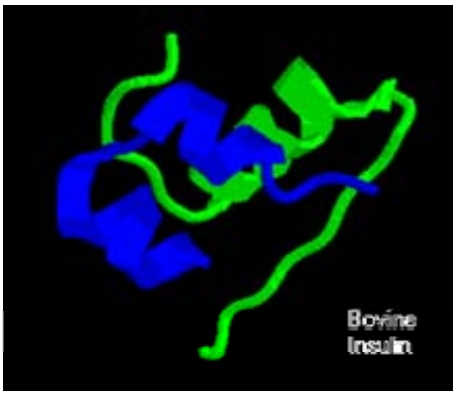
Endocrine Index Glossary

Insulin Synthesis and Secretion

Structure of Insulin

Insulin is a rather small protein, with a molecular weight of about 6000 Daltons. It is composed of two chains held together by disulfide bonds. The figure to the right shows a molecular model of bovine insulin, with the A chain colored blue and the larger B chain green. You can get a better appreciation for the structure of insulin by manipulating such a model yourself.

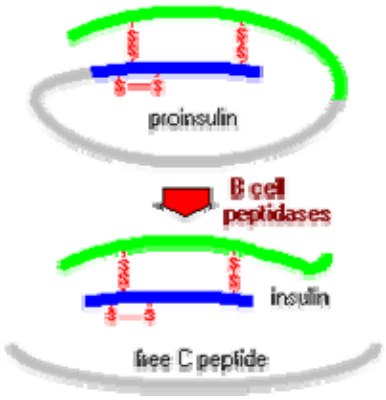


The amino acid sequence is highly conserved among vertebrates, and insulin from one mammal almost certainly is biologically active in another. Even today, many diabetic patients are treated with insulin extracted from pig pancreas.

Biosynthesis of Insulin

Insulin is synthesized in significant quantities only in beta cells in the pancreas. The insulin mRNA is translated as a single chain precursor called preproinsulin, and removal of its signal peptide during insertion into the endoplasmic reticulum generates proinsulin.

Proinsulin consists of three domains: an amino-terminal B chain, a carboxy-terminal A chain and a connecting peptide in the middle known as the C peptide. Within the endoplasmic reticulum, proinsulin is exposed to several specific endopeptidases which excise the C peptide, thereby generating the mature form of insulin. Insulin and free C peptide are packaged in the Golgi into secretory granules which accumulate in the cytoplasm.



When the beta cell is appropriately stimulated, insulin is secreted from the cell by exocytosis and diffuses into islet capillary blood. C peptide is also secreted into blood, but has no known biological activity.

Control of Insulin Secretion

Insulin is secreted in primarily in response to elevated blood concentrations of glucose. This makes sense because insulin is "in charge" of facilitating glucose entry into cells. Some neural stimuli (e.g. sight and taste of food) and increased blood concentrations of other fuel molecules, including amino acids and fatty acids, also promote insulin secretion.

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Physiologic Effects of Insulin

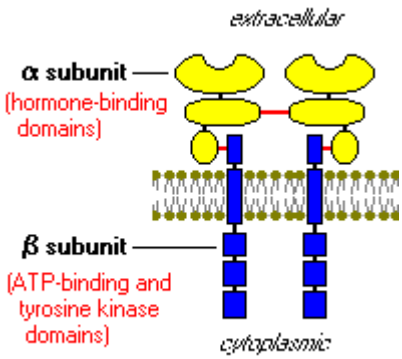
Stand on a streetcorner and ask people if they know what insulin is, and many will reply, "Doesn't it have something to do with blood sugar?" Indeed, that is correct, but such a response is a bit like saying *"Mozart? Wasn't he some kind of a musician?"*

Insulin is a key player in the control of intermediary metabolism, and the big picture is that it organizes the use of fuels for either storage or oxidation. Through these activities, insulin has profound effects on both carbohydrate and lipid metabolism, and significant influences on protein and mineral metabolism. Consequently, derangements in insulin signalling have widespread and devastating effects on many organs and tissues.

