

Table of Contents

Page 1 of 4

Module 6: Regulation Eating Behavior, Insulin, & Glucose Homeostasis

LM-6 Homework

Quiz 6-LM 6

Discussion Board: Part 2 of the Interest to Action Assignment or Extra Credit

Eating Behavior, Insulin, & Glucose Homeostasis

When automatically you can see the content of this page, click on the link below to see the content of this page.

Module 6: Regulation Eating Behavior, Insulin, & Glucose Homeostasis

Page 1 of 4

about:

stories you might have heard this week

campus or community events you're aware of that you might attend or would like others to know about

ing, you have changed or been thinking about that's related to *last* week's discussion on... Energy

post in the extra credit class discussion your observations and/or news.

Regulation of Eating Behavior & Interactions of Diet with Metabolism

review the different factors that regulate our eating behavior and the major hormones that play roles in how the macronutrients we consume are metabolized.

By the end of this lecture, you should be able to:

1. Gain an understanding of the complexity of factors influencing food intake and eating behaviors
2. Identify the different mechanisms affecting satiety
3. Develop a fundamental understanding of short-term and long-term factors that influence food intake
4. Understand the role of insulin and glucagon in metabolic homeostasis

Quick message from your instructor: Pre-diabetes affects about 1 in 3 people! This module lays the groundwork for understanding that disease and others. This module is going to give your brain a good workout and its worth it. You will be the one in your family and the one your clients turn to to help them understand this too common condition. We need more people who can explain things so, thank you, ahead of time, for your hard work.

Hunger and Satiety

Everyone who is gaining weight consumes *more calories than their body needs* for daily activity. This does NOT mean obese people are “gluttons”- some obese people eat less than people who are not obese. Food intake is both an emotional and very complex metabolic process. This Learning Module will help you gain an understanding of the physiological factors related to the drive to eat.

Hunger is a body reaction that has served us well since the dawn of time. Hunger was an important survival mechanism for early peoples, prompting them to hunt and forage for food to power up and survive. In light of the modern obesity epidemic, the field of research on appetite has blossomed, diverging into many paths that explore aspects such as genetics, hormone regulation, behavior, psychology, and diet. Researchers are digging into everything from appetite-regulating neuropeptides and genetic characteristics in people who are obese to disinhibition behavior and the effects of food stimuli on hunger, hoping to gain insight into what makes us hungry and what quells the growling stomach.

Hunger is defined as the “physiological” desire to eat. We have all experienced the feeling of the “need” for food - the “hunger pains” felt when one has not eaten for some time. Hunger can also make us feel cranky, shaky, and sometimes result in a headache. There is research evidence that people who are obese or obesity prone experience the sensation of hunger more intensely and or experience relief from hunger, upon eating, more slowly (and only after consuming more calories).

Appetite is defined as a “psychological” drive to eat. It can be thought of more as an interest in or desire to eat. Appetite is related to cravings, which are defined as strong desires for a particular food. Although not dependent on hunger, appetite can stem from hunger.

Appetite can be distinguished from hunger in that appetite is often a pleasant sensation (versus the feeling of discomfort that accompanies hunger) based on previous experiences that causes you to seek food for the purpose of tasting and enjoying it. In other words, appetite is a strong desire for something – in this case food. There is also research suggesting that people who are obese or obesity prone have a different appetite experience. Research suggests that appetite and/or eating behavior is influenced by:

- Variety. When offered a variety of flavors, textures, colors, foods, people (and even animals) tend to eat more.
- Food insecurity. People (and animals) who are insecure about where and when they will get their next meal tend to eat more when food is available.
- Feasting traditions, reward traditions, and social circumstances often encourage humans to eat more than needed to satisfy hunger.
- Skipping breakfast or waiting too long to eat between meals can also stimulate over eating. People become so hungry that when they finally do eat, they over eat. Thus it's important to remember that fasting or strict dieting can back-fire and lead to binge eating and other eating disorders.
- Eating highly palatable, energy dense, and easy to consume foods (donuts, pizza, macaroni & cheese, fast food burgers) tends to stimulate over eating while low calorie, high fiber and nutrient foods like fruits, vegetables, and legumes inhibits appetite due to a volume effect.
- Serving size. People tend to eat the amount that they are served.
- Personal memories and associations can encourage or discourage consumption of certain foods.
- Fructose consumption in beverages does not decrease the hunger hormone ghrelin, therefore the amount of food needed to feel satiated is not reduced, multiplying the total calories consumed.

Consider for a minute what food memories, stories, or associations you have. Most people have happy memories where food is involved such as baking cookies with Grandma or drinking sweet tea with a favorite cousin. What memories and associations affect your appetite?

Satiety is the feeling of fullness and the desire to stop eating. It is the predominate feeling at the end of a meal. Obese and obesity prone people seem to experience satiety later, after consuming more calories and may experience hunger and appetite differently as well.

Hunger, appetite, and satiety are affected both by the function of the gastrointestinal (GI) tract and hormones such as cholecystokinin (CCK), leptin, insulin, and ghrelin among others.

There are many signals that contribute to the regulation of energy intake in order to maintain energy homeostasis, both short-term and long-term. The short-term signals are essentially the nutrients (such as amino acids, glucose, and fatty acids) and gastrointestinal (GI) hormones (e.g., CCK) that act to limit the size of individual meals. The long-term signals, such as insulin and leptin, are activated by long-term energy intake and body composition.

Maintaining Homeostasis

Homeostasis refers to the body's ability to maintain balance. The body has to maintain energy homeostasis. For example, it has to keep blood glucose levels steady. It has to keep enough nutrients in circulation so cells can absorb them and form the ATP they need to function. In most cases, the body does a great job of maintaining body weight homeostasis. Consider that, to gain one pound of fat, you must consume an extra 3,500 calories. Consider too that an average person, eating 2,000-2,500 calories per day, eats about 800,000 calories in a year. To gain a pound a year means a .004 error or 10 calorie per day error. Metabolic energy homeostasis is critical to survival and that is why the body has complicated systems for maintaining it.

The obesity pandemic is related to a miss match between our biochemistry (designed for low food availability and high levels of activity) and our modern environment (plenty of food and little need to move). Some people think individuals should avoid obesity by learning to resist the environment and over-ride their appetite and hunger cues. Other people think we should modify the environment and government policies so that it's not so difficult to resist our appetites and become over weight.

