Pancreatic islets endocrinology
Insulin

Insulin is a 51-amino acid peptide hormone comprising two polypeptide chains, the A and B chains, which are linked by disulphide bridges (Figure 1). Insulin is synthesized in the β-cells of the islets of Langerhans in the pancreas (Figure 1).

The other endocrine cell types of the islet are the α-cells producing glucagon, the δ-cells producing somatostatin, the ε-cells producing ghrelin and the pancreatic polypeptide (PP) cells producing pancreatic polypeptide. The β-cells are the most numerous, tend to be located more centrally in islet structures and are surrounded by the other cell types. Insulin is synthesized on the ribosomes of the rough endoplasmic reticulum (RER) as a single amino acid chain precursor molecule called preproinsulin . After removal of the signal peptide, proinsulin is transferred from the RER to the Golgi apparatus, where soluble zinc-containing proinsulin hexamers are formed. The prohormone convertase enzyme, PC1/3, finally acts outside the Golgi apparatus to produce the mature insulin and connecting peptide (C-peptide). In the pancreatic islet, both insulin and C-peptide are released simultaneously in equimolar quantities by exocytosis in response to a number of stimuli, including glucose and amino acids (Table 11.5).

Table 11.5 Factors regulating insulin release from the β-cells of the pancreatic islets

Insulin secertion increased by	Insulin secretion decreased by
Nutrients	Nutrients
Raised glucose	Low glucose
Amino acids	Hormones
Hormones	Somatostatin
Glucagon	NPY
Gastrin, secretin	Ghrelin
Cholecystokinin	Pancreatic innervation
GIP	Signalling via sympathetic β receptors
GLP-1	Adipokines
Pancreatic innervation	Leptin
Signalling via sympathetic α-receptors	Resistin
Parasympathetic stimulation	Stress
Adipokines	Exercise
Adiponectin	Hypoxia
	Hypothermia
	Surgery
	Severe burns

GIP, glucose-dependent insulinotrophic peptide (previously known as 'gastric inhibitory peptide'); GLP-1, glucagon-like peptide 1; NPY, neuropeptide Y.

