

Voltage-Gated Ion Channels and Hereditary Disease

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Lehmann-Horn, Frank, and Karin Jurkat-Rott. Voltage-Gated Ion Channels and Hereditary Disease. *Physiol. Rev.* 79: 1317–1372, 1999.—By the introduction of technological advancement in methods of structural analysis, electronics, and recombinant DNA techniques, research in physiology has become molecular. Additionally, focus of interest has been moving away from classical physiology to become increasingly centered on mechanisms of disease. A wonderful example for this development, as evident by this review, is the field of ion channel research which would not be nearly as advanced had it not been for human diseases to clarify. It is for this reason that structure-function relationships and ion channel electrophysiology cannot be separated from the genetic and clinical description of ion channelopathies. Unique among reviews of this topic is that all known human hereditary diseases of voltage-gated ion channels are described covering various fields of medicine such as neurology (nocturnal frontal lobe epilepsy, benign neonatal convulsions, episodic ataxia, hemiplegic migraine, deafness, stationary night blindness), nephrology (X-linked recessive nephrolithiasis, Bartter), myology (hypokalemic and hyperkalemic periodic paralysis, myotonia congenita, paramyotonia, malignant hyperthermia), cardiology (LQT syndrome), and interesting parallels in mechanisms of disease emphasized. Likewise, all types of voltage-gated ion channels for cations (sodium, calcium, and potassium channels) and anions (chloride channels) are described together with all knowledge about pharmacology, structure, expression, isoforms, and encoding genes.

I. INTRODUCTION

Life's chemistry of aqueous solutions employs ions as carriers of cell signals. Such a signal is the action potential. That such a simple all-or-nothing signal should require highly complex proteins and ion channels, rather than just a particle within membrane bilayer, was unknown when Hodgkin and Huxley first described the pro-

cesses of activation and inactivation of cation currents during the action potential in the early 1950s. In the meantime, whole families of channels with high diversity of structure and function have been described. More than conveying rapid excitation by action potentials alone, other internal cell processes are initiated by ion signals. Accordingly, the expression of these proteins is not restricted to excitable cells such as neurons or muscle but

can be observed in external and internal membranes of almost all cells.

It was by electrophysiological characterization of functional channel disturbances in skeletal muscle that the underlying genetic cause for the first ion channel disease was detected. Since then, over a dozen such disorders have been described that have some striking clinical similarities leading to the coining of the terms *ion channel diseases* or *ion channelopathies*. Elucidating the pathogenesis of hereditary ion channel diseases with electrophysiological methods has given rise to new approaches for basic research and has greatly contributed to knowledge of structure-function relationships of voltage-gated ion channels. They will be decisively involved in developing strategies for specific therapy in the future. In this review, basic patterns of structure and function of voltage-gated ion channels as well as functional changes brought about by naturally occurring mutations are discussed.

Further literature relevant to this topic may be found in reviews and handbooks of the structure and function of voltage-gated ion channels in general (8, 74, 197, 372) as well as for sodium (166, 255, 389), potassium (78, 171, 242, 402, 571), calcium (201, 317, 352, 395, 538), and chloride channels (231, 232, 414). Reviews on skeletal muscle ion channel disorders (22, 65, 200, 204, 239, 286–288, 313, 408) and cardiac channelopathies (252) have also been published as well as on neurological ion channel diseases (48, 169, 180). Overviews of the whole spectrum of voltage-gated channelopathies are also available (59, 145, 287, 288).

II. CHANNEL FUNCTION AND STRUCTURE

Ion-conducting membrane channels are opened by ligands or voltage changes (usually depolarization) and closed by a delayed inactivation that is simultaneously initiated with the activation. Sustained exposure to the ligand or the depolarization may lead to reopenings of the channel if the circumstances (time, voltage) allow the channel to recovery from the inactivated state. The ion-conducting pore is highly selective for a specific ion as in most voltage-gated channels, or it conducts cations or anions without high selectivity as in most ligand-gated channels. The structures of the pore, its selectivity filter, and its activation and inactivation gates show high evolutionary conservation that allows one to make deductions on structure-function relationships from one channel type to the next.

A. Voltage-Gated Cation Channels

1. General characteristics

Voltage-sensitive cation channels usually have at least one open state and two closed states, the resting

state from which the channels can be activated, i.e., opened. At the resting potential, their open probability is extremely low, meaning that only very few channels open randomly. Depolarization causes channel activation by markedly increasing open probability. During maintained depolarization, open probability is time-dependently and not voltage-dependently reduced by channel inactivation, leading to a closed state from which the channels cannot immediately be reactivated. Instead, inactivated channels require repolarization and a certain time for recovery from inactivation. On the other hand, repolarization of the membrane before the process of inactivation will deactivate the channel, i.e., reverse activation leading to the closed resting state from which the channels can be activated. In this most simple approximative model, transitions from one state to another are possible in both directions, permitting also the transition from the resting to the inactivated state at depolarization as well as the recovery from inactivation via the open state. Forward and backward rate constants for the transitions determine the probabilities of the various channel states (Fig. 1).

A) STRUCTURE OF α -SUBUNITS. Basic motif of this essential subunit is a tetrameric association of a series of six transmembrane α -helical segments, numbered S1-S6, connected by both intracellular and extracellular loops, the interlinkers (Figs. 2 and 3). Voltage-gated sodium and calcium channels and at least the potassium channels of the *Shaker* family show varying subunit composition. Of these, the α -subunit determines main characteristics of the complex conveying ion selectivity and containing the ion-conducting pore, voltage sensors, gates for the different opened and closed channel states, and binding sites for endogenous and exogenous ligands.

B) α -SUBUNIT PORE REGION. The pore region of voltage-gated potassium channels, the S5-S6 interlinker (P-region), was first defined by studies of external and internal binding sites of a pore-blocking agent, tetraethylammonium (TEA) (247, 248, 258, 323, 587). A combination of site-directed mutagenesis and toxin binding studies showed that neutralization of specific negative residues of this so-called SS1-SS2 or P-region abolished the ability of positively charged toxins to physically block the potassium channels and altered their ion specificity (371, 530, 587). This suggested that the P-region contributed to the lining of the channel pore and the negative charges surrounding the external mouth of the pore forming the selectivity filter of the channel. Selectivity filters are common structures in all voltage-gated cation channels, and modifications in only a few decisive residues in the P-region may make the pore selective for a different cation (155). For the sodium channel, for example, substitution of lysine and alanine residues by glutamate made the pore selective for calcium (193, 392).

C) ACTIVATION. Activation results from a depolarization-induced conformational change of the protein leading to

Voltage-gated Na⁺-channel

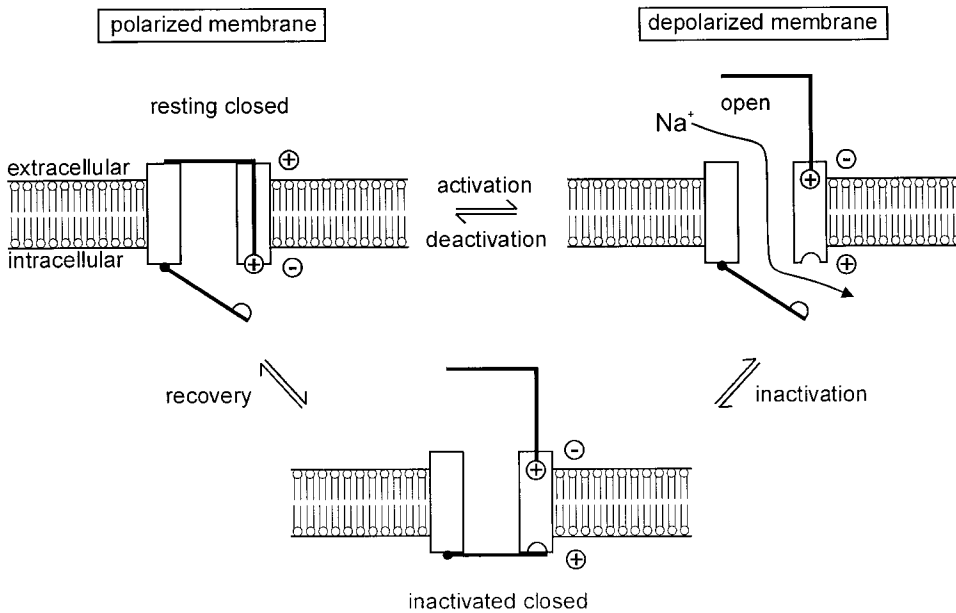


FIG. 1. Scheme of 3 states of sodium channel that opens rapidly upon depolarization and then closes to a fast inactivated state from which it reopens very rarely. Repolarization of membrane, initiated by inactivation of channel, leads to recovery from inactivation (= resting state) from which activation is again possible. Outward movement of voltage sensor upon depolarization results in both opening of pore and exposure of a docking site for inactivation gate. (Scheme developed in collaboration with Dr. W. Melzer.)

the opening of the ion-conducting pore. Even when the pore is pharmacologically blocked, charge movements in the electrical membrane field are measurable, the so-called gating current, associated with movements of the highly conserved α -helical S4 segments carrying arginines or lysines at every third amino acid residue. Replacing the positive charges with neutral or negatively charged residues reduces the steepness of the voltage dependence of activation (519), making them candidates for the voltage

sensor of the channel. Size and shape of the hydrophobic (neutral) residues between the positive charges are equally important for the ability of S4 to move (21). During their outward movement, the S4 segments seem to move in a spiral path ("sliding helix" or "helical screw" model) outward through "canaliculi" of the channel protein, the outer charges becoming exposed on the cell surface while the inner charges become buried in the membrane during activation (335, 583).

α -subunits

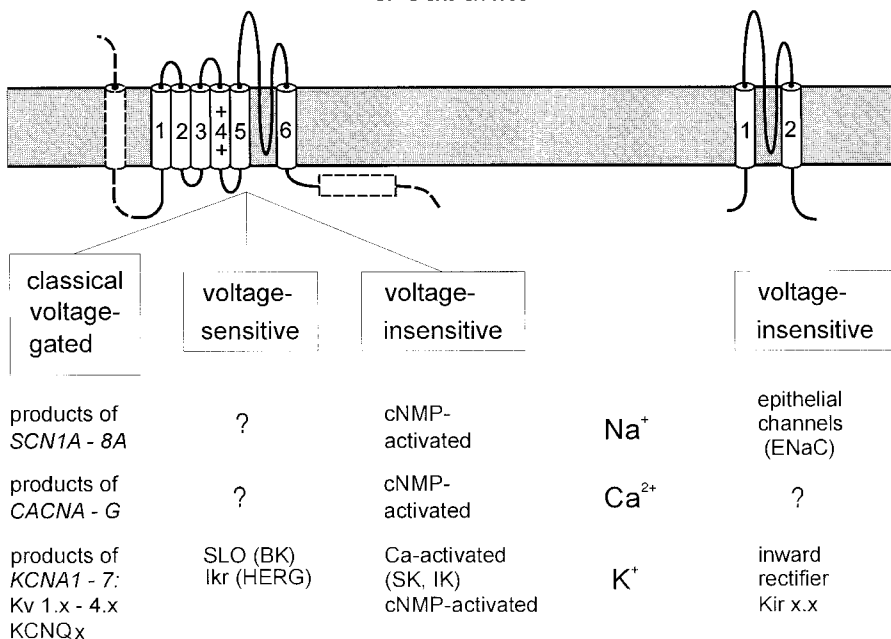


FIG. 2. Classification of elementary units of cation channel α -subunits on basis of their relation of transmembrane to pore segments. All functional voltage-gated α -subunits consist of 4 units of 6 transmembrane segments each including voltage sensor (segment 4) characterized by several positive amino acid residues. All 4 units are encoded by a single sodium (or calcium) channel gene, whereas potassium channel genes code for only 1 unit. Although cyclic nucleotide monophosphate (cNMP)-activated channels contain a positive segment 4, they are not voltage sensitive at all, maybe due to uncoupling of sensor and activation gate. x, 1...n.

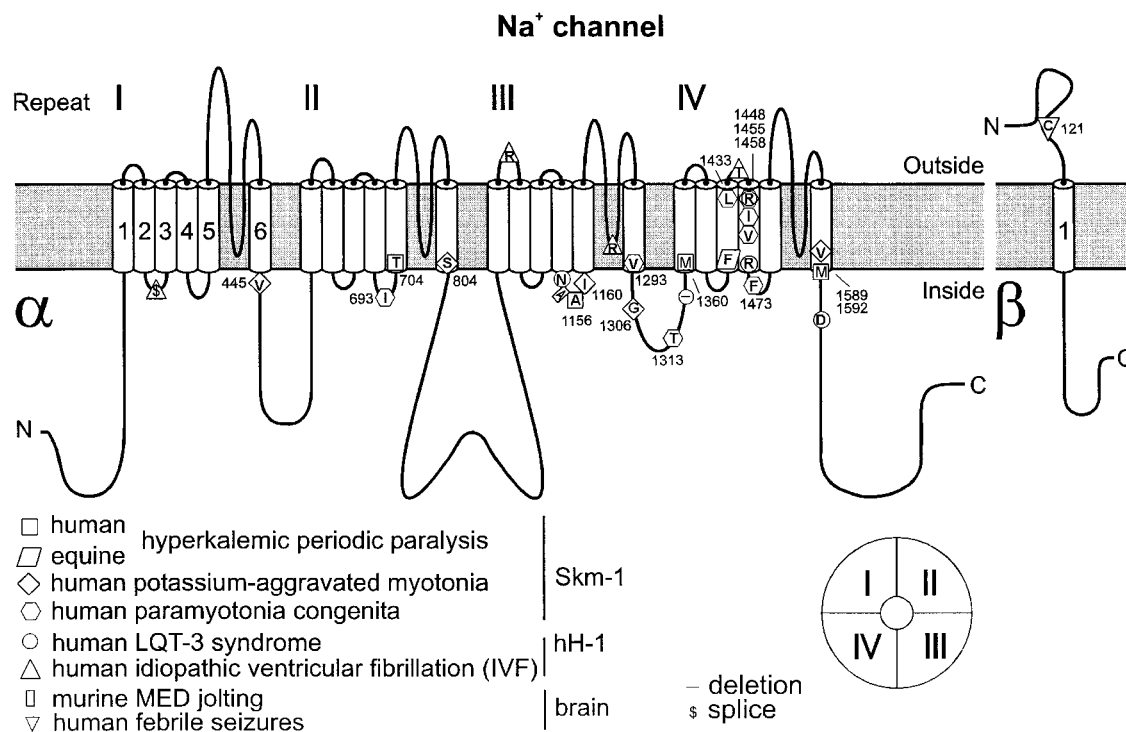


FIG. 3. Subunits of voltage-gated sodium channel. α -Subunit consists of 4 highly homologous domains (repeats I-IV) containing 2 transmembrane segments each (S1-S6). S5-S6 loops form ion-selective pore, and S4 segments contain positively charged residues conferring voltage dependence to protein. Repeats are connected by intracellular loops; one of them, III-IV linker, contains supposed inactivation particle of channel. β_1 and β_2 are auxiliary subunits. When inserted in membrane, 4 repeats of protein fold to generate a central pore as schematically indicated on *bottom right*. To date, mutations have been described for α -subunits of various species and tissues: human and equine adult skeletal muscle (Skm-1), human heart (hH-1), and murine brain. So far, only 1 mutation has been reported for a sodium channel subunit, i.e., 1 of human brain. Conventional 1-letter abbreviations are used for replaced amino acids whose positions are given by respective numbers of human skeletal muscle channel. Different symbols used for point mutations indicate resulting diseases as explained at *bottom left*.

D) INACTIVATION AND RECOVERY FROM INACTIVATION. Voltage-gated channels usually display two modes of inactivation, fast and slow. These nonconducting inactivated states are probably mediated by different molecular mechanisms. Fast inactivation describes the rapid and complete decay of currents observed in response to short millisecond depolarizations. Slow inactivation occurs when cells are depolarized for seconds or minutes. Recovery from inactivation takes place at membrane repolarization on similar time scales as inactivation itself.

E) FAST INACTIVATION. From studies employing intracellular perfusion of the giant axon with the proteolytic enzyme pronase that abolishes sodium channel inactivation (19), it has become obvious that the inactivation gate is accessible to cytoplasmic agents. The absence of charge movements during inactivation suggested the localization of the inactivation gate outside the membrane voltage field. Based on these studies, Armstrong and Bezanilla (18, 37) proposed a ball-and-chain model in which the ball, tethered to the cytoplasmic side of the channel by a chain, swings into the inner mouth of the pore where it binds and blocks ion fluxes. Although originally proposed for the sodium channel, this model has quite con-

vincingly been shown for fast-inactivating potassium channels where the pore-blocking ball is part of or attached to the NH₂ terminal (so-called N-type inactivation) (203). For sodium channels, one or more of the cytoplasmic loops that connect the various domains could be involved in fast inactivation. That the loop between domains III and IV is essential was demonstrated by antibodies specifically directed against this region which slowed fast inactivation (547). Mutagenesis experiments confirmed the sodium channel III/IV loop as the putative inactivation gate. With elimination of the III/IV interlinker by mRNA cleavage and coexpression of the two resulting partial mRNA in *Xenopus* oocytes, inactivation was markedly slowed (519). The inactivation particle itself, i.e., the ball, seems to consist of three consecutive amino acids near the middle of the loop, namely, a phenylalanine flanked by two other hydrophobic amino acids (573). Functional similarity allows this III/IV loop of the sodium channel even to confer fast inactivation to slowly inactivating potassium channels (391).

Because of the resemblance of this III-IV loop to the hinged lids of allosteric enzymes controlling substrate access, a slight modification of the ball-and-chain model

Hinged-lid model for Na channel inactivation

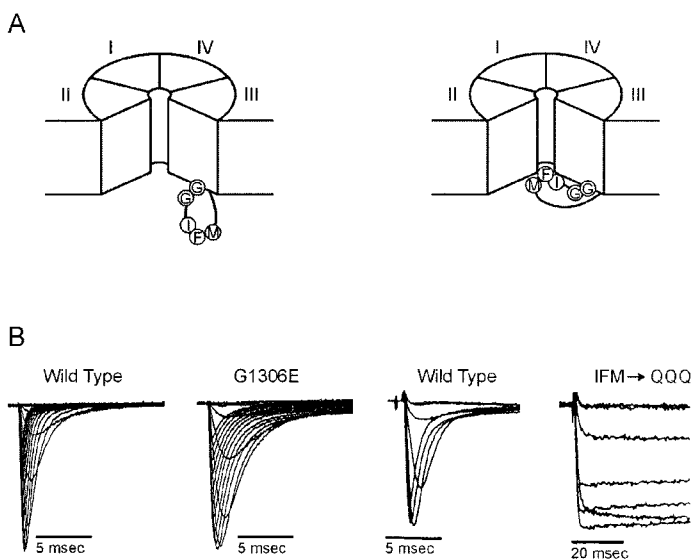


FIG. 4. Hinged-lid model of fast inactivation of sodium channels and effects of mutations at various locations on current decay. A: bird's eye view of channel consisting of 4 similar repeats (I—IV). Channel is cut and spread open between repeats II and III to allow view on intracellular loop between repeats III and IV. Loop acts as inactivation gate whose "hinge" GG (= a pair of glycines) allows it to "swing" between 2 positions, i.e., noninactivated channel state (pore open; left) and inactivated state (pore blocked by "plug" IMF = amino acid sequence isoleucine, phenylalanine, methionine; right). [Modified from West et al. (573).] B: substitution of E (Glu) for Gly-1306 slows channel inactivation (left panels, cf. fast current decay in wild-type channel on far left) and leads to a life-threatening form of potassium-aggravated myotonia. Designed substitution of QQQ (Gln-Gln-Gln) for IFM (Ile-Phe-Met) completely abolishes channel inactivation (right panels) proving that loop between repeats III and IV is indeed inactivation gate. [Modified from West et al. (573) and Mitrovic et al. (361).] Bottom: effects of disease mutations on current. ↑, increased; ∅, no change.

Main electrophysiological features of sodium channelopathies

location of mutations	putative function of location	slowing of inactivation	persistent current	acceleration of recovery from inactivation	shift of inactivation curve	resulting disease
segment α I/VS4	voltage sensor	↑↑	↑	↑	←	paramyotonia congenita
loop III/IV of α subunit	inactivation gate	∅	↑	∅/↑	∅/→	potassium-aggravated myotonia LQT syndrome type 3
intracellular ends of α segments	acceptor of inactivation gate	∅	↑↑	↑	∅	hyperkalemic periodic paralysis
N-terminus β subunit	modifying part	?	↑	?	?	epilepsy with febrile convulsions

was proposed (Fig. 4). According to this hinged-lid model, the inactivation particle acts as a latch of a putative catch to be identified, and one of the hinges consists of a pair of glycines situated in the vicinity of the phenylalanine (391, 573). In potassium channels, the S4-S5 interlinkers putatively adjacent to the intracellular orifice of the pore may act as the acceptor for the N-type inactivation particle (202, 217, 497). Similar but not identical parts of the supposed S4-S5 helices and adjacent amino acids of the transmembrane segments S5 and S6 may form the catch of the sodium channel (136, 295, 344, 345, 363).

F) SLOW INACTIVATION. Slow inactivation, also called core-associated or C-type inactivation, is not only kinetically distinct from fast inactivation, it also involves different structural elements. Present in almost all voltage-gated cation channels, it is detectable even when fast inactivation has been destroyed. It is the only inactivation possibility in potassium channels devoid of the ball. In potassium channels, C-type inactivation is influenced by cations of external and internal solutions that interact

with certain amino acids of the ion-conducting pore (foot-in-the-door model of gating; Refs. 172, 315). The removal of inactivation by a point mutation in the pore led to the depiction of another term, the P-type (pore-type) inactivation (105). Further inactivation mechanisms involving modification of the intracellular vestibule by an auxiliary subunit have been described (365, 375).

G) α-SUBUNIT TERTIARY STRUCTURE. Out of the homology of the four domains in sodium, calcium, and many potassium channels, a fourfold symmetry surrounding a central pore lined by the S5-S6 interlinkers dipping down into the membrane has been proposed. The S5 and S6 segments are thought to be located near the pore while the adjacent S4 segments are proposed to move outward upon depolarization in a space independent of the ion-conducting pore, and the S1-S3 segments are suggested to be situated adjacent to the lipid bilayer because of their amphipathic helical structure which allows interaction with lipid and polypeptides (181). The selectivity filter is the most narrow portion of the pore. A model for the selectivity filter

was developed for the potassium channel from *Streptomyces lividans* in which main chain carbonyl oxygen lines the selectivity filter, which is held open by structural constraints to coordinate potassium ions but not smaller sodium ions. The selectivity filter contains two potassium ions, promoting ion conduction by exploiting electrostatic repulsive forces to overcome the interattractive forces (114).

H) ADDITIONAL SUBUNITS AND CHANNEL-ASSOCIATED MEMBRANE PROTEINS. Quarternary structure and channel function are dependent on additional subunits that may modify voltage sensitivity, kinetics, expression levels, or membrane localization (178). The auxiliary subunits of the different cation channels do not share homologous structures, indicating a large variety in possible mechanisms of channel modification. Usually, one of at least two different β -subunits may bind to a single α -subunit, e.g., the complete potassium channel tetramer binds up to four β_2 -subunits. Although all cation channels consist of α - and optional β -subunits, only calcium channels consist of two additional proteins, α_2 and δ encoded by a single gene, the transmembrane δ -subunit covalently binding the extracellular α_2 -subunit by disulfide bonds. Specific for skeletal muscle, an additional transmembrane γ -subunit facilitating inactivation had been described (229). Recently, a similar subunit has been found for the brain (300). Link of α -subunits to the underlying cytoskeleton by associated proteins like ankyrin and spectrin that bind to the brain sodium channel may help to control the mobility of the channels within the fluid lipid bilayer, thus enabling cell membrane topology (508).

