Chapter 5

Endocrine Regulation of Glucose Metabolism

Overview of Glucose Homeostasis

Glucose metabolism is critical to normal physiological functioning. Glucose acts both as a source of energy and as a source of starting material for nearly all types of biosynthetic reactions. The diagram shows the major players in the regulation and utilization of plasma glucose.

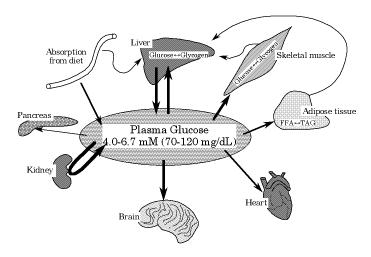


Figure 1. The organs that control plasma glucose levels. The normal plasma glucose concentration varies between about 70 and 120 mg/dL (3.9-6.7 mM). Note that whole blood glucose values are about 10-15% lower than plasma values due to the removal of cellular components during preparation of plasma.

The brain uses about 120 grams of glucose daily: 60-70% of the total body glucose metabolism. The brain has little stored glucose, and no other energy stores. Brain function begins to become seriously affected when glucose levels fall below ~40 mg/dL; levels of glucose significantly below this can lead to permanent damage and death. The brain cannot use fatty acids for energy (fatty acids do not cross the bloodbrain barrier); ketone bodies can enter the brain and can be used for energy in emergencies. The brain can only use glucose, or, under conditions of starvation, ketone bodies (acetoacetate and hydroxybutyrate) for energy.

The diet is one source of circulating glucose, and provides carbon and energy sources for liver gluconeogenesis.

The **liver is the major metabolic regulatory organ**. About 90% of all circulating glucose not derived directly from the diet comes from the liver. The liver contains significant amounts of stored glycogen available for rapid release into circulation, and is capable of synthesizing large quantities of glucose from substrates such as lactate, amino acids, and glycerol released by other tissues. In addition to controlling plasma glucose, the liver is responsible for synthesis and release of the lipoproteins that adipose and other tissues use as the source of cholesterol and free

fatty acids. During prolonged starvation, the liver is the source of both glucose and the ketone bodies required by the brain to replace glucose. The liver uses glycolysis primarily as a source of biosynthetic intermediates, with amino acid and fatty acid breakdown providing the majority of its fuel.

Like the liver, the kidney has the ability to release glucose into the blood. Under normal conditions gluconeogenesis in the kidney provides only a small contribution to the total circulating glucose; however, during prolonged starvation, the kidney contribution may approach that of the liver. Kidney function is critical for glucose homeostasis for another reason; plasma glucose continuously passes through the kidney and must be efficiently reabsorbed to prevent losses.

The **muscle cannot release glucose into circulation**; however, its ability to rapidly increase its glucose uptake is critical for dealing with sudden increases in plasma glucose. Skeletal muscle has an additional role in maintaining plasma glucose levels: it releases free amino acids into circulation to serve as substrates for liver gluconeogenesis. The muscle can use glucose, fatty acids, and ketone bodies for energy. The muscle normally maintains significant amounts of stored glycogen, small amounts of fatty acids, and contains a large pool of protein that can be broken down in emergencies. The resting muscle uses fatty acids as its primary energy source; however, glucose (from its own glycogen stores and from circulation), is preferred for rapid energy generation (*e.g.* in sudden exercise).

The adipose tissue is the major site of fatty acid storage. Fatty acids are stored in the form of triacylglycerol, which is synthesized in the adipose tissue from glycerol-phosphate and free fatty acids. The glycerol-phosphate used must be derived from glycolysis in the adipose tissue; free glycerol cannot be phosphorylated because adipocytes lack the relevant kinase. In conditions when liver gluconeogenesis is necessary the adipose tissue supplies free fatty acids and glycerol to the circulation to be taken up by the liver as substrate.

Finally, the pancreas is the source of insulin and glucagon, two of the most important metabolic regulatory hormones. The synthesis, release, and actions of these hormones is the major subject of this chapter.

Glycolysis and Gluconeogenesis

Glycolysis (Figure 2) is a major energy production pathway used at least to some degree in all cells. In addition, glycolytic intermediates and products act as carbon sources for nearly all biosynthetic reactions, and the reducing equivalents required for most biosynthetic reactions are derived from the flow of glucose through the pentose phosphate pathway. Glucose homeostasis is thus of central importance in metabolism and is heavily regulated.

