Perspective

Sodium-Calcium Exchange in Excitable Cells: Fuzzy Space

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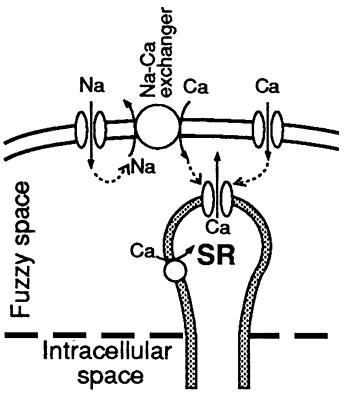
THE CONCENTRATION OF INTRACELLULAR CALCIUM ($[Ca^{2+}]_i$) is an important cellular signal. The Na^+-Ca^{2+} exchange mechanism helps to regulate $[Ca^{2+}]_i$ in diverse cells, including heart cells, retinal photoreceptors, smooth muscle cells, epithelial cells, and neurons (*1*). Because so much has been learned about the Na^+-Ca^{2+} exchanger since it was identified 23 years ago (*2, 3*), many investigators may be surprised by the findings in this issue of *Science* of Leblanc and Hume (*4*) and Bridge, Smolley, and Spitzer (*5*), and their implications.

The Na^+-Ca^{2+} exchanger is a protein that uses the electrochemical gradient for Na^+ into the cell to "pump" Ca^{2+} out with a stoichiometry of 3 Na^+ to 1 Ca^{2+}, generating an inward current (*5–7*). At potentials positive to its reversal potential, it "pumps" in the opposite direction, producing Ca^{2+} entry and generating outward current. In the heart, changes in $[Ca^{2+}]_i$ attributed to Na^+-Ca^{2+} exchange have generally been slow {that is, the development of tonic tension, setting resting $[Ca^{2+}]_i$, and contributing to relaxation (*8*)}. Bridge *et al.* provide compelling evidence that the Ca^{2+} that enters the heart cell during excitation is extruded by the Na^+-Ca^{2+} exchanger. However, Leblanc and Hume (*4*) report that the Na^+-Ca^{2+} exchanger may be involved in faster events. They find that excitation-contraction (EC) coupling in heart muscle can occur in the absence of Ca^{2+} current (I_{Ca}) [contrary to the conclusion of (*9*)] and is triggered by influx of Ca^{2+} via Na^+-Ca^{2+} exchange.

The elevation of $[Ca^{2+}]_i$ arises as a result of the influx of Na^+ through Na^+ channels (I_{Na}) that activates the Na^+-Ca^{2+} exchanger to transport Ca^{2+} into the cell (*4*). This $[Ca^{2+}]_i$ then activates Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum (SR), which leads to contraction (*10*). The role of I_{Na} in EC coupling has been overlooked previously, presumably because it has been suppressed intentionally during experiments (*11, 12*) and because it may play a secondary, contributing role physiologically.

How high must intracellular Na^+ rise to activate the Na^+-Ca^{2+} exchange? The Na^+-Ca^{2+} exchanger is activated by depolarization, but by itself does not bring in enough Ca^{2+} to activate Ca^{2+}-induced Ca^{2+} release with normal $[Na^+]_i$ ($\approx$ 8 m*M*) (*11*); therefore a significant elevation of $[Na^+]_i$ is needed to sufficiently activate the Na^+-Ca^{2+} exchanger (*7*). In a typical guinea pig ventricular muscle cell, 10 by 20 by 100 μm, a 50-nA Na^+ current with an inactivation time constant of 1 ms (*13*) would cause a spatially averaged increase of $[Na^+]_i$ of around 25 μ*M*. This minimal elevation above the normal $[Na^+]_i$ would not significantly alter the Na^+-Ca^{2+} exchange nor, therefore, $[Ca^{2+}]_i$ (*7*). Therefore, if I_{Na} can activate Na^+-Ca^{2+} exchange, the volume into which entering Na^+ ions are distributed must be restricted (at least in the short term). If the diffusional distance is limited to 100 Å below the surface membrane (not including any invaginations), the restricted volume is about 0.3% of the total. With such a restriction on diffusion, an elevation of $[Na^+]_i$ of 8 m*M* would be achieved, thereby doubling $[Na^+]_i$. Although this $[Na^+]_i$ could activate the influx of Ca^{2+} via Na^+-Ca^{2+} exchange sufficiently to trigger Ca^{2+}-induced Ca^{2+} release, its calculation is based on untested assumptions. The characterization of the Na^+-Ca^{2+} exchanger by Miura and Kimura (*7*) would predict that $[Ca^{2+}]_i$ would rise in this hypothesized restricted volume by between 1 and 10 μ*M* per millisecond (assuming no buffering).

Therefore, to fit the experiments of Leblanc and Hume with known properties of the Na^+-Ca^{2+} exchanger, one must postulate the existence of a functionally restricted intracellular space accessible to Na^+ channels, the Na^+-Ca^{2+} exchanger, and some of the SR. L-type Ca^{2+} channels, which contribute to Ca^{2+}-induced Ca^{2+} release, must have access to this restricted space, given the complex manner in which Ca^{2+}-induced Ca^{2+} release is influenced by I_{Ca} (*10–12, 14*). The clear implication from the paper by Bridge *et al.* (*5*) in this issue of *Science* and from Crespo, Granthan, and Cannell (*15*) is that the Na^+-Ca^{2+} exchanger also has access to the entire pool of cytoplasmic Ca^{2+}, as it is responsible for extruding Ca^{2+} from the myocyte that enters through I_{Ca}. Additionally, of course, the Ca^{2+} released from the SR must be able to activate the contractile proteins. Thus, the diffusional limitations and the physical structure of this space are crucial but poorly conceptualized. The space, with unknown molecular anatomy, must severely impede the movement of small ions and yet allow equilibration with the cytoplasm over longer times.



Leblanc and Hume show clearly that I_{Na} can make a significant contribution to EC coupling in heart and Bridge *et al.* show the fundamental importance of Na^+-Ca^{2+} exchange to cellular Ca^{2+} homeostasis and to relaxation. Furthermore, the findings of Leblanc and Hume support the growing evidence that EC coupling in heart muscle involves a Ca^{2+}-induced Ca^{2+} release mechanism that has complex activation and termination mechanisms. These new results on the Na^+-Ca^{2+} exchanger and EC coupling in heart also imply that the cellular architecture of heart cells may involve an incomplete barrier to diffusion underneath the sarcolemmal membrane.

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