The Insulin Receptor and Mechanism of Action

Like the receptors for other protein hormones, the receptor for insulin is embedded in the plasma membrane. The insulin receptor is composed of two alpha subunits and two beta subunits linked by disulfide bonds. The alpha chains are entirely extracellular and house insulin binding domains, while the linked beta chains penetrate through the plasma membrane.

The insulin receptor is a tyrosine kinase. In other words, it functions as an enzyme that transfers phosphate groups from ATP to tyrosine residues on intracellular target proteins. Binding of insulin to the alpha subunits causes the beta subunits to phosphorylate themselves (autophosphorylation), thus activating the catalytic activity of the receptor. The activated receptor then phosphorylates a number of intracellular proteins, which in turn alters their activity, thereby generating a biological response.



Several intracellular proteins have been identified as phosphorylation substrates for the insulin receptor, the best-studied of which is *insulin receptor substrate 1* or IRS-1. When IRS-1 is activated by phosphorylation, a lot of things happen. Among other things, IRS-1 serves as a type of docking center for recruitment and activation of other enzymes that ultimately mediate insulin's effects. A more detailed look at these processes is presented in the section on Insulin Signal Transduction.

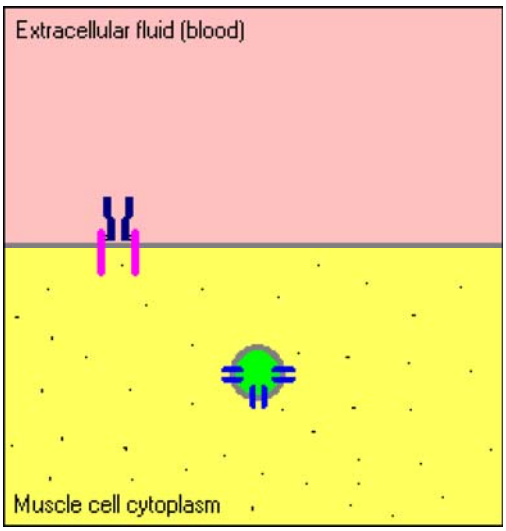
Insulin and Carbohydrate Metabolism

Glucose is liberated from dietary carbohydrate such as starch or sucrose by hydrolysis within the small intestine, and is then absorbed into the blood. Elevated concentrations of glucose in blood stimulate release of insulin, and insulin acts on cells thoughout the body to stimulate uptake, utilization and storage of glucose. The effects of insulin on glucose metabolism vary depending on the target tissue. Two important effects are:

1. **Insulin facilitates entry of glucose into muscle, adipose and several other tissues.** The only mechanism by which cells can take up glucose is by facilitated

diffusion through a family of hexose transporters. In many tissues - muscle being a prime example - the major transporter used for uptake of glucose (called GLUT4) is made available in the plasma membrane through the action of insulin.

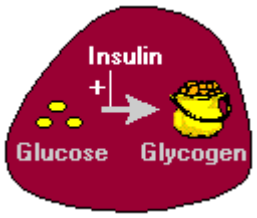
When insulin concentrations are low, GLUT4 glucose transporters are present in cytoplasmic< vesicles, where they are useless for transporting glucose. Binding of insulin to receptors on such cells leads rapidly to fusion of those vesicles with the plasma membrane and insertion of the glucose transporters, thereby giving the cell an ability to efficiently take up glucose. When blood levels of insulin decrease and insulin receptors are no longer occupied, the glucose transporters are recycled back into the cytoplasm.



The animation to the right depicts how insulin signalling leads to translocation of glucose transporters from the cytoplasm into the plasma membrane, allowing glucose (small blue balls) to enter the cell. Click on the "Add Glucose" *button to start it.*

It should be noted here that there are some tissues that do not require insulin for efficient uptake of glucose: important examples are brain and the liver. This is because these cells don't use GLUT4 for importing glucose, but rather, another transporter that is not insulin-dependent.

2. **Insulin stimulates the liver to store glucose in the form of glycogen.** A large fraction of glucose absorbed from the small intestine is immediately taken up by hepatocytes, which convert it into the storage polymer glycogen.



