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Ion channel diseases

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Ion channels serve many functions apart from electrical signal transduction: chemical signalling (Ca^{2+} as a second messenger), transepithelial transport, regulation of cytoplasmic or vesicular ion concentration and pH, and regulation of cell volume. Therefore, ion channel dysfunction can cause diseases in many tissues. The list of human diseases known to be associated with defects in ion channels has grown considerably during the past years. This review gives a short overview of known channelopathies, and focuses in particular on recent findings and on channelopathies that have significantly advanced our physiological insight.

Ion channels provide pores for the passive diffusion of ions across biological membranes. They are often highly selective for a particular ionic species, leading to a classification into sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), chloride (Cl^-) and unspecific cation channels. The direction of net ion transport, which is associated with an electric current, depends on the electrochemical gradient for the relevant ionic species. These gradients are established by an interplay of active pumps, co-transporters and ion channels. Ion channels can close and open in a process called gating. This allows many types of regulation. Thus, there are ligand-gated channels (e.g. post-synaptic GABA- or glutamate-receptor channels), voltage-gated, swelling- or stretch-activated, and heat- or cold-activated channels. In addition, channels may be regulated by calcium, pH, phosphorylation and lipids. Many, but not all, channels are oligomers of identical or homologous pore-forming α subunits. They are often present in a complex with β and sometimes γ subunits, which may be essential for their function or may modulate their properties.

Channels reside not only in the external (plasma) membrane, but also in membranes of intracellular organelles such as the endoplasmic reticulum, endosomes, lysosomes and mitochondria. Gap junction channels connect the cytoplasm of adjacent cells and are formed by closely opposed hemichannels in their respective plasma membranes. While the role of ion channels in generating the electric currents (the basis of neuronal signalling) is probably known best, channels have many other functions. For instance, ion channels are crucial for the transepithelial transport of salt and water, for the regulation of cellular volume and pH, for the acidification of intracellular organelles, and (in particular in the case of Ca^{2+} channels), for chemical signalling. Hence, although many ion channel diseases affect the neuromuscular system and cause diseases such as epilepsy, ataxia, myotonia and cardiac arrhythmia, they may affect many other organs. Defects in transepithelial transport underlie, for example, cystic fibrosis and several forms of Bartter syndrome, mutations in ATP-sensitive K^+ channels severely affect insulin secretion, and mutations in endosomal and lysosomal Cl^- channels can cause kidney stones and osteopetrosis, respectively. As ion channels can be studied by electrophysiological techniques, the consequences of human channel mutations are often understood in considerable detail.

Mutations in ion channel genes may cause either a loss or a gain of channel function. Loss-of-function mutations in ion channels often lead to recessive disease, as is the case with *CFTR* mutations in cystic fibrosis (1) or with *CLCNKB* mutations in Bartter syndrome (2,3). However, as many ion channels are multimeric complexes, certain loss-of-function mutations may give rise to dominant-negative mutants. These can reduce channel function below the 50% level expected from non-interacting proteins in a heterozygous patient. Whilst such dominant-negative effects can reduce channel function down to one-quarter of wild-type with dimeric channels (e.g. CLC Cl^- channels), the effect can be much stronger (reduction up to one-sixteenth) with tetrameric channels (e.g. K_v K^+ channels). Depending on the presence or absence of dominant-negative effects, mutations in the same gene may result in recessive or dominant disease. An example is the muscle Cl^- channel ClC-1: its mutation can give either rise to recessive (Becker-type) or dominant (Thomsen-type) myotonia congenita (4–7). This distinction is not absolute. There are mutations with borderline dominant-negative effects that may result in dominant myotonia in some and recessive myotonia in other families (8). As a general rule, patients with recessive mutations (in a homozygous state) are more severely affected than (heterozygous) patients with dominant mutations, since the latter, but not the former, patients have residual channel

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function. In some cases, the more severe loss of channel function may lead to qualitatively new symptoms: patients heterozygous for dominant-negative mutations in the K^+ channel gene *KCNQ1* present with severe cardiac arrhythmia in the Romano–Ward variant of the long-QT syndrome, whereas the total loss of channel function resulting from homozygous recessive mutations additionally entails congenital deafness in the Jervell–Lange–Nielsen syndrome (9,10). In some cases, expression levels of currents do not tolerate even a 25–50% decrease in amplitude. For instance, mutations in *KCNQ2* and *KCNQ3* that lack a dominant-negative effect cause dominant neonatal epilepsy (benign familial neonatal convulsions, BFNC) by haploinsufficiency (11).

Gain-of-function mutations are most often associated with dominant inheritance of the disease. Mutations in various isoforms of voltage-dependent Na^+ channels cause paramyotonia, cardiac arrhythmia and epilepsy because they result in additional, late Na^+ currents due to defective inactivation (12–15). Mutations in the epithelial Na^+ channel ENaC that result in an increased plasma membrane expression cause dominant hypertension in Liddle syndrome (16,17).

The number of known ion channel diseases (channelopathies) has increased dramatically over the past decade (Table 1). Disease genes were identified by positional cloning [e.g. *CFTR* (1), *KCNQ1* (18), *CLCN5* (19) and *BSND* (20)], by candidate gene approaches [e.g. *CLCN1* (5)], by positional candidate approaches [e.g. *KCNQ2* (21,22) and *KCNQ4* (23)], or on the basis of phenotypes obtained from knockout mouse models [e.g. *CLCN7* (24)]. Two excellent comprehensive reviews on this topic were published three years ago (25,26). The present review will focus on recently identified ion channel diseases and on channelopathies that are particularly important for physiological understanding.

