Phospholamban Structure and Phosphorylation

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Summary

Phospholamban is a small protein which is intrinsic to cardiac sarcoplasmic reticulum. Its 52 amino acid primary sequence contains an N-terminal cytosolic domain, which contains phosphorylation sites for cAMP- and calcium and calmodulin-dependent protein kinases, and a C-terminal membrane spanning domain. Phospholamban is known to regulate the activity of the SR calcium ATPase, which is of primary importance in diastolic calcium sequestration. Phospholamban phosphorylation is known to occur after beta-adrenergic stimulation, or other cAMP-dependent inotropic treatments.

In intact hearts, phospholamban is phosphorylated at serine-16 and threonine-17 following beta agonist exposure, residues phosphorylated very specifically in vitro by cAMP- and calcium and calmodulin-dependent protein kinases, respectively. In Langendorff perfused hearts, varying perfusate calcium had a marked effect on the rate of phospholamban dephosphorylation, suggesting calcium and calmodulin-dependent protein kinase functions to control the durability of phospholamban phosphorylation, which must be initiated by cAMP-dependent protein kinase.

Purification and structural analysis of phospholamban suggested that monomers could interract through their hydrophobic C-terminal domains to form pentamers, and a quaternary structure model suggests pentameric phospholamban could form an ion channel in the sarcoplasmic reticulum. We predict that this interraction may be phosphorylation-dependent, requiring dissociation of monomers from the calcium ATPase. Phospholamban, purified by our methods, has now been shown to conduct calcium ions across artificial bilayers (Kovacs et al. (1988) J Biol Chem). Further investigation into the function of phospholamban may prove very enlightening. Phosphorylation-dependent stimulation of SR calcium ATPase, accompanied by formation of phosphorylation-dependent calcium release channels, could provide a unifying mechanism to account for accelerated contraction and relaxation produced by beta agonists.

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