ELSEVIER

Clinical Neurophysiology 112 (2001) 2–18

www.elsevier.com/locate/clinph

Invited review

Disorders of membrane channels or channelopathies

Gastone G. Celesia*

Department of Neurology, Loyola University Chicago, Stritch School of Medicine, 2160 S. First Avenue, Maywood, IL, USA

Accepted 27 September 2000

Abstract

Objective: To review the structure and function of membrane ion channels with special emphasis on inherited nervous system channel disorders or channelopathies.

Results: Channels are pores in the cell membrane. Through these pores ions flow across the membrane and depolarize or hyperpolarize the cell. Channels can be classified into 3 types: non-gated, directly gated and second messenger gated channels. Among the important directly gated channels are voltage gated (Na^+, K^+, Ca^{2+}, Cl^-) and ligand gated (ACh, Glutamate, GABA, Glycine) channels. Channels are macromolecular protein complexes within the lipid membrane. They are divided into distinct protein units called subunits. Each subunit has a specific function and is encoded by a different gene. The following inherited channelopathies are described. (1) Sodium channelopathies: familial generalized epilepsy with febrile seizures plus, hyperkalemic periodic paralysis, paramyotonias, hypokalemic periodic paralysis; (2) potassium channelopathies: benign infantile epilepsy, episodic ataxia type 1; (3) calcium channelopathies: episodic ataxia type 2, spinocerebellar ataxia type 6, familial hemiplegic migraine, hypokalemic periodic paralysis, central core disease, malignant hyperthermia syndrome, congenital stationary night blindness; (4) chloride channelopathies: myotonia congenitas; (5) ACh receptor channelopathies: autosomal dominant frontal lobe nocturnal epilepsy, congenital myasthenic syndromes; (6) glycine receptor channelopathies: hyperekplexia.

Conclusions: Studies of human inherited channelopathies have clarified the functions of many ion channels. More than one gene may regulate a function in a channel, thus different genetic mutations may manifest with the same disorder. The complex picture of the genetic and molecular structures of channels will require frequent updates.

Keywords: Channelopathies; Ion channels; Congenital myasthenic syndrome; Epilepsy; Periodic paralysis; Hemiplegic migraine; Episodic ataxia; Central core disease; Myotonia

1. Introduction

A better understanding of cell membrane structures and channel functions has been achieved in recent years by 3 scientific advances, the patch-clamp technique, the use of selective neurotoxins, and the cloning and sequencing of genes. Channels are membranous structures formed by aggregated proteins and contain aqueous central pores that allow the passage of ions. Channels control the flow of ions in and out of the cell causing depolarization and hyperpolarization of the cell. The patch-clamp technique measures the activity of a single ion directly by recording the current flow through a single open channel (Neher and Sakmann, 1976; Owens and Kullberg, 1989). Neurotoxins selectively inactivate different sites of the ion channel thus allowing both the identification of channel components and the determination of their functions (Hille and Catterall, 1999). The protein aggregates that form the channels are encoded by different genes and the genes for many of these channels have been cloned and their structures identified (Fontaine et al., 1997; Mody, 1998; Hille and Catterall, 1999; Barchi, 1999). In this review we will describe the structures of the various membrane channels, discuss their physiology, and then review the effects of channel disorders as causative agents for diseases of the nervous system.

2. Ion channels

Ion channels are fundamental in membrane potential generation. They either produce action potentials or graded potentials, the base for communication among neurons. During excitation some channels open, others close and ions move through the membrane producing potential changes. The changes in membrane potential generate either 'all or none' action potentials or graded potentials causing an increase or decrease in cell membrane polarization. Channels have specific properties as summarized by Siegelbaum and Koester (2000): '(1) they conduct ions; (2) they

* Corresponding author. Fax: +1-708-216-8784.
E-mail address: gcelesi@lumc.edu (G.G. Celesia).

1388-2457/01/$ - see front matter CLINPH 2000081
PII: S1388-2457(00)00496-X

recognize and select among specific ions, and (3) they open and close in response to specific electrical, mechanical or chemical signals.' The resting membrane potential as well as the activation of the membrane potential depends on a variety of ion channels and other membrane transporters. Channels are widely distributed in the nervous system and are present in the cell soma, dendrites, axons and at the synapses (Koester, 2000a). In the muscles they are present both at the neuromuscular junction and in the muscle membrane (Aidley and Stanfield, 1996). The number and the type of channels differ in relation to the cell type and its location (Hille and Catterall, 1999). In the axons the majority of ion channels are Na^+ and K^+ channels, in myelinated fibers there is a high concentration of Na^+ channels in the node of Ranvier, and in the neuromuscular junction there is a high concentration of nicotinic ACh ligand-gated channels. Cl^- channels are particularly important in muscle cells where they account for 70% of the resting membrane conductance (Davis and Hanna, 1999).

Several types of channels have been identified in cells membranes (Table 1): non-gated, directly gated and second messenger gated channels. Non-gated channels open or

Table 1
Nervous system channels

Channel type	Ions involved	Effector mechanism
Non-gated channels		
Na^+	Na^+	Concentration gradient[a]
K^+	K^+	Concentration gradient[a]
Cl^-	Cl^-	Concentration gradient
Directly gated channels		
Voltage-gated		
Na^+	Na^+	Membrane electrical fields
K^+	K^+	Membrane electrical fields
Ca^{2+}	Ca^{2+}	Membrane electrical fields
Cl^-	Cl^-	Membrane electrical fields
Ligand-gated		
ACh		Transmitter binding
Nicotinic	Na^+, K^+, Ca^{2+}	Nicotinic ACh binding
Glutamate		Transmitter binding
NMDA	Na^+, Ca^{2+}, Mg^{2+}	Glutamate bindings
AMPA	Na^+, Ca^{2+}	Glutamate bindings
KA	?	Glutamate bindings
GABA		Transmitter binding
$GABA_A$	Cl^-	GABA binding
$GABA_B$	Cl^-	GABA binding
Glycine		Transmitter binding
GLRA1	Cl^-	Glycine binding
GLRA2	Cl^-	Glycine binding
GLRA3	Cl^-	Glycine binding
Cyclic nucleotide-gated		Cyclic nucleotide binding
cGMP (retinal)	Na^+, K^+	Light activated the cGMP that directly affect the Na^+ channel
cGMP, cAMP	Na^+, K^+, Ca^{2+}	Direct activation of channel by cGMP or cAMP
Proton-gated		
ASIC alpha	Na^+	Low pH
ASIC beta	Na^+	Low pH
DRASIC	Na^+, Ca^{2+}	Low pH
MDEG-1	?	Low pH
Capsaicin	?	Heat, low pH
Mechanically-gated	Na^+, Cl^-	Mechanical pressure or stretch
Second messenger gated		Transmitter bindings and secondary ion channel activation by phosphorylation, or via cAMP, cGMP
G-protein receptor	Na^+, K^+, Ca^{2+}	
Muscarinic Ach receptor[b]	K^+	Via GTP proteins regulates K^+ channels
Serotonin receptor	K^+	Via cAMP, protein kinase, phosphorylation, followed by closure K^+ channel
Alpha1D adrenergic receptor	Ca^{2+}	?

[a] Sodium potassium pump balances the passive flux of Na^+ and K^+ by active transport against the gradient via ATP.

[b] Most muscarinic receptors are activated via the interaction of the receptor with a G-protein with either inhibition of adenylyl cyclase or stimulation of phospholipase C, and less frequently via regulation of potassium channels.

close in relation to simple ion concentration gradients, whereas gated channels require a 'key' to open the gate of the channel. Opening and closing of channels involves conformational changes of the channel. Only some of the conformational changes are understood. Siegelbaum and Kooester (2000) propose 3 physical models for the opening and closing of the channels, a localized change in one region of the channel, a general structural change involving the length of the channel and a blocking particle that swings into and out of the channel mouth.

The channels are macromolecular protein complexes within the lipid membrane. Structurally they are often divided into distinct protein units called channel subunits. Each subunit has a different function and is encoded by different genes (Hille and Catterall, 1999). Most of the channels contain a principal subunit and 3–4 auxiliary subunits (Fontaine et al., 1997; Hille and Catterall, 1999). The principal subunit in the voltage-gated channels is the α subunit and is capable of carrying out the functions of the channels (Fig. 1). In Na^+, K^+ and Ca^{2+} channels the principal subunit is functionally independent whereas the auxiliary subunits, according to Hille and Catterall (1999) 'improve expression and modulate physiological properties'. Recently Doyle et al. (1998), using high-resolution X-ray crystallography, have visualized the K^+ channel. The channel is formed by 4 polypeptide subunits arranged symmetrically around the central pore.

Ion channels often undergo 3 states: open, and two closed states, resting closed and inactivated closed. Fig. 1 shows a cartoon of the Na^+ channel and its two gates, the activation and the inactivation gate.

