New Antiepileptic Drugs: From Laboratory to Patient

Ley Sander MD MRCP PhD
National Society for Epilepsy
UCL Institute of Neurology
National Hospital for Neurology and Neurosurgery

Overview

- **Epilepsy is a symptom complex**

- **It is not like diabetes, but is more analogous to anaemia**

- **Epilepsy is the result an underlying disease of the brain**

- **At the moment we treat symptom – seizures.**

Definition

- Epilepsy is the propensity to have seizures "One swallow does not make a summer"

- Epileptic Seizures are synchronous and excessive discharges in the cortex that lead to a clinically discernable event
  - Many different seizure types

Seizure Types

- Most common seizure type are convulsive attacks
  - **Primarily Generalised**
  - **Secondarily Generalised**

- Partial seizures present in many ways
  - **Complex partial with impairment of consciousness**
  - **Simple partial with no impairment**

- Other seizure types rarer
  - **Absences, Myoclonic, tonic, atonic**

The incidence

- **Incidence of new cases of epilepsy:**

  - ➤ **Developed world: 40 - 80/100,000/year**
    - ✓ 50/100,000/year

  - ➤ **Developing world: 80 - 190/100,000/year**
    - ✓ 120/100,000/year

- **Incidence of single seizures:**
  - ➤ 20 - 30/100,000/year

The prevalence

- Prevalence of active epilepsy (independent of location):
  - 5 - 10/1,000   (50% because on AEDS)
    - Severe epilepsy: 1 - 2/1,000

- Cumulative Incidence (lifetime prevalence):
  - 2 - 5%

Numbers in the UK

- 30 000 new cases a year

- 300 000 - 400 000 cases

- 72 000 - 80 000 cases of severe epilepsy

Population 59,000.000

Emerging Anti-epileptic Drugs

- Goals of anti-epileptic treatment
- Past and present AEDs
- The need for new drugs
- Discovering new drugs
- Targets for new drugs
- Future AEDs
- Conclusions

Goals of Anti-epileptic Treatment I

- Complete seizure freedom
  - 50% seizure reduction of little benefit

- No adverse effects
  - long term treatment - long term effects?
  - cognitive effects can be debilitating
  - non-teratogenic

Goals of Anti-epileptic Treatment II

- Non-obtrusive treatment
  - once or twice daily
  - No drug interactions

- Maintenance of a normal lifestyle

- Reduction in morbidity and mortality

'There is scarcely a substance in the world, capable of passing through the gullet of man, that has not at one time or other enjoyed a reputation of being an anti-epileptic.'

Sir Edward Henry Sieveking, circa 1900

Some Antiepileptic Drugs Used at Queen Square Circa 1880

- Bromide*
- Digitalis
- Belladonna*
- Atropine
- Cannabis*
- Opium*
- Zinc*
- Borax
- Iron
- Sesame oil*
- Hyoscine
- Ergot
- Sclerotic Acid
- Gelsemium
- Curare

- Iron
- Strophantus
- Camphor
- Mistletoe
- Turpentine
- Nitrate of silver
- Sulphate of copper
- Calabar bean
- Nitroglycerine
- Nitrite of Amyl
- Iodide of potassium
- Hydrocyanic acid
- Bromalin
- Chloral
- Osmic acid

Current antiepileptic drug treatment

- Symptomatic
  - Treat seizures and not epilepsy

- Empirical rather than rational!
  - Shoot in the dark and hope it works!

- No "curative", antiepileptogenic or disease modifying treatment

The conventional or Legacy AEDs

- Acetazolamide
- Benzodiazepines
  - Clobazam
  - Clonazepam
  - Clorazepate
  - Lorazepam
  - Nitrazepam
- Bromides
- Carbamazepine
- Ethosuximide
- Ethotoin
- Mephenytoin
- Mephobarbital
- Methsuximide
- Phenobarbital
- Phenytoin
- Primidone
- Sodium Valproate
- Sulthiame

"New" Antiepileptic Drugs

✝ - Progabide   (1987 - 1996)
✝ - Vigabatrin   (1989 - 1997)
✝ - Felbamate   (1993 - 1995)

- 1990 -   Oxcarbazepine
- 1990 -   Zonisamide*
- 1990 -   Lamotrigine
- 1993 -   Gabapentin
- 1993 -   Piracetam
- 1995 -   Topiramate
- 1996 -   Tiagabine
- 1999 -   Levetiracetam
- 2004 -   Pregabalin

