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PhD Dissertation

Entitled

THE MOLECULAR BASIS OF DIABETIC CARDIOMYOPATHY

by

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Abstract

Diabetes mellitus (DM) is a major and worsening global health problem. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of DM and the global epidemic of obesity largely explains the dramatic increase in the incidence and prevalence of T2DM over the past 20 years. Cardiovascular complications are the major cause of morbidity and mortality in diabetic patients. The electrocardiogram (ECG) of diabetic and obese patients is frequently disturbed. The aim of this project was to characterize and clarify the molecular basis of electro-mechanical dysfunction in the hearts of type 2 diabetic and type 2 diabetic/obese patients. Experiments were performed in Zucker diabetic fatty (ZDF), Zucker fatty (ZF) and Zucker lean (ZL) rats. *In vivo* biotelemetry experiments were performed to establish how the ECG was altered by diabetes and diabesity. Experiments were also carried out in isolated heart to further investigate how diabetes and diabesity affects the electrical conduction system of the heart. Whole cell patch clamp techniques were used to assess the effects of diabetes and diabesity on ion channel currents. Molecular biology and electron microscopy techniques were employed to assess proteins and structures associated with cardiac muscle contraction. Heart rate (HR) was reduced by ageing and by diabesity in the absence of changes in physical activity and body temperature. Reductions in heart rate variability linked with altered sympathovagal drive may partly underlie disturbed HR in the ZDF rat even in the absence of autonomic nervous system control in the isolated perfused heart. Amplitude of shortening is generally well preserved in ZDF myocytes. There was evidence of altered time course of the Ca^{2+} transient and shortening in ventricular myocytes from ZDF rat. Molecular and structural defects in the ZF and ZDF rat heart were observed. The results suggest that sarcoplasmic reticulum (SR) Ca^{2+} handling as well as energy utilization are compromised in ZDF and ZF myocytes. Myocyte contraction and relaxation may also be affected in the ZDF and ZF rat due to protein and structural defects. Isoprenaline was less effective at generating an increase in the AMP of shortening in ZDF and ZF compared to ZL myocytes and defects in Ca^{2+} signaling, and in particular SR Ca^{2+} transport, might partly underlie these abnormalities.

Keywords: Heart, Diabetes, Obesity, Diabetic Cardiomyopathy, Zucker diabetic fatty rat, Zucker fatty rat, Zucker lean rat