The gate may be activated by a variety of mechanisms

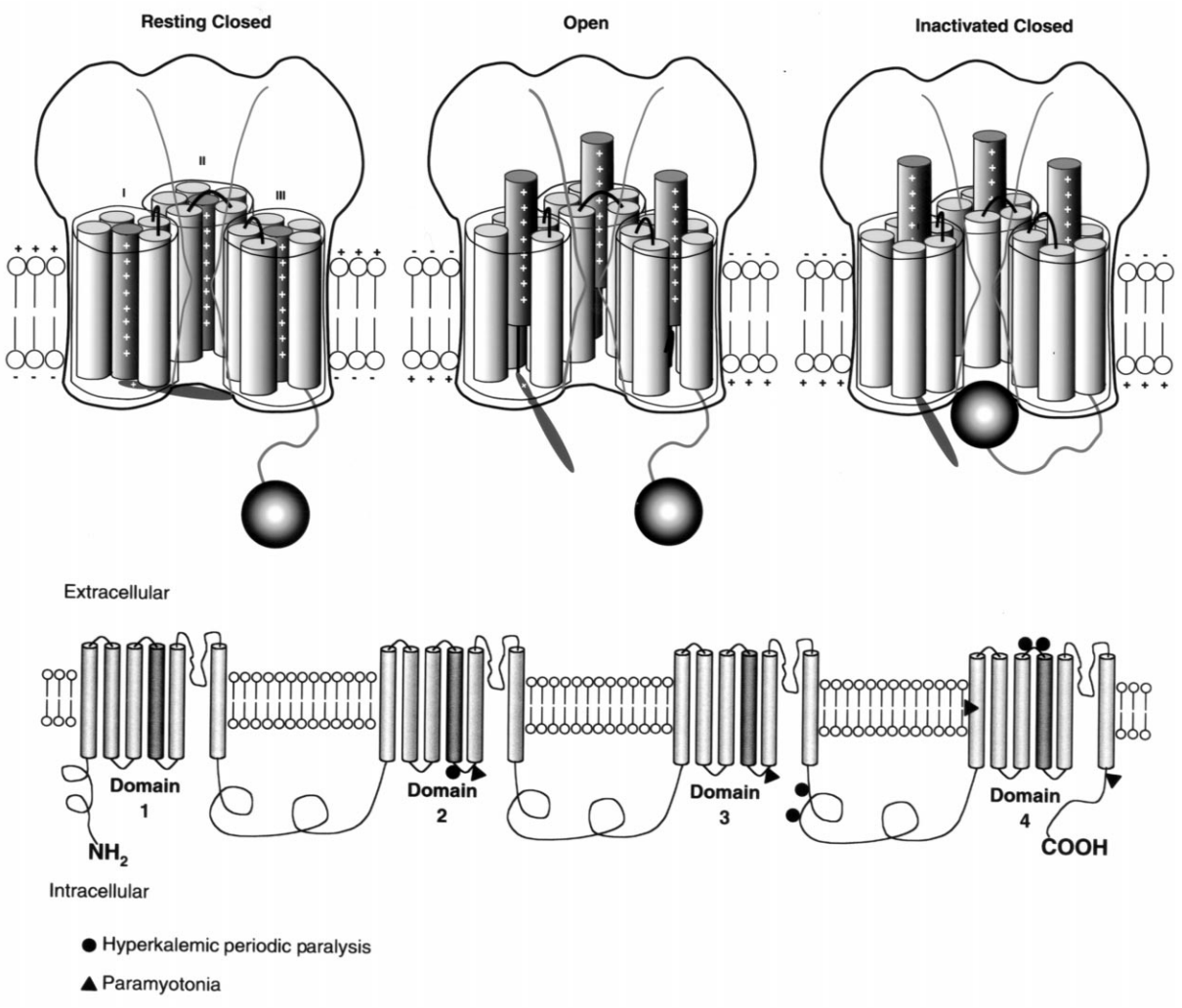

Fig. 1. (Upper) Three-dimensional model of the sodium channel in the resting closed, open and inactivated state. The subunits of the Na^+ channel are composed of 4 common repeated domains. Only 3 domains are shown here to visualize the pore. The central pore is surrounded by the 4 repeated domains. Each of the 4 domains is constituted by 6 cylinders, which represent the 6 α-helices. In the figure one of the cylinders is removed to show the positively charged S4 helix. When the cell is depolarized the change in the electrical field drives the S4 region towards the extracellular part of the membrane thus opening the activation gate. (Lower) Cartoon of the sodium channel alpha subunit. It contains 4 repeat domains. Each domain contains 6 transmembrane alpha helical segments. The 4th segment (drawn darker) is the voltage sensor for the channel. A stretch of amino acids, the P region between alpha helices 5 and 6 forms a loop that dips into the membrane. Most mutations are located in domains 3 and 4.

including voltage, mechanical changes, pH changes, and binding of ligands such as neurotransmitters, or indirectly by activation of the second messenger system. Thus gated-channels have been classified by the mechanisms of their activation: voltage-gated, ligand-gated, proton-gated, etc. Channels tend to be preferentially permeable to specific ions: sodium, potassium, chloride and calcium. Although other ion channels have been identified such as hydrogen, etc. we will limit our review to Na^+, K^+, Cl^-, and Ca^{2+} ions.

Non-gated channels are channels that allow the flux of ions by the mechanism of concentration gradient. The flux of ions is passive and involves Na^+ and K^+ with K^+ going out of the cell and Na^+ entering the cell. The membrane potential can be calculated with the Nernst equation (Koester, 2000a,b). This tendency of K^+ to efflux and Na^+ to influx the cell is balanced by the Na^+–K^+ pump that actively moves the two ions against their electrochemical gradient using energy from the hydrolysis of ATP. Non-gated channels include Na^+ and K^+ channels found in both neurons and glial cells (Koester, 2000a,b). In resting neurons the membrane potential is constant because the efflux of K^+ is balanced by the influx of Na^+ via non-gated channels. When the cell is activated the excitatory synaptic potential triggers the voltage-gated Na^+ channel to open causing an influx of Na^+ which is greater than the K^+ efflux. Voltage-gated Na^+ and then K^+ channels mediate the depolarization and repolarization of the cell following excitation.

As shown in Table 1 there are a large number of directly gated channels that are activated by various mechanisms and will be discussed briefly.

Voltage-gated channels are channels whose conductance is affected by changes in membrane potentials. These channels have voltage sensors sensitive to membrane electrical fields. These sensors will trigger conformational changes effectively opening or closing the gates that determine the permeability of the channel. The voltage-gated family includes Na^+, K^+, Ca^{2+}, Cl^- channels. The nervous system contains a great variety of voltage-gated channels. At least 4 variants of K^+ channels have been described in neurons. We know that there are 10 types of Na^+ and 3 types of Ca^{2+} voltage-gated channels (Koester, 2000a,b). Additional types may be identified in the future.

Proton-gated channels are sensitive to pH changes. The activating mechanism of these channels is a low pH. Three proton-gated channels have been cloned: dorsal root acidic sensing channel (DRASIC), acidic sensing ion channel (ASIC) and mammalian degenerin homologue (MDEG-1). Changes toward low pH will open the channel gate to Na^+, and in DRASIC also to Ca^{2+}. These channels are widely distributed in the nervous tissue (Meyer et al., 2000; Chen et al., 1998; Babinski et al., 1999). ASICs have two variants: ASIC-alpha and ASIC-beta. ASIC-beta is expressed exclusively in sensory neurons (Chen et al., 1998). The function of these channels is not known, although their preponderant expression in sensory neurons suggests a role in sensory transduction and nociception. Recently a vanilloid-activated cation channel has been identified and cloned in mice (Caterina et al., 2000). This channel, named capsaicin receptor, is present in small and medium neurons of dorsal roots, trigeminal and other sensory ganglia. It is part of the pain pathway and it responds to heat, cold and acid. Its relationship to proton-gated channels is uncertain. Whether these channels represent a separate ion channel family or a subset of the proton family is not clear. Mice lacking capsaicin receptors do not respond to heat or vanilloid-pain evoked stimuli, but react normally to mechanical nociceptive stimuli (Caterina et al., 2000).

Ligand-gated channels are ion channels whose change in conductance is regulated by its binding to a neurotransmitter or other chemical structure. The neurotransmitter-known ligands activating these channels are: glutamate, glycine, GABA, and ACh. The complexity of ligand-gated channels is not completely known. The most studied is the nicotinic ACh receptor channel at the neuromuscular junction. As shown in Fig. 2 the receptor is an intrinsic membrane protein with 5 distinct subunits (alpha to gamma). In the muscle the α subunit is expressed in two copies. Each subunit contains 4 alpha helical domains labeled M1 to M4. The M2 domain forms the channel pore. The amino acids in the outer and inner boundaries of the M2 domain are negatively charged constituting a selective filter for cations. In contrast to voltage-gated channels that are allowing either Na^+ or K^+ influx, the ACh receptor as it opens becomes permeable to Na^+, K^+ and Ca^{2+} (Hille and Catterall, 1999; Kandell and Siegelbaum, 2000). The muscarinic ACh channel is not a directly gated channel but operates via activation of the G-protein receptor and will be discussed later.

Glutamate receptors are present in the nervous system in two forms: the ionotropic and the metabotropic forms. The metabotropic receptor belongs to the family of G-protein-coupled receptors and will not be discussed here. The ionotropic glutamate receptor channels are further subdivided into NMDA, AMPA/KA and KA (Kainic) receptor channels. GABA receptors are subdivided into two classes: $GABA_A$ and $GABA_B$. The $GABA_A$ receptor consists of 5 subunits. There are differences in the combination of subunits in the various species and in the different brain regions. Less is understood about the $GABA_B$ receptor. As the transmitter binds to the receptor (two binding sites need to be activated in the $GABA_A$ receptor) the channel opens and allows the flux of chlorides (Cl^-) into the cell. Glycine-gated channels are similarly Cl^- channels. Both GABA and Glycine are inhibitory ion channels.

Ligands can also be other chemical structures such as cyclic nucleotides. Channels responding to such signals are named cyclic nucleotide-gated (CNG) channels. The cyclic nucleotide binds directly to the channel and activates it. cGMP and cAMP channels have been identified both in the retina and olfactory bulb. In the retina the cGMP is activated by light causing the channel to close and hyperpolarize the photoreceptor. Darkness in contrast opens the

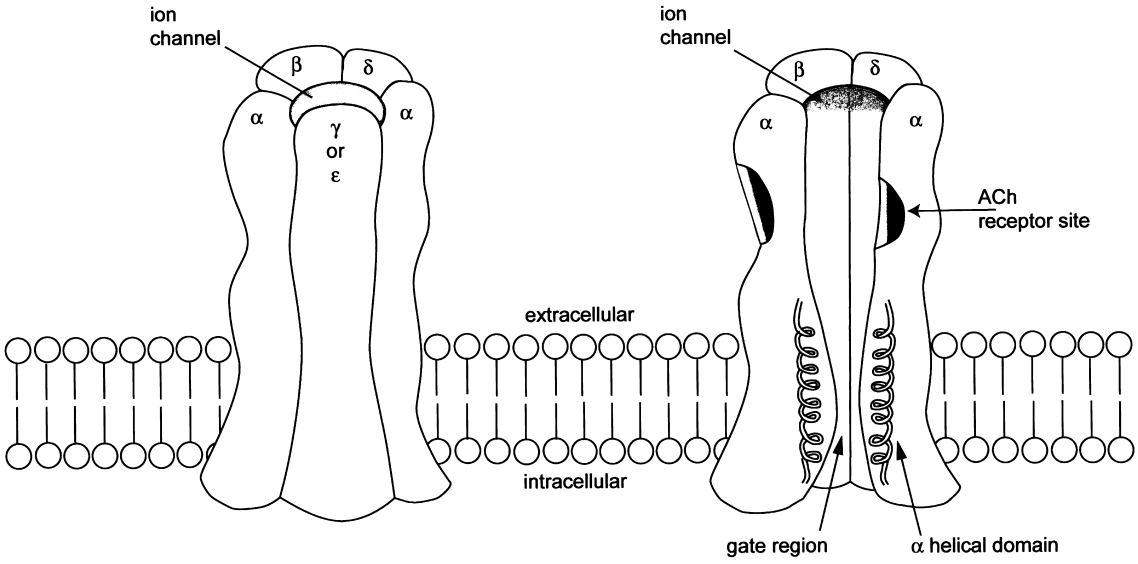

Fig. 2. Three dimensional model of the muscle nicotinic ACh receptor. On the left the 5 subunits are shown, while on the right the receptor is cut and the γ or ϵ subunit removed to show the internal channel. Note the gating region deep in the bilayer membrane region. The α-helical domains and the receptor sites are shown. Note that the γ subunit present in the human fetus is then replaced in the adult by the ϵ subunit.

channel to the influx of Na^+ ions and thus depolarizes the photoreceptors (Dzeja et al., 1999; Tessier-Lavigne, 1999). In the olfactory epithelium 3 molecules of cAMP activate the CNG channel. The channel opens and an influx of Na^+ and Ca^{2+} cations enter the neuron leading to a depolarization of the cell (Komatsu et al., 1999; Firestein et al., 1999).

Mechanically-gated channels are channels that are activated by pressure or stretching. They have been found in sensory and motor neurons (Tavernarakis et al., 1997; Zhang et al., 2000). Walker et al. (2000) have cloned an ion channel from the neurons of the sensory bristle of the fruit fly and have demonstrated that movements of the bristles are converted into electrical impulses. They also showed that mutation of the receptor virtually abolished mechano-induced sensory signaling. They further suggest that the fruit fly bristles are good models for the hair cells of the human ear. This study may lead to a better understanding of inherited sensory-neural deafness.

Second messenger-gated channels are channels which may open or close by indirect intracellular action of second messengers. For instance the muscarinic ACh receptor activates the membrane G-protein receptor and then the closure of the K^+ channel. The process in these systems consists of two steps: ligand binding that initiates the chemical process leading to the second step of gate control. The secondary ion channel activation is via phosphorylation or via cAMP or cGMP (Bevans et al., 1998). Examples of second messenger-gated channels are the muscarinic ACh receptor, the serotonin and the adrenergic receptors (Table 1).

