New Molecular Targets for Antiepileptic Drugs: $\alpha_2\delta$, SV2A, and K_v7/KCNQ/M Potassium Channels

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Abstract

Many currently prescribed antiepileptic drugs (AEDs) act via voltage-gated sodium channels, through effects on γ-aminobutyric acid–mediated inhibition, or via voltage-gated calcium channels. Some newer AEDs do not act via these traditional mechanisms. The molecular targets for several of these nontraditional AEDs have been defined using cellular electrophysiology and molecular approaches. Here, we describe three of these targets: $\alpha_2\delta$, auxiliary subunits of voltage-gated calcium channels through which the gabapentinoids gabapentin and pregabalin exert their anticonvulsant and analgesic actions; SV2A, a ubiquitous synaptic vesicle glycoprotein that may prepare vesicles for fusion and serves as the target for levetiracetam and its analog brivaracetam (which is currently in late-stage clinical development); and K_v7/KCNQ/M potassium channels that mediate the M-current, which acts a brake on repetitive firing and burst generation and serves as the target for the investigational AEDs retigabine and ICA-105665. Functionally, all of the new targets modulate neurotransmitter output at synapses, focusing attention on presynaptic terminals as critical sites of action for AEDs.

Introduction

Since the 1940s, the discovery of antiepileptic drugs (AEDs) has been based on the screening of structurally diverse chemical compounds using predictive animal models. Virtually all of the more than 25 distinct chemical entities that have been marketed for the treatment of epilepsy had their origins in this development strategy. Because a consideration of molecular mechanism does not play a role in the development process, AEDs often reach the market with little understanding of their pharmaco-dynamic effects. However, there has been an evolving understanding of the mechanisms of the clinically used AEDs and the molecular targets on which they act [1]. Until recently, there has been a consensus that the major targets are voltage-gated sodium channels; components of the γ-aminobutyric acid (GABA) system, including receptors, the GAT-1 GABA transporter, and GABA$_A$ GABA transaminase; and voltage-gated calcium channels [2]. In 1993, gabapentin was reported to bind with high affinity to a site in neuronal membranes, which was subsequently demonstrated to represent the $\alpha_2\delta$ protein [3]. Although the implications of this observation were not well appreciated at the time, it marked the beginning of a new era in which AED targets are identified using molecular approaches. This has resulted in an expansion in the range of known targets for clinically effective AEDs. It is noteworthy that the traditional process by which new AEDs are discovered, using animal models that are unbiased with respect to mechanism, enabled the identification of these new targets [4].

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Any brain constituent that plays a role in neuronal excitability mechanisms is a potential AED target. There are thus a large range of prospective targets, such as voltage-gated ion channels (143 subunit genes), ligand-gated ion channels (71 subunit genes), gap junctions (4 connexins genes), G-protein coupled receptors (approximately 600 genes), plasma membrane neurotransmitter transporters (13 genes), neurotransmitter metabolic enzymes, other enzymes affecting ion channel function (such as kinases and phosphatases), and components of the synaptic release machinery (estimated at 50–100 proteins) [5]. A small subset of these potential targets has been validated because of the availability of drugs that act specifically on the targets and the demonstration that the drugs have anticonvulsant activity in animals. This article focuses on several novel targets that have not only been validated in animal models, but also for which there is evidence of clinical efficacy in the treatment of epilepsy in humans. These targets are $\alpha_2\delta$, the high-affinity binding site for gabapentin and pregabalin; SV2A, a synaptic vesicle protein to which levetiracetam and brivaracetam (a related compound in development) bind; and M-type potassium channels, through which the investigational AED retigabine acts.

$\alpha_2\delta$: The Target for Gabapentinoids

Gabapentin was originally developed as an analog of the inhibitory neurotransmitter GABA. GABA, an amino acid, was modified by addition of a cyclohexane ring to increase its lipophilicity so as to allow passive blood-brain barrier transport [6]. However, gabapentin was subsequently found not to interact with either $GABA_A$ or $GABA_B$ receptors or other components of GABA systems. Pregabalin is similar chemically to gabapentin in that it is an analog of GABA and has comparable vivo anticonvulsant activity in animal models. Together, they are referred to as gabapentinoids.

