A Novel Ca\(^{2+}\) Channel in Vascular Smooth Muscle?

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Contraction of vascular smooth muscle cells (VSMCs) requires an increase in \([Ca^{2+}]\). This increase can occur via Ca\(^{2+}\) release from the sarcoplasmic reticulum or by influx of Ca\(^{2+}\) from the extracellular space through voltage-dependent Ca\(^{2+}\) channels (VDCCs) or receptor operated nonselective cation channels. A number of studies using dissociated or cultured VSMCs with origins from a range of vascular beds have demonstrated, using electrophysiological and molecular techniques, that a major contribution to Ca\(^{2+}\) influx in response to membrane depolarization and/or vasoactive agents is mediated via VDCCs. Two types of VDCCs have been recorded in VSMCs: L- and T-type. The L-type Ca\(^{2+}\) current is classified as high voltage activated (HVA) because it activates at membrane potentials at or more positive than −40 mV. The L-type class of VDCCs has a distinct pharmacology. L-type VDCCs are dihydropyridine (DHP) sensitive, and molecular cloning has confirmed that these channels contain unique domains on the pore-forming α subunit that confer this sensitivity. Because the L-type VDCC is a major contributor to vascular tone, its unique pharmacology has been exploited to treat cardiovascular disorders such as hypertension. However, the ubiquitous expression of L-type Ca\(^{2+}\) channels in many cell types causes undesirable side effects when DHPs are clinically used.

Fewer published studies have shown that T-type Ca\(^{2+}\) current exists in smooth muscle cells. Unlike the HVA channels, electrophysiological data show that T-type Ca\(^{2+}\) current is DHP insensitive and activates at more negative membrane potentials. Additionally, T-type Ca\(^{2+}\) current inactivates whereas HVA channels show relatively little inactivation during a depolarizing voltage step. At first glance, this would seem a likely therapeutic target. However, the physiological role of this current component in VSMCs remains unclear. In fact, molecular evidence is needed in VSMCs to confirm that this current component is actually carried via T-type Ca\(^{2+}\) channels. In this issue of Circulation Research, Morita et al. use RT-PCR in an attempt to uncover the DHP-insensitive component of the Ca\(^{2+}\) current in RNA isolated from terminal mesenteric resistance arterioles of the guinea pig to be DHP insensitive. When VSMCs from more distal arterioles in the mesenteric vascular bed are examined, the DHP-insensitive current approached 100% of the total Ca\(^{2+}\) current. The extremely high expression is not paralleled by previous studies of non-L-type Ca\(^{2+}\) current in VSMCs. This study opens the possibility of a new therapeutic target for the management of vascular resistance.

A traditional interpretation of the data presented by Morita et al. may lead to the conclusion that the residual Ca\(^{2+}\) current was T-type, as previously found in other smooth muscle cell types, or R-type, which has not been found previously in VSMCs. Perez-Reyes’ group, in 1998 and 1999, has cloned and characterized the α subunits that underlie T-type Ca\(^{2+}\) current: α\(_{1G}\), α\(_{1H}\), and α\(_{1I}\). Assigning a molecular identity to these channels has shifted previous notions that α\(_{1E}\) was the mediator of LVA current and provides further evidence that α\(_{1E}\) is the molecular equivalent of R-type Ca\(^{2+}\) current. R-type Ca\(^{2+}\) current, so named because it is resistant to antagonists used to identify other Ca\(^{2+}\) channel subtypes, is predominantly neuronal and activates at membrane potentials near −50 mV. Despite its obviously distinct activation characteristics, R-type Ca\(^{2+}\) current is classified as HVA current on the basis of the sequence homology of the α subunit compared with other HVA channels and on other electrophysiological characteristics that are more like HVA channels. In fact, one could speculate that because T- and R-type Ca\(^{2+}\) current are very similar in their kinetic and pharmacological profiles, what was previously characterized as T-type Ca\(^{2+}\) current in VSMCs could indeed be a regulated R-type Ca\(^{2+}\) current (ie, channel phosphorylation, β subunit assembly, or other protein-protein interactions).

Morita et al. compare the characteristics of the DHP-insensitive current in guinea pig mesenteric arteriolar VSMCs with characteristics of both T- and R-type Ca\(^{2+}\) current. Although the activation parameters of the current in question are similar to those of R-type Ca\(^{2+}\) current, the inactivation parameters, particularly the time constant of inactivation, are strikingly similar to those of T-type Ca\(^{2+}\) current. Permeability analysis reveals that the DHP-insensitive current in this study is more similar to R-type Ca\(^{2+}\) current. However, pharmacological analysis of the current, according to traditional criteria such as nickel and cadmium sensitivity, does not clearly define it as R-type Ca\(^{2+}\) current. These conflicting data seem to make classification of this Ca\(^{2+}\) current as T-type or R-type unfeasible (see Table in Morita et al. for further clarification).

Molecularly, Morita et al. use RT-PCR in an attempt to uncover the DHP-insensitive component of the Ca\(^{2+}\) current in RNA isolated from terminal mesenteric resistance arterioles of guinea pig. Although α\(_{1E}\), the equivalent of the DHP-sensitive current, mRNA is present, α\(_{1E}\) cannot be amplified under the same conditions that reveal α\(_{1E}\) presence...
in mRNA isolated from cerebellum. Despite the availability of the sequence for T-type Ca\(^{2+}\) channels, Morita et al\(^8\) do not attempt to classify their current as LVA, and as such, do not probe for its presence using RT-PCR. Regardless of this oversight, the evidence presented in this study points to the possibility of a novel Ca\(^{2+}\) channel with characteristics overlapping both R-type and T-type current and perhaps bridges the gap between LVA and HVA Ca\(^{2+}\) channel families.

The relatively large expression of the DHP-insensitive current, approaching 100% of the total Ca\(^{2+}\) current in the mesenteric terminal arterioles, argues for a more significant role of non–L-type Ca\(^{2+}\) current in maintenance or alteration of vascular tone than has been suggested.\(^1\) However, before a ubiquitous role of this current is assigned, more arteriolar preparations from a number of different vascular beds must show both electrophysiological and molecular evidence of non–DHP-sensitive Ca\(^{2+}\) current. In fact, in VSMCs from a number of small arteriolar preparations, including those of the kidney, no DHP-insensitive Ca\(^{2+}\) current component is resolved.\(^1\) Given that the tone of small resistance arterioles contributes more significantly to alterations in blood pressure than does the tone of larger conduit vessels, perhaps the DHP-insensitive Ca\(^{2+}\) current, reported by Morita et al,\(^8\) is a more rational, more effective therapeutic target than L-type Ca\(^{2+}\) current. A novel Ca\(^{2+}\) current type, or even R-type Ca\(^{2+}\) current, in these vessels would be an exciting target for clinical agents without many of the cardiovascular side effects.

The findings presented by Morita et al\(^8\) fuel curiosity regarding the molecular identity of the Ca\(^{2+}\) currents in resistance arterioles, which hopefully will be elucidated in the near future. If the current is indeed carried via a novel Ca\(^{2+}\) channel subtype, structural analysis of this channel compared with the HVA and LVA families is likely to reveal nonconserved gating regions that can be exploited for rational drug design for the treatment of cardiovascular diseases. Data presented in Morita et al\(^8\) will no doubt spark interest in the molecular identity of the DHP-insensitive Ca\(^{2+}\) current component in mesenteric resistance arterioles, not only for potential therapeutic value but also for reinvestigation of former dogma regarding the role of non–L-type Ca\(^{2+}\) current in vascular smooth muscle cells.

References


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