21. PANCREATIC FUNCTION AND METABOLISM

ISLETS OF LANGERHANS

Some pancreatic functions had already been discussed in the digestion section. In this one, the emphasis will be placed on the endocrine function of the pancreas. The structures of interest are the Islets of Langerhans (Fig. 21-1, 21-2).

Among the islets there are also D cells which secrete somatostatin and F cells, which produce pancreatic polypeptide.

Pancreatic secretions

- In addition to the digestive enzymes, the pancreas serve an important endocrine role
- Produces
  - Insulin
  - Glucagon
  - Pancreatic polypeptide
  - Somatostatin
  - Amylin

Insulin

Because of its clinical importance insulin is the most studied hormone from the islets. Insulin has been traditionally associated with the metabolism of carbohydrate, more precisely with circulatory glucose concentration. In reality, insulin also participates in metabolism of fat and protein, especially under abnormal conditions. Insulin is a protein molecule that circulates free and has a half life of about 6 min (Fig. 21-5).

These endocrine islets have a variety of cells, each in charge of producing a specific hormone (Figs. 21-3, 21-4). The alpha cell produces glucagons, while the beta cells secrete both insulin and amylain.
Insulin secretion. The mechanism of release is presented in figure 21-6. The circulatory glucose enters the cell through an active mechanism. At the same time other molecules of glucose bind to a membrane bound receptor which then activates the G protein to increase the intracellular cAMP. This, together with the intracellular glucose, and supported by calcium, trigger the activation of proinsulin to insulin and its release by exocytosis.

As long as the insulin molecules remain bound, the channel stays in the membrane. Upon release of insulin the channels are internalized and further glucose incorporation ceases.

GLUCOSE METABOLISM

The general pattern of glucose metabolism is influenced by insulin as presented in figure 21-8. The green lines denote enhanced activity induced by insulin, while those in red are steps which are inhibited. Yellow lines indicate no change in the rate of action.

The brain is a tissue which depends on glucose as its only source of energy; thus, when glucose is scarce the CNS takes priority in its utilization. This is reflected in the brain’s ability to uptake glucose from circulation without the mediation of insulin. Similarly liver cells and erythrocytes have similar capacity freely internalize glucose (Fig 21-9).
Once a molecule of glucose enters a cell, it is phosphorylated by the enzyme glucokinase and, after phosphorylation the molecule cannot leave the cell (Fig. 21-10). To be able to migrate out of the cells the phosphorylated glucose has to be dephosphorilated. This step is carried out by the enzyme glucose-6-phosphatase, which is only present in liver cells. This peculiarity implies that once a molecule of glucose enters into a muscle, or fat cell, it can no longer be exported as glucose. It has to be further metabolized intracellularly for its storage or production of cellular energy. The only tissue that has the capacity of dephosphorilating glucose-6 phosphate to glucose for exporting it into circulation is the liver. The possible pathways of glucose are described in figure 21-11.

### Use of glucose
- Brain tissue uses only glucose as fuel
- Brain can uptake glucose from circulation independently of insulin
- Only few types of cells permit free transport of glucose onto themselves
  - Brain
  - Liver
  - Erythrocytes

The importance of glucose in circulation resides in the fact that brain tissue depends on glucose as a source of energy for its functioning. The uptake of glucose by brain cells is done independently of insulin. Similar capacity exists in liver cells and in erythrocytes (Fig. 21-11).
The sequences of events which follow release of insulin into circulation is such, that after a few seconds there is an increase in uptake of glucose by muscle and adipose cells (Fig. 21-12).

Glucose is rapidly phosphorylated intracellularly and enters the metabolic pathways described before. Another effect within 10 minutes of the increase in circulatory insulin is an increase in amino acid uptake by cells. Many of the enzymes leading to further metabolic enhancement are elevated within 10 to 15 minutes and after hours of insulin stimulation an increase in the translation of mRNA is observed (Fig. 21-12).

Role of insulin

The role of insulin, therefore, can be summarized as a hormone that lowers circulatory concentration of glucose, amino acids and, to certain extent fatty acids. It enhances the storage of these building blocks into larger molecules such as glycogen, triglycerides and proteins (Fig. 21-13).

