Epileptogenesis: A Clinician’s Perspective

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Epileptogenesis

- The process of development and sustaining the propensity to recurrent seizures

- **Primary epileptogenesis**
  Transformation of a “normal” brain to one that generates seizures

- **Secondary epileptogenesis**
  Development of secondary (often mirror) foci
  Evidence that seizures themselves contribute to the process
Epileptogenesis

Approaches to Epileptogenesis in Man

- Aetiology ("initiating lesion")
- Natural history
- Imaging studies
- Study of chronic epileptic tissue (peri-operative)
- Drug responsiveness/resistance
**Epileptogenesis - Natural History**

**Adult Partial Epilepsy**
- Post-traumatic and post-stroke epilepsy
  - Characteristically delay of months or years before epilepsy begins
- “Cryptogenic” partial epilepsies
  - Usually no known initiating event

**Initiating Event**

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Silent Interval  CHRONIC EPILEPSY

months-years
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**Childhood Symptomatic Partial Epilepsy**
- Post-traumatic and Post-stroke epilepsy
  - Characteristically delay of months or years before epilepsy begins
- Congenital tumours/migrational abnormalities
  - Epilepsy often begins in mid childhood or adolescence
- Chronic Temporal Lobe Epilepsy
  - Begins in mid childhood or adolescence, prolonged febrile seizure in infancy
**Epileptogenesis - Natural History**

Injury in infancy or early childhood

- Silent Interval
- Seizures
- Deceitful interval
- CHRONIC

*childhood* → *early teens* → *late teens*

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**Epileptogenesis - Natural History**

Genetic (idiopathic) epilepsies

Gene defect

- "Silent Interval" → EPILEPSY → Remission

*Birth* → *months-years*
Epileptogenesis - Natural History

- Genetic (idiopathic) epilepsies

Gene defect

“Silent Interval” EPILEPSY

Many years

Birth

Developmental Changes and Epileptogenesis
Benign Familial Neonatal-Infantile Seizures: SCN2A

Neonatal onset
Infantile onset

Voltage-gated sodium channel
in 3D
Exon splicing yields adult and neonatal forms of SCN2A - Related to epileptogenesis

Exon 25

YVTEFVNLGNVLALRTFRVLKISVIP

YVTEFVLGNVLALRTFRVLKISVIP

Modified from Lerche et al., 2001
L1563V decreases the rate of inactivation in neonatal form

Neonatal

**Developmental changes and Epileptogenesis SCN2A & BFNIS**

- Neonatal (6N) form is less excitable than adult form (6A)

- This reduced sodium channel excitability may be important for protecting against seizures in infancy, a time when the brain is more susceptible to seizures

- Mutation only alters function of neonatal isoform
  - The L1563V mutation reverses the "inhibitory" effects of the neonatal exon
  - ? mechanism underlying development of BFNIS in this family, an age-dependent benign epilepsy
Epileptogenesis: Human Epileptic Tissue

- Technically very challenging
  - Control tissue a major issue
  - Tissue slice is a “reduced” system
  - Limited window for experiments
  - One time point
  - Very “chronic” tissue

Epileptogenesis: Human Epileptic Tissue

- Laborious electrophysiological studies have not yielded a coherent signature of human epileptogenic cortex

- Recent interest in molecular changes in receptors
  - Not yet consistent
Epileptogenesis: Aetiology

Numerous (>300) genetic disorders cause symptomatic epilepsies
- Chromosomal syndromes (Trisomy 21, Ring 20 etc...)
- Storage diseases (Tay-Sachs, Lafora etc...)
- Amino-acidopathies (Phenylketonuria, hyperglycinemias etc...)
- Cortical Malformation disorders (Double cortex syndrome, Tuberous sclerosis etc...)

No common theme explaining epileptogenesis but
Maturation patterns of epilepsy evident in these disorders
Account for a tiny minority of cases

Hauser et al
## Idiopathic Epilepsies: Monogenic Inheritance 2006

### Voltage-gated Channelopathies

**Benign Familial Neonatal Seizures**
- Potassium channel genes: *KCNQ2, KCNQ3*

**Benign Familial Neonatal-Infantile Seizures**
- Sodium channel gene: *SCN2A*

**Generalized Epilepsy with Febrile Seizures Plus / SMEI**
- Sodium channel genes: *SCN1B, SCN1A, SCN2A*

**Autosomal Dominant Partial Epilepsy with Auditory Features**
- Potassium channel subunit: *LGII*

### Ligand-gated Channelopathies

**Autosomal Dominant Nocturnal Frontal Lobe Epilepsy**
- Nicotinic receptor subunit genes: *CHRNA4, CHRNA2*

**Idiopathic Generalized Epilepsy /GEFS+**
- GABA receptor subunit gene: *GABRG2*

**Juvenile myoclonic epilepsy**
- GABA receptor subunit gene: *GABRA1*

## Idiopathic Epilepsies; Complex Inheritance Susceptibility Genes: 2006

### Juvenile Myoclonic Epilepsy
- Novel protein; pro-apoptotic, calcium sensing: *EFHC1* **
- Transcriptional regulator: *BRD2 (??)*

### Childhood Absence Epilepsy
- Calcium T channel gene: *CACNA1H**

### Idiopathic Generalized Epilepsy
- Chloride channel gene: *CLCN2*
- GABA delta subunit gene: *GABRD*
GABA<sub>A</sub> Receptor Sub-unit Composition

GABA<sub>A</sub> Synapse

GABA<sub>A</sub> Receptor Changes in the Silent Interval

Brooks-Kayal et al 1998
Conclusions

- Understanding epileptogenesis is a major priority
- Likely to be many mechanisms
- Intertwined with developmental changes
- Ion channel changes may be critical