I) VOLTAGE-INSENSITIVE CATION CHANNELS. Cyclic nucleotide-gated channels share common structural features with the voltage-sensitive channels, e.g., the α -subunit composition with the four domains of six segments each as well as a voltage-sensing positive charge motif in the S4 (Fig. 2) that in the physiological voltage range is stabilized in an activated conformation that is permissive for pore opening (527). Functional channels show less selectivity for a specific cation, and they are activated by direct binding of cAMP or cGMP to the intracellular COOH terminus. Calcium ions permeate the channels and thereby block the pore for sodium, a mechanism important for biofeedback regulation of cyclic nucleotide synthesis and degradation. This block from the extracellular side of the pore takes place in a voltage-dependent fashion and is dependent on glutamate residues in the P-region, a selectivity filter also found in voltage-dependent calcium channels (see sect. II A 3 B). Replacement of glutamate by glycine therefore reduces calcium permeability. A human disease is linked to mutations in channels of this group, i.e., missense and nonsense changes in the α -subunit of cGMP channels: autosomal recessive retinitis pigmentosa (118), not further described in this review.

2. Sodium channels

Membrane depolarization of excitable cells causes sodium channel activation in a positive-feedback mechanism along both the concentration gradient and the electric field. The resulting increase in sodium conductance of the membrane is associated with further depolarization and activation of further sodium channels. This produces an action potential that rises to a peak close to the sodium equilibrium potential within ~ 1 ms. The channel's intrinsic inactivation occurs within a few milliseconds (Fig. 5) and leads under unclamped, i.e., natural, conditions to repolarization of the membrane even in the absence of any voltage-gated potassium channels. After an action potential, the cell membrane is inexcitable for a short period of time, the so-called refractory period. The duration of this period of time is regulated by the kinetics of recovery of the channels from inactivation and is the limiting factor for the firing rate of the cells (Fig. 1).

A) SODIUM CHANNEL α -SUBUNITS. Ten different genes have been identified in the human genome that are known to encode four-domain α -subunits of voltage-gated sodium channels (*SCN1A* to *SCN10A*, Table 1). Because voltage-gated sodium channels are responsible for the fast component of action potentials, most of these genes are expressed in excitable tissues such as brain, peripheral nerve, and skeletal muscle. Most important in the context of this review are *SCN4A* and *SCN5A*, the genes associated with diseases in humans: hyperkalemic periodic paralysis (also in horses, see Fig. 6), paramyotonia congenita, potassium-aggravated myotonia (see sect. III A), and long Q-T syndrome 3 (see sect. IV). Although the product of *SCN4A* is the only sodium channel α -subunit detectable in the fully differentiated and innervated skeletal muscle, *SCN5A* is expressed in both cardiac muscle and in fetal skeletal muscle. Additionally, *SCN8A* is a candidate gene for inherited neurodegenerative diseases due to a deletion in the mouse homolog causing motor end-plate disease and ataxia (MED jolting, Fig. 3). Even in the fruit fly *Drosophila melanogaster*, mutations in the para locus encoding a neuronal voltage-gated sodium channel that is very similar to those of vertebrate sodium channels causes paralysis (see sect. VA).

B) PORE REGIONS IDENTIFIED BY TOXIN BINDING. Most α -subunits expressed in brain and skeletal muscle are sensitive to tetrodotoxin (TTX), which blocks ion flux through the sodium channels by binding to the proximal part of the S5-S6 interlinker of repeat I and thereby occludes the external mouth of the pore in micromolar concentrations. Binding of TTX in these channels is conferred by an aromatic amino acid (Tyr or Phe) not present in the product of *SCN5A*, which is ~ 200 -fold less sensitive to the toxin due to a cysteine residue at an equivalent position (83, 465). Origins of this obviously extremely poisonous substance are liver and ovaries of the Puffer fish *Fugu*

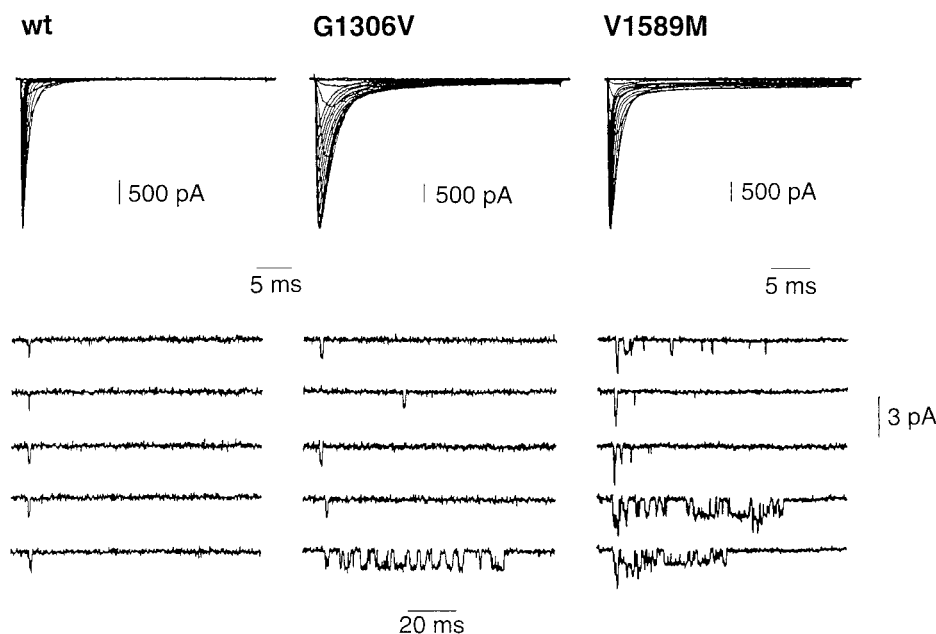


FIG. 5. Two examples of faulty inactivation of mutant sodium channels of skeletal muscle. Patch-clamp recordings from normal (wt), Gly-1306-Val, and Val-1589-Met channels expressed in HEK 293 cells. *Top panels:* families of sodium currents recorded at various test potentials in whole cell mode show slowed decay and failure to return completely to baseline. Slowed inactivation is more pronounced with Gly-1306-Val; persistent inward sodium current is larger for Val-1589-Met. *Bottom panels:* traces of 5 single-channel recordings each obtained by clamping membrane potential to -20 mV. Mutant channels show reopenings that are reason for "macroscopic" current alterations shown in *top panels*. [Modified from Mitrovic and co-workers (361, 363).]

whose flesh and testes are an exquisite Japanese dish. Separation of the ovaries from the testes in the hermaphrodite fish is a prerequisite for consumption, a task requiring expertise if the physiologically interested gourmet is to survive.

Sea anemone toxin (ATX) and α -scorpion toxin (α -ScTX) also bind to the extracellular surface of the channel at overlapping sites of the S3-S4 loop of repeat IV, in particular to a glutamate residue only present in the neuronal subunit (439). Both ATX and α -ScTX impair fast inactivation, although the inactivation particle, part of the III-IV interlinker, can block the channel from the intracellular side. Slowing of fast inactivation may be explained by inhibition of the depolarization-induced outward movement of IVS4 that initiates both activation and coupled fast inactivation. A similar depolarization-induced movement of IIS4 is needed for the binding of β -ScTX to its extracellular end and to a receptor site that includes a highly conserved glycine in the adjacent S3-S4 loop, thereby shifting the voltage dependence of activation to more negative potentials and enhancing the closed state inactivation (75a). Extracellular application of another excitotoxin, δ -conotoxin P_{VIA}, produced by the inedible fish-hunting purple cone snail, *Conus purpurascens*, also slows fast inactivation, resulting in increased sodium current and membrane depolarization (488, 531).

C) STRUCTURES MEDIATING INACTIVATION. Disturbance of fast inactivation is not only a popular toxin mechanism but also is decisive for sodium channel disease pathogenesis (66, 68, 283, 284, 289), indicating a crucial function in the ability of cells to maintain their homeostasis. Regions important for the inactivation process in the sodium channel were identified by deletion of 10 amino acids at the NH₂-terminal end of the inactivation loop between re-

peats III and IV, which completely blocked fast channel inactivation (390). The inactivation particle itself is thought to be formed by three hydrophobic amino acids (Ile-Phe-Met) downstream within this loop, whereby replacement of Phe-1489 (of the rat brain IIa sodium channel corresponding to Phe-1311 in the human skeletal muscle isoform) alone already led to abolishment of fast inactivation (573) (Fig. 4). A cysteine substitution for phenylalanine is only accessible to intracellular thiol reagent in the hyperpolarized state, i.e., when the channel is not inactivated (254). The interaction of the inactivation particle with its receptor is likely to be hydrophobic, since there is a close correlation between the hydrophobicity of the Ile-Phe-Met substitutions studied and the extent of inactivation. Current research focuses on the hydrophobic parts of the putative intracellular orifice of the pore or its surrounding protein parts which may act as receptor of the inactivation particle (136, 295, 345). Identification of this acceptor site may give a clue to which residues contribute to the intracellular mouth of the permeation pathway.

D) VOLTAGE DEPENDENCE OF INACTIVATION. Fast inactivation derives most of its voltage dependence from coupling to activation. The conformational changes resulting from depolarization-induced activation increase the rate of inactivation. Although the structural nature of this coupling is unknown, electrophysiological experiments on naturally occurring mutants revealed that mutations in segment S4 of domain IV selectively affect the voltage dependence of inactivation time constants (76, 377).

E) SODIUM CHANNEL β -SUBUNITS (FIG. 3). Several different genes encoding β -subunits seem to exist (Table 1); however, only one, *SCN1B*, has been localized, and two gene products have been characterized to date. Only β_1 is

TABLE 1. *Sodium channels*

Gene	Accession ID	Gene Locus	Sodium Channel Type/Disease	Tissue Expression	Reference No.
<i>SCN1A</i>	GDB: 118870 S71446	2q24	<i>SCN1</i> , vg type I, α -subunit (280 kDa)	Brain	330
<i>SCN1B</i>	GDB: 127281 U12188-12194 L16242, L10338	19q13.1	Hs.89634, vg type I, β_1 -subunit (38 kDa)	Brain, heart, skeletal muscle	221, 328, 341
<i>SCN2A1</i>	GDB: 120367	2q23	<i>SCN2A</i> , HBSCI, vg type II, α_1 -subunit (280 kDa)	Brain, peripheral nerve	7a
<i>SCN2A2</i>	GDB: 133727	2q23-24.1	HBSCII, vg type II, α_2 -subunit	Brain	7a
<i>SCN2B</i>	GDB: 118871 AF049498		vg type II, β_2 -subunit (33 kDa)		222
<i>SCN3A</i>	GDB: 132151 S69887	2q24-31	vg type III, α -subunit (280 kDa)	Brain	331
<i>SCN4A</i>	GDB: 125181 L04216-LO4236	17q23.1-25.3	SkM1, vg type IV α -subunit (260 kDa), hyperkalemic periodic paralysis, paramyotonia congenita, potassium-aggravated myotonia	Skeletal muscle	144, 342, 564
<i>SCN4B</i>	GDB: 125182		vg type IV, β -subunit		
<i>SCN5A</i>	GDB: 132152	3p21	SkM2, hH1, vg type V, α -subunit, long Q-T syndrome 3	Heart, fetal skeletal muscle	155a, 160a
<i>SCN6A</i>	GDB: 132153	2q21-23	Hs.99945, vg type VI, α -subunit	Heart, uterus, fetal and denervated skeletal muscle	158, 159
<i>SCN7A</i>	GDB: 228137		vg type VII, α -subunit		402a
<i>SCN8A</i>	GDB: 631695	12q13	vg type VIII, α -subunit, motor end-plate disease + ataxia in mice	Brain, spinal cord	107, 401
<i>SCN9A</i>	GDB: 3750013		vg type IX, α -subunit, neuroendocrine type	Thyroid and adrenal gland	259
<i>SCN10A</i>	GDB: 3750014	1pter-p36.3	hPN3, vg type X	Sensory neurons, dorsal root ganglia	422a
<i>SCNN1A</i>	GDB: 366596 Z92978	12p13	<i>SCNN1</i> , nvg type I α -subunit of ENaC	Kidney, lung, colon	349, 516
<i>SCNN1B</i>	GDB: 434471	16p12.2-p12.1	nvg 1 β -subunit, Liddle's syndrome, pseudohypoaldosteronism I	Kidney, lung, colon	516, 549
<i>SCNN1D</i>	GDB: 6053678	1p36.3-p36.2	DnaCh, nvg 1 δ -subunit	Kidney, lung, colon	554, 555
<i>SCNN1G</i>	GDB: 568759 X87160 U53835-U53853	16p12.2-p12.1	nvg 1 γ -subunit, Liddle's syndrome, pseudohypoaldosteronism I	Kidney, lung, colon	549

Gene names, accession numbers, protein names, and tissue expression of voltage-gated (vg) and non-voltage-gated (nvg) sodium channels are listed. When no information on tissue expression in humans was available, data for other mammals are given. GDB, genome database (<http://gdbwww.gdb.org>); GB, GenBank (<http://www.ncbi.nlm.nih.gov/Entrez>).

expressed in skeletal muscle, whereas brain and heart additionally express β_2 , which is covalently bound to the α -protein (187) by disulfide bonds (222). Sequence analysis of the noncovalently bound β_1 suggests a structure consisting of a single transmembrane segment with an extracellular NH₂ terminal containing glycosylation sites (221). The 1:1 stoichiometry of $\alpha\beta$ -binding indicates only one of the four domains to mediate the binding site (268) that is located in the extracellular parts of the S5-S6 loops of the second and fourth domain (329). In *Xenopus* oocytes, the heterologously expressed α -subunit shows slower inactivation than when coexpressed with the β -subunit, with the slowing corresponding to additional channel reopenings or bursts (221, 266, 267). This suggests at least two gating modes, the one with the faster inactivation being stabilized by β_1 (220, 223, 234, 477). Site-directed mutagenesis of β_1 showed that small deletions in the extracellular domain slow both inactivation

and recovery from inactivation, whereas deletion of the intracellular COOH terminus had no effect (82).

Although in *Xenopus* oocytes the β_1 -subunit increased functional expression and current amplitude, shifted the steady-state activation and inactivation curves toward more negative potentials, and accelerated recovery from inactivation (328) of the α -skeletal subunit, it had no effect on the gating of the cardiac channel (328). In mammalian cells without endogenous β_1 -production, co-expression of β_1 had similar effects except for the almost missing acceleration of the already fast inactivation of the channel (223). This suggests the change in kinetics may be due to posttranslational modifications (phosphorylation and glycosylation) or lack of compatible endogenous auxiliary subunits in amphibian cells compared with mammalian expression systems. It is the β_1 -subunit that shows mutations causing human disease: febrile seizures and generalized epilepsy (see sect. vA, Fig. 3).



EXPLANATION FOR PARALYTIC ATTACKS IN HYPERKALEMIC PERIODIC PARALYSIS PATIENTS

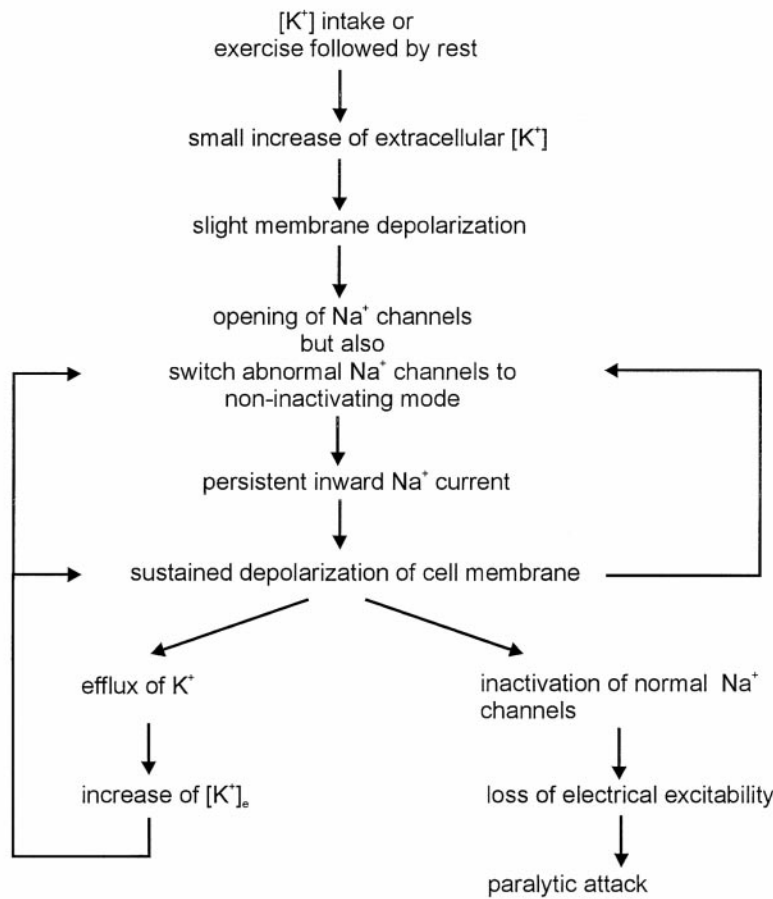


FIG. 6. *Top*: a paralytic attack in hyperkalemic periodic paralysis elicited by rest after exercise. A naturally occurring animal model, affected quarter horse, is shown. (Courtesy of Dr. E. P. Hoffman.) *Bottom*: sequence of cellular events in hyperkalemic periodic paralysis patients that may result in muscle paralysis. $[K^+]_e$, extracellular K^+ .

F) VOLTAGE-INSENSITIVE SODIUM CHANNELS. A novel gene superfamily (SCNN, Table 1) that encodes voltage-insensitive ion channels involved in neurotransmission and in the control of cellular and extracellular volume as well as of distinct functions, such as mechanotransduction, con-

tains the amiloride-sensitive epithelial sodium channel (ENaC) (64). This heteromultimeric protein, made up of three homologous subunits, α , β , and γ , each containing only two transmembrane segments, is rate-limiting for electrogenic sodium reabsorption in the distal part of the

renal tubule, the distal colon, and the airways (60). Expression of the α -protein is obligatory for the channel to function. A gain or change of function in human ENaC has been described in Liddle's syndrome, an autosomal dominant form of salt-sensitive hypertension (pseudohyperaldosteronism) resulting from point mutations in the β - or γ -subunits (470, 486), whereas loss-of-function mutations cause salt wasting with hyperkalaemic acidosis (pseudohypoaldosteronism type I; Refs. 79, 176, 515). Because voltage-insensitive channels are not the topic of this review, these diseases are not discussed in more detail.

3. Calcium channels

In axon terminals and sarcolemma, calcium influx is mediated along the electrochemical gradient by voltage-gated calcium channels. As in sodium channels, membrane depolarization activates them in a positive-feedback mechanism. In contrast to sodium channels, rate constants for activation and the channel's intrinsic inactivation are slower so that repolarization of the membrane is delayed.

A) CLASSIFICATION. Voltage-gated calcium channels are classified into transient (T-type) and long-lasting (L-type) currents according to their inactivation properties, and B (brain), N (neuronal), P (Purkinje cell), and R (toxin resistant) channels are distinguished depending on their tissue expression pattern and toxin sensitivity. Although T-type channels are low-voltage activated (LVA), the thresholds for L-type and P-types are high-voltage activated (HVA). Pharmacologically, N-type channels are blocked by ω -conotoxin M_{VIC} (198) and P-type channels by the funnel web spider toxin ω -Aga_{IVA} and by ω -conotoxin G_{IVA} (359). L-type channels are very sensitive to dihydropyridines (DHP; e.g., nifedipine), phenylalkylamines (e.g., verapamil), and benzothiazepines (e.g., diltiazem), which has led to the term *dihydropyridine receptor*, a misnomer because it suggests ligand activation when, in fact, the channel is activated voltage dependently. R-type channels are resistant to these toxins and drugs; they are opened by a depolarization smaller than that needed for HVA channels such as L-type channels and larger than that necessary for LVA channels like the T-type channels (426).

Voltage-gated calcium channels and especially the cardiac L-type channel are modulated by cAMP-dependent protein kinase A via certain G_s proteins (586). The α_1 -subunits of N, P, and R channels may be voltage-dependently inhibited by G proteins by a direct interaction between the G $\beta\gamma$ complex and the α_1 -subunit (111, 194, 208), e.g., somatostatin, carbachol, ATP, and adenosine are able to reduce inward current amplitude and to slow inactivation, effects that can be prevented by pertussis toxin (348), a G protein inhibitor. These stimulatory or inhibitory receptor-coupled mechanisms may coexist

in synapses of the autonomous nervous system and its effector cells.

B) CALCIUM CHANNEL α -SUBUNIT ENCODING GENES. Eight different α_1 -subunit genes (*CACNA* to *GACNG*, Table 2) with homologous structure of their products to the sodium α -subunits have been published in vertebrates (Fig. 2). The high selectivity for calcium over sodium is conferred by a group of conserved glutamate residues forming a high-affinity calcium binding site in the pore exhibiting an apparent dissociation constant of ~ 700 nM (582). Nevertheless, the channel conducts a reasonably high calcium flux, probably by the vicinity of a second binding site. When only one of the sites is occupied, which is the case at low concentration, calcium is bound tightly. However, as soon as the probability of double occupancy increases at higher calcium concentration, electrostatic repulsion drastically reduces the time that the ions spend at the site and calcium flows through the channel along its electrochemical gradient. Therefore, monovalent cations (e.g., sodium) pass the channel in the absence of divalents, micromolar calcium blocks the monovalent current, and millimolar external calcium leads to an almost pure calcium inward current (10). This binding site is conserved through all α_1 -subunits of the calcium channel family.

C) CALCIUM CHANNEL α -SUBUNITS OF BRAIN (FIG. 7 AND PARTICULARLY FIG. 17 IN SECTION VC). The neuronal α_{1A} channel expressed in brain, presynaptic membrane of neuromuscular junction, axon-associated Schwann cells, and distal kidney convolute tubule is a master of disguise (574). Its subcellular localization in the cerebellum, for example, is determined by at least 10 different splice variants known to date, i.e., BI-1 is mainly expressed in the dendrites while rBA is located primarily in the membrane of soma and axon terminal (460). Not only the multiple splice variants modify its gating properties but also the variability in coexpression of auxiliary subunits (596). The resulting electrophysiological properties exhibit such different characteristics as the rapidly inactivating Q-type current (granular cell-type calcium channel) and the slowly inactivating P-type current (Purkinje cell calcium channel; Ref. 502) originally thought to be mediated by two totally different voltage-gated calcium channels. Additional variations result from interaction with N-type channels in vesicle formation and neurotransmitter release. The II-III loop of the protein binds syntaxin, which in turn has a functional effect on the PQN channel complex. Mutations in α_{1A} cause familial hemiplegic migraine, episodic ataxia type 2, and spinocerebellar atrophy type 6 in humans as well as ataxia and seizures in mice (*tottering* and *leaner*) (see sect. VC).

