Antiepileptic drugs in neuroprotection

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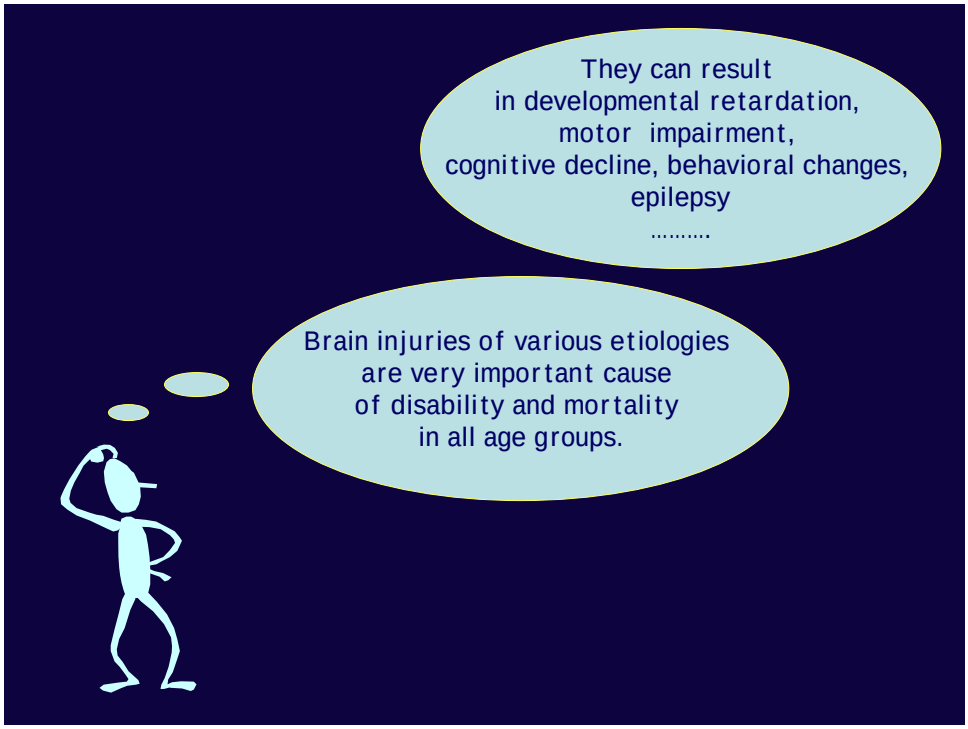


Incidence of selected brain injuries:

- Stroke

183 per 100 000

- 4/1000 in neonates
- 2.7/100 000 in children

- Head trauma

101 major TBI per 100 000

Higher rate in adolescents and young adults

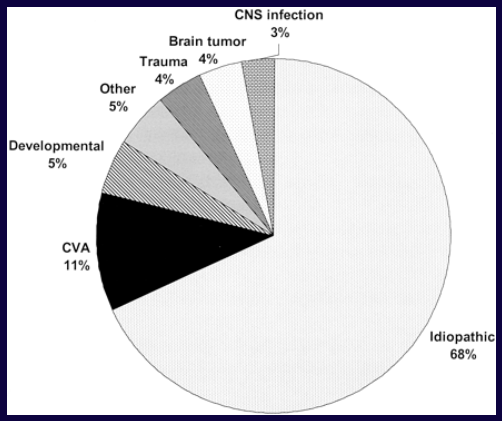
- Status epilepticus

prevalence 0.1%

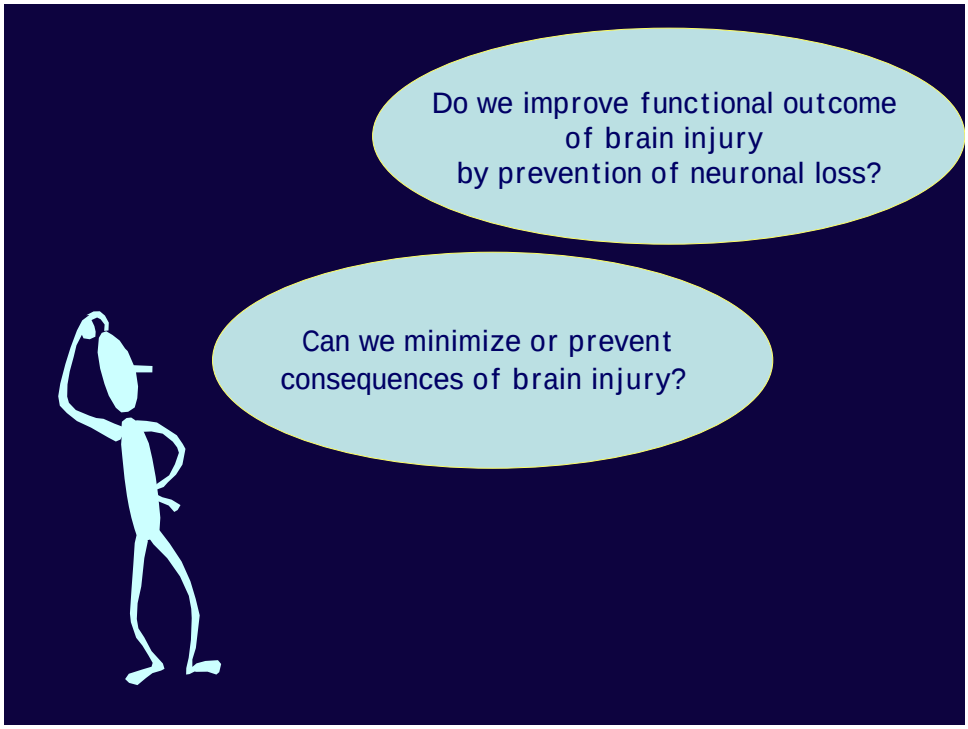
- 180 000 episodes of SE per year in USA and 365 000 episodes in Europe)
- 50% of the cases occurring in children younger than 2 years