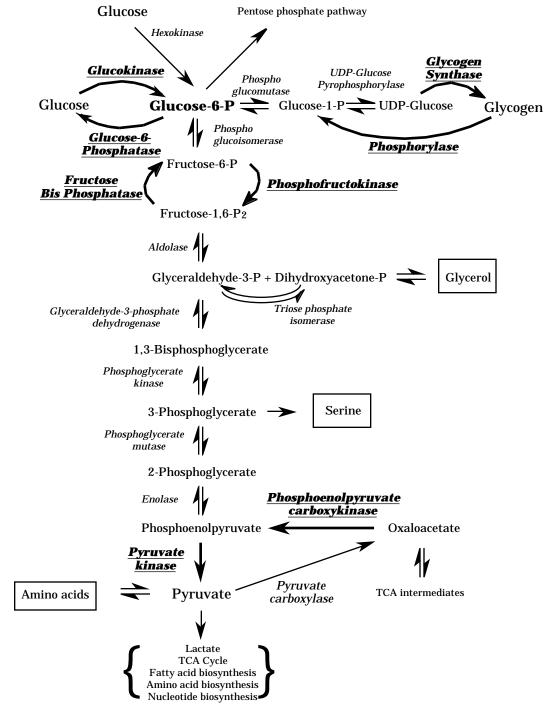


Figure 2. The glycolytic, gluconeogenic, pentose phosphate, and glycogen synthetic pathways. The primary regulated steps are catalyzed by the underlined enzymes. Note the convergence of the pathways at glucose-6-phosphate. Note also that although glucose can be phosphorylated in all tissues, the reversal enzyme glucose-6-phosphatase is only found in liver and kidney.

Metabolism of free glucose begins with a phosphorylation reaction that yields glucose-6-phosphate. This reaction is catalyzed by hexokinase in most tissues.

Hexokinase has a relatively high affinity for glucose; in most tissues the rate of the hexokinase reaction is limited by the rate of glucose import into the cell, or by glucose-6-phosphate inhibition of the enzyme. In the liver and pancreas, another enzyme, glucokinase, also catalyzes this reaction. Unlike hexokinase, glucokinase has relatively low affinity for glucose and is regulated by glucose regulatory hormones; glucokinase thus acts as a mechanism for the liver to remove excess glucose from circulation. In liver, although not in pancreas, glucokinase protein synthesis is regulated by insulin and glucagon.

The K_m of hexokinase is <1 mM. Hexokinase is therefore saturated at physiological glucose concentrations; its activity is controlled by either glucose uptake (in most tissues), a combination of uptake and the amount of the enzyme present (in liver), or (in conditions of high glucose availability), by inhibition of the enzyme by glucose-6-phosphate. In contrast, the K_m of glucokinase is ~10 mM (180 mg/dL); therefore the rate of the glucokinase reaction is essentially linearly proportional to the plasma glucose concentration, with half-maximal activity not achieved until glucose levels reach the hyperglycemic range; glucokinase is not regulated by glucose-6-phosphate.

The phosphorylation of glucose prevents the glucose molecule from leaving the cell. Since, except in liver and kidney, cells lack the ability to remove the phosphate, the hexokinase reaction is essentially a signal that the cell intends to retain the glucose molecule. Although the phosphorylation step is often referred to as the first step in glycolysis, glucose-6-phosphate is not necessarily committed to the glycolytic pathway; it can also be a substrate for glycogen synthesis or be diverted to the pentose phosphate pathway. In the liver and kidney, the enzyme glucose-6-phosphatase removes the phosphate and allows the release of glucose to circulation.

The first committed step, and primary regulatory step in the glycolytic pathway is catalyzed by phosphofructokinase. This enzyme is regulated by several hormones and by the energy state of the cell. The effect of the hormones on phosphofructokinase activity is tissue-dependent (e.g. insulin increases phosphofructokinase activity in liver, but inhibits the activity in muscle).

Phosphofructokinase is activated by fructose-2,6-bis-phosphate, AMP, and ammonia (an amino acid breakdown product) and is inhibited by ATP and citrate. In muscle, epinephrine increases the level of fructose-2,6-bis-phosphate; in liver, epinephrine and glucagon decrease fructose-2,6-bis-phosphate levels by stimulating phosphorylation of the bifunctional enzyme fructose-2,6-bis-phosphatase/fructose-6-phosphate 2-kinase. Fructose-1,6-bis-phosphatase is regulated by same compounds as phosphofructokinase, but in the opposite direction.

