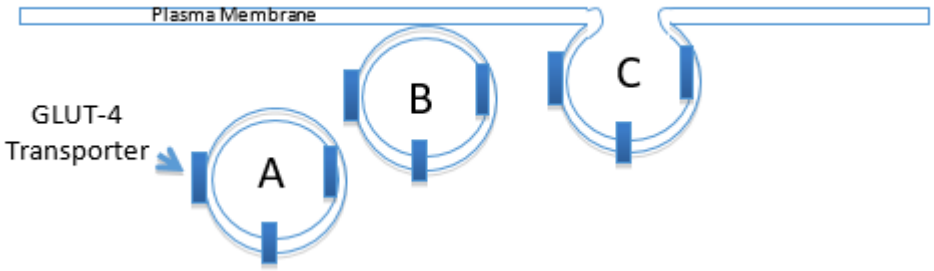
5.6.1

Insulin and Glucagon

Skeletal Muscle

Since glucose is a polar molecule, it cannot easily cross the plasma membrane and requires special transport proteins called **GLUT transporters** to enter the cell. There are several different GLUT transporters. We differentiate the different ones by giving them numbers, GLUT-1, GLUT-2, GLUT-3, etc. To date, only one of the GLUT transporters has been shown to require insulin for its action. That transporter is **GLUT-4** and that is the one found in skeletal muscle. Therefore, in the absence of insulin skeletal muscle cells cannot import glucose into the cell. The truth is that without insulin the skeletal muscle cells do not even have the transporters in their plasma membrane. They are found in the membranes of vesicles inside the cell. When insulin binds to its receptor a signal is sent to the vesicles initiating the process of exocytosis. In this process the membrane of the vesicles containing GLUT-4 transporters fuses with the plasma membrane, incorporating the vesicular membrane into the plasma membrane. The GLUT-4 transporters that were in the vesicular membrane are now part of the plasma membrane and allow glucose to enter the muscle cell. See image below.



Insertion of GLUT-4 transporters into the plasma membrane of a muscle cell. (A) GLUT transporters shown in the membrane of a secretory vesicle. (B) Vesicle move to the plasma membrane. (C) Vescicular membrane has fused with the plasma membrane, inserting the transporters.

Image created by BYU-Idaho 2012

Once the glucose gets into the cell, insulin promotes the conversion of glucose into **glycogen** (**glycogenesis**). Recall that glycogen is a large storage polymer made of glucose subunits. In addition, insulin promotes the utilization of glucose for energy by stimulating **glycolysis** and the oxidation of glucose.

Amino acids in the blood also stimulate insulin secretion. This is because insulin promotes the uptake of amino acids into skeletal muscle cells where they are used to synthesize new proteins.

Due to these actions we say that insulin promotes **anabolic reactions**. These reactions result in the storage of energy sources in the form of glycogen and proteins. We will see similar actions in both adipose tissue and the liver.

Adipose Tissue (Fat Cells)

The action of insulin in **adipose tissues** is similar to the action in skeletal muscle. Fat cells utilize GLUT-4 transporters to import glucose, therefore, insulin increases glucose uptake by these cells. Adipose cells store some energy in the form

of glycogen, but most of the glucose that enters the cell is used to make fatty acids that can then be converted to fat (**triglycerides**) and stored for future energy needs. Insulin also promotes free fatty acid uptake from the blood which enhances triglyceride formation. Additionally, insulin decreases the activity of the enzyme called hormone-sensitive triglyceride lipase. This enzyme converts triglycerides back to free fatty acids.

