Mechanisms of action of antiepileptic drugs

Epilepsy affects up to 1% of the general population and causes substantial disability. The management of seizures in patients with epilepsy relies heavily on antiepileptic drugs (AEDs). Phenobarbital, phenytoin, carbamazepine and valproic acid have been the primary medications used to treat epilepsy for several decades. Since 1993 several AEDs have been approved by the US FDA for use in epilepsy. The choice of the AED is based primarily on the seizure type, spectrum of clinical activity, side effect profile and patient characteristics such as age, comorbidities and concurrent medical treatments. Those AEDs with broad-spectrum activity are often found to exert an action at more than one molecular target. This article will review the proposed mechanisms of action of marketed AEDs in the US and discuss the future of AEDs in development.

KEYWORDS: AEDs ■ anticonvulsant drugs ■ antiepileptic drugs ■ epilepsy ■ mechanism of action ■ seizures

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The therapeutic armamentarium for the treatment of seizures has broadened significantly over the past decade [1]. Many of the newer antiepileptic drugs (AEDs) have clinical advantages over older, so-called 'first-generation' AEDs in that they are more predictable in their dose–response profile and typically are associated with less drug–drug interactions. In addition, many of the newer AEDs also have unique mechanisms of action compared with previously available agents. First-generation AEDs are proposed to have a couple of primary mechanisms of action. Sodium channel blockade and GABA potentiation both result in a reduction of neuronal discharge. More recent AEDs that have been approved have provided more of a variety in drug targets, such as specific GABA subunits and synaptic vesicle inhibition. Currently, there are several viable agents in the AED pipeline that expand the spectrum of effective mechanisms of action even further (Table 1).

Such a variety of pharmacologic targets for the treatment of seizures is desirable for several reasons. First, more specific targeting of receptors implicated in seizure propagation may lead to less adverse effects (both neurologic and otherwise). Second, currently available AEDs are not often broadly active in numerous models of seizure. By increasing the variety of pharmacologic targets, less common and more treatment refractory seizure disorders may gain viable treatment options. Finally, utilizing a combination of AEDs with multiple mechanisms of action may allow for synergistic activity, particularly for patients with refractory seizures. The aim of this article is to discuss the past, present and future of AED pharmacology and mechanisms of action.

First-generation AEDs

Broadly, the mechanisms of action of AEDs can be categorized by their effects on the neuronal action potential or their post-synaptic inhibition of neuronal impulse generation. Inhibition of the neuronal action potential is typically focused on the activation of voltage-gated channels involved in the electrical propagation of the seizure. Sodium channels are integral to the action potential and neuronal depolarization. The fulfilled action potential typically results in the release of a neurotransmitter, which further propagates the signal at a neuronal synapse or results in a terminal effect on the brain or other neurons leading to extracranial organs.

■ Sodium channel blockade (fast inactivation)

Inhibition of sodium channels is the most common mechanism of action of the early first-generation AEDs (Figure 1). During the neuronal action potential, sodium concentrations spike upwards once the depolarization threshold is reached. The large extracellular sodium concentration, as well as negative electrical gradient inside the cell, creates a significant influx of sodium when the voltage-gated sodium channels are opened. Agents such as first-generation AEDs phenytoin, carbamazepine and valproate, as well as second generation AEDs

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Table 1. Summary of antiepileptic drugs' proposed mechanisms of action.

Mechanism of action	Effect on neuronal transmission	First-generation AEDs	Second/third-generation AEDs	AEDs under development
Sodium channel blockade (fast inactivation)	Slowed recovery from inactivated state	Phenytoin Carbamazepine Valproate	Topiramate Zonisamide Oxcarbazepine Lamotrigine Felbamate Rufinamide	
Calcium channel blockade	Post-synaptic inhibitory action	Ethosuximide (T-type) Valproate	Topiramate Zonisamide (T-type) Gabapentin Lamotrigine Pregabalin	
GABA agonism/potentiation	Inhibitory activity by permitting hyperpolarization	Benzodiazepines Barbiturates Valproate	Felbamate Topiramate Vigabatrin Stiripentol	Retigabine Neurosteroids
NMDA receptor blockade	Decreased excitatory synaptic activity		Felbamate	
AMPA receptor blockade	Decreased excitatory synaptic activity		Topiramate	
SV2a vesicle inhibition	Decreased excitatory synaptic activity		Levetiracetam	Seletracetam Brivaracetam
Sodium channel blockade (slow inactivation)	Recovery of neurons from prolonged depolarization		Lacosamide	
Potassium channel blockade		Oxcarbazepine	Topiramate	
Potassium channel activation				Retigabine

