

Review

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Neurological potassium channelopathies

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Summary

Potassium channel dysfunction has been implicated in a variety of genetic and acquired neurological disorders that are collectively referred to as the potassium channelopathies. These include acquired neuromyotonia, episodic ataxia type-1, hereditary deafness syndromes, benign familial neonatal convulsions and hypokalaemic periodic

paralysis. Insight into potassium channel structure and function is crucial to understanding the pathophysiology of these conditions. This article describes potassium channel structure and function and then outlines what is known about the immunology and genetics of the neurological potassium channelopathies.

Introduction

Potassium channels are the most diverse class of ion channels. A variety of genetic and acquired potassium channel defects have been described, and the term *potassium channelopathy* is used to refer to those conditions that are pathophysiologically linked to potassium channel dysfunction.

Insight into the diversity of potassium channels has been gained from the combined approaches of physiology and molecular biology. This has led to a confusing array of terminology used in the description of potassium channels, with some names based on electrophysiological properties such as rectification or voltage-dependence, some based on molecular cloning (e.g. KCNA, KCNQ), and yet others based on the relationship to disease (e.g. KvLQT1 in the long QT-syndrome) or homology to potassium channels cloned from other species (e.g. human *ether-a-go-go* related gene [HERG]). At this time, it is not possible to construct a unifying classification schema that incorporates all molecularly-defined subunits as well as all physiologically-defined potassium channels.

The approach adopted in this review is simply to group potassium channels into one of three major classes: voltage-sensitive; calcium-sensitive; and inwardly-rectifying. Whilst this classification is based primarily on the structure of these different classes of channels, the discussion will also focus on their function and how this relates to disease.

Structure

Potassium channels comprise a pore-forming α -subunit and an accessory β -subunit (Figure 1). The α -subunit of the voltage-sensitive potassium channel (K_v) class comprises six transmembrane segments with the defining 'pore-domain' between S5 and S6 looping into the plasma membrane. The 'six-transmembrane structure' bears homology to each of the four domains of voltage-gated sodium and calcium channels. The fourth membrane spanning segment (S4) is highly (positively) charged and serves as a voltage-sensor.¹ Four K_v subunits