RENAL DISORDERS

The glomerula of the kidney filter ~125 ml of plasma per minute, retaining blood cells and plasma proteins in the capillaries, and allowing water, salts, organic solutes such as glucose and amino acids and also low-molecular-weight proteins to pass through into the $>1.2 \times 10^6$ renal tubules. Many components of the primary filtrate are reabsorbed as the fluid passes the tubular epithelium. This process depends on a complex interplay between ion channels, pumps and transporters.

Direct defects in renal transepithelial transport

Bartter syndrome is a group of closely related hereditary tubulopathies characterized by renal salt wasting, hypokalemic metabolic alkalosis and hyperreninemic hyperaldosteronism with normal blood pressure. Several clinical variants have been described, all of which follow an autosomal recessive trait: a severe antenatal form with or without deafness, and the classic Bartter syndromes that occur in infancy or early childhood. The renal salt loss in Bartter syndrome is caused by impaired transepithelial transport in the thick ascending limb of the loop of Henle. The molecules involved have been identified, and mutations in either component of this transport system can cause Bartter syndrome (Fig. 1: inset). Filtrated NaCl is taken up through the apically expressed Na–K–2Cl co-transporter NKCC2 (*SLC12A1*), which uses the Na^+ gradient across the membrane to transport Cl^- and K^+ into the cell. This transport protein is mutated in severe antenatal forms of Bartter syndrome (Bartter syndrome type I) without deafness (27). The K^+ ions must be recycled over the apical membrane by the K^+ channel ROMK/Kir1.1, and mutations in its gene (*KCNJ1*) are indeed the cause of Bartter syndrome type II (28). Na^+ leaves the cell actively via the basolateral (Na,K)ATPase. In contrast, Cl^- diffuses passively through basolateral ClC-Kb chloride channels (*CLCNKB*) (2), which need the recently identified β subunit barttin (*BSND*) for their transport to the surface (3). Whereas mutations in *CLCNKB* cause Bartter syndrome type III (2), mutations in *BSND* additionally lead to congenital sensorineural deafness in Bartter syndrome type IV (20). The role of barttin and ClC-K channels in the inner ear is discussed below.

Mutations of the epithelial Na^+ channel ENaC, a heteromeric complex of three homologous proteins with unknown stoichiometry, lead to either hereditary hypertension or hypotension. In the principal cells of the collecting duct, Na^+ enters the cell passively through apical ENaC channels. It is then extruded by the basolateral (Na,K)ATPase. ENaC is highly regulated by aldosterone and ADH. Because Na^+ absorption is accompanied by increased water retention, its pathophysiological increase leads to volume expansion and raises the blood pressure. In Liddle syndrome, a rare, severe form of autosomal dominant salt-sensitive hypertension with secondary hypokalemia and metabolic acidosis, specific mutations of the β or γ subunit of ENaC have been identified (16,17). Mutations in the β subunit affect a motif characterized by the amino acid sequence PPPxY. This interferes with the binding of ENaC to ubiquitin ligases that normally downregulate channel activity by stimulating channel internalization and degradation (29–31). The ensuing increased presence of ENaC in the apical membrane results in increased Na^+ reabsorption (gain of function) and hypertension. In contrast, mutations in the α, β, and γ subunits of ENaC that lead to a loss of function of channel activity are associated with autosomal recessive pseudohypoaldosteronism type 1 (PHA1) (32). This disorder is characterized by marked hypotension and dehydration of newborns and infants due to an excessive loss of Na^+ and water.

Defective renal tubular endocytosis leading to kidney stones

Dent's disease (X-linked hypercalciuric nephrolithiasis) is caused by mutations in *CLCN5* (19). This syndrome is characterized by low-molecular-weight proteinuria with a variable presence of hypercalciuria, hyperphosphaturia, nephrocalcinosis and kidney stones. *CLCN5* encodes a Cl^- channel (ClC-5) that is expressed in endosomes of the proximal tubules (33,34) (Fig. 2). By shunting the current of the electrogenic H^+–ATPase, ClC-5 is crucial for the efficient acidification of renal endosomes. As shown in a knockout mouse model (35), its loss of function severely reduces receptor-mediated and fluid-phase endocytosis, as well as the endocytotic retrieval of plasma membrane proteins. This also affects the apical endocytosis of parathyroid hormone and vitamin D, resulting

