Ion Channels and Epilepsy

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Helmut Kubista – **Ion channels and Epilepsies**

**Literature:**


Helbig I, Lowenstein DH (2013). *Genetics of the epilepsies: where are we and where are we going?* Curr Opin Neurol. 26:179-185.


**What is Epilepsy?**

umbrella term for a variety of more than 40 clinical syndromes (signs + symptoms) that affect 0.5 – 1% of the population worldwide  

~ 50 million people affected!

cardinal feature is a predisposition to recurrent unprovoked seizures

**Seizures**: episodic, abnormal, synchronized electrical activity of neuronal circuits which manifests as alteration in mental state, as motor symptoms or various other psychic symptoms

5% of the people experience at least one seizure in their lifetime

- **epileptic seizures** are classified according to their source within the brain, e.g. generalized or focal (partial) seizures and to their effects on the body (absence, tonic, clonic, myoclonic, …).

- **epileptic syndromes** are categorized by their aetiology (idiopathic, symptomatic, cryptogenic), the type of seizure, hereditary aspects, the age of onset, the prognosis, characteristic EEG findings, …
Forms of generalized epilepsies

- Grand mal seizure
- Absence seizure
human epileptic seizures

- partial seizures
  - simple p.s.
  - complex p.s.
  - secondary generalized p. s.
- generalized seizures
  - absence
  - atonic seizures
    - myoclonic s.
    - tonic-clonic s.
      - clonic s.
      - tonic s.
EPILEPTIC SEIZURE

- Idiopathic
- Cryptogenic
- Symptomatic
In humans, seizure susceptibility peaks in the first few months after birth, and then declines from 5 years through adolescence.

Secondary increases in aged population (acquired epilepsies)
Ätiologie symptomatischer Epilepsien

[Bar chart showing the distribution of different causes of symptomatic epilepsy across different age groups (0-4, 5-14, 15-24, 25-44, 45-64, >64). The causes include neurodegenerative diseases, vascular injuries, tumors, trauma, infections, and developmental anomalies.]
**Ion Channels and Epilepsy**

1.) electrical activity (both normal and pathological) is due to the activation/inactivation of ion channels

   many AEDs act on ion channels

2.) ion channels are modulated in the process of epileptogenesis (e.g. acquired epilepsies)

3.) rare monogenic idiopathic epilepsies are due to defects in ion channels

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**Diagram:**

- **Monogenic:** Gene → Protein → Epilepsy
- **Oligogenic:** Gene → Protein → Epilepsy
- **Polygenic:** Gene → Protein → Epilepsy
SYMPOSIUM REVIEW

Ion channels in genetic and acquired forms of epilepsy

Holger Lerche¹, Mala Shah², Heinz Beck³, Jeff Noebels⁴, Dan Johnston⁵ and Angela Vincent⁶

