ENDOCRINE PANCREAS & FUEL HOMEOSTASIS

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LEARNING OBJECTIVES

1. Explain the two metabolic states of fed and fasting and the minute to minute regulation of these states by hormones.
2. Identify the major hormones secreted by the pancreas, their cells of origin and their chemical nature.
3. Identify the time course for the onset and duration for the biological actions of insulin and of glucagon.
4. Describe the relationship between blood glucose concentrations and insulin secretion.
5. List the major target organs for insulin and the effect of insulin on these organs.
6. Describe the control of glucagon secretion.
7. Identify the target organ for glucagon.
8. Identify disease states caused by a lack of insulin or by resistance to insulin and describe the principle symptoms of each.

METABOLIC STATES

Metabolism is classified as one of two states, fed and fasting.

Fed or anabolic state occurs immediately after a meal when the energy of nutrients (carbohydrate, protein, or fat) is transferred to high energy compounds for immediate use or for storage. Peripheral tissues (predominantly skeletal muscle) buffer ingested glucose by storing it as glycogen.

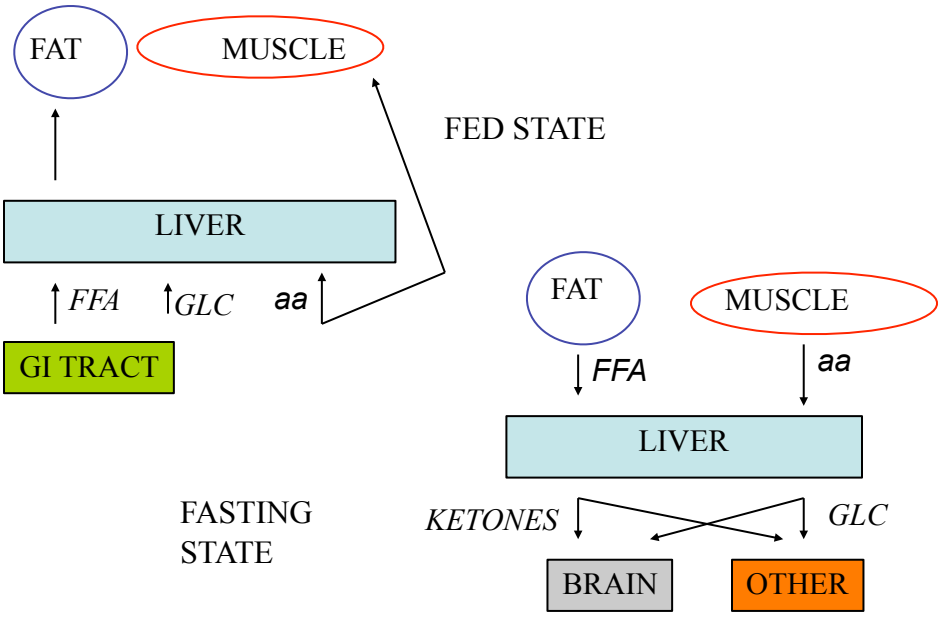

Figure 1. Changes in fuel depots associated with fed and fasted states.

Fasted or catabolic state occurs later when the level of available nutrients decreases in the blood, and the stored reserves (initially glycogen) are mobilized to perform work or to generate heat. During prolonged fasting, fat oxidation and ketone bodies are used to meet whole body energy requirements.

One of the most important aspects of metabolism is the regulated use of carbohydrates, proteins and fat to generate glucose. Plasma glucose is closely regulated (80-100 mg/dL) because it is the primary fuel metabolized by the brain. Minute-to-minute regulation of glucose levels depends on the opposing actions of two pancreatic hormones, **insulin and glucagon**. The secretion of these two hormones is controlled in a reciprocal manner by blood glucose levels (Fig 2).

High insulin to low glucagon ratio (Fig 2) occurs in the fed state activating anabolic pathways, such as storage of glucose and fatty acids as triglycerides (fats). Insulin is secreted from the pancreatic islet beta cells when blood glucose levels are higher than 100 mg/dL.

