

ENCYCLOPEDIA ARTICLE

Insulin

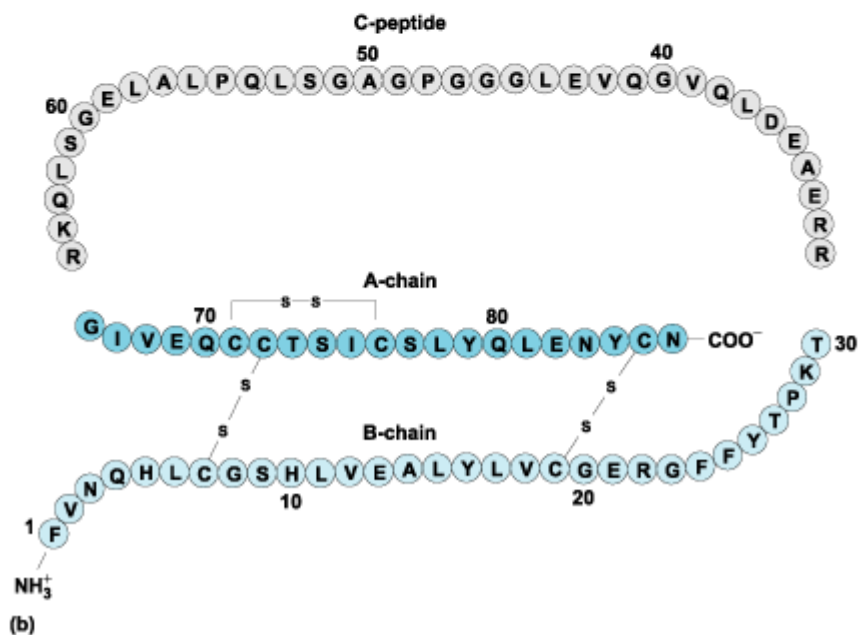
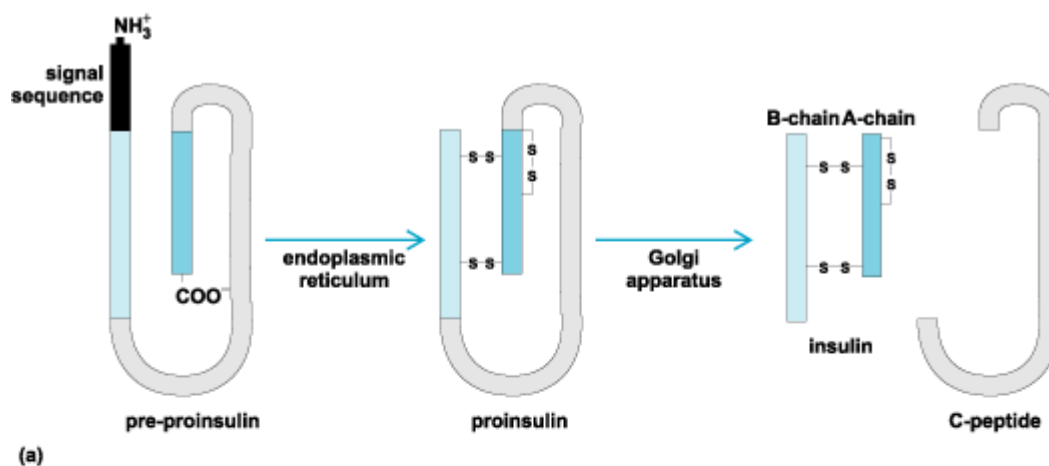
One of the hormones produced by the beta cells of the pancreas, which are located in the islets of Langerhans.

Biosynthesis

Insulin participates in carbohydrate and fat metabolism. Along with insulinlike growth factors (IGF1 and IGF2), it regulates a variety of metabolic and growth-related effects in target tissues, including stimulation of glucose transport, glycogen synthesis, lipogenesis, gene transcription, and deoxyribonucleic acid (DNA) synthesis. Moreover, the insulin/IGF signaling system promotes cell growth and survival, and is essential for normal reproductive capacity. When insulin becomes unavailable or fails to function, diabetes ensues. See also: Carbohydrate metabolism; Hormone; Lipid metabolism; Pancreas