<p>| Table 1. Genes and proteins mutated in idiopathic epilepsies and epileptic encephalopathies |
|---------------------------------|-------------------|-------------------|-------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Abbreviation</strong></th>
<th><strong>Gene</strong></th>
<th><strong>Protein</strong></th>
<th><strong>References</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Idiopathic focal epilepsies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign familial neonatal seizures</td>
<td>BFNS1/EBN1</td>
<td>KCNQ2</td>
<td>Kᵥ7.2 (K⁺ channel)</td>
</tr>
<tr>
<td></td>
<td>BFNS2/EBN2</td>
<td>KCNQ3</td>
<td>Kᵥ7.3 (K⁺ channel)</td>
</tr>
<tr>
<td></td>
<td>BFNIS</td>
<td>SCN2A</td>
<td>Naᵥ1.2 (Na⁺ channel)</td>
</tr>
<tr>
<td>Benign familial neonatal-infantile seizures</td>
<td>ADNFLE</td>
<td>CHRNA4</td>
<td>α₄ subunit (nACh) receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHRNBB2</td>
<td>β₂ subunit (nACh) receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHRNA2</td>
<td>α₂ subunit (nACh) receptor</td>
</tr>
</tbody>
</table>
## Idiopathic generalized epilepsies and associated syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mutation</th>
<th>Gene</th>
<th>Protein</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood absence epilepsy with febrile seizures</td>
<td>CAE+FS</td>
<td>GABRG2</td>
<td>$\gamma_2$ subunit (GABA&lt;sub&gt;A&lt;/sub&gt; receptor)</td>
<td>Wallace et al. 2001</td>
</tr>
<tr>
<td>Absence epilepsy and episodic ataxia</td>
<td>CAE+EA2</td>
<td>CACNA1A</td>
<td>Ca&lt;sub&gt;V&lt;/sub&gt;2.1 (Ca&lt;sup&gt;2+&lt;/sup&gt; channel)</td>
<td>Jouveneau et al. 2001; Imbrici et al. 2004</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>JME</td>
<td>GABRA1</td>
<td>$\alpha_1$ subunit (GABA&lt;sub&gt;A&lt;/sub&gt; receptor)</td>
<td>Cossette et al. 2002</td>
</tr>
<tr>
<td>Genetic (generalized epilepsy with febrile seizures plus (GEFS+))</td>
<td>GEFS+</td>
<td>EFHC1</td>
<td>EF hand motif protein</td>
<td>Suzuki et al. 2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCN1A</td>
<td>Na&lt;sub&gt;V&lt;/sub&gt;1.1 (Na&lt;sup&gt;+&lt;/sup&gt; channel)</td>
<td>Escayg et al. 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCN1B</td>
<td>$\beta_1$ subunit (nACh receptor)</td>
<td>Wallace et al. 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GABRG2</td>
<td>$\gamma_2$ subunit (GABA&lt;sub&gt;A&lt;/sub&gt; receptor)</td>
<td>Baulac et al. 2001</td>
</tr>
<tr>
<td>Generalized epilepsy and paroxysmal dyskinaesia</td>
<td>GEPD</td>
<td>KCNMA1</td>
<td>K&lt;sub&gt;Ca&lt;/sub&gt;1.1 (K&lt;sup&gt;+&lt;/sup&gt; channel)</td>
<td>Du et al. 2005</td>
</tr>
</tbody>
</table>

## Epileptic encephalopathies

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mutation</th>
<th>Gene</th>
<th>Protein</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dravet syndrome (severe myoclonic epilepsy of infancy)</td>
<td>SMEI</td>
<td>SCN1A</td>
<td>Na&lt;sub&gt;V&lt;/sub&gt;1.1 (Na&lt;sup&gt;+&lt;/sup&gt; channel)</td>
<td>Claes et al. 2001</td>
</tr>
<tr>
<td>Other syndromes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal epilepsy and episodic ataxia</td>
<td>EA1+FE</td>
<td>KCNA1</td>
<td>K&lt;sub&gt;V&lt;/sub&gt;1.1 (K&lt;sup&gt;+&lt;/sup&gt; channel)</td>
<td>Zuberi et al. 1999</td>
</tr>
</tbody>
</table>
single gene defects of ion channels can cause epileptic seizures (e.g. KCNQ→BFNS) even focal and spontaneously remitting ones (ADNFLE, childhood epilepsies!)

both loss and gain of function of the channel can be epileptogenic e.g. both an increase and decrease in sodium channel activity can result in GEFS+!

penetrance never 100%, suggesting that the gene defects are only epileptogenic in a certain phenotypical environment. Healthy relatives of patients with ideopathic epilepsies were found to show epileptiform EEG abnormalities.

- allelic imbalance: the expression levels of mutant versus normal mRNA are differentially regulated in phenotypically affected and unaffected individuals

- „mosaicism“: the mutation may be restricted to certain cell lineages.

