proximal tubule cells. Mouse models suggest that ClC-5 mutations

result in reduced uptake of protein (including parathyroid hormone) by the proximal tubules. This leads to im- paired metabolism of calciotropic hormones and ultimately to hyperphosphaturia and kidney stones. Nephrogenic diabetes insipidus Familial nephrogenic diabetes insipidus (NDI) results from im- paired water uptake by the kidney tubules. The diseases manifests within the first few weeks of life and is characterized by the excretion of large amounts of hypotonic urine and excessive thirst. In early infancy these may not be noticed and the disease is often recognized by signs of dehydration, such as poor feeding, poor weight gain, ir- ritability, and fever. In most cases, familial NDI is caused by a muta- tion in the vasopressin receptor, but in some families it results from loss-of-function mutations in the aquaporin 2 (AQP2) gene. AQP2 is expressed exclusively in the collecting duct of the kidney and plays a fundamental role in the production of a concentrated urine because it acts as a water channel. Vasopressin stimulates water uptake by causing the insertion of AQP2 channels into the apical membranes of the principal cells of the collecting duct, thereby enhancing water uptake. Loss-of-function mutations in AQP2 result in a dramatic re- duction in water channels, thereby accounting for the polyuria. Polycystic kidney disease Autosomal dominant polycystic kidney disease is characterized by the gradual development of multiple fluid-filled renal cysts that ul- timately lead to kidney failure. It is one of the most common in- herited human diseases and caused by mutations in the either the transient receptor potential polycystin 2 channel (TRPP2, PDK2) or polycystin-1 (PDK1). TRPP2 is Ca^{2+} permeable nonselective cation channel found in both the plasma membrane and several subcellular compartments where it appears to have different functions. PDK1 associates with TRPP2 to form a large receptor-channel complex. How the mutations cause the disease is poorly understood. Other channelopathies Cystic fibrosis Of all the channelopathies, the best known is probably cystic fibrosis (CF). Its clinical features are described in Chapter 18.10. Cystic fi- brosis is a recessively inherited disorder that results from mutations in an epithelial chloride channel known as the cystic fibrosis transmem- brane conductance regulator (CFTR). Although its primary sequence is highly homologous to that of the ATP-binding cassette transporters, it is now well established that CFTR functions as a chloride channel. It also regulates the activity of the epithelial Na^+ channel. All disease-causing CF mutations result in the complete absence or a marked reduction in CFTR function. Those which result in the total loss of channel activity, either because the protein does not reach the plasma membrane or because it is present but completely inactive, give rise to a severe form of the disease. Mutations that re- sult in a reduced Cl^- current are associated with a milder form of the disease. Compound heterozygotes carrying one allele with a severe mutation and another with a mild mutation will have significant re- sidual channel activity and therefore a mild form of the disease. Although a large number of mutations (more than 2000) have been identified in CFTR, it is uncertain how the loss of channel function gives rise to the clinical features of the disease, especially in the lungs. However, it is recognized that lack of Cl^- and HCO_3^- se- cretion leads to the accumulation of sticky mucous and increases the risk of bacterial infection. Insulin secretory disorders The pancreatic β-cell ATP-sensitive K^+ (K_{ATP}) channel consists of two types of subunit: a pore-forming subunit Kir6.2 (KCNJ11), and a regulatory subunit SUR1 (ABCC8). Loss-of-function mutations in either subunit cause congenital hyperinsulinaemia (CHI) whereas gain-of-function mutations lead to neonatal diabetes. This is because the K_{ATP} channel plays a crucial role in glucose-stimulated insulin secretion. When the plasma glucose level is low (less than 3 mM), the channel is open and keeps the β-cell membrane potential at a hyperpolarized level. When plasma glucose levels rise, increasing glucose uptake and metabolism by the β-cell, ATP levels rise causing K_{ATP} channels close. This produces a membrane depolarization that activates voltage-gated Ca^{2+} channels, increases Ca^{2+} influx, and so stimulates insulin release. Two classes of therapeutic

drugs modulate insulin secretion by interacting with KATP channels. Sulphonylureas inhibit channel activity and are used to enhance insulin secretion in patients with type 2 diabetes mellitus, whereas K-channel openers (e.g. diazoxide) activate KATP channels, hyperpolarizing the β-cell and preventing insulin release.