Particularly in liver and muscle, the flow of glucose to the glycolytic pathway is regulated the combination of hormonal influences (insulin, cortisol, and epinephrine, and, in liver, glucagon) and by the ATP:AMP ratio. When the ATP:AMP ratio is high, energy generated has met or exceeded requirements, and glycolysis decreases. It is primarily this mechanism that controls the ratio of glycogen synthesis to glycolysis in liver during insulin stimulation (insulin stimulates both pathways).

Pyruvate kinase is the last regulated step of glycolysis. Liver pyruvate kinase is phosphorylated by cAMP-dependent protein kinase, which inhibits the activity of

the enzyme; liver pyruvate kinase is also regulated by several allosteric effectors. Muscle uses a different isozyme of pyruvate kinase; muscle pyruvate kinase is not inhibited by phosphorylation.

Liver pyruvate kinase gene expression has been shown to be stimulated by glucose metabolites directly activating transcription factors. Glucose metabolites are also thought to increase GLUT2 and (in -cells) insulin gene expression. These findings suggest that glucose can act to regulate its own metabolism in a fashion at least partially independent of insulin, and may prove useful in developing new therapies for diabetes.

Gluconeogenesis (Figure 2) is the reverse of glycolysis. Many of the enzymes involved are easily reversible, and are common to both pathways. However, the reactions catalyzed by phosphofructokinase and pyruvate kinase are not reversible. The gluconeogenic pathway must use different enzymes to reverse these steps. These enzymes (phosphoenolpyruvate carboxykinase and fructose-bis-phosphatase) are the ones regulated by hormonal stimuli.

Under normal circumstances, alanine is the preferred liver gluconeogenic substrate. However, all amino acids except leucine can be used as substrate for gluconeogenesis. Alanine and glutamine are the major (~50% of total) amino acids released by muscle, although they comprise only about 15% of muscle protein. Alanine is produced in muscle from pyruvate derived from both glycolysis and amino acid metabolism.

Gluconeogenesis is inhibited by ethanol (ethanol metabolism in the liver uses up NAD, and therefore prevents the conversion of lactate to pyruvate). In normal individuals, liver glycogen breakdown yields sufficient glucose to maintain plasma levels until the ethanol has been metabolized. In conditions of malnutrition or poorly managed diabetes mellitus, ethanol inhibition of gluconeogenesis may result in hypoglycemia.

Pancreatic Anatomy and Function

The pancreas has two major functions: it produces and releases digestive enzymes, and it produces and releases the two major hormones responsible for the endocrine control of glucose metabolism: insulin and glucagon.

The exocrine pancreas comprises about 98% of the mass of the organ. The acinar cells synthesize and secrete the digestive enzymes (trypsin, chymotrypsin, elastase, amylase, and others) that break down food into simpler components that can be absorbed by the intestine.

The endocrine pancreas is comprised of small groups of cells distributed throughout the organ. These groups, the Islets of Langerhans, consist of four cell types (, , , and F). The islet composition varies in different parts of the pancreas (posterior primarily F-cells with some -cells, and anterior primarily -cells with some and smaller amounts of -cells). Each cell type secretes one major hormone: the -cells are the insulin producing cells, while the -cells produce glucagon, the -cells

produce somatostatin, and the F cells produce Pancreatic Polypeptide.

The function of pancreatic somatostatin appears to be limited to inhibition of insulin and glucagon release; the function of Pancreatic Polypeptide is unknown. The control of insulin and glucagon release is discussed in detail in the next few sections.

Synthesis and Release of Insulin

Insulin is a peptide hormone. It is synthesized in the rough endoplasmic reticulum as part of an 11.5 kDa precursor protein called pre-proinsulin. The endoplasmic reticulum-targeting sequence is cleaved during peptide synthesis to release proinsulin. Proinsulin is packaged into secretory vesicles, where it is processed into the mature peptide hormone (Figure 3).

The half-life of circulating insulin is about 5 minutes; the major sites of degradation are the liver and kidney. Under normal conditions, some proinsulin secretion occurs, amounting to 3-5% of the insulin secretion; during periods of high rates of insulin release, the processing tends to be less complete, and therefore proinsulin release constitutes a larger proportion of the total released peptides. The released proinsulin has a longer half-life than insulin. It cross-reacts with the insulin RIA, and therefore plasma "insulin" levels include about 10-20% proinsulin. Proinsulin has some activity, but only ~10% of that of insulin.