Causes of epilepsy

The proportions of epilepsy from each type of brain injury approximate the attributable risk for that brain injury



(Herman, 2002)



Neuroprotection

- Which drugs to use
- When to start treatment
- How long to continue neuroprotective therapy
- How to select patients

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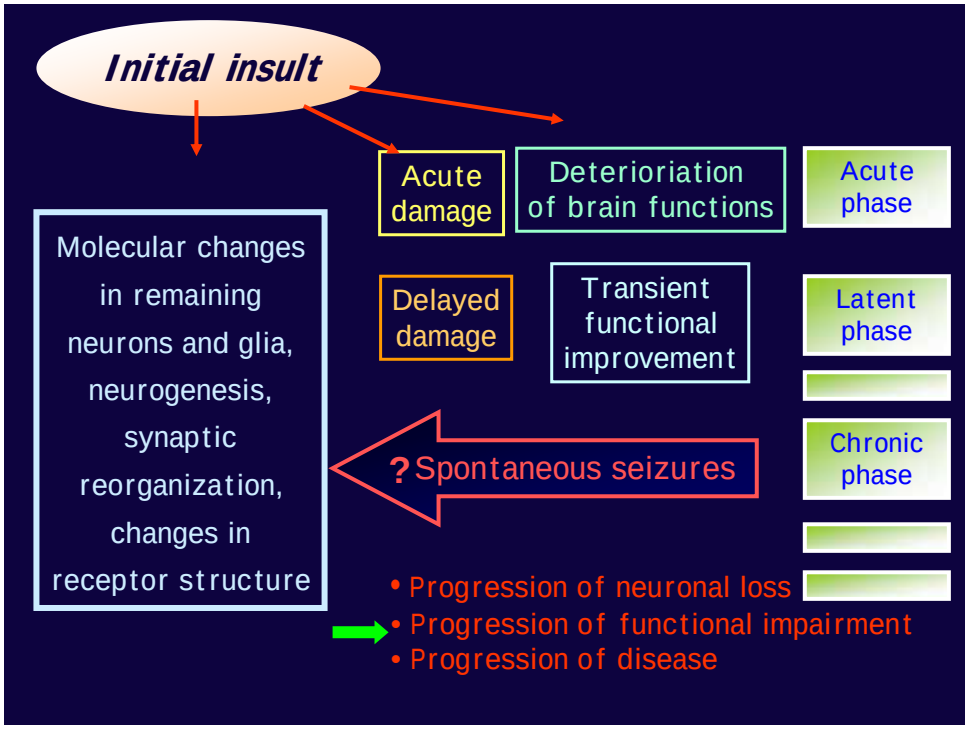
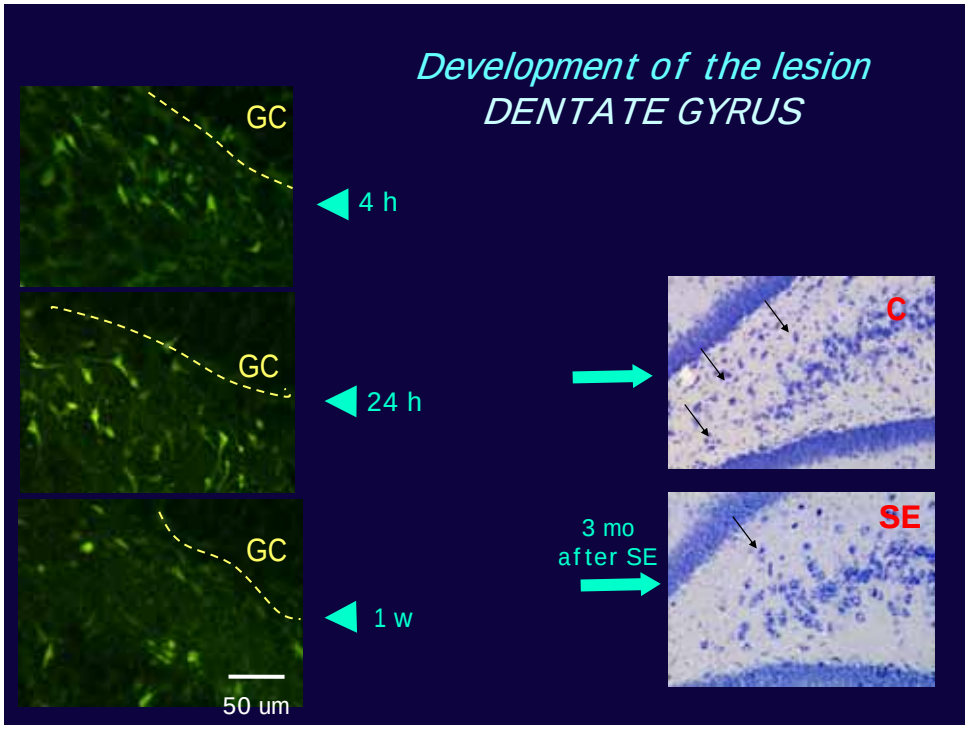
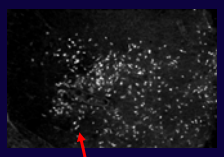
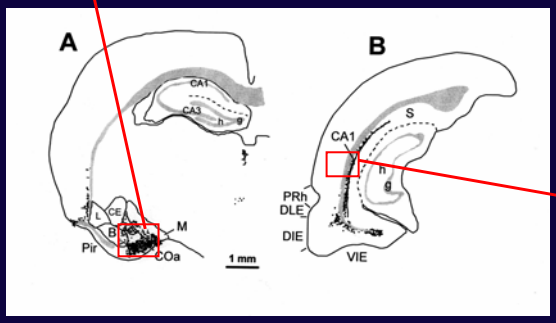

