

# Epileptogenesis: A Clinician's Perspective

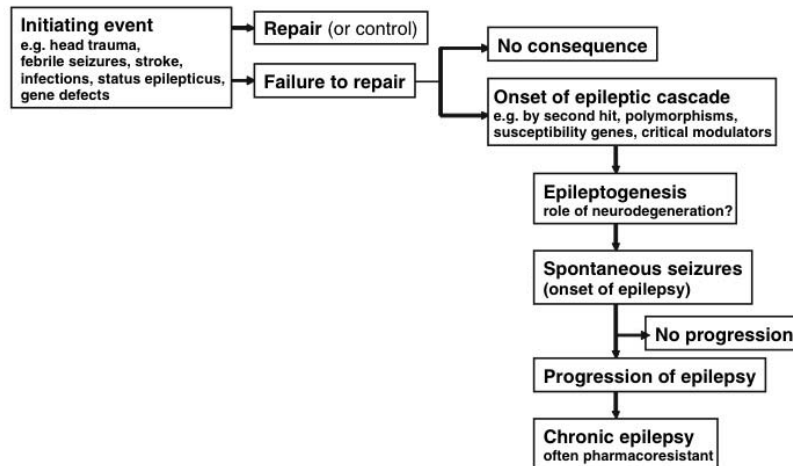
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## Epileptogenesis

- 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

## Steps in epilepsy development, progression and pharmacological intervention



*Loscher 2006*

## Epileptogenesis

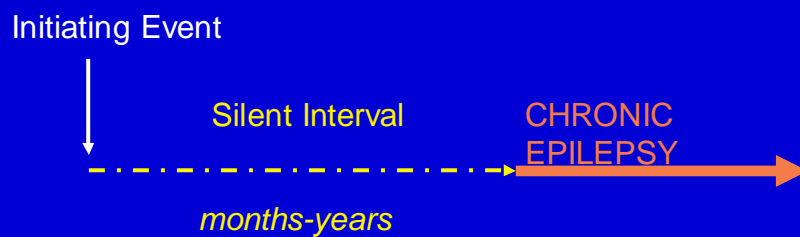
### Approaches to Epileptogenesis in Man

- 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

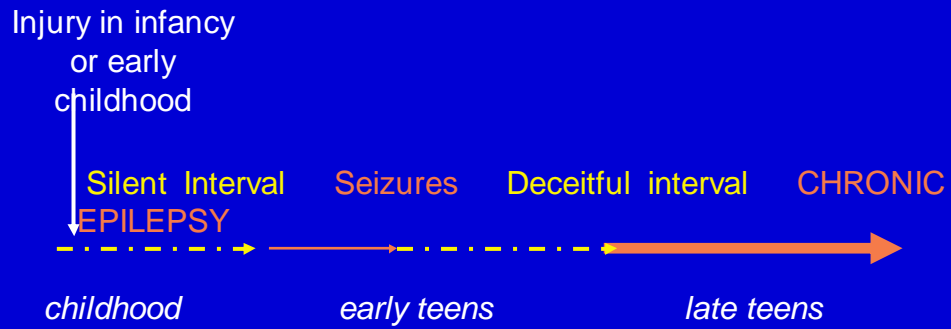


## Epileptogenesis - Natural History

### Childhood Symptomatic Partial Epilepsy

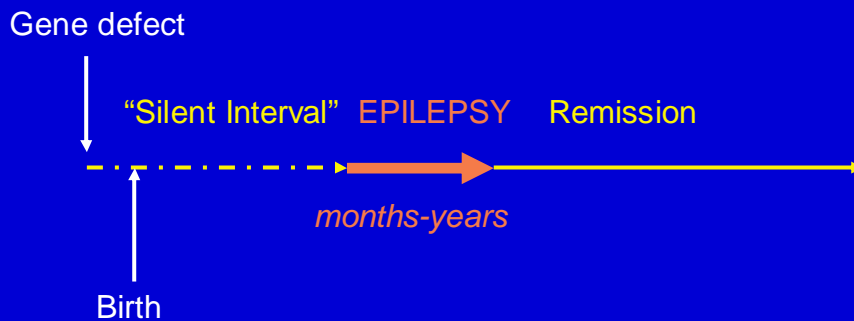
- Post-traumatic and Post-stroke epilepsy  
Characteristically delay of months or years before epilepsy begins
- Congenital tumours/migrational abnormalities  
Epilepsy often begins in mid childhood or adolescence
- Chronic Temporal Lobe Epilepsy  
Begins in mid childhood or adolescence, prolonged febrile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

