18. PANCREATIC FUNCTION AND METABOLISM

ISLETS OF LANGERHANS
Some pancreatic functions have 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. 18-1, 18-2).

These endocrine islets have a variety of cells, each in charge of producing a specific hormone (Figs. 18-3, 18-4). The alpha cell produces glucagons, while the beta cells secrete both insulin and amylin.

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

Pancreatic secretions
- In addition to the digestive enzymes the pancreas serves 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 carbohydrates, more precisely with circulatory glucose concentration. In reality insulin also participates in the metabolism of fat and protein, especially under abnormal conditions. Insulin is a protein molecule that circulates freely and has a half-life of about 6 mins (Fig. 18-5).
Insulin secretion. The mechanism of release is presented in figure 18-6. 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.

The conversion of proinsulin to insulin is achieved by the activation of a specific endopeptidase, which cleaves a section of the proinsulin called the C chain or connective peptide. This leaves insulin as a 191 amino acid molecule formed by two protein chains, attached by two disulfide bonds and folded in a specific manner, to confer the biological activity.

The action mechanism of insulin is slightly different than that of other hormones. To trigger the phosphorylation, which will lead to the final hormonal effect, two molecules of insulin have to simultaneously bind to a complex receptor. This receptor is made of a protein tetramer, to make two extracellular α proteins. These will connect to two β transmembrane proteins, as effector proteins since they connect to the intracellular signal molecules.

Through phosphorylation, many of the effects of insulin are realized; but, the most important action, the incorporation of glucose into the cells is carried out by the movement of special channels into the membrane. This effect is maintained, as long as the insulin is bound to the receptors (Fig. 18-7).

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 18-8. The green lines denote enhanced activity induced by insulin, while those in red are steps that are inhibited. Yellow lines indicate no change in the rate of action.

The brain is a tissue that 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 a similar capacity to freely internalize glucose (Fig 18-9).
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. 18-10). To be able to migrate out of the cell, the phosphorylated glucose has to be dephosphorylated. 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 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 dephosphorylating glucose-6-phosphate to glucose, for exporting it into circulation, is the liver. The possible pathways of glucose are described in figure 18-11.

**Metabolic pathway of glucose in muscle**

- Once inside a cell, glucose is phosphorylated by the enzyme glucokinase
- Once phosphorylated glucose cannot cross the cell membrane (leave the cell)
- Unlike the liver, muscle tissues lacks glucose-6-phosphatase
- Cannot release glucose into circulation
- Can only use it for its own metabolism
  - Storage
  - Energy

**Use of glucose**

- Brain tissue can only glucose as a 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. 18-11).
The sequence of events, which follow the release of insulin into circulation is such, that after a few seconds there is an increase in the uptake of glucose by muscle and adipose cells (Fig. 18-12).

Glucose is rapidly phosphorylated intracellularly and enters the metabolic pathways as described previously. 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. 18-12).

### Sequence of events following insulin elevation

- **After seconds of attachment**
  - Increased glucose uptake by cells
    - Muscle and adipose cells not on neurons
    - Glucose is phosphorylated
    - Enters metabolic pathway
  - Permeability to aa increases
- **After 10-15 minutes**
  - Increases internal enzymes
- **After hours or days**
  - Increases translation of mRNA

### Role of insulin

The role of insulin, therefore, can be summarized as a hormone that lowers the circulatory concentration of glucose, amino acids and, to a certain extent fatty acids. It enhances the storage of these building blocks into larger molecules such as glycogen, triglycerides and proteins (Fig. 18-13).

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. 18-14).

In the 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 the release of free fatty acids into circulation. By promoting the uptake of glucose, insulin provides the base for synthesis of glycerol and free fatty acids in adipocytes (Fig 18-15).

### Role of insulin

- Lowers the circulatory concentrations of glucose, fatty acids and amino acids
- Enhances 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 the liver

The effects of insulin on protein metabolism can be viewed as a series of steps leading to promote protein synthesis (Fig. 18-16).

Insulin enhances amino acid uptake by cells, increases rate of mRNA translation and, as a counterpart inhibits catabolism in muscle and reduces gluconeogenesis in the liver, which then spares the use of amino acids.
When there is a deficiency in insulin production, the storage of protein stops because amino acids are used for gluconeogenesis by deamination (Fig. 18-17).

**Effect of insulin on protein metabolism**

- **Protein storage stops**
  - Increases plasma amino acids concentration
  - Used for gluconeogenesis
  - Conversion to urea and excreted
- **Overall protein wastage**
- **Causes weakness**
- **Organ malfunction**

**Insulin catabolism**

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

**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. 18-19).

**Effect of the lack of insulin on protein metabolism**

- **Protein storage stops**
  - Increases plasma amino acids concentration
  - Used for gluconeogenesis
  - Conversion to urea and excreted
- **Overall protein wastage**
- **Causes weakness**
- **Organ malfunction**

**Glucagon**

- 29 amino acid protein
- Produced by alpha cells
- Released when circulatory glucose is low
- Contributes to elevation of circulatory glucose

This translates in an overall protein wastage, which initially causes muscle weakness and overall weakness, in the long term, it 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. 18-18).
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. 18-20).

**Effect of glucagon on glucose metabolism**

- **Promotes glycogenolysis**
  - Through a complex enzymatic cascade
- **Increases gluconeogenesis in the liver**
  - Promotes amino acid uptake
  - Converts them to glucose

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 inhibits the capacity of the liver to store triglycerides and 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. 18-21).

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. 18-22).

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 activates the enzyme adipose cell lipase making available substrate for energy metabolism. At the same time it prevents the liver from storing triglycerides, making them available as an energy source in the organism. Less explained are the reasons for the enhancement of heart strength, the increased irrigation of the kidneys, as well as the improved bile secretion but also the inhibition of gastric secretion observed under a very high concentration of glucagon (Fig. 18-23).

**Regulation of glucagon secretion**

- **High circulatory glucose inhibits secretion**
- **Low concentration enhances secretion**
- **Increased circulating amino acids increase secretion**
  - Permits conversion to glucose
- **Exercise increases glucagon secretion**

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 18-25.
ABNORMALITIES

The most common pathophysiology associated with the pancreas is diabetes (http://www.executec.com/diabetes.htm or, http://www.thepetcenter.com/gen/d.html). Two types of diabetes have been identified. Diabetes Mellitus Type I, which is insulin dependent and is due to a problem with the capacity of the pancreas to secrete insulin. Juvenile diabetes is part of this syndrome. The Type II or non-insulin dependent is the result of a decreased sensitivity of tissue to insulin. It is also known as insulin resistance. The diabetes manifested by adults is usually this type (Fig. 18-26).

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 is manifested by having a high glucose concentration in circulation and, as a result, by a significant loss of glucose in the urine, which causes osmotic diuresis and polyuria. The consequences of this type of diabetes are significant changes to several tissues, which include the 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.

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

**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

**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 a decrease in sensitivity of tissue to insulin (insulin resistance)
    - Adult-onset diabetes
Animals with diabetes also switch their metabolism to use more fats. This causes metabolic acidosis, which in turn triggers many metabolic abnormalities. Obese animals are more vulnerable (Fig. 18-27).

**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 18-27. Causes and consequences of type I 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 in severe cases can evolve into a diabetic coma and death (Fig. 18-28).