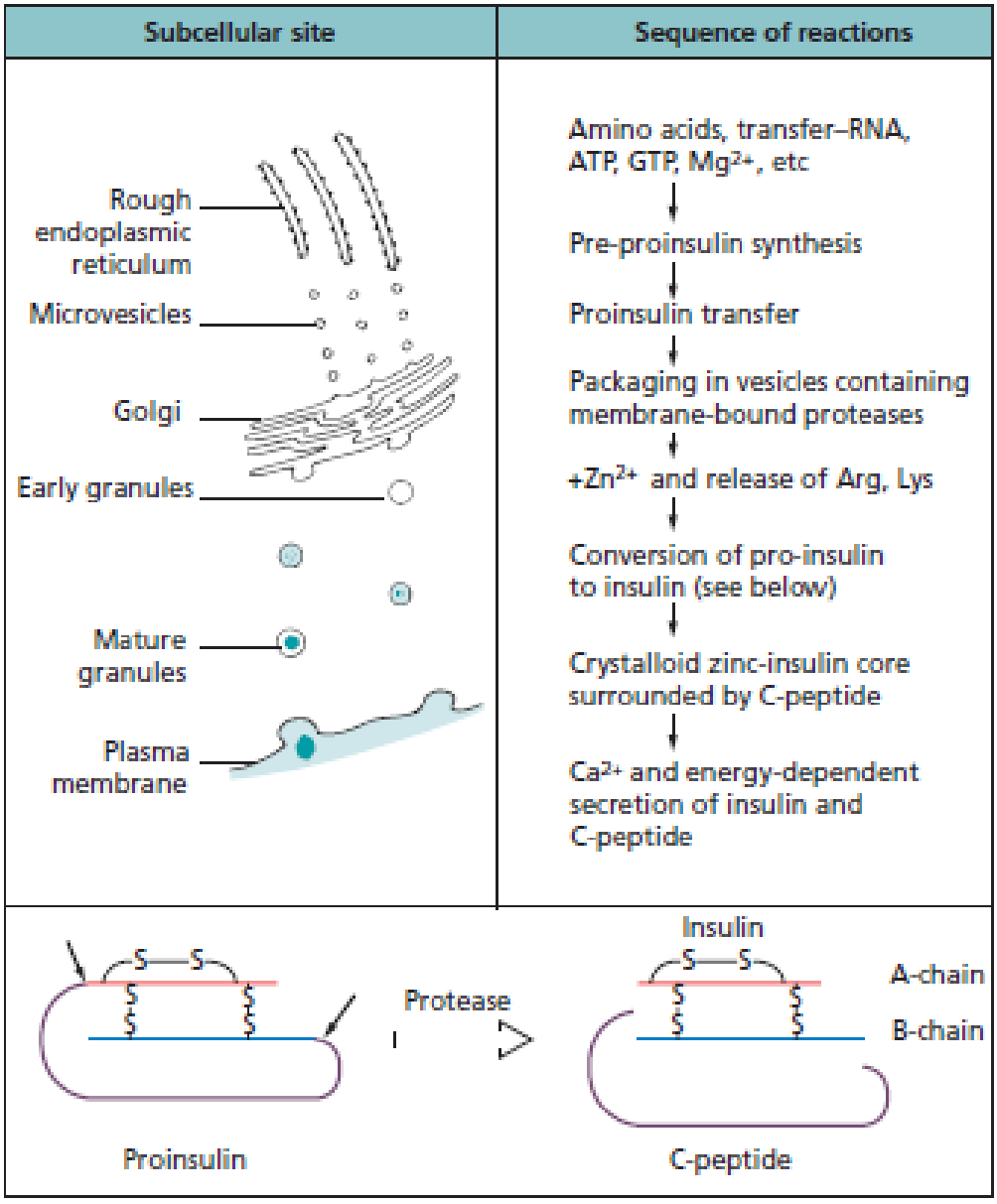

Figure 1: Insulin synthesis and secretion from the β-cells of pancreatic islets of Langerhans. Protein synthesis on the rough endoplasmic reticulum yields pre-proinsulin, which is transferred into the lumen of the endoplasmic reticulum. Hydrolysis yields proinsulin, which is then transferred to the Golgi apparatus approximately 20 min after the initiation of protein synthesis. Proinsulin is enclosed in vesicles that carry specific proteases bound to the membrane. Over a period of 30 min to 2 h, the specific proteases act on proinsulin to release C-peptide and insulin within the granule. When the cells are stimulated, e.g. by a rise in blood glucose, an energy-dependent and Ca2+-dependent fusion of the granules with the cell membrane releases the contents into the bloodstream.

The lower portion of the illustration shows a schematic diagram of the structures of proinsulin and insulin. Proinsulin, on the left, is cleaved at two points (arrows) by specific proteases packaged into early β-cell granules. The C-peptide is cleaved from a single-chain peptide to leave insulin, which then has two chains, A and B, linked by two disulphide bridges, with the A

chain also carrying an intrachain disulphide bridge. Proinsulin contains 86 amino acids, while insulin has 21 amino acids in the A chain and 30 in the B chain.

Secretion

In response to nutrients following a meal, insulin is secreted in a coordinated pulsatile fashion from the β-cells ; first there is an acute rapid 'first phase' release of insulin, lasting for a few minutes, followed by a less intense more sustained 'second phase'. Pancreatic β-cells also secrete 0.25– 1.5 units of insulin/h during the fasting state. Although at a low-level, this background secretion accounts for over 50% of total daily insulin production. Glucose is the principal stimulus for insulin secretion, though other macronutrients, and hormonal and neuronal factors may alter this response (Table 11.5). When glucose enters the β-cell via a family of high-capacity glucose transporters (GLUT 1–3, mainly GLUT-2), it undergoes phosphorylation by the enzyme glucokinase and metabolism by glycolysis to produce ATP (Figure 11.9). The rise in ATP closes a type of potassium channel, the potassium inward rectifying channel type 6.2 (KIR6.2), on the cell surface, leading to depolarization of the membrane. This is followed by an influx of calcium ions which triggers insulin granule translocation to the cell surface and the hormone's release by exocytosis.

