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PERSPECTIVES

The L-type calcium channel C-terminus: sparking interest beyond its role in calcium-dependent inactivation

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It is well established that members of the Ca_v1 (L-type) calcium channel family trigger a number of critical cellular responses. In skeletal muscle, $Ca_v1.1$ calcium channels mediate excitation–contraction (EC) coupling by acting as voltage sensors that trigger the opening of ryanodine receptors and, thus, calcium release from the sarcoplasmic reticulum (SR). The changes in membrane potential are transduced to the ryanodine receptor through physical interactions with the second intracellular loop of the $Ca_v1.1$ calcium channel α_1 subunit (Tanabe *et al.* 1990). This interaction also alters L-type calcium channel function, thereby providing for a possible feedback mechanism for the regulation of skeletal muscle EC coupling (Nakai *et al.* 1996). In heart and smooth muscle, calcium influx through $Ca_v1.2$ channels results in calcium-induced calcium release from ryanodine-sensitive internal stores, which subsequently triggers muscle contraction. This process is initiated by calcium 'sparks' (i.e. highly localized rises in intracellular calcium concentrations near the inner mouth of the L-type calcium channel pore; Cheng *et al.* 1993). Similar to the feedback regulation of skeletal muscle EC coupling, the increase in local calcium concentration regulates calcium channel activity *per se* through calcium-dependent inactivation, a process that is critically dependent on calmodulin binding to an IQ motif in the C-terminal region of the L-type calcium channel α_1 subunit (Peterson *et al.* 1999). The introduction of dominant negative calmodulin mutants into cardiac myocytes disrupts calcium-dependent inactivation, which then culminates in a fivefold prolongation of cardiac action potentials (Alseikhan *et al.* 2002). This clearly underlines the physiological significance of such feedback inhibition.

An article by Woo *et al.* (2003) in this issue of *The Journal of Physiology* suggests an additional function of the L-type channel C-terminus–calmodulin complex in regulating calcium sparks and calcium-induced calcium release in cardiac myocytes. Woo and colleagues used a combination of electrophysiological recordings and two-dimensional confocal calcium imaging to explore the role of the $Ca_v1.2$ C-terminus in the regulation of calcium signalling in cardiac myocytes. Intracellular dialysis of myocytes with a short $Ca_v1.2$ C-terminus calmodulin-binding peptide (located upstream of the IQ locus) resulted in an increase in the frequency of spontaneous calcium sparks and in an increased rate of caffeine-induced SR calcium release. Although L-type calcium channel function *per se* was not affected, the overall size of the calcium transients was increased. Mutant peptides that are incapable of associating with calmodulin were ineffective, indicating that the regulation of calcium sparks is dependent on a physical association between the L-type calcium channel C-terminus and calmodulin. Surprisingly, the observed effects occurred selectively at the central portion of the myocyte where, unlike at the periphery, calcium channels and ryanodine receptors do not appear to be colocalized. The latter observation suggests that the $Ca_v1.2$-C-terminus–calmodulin complex only has access to those ryanodine receptors that are not already colocalized with calcium channels, thus perhaps implying that the receptors expressed at the periphery are already sensitized by interactions with endogenous L-type channels. Taken together, the authors present intriguing evidence suggesting that cardiac ryanodine receptor function, and thus presumably cardiac muscle contraction, could be regulated by dynamic interactions with the L-type calcium channel–calmodulin complex. In view of evidence showing that calmodulin interactions with the C-terminus of $Ca_v1.2$ calcium channels triggers cAMP response element-binding protein (CREB)-mediated gene transcription in neurons (Dolmetsch *et al.* 2001; Mermelstein *et al.* 2001), this suggests that the calmodulin–L-type channel complex may act as a multifaceted signalling entity in excitable cells.

Although the data presented by Woo *et al.* are interesting, further experimentation will be necessary to confirm the presence of L-type channel–calmodulin–ryanodine receptor complexes in cardiomyocytes and to elucidate the exact underlying molecular determinants, such as the identification of interaction sites on the ryanodine receptor molecule. Moreover, it will be necessary to establish a putative role of these interactions in regulating cardiac action potential properties, perhaps by utilizing elegant viral infection approaches such as those developed by the Yue laboratory (Aklseikhan *et al.* 2002). Finally, in view of increasing evidence of a voltage-dependent component of cardiac EC coupling (for review, see Ferrier & Howlett, 2001), it will be important to examine whether voltage-dependent changes in the interactions between calmodulin, L-type channels and cardiac ryanodine receptors could account for such a mechanism.

Clearly, the regulation of calcium signalling in cardiac myocytes remains a complex issue. Nonetheless, the work of Woo *et al.* has opened novel avenues for investigations that may ultimately bring us closer to understanding the molecular details underlying the control of cardiac function.

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