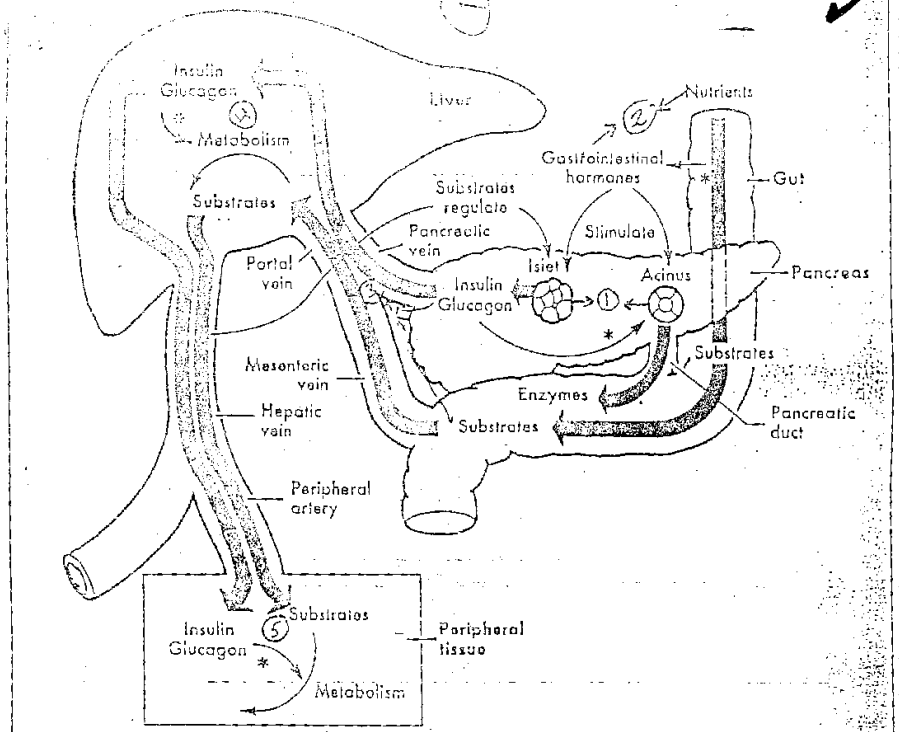

FIGURE 37-1 A schematic view of the pivotal location of the pancreatic islets. Secretion of the islet hormones insulin and glucagon is coordinated with secretion of exocrine pancreatic enzymes. Both are stimulated by entry of nutrients into the gastrointestinal tract and by gastrointestinal hormones. Islet hormones are secreted into the portal vein and thereby reach the liver with the substrate products of nutrient digestion. Within the liver they affect the metabolism of the ingested substrates. Islet hormones that pass through the liver with substrates affect disposition of these substrates by peripheral tissues. In turn these substrates feed back on the pancreatic islets to modulate the secretion of insulin and glucagon.