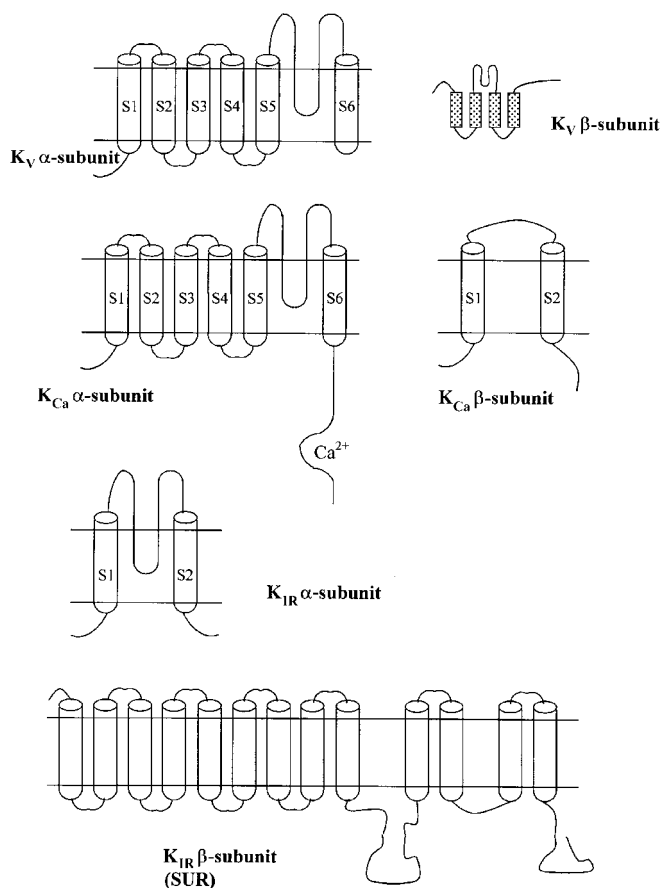


Figure 1. The α and β subunits of three groups of K^+ channels are shown. The voltage-sensitive and calcium-sensitive K^+ channels share a similar structure with six transmembrane regions and the pore-domain formed by the S5-S6 loop. The calcium-sensitive K^+ channels differ in that they contain a long C-terminal cytoplasmic tail which is thought to bind small molecules such as calmodulin and to function in regulating the calcium-sensitivity of the channel. The inwardly-rectifying K^+ channels comprise two transmembrane domains connected by an intervening pore-domain. The S1 and S2 regions of these channels bear homology to the S5 and S6 segments of the voltage and calcium-sensitive K^+ channels. The β subunits of the voltage-sensitive K^+ channels are entirely intracellular. The shaded rectangles in this diagram represent putative α -helical domains. In contrast, the β -subunits of the calcium-sensitive K^+ channels contain two transmembrane segments. The sulphonylurea receptor (SUR) forms the β -subunit of the ATP-sensitive K^+ channel inwardly rectifying. The SUR is a member of the ATP-binding cassette (ABC) protein.

assemble to form functional voltage-sensitive potassium channels.

The β -subunits assemble into a tetrameric structure without membrane-spanning sequences that interacts with the intracellular surface of the K_V α -subunits.² Four such β -subunits have been cloned, three representing splice variants of a single gene and the fourth derived from a related gene.³ The β -subunits alter the function of the α -subunits either by accelerating the inactivation of the potassium current or by altering surface expression of the potassium channel complex.⁴

The calcium-activated potassium channels (K_{Ca}) are structurally similar to the K_V , but have in addition, a long C-terminal extension that is presumed to function in sensing calcium levels or for modulation by other small molecules (e.g. calmodulin).¹ The β -subunits that associate with K_{Ca} α -subunits

have two transmembrane segments, and function to increase the calcium-sensitivity of the channel. Functional coupling between the α and β subunits is regulated by intracellular calcium concentrations.

The inwardly-rectifying potassium channels (K_{IR}) may be conceptualized as a functional fragment of the K_V , with the conserved pore domain linking two transmembrane sequences with homology to S5 and S6 of K_V .¹ Some members of this class are regulated by intracellular concentrations of ATP. The β -subunit of the ATP-sensitive K^+ channel ($K_{IR6.2}$) belongs to the ATP-binding cassette (ABC) protein superfamily, and is otherwise known as the sulphonylurea receptor (SUR). In pancreatic β -cells, SUR1 and $K_{IR6.2}$ combine to form the K_{ATP} channel, whereas in the heart and skeletal muscle, SUR2A combines with $K_{IR6.2}$ to form the K_{ATP} channel.⁴

Function

The resting membrane potential of a cell is a function of the differential distribution of the most abundant ions between the inside and outside of the cell. In living cells, the intracellular concentration of K^+ is much greater than that found in the extracellular space. The outward flow of positively charged K^+ ions generates a negative potential across the membrane. The net flow of K^+ ions ceases when the concentration gradient driving K^+ ions out of the cell is balanced by the electrical gradient that retards the efflux of positively-charged ions. A similar balance exists for other major ions such as Na^+ and Cl^- , but the relatively greater permeability to K^+ ions determines that the resting membrane potential of the cell is closest to the resting potential for K^+ .

Rectification refers to the ability of an ion-channel to pass ions through a membrane more easily in one direction than the other given an equivalent driving force generated by voltage. *Rectification* is an electrophysiological property that should not be confused with the direction of ionic flux. Under physiological conditions, the *inwardly rectifying* K^+ channel passes an outward K^+ current only in a narrow voltage range around the resting membrane potential. The outward currents through these channels in response to small depolarizations tend to repolarize the membrane and thus to resist the voltage change. However, a large depolarization leads to blockage of the inwardly-rectifying K^+ channel and action potential firing is thus facilitated. Inwardly-rectifying K^+ channels thus play an important role in setting the resting membrane potential and in regulating overall cell excitability. *Outwardly-rectifying* K^+ channels are voltage-sensitive K^+ channels that carry large outward currents at positive membrane potentials, but negligible currents at negative potentials. *Delayed rectifiers* also belong to the class of voltage-sensitive K^+ channels, but exhibit a delayed onset of activation following depolarization, and thus exhibit an extreme form of outward rectification. Both of these channels, therefore, are active when the cell is depolarized and thus mediate repolarization by passing large outward K^+ currents.

The M-channel is a voltage-sensitive K^+ channel that is highly expressed in the cortex and hippocampus. This channel opens occasionally at resting membrane potential, and is slowly activated by

membrane depolarization. These slow kinetics implicate M-channels in generating a delayed membrane hyperpolarization after a cell receives an excitatory input. This channel derives its name from the observation that it is suppressed by muscarinic acetylcholine receptor activity.