Insulin has several effects in liver which stimulate glycogen synthesis. First, it activates the enzyme hexokinase, which phosphorylates glucose, trapping it within the cell. Coincidently, insulin acts to inhibit the activity of glucose-6-phosphatase. Insulin also activates several of the enzymes that are directly involved in glycogen synthesis, including phosphofructokinase and glycogen synthase. The net effect is clear: *when the supply of glucose is abundant, insulin "tells" the liver to bank as much of it as possible for use later.*

A well-known effect of insulin is to decrease the concentration of glucose in blood, which should make sense considering the mechanisms described above. Another important consideration is that, as blood glucose concentrations fall, insulin secretion ceases. In the absense of insulin, a bulk of the cells in the body become unable to take up glucose, and begin a switch to using alternative fuels like fatty acids for energy. Neurons, however, require a constant supply of glucose, which in the short term, is provided from glycogen reserves.

When insulin levels in blood fall, glycogen synthesis in the liver diminishes and enzymes responsible for breakdown of glycogen become active. Glycogen breakdown is stimulated

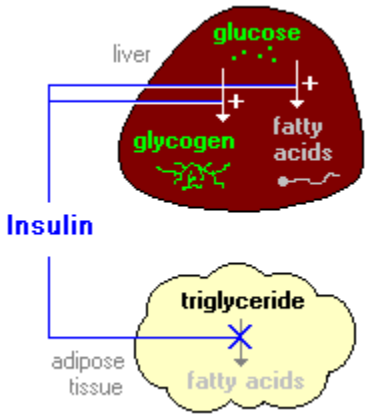
not only by the absense of insulin but by the presence of glucagon, which is secreted when blood glucose levels fall below the normal range.

Insulin and Lipid Metabolism

The metabolic pathways for utilization of fats and carbohydrates are deeply and intricately intertwined. Considering insulin's profound effects on carbohydrate metabolism, it stands to reason that insulin also has important effects on lipid metabolism, including the following:

Insulin promotes synthesis of fatty acids in the liver. As discussed above, insulin is stimulatory to synthesis of glycogen in the liver. However, as glycogen accumulates to high levels (roughly 5% of liver mass), further synthesis is strongly suppressed.

When the liver is saturated with glycogen, any additional glucose taken up by hepatocytes is shunted into pathways leading to synthesis of fatty acids, which are exported from the liver as lipoproteins. The lipoproteins are ripped apart in the circulation, providing free fatty acids for use in other tissues, including adipocytes, which use them to synthesize triglyceride.



Insulin inhibits breakdown of fat in adipose tissue by inhibiting the intracellular lipase that hydrolyzes triglycerides to release fatty acids.

Insulin facilitates entry of glucose into adipocytes, and within those cells, glucose can be used to synthesize glycerol. This glycerol, along with the fatty acids delivered from the liver, are used to synthesize triglyceride within the adipocyte. By these mechanisms, insulin is involved in further accumulation of triglyceride in fat cells.

From a whole body perspective, insulin has a fat-sparing effect. Not only does it drive most cells to preferentially oxidize carbohydrates instead of fatty acids for energy, insulin indirectly stimulates accumulation of fat in adipose tissue.

Other Notable Effects of Insulin

In addition to insulin's effect on entry of glucose into cells, it also stimulates the uptake of amino acids, again contributing to its overall anabolic effect. When insulin levels are low, as in the fasting state, the balance is pushed toward intracellular protein degradation.

Insulin also increases the permiability of many cells to potassium, magnesium and phosphate ions. The effect on potassium is clinically important. Insulin activates sodium-potassium ATPases in many cells, causing a flux of potassium into cells. Under certain circumstances, injection of insulin can kill patients because of its ability to acutely suppress plasma potassium concentrations.