As channels are made up of protein aggregates, the channel structure is determined by gene encoding of the various proteins that make up the channel (Mody, 1998). Different genes encode each protein subunit. Furthermore there are several isoforms of a protein and each isoform is encoded by another gene. We know of more than 50 genes encoding channel subunits (Hille and Catterall, 1999). Gene mutations can easily alter the structure of a given channel and produce aberration in channel function. The elucidation of the molecular structures and the genetic encoding of these channels increase our understanding of their function and their role in inherited diseases. As we further identify the function of channel subunits we may be able to devise specific and novel targeted therapies.

3. Disorders of channel function or channelopathies

Channels have a fundamental role in neuronal signaling thus channel dysfunction may result in a variety of neurological disorders that span from myopathies to epilepsy. Disorders of channel function are called channelopathies (Ashcroft, 1999; Ptacek, 1998, 1999; Davis and Hanna, 1999; Lehmann-Horn and Jurkat-Rott, 1999; Mody, 1998; Fontaine et al., 1997). Various pathological processes can affect channel function including autoimmune, toxic and genetic causes. Among the acquired channelopathies the most common are disorders of the nicotinic ACh receptor. The prototype is myasthenia gravis, an autoimmune disorder where antibodies are targeted at the neuromuscular junction nicotinic ACh receptor. Other autoimmune disorders are Rasmussen's encephalitis and Isaac's syndrome. Rasmussen's encephalitis is caused by antibodies against the glutamate receptor GluR3 (Gibbs et al., 1998; Palmer et al., 1999). Isaac's syndrome is a neuromytonia caused by the presence of antibodies to peripheral nerve potassium channels (Hart et al., 1997). Toxins can also selectively

affect various channels; for example the snake venom alpha-bungarotoxin blocks the nicotinic ACh receptor, whereas the scorpion venom toxin blocks the voltage sensor of the Na^+ channel. Similarly drugs have been developed to block the functions of specific channels. For example, 4-amino-pyridine blocks the K^+ channel and curare blocks the nicotinic ACh receptor at the neuromuscular junction.

In this review we will discuss only inherited channelopathies affecting the nervous system. There is as yet no consensus in the classification of channelopathies thus we classified these disorders in relation to the channel involved (Table 2).

A characteristic of channel disorders is the intermittent nature of the patient symptoms. Why are these disorders episodic? Ptacek (1999) suggests that the mutation causing inherited channelopathies produces 'changes in membrane excitability' that 'can predispose to episodic disorders in excitable tissues'. He further proposes that significant mutations may have profound consequences on membrane excitability resulting in 'a lethal phenotype' (Ptacek, 1999). This would explain why we do not have channel disorders that manifest with progressive unremitting neurological deficits.

There are several basic principles that apply to disorder of channel function. They are: location selectivity, channel interdependency, genetic heterogeneity and phenotype heterogeneity principles.

3.1. Location selectivity principle

The anatomical location of specific channel types determines their function. The composition of the subunit of a specific channel type differs in different locations of the brain and nervous system. Different genes encode specific channels based on their anatomical location and their subunit structure. For example, nicotinic ACh receptor channels in the frontal lobe are structurally and functionally different from the nicotinic ACh receptor channels at the neuromuscular junction. Frontal lobe ACh receptors are not blocked by curare in contrast to the neuromuscular ACh receptors. Furthermore, these two different types of channels are encoded by different genes (see Table 2). Gene mutations of a specific channel, therefore, may cause very diverse disorders in relation to the location of the channel affected. For instance a mutation in gene SCN1B produces a disruption in the central nervous Na^+ channel and causes febrile seizures, whereas a mutation of the gene SCN4A causes disruption of the function of the muscle Na^+ channel resulting in hyperkalemic periodic paralysis.

3.2. Channel interdependency

The normal excitability of neuronal and muscle membranes requires the integrated function of many ion channels. We know for instance that action potentials in neuronal membranes result from the rapid increase in Na^+ conductance via Na^+ channels, whereas activation of the K^+ channel assists in membrane repolarization. Both channels are required to maintain normal membrane function. Similarly a second messenger channel can secondarily activate a voltage-gated channel. Thus it is possible to predict that malfunctions of different channels may result in similar, if not identical, clinical epiphenomena.

3.3. Genetic heterogeneity principle

Some functions may be regulated by more than one gene, thus different genetic mutations may result in the same disease phenotype. This is exemplified by at least 56 mutations causing congenital myasthenic syndromes. Although the channel dysfunction may have different mechanisms, the final disorder remains a dysfunction of the neuromuscular junction. In some cases the genetic heterogeneity may be related to different isoforms of protein subunits of a channel. We know that different genes encode different isoforms of the α subunit of the Na^+ channel. In most instances, however, the heterogeneity is related to allelic variants. Two copies of one gene are called alleles; if the two alleles are identical we use the term 'homozygous' for that locus. Most of the alleles vary in their nucleotide sequence. In genetic disorders, mutation of one allele may be due to different changes in the nucleotide sequence all producing the same defect. For instance mutations in gene locus SCN4A may be due to a substitution of threonine residue with methionine at codon 704 (SCN4A, THR704MET) or substitution of valine for methionine at codon 1592 (SCN4A, MET1592VAL). Both of these two allelic variants cause the same disorder of the sodium channel: hyperkalemic periodic paralysis. In summary different genetic mutations may cause the same phenotype.

3.4. Phenotype heterogeneity principle

Similar genetic mutations will cause different phenotypes. For example similar mutations in the same muscle Na^+ channel results in either hyperkalemic periodic paralysis or paramyotonia congenital (Fig. 1) or other myotonic disorders (Table 2).

Griggs and Ptacek (1999) have pointed out that different portions of an ion channel have different functions thus the site of the mutation on the same gene 'will determine the nature of the physiological defect'.

Mutations in the protein produce a defective protein that causes channel dysfunction. Three physiological mechanisms have been described (Ashcroft, 1999; Lehmann-Horn and Jurkat-Rott, 1999) in malfunctioning channels:

1. Gain of function: the ion channel increases its function, e.g. in slow-channel congenital myasthenic syndrome, mutations in AChR subunits increase the response to ACh resulting in delayed channel closure and increased affinity of AChR for ACh.
2. Loss of function: the altered protein interferes with normal channel and cell function, e.g. in fast-channel congenital myasthenic syndrome, the mutations cause a decrease in synaptic response which results in brief activation

Table 2
Nervous system channelopathies[a]

Type of channelopathy specific disease	Gene map locus on chromosome	Gene mutation	Allelic variants
Voltage gated channelopathies			
Sodium channelopathies			
Familial generalized epilepsy with febrile seizures plus	2q24	SCN1A	ARG1648HIS; THR875MET
	19q13.1	SCN1B	CYS121TRP
	2q21-q33	Not yet identified	
	5q14-q15	FEB4	
Hyperkalemic periodic paralysis	17q23.1-q25.3	SCN4A	THR704MET; MET1592VAL
Paramyotonia congenita and variants	17q23.1-q25.3	SCN4A	ARG1448CYS; ARG1448HIS; ILE1160VAL; LEU1433ARG; SER804PHE; GLY1306VAL; THR1313MET
Paramyotonia congenita/hyperkalemic periodic paralysis	17q23.1-q25.3	SCN4A	ALA1156THR
Paramyotonia congenita without cold paralysis	17q23.1-q25.3	SCN4A	VAL1293ILE
Potassium-aggravated myotonia	17q23.1-q25.3	SCN4A	VAL1589MET
Myotonia fluctuans and myotonia atypical	17q23.1-q25.3	SCN4A	GLY1306ALA; VAL445MET
Hypokalemic periodic paralysis	17q23.1-q25.3	SCN4A	
Potassium channelopathies			
Benign infantile epilepsy or neonatal convulsions	20q13.3	KCNQ2	TYR284CYS; ALA306THR; 5BP INS; 1-BP DEL,1846T
	8q24	KCNQ3	
Episodic ataxia type 1	12p13	KCNA1	VAL408ALA; ARG239SER; VAL174PHE; PHE249ILE; PHE184CYS; GLU325ASP; THR226ALA;VAL404ILE; ILE176ARG
Calcium channelopathies			
Episodic ataxia type 2	19p13.1	CACNL1A4, CACNA1A	1 BP DEL 4073C; IVS24DS-G-A + 1; ARG1666HIS;(CAG)n expansion
Spino-cerebellar ataxia type 6	19p13	CACNA1A	(CAG)n expansion; GLY293ARG
Familial hemiplegic migraine	19p13.1	CACNL1A4,CACNA1A	ARG192GLN; THR666MET; VAL714ALA; ILE1811LEU
Familial hemiplegic migraine/progressive ataxia	19p13	CACNA1A	ASP715GLU
Hypokalemic periodic paralysis	1q32	CACNL1A3,CACNA1S,CCHL1A3	ARG1239HIS; ARG1239GLY; ARG528HIS; ARG1086HIS
Central core disease	19q13.1	RYR1	ARG2434HIS; ILE403MET; ARG2163HIS; ILE4898THR
Malignant hyperthermia syndrome/central core disease	19q13.1	RYR1	ARG163CYS
Malignant hyperthermia syndrome	19q13.1	RYR1	ARG614CYS; ARG248GLY;GLY341ARG; GLY2433ARG; ARG2458CYS; ARG2458HIS; ARG2163CYS
	1q32	CACNA1S	ARG1086HIS
	17q11.2-q24	SCN4A?	
	3q13.1	not yet identified	
	7q21-q22	CACNL2A	
Congenital stationary night blindness	Xp11.23	CACNA1F	GLY369ASP; ARG958TER; 991C INS; ARG830TER
	Xp21.1	CACNA1F	
	3p22-p21.3	GNAT1	GLY38ASP
	4P16.3	PDE6B	HIS258ASN
Chloride channelopathies			
Myotonia congenita autosomal dominant	7q35	CLCN1	GLY230GLU; PRO480LEU; GLN552ARG; ILE290MET; 14 BP DEL

Table 2 (*continued*)

Type of channelopathy specific disease	Gene map locus on chromosome	Gene mutation	Allelic variants
Myotonia congenita autosomal recessive	7q35	CLCN1	IVSDS, G-A + 1;ARG496SER;GLY482ARG; GLU291LYS; PHE413CYS; ARG317GLN; GLY499ARG
Ligand-gated channelopathies			
ACh receptor channelopathies			
Autosomal dominant frontal nocturnal epilepsy	20q13.2	CHRNA4	SER248PHE; 3BP INS, 776GCT
	15q24	ENFL2	
Congenital myasthenia gravis syndromes			
Familial infantile myasthenia gravis	17p13	MGI, FIMG	
Myasthenia gravis neonatal transient	2q33-q34	CHRNG,ACHRG	
Slow channel syndromes	17p12-p11	CHRNB1, ACHRB	VAL266MET; LEU263MET; 1276DEL9; EX8DEL
	2q24-q32	CHRNA1	SER269ILE; GLY153SER; THR254ILE; VAL156MET; ASN217LYS
Endplate acetylcholinesterase deficiency	3p24.2	COLQ	215-BP DEL NT107; GLU214TER; SER169TER; ARG282TER; 1-BP DEL 1082C
Glycine receptor channelopathies			
Hyperekplexia (familial startle disease)	5q32	GLRA1	ARG271LEU, ARG271GLN, ILE244ASN, TYR279CYS, GLN266HIS
Hyperekplexia (familial startle disease) and spastic paraparesis	5q32	GLRA1	LYS276GLU, PRO250THR; 1-BP INS 788C; TYR431SER; ARG315TER; IVS16DS A-G, +3

[a] A, adenine; ALA, alanine; ARG, arginine; ASN, asparagine; ASP, aspartic acid; BP, base pair; C, cytosine; CYS, cysteine; DEL, deletion; DS, D segment; EX, exon; G, guanine; GLN, glutamine; GLU, glutamic acid; GLY, glycine; HIS, histidine; ILE, isoleucine; INS, insertion; IVS, intron mutation; LEU, leucine; LYS, lysine; MET, methionine; PHE, phenylalanine; PRO, proline; SER, serine; T, thymine; TER, terminus; THR, threonine; TRP, tryptophan; TYR, tyrosine; VAL, valine.

episodes and reduces the probability of channel opening.
3. Dominant negative effects: the altered protein interferes with the activity of the normal protein, e.g. in spinocerebellar ataxia, mutations in the 1α subunit interfere with the assembly of P/Q channels (Ashcroft, 1999).

