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Is levetiracetam different from other antiepileptic drugs? Levetiracetam and its cellular mechanism of action in epilepsy revisited

Rainer Surges, Kirill E. Volynski and Matthew C. Walker

***Abstract*:** Levetiracetam (LEV) is a new antiepileptic drug that is clinically effective in generalized and partial epilepsy syndromes as sole or add-on medication. Nevertheless, its underlying mechanism of action is poorly understood. It has a unique preclinical profile; unlike other antiepileptic drugs (AEDs), it modulates seizure-activity in animal models of chronic epilepsy with no effect in most animal models of acute seizures. Yet it is effective in acute *in-vitro* 'seizure' models. A possible explanation for these dichotomous findings is that LEV has different mechanisms of actions, whether given acutely or chronically and in 'epileptic' and control tissue. Here we review the general mechanism of action of AEDs, give an updated and critical overview about the experimental findings of LEV's cellular targets (in particular the synaptic vesicular protein SV2A) and ask whether LEV represents a new class of AED.

***Keywords*:** levetiracetam, SV2A, antiepileptic drugs, synaptic transmission, epilepsy, ion channels

Introduction

Antiepileptic drug (AED) development has mainly taken place through trial and error. AEDs have been screened in animal models of seizures and epilepsy, often with an incomplete knowledge of their mechanism of action [Walker *et al.* 2004]. Indeed, the identification of drugs acting at putative 'antiepileptic' targets has rarely translated into successful AED therapies, because the drugs are often poorly tolerated or have poor efficacy. Moreover, AEDs that were designed to act at specific targets (e.g., gabapentin, lamotrigine) work via different mechanisms. Consequently, the underlying mechanism of action of an individual drug may only become apparent after its widespread clinical use. However, growing evidence suggests that many of the drugs that we use fall into one or more specific mechanistic groups – drugs that act at sodium channels, calcium channels or the GABAergic system [Walker and Fisher, 2004]. Other putative and potential targets include potassium channels, hyperpolarization-activated cation channels, and glutamate receptors. Here we briefly review the mechanism of action of AEDs and ask whether levetiracetam (LEV) represents a new class of AED.

Main targets for AED

Sodium channels

Sodium channels provide the major target for a number of AEDs including phenytoin, carbamazepine, oxcarbazpine, and lamotrigine. Voltage-gated sodium channels are critical for action potential (AP) generation and propagation [Catterall, 2000a]. The sodium channel exists in three principal conformational states: at hyperpolarized potentials the channel is in the resting closed state; with depolarization the channel opens and permits the conduction of sodium ions; the channel then enters a nonconducting, inactivated state. This inactivation is removed (termed deinactivation) by hyperpolarization. In this manner, depolarization results in a transient inward sodium current that rapidly inactivates. In addition to these three states, there is also a slow inactivated state, which occurs with sustained or repeated depolarizations. This state

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is selectively enhanced by the new AED, lacosamide [Errington *et al.* 2008].

Phenytoin, lamotrigine, oxcarbazepine, and carbamazepine bind to and stabilize the inactivated state of the sodium channel [Kuo, 1998]. This has two effects: a greater proportion of channels are inactive at hyperpolarized membrane potentials, and second there is a delay in deinactivation. The effect on the excitability of neurons is 2-fold. The rate at which an axon can 'fire' is critically determined by the rate at which the sodium channels deinactivate. If this time is increased, then the 'refractory period' is prolonged, inhibiting sustained repetitive firing [McLean and Macdonald, 1983]. In addition, since these drugs bind to channels in their inactive state, then the greater the number of channels that have entered this state, the greater the drug binding. This results in a 'use dependent' phenomenon in which repetitive firing results in greater amounts of the drug bound and so greater inhibition. In addition, these drugs inhibit the persistent sodium current, which mediates long-lasting depolarizations [Lampl *et al.* 1998]. Other AEDs such as valproate, topiramate, and zonisamide may also have similar effects on sodium channels, but have been less well characterized.