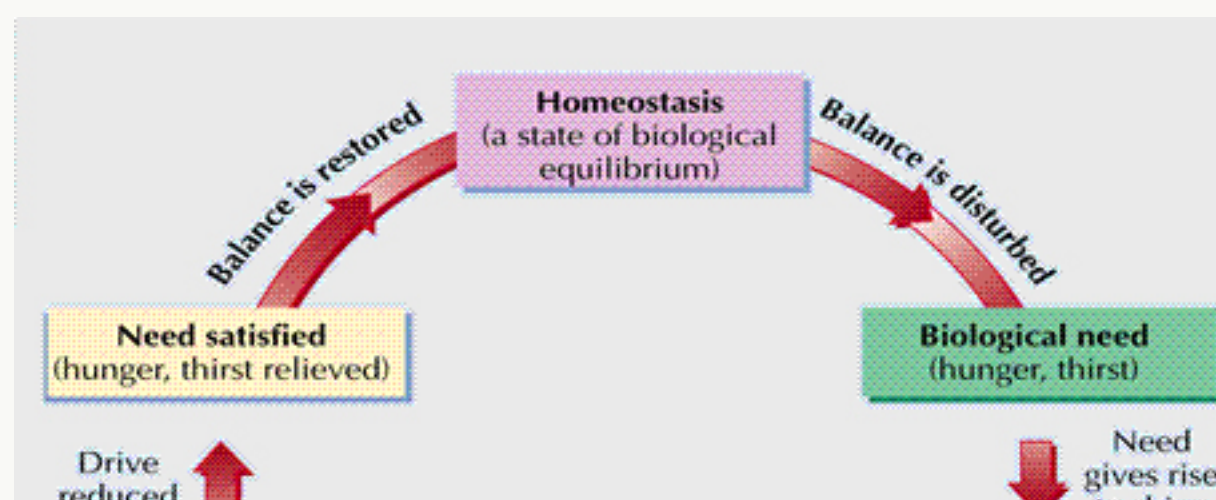
What approach do you think is best?

1) Leave the environment as it is and teach people to resist the environment better.

2) Change the environment so eating well and exercising is easier than it is today.

My personal belief is that we need both and, since agricultural policy and environment are what primarily got us into this problem (see module 1), we should emphasize efforts in these areas in order to get us past this problem.

To begin our discussion of eating behavior regulation, let's start with the role of the brain in this process. Our brain works to with the rest of the body to maintain homeostasis.



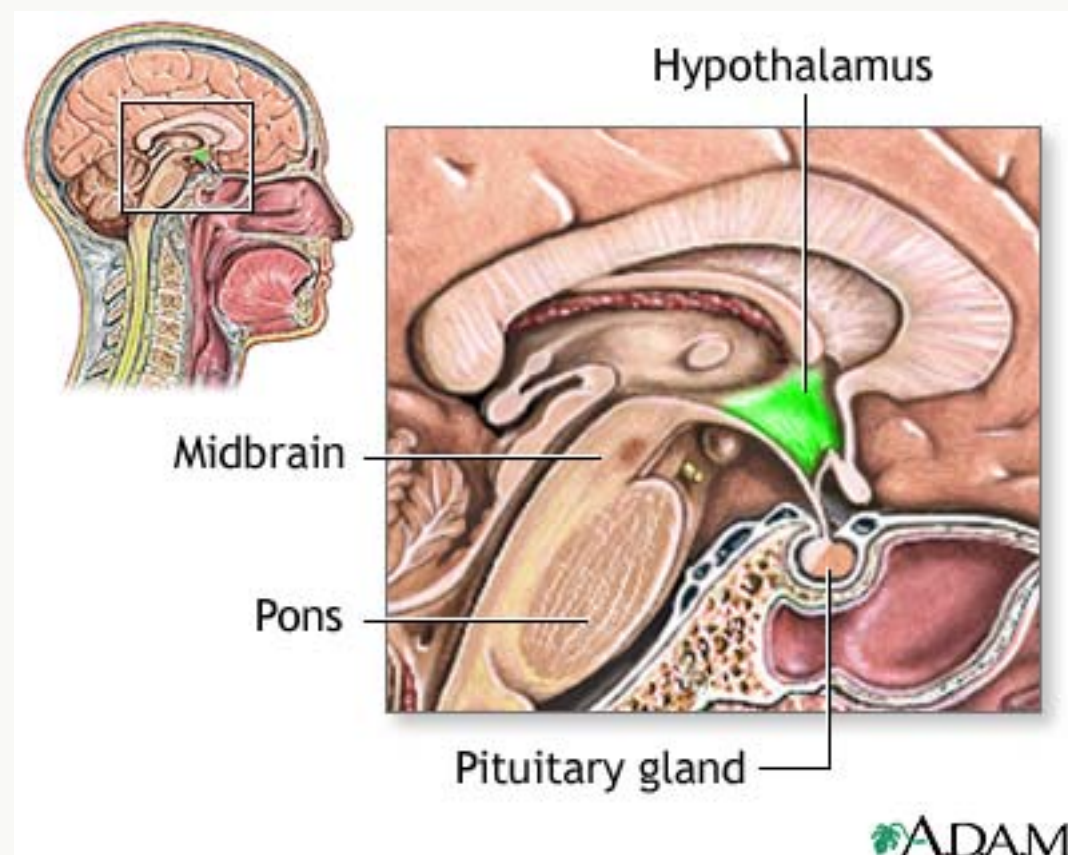


Brain Control of Hunger & Satiety

The brain acts as the “Central Regulator” of metabolic homeostasis and weight and integrates body systems, including recognition of hunger, appetite, and satiety. In this figure, the biological need for energy (hunger) is followed by the drive and goal-directed behavior (appetite/food consumption), followed by the need being satisfied (satiety). Much research has focused on the possible location of specific regions of the brain that control hunger, satiety and energy balance. The hypothalamus is located at the base of the brain and represents the main control center of the autonomic nervous system. The autonomic nervous system regulates involuntary and vital function including body temperature, hunger, thirst, fatigue, and anger.

The hypothalamus regulates:

- Appetite & hunger
- Emotions
- Energy expenditure
- Temperature regulation
- Water balance
- Hormone secretion



The many tasks of the hypothalamus make it harder for scientists to find ways to “turn down” people's appetite signals. Tinkering with appetite can affect other things too including emotions.

Ventromedial nucleus/hypothalamus (VMH) a sub-area of the hypothalamus regulates energy storage and energy expenditure. There are afferent (incoming) and efferent (outgoing) systems that control energy balance. The VMH receives meal to meal information from the GI tract. It receives information from adipose cells about how full they are. This information comes to the VMH part of the brain primarily through the hormones leptin and insulin. Destruction of the VMH will result in uncontrolled eating.