A brief description of the various genetic channelopathies will follow.

4. Sodium channelopathies

Sodium channelopathies are disorders of the Na^+ channel that includes a variety of diseases: generalized epilepsy with febrile seizures plus, hyperkalemic periodic paralysis, paramyotonia congenita, potassium aggravated myotonia, and hypokalemic periodic paralysis (Table 2). So far there are 23 described missense mutations in the Na^+ muscle channel affecting the alpha subunit (Bulman et al., 1999).

Generalized epilepsy with febrile seizures plus (GEFS+) is a syndrome of febrile seizures occurring in families and has an autosomal dominant inheritance (Singh et al., 1999). The syndrome is characterized by febrile seizures that may persist after 6 year of age or be associated with generalized seizures not precipitated by fever. GEFS+ is a classic example of genetic heterogeneity with so far at least 4 mutations in different gene loci producing the same phenotype (Nakayama et al., 2000; Pfeiffer et al., 1999; Wallace et al., 1998; Baulac et al., 1999; Singh et al., 1999). Wallace et al. (1998) have identified a family in Australia with a dominant inheritance and determined, by linkage analysis, that the affected gene map locus was in the region of 19q13.1 with a mutation in gene SCN1B affecting the Na^+ channel. They elegantly demonstrated in *Xenopus laevis* oocytes that this mutation interferes with the ability of the channel β-1 subunit to modulate gating kinetics, possibly leading to membrane hyper-excitability.

Baulac et al. (1999) describe a family with GEFS+ and found the abnormality of the gene map locus on chromosome 2q21-q33. Escayg et al. (2000) identified two mutations in two separate families affecting the SCN1A gene on locus 2q24. Another family with GEFS+ was found in Utah and mapped to chromosome 2q23-24 (Pfeiffer et al. 1999). These genes encode different isoforms of the α subunit of the sodium channel. Other families have been studied and as shown in Table 2 other gene loci have been detected. There are other families with GEFS+ that may have as yet not identified genetic abnormalities.

Hyperkalemic periodic paralysis is an inherited disorder due to mutations in the sodium channel gene SCN4A (George et al., 1991). Patients with this disorder suffer from recurrent attacks of muscle weakness. The weakness can be precipitated by administering potassium and often alleviated by administering calcium. Progressive muscle weakness has also been described. There are close links between this disorder and paramyotonia congenita. Ptacek et al. (1991), and McClatchey et al. (1992) suggest that the two diseases are allelic disorders.

Paramyotonia congenita is characterized by myotonia that increases by exposure to cold and by occasional episodes of flaccid paresis. McClatchey et al. (1992) identified two point mutations in the SCN4A gene. They suggested that the mutation leads to a substitution of valine for glycine in the sodium channel. The glycine-glycine pair present in a normal sodium channel is then substituted by the valine. The valine is more rigid than glycine thus stiffening the domain. At normal temperature the channel functions normally but a minor drop in temperature interferes with the movement of the protein loop resulting in an abnormal sodium flux. Hayward et al. (1999) have shown in an elegant set of experiments that missense mutations of muscle sodium channels in hyperkalemic periodic paralysis, paramyotonia congenita and potassium-aggravated myotonia cause 'gain-of-function defects in the channel'. In their electrophysiological studies they showed that the mutation impairs the Na^+ channel slow inactivation (Fig. 3) causing an 'aberrant depolarized shift in the resting potential that renders the muscle electrically inexcitable and results in flaccid paralysis' (Hayward et al., 1999). They further showed that different mutations in the SCN4A gene may results in different clinical disorders.

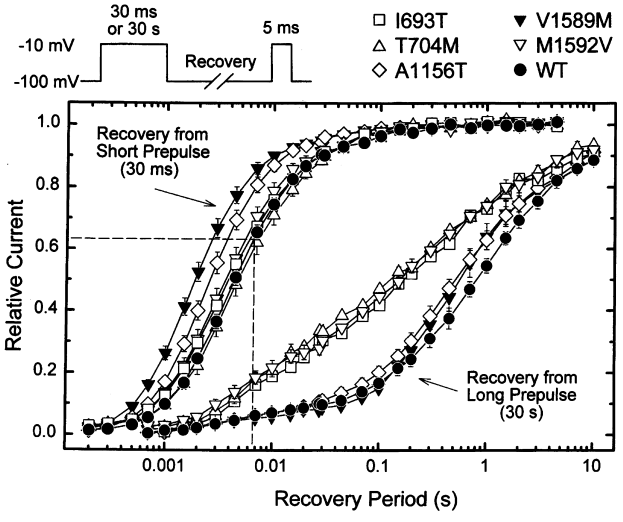

Fig. 3. Slow inactivation is impaired by mutations associated with periodic paralysis (T704M, M1592V) or cold induced weakness (I693T). The kinetics of recovery from inactivation following 30 ms or 30 s conditioning pulsing to −10 mV for wild-type (WT) and mutant channels are shown. Relative current is the amplitude of the peak Na current elicited after the recovery period, divided by the maximal peak Na current measured at the start of the conditioning pulse. The dashed line shows a time constant of ~7 ms for recovery from fast inactivation for WT channels. The V1589M and A1156T channels exhibited accelerated recovery from fast inactivation (data from 30-ms conditioning pulse, left) but normal slow inactivation (SI) (data from 30-s pulses, right). The I693T, T704M and M1592V channels had normal recovery from fast activation but accelerated recovery from SI, implying destabilization of the low-inactivated state. Open symbols depict mutations from which paralytic weakness is a prominent clinical finding. (Reprinted with permission from Hayward et al., 1999).

A persistent current of sodium into the cell produces a sequential depolarization that will be manifested by sustained muscle contraction or myotonia (Davis and Hanna, 1999). There are various allelic varieties of both hyperkalemic periodic paralysis and paramyotonia congenita (see Table 2).

Hypokalemic periodic paralysis is an autosomal dominant disease, usually affecting the function of the calcium channel. However, Bulman et al. (1999) have described a family with this disorder that had an abnormality of the α-1 Na^+ channel subunit producing an alteration of the 'outermost positive charge in the membrane spanning segments DII/S4, which is involved in voltage sensing' (Bulman et al., 1999). Hypokalemic periodic paralysis is a prototype of genetic heterogeneity and although caused most often by a Ca^{2+} channel dysfunction, it can also be caused by a Na^+ channel abnormality.

5. Potassium channelopathies

Disorders of the potassium channels have been identified in two diseases: benign familial neonatal convulsions and episodic ataxia type 1.

Benign familial neonatal convulsions (benign infantile epilepsy) are characterized by neonatal convulsions that clear spontaneously after a few weeks. Seizures onset occurs on day 3 in 42% of cases followed by complete remission during the first 6 weeks of the newborn life. The neonate will have subsequent normal development. This disorder shows autosomal dominant inheritance. As shown in Table 1, the disease is caused by mutations in two voltage-gated K channel genes KCNQ2 or KCNQ3 (Bievert et al., 1998; Charlier et al., 1998; Singh et al., 1998; Lerche et al., 1999). Bievert et al. (1998) have shown that a decreased potassium current impairing repolarization of the cell membrane causes convulsions in this disorder. They postulate that the decreased current results in hyperexcitability of the central nervous system neurons.

Why are seizures in this entity only seen in the neonatal period and why do the seizures remit after a few weeks? Lerche et al. (1999) suggest two possible explanations: (1) the brain is more likely to develop seizures in premature state than later in life; (2) differential expression of K^+ channels during maturation. They further suggest that KCNQ channels may play a dominant role during the first weeks of life or KCNQ may be up-regulated during this period or other K^+ voltage-gated channels have not reached their full expression level (Lerche et al., 1999).

Episodic ataxia type 1 is an autosomal dominant inherited disorder characterized by episodes of paroxysmal cerebellar ataxia and is often associated with myokymia. The disorder has been located to chromosome 12p13 and attributed to mutation of the potassium channel gene KCNA1 (Browne et al., 1994; Brandt and Strupp, 1994). There are many allelic variants of this disorder, as shown in Table 2.

6. Calcium channelopathies

Ca^{2+} channels have many functions: they mediate the entry of Ca^{2+} ions into excitable cells and are involved in muscle contraction, and hormone and neurotransmitter release by a variety of calcium directed processes. Ca^{2+} channels are heterogeneous both in function and structure. Each channel type has been cloned (Putney, 1999). Each channel consists of a major pore-forming α-1 subunit and other auxiliary subunits. The subunits include beta, alpha-2, delta and gamma subunits (De Waard et al., 1996). Based on the pharmacological and biophysical properties Ca^{2+} channels have been classified as L-, N-, T-, P-, Q- and R- types (Catterall, 1996). The major α-1 subunit has at least 6 isoforms (Dunlap et al., 1995). An important skeletal muscle Ca^{2+} channel is located in the muscle sarcoplasmic reticulum, the ryanodine receptor (RYR) and is coupled in the t-tubule membrane. This arrangement permits the rapid release of stored Ca^{2+} when the action potential reaches the tubule (Putney, 1999).

Calcium channelopathies are thus very variable and include at least 7 disorders varying from retinal abnormalities to migraine (see Table 2). Genetic heterogeneity has been demonstrated in various calcium disorders (for example, see the susceptibility to malignant hyperthermia syndrome) thus different families may have different mutations causing the same disorder (Fagerlund et al., 1994; Plassart et al., 1994; Moleshi et al., 1998; Ptacek, 1998). Table 2 will became more complex as new mutations are identified.

Familial hemiplegic migraine (FHM) is an autosomal dominant disorder characterized by migraine often associated with motor weakness. The weakness consists of hemiplegia occasionally associated with some impairment of consciousness. At least 4 allelic forms of FHM are known: ARG192GLN, THR666MET, VAL714ALA, ILE1811LEU (Table 2).

Episodic ataxia type 2 (EA2) is an inherited disorder characterized by episodes of paroxysmal cerebellar ataxia often associated with nystagmus and showing a beneficial response to acetazolamide. The disorder is localized to chromosome 19p13.1. The following allelic forms of EA2 have been identified: 1-BP DEL-4073C, IVS24DS-G-A + 1, ARG1666HIS, (CAG)n expansion. Spinocerebellar ataxia type 6 is an autosomal dominant disorder characterized by progressive ataxia of all extremities, dysarthria, nystagmus and impairment of vibratory and position sense. The disease progresses over 10-30-years leading to severe impairment of gait. The disorder is caused by expansion of CAG repeat in the coding region of one isoform of the alpha 1A Ca^{2+} channel subunit (Takahashi et al., 1998; Jodice et al., 1997; Ishikawa et al., 1999) or by a replacement of a glycine by an arginine (Yue et al., 1997).