For more information about drug–drug interactions and adverse effects with individual agents, readers may refer to the prescribing information for the individual agents or several recent reviews [37–40].
AED: Antiepileptic drug; NMDA: N*-methyl-*D*-aspartate; SV2a: Synaptic vesicle protein 2a.*

oxcarbazepine and lamotrigine, work in this manner. The principle example of a sodium channel blocker is phenytoin, which blocks voltage-gated sodium channels in the motor cortex and seems to block repetitive firing of neurons, but has little impact on neurons with a low rate of firing [2,3]. Therefore, there is a greater effect of phenytoin on neurons with more pronounced depolarization or more frequent firing.

Phenytoin reduces inward sodium movement by binding to inactivated voltage-gated channels after depolarization and modifying their sodium permeability. This results in an increase in the inactivation (or refractory) period of frequently firing neurons. Phenytoin also appears to diminish the amplitude of the action potential and slows neuronal conduction, both likely related to sodium channel inhibition [3]. Interestingly, it appears as though lamotrigine, carbamazepine and phenytoin all bind to the same receptor on the extracellular aspect of the voltage-gated sodium channel, suggesting that each of the drugs may compete with the other for occupancy of available receptors [4].

GABA potentiation

Potentiation or agonism of GABA receptors and their inhibitory chloride channels is another common mechanism of action for first-generation AEDs, particularly benzodiazepines. Rather than modifying the influx of cations, GABA agonists push the neuron to hyperpolarization by opening chloride channels. Barbiturates also activate GABA receptors by binding to a different site than benzodiazepines. Valproic acid promotes the formation and inhibits the endogenous degradation of GABA, although the clinical impact of this mechanism of action is ill-defined [2].

Benzodiazepines bind to $GABA_A$ receptors between the α and γ subunits, primarily α-1 and γ-2 [5]. This extracellular binding opens the chloride channel and permits chloride influx due to the extracellular concentration gradient. Various α subunits are present in human neurons, most of which exhibit similar benzodiazepine binding. Subsequent hyperpolarization decreases the membrane potential of neurons, making generation of an action potential more unlikely and abrogating the depolarized state of activated neurons.

Barbiturates binding to $GABA_A$ receptors differs from benzodiazepines in that the binding site is in the membrane portion of the receptor [5]. This induces a conformational change in the chloride channel that permits influx. Barbiturates also appear to potentiate GABA (and benzodiazepine) activity by enhancing the inhibitory response to endogenous GABA [2]. Barbiturates vary subtly in their structure, which confers a spectrum of sedative effects (i.e., pentobarbital and thiopental being very sedating, phenobarbital being minimally sedating).

Calcium-channel blockade

Blockade of calcium channels also confers some antiepileptic activity. Calcium channels are evident in presynaptic neurons and are involved in neuronal depolarization. Ethosuximide is a unique agent used for absence seizures, which appears to inhibit low threshold calcium channels in thalamic neurons [2]. Valproate appears to have similar activity at these T-channels, which also makes this agent helpful for absence seizures. Some evidence suggests that phenytoin may have some activity in inhibiting calcium channel activation presynaptically. Other agents such as felbamate, which antagonizes glutamate–NMDA receptors, and barbiturates, which attenuate the response to excitatory neurotransmitters such as glutamate, inhibit calcium influx postsynaptically.

New generation of AEDs

The current and future generations of AEDs will include a variety of new pharmacologic targets, more specific binding of previously targeted mechanisms of action and molecules similar to currently available AEDs that exhibit dramatically decreased rates of toxicity. Drug development efforts are also aimed at providing AEDs that are more tolerable and less associated with complex drug–drug interactions.

SV2a vesicle inhibition

Levetiracetam is the first of several agents able to inhibit the synaptic vesicle protein 2a (SV2a) [6]. SV2a appears to be integral to the process of neurotransmitter exocytosis into the synaptic cleft. Inhibition of this protein appears to result in a broad-spectrum attenuation of excitatory activity. Brivaracetam and seletracetam are more potent inhibitors of this presynaptic protein and may provide an even broader spectrum of antiepileptic activity over levetiracetam if they ultimately garner US FDA approval [7]. In particular, brivaracetam may have added activity, as it also inhibits fast inactivation of voltage-gated sodium channels [8,9].