Initial insult
Acute damage
Deterioriation of brain functions
Acute phase
Molecular changes in remaining neurons and glia, neurogenesis, synaptic reorganization, changes in receptor structure
Delayed damage
Transient functional improvement
Latent phase
? Spontaneous seizures
Chronic phase
• Progression of neuronal loss
• Progression of functional impairment
• Progression of disease

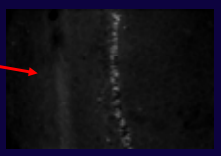

Development of the lesion
DENTATE GYRUS
GC
4 h
GC
24 h
GC
1 w
50 um
C
3 mo after SE
SE

Continuous neurodegeneration



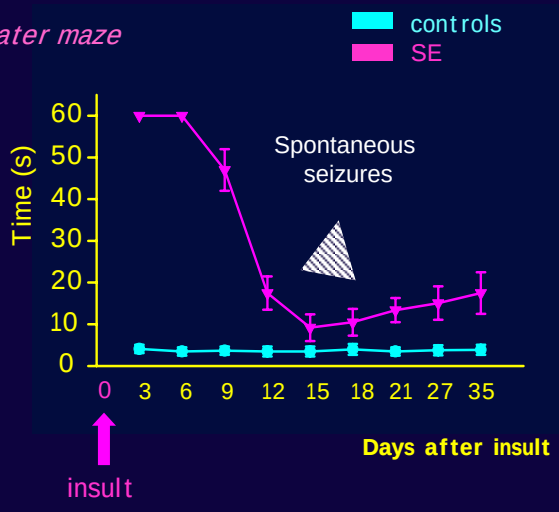
Degenerating neurons 5 mo after SE
(animal with spontaneous seizures)

