Potassium Channelopathies: Consequences and Impact on Treatment

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Potassium Channelopathies and Epilepsy

- Variety of seizure disorders and syndromes
- Inherited channelopathy
- De novo channelopathy
- Acquired or transcriptional channelopathy
- Loss AND gain of function mutations
Inward Rectifier Family – KCNJ1-6, 8-16

Twin Pore Channels – KCNK1-7, 9-18

6 Transmembrane K⁺ Channels

Voltage-Activated K⁺ Channels

KCNN1-4
Ca²⁺-Activated K⁺ Channels

KCNMA1 Ca²⁺ and Voltage Activated Channels

KCNQ1-LQTS/SUDEP?
KCNQ2, KCNQ3 - Benign Familial Neonatal Convulsions

Shaker-related Family
KCNA1-7, 10 (Shaker)
KCNB1-2 (Shab)
KCNC1-4 (Shaw)
KCND1-3 (Shal)

Eag-related family
KCNH1-8

KvLQT-related family
KCNQ1-5

Slo-related family

KCNMA1 - Generalized Epilepsy and Paroxysmal Dyskinesia

KCNJ10 EAST Syndrome
KCNJ11 DEND Syndrome

KCNA1 Episodic Ataxia 1, Partial Seizures, SUDEP?
KCND2 Temporal Lobe Epilepsy

Brenner and Wilcox, in press
Mutations in \textit{KCNQ2} and \textit{KCNQ3}

Benign Familial Neonatal Convulsions (BFNC)

- Generalized and partial seizures
- Onset usually within first few days and can be as late as 13 months
- Incomplete penetrance
- Can also occur \textit{de novo}
- Spontaneous resolution
  - (with or without anticonvulsant treatment)
- Normal psychomotor skill, development, and learning ability in most, \textit{but not all patients}
- Greatly increased risk of developing adult onset epilepsy – BENIGN???? Seizure susceptibility gene?

\textit{(Singh et al, Charlier et al*) (Biervert et al, Schroeder et al, Lerche et al)}
KCNQ2 and KCNQ3 Subunits Co-Assemble to Form the M-channel

- Unique channel that is gated by voltage and GPCRs
- Muscarinic ACh receptor activation will close channel and depolarize cell
- Helps set and maintain resting membrane potential
- Influences action potential firing rates
- Mechanism of action for retigabine (Ezogabine®)

69 Mutations in \textit{KCNQ2} Have Been Identified in Families with BFNC

Only Four Mutations Have Been Identified in the *KCNQ3* Gene in Families with BFNC

KCNQ2 Is Highly Concentrated at the Axon Initial Segment (AIS)

Pan et al., J Neurosci 26:2599 –2613, 2006
Neurons in Mice With a *Kcnq2* Haploinsufficiency Are More Excitable

Retigabine Is Not as Effective in Mice With a *Kcnq2* Haploinsufficiency

Retigabine Is Less Potent In Mice With a $Kcnq2$ Haploinsufficiency

Therapeutic Implications of Mutations in \textit{KCNQ2} and \textit{KCNQ3}

- Increased seizure susceptibility
  - Are patients at risk following insults?
- Altered pharmacology has implications for clinical trials
- The right compound for the right patient:
  - pharmacogenomics
Potassium Channelopathies and Sudden Unexplained Death in Epilepsy (SUDEP)

*KCNQ1* (Kv 7.1): expressed in heart and CNS

*KCNA1* (Kv 1.1): expressed mainly in CNS
SUDEP

- Patients with epilepsy die unexpectedly at a rate up to 24 times greater than the general population.
- SUDEP may account for up to 18% of all deaths in patients with epilepsy.
- AES & EFA Joint Task force recommends discussing SUDEP with patients and families.
- Clinical risk factors for SUDEP:
  - early onset intractable epilepsy
  - males, aged 20-40 years
  - generalized seizures
  - exposure to multiple anticonvulsant medications
  - poor compliance with medications
Potential Mechanisms Hypothesized to Result in SUDEP

- Intrinsic cardiac problem, e.g. LQTS mutations
- Cardiac failure mediated by autonomic dysregulation
- Apnea due to central respiratory depression
Loss of Function Mutations in *KCNQ1* Result in Long QT Syndrome and Cause Seizures in Mice

- A slow delayed rectifier potassium current ($I_{KS}$) in human cardiac myocytes
- Not thought to be expressed in CNS
KCNQ1 Potassium Channels and Seizures in Mouse Forebrain

Goldman et al., Sci Trans Med, 2009
KCNQ1 Potassium Channels in Mouse Vagal Nerve Nuclei

Cortical Discharges Often Trigger Cardiac Asystole

Goldman et al., Sci Trans Med, 2009
**KCNQ1** Potassium Channel Mutations in Heart and Brain

- Hundreds of LQTS mutations have been identified for **KCNQ1**
  - Loss of function

- Seizure disorders have been observed with greater than expected frequency in patients with LQTS

- Excessive autonomic activity can influence cardiorespiratory function
Loss of Function Mutations in \textit{KCNA1} (Kv1.1) Can Result in Epilepsy

- T226R and A242P mutations in \textit{KCNA1} result in partial epilepsy
  - Reduce expression or trafficking of channels
- \textit{Kcnai} knockout mice have seizures and die prematurely
- Enhanced excitability related to axonal repolarization and propagation
EEG–ECG Recordings Reveal Interictal and Ictal Cardiac Abnormalities in *Kcna1*−/−

KCNA1 Is Present In Vagus Nerve Axons: Enhanced Parasympathetic Activity in Knockout Mice?

Therapeutic Implications of Potassium Channelopathies and SUDEP

- Screen for heart rhythm disorders to reduce the risk
- Follow up with genetic screening and pharmacotherapy where indicated
*KCNJ11* (K$_{IR}$ 6.2; K$_{ATP}$) Channelopathy: Delay, Epilepsy, and Neonatal Diabetes (DEND) Syndrome

- Gain of function mutation
- Neonatal-onset diabetes
- Developmental delay
- Neonatal seizures
- Infantile spasms
- Intractable seizures
$K_{ATP}$ Gating

Treatment for DEND with Glibenclamide

- Binds to the SUR receptor
- Closes the channel
- Depolarizes cells in pancreas and allows insulin release
- Seizures come under control
- Development resumed


J Physiol 572.3 (2006) 617–624
A large number of familial and *de novo* channelopathies in potassium channels underlie, or are associated with, many types of epilepsy.

Both loss of function and paradoxically, gain of function mutations:

- Missense/nonsense
- Splicing mutations
- Small and gross deletions
- Small and gross insertions
- Indels
Potassium Channelopathies: Consequences and Impact on Treatment

Recent advances in genetics and animal models provide information to guide treatment

- Reduce risk of SUDEP
- Identify seizure susceptibility genes
  - Many forms of epilepsy likely to be multifactorial
- Novel drug targets and personal pharmacogenomics
- Basic mechanisms underlying epilepsy
ARS question to be placed here

(if applicable)