D) CALCIUM CHANNEL α -SUBUNITS OF THE VARIOUS MUSCLE TYPES (FIG. 7). Different splice variants of the same gene, *CACNA1C*, encode the L-type calcium channel of heart (α_{1Ca}) and smooth muscle (α_{1Cb}), whereas the main subunit of the L-type calcium channel of skeletal muscle, α_{1S} ,

TABLE 2. *Calcium channels*

Gene Name	Accession ID	Gene Locus	Calcium Channel Type/Disease	Tissue Expression	Reference No.
<i>CACNA1A</i> <i>CACNLI4</i>	GDB: 126432 Z80114-Z80155, X99897, U79666	19p13 19p13.1	P/Q-type α_{1A} -subunit, episodic ataxia 2, familial hemiplegic migraine, spinocerebellar ataxia 6; <i>tottering</i> , <i>leaner</i> , and <i>rolling</i> mice	Brain (cortex, bulbus, olfactorius, hippocampus, cerebellum, brain stem), motoneurons, kidney	104, 112, 320, 378, 425, 509
<i>CACNA1B</i> <i>CACNLI5</i>	GDB: 580689 M94172, M94173	9q34	<i>CACNN</i> , N-type α_{1B} -subunit	Central, peripheral nervous system	104, 112
<i>CACNA1C</i> <i>CACNLI1</i>	GDB: 126094 L29536, L29534, L29529	12p13 12p13.3	<i>CCHLIA1</i> , L-type α_{1C} -subunit	Heart, fibroblasts, lung, smooth muscle (2 splice variants)	276, 403, 479
<i>CACNA1D</i> <i>CACNLI2</i>	GDB: 128872	3p14.3 3p21.3/2?	<i>CCHLIA2</i> , L-type α_{1D} -subunit	Brain, pancreas, neuroendocrine	87, 575, 580
<i>CACNA1E</i> <i>CACNLI6</i>	GDB: 434408	1q25-31	R-type α_{1E} -subunit	Brain, skeletal muscle (end plate)	104, 112, 503
<i>CACNA1F</i> <i>CACNLI7</i>	GDB: 6053864 AF27984	Xp11.23-11.22 17q22	α_{1F} -Subunit T-type α_{1G} -subunit	Retina Brain	28, 138, 518 394
<i>CACNA1S</i> <i>CACNLI3</i>	GDB: 126431 Z22672, L33798 U30666-U30707	1q31-32	L-type α_{1S} -subunit (5% 212, 95% 190 kDa), malignant hyperthermia 5, hypokalemic periodic paralysis	Skeletal muscle (brain, kidney)	117, 170, 201
<i>CACNA2</i> <i>CACNL2A</i>	GDB: 132010 Z28613, Z28609 Z28605, Z28602 Z28599, M76559	7q21-22	<i>CACNA2</i> , <i>CACNA2D1</i> , α_2/δ -subunit (175 kDa), MHSS	α_{2A} : skeletal muscle, heart, brain, ileum; α_{2B} : brain; $\alpha_{2C/D}$: aorta	73, 126, 209, 405, 471
<i>CACNB1</i> <i>CACNLB1</i>	GDB: 132012 GDB: 1073281 U86952-U86961 M76560, L06111	17q21-22	β_1 -Subunit (524 aa, 54 kDa)	β_1A/M : skeletal muscle β_1B/C : brain, heart, spleen	170, 210, 404, 406, 454, 575
<i>CACNB2</i> <i>CACNLB2</i>	GDB: 132014 Q08289	10p12	MYSB, β_2 -subunit	$\beta_2A/B/E$: brain, heart, lung, aorta	206, 443, 529
<i>CACNB3</i> <i>CACNLB3</i>	GDB: 341023 L27584	12q13	β_3 -subunit (482 aa)	Brain, heart, lung, spleen, skeletal and smooth muscle, aorta, trachea, ovary, colon	94, 206, 386, 580
<i>CACNB4</i> <i>CACNG</i> <i>CACNLG</i> <i>CACNG2</i>	GDB: 6028693 GDB: 132015 L07738	2q22-23 17q24	β_4 -subunit, <i>lethargic</i> mice γ -Subunit (222 aa, 30 kDa) γ_2 -Subunit, <i>stargazin</i> , <i>absence epilepsy</i> <i>stargazer</i> , <i>wagglers</i> mice	Brain, kidney Skeletal muscle, lung Brain	72, 529, 556 45, 210, 211, 229, 576 300
<i>RYR1</i>	GDB: 120359	19q13.1	Ryanodine receptor 1, Ca release channel, 3 splice variants, malignant hyperthermia 1, central core disease	Skeletal muscle, testis, brain, submaxillary and adrenal glands, spleen	163, 324, 340, 597
<i>RYR2</i>	GDB: 125278	1pter-qter 1q42.1-43	RYR2, calcium release channel	Heart, smooth muscle	380
<i>RYR3</i>	GDB: 138451	15q14 15q14-15	RYR3, calcium release channel	Brain, neonatal skeletal muscle, adult diaphragm	96, 429, 504, 528

Gene names, accession numbers, protein names, and tissue expression of voltage-gated calcium channels are given. Ryanodine receptor, a ligand-gated channel, is included since it is under control of voltage-gated L-type channel in skeletal muscle. When no information on tissue expression in humans was available, data for other mammals are given. aa, Amino acids.

is encoded by another gene, *CACNAIS*. Physiologically, two α_{1S} -isoforms are expressed: the rare 212-kDa complete protein and a likewise functional truncated form of 190 kDa comprising 95% of total channel population resulting by posttranslational proteolysis at amino acid 1690 (24, 106). An additional variant has been suggested to

exist, at least in postnatal skeletal muscle (332). Further functional alterations have also been demonstrated, i.e., by phosphorylation; however, the physiological importance of these alterations, which are acknowledged for the cardiac channel, seems questionable for skeletal muscle (140). Mutations in α_{1S} cause hypokalemic periodic

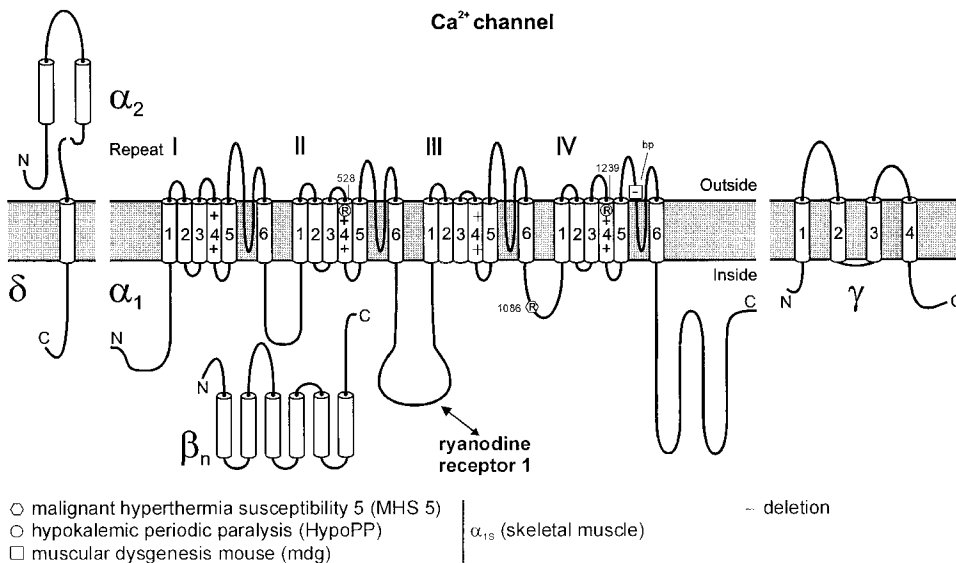


FIG. 7. Subunits of voltage-gated calcium channel. α -Subunit resembles that of sodium channel; however, function of various parts, e.g., III-IV linker, may not be same. α_2/δ , β_1 to β_4 , and γ are auxiliary subunits. Mutations shown here, α_{1S} -subunit of skeletal muscle L-type calcium channel (= dihydropyridine receptor), have been described for humans (HypoPP, MHS 5) and mice (mdg). Mutations have been also reported for α_{1A} -subunit of brain P/Q-type channel (see Fig. 17) and β_4 -subunit causing tottering mice. Conventional 1-letter abbreviations are used for replaced amino acids whose positions are given by respective numbers of α_{1S} -subunit. Symbols used for point mutations indicate resulting diseases as explained at *bottom left*.

paralysis and malignant hyperthermia susceptibility type 5 in humans as well as muscular dysgenesis in mice (see sect. III B).

E) ADDITIONAL SUBUNITS OF CALCIUM CHANNELS (FIG. 7). Even though the α_1 -subunits form functional channels by themselves, maximally four additional subunits, α_2 , β , γ , and δ copurified. The extracellularly located α_2 protein is anchored by disulfide bonds to the membrane-spanning subunit (230, 178), and the two proteins are encoded by a single gene. It was originally thought to possess an ion-conducting pore since expression in cells devoid of functional calcium channels resulted in an appreciable calcium current. In the meantime, this phenomenon can be explained by the drastic increase in expression of endogenous α_1 -subunits by coexpression of α_2/δ -subunit (179). This subunit, which can bind the anticonvulsant drug gabapentin, not only increases α_1 -expression rates and current density, but also accelerates inactivation kinetics and slightly shifts both steady-state inactivation and activation curves in hyperpolarizing directions (494).

Coexpression of any of the four β -subunits with α_{1A} markedly increases the number of channel complexes inserted into the membrane and the current amplitude (51). For α_{1S} , β -coexpression increased the number of DHP binding sites and accelerated current activation kinetics, however, without increasing current density (276, 546). Similar effects have been noted for α_{1C} when expressed in oocytes increasing both rate of activation and current density (393, 572). In addition to the intracellular I/II loop, the COOH terminal also seems to act as a binding site for β (556). The type of β can decisively determine current characteristics of the whole channel complex, i.e., β_{2A} induces the P-type current and β_{1B} and β_3 induce the Q-type current when coexpressed with α_{1A} (509). β_1 is an intracellular acidic protein and binds to the loop connecting domains I and II of the α_1 -subunit, distinct from the

consensus site for the G protein $\beta\gamma$ -complex (111). On the other hand, β_3 is capable of differential modulation of G protein inhibition of α_{1A} and α_{1B} subunits (437). Mutations in β_4 are found in the *lethargic* mouse (see sect. vC).

The γ -subunits consist of four transmembrane segments and are expressed in skeletal muscle and brain. Coexpression with skeletal muscle γ -subunits with cardiac α_1 -subunits in amphibian and mammalian cell systems moderately increased calcium current amplitude and inactivation rate. The main effect is a marked shift of the voltage dependence of inactivation in the hyperpolarizing direction (494, 293). The brain γ -subunit stargazin has a similar effect when coexpressed with the P/Q-type calcium channel, and mutations therein cause absence epilepsy in the *stargazer* mouse (300) (see sect. vC). Additional γ -subunits may exist (124).

F) OTHER CALCIUM CHANNELS. Two distinct classes of channels mediating release of calcium ions from intracellular stores have been identified: they are sensitive either to inositol 1,4,5-trisphosphate (InsP₃) or to a nonphysiological ligand, the plant alkaloid ryanodine. The latter, the ryanodine receptor, releases calcium from the sarcoplasmic reticulum (SR) or endoplasmic reticulum (ER), an essential step for contraction of skeletal, heart, and smooth muscle (Figs. 8 and 9). In the heart, calcium release is initiated by the calcium influx through the fast-activating T-type calcium channel and maintained by L-type channels during the plateau phase of the action potential. Calcium activates RYR2, the ryanodine receptor expressed in cardiac and smooth muscle. In skeletal muscle, calcium release is initiated by the surface membrane action potential, which spreads via the transverse tubular (t-tubular) system within the fiber. A depolarization of the tubular membrane activates the L-type calcium channel leading to a fast conformational change of one or more intracellular loops which open RYR1, the ryanodine receptor expressed in skeletal muscle. This signal

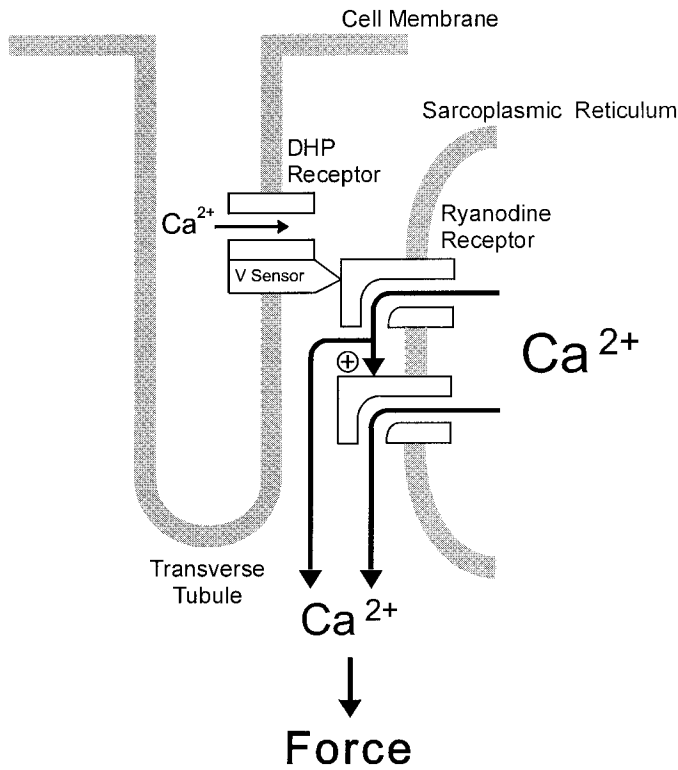


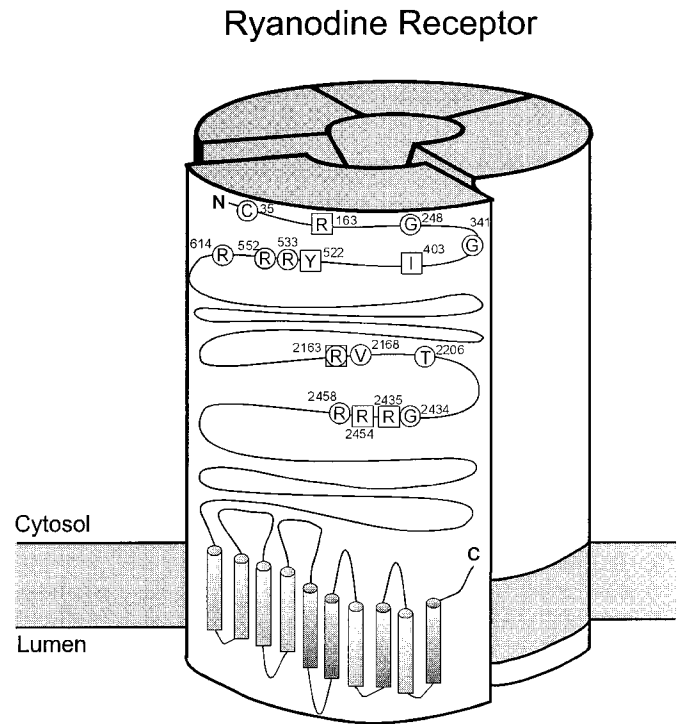
FIG. 8. Triadic junction between a transverse tubule and sarcoplasmic reticulum: position of 2 calcium channels of skeletal muscle, L-type calcium channel, also called dihydropyridine (DHP) receptor, and calcium release channel, also called ryanodine receptor. Coupling between the 2 channels is not fully elucidated. Mutations in respective genes cause hypokalemic periodic paralysis, malignant hyperthermia, or central core disease.

transmission between the t-tubular and SR membrane is referred to as excitation-contraction (EC) coupling (for review, see Ref. 149).

Ryanodine receptors are among the largest known proteins consisting of homotetramers each over 5,000 amino acids with a molecular mass of ~565 kDa. Morphological studies revealed a quatrefoil structure with the hydrophobic parts of the four subunits forming a membrane-spanning base plate and the hydrophilic segments forming a cytoplasmic domain, the foot, which bridges the gap between t-tubular and SR membrane. Despite of the huge size, RYR1 channels can be functionally expressed by transient transfection and reveal very similar characteristics to those of the native channel, e.g., a calcium conductance of 116 pS in 50 mM calcium and an open time constant of 0.22 ms (85). RYR1 mutations cause susceptibility to malignant hyperthermia, type 1, a potentially lethal event during general anesthesia, and some of them lead to central core disease, a congenital myopathy (325) (see sect. III B).

4. Potassium channels

Membrane depolarization activates voltage-gated potassium channels that, once opened, conduct potassium



- malignant hyperthermia (MH)
- ◻ malignant hyperthermia/central core disease (MH/CCD)

FIG. 9. Cartoon of homotetrameric ryanodine receptor, calcium release channel situated in membrane of sarcoplasmic reticulum (SR). Cytosolic part of protein complex, the so-called foot, bridges gap between transverse tubular system and SR. Mutations have been described for skeletal muscle ryanodine receptor (RYR1) that cause susceptibility to malignant hyperthermia and central core disease. Conventional 1-letter abbreviations are used for replaced amino acids whose positions are given by respective numbers of human RYR1. [Modified from Melzer et al. (352).]

ions along the concentration gradient against the electric field. This outward current leads to repolarization of the membrane. In addition to voltage-gated channels, there is a large spectrum of potassium channels more or less sensitive to membrane potential and activated or blocked by endogenous ligands. Voltage-insensitive potassium channels convey background conductance and therefore determine the resting membrane potential of cells, excitable and nonexcitable. They also play a role in volume regulation and signal transduction.

Potassium channels constitute the most diverse class of ion channels with respect to kinetic properties, regulation, pharmacology, and structure (Tables 3 and 4). In vertebrates, over 13 subfamilies have been described, 8 of which show the typical voltage-dependent channel structural features with voltage sensor, toxin binding sites, and a single ion-conducting pore. Because of the high variability in structure, the channels can be classified according

TABLE 3. *Classical voltage-gated potassium channels*

Gene	Accession ID	Gene Locus	Potassium Channel Type/Disease	Tissue Expression	Reference No.
<i>KCNA1</i>	GDB: 127903 L02750	12p13	RBK1, HUK1, MBK1, AEMK, Kv1.1, <i>Shaker</i> homolog 1, <i>Shaker</i> , episodic ataxia 1 (with myokymia)	Brain, nerve, heart, skeletal muscle, retina, pancreatic islet	100, 579
<i>KCNA1B</i>		3q26.1	Kv β 1.1, Kv β 1.3 (splice product), β -subunit		478
<i>KCNA2</i>	GDB: 128062 X17622	12pter-qter	HK4, Kv1.2, <i>Shaker</i> homolog 2	Brain, nerve, heart, pancreatic islet	173
<i>KCNA2B</i>		1p36.3	Kv β 1.2, β -subunit		478
<i>KCNA3</i>	GDB: 128079 L23499	1p13.3	Hs.1750, MK3, HLK3, HPCN3, Kv1.3, <i>Shaker</i> homolog 3	Skeletal muscle, lymphocytes (brain, lung, thymus, spleen)	143, 277
<i>KCNA4</i>	GDB: 126730 M60450 M55514	11p14	Hs.89647, Hs.1854, HK1, HPCN2, Kv1.4, <i>Shaker</i> homolog 4	Brain, nerve, heart, fetal skeletal muscle, pancreatic islet	396, 579
<i>KCNA4L</i>	GDB: 386059	11q14	<i>Shaker</i> homolog type 4-like		396
<i>KCNA5</i>	GDB: 127904 M83254 M60451	12p13.3-13.2 12p13 12p13.33-13.31	Hs.89509, HK2, HPCNI, Kv1.5 <i>Shaker</i> homolog 5	Brain, heart, kidney, lung, skeletal muscle, pancreatic islet	277
<i>KCNA6</i>	GDB: 128080 X17622	12p13	HBK2, Kv1.6, <i>Shaker</i> homolog 6	Brain, pancreatic islet	427
<i>KCNA7</i>	GDB: 127905	19q13.3	HAK6, Kv1.7 <i>Shaker</i> homolog 7		243, 277, 346
<i>KCNA8</i>			see <i>KCNQ1</i>		
<i>KCNA9</i>			see <i>KCNQ1</i>		
<i>KCNA10</i>	GDB: 5885822		<i>Shaker</i> homolog type 10, cGMP activated		379
<i>KCNB1</i>	GDB: 128081	20q13.2	Kv2.1, <i>Shab</i> homolog 1	Brain, heart, kidney, retina, skeletal muscle	9, 351
<i>KCNB2</i>			Kv2.2, <i>Shab</i> homolog 2	Brain, heart, retina	
<i>KCNC1</i>	GDB: 128082 S56770 M96747	11p15.1	Kv3.1, <i>Shaw</i> homolog 1	Brain, skeletal muscle, spleen, lymphocytes	
<i>KCNC2</i>	GDB: 127906	19q13.3-13.4	Kv3.2, <i>Shaw</i> homolog 2	Brain	183, 346
<i>KCNC3</i>	GDB: 127907	19q13.3	Kv3.3, <i>Shaw</i> homolog 3	Brain, liver	183, 346
<i>KCNC4</i>	GDB: 127908	1p21	Kv3.4, HKSHIIC, <i>Shaw</i> homolog 4	Brain, skeletal muscle	162, 346, 451
<i>KCND1</i>	GDB: 128083		Kv4.1, <i>Shal</i> homolog 1	Brain	
<i>KCND2</i>	GDB: 134771		RK5, Kv4.2, <i>Shal</i> homolog 2	Brain, heart, aorta	
<i>KCND3</i>	GDB: 134772		Kv4.3, KSHIVB, <i>Shal</i> homolog 3		

Gene names, accession numbers, protein names, and tissue expression of classical voltage-gated (Kv: rapidly inactivating A-type and slowly inactivating delayed rectifier) channels are given. When no information on tissue expression in humans was available, data for other mammals are given. aa, Amino acids.

to the number of pore regions (P) and the number of helical structures that were thought to correspond to the number of transmembrane segments (termed T or S in the voltage-gated and M in the 4 ligand-gated channels).

As to be expected by their diversity, even voltage-gated potassium channels are expressed in nonexcitable tissues. This knowledge, which seems taken for granted today, was gained by a shift of weather-altering water currents in which giant squids roamed about near the coast of Irvine, California. Because of the absence of their beloved experimental animal, the potassium channel scientists were in immediate need of other plentiful research material, a problem they solved by changing to human blood lymphocytes also expressing the potassium channels of interest.