Table 1. Known ion channel diseases

Channel	Gene	Channel-forming unit/ligand	OMIM	Disease
Cation channels:				
CHRNA1/ACHRA	*CHRNA1*	α, ACh	100690	Myasthenia congenita
CHRNA4	*CHRNA4*	α, ACh	118504	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNB2	*CHRNB2*	β, ACh	118507	Autosomal dominant nocturnal frontal lobe epilepsy
Polycystin-2	*PKD2*	α	173910	Autosomal dominant polycystic kidney disease (ADPKD)
CNGA3	*CNGA3*	α, cGMP	600053	Achromatopsia 2 (color blindness)
CNGB1	*CNGB1*	β, cGMP	600724	Autosomal recessive retinitis pigmentosa
CNGB3	*CNGB3*	β, cGMP	605080	Achromatopsia 3
Sodium channels:				
$Na_v1.1$	*SCN1A*	α	182389	Generalized epilepsy with febrile seizures (GEFS+)
$Na_v1.2$	*SCN2A*	α	182390	Generalized epilepsy with febrile and afebrile seizures
$Na_v1.4$	*SCN4A*	α	603967	Paramyotonia congenita, potassium aggressive myotonia, hyperkalemic periodic paralysis
$Na_v1.5$	*SCN5A*	α	600163	Long-QT syndrome, progressive familial heart block type I, Brugada syndrome (idiopathic ventricular arrhythmia)
SCN1B	*SCN1B*	β	600235	Generalized epilepsy with febrile seizures (GEFS+)
ENaCα	*SCNN1A*	α	600228	Pseudohypoaldosteronism type 1 (PHA1)
ENaCβ	*SCNN1B*	β	600760	PHA1, Liddle syndrome (dominant hypertension)
ENaCγ	*SCNN1G*	γ	600761	PHA1, Liddle syndrome
Potassium channels:				
$K_v1.1$	*KCNA1*	α	176260	Episodic ataxia with myokymia
KCNQ1/K_vLQT1	*KCNQ1*	α	192500	Autosomal dominant long-QT syndrome (Romano–Ward) Autosomal recessive long-QT syndrome with deafness (Jervell–Lange–Nielsen)
KCNQ2	*KCNQ2*	α	602235	BFNC (epilepsy), also with myokymia
KCNQ3	*KCNQ3*	α	602232	BFNC (epilepsy)
KCNQ4	*KCNQ4*	α	603537	DFNA2 (dominant hearing loss)
HERG/ KCNH2	*KCNH2*	α	152427	Long-QT syndrome
Kir1.1/ROMK	*KCNJ1*	α	600359	Bartter syndrome (renal salt loss, hypokalemic alkalosis)
Kir2.1/IRK/KCNJ2	*KCNJ2*	α	600681	Long-QT syndrome with dysmorphic features (Andersen syndrome)
Kir6.2/K_{ATP}	*KCNJ11*	α	600937	Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
SUR1	*SUR1*	β	600509	PHHI
KCNE1/MinK/ISK	*KCNE1*	β	176261	Autosomal dominant long-QT syndrome (Romano–Ward) Autosomal recessive long-QT syndrome with deafness (Jervell–Lange–Nielsen)
KCNE2/MiRP1	*KCNE2*	β	603796	Long-QT syndrome
KCNE3/MiRP2	*KCNE3*	β	604433	Periodic paralysis
Calcium channels:				
$Ca_v1.1$	*CACNA1S*	α	114208	Hypokalemic periodic paralysis, malignant hyperthermia
$Ca_v1.4$	*CACNA1F*	α	300110	X-linked congenital stationary night blindness
$Ca_v2.1$	*CACNA1A*	α	601011	Familial hemiplegic migraine, episodic ataxia, spinocerebellar ataxia type 6
RyR1	*RYR1*	α	180901	Malignant hyperthermia, central core disease
RyR2	*RYR2*	α	180902	Catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia type 2
Chloride channels:				
CFTR	*ABCC7*	α	602421	Cystic fibrosis, congenital bilateral aplasia of vas deferens
ClC-1	*CLCN1*	α	118425	Autosomal recessive (Becker) or dominant (Thomsen) myotonia
ClC-5	*CLCN5*	α	300008	Dent's disease (X-linked proteinuria and kidney stones)
ClC-7	*CLCN7*	α	602727	Osteopetrosis (recessive or dominant)
ClC-Kb	*CLCNKB*	α	602023	Bartter syndrome type III
Barttin	*BSND*	β	606412	Bartter syndrome type IV (associated with sensorineural deafness)
GLRA1	*GLRA1*	α, glycine	138491	Hyperekplexia (startle disease)
GABAα1	GABRA1	α, GABA	137160	Juvenile myoclonus epilepsy
GABAγ2	*GABRG2*	γ, GABA	137164	Epilepsy
Gap junction channels:				
Cx26	*GJB2*		121011	DFNA3 (autosomal dominant hearing loss) DFNB1 (autosomal recessive hearing loss)
Cx30	*GJB4*		605425	DFNA3
Cx31	*GJB3*		603324	DFNA2
Cx32	*GJB1*		304040	CMTX (X-linked Charcot–Marie–Tooth neuropathy)

The third column classifies channel proteins into α, β, and γ subunits, where α subunits are always directly involved in pore formation. Several β subunits are only accessory (i.e. do not form pores), as is the case, for example, with SCN1B and barttin. Others (e.g. of ENaC and GABA receptors) participate in pore formation. For ligand-gated channels, the ligand is given. Note that GABA and glycine act from the extracellular side, whereas cGMP is an intracellular messenger.

