Anticonvulsants as Anxiolytics, Part 2

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 may also prove to be novel anxiolytics.*

Activation of fear circuits is a leading hypothesis for explaining symptoms in anxiety disorders,[1–3] and returning neurotransmission in these circuits to a more normal pattern may reduce certain symptoms.[4] For example, anticonvulsants may theoretically reduce seizures by decreasing excessive output from epileptic neurons, and could, by analogy, reduce symptoms of anxiety if these agents were also able to decrease neuronal activation within fear circuits.[1–4] A newly discovered mechanism of reducing neurotransmission is employed by the anticonvulsants pregabalin and gabapentin: they bind to a specific subunit of one type of calcium channel—namely, the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels—which leads to reduction of neurotransmitter release.[5–10] If this reduction happens in amygdala-centered fear circuits, it might have anxiolytic actions.

KNOW YOUR CALCIUM CHANNELS: VOLTAGE-SENSITIVE OR LIGAND-GATED?

Most clinicians have heard of calcium channels, but only recently has it become clear that there are multiple subtypes of calcium channels, some regulated directly by voltage and others regulated directly by neurotransmitters, with each having unique physiologic functions as well as differential selectivity for specific drugs.[11] For example, calcium channels regulated by the charge across the membrane where they reside are called "voltage sensitive" or "voltage gated" whereas calcium channels regulated by neurotransmitters are called "ligand gated."

Voltage-Sensitive Channels

Two subtypes of calcium channels in the voltage-sensitive family—known as N and P/Q channels—regulate neurotransmitter release during synaptic neurotransmission.[11] On the one hand, when calcium flow through these presynaptic channels is increased during neurotransmission, neurotransmitter release is thus enhanced. On the other hand, when the $\alpha_2\delta$ ligands pregabalin and gabapentin bind to these channels and thereby decrease calcium flow through them, the release of several neurotransmitters from presynaptic neurons is decreased.[5–10]

Another subtype of voltage-gated calcium channels is an L channel, which resides in membranes of vascular smooth muscle and is blocked by antihypertensives commonly known as "calcium channel blockers."[11] Such drugs lower blood pressure but have neither anticonvulsant nor anxiolytic actions.

Ligand-Gated Channels

An example of a ligand-gated calcium channel is the NMDA (or *N*-methyl-D-aspartate) glutamate receptor complex, one of the key mediators of excitatory postsynaptic neurotransmission.[12] A novel drug for the treatment of Alzheimer's disease, memantine, binds loosely to the NMDA receptor complex, and the hallucinogen phencyclidine binds tightly to the NMDA receptor complex, but $\alpha_2\delta$ ligands do not bind to the NMDA receptor complex. Thus, postsynaptic ligand-gated cal-

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cium channels may cooperate with presynaptic voltage-gated calcium channels during neurotransmission, but their functions and pharmacology are quite unique.

COULD $\alpha_2\delta$ LIGANDS BE NOVEL ANXIOLYTICS?

Preclinical studies have established the anxiolytic actions of the $\alpha_2\delta$ ligand pregabalin.[13] Some preliminary clinical data have suggested that the $\alpha_2\delta$ ligand gabapentin may have anxiolytic properties after a case series reported marked clinical improvement with gabapentin as adjunctive therapy in patients with treatment-refractory anxiety disorders.[14] Also, a placebo-controlled study[15] in social phobia has shown that gabapentin reduced anxiety symptoms. Another study[16] in panic disorder found no overall gabapentin/placebo differences, only improvement in the more severely ill patients.

Take-Home Points

- Activation of neurotransmission in fear circuits may underlie symptoms in anxiety disorders.
- Agents such as pregabalin and gabapentin that target the $\alpha_2\delta$ subunits of voltage-gated calcium channels can reduce neurotransmission in activated neuronal circuits by reducing the release of neurotransmitters.
- Reducing neurotransmission in fear circuits could hypothetically reduce symptoms in anxiety disorders.

Compared with studies for gabapentin, much better designed studies of anxiety have been conducted for pregabalin, a higher-potency analog to gabapentin with better bioavailability and potentially more consistent clinical effects. Multicenter, placebo-controlled comparator trials of pregabalin in generalized anxiety disorder suggest comparable efficacy to benzodiazepines[17–19] and venlafaxine,[20] and these findings have been filed with the U.S. FDA for marketing approval in this indication. Preliminary findings with pregabalin in social phobia are also promising, and studies in other anxiety disorders, including panic disorder, are ongoing. Thus, it appears that the high-potency $\alpha_2\delta$ ligand pregabalin is promising to become a new anxiolytic with a novel mechanism of action.

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