A) CLASSICAL VOLTAGE-GATED α -SUBUNITS: KV AS HUMAN HO-

MOLOGS OF *SHAKER*, *SHAB*, *SHAW*, AND *SHAL* (FIG. 2). These channels inactivate at different rates and to a varying extent (fast N-type and slow C-type inactivation). The rapidly inactivating A-type Kv channels operate in the subthreshold range of an action potential and play a key role in the generation of pre- and postsynaptic signals; the slowly inactivating, delayed rectifying channels repolarize the cell membrane during an action potential and reduce cell excitability. Both types are found in almost all eukaryotic cells of the animal and plant kingdom (450) and are not only present in nerve or muscle cells, but also in lymphocytes, pancreatic islet cells, and others (173). The α -subunits, typically forming tetramers, contain six transmembrane segments (6T). Four potassium channel families show this pattern (name of the corresponding gene in parentheses), namely, *Shaker*/Kv1 (*KCNA*), *Shab*/Kv2

TABLE 4. *Additional potassium channels*

Gene	Accession ID	Locus	Potassium Channel Type/Disease	Tissue Expression	Reference No.
<i>KCNE1</i>	GDB: 127909	21q22.1-22.2	MinK, ISK, vg Isk homolog 1 (129 aa), long Q-T syndrome 5	Kidney, submandibular gland, uterus, heart, cochlea, retina	86, 366, 458, 506
<i>KCNMA1</i>	GDB: 386031 U09383-4 U02632	10pter-qter 7q32.1	SLO, Hs.62679, α -subunit member 1, α -subunit of maxiK or BK channel	Fetal skeletal muscle	5, 385
<i>KCNMB1</i>	GDB: 6099615 U42600	5q34	hSLO- β , β -subunit member 1 (191 aa), β -subunit of maxiK or BK channel	Smooth, fetal skeletal muscle, brain (hippocampus, corpus callosum)	537
<i>KCNN1</i>	U69883		SK(Ca)1, small-conductance Ca-activated K channel, apamin-insensitive	Brain, heart	263
<i>KCNN2</i>			SK(Ca)2, apamin sensitive	Brain, adrenal gland	263
<i>KCNN3</i>	Y08263 AA285078	1q?	SK(Ca)3, small-conductance Ca-activated K channel, intermediate apamin sensitivity	Brain, heart, (human embryonic) skeletal muscle, liver	77, 263
<i>KCNN4</i>	AF022150 AF022797 AF033021 AF000972	19q13.2	IK1, intermediate-conductance Ca-activated K channel, KCa4, SK4, <i>Gardos</i> channel	T lymphocytes, colon, smooth muscles, prostata, red blood cells, neurons	161, 219, 236, 263, 312
<i>KCNQ1</i>	GDB: 741244 U40990	11p15.5	KCNA9, (KV)LQT1, KQT-like subfamily member 1, long Q-T syndrome 1	Heart, cochlea, kidney, lung, placenta, colon	244, 506, 566
<i>KCNQ2</i>	GDB: 9787229, Y15065, AF033348	20q13.3	KQT-like subfamily member 2 (872 aa)	Brain	39, 495
<i>KCNQ3</i>	GDB: 9787230 AF033347	8q24.22-24.3	KQT-like subfamily member 3 (825 aa)	Brain	80
<i>HERG</i>	GDB: 407638	7q35-36	HERG, similar to ether-à-go go (<i>eag</i>), <i>Ikr</i> , long Q-T syndrome 2	Brain, heart	101, 235, 464, 506, 536
<i>KCNJ1</i>	GDB: 204206 U65406, U12541	11q24	ROMK1, Kir1.1, Hs.463, Bartter/hyperprostaglandin E syndrome	Kidney, pancreatic islets	41, 490, 585
<i>KCNJ2</i>	GDB: 278364 U12507	17pter-qter	IRK1, Kir2.1, Hs.1547	Muscle, neural tissue, heart	422
<i>KCNJ3</i>	GDB: 278325 U50964	2q24.1	GIRK1, Kir3.1	Heart, cerebellum	475, 514
<i>KCNJ4</i>	GDB: 374080 Z97056	22q13.1	HIR, HRK1, HIRK2, Kir2.3	Heart, skeletal muscle, brain	58, 327
<i>KCNJ5</i>	GDB: 547948	11q24	CIR, KATP1, GIRK4, Kir3.4	Heart, pancreas	539
<i>KCNJ6</i>	GDB: 547949 U24660	21q22.1	KCNJ7, GIRK2, KATP2, BIR1, Kir3.2, ataxia, <i>weaver</i> mice	Cerebellum, pancreatic islet	459
<i>KCNJ8</i>	GDB: 633096	12p11.23	Kir6.1, uKATP, ubiquitous K _{ATP} α -subunit	Brain, heart, skeletal, smooth muscle, others	214
<i>KCNJ10</i>	GDB: 3750203	1q22-23	Kir1.2, Kir4.1	Glia	491
<i>KCNJ11</i>	GDB: 7009893	11p15.1	Kir6.2, BIR, K(ATP) α -subunit, hyperinsulinemic hypoglycemia	Pancreatic islets	212
<i>KCNJ12</i>	GDB: 4583927	17p11.1	Kir2.2		205
<i>KCNJ15</i>	GDB: 6275865	21q22.2	Kir4.2		167
<i>KCNJN1</i>	GDB: 6108062		Kir2.2v, subfamily inhibitor 1		369
<i>SUR1</i>	GDB: 591370	11p15.1	SUR(1), sulfonylurea receptor, K(ATP) β -subunit, hyperinsulinemic hypoglycemia	Pancreatic islets	7, 533
<i>SUR2</i>		12p12.1	SUR2, SUR2A,B, sulfonylurea receptor 2 (1545-aa), β -subunit of K(ATP)	2A: heart, 2B: brain, liver, skeletal, smooth muscle, urinary bladder	89, 213, 224
<i>KCNK1</i>	GDB: 6045446	1q42-43	DPK, TWIK1	Kidney	296, 297, 299
<i>KCNK2</i>		1q41	TREK1	Brain	137, 298
<i>KCNK3</i>	GDB: 9773281	2p23	TASK	Kidney	123, 299

Voltage-gated (*LQT*), voltage-sensitive (*SLO*, *Ikr*), and voltage-insensitive potassium channels (calcium-activated, SK and IK, as well as the inward rectifiers, Kir) are listed. Brackets indicate adjacent genes.

(*KCNB*), *Shaw/Kv3* (*KCNC*), and *Shal/Kv4* (*KCND*) (78). Compatibility to aggregate as homotetramers (or within a channel subfamily also as heterotetramer) is conferred by a part of the intracellular NH₂ terminal (303). Tetramers

show fast N-type inactivation if the NH₂ terminal of one of the α -subunits carries the inactivation "ball," e.g., when Kv1.4 is involved. In the absence of the "N-type ball," rapid inactivation can also be achieved by the β_1 -subunit

(322, 428, 485) as for Kv1.1, but, in the presence of an N-type inactivation prevention (NIP region) as in Kv1.6, fast inactivation cannot be achieved even in heteromultimers with Kv1.4. Until now, one human disease is known to be associated to mutations in Kv1.1: episodic ataxia type 1 (see sect. vC).

Voltage-gated potassium channels with unusual characteristics are encoded by the *KCNQ* family. Heterologous expression of *KCNQ1* cDNA encoding a heart potassium channel led to currents whose kinetics were unlike known cardiac potassium currents showing more rapid activation and greater degree of inactivation than the slow delayed rectifier, I_{ks}, despite a common pharmacology such as potentiation by cAMP and blockage by clofilium (584). However, when coexpressed with *KCNE1* cDNA encoding MinK (see below), the potassium current density was much greater and became indistinguishable from I_{ks}. Heterologous expression of *KCNQ2* yielded a slowly activated current with a threshold at -60 mV and full activation at 0 mV with similarities to *KCNQ1* in voltage dependence and kinetics, but coexpression with MinK (*KCNE1*) did not change current characteristics (39). Mutations in *KCNQ1* cause the long Q-T syndrome type 1 (see sect. iv), and mutations in *KCNQ2/3* cause benign neonatal convulsions (see sect. vB).

B) VOLTAGE-SENSITIVE α -SUBUNITS: SLO OR B_K AND IKR OR HERG (FIG. 2). HERG channels have an intracellular NH₂ terminus, whereas SLO has an extracellular one. Consequently, SLO possesses an additional transmembrane segment, called S0 (559). SLO, encoded by *KCNMA1*, is known as the large-conductance (>150 pS with symmetrical potassium concentrations) calcium-activated channel or B_K (B for big) channel that requires massive depolarization for activation in the absence of intracellular calcium. It possesses four additional hydrophobic segments S7-S10 that are thought to be associated with the inner surface of the membrane and convey calcium sensitivity. A β -subunit, hSLO-beta, interacts with SLO and increases its sensitivity to charybdotoxin and intracellular calcium.

Nearly a decade ago, I_{kr} (r for rapid) was electrophysiologically described as a relatively fast delayed rectifier in cardiac myocytes and contrasted to the very slow delayed-rectifying potassium current, I_{ks} (s for slow; Ref. 578). Surprisingly, it showed similarity to the *Drosophila* ether-a-go-go (*eag*) potassium channel, leading to the term *human ether-a-go-go-related gene* (HERG). Heterologous expression indeed showed a potassium channel with gating and pharmacological properties similar to the I_{kr} current. A unique feature of the voltage-dependent gating of this channel is the relatively fast C-type inactivation due to high sensitivity to extracellular cations as well as the slow activation and deactivation in comparison with the rapid inactivation. This combination of gating kinetics produces a novel inward-rectifying behavior of the channel: inactivation is faster than activation so

that membrane depolarization is not associated with an outward current, and recovery from inactivation is faster than deactivation so that repolarization causes a long-lasting tail current (474, 501). The NH₂ terminus stabilizes the open state and, by a separate mechanism, promotes C-type inactivation (565). Two alternatively processed, cardiac-specific isoforms have been identified: a splice variant that has a much shorter NH₂ terminus (280, 314) and another with a truncated COOH terminus that prevents current generation (274). When coexpressed with the full-length cDNA or by itself, the truncated NH₂-terminal isoform displays faster deactivation gating kinetics (280, 314). Heteromers may form the channels responsible for I_{kr} in vivo. HERG mutations cause the long Q-T syndrome type 2 (see sect. iv).

C) VOLTAGE-INSENSITIVE α -SUBUNITS: CYCLIC NUCLEOTIDE-GATED, SK, AND IK (FIG. 2). Although these channels contain similar structures as the voltage-gated α -subunits, i.e., S4 segments with positive residues at almost every third amino acid, they are not activated by depolarization. Cyclic nucleotide monophosphate (cNMP)-gated potassium channels possess an intracellularly located helical segment conveying a cyclic nucleotide binding site situated at the COOH terminus. These channels are not specific for potassium because the specificity filter is altered with the GYGD motif typical for the voltage-gated channels missing (189, 190). Calcium-gated voltage-insensitive potassium channels with small (SK1-3; ~10 pS) and intermediate (IK; ~40 pS) conductance also show the typical 6T structure; the latter is sensitive to charybdotoxin and clomifazole and probably represents the Gardos channel (the Gardos effect is an increase in potassium conductance at ATP depletion in the presence of extracellular calcium as originally reported for red blood cells). The various SK/IK types are resistant to TEA; however, they differ in their affinity to gallamine, D-tubocurarine, and apamin, a bee venom (218, 551). KCa4, SK4, and IK1 seem to be products of the same gene. Because SK and IK are activated by high intracellular calcium, which may result from cell activity, e.g., calcium influx during action potentials or calcium release from intracellular stores, their hyperpolarizing effect may terminate a burst of action potentials. All these channels are not gated by voltage and are therefore not discussed further in this review, even though myotonic dystrophy, the most frequent muscle disorder of human adults, may be related to an abnormal expression of an apamin-sensitive potassium channel (for review, see Ref. 186).

D) 2T/1P α -SUBUNITS: THE INWARD GOING RECTIFIERS (FIG. 2). The simplest motif for voltage-insensitive potassium channel α -subunits are protein tetramers each consisting of only two membrane-spanning segments (M1 and M2) and an interlinker forming the pore. Its architecture has been recently demonstrated by crystallization of the corresponding *S. lividans* channel (17, 114). The homologous human channels

are the inward-going rectifiers, K_{ir} , that are encoded by the over 15 genes of the *KCNJ* family. Rectification results from internal blockade by magnesium ions and the ubiquitously cytoplasmic polyamines such as spermine. Grade of rectification is determined by an important amino acid residue in M2 near the cytoplasmic side of the cell, whereby a negatively charged aspartate confers strong rectification and a neutral asparagine confers weak rectification (571). Although the NH_2 terminal does not carry an inactivation particle, fast inactivation is conferred by spermine. The presence of a lysine residue in the NH_2 terminal conveys sensitivity to pH (134).

$K_{ir3.4}$ and $K_{ir3.2}$ are well known as potassium channel α -subunits that are blocked by intracellular ATP and unblocked at energy depletion (KATP1 and KATP2, respectively), whereas ROMK1 shows a paradoxical effect with ATP activating the channel (199). $K_{ir6.1}$ and $K_{ir6.2}$ interact with the sulfhydrylurea receptors SUR1 and SUR2 (see below) forming hetero-octameric K_{ATP} channel complexes with a $(SUR-K_{ir6.x})_4$ stoichiometry and a tetrameric pore of 76 pS in the fully open state (13, 93), even though neither subunit alone exhibits channel activity. K_{ATP} complexes modulate insulin secretion and are activated by MgADP, cromakalim, pinacidil, and diazoxide and are inhibited by ATP and sulfonylureas, e.g., glibenclamide (213). Some of the inward-going rectifiers of the 2T/1P group are also directly gated by G proteins (GIRK1,2,4), e.g., GIRK1 is opened by parasympathetic nerve stimulation via activation of muscarinic acetylcholine receptors resulting in slower heart rate (272).

Several diseases are caused by mutations in channels encoded by genes of the *KCNJ* family: GIRK2, $K_{ir6.2}$, and ROMK1. A missense mutation in the pore region of the GIRK2 channel causes ataxia in homozygous *weaver* mice that reveal a lack of differentiation of cerebellar granule cells (388). To date, this is the only one gain-of-function potassium channelopathy. Mutations in the pancreatic islet inward rectifier subunit, $K_{ir6.2}$, cause a recessive disease, persistent hyperinsulinemic hypoglycemia of infancy (534), and mutations in ROMK1 or other channels or transporters that are involved in transepithelial chloride transport in the thick ascending limb of Henle, such as the basolateral chloride channel and a basolateral K-Cl cotransporter, lead to an impairment of the furosemide-sensitive salt reabsorption and cause the hyperprostaglandin E syndrome, also termed antenatal variant of Bartter syndrome (215, 492, 109). Because G protein-coupled and ATP-dependent inward rectifiers belong to the group of voltage-insensitive potassium channels, these diseases are not discussed in more detail here.

E) 4T/2P α -SUBUNITS. Next to the 2T/1P type, 4T/2P types of channels have recently been cloned in humans and are encoded by the *KCNK* gene family. Each subunit is equivalent to two core complexes, M1-P-M2-M3-P-M4. Pore function has not been clarified sufficiently, with presumably only

one pore being functional at a given time. This basic structure is found in TWIK (twin P-domain weakly inward-rectifying potassium channel encoded by *KCNK1*) and TASK (TWIK-related acid-sensitive potassium channel encoded by *KCNK2*) channels; the latter senses external pH variations near physiological pH (123). Both are weak inward rectifiers, probably involved in background potassium membrane conductance. The TREK channel (TWIK-related potassium channel encoded by *KCNK3*) acts as an outward rectifier (137). Other potassium channels such as ORK, a 4T/2P outward rectifier, or 8T/2P channels (6T as in voltage-gated channels plus 2T as in inward rectifiers) have been yet been identified in humans.

F) DEFINITIVE AND PUTATIVE β -SUBUNITS. Several sequences and structures turned out to conduct potassium ions only when associated with one of the above-mentioned α -subunits. Of the β -subunit family interacting with the voltage-gated α -subunit from the cytoplasm, two are known: the β_1 -subunit encoded by *KCNA1B* that confers N-type inactivation as well as the β_2 -subunit encoded by *KCNA2B* that increases the expression rate of the whole channel complex (428). A structurally different β -subunit, *hslo-beta*, which contains two transmembrane segments, interacts with SLO and increases its sensitivity to charybdotoxin (185) and to intracellular calcium concentrations >100 nM that occur during cellular excitation and that functionally couple the two subunits (347). MinK proteins (also called ISK or Isk; encoded by *KCNE1*) contain a single transmembranous domain and conduct slowly activating potassium currents when expressed in oocytes and other cell lines that express *KCNQ* channels. The resulting currents are similar to those recorded in cardiac and some epithelial cells and are modulated after activation of various second messenger systems. MinK is suggested to act as the β -subunit with so far unclear stoichiometry. The COOH terminus of MinK is supposed to interact with the pore region of *KCNQ* channels, resulting in prolonged openings and smaller single-channel conductance. Mutations in MinK cause long Q-T syndrome type 5 (see sect. IV). Various other transmembrane β -subunits with tissue specificity are identified or postulated to exist for inward going rectifiers. Mutations in SUR1, the β -subunit of the K_{ATP} channel exclusively expressed in pancreatic islet lead to the same disease as $K_{ir6.2}$ mutations, i.e., hyperinsulinemic hypoglycemia of infancy (122, 533; not further discussed here).

B. Voltage-Gated Anion Channels

The voltage-dependent anion channel (VDAC) is a small, abundant pore-forming protein found in the outer membranes of all eukaryotic mitochondria and in the membranes of other intracellular organelles as well as in the plasmamembrane. Four human VDAC isoforms are known (40). The VDAC protein is believed to form the

TABLE 5. *Voltage-gated chloride channels*

Gene Name	Accession ID	Chromosome Location	Chloride Channel Type/ Disease	Tissue Expression	Reference No.
<i>CLCN1</i>	GDB: 1346887 Z25752-68 L25587	7q32-qter	CLC1, 988 aa, major skeletal muscle channel, myotonia congenita	Skeletal muscle, placenta	262, 511
<i>CLCN2</i>	GDB: 270664	3q27-28	CLC2	Ubiquitous, kidney (S3 segment of the proximal tubule)	90, 373, 532
<i>CLCN3</i>	GDB: 270665 AF029346 X78520	4q33 4q32 4pter-qter	CLC3, protein kinase C-regulated channel (760 aa)	Brain, skeletal muscle, lung, retina, kidney (type B intercalated cells of connecting tubule and collecting duct)	44, 358, 373, 457, 521
<i>CLCN4</i>	GDB: 270666 X77197	Xp22.3	CLC4	Skeletal muscle, brain, heart, kidney, retina	232, 545
<i>CLCN5</i>	GDB: 270667 X91906	Xp11.22	CLC5 (746 aa), X-linked nephrolithiasis	Kidney (type A intercalated cells of connecting tubule and collecting duct)	139, 309, 373
<i>CLCN6</i>	GDB: 3929143 AF009247-57 X83378	1p36	CLC6, KIAA0046 (97 kDa)	Ubiquitous	47
<i>CLCN7</i>	GDB: 3929156 Z67743	16p13	CLC7 (89 kDa)	Brain, testes, skeletal muscle, kidney	47
<i>CLCNKA</i>	GDB: 698471	1p36	CLC-Ka, CLC-K1 kidney-specific channel	Kidney inner medulla, thin ascending limb of Henle	47, 457, 541
<i>CLCNKB</i>	GDB: 698472	1p36	CLC-Kb, CLC-K2 kidney-specific channel, Bartter III	Kidney, thin ascending limb of Henle and collecting ducts	457, 522

Listed are gene names, accession numbers, protein names, and tissue expression for voltage-gated chloride channels. When no information on tissue expression in humans was available, data for other mammals are given. aa, Amino acids.

major pathway for movement of adenine nucleotides and anions. In contrast to the channels discussed in the following section, the anion selectivity is low and, dependent on the membrane potential, monovalent and perhaps divalent cations are also conducted.

1. Chloride channels

Chloride channels are present in the plasma membrane of most cells playing important roles in cell volume regulation, transepithelial transport, secretion of fluid from secretory glands, and stabilization of membrane potential. They can be activated by extracellular ligands, intracellular calcium, cAMP, G proteins, cell swelling, mechanical stretch, and transmembrane voltage. Because mechanisms of activation may overlap, and expression of a given channel may not be restricted to a certain cell type, the classification is intriguing. Of the three superfamilies, the first consists of ligand- or transmitter-gated chloride channels that are predominantly expressed in nervous tissue. Here, the chloride conductance is important for inhibitory synapses at which the membrane will be hyperpolarized by opening of transmitter-gated anion channels such as GABA_A and glycine receptor channels mediating chloride influx. These channels consist of four transmembrane domains and may associate as pentamers. The second superfamily includes the ATP-binding

cassette channels and cystic fibrosis transmembrane conductance regulator (CFTR) consisting of two blocks of six transmembrane domains followed by two nucleotide binding domains (520). The third superfamily is composed of the voltage-gated chloride channels, present in excitable and epithelial cells.

Voltage-dependent chloride channels also fulfill a variety of functions depending on their tissue distribution, i.e., stabilization of the membrane potential, regulation of cell volume, and concentration of extracellular medium (232). The channels can be found both in plasmalemma and in the lining of internal organelles. In axons, voltage-dependent chloride conductance is so small that it is usually neglected, whereas that of skeletal muscle is even larger than the resting conductance for potassium (49). Nevertheless, its electrophysiological identification and characterization at the single-channel level turned out to be very difficult. The reason why is its very low single-channel conductance near 1 pS as estimated from noise analysis (414). The large macroscopic chloride conductance, therefore, must result from an extremely high channel density in the skeletal muscle membrane.

A) CHLORIDE CHANNEL ENCODING GENES. Nine different human genes have been identified (*CLCN1* to *CLCN7*; *CLCNA/B*, Table 5) to encode voltage-gated chloride channels, termed CLC1 to CLC7, CLCKA, and CLCKB,

CLC-1 channel

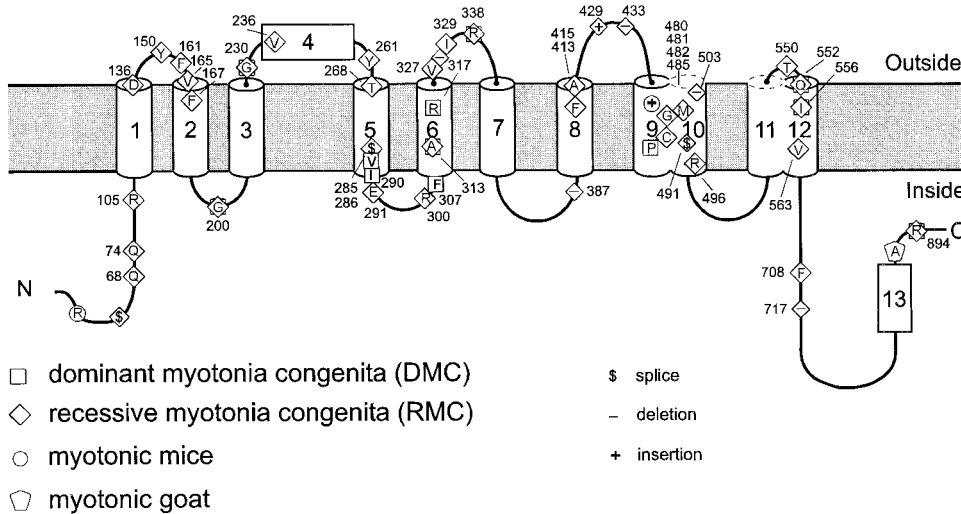


FIG. 10. Shown is a revision (256, 356, 472) of original membrane topology model that was based on hydrophathy analysis (233) of skeletal muscle chloride channel monomer, CLC-1, which is functional as homomeric channel complex. Different symbols used for known mutations leading to dominant Thomsen-type myotonia, recessive Becker-type myotonia, recessive myotonic mice, and dominant myotonic goat are explained on *bottom left*. Conventional 1-letter abbreviations were used for replaced amino acids located at positions given by respective numbers of human protein. [Modified from Pusch and Jentsch (414).]

that do not structurally resemble any other ion channel family. According to hydrophobicity blots performed on the first recognized family member, the CLC0 channel from the electric organ of *Torpedo*, 13 putative transmembrane helical segments were originally assumed (233). Later, by a combination of glycosylation and electrophysiological experiments on mutant proteins, it became clear that both the NH₂ and COOH terminals must be located intracellularly and that the S8-S9 interlinker is extracellular because of a glycosylation site. Two different possibilities of configuration arose from these results, namely, a model that places S4 extracellularly and the hydrophobic core of S9-S12 crosses the membrane several times (Fig. 10; Refs. 232, 415, 472) or, alternatively, a model that places S2 extracellularly (2, 356).

B) CHLORIDE CHANNEL STRUCTURE. Coexpression of wild-type CLC0 with naturally occurring mutant that change the single-channel conductance resulted in chloride channels with different conductance levels and largely independent pores (319, 357). This suggests CLC0 channel proteins to consist of “double-barrelled” homodimers with two functional off-axis pores each with its own independent activation gate but with a single slow inactivation gate in common. Closely related members of the same subfamily may assemble as heterodimers such as the voltage-dependent skeletal muscle chloride channel CLC1 (133) and the voltage- and volume-sensitive ubiquitously expressed CLC2. The CLCN proteins show a typical chloride over iodide specificity, are blockable by unspecific agents only, and can both be inwardly (CLC1 and CLC2) or outwardly rectifying (CLC5). The latter conducts noninactivating currents detectable only at voltages more positive than -20 mV (513, 310). The other mammalian genes such as the widely expressed *CLCN3* and *CLCN4*, the kidney-specific genes *CLCNKA* and *CLCKB*,

and the ubiquitously expressed *CLCN6* and *CLCN7* genes could not be functionally expressed as chloride channels or their expression has been controversially discussed. Mutations in *CLCN5* cause a recessive form of nephrocalcinosis (see sect. vi).