Low insulin to high glucagon ratio (Fig 2) occurs in the fasting and "fight or flight' states resulting in increased levels of blood glucose. Glucose is released into the blood by the break down of glycogen (glycogenolysis) and fat (lipolysis). Glucagon is secreted from the pancreatic islet alpha cells when blood glucose levels are lower than 80 mg/dL.

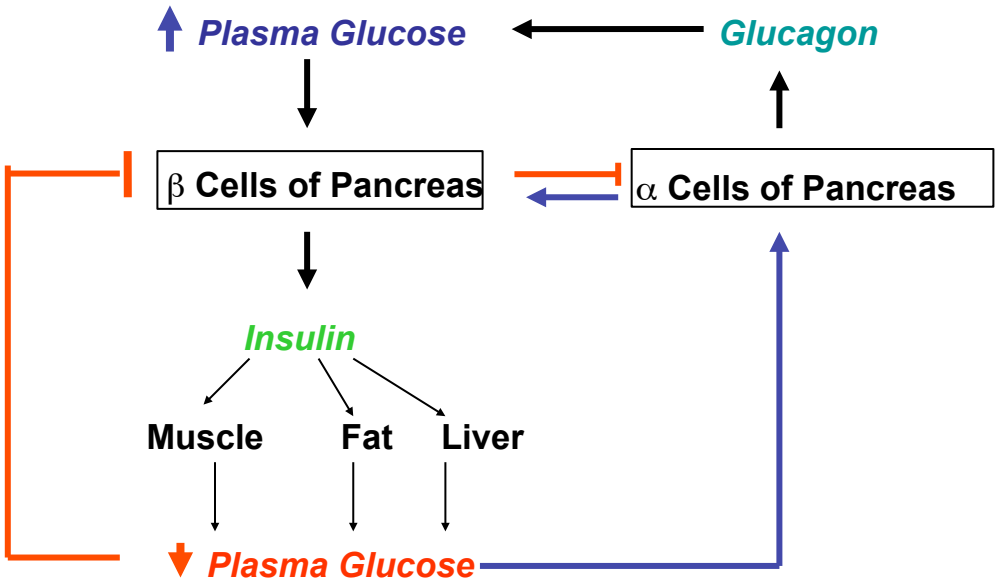

Figure 2. Feedback between glucose concentration and insulin secretion.

PANCREAS SECRETES INSULIN & GLUCAGON

The endocrine cells of the pancreas are located in islets. The islets contain four distinct cell types, each secreting a different peptide hormone.

Approximately 75% of the islet cells are β cells which produce insulin. Another 20% are α cells that secrete glucagon. The δ cells produce the paracrine, somatostatin (SRIF). Which inhibits both insulin and glucagon secretion.

Insulin is secreted from the pancreas by a process called **glucose stimulated insulin secretion** (GSIS) (Fig 3).

GSIS: Glucose Stimulated Insulin Secretion

Figure 3. Insulin secretion is regulated by glucose in β cells.

Insulin is secreted in a biphasic manner. The initial burst reflects the release of preformed secretory vesicles; it lasts 5-15 minutes. The second more gradual and sustained secretion (30 min) is due to the release of newly synthesized insulin molecules.

The half life of insulin, like most protein hormones, is short (~ 5 minutes). Most of secreted insulin is degraded by the liver and kidney.

Insulin secretion is regulated by factors other than glucose (Fig 4). Both an increase in plasma amino acids and the feed forward signaling by glucagon like peptide from the small intestine will lead to secretion of insulin.

INHIBITION OF INSULIN SECRETION

There are several potent inhibitors of insulin secretion including **somatostatin** and the catecholamines **(epinephrine and norepinephrine) (Fig 4)**. While the paracrine role of pancreatic somatostatin in regulating insulin secretion is not well understood, the antagonistic effect of catecholamines is consistent with their role in mobilizing glucose stores during periods of stress.

