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Chapter 8

Sodium channelopathies in skeletal muscle and brain

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Introduction

Channelopathies

Ion channel disorders are rare inherited diseases providing interesting models to study dysfunction of excitability in vivo and in vitro. The first so-called 'channelopathies' identified were skeletal muscle diseases, the myotonias and hyperkalemic periodic paralysis (HyperPP), which are sodium or chloride channel disorders. Within the last 5–10 years, complementary genetic and electrophysiological investigations led to the continuously growing list of channelopathies. Beside skeletal muscle, the channelopathies affect in particular other excitable tissues such as heart muscle and the nervous system. Typical examples are inherited cardiac arrythmias, episodic ataxias, familial hemiplegic migraine and some familial idiopathic epilepsy syndromes, but also kidney stones or hypertension can be caused by ion channel defects. The responsible genes encode for subunits of sodium, potassium, calcium or chloride channels which are gated by membrane voltage, ligands such as acetylcholine or γ-amino-butyric-acid (GABA) or other factors (for a recent comprehensive review see Lehmann-Horn and Jurkat-Rott 1999). This article will focus on the pathophysiological concepts of the sodium channelopathies found in skeletal muscle and brain, namely HyperPP, paramyotonia congenita (PC), potassium aggravated myotonia (PAM), hypokalemic periodic paralysis type 2 (HypoPP2), generalized epilepsy with febrile seizures plus ($GEFS^+$) and severe myoclonic epilepsy of infancy (SMEI).

Structure and function of voltage gated sodium channels

Voltage gated sodium channels are membrane spanning proteins responsible for the initiation and propagation of action potentials in nerve and muscle cells. In response to membrane depolarization, the channels open from the resting, closed state, and then inactivate spontaneously. Upon repolarization they will recover from inactivation. Beside these fast gating mechanisms which occur on a time scale of milliseconds and regulate the time course of an action potential there is a slow inactivation mechanism acting on a time scale of seconds. This slow gating process may decrease channel availability during series of action potentials or long-lasting membrane depolarization. Sodium channels

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consist of one α- and one or several β-subunits. The functionally important α-subunit contains four domains (I–IV) of six transmembrane segments each (S1–S6). All S4 segments contain positively charged residues conferring voltage dependence to the channel protein; the S5–S6 loops form the ion conducting pore and the cytoplasmic linker between domains III and IV contains the supposed inactivation particle. There are several genes encoding different α-subunits (SCN1A-SCN11A) that are expressed specifically in skeletal muscle (SCN4A), heart muscle (SCN5A) and neuronal tissue; four subunits (SCN1A, SCN2A, SCN3A and SCN8A) are considered to be responsible for the sodium current in brain. There are three genes for auxiliary β-subunits (SCN1B–SCN3B), that are all expressed in brain; the β_1-subunit is also expressed in skeletal and heart muscle (reviewed by Lehmann-Horn and Jurkat-Rott 1999; Catterall 2000; Goldin et al. 2000).

Sodium channelopathies in skeletal muscle

Hyperkalemic periodic paralysis, paramyotonia congenita and potassium aggravated myotonia: gain-of-function sodium channelopathies

2.1.1 Clinical features

All three diseases are transmitted as a dominant with complete penetrance except for a few families with rare mutations. PC is characterized by paradoxical myotonia, defined as muscle stiffness increasing with continued activity. This is in contrast to the chloride channel myotonias Thomsen and Becker showing the so-called warm-up phenomenon when myotonia is alleviated by continued exercise. PC patients furthermore suffer from severe worsening of the myotonia by cold, and muscle weakness occurs after long lasting exposure to cold.

Episodes of flaccid muscle weakness lasting 15 min to hours are the hallmark of HyperPP. They go along with a high serum potassium level and are triggered by rest after exercise or potassium loading. HyperPP can be accompanied by interictal myotonia and some patients develop a myopathy with permanent muscle weakness.