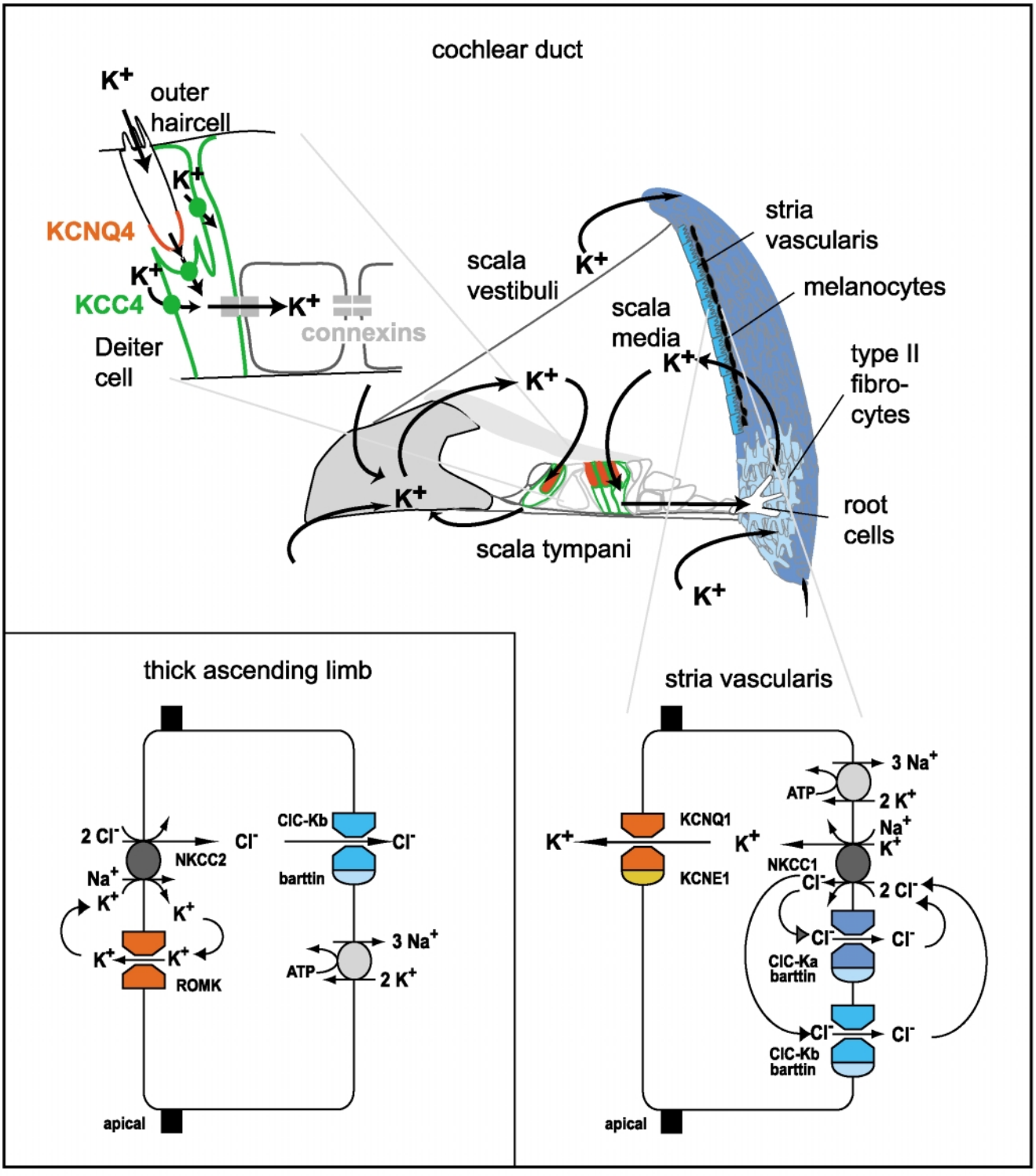

Figure 1. Transport pathways in the inner ear and in the kidney (thick ascending limb). The main diagram shows a cochlear duct, highlighting the proposed K^+ ion recycling pathways. Hearing depends on a high K^+ concentration (150 mM) bathing the apical membranes of sensory hair cells. During sound stimulation, K^+ enters the hair cells via apical mechanosensitive cation channels. K^+ exits from outer hair cells, probably through KCNQ4 K^+ channels. K^+ is then taken up via the K–Cl co-transporter KCC4 by supporting Deiters cells (shown in detail at top left). K^+ passes fibrocytes of the lateral wall through gap junctions to the stria vascularis, where it is pumped into the endolymph. In strial marginal cells (magnified below), basolateral NKCC1 raises intracellular K^+ concentration. Parallel ClC-Ka/barttin and ClC-Kb/barttin channels recycle Cl^-. K^+ exits through apical channels containing KCNQ1 subunits and KCNE1 subunits. Loss of KCNQ1, KCNE1, NKCC1 or barttin causes deafness in humans and mice. Neither loss of ClC-Ka nor of ClC-Kb alone entails deafness. In cells of the renal thick ascending limb (inset), apical NKCC2 co-transporters driving Cl^- uptake require ROMK to recycle K^+. Cl^- exits through channels containing ClC-Kb α subunits and barttin β subunits. Mutations in all four genes cause Bartter syndrome.