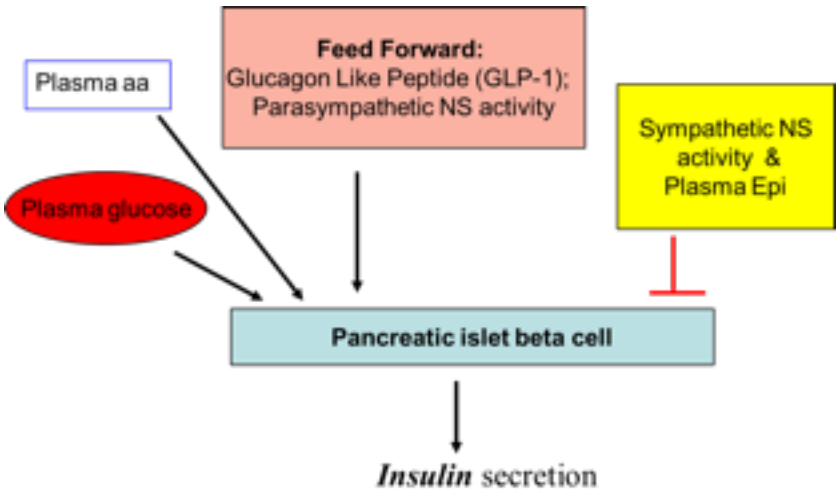

Figure 4. Positive and negative regulation of secretion by the pancreatic beta cell.

EFFECTS OF INSULIN

The primary targets for insulin are liver, skeletal muscle, and fat. Insulin has multiple actions in each of these tissues, the net result of which is fuel storage (glycogen or fat).

Glucose enters the circulation either from the diet or from synthesis in the liver. It enters all cells via the glucose transporter (GLUT). To prevent glucose from leaving the cells via this transporter, the glucose is rapidly phosphorylated to glucose-6-phosphate. There is a family of glucose transporters (e.g., GLUT 1, GLUT 2, GLUT 4). In skeletal muscle and fat cells, insulin binds to the insulin receptor which causes the active recruitment of the glucose transporter, GLUT 4, to the cell surface. Once located at the cell surface, GLUT 4 increases the amount of glucose that enters fat and skeletal muscle cells. The GLUT4 action enables a rapid removal of glucose from the circulation thereby restoring plasma levels to 80-100 mg/dL.

INSULIN DEFICIENCY

Problems arise from:

- **Reduced glucose uptake into various tissues (energy starvation).**
- **Increased release of glucose from the liver (hyperglycemia)**

The effect of these two deficiencies is simple:

- **Too little glucose inside cells.**
- **Too much glucose in the blood (hyperglycemia)**

Glucose deficiency inside cells shifts the energy source to protein, fat, and glycogen. A first consequence is protein deficiency and the second consequence is an increase in free fatty acids and triglycerides from increased lipolysis. The liver uses these products to generate ketones which are acids. The brain does not store fuel. It uses glucose (primarily) and ketones which are supplied by the blood to drive its metabolism. In excess, circulating ketones can lead to metabolic acidosis (lower blood pH).

Hyperglycemia (excess glucose in the blood) can lead to cellular dehydration. Once the kidney reaches its threshold for glucose reabsorption, glucose is excreted in the urine. This leads to an increased output of urine and loss of electrolytes. Long term hyperglycemia can lead to vascular injury resulting in blindness and end-stage renal disease.

PATHOLOGY

Diabetes mellitus: IDDM (type I) and NIDDM (type II)
Symptoms include frequent urination, increased thirst, increased food consumption, and weight loss.

Diabetes mellitus is diagnosed by a blood glucose value > or = 126 mg/dL following an overnight fast (FOG) and by an oral glucose tolerance test (OGTT) of 200 mg/dL or higher (Table 1).

Table 1. Diagnostic Values For Diabetes Mellitus.

	Normal (mg/dL)	Prediabetic (mg/dL)	Diabetic (mg/dL)
Fasting Overnight Glucose (FOG)	80- 00	100-125	126 or higher
Oral Glucose Tolerance Test (OGTT)	140 or less	140-200	200 or higher

In the Oral Glucose Tolerance Test (OGTT), a subject is given 75 mg of glucose orally. Timed blood draws are tested for glucose (Table 1). In normal subjects, the plasma glucose returns to 80-100 mg/dL by 2 hours after ingestion of glucose. In the diabetic subject, plasma glucose remains elevated even 4 hours after ingestion of the glucose.

Insulin-dependent diabetes mellitus (IDDM, type I) - these patients do not produce sufficient amounts of insulin and therefore they must be injected with insulin daily.

