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Insulin as an Anti-Inflammatory and Antiatherogenic Modulator

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Data demonstrate the anti-inflammatory effects of insulin and proinflammatory effects of glucose. These data provide a mechanistic justification for the benefits of maintaining euglycemia with insulin infusions in hospitalized patients. Regimens that infuse fixed doses of insulin with high rates of glucose are usually associated with hyperglycemia, which may neutralize the beneficial effects of insulin. Therefore, we propose that such regimens should be avoided and instead replaced by insulin infusions that normalize and maintain blood glucose at a reasonably low level and ensure that plasma insulin is maintained at levels high enough to provide clinically relevant anti-inflammatory and cardioprotective effects. Trials to test this hypothesis are in progress. (J Am Coll Cardiol 2009;53:S14–20) © 2009 by the American College of Cardiology Foundation

Since its discovery in 1921, insulin has been considered a key metabolic hormone with profound effects on glucose and lipid metabolism as well as cardiovascular function, as reviewed elsewhere in this supplement. Additionally, over the past decade, data have emerged on the different effects of insulin and hyperglycemia on inflammatory processes. This article will summarize these data and discuss their implications for management of patients with acute myocardial infarction (AMI).

Proinflammatory Effect of Glucose

Our group has shown that acute challenge with 75-g glucose given orally causes an increase in superoxide radical generation by polymorphonuclear leukocytes and mononuclear cells and increased expression of p_{47}^{phox}, an essential component of the enzyme nicotinamide adenine dinucleotide phosphate hydrogen oxidase, which converts molecular O_2 to superoxide radical (1). Downstream consequences include activation of redox-sensitive proinflammatory transcription factors such as nuclear factor-kappa B (NF-kB), activator protein-1, early growth response-1, and hypoxia inducible factor-alpha, with concomitant increases in expression of matrix metalloproteinases and tissue factor by mononuclear cells (2,3). Likewise, Esposito et al. (4) demonstrated that the induction of steady-state hyperglycemia with intravenous glucose infusion with concomitant inhibition of endogenous insulin secretion with somatostatin led to an increase in plasma tumor necrosis factor-alpha and interleukin-6 concentrations. Finally, Monnier et al. (5) correlated acute glucose excursions with induction of oxidative stress in subjects with type 2 diabetes mellitus.

Hyperglycemia-related oxidative stress reduces the bioavailability of nitric oxide (NO) because superoxide radical combines with NO to form peroxynitrite. NO causes vasodilation and has inhibitory effects on platelet adhesion and aggregation (6,7). In addition, tissue factor is an activator of the extrinsic pathway of coagulation and is involved in the conversion of prothrombin to thrombin (3). Thrombin is a potent platelet aggregator and induces the conversion of fibrinogen to fibrin. Thrombin also triggers proinflammatory pathways, while platelets release CD40 ligand, a powerful inflammatory trigger (8). Thus, inflammation caused by elevated glucose concentrations induces a vasoconstrictive, prothrombotic state and thrombosis begets further inflammation. Moreover, elevated plasma levels of the inflammatory marker C-reactive protein (CRP) are associated with increased incidence of arrhythmias (9). These mechanisms may contribute to the adverse outcomes associated with hyperglycemia in patients with acute coronary syndromes (ACS) (10–13). Hyperglycemia is also associated with a reduction in spontaneous reperfusion, reduced rate of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, and a higher rate of no reflow after primary percutaneous coronary intervention in AMI (14,15). Moreover, chronic hyperglycemia and high hemo-

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globin A1c levels are associated with a lower percutaneous coronary intervention success rate in people with diabetes (16).

Reactive Oxygen Species Suppression and the Anti-Inflammatory Effects of Insulin

Insulin induces expression of endothelial NO synthase through the activation of phosphatidylinositol kinase (PI_3) and AkT kinase (protein kinase B), an insulin signaling mechanism similar to that which mediates the uptake of glucose through the glucose transporter (17). In turn, endothelial NO synthase generates NO. Human studies have demonstrated that insulin increases blood flow at the arterial, venous, and microcirculatory levels (18), effects that are NO-dependent. Insulin also inhibits platelet aggregation via a NO-dependent effect (7).

