# Mechanism of Action of $\alpha_2\delta$ Ligands: Voltage Sensitive Calcium Channel (VSCC) Modulators

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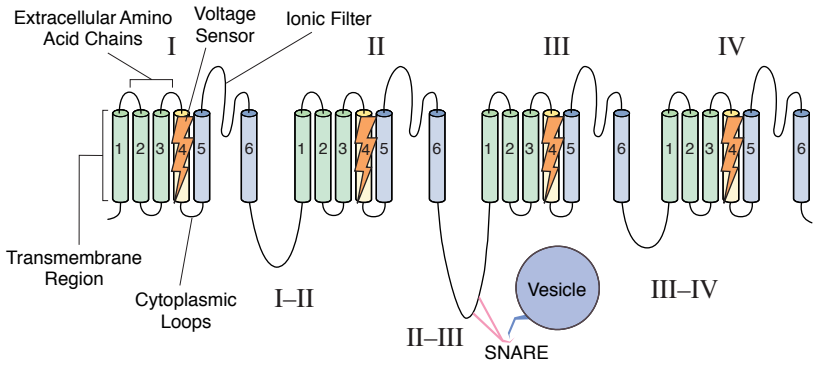
**Issue:** *Voltage sensitive calcium channels (VSCCs) have unique structures and functions that distinguish them from other ion channels, especially the voltage sensitive sodium channels (VSSCs). Modulation of VSCCs by certain drugs such as pregabalin and gabapentin via binding to the $\alpha_2\delta$ subunits of VSCCs can lead to anticonvulsant, anxiolytic, and chronic pain–relieving actions.*

Ion channels that are sensitive to changes in the charge across neuronal membranes are known as voltage sensitive or voltage gated ion channels and are critical to neurotransmission in the central nervous system.[1–5] Two major classes include those that conduct sodium ions, and are thus known as voltage sensitive sodium channels or VSSCs,[6] and those that conduct calcium ions, known as voltage sensitive calcium channels (VSCCs).[5] There are both similarities and important distinctions to the structures of these 2 classes of ion channels. Both have $\alpha$ units that form a pore to conduct the ion from outside the cell to the inside. Both have additional regulatory subunits, but those associated with VSSCs are much different than those associated with VSCCs. Specifically, an important $\alpha_2\delta$ subunit is uniquely associated with VSCCs and is specifically bound with high affinity and selectivity by 2 agents in a new therapeutic class known as $\alpha_2\delta$ ligands.[2,3] This binding action seems to confer anticonvulsant effects,[1] anxiolytic actions,[2] and activity in reducing chronic neuropathic pain.[3] Here we illustrate the structure and function of VSCCs, including their $\alpha_2\delta$ subunits, and show the similarities and differences of VSCCs compared with VSSCs, which were illustrated last month.[6]

**Figure 1. Four Subunits Connect to Form the Pore-Forming $\alpha_1$ Subunit of a Voltage Sensitive Calcium Channel (VSCC)**




Shown here is the connecting of 4 subunits of a voltage sensitive calcium channel (VSCC) that together form the pore of a calcium channel, also known as the "pore-forming" $\alpha$ unit. Just as for VSSCs,[6] segment 4 of each subunit of a VSCC is a voltage sensor capable of detecting changes in voltage across the neuronal transmembrane and reacting by changing the conformation of the pore, resulting in opening or closing of the channel. For VSCCs, the extracellular segments between segments 5 and 6 form an ionic filter that is configured to allow only calcium to enter the cell through the channel.

When 4 subunits are linked together, they form the pore-forming $\alpha$ unit of a VSCC, as shown here. The intracellular segments that connect each of these 4 subunits are sites of regulatory action. For VSCCs, the segment between the second and third subunits (II–III) can interact with SNARE proteins, allowing it to connect with synaptic vesicles and facilitate the vesicle's release of neurotransmitter.

