

Psychopharmacology of Anticonvulsants: Levetiracetam as a Synaptic Vesicle Protein Modulator

Stephen M. Stahl, M.D., Ph.D.

Issue: *A novel mechanism of action has recently been described for levetiracetam, a member of a new class of anticonvulsants. Levetiracetam binds selectively and with high affinity to a synaptic vesicle protein known as SV2A, thought to be involved with synaptic vesicle exocytosis and presynaptic neurotransmitter release.*

Anticonvulsants reduce seizures by a variety of unique pharmacologic mechanisms of action.¹⁻⁷ Not only are the distinct pharmacologic mechanisms of action for each individual anticonvulsant being clarified but so are the therapeutic profiles for these agents. Thus, some anticonvulsants are also linked to therapeutic actions in anxiety disorders,^{2,3,7} others in chronic pain disorders,^{4,7} and still others in bipolar disorder.^{5,6} As pharmacologic action is better understood, so is the full therapeutic spectrum for each agent.

Recently, yet another novel action has been described for a new class of anticonvulsant exemplified by levetiracetam, namely, the selective and high affinity binding to a protein involved in synaptic vesicle function called the SV2A protein.^{8,9} SV2A has

already proved an effective therapeutic target in reducing seizures and also holds promise for therapeutic application in conditions characterized by excessive neurotransmitter release in pathologically active neuronal circuits such as bipolar disorder¹⁰ and chronic neuropathic pain.^{11,12}

WHAT IS SV2A?

Synaptic vesicles are composed of numerous proteins, some of which act as transporters.^{8,9,13-15} A protein specific to synaptic vesicles, denoted SV2, is a 12 transmembrane region glycoprotein present in all neural cells and occurring in 3 isoforms, SV2A, SV2B, and SV2C.¹³⁻¹⁵ SV2A is the most widely distributed isoform and is ubiquitous not only throughout the CNS, but also in endocrine cells. SV2B is brain specific, but not widely distributed, and SV2C is a minor isoform in brain.

The SV2 synaptic vesicle proteins are structurally similar to vesicular transporters for neurotransmitters, but it is not known what, if anything, SV2s transport, nor in which direction.¹³⁻¹⁵ However, it is known that SV2 synaptic vesicle proteins are not identical to any of the 4 different ve-

sicular transporters for neurotransmitters that have been described (i.e., 1 for acetylcholine; 1 for serotonin, dopamine, norepinephrine, and epinephrine; 1 for GABA and glycine; and 1 for glutamate). It is also known that in order for neurotransmitter vesicular transporters to transport their neurotransmitters into the synaptic vesicle, they rely upon an electrochemical gradient generated by [H⁺]ATPase. It is plausible that SV2s transport an ion linked to this process, perhaps chloride or calcium itself.¹³⁻¹⁵

WHAT IS THE FUNCTION OF SV2A?

SV2A synaptic vesicle proteins are essential, since knockout mice without them develop severe seizures soon after birth and die within 3 weeks. Neurons isolated from animals lacking SV2As exhibit altered neurotransmission, but without changes in either the density or the morphology of synapses or synaptic vesicles.¹³⁻¹⁵ This suggests that SV2As act as a modulator of synaptic vesicle exocytosis, perhaps even moving a substrate out of vesicles as part of the process of fusion of the vesicle to the presynaptic neuronal membrane. SV2As thus ap-

BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.

From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

pear to have a crucial role in the regulation of synaptic vesicle function, although not in the formation or shape of vesicles.

HOW DOES LEVETIRACETAM ACT UPON SV2As?

Determining the effect of levetiracetam on SV2A function is complicated both by an incomplete knowledge of what SV2A does and also by the unusual pharmacology of levetiracetam, which lacks effects on electrophysiology of normal brain tissue and neurons but acts on abnormal electrophysiology of neurons.^{8,9} This selective action is reminiscent of the mechanism of action postulated for $\alpha_2\delta$ ligands that seem to act more upon abnormally activated neurons than on normal neurotransmission.^{3,4,7}

That knockout mice lacking SV2A exhibit seizures whereas levetiracetam inhibits seizures suggests that levetiracetam must not be working simply as an antagonist of SV2A (or it would be proconvulsant rather than anticonvulsant). Instead, levetiracetam binding may enhance an SV2A

Take-Home Points

- ◆ Anticonvulsants act by numerous and different mechanisms to reduce seizures.
- ◆ A new mechanism of action has recently been described for the anticonvulsant levetiracetam that is distinct from that of all other anticonvulsants, namely binding to the SV2A synaptic vesicle protein.
- ◆ This action should theoretically modulate excessive neuronal activation, and thus levetiracetam may not only be a therapeutic agent for epilepsy, but also has theoretical appeal for other states hypothetically linked to excessive neuronal activation, such as bipolar disorder, chronic neuropathic pain, and anxiety disorders.