Studies with [3H]gabapentin demonstrated high-affinity binding in brain, and the binding site was subsequently identified as $\alpha_2\delta$, which is an auxiliary subunit of voltage-gated calcium channels [3,7]. In 2001, two additional $\alpha_2\delta$ proteins were identified, designated $\alpha_2\delta$-2 and $\alpha_2\delta$-3 [8]. The original form, referred to now as $\alpha_2\delta$-1, has the highest binding affinity (K_d, 59 nM). Gabapentin also binds to $\alpha_2\delta$-2 (K_d, 153 nM) but does not bind to $\alpha_2\delta$-3 or to $\alpha_2\delta$-4, which is expressed mainly in endocrine and peripheral tissues [9]. The $\alpha_2\delta$ proteins are derived from a single gene, the product of which is extensively modified posttranslationally. Mutagenesis and deletion experiments have identified critical regions within the $\alpha_2\delta$ protein that are required for gabapentin binding [10]. In these experiments, it was found that the arginine at position 217 is required for [3H]gabapentin binding [11]. A transgenic mouse was created in which the wild-type $\alpha_2\delta$-1 gene was replaced with one encoding a mutated protein in which the arginine at position 217 was replaced by alanine [12••]. These R217A mutant mice had reduced [3H] pregabalin binding in the neocortex, amygdala, entorhinal cortex, and hippocampus [13]. Although the mutant mice exhibited pain responses and seizures that were indistinguishable from those of wild-type controls, pregabalin (30 mg/kg) had no analgesic activity, although it was analgesic in wild-type controls) [12••]. The mutant mice showed a persistent but diminished anticonvulsant response to pregabalin in the maximal electroshock test (Vartanian and Baron, unpublished data). These results indicate that $\alpha_2\delta$-1 binding is required for the analgesic activity of pregabalin and contributes to its anticonvulsant activity. Binding to $\alpha_2\delta$-2 could also play a role in the anticonvulsant activity, thus accounting for the anticonvulsant response in the mutant animals. Indeed, although [3H]gabapentin binding is markedly reduced in R217A mice, it is not eliminated [13]. Areas relevant to seizures, including the hippocampus and amygdala, show 9% to 46% residual binding, which is presumably to $\alpha_2\delta$-2. Structure-activity studies with a variety of compounds related to gabapentin and pregabalin, in which there is a strong correlation between $\alpha_2\delta$ binding affinity and anticonvulsant activity [14,15], further support a role of $\alpha_2\delta$ in the anticonvulsant activity of gabapentinoids.

Spontaneous and induced mutations affecting the $\alpha_2\delta$-2 gene have been associated with epilepsy and enhanced seizure susceptibility in mice. Various alleles of the mouse strain ducky, which have disruptions or modifications in the *Cacna2d2* gene that are predicted to alter $\alpha_2\delta$-2 expression or structure, demonstrate absence epilepsy [16,17]. In addition, mice with targeted disruption of the *Cacna2d2* gene exhibit a markedly reduced threshold for pentylenetetrazol seizures [18]. As of yet, no mutations in $\alpha_2\delta$-1 have been associated with epilepsy in mice, nor are there examples in which any of the $\alpha_2\delta$ genes have been linked to human epilepsy.

The exact mechanism whereby gabapentinoid binding to the $\alpha_2\delta$ proteins protects against seizures has not been fully defined. It is plausible that the functional effects of a gabapentinoid binding could relate to the role of $\alpha_2\delta$ as a subunit of calciuim channels (through effects on calcium influx), but $\alpha_2\delta$ could have other cellular functions that might be relevant to the actions of gabapentinoids [19]. It has been suggested that the actions of gabapentinoid $\alpha_2\delta$ ligands to reduce neurotransmitter release may not require inhibition of calcium influx, and therefore may be mediated by an interaction of $\alpha_2\delta$ (or the calcium-channel complex containing $\alpha_2\delta$) with synaptic proteins involved in the release or trafficking of synaptic vesicles [20]. Because little is known about these potential interactions, we focus here on $\alpha_2\delta$ as a component of voltage-gated calcium channels.

