

Anticonvulsants and the Relief of Chronic Pain: Pregabalin and Gabapentin as $\alpha_2\delta$ Ligands at Voltage-Gated Calcium Channels

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Issue: *Anticonvulsants that act as ligands at $\alpha_2\delta$ subunits of voltage-gated calcium channels are proving to be novel treatments for chronic pain.*

Recent BRAINSTORMS features have highlighted the fact that anticonvulsants have several different mechanisms of action¹ and that some of these mechanisms may also have therapeutic applications in anxiety disorders.^{2,3} Last month we specifically reviewed a novel class of anticonvulsants with actions as ligands at the $\alpha_2\delta$ subunit of voltage-gated calcium channels.³ A new entrant to this class, pregabalin, is not only an effective anticonvulsant, presumably due to its ability to reduce neurotransmitter release from activated epileptic neurons, but is also a promising new anxiolytic, hypothetically due to its ability to reduce neurotransmitter release from activated neurons in fear circuits.³ Here we discuss how $\alpha_2\delta$ ligands may also be effective treatments for chronic pain conditions. In fact, new studies suggest that pregabalin is a novel treatment for

2 chronic pain conditions for which there are, as yet, no approved treatments, namely diabetic peripheral neuropathy and fibromyalgia.⁴⁻⁶

NEUROTRANSMISSION AND CHRONIC PAIN

Acute pain and its neuroanatomic basis are well characterized, but the pathophysiology of chronic pain is less well understood. One notion is that pain circuits become modified over time in a process called "central sensitization" so that neurons in the pain pathway become chronically activated, transmitting painful sensations in an ongoing manner.⁷ This continual activation may be occurring in some of the most difficult-to-manage chronic pain conditions, including diabetic peripheral neuropathy, fibromyalgia, post-herpetic neuralgia, and trigeminal neuralgia.

of reducing neurotransmission by several distinct mechanisms,^{1,8} they have been investigated as potential treatments for chronic pain. Those that reduce neurotransmission by blocking voltage-gated sodium channels include lidocaine, carbamazepine, and lamotrigine,^{1,8,9} but only topical application of lidocaine is specifically recommended for the treatment of neuropathic pain.¹⁰ Presumably, blocking sodium channels could interfere with the propagation of nerve impulses throughout the pain pathway and thereby relieve pain.^{8,9}

$\alpha_2\delta$ LIGANDS AS NOVEL TREATMENTS FOR CHRONIC PAIN

Other anticonvulsants, namely pregabalin and gabapentin, reduce neurotransmission in activated neurons by blocking voltage-gated presynaptic N and P/Q calcium channels.^{3,11-13} N- and P/Q-type calcium channels regulate the release of neurotransmitters during synaptic neurotransmission; when calcium flows through these presynaptic channels, neurotransmitter is released. Pregabalin and gabapentin bind with high affinity to a specific subunit of these presynaptic calcium channels.^{3,11-13} This subunit is called the $\alpha_2\delta$ subunit, and these anticonvulsants are therefore called $\alpha_2\delta$ ligands. When

SODIUM CHANNEL BLOCKING ANTICONVULSANTS FOR CHRONIC PAIN

One hypothetical means of reducing chronic pain in such conditions may be to reduce neurotransmission in activated neurons within the pain pathway. Since anticonvulsants are capable

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.

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pregabalin and gabapentin bind to the $\alpha_2\delta$ subunit, they decrease calcium flow through the channel and therefore decrease neurotransmitter release from the presynaptic neuron, which presumably leads not only to anticonvulsant actions but to anxiolytic and antineuralgic (chronic pain-reducing) actions.^{3,11-13}

Presynaptic N and P/Q calcium channels are not to be confused with another subtype of voltage-gated calcium channel known as the L channel, which resides in membranes of vascular smooth muscle and is blocked by antihypertensives commonly known as "calcium channel blockers."^{3,14} Such drugs lower blood pressure but have no anticonvulsant, anxiolytic, or antineuralgic actions. Presynaptic N and P/Q calcium channels are also not to be confused with ligand-gated calcium channels such as the NMDA (*N*-methyl-D-aspartate) glutamate receptor, one of the key mediators of excitatory postsynaptic neurotransmission, which is loosely bound by the novel drug for the treatment of Alzheimer's disease, memantine, and tightly bound by the hallucinogen phencyclidine, neither of which acts at N or P/Q calcium channels.³

Preclinical studies have established the pain-relieving actions of the $\alpha_2\delta$ ligands pregabalin and gabapentin.^{15,16} Gabapentin is FDA approved for postherpetic neuralgia and is specifically recommended for the treatment of neuropathic pain.¹⁰ Pregabalin is a higher-potency analog of gabapentin with better bioavailability and potentially more consistent clinical effects. Numerous recent controlled clinical studies demonstrate efficacy in a variety of chronic pain conditions,⁴⁻⁶ including 2 for which there is no currently approved treatment, namely diabetic peripheral neuropathy⁵ and fibromyalgia.⁶ Pregabalin is under re-

Take-Home Points

- ◆ Continuous activation of neurotransmitter release in pain pathways may hypothetically underlie painful symptoms in diabetic peripheral neuropathy, post-herpetic neuralgia, fibromyalgia, and other chronic pain syndromes.
- ◆ The anticonvulsants pregabalin and gabapentin target the $\alpha_2\delta$ subunit of voltage-gated calcium channels and reduce neurotransmission in activated neuronal circuits by reducing the release of numerous neurotransmitters.
- ◆ Decreasing neurotransmission in pain pathways could hypothetically reduce painful symptoms in a wide variety of chronic pain syndromes.

view by the FDA for the treatment of chronic pain as well as epilepsy and anxiety. Thus, $\alpha_2\delta$ ligands may have a novel mechanism of action with implications for potentially broad therapeutic actions, i.e., the therapeutic potential of diminishing neurotransmission in activated neurons not only in the pain pathway of chronic pain conditions but also in the fear pathway of anxiety disorders and in epileptic neurons. ◆

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