Hyperglycemic stress induces cardiac arrhythmia via O-linked glycosylation of CaMKII

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Ca^{2+}-calmodulin dependent protein kinase II (CaMKII) is a nodal regulatory protein in both the heart and brain. Chronic CaMKII activation is associated with a number of cardiovascular pathologies. For example, CaMKII activation during heart failure can directly induce changes in ion channel gating, Ca^{2+} handling, and apoptotic signaling pathways. Here we present data demonstrating a direct link between CaMKII activity and hyperglycemia, a mechanism that may contribute to structural and electrical remodeling of the heart in patients with diabetes mellitus. Indeed, more than 180 million people around the world suffer from diabetes, a key risk factor for heart disease and neurodegenerative disorders. We describe the novel observation that a covalent modification of CaMKII by O-linked N-acetylglucosamine (O-GlcNAc) is enhanced significantly during hyperglycemia. O-GlcNAc modification of CaMKII results in autonomous activation of the kinase even after $[Ca^{2+}]$ declines via a mechanism similar to phosphorylation or oxidation of the kinase. We also show that O-GlcNAc modified CaMKII is increased in heart and brain from both diabetic humans and rats. In isolated cardiac myocytes, both acute enhancement of glucose concentration as is observed in diabetes and pharmacological enhancement of O-GlcNAc modification significantly enhances CaMKII-dependent activation of spontaneous sarcoplasmic reticulum (SR) Ca^{2+} release events (sparks). Ca^{2+} sparks are thought to underlie arrhythmogenesis and cardiac pathology. We show an increase of arrhythmic events in perfused rat hearts exposed to acute elevation of glucose concentration. Importantly, glucose dependent arrhythmogenesis was found to be O-GlcNAc- and Ca^{2+}-dependent, suggesting a key role for O-GlcNAc signaling in diabetic arrhythmia. Thus, O-GlcNAc modification of CaMKII is a newly discovered signaling event that contributes critically to cardiac pathophysiology in diabetes and other diseases.