In contrast to HyperPP and PC, patients with PAM only rarely experience weakness and are usually not cold-sensitive. They show a generalized myotonia of variable degree (mildest form: myotonia fluctans, most severe form: myotonia permanens) which is often indistinguishable from Thomsen myotonia, the dominant form of the chloride channel myotonias. A clinical difference which may be used as a diagnostic tool is the sensitivity to oral potassium intake.

2.1.2 Genetics and pathophysiology

Electrophysiological studies on muscle biopsies from patients with HyperPP and PC revealed a membrane depolarization caused by an abnormal sodium inward current which was the first hint that the voltage gated sodium channel might be the site of the defect in these diseases (Lehmann-Horn et al. 1987). Subsequent genetic studies detected the first disease causing mutation within an ion channel gene, SCN4A encoding the α-subunit of the adult skeletal muscle sodium channel (Rojas et al. 1991). Subsequently, several mutations were found in SCN4A causing HyperPP or PC. The detection of SCN4A mutations in patients with dominant myotonia led to the description of the separate clinical entity PAM (Lerche et al. 1993) and up to now there are more than 20 mutations known causing one of these three disorders (Fig. 1A, reviewed by Lehmann-Horn and Jurkat-Rott 1999; Mitrovic and Lerche 2000).

Patch-clamp studies investigating the functional consequences of these mutations were first performed on muscle fibers from patients (Cannon et al. 1991; Lehmann-Horn et al. 1991; Lerche et al. 1993) and later in heterologous expression systems where wild-type or mutant cDNA of SCN4A was transfected into human embryonic kidney cells (Cannon and Strittmatter 1993; Cummins et al. 1993; Chahine et al. 1994; Mitrovic et al. 1994, 1995). All of these studies revealed defects in fast inactivation of the sodium channel, showing an increased number of channel reopenings causing a persistent sodium current and/or slowing of the inactivation time course (Figs. 1B, and 1C). These findings correlated to the abnormal sodium inward current observed in muscle biopsies from patients (Lehmann-Horn et al. 1987).