Of particular interest is the linkage between these 3 different hereditary disorders. It has been shown that familial hemiplegic migraine and episodic ataxia type 2 are both caused by a mutation in the same gene CACNA1A (Ophoff

et al., 1996). It is further known that some patients with FHM also experience occasional episodes of ataxia during an attack of migraine and some patients have cerebellar ataxia (Tournier-Lasserve, 1999). Usually the CACNA1A mutations are different for FHM and EA2, however Jen et al. (1999) have shown in one family that truncating mutations of the same gene CACNA1A may in some EA2 patients cause paroxysmal episodes of ataxia and transient hemiplegia. One patient also had migraine headaches. Fontaine et al. (1997) suggest that EA2 is due to loss of function mutation whereas FHM is caused by a gain of function mutation. Hans et al. (1999) introduced 4 missense mutations (responsible for FHM) into the human α-1A-2 subunits and investigated their functional dysfunction in vivo in human embryonic renal cells. They recorded single-channel and whole-cell patch clamp potentials and noted the effects of various mutations. Mutation R192Q increased the density of functional P/Q type channels and their probability of being open. Other mutations had different effects: some increased the channel conductance others decreased the rate of recovery from inactivation. They concluded that FHM mutations might lead to either gain or loss of function of human P/Q-type calcium channels. Hans et al. (1999) demonstrated that different mutations in the α 1A calcium channel subunit produces different changes in the channel conductance. Mutation T666M in the pore loop of domain II decreased the density of functional channels and their conductance. Other mutations affected the rate of recovery from inactivation. Phenotypic variety may therefore be multifactorial including allelic variants, genetic polymorphism elsewhere in the gene or at other channel loci, resulting in a net effect on the polarity of the membrane (Ophoff et al., 1996).

The question that remains unsolved is how various mutations may lead to the same or different phenotypes. Is the phenotype purely under genetic control or are environmental factors modifying the phenotype? Hopefully future studies will clarify these issues.

Hypokalemic periodic paralysis is the most frequent cause of periodic paralysis. It is an autosomal dominant disorder with reduced penetrance in females. The classic picture is weakness associated with low potassium serum levels. The episodic attacks of weakness may be precipitated by exercise or by high carbohydrate meals. In a European pedigree Fontaine et al. (1994) localized the genetic defect on chromosome 1q31-q32 and mapped the locus at the CACNA1S. Ptacek et al. (1994) in a large American family found the deficit similarly related to mutations in the gene CACNA1S. This is the gene encoding the muscle dihydropyridine (DPH)-sensitive calcium channel α-1 subunit.

Ptacek et al. (1994) found a substitution of an arginine by a histidine at position 1239. Several allelic variants have been identified including ARG1239HIS, ARG1239GLY, and ARG528HIS (Ptacek et al., 1994; Elbaz et al., 1995; Boerman et al., 1995). Genetic heterogeneity is present in hypokalemic periodic paralysis with other families having different mutations including one pedigree with a mutation causing a deficit in the Na^+ channel (Bulman et al., 1999).

Malignant hyperthermia syndrome is an autosomal dominant inherited disorder characterized by a crisis when the subject is exposed to the administration of inhalation anesthetics or muscle relaxants. The clinical picture is characterized by muscle rigidity, tachycardia, rising end tidal CO_2, unstable or raising blood pressure, lactic acidosis and fever. The disorder is potentially lethal. As shown in Table 2, the disorders are genetically heterogeneous affecting different loci and different calcium receptor subunits (Fagerlund et al., 1992; Moleshi et al., 1998; OMIM, 2000; Monnier et al., 1997). Brandt et al. (1999) reports that 21 ryanodine receptor (RYR1) mutations have been so far identified in families with malignant hyperthermia.

Central core disease is a myopathy that manifests in infancy usually as a hypotonic or floppy infant. The disorder is autosomal dominant but with variable expression. Diagnosis is made by muscle biopsy showing characteristic central core lesions. Central core disease is due to mutations in the RYR1 calcium receptor and is occasionally associated with malignant hyperthermia (Brandt et al., 1999; Lynch et al., 1999; Phillips et al., 1996; O'Brien et al., 1995; Quane et al., 1993).

Congenital stationary night blindness is a non-progressive retinal disorder characterized by a decrease of visual acuity and loss of night vision. The disorder is due to a mutation in the retina-specific Ca^{2+} channel alpha-1 subunit gene (Bergen et al., 1996; Boycott et al., 1998). Multiple mutations have been identified in different families involving either Xp11.23, X21.1, 3p22-p21.3, or 4p16.3 gene loci (Strom et al., 1998; Ngo et al., 1993; Dryja et al., 1996; Gal et al., 1994).

6.1. Chloride channelopathies

Skeletal muscle excitability and particularly conductance is regulated in part by the muscle chloride channel CLC-1. Reduction in resting membrane conductance may cause electrical instability and myotonia.

Mytonia congenita is a syndrome of muscular hypertrophy and myotonia and can be recessive or autosomal dominant. The disorder is due to mutation in the skeletal muscle chloride channel CLCN1 located on chromosome 7 (Fahlke et al., 1997; Kubish et al., 1998; Papponen et al., 1999). Several mutations have been described (see Table 2).

So far no other neurological diseases are known to be associated with chloride channel abnormalities.

6.2. ACh receptor channelopathies

Nicotinic ACh receptors have distinct ligand properties in the central nervous system neurons and in neuromuscular junctions (Taylor and Brown, 1999). The central neuronal nicotinic receptor mediates fast signal transmission at synapses and is not blocked by bungaratoxin or other snake venoms. Two major syndromes are caused by ACh

receptor abnormalities: nocturnal frontal lobe epilepsy and congenital myasthenic syndromes.

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is inherited epilepsy characterized by seizures that occur exclusively in drowsiness or sleep. Video-EEG monitoring has shown that these seizures occur in clusters and they originate in the frontal region. The onset of the seizures is usually in the first or second decade. They persist throughout adult life. Motor activity, moaning, shouting or other psychomotor activity characterizes the seizures. Oldani et al. (1998), however, reported a series of 40 patients and stated that they presented 'a wide clinical spectrum, ranging from nocturnal enuresis to sleep-related violent behavior, thus including all main features of the so-called 'typical' parasomnias'. A proper differential diagnosis between the various entities will necessitate prolonged EEG/video monitoring and polysomnography. The disorders (Table 2) are genetically heterogeneous affecting the α subunit nicotinic ACh receptor channel. Two groups of investigators (Bertrand et al., 1998; Figl et al., 1998) have shown in *Xenopus* oocytes that mutations in the ACh receptor channel influence ACh responses. Figl et al. (1998) reported the following effects: potentiation of the responses during a train of brief 100 nM ACh pulses, a delayed rise time of the ACh response, and a reduced extracellular Ca^{2+}-induced increase in the ACh response. These changes may trigger ADNFLE by suddenly increasing ACh release. Bertrand et al. (1998) noted that some mutations affect the desensitization properties of the receptor resulting in increased probability of achieving an active state. This change in receptor property may reduce the permeability to calcium thus resulting in increased sensitivity that might produce ADNFLE. Kuryatov et al. (1997) have shown that some of the mutations produced faster desensitization, slower recovery from desensitization, less inward rectification and poor Ca^{2+} permeability (Fig. 4). The result is a reduction of ACh receptor function. They postulated that the ACh receptors are part of an inhibitory circuit regulating the release of presynaptic GABA. The reduction in ACh receptor function will result in hyperexcitability causing epilepsy.

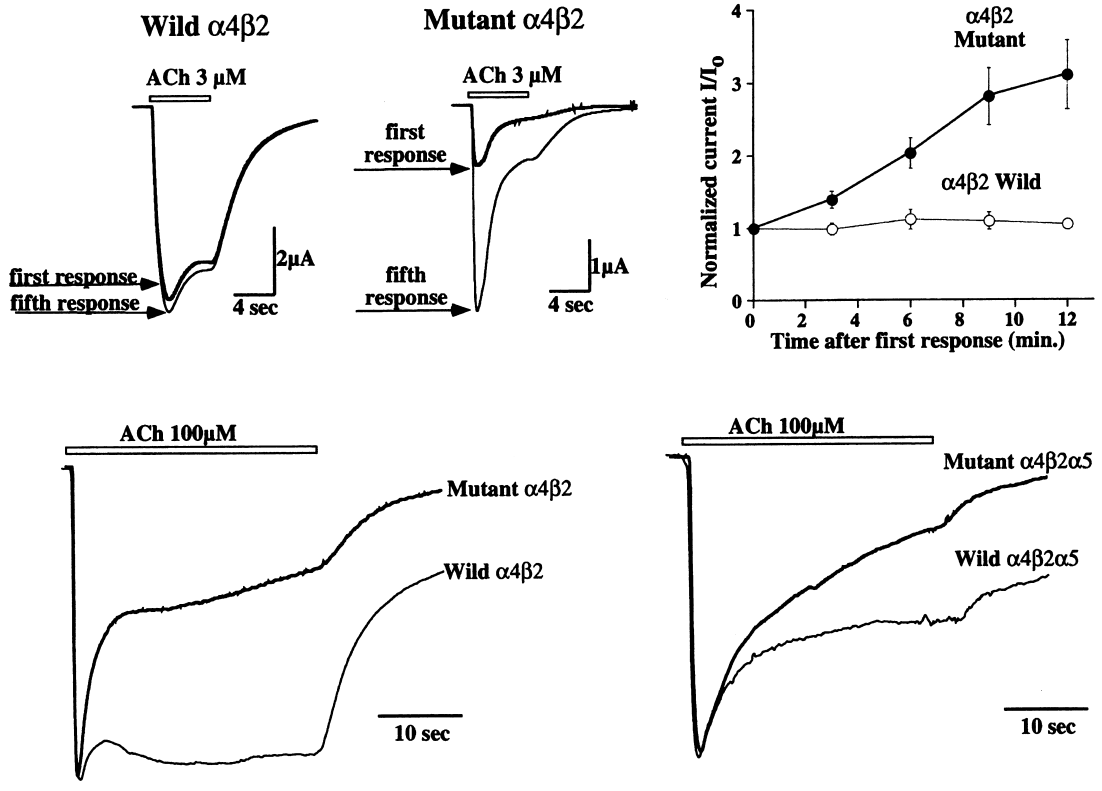

Fig. 4. Functional differences between wild-type and mutant α4β2 AchRs. (Top) Use-dependent functional up-regulation of the responses mediated by mutant α4β2 AchRs. (Left) Currents induced by the first and fifth application of 3 nM ACh are shown for oocytes expressing wild-type and mutant α4β2 AchRs. Oocytes that did not have previous exposure to the agonists were held at −50 mV. ACh was applied at 2-min interval. (Right) Plot of the agonist response peak amplitude on the initial 5 consecutive applications of 3 μV ACh on the oocytes expressing wild-type (open circles) or mutant α4β2 AchRs (filled circles). Currents were normalized to the peak amplitude of the first response. (Bottom) S247F mutation causes significant changes in the desensitization of the α4β2 and α4β2α5 AChRs. (Left) Comparison of the time course of the superimposed normalized averaged currents mediated by the wild-type (thin traces) and mutant α4β2 AchRs (thick traces). (Right) Comparison of time course for the wild-type and mutant α4β2α5 AchRs. Averaged currents were obtained from 15 to 22 oocytes by normalizing to the same current amplitude. Oocytes were held at −50mV. Both perfusion and agonist solutions contained no Cl^- ions to prevent contamination with endogenous Ca^{2+}-dependent Cl^- current. Oocytes were preincubated in Cl^--free media for 4–16 h. (Reprinted with permission from Kuryatov et al., 1997).