## Epileptogenesis - Natural History



## Epileptogenesis - Natural History

Genetic (idiopathic) epilepsies

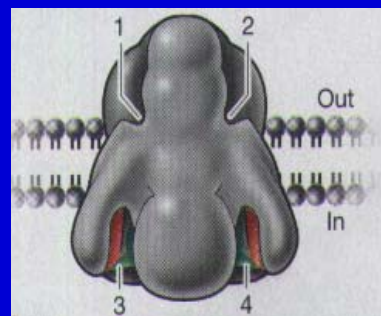
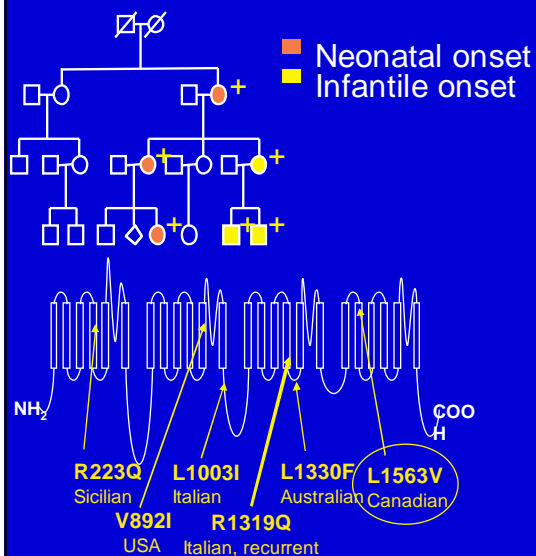


