

Featured research

Abstracts and commentaries

Insulin resistance, abnormal energy metabolism and increased ischemic damage in the chronically infarcted rat heart

Murray AJ, Lygate CA, Cole MA, et al. *Cardiovasc Res.* 2006; 71:149–157.

Many patients with heart failure have whole-body insulin resistance and decreased myocardial fluorodeoxyglucose uptake during insulin clamp and decreased glucose transporter activity. Impaired myocardial glucose uptake may contribute to the progression to failure, although the mechanisms for this are not completely understood. Glucose enters heart cells via the facilitative glucose transporters, GLUT 1 and GLUT 4. A large proportion of GLUT 1, the least abundant transporter, resides in the plasma membrane and mediates basal glucose uptake. GLUT 4 resides in intracellular vesicles under basal conditions and translocates to the plasma membrane in response to insulin, ischemia, and exercise. Hence, GLUT 4 translocation represents the major mechanism by which glucose uptake to the cardiomyocyte can be increased. In this study, the authors determined whether there is a link between insulin resistance and ischemic damage in the chronically infarcted rat heart, postulating that the heart would have decreased insulin sensitivity, with lower GLUT 4 glucose transporter protein concentrations as a result of high circulating free fatty acid (FFA) concentrations. A decreased capacity for glucose uptake would decrease glycolytic adenosine triphosphate (ATP) production and thereby increase ischemic injury in the infarcted heart.

Commentary

In-vivo left ventricular ejection fractions, measured using echocardiography, were 40% lower in

chronically infarcted rat hearts (10 weeks after coronary artery ligation) than in sham-operated control rats. In response to insulin stimulation, uptake of D-[2-³H]glucose was 42% lower in isolated, perfused, infarcted hearts. Myocardial GLUT 4 glucose transporter protein concentrations were 28% lower in the infarcted hearts. They correlated positively with ejection fractions and negatively with concentrations of plasma FFAs. Compared with controls, chronically infarcted hearts had 46% less total glucose uptake and 3-fold faster ATP hydrolysis, measured using phosphorus-31 nuclear magnetic resonance spectroscopy, during low-flow ischemia (32 min, 0.4 ml/min per gram wet weight). During reperfusion, recovery of left ventricular developed pressure in infarcted hearts was 42% less than that in control hearts. It should be noted that the high circulating concentrations of FFAs in rats with chronically infarcted hearts reflected those found in patients with congestive heart failure; they correlated negatively with cardiac ejection fractions and myocardial GLUT 4 protein concentrations. Decreased myocardial concentrations of GLUT 4 may have contributed to the reduced glucose uptake in response to insulin and during low-flow ischemia. In turn, reduced glucose uptake resulted in lower glycolytic production of ATP and greater loss of ATP during ischemia, and therefore impaired functional recovery during reperfusion. The 28% decrease in GLUT 4 protein may not have been the only reason for the 45% decrease in glucose uptake with insulin stimulation or ischemia. It is possible that there were also changes in expression or activity of other proteins, such as GLUT 1 or proteins of the insulin-signaling pathway, that may have affected glucose uptake in the heart. Further studies might reveal other defects in the ability of the infarcted heart to take up and metabolize glucose.

Danielle Feuvray

Effects of metabolic modulation by trimetazidine on left ventricular function and phosphocreatine/adenosine triphosphate ratio in patients with heart failure

Fragasso G, Perseghin G, De Cobelli F, et al. *Eur Heart J*. 2006;27:942–948.

The addition of trimetazidine to standard treatment has been shown to improve left ventricular function in patients with heart failure. The aim of this study was to use in-vivo phosphorus-31 magnetic resonance spectroscopy (^{31}P -MRS) for non invasive assessment of the effects of trimetazidine on left ventricular cardiac phosphocreatine and adenosine triphosphate (PCr : ATP) ratios in patients with heart failure. In a double-blind, crossover study, 12 patients with heart failure were allocated randomly to groups receiving placebo or trimetazidine (20 mg three times a day) for two periods of 90 days. At the end of each period, all patients underwent exercise testing, two-dimensional echocardiography, and MRS. New York Heart Association (NYHA) class, ejection fraction, maximal rate–pressure product, and metabolic equivalent of task units (METs) were evaluated. Relative concentrations of phosphocreatine and ATP were determined by cardiac ^{31}P -MRS. With trimetazidine, NYHA class decreased from 3.04 ± 0.26 to 2.45 ± 0.52 ($P = 0.005$), whereas ejection fraction increased from $34 \pm 10\%$ to $39 \pm 10\%$ ($P = 0.03$) and METs increased from 7.44 ± 1.84 to 8.78 ± 2.72 ($P = 0.03$). The mean cardiac PCr : ATP ratio was 1.35 ± 0.33 with placebo, but was increased by 33%, to 1.80 ± 0.50 ($P = 0.03$), with trimetazidine. It was concluded that trimetazidine improved functional class and left ventricular function in patients with heart failure. These effects are associated with the observed trimetazidine-induced increase in the PCr : ATP ratio, indicating preservation of the myocardial high-energy phosphate concentrations.