The hypothalamus communicates hunger, satiety, and energy expenditure signals to the rest of the brain and body through the autonomic nervous system:

- The autonomic nervous system is composed of two parts:
 1. sympathetic nervous system, responsible for the fight or flight, energy expenditure responses, and
 2. the parasympathetic nervous system, responsible for functions such as food digestion and absorption. The Vagus nerve, part of the parasympathetic system, directly tells the brain whether the stomach is empty or full and whether the blood levels of glucose, amino acids, and fatty acids are high or low.

The VMH integrates the sympathetic and parasympathetic signals, which leads to one of two body states/sensations:

1. A feeling and response of: *I don't need any more food and I have energy to burn.*
2. A feeling and response of: *I'm hungry and I need to store energy (instead of burn it).*

There is a delicate balance and feedback loop between the sympathetic and parasympathetic systems.

Cytokines, Neuropeptides, hormones, and enzymes that influence food intake

I like to picture the nervous system as a "highway" system where the spinal chord is the main highway, the brain is the main "station" and, out in the peripheries of the body, you have country roads (nerves). The parasympathetic and sympathetic

nervous systems includes the nerve "highways" and the "cars" on the roads include neuropeptides, cytokines, hormones and enzymes. Some of the "cars" on the nervous system roads increase hunger while others decrease hunger.

Khan Academy, in 3 short minutes, does a super job of explaining hormones and hunger. Please watch this short video: <https://www.youtube.com/watch?v=EVkFPeP5sFI>

Symbolically "Cars" or signals that increase hunger include:

- Neuropeptide Y (NP-Y) (from brain)
- Galanin (brain)
- Ghrelin (stomach)
- Dopamine (brain)
- Interleukin-6 (immune system)

Symbolically "Cars" or signals that decrease hunger include:

- Glucagon-like peptide (GLP-1) (small intestine and stomach)
- Serotonin (brain)
- Cholecystikinin (CCK) (duodenum the first segment of the small intestine)
- Peptide YY (PYY) (from ilium and colon or lower small intestine and large intestine)
- Leptin (adipose)
- Norepinephrine (brain and adrenal gland)

Role of the Digestive System

The GI tract plays important roles in regulation of eating behavior...

The digestion process begins in the mouth and stomach and it continues through the small intestine.

There are many tissues involved in both the digestion and absorption of food including:

- Oral cavity
- Esophagus
- Stomach
- Small intestine (SI)
- Colon
- Salivary glands

Nose and Mouth:

A complex process begins when food is smelled or enters the mouth. Food consumption stimulates numerous processes within the gastrointestinal tract, beginning in the mouth. The smell and taste of food is important in the initiation and termination of eating. Most people would say that the taste of a favorite food becomes less enticing as a meal progresses. In addition, volume of food, nutrient content and caloric content affect food consumption. Both human and animal studies suggest that increasing variety increases food intake.

Stomach:

Stomach distention is frequently used by individuals to express their feelings of fullness or hunger. Food intake causes expansion (distention) of the abdomen and stimulation of the GI tract. Gut peptides are produced by the intestinal mucosal cells in response to the presence of food in the GI tract. They regulate motility and the secretions of the intestine, pancreas, liver, and gall bladder.

Digestion is typically defined by three phases, including the cephalic, gastric, and intestinal phases.

The **cephalic** phase consists of reflexes initiated by sensory receptors in the brain, nose, eyes, and mouth. Even before food enters the stomach, the sight, smell, taste, or thought of food initiates this reflex. These stimuli trigger the vagus nerve to stimulate salivary glands and stomach secretions.

In the **gastric** phase, food distends the stomach and stretches receptors in the stomach walls. These nerve impulses cause waves of peristalsis and stimulate the release of gastric juice from parietal cells, chief cells, and mucous cells. Along with releasing of gastric acid, gastrin also increases motility of the stomach. A hormone called glucagon-like peptide (GLP) is released, tells the pancreas to get ready to release insulin, tells the liver to stop releasing sugar into the blood (because soon it will come from the GI) and tells the hypothalamus to stop paying so much attention to hunger signals.

The **intestinal** phase occurs when receptors in the small intestine are activated. The enzymes and hormones released in the

intestinal phase actually slow the release of the stomach contents (chyme) into the small intestine.

When chyme containing fatty acids and glucose leaves the stomach and enters the small **intestine**, it triggers the small intestine cells to release two hormones into the blood that affect the stomach: secretin and cholecystokinin (CCK).

Secretin mainly decreases gastric secretions, whereas **CCK** mainly inhibits stomach emptying.

Gastrointestinal Hormones & Neuropeptides

Cholecystokinin (CCK) from the upper small intestine, is stimulated by the presence of fat and protein in the duodenum, and in turn stimulates the contraction of the gall bladder to eject bile and the pancreas to release digestive enzymes. The effect of this gut peptide is also to reduce desire for continued eating/food intake. However, the effect of CCK and other gut peptides is limited to a specific meal and CCK administration does not affect long-term energy homeostasis.

Summary of Cholecystokinin (CCK)

- Secreted by the duodenum (upper small intestine)
- Stimulated by fat and protein in GI tract
- Stimulates secretion of pancreatic enzymes
- Signals the gallbladder to contract sending bile through the common bile duct into the duodenum
- Says to your brain and body as you sit at the table, "Okay, you're full now. You can stop eating. We need to do some digesting."
- The mechanism by which it says "stop eating" is by inhibiting Neuropeptide Y which is a hunger signal

For more on **CCK** [click here](#).

Ghrelin does the opposite of of Cholecystokinin and it is involved in longer term regulation.

Ghrelin, is predominately produced by epithelial cells in the stomach. Ghrelin receptors in the feeding center of the hypothalamus stimulate eating behaviors.

- Production increases in response to fasting
- The more the levels increase, the hungrier you feel.
- This is the messenger from the stomach to the brain that says, "I'm empty and hungry!"
- Levels are reduced with the presence of food in the stomach.
- Stimulates cells in the pituitary to secrete growth hormone
- Stimulates gastric emptying
- Inhibits lipolysis (break down and mobilization of fat from adipose)
- Likely acts in long-term regulation
- Gastric bypass surgery greatly reduces ghrelin secretion

For more information on **Ghrelin** [click here](#).

Adipose:

Leptin is a hormone made and released by adipose tissue that signals the hypothalamus to dial back appetite. Leptin is a long-term signal. It's affected by fat cell size not by the size of a meal. Most obese people have adequate leptin levels but are leptin resistant, the brain doesn't "hear" the leptin signal. Their hypothalamus can't see the leptin signal, so their brains think they are starving, and will therefore try to increase energy storage. When people lose weight their leptin sensitivity is often restored. This suggests that obese people are not leptin deficient but rather leptin resistant. Leptin resistance may be a key part to the obesity epidemic. H.Munsberg et al. **Nat. Neurosci.** 8(2005):566-70.