The C-peptide also has a longer half-life than insulin. Measurement of C-peptide is useful for monitoring pancreatic -cell activity because it does not cross-react in the insulin RIA and is not present in therapeutic insulin preparations.

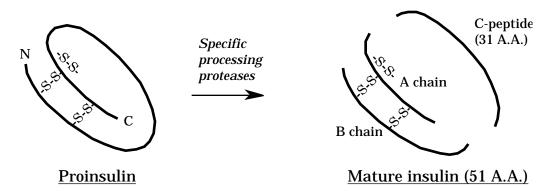


Figure 3. Cleavage of proinsulin to form insulin and C-peptide.

Mature insulin is composed of two peptide chains (the A and B-chains) linked by disulfide bonds. A connecting sequence, termed the C-peptide, is removed to produce the mature hormone; the mature hormone and the C-peptide are released by the -cells in equimolar amounts along with small amounts of unprocessed proinsulin. Cleavage of proinsulin is catalyzed by a protease that recognizes dibasic sequences (e.g. Lys-Arg). An exopeptidase then removes the basic residues to yield the mature insulin and C-peptide. (This system is also responsible for the processing (in other cell types) of a variety of peptide hormone precursors, such as glucagon and ACTH.)

The mature insulin forms hexameric crystals with zinc ions in the secretory vesicles. This process is

thought to increase the amount of insulin that can be stored in vesicles of a given size. The crystals dissolve upon release into circulation.

The C-peptide was long thought to be inactive. Recent studies, however, have suggested that some complications of diabetes may actually be alleviated or prevented by injection of C-peptide. The mechanism by which C-peptide may be acting is under investigation.

Insulin is released from the -cell in response to elevated plasma glucose, mannose, and some amino acids, especially leucine (Figure 4). Stimulation of insulin release by glucose can be enhanced by other hormones (especially those released by the gut, such as gastrin inhibitory peptide and cholecystokinin; this is why insulin release due to oral administration is greater than release due to intravenous infusion of glucose), by arginine and some other amino acids, and by -adrenergic agonists. Insulin release is inhibited by somatostatin, by cortisol, and by catecholamines acting via -adrenergic receptors. Although specific and -adrenergic agonists have opposite effects on insulin release, the net effect of physiological catecholamine action is strongly inhibitory.

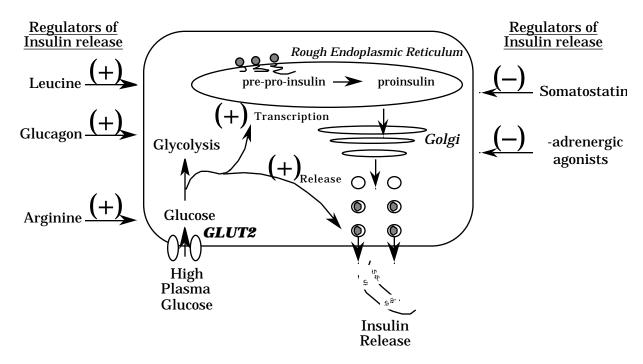


Figure 4. Insulin release is affected by a variety of different positive and negative stimuli.

Prolonged high levels of glucose decrease the -cell response to the glucose stimulation, without altering -cell responsiveness to other stimuli. Although not completely understood, this appears to be due at least in part to a decrease in the amount of GLUT2 glucose transporter in the -cell membrane. Prolonged elevation of glucose (such as that caused by hypersecretion of glucocorticoids) may exhaust the -cell stores of insulin and exceed the ability of the -cell to synthesize additional hormone, resulting in hyperglycemia; it is possible that this down-

regulation of GLUT2 is one mechanism for reducing risk of -cell exhaustion.

Transcription of the insulin gene and translation of the insulin mRNA are stimulated by glucose. Acute increases in glucose levels largely affect secretion of pre-formed insulin from secretory vesicles and mRNA translation and stability, while chronic increases in glucose levels increase transcription of insulin mRNA. Increases in transcription and translation require some time to become effective. Stimulation with glucose may therefore result in two phases of insulin release (Figure 5); a rapid phase, due to release of pre-formed hormone from mature vesicles, and a slower phase requiring synthesis of new protein. During onset of Type I diabetes the rapid phase disappears first, because basal insulin secretion rates become such a large proportion of the remaining -cell capacity that storage of pre-formed insulin in vesicles is no longer possible.