The more specific effects can be summarized as: In carbohydrates, insulin promotes the absorption of glucose and its conversion to glycogen in muscle cells (Fig. 21-14).

In liver the same pattern occurs, but the storage is usually of a short term nature. It also inhibits gluconeogenesis in the liver. With respect to fat; in the liver, insulin promotes fat synthesis. This commences after the glycogen deposits are filled. The liver can, then, export fats as VLDL, which is taken by adipose tissue and stored as fat. Insulin also inhibits hormone sensitive lipase from adipocytes, thus preventing release of free fatty acids into circulation. By promoting uptake of glucose, insulin provides the base for synthesis of glycerol and free fatty acids in adipocytes (Fig 21-15).

**Role of insulin**
- **Lower the circulatory concentrations of glucose, fatty acids and amino acids**
- **Enhance storage of these in large molecules**
  - Glycogen
  - Triglycerides
  - Proteins

**Effect of insulin on carbohydrates**
- **Muscle absorption of glucose**
  - Conversion of glucose to glycogen for storage
- **Liver uptake of glucose**
  - Conversion of glucose to glycogen for short storage
- **Inhibition of gluconeogenesis in liver**

The effects of insulin on protein metabolism can be viewed as a series of steps leading to promote protein synthesis (Fig. 21-16).

Insulin enhances amino acid uptake by cells, increases rate of mRNA translation and, as a counterpart inhibits catabolism in muscle and reduces gluconeogenesis in liver, which then spares use of amino acids.
When there is deficiency of insulin production, the storage of protein stops because amino acids are used for gluconeogenesis by deamination (Fig. 21-17).

### Effect of insulin on fat metabolism
- After deposit of glycogen are full (6% liver weight) promotes synthesis of fat in liver
- Exported to circulation as VLDL
  - Uptake by adipose tissue
  - Stored as fat
- Inhibit hormone-sensitive lipase (no FFA release from adipocytes)
- Promotes glucose uptake in adipocytes
  - Synthesis of glycerol and FFA

**Figure 21-15. Role of insulin on fat metabolism**

### Effect of insulin on protein metabolism
- Promotes protein synthesis and storage
  - Increase uptake of amino acids
  - Increase translation of mRNA
    - Turn on ribosomal assembly
  - Inhibits catabolism
  - In liver reduces gluconeogenesis (amino acid sparing)

**Figure 21-16. Role of insulin on protein metabolism**

This translates in an overall protein wastage, which initially caused muscle and overall weakness and, in the long term, can cause some malfunctions. Insulin is catabolized in the liver by the action of an enzyme, insulinase. The first step is to sever the disulfide bonds and then chop the molecule into smaller peptides and amino acids (Fig. 21-18).

### Insulin catabolism
- Takes place in liver and kidney
  - Enzyme insulinase
- Disulfide bonds are reduced
- Peptide enzymes chop chains into small peptides and amino acids

**Figure 21-18. Catabolism of insulin**

### Effect of lack of insulin on protein metabolism
- Protein storage stops
  - Increase plasma amino acids concentration
  - Used for gluconeogenesis
  - Conversion to urea and excreted
- Overall protein wastage
- Causes weakness
- Organ malfunction

**Figure 21-17. Consequences of insulin deficiency in protein metabolism**

### Glucagon
The next hormone produced by the alpha cells of the islets of Langerhans is a 29 amino acid protein called glucagon. It is released in response to low circulatory concentrations of glucose and its main role is to elevate the levels of glucose in circulation (Fig. 21-19).

The specific effects can be summarized as promoting glycogenolysis through a complex enzymatic cascade and increasing gluconeogenesis in the liver by increasing the rate of amino acid uptake and converting them into glucose (Fig. 21-20).
Glucagon also counteracts the effect of insulin in other areas. It activates the enzyme adipose lipase, thus, making free fatty acids available to be used as an energy source. It also inhibits the capacity of the liver to store triglycerides. It also enhances heart strength and augments irrigation of the kidney. Finally, it contributes to the digestive process by enhancing bile secretion and reducing gastric acid secretion.

Glucagon secretion. Secretion of glucagon is regulated mainly by the serum concentration of glucose (Fig. 21-21).