## Epileptogenesis - Natural History

- Genetic (idiopathic) epilepsies

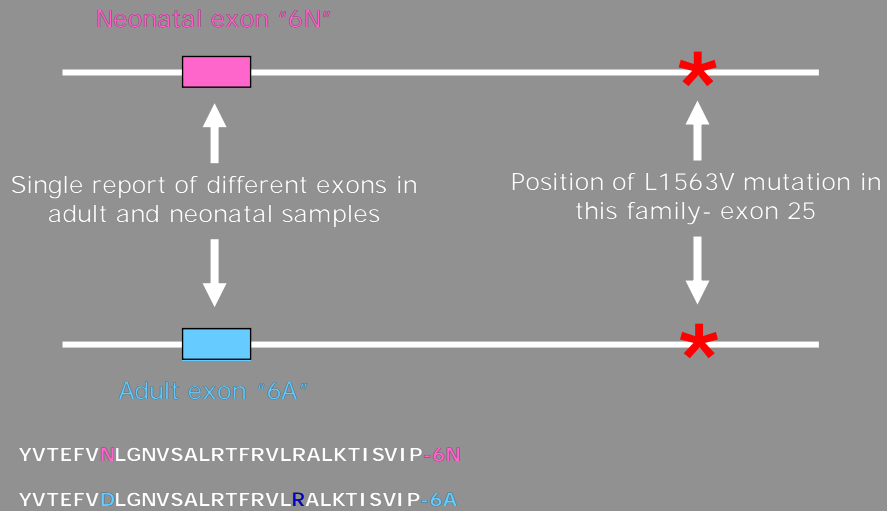


## Developmental Changes and Epileptogenesis Benign Familial Neonatal-Infantile Seizures: *SCN2A*

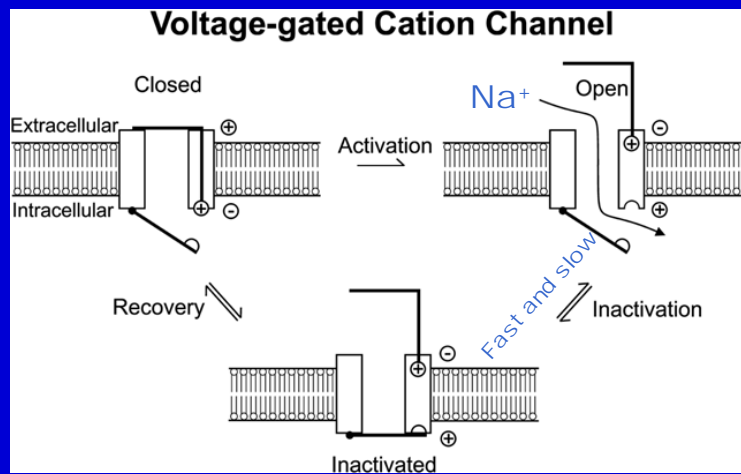


Voltage-gated sodium channel  
in 3D  
Sato et al Nature 2001

## Exon splicing yields adult and neonatal forms of SCN2A - ? Related to epileptogenesis



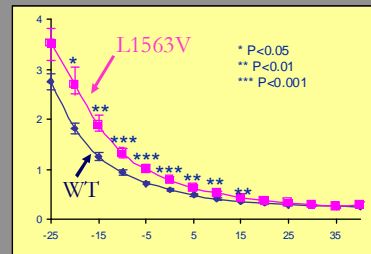
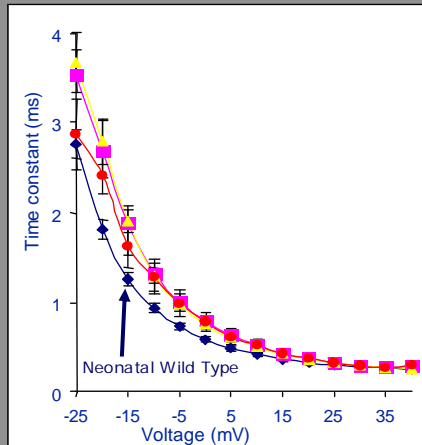
## States of the sodium channel



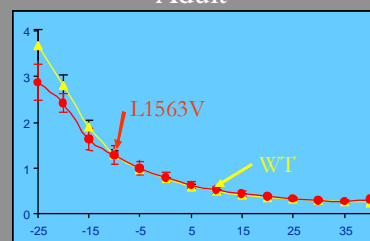
Modified from Lerche et al., 2001

## L1563V decreases the rate of inactivation in neonatal form

Neonatal



Adult



*Xu et al 2007*

## 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**

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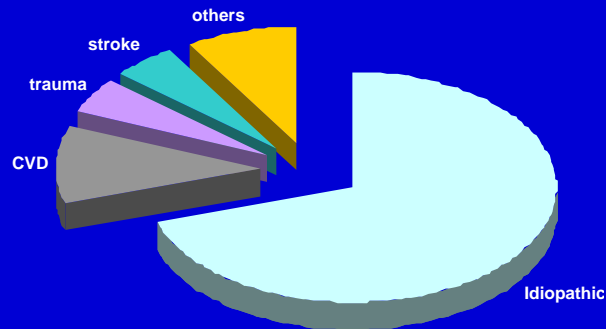
- Technically very challenging
  - Control tissue a major issue
  - Tissue slice is a “reduced” system
  - Limited window for experiments
  - One time point
  - Very “chronic” tissue

## **Epileptogenesis: Human Epileptic Tissue**

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- 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

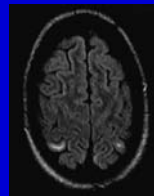
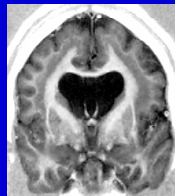
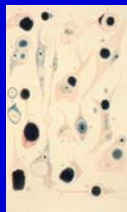


*Hauser et al*

## 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*  
Maturational patterns of epilepsy evident in these disorders  
Account for a tiny minority of cases