Studies of calcium flux measured with fluorescent probes in synaptosomes from rat neocortex [21] or human brain tissue obtained at epilepsy surgery [22] have indicated that both gabapentin and pregabalin reduce calcium influx into presynaptic terminals. In addition, gabapentin and pregabalin have been shown to produce subtle but reproducible reductions in the calcium-dependent release of glutamate and other neurotransmitters, including nor-epinephrine, serotonin, and dopamine, from neocortical tissues [23,24]. However, studies examining the direct actions of gabapentin and pregabalin on calcium channel currents have been equivocal [25]. Whereas some investigators have shown small inhibitory effects on release, others have failed to detect such actions. It has also been difficult to reproducibly demonstrate robust acute effects on synaptic transmission. A recent report has proposed that the action of gabapentin is not to directly reduce calcium channel activity, but rather to inhibit trafficking and plasma membrane expression of $\alpha_2\delta$ and the channel complex of which it is a component [26••]. Interestingly, gabapentin must enter neurons to exert this effect on trafficking, which it does via transport by the system-L transporter. It has been speculated that gabapentin displaces an endogenous positive modulatory substance (perhaps L-leucine) that is required for trafficking. Thus, according to this theory, the action of gabapentinoids would depend upon the turnover of calcium channels. The rate of turnover has not been well defined, but it would have to be sufficiently fast to explain the rapid action of gabapentin in animal seizure models, where pretreatment with gabapentin for 60 to 120 minutes or less can confer seizure protection [27–29]. This proposed mechanism represents an entirely novel action for an AED, which contrasts with the usual view that AEDs directly (or perhaps indirectly in the case of topiramate) modulate channel activity [1]. Clearly, there is much more to be learned about the functional roles of $\alpha_2\delta$ proteins before it will be possible to gain a complete understanding of the mechanism of action of gabapentinoid AEDs.

SV2A: The Target for Levetiracetam and Brivaracetam

SV2A, a membrane glycoprotein present in the synaptic vesicles of neurons and the secretory vesicles of endocrine cells [30], is believed to be present in virtually all neurons of vertebrates. SV2A has a structure that is homologous to bacterial and eukaryotic transporters; however, a transport function of SV2A has not been demonstrated. Various hypotheses have been advanced for the function of SV2A, such as trapping soluble neurotransmitter molecules, diminishing intravesicular osmotic pressure, modifying synaptic vesicle exocytosis by binding

to synaptotagmin I, and serving as a scaffold protein to regulate vesicle shape or participate in vesicle trafficking [31]. None of these proposed mechanisms have been verified. Recently, Custer et al. [32•] have proposed that SV2A is a positive modulator of low-frequency synaptic transmission that may act by preparing vesicles for fusion. These authors found a reduction in excitatory synaptic potential responses in hippocampal neuron cultures from mice in which SV2A had been deleted by gene targeting. The reduction was restricted to low-frequency trains of stimuli or to the initial synaptic responses to trains, and appeared to be due to a smaller, readily releasable pool of vesicles, leading to a reduction in initial release probability. Synapses were morphologically normal and there was no change in the number of docked vesicles. This led the authors to conclude that SV2A does not influence docking but rather has a role in facilitating "priming" (the events that render docked vesicles competent for calcium-triggered fusion). It is not apparent how functional alterations in the activity of SV2A and the resultant effects on vesicle dynamics might influence epileptic excitability. However, SV2A knockout mice develop severe seizures and die within the first weeks of life [33]. Heterozygous animals do not show spontaneous seizures, but they do exhibit enhanced seizure susceptibility [34]. Thus, there is a link between SV2A and epilepsy, although the physiologic basis remains to be elucidated. Although its functional role is not well understood, SV2A exhibits two well-accepted interactions with xenobiotics. First, botulinum neurotoxin A binds to SV2A (and its B and C isoforms), which allows the toxin to enter neurons [35]. Second, the AED levetiracetam and its analogs bind to SV2A, and this interaction seems to mediate the anticonvulsant activity of the drugs. In 1995, [^{3}H]levetiracetam was found to exhibit saturable binding to an abundant site in the brain with K_d of 780 nM [36]. Further studies using a higher-affinity analog, UCB 30889, showed that the binding site was SV2A [37]. There was a high correlation between the binding affinities of a series of levetiracetam analogs and their potencies for protection against audiogenic seizures in mice, suggesting that SV2A is the molecular target for anticonvulsant activity. Using this binding assay to screen a library of 12,000 compounds, brivaracetam, the *n*-propyl analog of levetiracetam, was identified as having 10-fold greater affinity than levetiracetam for sites in brain labeled with [^{3}H]levetiracetam [38]. Brivaracetam was more potent than levetiracetam in several animal seizure models and may have an expanded spectrum of activity. Like levetiracetam, it demonstrates a large separation between the doses conferring seizure protection and acute neurologic impairment. A recent phase 2 clinical trial in 208 patients demonstrated that brivaracetam produced a dose-dependent reduction in the frequency of seizures in adults with refractory partial seizures [39]. Remarkably, brivaracetam had an adverse event profile indistinguishable from placebo. The results of the clinical trial provide ultimate validation of SV2A as an AED target because binding to this site was the initial screen used to select brivaracetam for further development.