C) CLC1, THE SKELETAL MUSCLE CHLORIDE CHANNEL. CLC1 (Fig. 10), the main chloride channel of skeletal muscle, is functional when expressed in *Xenopus* oocytes (512) or human embryonic kidney cells (414) without any other subunits. The channel conducts over the whole physiological voltage range, showing inward rectification in the negative potential range. It is activated upon depolarization and deactivated with hyperpolarizing voltage steps to a non-zero steady-state level. The very small channel conductance of ~1 pS makes single-channel measurements almost impossible to perform (414). As already known from macroscopic experiments (57, 384), the channel can be blocked by external iodide ion and by low concentrations of 9-anthracene carboxylic acid, a typical inhibitor of chloride channels in general (414, 512).

Not much is known about CLC1 structure-function relationship until now. Fahlke and Rüdell (131) showed a negative charge in S1 to be involved in the voltage-sensing mechanism and postulated that the intracellular mouth of the pore changes its affinity to a putative gating particle in three different grades, thus mediating the three known gating modes differentiated by their time course: fast, slow, or time independent. The grading could result from a set of two negatively charged voltage sensors combining to three different states. This model is able to explain all macroscopic gating properties described so far. The cytoplasmic face of the pore vestibule may be associated with a phosphorylation site for protein kinase C as suggested by an increase of nondeactivating channels and

reduction of single-channel conductance without change in voltage sensitivity of channel gating after protein kinase C activation (441). Mutations in *CLC1* cause dominant or recessive myotonia congenita (see sect. III C).

D) VOLTAGE-INSENSITIVE EPITHELIAL CHLORIDE CHANNELS. In contrast to the *CLC* family, cAMP-activated chloride channels have 12 putative membrane segments arranged in 2 separate blocks of 6 each per block that is followed by a nucleotide binding domain NBD1 and NBD2, respectively. The CFTR is an ATP-binding cassette transporter (ABC transporter) that forms monomeric channels with a single pore. The CFTR has a special feature of a nonconserved R-domain (regulatory domain) that confers regulation by cAMP-dependent phosphorylation. The function of CFTR in the sense of an ion channel was long controversially discussed (for review, see Ref. 110). The channel hypothesis was finally strengthened by single-channel experiments showing charged residues in M1 and M6 to be responsible for chloride selectivity or dependence of the conductance on the chloride mole fraction. For completeness, another nucleotide-sensitive chloride channel, *ICln*, is mentioned. It is an epithelial channel that regulates cell volume and is activated by tension due to cell swelling (177).

E) GLYCINE RECEPTORS. Glycine receptors (GlyR) are located in synapses of the central nervous system. These chloride channels are composed of variants of α - and β -subunits in a pentameric ($3\alpha-2\beta$) arrangement around a central pore. All subunits show similar structure with a large extracellular NH_2 terminus (responsible for ligand binding in α -subunits) followed by four transmembrane segments M1-M4 of which M2 forms the pore. Mutations in α -subunits occur naturally in the *spasmodic* mouse, in that a point mutation leads to lower agonist affinity, and in the *oscillator* mouse, in that a microdeletion with frame shift leads to complete loss of the GlyR_A protein. Additionally, an insertion resulting in aberrant splicing of GlyR_B and decreased receptor expressivity is known in *spastic* mice. In humans, only mutations in the gene *GLRA1* encoding the α_1 -subunit have been described leading to startle disease, hyperekplexia, or stiff baby syndrome, a single entity, often misdiagnosed as myotonia congenita (for review, see Ref. 31).

III. SKELETAL MUSCLE CHANNELOPATHIES

A. Skeletal Muscle Sodium Channelopathies

1. Hyperkalemic periodic paralysis, paramyotonia congenita, and potassium-aggravated myotonia in humans

Before *SCN4A*, the gene encoding the α -subunit of the human adult skeletal muscle sodium channel, was cloned, an extensive electrophysiological survey, carried

out with excised muscle specimens of all kinds of myotonia patients, had found that in two rare hereditary conditions the inactivation of the sodium channels was defective (284, 289). These dominantly inherited diseases are hyperkalemic periodic paralysis (HyperPP) and paramyotonia congenita (PC). Hyperkalemic periodic paralysis is characterized by episodes of flaccid muscle weakness associated with hyperkalemia with signs of myotonia in the interval between attacks; PC is characterized by a stiffening of the muscles during exercise or exposure to cold, which can merge into flaccid weakness that may last several hours even when the muscles were rapidly rewarmed. A third allelic disorder, potassium-aggravated myotonia (PAM), is characterized by severe permanent myotonia or fluctuating muscle stiffness that is most prominent ~ 20 min after exercise (delayed onset myotonia; Refs. 433, 434); the mild form is symptomatically very similar to classical dominant myotonia congenita Thomsen (which is now known to be a chloride channel disease; Ref. 262). Genetic studies of large families performed with an intragenic marker quickly revealed that the diseases are indeed linked to *SCN4A* (144). Intron-exon boundaries of the gene are known; primer sets consisting of intron sequences for amplification of all 24 exons by use of PCR are available (157). To date, 21 missense mutations have been discovered, leading to the different symptoms described above (Fig. 3).

The three allelic diseases do not always appear in their pure forms, e.g., PC patients often suffer from spontaneous episodes of weakness that may go along with an elevated serum potassium level. However, HyperPP patients do not show substantial stiffness when cooled, and muscle weakness never occurs in PAM. Although intermediate forms are frequent, it seems reasonable to retain them as separate diseases because, in the pure forms, not only the symptoms but also the recommended treatment differ (431).

As in most other channelopathies, the clinical symptoms and signs of the three diseases, muscle stiffness and, in two of them, muscle weakness, are not present all the time; rather, they are elicited by typical stimuli. A typical trigger for an episode of weakness in HyperPP would be rest after a heavy work load; stiffness and weakness in PC is triggered by muscle exercise during exposure of the muscles to cold, and ingestion of potassium-rich food may induce muscle stiffness in patients having PAM. All these symptoms disappear spontaneously within a few hours. Nevertheless, the episodes hamper the patient's life considerably, although they may be prevented to a certain extent by proper behavior and symptomatic treatment with drugs (for review, see Ref. 281).

The key symptoms of stiffness and weakness are caused by the same pathogenesis mechanism, namely, a long-lasting depolarization of the muscle fiber membranes (284, 289). Keeping in mind that there are two channel

TABLE 6. *SCN4A* mutations

Genotype	Channel Region	Mutation	Exon	Phenotype	First Report
<i>Hyperkalemic periodic paralysis</i>					
C2188T	IIIS ₅ _i	Thr-704-Met	13	Permanent weakness (non)myotonic most frequent	410
G3466A	IIIS4-S5	Ala-1156-Thr	19	Reduced penetrance	343
A4078G	IVS1	Met-1360-Val	23	Reduced penetrance	553
A4774G	IVS6 _i	Met-1592-Val	24	Myotonic, frequent	440
<i>Paramyotonia congenita</i>					
T2078C	IIIS4-S5	Ile-693-Thr	13	No paralysis	399
G3877A	IIIS6 _i	Val-1293-Ile	21	No paralysis	261
C3938T	III/IV	Thr-1313-Met	22	Frequent	343a
T4298G	IVS3	Leu-1433-Arg	24		411
C4342T	IVS4	Arg-1448-Cys	24	Potential atrophy	409
G4343A	IVS4	Arg-1448-His	24		409
G4343C	IVS4	Arg-1448-Pro	24	Potential atrophy	294
T4418C	IVS4-S5	Phe-1473-Ser	24		141
<i>Potassium-aggravated myotonias</i>					
G1333A	IS6 _i	Val-445-Met	9	Painful myotonia	442
C2411T	IIIS6 _i	Ser-804-Phe	14	Paramyotonic features	343
				Myotonia fluctuans	434
A3478G	III-IV	Ile-1160-Val	19	Acetazolamide responsive	413
G3917A	III-IV	Gly-1306-Glu	22	Myotonia permanens	292
G3917C	III-IV	Gly-1306-Ala	22	Myotonia fluctuans	292
G3917T	III-IV	Gly-1306-Val	22	Paramyotonic features	343a
				Myotonia	292
G4765A	IVS6 _i	Val-1589-Met	24	Myotonia	192

Gene encodes α -subunit of human skeletal muscle sodium channel. i, Internal end of a transmembrane segment (S) situated in one of 4 repeats (I-IV).

populations, mutant and wild type, the pathogenesis of the diseases may be explained. When the membrane depolarization caused by the mutant channels is mild, 5–10 mV, wild-type sodium channels can recover from inactivation during an action potential and be reactivated by mutant channels leading to repetitive firing, which is the basis for the involuntary muscle activity that patients experience as muscle stiffness. This hyperexcitable state can be computer simulated (67) and mimicked by anemone toxin (68). When the depolarization is strong, 20–30 mV, the majority of the intact sodium channels adopt the state of inactivation rendering the muscle fibers inexcitable, which is the basis of the muscle weakness (284, 289). Heterologous expression of mutant human sodium channel cDNA and patch-clamp studies of the resulting currents confirmed these early results and made further specification of the altered channel inactivation for the various mutations possible (Figs. 4 and 5). Several features of channel inactivation were changed, such as the speed of current decay after a depolarization step, the current fraction that persists after the decay, the speed of the recovery from inactivation, the position of the steady-state inactivation curve, and/or the degree of uncoupling of inactivation from activation (76, 362). Careful investigation revealed that the changes of inactivation are not quite the same with different mutants. For example, slow-

ing of the current decay was most pronounced with substitutions for Arg-1448 causing paramyotonia (76, 294), whereas a large persistent sodium current was found for the mutants Met-1592-Val (HyperPP, Ref. 70) and Val-1589-Met (PAM, Ref. 362). Persistent current should be decreased by slow channel inactivation (452); however, this type of inactivation (569) seems to be disturbed by some HyperPP mutants situated at the cytoplasmic ends of segments S5 and S6 (99, 188). In contrast, mutations within the III-IV linker abolish fast inactivation and have no effect on slow inactivation (99, 188).

As it turned out, a number of the 21 substitutions are situated in the “inactivating” linker between repeats III and IV or in the “voltage-sensing” segment S4 of repeat IV. Almost all remaining mutations are situated at the inner side of the membrane where they could impair the docking site for the inactivation particle (Table 6). Three of the mutations in the III/IV linker (Gly-1306-Glu, Ala, Val) effect different amino acid substitutions for one of a pair of glycines proposed to act as the “hinge” for the inactivation gate. They all cause PAM, and interestingly, the more the substituting amino acid differs from the physiological Gly-1306 (longer side chains and/or greater charge), the more enhanced is the membrane excitability, and the more severe are the clinical symptoms. Glutamic acid, an amino acid with a long side chain, causes permanent

myotonia, the most severe form of the disease; valine, having a side chain of intermediate size, causes moderate exercise-induced myotonia; and alanine, with a short side chain, results in a benign, often "subclinical" form of myotonia. Thus the natural mutations affecting Gly-1306 provided evidence that increased rigidity of the amino acid chain at the position of the highly conserved pair of glycines increasingly hampers channel inactivation (361). Unexpectedly, mutations at this hinge site altered, in addition to channel inactivation, also activation and deactivation. A similar correlation between the difference of physiological and mutant amino acid on one side, and the severity of clinical symptoms on the other, exists for three paramyotonia-causing substitutions located in an identical position (Arg-1448-Cys,His,Pro) near the extracellular face of IVS4. This finding led to the systematic application of site-directed mutagenesis in this supposed channel activation domain. The mutations primarily affected channel inactivation (76). Therefore, it was hypothesized that depolarization-induced movements in IVS4 concern both the inactivation gate and the docking site for the inactivation particle (583).

Contrary to what one could have expected, in the heterologous expression system neither extracellular potassium nor low temperature had a direct effect on any of the mutant channels investigated. The mechanism by which cold enhances muscle stiffness in PC patients is not completely clear. Both fast inactivation constant and persistent current increase with cooling, and mutant and normal channels reveal the same temperature dependence; however, the absolute figures are larger for mutant channels at any temperature. Therefore, it has been proposed that a certain threshold has to be exceeded in cold environment to induce myotonic and/or paralytic symptoms (141). In contrast to the cold-induced symptoms, the pathogenesis of the potassium-induced stiffness and paralysis is very obvious; the physiological depolarization, which follows an elevation of serum potassium according to the Nernst equation, increases the open probability of the sodium channels and unmasks their inactivation defect. Therefore, potassium exerts its effect via the depolarization, an effect which cannot be observed under the experimental voltage-clamp conditions (see Fig. 6).

2. Equine HyperPP

A condition equivalent to human HyperPP in humans has become known in the quarter horse (Fig. 6), a common breed of race horses in the United States (98, 397). It has the highest incidence of all known inherited disorders of horses. The symptoms are similar to those described above for the human disease, but the condition seems to be sometimes more serious than in humans because some affected horses have died from attacks (505). The hyperexcitability of the muscles causes hypertrophy resulting

in particular beauty of the affected quarter horses and makes them show winners instead of race winners. A point mutation, a F1421L substitution situated in the third segment of domain IV (Fig. 3), was identified in the equine muscle sodium channel (448, 449) that showed functional alterations of the mutant comparable to human HyperPP at the molecular level (69, 184).

All affected horses (4.4% of the quarter horses in the United States) trace to the sire Impressive as first-, second-, or third-generation descendants. These are an ideal model for the study of the cellular and physiological factors dictating the onset and severity of attacks and the relationship between exercise, systemic potassium, catecholamines, and other factors influencing muscle metabolism. In addition, the hyperkalemic horse has been used to show the first correlation of levels of mutant mRNA relative to normal mRNA as a likely determinant of clinical severity in dominantly inherited disease (594). Accordingly, homozygous animals have laryngeal and pharyngeal dysfunction during exercise not observed in heterozygous animals, even though the weakness from any myotonia does not seem more severe (71, 336).

3. Effects of therapy of skeletal muscle sodium channelopathies

Local anesthetics and antiarrhythmic drugs of class 1B, such as mexiletine and other lidocaine analogs, very effectively prevent muscle stiffness and weakness occurring in paramyotonia congenita (PC) with cooling (432, 517) and relieves stiffness in potassium-aggravated myotonia (PAM). A reduction of stiffness is also seen in genetically and pathogenetically different types of myotonia, e.g., the chloride channel myotonias and myotonic dystrophy (445). This beneficial effect is due to the well-known use-dependent block of sodium channels exerted by these agents (197). The block prevents the repetitive firing of action potentials, the last common pathway of the generation of myotonic muscle stiffness. However, this "unspecific" antimyotonic effect seems to be most pronounced in PC and PAM, probably as this treatment is causative for those sodium channel diseases that are induced by a destabilized inactivation state. Mexiletine stabilizes the inactivated channel by a hyperpolarizing shift in steady-state inactivation and slowing of recovery from inactivation (135, 141).

The effects of mexiletine have been studied in cell lines expressing sodium channel mutations situated in regions known to be essential for channel inactivation. Compared with wild type, the use-dependent block was increased for R1448C, located in the IVS4 voltage sensor, and decreased for F1473S (IVS4-S5), G1306E, and T1313M, both within the III-IV loop (135, 141). For the latter mutation only, reduced affinity of the drug to the inactivated state has been reported, suggesting both less

beneficial drug effects for this mutation and a binding site for local anesthetics and antiarrhythmics in this loop. Data on minor therapeutical effects are not available for this mutation, and studies on drug binding mainly focus on the cytoplasmic end of segment IVS6 (417, 423). In agreement with the beneficial response of lidocaine analogs on sodium channel myotonia, studies on cardiac sodium channel mutations causing long QT syndrome type 3, including those in the III-IV loop, revealed a preferential suppression of channel reopenings, the event of slowed and incomplete current inactivation at the molecular level (35, 562, see also sect. IV C).

In contrast to the relief of stiffness and the prevention of cold-induced weakness, the spontaneous and potassium-induced attacks of weakness typical for HyperPP and also occurring in many PC patients are not influenced by mexiletine (431). Fortunately, diuretics such as hydrochlorothiazide and acetazolamide can decrease frequency and severity of paralytic episodes by lowering serum potassium (281, 431) and perhaps by shifting the pH to lower values (284).

B. Skeletal Muscle Calcium Channelopathies

There are two major types of calcium channels expressed in adult skeletal muscle, the so-called dihydropyridine receptor (DHPR) and the ryanodine receptor (RYR1) (Figs. 7 and 9). Both are situated in the triadic junctions of the t-tubular system and the SR, respectively (see Fig. 8). The DHPR, located in the t-tubular membrane, is an L-type voltage-dependent calcium channel that is sensitive to DHP. Located in the SR membrane, RYR1 is itself not voltage dependent, but coupled to the DHPR.

In contrast to the cardiac muscle, the voltage-gated L-type calcium channel of skeletal muscle appears to be physiologically unimportant as an ion-conducting channel. However, it functions as voltage sensor of the RYR1 that releases calcium from the SR, initiating contraction (352). The α_{1S} -subunit of the α_{1S} - α_2 - δ - β_1 - γ pentameric DHPR complex interacts with the RYR1 via the II-III interlinker (290, 525). Disease-causing mutations are known in the genes for both channels. Certain point mutations in *CACNAS*, encoding the α_{1S} -subunit of DHPR, cause familial hypokalemic periodic paralysis in humans, a disease characterized by disturbed muscle excitation. A stop mutation in the murine gene leads to muscular dysgenesis in mice homozygous for the truncated subunit. Other point mutations in this gene, as well as mutations in the RYR1 gene, cause human malignant hyperthermia, i.e., defective EC coupling. One of these RYR1 mutations has been also identified in the porcine stress syndrome.

1. Hypokalemic periodic paralysis

A) A HUMAN L-TYPE CALCIUM CHANNELOPATHY. Familial hypokalemic periodic paralysis (HypoPP) is a disease that still baffles clinicians and basic scientists, although the genetic cause of this dominantly inherited disease has been found. Although it is the most common form of the periodic paralyzes in humans, it is still a rare disease showing a prevalence of only 1:100,000. The major symptoms of dyskalemic periodic paralysis, i.e., episodes of generalized paralysis, may occur less frequently and be on average of longer duration than in HyperPP, but there are many cases where differential diagnosis requires considerable skill of the physician. Decisive for classification is the level of serum potassium during a paralytic attack, which may fall below 2 mM in HypoPP, whereas in the hyperkalemic form, it may rise above 4.5 mM. The hypokalemia is assumed to be caused by stimulation of the sodium-potassium pump by insulin, which is one physiological mechanism by which potassium ions are transported from the extracellular space into the intracellular compartment. Low external potassium concentration theoretically approaching zero may cause electrical destabilization of the cell membrane because the potassium equilibrium then becomes very negative and the potassium conductance approaches zero. Even in normal muscle, external potassium concentrations <1.0 mM cause membrane depolarization, and any increase in external potassium will cause normalization and stabilization of the resting potential (reviewed in Ref. 281).

B) MUTATIONS IN THE L-TYPE CALCIUM CHANNEL (FIG. 7). A systematic genome-wide search in members of three families demonstrated that the disease is linked to chromosome 1q31-32 and cosegregates with the gene encoding the L-type calcium channel (DHPR) α_{1S} -subunit (146) that is located in this region (117, 170). Sequencing of cDNA derived from muscle biopsies of patients revealed three mutations so far. Two of these are analogous, predicting arginine to histidine substitutions within the highly conserved S4 regions of repeats II and IV (Arg-528-His and Arg-1239-His, respectively); the third predicts a rare arginine to glycine substitution in IVS4 (Arg-1239-Gly) (42, 125, 147, 175, 240, 412).

Even though the first report on the L-type current in myotubes of a single HypoPP patient carrying the R528H mutation and expressing both wild-type and mutant channels revealed a left shift in steady-state inactivation (496), later studies could not confirm it (241, 365a). Instead, a significant slowing of the rate of activation and mild reduction of current density was found using modified myotube preparations (365a). Expression of the rabbit channel in a fibroblast cell line showed a reduction of current density to be the only detectable effect of the amino acid exchange (278). Introduction of an Arg-528-His equivalent into the human cardiac α_1 -subunit and expression in hu-

man embryonic kidney cells displayed only barely significant changes in voltage dependence of activation and inactivation of the L-type current. Similarly, functional expression of rabbit skeletal muscle α_1 -subunit, carrying the human mutation, in a muscular dysgenesis mouse (*mdg*) cell line showed normal L-type calcium currents and calcium transients (241). The Arg-1239-His mutation has so far only been studied in patient myotubes that revealed reduced L-type current amplitudes (496).

How a potentially pathological L-type calcium current is related to hypokalemia-induced attacks of muscle weakness can only be speculated. Because electrical muscle activity, evoked by nerve stimulation, is reduced or even absent during attacks (127, 306), a failure of excitation is more likely than a failure of EC coupling. Nevertheless, the hypokalemia-induced, large membrane depolarization observed in excised muscle fibers (446) might also reduce calcium release by inactivating sarcolemmal and t-tubular sodium channels and would explain why repolarization of the membrane by activation of ATP-sensitive potassium channels restores force (168). The fact that HypoPP patients often show a deviation from normal controls in the *in vitro* contracture test for malignant hyperthermia susceptibility could also be due to fiber depolarization (282). New clues to the underlying pathogenesis may be gained by identification of additional causative genes as suggested by genetic heterogeneity of the disease (398).

2. Muscular dysgenesis mice (*mdg*)

A) A NATURAL KNOCK-OUT FOR THE L-TYPE CALCIUM CHANNEL. An autosomal recessive mouse mutant has been described with homozygous animals dying at birth because of nonfunctional respiration caused by a deletion of a single nucleotide in the gene encoding the L-type calcium channel (DHPR) α_1 -subunit (81, Fig. 7) leading to a premature stop codon. In the muscles of homozygous animals, the altered mRNA is present only at low levels (524), and α_1 -subunits are immunologically not detectable (260). Action potentials can be elicited in these muscles, but they do not trigger contractions. Mice heterozygous for the deletion are not distinguishable from normal mice. Because the truncated protein, resulting from the premature stop, is thought to be nonfunctional, one-half of normal quantity of L-type calcium channels may be sufficient for normal EC coupling (if expression rate of the normal gene can be considered unchanged).

Myotubes can be cultured from the muscle of newborns and studied in primary culture (3, 25–27). The DHP-sensitive L-type current and EC coupling are both absent (27). However, L-type currents were present after rabbit cDNA encoding the α_1 -subunit had been injected into nuclei of these myotubes (524). Recently, next to primary cells, an *mdg* cell line has been successfully used as an

expression system for the characterization of the structure-function relationship of the L-type calcium channel α_1 -subunit (241).

3. Malignant hyperthermia

A) DRUG-INDUCED, POTENTIALLY LETHAL EVENT IN CARRIERS OF VOLTAGE- OR LIGAND-GATED CALCIUM CHANNEL MUTATIONS. Malignant hyperthermia (MH) is, in the strict sense of the word, not a disease but a genetic predisposition of clinically inconspicuous individuals to respond abnormally when exposed to volatile anesthetics or depolarizing muscle relaxants (52, 108). A pathologically high increase of the myoplasmic calcium concentration during exposure to the triggering agents (207) during exposure to the triggering agents underlies the MH susceptibility (MHS) that leads to increased muscle metabolism and heat production resulting in symptoms of muscle rigidity, hyperthermia associated with metabolic acidosis, hyperkalemia, and hypoxia. The metabolic alterations usually progress rapidly and, without immediate treatment, up to 70% of the patients may die (174). Early administration of dantrolene, an inhibitor of calcium release from the SR, has successfully aborted numerous fulminant crises and has reduced the mortality rate to presently 10%.

Malignant hyperthermia susceptibility is genetically heterogeneous in humans. In many families, mutations in the gene encoding the skeletal muscle RYR1 (Fig. 9), a calcium channel which is not voltage dependent on its own but under the control of the voltage-dependent L-type calcium channel (Fig. 8), can be found. Additionally, two mutations in the α_1 -subunit of the DHPR, the voltage sensor of RYR1, have been described (see sect. $\text{III B } 3c$) underlining the functional link between the two protein complexes. Another possible locus contains the gene encoding the α_2/δ -subunit of the DHPR (209, 471).