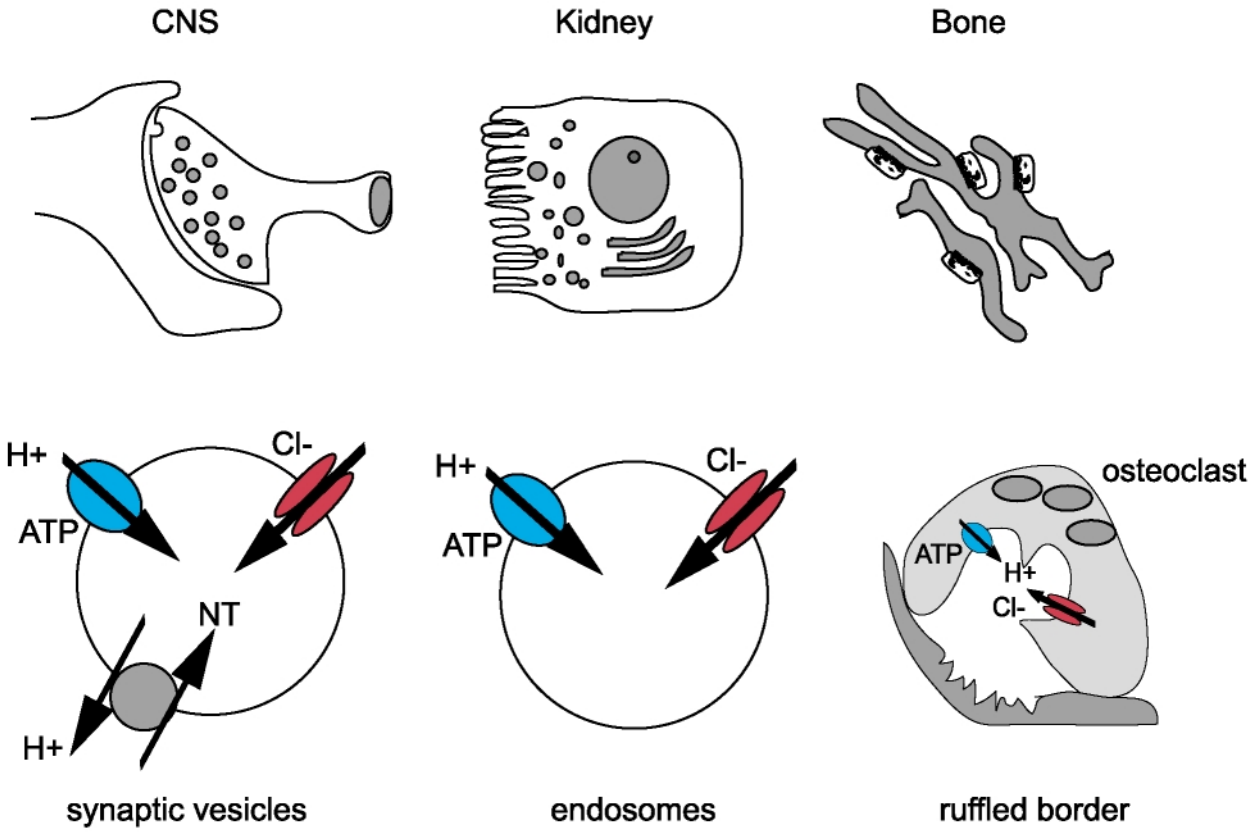

Figure 2. Chloride channels play a major role in acidifying synaptic vesicles, endosomes and lysosomal compartments. Intracellular chloride channels such as ClC-3 are present in synaptic vesicles, where they contribute to their acidification. The electrochemical H^+ gradient is used to load synaptic vesicles with neurotransmitters (NT). By shunting the current of the electrogenic H^+–ATPase, ClC-5 is crucial for the efficient acidification of renal endosomes. Loss of ClC-5 leads to Dent's disease, which is characterized by low-molecular-weight proteinuria with variable presence of hypercalciuria, hyperphosphaturia, nephrocalcinosis and kidney stones. ClC-7 provides the chloride conductance required for efficient proton pumping by the H^+–ATPase of the osteoclast ruffled border. Loss of function leads to a defect in bone degradation, resulting in osteopetrosis.

in secondary disturbances of renal phosphate and calcium handling (35).

Formation of renal cysts

In autosomal dominant polycystic kidney disease (ADPKD), the structure of the kidney is progressively destroyed by cysts that develop from renal tubules. This process ultimately leads to renal failure in 50% of affected patients. Mutations in two different genes have been identified in ADPKD: *PKD1* and *PKD2*, encoding the membrane proteins polycystin-1 (36,37) and polycystin-2 (38), respectively. Polycystin-2 shares structural features with the transient receptor potential (TRP) channel superfamily. It was speculated that polycystin-1 is essential for the translocation of polycystin-2 to the plasma membrane, where a complex of both proteins is thought to form a cation-selective ion channel (39). However, an alternative view is that polycystin-2, which is abundantly expressed in the endoplasmic reticulum, is a calcium-activated, high-conductance ER channel that is permeable to divalent cations and may act as a calcium release channel (40). The mechanism by which mutations in these proteins lead to cysts is still obscure (41). Knockout mouse models show several malformations (42,43), and it was concluded that polcystin-2 is involved in determining the right–left axis (44).

ENDOCRINE DISORDERS

ATP-sensitive K^+ channels of pancreatic β cells are formed by pore-forming α subunits (Kir6.2, encoded by *KCNJ11*) and associated sulfonylurea receptors (SUR1). They are inhibited by intracellular ATP, thereby linking their activity to the metabolism of the cell. When blood glucose rises, the uptake and metabolism of glucose leads to an increase of the intracellular ATP concentration in β cells. The ensuing closure of K_{ATP} channels results in membrane depolarization, activation of voltage-dependent Ca^{2+} channels, a rise in intracellular Ca^{2+}, and the exocytosis of insulin-containing granules. The associated transmembrane protein SUR1 is necessary for the surface expression of the channel (45), and is important for its regulation. Moreover, it is the target for oral antidiabetics such as glibenclamide and other sulfonylureas, which increase insulin secretion by inhibiting K_{ATP} channels. Mutations in either *KCNJ11* or *SUR1* underlie familial persistent hyperinsulinemic hypoglycemia of infancy (PHHI) (46,47). PHHI is an autosomal recessive disorder that usually manifests at birth or within the

first year of life. The K^+ channel opener diazoxide is sometimes used to treat PHHI.

BONE DISEASES

Mutations in the Cl^- channel gene *CLCN7* are associated with a severe autosomal recessive form of osteopetrosis (24), as well as with less severe, autosomal dominant osteopetrosis (48). ClC-7 resides in membranes of late endosomes and lysosomes (24), and thus occurs downstream from ClC-5 (33,35) in the endocytotic pathway. In osteoclasts, it is inserted together with the H^+–ATPase into the ruffled border (Fig. 2). This specialized membrane acidifies the bone resorption lacuna. The disruption of ClC-7 in mice leads to a severe osteopetrotic phenotype (24). Although osteoclasts are present in normal numbers, they fail to resorb bone because they cannot acidify the lacuna (24). Thus, similar to the role of ClC-5 in the acidification of proximal tubule endosomes (35), ClC-7 may be needed to balance the current of the electrogenic H^+–ATPase. This model is supported genetically by the identification of mutations in the a3 subunit of the H^+–ATPase in osteopetrotic patients (49,50), as well as in osteopetrotic *oc* mice, which lack the a3 subunit. In addition to the osteopetrotic phenotype, ClC-7 KO mice show severe retinal and central nervous system (CNS) degeneration (24). This may also apply for humans with the recessive, but not with the less severe dominant, form of *CLCN7* osteopetrosis.