Calcium channels

Calcium channels are also putative targets for AEDs, as they regulate not only neuronal excitability but also neurotransmitter release [Catterall, 2000b]. The voltage-gated calcium channels expressed in the brain can be subdivided into four main classes, L-, P/Q-, N-, and T- type channels. L-, P/Q-, and N-type channels are high-voltage activated (HVA) channels that require significant depolarization to open, while the T-type channel is a low-voltage activated (LVA) channel and is opened by relatively small depolarizations.

The L-type channels are mainly expressed postsynaptically. L-type channels are slowly inactivated thereby permitting sustained calcium entry following a depolarization. Calcium entering through L-type calcium channels may play a role in activity-dependent gene expression and synaptic plasticity. Some AEDs (such as carbamazepine) have been proposed to antagonise L-type calcium channels but the relevance of this to their antiepileptic effect is unclear [Ambrosio *et al.* 1999].

N- and P/Q-type channels are expressed at synaptic boutons where they mediate calcium entry necessary for neurotransmitter release. These channels rapidly inactivate, resulting in brief calcium transients. This calcium entry then triggers exocytosis of presynaptic vesicles. N- and P/Q–type calcium channels can be modulated by G-protein linked receptors such as $GABA_B$ receptors. Inhibition of these channels would be expected to decrease neurotransmitter release. Gabapentin's and pregabalin's effect on HVA calcium channels is complex and novel; they both show strong and specific binding for the $\alpha 2\delta$ auxillary calcium channel subunit and may modulate P/Q-type calcium channels [Dooley *et al.* 2007].

T-type calcium channels are activated at relatively hyperpolarized potentials. They open with small depolarization and then rapidly inactivate. They have been proposed to contribute to the generation of physiological rhythms within the thalamus, and have been implicated in the generation of spike-wave discharges associated with absence epilepsy [McCormick and Contreras, 2001]. There is evidence that ethosuximide mediates its effect through binding to and stabilizing the inactivated state of the T-type calcium channel [Gomora *et al.* 2001]. Other drugs such as zonisamide and valproate have also been suggested to act at this channel [Todorovic and Lingle, 1998; Suzuki *et al.* 1992].

GABAergic system

Gamma amino butyric acid (GABA) is the major inhibitory neurotransmitter in the brain. It is formed and degraded in the GABA shunt. Glutamic acid decarboxylase (GAD) converts glutamate to GABA. Promotion of GABA synthesis has been proposed to contribute to the action of some AEDs including valproate [Löscher, 1989].

GABA is released into the synaptic space where it acts on two receptor types: ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors (a third type, termed $GABA_C$ receptors, is present predominantly in the retina) [Bormann, 2000]. Benzodiazepines act at specific $GABA_A$ receptor subtypes [Mehta and Ticku, 1999], increasing the affinity of $GABA_A$ receptors for GABA, and the probability of receptor opening. Topiramate also potentiates $GABA_A$ receptor currents in a subunit specific manner [Simeone *et al.* 2006]. Barbiturates are less selective for $GABA_A$ receptor subtypes, and prolong receptor

opening times. Drugs that act at $GABA_B$ receptors have been less useful as AEDs, probably because $GABA_B$ receptors have a complex function acting postsynaptically to decrease neuronal excitability but also presynaptically decreasing GABA release.

GABA is taken up by glial and neuronal GABA transporters, inhibition of which is another AED target (tiagabine) [Rekling *et al.* 1990]. Inside the cell, GABA is degraded by GABA transaminase to succinic semialdehyde, and inhibition of this enzyme by the AED vigabatrin increases GABAergic transmission [Gale and Iadarola, 1980].