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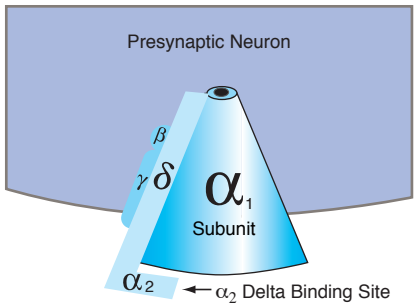
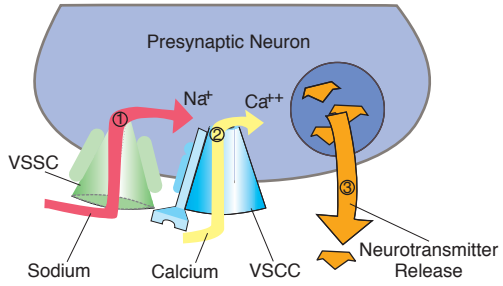
Figure 2. Calcium Channel With Multiple Subunits



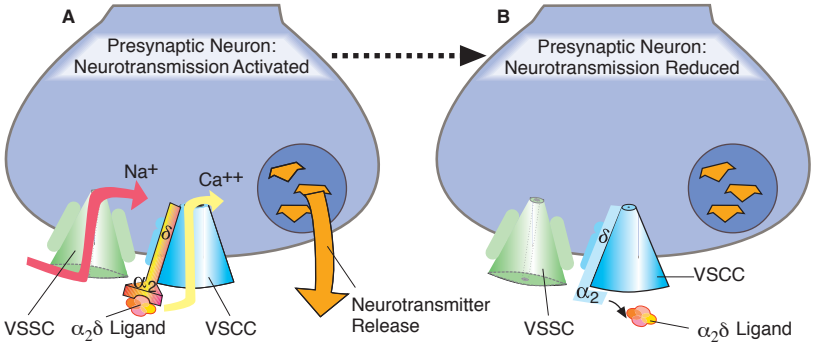

When the 4 subunits of the pore-forming α unit, shown strung together in Figure 1, are arranged in a circle, they form the channel for calcium ions. The calcium channel shown here comprises not only the pore-forming $\alpha_1$ subunit, but also several other subunits that are thought to exert regulatory influence on the ion channel, namely the β, γ, and $\alpha_2\delta$ subunits. A binding site for $\alpha_2\delta$ ligands is shown near the terminal of the extracellular portion of the $\alpha_2\delta$ subunit. Ligands bind preferentially to this site when the channel is open or activated (as shown in Figures 3 and 4) rather than when it is closed as shown here.

Figure 3. Role of Ion Channels in Neurotransmission




First, sodium enters the neuron through a voltage sensitive sodium channel (VSSC) as an action potential arrives in the axon terminal (arrow 1). Second, sodium's entry changes the voltage across the membrane of the neuron, and when the voltage change is sensed by the voltage sensitive calcium channel (VSCC), calcium then enters the neuron as well (arrow 2). Third, calcium's entry triggers neurotransmitter release from synaptic vesicles (arrow 3). Activation of neurotransmission can be a normal physiologic activity, but if excessive, can lead to epilepsy, anxiety, or pain, depending on where the neurons that are activated are located.

Figure 4. Actions of $\alpha_2\delta$ Ligands Inhibit Calcium Flux Through Voltage Sensitive Calcium Channels




The $\alpha_2\delta$ ligands such as pregabalin and gabapentin can bind to the activated voltage sensitive calcium channel (VSCC) at the $\alpha_2\delta$ subunit (A), which reduces calcium flow through the channel and diminishes neurotransmitter release (B). This inhibition of calcium entry with subsequent reduction of neurotransmitter release may be the mechanism by which $\alpha_2\delta$ ligands reduce symptoms associated with activation of neurons, such as anxiety, pain, and epilepsy.

## REFERENCES

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## Take-Home Points

- Voltage sensitive calcium channels (VSCCs) have a specific subunit, known as the $\alpha_2\delta$ subunit, that regulates the release of neurotransmitters from presynaptic nerve terminals by controlling the opening and closing of the calcium channel.
- Drugs such as pregabalin and gabapentin that target VSCCs by binding to this subunit are known as $\alpha_2\delta$ ligands and have anticonvulsant, anxiolytic, and chronic pain-relieving actions.
- VSCCs are distinct in structure and function from other ion channels in the CNS.