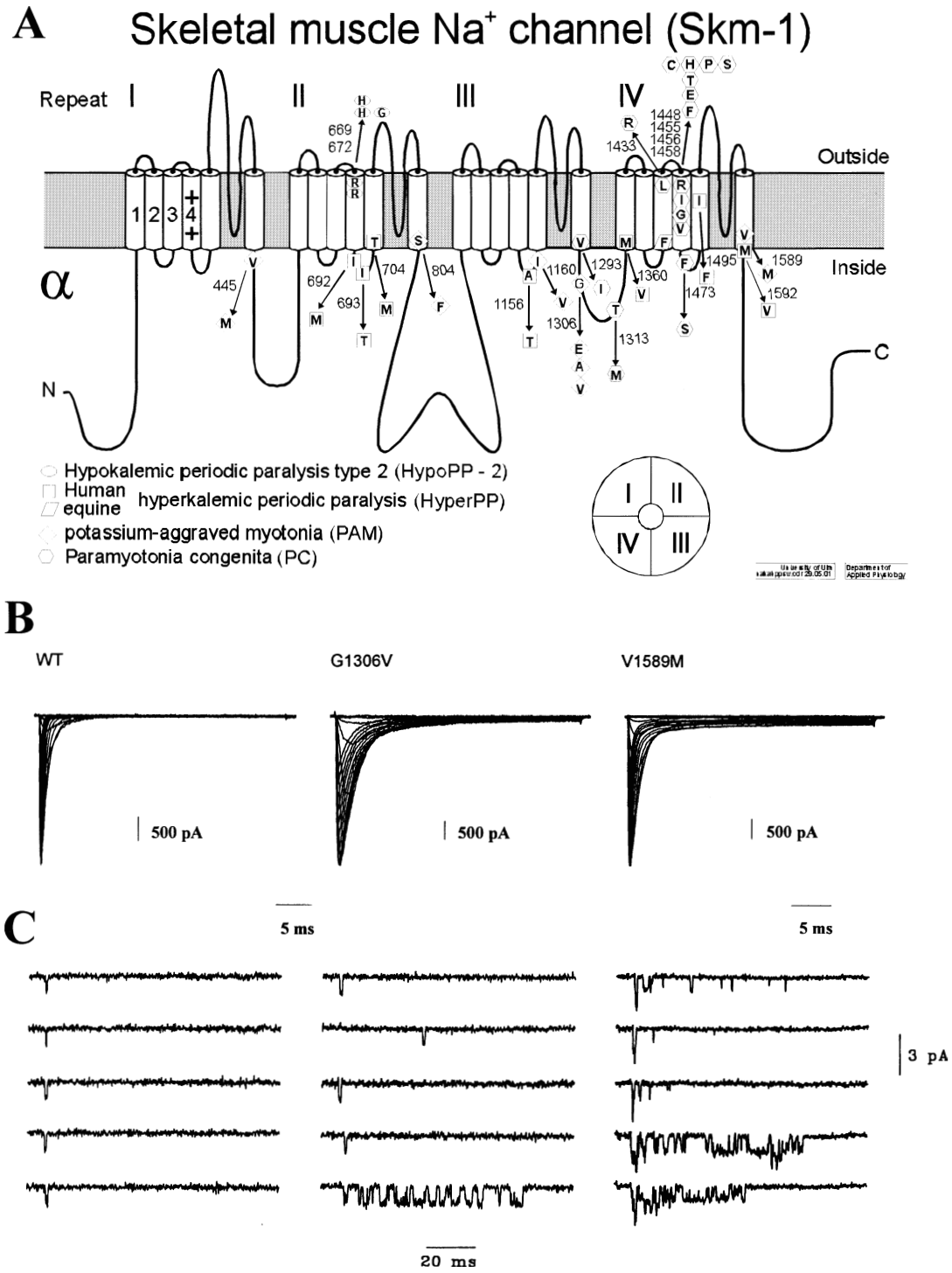


Fig. 1. (A) Proposed structure of the voltage gated skeletal muscle Na^+ channel α-subunit containing mutations causing HyperPP, PC, PAM or HypoPP2. Na^+ channels consist of four highly homologous domains (I–IV) with six transmembrane segments each (S1–S6) forming a central pore (lower right). (B, C) Functional studies using heterologous expression in human embryonic kidney cells and the whole cell (B) and single channel (C) patch-clamp technique revealed slowing of the fast inactivation time course and/or an increased persistent sodium current (B), caused by more frequent reopenings of single channels (C) for these mutations causing PAM, compared to wild-type (WT) channels (modified after Mitrovic et al. 1994, 1995).

The pathophysiology of myotonia is explained by slight membrane depolarization due to a relatively small persistent sodium current rendering the sarcolemma hyperexcitable. In contrast, paralysis occurs with strong depolarization leading to inactivation of all sodium channels and inexcitability due to a large persistent current. This could be predicted by a computer model (Cannon et al. 1993) and indeed genotype–phenotype relationships showed in general milder inactivation defects for the myotonia causing mutations than for those causing paralysis (HyperPP; reviewed by Mitrovic and Lerche 2000). A key finding for HyperPP causing mutations was an additional impairment of slow inactivation (Cummins and Sigworth 1996) leading to a long lasting persistent current. This could not be found in any of the PAM or PC mutations (Hayward et al. 1997). A strong slowing of fast inactivation found in particular for PC causing mutations could explain the paradoxical myotonia, since most of the abnormal sodium inward current would flow during action potentials, i.e. should increase with continued activity (Lerche et al. 1996). Thus, HyperPP, PC and PAM are all caused by gain-of-function mutations of the voltage gated sodium channel of skeletal muscle.