K$_v$7/KCNQ/M Potassium Channel: The Target for Retigabine

In 1980, Brown and Adams [40] described the existence of a low-threshold, depolarization-activated potassium current that they referred to as the "M-current" because it was inhibited by the cholinergic agonist muscarine. The M-current is active in the voltage range for action potential initiation and is therefore of particular importance in regulating the dynamics of the neuronal firing [41]. The M-current turns on slowly following membrane depolarization, and it does not inactivate with sustained depolarization. Although the current was originally described in bullfrog sympathetic neurons, it is also present in brain neurons in the hippocampus, neocortex, and elsewhere [42]. In hippocampal pyramidal cells, M-current contributes to the medium duration (0.1 seconds) afterhyperpolarization that occurs after a single action potential or bursts of action potentials [43]. Depolarizing stimuli activate the M-current, which acts as a brake on repetitive action potential discharges and burst responses, so that neurons generate a regular, stimulus-graded spike output [44]. Thus, the M-current is uniquely suited to suppress bursting and epileptiform activity while permitting maintenance of responses to ordinary excitatory inputs [45].

The molecular identity of the potassium channels that underlie the M-current was uncovered as a result of studies in the late 1990s on a rare type of idiopathic generalized epilepsy [46, 47]. This form of epilepsy, benign familial neonatal convulsions, was found to be due to diverse mutations in novel potassium channel subunits, referred to as KCNQ2 (K_v7.2) and KCNQ3 (K_v7.2), which are homologous to a heart potassium channel subunit KvLQT1 (KCNQ1/K_v7.1). The potassium channel family that includes the cardiac KvLQT1 subunit and its KCNQ homologs is now referred to as K_v7 [48]. Shortly after the discovery of KCNQ2 and KCNQ3, it was demonstrated that the M-current channel is formed by these subunits as heteromultimers [49]. M-current can also be generated by KCNQ2 and KCNQ3 homomultimers and possibly also by heteromultimers with other KCNQ subunits, such as KCNQ5, which to date has not been linked to a human disease [50–54]. KCNQ2 mRNA is found throughout the rodent central nervous system, with high expression levels in the hippocampus, neocortex, and cerebellum [42], and KCNQ2 protein has high expression levels in hippocampus, neocortex, and amygdala [55]. KCNQ3 is also expressed in the hippocampus, neocortex, thalamus, and cerebellum [56].

The first immunocytochemical studies of KCNQ channels indicated that they have a somatodendritic distribution and are also expressed presynaptically [57]. Functional M-channels (most likely KCNQ2/KCNQ3 heteromers) are expressed by hippocampal interneurons as well as by principal cells [58]. More recent immunocytochemical studies and patch clamp recordings from different regions of the neuron have confirmed the somatic distribution of the channels in hippocampal neurons, but the channels were unexpectedly found to be absent from distal dendrites [59] (however see Yue and Yaari [45]). In other studies, immunohistochemical staining has demonstrated colocalization of KCNQ2 with voltage-dependent sodium channels at nodes of Ranvier [60]. In addition, immunoreactivity for KCNQ2 and KCNQ3 has been detected at axon initial segments [47,61•]. There is an emerging recognition of the similarities between nodes of Ranvier and axon initial segments, which are sites of action potential initiation and propagation, respectively [62]. The two axonal domains have similar molecular compositions: both are enriched in voltage-dependent sodium channels as well as various adhesion molecules and cytoskeletal proteins that serve to complex sodium channels, including the adaptor protein ankyrin-G. KCNQ2 and KCNQ3 have an ankyrin-G binding motif similar to that present in sodium channels, which is believed to mediate the interaction and retention of both channel types at the plasmalemma of the node and axon initial segment [61•].