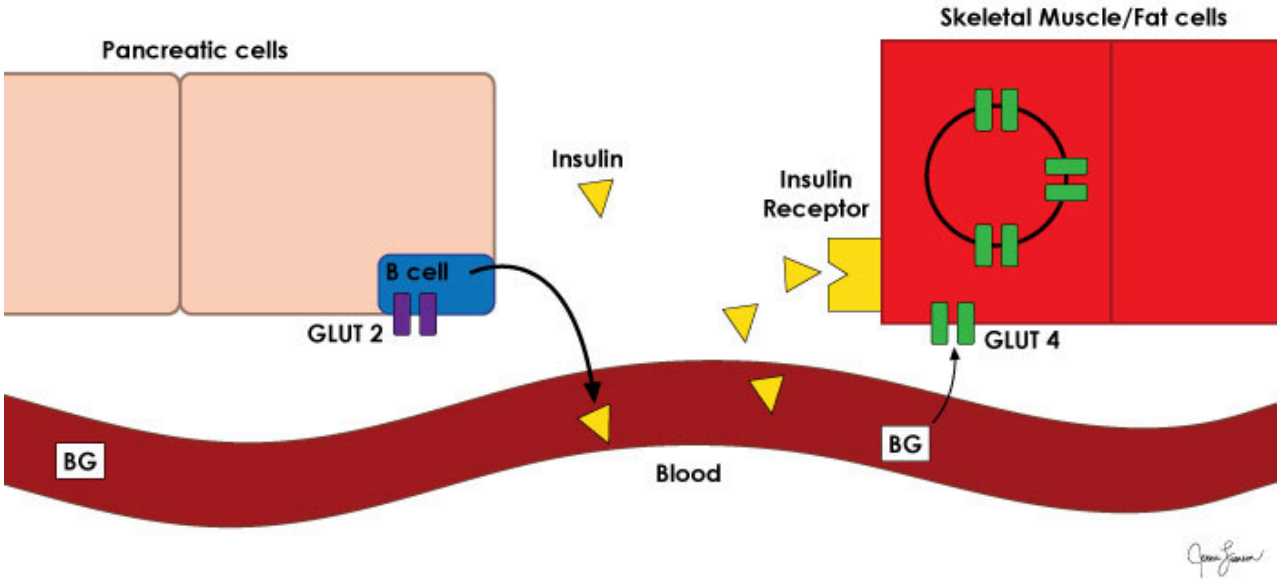
Liver

Liver cells are a bit different from muscle and fat cells. The glucose transporters in liver cells are **GLUT-2 transporters** that are always present in the membranes and do not require insulin. Nevertheless, insulin has a big impact on liver function. When glucose is plentiful, insulin promotes energy storage and activates the enzymes that convert glucose to glycogen. In addition, insulin inhibits the breakdown of glycogen. The liver plays an important role in regulating blood glucose levels, forming glycogen when glucose is plentiful and then converting glycogen back to glucose (**glycogenolysis**) when glucose levels in the blood decrease. Its like food storage, we store food in the good times and then use it in the bad. In the case of our bodies the good times are right after we eat and the bad times are several hours later. This mechanism maintains fairly constant and continuous supplies of glucose for our cells.

Another function of insulin in the liver is to inhibit **gluconeogenesis**, which is, the conversion of amino acids to glucose.