For more information on **leptin** [click here](#).

An Evening of Appetite Regulation:

It's 5 pm and ghrelin, produced in the stomach, is saying to the brain, "Hey there. We're on empty. Get some food would you?" You begin food seeking behavior and by 6 pm you're eating. At 6:20 the stomach and duodenum pipe up and say to the brain via GLP-1 and CCK respectively, "Put down the fork please. You're full and I'm busy digesting." At 8:20, PYY from further down in the intestine might say to the brain, "Hey we're still working on those curly fries. No bedtime snack for you!" However, if you've been starving yourself for several days, a lack of leptin from the fat cells might cause the brain to say, "We're over-riding the gut! Break-out the ice-cream." We're having that night time snack after all." Alternatively, you could have plenty of leptin, CCK, PYY and GLP-1 but everyone in your family is having some of that yummy Ben & Jerry's so, you do too.

Summary:

In summary, appetite regulation is complex. We covered only the major hormonal and neurological signals involved. Additionally, appetite regulation is intertwined with our most basic of drives and emotions.

Next we are going to turn to discussing how appetite and eating affect metabolism and the major hormones involved in maintaining the body's metabolic homeostasis.

Macronutrient Metabolism – Overview

If you're an audio visual learner, here is a great video that explains these concepts: <https://www.youtube.com/watch?v=ld2E72P8Fe0>

As we have learned, the primary energy source for the cells is ATP. All cells continuously use ATP, thus cells require a constant fuel supply to generate ATP

constant fuel supply to generate ATP.

Most cells partially or totally depend on glucose for ATP production. A key role of the liver is to maintain blood glucose levels in order to provide a constant supply of glucose to the cells.

- In a healthy human, blood glucose is kept within a fairly narrow range, about 70-140mg/dL. The body works hard, as you'll see, to maintain blood glucose in that range because the brain, red blood cells, and nerves must have a constant supply of glucose to "run" properly. These tissues can not utilize fat to make ATP. They rely on glucose.
- Glucose homeostasis is primarily maintained through the actions of insulin (an anabolic hormone) and glucagon (it's opposite, a catabolic hormone). These two also help to to regulate amino acids and lipids to meet needs of individual tissues.

Insulin

Insulin is a key hormone in the regulation of energy balance. Insulin is secreted by the beta- cells of the pancreas. Insulin levels increase in response to meals that contain carbohydrate (CHO) and protein (amino acids - AA).

- Secreted by pancreas when glucose levels in blood are high (after you’ve eaten).
- Insulin is secreted in the “fed” state (you’ve eaten and blood sugar and blood amino acid levels are rising as food is digested and absorbed by the intestine).
- Insulin functions to unlock the cell membrane and move glucose from blood into cells.
- Insulin also stimulates liver and, if you've exercised, muscle, to make glycogen. Glycogen is the storage form of glucose.

The actions of insulin on cells include:

- Increase cell uptake of glucose
- Increase protein synthesis
- Increased glycogen synthesis – insulin causes the storage of glucose in liver (and muscle) cells in the form of glycogen
- Increased fatty acid synthesis – insulin causes fat cells to take in blood lipids which are converted to triglycerides
- Decreased proteolysis – decreases the breakdown of protein.
- Decreased lipolysis – fat cells stop letting go of fat and start taking it in (and getting bigger) instead.
- Decreased gluconeogenesis – liver cells stop turning amino acids into glucose
- Increased amino acid uptake – cells to absorb circulating amino acids and use them to make proteins for building and repair

For more information on **insulin** [click here](#).

Glucagon

Glucagon is the other key hormone involved in nutrient homeostasis and energy metabolism. It is released by the alpha-cells of the pancreas and has the opposite effects of insulin on energy metabolism. Glucagon is released when blood glucose levels are low. Many hours after a meal, glucose stops coming out of the intestines and into the blood. Blood glucose levels start to drop.

- Secreted by pancreas when glucose levels in the blood are low
- Glucagon is secreted in the “fasting” state.
- Glucagon stimulates the liver to breakdown glycogen back into glucose and release it into the blood (glycogenolysis)
- The glucose is released into the blood between meals and during your over night fast ensuring that glucose is available for the brain, nervous system and red blood cells.
- Glucagon also stimulates breakdown of body protein into amino acids (glucogenic amino acids) and conversion of amino acids by the liver to blood glucose (gluconeogenesis)
- Glucagon inhibits uptake of glucose by muscle and other tissues and, in this way, it preserves the glucose for the brain, nerves, and red blood cells.

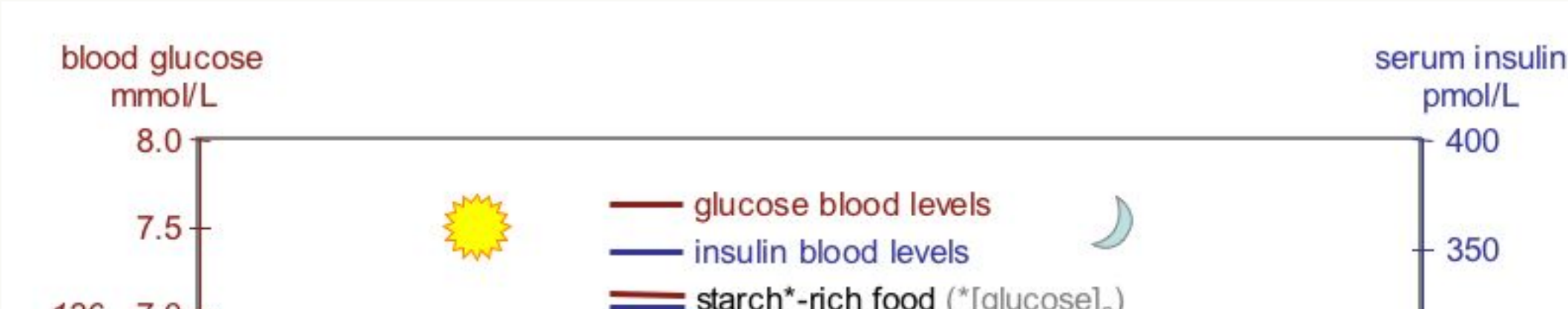
For more information on **glucagon** [click here](#).