Hypokalemic periodic paralysis type 2: a loss-of-function sodium channelopathy

HypoPP is clinically very similar to HyperPP but attacks go along with a marked decrease of the serum potassium level. Triggers are strenuous exercise often the day before the attack or excessive ingestion of carbohydrates which lead to a decrease of serum potassium. Genetic analyses revealed linkage to the skeletal muscle calcium channel gene CACNA1S and subsequent detection of mutations therein (HypoPP1). Functional studies of these calcium channel mutations could not explain the occurrence of membrane depolarization and paralysis (Lehmann-Horn and Jurkat-Rott 1999).

Only recently, mutations in the muscle sodium channel gene SCN4A were also detected in HypoPP families (HypoPP2; Bulman et al. 1999; Jurkat-Rott et al. 2000; Fig. 1A). In contrast to the gain-of-function mechanism found for the other sodium channelopathies, these mutations did not show an impairment but instead an enhancement of fast and/or slow inactivation (Jurkat-Rott et al. 2000; Struyk et al. 2000; unpublished results from our group). These findings can explain the observation of action potentials with a slower rate of rise and loss of overshoot as well as conduction slowing in muscle fibers (Jurkat-Rott et al. 2000) and should contribute to muscle weakness since the number of sodium channels available for an action potential will be reduced. However, it is difficult to explain membrane depolarization as the pathophysiology is not fully understood so far. Since all mutations are concentrated in the II/S4 segment (Fig. 1A) it is tempting to speculate that this channel region plays a very specific role in the pathophysiology which is not yet known.

Sodium channelopathies in brain: generalized epilepsy with febrile seizures plus and severe myoclonic epilepsy of infancy

Clinical features

GEFS$^+$ was first described in 1997 Scheffer and Berkovic et al. (1997) as a childhood-onset syndrome featuring febrile convulsions and a variety of afebrile epileptic seizure types within the same pedigree with autosomal dominant inheritance. Most common was the febrile convulsion syndrome (FS), often with febrile seizures persisting after the 6th year of life or in combination with afebrile generalized tonic-clonic seizures (called 'FS$^+$'). The phenotypes FS and FS$^+$ were found in about two-thirds of affected individuals. According to the additional seizure types occurring in the remaining one-third of the patients, phenotypes such as 'FS$^+$ with absences', 'FS$^+$ with myoclonic seizures' or 'FS$^+$ with atonic seizures' were described. The most severe phenotype was myoclonic astatic epilepsy (MAE). Also partial epilepsies occurred in rare cases ('FS$^+$ with temporal lobe epilepsy'). The penetrance was about 60%.

Severe myoclonic epilepsy of infancy is characterized by clonic and tonic-clonic seizures in the first year of life that are often prolonged and asso-

ciated with fever. Later, patients have afebrile generalized seizures such as myoclonic, absence or tonic-clonic, and also simple and complex partial seizures occur. Developmental stagnation with dementia occurs in early childhood. In contrast to GEFS$^+$, the syndrome is usually resistant to pharmacotherapy.