NMDA receptor blockade

N-methyl-D-aspartate (NMDA) receptor antagonists act on membrane-associated postsynaptic calcium channels [10]. The NMDA receptor interacts with the excitatory neurotransmitter, glutamate, and allows calcium influx into the neuron. This represents one of the major mechanisms for neurotoxicity during traumatic brain injury, stroke and status epilepticus. Several agents can inhibit the action of glutamate on the NMDA receptor, including topiramate and zonisamide [11]. Other older agents, such as felbamate and phenobarbital, may have some modicum of inhibition at the NMDA receptor, although it does not appear that this is the principal mechanism of action of these AEDs. The anesthetic ketamine also inhibits NMDA receptors, which likely imparts the efficacy of ketamine in late, refractory status epilepticus [12].

Potassium channel potentiation

In addition to increasing the level of newly synthesized GABA, retigabine's antiepileptic properties are largely due to its ability to activate and prolong the opening of neuronal potassium KCNQ2 (Kv7.2) and KCNQ3 (Kv7.3) channels [13,14].

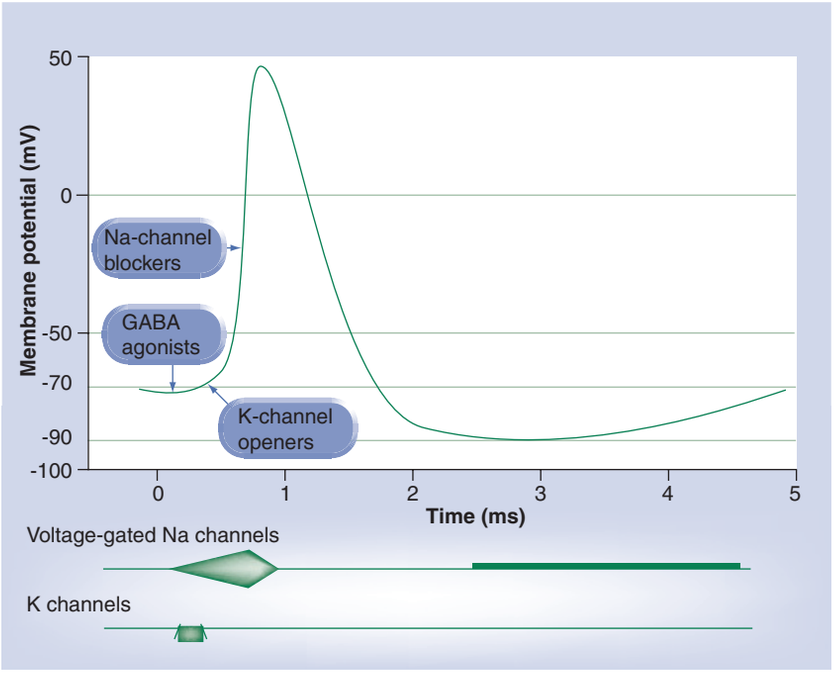

Figure 1. Effects of antiepileptic drugs on the neuronal action potential.

Sodium channel blockade (fast inactivation)

Rufinamide showed broad-spectrum anticonvulsant properties. The principal mechanism of action of rufinamide is considered to be suppression of neuronal hyperexcitability by prolongation of the inactive state of voltage-gated sodium channels. Rufinamide was found to be effective in the treatment of patients with Lennox–Gastaut syndrome [15,16].

Sodium channel blockade (slow inactivation)

Slow inactivation of voltage-dependent sodium channels appears to be a separate and novel mechanism of inhibiting sodium influx in depolarizing neurons. Lacosamide is the first AED available that promotes slow inactivation of sodium channels. Whereas fast inactivation of sodium channels with older AEDs, such as phenytoin and carbamazepine, tends to have effects on frequently firing neurons, slow inactivation occurs in neurons, which are repetitively discharged and have prolonged depolarization. Slow inactivation probably involves a structural alteration to the sodium channel that develops over a more prolonged period of time than fast-inactivation [17]. At this point, the clinical role of lacosamide seems to be a viable option for patients with refractory partial epilepsy and in status epilepticus [18,19].

GABA potentiation

Augmentation of GABAminergic inhibition of neurons can also be achieved by new methods aside from enhancing the endogenous activity of GABA (as previously discussed). Vigabatrin, a structural analog of GABA, inhibits GABA-transaminase, which is the enzyme responsible for degrading GABA in the synaptic cleft, thereby increasing GABA concentrations [11]. Tiagabine also increases GABA concentrations, but, unlike vigabatrin, does so by decreasing glial and neuronal uptake of GABA [11]. Topiramate, among its numerous mechanisms of antiepileptic activity, also appears to enhance GABA activity [20]. Retigabine, currently under review for approval by the FDA, also likely increases GABA synthesis [21]. Neuroactive steroids (e.g., ganaxolone) also augment GABA inhibition by binding a steroid receptor on the GABA complex, increasing the permeability of the chloride channel [22]. Stiripentol appears to enhance central GABA transmission by increasing the duration of opening of $GABA_A$ receptor channels in hippocampal slices. Stiripentol is the only drug specifically indicated for use in severe myoclonic epilepsy of infancy (also known as Dravet syndrome) [23,24].