Human insulin is composed of 51 amino acids with a molecular mass of 6000. It is synthesized from the proinsulin gene located on human chromosome 11 (11p15.5). The proinsulin gene encodes a protein called pre-proinsulin, which is targeted to the endoplasmic reticulum where the amino-terminal signal peptide (referred to in **Fig. 1** as the signal sequence) is removed to produce proinsulin. Proinsulin displays only 10% of the biological activity of insulin. The A-chain and the B-chain that form insulin are produced by removal of the C-peptide (residues 33–63) from the middle of proinsulin (Fig. 1). The C-peptide facilitates proper folding of proinsulin so that three disulfide bonds form correctly between the A- and B-chains to stabilize the shape of insulin needed for biological activity. No biological function has been assigned to the C-peptide, although it is packaged and secreted with insulin in equimolar amounts.

Insulin biosynthesis. (a) Schematic diagram. Pre-proinsulin is synthesized from the insulin gene and directed into the endoplasmic reticulum by the signal sequence, where it folds into a proper conformation that is stabilized by three disulfide bonds (—S—S—). The signal sequence is removed, and proinsulin is further processed in the Golgi apparatus, where the C-peptide is removed and packaged with insulin for secretion. (b) Primary amino acid sequence of human insulin and the C-peptide.



Physiological activity

The consumption of a carbohydrate meal causes an immediate rise in blood glucose concentration from 80 mg/dl to 130 mg/dl. Immediate insulin secretion then lowers blood glucose to the original level within 90 min. In healthy people, the blood contains about 0.2–1 ng/ml insulin before a meal and 1–5 ng/ml after the ingestion of a carbohydrate meal. Antibodies that specifically bind to insulin are used to determine precisely the concentration of insulin in blood. Similar methods measure the concentration of C-peptide in blood, which is used as an indicator that insulin is being produced in the beta cells, especially in people receiving insulin injections.

The blood glucose level is an important signal for insulin secretion. Glucose enters the pancreatic beta cells and increases the production of adenosine triphosphate (ATP), which directly stimulates insulin secretion. Other hormones released from cells in the small intestine during a meal travel to the beta cells to further promote insulin secretion. Upon secretion from the beta cells, insulin passes through the liver on its way to the peripheral tissues. Insulin-degrading enzyme is abundant in the liver, destroying about 50–60% of the secreted insulin as it passes through: the “half-life” of insulin in the body has been estimated to be 10–30 min. Insulin inhibits the production of glucose by the liver and increases the uptake of glucose by muscle and adipose tissues. Depending upon the tissue type, the glucose is used for energy (ATP production) or stored

as glycogen or fat. See also: Glucose

Diabetes

The role of pancreatic secretions to control blood sugar levels was demonstrated in 1889. Insulin purified from the pancreas was first used to treat diabetic patients in 1921. Over the following decades, clinicians and scientists revealed the system-wide effects of insulin in liver, muscle, and adipose tissues. By the middle 1930s, the widespread use of insulin revealed important differences between insulin-dependent (type 1) and non-insulin-dependent (type 2) diabetes. Antibodies against insulin were used in the 1950s to confirm that hyperinsulinemia—elevated insulin in the blood—is characteristic of type 2 diabetes. Cell surface insulin receptors were first identified in the 1970s, and their tyrosine kinase activity was discovered 10 years later. Remarkably, this steady scientific progress has not stemmed the worldwide diabetes epidemic that will take a huge toll in premature morbidity and mortality in the twenty-first century.

The inability of beta cells to detect glucose or secrete enough insulin causes diabetes mellitus. Diabetes mellitus is a complex disorder that arises from various causes, including dysregulated glucose sensing or insulin secretion [maturity-onset diabetes of youth (MODY)], autoimmune-mediated β -cell destruction (type 1), or insufficient compensation for peripheral insulin resistance (type 2). MODY is a rare and usually mild form of diabetes caused by one of many well-defined genetic mutations. By contrast, the complete lack of insulin production that occurs in type 1 diabetes and in the late stages of type 2 diabetes is catastrophic. The most obvious problem is a 5- to 10-fold elevated blood glucose level, which causes life-threatening symptoms of diabetes mellitus—polydipsia (excessive thirst), polyphagia (excessive hunger), and polyuria (excessive urine production). The complete absence of insulin is accompanied by the breakdown of triglyceride into fatty acids. Fatty acids are useful fuel materials, but when present in large amounts they form beta-ketoacids in the liver, which acidifies the blood resulting in coma. In addition to an increased fat breakdown, an increase in the breakdown of tissue proteins occurs. Insulin injection reverses all of these acute problems by favoring storage and swift intake of glucose into the tissues, by decreasing the breakdown of stored fat, and by promoting protein synthesis. Optimized insulin treatment also reduces the occurrence of long-term complications that impair eye and kidney function and damages nerves and blood vessels.

