Antiepileptic drugs in neuroprotection

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Brain injuries of various etiologies are very important cause of disability and mortality in all age groups.

They can result in developmental retardation, motor impairment, cognitive decline, behavioral changes, epilepsy

............
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)
Can we minimize or prevent consequences of brain injury?

Do we improve functional outcome of brain injury by prevention of neuronal loss?

Neuroprotection

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

...
Molecular changes in remaining neurons and glia, neurogenesis, synaptic reorganization, changes in receptor structure.

Initial insult

Acute damage

Deterioriation of brain functions

Acute phase

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

4 h

24 h

1 w

50 um

3 mo after SE

C

SE
Continuous neurodegeneration

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

Development of cognitive impairment after brain insult.

Morris water maze

controls
SE

Spontaneous seizures

Time (s)

0 10 20 30 40 50 60

Days after insult

insult

3 6 9 12 15 18 21 27 35
What do we know about neuroprotective, antiepileptogenic and disease-modifying effects of AEDs
Cl-GABA

Benzodiazepines
Barbiturates
Felbamate

GABA-T

GAT

GABA

GABA_A

GABA_B

GABA_T

GAD

Vigabatrin

Tiagabine

Ethosuximide
Trimetadone

Ca^2+ T-type

Protection of neurons against damage

Protections of brain functions

Disease-modifying effects

Epileptogenesis

NEUROPROTECTION
### Classical AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ischemia-induced damage</th>
<th>SE-induced damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>±0 or Ø</td>
<td>n.d.</td>
</tr>
<tr>
<td>Clobazam</td>
<td>n.d.</td>
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</tr>
<tr>
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Pitkanen, 2002

### New AEDs

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Pitkanen, 2002
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<th>Seizure frequency or duration</th>
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Pitkänen and Kubová; 2004

- Can neuroprotection prevent epileptogens?
- Can effective anti-epileptogenic treatment prevent cognitive impairment?
- Can 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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<th>DRUG</th>
<th>Kindling development</th>
<th>Seizure duration pretreatment</th>
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**Insult (SE, TBI, stroke)**

- **No damage**
  - **No significant consequences**
  - **epileptogenesis**

**Pharmacological intervention**

- **Seizure suppression**
  - "disease-modifying" drugs

**Prevention of pharmacoresistance**

- **Pharmacoresistant epilepsy**

**Epilepsy**

- **Progressive disease**
  - treatment sensitive
- **without progression**

**Neuroprotection**

- **Antiepileptic drugs**

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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

- **Epilepsy**
  - Treatment during or soon after injury only
- **Developmental delay**
- **Cognitive decline**
- **Behavioral changes**

Epileptogenesis

- Treatment during injury and latency period
- Treatment during latency period
Genetic factors

Brain maturation

Pharmacological intervention

Additional pathologies

Consequences

Genetic factors

Insult

Actual conditions