Interaction of Insulin and AMPK in the Ischemic Heart
Another Chapter in the Book of Metabolic Therapy?

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There has been a longstanding interest in the development of metabolic modulations to improve the outcome of myocardial ischemia. The glucose-insulin-potassium (GIK) regimen presents the classic example of such a quest. For more than four decades since GIK was first described, substantial evidence from animal research and small size clinical studies has supported the efficacy of GIK treatment for acute myocardial ischemia. However, a recent large clinical trial, CREATE-ECLA, showed no effect of GIK in patients with acute ST-segment elevation myocardial infarction. Although this is extremely disappointing for supporters of metabolic treatment, careful evaluations of why GIK got lost in translation will benefit future development of therapeutic strategies based on metabolic principles. The study by Folmes et al published in this issue of Circulation Research sheds some light on this matter.

Decreased perfusion during myocardial ischemia limits the delivery of oxygen and nutrients and decreases oxidative metabolism. Under these conditions, increased glycolytic ATP production becomes a critical energy source (Figure). Several mechanisms have been proposed to account for the increases in glucose uptake and glycolysis during myocardial ischemia. These include: α-adrenergic mechanisms, p38 activation, and, more recently, stimulation of AMPK-activated protein kinase (AMPK). AMPK acts as an intracellular energy sensor. Its activity is highly sensitive to the cellular AMP to ATP ratio. AMPK activity markedly increases in response to energy depletion (increased AMP/ATP) during myocardial ischemia. Previous studies suggested that the increased AMPK activity promoted glycolytic ATP production and, thereby, protected against ischemic injury. It was also suggested, however, that stimulation of fatty acid oxidation by AMPK during reperfusion was detrimental to postischemic recovery. This is because increased fatty acid oxidation would suppress glucose oxidation, whereas continued glycolysis will result in cytosolic proton production and intracellular acidosis (Figure). This uncoupling between the rates of glycolysis and glucose oxidation could be exaggerated when enhanced glycolysis occurred in the presence of high circulating fatty acids, because the latter would facilitate fatty acid oxidation, which suppresses glucose oxidation, thereby increasing the “uncoupling” and predisposing the reperfused myocardium to further injury.

Multiple mechanisms have been proposed to explain the benefit of providing insulin and glucose to ischemic hearts (Figure). First, this regimen enhances glycolytic ATP production during restricted perfusion and impaired oxidative ATP production. Second, high insulin will suppress the high blood fatty acid levels that are commonly observed in patients with acute ischemic syndrome. Third, activation of PI3K/Akt signaling by insulin promotes cell survival and protects against apoptosis. Finally, recent studies suggest that insulin, via activation of Akt, inhibits AMPK activity by phosphorylation of Ser 485 of α-AMPK. This interesting finding provides a mechanism by which insulin could antagonize the adverse effects of AMPK in postischemic hearts. The study by Folmes et al critically tested this hypothesis in isolated mouse hearts. They reported that although insulin inhibited AMPK activity and improved postischemic recovery in hearts perfused with glucose as the only substrate, the inhibitory effect of insulin on AMPK activity was not observed when palmitate was present in the perfusate at either low (0.2 mmol/L) or high (1.2 mmol/L) concentration. Furthermore, in contrast to the improved function observed in glucose-perfused hearts treated with insulin, insulin impaired the post-ischemic recovery in hearts perfused with the high concentration of palmitate.

Although this study was performed in vitro it illustrates several important considerations regarding metabolic modulation for the management of myocardial ischemia. One critical issue is the level of circulating fatty acids to which the heart is exposed during ischemia and reperfusion. The study reports that high levels of fatty acids, commonly observed in patients during acute stress, abolished the benefit of insulin. This result suggests that the insulin effects observed in ex vivo animal studies may not extend to clinical situations. However, a potential effect of GIK treatment is the insulin-mediated suppression of circulating fatty acid levels. If so, the peripheral effect of insulin may also serve or contribute to its cardiac action. Such an effect was only tested in small groups of patients in early studies of GIK treatment when the management of myocardial ischemia was drastically different from that of today. Low-molecular weight heparin used during reperfusion therapy releases lipoprotein lipase into circulation that could counteract the lowering of free fatty acids by insulin, thus the effect of insulin on plasma levels of free fatty acids should be reevaluated in today’s clinical studies.

The study by Folmes et al also suggests that the amount of insulin supplied to the heart might contribute to the differen-
tial outcomes observed among various studies. Insulin, at a concentration several orders of magnitude higher than physiological levels (100 nmol/L), has been shown to antagonize ischemia-induced activation of AMPK via Akt-mediated phosphorylation of S485/491 on α-AMPK. This observation adds to the previously proposed mechanisms for insulin-mediated myocardial protection and suggests that reperfusion with insulin can eliminate the adverse effects of AMPK activation. Using a high physiological level of insulin (100 mU/L or 0.6 nmol/L), however, Folmes et al did not observe differential phosphorylation of S485 on α-AMPK with insulin. There was also no inhibition of AMPK activity in hearts perfused with glucose and fatty acids although activation of Akt, and its effects on glucose metabolism were evident in these hearts. It was not determined though if an Akt-mediated prosurvival effect could be observed in these hearts. Nevertheless, the study raises the issue of what amount of insulin should be used and can be delivered to patients to achieve the desirable outcome. Currently, GIK clinical studies in patients during ischemia often monitor blood glucose rather than insulin levels. This apparently needs to change to understand the effects of insulin beyond modulation of glucose metabolism. Folmes et al have elegantly demonstrated that the insulin effect on glucose metabolism does not parallel its other biological effects especially those elicited by a different dose of insulin.

Although delivering therapy during ischemia is clinically challenging, it is important to recognize that the potential advantage of a metabolic intervention should be considered for both the ischemia and the reperfusion periods. Cardiac metabolism during ischemia plays an essential role in determining the extent of myocardial salvage by reperfusion. Whereas Folmes and colleagues primary focused on the reperfusion period, other studies have shown that modulation of glucose metabolism by either insulin or AMPK during low-flow ischemia, a simulation of under-perfusion, contributes significantly to postischemic recovery. Another interesting yet unanswered question raised by the study of Folmes et al is why insulin exerts opposite effects on postischemic recovery in hearts perfused with and without high concentrations of fatty acid. In hearts perfused with high concentration of fatty acid, insulin suppressed the fatty acid oxidation rate without an effect on AMPK activity. The net proton production from uncoupled glycolysis was essentially identical in reperfused heart receiving insulin regardless of whether they were reperfused with glucose or glucose plus palmitate, suggesting additional mechanism(s) may yet be discovered. In this regard, Folmes and colleagues have met the criteria for carrying out an excellent study; that is, to raise new questions for investigation. Defying predictions that the CREATE-ECLA Trial would put the issue of metabolic modulation therapy to rest, the study by Folmes has likely just opened a new chapter.

Acknowledgments

We thank Linda Johnson for her professional assistance in preparing the manuscript.

Sources of Funding

The authors’ work is supported by research funds from the National Institute of Health HL46033 (to J.A.B.), HL67970 and HL59246 (to R.T.). R.T. is an Established Investigator of the American Heart Association.

Disclosures

None.

References


**KEY WORDS:** insulin, AMPK, glucose, myocardial ischemia, metabolic modulation
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_Circ Res._ 2006;99:3-5
doi: 10.1161/01.RES.0000233142.26369.f6

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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