Sodium Calcium Exchange in the Heart
Necessity or Luxury?

David A. Eisner, Karin R. Sipido

The sodium calcium exchange (NCX) was first discovered in cardiac muscle and squid axon and has since been found in most cell types (see reviews). It accounts for the previously observed effects of sodium on cardiac contractility. The exchanger transports Na\(^+\) ions per Ca\(^{2+}\). This stoichiometry has three important consequences. Ca\(^{2+}\) fluxes and hence intracellular Ca\(^{2+}\) concentrations ([Ca\(^{2+}\)]\(_i\)) are very sensitive to intracellular Na\(^+\) concentration ([Na\(^+\)]\(_i\)), and therefore, even small changes of [Na\(^+\)], have large effects on contractility. In the case of vascular smooth muscle, the [Na\(^+\)]-dependence of NCX has been suggested to account for aspects of hypertension.

The activity of NCX is affected by membrane potential with depolarization hindering Ca\(^{2+}\) efflux and increasing Ca\(^{2+}\) influx. This voltage dependence may produce net Ca\(^{2+}\) entry into the cell at the start of the action potential and contribute to triggering Ca\(^{2+}\)-induced Ca\(^{2+}\) release from the sarcoplasmic reticulum (SR). Changes in the activity of NCX attributable to an increase in [Ca\(^{2+}\)]\(_i\), activate inward current. Specifically, (1) inward current activated by the systolic Ca\(^{2+}\) transient will contribute to maintaining the action potential plateau, and (2) current activated by abnormal Ca\(^{2+}\) release in diastole generates the delayed afterdepolarizations known to be a cause of triggered arrhythmias.

Effects of NCX on Systolic [Ca\(^{2+}\)]\(_i\)
NCX does not only control the cytoplasmic Ca\(^{2+}\) concentration but, indirectly, also regulates the amount of Ca\(^{2+}\) stored in the SR. This occurs because, on any one beat, the change of total Ca\(^{2+}\) in the cell is the difference between the influx of Ca\(^{2+}\) into the cell (largely via the L-type Ca\(^{2+}\) current) and the efflux (largely on NCX). In the steady state, influx and efflux must be equal and therefore if the influx is maintained constant from beat to beat so must the efflux. If there is less NCX, then a larger systolic Ca\(^{2+}\) transient will be required to activate the same efflux. Until this larger transient is achieved, influx will exceed influx and SR content will increase until they are equal.

One consequence of this is that SR Ca\(^{2+}\) content is decreased by maneuvers that decrease the ratio of the activities of SERCA to NCX. In the heart failure when SERCA activity decreases and that of NCX increases.

Ca\(^{2+}\) Removal by Mechanisms Other Than NCX
The only other known mechanism that can pump Ca\(^{2+}\) out of the cardiac cell is the plasma membrane Ca\(^{2+}\)-ATPase (PMCA). Lack of specific inhibitors has made it difficult to obtain a quantitative estimate of the activity of the PMCA compared with that of NCX. One approach is to release Ca\(^{2+}\) from the SR using the rapid application of caffeine. The Ca\(^{2+}\) cannot be taken back into the SR and the rate constant of its subsequent decay represents the rate of Ca\(^{2+}\) removal by other systems including NCX, PMCA, and possibly, mitochondria.

Effect of NCX Knockout
From this one would expect that cardiac function would be grossly abnormal in animals in which NCX is knocked out, and indeed, full knockout of NCX is embryonically lethal. The article in this issue of Circulation Research by Henderson et al uses the Cre/LoxP system to knock out NCX in 80% to 90% of cells in the ventricle at a slightly later point in development and restricted to the ventricle. Despite this gross insult, the animals live to adulthood and display only a 30% or so decrease of contractility, suggesting that the embryonic death in the whole animal knockout results from early developmental problems (possibly failure of the heart function).
beat) or from some tissue other than the heart. The authors checked that the reduction of NCX was not compensated for by increased expression of PMCA. Perhaps most striking are the results from single cells that showed that not only was the amplitude of the Ca\(^{2+}\) transient the same in control and knockout cells, but there was also no difference in its modulation by changing stimulus frequency or adding isoprorenaline. Indeed, the reader is challenged to cut out the traces from the article and attempt to identify which is from control versus knockout! There was also no difference in SR content between control and knockout cells. Interestingly, the amplitude of the L-type Ca\(^{2+}\) current was decreased to 50% of control and it was suggested that this reduction of Ca\(^{2+}\) entry might allow the PMCA alone to provide the required efflux. Although qualitatively in the right direction, there is a quantitative problem with this hypothesis. If in control cells the activity of the PMCA was equal to that of the NCX, then knocking out NCX could be compensated for exactly by decreasing Ca\(^{2+}\) entry to 50%. Even allowing for the possibility that the shorter action potential of the KO may further decrease Ca\(^{2+}\) entry, the required PMCA activity is greater than that found in previous work. A rough estimate of the activity of the PMCA can be obtained from the half times of decay of [Ca\(^{2+}\)]\(_i\), after applying caffeine. The decay rate in knockouts was 20% of that in controls, suggesting that, in controls, the PMCA accounts for \(\approx20\%\) of efflux. This value is comparable to the amount of extrusion by PMCA calculated from the decay of caffeine transients with NCX blocked by Ni in normal mouse myocytes\(^{25}\) and is consistent with the absence of upregulation of PMCA. To gain further insight then into the remarkably unaltered Ca\(^{2+}\) transients during field stimulation additional experiments will be needed. As indicated by the authors the Ca\(^{2+}\) influx, SR content and Ca\(^{2+}\) transients were measured in separate experiments. A comprehensive analysis of fluxes during voltage clamp may more clearly delineate the actual changes in Ca\(^{2+}\) influx and efflux, and might quantify the changes in fraction of Ca\(^{2+}\) entry versus Ca\(^{2+}\) cycling across the SR. The nature of the efflux pathways can then also be further characterized. Currently, it is also unclear what causes the significant decrease in cardiac function in vivo. A further study of Ca\(^{2+}\) transients at more physiological stimulation rates and temperature might reveal a more pronounced cellular deficit.

By showing that the heart can survive remarkably well in the absence of NCX, the work of Henderson et al emphasizes the need to better characterize fluxes carried by the PMCA in the heart. As pointed out by the authors, the data indicate the remarkable potential for adaptation to reduced NCX at the cellular level. Whereas in mice the NCX apparently is not a necessity, it is certainly no luxury either as evidenced by the shorter lifespan and mortality of females after giving birth. It is also important to keep in mind that the limited Ca\(^{2+}\) influx during the very brief action potential of the mouse myocyte is different from the Ca\(^{2+}\) influx during the action potential in larger mammals, including human. The consequences of reduced NCX may then be quite different, and not as well tolerated. With the development of pharmacological blockers of NCX well under way\(^{3,32}\) the role of the NCX in Ca\(^{2+}\) homeostasis will remain an important issue.

References


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