NEUROLOGICAL DISORDERS

Epilepsy and ataxia

Ion channels have key functions in the nervous system, including the generation, repression and propagation of action potentials. The opening of Na^+ channels depolarizes neurons, while the opening of K^+ channels will lead to hyperpolarization. The situation is more complex with Cl^- channels, because the cytoplasmic chloride concentration depends upon the cell type, and changes during development. Thus, an opening of Cl^- channels may lead to a hyperpolarization (as in most neurons of the adult CNS) or to a depolarization (as in early development). Given the very large transmembrane gradient of Ca^{2+}, Ca^{2+} currents will always be depolarizing. However, the role of Ca^{2+} as a second messenger is more important under most circumstances.

Taking these considerations into account, loss-of-function mutations in neuronal K^+ or Cl^- channels, or gain-of-function mutations in neuronal Na^+ channels, should give rise to hyperexcitability and perhaps epilepsy. While this indeed turns out to be true in some cases, it should be borne in mind that the systemic effect depends on the particular neuronal circuitry that is affected. For instance, ion channel mutations leading to a selective hyperexcitability of inhibitory interneurons are expected to rather decrease CNS excitability.

Although K^+ channel defects were long suspected to underlie some forms of epilepsy, this was proven only in 1998, when it was shown that mutations in *KCNQ2* and *KCNQ3* underlie benign familial neonatal convulsions, a generalized epilepsy of the newborn (21,22,51). KCNQ2 and KCNQ3 are neuron-specific K^+ channels that are broadly expressed in the CNS, where they assemble to heteromeric channels (11,52). KCNQ2/KCNQ3 heteromers are a molecular correlate of the M current (53). This current was first described in sympathetic neurons as a non-inactivating K^+ current that could be inhibited by muscarinic stimulation (hence its name 'M current') (54). M currents are involved in regulating the subthreshold excitability of neurons and their responsiveness to synaptic inputs. This physiological, extremely sensitive regulation of neuronal excitability probably explains why a small loss of M currents suffices to cause epilepsy (55). From *in vitro* studies, it was concluded that mutations found in BFNC reduce current amplitudes by merely 25% (11). Interestingly, the homozygous knockout of *KCNQ2* in mice is lethal, and heterozygous animals have a reduced seizure threshold (56). Recently, a particular mutation in the voltage sensor of KCNQ2 was shown to lead to neonatal epilepsy with myokymia (involuntarily contractions of skeletal muscles), pointing to a role of M currents in motor neuron control (57). A dominant form of episodic ataxia that is accompanied by myokymia was previously shown to be caused by mutations in the Kv1.1 K^+ channel (encoded by *KCNA1*) (58). This K^+ channel is strongly expressed in myelinated peripheral nerves and cerebellar interneurons, where it contributes to the repolarization of action potentials.

Mutations in pore-forming α and accessory β subunits of voltage-gated Na^+ channels of the CNS were found to underlie other forms of epilepsy (59–61). Mutations in the SCN1A α subunit (59) and in the SCN1B β subunit (60) cause generalized epilepsy with febrile seizures (GEFS+), while mutations in another α-subunit isoform (SCN2A) (61) yield a somewhat different clinical picture (generalized epilepsy with febrile and afebrile seizures). Similar to previous findings with skeletal muscle Na^+ channel mutations, for example in periodic paralysis (12), the mutant channels do not inactivate properly (15). Mutations in the Ca^{2+} channel gene *CACNA1A* (encoding $Ca_v2.1$) can cause ataxia and migraine (62,63), and this gene may also be associated with epilepsy (64). Mutations in another channel type whose opening leads to depolarization, namely two different subunits of the nicotinic acetylcholine receptor, have also been shown to be associated with epilepsy (65,66). Although the mutants have been studied in heterologous expression systems, the mechanism by which they lead to autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is incompletely understood (67).

Rather surprisingly, no unambiguous association with human genetic disease has been established so far for the major class of CNS excitatory neurotransmitter receptors, the glutamate receptors. The main inhibitory neurotransmitters, GABA and glycine, exert their fast inhibitory effect through ligand-gated Cl^- channels: the $GABA_A$ and glycine receptors. Because intracellular Cl^- is usually below its electrochemical equilibrium in adult neurons, opening of these receptors leads to a hyperpolarizing Cl^- influx. The sedative and anxiolytic effects of benzodiazepines depend on a modulatory upregulation of $GABA_A$ receptor activity. Only recently, two $GABA_A$ receptor subunit genes were found to be affected in epilepsy. Mutations in the γ_2 subunit of the $GABA_A$ receptor (*GABRG2*) were identified in childhood absence epilepsy and febrile seizures (68), as well as in generalized epilepsy with febrile seizures (GEFS+) (69).

A mutation of *GABRA1*, which encodes the α_1 subunit of the $GABA_A$ receptor, was recently associated with an autosomal dominant form of juvenile myoclonus epilepsy (70).