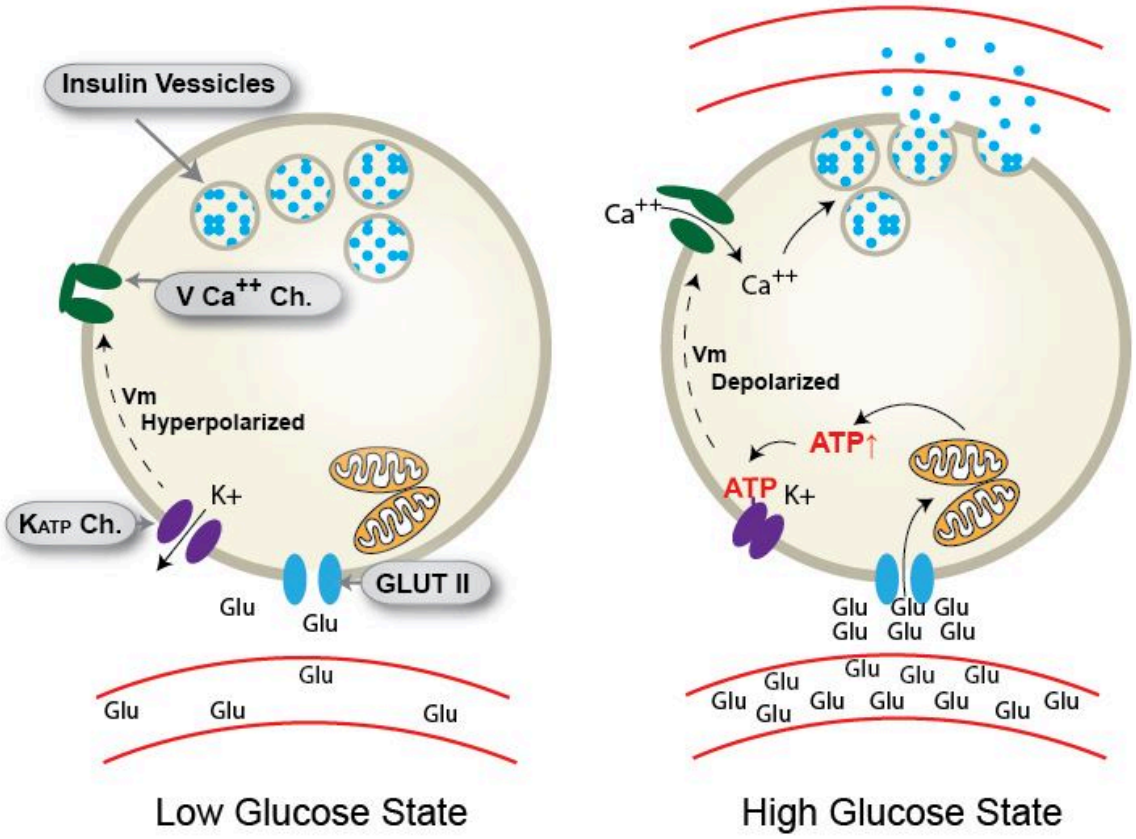
Thus, the overall action of insulin is to promote the uptake of glucose by the cells, the result of which lowers the levels of glucose in the blood. Also, it stimulates the storage of energy in the cells when nutrients are plentiful. Those storage molecules can later be broken down and released back into the blood to maintain a constant supply of energy to the cells. If it weren't for this system we would have to eat continually in order to maintain sufficient levels of glucose in our blood. The actions of insulin on the cells of the body are summarized in the table below.

Target Tissue	Actions
Skeletal Muscle	Increased number of GLUT-4 transporters in plasma membrane (increased glucose uptake) Increased glycogen synthesis (glycogenesis) Increase glycolysis and carbohydrate oxidation Increased amino acid uptake and protein synthesis
Adipose Tissue	Increased number of GLUT-4 transporters in plasma membrane (increased glucose uptake) Increased conversion of glucose to fatty acids Increased free fatty acid uptake from the blood Increased triglyceride (fat) formation
Liver	Increased glycogen synthesis (glycogenesis) Inhibition of glycogen breakdown (glycogenolysis) Inhibition of gluconeogenesis



Insulin attaches to insulin receptors on skeletal muscle and bone and stimulates the movement of GLUT-4 channels to the membrane to let glucose in. (BG= Blood Glucose)

Image created by BYU-Idaho student Jenna Fransen, Spring 2017



As blood glucose increases, this increases metabolism which increases ATP which attaches to and closes K+ channels which depolarize the cell and cause the release of insulin.

Image created by J. Shaw at BYU-Idaho Spring 2015

Regulation of Insulin

1. **Plasma glucose**: One of the stimuli of insulin secretion is elevated plasma glucose levels (the majority is through the incretins GLP-1 or GIP). Still, if the plasma glucose concentrations increase above 100mg/dL glucose uptake through the GLUT2 transporter in the beta cells is increased. Note: GLUT2 transporters are not dependent upon insulin like the GLUT4 transporters. Once in the beta cell the glucose is metabolized resulting in an increase in ATP production. Increased ATP interacts with ATP-sensitive K+ channels which causes them to close, resulting in depolarization of the cell membrane. The depolarization results in the opening of voltage-gated Ca2+ channels allowing Ca2+ to enter the cell. The increase in intracellular Ca2+ stimulates exocytosis of the insulin containing vesicles. When glucose levels drop below 100 mg/dL ATP levels drop, the K+ channels open and insulin secretion stops. This is a classic example of negative feedback control.