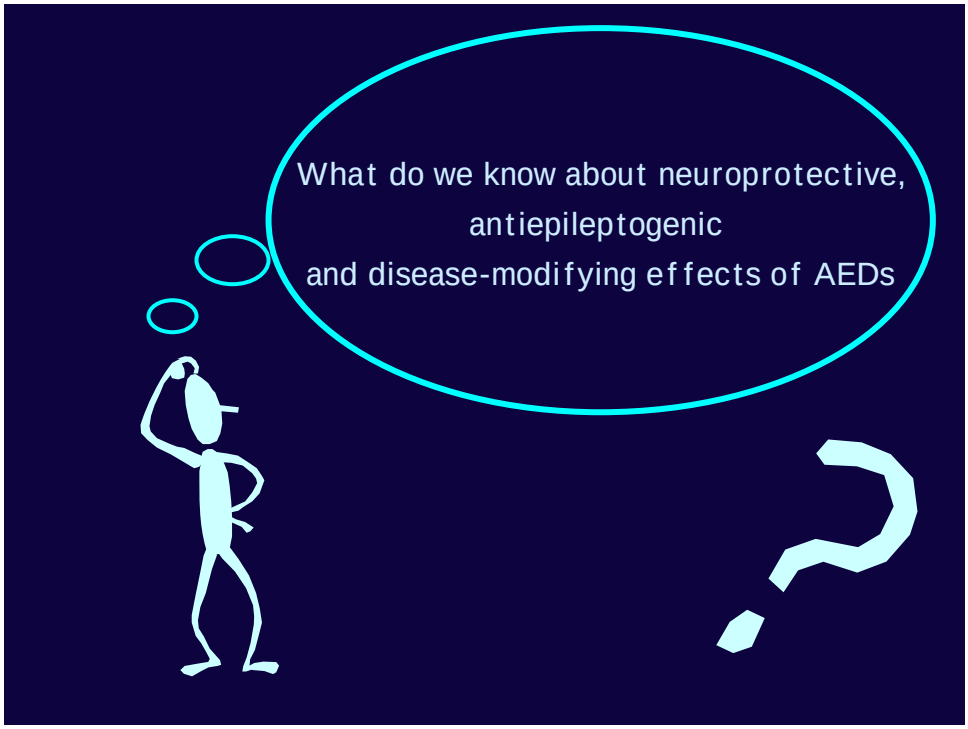


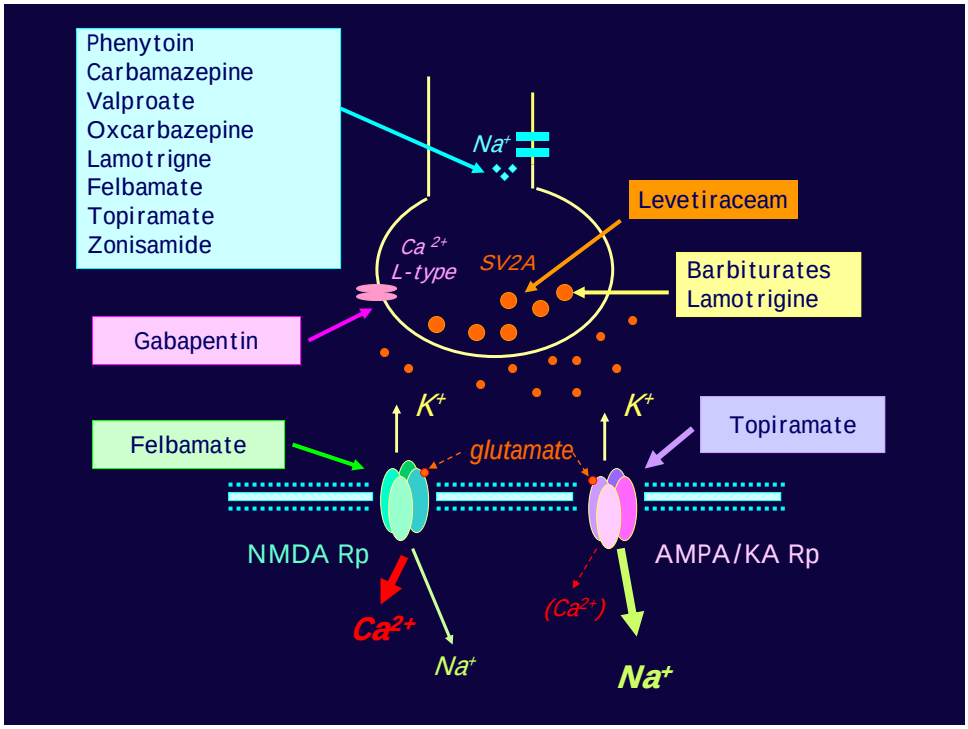


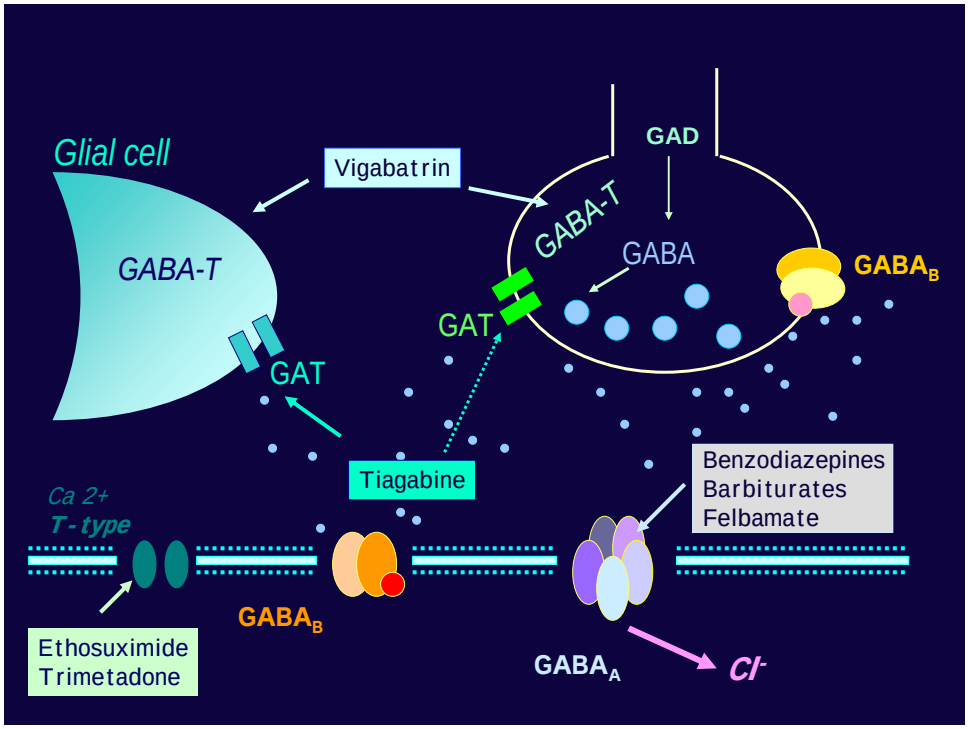
Development of cognitive impairment after brain insult.

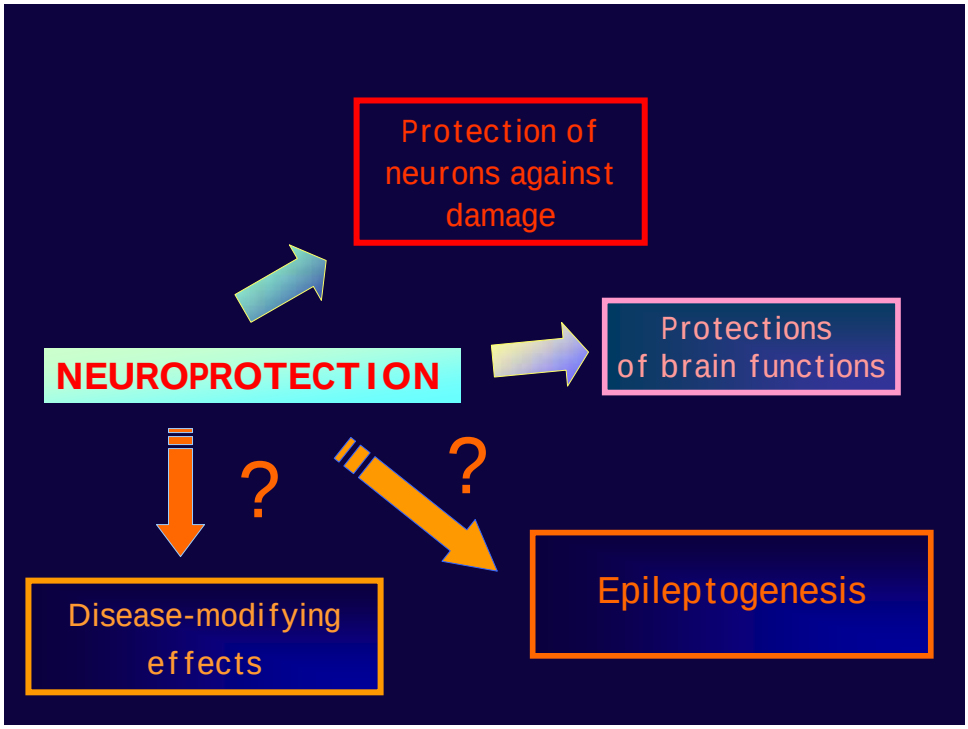
Morris water maze




What do we know about neuroprotective,
antiepileptogenic
and disease-modifying effects of AEDs


Phenytoin
Carbamazepine
Valproate
Oxcarbazepine
Lamotrigne
Felbamate
Topiramate
Zonisamide
Na+
Levetiraceam
Ca 2+
L-type
SV2A
Barbiturates
Lamotrigine
Gabapentin
K+
K+
Topiramate
Felbamate
glutamate
NMDA Rp
AMPA/KA Rp
Ca2+
Na+
(Ca2+)
Na+