Congenital myasthenic syndromes (CMS) are heterogeneous disorders with a similar clinical picture of respiratory and feeding difficulties at birth or ocular, bulbar symptoms exacerbated by crying during the first 2 years of life (Nichols et al., 1999). In contrast to neonatal myasthenia gravis that is caused by passive transfer of anti ACh receptor antibodies to the fetus by a myasthenic mother, the mother of CMS has no myasthenia. CMS have some characteristic laboratory findings: (1) repetitive motor nerve stimulation shows a decrement in amplitude of the compound action potential; (2) single fiber EMG shows increased jitter and blocking; (3) stimulation to a single supramaximal stimulus induces repetitive motor evoked responses; (4) anti-AChR antibodies are negative. These findings suggest the diagnosis of CMS, but do not differentiate between the various syndromes. The inheritance of CMS is either autosomal recessive or autosomal dominant. CMS are heterogeneous disorders caused by presynaptic, synaptic and postsynaptic defects. Engel et al. (1999) proposes the following classification of CMS: (1) presynaptic defects affecting the quantity, the size or the speed of release of ACh quanta or their packaging (Engel et al., 1990; Walls et al., 1993); (2) synaptic defects due to endplate acetylcholinesterase deficiency (Engel et al., 1977, 1999; Donger et al., 1998; Ohno et al., 1998); (3) postsynaptic defects due to either kinetic abnormalities of the ACh receptor or to AChR deficiency. Changes in the kinetic properties of the channel have been described as CMS slow-channel syndrome, fast-channel syndrome and mode-switching kinetic syndromes (Engel et al., 1990, 1999; Croxen et al., 1997; Milone et al., 1998).

Presynaptic CMS. Engel's group has described (Engel and Lambert, 1987; Mora et al., 1987) few infants with CMS that had normal endplate morphology but a decreased size of synaptic vesicles. Upon repeated nerve stimulation these patients showed an increase in the size of the vesicles. Mora et al. (1987) suggested that the increased size with nerve stimulation indicated a defect in the vesicle metabolism. The same group (Engel et al., 1990; Walls et al., 1993) described patients with CMS caused by a paucity of synaptic vesicles and related reduced quanta release. These authors showed, by microelectrode recording, a decrease in the number of ACh quanta released by nerve stimulation. Electron microscopy and labeled bungarotoxin binding showed that the endplate was anatomically normal.

Synaptic CMS are related to end plate acetylcholinesterase (AChE) deficiency (Table 2). Muscle histochemistry in these patients shows an absence or decrease of acetylcholinesterase at the end plate. This subset of myasthenia is due to a genetic defect in the collagenic tail of endplate acetylcholinesterase (COLQ). This collagenic tail attaches acetylcholineterase to the basal lamina of the endplate (Engel et al., 1998, 1999). The decreased AChE results in persistent stimulation of the endplate causing a desensitization of the AChR. Only 17 cases of this disorder have been described in the literature (Ohno et al., 1998; Donger et al., 1998; Engel et al., 1999).

Postsynaptic CMS are either related to abnormalities of AChR kinetics or to AChR deficiency (Engel et al., 1999). The most frequent type of postsynaptic CMS is the slow-channel syndrome. The slow-channel syndrome may manifest later in life. The slow-channel syndrome is usually characterized by limb weakness with little involvement of the bulbar muscles (eye and oropharynx). The genetic defect in slow-channel syndrome is caused by mutations of the alpha, beta or epsilon subunits of the ACh receptor. The complexity of genetic mutations is exemplified by a total of 56 mutations in the alpha-1, beta and epsilon AChR subunits reported to cause similar but genetically distinctive myasthenic syndromes (Croxen et al., 1997; Lindstrom, 1998; Nichols et al., 1999; Engel et al., 1999). It is now possible to analyze the effect of these mutations (using patch-clamping endplates of human intercostal muscles) on the activity of single ACh receptor channels. Abnormalities in AChR subunits in the slow-channel syndrome prolong the activation of the receptor by either delaying channel closure or increasing the affinity of the receptor for ACh (Engel et al., 1990; Milone et al., 1997; Croxen et al., 1997; Middleton et al., 1999). Milone et al. (1997) suggest that in the slow-channel myasthenic syndrome the neuromuscular transmission is compromised because there is: (1) cation overloading leading to degenerating junctional folds and loss of AChR; (2) an increased fraction of AChR is desensitized in the resting state; (3) physiological rates of stimulation elicit additional desensitization and depolarization block of transmission. In the fast channel syndrome, the post-synaptic response to ACh is markedly reduced. ACh induces short duration activation episodes (Engel et al., 1990). The neuromuscular junction shows a reduced ACh binding affinity and a decreased desensitization by ACh (Fig. 5). Anatomically the endplate and muscle are

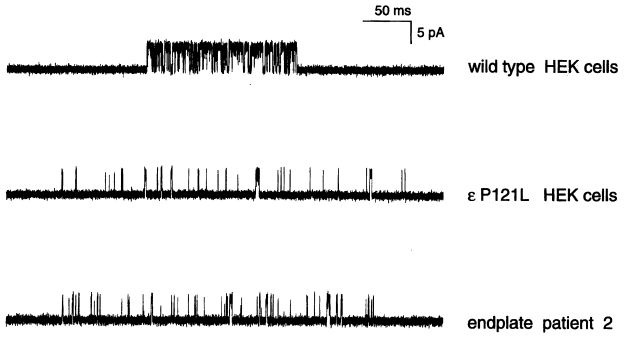

Fig. 5. CMS due to fast-channel mutations. Comparison of single channel current from endplate potential and engineered ϵP121L AChRs. Clusters of single-channel currents elicited by high concentrations of ACh are shown, with opening upward deflections. Wild-type corresponds to the engineered adult human AChR ($\alpha 2\beta\epsilon\delta$) in the presence of 50 μV ACh, ϵP121L to the engineered mutant AChR ($\alpha 2\beta\epsilon\delta$ P121L) in the presence of 200 μV ACh, and endplate potential to the AChR at an endplate potential from patient 2 in the presence of 50 μV ACh. Note that ACh release causes abnormally brief activation and channel opening in the mutants compared to the normal control (wild-type). (Reprinted with permission from Ohno et al., 1996).

normal (Engel et al., 1990). The other postsynaptic CMS are due to AChR deficiency. In these patients the post-synaptic response to ACh is reduced as demonstrated by a decreased amplitude of miniature endplate potentials (MEPP) and miniature endplate currents resulting in high or higher than normal quantal release of ACh. Structurally there is an increased number of endplates but the endplate region is smaller and simplified. AChR affinity is attenuated and AChR distribution is patchy (Ohno et al., 1995, 1997; Quiram et al., 1999). Sieb et al. (1998) described a family with CMS due to deficiency of endplate AChR and utrophin. They demonstrated a decreased in MEPP amplitude, but normal quantal content of endplate potentials. Structurally there was a reduced AChR density. They conclude that in this family CMS was related to a defect in development and/or maintenance of the post-synaptic cleft. They further suggested that utrophin plays a role in anchoring the AChRs at synaptic sites through adhesion to the underlying cytoskeleton (Sieb et al., 1998). Among the various AChR deficiencies is the demonstration by Engel and his collaborators (Engel et al., 1998, 1999; Ohno et al., 1996) that some cases of congenital myasthenic syndromes are due to mutations causing the presence of fetal AChR containing the γ subunit instead of the adult ϵ subunit. The fetal AChR is a low conductance channel in contrast to the high conductance channel of the adult AChR. Thus ACh release causes brief activation and reduced probability of channel opening.

From these elegant studies it appears that multiple molecular mechanisms may influence the duration of the opening of the ACh-receptor channel resulting in a destabilization of the neuromuscular junction. Once again we are witnessing genetic heterogeneity (Engel et al., 1998, 1999; Nichols et al., 1999; Quiram et al., 1999).

All of these syndromes are phenotypically similar and elucidation of their pathophysiology requires correlation of in vitro electrophysiological and molecular genetic studies (Engel et al., 1999). For a more detailed review of the congenital myasthenic syndromes see Engel et al. (1998, 1999).

6.3. Glycine receptor channelopathies

The glycine receptor mediates inhibition in the spinal cord and central nervous system. So far only one genetic disorder is known to be related to mutations of the glycine receptor α-1 subunit gene on locus 5q32, the familial startle disease or hyperekplexia.

Hyperekplexia or familial startle disease is a disorder characterized by an exaggerated startle reflex that may cause sudden myoclonus or falling in response to sudden stimuli. In some families startle disease is associated with spastic paraparesis (Saul et al., 1999; Elmslie et al., 1996). The abnormality of the glycine receptor results in a reduction of inhibition in the spinal cord.

7. Conclusion

This brief review shows the importance of genetic influence on the smooth functioning of various channels. As research continues and the genome project maps all human genes, there will be more additions to the present tables of channelopathies and a continuous addition of allelic variants.

Acknowledgements

Special thanks to Dr George J. Siegel for his insightful comments and advice in the preparation of this review article.

References

Aidley DJ, Stanfield PR, editors. Ion channels: molecules in action Cambridge: Cambridge University Press, 1996.

Ashcroft FM, editor. Ion channels and disease: channelopathies, San Diego, CA: Academic Press, 1999.

Babinski K, Le KT, Seguela P. Molecular cloning and regional distribution of a human proton receptor subunit with biphasic functional properties. J Neurochem 1999;72:51–57.

Barchi RL. Disorders of muscle excitability. In: Siegel GJ, Agranoff BW, Albers RW, Fischer SK, Uhler MD, editors. Basic neurochemistry, Philadelphia, PA: Lippincott–Raven, 1999. pp. 865–886.

Baulac S, Gourfinkel-An I, Picard F, Rosenberg-Bourgin M, Prud'homme J-F, Baulac M, Brice A, LeGuern E. A second locus for familial generalized epilepsy with febrile seizures plus maps to chromosome 2q21-q33. Am J Hum Genet 1999;65:1078–1085.

Bergen AAB, ten Brink JB, Riemslag F, Schuurman EJM, Meire F, Tjimes N, de Jong PTVM. Conclusive evidence for a distinct stationary night blindness locus in Xp21.1. J Med Genet 1996;33:869–872.

Bertrand S, Weiland S, Berkovic SF, Steilein OK, Bertrand D. Properties of neuronal nicotinic acetylcholine receptor mutants from human suffering from autosomal dominant nocturnal frontal lobe epilepsy. Br J Pharmacol 1998;125:751–760.

Bevans CG, Kordel M, Rhee SK, Harris AL. Isoform composition of connexin channels determines selectivity among second messengers and uncharged molecules. J Biol Chem 1998;273:2808–2816.

Bievert C, Schroeder BC, Kubisch C, Berkovic SF, Propping P, Jentsch TJ, Steinlein OK. A potassium channel mutation in neonatal human epilepsy. Science 1998;279:403–406.

Boerman RH, Ophoff RA, Links TP, van Eijk R, Sandkuijl LA, Elbaz A, Vale-Santos JE, Wintzen AR, van Deutekom JC, Isles DE, Fontaine B, Padberg GW, Frants RR. Mutation in DHP receptor alpha-1 subunit (CACLN1A3) (sic) gene in a Dutch family with hypokalemic periodic paralysis. J Med Genet 1995;32:44–47.

Boycott KM, Pearce WG, Musarella MA, Weleber RG, Maybaum TA, Birch DG, Miyake Y, Young RSL, Bech-Hansen NT. Evidence for genetic heterogeneity in X-linked congenital stationary night blindness. Am J Hum Genet 1998;62:865–875.

Brandt T, Strupp M. Episodic ataxia type 1 and 2 (familial periodic ataxia/vertigo). Audiol Neurootol 1994;2:373–383.

Brandt A, Schleithoff L, Jurkat-Rott K, Klinger W, Baur C, Lehmann-Horn F. Screening of ryanodine receptor gene in 105 malignant hyperthermia families: novel mutations and concordance with the in vitro contracture test. Hum Mol Genet 1999;8:2055–2062.