Mutations of the α_1 glycine receptor cause autosomal dominant hyperekplexia (startle disease) (71), which is characterized by marked muscular hypertonia in infancy and a grossly exaggerated response to unexpected stimuli. As the electrophysiological effect of GABA and glycine depends on the intracellular Cl^- concentration, one may speculate that mutations in transporters involved in intracellular Cl^- concentration regulation may also affect neuronal excitability. In fact, a locus for rolandic and idiopathic generalized epilepsy maps close to KCC3, a K–Cl co-transporter that is expressed in the CNS. Like other KCCs, it is expected to contribute to postsynaptic inhibition by lowering $[Cl^-]_i$. However, no mutations were found in *SLC12A6*, the gene encoding KCC3, in the linked families (72). In contrast, the disruption in mice of the neuronal-specific isoform KCC2 caused severe motor deficits due to defective GABA- and glycine-mediated synaptic inhibition, and led to early postnatal death (73). Mice with an incomplete gene disruption survived for a couple of weeks and displayed severe seizures (74).

Retinal diseases

Several retinal diseases are caused by ion channel mutations. One of the many genes mutated in retinitis pigmentosa (75,76) is the Ca^{2+} channel gene *CACNA1F*, which encodes the $Ca_v1.4$ isoform. Mutations in different subunits of cGMP-gated cation channels, which play crucial roles in the signal transduction of photoreceptors, are associated with certain forms of color blindness (achromatopsia) (77,78). Photoreceptor degeneration was observed in mouse models with disrupted Cl^- channel genes encoding ClC-2 (79), ClC-3 (80) or ClC-7 (24). No human diseases corresponding to the first two mouse models have been described so far. However, the retinal degeneration is likely to occur also in osteopetrotic patients who carry ClC-7 mutations on both alleles (24).

Deafness

Hearing loss is the most common sensory defect in humans. There are a large number of monogenic forms that have yielded considerable insight into the physiology of hearing (81). Several deafness genes affect the ionic homeostasis of the inner ear. The fluid surrounding the upper surface of hair cells, the endolymph, has a high K^+ and low Na^+ concentration and is maintained at a high resting potential of around +100 mV. This ionic composition and voltage depend on active transport processes in a specialized epithelium, the stria vascularis (Fig. 1). The unique composition of the endolymph is needed because the apical mechanosensitive channels of sensory hair cells function as K^+ channels. Thus, both the influx as well as the efflux of K^+ can occur purely passively, avoiding a direct input of energy that would be necessary to drive the (Na,K)ATPase if Na^+ ions were used instead of K^+. The sound-induced relative movement of the basilar and tectorial membrane deflects the cilia of sensory hair cells and opens mechanosensitive channels. The resulting K^+ influx depolarizes the hair cell, leading to the exocytosis of synaptic vesicles. K^+ leaves outer hair cells presumably through KCNQ4 K^+ channels at the basolateral side (Fig. 1) (82). *KCNQ4* is mutated in patients with autosomal dominant progressive hearing loss (DFNA2) (23). Most human mutations exert a dominant-negative effect on coexpressed wild-type KCNQ4 subunits (23). After leaving outer hair cells, K^+ must be removed, partially by uptake into Deiters cells. This uptake probably occurs through the K–Cl co-transporter KCC4 (*SC12A7*), which is highly and specifically expressed in these supporting cells (83). In the inner ear potassium-recycling model (Fig. 1), K^+ then diffuses through a gap junction system connecting Deiters cells to adjacent epithelial cells. K^+ further passes through a distinct fibrocyte gap junction system to the stria vascularis. At least three connexin genes, *GJB2*, *GJB3* and *GJB6*, all of which are expressed in this gap junction system, are involved in human genetic deafness (84–87). K^+ is then pumped into the marginal cells of the stria vascularis by the combined activity of the (Na,K)ATPase and the Na–K–2Cl co-transporter NKCC1. Mice lacking NKCC1 are deaf owing to defective endolymph secretion (88–90). To allow efficient uptake of K^+, Cl^- ions taken up by the co-transporter have to be recycled across the basolateral membrane, in a process resembling the apical K^+ recycling in the renal thick ascending limb (Fig. 1: inset). We now know that this recycling occurs through ClC-Ka/barttin and ClC-Kb/barttin Cl^-channels (3). Mutations in the β subunit barttin lead to both renal salt loss and deafness in Bartter syndrome type IV (20), because it is a common subunit of ClC-Ka and ClC-Kb. In contrast, symptoms in Bartter syndrome type III are restricted to renal salt loss, because the lack of functional ClC-Kb can be compensated by ClC-Ka/barttin channels in the inner ear, but not in the kidney. K^+ is then secreted into the endolymph through apical KCNQ1/KCNE1 K^+ channels. Homozygous loss-of-function mutations in either gene cause the Jervell–Lange–Nielsen syndrome, which is characterized by cardiac arrhythmia associated with congenital deafness (91–93).

CARDIAC ARRHYTHMIAS

Each heartbeat is initiated by a depolarization that begins in a group of specialized pacemaker cells and then spreads through the heart. The 'action potential' of cardiac myocytes is extremely long compared with that of neurons, since a continuous influx of calcium during the plateau phase is needed for cardiac contraction. As in neurons, the fast initial depolarization is mainly mediated by voltage-gated Na^+ channels, although the heart uses a different isoform ($Na_v1.5$, encoded by *SCN5A*). Mutations in *SCN5A* (94) underlie one form of the long-QT syndrome, a severe cardiac arrhythmia associated with a prolonged QT interval in electrocardiograms. The incomplete inactivation of mutant channels cause late, depolarizing Na^+ currents (14). K^+ channels are responsible for the repolarization of the cardiac action potential, as in neurons. There are distinct contributions from several K^+ channels that display different voltage-dependences and kinetics. For instance, the extremely slow voltage activation of KCNQ1/KCNE1 heteromers (95,96) is important for these exceedingly long action potentials. Mutations in several genes encoding components of the repolarizing K^+ current have been

