Metabolic Consequences of Hyperglycemia and Insulin Resistance

PAUL S. JELLINGER, MD, MACE
The Center for Diabetes & Endocrine Care
University of Miami
Hollywood, Florida

Insulin is a pleiotropic hormone that exerts a multitude of effects on metabolism and various cellular processes in the body. The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and the heart and to suppress the production of glucose and very-low-density lipoprotein in the liver. Other metabolic effects of insulin include inhibition of glucose release from the liver, inhibition of the release of free fatty acids (FFAs) from adipose tissue, and stimulation of the process by which amino acids are incorporated into protein. Insulin resistance (IR) is a condition in which defects in the action of insulin are such that normal levels of insulin do not trigger the signal for glucose absorption. An excess of FFAs is implicated in the pathogenesis of IR. The effects of this condition can have profound pathophysiologic effects on various organs and tissues of the body. For example, IR is associated with impaired insulin signaling, impaired fibrinolysis, and inflammation. The clinical consequences include hyperglycemia-induced tissue damage, hypertension, dyslipidemia, metabolic syndrome, and cardiovascular disease. Pharmacotherapies that target IR include metformin and the thiazolidinediones. Endocannabinoid antagonists, agents that target obesity and associated cardiovascular and metabolic risk factors, are currently being developed. (*Clinical Cornerstone.* 2007;8[Suppl 7]:S30–S42).

A recent study reported a statistically significant correlation between blood glucose levels and mortality.[1] In this study, data on exposure to higher than optimum blood glucose levels were collected from 65 data sources in 52 countries, representing 74% of the world population. The data sources included individual-level data from population-representative health examination surveys, exposure data from systematic reviews of published studies, data provided by individual investigators, and empirically derived models. In addition, relative risks for ischemic heart disease and stroke mortality were obtained from a meta-analysis of >200,000 participants in the Asia-Pacific region extrapolated to all populations, with adjustment for other cardiovascular risk factors. The investigators found that higher than optimum blood glucose levels account for 21% of deaths from ischemic heart disease and 13% of deaths from stroke worldwide. This burden of mortality is >2 times greater than that due to diabetes alone. They concluded that higher than optimum blood glucose is a leading cause of cardiovascular mortality in most regions of the world. Other studies also suggest a positive continuous association between blood glucose levels and cardiovascular risk.[2] The hyperglycemia that occurs with insulin resistance (IR) can have deleterious effects on organs and tissues in the body (**Figure 1**).[3] This paper will review the pathophysiology of hyperglycemia and IR, describe the metabolic consequences of IR at the cellular and organ levels, and present pharmacotherapeutic options that target IR and obesity and the associated cardiovascular and metabolic risk factors.

NORMAL ACTIONS OF GLUCOSE AND GLUCOSE METABOLISM

Glucose is the required metabolic fuel for the brain under physiologic conditions. Other organs, however, can use both glucose and fatty acids to generate energy. The process of glucose homeostasis maintains plasma glucose levels within a narrow range, usually between 60 and 150 mg/dL (3.3 and 8.3 mmol/L).[4] Because glucose is a hydrophilic molecule, specific carrier proteins—glucose transporter (GLUT) proteins—are required to allow glucose to cross cell membranes down its concentration gradient. Five GLUT proteins have been identified. One of

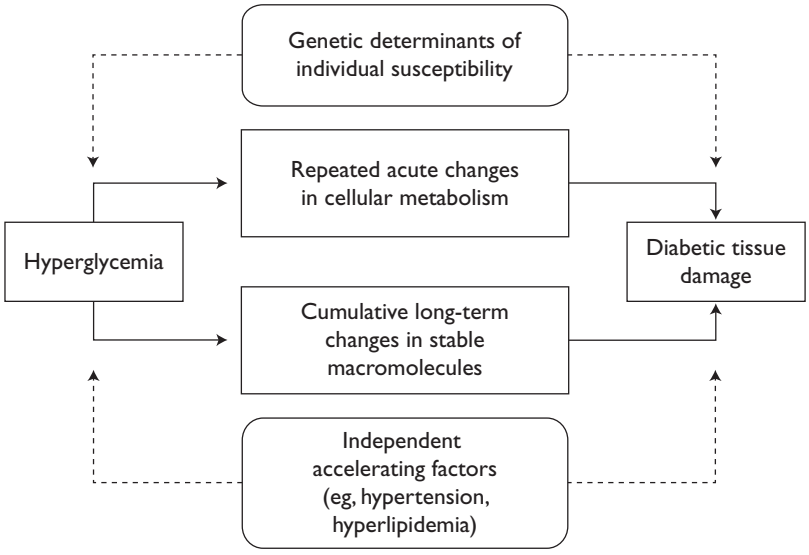

Figure 1. General features of hyperglycemia-induced tissue damage. Adapted with permission.[3]

these proteins, GLUT-4, is located on the cell membranes of muscle cells and adipocytes. In the absence of insulin, GLUT-4 exists in membrane vesicles located within the cytosol of cells. Insulin binding to its receptor initiates a signaling cascade that promotes the translocation of GLUT-4 to the plasma membrane, thus permitting the movement of glucose into the cell.

NORMAL ACTIONS OF INSULIN

Insulin is a pleiotropic hormone that exerts a multitude of effects on metabolism and various cellular processes in different tissues and organs of the body. The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and the heart and to suppress the production of glucose and very-low-density lipoprotein (VLDL) in the liver.[5] Other metabolic effects include inhibition of glucose release from the liver, inhibition of the release of free fatty acids (FFAs) from adipose tissue, and stimulation of the process by which amino acids are incorporated into protein.[6]

Some of the actions of insulin can be considered antiatherogenic.[5] For example, in blood vessels, insulin increases the production of nitric oxide (NO), which has a vasodilatory effect.[7] Insulin also inhibits platelet aggregation[8] and type-1 plasminogen activator inhibitor (PAI-1).[9] Insulin has been hypothesized to be a growth factor that stimulates vascular cell growth and synthesis of matrix proteins.[10,11]

KEY POINT

The main metabolic actions of insulin are to stimulate glucose uptake in skeletal muscle and the heart and to suppress the production of glucose and VLDL in the liver.

GLUCOSE PRODUCTION AND UTILIZATION

The balance between glucose production and utilization is regulated by a network of hormones, neural pathways, and metabolic signals. Insulin plays a pivotal role in this process. In the fasting state, insulin secretion is suppressed, which leads to increased gluconeogenesis in the liver and kidneys and increased glucose generation by the breakdown of liver glycogen. In the fed state, insulin released from pancreatic β-cells reverses this process by inhibiting glycogenolysis and gluconeogenesis, enhancing peripheral glucose uptake and utilization, and reducing lipolysis and proteolysis. The net result is that excess glucose is converted into glycogen, triglycerides (TGs), and proteins. When more glucose is present in liver cells than can be metabolized or stored as glycogen, insulin causes the excess glucose to be converted into FFAs. These FFAs are packaged as TGs in VLDL, transported in the blood in this form, and deposited as fat in adipose tissue.[12]