different mutations in the same gene can cause distinct syndromes (e.g.: ClC-2: JAE vs. JME vs. EGMA), although electrophysiological data indicate identical ion channel defects the heterologous expression systems are not able to distinguish between missense mutations that lead to mild disease in vivo and those that lead to severe disease, e.g. SCN1A: R1648C (SMEI mutation) and R1648H (GEFS+)

different syndromes in one family are frequently observed (overlapping action of epilepsy genes, change of one syndrome to another in a single epilepsy patient possible
**BFNS: benign familial neonatal seizures** (formerly benign familial neonatal convulsions: BFNC)

brief unprovoked partial or generalized seizures

**onset:** a few days after birth (first seizures appear on PND 2 to 3)

seizures last from a few seconds to 3 minutes

**tonic phase** at the beginning (tonic posture of trunk and limbs)
accompained by tachycardia or apnoe

then **clonic phase** starts with vocalisation (e.g. shrill cry), ocular symptoms
(e.g. rapid blinking of the eyes) or chewing movements, rhythmic shaking of
upper limbs

frequency of seizures as high as 20 to 30 episodes per day

progression: **spontaneous remission by 16 months of age**, however: increased seizure risk in later life

**associated channelopathies:**

• **KCNQ2** (48 mutations described!) and less frequently **KCNQ3** channel mutations, loss-of-function of
**M-type potassium channels**

(penetrance ~ 85 %)
KCNQ = $K_v$ 7.x

Heart, lung, kidney

CNS

CNS

Inner ear

CNS
M-current $K^+$ channels

KCNQ2

KCNQ3

○ benign familial neonatal convulsions
ADNFLE: autosomal dominant nocturnal frontal lobe epilepsy

focal-onset frontal lobe seizures

during stage 2 sleep (never in REM sleep)

patients wake up, experience an aura with generalized
tingling or shiver, fear, breathless feeling or
auditory hallucinations

seizure starts with bizarre vocalizations: moaning, gasping
or grunting

then prominent motor activity such as hyperkinetic thrashing movements with bipedal and bimanual
automatisms, tonic contraction and sustained dystonic posturing with forced hyperextension

onset: 9-11 years, seizures persist through adult life
seizure frequency: typically 2-3 per night, not necessarily every night

duration: typically less than a minute

associated channelopathies:

• nAChR subunit (α4 and β2) mutations have been associated with ADNFLE (penetrance 70%)
Nicotinic receptors in epilepsy

Figure 2. A representation of presynaptic nicotinic acetylcholine receptors (nAChRs). The nAChRs are positioned so they can influence the release of another neurotransmitter, which is released by the presynaptic terminal (Pre) onto the postsynaptic bouton (Postsynaptic). Evidence indicates that nAChRs initiate an increase of calcium in the presynaptic terminal. The calcium then enhances the release of the neurotransmitter.

Figure 4. A representation of fast nicotinic synaptic transmission. Only nicotinic acetylcholine receptors (nAChRs) are represented on the postsynaptic bouton in this simplified picture. Two presynaptic nAChRs are also shown.
Mutations in ADNFLE

- α4
- β2
- autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
The Rodrigues-Pinguet model of epileptiform activity in ADNFLE

Rodrigues-Pinguet et al., 2003
Rodrigues-Pinguet et al., 2005

nAChR mutants cause a reduction in autoinhibition of nicotinic facilitation of glutamate neurotransmission, but do not alter inhibitory GABAergic transmission.
Single gene defects of ion channels can cause epileptic seizures (e.g. KCNQ → BFNS) even focal and spontaneously remitting ones (ADNFLE, childhood epilepsies!)

Both loss and gain of function of the channel can be epileptogenic e.g. both an increase and decrease in sodium channel activity can result in GEFS+!

Penetrance never 100%, suggesting that the gene defects are only epileptogenic in a certain phenotypical environment. Healthy relatives of patients with ideopathic epilepsies were found to show epileptiform EEG abnormalities.

- Allelic imbalance: The expression levels of mutant versus normal mRNA are differentially regulated in phenotypically affected and unaffected individuals
- "Mosaicism": The mutation may be restricted to certain cell lineages.