The Need for Even More New AEDs

- To improve the outcome of people with chronic epilepsy

- To improve on established AEDs as first line therapy:
  - efficacy
  - safety
  - pharmacokinetics (metabolism of the drug)
  - cost-effectiveness

New AEDs: Impact on Prognosis

- In chronic epilepsy the impact of the new AEDs has been small – at best 10 – 20% seizure free
  - Levetiracetam
  - Topiramate
  - Lamotrigine

- In newly diagnosed epilepsy, little difference between new and conventional AEDS in outcome, but new AEDs are better tolerated

- Most new AEDs have not lived up to expectations!

Current anti-epileptic drug treatment

- Symptomatic
  - Treat seizures and not epilepsy

- Empirical rather than rational
  - Shoot in the dark and hope it works!

- "Curative", anti-epileptogenic or disease-modifying treatment urgently needed

Discovering AEDs I

- Secondary use of drugs
  - Phenobarbital
  - Carbamazepine

- Screening
  - Phenytoin
  - Ethosuximide

- Modification of existing drugs
  - Oxcarbazepine
  - Pregabalin

Discovering AEDs II

- Serendipity
  - Sodium Valproate
  - Levetiracetam
  - Topiramate

- "*Rational*" or target oriented design
  - Vigabatrin
  - Lamotrigine
  - Gabapentin
  - Tiagabine

Phenobarbital: Secondary Use of a Drug

- Launched in Germany as a "sleeping pill" in 1911

- Dr Hauptman, a psychiatry registrar in Freiburg, could not sleep because of patients' seizures!

- Prescribed Phenobarbital to the patients… and the rest is history!!!

Valproate: Serendipity

- French laboratory was screening AEDs in the mid 1950's

- Many different compounds had identical efficacy profiles

- Solvent for all was valproate… and the rest is history!

Phases of Drugs Development: Why Does It Take So Long to Get a Drug on Prescription!

- Identifying a potentially useful compound

- Pre-clinical development
  - Testing in animal models of epilepsy
    - Efficacy and tolerability
    - Pharmacokinetics (metabolism of the drug)

  - Assessing toxicology in animals
    - Potential carcinogenicity (cancer-causing)
    - Potential mutagenicity

3 – 15 years

Phases of Drugs Development: Why Does It Take So Long to Get a Drug on Prescription!

- ## Clinical development

  - ### Phase I: Drug tested in a small group of healthy people to evaluate safety, the safe dosage range, and identify side effects

  - ### Phase II: Drug given to a small group of people with the condition to see if it is more effective than placebo, and to evaluate its safety

    2 - 5 years

Phases of Drugs Development: Why Does It Take So Long to Get a Drug on Prescription!

- Clinical development

  - **Phase III:** The drug is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to other drugs or placebo, and collect safety information

