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Mechanisms and consequences of impaired stimulation of myocardial glucose uptake in the metabolic syndrome

The capacity of the heart muscle to derive energy from a wide variety of substrates provides the myocardium with remarkable adaptability in the face of the ever-changing metabolic status of the organism. Among the myocardial substrates, glucose accounts for less than 25% of the energy production under normal conditions. Glucose is however unique among myocardial substrates because 1) energy can be obtained from glucose through glycolysis even in situations of ischemia, such as occurs during coronary occlusion and 2) ATP obtained from glycolysis, although scarce, is of paramount importance for the maintenance of ionic homeostasis. The importance of stimulation of glucose metabolism for post-ischemic recovery is illustrated by the poor recovery of GLUT4-null hearts, which are incapable of stimulation of glucose transport.

The Western diet is characterized by overconsumption of fatty and sugary food, leading to a worldwide epidemic of obesity and type II diabetes, termed the metabolic syndrome or “diabesity”. The increased cardiovascular risk associated with the metabolic syndrome is usually explained by the higher prevalence of atherosclerosis and thus of myocardial infarction. However, experimental and clinical data suggest that the metabolic syndrome also increases the severity of infarcts. In the metabolic syndrome circulating glucose, fatty acids (FA), lipoproteins and proinflammatory cytokines are increased, chronically exposing the myocardium to an altered metabolic milieu. We recently observed that FA, Very-Low Density Lipoproteins (VLDL) and the cytokine Cardiotrophin-1 (CT-1) impair the stimulation of glucose transport into cardiomyocytes by physiologic – insulin – or pathologic – metabolic stress - stimulators.

Our lab is currently working towards the goals of 1) determine the cellular mechanisms of myocardial stimulated glucose transport impairment and 2) evaluate the consequences of this impairment in situations of myocardial metabolic stress.

To these ends, isolated adult rat cardiomyocytes are exposed *in vitro* to cytokines and metabolites previously identified to impair glucose metabolism in cardiomyocytes. Glucose metabolism in cardiomyocytes is assessed in response to insulin, chemically induced metabolic stress or simulated ischemia. Intracellular signaling and events leading to increased or impaired glucose transport are investigated by biochemical and cell imaging methods. Also, the capacity of the cardiomyocytes to withstand prolonged metabolic stress is evaluated.

The functional consequences of impaired glucose transport will be further assessed in isolated perfused heart experiments, wherein myocardial function can be studied together with metabolism, both in normal and ischemia-reperfusion conditions.

Although the impact of the metabolic syndrome on cardiovascular morbidity is well known, research has mostly focused on the development of atherosclerosis. Our research could shed light on how the metabolic syndrome directly affects one of the tissues that most severely suffers from atherosclerosis-induced events, the myocardium.