Browne DL, Gancher ST, Nutt JG, Brunt ERP, Smith EA, Kramer P, Litt M. Episodic ataxia/myokymia syndrome is associated with point muta-

tion in the human potassium channel gene, KCNA1. Nat Genet 1994;8:136–140.

Bulman DE, Scoggan KA, van Oene MD, Nicolle MW, Hahn AF, Tollar LL, Ebers GC. A novel sodium channel mutation in a family with hypokalemic periodic paralysis. Neurology 1999;53:1932–1936.

Catterall WA. Molecular properties of sodium and calcium channels. J Bioenerg Biomembr 1996;28:219–230.

Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, et al. Impaired nociception and pain in mice lacking the capsain receptor. Science 2000;288:306–313.

Charlier C, Singh NA, Ryan SG, Lewis TB, Reus BE, Leach RJ, Leppert M. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. Nat Genet 1998;18:53–55.

Chen CC, England S, Akopian AN, Wood JN. A sensory neuron-specific, proton-gated ion channel. Proc Natl Acad Sci USA 1998;95:10240–10245.

Croxen R, Newland C, Beeson D, Oosterhuis H, Chauplannaz G, Vincent A, Newsom-Davis J. Mutations in different functional domains of the human muscle acetylcholine receptor alpha subunit in patients with the slow-channel congenital myasthenic syndrome. Hum Mol Genet 1997;6:767–774.

Davis NP, Hanna MG. Neurological channelopathies: diagnosis and therapy in the new millennium. Ann Med 1999;31:406–420.

De Waard M, Gurnett CA, Campbell KP. Structural and functional diversity of voltage-activated calcium channels. Ions Channels 1996;4:41–87.

Donger C, Krejci E, Serradell AP, Eymard B, Bon S, et al. Mutation in the human acetylcholinesterase-associated collagen gene, COLQ, is responsible for congenital myasthenic syndrome with end-plate acetylcholinesterase deficiency (Type Ic). Am J Hum Genet 1998;63:967–975.

Doyle DA, Cabral JM, Pfuetzner RA, Kuo A, et al. The structure of the potassium channel: molecular basis of K^+ conduction and selectivity. Science 1998;280:69–77.

Dunlap K, Luebke JL, Turner TJ. Exocytotic Ca^{2+} channels in mammalian central neurons. Trends Neurosci 1995;18:89–98.

Dryja TP, Hahn LB, Reboul T, Arnaud B. Missense mutation in the gene encoding the alpha subunit of rod transducin in the Nougaret form of congenital stationary night blindness. Nat Genet 1996;13:358–365.

Dzeja C, Hagen V, Kaupp UB, Frings S. Ca^{2+} permeation in cyclic nucleotide-gated channels. EMBO J 1999;18:131–144.

Elbaz A, Vale-Santos J, Jurkat-Rott K, Lapie P, Ophoff RA, Bady B, Links TP, Piussan C, Vila A, Monnier N, Padberg GW, Abe K, et al. Hypokalemic periodic paralysis and the dihydropyridine receptor (CACNL1A3): genotype/phenotype correlation for two predominant mutations and evidence for the absence of a founder effect in 16 caucasian families. Am J Hum Genet 1995;56:374–380.

Elmslie FV, Hutchings SM, Spencer V, Curtis A, Covanis T, Gardiner RM, Rees M. Analysis of GLRA1 in hereditary and sporadic hypereklepxia: a novel mutation in a family cosegregating for hyperekplexia and spastic paraparesis. J Med Genet 1996;33:435–436.

Engel AG, Lambert EH. Congenital myasthenic syndromes. Electroenceph clin Neurophysiol Suppl 1987;39:91–102.

Engel AG, Lambert EH, Gomez MR. A new myasthenic syndrome with endplate acetylcholinesterase deficiency, small nerve terminal, and reduced acetylcholine release. Ann Neurol 1977;1:315–330.

Engel AG, Walls TJ, Nagel A, Uchitel O. Newly recognized congenital myasthenic syndromes. I. Congenital paucity of synaptic vesicles and reduced quantal release. II. High conductance fast-channel syndrome. III. Abnormal acetylcholine receptor (AChR) interaction with acetylcholine. IV. AChR deficiency and short channel-open time. Prog Brain Res 1990;84:125–137.

Engel AG, Ohno K, Wang HL, Milone M, Sine SM. Molecular basis of congenital myasthenic syndromes: mutations in the acetylcholine receptor. Neuroscientist 1998;4:185–194.

Engel AG, Ohno K, Sine SM. Congenital mysthenic syndromes: recent advances. Arch Neurol 1999;56:163–167.

Escayg A, MacDonald BT, Meisler MH, Baulac S, Huberfeld G, An-Gourfinkel I, Brice A, LeGuern E, Moulard B, Chaigne D, Buresi C, Malafosse A. Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS + 2. Nat Genet 2000;24:343–345.

Fagerlund T, Islander G, Ranklev E, Harbitz I, Mokleby E, Berg K. Genetic recombination between malignant hyperthermia and calcium release channel in skeletal muscle. Clin Genet 1992;41:270–272.

Fahlke C, Beck CL, George Jr AL. A mutation in autosomal dominant myotonia congenita affects pore properties of the muscle chloride channel. Proc Natl Acad Sci USA 1997;94:2729–2734.

Figl A, Viseshakul N, Shafaee N, Forsayeth J, Cohen BN. Two mutations linked to nocturnal frontal lobe epilepsy cause use-dependent potentiation of the nicotinic ACh response. J Physiol 1998;513(3):655–670.

Firestein SJ, Margolskee RF, Kinnamon S. Molecular biology of olfaction and taste. In: Siegel GJ, Agranoff BW, Albers RW, Fischer SK, Uhler MD, editors. Basic neurochemistry, Philadelphia, PA: Lippincott–Raven, 1999. pp. 985–1006.

Fontaine B, Vale-Santos J, Jurkat-Rott K, Reboul J, Plassart E, Rime C-S, Elbaz A, Heine R, Guimaraes J, Weissenbach J, Baumann N, Fradeau M, Lehmann-Horn F. Mapping of the hypokalemic periodic paralysis (HypoPP) locus to chromosome 1q31-32 in three European families. Nat Genet 1994;6:264–272.

Fontaine B, Plassart-Sciess E, Nicole S. Diseases caused by voltage-gated ion channels. Mol Aspects Med 1997;18:415–463.

Gal A, Xu S, Piczenik Y, Eiberg H, Duvigneau C, Schwinger E, Rosenberg T. Gene for autosomal dominant congenital stationary night blindness maps to the same region as the gene for the beta-subunit of the rod photoreceptor cGMP phosphodiesterase (PDEB) in chromosome 4p16.3. Hum Mol Genet 1994;3:323–3265.

George Jr AL, Ledbetter DH, Kallen RG, Barchi RL. Assignment of a human skeletal muscle sodium channel alpha-subunit gene (SCN4A) to 17q23.1.1-25.3. Genomics 1991;9:555–556.

Gibbs III JW, Morton LD, Amaker B, Ward JD, Holloway KL, Coulter DA. Physiological analysis of Rasmussen's encephalitis: patch clamp recordings of altered inhibitory neurotransmitter function in resected frontal cortical tissue. Epilepsy Res 1998;31:13–27.

Griggs RC, Ptacek LJ. Mutations of sodium channels in periodic paralysis: can they explain the disease and predict treatment? Neurology 1999;52:1309–1310.

Hans M, Luvisetto S, Williams ME, Spagnolo M, Urrutia A, Tottene A, Brust PF, Johnson EC, Harpold MM, Stauderman KA, Pietrobon D. Functional consequences of mutations in the human alpha 1A calcium channel subunit linked to familial hemiplegic migraine. J Neurosci 1999;19:1610–1619.

Hart IK, Waters C, Vincent A, et al. Autoantibodies detected to expressed K^+ are implicated in neuromyotonia. Ann Neurol 1997;41:238–246.

Hayward LJ, Sandoval GM, Cannon SC. Defective slow inactivation of sodium channels contributes to familial periodic paralysis. Neurology 1999;52:1447–1453.

Hille B, Catterall WA. Electrical excitability and ion channels. In: Siegel GJ, Agranoff BW, Albers RW, Fischer SK, Uhler MD, editors. Basic neurochemistry, Philadelphia, PA: Lippincott–Raven, 1999. pp. 119–137.

Ishikawa K, Fujigasaki H, Saegusa H, Ohwada K, Fujita T, Iwamoto H, Komatsuzaki Y, Toru S, Toriyama H, Watanabe M, Ohkoshi N, Soji S, Kanazawa I, Tanabe T, Mizusawa H. Abundant expression and cytosplasmic aggregation of alpha-1A voltage-dependent calcium channel protein associated with neurodegeneration in spinocerebellar ataxia type 6. Hum Mol Genet 1999;8:1185–1193.

Jen J, Yue Q, Nelson SF, et al. A novel nonsense mutation in CACNA1A causes episodic ataxia and hemiplegia. Neurology 1999;53:34–37.

Jodice C, Mantuano E, Veneziano L, Trettel F, Sabbadini G, Calandriello L, Francia A, Spadaro M, Pierelli F, Salvi F, Ophoff RA, Frants RR, Frontali M. Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the CACNA1A gene on chromosome 19p. Mol Genet 1997;6:1973–1978.

Kandell ER, Siegelbaum SA. Signaling at the nerve-muscle synapse:

directly gated transmission. In: Kandel ER, Scharrtz JH, Jessel TM, editors. Principles of neural science, New York: McGraw–Hill, 2000. pp. 1187–1206.

Koester J. Membrane potential. In: Kandel ER, Scharrtz JH, Jessel TM, editors. Principles of neural science, New York: McGraw–Hill, 2000a. pp. 125–139.

Koester J. Propagated signaling: the action potential. In: Kandel ER, Scharrtz JH, Jessel TM, editors. Principles of neural science, New York: McGraw–Hill, 2000b. pp. 150–169.

Komatsu H, Jin YH, L'Etoile N, Mori I, Bargmann CI, Akaike N, Ohshima Y. Functional reconstruction of a eteromeric cyclic nucleotide-gated channel of Caenorhabditis elegans in cultured cells. Brain Res 1999;821:160–168.

Kubish C, Schmidt-Rose T, Fontaine B, Bretag AH, Jentsch TJ. CIC-1 chloride channel mutations in myotonia congenita: variable penetrance of mutations shifting the voltage dependence. Hum Mol Genet 1998;7:1753–1760.

Kuryatov A, Gerzanich V, Nelson M, Olale F, Lindstrom J. Mutation causing autosomal dominant nocturnal frontal lobe epilepsy alters Ca^{2+} permeability, conductance, and gaiting of human a4b2 nicotinic acetylcholine receptors. J Neurosci 1997;23:9035–9090.

Lehmann-Horn F, Jurkat-Rott K. Voltage-gated ion channels and hereditary disease. Physiol Rev 1999;79:1317–1371.

Lerche H, Bievert C, Alekov AK, Schleithoff L, Lindner M, Klinger F, Bretscheiner F, Mitrovic N, Jurkat-Rott K, Bode H, Lehmann-Horn F, Steilein OK. A reduced K^+ current due to a novel mutation in KCNQ2 causes neonatal convulsions. Ann Neurol 1999;46:305–312.

Lindstrom J. Mutations causing muscle weakness. Proc Natl Acad Sci USA 1998;95:9070–9071.

Lynch PJ, Tong J, Lehane M, Mallet A, Giblin L, Heffron JJ, Vaughan P, Zafra G, MacLennan DH, McCarthy TV. A mutation in the transmembrane/luminal domain of the ryanodine receptor is associated with abnormal Ca(2+) release channel function and sever central core disease. Proc Natl Acad Sci USA 1999;96:4164–4169.