  - **Phase IV:** Studies are done after the drug has been marketed to gather information on the drug's effects in various populations, and any side effects associated with long-term use
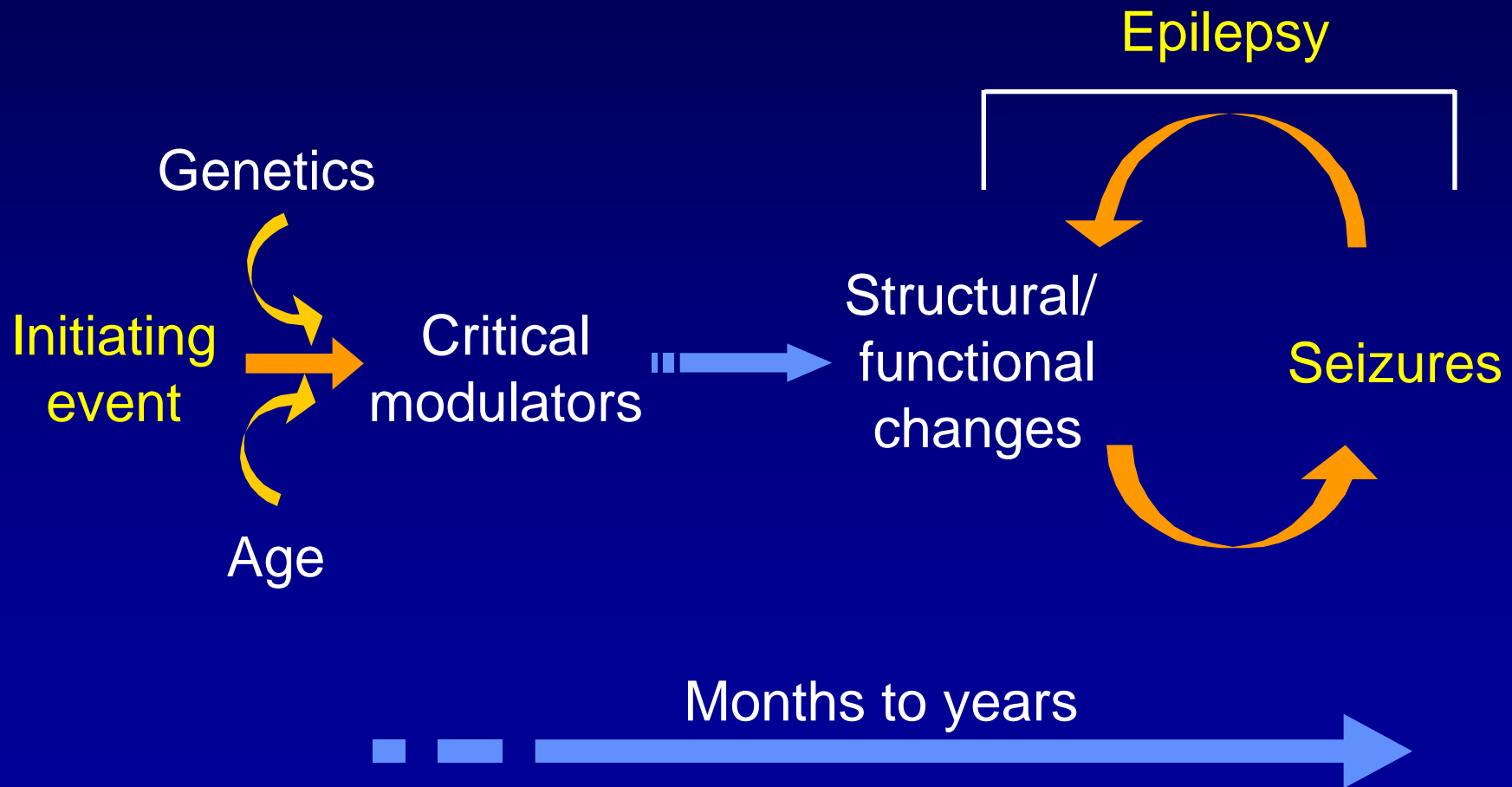
  2 – 10 years