Calcium channel blockade

Gabapentin was initially synthesized to mimic the chemical structure of GABA, but it is not believed to act on the same brain receptors. Gabapentin was shown to bind to the $\alpha 2\delta$ subunit of the voltage-dependent calcium channel in the CNS [25].

Like gabapentin, pregabalin binds to the $\alpha 2\delta$ subunit of the voltage-dependent calcium channel in the CNS. Pregabalin decreases the release of neurotransmitters such as glutamate (excitatory neurotransmitter), noradrenaline and substance P. Pregabalin increases neuronal GABA levels by producing a dose-dependent increase in glutamic acid decarboxylase (GAD). GAD converts glutamate into the inhibitory GABA [26].

AMPA receptor blockade

Perampanel, currently in Phase III development for epilepsy, has shown in preclinical studies to inhibit AMPA-induced increases in intracellular calcium concentration [27]. Agents that inhibit or decrease the AMPA receptor activity have the potential to reduce excessive excitatory responses and confer neuroprotection [28].

General characteristics of future AEDs

The future of AED development will likely incorporate many of our currently available drug entities, while also building upon new science and discovery in drug delivery. Many of the older AEDs are limited by severe adverse effects, cumbersome drug–drug interactions and a narrow therapeutic index. Felbamate is a unique example of a newer AED with severe toxicity and adverse event problems. Severe aplastic anemia and hepatic failure have both occurred with felbamate. It seems as though the reactions are idiosyncratic with little indication of predictive factors for developing one of these devastating side effects. Phenytoin is another example of an AED with characteristic adverse effects. Some adverse effects are drug entity-specific, such as the risk of hydantoin hypersensitivity syndrome, which presents as a Stevens–Johnson Syndrome-like rash, usually after 1–2 weeks of use. Other effects are related to the intravenous formulation, such as purple-glove syndrome, which causes digital thrombosis and ischemia, likely due to the dramatically elevated pH of the phenytoin solution for injection.

Newer AEDs that are available now or are likely to be available in the future are less associated with severe reactions. A classic example of this is the development of the more water soluble prodrug, fosphenytoin. This improved method of delivering phenytoin intramuscularly or intravenously has mitigated the formulation-related adverse effects to some extent, although the drug entity-specific adverse effects remain.

Drug–drug interactions with older AEDs are frequent and commonly alter concomitantly administered medications. The cytochrome p450 (CYP450) system participates prominently in a host of endogenous metabolic pathways [29]. Several of these, including exogenous drug metabolism, vitamin D and bone metabolism, gonadal steroid metabolism and the metabolism of cholesterol and other markers of vascular risk, have been shown to be affected by the inducing AEDs. Hepatic induction by barbiturates, carbamazepine and phenytoin can decrease the serum concentrations of other hepatically metabolized medications, typically by induction of the CYP450 enzyme system. Patients with complicated medication regimens for other disease states, such as HIV, are particularly affected by these drug–drug interactions [30]. Other medications, such as warfarin, cyclosporine, voriconazole and many other hepatically metabolized AEDs such as felbamate and carbamazepine, may have lower serum concentrations after enzyme induction. Inhibition of hepatic metabolism is also evident with some AEDs such as valproic acid. These agents can increase some concomitant medications (such as amitriptyline, lamotrigine and nifedipine) to potentially toxic concentrations [31]. The classic complex drug–drug interaction between AEDs is phenytoin and valproic acid, where phenytoin induces valproic acid metabolism. Simultaneously, valproic acid inhibits phenytoin metabolism and increases the fraction of unbound drug due to another type of drug–drug interaction mechanism, displacement of plasma protein binding. Newer AEDs, such as lacosamide, pregabalin and levetiracetam, do not induce or inhibit hepatic CYP450 enzyme function, therefore making these drugs much less likely to impact the biotransformation of concomitant medications [32,33].