High glucose inhibits secretion, while low concentration enhances it. Its production is also influenced by the presence of amino acids in circulation which are converted to glucose. Physical exercise also increases glucagon secretion (Fig. 21-22).

When the concentration of glucagon increases significantly it starts exerting a variety of other effects. Most of these effects are consistent with its main role of generating available energy in the form of glucose. Glucagon activate the enzyme adipose cell lipase making available substrate for energy metabolism. At the same time it avoids that the liver store triglycerides making them available as an energy source in the organism. Less explained are the reasons for the enhancement of heart strength and the increased irrigation of the kidneys as well as the improved bile secretion but inhibition of gastric secretion observed under very high concentration of glucagon (Fig. 21-23).

The other hormone produced in the Islets of Langerhans is somatostatin. This hormone acts in the islets themselves by inhibiting the production of both glucagons and insulin (Fig. 20-24).

It also exerts an effect in the stomach, duodenum and gallbladder, where it reduces motility. Furthermore, somatostatin slows down secretory and absorptive
processes in the small intestine. The interaction between insulin, glucagon and somatostatin producing cells is shown in figure 21-25.

### Other effects of glucagon

- **Activates adipose cell lipase**
  - Makes available fatty acids for energy
- **Inhibits storage of triglycerides in liver**
- **Enhances heart strength**
- **Increases irrigation of kidney**
- **Enhances bile secretion**
- **Inhibits gastric secretion**

![Figure 21-23. Further effects of glucagon](image)

### Somatostatin inhibits glucagon and insulin

- **Acts locally in islets**
- **SS decreases stomach, duodenum and gallbladder motility**
- **SS inhibits secretion and absorption by the GIT**
- Amylin is a protein produced by the pancreas which selectively inhibits insulin stimulated glucose utilization and glycogen deposition in muscle
- **Amylin does not affect adipocyte glucose metabolism**

![Figure 21-24. Role of somatostatin](image)

### Pathophysiology

- **Diabetes Mellitus**
- **Type I diabetes (Insulin-dependent)**
  - Due to lack of insulin production
  - Juvenile diabetes mellitus
- **Type II diabetes (non insulin-dependent)**
  - Due to decrease sensitivity of tissue to insulin (insulin resistance)
  - Adult-onset diabetes

![Figure 21-25. Regulatory interaction between pancreatic cells](image)

Type I diabetes is usually the result of some type of damage to the beta cells of the islets. This can be caused by a viral infection, an autoimmune problem or genetic predisposition. It is characterized for appearing at an early age and manifests itself very rapidly. It manifests by having high glucose concentration in circulation and, as a result by a significant loss of glucose in urine, which causes osmotic diuresis and polyurea. The consequences of this type of diabetes are significant changes to several tissues, which include malfunction of blood vessels, increase risk of heart attack or stroke, kidney disease...
retinopathy and blindness and, in extreme cases, can trigger ischemia leading to gangrene in limbs.

Animals with diabetes also switch their metabolism to use more fats. This causes metabolic acidosis which in turn triggers many metabolic abnormalities. More vulnerable are obese animals (Fig. 21-27).

**Type I diabetes**

- **Damage of B cells**
  - Viral infection, autoimmune disorder, genetic predisposition
  - Appears at a young age
  - Very rapidly
- **High glucose concentration**
  - Loss of glucose in urine
  - Osmotic diuresis (dehydration)
  - Polyurea
- **Structural changes in tissue**
  - Malfunction of blood vessels
  - Risk of heart attack, stroke, kidney disease, retinopathy and blindness, ischemia and gangrene of limbs
  - Also neurological problems
- **Switch to use of fats**
  - Causes metabolic acidosis
  - Diabetic coma... death

**Type II diabetes**

- Accounts for 80-90% of cases
- Manifest at mature age (adult onset diabetes)
- Increased plasma insulin
- Many metabolic abnormalities
  - Except ketosis
- Patients usually obese
  - Can be managed through diet

**Figure 21-28. Characteristics of type II diabetes**

Type II diabetes is more common and accounts for over 80% of the cases. Usually it manifests at an advanced age, it is characterized by increased plasma insulin and can evolve to diabetic coma and death (Fig. 21-28).