B) MHS DUE TO RYR1 MUTATIONS (FIG. 9). To date, more than 20 disease-causing point mutations in RYR1 have been identified in humans, all situated in the long NH_2 terminus of the protein, the so-called foot of the channel complex (see Fig. 9 and Table 7) which contains the binding sites for various activating ligands like calcium (μM), ATP, calmodulin (which binds in the absence of calcium), caffeine and ryanodine (nM), and inactivating ligands like calcium ($>10 \mu\text{M}$) and magnesium in millimolar concentrations (97, 350). The diagnostically important increased sensitivity of MHS muscle to caffeine is considered to be caused by an altered RYR1 function. Functional tests, so far only performed with porcine muscle (see sect. $\text{III B } 5$, the porcine stress syndrome, an MH equivalent) in isolated SR vesicles, have shown that calcium regulation is disturbed. Lower calcium concentrations activate the channel to a higher than normal level, and higher than normal calcium concentrations are required to inhibit the channel (355). Investigations of re-

TABLE 7. *CACNA1S* and *RYR1* mutations

Genotype	Exon	Mutation	Disease State	Frequency	First Report
<i>DHPRa1: HypoPP or MH</i>					
G1583A	11	Arg-528-His	HypoPP	40%	240
C3256T	26	Arg-1086-Cys	MH	1 Family	239
G3257A	26	Arg-1086-His	MH	1 Family	364
C3715G	30	Arg-1239-Gly	HypoPP	3%	412
G3716A	30	Arg-1239-His	HypoPP	40%	240, 412
<i>RYR1: MH and/or CCD</i>					
T103C	2	Cys-35-Arg	MH	1 Family	321
C487T	6	Arg-163-Cys	MH, CCD	2%	418
G742A	9	Gly-248-Arg	MH	2%	165
G1021A	11	Gly-341-Arg	MH	6%	420
C1209G	12	Ile-403-Met	CCD	1 Family	418
A1565C	14	Tyr-522-Ser	MH, CCD	1 Family	419
C1654T	15	Arg-552-Trp	MH	1 Family	249
C1840T	17	Arg-614-Cys	MH	4%	164
G1841T	17	Arg-614-Leu	MH	2%	421
C6487T	39	Arg-2163-Cys	MH	4%	334
G6488A	39	Arg-2163-His	MH, CCD	1 Family	334
G6502A	39	Val-2168-Met	MH	7%	334
C6617T	40	Thr-2206-Met	MH	1 Family	334
C6617B	40	Thr-2206-Arg	MH	1 Family	46a
G7303A	45	Gly-2434-Arg	MH	4%	250
G7307A	45	Arg-2435-His	MH, CCD	1 Family	593
C7360T	46	Arg-2454-Cys	MH	1 Family	46a
C7372T	46	Arg-2458-Cys	MH	4%	333
G7373A	46	Arg-2458-His	MH	4%	333

These genes encode α_1 -subunit of L-type calcium channel (dihydropyridine receptor, DHPR) of t-tubular membrane and calcium release channel (ryanodine receptor, RYR1) of sarcoplasmic reticulum, respectively. Both proteins are involved in excitation-contraction coupling of skeletal muscle. HypoPP, hypokalemic periodic paralysis; MH, malignant hyperthermia; CCD, central core disease.

constituted RYR1 in lipid bilayers, designed to find the reason for the increased caffeine sensitivity of MHS muscle, led to controversial results. Electrophysiological single-channel measurements on RYR1 did not show increased caffeine sensitivity (487), whereas pharmacological studies showed increased sensitivity (195). Functional characterization of the various mutations in the NH₂ terminus and the central part of the "foot" revealed similar results, i.e., increased sensitivity of the mutant RYR1 to activating concentrations of calcium and exogenous and diagnostically used ligands such as caffeine, halothane, and 4-chloro-*m*-cresol (382, 430, 535). Overexpression of a mutated ryanodine receptor in normal human primary muscle cells also led to an increased calcium response during exposure to a triggering agent (75). A reduced inhibition of calcium release by magnesium has been reported for MHS muscle and proposed as the major pathomechanism of MH (279).

C) MHS CAUSED BY L-TYPE CHANNEL α_1 -SUBUNIT MUTATIONS (FIG. 7). Recently, cosegregation of the MHS trait with markers on chromosome 1q32 was shown for two families. Screening for causative mutations in the candidate gene, *CACNA1S*, revealed arginine-1086 to histidine and cysteine transitions in the intracellular interlinker connecting domains III and IV of the protein, a region whose

significance for EC coupling is unknown (Fig. 7; Refs. 239, 364).

4. Central core disease

Allelic to MH is central core disease (CCD), a congenital autosomal dominantly transmitted proximal myopathy with structural alterations mainly of type 1 fibers. Name giving are central areas along the whole fiber length that contain structured or unstructured myofibrils and lack of mitochondria. Affected individuals show hypotonia upon birth (floppy infant syndrome). Later in life, muscle strength usually improves except for rare cases showing progressive muscle weakness. Exercise-induced muscle cramps are often reported. Some patients suffered from an event indicative of MH and revealed a positive result in the diagnostic in vitro contracture test (489). This observation induced genetic linkage studies on chromosome 19q12-13.2, the first MHS locus, that indeed confirmed this hypothesis (182, 246). Mutations in RYR1 were reported thereafter (see Table 7 and Fig. 9). Even though events similar to MH may occur in numerous muscle disorders during general anesthesia, a genetic relation exists with certainty only in CCD and possibly also in King-Denborough syndrome, which is characterized by dwarfism, scoliosis, ptosis, and further skeletal or muscu-

lar symptoms (257). Data on the molecular genetics of the latter disease are still missing. Lethal events during anesthesia have been reported for both of these rare diseases.

5. Porcine stress syndrome

An important clue to which chromosomal region might bear the most common human MHS locus was provided by an animal model, porcine stress syndrome. In predisposed animals, MH crises can be triggered not only by the volatile anesthetic halothane but also by physical and psychological stress as endorsed by transport to the slaughterhouse (360, 499). Originally, only swine homozygous for this trait were thought to be susceptible; however, later studies showed that the syndrome can be also triggered in heterozygous animals and that their muscles react abnormally when exposed to various agents (152, 481, 570). Soon after linkage of this syndrome to the so-called halothane locus, the corresponding cluster of genes was linked to MHS in several families and localized to human chromosome 19q12–13.2, a region containing RYR1 (324, 340). In the animal model, the first RYR1 mutation, an Arg-615-Cys, was detected (150, 381), which corresponds to the most frequent human mutation, Arg-614-Cys substitution (164).

Stress-susceptible pigs had more muscle mass and their meat was less fat; therefore, the trait was initially selectively bred. Nowadays, because of the higher loss numbers during transport and the reduced meat quality of stressed animals (so-called PSE meat that is pale, soft, and exudative pork), strict care in breeding is taken to achieve exclusively stress-resistant sows (mutation to be excluded), stress-susceptible boars, and heterozygous litters. The latter are characterized by large muscle mass, similar to susceptible pigs, and stress resistance, similar to MH-negative swine. These animals are also important for research because porcine and human syndromes are virtually identical in most aspects, including changes in vital signs, metabolism, acid-base balance, temperature, and muscle contracture. Novel anesthetics that do not trigger an MH reaction in swine are considered as safe in MHS humans.

C. Skeletal Muscle Chloride Channelopathies

Myotonia, at least in humans, may not only be due to sodium channel mutations as in PAM but also to changes in the chloride channel CLC1 as in autosomal dominant Thomsen myotonia. The clinical symptoms of both are almost indistinguishable despite two totally different disease pathogenesis mechanisms, namely, disturbed inactivation of the sodium channel, leading to depolarization and hyperexcitability, versus instability of the resting potential, as seen for defects in the chloride channel.

1. Myotonia congenita

A) THOMSEN'S DISEASE AND BECKER-TYPE MYOTONIA. Congenital myotonia (muscle tension) may show both dominant and recessive (32) modes of transmission, both of which may be caused by mutations in *CLCN1*, the gene encoding the major skeletal muscle chloride channel. Muscle stiffness is temporary and can affect every skeletal muscle of the body. Myotonic stiffness is most pronounced when a forceful movement is abruptly initiated after the patient has rested for 5–10 min. For instance, after making a hard fist, the patient may not be able to extend the fingers fully for several seconds. Myotonia decreases or vanishes completely when the same movement is repeated several times (warm-up phenomenon), but it always recurs after a few minutes of rest. On rare occasions, a sudden, frightening noise may cause instantaneous generalized stiffness. The patient may then fall to the ground and remain rigid and helpless for some seconds or even minutes. Typically, myotonic muscles reveal a characteristic pattern in the electromyogram (EMG), i.e., bursts of repetitive action potentials with amplitude and frequency modulation, so-called dive-bombers in the EMG loudspeaker.

Both the dominant and the recessive forms are caused by mutations in the same gene (262). The intensive search for mutations that followed this discovery showed that the dominant form is very rare, since <10 different families have been identified at the molecular level to date. The recessive form is much more common, and the estimation by Becker (33) of a frequency between 1:23,000 and 1:50,000 might still hold. Males seem to be affected predominately over females with a ratio of 3:1 when only taking the typical clinical features into account. However, family studies disclose that women are affected at the same frequency, although to a much lesser degree.

B) MOLECULAR PATHOLOGY. The muscle stiffness is caused by the fact that, after voluntary excitation, the membranes of individual muscle fibers may continue for some seconds to generate runs of action potentials. This activity prevents immediate muscle relaxation from occurring. Experiments with muscles of an animal model, the myotonic goat (see sect. III C 2), showed that the overexcitability is caused by a permanent reduction of the resting chloride conductance of the muscle fiber membranes (56). The high chloride conductance is necessary for a fast repolarization of the t-tubular membranes, in particular, when these tend to become depolarized by potassium accumulated in the tubules during tetanic muscle excitation (6). This pathology was also shown to exist in human dominant and recessive myotonia congenita (148, 307, 447).

The starting point for an understanding of myotonia congenita on the molecular level was the cloning of the chloride channel, *ClC0*, from the electric organ of the fish

TABLE 8. *CLCN1* mutations causing myotonia congenita

Genotype	Segment	Region	Mutation	Trait	First Report
+3/A→T	Intron 1	NH ₂ terminal	Splice site	Recessive	498
C202T	Exon 2	NH ₂ terminal	Gln-68-Stop	Recessive	593
C220T	Exon 2	NH ₂ terminal	Gln-74-Stop	Recessive	326
C313T	Exon 3	NH ₂ terminal	Arg-105-Cys	Recessive	354
A407G	Exon 3	S1	Asp-136-Gly	Recessive	191
A449G	Exon 4	S1-S2	Tyr-150-Cys	Recessive	326
T481G	Exon 4	S1-S2	Phe-161-Val	Recessive	400
T494G	Exon 4	S2	Val-165-Gly	Recessive	354
C501G	Exon 4	S2	Phe-167-Leu	Recessive	160
G598A	Exon 5	S2-S3	Gly-200-Arg	Dominant	326
G689A	Exon 5	S3-S4	Gly-230-Glu	Dom./rec.	156, 592
G706C	Exon 6	S4	Val-236-Leu	Recessive	271
A782G	Exon 7	S4-S5	Tyr-261-Cys	Recessive	326
G854A	Exon 8	S5	Splice site	Recessive	400
G854A	Exon 8	S5	Gly-285-Glu	Recessive	271
T857C	Exon 8	S5	Val-286-Ala	Dominant	271
C870G	Exon 8	S5-S6	Ile-290-Met	Dominant	265, 285
G871A	Exon 8	S5-S6	Glu-291-Lys	Recessive	354
C898T	Exon 8	S5-S6	Arg-300-Stop	Recessive	160
T920C	Exon 8	S5-S6	Phe-307-Ser	Dom./rec.	271, 400
G937A	Exon 8	S6	Ala-313-Thr	Dom./rec.	400
G950A	Exon 8	S6	Arg-317-Gln	Dominant	354
G979A	Exon 8	S6-S7	Splice site	Recessive	316
T986C	Exon 9	S6-S7	Ile-329-Thr	Recessive	160, 354
G1013A	Exon 9	S6-S7	Arg-338-Gln	Dom./rec.	160, 592
1095-96Δ	Exon 10	S7	fs 387-Stop	Recessive	354
T1238G	Exon 11	S8	Phe-413-Cys	Recessive	262
C1244T	Exon 11	S8	Ala-415-Val	Recessive	326
1262insC	Exon 12	S8-S9	fs 429-Stop	Recessive	354
1278-81Δ	Exon 12	S8-S9	fs 433-Stop	Recessive	191
C1439T	Exon 13	S9-S10	Pro-480-Leu	Dominant	511
1437-50Δ	Exon 13	S9-S10	fs 503-Stop	Recessive	353
C1443A	Exon 13	S9-S10	Cys-481-Stop	Recessive	461
G1444A	Exon 13	S9-S10	Gly-482-Arg	Recessive	354
A1453G	Exon 13	S9-S10	Met-485-Val	Recessive	354
G1471A	Exon 13	S10	Splice site	Recessive	354
G1488T	Exon 14	S10-S11	Arg-496-Ser	Recessive	316
C1649T	Exon 15	S11-S12	Thr-550-Met	Recessive	482
A1655G	Exon 15	S12	Gln-552-Arg	Dom. levior	285
T1667A	Exon 15	S12	Ile-556-Asn	Dom./rec.	271, 400
G1687A	Exon 15	S12	Val-563-Ile	Recessive	461
C2124G	Exon 17	COOH terminal	Phe-708-Leu	Recessive	461
G2149Δ	Exon 17	COOH terminal	Glu-717-Stop	Recessive	400
C2680T	Exon 23	COOH terminal	Arg-894-Stop	Dom./rec.	354

Gene encodes major chloride channel of skeletal muscle. fs, Frame shift due to an insertion (ins) and/or deletion (Δ); sp, splice site mutation; both events cause altered amino acid sequence usually followed by premature termination, sometimes indicated by the given stop codon number.

Torpedo marmorata (233). Murine skeletal muscle chloride channel cDNA was then cloned by homology screening (510). This was followed by demonstration of linkage of both dominant and recessive myotonia congenita to chromosome 7q35 (262). *CLCN1*, the gene encoding the chloride channel, is responsible for the high resting membrane conductance of skeletal muscle cells. It spans at least 40 kb and contains 23 exons whose boundaries have been located (316).

Functional expression of *CLCN1* has been accomplished in *Xenopus* oocytes (232, 414, 415, 512), human embryonic kidney (HEK-293) cells (132), and the insect cell line Sf9 (20). The resulting currents were similar to those found in native muscle fibers (131). Electrophysiological studies of wild-type and mutant channel proteins

have provided first insight into the pharmacology and structure-function relationships of CLC-1 and have led to the identification of regions involved in gating and permeation (128, 130, 132, 275, 416, 455, 511). Inferences from experiments with the chloride channel of *Torpedo* electric organ, CLC-0 (319, 357), and studies of CLC-1 constructs (129) strongly suggest that functional channels are formed as homodimers.

More than 30 point mutations and three deletions have been found in the channel gene, and they cause either dominant or recessive myotonia congenita (Fig. 10, Table 8) by producing change or loss of function of the gene product. Gene dosage effects of loss-of-function mutations may lead to a recessive or dominant phenotype, depending on whether 50% of the gene product (supplied

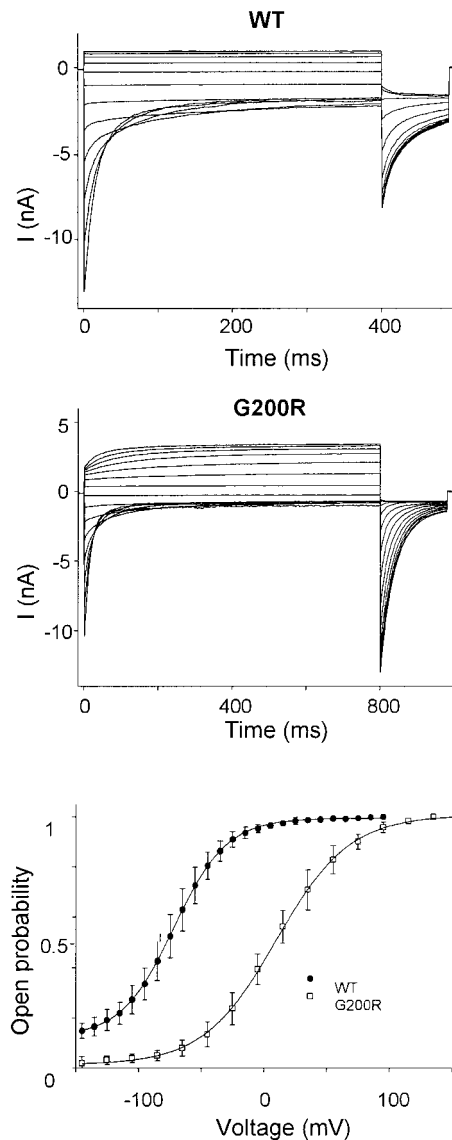


FIG. 11. Behavior of human skeletal muscle CIC-1 channels expressed in a mammalian cell line. Compared are currents of normal (WT) and mutant (Gly-200-Arg) channels, with the latter causing dominant myotonia in humans (Thomsen type). *Top and middle panels:* macroscopic currents, recorded in patch-clamp whole cell mode, were activated from a holding potential of 0 mV by voltage steps to potentials of 145 to -95 mV, and deactivated after 400 ms by polarization to 105 mV. *Bottom panel:* voltage dependence of relative open probability that is much reduced for mutant channel in physiological potential range. All mutations that cause such a voltage shift have dominant effects. [Modified from Wagner et al. (552).]

by the normal allele) is or is not sufficient for normal function. Experiments with myotonia-generating drugs showed that blockade of 50% of the physiological chloride current is not sufficient to produce myotonic activity. This could be the reason why heterozygous carriers of recessive mutations that completely destroy the protein's functions have 50% chloride current reduction and are, therefore, without clinical myotonia. Dominant inheritance is explained by a mutant gene product that can bind to

another protein (form channel dimers) and, in doing so, changes its function in the sense of a dominant negative effect. The most common feature of the thereby resulting chloride currents in dominant myotonia is a shift of the activation curve toward more positive membrane potentials reducing the total chloride conductance (Fig. 11). Surprisingly, the degree of the shift and clinical severity sometimes disagree, e.g., Gln-552-Arg causes an unusually large potential shift however a very mild clinical phenotype, myotonia levior (285, 416).

C) EFFECTS OF THERAPEUTIC DRUGS. Many myotonia congenita patients can manage their disease without medication. Should treatment be necessary, myotonic stiffness responds well to drugs that reduce the increased excitability of the cell membrane by interfering with the sodium channels, i.e., local anesthetics, antifibrillar and antiarrhythmic drugs, and related agents. These drugs suppress myotonic runs by decreasing the number of available sodium channels and have no known effect on chloride channels. Of the many drugs tested that can be administered orally, mexiletine is the drug of choice (445).

2. Myotonic goats

About 30 years after the first description of myotonia in humans by Thomsen in 1876 (534a), White and Plaskett (570a) described a breed of "fainting" goats raised in Tennessee (Fig. 12). The animals tended to have attacks of extreme muscle stiffness when attempting a quick forceful motion so that they often fell to the ground for 5–20 s with extension of the limbs and neck. The disease was recognized as "a form of congenital myotonia in goats" (91). It was excised external intercostal muscle from this strain that the American pharmacologist Shirley H. Bryant used in the 1960s for his famous electrophysiological studies of the membrane conductance (56). These studies led him to the conclusion that the fundamental electrical abnormality of resting myotonic fibers is a reduced chloride conductance. Studies on the same muscle from the myotonic goat also first elucidated the role of the t-tubular system in generating repetitive action potentials (6). Curiously, the myotonic goat did not play a role in the finding of the genetic defect causing the reduced chloride conductance. Long after the gene encoding the muscle chloride channel was localized and cloned for mouse (510) and human (262), finally the autosomal dominant goat mutation in the homologous gene was found (30). It is due to an Ala-885-Pro substitution in the COOH terminal of the chloride channel protein (Fig. 10) that results in a right shift of the activation curve comparable to human dominant mutations.



FIG. 12. Severe muscle stiffness in myotonic goats, a naturally occurring animal model of dominant myotonia, provoked by noise. (Courtesy of Drs. S. Bryant and A. L. George.)

3. Myotonic mice

In the late 1970s, two spontaneous mouse mutations were detected (as reviewed in Ref. 444), one in the A2G strain in London and the other in the SWR/J strain in Bar Harbor, Maine. The behavioral abnormalities of the affected animals were very similar, and in both mutations the traits were transmitted as an autosomal recessive trait. The British scientists were struck by the observation that from *days 10 to 12* onward the affected animals had difficulty in righting themselves when placed supine and therefore called the mutation *adr* for “arrested development of righting response”

(Fig. 13). The Americans observed that shaking the cage provoked sustained extension of an animal’s hindlimbs, and because electrical myotonia was recorded in the EMG from the stiff muscles, this strain was called *mto* for “myotonic.” As far as the phenotype is concerned, the two models of myotonia are virtually indistinguishable and, as in the myotonic goat, the reason for the abnormal excitability is a reduced chloride conductance. The assumption of interspecies conservation of the genomic structure in the vicinity of the *adr* locus found for the mice led Jockusch (237) to predict that the Becker myotonia gene is located on the human



FIG. 13. Severe muscle stiffness in a myotonic ADR mouse (*left*) induced by muscle activity compared with a normal control mouse (*right*). Both animals had been laid on back at same time and tried to right themselves.

Cardiac (and inner ear) K⁺ channels

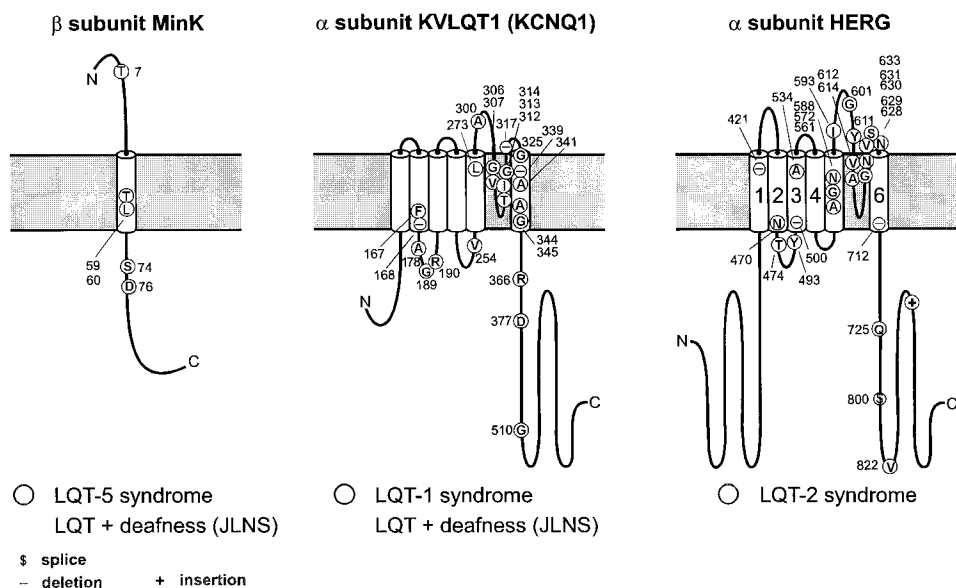


FIG. 14. Cartoon of various cardiac potassium channels. KVLQT1 and HERG are α -subunits, and MinK is a β -subunit interacting with KVLQT1 and forming a functional channel complex. Heterozygosity of a single mutation in either KVLQT1 or MinK subunits causes long QT syndromes 1 or 5; homozygosity of a mutation or compound heterozygosity leads to inner ear deafness and a more severe long QT syndrome. Heterozygous HERG mutations cause LQT-2. Conventional 1-letter abbreviations are used for replaced amino acids.

chromosome 7 before the major chloride channel, *ClC1*, of mammalian skeletal muscle was cloned. When this was finally accomplished (512), the spontaneous mutation of the *adr* mouse was soon identified, which destroys the gene's coding potential for several membrane-spanning domains (Fig. 10; Ref. 510). From this and the lack of recombination between the *ClC-1* gene and the *adr* locus, it was concluded that a lack of functional chloride channels is the primary cause of mouse myotonia.