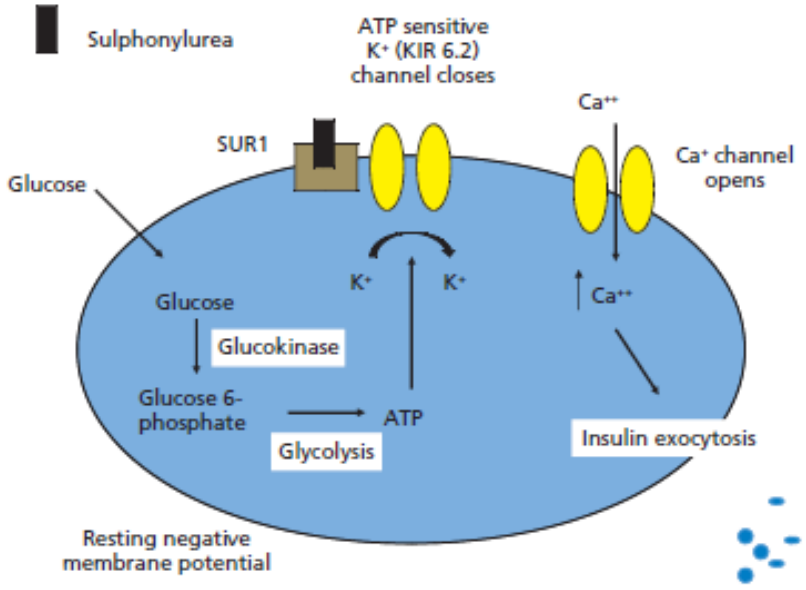

Figure 2: Mechanism of insulin secretion. After uptake, glucose is metabolized within the β-cell to generate ATP. The increase in ATP closes ATP sensitive potassium (KIR 6.2) channels in the cell membrane and prevents potassium ions from leaving the cell. This depolarizes the cell

membrane, which in turn opens voltage-gated calcium channels in the membrane allowing calcium ions to enter the cell and be released from intracellular stores. The increase in intracellular calcium initiates insulin granule exocytosis.

This process can be divided in two: glucose sensing and insulin secretion. Normal β-cell function is dependent on the exquisite coupling of glucose sensing and insulin secretion. For instance, inactivating mutations in glucokinase causes a form of MODY and activating mutations in KIR6.2 or SUR1 can cause permanent neonatal diabetes. In contrast, inactivation of KIR6.2 or SUR1 can uncouple secretion from glucose sensing and cause a rare syndrome of excessive insulin production and hypoglycaemia, called congenital hyperinsulinism.

Action

Insulin exerts its biological actions by binding to the insulin receptor on the target cell surface. The insulin receptor is a heterotetramer consisting of two α- and two β-glycoprotein subunits linked by disulphide bonds. Insulin binds to the extracellular α-sub-units, resulting in conformational change enabling ATP to bind to the intracellular component of the β-subunit; this triggers phosphorylation of the β-subunit, conferring tyrosine kinase activity. Tyrosine phosphorylation of intracellular substrate proteins, known as insulin responsive substrates (IRSs), ensues, and these can then bind other signalling molecules that in turn mediate further cellular actions of insulin (Figure 3).