Glial cell
GABA-T
Vigabatrin
GAD
GABA-T
GABA
GABA$_B$
GAT
GAT
Tiagabine
Benzodiazepines
Barbiturates
Felbamate
Ca 2+
T - type
Ethosuximide
Trimetadone
GABA$_B$
GABA$_A$
Cl$^-$


Protection of neurons against damage
NEUROPROTECTION
Protections of brain functions
?
?
Disease-modifying effects
Epileptogenesis

Classical AEDs

	Ischemia-induced damage	SE-induced damage
Carbamazepine	±0 or ⇩	n.d.
Clobazam	n.d.	n.d.
Clonazepam	⇩	n.d.
Ethosuximide	n.d.	n.d.
Oxcarbazepine	n.d.	n.d.
Phenobarbital	n.d.	±0 or ⇩
Phenytoin	±0 or ⇩	n.d.
Primidone	n.d.	n.d.
Valproate	n.d.	±0 or ⇩

Pitkanen, 2002

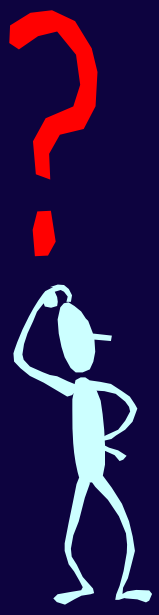
New AEDs

	Ischemia-induced damage	SE-induced damage
Felbamate	⇩	⇩
Gabapentin	n.d.	⇩
Lamotrigine	⇩	⇩
Levetiracetam	n.d.	±0
Tiagabine	⇩	n.d.
Topiramate	⇩	⇩
Vigabatrin	⇩	±0 or ⇩
Zonisamide	⇩	n.d.

Pitkanen, 2002

DRUG	Effects on memory impairment	Seizure frequency or duration
Carbamazepine	n.d.	⇩
Felbamate	⇩	⇩
Gabapentin	±0	n.d.
Lamotrigine	⇩	±0
Levetiracetam	n.d.	±0 or ⇩
Phenobarbital	±0 or ⇧	±0
Phenytoin	n.d.	±0
Topiramate	±0	⇩
Valproate	⇩	±0
Vigabatrin	±0	±0

Pitkänen and Kubová; 2004



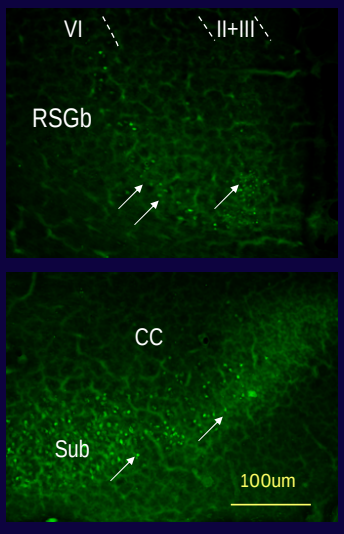
- Can neuroprotection prevent epileptogenes?
- Can effective anti-epileptogenic treatment prevent cognitive impairment?
- Can be the same therapeutic schedule used for different ages and for different insults?
- Is there genetic predisposition to develop epilepsy after the initial insult?

Future challenges

- Effects of neuroprotection on glial cells and their functions
- Additional effects of neuroprotective drugs (on metabolisms, vascularization, synaptic reorganization, etc.)
- Age-specific pattern of brain injury
- Age-specific effects of neuroprotective drugs

Neurotoxic effects of AED

- Some classical AEDs exhibit neurotoxic effects *in vivo* in immature brain (phenytoin, diazepam, phenobarbital)



What I am missing

- Detailed time profile of possible consequences – some changes can be transient
- Spontaneous behavior (open field)
- Anxiety (elevated plus maze, open field)
- Social behavior
- Non-associative learning (habituation)

What I am missing

- More different tests to assess cognitive impairment
- VideoEEG monitoring at different time points
- Histological evaluation both limbic and extralimbic structures at different time points after insult