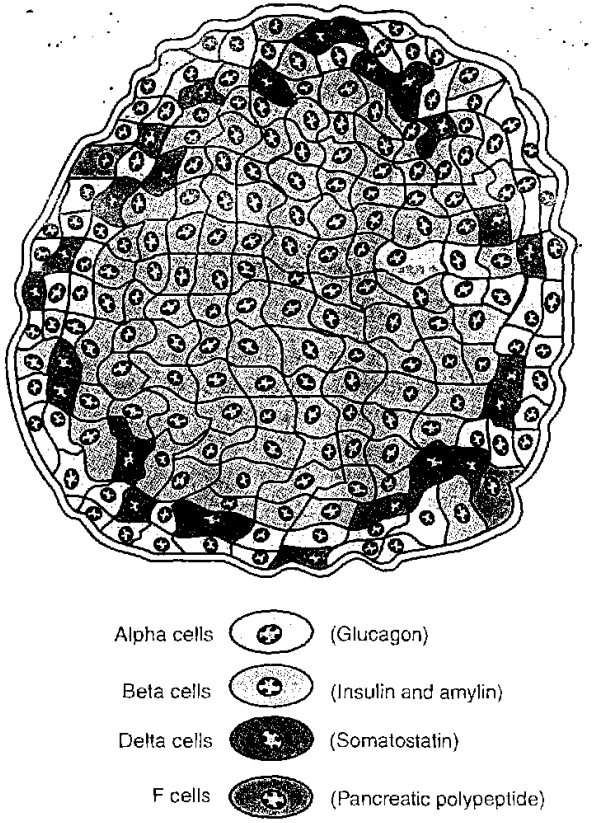

FIGURE 34.1 Major cell types in a typical islet of Langerhans. Note the distinct anatomic arrangement of the various cell types. (Modified from Orci L, Unger RH. Functional subdivision of islets of Langerhans and possible role of D cells. Lancet 1975;2:1243–1244.)

Amylin is a 37–amino acid peptide that is almost exclusively expressed within pancreatic beta cells, where it is copackaged with insulin in secretory granules. Preclinical data indicate that amylin acts as a neuroendocrine hormone that complements the actions of insulin in postprandial glucose homeostasis via several mechanisms. These include a suppression of postprandial glucagon secretion and a slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption.

Table 19–1. Cell types in pancreatic islets of Langerhans.

Cell Types	Approximate % of Islet Mass	Secretory Products
A cell (α)	20%	Glucagon, proglucagon
B cell (β)	75%	Insulin, C peptide, proinsulin
D cell (δ)	3–5%	Somatostatin
F cell (PP cell)	< 2%	Pancreatic polypeptide

Pancreatic islets of Langerhans comprise 1% to 2% of the mass of pancreas and are scattered through out the organ

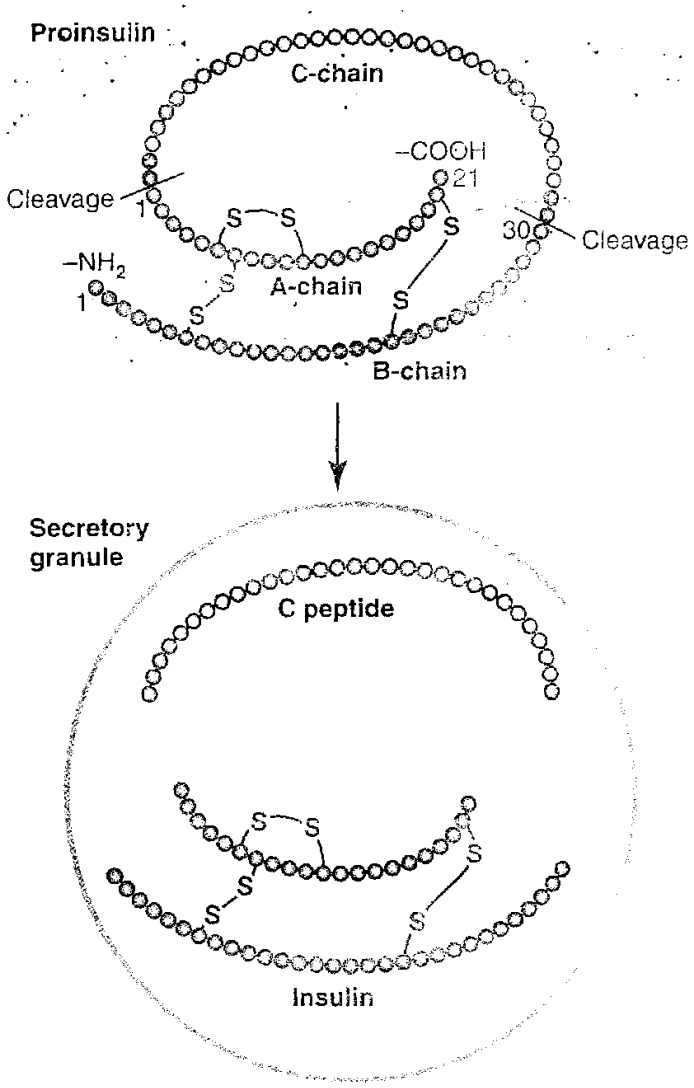

Figure 78-2 Schematic of the human proinsulin molecule, which is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide), and insulin, which is composed of the A and B chains connected by disulfide bonds. The C peptide and insulin are packaged in granules and secreted in equimolar amounts, along with a small amount of proinsulin.