The new information on the subcellular localization of M-current channels has allowed a refinement in the understanding of the role the channels play in regulating neuronal excitability and the inhibition of epileptiform discharges. In hippocampal pyramidal neurons, spikes are probably initiated in the axon distal to the initial segment [63]. The initial segment therefore lies between the somatodendritic compartment and the true spike-initiation site. M-channels at this pivotal location are well positioned to gate transmission of somatodendritic depolarizations to the site of action potential generation. Because M-channels are slow to activate, rapid depolarizations are relatively unaffected by the axon initial-segment M-current. In contrast, more prolonged somatodendritic depolarizations, such as those that occur during epileptiform activity, would be attenuated and less likely to activate action-potential firing at the spike-initiation zone. In addition, initial-segment M-channels may block retrograde spike invasion into the somatodendritic compartments, electrically isolating the axon from the remainder of the neuron. Spikes generate an afterdepolarization (driven by subthreshold-persistent sodium current), which triggers further spiking so that bursting occurs. The M-current limits the size and duration of the afterdepolarization, preventing its escalation into a somatic spike burst [44].

Although M-channels in central and peripheral neurons have been localized by immunocytochemistry to nodes [60,64], they have not yet been demonstrated anatomically on nerve terminals. Nevertheless, the selective M-current blocker linopirdine can enhance the depolarization-induced release of various neurotransmitters in brain slices [65] and isolated nerve terminals [66], suggesting a presynaptic localization. Recent evidence supports the view that presynaptic M-channels serve to inhibit neurotransmitter release [67,68]. For example, in cultured hippocampal neurons, activation of M-channels reduces the frequency of spontaneous EPSCs [69]. Although calcium influx is conventionally believed to be the exclusive trigger for neurotransmitter release, there is evidence that release is modulated by voltage [70]. Therefore, the control of neurotransmitter release by M-current may simply be the result of changes in axon terminal membrane potential.

Given the critical role of M-current in regulating the transition to bursting, it is of interest that mutations in *KCNQ2*, and rarely *KCNQ3*, are associated with benign familial neonatal convulsions, a condition that is characterized by frequent unprovoked seizures beginning in the first days of life and resolving after weeks to months. The mutations reside predominantly in the pore region or the long cytoplasmic C-terminus, and also in the S4 voltage sensor and the S1–S2 region [47]. In many cases, the mutations cause nearly a complete loss of function of the homomeric expressed channels, but in heteromeric KCNQ2/KCNQ3 channels there is a 20% to 25% reduction in current. Thus, only a relatively small reduction in current leads to the epileptic phenotype. Complete elimination of the current is lethal in genetically altered mice [71]. Heterozygous animals develop normally and lack spontaneous epileptic activity but are more susceptible to pentylenetetrazol-induced seizures. Similar phenotypes are observed in mice homozygous or heterozygous for the spontaneous Szt1 mutation, which involves the region of the *Kcnq2* gene that encodes the C-terminus of KCNQ2, as well as other genes [72, 73].

Because reducing M-current enhances neuronal excitability and predisposes to seizures, enhancing M-current might be expected to protect against seizures [41]. Experimental support for this concept was first provided when it was shown that retigabine (a powerful AED) could open potassium channels in cultured neuronal cells [74]. Retigabine was subsequently found to be a specific opener of M-current channels [75–77], with effects on KCNQ2–5 and the most potent activity on KCNQ3. The main action of retigabine is to shift the current–voltage curve for activation of the channels to the left so that they open at more hyperpolarized membrane potentials [78,79]. In addition, retigabine increases the rate at which the channels activate and slows the rate at which they deactivate. These effects appear to be due to an interaction of retigabine with a key tryptophan residue in the S5 domain of the channel [80••81]. This residue is not present in the cardiac KvLQT1 channel, which is resistant to retigabine, thus accounting for a lack of cardiotoxicity of the drug. Wuttke et al. [80••] have proposed that retigabine binds to a hydrophobic pocket in the cytoplasmic domains of S5 and S6, thus stabilizing the open state of the channel (see also Maljevic et al. [47]).