Calcium-sensitive K^+ channels are activated by a rise in the intracellular calcium concentration. They are primarily responsible for mediating fast and slow afterhyperpolarizations (AHPs). Fast AHPs contribute to repolarization of the cell after the action potential spike and slow AHPs play a role in regulating spike frequency.

The K_{ATP} channel is widely distributed in tissues as diverse as pancreatic β -cells, skeletal muscle, smooth muscle, neurons and epithelial cells. In all these cell types, a rise in intracellular ATP concentration results in inhibition of channel activity. In this way, the electrical activity of the cell is coupled to cellular metabolism.

Clinical disorders

Most of the neurological potassium channelopathies have been linked to dysfunction of a voltage-sensitive potassium channel. Neuromyotonia, episodic ataxia type-1 and benign familial neonatal convulsions appear to result from acute dysfunction of the relevant potassium channel. In the Jervell-Lange Nielsen and other hereditary deafness syndromes, however, the pathology is the consequence of cumulative damage that results from long-standing potassium channel dysfunction. Hypokalaemic periodic paralysis, although arising from a primary defect in voltage-gated calcium channel function, seems to derive part of its pathophysiology from dysfunction of the K_{ATP} channel. This may explain why attacks of paralysis are triggered by factors such as exercise and carbohydrate ingestion. A variety of other diseases are only circumstantially linked to potassium channel dysfunction. Brief reference is made to these disorders in Table 2 but they will not be discussed in any detail.

Acquired neuromyotonia

Acquired neuromyotonia^a (Isaacs' syndrome) is a clinical condition characterized functionally by hyperexcitability of peripheral nerves manifesting as continuous muscle fibre activity. This leads

^a The terms 'neuromyotonia' and 'myokymia' are also used to refer to specific electromyographic patterns and are more accurately referred to as neuromyotonic and myokymic discharges. The former refers to a burst of motor unit action potentials firing at 150–300 Hz for several seconds, often starting and stopping abruptly and waning in amplitude. In contrast, a myokymic discharge represents the spontaneous firing of single motor units as doublet, triplet or multiplet discharges at irregular intervals.

Table 1 Summary of neurological potassium channelopathies

Channel type	Structural information*	Physiological function	Disease association
<i>Voltage-sensitive K⁺ channel</i> K _V (delayed rectifier)	Homo/heteromultimer of K _V 1 (shaker), K _V 2 (shab), K _V 3 (shaw, KCNC) and K _V 4 (shal)	Action potential repolarization	Neuromyotonia EA-1
K _{Vs} (slow delayed rectifier)	Tetramer of K _V 5 (K _V LQT1, KCNQ1, KCNA8) subunits; associated with KCNE1 (<i>minK</i>)	Extrusion of K ⁺ into endolymph	JLN
K _M (M-channel)	Heteromultimer of KCNQ2 and KCNQ3	Delayed membrane hyperpolarization after excitatory input	BFNC
K _V (? outward rectifier)	Tetramer of KCNQ4	K ⁺ efflux from outer hair cells	Deafness
<i>Inward rectifier K⁺ channel</i> K _{ATP}	Heteromultimer of α -subunits drawn from K _i ,6.1 or 6.2	Stabilization of resting membrane potential	HOPP

*Alternative subunit nomenclature is indicated in parentheses. EA1, episodic ataxia type-1; JLN, Jervell Lange Nielsen syndrome; BFNC, benign familial neonatal convulsions; HOPP, Hypokalaemic periodic paralysis.

Table 2 Neurological disorders that may be associated with potassium channel dysfunction

Disorder	K ⁺ channel	Evidence	Proposed pathophysiology	References
Schizophrenia	Ca ²⁺ -dependent K ⁺ channel (SK _{Ca}) subunit (KCNN3)	Allele frequency differs between schizophrenia and control populations. Hypothesis is that a CAG polymorphism in KCNN3 represents a susceptibility allele for the development of schizophrenia	SK _{Ca} current is important in the inactivation of the NMDA receptor. Hypothesis is based on observations (1) that NMDA-R antagonists induce a schizophrenia-like syndrome and (2) antipsychotics used in treatment of schizophrenia are NMDA-R antagonists	43, 44
Paroxysmal choreoathetosis/episodic ataxia	Voltage-sensitive K ⁺ channel	Linkage to a cluster of K ⁺ channel genes (related to KCNA1 of EA-1) on chromosome 1p	Similar to that proposed for KCNA1 dysfunction in EA-1 (see text)	45
Alzheimer's disease	Platelet Ca ²⁺ -dependent K ⁺ channel	Reduced sensitivity of K _{Ca} to charybdotoxin, apamin and α -dendrotoxin in a ⁸⁶ Rb ⁺ efflux assay	Unknown	46