Commentary

Evidence that a metabolic approach with trimetazidine improves left ventricular function in patients with heart failure continues to accumulate. This randomized double-blind crossover study comparing trimetazidine 20 mg three times daily with placebo in patients whose heart failure was well-controlled demonstrated a beneficial effect of trimetazidine on functional class, ejection fraction, and exercise time as a result of its metabolic actions. The prognosis for patients with heart failure remains poor, even when all evidence-based medicine is in place (angiotensin converting enzyme inhibitors, β -blockade, antiplatelet or anticoagulant therapy, and diuretics, including spironolactone), so that the possibility of additional

benefit, however small, from metabolic manipulation of the ischemic process remains an interesting and potentially exciting option. This paper therefore adds to the scientific need for a prognostic and symptomatic longer-term study of trimetazidine in addition to conventional treatment in patients with heart failure and left ventricular dysfunction. *Heart and Metabolism* issue 27 reviewed the metabolic approach to heart failure and provided a comprehensive review, to which the present issue (32) and this paper now add.

Graham Jackson

AMP-activated protein kinase activates p38 mitogen-activated protein kinase by increasing recruitment of p38 MAPK to TAB1 in the ischemic heart

Li J, Miller EJ, Ninumiya-Tsuji J, Russell RR III, Young LH. *Circ Res*. 2005;97:872–879.

AMP-activated protein kinase (AMPK) promotes glucose transport, maintains ATP stores, and prevents injury and apoptosis during ischemia. AMPK has several direct molecular targets in the heart, but also may interact with other stress-signaling pathways. This study examined the role of AMPK in the activation of the p38 mitogen-activated protein kinase (MAPK). In isolated heart muscles, the AMPK activator, 5-aminoimidazole-4-carboxy-amide-1- β -D-ribofuranoside (AICAR) increased p38 MAPK activation. In AMPK-deficient mouse hearts, expressing a kinase-dead α_2 catalytic subunit, p38 MAPK activation was markedly reduced during low-flow ischemia (2.3-fold, compared with 7-fold in wild-type hearts; $P < 0.01$) and was similarly reduced during severe no-flow ischemia in kinase-dead hearts ($P < 0.01$ compared with ischemic wild-type). Knockout of the p38 MAPK upstream kinase, MAPK kinase 3 (MKK3), did not affect ischemic activation of either AMPK or p38 MAPK in transgenic $mkk3^{-/-}$ mouse hearts. Ischemia increased the recruitment of p38 MAPK to transforming growth factor- β -activated protein kinase 1 binding protein 1 (TAB1), a scaffold protein that promotes p38 MAPK autophosphorylation. Moreover, TAB1 was associated with the α_2 catalytic subunit of AMPK. Recruitment of p38 MAPK to TAB1–AMPK complexes required the activation of AMPK and was reduced in ischemic AMPK-deficient transgenic mouse hearts. The potential role of p38 MAPK in mediating the downstream action of AMPK to promote glucose transport was also assessed. The p38 MAPK inhibitor, SB203580, partially

inhibited both AICAR- and hypoxia-stimulated uptake of glucose and translocation of glucose transporter 4. Activation of p38 MAPK by anisomycin also increased glucose transport in heart muscles. Thus AMPK has an important role in promoting the activation of p38 MAPK in the ischemic heart by inducing the autophosphorylation of p38 MAPK through interaction with the scaffold protein, TAB1.

Commentary

Myocardial ischemia is complex! A multitude of changes occur within the myocardium that appear to be energy-dependent yet occur when the high-energy phosphate “charge” is low. One such change is the phosphorylation of a mitogen-activated protein kinase known as p38 (p38 MAPK) [1]. This kinase is activated during ischemia by the phosphorylation of two amino acids on a loop within the enzyme that normally prevents substrates from binding. The ATP-dependent dual phosphorylation therefore activates p38 MAPK. The activation of p38 MAPK has a number of consequences – some good; many bad [2].

Although p38 MAPK is known to become dually phosphorylated during ischemia, the underlying mechanisms are poorly understood and rather strange. For example, a compound known as SB203580, which inhibits the kinase activity of p38 MAPK, inhibits the dual phosphorylation step [3]. This and other observations suggest that, in fact p38 MAPK activates itself by autophosphorylating its own activation loop [3]. Superficially, this seems rather odd. How can a kinase normally regulated by dual phosphorylation manage to perform this crucial step on its own, yet still be regulated physiologically? The article by Li et al may seem a little *recherche*, but does address this fundamental question. They show that mouse hearts containing an abnormal form of AMPK do not dual-phosphorylate p38 MAPK in a normal way during ischemia. Moreover, compounds that activate AMPK seem to dual-phosphorylate p38 MAPK. In keeping with the findings of other studies [1,3], the activation

of AMPK seemed to promote the association of p38 MAPK with a scaffold protein known as TAB1. This protein scaffold is believed to bind p38 MAPK and cause the change in conformation that allows it to autophosphorylate its own activation loop. Thus AMPK senses the metabolic milieu, activates, and in turn promotes the association between p38 MAPK and TAB1 that causes p38 MAPK autoactivation. What makes the story even more interesting is that this form of p38 MAPK activation, under this circumstance, seems to contribute to some of the changes associated with the activation of AMPK, including a translocation of the proteins of glucose uptake to the cell-surface membrane. These proteins are involved in the enhanced utilization of glucose needed for glycolysis to support myocardial anaerobic metabolism. The ultimate question is whether this is something that should be promoted, or inhibited, during ischemia? Unfortunately, this is a difficult question to answer; glycolysis without matched glucose oxidation could aggravate the accumulation of lactate and intracellular acidosis. This scenario is believed to lead to cellular accumulation of sodium and calcium, and to increase the probability of mitochondria self-destructing at reperfusion. Thus, although this paper adds credence to the central importance of AMPK in orchestrating responses to metabolic stress, it remains unclear whether all such responses are truly adaptive.

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