In vitro studies showed that insulin suppressed intracellular adhesion molecule-1, monocyte chemoattractant protein-1 expression, and NF-kB binding in human aortic endothelial cells (19). In obese subjects, who typically are insulin resistant and have chronic inflammation, we further showed that low-dose insulin infusion (2 U/h) suppressed reactive oxygen species generation and p_{47}^{phox} expression in mononuclear cells and suppressed NF-kB and early growth response-1 (20,21). Both the binding and expression of early growth response-1 and its protein were also suppressed, whereas inhibitor kappa B, the intracellular inhibitor of NF-kB, was increased. Plasma concentrations of intracellular adhesion molecule-1, monocyte chemoattractant protein-1, matrix metalloproteinase-2 and -9, tissue factor, and plasminogen activator inhibitor-1 also dropped significantly following the insulin infusion during which plasma glucose concentrations were maintained at a normoglycemic and constant level (20,21). We further showed in obese subjects that vascular endothelial growth factor, a cytokine that may contribute to neovascularization of the retina in the pathogenesis of diabetic retinopathy and cause expansion of experimental MI extent in the rat (22) was also suppressed by insulin (23). Taken together, these findings support potent and comprehensive anti-inflammatory and antioxidant effects for insulin. Onset is rapid, within 2 h, with the magnitude of this observed effect similar to that of 100 mg of hydrocortisone given intravenously.

Suppressive Effect of Insulin on Toll-Like Receptors (TLRs)

TLRs are a class of pathogen-recognition receptors that bind to bacterial, fungal, and viral products and induce inflammation through the subsequent activation of proinflammatory transcription factors. TLR-4 is the specific receptor for the lipid-A moiety of endotoxin and, therefore, mediates inflammatory changes induced by endotoxins (24). TLR-4 has also been shown to mediate diet-induced obesity, insulin resistance, and vascular inflammation (25,26). Thus, it is plausible that TLR-4 suppression by insulin is implicated in endotoxin-mediated inflammation, diet-induced obesity, insulin resistance, vascular inflammation, and atherogenesis. TLR-2 binds to lipopeptides, glycolipids, and peptide glycerol, which might play a role in ischemia-reperfusion–induced myocardial injury (27,28). Our most recent studies in patients with type 2 diabetes have shown that insulin infusion (2 U/h) suppresses both TLR-2 and -4 and PU1, the key transcription factor involved in the biosynthesis of TLRs (29).

Abbreviations and Acronyms

- **ACS** = acute coronary syndromes
- **AMI** = acute myocardial infarction
- **CABG** = coronary artery bypass graft
- **CRP** = C-reactive protein
- **GIK** = glucose, insulin, potassium
- **ICU** = intensive care unit
- **NF-kB** = nuclear factor-kappa B
- **NO** = nitric oxide
- **SAA** = serum amyloid A
- **TLR** = toll-like receptor

Anti-Inflammatory and Cardioprotective Effects of Insulin in Experimental Models

In a rat isolated heart preparation, the addition of insulin, even without glucose and potassium, at the time of reperfusion following the ligation of the anterior descending coronary artery reduced the size of the infarct by 45% (30). This was attributed to an antiapoptotic action of insulin, mediated via PI_3 kinase, AkT, BAD, and NO synthase phosphorylation (31). In a canine model of low-flow ischemia, insulin improved contractile function and myocardial metabolic efficiency without alteration of adenosine triphosphate, phosphocreatine, and phosphate levels (32). In an in vivo canine model of AMI, glucose and potassium infusion induced hyperglycemia and was shown to increase infarct size, but the administration of insulin with glucose and potassium, or insulin alone, reduced infarct size and improved left ventricular function (33). In total, the benefits of insulin were attributed to its antiapoptotic effect, suggesting that insulin is the main beneficial component of glucose, insulin, and potassium (GIK) infusion.

Another study in an in vivo rat model with AMI showed that induced hyperglycemia during ischemia was associated with increased infarct size (34). Hyperglycemia also neutralized the benefits obtained by GIK infusion during reperfusion, because the antiapoptotic effect of insulin, mediated via a PI_3 kinase-dependent pathway, was inhibited. These findings underscore the need to avoid hyperglycemia and maintain adequate insulin concentration during insulin infusion in ACS.

In other animal studies, insulin was shown to suppress endotoxin-induced proinflammatory transcription factors and genes regulated by them (35). These effects were shown during euglycemic conditions and, thus, are independent of any changes in glucose concentrations. A suppressive effect of insulin on proinflammatory factors has also been demonstrated in rats exposed to thermal injury (36). Insulin treatment in a rat model of endotoxemia has been shown to decrease endotoxin-induced increase in poly(adenosine