to the characteristic clinical manifestations of myokymia^a (continuous undulating muscle twitching caused by spontaneous motor nerve discharges), muscle cramps, impaired muscle relaxation, stiffness, increased sweating and occasionally by muscle weakness. Serum levels of creatine kinase may be elevated, and some patients may also have central nervous system symptoms including insomnia, mood changes and hallucinations.⁵ The association of neuromyotonia with these CNS manifestations has been designated Morvan's syndrome.⁶

The continuous muscle fibre activity, which characterizes this syndrome, is generated by hyperexcitability of the terminal arborizations of motor nerves. This hyperexcitability is the result of impaired function of delayed rectifier K⁺ channels that are ordinarily responsible for neuronal repolarization following action potential firing.

Isaacs, who first described this clinical syndrome in 1961, suggested that the pathology arose from the terminal arborization of motor nerves.⁷ His original conclusion was based on the observation that the muscle fibre activity persisted following proximal nerve block by local anaesthetic, but that it was abolished by curare blockade of neuromuscular transmission. The next step in defining the pathophysiology of neuromyotonia followed its recognition as an (auto)immune disorder. This possibility was raised by the observation that neuromyotonia may occur as a paraneoplastic syndrome,⁸ and the recognition that patients with the disease might respond to plasmapheresis.⁹ Sinha and colleagues investigated in mice the effects of passive transfer of serum and purified IgG from a patient with neuromyotonia. They demonstrated an increased resistance to d-tubocurarine at the neuromuscular junction of the phrenic nerve-diaphragm preparation from mice treated with neuromyotonia serum or IgG.⁹ Subsequent study of neuromuscular transmission in these mice demonstrated normal miniature end-plate potential frequency and amplitude, but a significantly increased quantal content.¹⁰

The quantal content refers to the number of quanta (vesicles) of neurotransmitter released in response to a single depolarizing stimulus. The quantal content is determined by the duration of the presynaptic action potential and the resulting magnitude of the calcium influx into the presynaptic nerve terminal. One possible explanation for the increased quantal content observed in the mice after passive transfer of neuromyotonia IgG, is a prolongation of the duration of the presynaptic nerve terminal action potential. The delayed rectifier K⁺-channel mediates action potential repolarization and prolongation of the action

potential could result from a reduction in the number or function of these K⁺ channels. Moreover, the physiological effect of the neuromyotonia IgG was similar to that induced by agents such as α -dendrotoxin that blocks certain voltage-gated K⁺-channels. This led to the suggestion that patients with neuromyotonia might harbour antibodies directed against this class of K⁺ channels.

The early reports of the presence of anti-potassium channel antibodies in the serum of patients with neuromyotonia were based on an immunoprecipitation assay. Extracts of human frontal cortex were labelled with ¹²⁵I- α -dendrotoxin, which binds to a variety of potassium channels, and then immunoprecipitated with serum derived from patients with neuromyotonia.¹⁰ The sensitivity and potassium channel subtype specificity were subsequently improved by the development of a molecular immunohistochemical assay which involved the expression of different potassium channel types in *Xenopus* oocytes which were then stained with human serum and fluorescent-labelled antibodies. Using this assay, Hart and colleagues were able to demonstrate immunoreactivity to KCNA6 (11/12 sera), KCNA2 (10/12 sera) and to KCNA1a (5/12 sera).¹¹ Using the whole-cell patch clamp technique, Sonoda and colleagues have since shown that the K⁺ current is reduced by 25–80% after culture of rat pheochromocytoma PC12 cells in neuromyotonia sera for 3–6 days.¹²

In summary, therefore, patients with acquired neuromyotonia harbour antibodies directed against voltage-gated K⁺ channels. These antibodies reduce the K⁺ current conducted by these channels and thus lead to a prolongation of the nerve action potential. This results in increased neurotransmitter release that manifests clinically as muscle hyperexcitability (Figure 2).