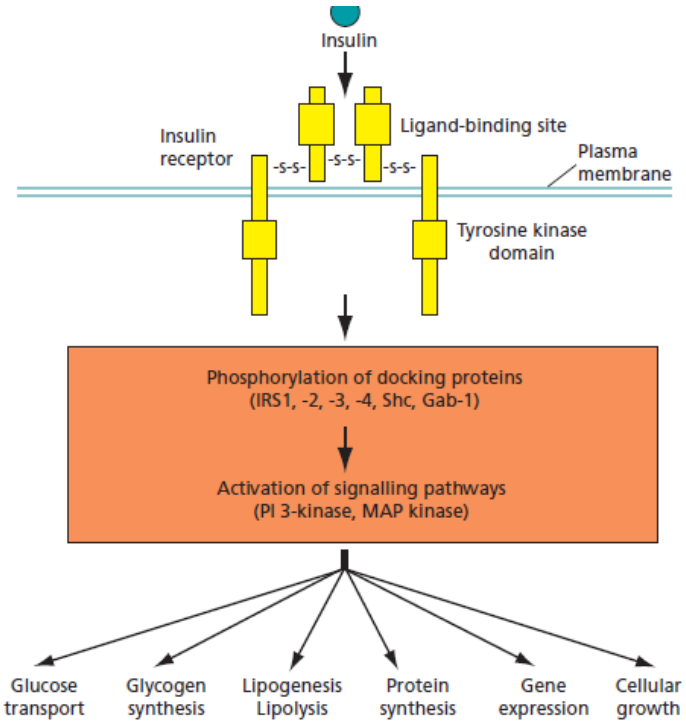

Figure 3: Insulin signalling cascade. IRS, insulin receptor substrate; PI, phosphatidylinositol; MAP, mitogen-activated protein.