Inhibition of excitatory transmitter output at synapses is a key mode of action of AEDs [1], and modulation of synaptic release is the likely action for the other two targets discussed in this review. Modulation of presynaptic release by M-channels could also represent an important way in which M-channel openers such as retigabine protect against seizures. However, it is certainly not the only mechanism, as retigabine was able to abolish nonsynaptic bursting in hippocampal neurons [82]. The mechanisms of neuronal synchronization in this situation are obscure, but because synaptic transmission was absent in these experiments, the action of retigabine must relate to its effects on intrinsic neuronal excitability. In rodents, KCNQ2 and KCNQ3 show a gradual maturation so that the characteristic adult axonal distribution of the channels is not present in the early postnatal period [55,56]. Understanding the human

developmental expression patterns of these channels will provide insights into the response to KCNQ openers in infants and children.

Validation of KCNQ potassium channels as an AED target has come from several recent clinical trials of retigabine [83]. A phase 2 dose-ranging study in 399 patients with partial seizure demonstrated a dose-dependent reduction in seizures [84•]. Two unpublished phase 3 trials (Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy [RESTORE] 1 and 2) in 305 and 593 patients, respectivly, have confirmed the results of the phase 2 study.

The efficacy of retigabine in these various clinical trials strongly supports the concept that positive modulation of M-current (reduction in the threshold for activation) can confer seizure protection. However, retigabine has some known pharmacologic actions distinct from its effects on KCNQ channels; most notably, it potentiates $GABA_A$ receptor responses at similar or perhaps slightly higher concentrations than are effective on potassium channels [85]. Therefore, it is of interest that a structurally dissimilar KCNQ activator, ICA-27243, which is more selective and does not affect $GABA_A$ receptor responses, also exhibits anticonvulsant activity [86–88]. This confirms the validity of KCNQ channels as an anticonvulsant target, at least in animal models. An additional orally bioavailable selective KCNQ activator, ICA-105665, with activity in chemoconvulsant (pentylenetetrazol), electroshock, and kindling models, is entering clinical development (Rigdon, personal communication).

Conclusions

The discovery of the new AED targets discussed in this review was based on the availability of anticonvulsant molecules identified as having protective activity in animal seizure models. With these molecules in hand, a program of research was initiated that eventually led to the identification of the novel targets. In the case of $\alpha_2\delta$ and SV2A, affinity ligands were used to localize the distribution of the targets and as fishhooks to snare the target for either automated sequencing or determination of molecular weight. Proof that the target is relevant to anticonvulsant activity was ultimately based on the use of genetically engineered mice. In the case of K_v7/KCNQ/M potassium channels, the target was discovered through cellular electrophysiology informed by genetic studies in a rare idiopathic epilepsy syndrome. The knowledge of the targets has been utilized to discover follow-on compounds with improved properties that act by similar mechanisms. Pregabalin, an analog of gabapentin, has already reached the market. Levetiracetam spawned the analog brivaracetam, which was identified specifically as a result of its high affinity for the levetiracetam binding site. There are a host of KCNQ openers in various stages of development, some of which are structurally related to retigabine and others that are not [42,69]. Clearly, the new set of targets discussed in this review are providing opportunities for the rational discovery of AEDs in a way that was not possible when animal models were the only tool.

A common theme for the three molecular targets discussed in this review is that they are all localized to nerve terminals, where they play diverse roles in regulating neurotransmitter release. Actions on presynaptic mechanisms are likely to be the primary way in which AEDs that target $\alpha_2\delta$ and SV2A confer seizure protection. Because K_v7/KCNQ/M potassium channels are also localized presynaptically, where they regulate release, AEDs that open these channels also likely act in part through regulation of release (although effects on somatodendritic and axon initial segment channels are likely relevant as well). The concept that AEDs act presynaptically to modulate transmitter release contrasts with conventional notions that AEDs confer seizure protection by inhibiting repetitive action-potential generation, influencing rhythm-generating mechanisms, or enhancing postsynaptic inhibition. The discovery and characterization of the new targets focuses attention on presynaptic mechanisms as a key mode of action for AEDs. In fact, it is likely that sodium channel–blocking

AEDs, including phenytoin, carbamazepine, and lamotrigine, ultimately confer seizure protection by affecting excitatory neurotransmitter output at synapses [1].

The identification of AEDs that act on new targets has not yet led to a "magic bullet" that reliably eliminates seizures in drug-refractory patients. Nevertheless, newer AEDs have provided improvements in safety, tolerability, and pharmacokinetics, and they offer a broader range of options. It remains to be seen whether the agents in the development pipeline that act through the targets discussed in this review, including brivaracetam and retigabine, will offer more substantial benefits.

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