Episodic ataxia type 1

Episodic ataxia type 1 (EA-1) is an autosomal dominant condition in which affected individuals experience continuous myokymia as well as attacks of cerebellar ataxia and dysarthria. The attacks are brief, usually lasting from seconds to minutes, and are precipitated by startle, emotion or exercise. Acetazolamide may be of benefit in reducing attacks in some families, and anticonvulsants may similarly reduce the attacks and myokymia in some patients. Several point mutations have now been described in the KCNA1 (K_V1.1) potassium channel on chromosome 12p in patients with this disorder.¹³

Expression of the various mutant K_V1.1 proteins in *Xenopus* oocytes yields functional channels with reduced currents and altered gating properties

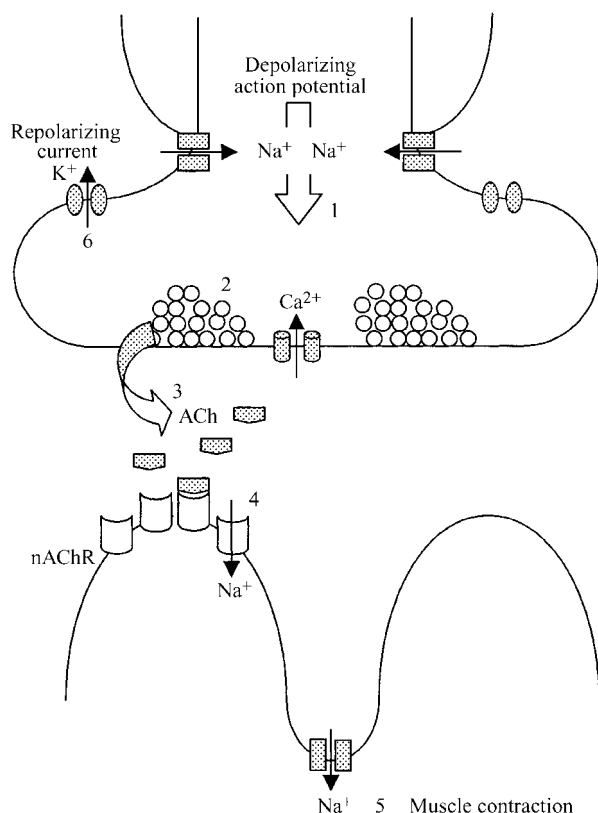


Figure 2. The action potential, mediated by Na^+ entry through voltage-gated sodium channels (1), invades and depolarizes the nerve terminal. This activates voltage-gated calcium channels which leads to entry of Ca^{2+} (2) and release of quanta (vesicles) of acetylcholine (ACh) (3). ACh diffuses across the synapse and binds to nAChRs (nicotinic acetylcholine receptors), which are concentrated on post-junctional folds of the muscle membrane. nAChRs are blocked by d-tubocurarine. Activation of the nAChR leads to Na^+ influx (4) and depolarization of the motor end-plate, which leads to activation of muscle voltage-gated sodium channels and muscle contraction (5). Presynaptic voltage-sensitive potassium channels are activated by nerve terminal depolarization, and result in repolarization (6) and termination of the nerve action potential. Reduced K^+ channel activity in neuromyotonia leads to prolongation of the action potential, increased release of acetylcholine-containing vesicles, and muscle hyperactivity.

(negatively shifted voltage-dependence of activation, with accelerated activation and deactivation). Co-expression of mutant and wild-type subunits reduces the overall delayed rectifier K^+ current, resulting in inefficient neuronal repolarization following an action potential.^{14,15}

KCNA1 is widely expressed in the nervous system, but is highly concentrated on the axons and nerve terminals of the cerebellar basket cells¹⁶ and at the juxtanoal regions of the myelinated axons in the peripheral nervous system. Dysfunction of voltage-sensitive potassium channels at these

sites is thought to underlie the clinical manifestations of EA-1. Basket cells are inhibitory interneurons that form synapses on the proximal segments of Purkinje cell axons. As such, they are well positioned to play an important role in regulating cerebellar output. Blockade of KCNA1 voltage-sensitive potassium channels with α -dendrotoxin causes a dramatic increase in spontaneous inhibitory post-synaptic potentials recorded in Purkinje cells, in keeping with the notion that KCNA1 regulates the excitability of the basket-cell presynaptic terminal.¹⁷ Mutations in KCNA1 that similarly reduce channel function thus impair cerebellar modulation of movement.