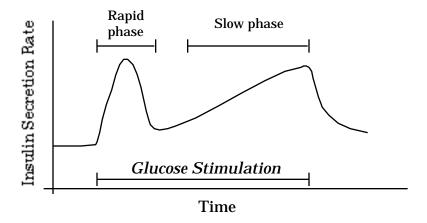


Figure 5. The two phases of insulin secretion observed during prolonged stimulation with glucose. The rapid phase represents release of previously synthesized hormone; the slow phase represents the induction of new hormone synthesis (the delay is due to the time required for transcription, protein synthesis and post-translational processing. *Time scales*: rapid phase begins less than one minute after stimulation, and ends about 10 minutes later; slow phase begins about 15-20 minutes after initial stimulation, and ends when stimulation ends.

Mechanism of Insulin Action

Insulin action is mediated by the insulin receptor, a complex multi-subunit cell surface glycoprotein. Binding of insulin activates the intrinsic tyrosine kinase activity of the receptor. Tyrosine phosphorylation of the insulin receptor itself and of some other proteins is thought to be required for insulin action. As a result of these phosphorylation (and probably other) events, a number of other intracellular proteins are activated, including several kinases, phosphatases, and transcription factors. One important enzyme activated by the second messenger cascade is phosphodiesterase, which decreases cellular cAMP levels. Insulin action is illustrated in Figure 6.

Acute increases in insulin levels result in phosphorylation or de-phosphorylation of existing proteins (e.g. the enzymes involved in the glycolytic and gluconeogenic pathways), which have rapid but transient effects on their activity. High levels of

insulin, or prolonged stimulation by insulin results in alterations in the rate of transcription of a variety of genes, and therefore in increased or decreased capacity for the processes mediated by those gene products.

Prolonged high levels of insulin result in **desensitization** (de-coupling of the receptor from the cellular responses) and **down-regulation** (decreased amounts of the receptor on the cell-surface). These phenomena protect the cell from overstimulation (similar effects are seen with a number of other hormones). Desensitization and down-regulation of the insulin receptor are important in Type II diabetes, since these phenomena occur upon prolonged high levels of insulin and contribute to the insulin resistance that characterizes the disorder. It is therefore preferable, although not always possible, to avoid use of exogenous insulin for Type II diabetics, since this tends to further down-regulate the receptor and worsen the desensitization that has already occurred.

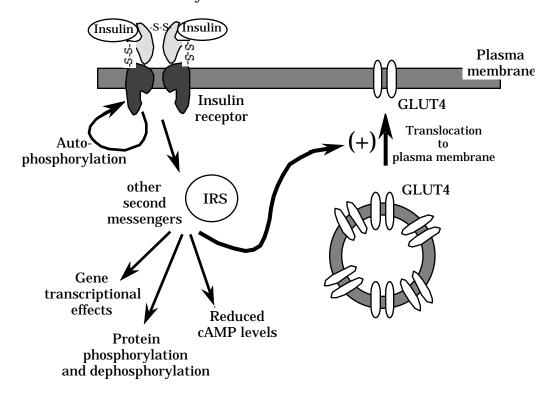


Figure 6. Intracellular effects of insulin binding to the insulin receptor. Insulin binding activates the insulin receptor tyrosine kinase. The phosphorylation of various intracellular proteins results in changes in activity of the proteins, in altered gene transcription rates for specific genes, and (in muscle and adipose tissue) in translocation of the GLUT4 glucose transporter to the plasma membrane, and therefore increased glucose uptake into these tissues.

Insulin receptor phosphorylates at least four insulin receptor substrate proteins (IRS-1 through IRS-4) on tyrosine residues. The *tyrosine phosphorylated* forms of the IRS proteins are thought to act as second messengers for a variety of intracellular responses. *Serine phosphorylation* of the IRS proteins or of the insulin receptor, in contrast, attenuates or abolishes the effect of insulin. Thus, insulin acting alone has "insulin action"; other hormones may decrease or prevent these actions by increasing activity of some serine kinases.

One important short term effect of insulin action is a translocation of the GLUT4 glucose transporter to the cell surface in muscle and adipose tissue. Stimulation of the cell for longer periods results in altered rates of transcription of a variety of proteins, including decreased rate of GLUT4 transcription.

At least five different glucose transport proteins are known. These proteins mediate the passive (*i.e.* non-energy dependent) transport of glucose across the plasma membrane of various cell types. They were named in order of discovery.