Insulin Deficiency and Excess Diseases

Diabetes mellitus, arguably the most important metabolic disease of man, is an insulin deficiency state. It also is a significant cause of disease in dogs and cats. Two principal forms of this disease are recognized:

- **Type I or insulin-dependent diabetes mellitus** is the result of a frank deficiency of insulin. The onset of this disease typically is in childhood. It is due to destruction pancreatic beta cells, most likely the result of autoimmunity to one or more components of those cells. Many of the acute effects of this disease can be controlled by insulin replacement therapy. Maintaining tight control of blood glucose concentrations by monitoring, treatment with insulin and dietary management will minimize the long-term adverse effects of this disorder on blood vessels, nerves and other organ systems, allowing a healthy life.
- **Type II or non-insulin-dependent diabetes mellitus** begins as a syndrome of insulin resistance. That is, target tissues fail to respond appropriately to insulin. Typically, the onset of this disease is in adulthood. Despite monumental research efforts, the precise nature of the defects leading to type II diabetes have been difficult to ascertain, and the pathogenesis of this condition is plainly multifactorial. Obesity is clearly a major risk factor, but in some cases of extreme obesity in humans and animals, insulin sensitivity is normal. Because there is not, at least initially, an inability to secrete adequate amounts of insulin, insulin injections are not useful for therapy. Rather the disease is controlled through dietary therapy and hypoglycemic agents.

Hyperinsulinemia or excessive insulin secretion is most commonly a consequence of insulin resistance, associated with type 2 diabetes or the metabolic syndrome. More rarely, hyperinsulinemia results from an insulin-secreting tumor (insulinoma) in the pancreas. Hyperinsulinemia due to accidental or deliberate injection of excessive insulin is dangerous and can be acutely life-threatening because blood levels of glucose drop rapidly and the brain becomes starved for energy (insulin shock).

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Last updated on August 1, 2009.

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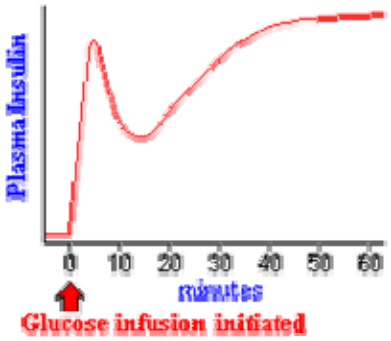
Our understanding of the mechanisms behind insulin secretion remain somewhat fragmentary. Nonetheless, certain features of this process have been clearly and repeatedly demonstrated, yielding the following model:

- Glucose is transported into the beta cell by facilitated diffusion through a glucose transporter; elevated concentrations of glucose in extracellular fluid lead to elevated concentrations of glucose within the beta cell.
- Elevated concentrations of glucose within the beta cell ultimately leads to membrane depolarization and an influx of extracellular calcium. The resulting increase in intracellular calcium is thought to be one of the primary triggers for exocytosis of insulin-containing secretory granules. The mechanisms by which elevated glucose levels within the beta cell cause depolarization is not clearly established, but seems to result from metabolism of glucose and other fuel molecules within the cell, perhaps sensed as an alteration of ATP:ADP ratio and transduced into alterations in membrane conductance.
- Increased levels of glucose within beta cells also appears to activate calcium-independent pathways that participate in insulin secretion.

Stimulation of insulin release is readily observed in whole animals or people. The normal fasting blood glucose concentration in humans and most mammals is 80 to 90 mg per 100 ml, associated with very low levels of insulin secretion.



The figure to the right depicts the effects on insulin secretion when enough glucose is infused to maintain blood levels two to three times the fasting level for an hour. Almost immediately after the infusion begins, plasma insulin levels increase dramatically. This initial increase is due to secretion of preformed insulin, which is soon significantly depleted. The secondary rise in insulin reflects the considerable amount of newly synthesized insulin that is released immediately. Clearly, elevated glucose not only simulates insulin secretion, but also transcription of the insulin gene and translation of its mRNA.

