Editors

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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 Ca\(^{2+}\) 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 Ca\(_V\)\(_{1\alpha}\) subunit of the voltage-gated calcium channel complex in mammals.\(^6\) Sequence comparisons among Ca\(_V\)\(_{1\alpha}\) genes from several genomes reveal three major families, Ca\(_V\)\(_{1\alpha}\), Ca\(_V\)\(_{2\alpha}\), and Ca\(_V\)\(_{3\alpha}\).\(^6\)

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 dependence of 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 Ca\(^{2+}\) channel subtype. Low-voltage-activated, T-type, Ca\(^{2+}\) channels that contain Ca\(_V\)\(_{3\alpha}\) subunits (\(\alpha_{\text{C}}\), \(\alpha_{\text{IB}}\), \(\alpha_{\text{III}}\)) 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 were established, and although simple, this remains a useful and informative way for distinguishing among different classes of calcium channels.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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L-type Ca\textsubscript{v}1.3\textsubscript{\alpha} channels activate at negative membrane potentials similar to T-type Ca\textsubscript{v}3.1 channels. Normalized, peak current-voltage relationships for L-type Ca\textsubscript{v}1.3\textsubscript{\alpha}, T-type Ca\textsubscript{v}3.1\textsubscript{\alpha}, and L-type Ca\textsubscript{v}1.2\textsubscript{\alpha} are compared. Activation midpoints (V\textsubscript{1/2}) are approximately −30 mV for L-type Ca\textsubscript{v}1.3\textsubscript{\alpha} and T-type Ca\textsubscript{v}3.1\textsubscript{\alpha}, and −5 mV for L-type Ca\textsubscript{v}1.2\textsubscript{\alpha}. Curves were generated by a Boltzmann-GHK function using parameters obtained from recombinant channels expressed in Xenopus oocytes recorded under similar conditions (10 mmol/L extracellular barium\textsuperscript{20,29}).

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

Do all L-type Ca\textsuperscript{2+} channels that contain Ca\textsubscript{v}1.3\textsubscript{\alpha} subunit activate at hyperpolarized voltages? The answer is probably yes, based on recent functional analyses of recombinant Ca\textsubscript{v}1.3\textsubscript{\alpha} channels.\textsuperscript{20–22} The Figure compares peak current voltage relationships of Ca\textsubscript{v}1.3\textsubscript{\alpha} L-type channels to high voltage-activated Ca\textsubscript{v}1.2\textsubscript{\alpha} L-type, and to low voltage-activated Ca\textsubscript{v}3.1\textsubscript{\alpha} T-type channels. The large difference in voltage dependence of activation between the two L-type Ca\textsuperscript{2+} channels is as striking as the similarity in the activation thresholds of Ca\textsubscript{v}1.3\textsubscript{\alpha} L-type and Ca\textsubscript{v}3.1\textsubscript{\alpha} T-type channels.\textsuperscript{20,23} While properties of calcium channels are influenced by several factors including association with specific auxiliary subunits, the similar features of Ca\textsubscript{v}1.3\textsubscript{\alpha} subunits cloned from different tissues,\textsuperscript{20–22} combined with two gene ablation studies in mice,\textsuperscript{17,18} favor the conclusion that low voltage-dependent activation is an intrinsic feature of Ca\textsubscript{v}1.3\textsubscript{\alpha}-containing L-type Ca\textsuperscript{2+} channels. Clearly, significant functional differences exist among L-type Ca\textsubscript{v}1\textsubscript{\alpha} genes.

If Ca\textsubscript{v}1.3\textsubscript{\alpha}-containing L channels activate at hyperpolarized membrane potentials, it is rather surprising that this feature has not been highlighted in previous studies of cloned and heterologously expressed channels. Although other factors almost certainly influence channel properties, the concentration of extracellular divalent cation has large effects on the voltage dependence of activation as a result of charge screening and is a factor that differs significantly among studies. For unknown reasons, achieving high expression screening and is a factor that differs significantly among tissues,\textsuperscript{20} favor the conclusion that low voltage-activated T-type channels are very low in the SA node, particularly when compared with Ca\textsubscript{v}3.1\textsubscript{\alpha} T-type mRNA.\textsuperscript{16} The availability of a selective inhibitor of Ca\textsubscript{v}1.3\textsubscript{\alpha}-containing L channels would prove a useful tool to determine the relative contribution of this channel to SA node function. Classic L-type Ca\textsuperscript{2+} channel blockers are not useful in this regard. Recent studies of recombinant Ca\textsubscript{v}1.3\textsubscript{\alpha} L-type channels suggest a relatively low sensitivity to block by dihydropyridines compared with Ca\textsubscript{v}1.2\textsubscript{\alpha} L-type channels.\textsuperscript{20,21} It will be of interest to establish whether a unique splice isoform of Ca\textsubscript{v}1.3\textsubscript{\alpha} mRNA is expressed in the SA node. There is evidence for some level of atrial-specific splicing of Ca\textsubscript{v}1.3\textsubscript{\alpha} RNA in the S3–S4 linker of domain IV of the channel.\textsuperscript{25} Splicing at this site shifts the voltage dependence of activation by <10 mV and does not seem to influence dihydropyridine binding.\textsuperscript{26} Finally, given the emphasis placed on similarities between Ca\textsubscript{v}1.3\textsubscript{\alpha} L-type and T-type Ca\textsuperscript{2+} channels in terms of their activation thresholds, it is worth noting features that distinguish these channels. Whereas T-type Ca\textsuperscript{2+} channels undergo prominent voltage-dependent inactivation, Ca\textsubscript{v}1.3\textsubscript{\alpha} L-type Ca\textsuperscript{2+} channels show weak voltage-dependent, but strong calcium-dependent, inactivation. Further, Ca\textsubscript{v}1.3\textsubscript{\alpha} L-type Ca\textsuperscript{2+} channels deactivate rapidly compared with T-type Ca\textsuperscript{2+} channel subtypes that dominate in heart.

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