GLUT1 and GLUT3 are found in most tissues and are especially important in transport of glucose into the brain. GLUT1 and GLUT3 have a high affinity for glucose, and therefore transport glucose efficiently throughout the normal range of plasma glucose concentration.

GLUT2 is found primarily in pancreas and liver. It has a low affinity for glucose and therefore mediates glucose transport only during high plasma glucose levels. GLUT2 is the transporter that is responsible for allowing the -cells to sense hyperglycemia, and for transporting high glucose levels into the liver for storage.

GLUT4 is the primary hormonally-responsive transporter. GLUT4 is found primarily in muscle and adipose tissue, where it is normally sequestered in intracellular vesicles; it is translocated to plasma membrane in response to insulin, resulting in enhanced glucose uptake. In contrast, cortisol decreases the amount of GLUT4 in the plasma membrane. Prolonged high levels of the hormones that affect GLUT4 localization result in effects on GLUT4 gene transcription in the opposite direction of the effects on activity; thus GLUT4 gene transcription is increased by high levels of glucocorticoids and inhibited by high levels of insulin. However, GLUT4 expression is also reduced by low insulin states, such as in muscle during fasting, and in insulin-resistant adipose tissue.

The remaining GLUT gene products are much less important for glucose transport. GLUT5 is found in gut, liver and spermatozoa, and is thought to function primarily as a fructose transporter. GLUT6 is thought to be a non-functional pseudogene. GLUT7 is an intracellular liver protein responsible for glucose-6-phosphate transport into the endoplasmic reticulum.

In contrast to the passive transport mediated by GLUT gene products, the kidney and intestine contain active (energy dependent) glucose pumps that catalyze the transport of glucose against a concentration gradient. These pump proteins are responsible for the absorption of glucose from the diet and the reabsorption of glucose in the kidney.

The kidney is very efficient under normal conditions; however, at plasma glucose concentrations above about 180 mg/dL, the kidney pump becomes saturated. Glucose from concentrations above 180 mg/dL therefore ends up in the urine.

Insulin Action in Target Tissues

The liver is the main site of action of the pancreatic hormones. Because blood flow from the pancreas proceeds directly to the liver, and because the liver is the major site of inactivation of most peptide hormones, the liver is exposed to higher levels of pancreatic hormones than any other tissue.

In liver, insulin stimulates glycogen synthesis and inhibits glycogen breakdown. It also stimulates glycolysis and inhibits gluconeogenesis. In addition to its effects on

glucose metabolism, insulin has a variety of anabolic actions in the liver, stimulating lipid synthesis and release and protein synthesis, and inhibiting the breakdown of these compounds.

The liver has some ability to respond directly to high levels of plasma glucose by increasing glucose uptake and glycogen synthesis in an insulin-independent manner; however, the majority of liver glucose regulatory functions require insulin action. The liver has about 300,000 insulin receptors per cell (a very large number), but experiences maximal response to insulin when a small fraction of the receptors are occupied; this allows the organ to respond to insulin even when the plasma insulin concentration is less than the K_d for the receptor.

In muscle, insulin stimulates amino acid uptake and protein synthesis, and glucose uptake and incorporation into glycogen. The muscle plays an important role in absorbing the majority (80-95%) of sudden increases in plasma glucose levels, such as those observed during a rich carbohydrate meal. The muscle expresses significant amounts of the GLUT4 glucose transporter, which, upon insulin stimulation, is translocated to the plasma membrane (see Figure 6), allowing a massive increase in glucose uptake. During exercise the muscle becomes more sensitive to insulin action and therefore retains the ability to import glucose from circulation in spite of the exercise-induced reduction in insulin levels.

Insulin stimulates glucose uptake into adipose tissue, and has three major actions which result in net fat deposition: 1) insulin increases the amount of lipoprotein lipase, an enzyme that mediates release of free fatty acids from circulating lipoproteins; 2) insulin stimulates synthesis of glycerol-phosphate (required for triacylglycerol synthesis) from glucose; and 3) insulin inhibits hormone-sensitive lipase, the enzyme responsible for the first step in triacylglycerol breakdown.

The brain does not depend on insulin for glucose uptake, and insulin probably does not have a direct metabolic role in the CNS. However, some evidence suggests that insulin may act as a behavioral modulator, with high levels of insulin promoting decreased food intake, and low levels acting as a caloric deprivation signal. Since these behaviors are extremely complex and therefore difficult to measure accurately, and since insulin is only one of many hormones and other stimuli that affect feeding behavior, the role of insulin in the CNS is poorly understood.

