Abstract

Control of Glucose Output from the Liver in Normal and Diabetic States

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I shall review some remarkable advances of the past 10 years in our knowledge of how hepatic glucose production is controlled in health and in diabetes. Many seemingly well established concepts have been drastically altered or discarded as a result of new discoveries. I will show evidence that minute to minute regulation of glycogenolysis and gluconeogenesis is achieved by delicate adjustments in the balance of glucagon and insulin secretion. Virtually every condition involving normal or pathological hyperglycemia, including juvenile and maturity onset diabetes, is associated with a high glucagon to insulin activity ratio. Glucagon activates glycogen breakdown to glucose, inhibits resynthesis of glycogen and promotes glucose production from lactate and amino acids through gluconeogenesis. These hormone actions are the end result of a long chain of molecular events which begin with a hormone receptor interaction on the plasma membrane of the liver cell. This interaction activates adenylate cyclase in a complex reaction involving GTP and physical rearrangements of at least three membrane proteins. The activation raises cyclic AMP which in turn activates a cyclic AMP dependent protein kinase system. The cyclic AMP binds to an inhibitory subunit of the protein kinase holoenzyme and releases an active catalytic subunit. The latter phosphorylates and changes the activity of several enzymes which control the rate of glucose formation. These enzymes have now been identified in many cases and their action and regulation will be described. Epinephrine also activates glucose production. This hormone action is mediated by the catecholamine alpha receptor system which involves Ca as the intracellular "messenger" rather than cyclic AMP. Protein kinases have been found recently which are activated by Ca and calmodulin and which affect glucose production. Insulin opposes the effects of glucagon and epinephrine as a consequence of at least 2 actions. First, insulin lowers cyclic AMP levels (by activating a diesterase which destroys cyclic AMP), and second, by lowering the intracellular level of Ca. In untreated diabetes, gluconeogenesis becomes the main source of blood glucose and is chronically stimulated by glucagon and glucocorticoids. Chronic stimulation induces increased synthesis as well as activation of key enzymes of the gluconeogenic pathway. Acceleration of this pathway is now much better understood and depends on interruption of two back reactions which impede substrate flow to glucose. Fructose 1,6-bisphosphate and possibly a new factor, fructose 2,6-bisphosphate, are allosteric activators for the pathway, and their levels are glucagon controlled.