Other targets

Potassium channels

Potassium channels form one of the most diverse groups of ion channels and have a critical role in determining neuronal excitability [Jan and Jan, 1997]. Persistent potassium currents play a crucial part in determining the resting membrane potential of neurons. Voltage-gated potassium channels can influence the resting membrane potential but also repolarize neurons following AP, thereby influencing neurotransmitter release. In addition, the rate of repolarization by potassium channels, affects the ability of a neuron to sustain rapid repetitive firing. Voltage-gated potassium channels in the brain can be subdivided into: channels that rapidly activate and inactivate (A-type channels), channels that open upon depolarization but do not significantly inactivate (delayed rectifier channels) and channels that close upon depolarization but are open at the resting potential (inward rectifying channels). There are other potassium channels that are similar in structure to the voltage-gated potassium channel, but are opened by intracellular calcium (calcium-activated potassium channels that mediate the afterhyperpolarization) or by cyclic nucleotides (mainly present in the retina where they mediate photoreceptor responses). There are also specific potassium channels that are inactivated by acetylcholine – termed M-type channels. Although, modulation of potassium channels would seem to be an ideal target for AEDs, most drugs have no or poorly characterized effects on potassium channels. However, phenytoin blocks the delayed rectifier potassium channels in neuroblastoma cells and retigabine, a putative AED, has as its main mode of action potentiation of potassium M-type channels [Wuttke *et al.* 2005; Tatulian *et al.* 2001; Nobile and Lagostena, 1998].

HCN channels

HCN channels are permeable to both potassium and sodium and mediate a current termed the H-current. These channels are activated at hyperpolarised potentials and deactivated at depolarized potentials. H-currents depolarize neurons from the resting membrane potential and have an important role in potentiating and maintaining oscillations [Robinson and Siegelbaum, 2003]. They may play a part in terminating thalamic oscillations and the generation of spike-wave discharges of absence epilepsy. The H-current is also highly expressed in dendrites where it shunts excitatory inputs. Lamotrigine has been shown to enhance the H-current in dendrites [Poolos *et al.* 2002]. Likewise, gabapentin has been demonstrated to increase the H-current in pyramidal neurons [Surges *et al.* 2003]. This may have two potentially antiepileptic effects: in the hippocampus it would inhibit excitatory transmission to the soma, explaining the efficacy of lamotrigine and gabapentin in partial epilepsy. In the thalamus, it may inhibit or terminate spike-wave discharges and, therefore, could explain the efficacy of lamotrigine against absence seizures.

Glutamate and glutamate receptors

Glutamate is the major excitatory transmitter in the central nervous system and acts at distinct receptor types: N-methyl-D-aspartate (NMDA), nonNMDA [consisting of alpha- amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid (KA) sensitive receptors] and metabotropic glutamate receptors. Inhibition of these receptors would seem to be an ideal target for AEDs, but such compounds have been associated with unacceptable side-effects. NMDA receptors influence memory, cognition, and learning and NMDA receptor antagonists have had unacceptable side effects in clinical use. Felbamate and remacemide, however, may modulate NMDA receptor-mediated transmission [Subramaniam *et al.* 1996; White *et al.* 1995].

Topiramate at high concentrations acts at AMPA/kainate receptors; whether this is responsible for its antiepileptic effect or dose-related side effects is unknown [Angehagen *et al.* 2004]. Low doses of phenobarbitone have been shown to block

AMPA receptors in the cerebral cortex [Sawada and Yamamoto, 1985], but the significance of this finding and its overall contribution towards the antiepileptic effects of phenobarbitone remains to be established. There are other drugs in clinical trials such as talampanel that are AMPA receptor antagonists.

Levetiracetam

LEV is a water soluble pyrrolidone derivative ((S)-α-ethyl-2-oxo-pyrrolidine acetamide), whose chemical structure differs from other AEDs. Since its approval for clinical use in 2002, LEV has become a widely used AED that is effective in partial and generalized epilepsy syndromes as sole or add-on medication [De Smedt *et al.* 2007]. Usual antiepileptic plasma concentrations range from trough levels between 35 and 100 μM (5.95–17 μg/ml) to peak levels between 90 and 250 μM (15.3–42.5 μg/ml) [Rigo *et al.* 2002; Patsalos, 2000]. Importantly, serum levels of LEV are very similar to corresponding LEV levels found in the brain tissue of individual patients [Rambeck *et al.* 2006]. Unlike other AEDs, LEV is probably not a substrate for multidrug transporters [Potschka *et al.* 2004].