The Quest for Potential New Antiepileptic Therapies I

- Old targets of drugs revisited
  - Inhibitory Transmission (GABAergic system)
  - Excitatory Transmission (NMDA receptor modulation)
  - Ion Channels
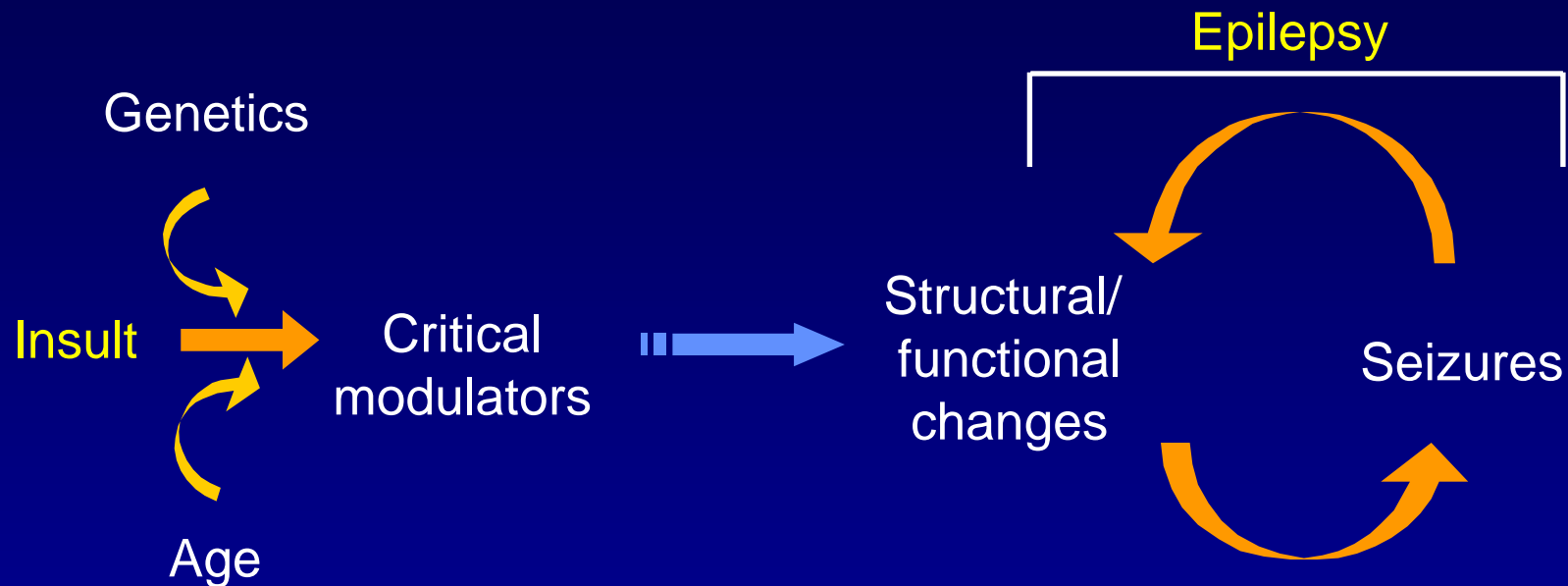   - Sodium
    - Calcium
    - Potassium

The Quest for Potential New Antiepileptic Therapies II

- Novel targets in the functional "cascade" of epilepsy
  - "Disease Modification"
    - Anti-epileptogenic

Functional cascade in refractory epilepsy

Epilepsy

Genetics

Initiating event

Age

Critical modulators

Structural/ functional changes

Seizures

Months to years

Potential new targets for treatment

Genetics

Insult → Critical modulators → Structural/ functional changes ⇄ Seizures

Age

Epilepsy

- BLOCK induction of critical modulators
- PREVENT structural and functional changes that contribute to increased excitability
- Identify and TREAT PROPHYLACTICALLY people at risk
- ?? PREVENT/DELAY the emergence of therapy-resistant epilepsy ??

The Quest for Potential New Antiepileptic Therapies III

- Role of gap junction?
  - Do epileptic discharges travel sideways?!

The Quest for Potential New Antiepileptic Therapies IV

- Novel approaches to drug delivery
  - Local delivery to epileptic focus

- "New" Neurotransmitter systems?
  - SV2A story!

The Quest for Potential New Antiepileptic Therapies V

- Mechanisms of Drug Resistance
  - Transporter Proteins

- Pharmacogenetics

Mechanisms of Drug Resistance

- MDR genes promotes resistance to drugs
  - Transporter Proteins

- Many AEDs need "transporters" to get into the brain

- Role in resistance to AEDs?

- Manipulation of transporter proteins?

Pharmacogenetics

- Susceptibility to epilepsy may be genetically determined
  - interaction with environment?

- Response to AEDs may be genetically determined

- Need to work out the "genetic blueprints" of the epileptic process and of drug sensitivity
  - Will this identify responders to drugs?
  - Will this identify people at risk of side effects?

The Quest for Potential New Antiepileptic Therapies VI

- Local thermo-regulation

  - At site of epileptic focus

- Deep brain stimulation

AEDs in the Pipeline

Phase I	*Phase II*	*Phase III*
AWD 131-138	BIA-2093	Losigamone
CGX 1007#	Carabersat*	Milacemide
DP-VPA	Fluorofelbamate	**Lacosamide**
Seletracetam	**Brivaracetam**	Stiripentol
Isovaleramide	MDL27192	Ganaxolone
	Safinamide	Rufinamide
	Talampanel*	
	Valrocemide	

Emerging AEDs: Conclusions I

- New antiepileptic drugs are still needed

- Anti-epileptogenic rather than anti-seizure

Emerging AEDs: Conclusions II

- New ways to assess potential therapies need to be developed

- Pharmacogenetics hold most promises!
  - 10 years away?

- Nevertheless, promising new AEDs are in the pipeline!!