The function of the KCNA1-containing channels concentrated at the juxtanoal regions of myelinated axons in the peripheral nervous system is to repolarize the neuron following action potential firing. The mechanism whereby their dysfunction leads to myokymia is similar to that proposed for patients with acquired neuromyotonia (Figure 2).

The demonstration that the same K^+ channel that is mutated in EA1 is also targeted by autoantibodies in neuromyotonia, raises as many questions as it answers. It does provide a convenient explanation for the continuous muscle fibre activity that is common to both conditions, but it leaves unexplained why episodic ataxia is not a feature of acquired neuromyotonia. It is tempting to speculate that this may simply be a function of failure of autoantibodies to cross the blood brain barrier. If this were the case, however, it would leave unexplained the central nervous system manifestations (insomnia, mood changes and hallucinations) that are reported in patients with neuromyotonia. On the other hand, it is not clear to what extent these CNS symptoms are integral to the disease process. An alternative (although unproven) hypothesis is that mood changes and insomnia might represent the individuals' response to the disease process.

Homozygous deletion of the mouse $\text{K}_V1.1$ gene has been shown to cause severe epilepsy, raising the question of whether the KCNA1 gene may also be involved in some forms of human epilepsy. Consistent with this suggestion is the demonstration of mutations in other voltage-gated potassium channels (see discussion relating to BFNC below) and the increased incidence of epilepsy amongst patients with EA-1.¹⁸

Benign familial neonatal convulsions

Benign familial neonatal convulsions (BFNC) is an autosomal dominant condition characterized by neonatal seizures in otherwise healthy newborns.

Seizures usually begin between the first and fourteenth days of life and typically remit spontaneously by 6 weeks of age. The risk of subsequent epilepsy is about 15%. The seizures are clinically heterogeneous and include eye deviation, tonic posturing, focal clonic activity and apnea with evolution to generalized convulsions.¹⁹

Early studies demonstrated BFNC to be genetically heterogeneous. The two genes on chromosomes 20q and 8q encode highly homologous potassium channel subunits, KCNQ2 and KCNQ3.^{20–22} Expression of either subunit alone in *Xenopus* oocytes results in small currents, but co-expression of the two genes yields a channel with currents 10–50 times larger,²³ and with the gating properties of the neuronal M-channel.²⁴ *In-situ* hybridization has demonstrated overlapping patterns of expression of KCNQ2 and KCNQ3.²⁴ These data cohere to suggest that KCNQ2 and KCNQ3 coassemble *in vivo* to form the M-channel. This molecular mechanism would explain why patients with BFNC linked to the loci on chromosomes 20q and 8q are clinically indistinguishable.

Functional expression of the disease causing missense mutations in these subunits are associated with a variable reduction (20–95%) in current magnitude.^{23,25} Coexpression of mutant and wild-type subunits yielded potassium currents of similar amplitude, essentially excluding a dominant negative effect.²⁵ Rather, these results are consistent with neuronal excitability being critically dependent on the absolute magnitude of KCNQ2/KCNQ3 potassium channel current.

Reduced activity of the M-channel would be expected to cause neurons to become slightly depolarized and to fire multiple action potentials rhythmically after receiving excitatory inputs. The known functional effects of the KCNQ2 and KCNQ3 mutations are thus consistent with the clinical phenotype of seizures. It is unclear, however, why these mutations preferentially lead to seizures in the neonatal period. Possibilities include that the neonatal brain simply has a lower seizure threshold, or that potassium channel subunit expression is developmentally regulated, with neuronal excitability more dependent on the M-channel than on other voltage-sensitive potassium channels in the neonatal period.

Hereditary deafness syndromes

The Jervell-Lange Nielsen (JLN) syndrome is an autosomal recessive disorder characterized by sensorineural deafness and prolongation of cardiac repolarization that manifests on the surface ECG as a prolonged QT interval. As a result of this cardiac

abnormality, these patients are prone to the development of fatal ventricular arrhythmias, especially torsades de pointes.

JLN is genetically heterogeneous, with mutations described in two K⁺ channel genes, KCNQ1 on chromosome 11p15.5^{26,27} and KCNE1 on chromosome 21q22,^{28–30} both of which are expressed in the inner ear and in the heart. In the inner ear, KCNQ1 is expressed on the apical surface of the marginal cells of the stria vascularis. KCNE1 encodes a K⁺ channel subunit that interacts with KCNQ1 to form a slow delayed rectifier K⁺ channel (K_{Vs}) that is tonically active and that is thought to pass K⁺ ions into the endolymph (Figure 3).

