The control of intracellular Na⁺ levels has long been known to be a crucial part of the regulation of cardiac contractility and the treatment of heart failure. Cardiac glycosides have been used to improve the symptoms of heart failure since William Withering published trials of a foxglove extract obtained from a gypsy woman in the late 1700’s. The active ingredients, digitalis and digoxin, were found to target sodium pump activity in the 1950’s, and the sodium pump was identified as Na,K-ATPase by Nobel Laureate Jens Skou in the 1970’s. Recent studies have established that digitalis does not improve survival in heart failure, but American College of Cardiology/American Heart Association guidelines recommend its use in combination with ACE inhibitors and β-adrenergic blockade in patients with symptomatic left ventricular systolic dysfunction.

A modest level of inhibition of Na,K-ATPase by digitalis slightly raises cardiac intracellular Na⁺ concentrations, which in turn decreases the driving force for Ca²⁺ extrusion via NCX1, the Na⁺:Ca²⁺ exchanger. In the therapeutic range, the extra cytoplasmic Ca²⁺ will be loaded into the sarcoplasmic reticulum, resulting in normal diastolic Ca²⁺ concentrations but improved systolic Ca²⁺ release, and thus improved contractility. β-adrenergic stimulation, on the other hand, improves the loading of the sarcoplasmic reticulum (SR) by acting on the Ca²⁺-ATPase, SERCA. β-adrenergic stimulation improves SR loading by phosphorylating a small regulatory membrane protein, phospholamban, which otherwise acts to reduce the affinity of SERCA for Ca²⁺. The phosphorylation relieves the basal Ca²⁺ ATPase inhibition.

Although the importance of the Na,K-ATPase in management of heart failure is clear, how the cellular mechanisms are integrated remains an intriguing area of research. β-adrenergic stimulation increases sodium pump activity, which in the simplistic analysis above would suggest that it would oppose the effect of β-adrenergic stimulation on the Ca²⁺ ATPase. Heart failure is generally accompanied by a reduction in Na,K-ATPase levels, particularly of certain of its isoforms. This reduction may play the same role as exogenous digitalis as part of the homeostatic response to cardiac dysfunction.

In this issue of *Circulation Research*, Bossuyt et al¹ have used a rabbit model of heart failure and human tissue samples to address some of these problems. They have established in the past that the rabbit cardiomyocytes sustain an elevated intracellular Na⁺ concentration without a net change in the level of pump activity measured electrophysiologically² and ascribed the higher concentration to increased influx through other pathways. Here they ask what happened to the amounts of Na,K-ATPase expressed, and they report that the amounts of all 3 of its α isoforms are reduced by roughly a third compared with healthy cells. These values are the amounts of Na,K-ATPase protein detected on blots of equal aliquots of protein of total cell lysates, and thus any remaining hypertrophy in the myocytes from the failing hearts will reduce the measured ratio of Na,K-ATPase to total protein in addition to any change in Na,K-ATPase expression per cell. This is, nonetheless, the important measurement of pump content because it is proportional to the cell mass and volume.

In prior work they found that pump activity measured as the rate of Na⁺ concentration decline was unchanged in myocytes from failing hearts.³ This implies that pump activity must have been increased to compensate for the effect of hypertrophy on pump concentration. In the present article, they show evidence that this is a consequence of regulation of the Na,K-ATPase by another small single-span membrane protein, phospholemman.

Phospholemman should not be confused with phospholamban, despite the similar names. Both were originally discovered as abundant small phosphoproteins in cardiac or skeletal muscle membrane fractions, but fractionation of membranes revealed that phospholamban is in sarcoplasmic reticulum and phospholemman in the sarcolemma. Structurally, they are unrelated other than being small and having a hydrophobic membrane span. They even have opposite orientations: the N terminus of phospholamban is in the cytoplasm, whereas the C terminus of phospholemman in the cytoplasm. Curiously, though, there is strong homology in the short phosphorylation motif sequence. Despite the obvious lack of evolutionary relationship, the 2 proteins bind to and regulate 2 closely-related ion transport ATPases, SERCA and Na,K-ATPase.

Phospholemman was shown to associate with Na,K-ATPase and change its kinetic properties after its homology to the Na,K-ATPase γ subunit was recognized.⁴ In oocytes, it reduced affinity for Na⁺, which should be a physiologically inhibitory effect, but blocking antibodies reduced activity, suggesting a stimulatory effect. In a phospholemman knock-out mouse, reduced total Na,K-ATPase activity was found in partially purified enzyme relative to littermate controls,⁵ which could be attributable to loss of a stimulatory effect. These apparent discrepancies may be resolved when the

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Phospholemman

**A New Force in Cardiac Contractility**

Kathleen J. Sweadner
effects of phosphorylation of phospholemman in oocytes and normal mouse cardiomyocytes are clarified, because phosphorylation of phospholemman appears to increase Na,K-ATPase activity.\textsuperscript{6,7} In measurements of Na\(^+\) decline and pump current using cardiac myocytes from the same knockout mice, apparent affinity for Na\(^+\) was higher than in littermate control myocytes. Furthermore, \(\beta\)-adrenergic stimulation increased Na\(^+\) affinity in normal myocytes, but the already-high affinity was unaffected in the phospholemman knockout.\textsuperscript{8}

In healthy myocytes, \(\beta\)-adrenergic stimulation of SERCA will increase Ca\(^{2+}\) loading of sarcoplasmic reticulum, whereas \(\beta\)-adrenergic stimulation of Na,K-ATPase will increase Ca\(^{2+}\) efflux from the cell via Na\(^+:\text{Ca}^{2+}\) exchange. The resulting net reduction of cytoplasmic Ca\(^{2+}\) is not what is wanted in failing heart, where Ca\(^{2+}\) stores are depleted.

The contribution by Bossuyt et al is an important one because it reveals a role for phospholemman interaction with Na,K-ATPase in heart failure. First, phospholemman coimmunoprecipitated with both \(\alpha1\) and \(\alpha2\) Na,K-ATPase isoforms. The expression level of phospholemman was lower in failing myocytes as well as in samples of human tissue. Most notably, the authors were able to demonstrate, using phosphorylation site-specific antibodies, that there was a dramatic increase in phospholemman phosphorylation in the failing heart samples.

The conclusions are complex: reduced Na,K-ATPase levels and reduced phospholemman levels would be expected to result in less pump activity in heart failure, but the enhanced phosphorylation of phospholemman apparently offsets the expected decrease in pump activity by stimulating the remaining pumps. With normal pump function, normal Na\(^+:\text{Ca}^{2+}\) exchange could be maintained in principle. This leaves room for improvement of sarcoplasmic reticulum Ca\(^{2+}\) loading by either inhibiting the sodium pump with digitalis or by reducing Na,K-ATPase activity (through net loss of phospholemman phosphorylation) with \(\beta\)-adrenergic blockade. This is consistent with the established clinical protocols.

A further recent idea has emerged that phospholemman also interacts with NCX1 and inhibits its activity (in both forward and reverse modes) as long as the protein kinase A phosphorylation site (Ser68) is available for phosphorylation.\textsuperscript{9} If \(\beta\)-adrenergic stimulation inhibits Na\(^+:\text{Ca}^{2+}\) exchange in parallel with stimulating Na,K-ATPase activity, the picture becomes complicated because the consequences for Ca\(^{2+}\) and contractility are not easy to predict. Na,K-ATPase and NCX1 colocalize in the sarclemma and are associated in a functional complex.\textsuperscript{10} Clearly, more investigation of the role of phospholemman in cardiac physiology will be fruitful.

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**References**


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