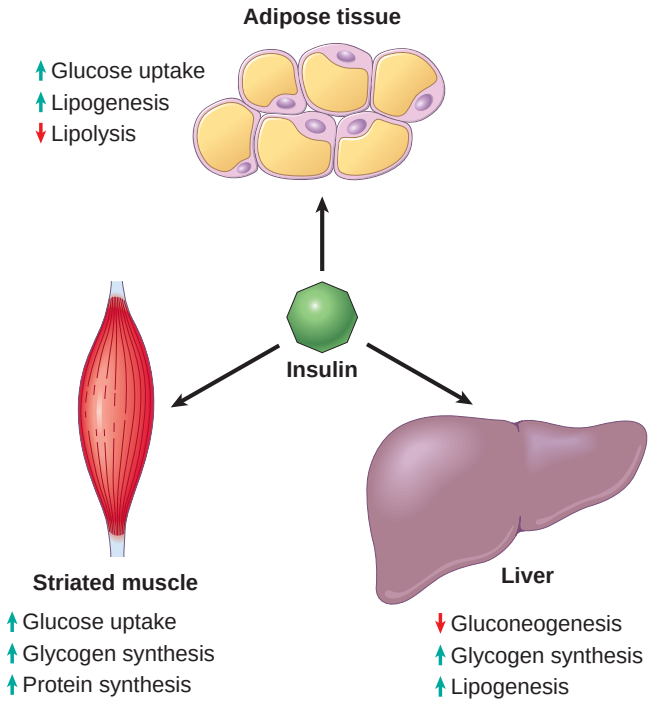

Figure 24-29 Metabolic actions of insulin in striated muscle, adipose tissue, and liver.

Insulin Action and Insulin Signaling Pathways

Insulin is the most potent anabolic hormone known, with multiple synthetic and growth-promoting effects (Fig. 24-29). The principal metabolic function of insulin is to increase the rate of glucose transport into certain cells in the body, thus increasing a major source of energy as well as metabolic intermediates that are used in the biosynthesis of cellular building blocks such as lipids, nucleotides, and amino acids. These cells are the *striated muscle cells* (including myocardial cells) and, to a lesser extent, *adipocytes,* which together represent about two thirds of the entire body weight. Glucose uptake in other peripheral tissues, most notably the brain, is insulin independent. In muscle cells, glucose is then either stored as glycogen or oxidized to generate ATP. In adipose tissue, glucose is primarily stored as lipid. Besides promoting lipid synthesis, insulin also inhibits lipid degradation in adipocytes. Similarly, insulin promotes amino acid uptake and protein synthesis, while inhibiting protein degradation. Thus, the anabolic effects of insulin are attributable to increased synthesis and reduced degradation of glycogen, lipids, and proteins. In addition, insulin has several *mitogenic* functions, including initiation of DNA synthesis in certain cells and stimulation of their growth and differentiation.

The molecular basis of insulin signaling is complex; the more pertinent mediators are summarized in Fig. 24-30. The *insulin receptor* is a tetrameric protein composed of two α- and two β-subunits. The β-subunit cytosolic domain possesses tyrosine kinase activity. Insulin binding to the α-subunit extracellular domain activates the β-subunit tyrosine kinase, resulting in autophosphorylation of the receptor and the phosphorylation (activation) of several intracellular substrate proteins, such as the family of insulin receptor substrates (IRS), which includes IRS1-IRS4 and GAB1. The substrate proteins, in turn, activate multiple downstream signaling cascades, including the PI3K and the MAP kinase pathways, which mediate the metabolic and mitogenic activities of insulin on the cell. Insulin signaling also facilitates the trafficking and docking of vesicles containing the insulin-sensitive glucose transporter protein GLUT-4 to the plasma membrane, which promotes glucose uptake. This process is mediated by AKT, the principal effector of the PI3K pathway, but also independently by the cytoplasmic protein CBL, which is a direct phosphorylation target of the insulin receptor.

Pathogenesis of Type I Diabetes Mellitus

Type 1 diabetes is an autoimmune disease in which islet destruction is caused primarily by immune effector cells reacting against endogenous β-cell antigens. Type 1 diabetes most commonly develops in childhood, becomes manifest at puberty, and progresses with age. Because the disease can develop at any age, including late adulthood, the previously used appellation "juvenile diabetes" is now considered inaccurate. Similarly, the older moniker "insulin-dependent diabetes mellitus" has been excluded from the current classification of diabetes because all forms of diabetes may be treated with insulin. Nevertheless, most patients with type 1 diabetes require insulin for survival; without insulin they develop serious metabolic complications such as ketoacidosis and coma.

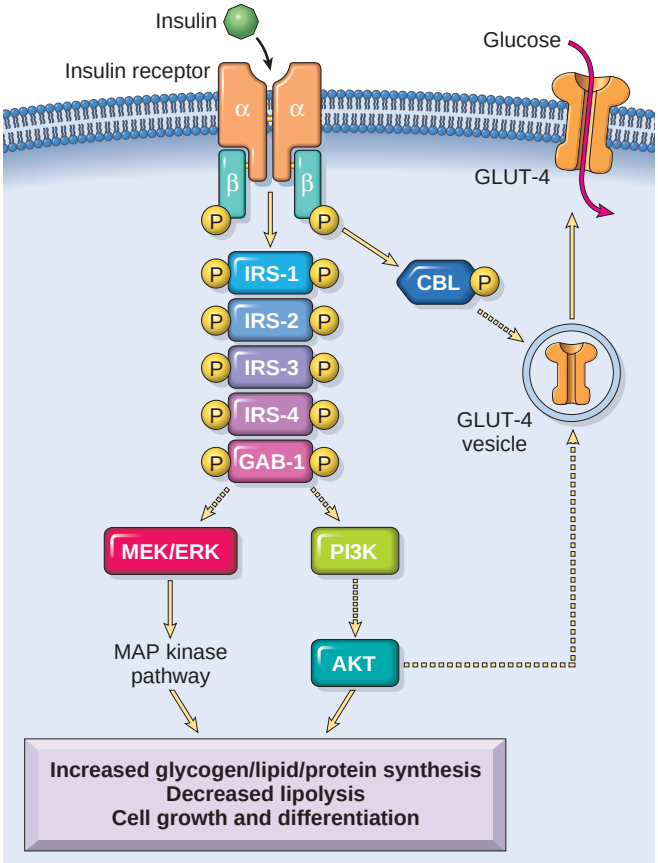

Figure 24-30 Insulin action on a target cell. The metabolic actions of insulin include promoting glycogen synthesis by activating glycogen synthase, and enhancing protein synthesis and lipogenesis while inhibiting lipolysis (see text). Dashed arrows represent intermediate proteins and binding partners that are not shown in this overview diagram.