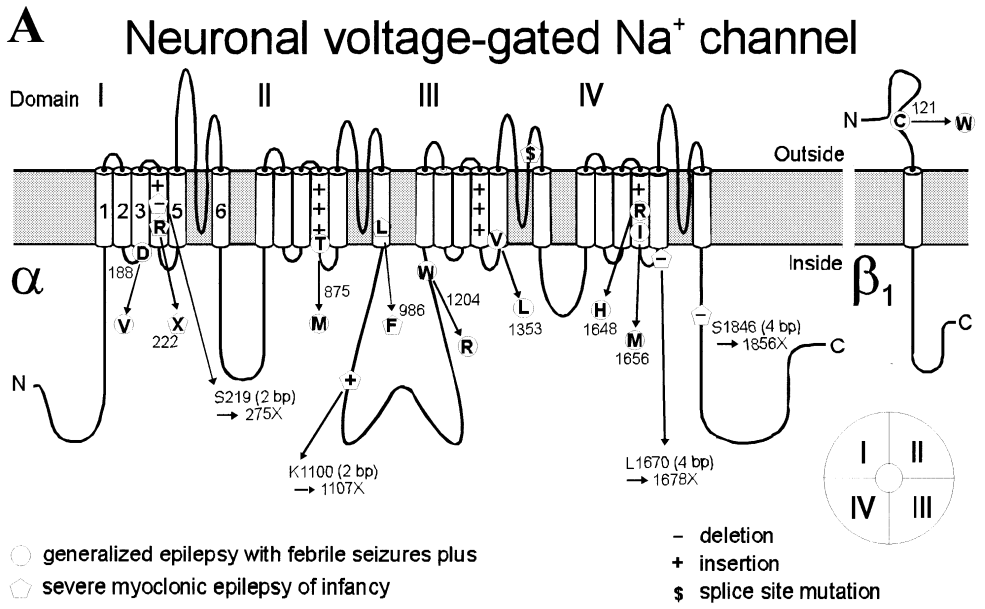
Genetics and pathophysiology

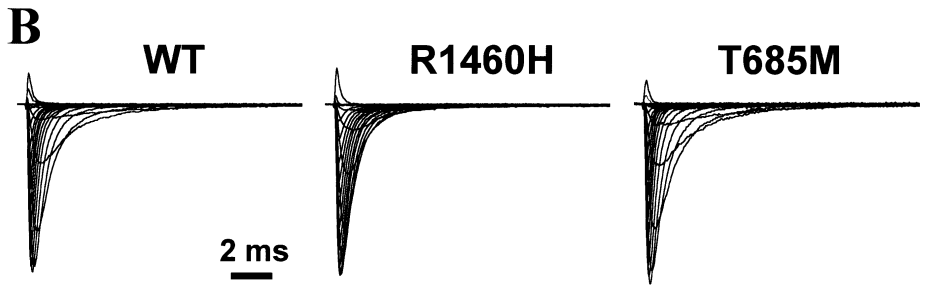
The first genetic defect in GEFS$^+$ was found by Wallace et al. (1998). The authors described linkage to chr 19q13 and identified a point mutation within the gene SCN1B encoding the β_1-subunit of the voltage gated Na^+ channel. The mutation predicts substitution of tryptophane for a cysteine residue at position 121, disrupting a disulfide bridge and changing the secondary structure of the β_1-subunit extracellular loop. This leads to a loss of β-subunit function resulting electrophysiologically in a slight slowing of the inactivation time course of the resulting Na^+ current (Wallace et al. 1998). Although the β_1-subunit is also expressed in skeletal muscle, interestingly these patients were not reported to suffer from myotonia like others carrying mutations within the skeletal muscle Na^+ channel α-subunit gene SCN4A. Hence, the brain seems to be more sensitive to such changes of excitability than skeletal muscle fibers, or alternatively, there are different disease causing mechanisms for both diseases, which is discussed in more detail further below.