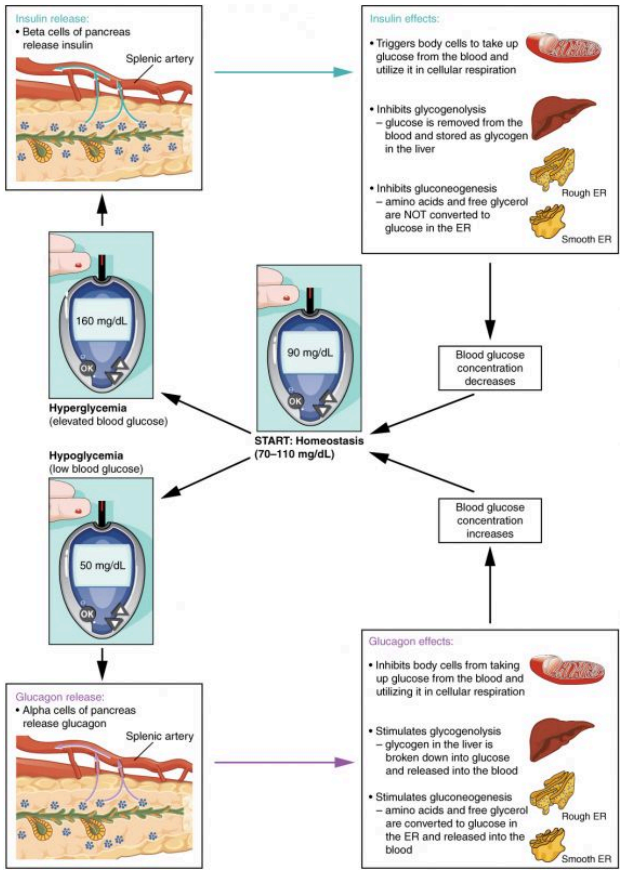
2. **Plasma amino acids**: amino acids in the blood have a similar, albeit slower effect than glucose on the release of insulin by the beta cells.

3. **Gastrointestinal hormones**: Prior to any increase in blood glucose or amino acids, insulin release will be increased 50% because of hormones released from cells in the intestines. The primary hormones involved are glucagon-like peptide-1 and gastric inhibitory peptide (these hormones are known collectively as incretins). Both hormones are released from cells of the small intestines in response to nutrient ingestion. This is a type of feed forward mechanism to help prevent a sudden surge in plasma glucose concentrations.

4. **Autonomic nervous system**: Parasympathetic activity increases insulin release while sympathetic activity decreases insulin release. It may seem odd that sympathetic activity decreases insulin release since that would limit glucose uptake in the very tissues that need additional energy during physical exertion, namely skeletal muscle. However, exercise results in incorporation of GLUT4 transporters in the active muscles allowing glucose to enter those muscles. Normally GLUT 4 requires insulin, but in this case exercise can incorporate the transporter even if insulin isn't present.

Glucagon

Glucagon, which is secreted by the alpha cells of the islets, generally opposes the actions of insulin in the liver. Glucagon stimulates the breakdown of glycogen to glucose and stimulates gluconeogenesis, both of which serve to increase the release of glucose into the blood and raise plasma glucose levels. The secretion of glucagon is stimulated by low blood sugar levels as well as increased levels of plasma amino acids. Recall that increased levels of amino acids also stimulate insulin secretion. This may seem as somewhat of a paradox. However, the simultaneous release of glucagon and insulin helps to prevent hypoglycemia (low blood glucose levels), especially with low carbohydrate diets. Thus, the ratio of glucagon to insulin plays a very important role in glucose metabolism.



Regulation of Blood Glucose Levels

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