Insulin and glucagon provide short-term regulation of plasma glucose levels

Other hormones involved in the regulation of plasma glucose

Insulin and glucagon play a pivotal role in the fine regulation of plasma glucose levels—indeed, insulin is the only hormone capable of lowering plasma glucose, and glucagon is the most important hyperglycemic hormone. Nevertheless, a number of other agents also contribute to the maintenance of a stable blood glucose, as well as mobilizing glucose when necessary. These hormones include adrenal corticosteroids, growth hormone, the catecholamines, and the thyroid hormones.

TABLE 18-4 SUMMARY OF GLUCOSE-COUNTERREGULATORY CONTROLS*

	Glucagon	Epinephrine	Cortisol	Growth hormone
Glycogenolysis	X	X		
Gluconeogenesis	X	X	X	X
Lipolysis	–	X	X	X
Inhibition of glucose uptake	–	–	X	X

*All the processes listed on the left—glycogenolysis, gluconeogenesis, lipolysis, and inhibition of glucose uptake—are opposed to insulin's actions and are stimulated by one or more of the glucose-counterregulatory hormones in the table. An X indicates that the hormone stimulates the process; no X indicates that the hormone has no major physiological effect on the process. Epinephrine stimulates glycogenolysis in both liver and skeletal muscle, whereas glucagon does so only in liver.

"To a great extent insulin may be viewed as the "hormone of plenty." Its secretion and plasma concentration are increased during the absorptive period and decreased during postabsorption, and these changes are adequate to cause most of the metabolic changes associated with these periods. In addition, opposed in various ways to insulin's effects are the actions of four major glucose-counterregulatory controls—glucagon, epinephrine and the sympathetic nerves to the liver and adipose tissue, cortisol, and growth hormone (Table 18-4). Glucagon and the sympathetic nervous system are activated during the postabsorptive period (or in any other situation with hypoglycemia) and definitely play roles in preventing hypoglycemia, glucagon being the more important. The rates of secretion of cortisol and growth hormone are not usually coupled to the absorptive-postabsorptive pattern; nevertheless, their presence in the blood at basal concentrations is necessary for normal adjustment of lipid and carbohydrate metabolism to the postabsorptive period, and excessive amounts of either hormone cause abnormally elevated plasma glucose concentrations.

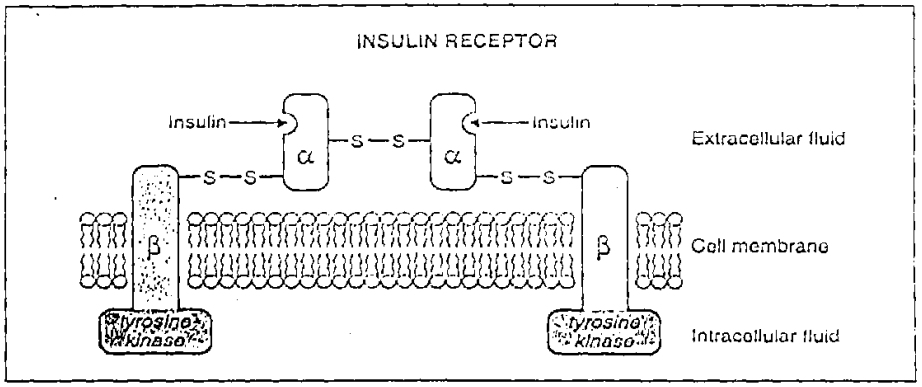

FIGURE 9-28. Structure of the insulin receptor. The two α subunits are connected by disulfide bonds; each α subunit is connected to a β subunit by a disulfide bond. The β subunits have tyrosine kinase activity.