3.4 Ion channels and disease 255 CHI is characterized by unregulated insulin secretion and pro- found hypoglycaemia that presents at birth or within the first year of life. This is because CHI mutations result in loss of KATP channel activity, which causes continuous depolarization of the β-cell, per- sistent Ca2+ influx and thereby constitutive insulin secretion. Some patients respond to treatment with diazoxide, but in others the most effective treatment is resection of the pancreas (more than 90% is usual). Many patients develop diabetes in later life. Mutations that impair ATP inhibition and so increase KATP channel activity cause neonatal diabetes (ND), by holding the β-cell hyperpolarized and preventing Ca2+ influx and insulin secretion even when plasma glucose rises. Around 50% of ND patients have KATP channel mutations. All have diabetes, usually presenting within the first six months of life, which may be either permanent or exhibit a remitting-relapsing time course. These patients were once thought to have an unusually early form of type 1 diabetes and thus were treated with insulin. Recognition that they possess activating KATP channel mutations has enabled more than 90% of patients to switch to sulphonylurea therapy: these drugs close the open KATP channels so stimulating endogenous insulin secretion. Importantly, glucose homeo- stasis is improved on sulphonylurea therapy, being lower and showing less fluctuations than on insulin therapy, which suggests the risk of dia- betic complications will be lower. In addition to diabetes, some muta- tions that produce a severe reduction in ATP inhibition cause muscle weakness, motor and mental developmental delay, and hyperactivity (iDEND syndrome), and occasionally also epilepsy (DEND syn- drome). This is because KATP channels are also expressed in neurones. The motor symptoms are sometimes helped by sulphonylureas, but the cognitive benefits are less clear. Because of the marked clinical benefits of sulphonylurea therapy, it is advisable to test all patients with diabetes presenting before six months for KATP channel mutations. KATP channels are also found in the heart, where they are composed of Kir6.2 and SUR2A; and in smooth muscle where they comprise Kir6.1 and either SUR2A or SUR2B (which differ only in their final 42 amino acids). Mutations in Kir6.1 or SUR2 cause Cantu syndrome. This is characterized by congenital hypertrichosis, macrocephaly, a distinctive facial appearance, cardiomegaly, a patent ductus arteriosus and various other symptoms. How the mutations cause the phenotype is unclear. Nonsyndromic deafness About 70% of all cases of prelingual deafness are nonsyndromic. The disorder shows marked genetic heterogeneity, but in some families it results from loss-of-function mutations in the gene (GJB2) encoding the gap junction channel connexin 26. Both recessive and dominant mutations have been described. Connexin 26 is expressed in the cochlea, but the mechanism by which the lack of functional connexin 26 leads to hearing loss remains obscure. In some individuals, muta- tions in connexin 26 are associated with Vohwinkel’s syndrome or other skin abnormalities. Many patients also suffer from deafness. Cancer A wide variety of ion channels have been implicated in tumour growth and metastasis. This is hardly surprising given that ion channels are involved in multiple processes involved in tumourigenesis, including cell cycle progression, proliferation, volume regulation, and cell death. Although we are unaware of a cancer caused by an ion channel mu- tation, enhanced expression of numerous ion channels has been found in many different types of cancer. For example, voltage-gated Na+ channels are upregulated in breast, lung, and prostate cancer (among others) and their enhanced activity potentiates migration, invasion, and metastasis in vivo. Chloride channels are important for glioma in- vasion, and a natural peptide inhibitor (chlorotoxin) labels glioma cells and

is a potential future tool both for glioma detection and for targeting of therapeutic agents. The K+ channel Kv10.1 is ectopically expressed in more than 75% of human tumours, and in mice blockade of this channel slows tumour growth. In many cases, however, the extent to which changes in ion channel expression are the cause or consequence of cancer are not fully understood. A recent investigation shows that persistent changes in the cell membrane potential, determined by al- tered expression of ion channels, can lead to clustering of negatively charged lipid in the inner membrane leaflet and recruitment of the sig- nalling protein K-Ras, which enhances its ability to promote cell prolif- eration. It is still unclear if targeting ion channel expression or activity will be of therapeutic benefit. Nevertheless, changes in ion channel ex- pression may provide a useful diagnostic biomarker. Concluding remarks Numerous ion channels are now known to play important roles in human disease, and recognition that this is the case has had a pro- found influence on both diagnosis and therapy. Identification of a specific channel mutation can now be accomplished much more quickly than was possible only a few years ago, enabling newly pre- senting patients to diagnosed and (where possible) treated without undue delay. Indeed, channelopathies have provided several ex- amples of personalized medicine, where therapy is tailored to the patient's genetic constitution. A genetic diagnosis also enables testing of family members, leading to identification of mutation car- riers and those at risk of the disease. It is important to remember, however, that genetic counselling can be complex: even where a mu- tation is not detected in either parent, a second child may be born with the same mutation due to parental mosaicism. FURTHER READING Ashcroft FM (2000). Ion channels and disease. Academic Press, San Diego, CA. Ashcroft FM (2006). From molecule to malady. Nature, 440, 440. Imbrici P, et al. (2016). Therapeutic approaches to genetic ion channelopathies and perspectives in drug discovery. Front Pharmaco, 7, 121. Lehmann-Horn F, Jurkatt-Rott K (1999). Voltage-gated ion channel and hereditary disease. Physiol Rev, 79, 1317–72. National Center for Biotechnology Information. http://www.ncbi. nlm.nih.gov/ Online Mendelian Inheritance in Man (OMIM). http://www.ncbi.nlm. nih.gov/omim/ Ptáček LJ (2015). Episodic disorders: channelopathies and beyond. Ann Rev Physiol, 77, 475–9. Washington University, Neuromuscular Disease Center. http:// www.neuro.wustl.edu/neuromuscular/mother/chan.html Zheng J, Trudeau MC (2015). Handbook of ion channels. CRC Press, Boca Raton, FL. Zipes DP (2013). Cardiac electrophysiology: from cell to bedside. Saunders, Philadelphia, PA.

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