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.

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.

On 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. Two major classes include those that conduct sodium ions, and are thus known as voltage sensitive sodium channels or VSSCs, and those that conduct calcium ions, known as voltage sensitive calcium channels (VSCCs). 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. This binding action seems to confer anticonvulsant effects, anxiolytic actions, and activity in reducing chronic neuropathic pain. 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.

**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, 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.
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.

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