The insulin resistance resulting from glucocorticoid action is also observed in the CNS. Individuals with low glucocorticoid levels generally have difficulty gaining weight; this may in part be due to the increased sensitivity to insulin (and consequent decreased feeding impulse) resulting from the low glucocorticoid action. Diabetics (in particular Type II diabetics) often exhibit significant weight gain in spite of restoration of insulin action; however, this is probably largely due to normalization of metabolism and prevention of glucose loss in the urine.

Glucagon

The other major regulatory hormone of the pancreas is glucagon, a 29 amino acid peptide synthesized as part of a 160 amino acid precursor. This precursor also contains several other peptide hormones: glucagon-like peptide-1 (GLP-1), glucagon-

like peptide-2 (GLP-2), and glicentin-related peptide. In the intestine, glucagon is not separated from glicentin-related peptide, resulting in a peptide called glicentin. GLP-1 may be further processed to a shorter form GLP-1[7-37], which (unlike GLP-1 itself) is a powerful stimulator of insulin release.

In serum samples, the glucagon RIA actually measures a mixture of proglucagon, glicentin, GLP-1, and GLP-2 as well as glucagon; glucagon normally comprises only 30-40% of the immunoreactive material measured.

Release of glucagon from the -cells is stimulated by low plasma glucose and by catecholamines and glucocorticoids. Release of glucagon is inhibited by insulin and somatostatin. Release of glucagon is also inhibited by glucose; it is not known whether this is a direct effect of glucose on the -cell, or an indirect consequence of elevated insulin levels.

Glucagon has actions opposite to those of insulin, and therefore functions to maintain plasma glucose levels between meals. However, unlike insulin, glucagon action is probably limited to the liver, with limited effects in other tissues. Glucagon stimulates liver amino acid uptake, gluconeogenesis, and glucose release, and inhibits glycolysis and fatty acid synthesis.

The glucagon receptor is coupled to adenylyl cyclase, and glucagon actions are mediated by elevation in cAMP levels. In general, actions of glucagon are mediated by increased phosphorylation of existing enzymes. Prolonged stimulation by glucagon may have some effects on gene transcription, usually in the opposite direction from that of insulin. If the insulin:glucagon ratio is low for a prolonged period (*i.e.* several days), an alteration in liver enzyme levels occurs, which causes increased production of ketone bodies.

Somatostatin

Somatostatin is released from the -cells under control of the same stimuli that result in insulin release. Somatostatin is thought to act primarily as a paracrine regulator of insulin release, preventing insulin levels from rising too rapidly. It may also have an endocrine role as an inhibitor of nutrient absorption in the gut, although this is not completely established. The somatostatin in circulation is thought to be derived from the pancreas, and not from the hypothalamus (which produces this peptide in order to inhibit growth hormone release from the pituitary).

Somatostatin is produced as part of a larger precursor. Pre-prosomatostatin (116 amino acids) is cleaved to release the 28 amino acid prosomatostatin upon transport into the endoplasmic reticulum. The 14 amino acid mature somatostatin is released from prosomatostatin by the dibasic processing protease system.

The Islet of Langerhans

One important regulator of pancreatic hormone release is the paracrine signaling that occurs within the islets. Insulin inhibits its own release, and also inhibits the release of glucagon. Glucagon inhibits its own release, and stimulates insulin release. Somatostatin inhibits the release of both insulin and glucagon. The local

changes in hormone levels act as a primary negative feedback mechanism to prevent excessive changes in pancreatic hormone levels. This is illustrated by the effects of untreated Type I diabetes mellitus, in which the loss of insulin inhibition of glucagon secretion results in overproduction of glucagon; the high levels of glucagon in the absence of insulin action throughout the body result in the severe metabolic changes of diabetic ketoacidosis (see Chapter 6).

Counter-regulatory Hormones

Glucagon (discussed above), the catecholamines epinephrine and norepinephrine, glucocorticoids, and growth hormone all act to raise plasma glucose levels. Their actions generally oppose those of insulin, and as a group, they are called counter-regulatory hormones. Due to the dependence of the brain on plasma glucose for energy, hypoglycemia can rapidly result in unconsciousness, brain damage, and death; the counter-regulatory hormones act to prevent hypoglycemia. It is thought that the variety of systems that oppose insulin action are in part a safety mechanism to prevent hypoglycemia; the influence of a variety of systems on glucose homeostasis also reflects the central importance of glucose in metabolism.