implicated in long-QT syndrome and other cardiac arrhythmias: *KCNQ1* (18), *HERG* (97), *KCNE1* (98), and *KCNE2* (99). Dominant-negative mutations in *KCNQ1* underlie the dominant Romano–Ward syndrome, whereas the total loss of function with mutations on both alleles additionally causes deafness in the Jervell–Lange–Nielsen syndrome (see above). The same holds true for its β subunit KCNE1. A K^+ channel (Kir2.1) is also involved in long-QT syndrome with dysmorphic features (Andersen syndrome) (100). Mutant Kir2.1 (KCNJ2) channels exert a dominant-negative effect on wild-type currents upon heterologous expression (100). Andersen syndrome usually occurs sporadically or follows an autosomal dominant trait. It is characterized by periodic paralysis, cardiac arrhythmia, and features such as short stature, scoliosis, clinodactyly, hypertelorism, small mandible and macrocephaly.

A different form of cardiac arrhythmia, catecholaminergic polymorphic ventricular tachycardia (also known as stress-induced polymorphic ventricular tachycardia), is caused by mutations in the intracellular calcium release channel ryanodine receptor 2 (RYR2) (101). Mutations in the same channel gene (*RYR2*) can cause arrhythmogenic right ventricular dysplasia type 2 (ARVD), an autosomal dominant cardiomyopathy, characterized by partial degeneration of the myocardium of the right ventricle, electrical instability and sudden death (102).

DISTURBANCES OF SKELETAL MUSCLE EXCITABILITY

The mammalian muscle is innervated by cholinergic synapses at motor endplates. Binding of acetylcholine to the nicotinic acetylcholine receptor (CHRNA1) leads to postsynaptic depolarization due to Na^+ influx. Mutations in *CHRNA1* resulting in prolonged channel activation are associated with congenital myasthenic syndromes (103). Rapsyn is critically involved in concentrating acetylcholine receptors in the postsynaptic membrane. Mutations in its gene cause endplate acetylcholine receptor deficiency and a myasthenic syndrome in humans (104). Depolarization at the motor endplate activates extrasynaptic voltage-gated Na^+ channels, resulting in an action potential, calcium release (mainly from intracellular stores) and muscle contraction. Mutations in the α subunit of the skeletal muscle isoform $Na_v1.4$ SCN4A were identified in paramyotonia congenita (105) and in hyperkalemic (106) and hypokalemic paralysis (107). Again, the underlying pathophysiological mechanism is mostly a defect in inactivation (12). Hypokalemic paralysis was also found to be associated with mutations in *CACNA1S* (108), which encodes the dihydropyridine receptor Ca^{2+} channel $Ca_v1.1$. Mutations in this gene were associated with malignant hyperthermia (109). Mutations in the ryanodine receptor gene *RYR1*, which encodes an intracellular calcium release channel, also cause malignant hyperthermia and the related central core disease (110–112).

Whereas neuronal action potentials are repolarized predominantly by K^+ channels, Cl^- conductance plays a major role in skeletal muscle. ClC-1 is the major skeletal muscle Cl^- channel. Mutations in *CLCN1*, encoding ClC-1, lead either to autosomal recessive (Becker myotonia) or, in the case of dominant-negative mutations, to autosomal dominant myotonia (Thomson myotonia) due to defective muscle relaxation after voluntary contraction (4–8). Recently, the MinK-related peptide 2 (MiRP2/KCNE3) was shown to form K^+ channels in skeletal muscle with Kv3.4/KCNC4. Mutations in *KCNC4* were proposed to underlie periodic paralysis in some patients (113).

CONCLUSIONS

The first ion channel was cloned in 1982 (114,115). Since then, advances in molecular biology and genetics have led to the discovery of many other ion channel genes. Some genes were in fact identified by positional cloning, such as that encoding CFTR, the cAMP-activated channel mutated in cystic fibrosis (1). While the pathophysiology of channelopathies is often known in considerable detail, because ion channels and their mutants can be studied by highly sensitive and elaborate biophysical techniques (even as single molecules in the patch-clamp technique), cystic fibrosis is an example of a disease whose complex pathophysiology remains incompletely understood 13 years after identification of the underlying gene.

Although many people associate ion channels only with excitable tissues, their function is not at all restricted to neurons or muscle. The important, and at first surprising, functions of ion channels in other tissues are now evident from human channelopathies and mouse knockout models. Dysfunction of ion channels can cause a broad spectrum of symptoms, ranging from hypertension (17) to endocrine disorders (46), kidney stones (19,35), and even dysmorphic features (24,100). More surprises are likely to come.

How does the identification of the genetic basis of a human disease benefit the individual patient? One obvious way is the development of diagnostic tests for genetic screening and prenatal diagnosis. Furthermore, ion channels mutated in human disease may be excellent targets for drug intervention—often in patients which do not carry a mutation in the respective gene. An excellent example is the identification (21,22,51) of the *KCNQ2* and *KCNQ3* K^+ channel subunits as the genes underlying a rare human neonatal epilepsy, BFNC. It turned out that retigabine, a novel antiepileptic drug that is in clinical trials, is a rather specific activator of precisely this channel (116,117). As another example, the discovery that mutations in the ClC-7 Cl^- channel cause osteopetrosis (24) suggests that specific inhibitors of this channel might be useful to treat the much more common osteoporosis. Thus, ion channel diseases have also fostered considerably our understanding of physiological and pathophysiological processes, and will contribute not only to a better diagnosis of genetic disease, but also to more generally applicable, novel therapeutic approaches.

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