Type 2 diabetes is the more prevalent form of the disease, affecting 18 million people in the United States alone. It develops more slowly and usually occurs in middle age, but is appearing with greater frequency in children and adolescents. Insulin resistance in muscle, liver, and adipose tissues is always associated with type 2 diabetes, and hyperinsulinemia prevents gross decompensation of glucose homeostasis in the early stages of type 2 diabetes. However, insulin resistance is associated with a cohort of systemic disorders—dyslipidemia, hypertension, cardiovascular disease, female infertility and neurodegeneration—which usually develop before the disease is diagnosed. See also: Diabetes

Commercial production

Human insulin was the first commercially available protein produced by recombinant DNA technology. The production is accomplished by inserting the gene for human insulin or proinsulin into a microorganism such as yeast or bacteria. While the microorganism grows, it produces the recombinant protein, which is purified and processed into biologically active insulin for injection. Treatment of diabetes with human insulin avoids the problems created by using insulin purified from animal sources, including the production of neutralizing antibodies.

The chemical characteristics of human insulin are exploited to produce insulin preparations that suit the treatment requirements of individual patients. Recombinant human insulin forms dimers in solution due to hydrogen bonding. Insulin dimers diffuse into the blood, where they separate into monomers that are

biologically available 30–45 min after injection. The addition of zinc to insulin promotes the formation of insulin hexamers that require extra time to dissolve and form biologically active monomers: Insulin hexamers display a slower onset but a longer duration of activity (up to 24 h), resulting in less frequent need for insulin injections. The duration of action of all forms of insulin is dependent on dose, site of injection, blood supply, temperature, and physical activity. Excess injected insulin causes severe hypoglycemia—blood sugar below its normal value—which damages neurons in the brain. For this reason, insulin should be injected subcutaneously and never intravenously or intramuscularly.

“Designer” insulin molecules with modified amino acid sequences can be produced by selectively changing the DNA sequence of the gene used in the process. These modifications alter the chemical behavior of insulin. For example, switching the order of the lysine and proline residues at the C-terminal end of the B-chain minimizes the formation of dimers and hexamers (Fig. 1). This designer insulin, called lyspro, displays almost immediate biological activity with short duration. It may be injected during a meal to prevent an excessive increase in plasma glucose after eating in certain patient populations. See also: Genetic engineering

Insulin receptors

Insulin action is initiated in cells by the binding of insulin to its cell receptor (**Fig. 2**). The insulin receptor is the prototype for a family of homologous integral membrane proteins composed of an extracellular insulin-binding domain that controls the activity of an intracellular tyrosine kinase. The 150-kilobase gene on chromosome 19, composed of 22 exons, encodes the human receptor precursor. During translation, two pro-receptors form disulfide-linked dimers that are glycosylated and cleaved to form a heterotetramer of two extracellular α -subunits and two transmembrane β -subunits. Insulin binds to the juxtaposed α -subunits, facilitating ATP binding and tyrosine autophosphorylation in the β -subunit, which activates the kinase and recruits cellular substrates: the first steps of signal transduction.