Effects on intermediate metabolism

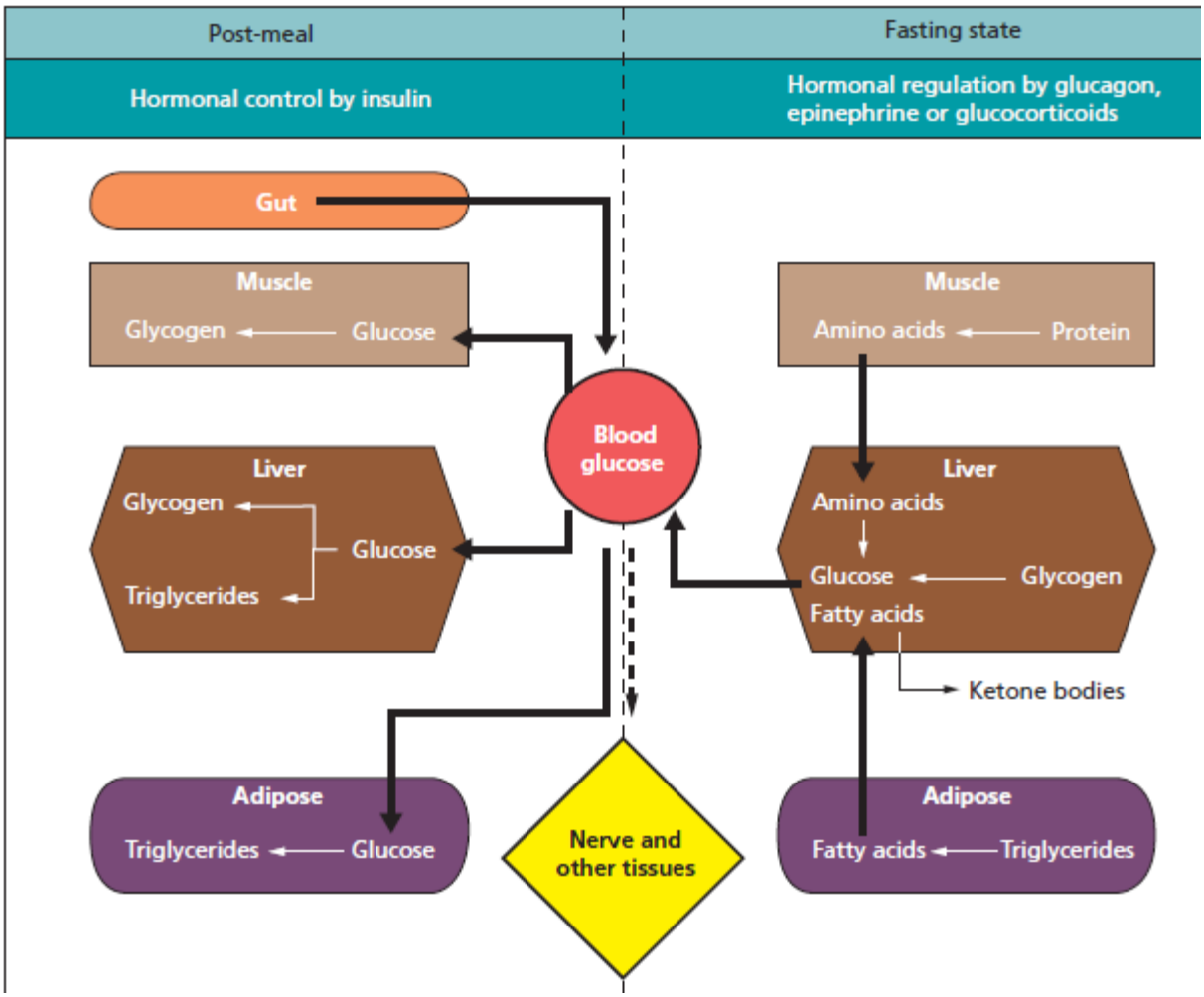

Figure 4: Regulation of blood glucose concentration. Tissue utilization of metabolites after a meal and in a fasting state are contrasted. Food is absorbed from the gut and increases the blood glucose concentration. Insulin facilitates absorption and stimulates the synthesis of glycogen and triglyceride storage in liver and adipose tissues. Approximately 90% of stored glucose is in the form of lipids. In the fasting state, amino acids are mobilized from muscle proteins to yield pyruvate in the liver, where gluconeogenesis and glycogenolysis are capable of maintaining the plasma glucose levels for utilization by brain, nerves and other tissues. Various hormones, including epinephrine, glucagon and glucocorticoids, exert a regulatory action at different sites in these tissues. Fatty acids, mobilized from adipose tissues under the control of a number of hormones (epinephrine, adrenocorticotrophic hormone, glucagon, growth hormone), provide a substrate for liver and muscle metabolism. Ketone bodies produced in the liver provide an energy source for muscle and brain during long periods of fasting.

Glucagon

Glucagon is a polypeptide with a molecular weight of ~3.5 kD. It is synthesized as a large precursor, pre-proglucagon, and is cleaved within the α-cells to the active hormone. Its secretion is stimulated by a fall in blood glucose and by amino acids. Release of glucagon is also under neural control; sympathetic adrenergic activation increases glucagon release. Glucagon plays an important part in preventing significant hypoglycaemia during fasting by antagonizing the actions of insulin. Its primary site of action is the liver where it binds to specific G-protein–coupled glucagon receptors that are linked to adenylate cyclase . This leads to the mobilization of glycogen and to the production of glucose from non-carbohydrate precursors by gluconeogenesis.

TypeI and TypeII Diabetes

"Juvenile onset" Diabetes—Type-I	*"Maturity onset" Diabetes—Type II*
1. Frequency—less	1. Frequency—more common.
2. Commences usually before 15 yrs of age. Males > than Females.	2. Occurs in middle aged individuals. Women are more.
3. Onset—rapid and abrupt	3. Onset—is insidious
4. ***Speedy Progression to Ketoacidosis and coma***	4. Usually mild. ***Ketoacidosis is rare.***
5. Usually patients are thin and underweight	5. Associated with obesity in 2/3 of cases. ***Usually detected during routine check-up of urine.***
6. Deficient Insulin: At first Juvenile diabetics produce more insulin than normal, but the β-cells soon become exhausted and patient becomes "overt" diabetics with atrophied β-cells and practically no insulin	6. β-Cells respond normally. Relative deficiency of insulin, which may be due to "insulin" antagonism.
7. Plasma insulin– It is almost absent. No insulin response is shown to glucose load.	7. Plasma insulin levels may be normal or even raised.
8. ***Insulin therapy–is necessary for control of these cases.***	8. ***Oral hypoglycaemic agents and dietary control are useful in treatment.***