Advanced and Supplemental Topics

- The Structure of Insulin

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Functional Anatomy of the Endocrine Pancreas

Physiologic Effects of Insulin

Last updated on June 15, 1999

Author: R. Bowen

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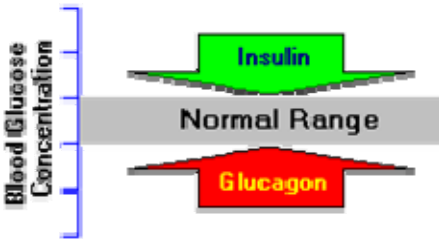
Glucagon

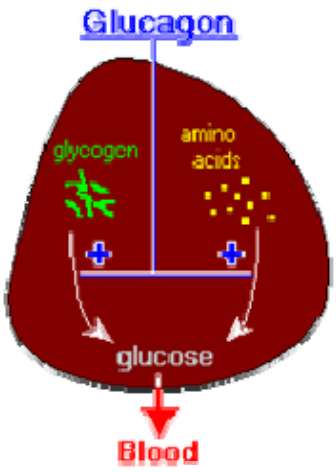
Glucagon has a major role in maintaining normal concentrations of glucose in blood, and is often described as having the opposite effect of insulin. That is, glucagon has the effect of increasing blood glucose levels.



Glucagon is a linear peptide of 29 amino acids. Its primary sequence is almost perfectly conserved among vertebrates, and it is structurally related to the secretin family of peptide hormones. Glucagon is synthesized as proglucagon and proteolytically processed to yield glucagon within alpha cells of the pancreatic islets. Proglucagon is also expressed within the intestinal tract, where it is processed not into glucagon, but to a family of glucagon-like peptides (enteroglucagon).

Physiologic Effects of Glucagon

The major effect of glucagon is to stimulate an increase in blood concentration of glucose. As discussed previously, the brain in particular has an absolute dependence on glucose as a fuel, because neurons cannot utilize alternative energy sources like fatty acids to any significant extent. When blood levels of glucose begin to fall below the normal range, it is imperative to find and pump additional glucose into blood. Glucagon exerts control over two pivotal metabolic pathways within the liver, leading that organ to dispense glucose to the rest of the body:



- **Glucagon stimulates breakdown of glycogen stored in the liver.** When blood glucose levels are high, large amounts of glucose are taken up by the liver. Under the influence of insulin, much of this glucose is stored in the form of glycogen. Later, when blood glucose levels begin to fall, glucagon is secreted and acts on hepatocytes to activate the enzymes that depolymerize glycogen and release glucose.
- **Glucagon activates hepatic gluconeogenesis.** Gluconeogenesis is the pathway by which non-hexose substrates such as amino acids are converted to glucose. As such, it provides another source of glucose for blood. This is especially important in animals like cats and sheep that don't absorb much if any glucose from the intestine - in these species, activation of gluconeogenic enzymes is the chief mechanism by which glucagon does its job.

Glucagon also appears to have a minor effect of enhancing lipolysis of triglyceride in adipose tissue, which could be viewed as an addition means of conserving blood glucose by providing fatty acid fuel to most cells.

Control of Glucagon Secretion

Knowing that glucagon's major effect is to increase blood glucose levels, it makes sense that **glucagon is secreted in response to hypoglycemia or low blood concentrations of glucose.**

Two other conditions are known to trigger glucagon secretion:

- Elevated blood levels of amino acids, as would be seen after consumption of a protein-rich meal: In this situation, glucagon would foster conversion of excess amino acids to glucose by enhancing gluconeogenesis. Since high blood levels of amino acids also stimulate insulin release, this would be a situation in which both insulin and glucagon are active.
- Exercise: In this case, it is not clear whether the actual stimulus is exercise per se, or the accompanying exercise-induced depletion of glucose.

In terms of negative control, glucagon secretion is inhibited by high levels of blood glucose. It is not clear whether this reflects a direct effect of glucose on the alpha cell, or perhaps an effect of insulin, which is known to dampen glucagon release. Another hormone well known to inhibit glucagon secretion is somatostatin.

Disease States

Diseases associated with excessively high or low secretion of glucagon are rare. Cancers of alpha cells (glucagonomas) are one situation known to cause excessive glucagon secretion. These tumors typically lead to a wasting syndrome and, interestingly, rash and other skin lesions.

Although insulin deficiency is clearly the major defect in type 1 diabetes mellitus, there is considerable evidence that aberrant secretion of glucagon contributes to the metabolic derangements seen in this important disease. For example, many diabetic patients with hyperglycemia also have elevated blood concentrations of glucagon, but glucagon secretion is normally suppressed by elevated levels of blood glucose.

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Last updated on June 15, 1999

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