IV. CARDIAC AND INNER EAR POTASSIUM CHANNELOPATHIES

A. Long Q-T Syndromes and Congenital Deafness

Of all the episodic disorders known to be caused by ion channels, Rolando Ward (RW) or long Q-T (LQT) syndrome is the most severe. It derives its name from the patients' electrocardiogram that shows an elongation of the Q-T interval as a result of disturbed myocardial repolarization. Typical for associated ventricular arrhythmias are Torsade de Pointes in which the QRS complex twists around the isoelectric axis in the electrocardiogram. Particularly at high activity of the sympathetic nervous system, it can cause ventricular arrhythmia, syncope, and sudden death in often young and otherwise healthy individuals (226). LQT syndrome is a genetically heterogeneous disorder of usually dominant inheritance for which five loci (LQT1–5) have been found. Three are potassium channel genes; one encodes a sodium channel, and the

gene the LQT4 syndrome located on chromosome 4q25–27 (476) has yet to be identified. Those families, which are not linked to any of the known loci, are termed as having LQT6.

1. Long Q-T syndrome type 1 (LQT1)

In 1991, the gene responsible for the most common type (50–60% of cases) LQT1 syndrome was mapped to the short arm of chromosome 11 (251). Positional cloning revealed that the mutated gene, termed *KCNQ1*, has 30% identity with the *Shaker* potassium channel gene (566). It encodes a potassium channel that is most likely involved in cardiac slow delayed repolarization. Heterologous expression of the wild-type *KCNQ1* cDNA produced potassium-selective channels with kinetics that were unlike any known potassium current in cardiac myocytes. When coexpressed with *KCNE1* cDNA encoding the potassium channel β -subunit MinK, also called ISK or Isk, the potassium current density was much greater and was indistinguishable kinetically and pharmacologically from the slow delayed rectifier current in heart, *I_{ks}* (23, 63, 463). Most of the LQT1-causing point mutations discovered were located near the pore region (S5-P-S6) (Fig. 14, middle; Table 9) and appear to have loss-of-function effects with reduction of current density and decrease the activity of wild type in a dominant negative fashion (Asp-222-Asn, 577, Leu-272-Phe; Ref. 484). One of them seems to exert very mild effects because it causes LQT1 (associated with normal hearing) only in a homozygous carrier (Ala-300-Thr). Relatively few mutations do indeed show a change of function, e.g., Arg-555-Cys in the COOH terminal resulted in a 50-mV positive shift of the voltage de-

TABLE 9. *KCNQ1* mutations causing long Q-T syndrome 1 or JLN syndrome

Genotype	Mutation	Region	First Report	Reported as	Disease
ΔTCG	Phe-167-Trp/ΔGly-168	S2	113	Phe-38-Trp/ΔGly-39	LQT1
G502C	Gly-168-Arg	S2	113		LQT1
T520C	Arg-174-Cys	S2-S3	113		LQT1
G532C	Ala-178-Pro	S2-S3	566	Ala-49-Pro	LQT1
G532A	Ala-178-Thr	S2-S3	526	Ala-49-Thr	LQT1
G565A	Gly-189-Arg	S2-S3	566	Gly-60-Arg	LQT1
Insertion	fs codon 190	S2-S3	1a		LQT1, JLNS
G569A	Arg-190-Gln	S2-S3	566	Arg-61-Gln	LQT1
Δ574-578	fs codon 192	S2-S3	1a		LQT1
G760A	Val-254-Met	S2-S3	566	Val-125-Met	LQT1
G781A	Glu-261-Lys	S4-S5	113		LQT1
G806A	Gly-269-Asp	S4-S5	113		LQT1
C817T	Leu-273-Phe	S5	566	Leu-144-Phe	LQT1
G898A	Ala-300-Thr	Pore	407		LQT1, homozygous
A914C	Trp-305-Ser	Pore	88		JLNS, homozygous
G916A	Gly-306-Arg	Pore	566	Gly-177-Arg	LQT1
Δ3 bp at 919	Splice site	Pore	302		LQT1
C926G	Thr-309-Arg	Pore	113		LQT1
C935T	Thr-312-Ile	Pore	566	Thr-183-Ile	LQT1
			456	Thr-182-Ile	
C939G	Ile-313-Met	Pore	526	Ile-184-Met	LQT1
G940A	Gly-314-Ser	Pore	453	Gly-185-Ser	LQT1
A944C	Tyr-315-Ser	Pore	113		LQT1
G949A	Asp-317-Asn	Pore	577	Asp-222-Asn	LQT1
			456	Asp-188-Asn	
C958G	Pro-320-Ala	Pore	113		LQT1
G973A	Gly-325-Arg	S6	113, 526		LQT1
Δ3 bp	ΔPhe-339	S6	1		LQT1
C1022A	Ala-341-Glu	S6	566	Ala-212-Glu	LQT1
C1022T	Ala-341-Val	S6	566	Ala-212-Val	LQT1
			453	Ala-212-Val	
			302	Ala-246-Val	
C1024T	Leu-342-Phe	S6	113		LQT1
C1031T	Ala-344-Val	S6	113		LQT1
G1032A	Splice site	S6	245, 302	sp/Ala-249	LQT1
G1034A	Gly-345-Glu	S6	566	Gly-216-Glu	LQT1
G1097C	Arg-366-Pro	S6	526	Arg-237-Pro	LQT1
G1111A	Ala-371-Thr	S6	113		LQT1
InsertionΔ	fs codon 544	COOH terminal	370	1244, -7 +8	JLNS, homozygous
C1663T	Arg-555-Cys	COOH terminal	113		LQT1

Numbering of the codons is for full-length human cardiac KvLQT1 clone (88, 584). Some original reports were based on partial clones (see reported as). fs, Frame shift due to an insertion (ins) and/or deletion (Δ); frame shift and splice site mutations cause altered amino acid sequence usually followed by premature termination. LQT1, long Q-T interval syndrome type 1; JLNS, Jervell and Lange-Nielsen syndrome.

pendence of activation when expressed alone and of 30 mV when coexpressed with wild type (88).

2. Long Q-T syndrome type 5 (LQT5)

With the new discovery that the I_{ks} channel complex is a heteromultimer of KVLQT1 and MinK subunits, families with LQT syndrome that had not been genetically linked to a specific locus were screened for mutations in *KCNE1*, expressed in heart and in marginal cells of the stria vascularis of the inner ear. This revealed mutations in *KCNE1* and thus defined it as another locus for LQT (Fig. 14, left; Ref. 507). Mutations in minK, especially those predicted to hinder coassembly with *KCNQ1* such as Leu-60-Pro and Thr-59-Pro, would be expected to alter the current density of I_{ks} in the heart. So far, two mutations located in the COOH terminal not inhibiting channel coassembly, Ser-74-Leu and Asp-76-

Asn, have been characterized by heterologous coexpression with *KCNQ1* in *Xenopus* oocytes show drastically reduced single-channel conductance (483, 507). The very slow deactivation of I_{ks} allows adaptive shortening of the action potential during tachycardia because the channels then deactivate incompletely (partially remain open). Therefore, functional disturbances of the channel complex during situations with elevated heart rate (physical or emotional stress) would have the most pronounced effect corresponding to the triggering situations of LQT syndrome in patients.

3. LQT1 and LQT5 with deafness

Mutations in both KVLQT1 and MinK have been shown to be responsible for Jervell and Lange-Nielsen syndrome (JLN), a recessively inherited disorder characterized by congenital bilateral deafness associated with

TABLE 10. *HERG mutations causing long Q-T syndrome 2*

Genotype	Region	Mutation	First Report
ΔA1261	S1	fs at codon 421	101, 304
A1408G	S2	Asn-470-Asp	101
C1421T	S2-S3	Thr-474-Ile	526
C1479G	S2-S3	Tyr-493-Stop	225
Δ1498-1524	S3	Δ500-508	101
C1600T	S4	Arg-534-Cys	225
G1681A	S5	Ala-561-Thr	103
C1682T	S5	Ala-561-Val	101
G1715A	S5	Gly-572-Cys	1a
A1762G	S5	Asn-588-Asp	1a
T1961G	Pore	Ile-593-Arg	36
G1801A	Pore	Gly-601-Ser	11
T1831C	Pore	Tyr-611-His	526
G1834T	Pore	Val-612-Leu	466
C1841T	Pore	Ala-614-Val	526
G1882A	Pore	Gly-628-Ser	101
A1885G	Pore	Asn-629-Asp	466
A1886G	Pore	Asn-629-Ser	466
T1888C	Pore	Val-630-Ala	1a
G1888C	Pore	Val-630-Leu	526
T1891G	Pore	Ser-631-Ala	598
A1898G	Pore	Asn-633-Ser	466
Δ2134-35	S6	fs at codon 712	225
C2173T	COOH terminal	Gln-725-Stop	225
G→C intron 3	COOH terminal	splice site	101
G2464A	COOH terminal	Val-822-Met	467
Dup(2539-69)	COOH terminal	fs	225

fs, Frame shift due to an insertion (ins) and/or deletion (Δ); frame shift and splice site mutations cause altered amino acid sequence usually followed by premature termination. Dup, duplication.

Q-T prolongation (Fig. 14) in accordance to the expression of the channel complex in the stria vascularis of the inner ear. Apparently deafness only occurs if the function of the channel complex is almost completely lost. Jervell and Lange-Nielsen syndrome is a rare disease thought to affect <1% of all deaf children. In two families, the disease is caused by a deletion-insertion event, leading to a frame shift and to a premature stop signal in the 3'-terminus of *KCNQ1* (370). In a family with consanguineous parents, a mutation in the same gene was homozygous in

the affected children (540). In another family, the index patient, congenitally deaf-mute, with recurrent syncopal events and a greatly prolonged Q-T interval, was homozygous for an Asp-76-Asn substitution, whereas heterozygous relatives had prolonged Q-T intervals only (120), compatible with the diagnosis of LQT5 syndrome associated with this mutation (507). Compound heterozygosity has been described (480). In contrast to dominant LQT syndromes, a JLN mutation truncating the COOH terminus of the KVLQT1 channel protein abolishes channel function without having a dominant-negative effect explaining the recessive mode of inheritance (577).

4. Long Q-T syndrome type 2 (LQT2)

After demonstration of linkage to chromosome 7q35–36 locus (101), several LQT-causative mutations in the *HERG* (human ether-a-go go related) gene were identified (Table 10). Heterologous expression of the channel produced a potassium channel with gating and pharmacological properties similar to the *I_{kr}*, the cardiac rapid delayed inward rectifier current. A unique feature of the voltage-dependent gating of this channel is relatively slow activation-deactivation in comparison with rapid inactivation. It is interesting to note that the very rapid inactivation of this 6T-1P channel is not of the N type as in *Shaker* because it is not eliminated by truncation of the NH₂ terminal (474). Instead, inactivation is highly sensitive to mutations in the pore region (Table 10) as found in LQT2 syndrome (501, 474, 196). *HERG* mutations suppress repolarization of the myocardial action potential, lengthening the Q-T interval by either loss of function or haploinsufficiency. A dominant negative effect is achieved by current reduction of the tetrameric channel complex. Both possibilities are suggested by heterologous expression of the LQT2-causing mutants that did not yield detectable current alone but showed different effects on coexpression with wild type: failure of protein incorporation into the membrane (Tyr-611-His, Val-822-Met; Ref. 595), inability to coassemble with the wild type (frame

TABLE 11. *SCN5A mutations*

Mutation	Region	Disease	First Report	Dysfunction	Reported by
sp intron 7	Truncation	IVF	84		
Arg-1232-Trp+	III/S1-S2	IVF	84	Inactivation shift	
Thr-1620-Met	IV/S3-S4				
Asn-1325-Ser	III/S4-S5	LQT3	567	Persistent current	121, 561
fs codon 1398	Truncation	IVF	84		
ΔLys-1505 to Gln-1507	III/IV loop	LQT3	568	Persistent current	35, 561
Arg-1623-Gln	IV/S4	LQT3	581	Slow inactivation	244
Arg-1644-His	IV/S4	LQT3	568	Persistent current	561
Asp-1790-Gly	COOH terminal	LQT3	34	Inactivation shift	15

Gene encodes cardiac α-subunit of sodium channel, and mutations cause long Q-T syndrome type 3 (LQT3) and idiopathic ventricular fibrillations (IVF). fs, Frame shift due to an insertion (ins) and/or deletion (Δ); frame shift and splice site (sp) mutations cause altered amino acid sequence usually followed by premature termination.

shift and deletions in pore region; Ref. 462), increased inactivation (Ala-614-Val, Val-630-Leu; Ref. 367), or reduced rectification (Ser-631-Ala; Ref. 598). Lack of the COOH terminus as a result of a disrupted splice donor site also reduces I_{kr} (sp/intron 3; Ref. 274).

5. Long Q-T syndrome type 3 (LQT3)

Finally, the most rare form, LQT3, has been shown to cosegregate with *SCN5A*, the gene encoding the α -subunit of the major cardiac sodium channel (235). Analysis on the molecular level revealed mutations in domains that are homologous to those found mutated in skeletal muscle channelopathies (Table 11, Fig. 3). Expression in *Xenopus* oocytes revealed that the mutant channels conduct a persistent inward current during membrane depolarization as in some of the skeletal muscle sodium channelopathies; single-channel recording indicated fluctuation between normal and noninactivating gating modes yielded prolonged bursts (deletion Lys-1505 to Gln-1507 in the III/IV loop; Ref. 35) or decreased stability of the inactivated state with frequent reopenings (Asn-1325-Ser in the S4-S5 loop of repeat IV; Ref. 121). Several mutations expressed in a mammalian cell line caused a sustained noninactivating current as well as alterations of voltage dependence and rate of inactivation (560, 561) and slowing of inactivation (Arg-1623-Gln; Ref. 244). One mutation located in the COOH terminal, Asp-1790-Gly, exerts a change of function only when coexpressed with β_1 shifting the voltage dependence of steady-state inactivation to the left in contrast to the above-described pathogenesis mechanism and in contrast to the putative extracellular α/β -binding site, thus suggesting an indirect effect (34).

B. Idiopathic Ventricular Fibrillation

Idiopathic ventricular fibrillation (IVF) in the presence of normal baseline Q-T intervals is an ion channel disorder allelic to LQT3. Two of the known mutations cause premature stop codons either in domain 1 or 4 of the sodium channel (Table 11, Fig. 3) and would be expected to cause loss of function (84). The third known case is linked to a double missense mutation of Arg-1232-Trp and Arg-1620-Thr. Heterologous expression of the latter revealed a depolarizing shift in the voltage dependence of steady-state inactivation and acceleration of recovery from inactivation, the opposite effect of antiarrhythmics of the lidocaine type (84).

C. Pathogenesis and Therapy

The plateau of the cardiac action potential is physiologically maintained by a delicate balance between inward (sodium and calcium) and outward (potassium) currents.

Membrane repolarization begins when outward current prevails over the inward current. Sustained inward current or reduced outward current may prolong the action potential and thus increase the Q-T interval. The delay in repolarization is caused either by suppression of repolarizing outward currents (438, 101) or by potentiation of depolarizing inward currents (46). This allows a reactivation of calcium currents (228) and secondary triggered activity due to early afterdepolarizations (523). β -Blockers are of benefit by suppressing sympathetic activity that may be associated with the initial increase in sympathetic tone preceding the Torsade de Pointes found in the hereditary forms of LQT only. Class I antiarrhythmics and local anesthetics such as mexiletine should be effective particularly on LQT3 because of their ability to prevent channel reopenings (14, 562). Raising the serum potassium concentration can increase outward HERG currents and may be effective in shortening the Q-T interval.

V. NEURONAL CHANNELOPATHIES

A. Neuronal Sodium Channelopathies

1. Generalized epilepsy with febrile seizures

Generalized epilepsy with febrile seizures (GEFS) is a recently described epilepsy syndrome comprising febrile seizures with childhood onset (1 yr), but unlike the typical febrile convulsions, attacks with fever continued beyond 6 yr or afebrile generalized seizures (tonic-clonic, myoclonic, myoclonic-astatic, absence, or atonic seizures) occurred usually to cease by the beginning of puberty (469). Recently, linkage to chromosome 19q13.1 was reported, and a point mutation was identified, Cys-121-Trp, in the gene encoding the voltage-gated sodium channel β_1 -subunit, *SCN1B* (558). The mutation disrupts a putative disulfide bridge normally maintaining an extracellular immunoglobulin-like fold (Fig. 3). Coexpression of the mutant β_1 -subunit with the rat brain IIA sodium channel α -subunit in *Xenopus* oocytes demonstrated that the mutation reverses the effect of the β -subunit on channel-gating kinetics leading to slowing of sodium current inactivation. This is similar to the effects of the skeletal muscle α -subunit mutations that cause myotonia and could explain neuronal hyperexcitability underlying GEFS. Lack of symptoms in heart and skeletal muscle also expressing *SCN1B* suggest tissue-specific effects of the β_1 -subunit on brain sodium channel isoforms.

2. Motor end-plate disease and ataxia in mice

Mouse motor end-plate disease is characterized by early-onset progressive paralysis of the hindlimbs and severe muscle atrophy due to alterations in neuromuscular transmission (16, 119). The cerebellar Purkinje cells

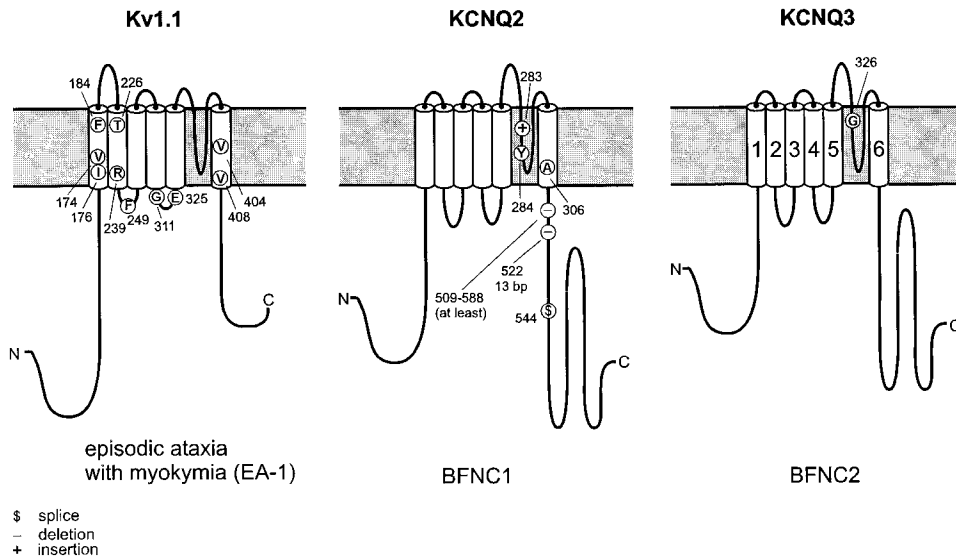
Neuronal K⁺ channels

FIG. 15. Cartoon of various neuronal potassium channel α -subunits: Kv1.1, KCNQ2, and KCNQ3. Mutations in voltage-gated Kv1.1, human homolog of *Shaker* channel, cause episodic ataxia with myokymia. Mutations in voltage-sensitive KCNQ2 and KCNQ3 lead to benign convulsions in neonatal humans (BFNC1 and -2). Conventional 1-letter abbreviations are used for replaced amino acids.

are degenerated and show a reduction in sodium-dependent spontaneous action potentials. Underlying genetic causes are splicing defects leading to premature stop codons by two naturally occurring alleles (*med*, *medj*) of the gene encoding the neuronal voltage-gated brain α -subunit, *Scn8a* (61, 264). An allelic recessive disorder is displayed by the jolting mouse (*medjo*) that suffers from no detectable morphological abnormality in skeletal muscle or peripheral nerve but disturbances of locomotion due to cerebellar impairment (cerebellar ataxia). The underlying mutation results in substitution of Thr for an evolutionarily conserved Ala residue in the cytoplasmic S4-S5 linker of domain III.

Scn8a is expressed in the gray matter of brain and spinal cord but not in skeletal or heart muscle. It is most closely related to the brain cDNA from the pufferfish *Fugu rubripes*, with 83% overall sequence identity and several shared insertions and deletions that are not present in other mammalian cDNA. The divergence of *Scn8a* from the other brain sodium channels thus must have occurred before the separation of fish and mammals and predates the origin of the gene cluster on chromosome 2. The subthreshold and the so-called resurgent sodium currents both mainly conducted by the noninactivating sodium channel type VIII (500) were drastically reduced in Purkinje neurons of *med* and jolting mice resulting in diminished spontaneous and evoked repetitive firing (424). Introduction of the jolting mutation into the rat brain IIA sodium channel shifted the voltage dependence of activation by 14 mV in the depolarizing direction, without affecting the kinetics of fast inactivation or recovery from inactivation. The shift in the threshold of the *Scn8a* channel could account for the reduced spontaneous activity of Purkinje cells, reduced inhibitory

output from the cerebellum, and subsequent loss of motor control observed in affected mice (264) (Fig. 3). The human homolog *SCN8A* maps to chromosome 12q13 and is an important candidate gene for inherited neurodegenerative disorders (401).

3. Paralysis in *Drosophila*

Para encodes a voltage-gated sodium channel expressed in neurons of the fruit fly *Drosophila melanogaster*. The transcript undergoes alternative splicing to produce several distinct channel subtypes resulting in proteins very similar to sodium channels of vertebrates (318). Mutations of *para* like smellblind (*sbl*) are associated with olfactory defects and temperature-sensitive paralysis (305). Molecular lesions within the *para* transcription unit consist of insertion of transposable elements that interfere with transcription or RNA processing of the sodium channel and result in a strongly reduced channel expression rate (154). Excitation of neurons in which the sodium channel is suppressed may thus be abortive under adversary circumstances such as elevated temperature, probably due to faster channel kinetics caused by conduction block (318). This is an example for haploinsufficiency, whereas all other sodium channelopathies are caused by gain-of-function mutations.

B. Neuronal Potassium Channelopathies

1. Benign neonatal convulsions

Autosomal dominant benign familial neonatal convulsions (BFNC) are characterized by brief and frequent

TABLE 12. *KCNA1* mutations

Genotype	Region	Mutation	First Report
C520A	S1	Val-174-Phe	54
T527A	S1	Ile-176-Arg	468
T551G	S1	Phe-184-Cys	53
A676G	S2	Thr-226-Ala	468
C677T	S2	Thr-226-Met	95
G715T	S2	Arg-239-Ser	54
T745A	S2/S3	Phe-249-Ile	54
Unpublished	S4/S5	Gly-311-Ser	591
G975C	S4/S5	Glu-325-Asp	53
G1210A	S6	Val-404-Ile	468
A1223G	S6	Val-408-Ala	54

Intronless gene encodes Kv1.1, the human analog of *Shaker* gene. Mutations cause episodic ataxia type 1.

generalized seizures, typically commencing within the first week of life and disappearing spontaneously within a few months. Seizure symptoms include tonic movements, shallow breathing, ocular signs (i.e., staring, blinking, or gaze deviations), and automatisms. The electroencephalogram shows generalized attenuation followed by slow waves, spikes, and burst suppression that correlate with symptoms. Interictally, patients show normal behavior and develop normal intelligence later in life. Seven mutations have been described in the voltage-sensitive potassium channel gene *KCNQ2* (39, 495, 291) and one in *KCNQ3* (80) that alter the structure of the pore region and/or COOH-terminal cytoplasmic domain leading to potential loss of function, gain of function, or dominant negative effects (Fig. 15). One of the *KCNQ2* mutants leading to a truncated channel protein has been expressed in *Xenopus laevis* oocytes but did not yield any detectable current. This suggests homotetramers to be nonfunctional. Coexpression with wild type at a ratio of 1:1 revealed a 50% current reduction without any support for a dominant negative effect of the mutation, indicating haploinsufficiency to be the decisive mechanism for disease pathogenesis (39).

