Convergence of glucose- and fatty acid-induced cardiomyocyte insulin resistance and abnormal E-C coupling

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Diabetic cardiomyopathy is characterized by both abnormal excitation-contraction (E-C) coupling and blunted insulin signaling. Hyperglycemia and elevated plasma fatty acids are typical complications of poorly controlled diabetes. We have previously shown that many of the abnormalities in E-C coupling associated with early stages of diabetes are recapitulated by culturing normal myocytes in a high glucose medium (e.g., prolonged action potentials and slowed cytosolic Ca^{2+} removal (attributable to impaired SERCA function), and slowed myocyte shortening/relengthening). We have recently shown that these high glucose myocytes are also insulin resistant (as measured by insulin-stimulated glucose uptake), and that both the mechanical dysfunctions and blunted insulin response are related to elevated PKC activity. Inhibition of PKC (with a non-specific inhibitor) prevents/reverses myocyte dysfunction and insulin resistance in both diabetic and high glucose myocytes. We now have evidence that certain fatty acids also induce both abnormalities, perhaps in a PKC dependent manner. Thus, questions remain as to whether there is a converging pathway which can account for these glucose- and fatty acid-induced changes and whether these effects are relevant to the cardiomyocyte dysfunctions seen in various animal models of diabetes. Preliminary evidence suggests that the hexosamine biosynthesis pathway may be a link to these dysfunctions associated with early stages of diabetes. Conclusions: We now have evidence that culturing cardiomyocytes in either high extracellular glucose or fatty acids produces similar mechanical dysfunctions as those seen in early stages of type 1 and type 2 diabetes. Furthermore, abnormal E-C coupling coincides with blunted insulin stimulated glucose uptake, independent of etiology (i.e., high glucose, high fatty acids or *in vivo* diabetes).