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The Underlying Mechanisms of Cardiac Dysfunction in Diabetes Mellitus

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Diabetic cardiomyopathy has been suggested to be caused by the intracellular Ca^{2+} overload in the myocardium. We have investigated the possible mechanism of the functional defect of cardiac sarcoplasmic reticulum (SR) in diabetic rats with respect to Ca^{2+}-ATPase and phospholamban (PLB) at the transcriptional and translational levels. 1) The maximal Ca^{2+} uptake and the affinity of Ca^{2+}-ATPase for Ca^{2+} were decreased in streptozotocin-induced diabetic rat cardiac SR. 2) The phosphorylation levels of PLB were increased in diabetic cardiac SR. However, phosphatase treatment of PLB prior to phosphorylation did not change the level of phosphorylation. 3) Levels of both mRNA and protein of PLB were significantly increased in diabetic rat hearts, whereas the mRNA and protein levels of SR Ca^{2+}-ATPase were significantly decreased. 4) Consequently, the relative PLB/ Ca^{2+}-ATPase ratio was 1.6 in diabetic hearts, and these changes correlated with changes in the EC_{50} of the SR Ca^{2+} uptake for Ca^{2+}. 5) Insulin treatment could reverse functional parameters of cardiac SR. In case of phospholamban, insulin treatment reverses mRNA and protein levels to normal levels. Minimal amount of insulin could reverse the protein levels; however, it could not reverse the mRNA level of SR Ca^{2+}-ATPase at all. 6) Thus, the decreased SR Ca^{2+} uptake appears to be largely attributed to the decreased SR Ca^{2+}-ATPase level, which is further impaired due to the inhibition by the increased level of phospholamban. 7) These results also indicate that insulin may be involved in the control of intracellular Ca^{2+} in the cardiomyocyte for the decrease in the mRNA for both SR Ca^{2+}-ATPase and PLB, which are unknown and needs further study. Supported by grant from KOSEF (95-0403-18-03-3)