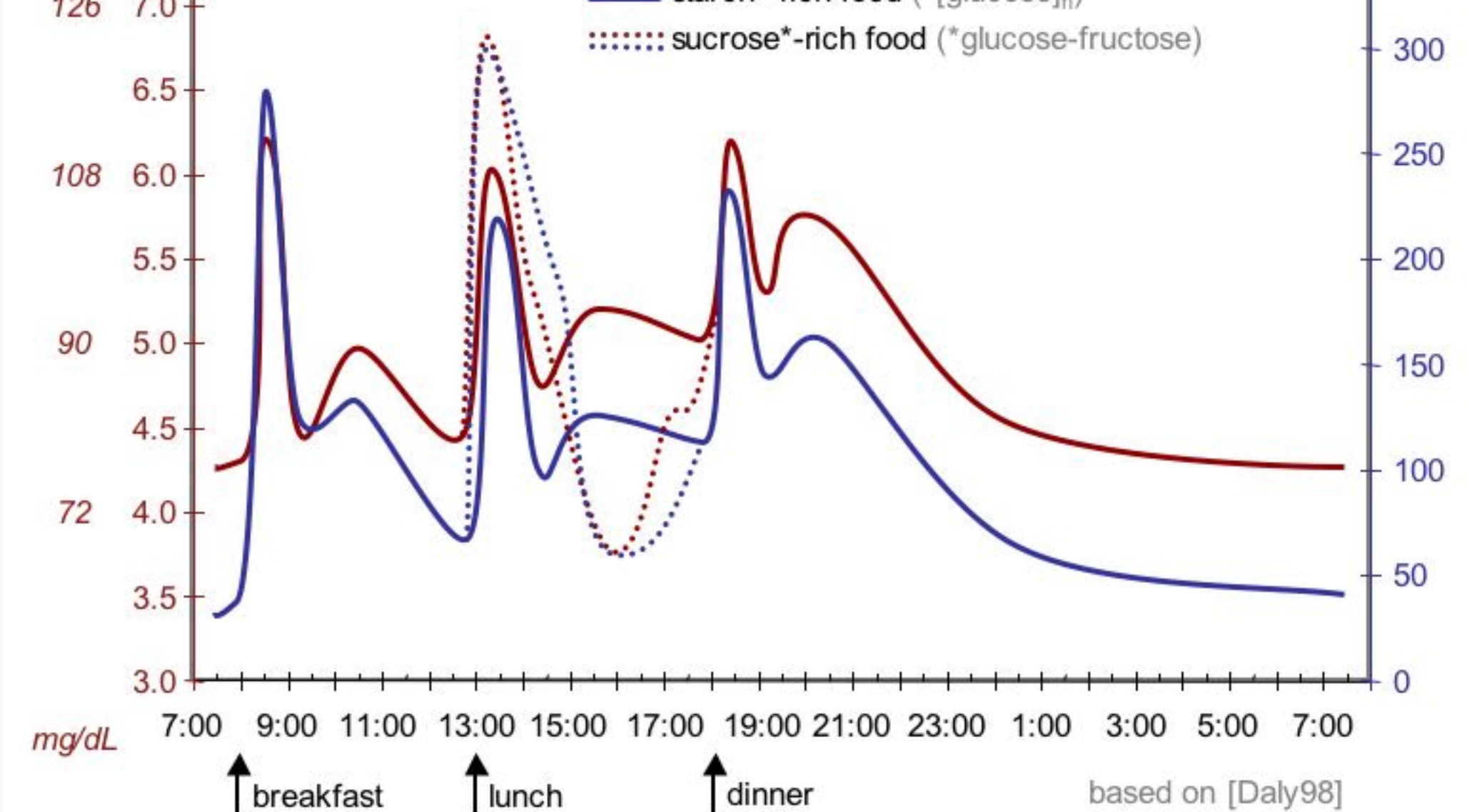
Metabolic Homeostasis

As mentioned, living cells require a constant source of fuels from which to derive ATP for the maintenance of normal cell function and growth. Therefore, a balance must be achieved between carbohydrate, fat, and protein intake. These nutrients are stored when present in excess of immediate need and mobilized when in demand.

The balance between need and availability is referred to as metabolic homeostasis. The intertissue integration required for metabolic homeostasis is achieved in three principal ways:

1. The concentration of nutrients or metabolites in the blood affects the rate at which they are used and stored in different tissues. So if there is plenty of blood glucose and insulin, tissues use lots of glucose to make ATP and some tissues also make glycogen. Our RQ would be high. If there isn't much glucose but plenty of fat (you ate bacon, avocado, and tomato salad) the body's cell will use fat to make ATP and your RQ will be low.
2. Hormones carry messages to individual tissues about the physiologic state of the body and nutrient supply or demand. So insulin and glucagon and other hormones send signals to cells about what to do. Insulin says to cells "Use carbohydrate to make ATP." Glucagon says, "Don't use carbohydrate. Burn fat to make ATP".
3. The central nervous system uses neural signals to control tissue metabolism, directly or through the release of hormones.





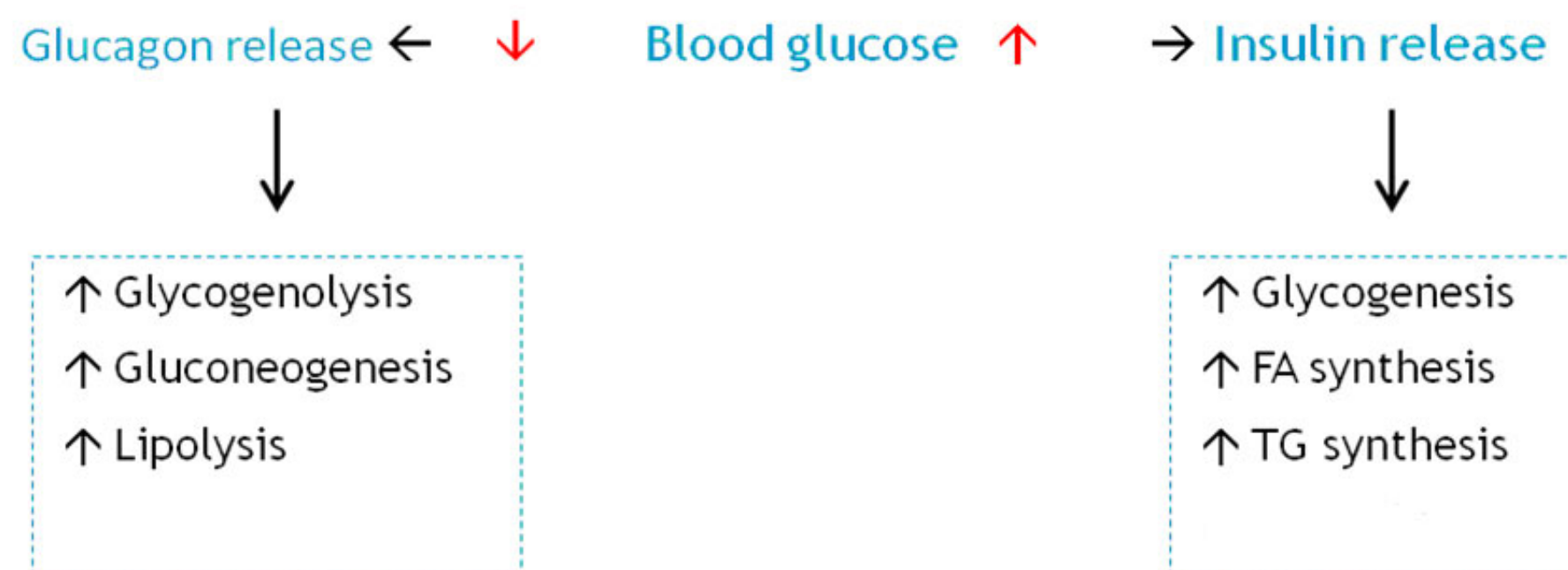
Role of Glucose in Metabolic Homeostasis