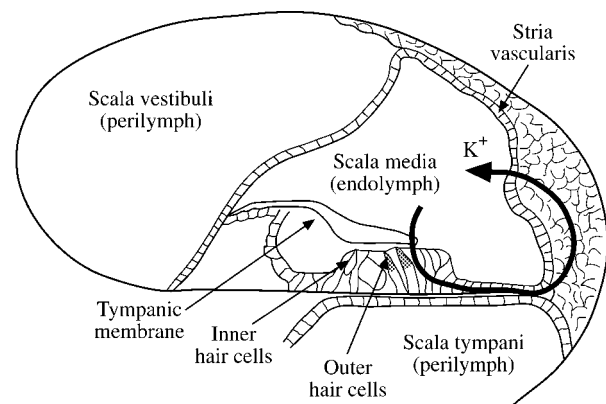


Figure 3. The function of the mammalian hearing apparatus, located in the snail-shaped cochlea, relies on a complex system of ion transport between perilymph- and endolymph-containing spaces. The scala tympani and scala vestibuli contain perilymph, which has an ionic composition similar to extracellular fluid (high Na⁺ and low K⁺). The scala media, however, contains endolymph with an ionic composition similar to intracellular fluid (low Na⁺ and high K⁺). These ionic concentrations and the endolymphatic membrane potential (+80mV) are maintained by ionic flux from the marginal cells, of the stria vascularis. The sensory hair cells have their apical ciliated surfaces facing endolymph and their basolateral surfaces immersed in perilymph. Acoustic vibrations cause deflection of the cilia of the sensory cells, and this in turn causes non-selective cation channels in the cilia to open and K⁺ to pass from the endolymph into the cytoplasm of the hair cell. K⁺ then leaves the basolateral surface of the hair cells to enter the perilymph and thence travels via two syncytial networks, to the marginal cells of the stria vascularis, which are responsible for pumping the K⁺ back into the endolymph. KCNQ1 and KCNE1 are expressed on the apical surface of the marginal cells of the stria vascularis and are tonically active, allowing the passage of K⁺ into the endolymph. Reduced activity of the K⁺ channels formed by these subunits underlies the JLN syndrome. KCNQ4 is expressed in the outer hair cells and permits the passage of K⁺ out of the hair cells. KCNQ4 is mutated in patients with non-syndromic progressive deafness.

The presence of homozygous or compound heterozygous mutations in either of these genes manifests as the autosomal recessive JLN syndrome. In contrast, heterozygous mutations result in the autosomal dominant form of the long QT syndrome (Romano-Ward syndrome), but without associated deafness. The implication appears to be that the deafness is inherited as an autosomal recessive trait and that the abnormality of cardiac repolarization is inherited as an autosomal dominant trait.

The mutations in KCNQ1 reported in patients with JLN result in the generation of premature stop codons and hence protein truncation.^{26,27} Functional expression of the mutant proteins alone yields no functional channels and co-expression with wild-type KCNQ1 channels in a 1:1 stoichiometry produces currents with an approximately 50% reduction in size.³¹ These observations are consistent with the known autosomal recessive mode of inheritance. Mutations in the KCNE1 gene have similarly been shown to reduce the K_{Vs} current.^{28,32} Disrupted function of K_{Vs} in the stria vascularis is predicted to disturb the delicate ionic balance of the endolymphatic scala vestibuli and hence the function of the sensory hair cells, resulting in deafness.

KCNQ4 is a potassium-channel subunit gene expressed in the outer hair cells and that is thought to play a role in the passage of K^+ from the cytoplasm of the hair cells to the epithelial cell syncytium. The KCNQ4 gene maps to chromosome 1p34, the locus for the non-syndromic dominant progressive deafness gene, DFN2. Point mutations that disrupt the canonical GYG sequences of the K^+ channel pore have been identified in families with this autosomal dominant condition.³³ The dominant effect of this mutation, and hence the dominant inheritance of this syndrome, is the result of the fact that this channel is assembled from four KCNQ4 subunits. A pore mutation in a single subunit results in dysfunction of the entire channel.

Hypokalaemic periodic paralysis

Hypokalaemic period paralysis (HOPP) is an autosomal dominant disorder in which affected individuals experience attacks of weakness lasting hours to days. The distinguishing features of this form of periodic paralysis is the hypokalaemia that accompanies the episodic paralysis and the absence of myotonia (cf. hyperkalaemic periodic paralysis). Attacks may be precipitated by stress, rest after exercise and events that lower serum potassium such as carbohydrate ingestion, insulin or diuretic use. Muscle fibres from patients with HOPP exhibit an abnormally depolarized resting membrane

potential with further depolarization (and paralysis) induced by insulin and hypokalaemia.