McClatchey AI, Van den Bergh P, Pericac-Vance MA, Raskind W, Verellen C, McKenna-Yasek D, Rao K, Haines JL, Bird T, Brown Jr RH, Gusella JF. Temperature-sensitive mutations in the III-IV cytoplasmic loop region of the skeletal muscle sodium channel gene in paramyotonia congenita. Cell 1992;68:769–774.

Meyer TM, Munsch T, Pape HC. Activity-related changes in intracellular pH in rat thalamic relay neurons. Neuroreport 2000;11:33–37.

Middleton L, Ohno K, Christodoulou K, Brengman J, et al. Chromosome 17p-linked myasthenia stem from defects in the acetylcholine receptor epsilon subunit gene. Neurology 1999;53:1076–1082.

Milone M, Wang HL, Ohno K, Prince R, Fukodome T, et al. Mode switching kinetics produced by a naturally occurring mutation in the cytoplasmic loop of the human acetylcholine receptor epsilon subunit. Neuron 1998;20:575–588.

Mody I. Ion channels in epilepsy. Int Rev Neurobiol 1998;42:199–226.

Moleshi R, Langlois S, Yam I, Friedman JM. Linkage of malignant hyperthermia and hyperkalemic periodic paralysis to the adult skeletal muscle sodium channel (SCN4A) gene in a large pedigree. Am J Med Genet 1998;76:21–27.

Monnier N, Procaccio V, Stieglitz P, Lunardi J. Malignant-hyperthermia susceptibility is associated with a mutation of the alpha-1-subunit of the human dihydropyridine-sensitive L-type voltage dependent calcium channel receptor in skeletal muscle. Am J Hum Genet 1997;60:1316–1325.

Mora M, Lambert EH, Engel AG. Synaptic vesicle abnormality in familial infantile myasthenia. Neurology 1987;37:206–214.

Nakayama J, Hamano K, Iwasaki N, Nakahara S, Horigome Y, Saitoh H, Aoki T, Maki T, Kikuchi M, Migita T, Ohto T, Yokouchi Y, Tanaka R, Hasegawa M, Matsui A, Hamaguchi H, Arinami T. Significant evidence for linkage of febrile seizures to chromosome 5q14-q15. Hum Mol Genet 2000;9:87–91.

Neher E, Sakmann B. Single-channel currents recorded from membranes of denervated frog muscle fibres. Nature 1976;260:799–802.

Ngo JT, Bateman JB, Klisak I, Mohandas T, Van Dop C, Sparkes RS. Regional mapping of a human rod alpha-transducin (GNAT1) gene to chromosome 3p22. Genomics 1993;18:724–725.

Nichols P, Croxen R, Vincent A, Rutter R, Hutchinson M, Newson-Davis J, Beeson D. Mutation of the acetylcholine receptor epsilon subunit promoter in congenital myasthenic syndrome. Ann Neurol 1999;45:439–443.

O'Brien RO, Taske NL, Hansbo PM, Matthaei KI, Hogan SP, Denborough MA, Foster PS. Exclusion of defects in the skeletal muscle specific region of the DHPR alpha-1 subunit as frequent cause of malignant hyperthermia. J Med Genet 1995;32:913–914.

Ohno K, Hutchinson DO, Milome M, et al. Congenital myasthenic syndrome caused by prolonged acetylcholine receptor opening due to a mutation in the M2 domain of the epsilon subunit. Proc Natl Acad Sci USA 1995;92:758–762.

Ohno K, Wang HL, Milone M, Bren N, Brengman JM, et al. Congenital myasthenic syndrome caused by decreased agonist binding affinity due to mutation in acetylcholine receptor epsilon subunit. Neuron 1996;17:157–170.

Ohno K, Quiram P, Milone M, et al. Congenital myasthenic syndromes due to heteroallelic nonsense/missense mutations in the acetylcholine receptor α subunit gene: identification and functional characterization of six new mutations. Hum Mol Genet 1997;6:753–766.

Ohno K, Brengman JM, Tsujino A, Engel AG. Human endplate acetylcholinesterase deficiency caused by mutations in the collagen-like tail subunit (ColQ) of the asymmetric enzyme. Proc Natl Acad Sci USA 1998;95:9654–9659.

Oldani A, Zucconi M, Asselta R, Modugno M, et al. Autosomal dominant nocturnal frontal lobe epilepsy: a video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome. Brain 1998;121:205–223.

OMIM™, Online Mendelian Inheritance in Man. National Center for Biotechnology Information, 2000. Database electronic resource available at: http://www.ncbi.nlm.gov/Omim/

Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type 2 are caused by mutations in the CA(2+) channel gene CACNL1A4. Cell 1996;87:543–552.

Owens JL, Kullberg R. In vivo development of nicotinic acetylcholine receptor channels in Xenopus myotomal muscle. J Neurosci 1989;9:1018–1028.

Palmer CA, Geyer JD, Keating JM, Gilliam F, Kuzniecky RI, Morawetz RB, Bebin EM. Rasmussen's encephalitis with concomitant cortical dysplasia: the role of GluR3. Epilepsia 1999;40:241–247.

Papponen H, Toppinen T, Baumann P, Myllyla V, Leisti J, Kuivaniemi H, Tromp G, Myllyla R. Founder mutations and the high prevalence of myotonia congenita in northern Finland. Neurology 1999;53:297–302.

Pfeiffer A, Thompson J, Charlier C, Otterud B, Varvil T, Pappas C, Barniz C, Gruenthal K, Khhn R, Leppert M. A locus for febrile seizures (FEB3) maps to chromosome 2q23-24. Ann Neurol 1999;46:671–678.

Phillips MS, Fujii J, Khanna VK, DeLeon S, Yokobata K, De Jong PJ, MacLennan DH. The structural organization of the human skeletal ryanodine receptor (RYR1) gene. Genomics 1996;34:24–41.

Plassart E, Elbaz A, Santos JV, Reboul J, Lapie P, Chauveau D, Jurkat-Rott K, Guimaraes J, Saudubray JM, Weissenbach J, Lehmann-Horn F, Fontaine B. Genetic heterogeneity in hypokalemic periodic paralysis (hypoPP). Hum Genet 1994;94:551–556.

Ptacek LJ. The place of migraine as a channelopathy. Curr Opin Neurol 1998;11:217–226.

Ptacek LJ. Ion channel diseases: episodic disorders of the nervous system. Semin Neurol 1999;19:363–369.

Ptacek LJ, George Jr AL, Barchi RL, Grigg RC, Riggs JE, Robertson M, Leppert MF. Identification of a mutation in the gene causing hyperkalemic periodic paralysis. Cells 1991;67:1021–1027.

Ptacek LJ, Tawil R, Griggs RC, Engel AG, Layer RB, Kwiecinski H, McManis PG, Santiago L, Moore M, Fouad G, Bradley P, Leppert MF. Dihydropyridine receptor mutations cause hypokalemic periodic paralysis. Cell 1994;77:863–868.

Putney JW. Calcium. In: Siegel GJ, Agranoff BW, Albers RW, Fischer SK, Uhler MD, editors. Basic neurochemistry, Philadelphia, PA: Lippincott–Raven, 1999. pp. 453–469.

Quane KA, Healy JMS, Keating KE, Manning BM, Couch FJ, Palmucci LM, Doriguzzi C, Fagerlund TH, Berg K, Ording H, Bendixen D, Mortier W, Linz U, Muller CR, Mc Carty TV. Mutations in the ryanodine receptor gene in central core disease and malignant hyperthermia. Nat Genet 1993;5:51–55.

Quiram PA, Ohno K, Milone M, Patterson MC, Pruitt NJ, Brengman JM, Sine SM, Engel AG. Mutation causing congenital myasthenia reveals acetylcholine receptor beta/delta subunit interaction essential for assembly. J Clin Invest 1999;104:1403–1410.

Saul B, Kuner T, Sobetzko D, Brune W, Hanefeld P, Meinck HM, Becker CM. Novel GLRA1 missense mutation (P250T) in dominant hepereklepxia defines an intracellular determinant of glycine receptor channel gating. J Neurosci 1999;19:869–877.

Sieb JP, Dorfler P, Tzartos S, Weaver UM, Ruegg MA, Meyer D, Baumann J, et al. Congenital mysthenic syndromes in two kingships with endplate acetylcholine and utrophin deficiency. Neurology 1998;50:54–61.

Siegelbaum SA, Koester J. Ion channels. In: Kandel ER, Scharrtz JH, Jessel TM, editors. Principles of neural science, New York: McGraw–Hill, 2000. pp. 105–125.

Singh NA, Charlier C, Stauffer D, DuPont BR, Leach RJ, Melis R, Ronen GM, Bjerre I, Quattlebaum T, Murphy JV, McHarg ML, Gagnon D, Rosales TO, Pfeiffer A, Anderson VE, Leppert M. A novel potassium channel gene, KCNQ2, is mutated an inherited epilepsy of newborns. Nat Genet 1998;18:25–29.

Singh R, Scheffer IE, Crossland K, Berkovic SF. Generalized epilepsy with febrile seizures plus: a common childhood-onset genetic epilepsy syndrome. Ann Neurol 1999;45:75–81.

Strom TM, Nyakatura G, Apfelstedt-Sylla E, Hellebrand H, Lorenz B, Weber BHF, et al. An L-type calcium channel gene mutated in incomplete X-linked congenital night blindness. Nat Genet 1998;19:260–263.

Takahashi H, Ikeuchi T, Honma Y, Hayashi S, Tsuji S. Autosomal dominant cerebellar ataxia (SCA6): clinical, genetic and neuropathological study in a family. Acta Neuropathol 1998;95:333–337.

Tavernarakis N, Shreffler W, Wang SL, Driscoll M. unc-8, a DEG/ENaC family member, encodes a subunit of a candidate mechanically gated channel that modulates c-elegans locomotion. Neuron 1997;18:107–119.

Taylor P, Brown JH. Acetylcholine. In: Siegel GJ, Agranoff BW, Albers RW, Fischer SK, Uhler MD, editors. Basic neurochemistry, Philadelphia, PA: Lippincott-Raven, 1999. pp. 213–242.

Tessier-Lavigne M. Visual processing by the retina. In: Kandel ER, Scharrtz JH, Jessel TM, editors. Principles of neural science, New York: McGraw–Hill, 1999. pp. 507–522.

Tournier-Lasserve E. CACNA1A mutations: hemiplegic migraine, episodic ataxia type 2, and the others. Neurology 1999;53:3–4.

Walker RC, Willingham AT, Zuker CS. A drosophila mechanosensory transduction channel. Science 2000;287:2229–2234.

Wallace RH, Wang DW, Singh R, Scheffer IE, George Jr AL, Phillips HA, Saar K, Reis A, Johnson EW, Sutherland GR, Berkovic SF, Mulley JC. Febrile seizures and generalized epilepsy associated with a mutation in the Na(+)-channel beta-1 subunit gene SCN1B. Nat Genet 1998;19:366–370.

Walls TJ, Engel AG, Nagel AS, Harper CM, Trastek VF. Congenital myasthenic syndrome associated with paucity of synaptic vesicles and reduced quantal release. Ann NY Acad Sci 1993;681:461–468.

Yue Q, Jen JC, Nelson SF, Baloh RW. Progressive ataxia due to a missense mutation in a calcium-channel gene. Am J Hum Genet 1997;61:1078–1087.

Zhang Y, Gao F, Popov VL, Wen JW, Hamill OP. Mechanically gated channel activity in cytoskeleton-deficient plasma membrane and vesicles from Xenopus oocytes. J Physiol (London) 2000;523:117–130.