function that inhibits abnormal neuronal activity in epileptic neurons. Without SV2As, presynaptic calcium accumulation during consecutive action potentials causes abnormal increases in neurotransmitter release that destabilize synaptic circuits and induce epilepsy.^{8,9,13-15} SV2As are involved in the calcium-dependent regulation of neurotransmitter release during repetitive stimulation,¹³⁻¹⁵ maybe even as

calcium transporters of some kind. Since abnormal buildup of residual calcium is not removed when SV2As are absent, it is conceivable that SV2As are calcium-dependent inhibitors of neurotransmitter release, and loss of SV2A function could mean loss of control of exocytosis. Adding levetiracetam to modulate SV2A function might restore the ability of a neuron to regulate its neurotransmitter release and thus reduce excessive neuronal activity, thereby reducing seizures.

Whatever the explanation of what levetiracetam does when it binds to SV2As, it is clear that this action is clearly unique from the main mechanisms currently established for the other anticonvulsants,¹ namely GABA facilitation, inhibition of voltage sensitive sodium channels, or inhibition of voltage sensitive calcium channels, none of which appear to be actions of levetiracetam. Understanding the mechanism of action of anticonvulsants can lead to novel uses for psychiatric disorders and rational combination treatments with agents that act by synergistic or complementary mechanisms. ◆

REFERENCES

1. Stahl SM. Psychopharmacology of anticonvulsants: do all anticonvulsants have the same mechanism of action? [BRAINSTORMS] *J Clin Psychiatry* 2004;65:149-150
2. Stahl SM. Anticonvulsants as anxiolytics, pt 1: tiagabine and other anticonvulsants with actions on GABA [BRAINSTORMS]. *J Clin Psychiatry* 2004;65:291-292
3. Stahl SM. Anticonvulsants as anxiolytics, pt 2: pregabalin and gabapentin as $\alpha_2\delta$ ligands at voltage-gated calcium channels [BRAINSTORMS]. *J Clin Psychiatry* 2004;65:460-461
4. Stahl SM. Anticonvulsants and the relief of chronic pain: pregabalin and gabapentin as $\alpha_2\delta$ ligands at voltage-gated calcium channels [BRAINSTORMS]. *J Clin Psychiatry* 2004;65:596-597
5. Stahl SM. Anticonvulsants as mood stabilizers and adjuncts to antipsychotics: valproate, lamotrigine, carbamazepine, oxcarbazepine and actions at voltage sensitive sodium channels [BRAINSTORMS]. *J Clin Psychiatry* 2004;65:738-739
6. Stahl SM. Mechanism of action of voltage sensitive sodium channel (VSSC) modulators [BRAINSTORMS]. *J Clin Psychiatry* 2004;65:894-895
7. Stahl SM. Mechanism of action of voltage sensitive calcium channel (VSCC) modulators [BRAINSTORMS]. *J Clin Psychiatry* 2004;65:1033-1034
8. Lynch BA, Lambeng N, Nocka K, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci U S A* 2004;101:9861-9866
9. Gillard M, Fuks B, Michel P, et al. Binding characteristics of [3H]ucb 30889 to levetiracetam binding sites in rat brain. *Eur J Pharmacol* 2003;478:1-9
10. Grunze H, Langosch J, Born C, et al. Levetiracetam in the treatment of acute mania: an open add-on study with an on-off-on design. *J Clin Psychiatry* 2003;64:781-784
11. Ardid D, Lamberty Y, Alloui A, et al. Antihyperalgesic effect of levetiracetam in neuropathic pain models in rats. *Eur J Pharmacol* 2003;473:27-33
12. Rowbotham MC, Manville NS, Ren J. Pilot tolerability and effectiveness study of levetiracetam for postherpetic neuralgia. *Neurology* 2003;61:866-867
13. Bajjalieh SM, Frantz GD, Weimann JM. Differential expression of synaptic vesicle protein 2 (SV2) isoforms. *J Neurosci* 1994;14:5223-5225
14. Crowder KM, Gunther JM, Jones RA, et al. Abnormal neurotransmission in mice lacking synaptic vesicle protein 2A (SV2A). *Proc Natl Acad Sci U S A* 1999;96:15268-15273
15. Janz R, Goda Y, Geppert M, et al. SV2A and SV2B function as redundant Ca^{2+} regulators in neurotransmitter release. *Neuron* 1999;24:1003-1016