The molecular defect underlying HOPP has been identified the α_{1S} (CACNA1S) gene on chromosome 1q31.³⁴ It encodes the pore-forming subunit of the skeletal muscle L-type voltage-gated calcium channel that, via an interaction with the ryanodine receptor, functions as a voltage-activated sensor for excitation-contraction coupling. Three point mutations in the voltage-sensor (S4) region of this gene have been identified in families with HOPP (reviewed in reference 35). Investigations of the functional effects of these mutations have not yielded consistent results. Current opinion is that they lead to reduced Ca^{2+} channel current density, but it has not been clear how this altered function produces the clinical phenotype.

Recent evidence suggests that defective function of the skeletal muscle ATP-sensitive potassium channel (K_{ATP}) may contribute to the pathogenesis of this disorder.^{36–38} Using macropatch-clamp recordings from muscle fibres of patients with HOPP, Tricarico and colleagues have demonstrated reduced resting outward K^+ current through the K_{ATP} channel as well as further inhibition of this current with hypokalaemia or the administration of insulin.³⁷ Similar effects have been observed in the K^+ -depleted rat model of this disorder.³⁹ On the basis of these results, the following model has been proposed, in which there is functional coupling between the Na^+/K^+ ATPase and the K_{ATP} channel in skeletal muscle. In healthy subjects, insulin activates the Na^+/K^+ ATPase, and leads to an influx of K^+ ions and transient hypokalaemia. Activation of the K_{ATP} channel, which mediates an outward K^+ current, compensates for the hypokalaemia and maintains muscle fibre hyperpolarization. In patients with HOPP, however, efflux of K^+ ions via K_{ATP} does not occur. The result is sustained hypokalaemia and membrane depolarization. This model explains the insulin-induced hypokalaemia and paralysis that occurs in HOPP, as well as the observation that K_{ATP} channel openers (diazoxide, cromakalim and pinacidil) are capable of repolarizing skeletal muscle and restoring muscle strength in patients with HOPP.⁴⁰ This model, however, does not provide an adequate link between the known mutations in the skeletal muscle voltage-gated calcium channel and the observed dysfunction of the K_{ATP} channel.

Conclusions

A notable feature of the K^+ channelopathies is that the clinical manifestations of all but one are paroxysmal, with the hereditary deafness

syndromes being the exception. In fact, many of the ion channelopathies are characterized by such episodic symptoms (reviewed in references 35, 41 and 42). It is for this reason that ion channel dysfunction is also hypothesized to contribute to the clinical expression of other paroxysmal conditions such as migraine and epilepsy.

This leaves open the question of how a stable genetic mutation is capable of causing paroxysmal dysfunction. The answer is probably multifactorial. In part, this periodicity relates to the nature of ion channels and their variable contribution to cell activity under different circumstances (e.g. transmembrane potential). An unchanging genetic mutation may thus exert a dynamic effect, based on the variable importance of the function of the particular ion channel in the context of other factors impacting on cellular excitability. Furthermore, no single ion channel determines the excitability or refractoriness of a neuron. The effect of disrupting the function of a single ion channel may be counterbalanced by a multitude of other factors impacting on cellular excitability. Depending on the delicate balance of excitatory and inhibitory influences at any point in time, the static dysfunction caused by particular genetic mutations may result in a varying effect.

In view of these speculations, how can the late onset and progressive nature of the hereditary deafness syndromes be explained on the basis of ion channel dysfunction? One attractive hypothesis is that it is not the acute ion channel dysfunction *per se* that causes the disease, but rather that intermittent ion channel dysfunction has a cumulative harmful effect. Abnormal K^+ conductance over a period of years may result in damage to the outer hair cells and thus progressive hearing loss.

The functional characterization of the genetic and immunological aberrations responsible for these disorders has greatly enhanced our understanding of the biology of K^+ channels and has provided remarkable insight into the pathophysiology of conditions as wide-ranging as deafness, ataxia, seizures, neuromyotonia and hypokalaemic periodic paralysis. It is hoped that these insights will further facilitate the development of new agents that modify K^+ channel function, and that these may be useful in the treatment of these and other more common clinical conditions.

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