Different mutations in the same gene can cause distinct syndromes (e.g.: ClC-2: JAE vs. JME vs. EGMA), although electrophysiological data indicate identical ion channel defects

The heterologous expression systems are not able to distinguish between missense mutations that lead to mild disease in vivo and those that lead to severe disease, e.g. SCN1A: R1648C (SMEI mutation) and R1648H (GEFS+)

Different syndromes in one family are frequently observed (overlapping action of epilepsy genes, change of one syndrome to another in a single epilepsy patient possible)
Mutations in α-subunits **R1648H**

Slow ramp: within 8 s from -120 to +40 mV

Lossin et al; Neuron 34, 877, 2002
both an increase and decrease in sodium channel activity can result in seizures!

Spamanato et al., 2001, J Neuroscience 21:7481–7490

Mutations in α-subunits R1648H

Mutations in α-subunits T875M
Yu et al; Nat Neurosci 9, 1142, 2006

~ 75% of $I_{Na}$ is carried by $Na_v1.1$ channels in hippocampal interneurons

$\leq 10\%$ $I_{Na}$ is carried by $Na_v1.1$ channels in hippocampal pyramidal neurons

(here, $Na_v1.2$ and $Na_v1.6$ predominate $I_{Na}$)
Ion Channels and Epilepsy

1.) electrical activity (both normal and pathological) is due to the activation/inactivation of ion channels

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3.) rare monogenic idiopathic epilepsies are due to defects in ion channels

monogenic  oligogenic  polygenic
<table>
<thead>
<tr>
<th>Channel/current</th>
<th>Form of epilepsy</th>
<th>Nature of change</th>
<th>Impact on cell excitability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCN channel/ HCN current $I_h$</td>
<td>Temporal lobe epilepsy (TLE)</td>
<td>Sustained reduction in current density following status epilepticus (SE) induction</td>
<td>Enhanced pyramidal and interneuron excitability</td>
<td>Dugladze et al. 2007; Jung et al. 2007; Marcelin et al. 2009; Shah et al. 2004; Shah et al. 2012; Shin et al. 2008; Wierschke et al. 2010</td>
</tr>
<tr>
<td>HCN channels/ HCN current $I_h$</td>
<td>Febrile seizure-induced epilepsy</td>
<td>Enhanced HCN channel expression and current</td>
<td>Enhanced rebound activity following inhibitory post-synaptic potentials (IPSPs)</td>
<td>Bender et al. 2003; Chen et al. 2001; Dyhrfjeld-Johnsen et al. 2008</td>
</tr>
<tr>
<td>HCN current $I_h$</td>
<td>Fragile X syndrome</td>
<td>Enhanced HCN channel current</td>
<td>Impaired long-term potentiation (LTP in pyramidal neurons)</td>
<td>Brager et al. 2012</td>
</tr>
<tr>
<td>$\text{Ca}_{\text{v}}3.2$ channels/ T-type $\text{Ca}^{2+}$ current</td>
<td>TLE</td>
<td>Transient elevation of expression and current from SE to chronic epilepsy</td>
<td>Enhanced pyramidal cell bursting</td>
<td>Becker et al. 2008; Su et al. 2002</td>
</tr>
<tr>
<td>$\text{K}_{\text{v}}4.2$ channels/ A-type $\text{K}^+$ current</td>
<td>TLE</td>
<td>Reduction 1 week after SE and persisting during chronic TLE</td>
<td>Enhanced pyramidal cell dendritic excitability</td>
<td>Bernard et al. 2004; Monaghan et al. 2008</td>
</tr>
<tr>
<td>BK channels</td>
<td>TLE</td>
<td>Reduction in expression during chronic TLE</td>
<td>??</td>
<td>Pacheco Otalora et al. 2008</td>
</tr>
<tr>
<td>$\text{K}_{\text{i}}2$ channels/ inward rectifier current</td>
<td>Chronic TLE</td>
<td>Enhanced expression</td>
<td>Reduced dentate gyrus granule cell excitability</td>
<td>Young et al. 2009</td>
</tr>
<tr>
<td>KCNN1 (SK1) KCNN2 (SK2) and KCNN3 (SK3) channels</td>
<td>TLE</td>
<td>Transient reduction during chronic TLE</td>
<td>Increased number of hippocampal population spikes</td>
<td>Oliveira et al. 2010</td>
</tr>
<tr>
<td>Persistent sodium current</td>
<td>TLE</td>
<td>Sustained increase following SE</td>
<td>Enhanced neuronal excitability</td>
<td>Agrawal et al. 2003; Chen et al. 2011; Epsztain et al. 2010; Hargus et al. 2011; Vreugdenhil et al. 2004</td>
</tr>
</tbody>
</table>

