THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

LEE BRODERICK BOCKUS

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
DEPARTMENT OF
BIOCHEMISTRY AND MOLECULAR BIOLOGY

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Room 109, Biomedical Research Center, OUHSC

Deficient Camp-Dependent Protein Kinase (Pka) Signaling and Phosphofructokinase 2 (Pfk2) Loss in the Type I Diabetic Heart Impair Cardiac Function and Metabolism

COMMITTEE IN CHARGE: Kenneth Humphries, Ph.D., Chair, Ann L. Olson, Ph.D., Zhongjie Sun, Ph.D., Hiroyuki Matsumoto, Ph.D., Augen Pioszak, Ph.D.

ABSTRACT: Diabetes mellitus causes cardiac dysfunction and heart failure that is associated with metabolic abnormalities and autonomic impairment. Autonomic control of ventricular function occurs intracellularly through the regulation of cAMP-dependent protein kinase (PKA). The diabetic heart has suppressed β-adrenergic responsiveness, yet little is known about how PKA signaling is affected. A PKA agonist was used acutely to evaluate its function in a mouse model of type 1 diabetes. We demonstrate that there is an impaired hemodynamic response to the agonist that is mediated by

reduced PKA substrate phosphorylation and PKA activity. The reduced response demonstrates post-receptor defects and occurs through reduced PKA catalytic subunit content in the cytoplasm and myofilaments. Compartment specific loss of PKA was reflected by the absence of phosphofructokinase 2 (PFK-2) phosphorylation, a cytosolic glycolytic regulator. Mechanistic studies with adult cardiomyocytes support a model in which lipids decrease metabolic flexibility by decreasing both PKA and PFK-2 phosphorylation. The improper activation of glycolysis in response to adrenergic stimulation led to the hypothesis that this defect is an important contributor to metabolic inflexibility and diabetic cardiomyopathy. Supporting this idea, we also found that PFK-2 content was substantially reduced in the diabetic heart. This loss of PFK-2 was also observed in fasting and a high fat diet type 2 diabetes model. To study the functional impact of PFK-2 loss, metabolomic analysis of fasted hearts was performed. Our data revealed elevated early glycolytic intermediates before the rate-limiting enzyme PFK-1 and reduced intermediates afterwards. Other allosteric regulators of PFK-1, in addition to the product of PFK-2, were not changed suggesting PFK-2 impairment is the primary reason for low glucose use in the fasted state. Media without insulin, with PI3K inhibition, or mTOR inhibition reduced PFK-2 content in adult cardiomyocytes. Further, we determined PFK-2 degradation is controlled by selective autophagy, which is upregulated in the diabetic heart. Reduced cardiac insulin signaling in both types of diabetes and fasting results in PFK-2 degradation via selective autophagy and impaired glycolysis. Overall, we present a contributory mechanism to explain deficient ventricular performance and metabolism in the diabetic heart.