Mechanism of Action of Voltage Sensitive Sodium Channel Modulators

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Issue: *Voltage sensitive sodium channels (VSSCs) have a unique structure that distinguishes them from other ion channels. Modulation of VSSCs can lead to mood stabilizing, anticonvulsant, and chronic pain relieving actions.*

The structure and function of ion channels for sodium, known as voltage sensitive sodium channels or VSSCs, are being elucidated at a rapid rate.[1] Numerous anticonvulsants modulate VSSCs,[2] especially those that have mood stabilizing actions.[3] Other therapeutic actions that may be associated with modulation of VSSCs include the enhancement of antipsychotic action in schizophrenia[3] as well as the relief of pain in trigeminal neuralgia and migraine.[4] Here we illustrate the structure and function of VSSCs and the actions of various drugs that modulate them. Next month we will illustrate another important type of ion channel, namely voltage sensitive calcium channels, or VSCCs.

Take-Home Points

- Voltage sensitive sodium channels (VSSCs) are targets for numerous anticonvulsants such as lamotrigine, carbamazepine, and oxcarbazepine and probably also valproate and topiramate.
- Modulation of VSSCs by some anticonvulsants can stabilize mood, augment antipsychotics in schizophrenia, and relieve certain neuropathic pain conditions.
- VSSCs are distinct in structure and function from other ion channels in the central nervous system, including those for calcium, known as voltage sensitive calcium channels or VSCCs.

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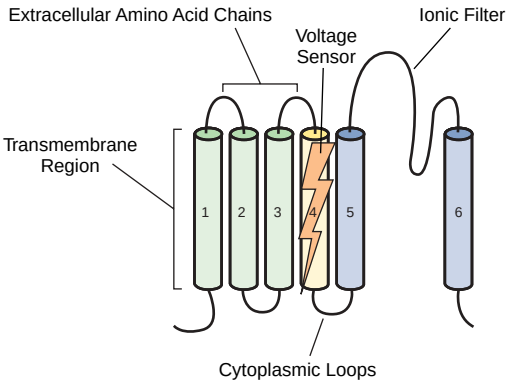
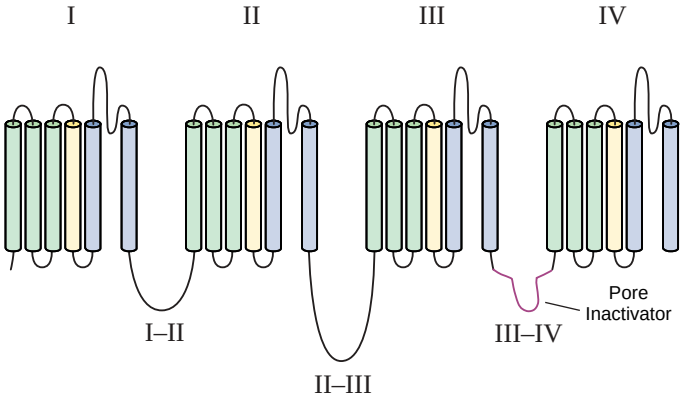
Figure 1. Subunit of a Voltage Sensitive Sodium Channel



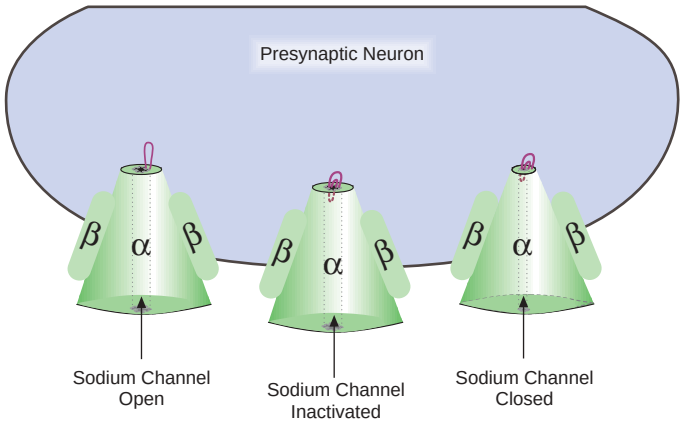
A voltage sensitive (also known as voltage gated) sodium channel is composed of subunits that have 6 transmembrane regions. Segment 4 is a voltage sensor and changes its conformation when it detects alterations in the charge across the neuronal membrane. The extracellular segments between the 5th and 6th transmembrane regions form an ionic filter that only allows the sodium ion to enter when the channel is open.

Figure 2. Four Subunits Connect to Form a Voltage Sensitive Sodium Channel



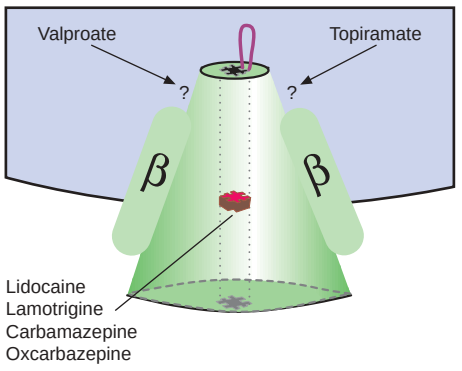
The "pore-forming" α unit of the voltage sensitive sodium channel is created when 4 of the subunits (Figure 1) are connected. Cytoplasmic segments that connect each of these 4 subunits are sites of regulatory action. For example, the segment between the third and fourth subunits (III–IV) forms a pore inactivator that can plug up the channel to stop the flow of sodium ions.

Figure 3. Three States of a Voltage Sensitive Sodium Channel (VSSC)



When the 4 subunits of the α pore-forming unit (shown stretched laterally in Figure 2) are arranged in a circle, they form the channel for sodium ions. Each VSSC shown here comprises not only the α pore-forming unit, but also 2 associated β units that are thought to exert regulatory influence on the ion channel. The first VSSC (on the left) is open, and sodium ions can flow through it into the neuron. The center VSSC is inactivated, and the pore inactivator is plugging up the open channel. In this state, the channel is rapidly inactivated and cannot conduct sodium ions into the cell. Finally, the VSSC on the far right is closed (and inactivated), a state in which ion flux is much reduced.

Figure 4. Pharmacologic Agents Having Actions Upon Voltage Sensitive Sodium Channels (VSSCs)



Various pharmacologic agents have actions upon VSSCs, which may explain their therapeutic effects in epilepsy, bipolar disorder, and pain. Effects of drugs on VSSCs may also explain side effects such as sedation and ataxia. Several agents bind to a specific site in the channel itself and are thus known as "open channel" or "use-dependent" inhibitors of VSSCs. Such drugs include lamotrigine, carbamazepine, oxcarbazepine, and lidocaine. Valproate and topiramate are also thought to act upon VSSCs, but at a different site that is not yet well characterized.