A new look at phospholamban in pressure-overload hypertrophy

Katherine A. Sheehan
Department of Physiology and Biophysics, Center for Cardiovascular Research, University of Illinois at Chicago, Chicago, Illinois

The question of the mechanisms of pathological cardiac hypertrophy and the relationship of changes in cellular function to a myriad of clinical symptoms has long been an important and intriguing puzzle to researchers. How is it that exercise induces signaling changes that are beneficial to heart function but pathological conditions such as hypertension or valvular disease are associated with a loss of hemodynamic function and neurohumoral response, although both produce muscular hypertrophy? What are the interactions between hypertrophic and contractile signaling pathways? One point of interest is the increase in sympathetic drive observed in the pressure-overloaded (PO) hypertrophic heart that is accompanied by decreased β-adrenergic sensitivity and diminished contractile reserve. This condition is significant to patients in that it causes a loss of ability to tolerate exercise and can lead to myocyte death and heart failure, but the cellular changes underlying the loss of contractile reserve are not entirely clear.

A number of researchers have identified mechanisms for this loss of contractile reserve, but this picture is not complete. One prominent mechanism involved in the loss of adrenergic response is a downregulation of β-adrenergic receptor (β-AR) density, which is improved by administration of β-blockers (4). Another is upregulation of β-receptor kinase 1 (or G protein-coupled receptor kinase 2, GRK2; see Ref. 1), which inactivates β-ARs and is reversible by exercise training (2).

In the current issue of the American Journal of Physiology-Heart and Circulatory Physiology, Mills et al. (3) have addressed the question of what downstream mechanisms may be involved in the diminution of adrenergic contractile reserve using a feline model of PO-induced left ventricular hypertrophy. They propose that altered abundance or basal phosphorylation state of target regulatory proteins, specifically phospholamban (PLB), is a central cause of the loss of inotropic responsiveness in PO animals. They have presented compelling in vivo evidence that aortic banded animals have a blunted systolic function that is not restored with dobutamine, concurrent with reduced total PLB and a significant increase in total PLB phosphorylation that is mainly attributed to the calmodulin kinase II site, Thr17. They also report that the less the response to dobutamine, the greater the level of Thr17 phosphorylation. Further experiments using single isolated ventricular myocytes elegantly support the whole heart results by reiterating the basic mechanism; paced cells have more frequent Ca2+ transients, higher basal Thr17 phosphorylation, and less response to isoproterenol.

This evidence yields intriguing implications as to the role of Ca2+-dependent processes in feedback regulation of β-adrenergic signaling and their changes in cardiac hypertrophy and failure. The evidence also redefines the nature of PLB signaling as both an integrator of Ca2+ and sympathetic pathways into a unified signal to the sarcoplasmic reticulum and as an element in modulating the β-adrenergic pathway itself. If intracellular Ca2+ fluxes change in response to other diseases or treatments, how can PLB modify adrenergic signaling under these conditions?

In that context, the data of Mills et al. (3) raise interesting questions in light of previous work in a rat model where the loss of sensitivity to isoproterenol in spontaneously hypertensive rats was associated with elevated abundance of PLB along with reduced phosphorylation at Ser16 and Thr17. Additionally, phosphorylation was restored at both of these sites by treadmill exercise training, increasing the Ca2+ available for release and, subsequently, contractility. This result is similar to the pacing of single cat myocytes in the increase of Thr17 phosphorylation while at the same time GRK2 was decreased, improving β-adrenergic responsiveness (2). Although there are obvious species differences in the two studies, why did PLB phosphorylation go down in the hypertensive rat and up in the PO cat when both had reduced adrenergic response? The changes in morphology, signaling, and function of the heart in these disease states leave many questions remaining to be answered, and this step in the progress of linking whole heart function to specific regulatory changes brings us closer to that goal.

REFERENCES