L-Type Calcium Channels
Highs and New Lows

Diane Lipscombe

Voltage-gated calcium channels are essential for coupling membrane depolarization to the influx of calcium in all excitable cells. The calcium that flows into excitable cells through voltage-gated calcium channels serves a dual function, generating both electrical and chemical signals. The intracellular events controlled by calcium are diverse and many. Excitable cells can select from a number of functionally distinct voltage-gated calcium channel subunits, whose activities are precisely tuned to support specific tasks. These include excitation-contraction coupling in muscle, excitation-secretion coupling in neurons, hair cells, and endocrine cells, and regulation of gene expression.1–5 Ten genes encode the main CaV1 channel complex in mammals.6 Sequence comparisons among CaV subunits from several genomes reveal three major families, CaV1α, CaV2α, and CaV3α.6

Even before the availability of selective toxins, several investigators demonstrated that multiple, functionally distinct classes of voltage-gated calcium channels are expressed in a variety of cell types including heart.8–11 This division was based on the presence of two distinct classes of calcium channels that differed significantly in their voltage-dependent activation. The concept of low-voltage-activated and high voltage-activated calcium channels was established, and although simple, this remains a useful and informative way for distinguishing among different classes of calcium channels.

Certain features have emerged from studies of voltage-gated calcium channels in heart and neurons that have established a set of standard criteria to define the presence of a specific Ca2+ channel subtype. Low-voltage-activated, T-type, Ca2+ channels that contain CaVα3α subunits (α6G, α1B, α1D) activate rapidly, deactivate slowly, exhibit pronounced voltage-dependent inactivation, and are insensitive to dihydropyridines and several other toxins that inhibit neuronal calcium channels. In studies of heart tissue, high voltage-activated calcium channels have become synonymous with L-type CaV1α (α1C, α1D)-containing channels that activate with slower kinetics, but deactivate more rapidly than T-type. They exhibit weak voltage-dependent inactivation, but strong calcium-dependent inactivation, and are sensitive to dihydropyridines.6,12 In neurons, high voltage-activated Ca2+ channels are further subdivided into dihydropyridine-sensitive, L-type and dihydropyridine-insensitive, P/Q-, N-, and R-type that contain CaV2α1 subunits (α1A, α1B, α1D).6,12,13

With low activation thresholds and pronounced voltage-dependent inactivation, T-type Ca2+ channels are optimized for contributing to depolarizing currents during the slow diastolic depolarization phase that supports pacemaking in the sinoatrial (SA) node.8,9,14,15 The presence of CaVα3α genes in SA nodal tissue of heart supports this view.16 L-type Ca2+ channels, on the other hand, until recently were implicated in later phases of the diastolic depolarization as the membrane potential depolarizes beyond about −30 mV. Their reliance on stronger depolarization for activation is consistent with the view that L-type Ca2+ channels do not contribute to initiation of the action potential. However, recent studies of CaV1α knockout mice, including those of Chiamvimonvat and colleagues reported in this issue of Circulation Research, offer strong evidence supporting a role for L-type Ca2+ channels in action potential initiation in the SA node.17,18 In both studies, mice lacking the L-type CaV1.3α1 gene exhibit significant SA node dysfunction characterized by sinus bradycardia. Other investigators also report complete hearing loss, consistent with prominent expression of CaV1.3α1 in inner hair cells of the cochlea.18,19

These findings are clearly paradoxical to classic descriptions of L-type Ca2+ channels as high voltage-activated. The explanation is relatively simple. CaV1.3α1 L-type Ca2+ channels are not high voltage-activated. Evidence supporting this conclusion is presented in both the Striessnig and Chiamvimonvat studies by comparing properties of native currents in wild-type and CaV1.3α1 knockout mice.17,18 Others studies characterizing the functional properties of recently cloned CaV1.3α1 subunits isolated from neurons and endocrine cells provide additional support.18,20–22

Striessnig and colleagues recorded from inner hair cells of the cochlea of CaV1.3α1−/− mice and showed selective loss of a low-threshold activating Ca2+ current. From this they inferred the presence of a similar current in SA node cells to explain the observed abnormalities in pacemaking in the same mice.18 Chiamvimonvat and colleagues now test this hypothesis directly by recording from the SA node and from isolated cells of wild-type and CaV1.3α1−/− mice.17 As reported in this issue of Circulation Research, the absence of CaV1.3α1 is associated with a reduced rate of SA node firing, diastolic depolarization rate slowing at relatively hyperpolarized voltages (−40 and −45 mV), and the loss of calcium current in isolated SA node cells that activates at relatively hyperpolarized membrane potentials.17 These new studies offer strong support that CaV1.3α1 ablation, SA node dysfunc-

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tion, and the loss of a low-threshold activating Ca\(^{2+}\) current in SA node cells are intimately linked.

Do all L-type Ca\(^{2+}\) channels that contain Ca\(_{v}1.3\alpha_{1}\) subunit activate at hyperpolarized voltages? The answer is probably yes, based on recent functional analyses of recombinant Ca\(_{v}1.3\alpha_{1}\) channels.20–22 The Figure compares peak current-voltage relationships of Ca\(_{v}1.3\alpha_{1}\) L-type channels to high voltage-activated Ca\(_{v}1.2\alpha_{1}\) L-type, and to low voltage-activated Ca\(_{v}3.1\alpha_{1}\) T-type channels. The large difference in voltage dependence of activation between the two L-type Ca\(^{2+}\) channels is as striking as the similarity in the activation thresholds of Ca\(_{v}1.3\alpha_{1}\) L-type and Ca\(_{v}3.1\alpha_{1}\) T-type channels.20,23 While properties of calcium channels are influenced by several factors including association with specific auxiliary subunits, the similar features of Ca\(_{v}1.3\alpha_{1}\) subunits cloned from different tissues,20–22 combined with two gene ablation studies in mice,17,18 favor the conclusion that low voltage-activated Ca\(_{v}1.3\alpha_{1}\) L-type channels undergo prominent voltage-dependent inactivation. Further, Ca\(_{v}1.3\alpha_{1}\) L-type Ca\(^{2+}\) channel subtypes that dominate in heart.25

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