The pharmacokinetics of older AEDs tend to exhibit marked inter-individual variability. Routine therapeutic drug monitoring is necessary for many of the older AEDs, such as phenobarbital, carbamazepine, valproic acid and phenytoin. Dosing is often based on body weight and fluctuations in bioavailability may require a wide range of doses among different patients, depending on their body size and composition. Extensive plasma protein binding (primarily albumin) is also often a factor that can affect the total concentration of some of the older AEDs, such as valproic acid and phenytoin. In addition, it is becoming more apparent that some older AEDs may be subject to pharmacogenetic variations in metabolic capacity, which may also affect the dose requirements of certain individuals. One of the focuses of the development of new AEDs appears to be the development of pharmaceutical preparations that yield consistent, predictable bioavailability that exhibit low interpatient variability and that are not subject to genetic polymorphisms that may impact the disposition and elimination of these medications.

Antiepileptic drug therapy may also be impacted by other advances aside from new agents. In models of drug-resistant epilepsy, it appears that drug efflux pumps may be responsible for pumping out AEDs, thereby making the tissue concentrations of pharmacotherapy lower than would be expected by the corresponding serum concentrations. Modulation of drug efflux transporters has the potential to reverse treatment failure in patients with drug-resistant epilepsy by preserving AED concentrations in astrocytes and neurons [34]. Unique drug-delivery strategies are already in use, such as osmotic pump tablets for extended-release preparations. However, novel strategies that maximize the delivery of the AED into the target tissue are promising alternatives under development. Nanoparticles appear to aid in the solubility of hydrophobic AEDs, as well as increase the blood–brain barrier penetration of medications. Liposomal formulations are amphiphilic carriers, which can be used to deliver AEDs in carefully selected locations based on temperature or pH. Liposomes can also facilitate the delivery of drug substances directly into the intracellular environment. Intranasal and rectal formulations for immediate delivery when the oral and intravenous routes are acutely unavailable are also already available, but being refined to optimize drug delivery and to expand the number of medications available by these alternative routes. Readers are referred to a recent excellent review on new drug-delivery options [35].

Conclusion & future perspective

As reviewed in this article, the current AEDs under development in Phase III trials include brivaracetam, ganaxolone, retigabine and

perampanel. A total of seven additional AEDs in development appear promising. These include: 2-deoxy-glucose, huperizine A, ICA-105665, NAX-5055, T-2007, valnoctamide and YK3089. The reader can find a more in-depth review on new AEDs in different stages of development in the progress report on new AEDs by Bialer *et al.* [36].

The currently available anticonvulsant agents suppress the symptoms of epilepsy but are not truly antiepileptic drugs. A rational approach to prevent epilepsy would be to use drugs to target abnormal brain mechanisms that are activated during the latent period of epileptogenesis following an acquired brain injury such as trauma or stroke.

There is a growing list of a number of mutations in ion channel genes that have been implicated in various human epilepsy syndromes. As we are thinking about new drugs for preventing the development of epilepsy or for the treatment of seizures, we need to be thinking about what other targets are involved in the control of seizures and develop new therapies that would be specific to a channelopathy or epileptic syndrome.

A better understanding and knowledge of the molecular mechanisms underlying some specific epileptic syndromes may prove more successful than mass screening techniques using animal models for some of the epilepsies.

There are no randomized controlled trials indicating that antiepileptic drugs should be chosen according to the mechanism of action and undertaking such trials might be useful.

Beyond seizures, the side effects of certain AEDs represent a burden to patients and the development of rational drug designs of blockers for specific subunits of the excitatory amino acid receptors may provide therapeutic activity without the side effects of nonspecific blockers.

Efforts in order to understand the relationship between target and effect should continue to provide important information about the neuropathology of the epileptic network and to facilitate the development of novel therapies for the prevention of epileptogenesis and the treatment of medically refractory epilepsy.

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Executive summary

- There are a number of multiple molecular targets for various antiepileptic drugs. They primarily include GABA receptors, glutamate receptors and voltage-gated ion channels. The end result of this is to stabilize neuronal function, reduce neuronal synchronization and reduce neurotransmitter and neuropeptide release. Several antiepileptic drugs of the first, second or third generation exert an action at more than one molecular target.

Future perspective

- Efforts should be made to develop new drugs with antiepileptic properties that would prevent epileptogenesis and the emergence of seizures in certain situations, such as brain injury, or that alter the underlying mechanisms of a particular epilepsy or prevent its progression.
- New therapies that would be specific to an epileptic syndrome should be developed as new mutations in ion channels implicated in certain epileptic syndromes have been discovered.
- In order to minimize side effects from antiepileptic drugs, drugs acting as blockers for specific subunits of the excitatory amino acid receptors should be designed.

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