Epinephrine is released by the adrenal medulla in response to hypoglycemia (as well as other stress stimuli), and as part of the preparation for exercise. Norepinephrine is released from sympathetic neurons. Both catecholamines have significant roles in maintaining glucose levels in exercise (especially in supporting the massive increase in glucose use by the muscle), and in stress-related conditions. Catecholamines stimulate glucagon release and inhibit insulin release, causing a decrease in insulin:glucagon ratio and therefore having indirect effects on liver glucose metabolism. Epinephrine also has direct effects in stimulating liver gluconeogenesis, muscle glycolysis, and glycogen breakdown in both tissues. (Note that glycolysis regulation by epinephrine is different in liver (inhibited) and muscle (stimulated); this is due in part to the presence of different isozymes of pyruvate kinase in the two tissues.) Catecholamine action is covered in more detail in Chapter 4.

Glucocorticoids (primarily cortisol in humans) are released from the adrenal cortex in response to stress; one such stress is a decrease in plasma glucose. Glucocorticoids stimulate gluconeogenesis and glycogen synthesis in the liver, and reduce muscle and adipose tissue glucose uptake. They also acutely inhibit insulin release, and over longer term, insulin action; prolonged cortisol hypersecretion can result in diabetes. Glucocorticoid synthesis, release, and action are covered in more detail in Chapters 2 and 3.

Growth hormone is released in response to falling plasma glucose levels. The actions of growth hormone related to increases in plasma glucose are poorly understood. The only established actions of growth hormone in this regard are a stimulation of lipolysis and an inhibition of insulin action. In acromegaly, the overproduction of growth hormone can lead to diabetes.

The effect of the metabolic regulatory hormones is summarized in Table I.

Table I. Hormonal Regulation of Metabolism

H	<u>ormonal</u>	<u>Regulation</u>	of Metabolism	<u>.</u>	
	Insulin	Glucagon	Epinephrine	Cortisol	Growth Hormone
Liver					
Glycogen breakdown					
Glycogen synthesis					
Gluconeogenesis					
Glycolysis					
Glucose release					
Glucose uptake					
Glucagon receptor					
Skeletal Muscle					
Glycogen breakdown					
Glycogen synthesis					
Glycolysis			†		
Glucose uptake			†		
Protein catabolism					
Amino acid uptake					
Amino acid release					
Adipose Tissue					
Lipolysis					
Glucose uptake					
Pancreas					
Insulin release					
Glucagon release					
Systemic Effects					
Insulin action	*				

 $^{^*}$ Note: Insulin obviously has "insulin actions", hence the $\,$; however, prolonged high levels of insulin decrease the insulin response in target tissues.

[†]Note: epinephrine effects on muscle glycolysis are relatively small except during exercise. Glucose uptake in muscle is stimulated by exercise, but is probably not directly affected by epinephrine.

Effect of Food Ingestion on Pancreatic Hormone Release

The pancreas alters its release of insulin and glucagon in response to changes in plasma glucose and other circulating nutrients. One major cause of these changes is eating. The response to a meal varies significantly depending on the composition of the food.

Intravenous infusion of glucose elicits a smaller rise in insulin release than does oral administration of an equivalent amount of glucose. The greater increase in insulin levels caused by actually eating is thought to be due to gastrointestinal peptide hormones. These peptides are released in response to food absorption and potentiate the glucose effect on insulin release.

When eating a meal rich in carbohydrate, insulin levels rise and glucagon levels fall. The decrease of glucagon is due to inhibition of its release by insulin, and to the elevation in plasma glucose.

When eating a meal rich in protein, insulin levels rise, because insulin secretion is stimulated by amino acids. Glucagon levels also rise; glucagon release is also stimulated by amino acids. In this case, unopposed insulin action would result in hypoglycemia, since little glucose is being absorbed; glucagon must increase to maintain plasma glucose.

When eating a mixed meal, insulin levels rise, and glucagon levels rise, fall, or remain unchanged as appropriate to maintain plasma glucose. The pancreas uses its ability to monitor the influx of nutrients, supplemented by signals in the form of intestinal peptide hormones, to regulate the disposal of the nutrients without allowing an undue change in plasma glucose (glucose levels usually rise to the upper limit of the normal range, ~120 mg/dL, but little further). Mimicking this tailored change in pancreatic hormone release is difficult to achieve by injections of insulin, and explains part of the problem faced by individuals with Type I diabetes.

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