Many tissues (e.g., the brain, red blood cells, the lens of the eye, the kidney medulla, exercising skeletal muscle) are dependent on glycolysis for all or a portion of their energy needs and require uninterrupted access to glucose on a second-to-second basis to meet their rapid rate of ATP utilization. This dependence dictates the special role of glucose in metabolic homeostasis.

In the adult, a minimum of 190 g dietary glucose is required per day; approximately 150 g for the brain and 40 g for other tissues. Significant decreases of blood glucose below 60 mg/dL limit glucose metabolism in the brain and elicit hypoglycemic symptoms, presumably because the overall process of glucose flux through the blood-brain barrier, into the interstitial fluid, and subsequently into the neuronal cells, is slow at low blood glucose levels.

The blood glucose concentration determines insulin secretion. When glucose levels are elevated above 80 mg/dL insulin secretion is stimulated. Insulin secretion increases relative to blood glucose levels up to 300 mg/dL. Fructose and galactose have no effect on insulin levels. (Remember, all monosaccharides are converted to glucose in the liver.)

Pathways Regulated by Insulin & Glucagon



Insulin is the major anabolic (synthesis) hormone that promotes the storage of nutrients: glucose storage as glycogen in liver and muscle, conversion of glucose to triglycerides in liver and triglyceride storage in adipose tissue, and amino acid uptake and protein synthesis in skeletal muscle. It also increases the synthesis of albumin and other blood proteins by the liver. Insulin promotes the utilization of glucose as a fuel by stimulating its transport into muscle and adipose tissue. At the same time, insulin acts to inhibit fat mobilization from fat cells; glucose mobilization from liver glycogen; and amino acid mobilization from muscle.

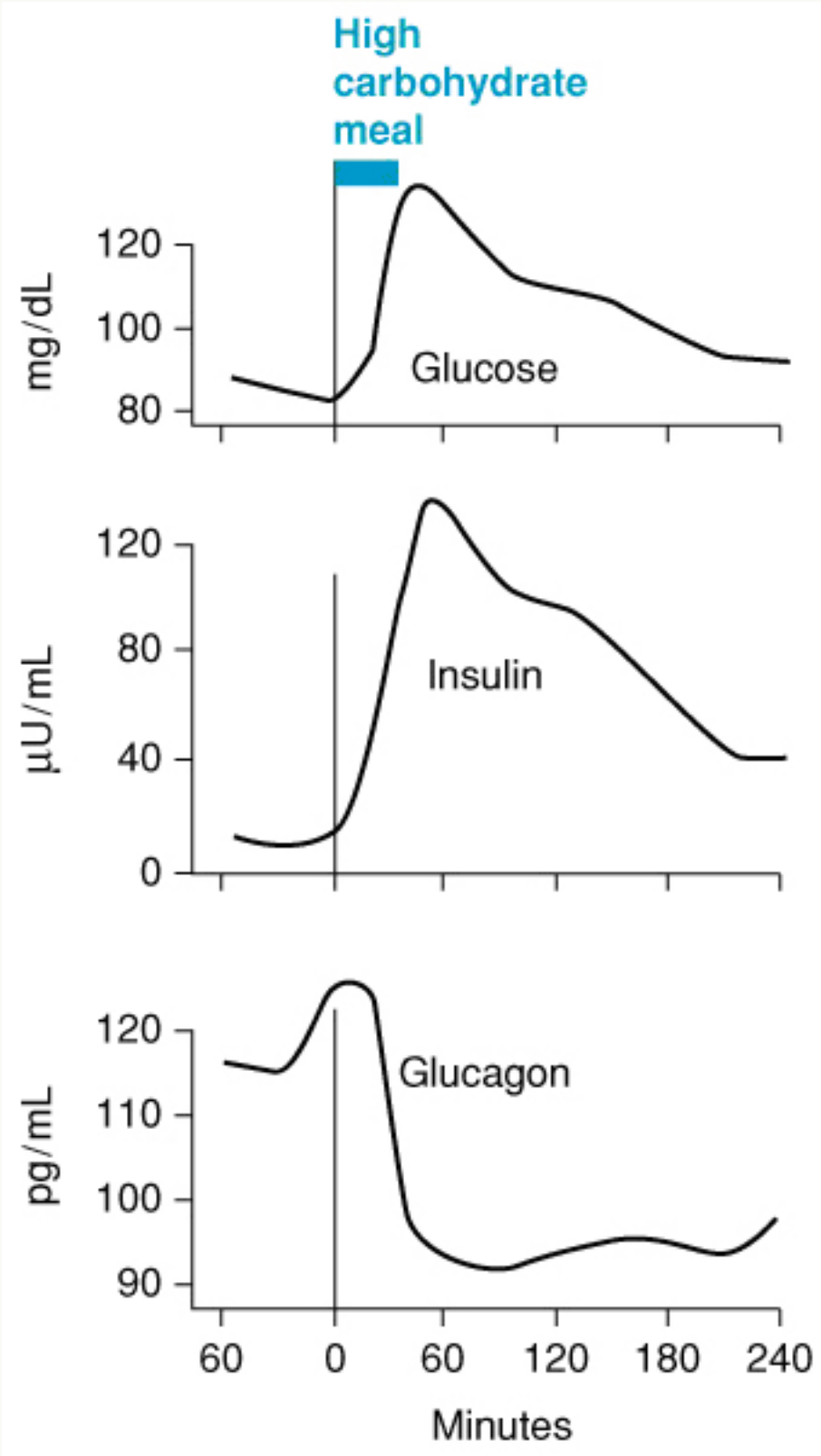
Glucagon acts to maintain fuel availability in the absence of dietary glucose by stimulating the release of glucose from liver glycogen, by stimulating gluconeogenesis from lactate, glycerol, and amino acids and, in conjunction with decreased insulin, by mobilizing fatty acids from fat cells to provide an alternate source of fuel. It acts principally on the liver and adipose tissue; it has no influence on skeletal muscle metabolism because muscle cells lack glucagon receptors.