Insulin receptors are found on many different cells in the body, including cells in which insulin does not increase glucose uptake. The receptor is made up of 2 α and 2 β glycoprotein subunits. The subunits are linked to each other and to β subunits by disulfide bonds. The α subunits bind insulin and are extracellular, whereas the β subunits span the membrane. The intracellular ends of the β subunits have tyrosine kinase activity. Binding of insulin triggers the tyrosine kinase activity of the β subunits, producing autophoisphorylation of the β subunits on tyrosine residues. This autophosphorylation in necessary for insulin to exert its biologic effects.

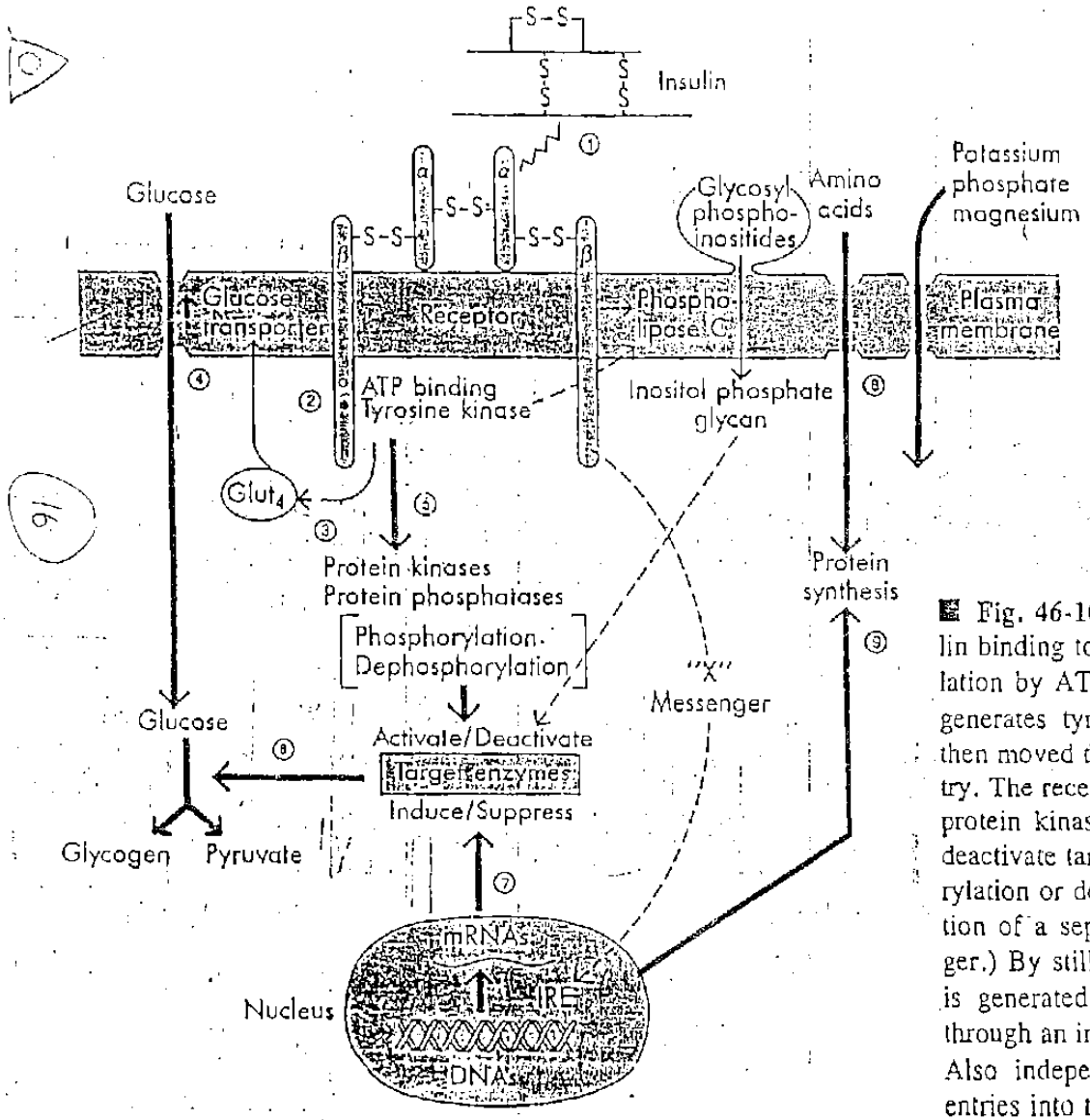

Fig. 46-10 Mechanisms of insulin action on cells. Insulin binding to α-subunit of its receptor causes autophosphorylation by ATP of an intracellular β-subunit receptor site that generates tyrosine kinase activity. Glucose transporters are then moved to the plasma membrane and facilitate glucose entry. The receptor tyrosine kinase is presumed to phosphorylate protein kinases and phosphatases, which in turn activate or deactivate target enzymes of glucose metabolism by phosphorylation or dephosphorylation. (This may be aided by generation of a separate inositol phosphate glycan second messenger.) By still undefined mechanisms, a transcription factor(s) is generated that stimulates or represses gene transcription through an insulin response element (IRE) in DNA molecules. Also independently potassium, magnesium, and phosphate entries into the cell are facilitated.

Table 78-1 Factors and Conditions That Increase or Decrease Insulin Secretion

Increase Insulin Secretion	Decrease Insulin Secretion
Increased blood glucose	Decreased blood glucose
Increased blood free fatty acids	Fasting
Increased blood amino acids	Somatostatin
Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)	α-Adrenergic activity
	Leptin
Glucagon, growth hormone, cortisol	
Parasympathetic stimulation; acetylcholine	
β-Adrenergic stimulation	
Insulin resistance; obesity	
Sulfonylurea drugs (glyburide, tolbutamide)	

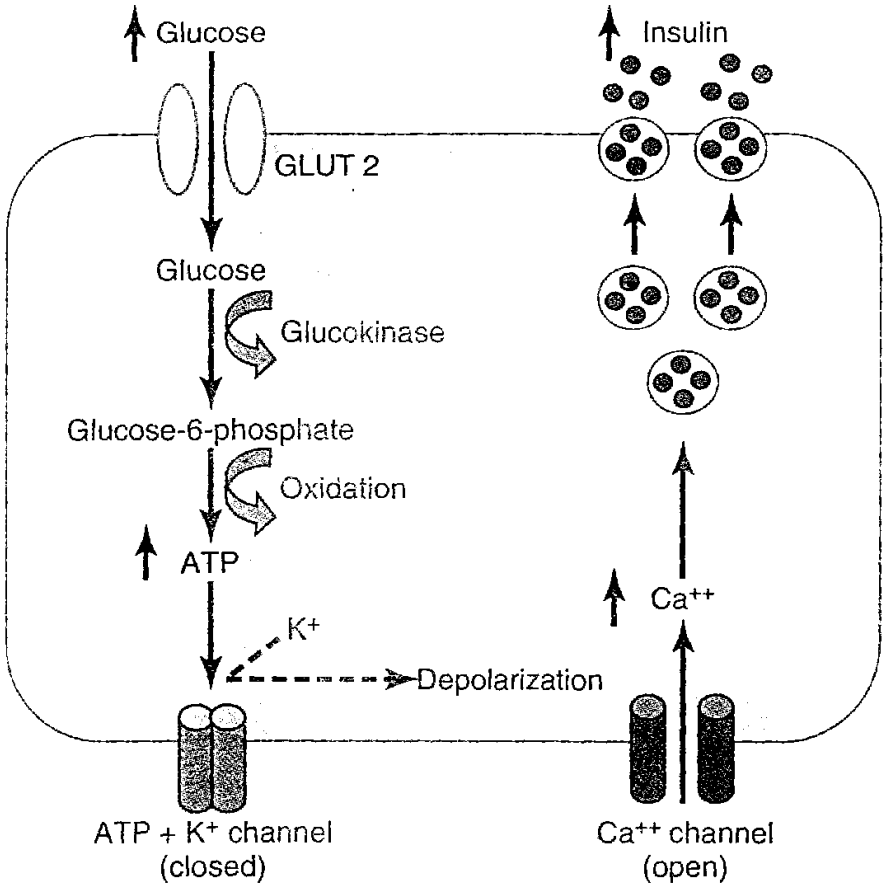

Figure 78-7 Basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

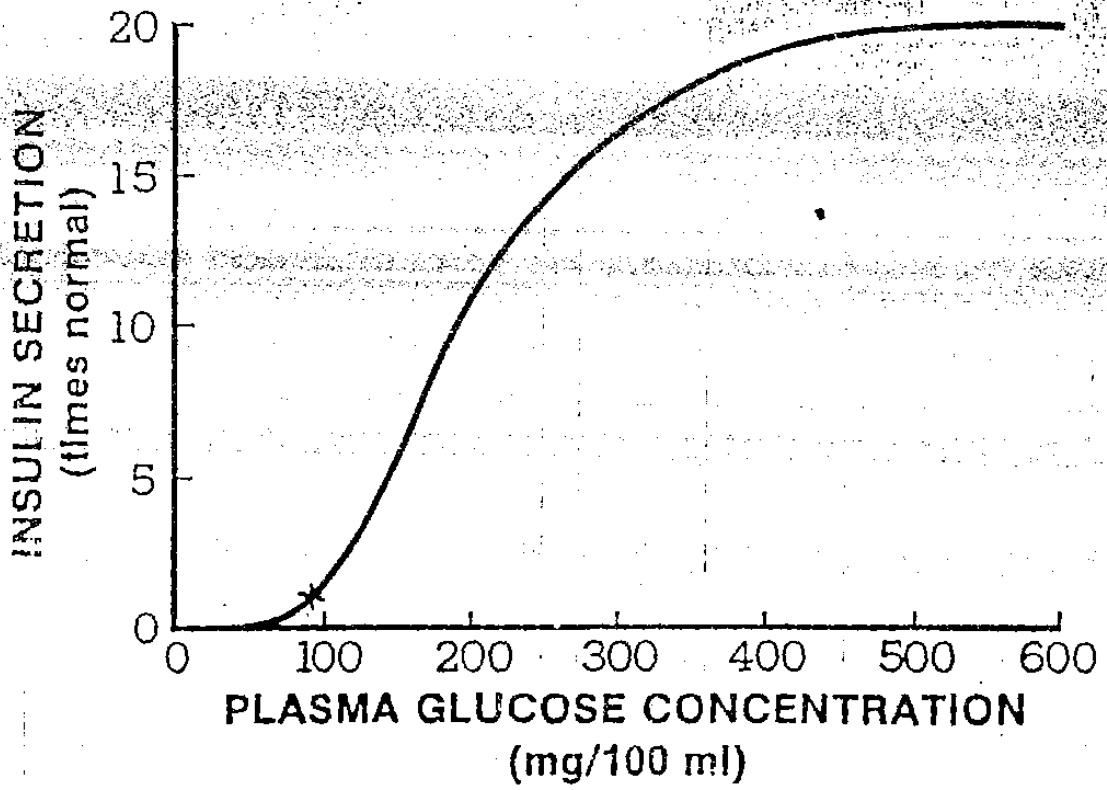

Figure 78–8. Approximate increase in insulin secretion at different plasma glucose levels.

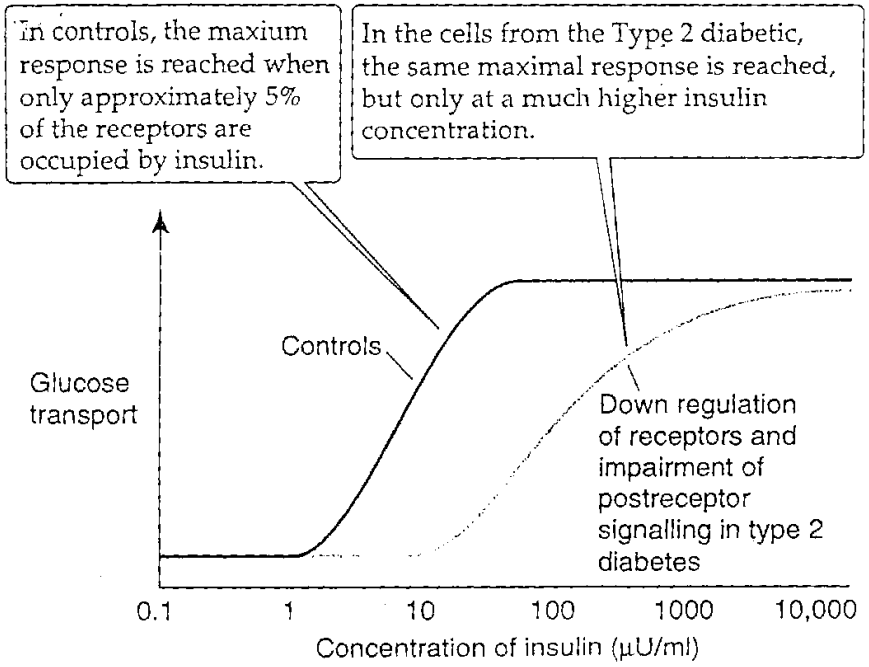

FIGURE 50--7. Response to insulin of normal and "downregulated" adipocytes.

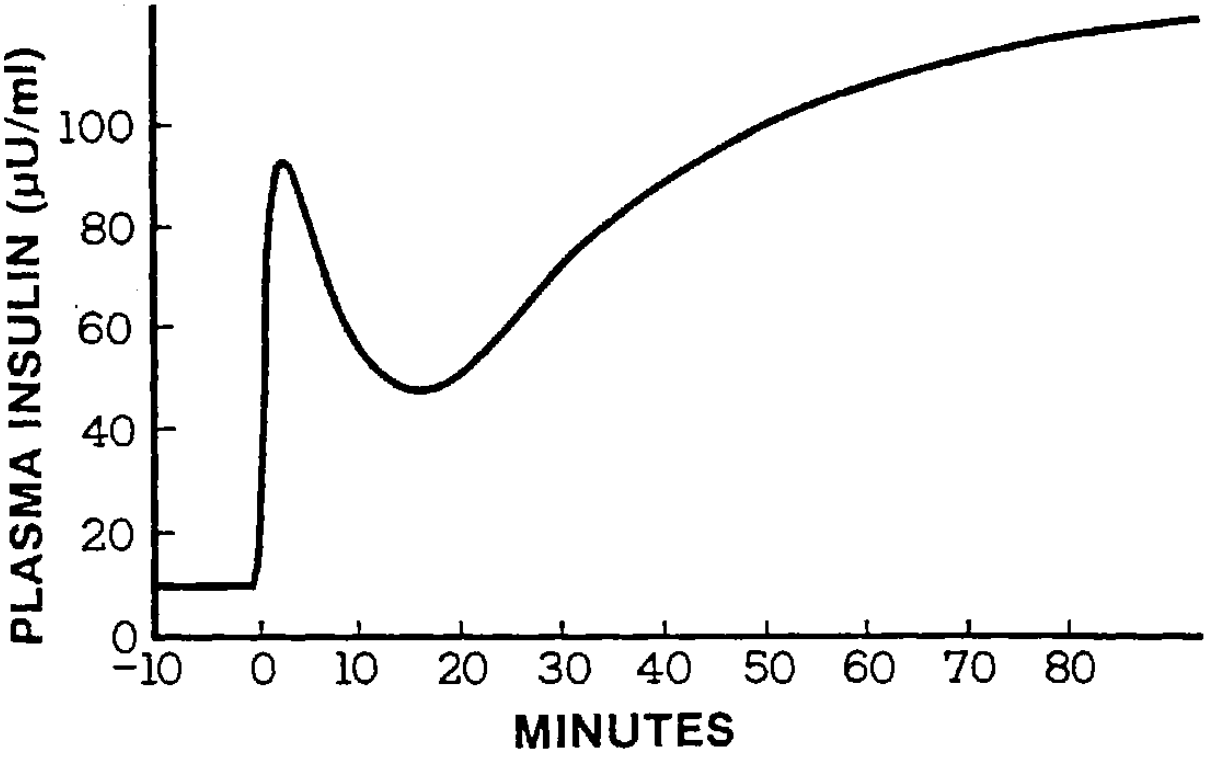

Figure 78–7. Increase in plasma insulin concentration following a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.