Review of the Mechanisms of Action of Antiepileptic Drugs

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Contents

Summary ................................................................. 469
1. Antiepileptic Drugs with Effects on Sodium Channels ................................................. 471
   1.1 Carbamazepine .................................................. 471
   1.2 Phenytoin ....................................................... 471
   1.3 Lamotrigine .................................................... 472
   1.4 Oxcarbazepine .................................................. 472
2. Antiepileptic Drugs with Effects on Calcium Channels ................................................ 472
   2.1 Ethosuximide .................................................... 473
3. Antiepileptic Drugs with Effects on γ-Aminobutyric Acid (GABA) Function ..................... 473
   3.1 Phenobarbital and Benzodiazepines .................................................. 473
   3.2 Gabapentin ....................................................... 474
   3.3 Vigabatrin ....................................................... 474
   3.4 Tiagabine ........................................................ 474
4. Antiepileptic Drugs with Multiple Mechanisms of Action ............................................. 474
   4.1 Valproic Acid .................................................... 474
   4.2 Felbamate ....................................................... 475
5. Conclusions .......................................................... 475

Summary

Antiepileptic drugs (AEDs) have measurable effects on neuronal membrane and synaptic function. These mechanisms of action partially predict effectiveness in animal models of epilepsy and in human epilepsy. Carbamazepine, phenytoin, lamotrigine, oxcarbazepine and valproic acid (sodium valproate) block voltage-dependent sodium channels. Ethosuximide reduces T-type calcium currents. Phenobarbital (phenobarbitone), benzodiazepines, gabapentin, vigabatrin, tiagabine, valproic acid and felbamate enhance the neuronal inhibition induced by γ-aminobutyric acid (GABA). Felbamate also decreases the activity of excitatory neurotransmitters.

AEDs with known mechanisms of action will further increase the range of options for patients with epilepsy. A rational approach to polytherapy may emerge in the near future, in which medications with complementary, synergistic mechanisms of action are used. Until then, cautious use of medications alone and in combination, with consideration given to mechanisms of action, will enable the large majority of patients with epilepsy to achieve the best possible control of their seizures within the limits of current therapy.
Approximately 0.5 to 1.0% of the population has epilepsy, a disorder characterised by recurrent, unprovoked seizures. Seizures are subdivided into partial and generalised types. Partial seizures originate in a focal region of the cortex and may or may not spread rapidly to other cortical areas, giving complex and simple subtypes, respectively. Generalised seizures begin synchronously in widespread, bilateral cortical regions. Approximately 70 to 80% of patients will achieve complete seizure control with minimal adverse effects on single-drug therapy, while combinations of antiepileptic drugs (AEDs) enable an additional 10 to 15% of patients to achieve seizure control without significant adverse effects.

Merritt and Putnam[1,2] are credited with the earliest attempt at testing compounds for potential use as AEDs, using an animal model of seizures. They demonstrated that phenytoin stopped maximal electroshock (MES) seizures in animals. After these pioneering efforts, other animal seizure models were described and other potential AEDs were developed that showed efficacy in these models. Still more recently, the cellular mechanisms of seizures have begun to be characterised, including abnormal neuronal membrane ionic conductance and abnormal synaptic influences of excitatory and inhibitory neurotransmitters. These discoveries have further helped to screen potential new AEDs.

With the rapid proliferation of animal seizure models, cellular theories of epileptogenesis and new AEDs, correlations have emerged between the in vitro cellular action of an AED, the animal model of epilepsy for which the AED is most effective and the type of human seizure that best responds to treatment with that AED. For example, carbamazepine and phenytoin both prevent MES-induced seizures and both inhibit voltage-dependent neuronal sodium channels (see sections 1.1 and 1.2). Both actions are predictive of efficacy against tonic seizures.

Insight into these correlations has given rise to the current era of AED development, and underscores the importance of understanding the basic mechanisms of AEDs.[3] These actions are summarised in table I.

This review focuses on the mechanisms of action of AEDs, including well established, newly approved and investigational AEDs. The AEDs have been subdivided into those that affect neuronal membrane ion channels, those that enhance γ-aminobutyric acid (GABA) function and those that have multiple mechanisms of action. Unless otherwise specified, the in vitro actions described in this

### Table I. Probable mechanisms of action of antiepileptic drugs

<table>
<thead>
<tr>
<th>Antiepileptic drug/class</th>
<th>Mechanism of action</th>
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</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Prolong GABA-mediated chloride channel openings</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Blocks voltage-dependent sodium channels</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Modifies low-threshold T-type calcium currents</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Blocks NMDA receptors; potentiates GABA-mediated inhibition</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Binds to gabapentin receptor</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Blocks voltage-dependent sodium channels, resulting in decreased release of glutamate and aspartate</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Blocks voltage-dependent sodium channels</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Blocks voltage-dependent sodium channels</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Inhibits GABA uptake into neurons and glia</td>
</tr>
<tr>
<td>Valproic acid (sodium valproate)</td>
<td>May block voltage-dependent sodium channels; enhances postsynaptic GABA-mediated inhibition</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Irreversibly inhibits GABA transaminase</td>
</tr>
</tbody>
</table>

**Abbreviations:** GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate.