TABLE 13.2
Ca_V Channel Terminology and Properties

Channel Subtype	Ca_V1	Ca_V2	Ca_V3
Former names	L-type	$Ca_V2.1$ = P/Q type $Ca_V2.2$ = N type $Ca_V2.3$ = R type	T-type
Activation threshold	High voltage	High voltage	Low voltage
Blocker	Dihydropyridines Phenylalkylamines Benzothiazepines	$Ca_V2.1$ blockers: ω-conotoxin MVIIC, ω-agatoxin IVA $Ca_V2.2$: blockers: ω-conotoxin GVIA, ω-conotoxin MVIIA $Ca_V2.3$ blocker: SNX-482	Mibefradil (*R*)-Efonidipine Kurtoxin

The major component of the Ca_V is the large α_1 subunit, consisting of approximately 2000 amino acid residues. This subunit has 24 TM segments, arranged in four linked homologous domains (I–IV), each comprising six transmembrane α-helices (S1–S6), including the positively charged voltage-sensing S4 segments, and the S5–S6 pore loops, with the pore loops and S6 segments believed to line the channel lumen; the structure of the α_1- and other Ca_V subunits is schematically shown in Figure 13.7a.

Ca_Vs are several thousand-fold selective for Ca^{2+} ions over Na^+ and K^+ and this amazing selectivity is created by a ring of four negatively charged glutamic acid residues projecting into the ion channel pore, one such residue being contributed by each of the four pore loops.

When expressed alone, the α_1 subunit can form a functional ion channel. But native Ca_Vs are multisubunit complexes in which the α_1 subunit interacts with a cytoplasmic β subunit, an extracellular membrane leaflet anchored α2δ subunit, and a 4-transmembrane spanning γ subunit (Figure 13.7b). The role of these subunits is to regulate surface expression, gating, and the pharmacological properties of Ca_Vs.

13.3.2 Physiological Roles of Voltage-Gated Calcium Channels

Ca^{2+} is an important second messenger molecule in eukaryotic cells where it initiates muscle contraction, neurotransmitter release, and activates many types of protein kinases. Many homeostatic mechanisms operate to keep intracellular $[Ca^{2+}] < 100$ nM under resting conditions. Outside the cell, $[Ca^{2+}]$ is 1–2 mM, creating a 10,000-fold concentration gradient. The Ca^{2+}-equilibrium potential is > +100 mV so Ca^{2+} always flows into a cell, when Ca_Vs are activated by depolarization. While the primary function of voltage-gated Na^+ and K^+ channels is to produce depolarization/re-polarization of the cell membrane, voltage-gated Ca^{2+} channels should be thought of as "gatekeepers" of calcium entry into excitable cells. Thereby, they constitute the principal entrance for calcium influx in nerves, endocrine, and muscle cells.

In muscle tissue, binding of Ca^{2+} to the protein troponin C allows myosin-mediated sliding of actin filaments, leading to shortening of muscle fibers. In skeletal muscle, the calcium necessary for this process actually comes from the sarcoplasmic reticulum and is released from this into the cytoplasm via ryanodine receptors. In this particular context, the Ca_V functions as a voltage sensor for the process—a direct interaction between the $Ca_V1.1$ α_1 subunit and the ryanodine receptors then activate the Ca^{2+} release.

Ca_Vs are also very important in cardiac and smooth muscle, where direct Ca^{2+}-influx through the Ca_V itself provides the Ca^{2+} necessary for muscular contraction. In cardiac muscle, $Ca_V1.2$ or $Ca_V1.3$ is responsible for the plateau phase of the cardiac AP which is important for cardiac muscle