## Idiopathic Epilepsies: Monogenic Inheritance 2006

### *Voltage-gated Channelopathies*

Benign Familial Neonatal Seizures	Potassium channel genes	<i>KCNQ2, KCNQ3</i>
Benign Familial Neonatal-Infantile Seizures	Sodium channel gene	<i>SCN2A</i>
Generalized Epilepsy with Febrile Seizures Plus / SMEI	Sodium channel genes	<i>SCN1B, SCN1A, SCN2A</i>
Autosomal Dominant Partial Epilepsy with Auditory Features	Potassium channel subunit	<i>LG1</i>

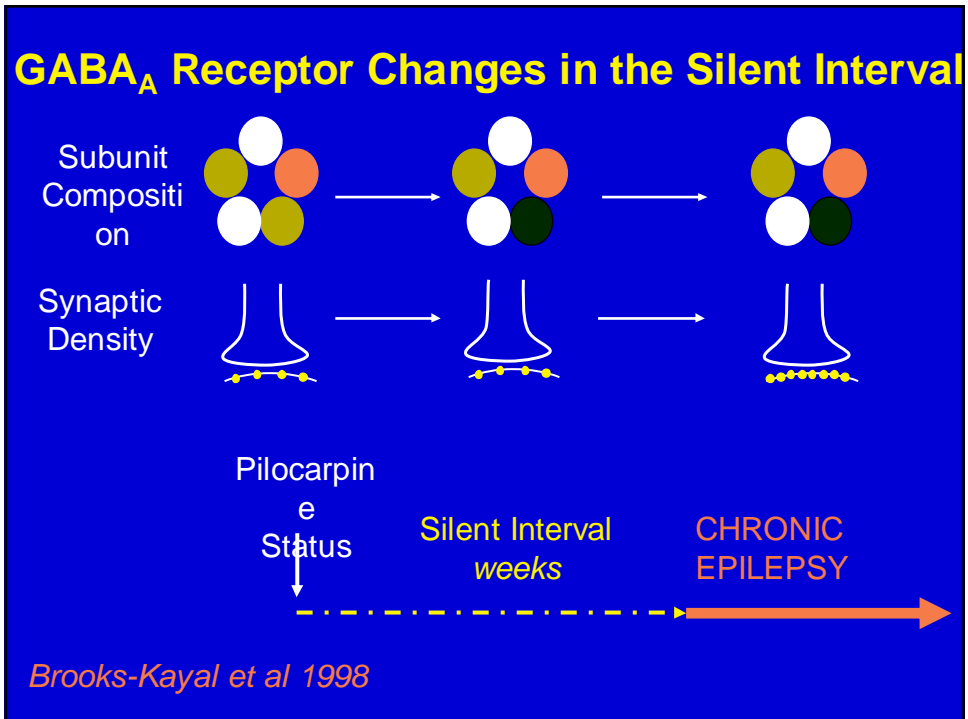
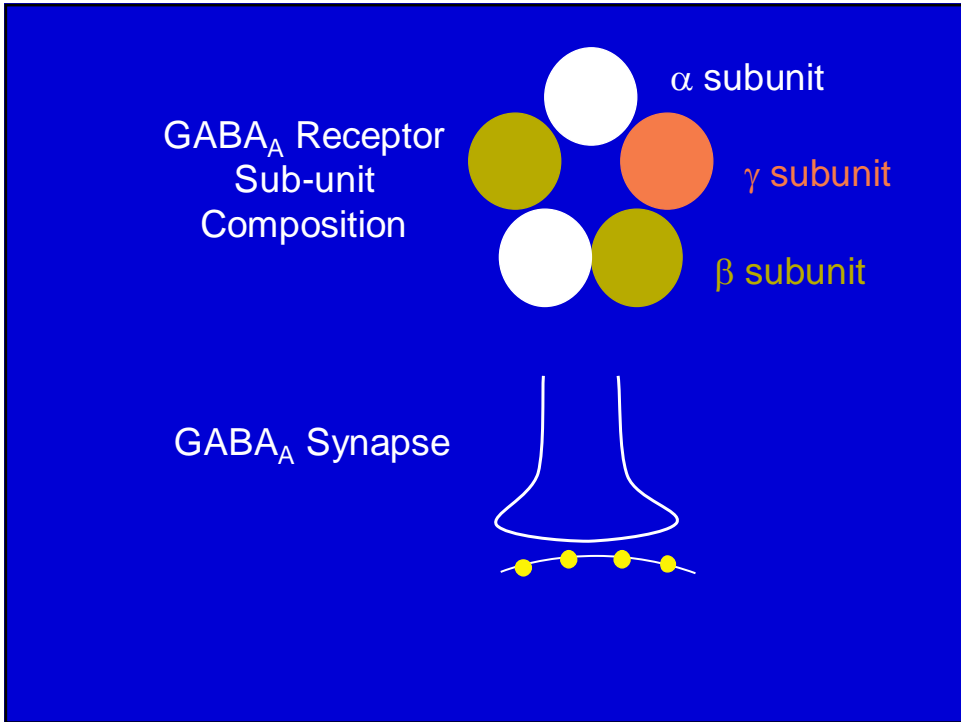
### *Ligand-gated Channelopathies*