2. *Shaker Drosophila*

A mutant of the fruit fly *D. melanogaster* episodically presents, and consistently responds to ether anesthesia, with jerking leg movements and was therefore named *Shaker*. Electrophysiological investigation of this mutant revealed potassium currents that inactivated much faster than those of wild-type *Drosophila* and led to the correct assumption that the *Shaker* mutation is located in a gene coding for the first voltage-gated potassium channel to be described (227).

3. Episodic ataxia type 1

A) A HUMAN ANALOG. Typically enough, the first vertebrate channelopathy detected involving a voltage-

gated potassium channel is linked to the human *Shaker* homolog *KCNA1* on chromosome 12p13 (308). Episodic ataxia type 1 is an autosomal dominant human disease characterized by episodic failure of excitation of cerebellar neurons and sustained hyperexcitability of the peripheral motoneurons (544). Onset of motion and exercise may provoke attacks of atactic gait and jerking extremity movements that last for seconds to minutes. Interictal twitching in facial muscles and those of distal extremities may occur, indicating that *KCNA1* is not only expressed in brain tissue but also in peripheral motoneurons. This so-called myokymia is associated with rhythmic activity of motor units in the EMG.

Several missense mutations have been detected in the resulting gene product Kv1.1 (Fig. 15, left; Table 12), most of which have been expressed in *Xenopus* oocytes. Although four of the mutants did not yield significant currents, others showed change of function leading to enhanced deactivation and C-type inactivation (Val-408-Ala in S6, Gly-311-Ser in S4-S5 loop) or right shift of voltage dependence of activation and slowing of time course of activation could be observed (Phe-184-Cys in S1, Val-1174-Phe in S1, Glu-325-Asp in S5, Thr-226-Ala/Met in S2) (4, 43, 102, 590, 591). Coexpression of the mutants with wild type mimicking in vivo conditions revealed current reduction between 26 and 100%, indicating a dominant negative effect interaction (4). Similar effects have been observed when these mutations were expressed in mammalian cells (Fig. 16; Ref. 50).

B) PATHOGENESIS. Disease pathogenesis might therefore be explained by a reduced repolarizing effect of the delayed rectifier leading to broadening of the action potentials and prolongation of transmitter release. Because of the strong expression of *KCNA1* in basket cells of the cerebellum, an imbalance between inhibitory and excitatory input could well destabilize motor control under stress or exercise leading to kinesigenic ataxia. Independently, myokymia may result from repetitive firing of affected peripheral motoneurons due to potassium current reduction which slows repolarization and hinders hyperpolarization after the action potential. The restriction of clinical symptoms to cerebellum and peripheral nerve despite almost ubiquitous expression in nervous tissue (548) may be due to the synergistic function of *KCNA2* which is capable of forming heteromultimers with the former (216, 563) generating the so-called dendrotoxin-sensitive delayed rectifier (436). Adequate treatment, as expected for neuronal hyperexcitability, consists of anticonvulsants such as carbamazepine. Interestingly, kinesigenic attacks also respond to some extent to acetazolamide (55, 153, 542).

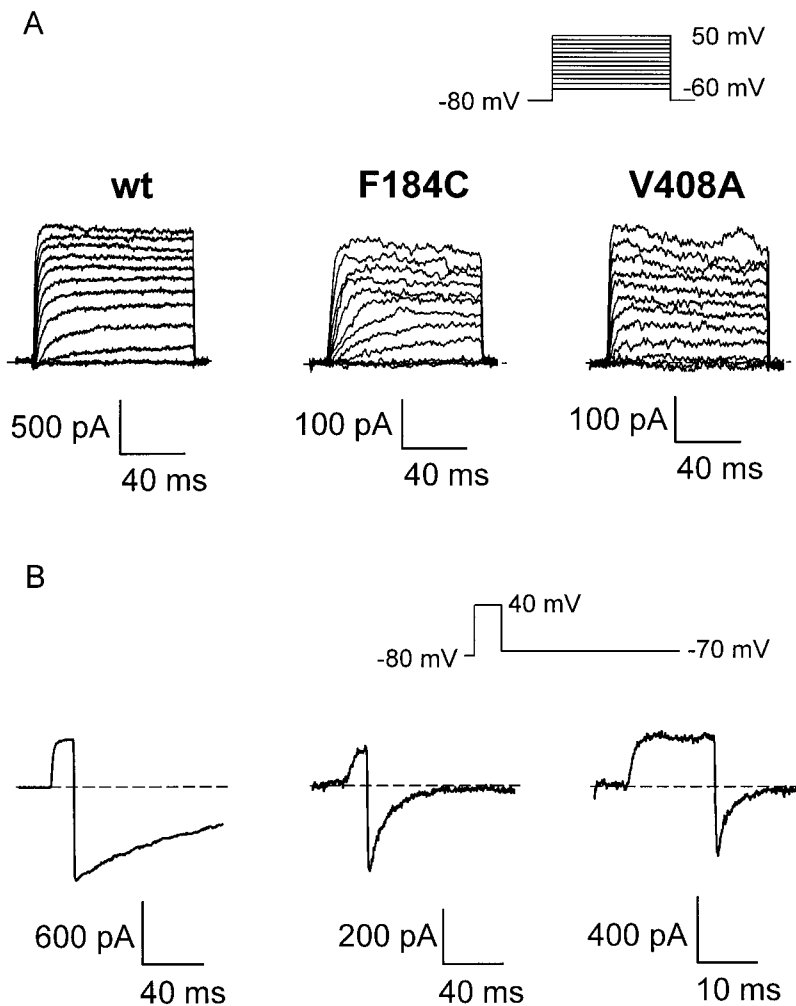


FIG. 16. Activation (A) and deactivation (B) of potassium currents through wild-type (WT) and mutant human Kv1.1 channels expressed in rat basophilic leukemia cells. Whole cell currents were elicited in response to depolarizing pulses. Phe-184-Cys mutant channels activate at 25 mV less negative potentials in physiological electrolyte gradients than WT and Val-408-Ala channels. In contrast, Val-408-Ala channels deactivate faster than WT and Phe-184-Cys channels (solutions containing symmetrical potassium concentrations). [Modified from Bretschneider et al. (50).]

C. Neuronal Calcium Channelopathies

1. Hemiplegic migraine and allelic ataxias: disorders of the human P/Q-type calcium channel

A clinically related dominantly inherited disease, episodic ataxia-type 2 (EA2), has been linked to chromosome 19p13 (543, 550). Patients present with attacks of ataxia triggered by emotional or alimentary stimuli and lasting for hours (387). They may be accompanied by headaches and cerebellar signs such as vertigo and dysarthria. In the interictal interval, spontaneous or gaze nystagmus may be observed. Matching the concomitant symptoms of EA2 patients, a familial form of headache, hemiplegic migraine (FHM) has been mapped to chromosome 19p13 for numerous families (238, 337). Individuals affected by this autosomal dominant disorder present with characteristic unilateral migrainous headaches accompanied by nausea as well as phono- and photophobia. Episodes are typically precipitated by an aura with symptoms of both hyper- and underexcitability such as aphasia, dysarthria, vertigo,

homonymous hemianopsia, cheiro-oral paresthesia, and hemiparesis. Some families additionally present with epilepsy, retinal degeneration, hypakusis, persistent cerebellar dysfunction, and Purkinje cell atrophy (376, 588). The underlying genetic causes are mutations in *CACN1A* on chromosome 19p13 encoding the α_1 -subunit of the voltage-gated P/Q-type calcium channel (Fig. 17; Refs. 378, 589). A progressive form of ataxia not involving the brain stem or retina in the neurodegenerational process, spinocerebellar ataxia (SCA6), is allelic (435, 596). Remarkably, the three allelic phenotypes are each associated with a different type of mutation. Although FHM is caused by missense point mutations suggesting change of function as pathogenic mechanism, EA2 mutations all lead to changes in posttranscriptional splicing or premature truncation that corresponds to loss of function and haploinsufficiency to be pathogenetically decisive. In contrast, the progressive disease SCA6 is associated with a trinucleotide expansion in the coding region as shown for several other neurodegenerative disorders.

Neuronal Ca²⁺ channel α_1 -subunit

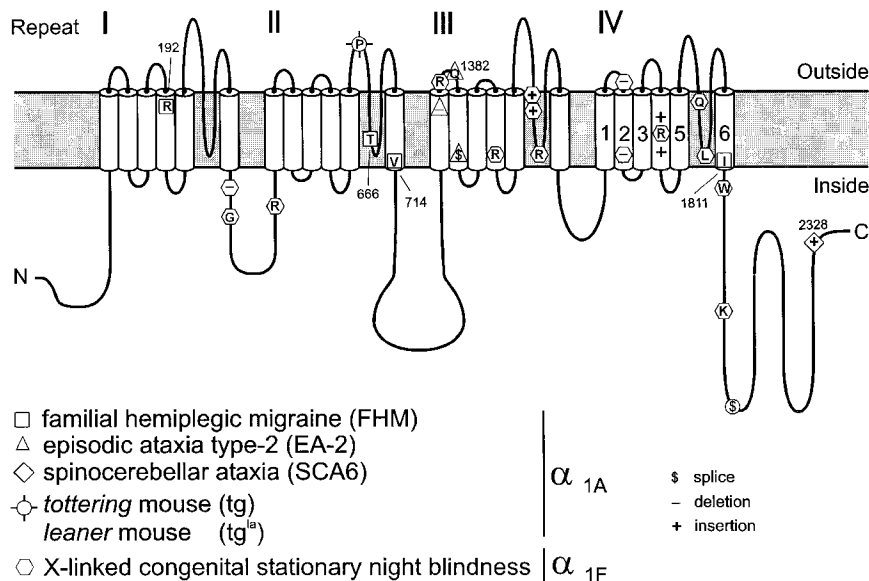


FIG. 17. Cartoon of α_{1A} -subunit of brain P/Q-type channel. To date, mutations have been described in humans (familial hemiplegic migraine, episodic ataxia type 2, and spinocerebellar ataxia type 6) and mice (*tottering*, *leaner*) as indicated by symbols at *bottom left*. Lethargic, *stargazer*, and *waggler* mice show similar clinical signs that are caused by mutations in other subunits of P/Q-type channel. Mutations in human α_{1F} -subunit cause X-linked congenital stationary night blindness. Different symbols used for various diseases are explained on *bottom left*. Conventional 1-letter abbreviations are used for replaced amino acids whose positions are given by respective numbers of human α_{1A} -subunit.

Six missense mutations for FHM in the *CACN1A* coding region have been described, all of which result in a comparable phenotype (378). Because of their localization in the voltage sensors or associated with P-region, a gain of function could be assumed to result from either a change in voltage dependence of gating, gating kinetics, or ion conductance and specificity, which all would result in membrane depolarization. Current pathogenesis models of migraine include an hypothesis on spreading depression that could well explain the aura initiating the attacks. Perhaps, in reality, *CACN1A* is more of an aura gene than a true migraine gene, and the pain may be a secondary effect of the long-lasting depolarization. Heterologous expression of four of the mutations in *Xenopus* oocytes revealed current inactivation to be slightly faster in mutants (Thr-666-Met, Val-714-Ala) and time course of recovery from channel inactivation to be accelerated (Val-714-Ala, Ile-1819-Leu) than in wild type in agreement with the depolarizing tendency expected (269).

2. *Tottering*, *leaner*, *rolling*, *lethargic*, *stargazer*, and *waggler* mice

In mice, four mutants of the murine *cacn1a* or associated genes exhibiting recessive effects have been described (Fig. 17; Refs. 115, 142). A *leaner* mutant presents with seizures homologous to human petit mal (absences), ataxia, and progressive cerebellar degeneration. At the molecular level, a splice donor sequence that is predicted to result in multiple transcripts can be found producing proteins with aberrant truncated COOH termini comparable to the situation in human EA2. A second mutant, *tottering* (*tg*), is caused by a missense mutation resembling one of hemiplegic migraine mutations in the putative pore-forming region of the second domain.

Affected animals show absencelike seizures also. The genetic background of *rolling Nagoya*, mice without seizures but showing poor limb coordination with falling and rolling over, has not been clarified, but the disorder is allelic to *tottering* (374). Animals with the fourth mutant, *lethargic* (*lh*), show absences and ataxia without neurodegeneration. The underlying mutation is in the β_4 -cosubunit and leads to protein truncation thereby deleting the region of interaction with the α_1 -subunit (62). *Stargazer* mice have spike-wave seizures characteristic of absence epilepsy,

TABLE 13. *CACNAF* mutations

Genotype	Exon	Region	Mutation	First Report
ΔC1023	9	I/II	fs at codon 341	29
G1106A	8	I/II	Gly-369-Asp	518
G1523A	13	I/II	Arg-508-Gln	518
C2488T	21	III/S1-S2	Arg-830-Stop	29
C2172T	24	III/S4	Arg-958-Stop	518
2972insC	27	III/S5-S6	fs at codon 991	29
3133insC	27	III/S5-S6	fs at codon 1045	518
C3145T	27	III/S5-S6	Arg-1049-Trp	518
ΔC3477	30	IV/S1-S2	fs at codon 1159	29
Δ3658-3669	30	IV/S2	fs at codon 1223	518
C3700T	33	IV/S4	Arg-1234-Stop	29
C4042C	35	IV/S5-S6	Gln-1348-Stop	518
T4091A	35	IV/S5-S6	Leu-1364-His	518
G4157A	37	COOH terminal	Trp-1386-Stop	29
A4771T	41	COOH terminal	Lys-1591-Stop	518

Gene codes for the α -subunit of retinal calcium channel. Mutations cause X-linked congenital stationary night blindness. S, transmembrane segment situated in one of the 4 repeats (I-IV); fs, frame shift due to an insertion (ins) and/or deletion (Δ) causing altered amino acid sequence usually followed by premature termination.

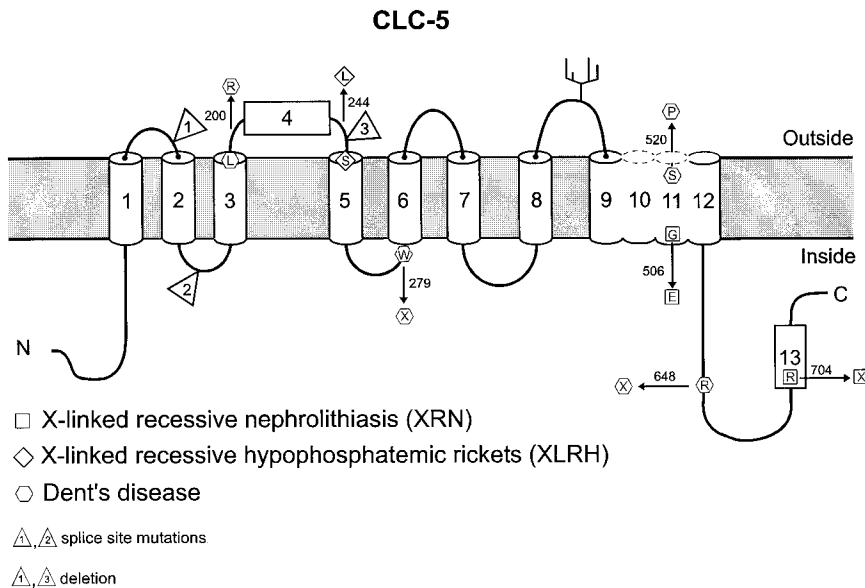


FIG. 18. Cartoon of human chloride channel monomer, CLC-5. Corresponding gene is located on X-chromosome and mainly but not exclusively expressed in kidney. All mutations identified to date cause loss or reduction of function and lead to a recessive type of nephrolithiasis with and without rickets. Conventional 1-letter abbreviations are used for replaced and substituting amino acids located at positions given by respective numbers. Various symbols are used for clinical diagnoses made for (male) patients carrying one of these mutations.

with accompanying defects in the cerebellum and inner ear. Genetic background is a disruption of a brain-specific calcium channel γ -subunit, *stargazin*. In the mutant, the *stargazin*-mediated effect of increased steady-state inactivation of P/Q-type channels is lacking, suggesting a loss of function/coassembly failure to be the mechanism of pathogenesis that leads to inappropriate calcium entry and neuronal depolarization (300). *Wagglers* is an allelic disorder characterized by whole body tremor, an unstable gait, and growth retardation in homozygous mice.

3. X-linked congenital stationary night blindness

X-linked congenital stationary night blindness (CSNB) is a recessive nonprogressive retinal disorder characterized by night blindness, decreased visual acuity, myopia, nystagmus, and strabismus. Two distinct clinical types can be distinguished: 1) complete CSNB with non-functional rods and normal cones and 2) incomplete CSNB with subnormal but measurable rod and cone function. Incomplete CSNB (CSNB2) is caused by missense and nonsense mutations predicting premature stop codons as *CACNF1* (Fig. 17, Table 13), an L-type retinal-specific calcium channel (28, 29, 518), indicating, most likely, a loss of function to be underlying the decrease in neurotransmitter release from photoreceptor presynaptic terminals.

VI. NEPHRONAL CHLORIDE CHANNELOPATHIES

Hypercalciuria, the most prevalent cause of nephrolithiasis, arises from various causes, mainly intestinal hyperabsorption, renal disturbances, or bone resorp-

tion. Some rare hereditary forms associated with hypercalciuria are caused by mutant ion channels or transporters.

A. Human Bartter Syndrome

Human Bartter syndrome is a clinically and genetically heterogeneous kidney disease. This autosomal recessive disorder is characterized by hyperreninism and hyperaldosteronism with hypokalemic metabolic alkalosis, hypercalciuria, and hypochloremia. Clinically, patients show edema, muscle weakness, vertigo, and hypotension. Three main phenotype variants have been described: classic syndrome, hypomagnesiemic variant, and antenatal subtype, the latter of which is the most severe type with life-threatening polyhydramnion due to fetal hyposthenuria and polyuria.

Three causative genes have been identified for this syndrome, each indicating different mechanisms for disease pathogenesis. Two of the genes are voltage-independent ion transporters or channels with loss-of-function mutations in the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter (encoded by *NKCC2*) and in the ATP-sensitive potassium channel ROMK (*KCNJ1*) (see Table 4). In the third genetic variant, Bartter syndrome type III, five missense mutations in a voltage-dependent chloride channel gene, *CLCNKB*, have been described (493). A reduction of chloride conductance by the mutations would agree with the observed reduction of the fractional reabsorption of chloride in the distal part of the ascending limb of the Henle loop, resulting in renal salt wasting, a theory awaiting confirmation by functional studies.

B. Human X-Linked Recessive Nephrolithiasis

Are there four clinical diagnoses for the same *CLC5* channelopathy? Four hypercalciuric nephrolithiasis disorders, Dent's disease, X-linked recessive nephrolithiasis, X-linked recessive hypophosphataemic rickets, and familial idiopathic low-molecular-weight proteinuria share common features of progressive proximal tubulopathy, characterized by low-molecular-weight proteinuria and hypercalciuric nephrocalcinosis. Additional symptoms include hypophosphatemic rickets, aminoaciduria, phosphaturia, glucosuria, kaliuresis, uricosuria, and impaired urinary acidification. Both females and males may exhibit hypercalciuria, nephrolithiasis, and low-molecular-weight proteinuria; however, only men develop renal insufficiency, consistent with an X-linked recessive gene defect. The diseases are caused by recessive mutations in the X-chromosomal gene *CLCN5*, encoding the voltage-sensitive *CLC5* channel (12, 253, 309–311, 368) with missense mutations all located in the transmembrane segments while nonsense and donor splice site mutations are all located in nonhelical loops (Fig. 18). Clinical variability between families with the same mutation is so great that differences in ethnic origin, diet, or an unidentified modifying gene have been proposed to account for the variance in phenotypes (253, 383).

Heterologous expression of wild-type *CLC5* in *Xenopus* oocytes resulted in outwardly rectifying chloride currents with mutants revealing abolition of currents or a marked reduction in current density that suggested loss of function to be the pathogenetic mechanism (309, 310). As in Bartter syndrome, reduced *CLCN5* function may indeed lead to a decreased chloride absorption in the proximal renal tubules, which in turn could result in decreased calcium absorption and nephrocalcinosis, but the pH-dependent low-molecular-weight proteinuria remains a mystery.

VII. CONCLUSIONS

In the past 9 years, research on ion channels has benefited tremendously from the discovery of channelopathies, a group of hereditary disorders associated with ion channel mutations in both humans and animals. Naturally occurring mutations causing disease indicated clear regions of functional importance in the channels that were then studied intensively and yielded much of our current knowledge on structure-function relationships of channel proteins today. One example is the chloride channel family that probably would not have been discovered to date had it not been for the clinical and functional studies launched to solve the intriguing pathogenesis of myotonia congenita. Differentiation of S4 segment function in the sense that repeat IV is important for

inactivation instead of activation would not have been described had there not been paramyotonia mutations associated with sodium channel *IVS4*. Even the cloning of the human *SCN4A* gene would perhaps have not yet been performed had it not been for the discovery of impaired sodium channel function in native muscle of periodic paralysis patients. Current research employing short-cuts derived from experiences in the past to accelerate genetic studies by candidate gene approach take advantage of the fact that ion channelopathies share many common features such as the attacklike symptoms of hyper- or under-excitability provoked by typical factors, additional progressive components related to cell degeneration, both associated with sustained membrane potential changes. Recurrent patterns of pathogenesis mechanisms associated with the mode of transmission already indicate functional consequences such as recessive mutations leading to loss of function and dominant mutations leading to change of function in the sense of gain of function (dominant positive effect) or loss of function (dominant negative effect in multimeric proteins or haplo-insufficiency). From the numerous ion channel genes cloned to date, multiple forms of disease genetically related to ion channels may be expected in the future that can serve as a model for understanding disease pathogenesis of more frequent nonhereditary idiopathic variants.

NOTE ADDED IN PROOF

Dominant deafness

In the meantime, the *KCNQ* gene family has been enlarged by a fourth member. *KCNQ4* maps to chromosome 1p34, a region including the *DFNA2* locus previously found to be linked to an isolated type of dominant deafness. The gene is expressed in the sensory outer hair cells of the cochlea. A mutation identified in a *DFNA2* pedigree changes a residue in the *KCNQ4* pore region and abolishes the potassium current of the tetrameric channel complex by a dominant negative effect. Whereas mutations in *KCNQ1* cause deafness by affecting endolymph secretion, the mechanism leading to *KCNQ4*-related hearing loss is intrinsic to outer hair cells (Kubisch, C., B. C. Schroeder, T. Friedrich, B. Lutjohann, A. El-Amraoui, S. Marlin, C. Petit, and T. J. Jentsch. *Cell* 96: 437–446, 1999).

Long QT syndrome and ventricular fibrillation

The second member of the *KCNE* gene family encoding potassium channel β -subunits has been cloned, characterized, and associated with cardiac arrhythmia. *KCNE2* encodes a MinK-related peptide 1 (MiRP1), a small membrane-spanning subunit that assembles with the *HERG* α -subunit protein and modifies its function. Unlike channels formed only with *HERG*, heteromeric complexes resemble native cardiac IKr channels in their gating, unitary conductance, regulation by potassium, and distinctive biphasic inhibition by class III antiarrhythmics. Three missense mutations associated with long Q-T syndrome and ventricular fibrillation have been identified in *KCNE2*. Mutants

form channels that open slowly and close rapidly, thereby diminishing potassium currents (Abbott, G. W., F. Sesti, I. Splawski, M. E. Buck, M. H. Lehmann, K. W. Timothy, M. T. Keating, and S. A. Goldstein. *Cell* 97: 175–187, 1999).

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