Insulin & Glucagon Release by Pancreas beta- and alpha-Cells

The release of insulin from the beta cells of the pancreas is dictated primarily by the blood glucose level. The highest levels

of insulin occur approximately 30 to 45 minutes after a high-carbohydrate meal. They return to basal levels as the blood glucose concentration falls, approximately 120 minutes after the meal.

The release of glucagon from the alpha cells of the pancreas, conversely, is controlled principally through suppression by glucose and insulin. Therefore, the lowest levels of glucagon occur after a high-carbohydrate meal. Because all of the effects of glucagon are opposed by insulin, the simultaneous stimulation of insulin release and suppression of glucagon secretion by a high carbohydrate meal provides an integrated control of carbohydrate, fat, and protein metabolism.



Physiologic Actions of Insulin & Insulin Counter-Regulatory Hormones

Insulin and glucagon are not the only regulators of fuel metabolism. The inter tissue balance between utilization and storage of glucose, fat, and protein is also accomplished by the circulating levels of other hormones involved in metabolic homeostasis (epinephrine and cortisol, among others).

These hormones oppose the actions of insulin by mobilizing fuels to provide energy for the cells. Different than insulin and glucagon being released in response to changing levels of glucose in the blood, epinephrine (also called adrenaline and the fight or flight hormone) and cortisol (the stress hormone) release is mediated by neuronal signaling. The release of these two hormones in the blood reflect, for the most part, a need for fuel to the cells. Epinephrine meets the immediate needs of cells; whereas cortisol works on a more long-term requirements for energy.

Hormone	Function	Major Metabolic Pathways Affected
Insulin (Anabolic)	- Promotes fuel storage after a meal - Promotes growth	- Stimulates glucose storage as glycogen (muscle and liver) - Stimulates fatty acid synthesis and storage after a high-carbohydrate meal - Stimulates amino acid uptake and protein synthesis
Glucagon (Catabolic)	- Mobilizes fuels - Maintains blood glucose during fasting	- Activates gluconeogenesis and glycogenolysis (breakdown of liver glycogen to glucose) during fasting - Activates fatty acid release from adipose tissue
Epinephrine (Catabolic)	Mobilizes fuels during acute stress	- Stimulates glucose production from glycogen (muscle and liver) - Stimulates fatty acid release from adipose tissue
Cortisol	Provides for changing	Stimulates amino acid mobilization from

(Catabolic)	requirements over the long-term	muscle protein • Stimulates gluconeogenesis • Stimulates fatty acid release from adipose tissue
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Insulin – Membrane GLUT-4

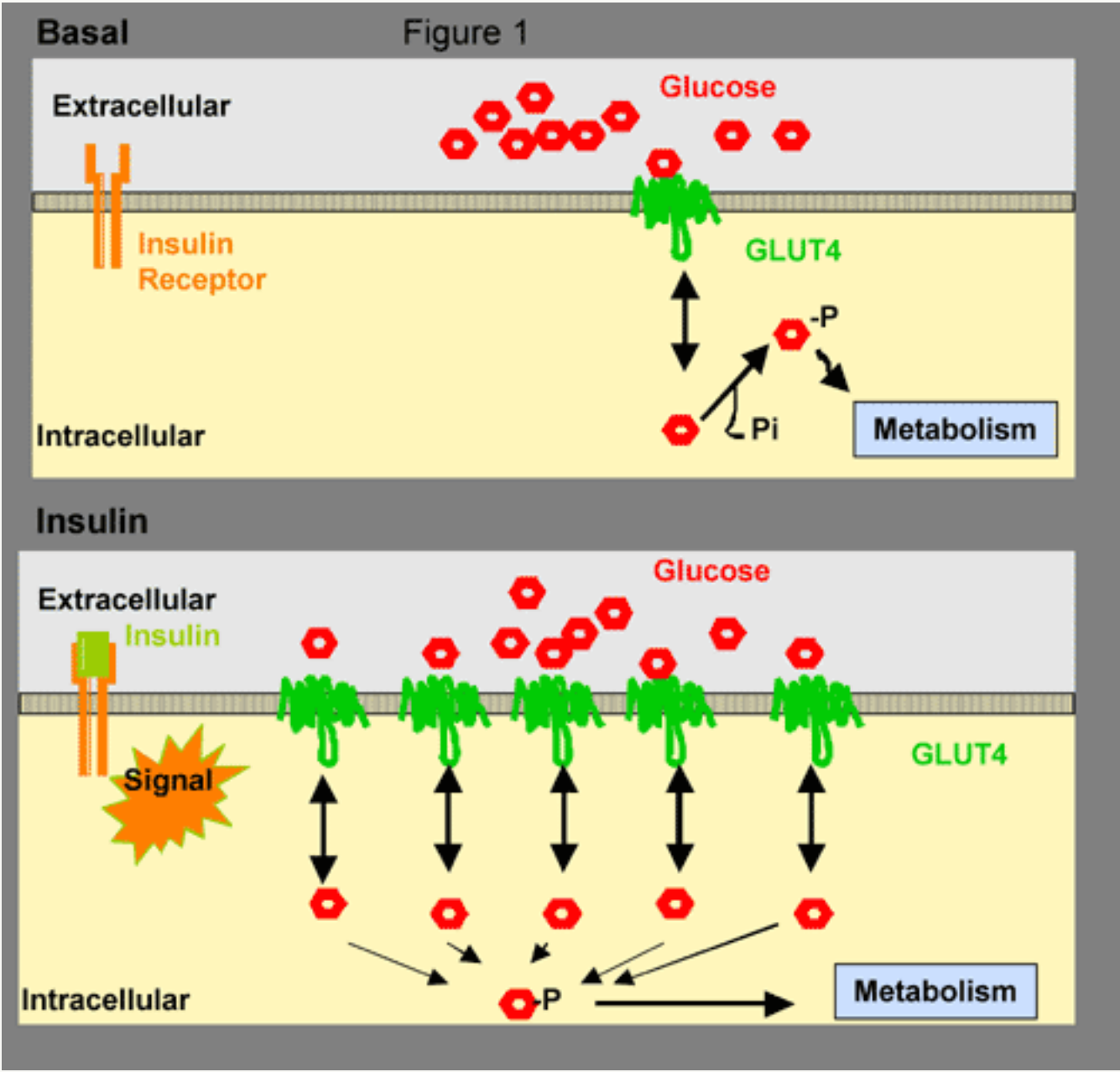
Below you'll find descriptions in words and in video of how insulin signals cells to take-up glucose.