- Developmental studies
- Multicentric studies

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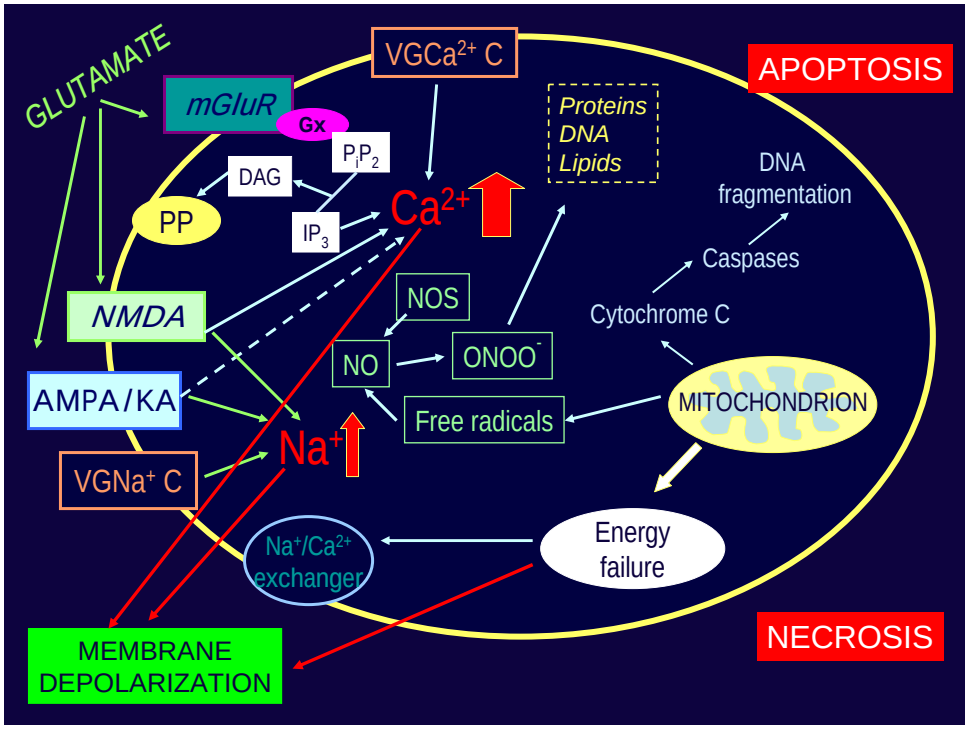
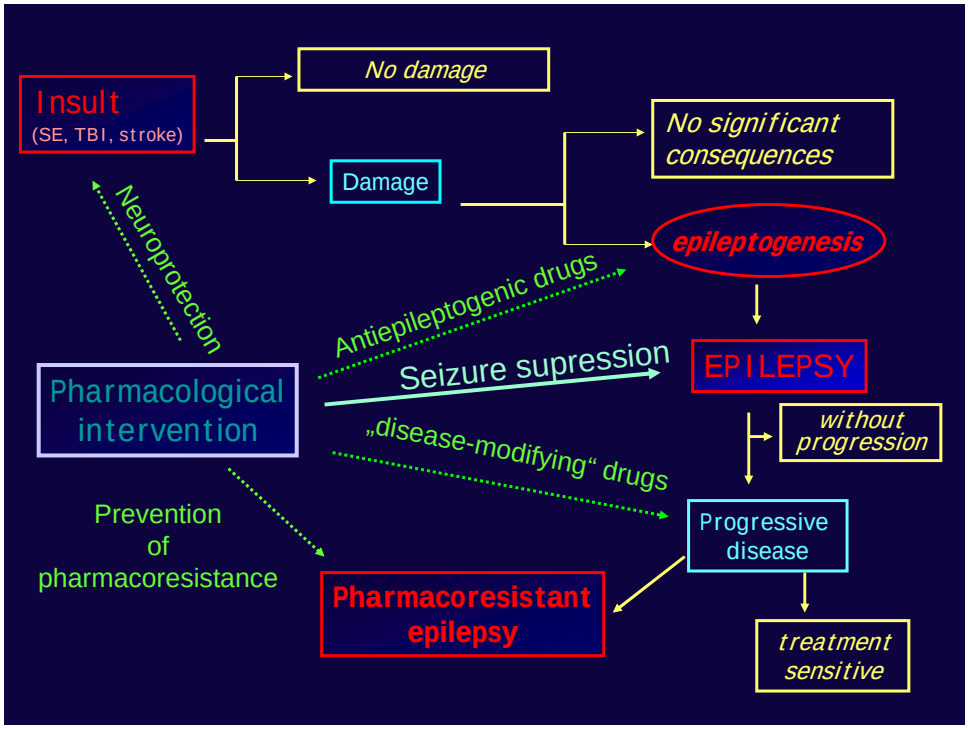


