13.4 VOLTAGE-GATED SODIUM CHANNELS

13.4.1 Structure and Molecular Biology of Voltage-Gated Sodium Channels

Functionally, Na_Vs are closed at the resting membrane potential and open when the membrane becomes depolarized, activation requiring membrane potentials of –70 to –30 mV, with some variation between different Na_V types. Most Na_Vs inactivate within ~1–10 ms in the presence of sustained depolarization. In certain types of neurons, a more persistent Na_V current with slow inactivation has also been identified.

At the molecular level, Na_Vs are composed of a large (~2000 amino acid residues) α-subunit which is structurally similar to the α_1-subunit of Ca_Vs, and forms the ion conducting pore (Figure 13.7a). The rapid inactivation of most Na_Vs is explained by the cytoplasmic domain III–IV linker (Figure 13.9b h motiv) which functions as a "hinged lid," that simply swings in to occlude the intracellular mouth of the pore.

Nine different Na_V α-subunits ($Na_V1.1$–$Na_V1.9$) have been cloned and all these display >50% amino acid identity with each other, so they compose one subfamily. The Na_V1 family has most likely arisen from a single ancestral gene and that their present diversity reflects gene duplication events and chromosomal rearrangements occurring late in evolution.

By analogy to the Ca_Vs, functional Na_Vs can be formed from expression of α-subunits alone although native Na_Vs are protein complexes composed by α-subunits and auxiliary subunits. Only a single class of auxiliary Na_V subunits (β-subunits) has been identified. β-Subunits are composed of a large extracellular part, through which it interacts with the α-subunit (Figure 13.7b) and a small C-terminal portion consisting of a single transmembrane segment. The function of the β-subunits can be divided into (1) modulation of the functional properties of Na_Vs, (2) enhancement of membrane expression, and (3) mediating interactions between Na_Vs and extracellular matrix proteins as well as various signal transduction molecules. Moreover, the β-subunits are also suggested to serve a number of non-Na_V channel-modulating roles, including modulation of brain development.

13.4.2 Physiological Roles of Voltage-Gated Sodium Channels

The biological importance of Na_Vs relies on their ability to cause depolarization of cell membranes. Most of the Na_V α-subunits are capable of detecting even very small increases in membrane potential and this makes the Na_Vs activate, and subsequently inactivate, on a ms timescale. This combination of high sensitivity toward depolarization and very rapid gating kinetics make Na_Vs perfect for initiating and conducting APs.

$Na_V1.1$, $Na_V1.2$, $Na_V1.3$, or $Na_V1.6$ subunits are expressed in virtually all neurons within the CNS, in particular at the base and along the entire length of the axon. When an excitatory synaptic signal (e.g., glutamate, released by a neighboring neuron, acting on AMPA receptors, see Chapter 15) is received, this generates a small depolarization of the neuronal membrane in the dendrites and cell body. This rather modest depolarization is sufficient for activating Na_Vs at the initial segment of the axon, leading to the generation of an AP. Once the AP reaches the nerve terminal, this will activate Ca_Vs, leading to release of neurotransmitter. The importance of these Na_Vs for AP initiation and conduction is also highlighted by the fact that point mutations in the genes encoding $Na_V1.1$, $Na_V1.2$, and $Na_V1.3$ which alter their functional properties, have been linked to certain forms of epilepsy.

Dorsal root ganglion (DRG) neurons are important for transmitting sensory signals, including pain, from the periphery to the CNS. Sensory stimulation leads to generation and conduction of APs in DRG neurons and these APs are mediated by Na_Vs. Na_Vs of DRG neurons contain the $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ subunits which are almost exclusively expressed in these neurons. It has also been shown that expression of these α-subunits is altered in a complex fashion in animal models