Non-insulin dependent diabetes mellitus (NIDDM, type II) - these patients are characterized by either insulin insufficiency due to beta cell dysfunction and/or by target cell receptor resistance. Following glucose ingestion, the diabetes type II patient will exhibit prolonged, elevated plasma glucose with either normal or elevated plasma insulin.

GLUCAGON

Glucagon is a peptide hormone secreted from the pancreatic islet **alpha** cells when glucose levels are less than 80 mg/dL. Glucagon circulates unbound in the plasma; it has a half- life of 6 minutes.

Glucagon is a peptide hormone. It binds a plasma membrane receptor which initiates a second messenger signaling cascade. The target tissue for glucagon is the liver. Glucagon causes the liver to secrete glucose leading to a net decrease in stored glycogen and an increase in plasma glucose.

In the absence of insulin, glucagon is secreted. Glucagon acts in a synergistic manner with cortisol and epinephrine to raise blood glucose levels (Fig 6).

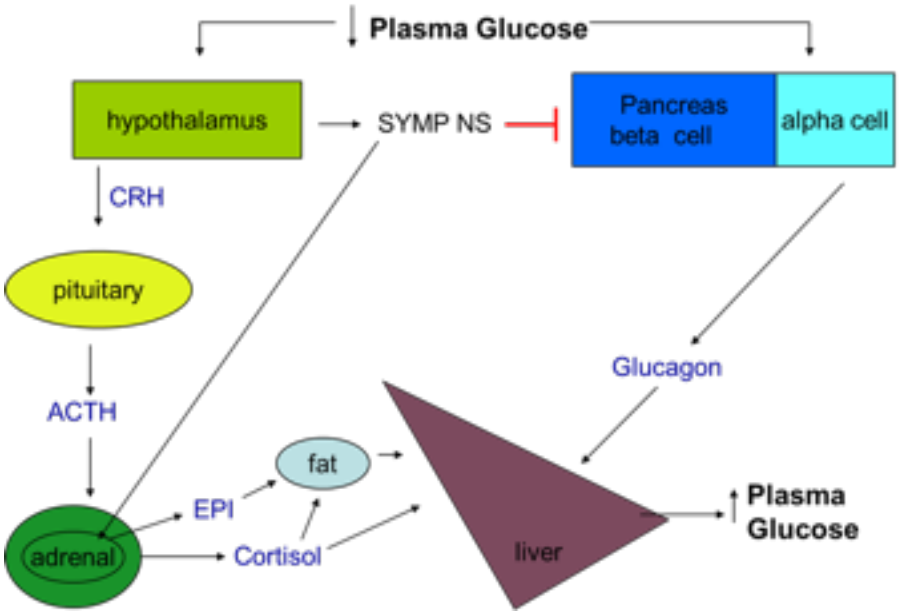

Figure 6. Synergy of glucagon, cortisol and epinephrine actions raises plasma glucose during stress.

GENERAL CONCEPTS

1. Endocrine pancreas produces insulin and glucagon which regulate fuel homeostasis in the fed and fasted states, respectively.
2. Insulin is secreted primarily in response to an increased blood glucose level. Glucagon is secreted in response to decreased blood glucose level.
3. In the fed state, insulin directs the storage of excess nutrients in the form of glycogen, triglycerides, and protein. The targets of insulin are liver, muscle, and adipose tissue.
4. In the fasting state, glucagon directs the movement of stored nutrients into the blood. Liver is the main physiological target of glucagon.
5. Diabetes mellitus occurs when there is a deficiency of insulin action as a result of either insufficient insulin secretion or resistance (receptor impairment) to insulin at its target tissue.

QUESTIONS

1. Which of the following will be elevated in the blood of a diabetic type I individual who is not well controlled?
   A. Adrenocorticotrophin (ACTH)
   B. Insulin
   C. Glucagon
   D. Insulin like growth factor 1

2. Which of the following inhibit insulin secretion from the pancreas?
   A. glucagon
   B. glucagon like peptide
   C. epinephrine
   D. norepinephrine
   E. C and D

3. During the fed (anabolic) state nervous tissue derives most of its metabolic energy from:

A. glucose
B. fatty acids
C. amino acids
D. ketones

ANSWERS

1. C is correct
2. E is correct
3. A is correct