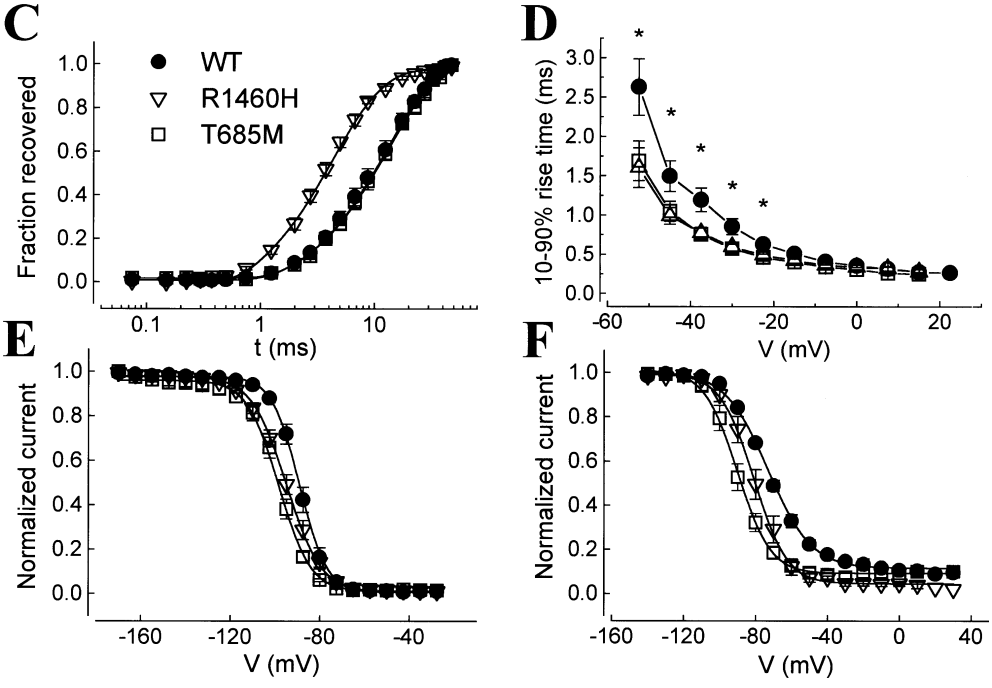
Subsequently, several groups found linkage to a cluster of genes encoding neuronal Na^+ channel α-subunits on chromosome 2q21–33 and the first 2-point mutations were detected in SCN1A, predicting amino acid changes within the voltage sensors (S4 segments) of domains II and IV (Escayg et al. 2000; Fig. 2A). Heterologous functional expression of these two mutations using the highly conserved gene SCN4A, human embryonic kidney cells (tsA201) and the whole cell patch-clamp technique revealed only subtle changes in sodium channel fast inactivation and activation and no persistent current (Alekov et al. 2000, 2001; Fig. 2). The most obvious alteration of the IV/S4 mutant was a 3-fold acceleration of recovery from inactivation (Fig. 2C). Little acceleration of the activation time course at potentials more negative than –20 mV compared to wild-type channels was found for both mutations (Fig. 2D). These were the only alterations increasing membrane excitability by shortening the refractory period after an action potential and the time of depolarization needed to elicit an action potential.

However, the most obvious difference in gating for the II/S4 mutation in comparison to the wild-type was an enhancement of both fast and slow inactivation of the channel. The steady-state fast and slow inactivation curves were shifted by –10 or –20 mV, entry into slow inactivation was accelerated and recovery from slow inactivation significantly slowed. These alterations were also found for the IV/S4 mutation, although less pronounced (Figs. 2E and 2F; Alekov et al. 2000, 2001). Hence, the disease causing mechanism of sodium channel

Fig. 2. (A) Proposed structure of the neuronal voltage gated Na^+ channel containing mutations causing GEFS$^+$ or SMEI in the α-subunit encoded by the gene SCN1A and the β_1-subunit encoded by SCN1B (Wallace et al. 1998; Escayg et al. 2000, 2001; Claes et al. 2001; Wallace et al. 2001). Both α-subunit mutations which were functionally examined so far (B–F) are located in the highly conserved voltage sensors (S4 segments) of domain II (T875M) and IV (R1648H), respectively. The β_1-subunit mutation disrupts a disulfide bridge between two cysteine residues in the extracellular loop that is essential for interaction with the α-subunit (see text). (B–F) Functional consequences of two SCN1A GEFS$^+$ mutations in II/S4 and IV/S4 (T875M, R1648H, A). The mutations were introduced in the highly homologous skeletal muscle α-subunit gene SCN4A (corresponding mutations T685M, R1460H) and studied in human embryonic kidney cells (tsA201) using the whole cell patch-clamp technique. (B) Families of raw current traces show only barely measurable differences in the time course of inactivation and no persistent Na^+ current at the end of the depolarizing test pulses for the mutations compared to wild-type (WT) channels. (C) A strong acceleration of the time course of recovery from inactivation was found for R1460H (shown at –100 mV). (D) Another significant difference was an acceleration of the time course of activation at potentials more negative than –20 mV, shown as a shortening of the rise time of the whole cell Na^+ current for both mutations. (E, F) Steady-state fast (E) and slow (F) inactivation curves. For both mutations inactivation is enhanced, resulting in a loss-of-function and decrease of membrane excitability in contrast to the gain-of-function mechanisms shown in (C, D) (modified after Alekov et al. 2000, 2001).


