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Dissertation

Title *Effects of Exercise and Pharmacological Intervention on Electromechanical Function of the Heart in the Goto-Kakizaki Type 2 Diabetic Rat*

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Defense Date 16 June 2015

Abstract

Type 2 diabetes mellitus (T2DM) accounts for more than 90% of cases of diabetes mellitus. Cardiovascular diseases are the major causes of morbidity and mortality in diabetic patients. A variety of diastolic and systolic dysfunctions have been reported. The severity of the abnormalities depends on the patients' age and diabetes duration. The aim of the study was to investigate the age-dependent, exercise and drug intervention on electromechanical function of the heart in the Goto-Kakizaki (GK) type 2 diabetic rat. mRNA expression was assessed in ventricular muscle with real-time RT-PCR. Ventricular myocytes shortening, intracellular Ca^{2+} transport and L-type Ca^{2+} current were measured with video edge detection, fluorescence photometry and whole cell patch clamp techniques, respectively. In vivo biotelemetry was used to measure the electrocardiogram (ECG). In young GK (8-10 weeks) rat, mRNA expression of *Atp1a3*, *Cacna1h*, *Scn1b*, *Hcn2* were up-regulated and *Slc9a1*, *Hcn4*, *Kcna2/4*, *Kcnj2* were down-regulated. Amplitude of ventricular myocyte shortening and intracellular Ca^{2+} transient were unaltered, time to peak shortening was prolonged and time to half decay of the Ca^{2+} transient was shortened in GK myocytes. Physical exercise is well established as a valuable form of non-pharmacological therapy. Experiments were performed in GK and control (10-11 months) following 2-3 months of treadmill exercise training. Expression of mRNA encoding *Tpm2*, *Gja4*, *Atp1b1*, *Cacna1g*, *Cacnb2*, *Hcn2*, *Kcna3* and *Kcne1* were up-regulated and *Gja1*, *Kcnj2* and *Kcnk3* were down-regulated in hearts of sedentary GK rats compared to sedentary controls. *Gja1*, *Cav3* and *Kcnk3* were up-regulated and *Hcn2* was down-regulated in hearts of exercise trained GK compared to sedentary GK controls. Amplitude of ventricular myocyte shortening, Ca^{2+} transients and L-type Ca^{2+} current were not significantly altered. The effects of the anti-diabetic drug Pioglitazone (PIO) on ventricular myocyte shortening and Ca^{2+} transport in addition to ECG were also investigated. PIO (0.1-10) μ M reduced the amplitude of shortening in ventricular myocytes from GK and control rats. PIO reduced the amplitude of the Ca^{2+} transient and modest reductions in L-type Ca^{2+} current in GK and control myocytes. Heart rate in GK rats was reduced. Although PIO reduced blood glucose in GK rats it had little effect on heart ECG.

Research Relevance and Potential Impact

Diabetes mellitus is a serious global and national health problem and cardiovascular complications are the major cause of morbidity and mortality in diabetic patients. Type 2 diabetes mellitus accounts for more than 90% of cases of diabetes and cardiovascular complications are the major cause of morbidity and mortality in diabetic patients. Experiments performed in this research project have provided further clarification of the cellular and subcellular basis of electromechanical dysfunction and the effects of exercise and drug intervention in type 2 diabetic heart. It is hoped that this mechanistic understanding will help to facilitate the development of new treatment strategies for this disease.

Relevant Publications

- Salem KA, Adrian TE, Qureshi MA, Parekh K, Oz M, Howarth FC. Shortening and intracellular Ca^{2+} in ventricular myocytes and expression of genes encoding cardiac muscle proteins in early onset type 2 diabetic Goto-Kakizaki rats. *Exp Physiol*. 2012 Dec; 97 (12):1281-91.
- Salem KA, Qureshi MA, Sydorenko V, Parekh K, Jayaprakash P, Iqbal T, Singh J, Oz M, Adrian TE, Howarth FC. (2012). Effects of exercise training on excitation-contraction coupling and related mRNA expression in hearts of Goto-Kakizaki type 2 diabetic rats. *Mol Cell Biochem*. 2013 Aug; 380 (1-2): 83-96.
- Salem KA, Jacobson M, Shafiullah M, Oz M, Adeghate E, Howarth FC. Effects of pioglitazone on electrical conduction in the Goto-Kakizaki type 2 diabetic rat heart (Accepted in JCERC)

Career Aspirations

My aspirations are to acquire a PhD degree in Medical Sciences (Pharmacology track) and then pursue a research and academic career. In the long term I would like to heighten awareness of the importance of research in our community.