Except for rare instances of the treatment of acute seizures, AED therapy involves a regular daily, therefore chronic, intake of medication. Therefore, acute *in-vitro* and *in-vivo* experimental paradigms do not necessarily reflect the clinical use of an AED. Moreover, there are various epilepsy-associated modifications of brain physiology, and therefore models of acute seizures differ from models of chronic epilepsy. Intriguingly, LEV modulates seizure activity in animal models of chronic epilepsy (kindling models, pilocarpine model, genetic absence epilepsy rats from Strasbourg GAERS) with no effect in most models of acute seizures [Glien *et al.* 2002; Klitgaard *et al.* 1998; Löscher and Hönack, 1993]. This is conisistent with the experimental observations that LEV only affects $GABA_A$ receptors from epileptic tissue or under conditions that occur during epilepsy, whereas it has no effect on $GABA_A$ receptors from controls [Palma *et al.* 2007; Rigo *et al.* 2002]. Taken together, these data suggest that LEV may preferentially work with chronic application or under chronic epilepsy-associated conditions. However, most of the experiments to investigate LEV's cellular mechanism of action have been performed by acute application, reporting its acute cellular effects. A further consideration is that LEV is now being proposed as an acute treatment for seizures. An intravenous formulation is available [Ramael *et al.* 2006] that has already been shown to terminate status epilepticus after acute intravenous application [Knake *et al.* 2008]. Interestingly, LEV is effective in one model of acute epilepsy (6 Hz psychomotor seizure model) [Shannon *et al.* 2005; Barton *et al.* 2001] with the maximal effect occurring 1 h after injection [Barton *et al.* 2001]. These findings suggest that LEV can have a rapid-onset effect in some acute seizure models. One possible explanation for these dichotomous findings in animal models of acute and chronic epilepsy is that LEV may have different mechanisms of action whether given acutely or chronically and in epileptic and control tissue (see subsequently).

Action of LEV on voltage-gated ion channels and regulation of intracellular ions

Neuronal excitability and firing behavior are crucially shaped by voltage-gated ion channels. Acute application of LEV at a relatively low concentration (10 μM) did not alter neuronal properties such as membrane potential, input resistance, AP amplitude, AP duration, or fast and slow afterhyperpolarization of CA3 pyramidal cells [Birnstiel *et al.* 1997]. However, at higher concentrations (similar to those used in clinical practice) there is substantial experimental evidence that acutely applied LEV (and prolonged application for up to 1 h) modulates cellular targets that are important for neuronal excitability and synaptic transmission (cf. Tables 1 and 2).

Voltage-gated ion channels

HVA Ca^{2+} currents in different cell preparations (acutely isolated striatal, neocortical, and hippocampal CA1 neurons, CA1 pyramidal neurons in slices) were inhibited by an average of 18–40% when LEV was acutely applied at different concentrations (1–300 μM) [Costa *et al.* 2006; Pisani *et al.* 2004; Lukyanetz *et al.* 2002; Niespodziany *et al.* 2001]. Pharmacological separation of different HVA Ca^{2+} channel subtypes revealed that mainly N-type, and to a lesser extent P/Q-type calcium channels were affected [Costa *et al.* 2006; Pisani *et al.* 2004; Lukyanetz *et al.* 2002]. Changes in steady-state activation or inactivation properties were not observed [Lukyanetz *et al.* 2002]. In contrast, LEV did not modulate amplitudes, steady-state activation/inactivation properties or kinetics of T-type Ca^{2+} currents

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