Regulation of the insulin/IGF signaling pathway. The diagram shows the relation between the insulin receptor and its principal substrates, including some of their downstream elements and mechanisms of inhibition. The IRb predominates in adult tissues and binds insulin with highest affinity (<1 nM); IRa predominates during fetal life and in adult brain, binds insulin with lower affinity (~ 1 nM), but has a similar affinity for IGF2. The homologous IGF1 receptor binds IGF1/2 with high affinity (<1 nM). Hybrid receptors display intermediate binding properties: IRb::IGF1R binds IGF1 better than insulin, whereas IRa::IGF1R binds insulin and IGF1/2 with approximately equal affinity. The receptor β -subunits are tyrosine-phosphorylated during ligand binding and recruit substrates for phosphorylation, including IRS1/2 through an interaction between the phosphorylated NPXY motif on the receptor and the PTB domain. This interaction is inhibited by JNK-mediated phosphorylation of Ser³¹², which causes insulin resistance. SOCS1/2 is an adapter protein that recruits IRS1/2 to an elongin B/C-based ubiquitin ligase, which promotes ubiquitination and degradation of the IRS-protein; proinflammatory cytokines like IL6 upregulate SOCS1/2. While proinflammatory cytokines inhibit IRS-protein signaling, cAMP agonists upregulate IRS2 through the activity of phosphorylated CREB. Tyrosine phosphorylation of IRS1/2 recruits and activates various SH2-domain-containing proteins, including the 85-kilodalton regulatory subunit of the PI 3-kinase. Activation of PI 3-kinase during association with IRS1/2 strongly stimulates the PKB cascades that phosphorylate various substrates, including BAD, GSK3 β , and Foxo1.

Tyrosine phosphorylation of IRS1/2 leads to the stimulation of the phosphatidylinositol 3-kinase (PI-3), which is composed of p85 and p110 subunits. PI-3 generates phosphatidylinositol 3,4,5-tris-phosphate (PI 3,4,5P₃) in the plasma membrane, which stimulates the activity of certain serine kinases in cells. One of these serine kinases, called protein kinase B (PKB), is especially important because it promotes the phosphorylation of other proteins, including BAD (important for cell survival), GSK3 β (cell growth and glycogen synthesis), and Foxo1 (regulation of gene expression) [Fig. 2].

Resistance

Since insulin resistance is an underlying cause of metabolic dysregulation and diabetes, understanding its molecular basis is an important goal. Genetic mutations are obvious sources of lifelong insulin resistance, but they are difficult to identify and usually associated with rare metabolic disorders. The idea that inflammation is associated with insulin resistance has been known for a long time, which provides a framework to understand how diet, acute or chronic stress, and obesity might cause insulin resistance. Familiar proinflammatory cytokines, including interleukin-6 (IL6) and tumor necrosis factor alpha (TNF α), ordinarily secreted from leukocytes during inflammation or from adipocytes in obese people, promote insulin resistance. These cytokines stimulate serine phosphorylation of IRS1/2, which inhibit their ability to undergo tyrosine phosphorylation. These cytokines also promote ubiquitination of IRS1/2, which targets them for degradation. Insulin resistance is also caused by protein or lipid phosphatases, including PTP1B, SHIP2, or PTEN. PTP1B is especially interesting because it resides in the endoplasmic reticulum, where it dephosphorylates the insulin receptor. This mechanism of action appears to confer selectivity toward the insulin receptor, so inhibitors of PTP1B might be least likely to cause unregulated cell growth.

Peripheral insulin resistance alone rarely causes diabetes, as β -cell failure is an essential feature of the disease. Why β -cells frequently fail to compensate for insulin resistance was difficult to determine until the IRS2-branch of the insulin/IGF signaling system was found to be essential for β -cell growth, function, and survival. Transgenic mouse experiments clearly show that upregulation of IRS2 potentiates compensatory insulin secretion in obese mice and prevents β -cell destruction. Recent work shows that the IRS2 gene in mice is strongly upregulated by cAMP agonists, including glucose and glucagon-like peptide-1 in β -cells, through pathways that activate CREB (Fig. 2). While many cAMP-mediated pathways oppose the action of insulin, the upregulation of IRS2 reveals an unexpected intersection of these important signals that prepares cells to respond during the next round of insulin secretion (Fig. 2). IRS2 upregulation might play a role in the beneficial health effects of many drugs that increase cellular cAMP levels. The positive effects of glucagon-like peptide-1 on β -cell function, peripheral insulin action, and neuronal function might be mediated in part by upregulation of IRS2.

Diabetes is a serious illness, but only one of the consequences of insulin resistance. The clinical effects of insulin resistance can be expected to increase, as the people become heavier and less fit. Whether better management of inflammatory responses can attenuate insulin resistance and diminish its consequences is an important area of investigation. Understanding how the IRS-proteins negotiate the conflicting signals generated during insulin and cytokine action might be a valuable starting point. However, too much insulin action might shorten our lives, so future work must better resolve the network of insulin responses that are generated in various tissues, and pinpoint the ones that prolong health as well as the ones that diminish it.

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