Insulin and Inflammation: Further Evidence and Discussion

Insulin is the main glucose homeostatic hormone in the body. Recently, I proposed that insulin also has anti-inflammatory actions.[1,2] This is supported by the observation that insulin blocks tumor necrosis factor (TNF) production in a dose-related manner,[3] and recombinant human TNF-induced reduction in food intake, decreased body weight gain, and interstitial pneumonitis, periportal inflammation in the liver, and increased weights of heart, lungs, kidney, and spleen are inhibited or reverted to normal by insulin administration.[4] Insulin suppressed carrageenan-induced paw edema[5] and inhibited superoxide anion ($O_2^{-\bullet}$) generation and TNF-α production by mononuclear cells.[6] It was also suggested that insulin suppresses the production of macrophage migration inhibitory factor, a proinflammatory molecule produced by a variety of cells and tissues.[1,2] The favorable effect exerted by the glucose–insulin–potassium regimen in acute myocardial infarction has been attributed to the anti-inflammatory action of insulin. Based on these findings, I suggested that continuous administration of insulin in the form of the glucose–insulin–potassium regimen (to avoid hypoglycemia that is likely to occur due to insulin infusion) could be beneficial in sepsis and septic shock and in critically ill patients. Hyperglycemia and impaired glucose use and tolerance are typical features seen in patients with sepsis and tissue trauma, leading to doubts as to whether insulin can really produce clinically significant effects during inflammatory disease.[7] It was also opined that the glucose–insulin–potassium regimen is unlikely to improve the survival of patients with sepsis (or significant trauma) and that the practical issues of the glucose–insulin–potassium regimen in surgical and critically ill patients, including dose, duration, and target insulin plasma concentration, need to be resolved. Some recent studies did confirm that insulin has antiinflammatory action and that intensive insulin therapy in critically ill patients reduces morbidity and mortality, at least in the surgical intensive care unit.

The transcription factor nuclear factor-κB (NF-κB) is a critical regulator of cytokine-inducible gene expression. Both TNF-α and interleukin-1, which are proinflammatory molecules, induce rapid translocation of NF-κB by producing degradation of inhibitory-κB (IκB). Phosphorylation of IκB leads to its dissociation from NF-κB and its nuclear translocation. Nuclear NF-κB regulates the genes that are involved in inflammatory responses such as hemopoietic growth factors, chemokines, and leukocyte adhesion molecules. Thus, NF-κB is a key mediator of the inflammatory responses of TNF-α.

Insulin infusion decreased the concentrations of intranuclear NFκB in mononuclear cells, increased IκB, and decreased the generation of reactive oxygen species and the levels of p47, the key protein of nicotinamide adenine dinucleotide phosphate oxidase in obese subjects.[8] In addition, a significant decrease in the concentrations of plasma soluble intercellular adhesion molcule-1, monocyte chemoattractant protein-1, and plasminogen activator inhibitor-1 was noted in these obese subjects after insulin administration.[8] Booth et al.[9] demonstrated that glucose induces acute inflammatory events in the rat as shown by increased leukocyte rolling, leukocyte adherence, and leukocyte transmigration through mesenteric venules associated with significant attenuation of endothelial nitric oxide release. In addition, they noted significantly increased expression of P-selectin on endothelial surfaces after exposure of mesenteric tissue to high glucose. Local application of insulin attenuated glucose-induced leukocyte rolling, adherence, and migration and increased P-selection expression, suggesting that glucose has proinflammatory actions and insulin has anti-inflammatory actions.[9]

Insulin and insulin-like growth factor-1 can phosphorylate and activate Janus kinase (JAK), JAK-1 and JAK-2, in intact cells, suggesting that the JAK family of non-receptor protein tyrosine kinases constitutes a novel type of signal transduction pathway that is activated by insulin and insulin-like growth factors.[10] Erythropoietin-mediated neuroprotection seems to involve cross-talk between JAK-2 and NF-κB signaling pathways.[11] Similar to erythropoietin, insulin and insulin-like growth factor-1 have been demonstrated to be neuroprotective in brain and spinal cord ischemia.[12] Activation of NF-κB has been reported to mediate neuronal apoptosis and prevent it.[11] These seemingly contradictory findings were explained by the fact that acute increases in NF-κB activate an apoptotic signaling pathway, whereas preconditioning stimuli such as a short exposure to hypoxia–ischemia with subsequent reperfusion lead to large increases in steady-state NF-κB activity, thereby providing neuroprotection.[11] Thus, activated JAK-2 can induce phosphorylation of IκB leading to nuclear translocation of NF-κB and NF-κB–dependent transcription of neuroprotective genes.[11] This could be one mechanism by which erythropoietin, insulin, and insulin-like growth factor-1 bring about their neuroprotective and anti-inflammatory actions.

If insulin has potent anti-inflammatory action, what could be its therapeutic implications? Hyperglycemia associated with insulin resistance is common in critically ill patients, even in those who do not have diabetes.[13–15] In a prospective, randomized, controlled study involving adults admitted to surgical intensive care unit and receiving mechanical ventilation, intensive insulin therapy (insulin infusion was given such that the blood glucose did not exceed 110 mg%, and the maximal dose of insulin was not more than 50 IU/h) substantially reduced mortality in the intensive care unit, in-hospital mortality, and morbidity.[16] Intensive insulin treatment reduced the number of deaths from multiple-organ failure with sepsis. Markers of inflammation were found to be less frequently abnormal in the intensive insulin treatment group than in the conventional treatment group (who received insulin sufficient to maintain plasma glucose levels between 180 and 200 mg%). It is interesting to note that the amount of insulin that I recommended (50 U) to obtain its anti-inflammatory actions in various inflammatory conditions is similar to what was used (the maximal dose was set at 50 IU/h) in this study.[16] This clinical study done in the surgical intensive care unit confirms that insulin has potent anti-inflammatory action and suggests that, in addition to its use in diabetes mellitus, it may have a much wider role in clinical medicine, as suggested previously.[1,2,17]

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