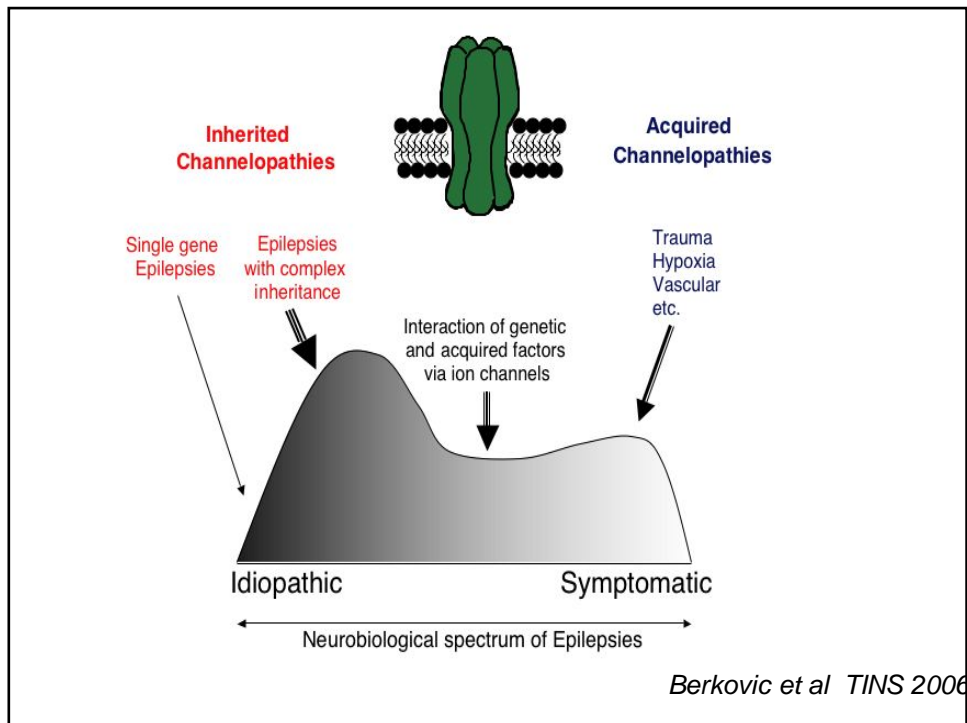
Autosomal Dominant Nocturnal Frontal Lobe Epilepsy	Nicotinic receptor subunit genes	<i>CHRNA4, CHRNB2, CHRNA2</i>
Idiopathic Generalized Epilepsy /GEFS+	GABA receptor subunit gene	<i>GABRG2</i>
Juvenile myoclonic epilepsy	GABA receptor subunit gene	<i>GABRA1</i>

## Idiopathic Epilepsies; Complex Inheritance Susceptibility Genes: 2006

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Juvenile Myoclonic Epilepsy	Novel protein; pro-apoptotic, calcium sensing Transcriptional regulator	<i>EFHC1</i> ** <i>BRD2</i> (??)
Childhood Absence Epilepsy	Calcium T channel gene	<i>CACNA1H</i> **
Idiopathic Generalized Epilepsy	Chloride channel gene GABA delta subunit gene	<i>CLCN2</i> <i>GABRD</i>





## Conclusions

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