Lerche et al., 2013 (review)
Sodium current alterations in the SE model of acquired epilepsy

Ketelaars et al., 2001
A-type current and epilepsy (Kv4.2)
Ayala et al., 1973
Fig. 2. Typical example of paroxysmal depolarization shift. Calibrations: 1 mv (surface tracing) and 10 mv (microelectrode tracing); 100 cycle/sec; Fig. 1 for other explanations.
THE STATUS EPILEPTICUS MODEL

Seizure Strength

↑ Status Epilepticus Latent (Silent) Period Spontaneous Seizures

(Continual Seizures over Several Hours)
Ben-Ari et al., 1989
Ben-Ari, 2001
Giant depolarizing potentials (GDP): brain network activity controlling the wiring of the developing brain (e.g. dendritic growth, spine generation) (papers by Y. Ben-Ari)
ROS formation!
(Waldbaum and Patel!)

CREB required (Zhu…Porter, 2012)

enhanced intracellular chloride (NKCC1up/KCC2down):
loss of interneurons/GABAergic inhibition↓

AMPAR↑, NMDAR↑

Kv4.2 upregulation (latent stage), downregulation (chronic stage)
NPY↑, but loss of NPY neurons later?
A B

control +caff

B

+caff

C D

caff + BayK "PDS"

caff + isra

Rubi et al., 2013
Rubi et al., 2013
Cation-chloride co-transporters play critical roles in the regulation of intracellular chloride. Alterations in the balance of NKCCs and KCCs may determine the switch from a hyperpolarizing to a depolarizing effect of GABA.

![Diagram showing NKCC1 and KCC2 transporters in immature and mature CNS neurons.](Image)

from Stein and Nicoll, 2003

NKCC1: Cl⁻ accumulation system  
KCC2: Cl⁻ extrusion system
Ben-Ari, 2006

GABA excitation early: triggers spikes

\[ E_{Cl} = -40 \text{ mV} \]

GABA inhibition in adult

\[ [Cl^-] = 7 \text{ mM} \quad E_{Cl} = -85 \text{ mV} \]

Immature CNS Neurons

Mature CNS Neurons

\[ E_{Cl} \]

\[ V_m \]

GABA

\[ \text{Cl}^- \]

\[ \text{GABA}_A \text{R} \]

\[ \text{Cl}^- \]

\[ \text{GABA}_A \text{R} \]

\[ \text{KCC2} \]

\[ \text{NKCC1} \]

\[ \text{NKCC1} \]

\[ \text{KCC2} \]
PDS: CREB phosphorylation effects on synaptic plasticity morphological changes from Kwon et al., 2011 „proximalisation“ !
Ätiologie symptomatischer Epilepsien
case example: artist and author Anja Zeipelt: basal skull fracture when inline-skating

„…first blackouts, stuttering, loss of words, progressive jerks, then seizures“

epilepsy develops in nearly 20% of civilians who survive severe head trauma, with the first seizure occurring several months to several years after the initial injury. (Staley, Helllier and Dudek, 2005)

PDS are known to cause transitory cognitive impairment
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   many AEDs act on ion channels

2.) ion channels are modulated in the process of epileptogenesis (e.g. acquired epilepsies)

3.) rare monogenic idiopathic epilepsies are due to defects in ion channels

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**Diagram: Genes, Proteins, and Epilepsy**

- **Monogenic:** Gene → Protein → Epilepsy
- **Oligogenic:** Gene → Protein → Epilepsy, Gene → Protein → Epilepsy, etc.
- **Polygenic:** Multiple genes and proteins contribute to epilepsy

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**Categories:**
- Monogenic
- Oligogenic
- Polygenic
Mode of Action of Anti-Epileptic Drugs
Phenytoin suppresses „epileptiform activity in the culture dish“