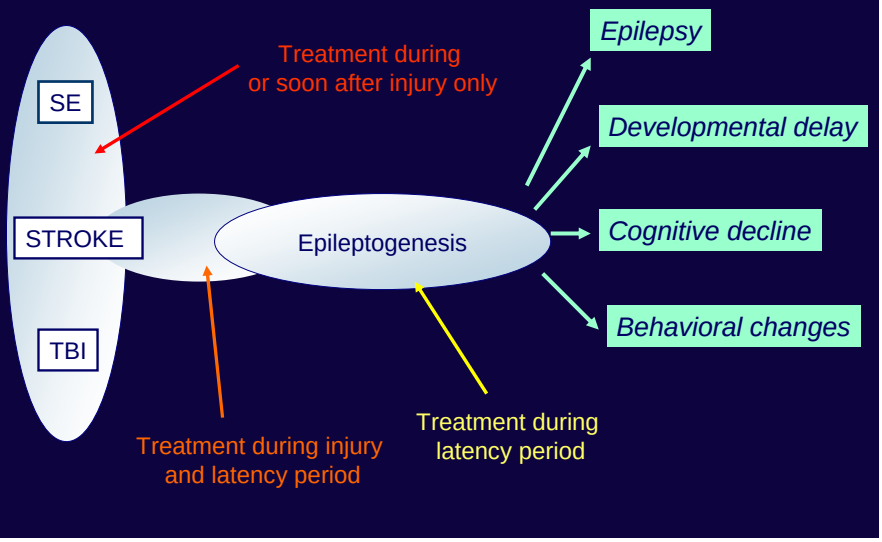
DRUG	Kindling development	Seizure duration pretreatment		SE induced damage
		Spontaneous seizures	Fully kindled seizures	
Carbamazepine	± 0 or ↑	↓	↓	± 0 or ↓ or ↑
Clobazam	↓	n.d	↓	n.d
Clonazepam	↓	n.d	↓	n.d
Ethosuximide	↓	↓	± 0	n.d
Felbamate	n.d	n.d	± 0 or ↓	n.d
Gabapentin	n.d	n.d	± 0 or ↓	n.d
Lamotrigine	± 0 or ↓ or ↑	± 0	↓	± 0 or ↓
Levetiracetam	↓	± 0 or ↓	↓	n.d
Oxcarbazepine	± 0 or ↑	n.d	n.d	n.d
Phenobarbital	↓	n.d	↓	↓
Phenytoin	± 0 or ↑	n.d	↓	± 0
Primidone	n.d	n.d	± 0	n.d
Tiagabine	↓	n.d	↓	↓
Topiramate	↓	n.d	± 0 or ↓	n.d
Valproate	↓	↓	↓	± 0
Vigabatrin	↓	± 0	↓ or ↑	↓
Zonisamide	n.d	n.d	↓	n.d

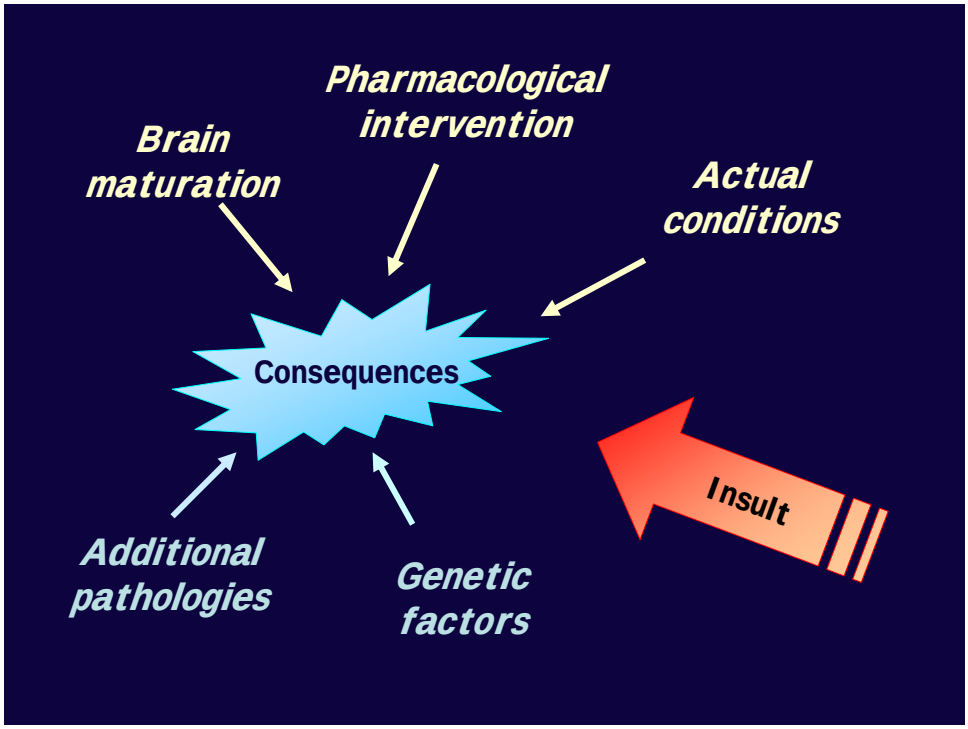


Physicians have access to a vast array of options for managing epilepsy. However, none of the past century's innovations have achieved the ultimate goal

a cure of epilepsy …

Possible timing of neuroprotection




Pharmacological intervention
Brain maturation
Actual conditions
Consequences
Insult
Additional pathologies
Genetic factors