A
Neuronal voltage-gated Na+ channel
Domain I
II
III
IV
Outside
Inside
α
β1
N
C
121
W
188
V
X
222
S219 (2 bp)
→ 275X
875
M
986
F
1204
W
R
L
1353
H
1648
M
1656
S1846 (4 bp)
→ 1856X
K1100 (2 bp)
→ 1107X
L1670 (4 bp)
→ 1678X
generalized epilepsy with febrile seizures plus
severe myoclonic epilepsy of infancy
- deletion
+ insertion
$ splice site mutation


B
WT
R1460H
T685M
2 ms


C
Fraction recovered
WT
R1460H
T685M
t (ms)
D
10-90% rise time (ms)
V (mV)
E
Normalized current
V (mV)
F
Normalized current
V (mV)

mutations found in GEFS$^+$ might be completely different from those causing disorders of skeletal muscle. The increase of excitability due to acceleration of recovery from fast inactivation or of the activation time course – which would have to exert its effect on excitatory neurons to explain the occurrence of epileptic seizures – may be too small, in particular for the II/S4 mutation. Enhancement of both fast and slow inactivation would decrease membrane excitability by reducing the number of available sodium channels. When acting on inhibitory neurons, this effect could be responsible for the occurrence of synchronous activity in neuronal circuits causing epileptic seizures.

Two recent advances in the genetics of idiopathic epilepsies support the hypothesis that a decrease of excitability of inhibitory neurons is the most important disease causing mechanism for GEFS$^+$ causing sodium channel mutations. First, mutations in two GEFS$^+$ families were found in the γ_2-subunit of $GABA_A$ receptors that both decrease the activity of the receptor (Wallace et al. 2001a,b; Baulac et al. 2001). Hence, for these mutations undoubtedly a decrease of excitability in inhibitory neurons is the pathophysiological mechanism causing seizures. Second, novel mutations were identified in SCN1A causing a more severe phenotype than GEFS$^+$, that is SMEI (Claes et al. 2001). Most of these mutations predict an early stop codon and a truncated protein without function, with regard to all we know about structure-function relationships of this channel (Catterall 2000). Thus, SMEI is a loss-of-function sodium channel disorder caused by haploinsufficiency and from a genetic point of view a severe allelic variant of GEFS$^+$. Finally, the loss of β_1-subunit function by the SCN1B mutation could also induce a loss-of-function of the sodium channel, since one of the major effects of the β_1-subunit upon coexpression with the α-subunit is to increase the current amplitude (Catterall 2000)

Conclusions

HyperPP, PC and PAM, are gain-of-function sodium channelopathies of skeletal muscle. The inactivation defect common to all mutations can fully explain the phenotypes of myotonia and/or paralysis via a slight or strong membrane depolarization, respectively. HypoPP2 is a loss-of-function sodium channelopathy, but the described enhancement of fast and/or slow inactivation can only explain part of the pathophysiological features of this disease. In brain, SMEI is caused by haploinsufficiency of the SCN1A gene, thus a loss-of-function sodium channelopathy. It is a severe allelic variant of GEFS$^+$, which is probably also caused by a loss-of-function due to enhanced fast and slow inactivation of the sodium channel. This can explain the occurrence of epileptic seizures by a decrease of excitability of inhibitory neurons. However, for at least one GEFS$^+$-mutation in SCN1A, there are also gain-of-function mechanisms such as a strong acceleration of recovery from inactivation which would increase membrane excitability. Therefore, in GEFS$^+$ the equilibrium of excitatory and inhibitory neurons might be disturbed in two different ways.

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