Here is the two minute video: <https://www.youtube.com/watch?v=RL7YQQ3Qjs8>

How insulin stimulates glucose uptake by cells:

- Insulin binds with an insulin receptor on the cell membrane, which activates a protein known as insulin receptor substrate molecule 1 (IRS-1).
- IRS-1 activates the enzyme phosphatidylinositol-3 (PI-3) kinase.
- PI-3 activates a cascade of reactions that ultimately stimulate the translocation of glucose transporter 4 (GLUT4) to the cellular membrane.
- GLUT4 is the insulin-regulated glucose transporter found in adipose tissues and muscle cells (skeletal and cardiac) and allows the movement of glucose across the membrane into the cell.
- In the absence of insulin, GLUT4 is sequestered (held) in the interior of muscle and fat cells, within the lipid bilayer of storage vesicles.
- Insulin induces the movement of GLUT4 from intracellular storage sites to the outer cell membrane.
- Once at the cell surface, GLUT4 facilitates the passive diffusion of circulating glucose down its concentration gradient into muscle and fat cells.
- Once inside cells, glucose is rapidly phosphorylated. Glucose-6-phosphate cannot diffuse back out of cells, which also serves to maintain the concentration gradient for glucose to passively enter cells.

Muscle contraction also stimulates the cell to translocate GLUT4 receptors to the surface. This is especially true in cardiac muscle, where continuous contraction can be relied upon; but is observed to a lesser extent in skeletal muscle.



Not all tissues need insulin to allow glucose to enter

Some tissues, instead of GLUT-4, have insulin-*independent* systems for glucose transport. For example, hepatocytes, erythrocytes, and cells of the nervous system, intestinal mucosa, renal tubules, and cornea do not require insulin for glucose uptake. Instead they have an active transport system that uses ATP to get glucose across the cell membrane.



Insulin-sensitive		Most tissues (for example, skeletal muscle and adipose tissue)
	Epithelia of intestine Renal tubules Choroid plexus	Erythrocytes Leukocytes Lens of eye Cornea Liver Brain
Insulin-insensitive		

Consider the following eating strategies to combat hunger

Solids Over Beverages

Americans live in a beverage society. Consumers tote sports drinks and sweetened beverages, consume large quantities of soda, and have become addicted to flavored coffee drinks. Many people don’t realize that they’re often chugging hundreds of calories.

But how do calories consumed in beverages affect satiety? A 2008 ***Appetite*** study investigated the effects of eating different forms of apples on satiety. The results showed that the whole apple increased satiety more than applesauce or apple juice.

Low-Calorie Starters

It may be good advice to start a meal with a low-calorie appetizer to calm the appetite. Evidence suggests that when people opt for a low-calorie first course, even though they may increase the volume they consume for the entire meal, the intake is lower. Soups and salads are examples of low-calorie appetizers that can take the bite out of hunger.

Whole Fruits and Vegetables Galore

If a client is fighting hunger pangs, fruits and vegetables should be his or her first line of defense. Foods that have higher water content allow you to have a bigger portion with the same calorie content. Eating low-energy-dense foods such as fruits and vegetables maintains satiety while reducing energy intake. People can incorporate fruits and vegetables into the diet in many ways—for example, by bulking up recipes or simply including more servings of whole fruits and vegetables at meals or snacks. Think veggie lasagna with a large green salad and fruit for dessert, and you’ve got the picture.

Filling Up on Fiber

Fiber appears to work on hunger in many ways: by displacing available calories and nutrients from the diet including: increasing chewing, which limits intake by promoting the secretion of saliva and gastric juices, resulting in stomach expansion and increased satiety; and reducing the absorption efficiency of the small intestine. In a 2001 research summary published in ***Nutrition Reviews***, researchers found that with ad libitum energy intake, the average effect of increasing dietary fiber across all of the studies indicated that an additional 14 grams of fiber per day resulted in a 10% decrease in energy intake and a weight loss of more than 1.9 kilograms through about 3.8 months of intervention.

Portion Size Matters

Portion size significantly affects weight and satiety. Satiety is linked with our view of what a “normal” portion size is. In a recent survey conducted by the American Institute for Cancer Research, seven out of 10 Americans said they finish their restaurant entrées all or most of the time, regardless of the entrée size.

In a 2004 study published in the ***American Journal of Clinical Nutrition***, study participants were served a lunch entrée at one of two levels of energy density in one of three portion sizes. Subjects consumed 56% more energy when served the largest portion of the high-energy-dense entrées compared with when they were served the smallest portion of the low-energy-dense entrée. Despite the 56% difference in energy intake between the two entrées, participant ratings of hunger and fullness did not differ after the meals. Helping people visualize

two entrees, participant ratings of hunger and fullness did not differ after the meals. Helping people visualize appropriate portion sizes is key to getting them to realize that the mound of spaghetti on their plate at their local Italian restaurant is five times too much.

Don't Skip

Some research suggests that those who skip breakfast tend to weigh more and make up for lost calories—and then some—during the day. It's common sense that skipping meals increases hunger, which can lead to poorer food choices, over compensation, and even binge-eating behavior. Fasting followed by gorging pattern of food intake has been shown to enhance lipogenesis (fat synthesis) and increase body weight, which may be due to large fluctuations in storage and mobilization of nutrients. It is thought that in a state of energy balance, increasing meal frequency may prevent large metabolic fluctuations. So what frequency of meals is the perfect combination?

A 2008 study in the ***British Journal of Nutrition*** found that eating three meals compared with two meals with the same amount of energy increased satiety over 24 hours.

Summary:

- Appetite and hunger regulation is complex. (We only looked a few of the signals involved.)
- The same pathways that regulate hunger and appetite are also involved in other physiological and psychological pathways. This is probably why developing appetite suppressing medications have proven to be so difficult and even risky.
- Insulin and glucagon work together to maintain relatively steady levels of nutrients in the blood. They also affect hunger and appetite.
- There are both long term and short term appetite regulation signals.
- The brain, intestines, fat cells, pancreas, liver, and other organs are all involved in a “conversation” that does a better job of guarding against weight loss than it does guarding against over consumption.
- Insulin signals GLUT-4 (the main glucose transporter) to go to the surface of cell membrane and let glucose enter insulin sensitive cells.
- There are several controllable factors that tend to stimulate people to over eat.

