Section Summary (continued)

During the fasting phase the activity of the parasympathetic nervous system falls, and the activity of the sympathetic nervous system increases. In response, the level of insulin falls, and the levels of glucagon and the adrenal catecholamines rise. These events cause liver glycogen to be converted to glucose and triglycerides to be broken down into glycerol and fatty acids. In the absence of insulin, only the central nervous system can use the glucose that is available in the blood; the rest of the body lives on fatty acids. Glycerol is converted to glucose by the liver, and the glucose is metabolized by the brain.

What Starts a Meal?

Regulation of body weight requires a balance between food intake and energy expenditure. If we ingest more calories than we burn, we will gain weight. Assuming that our energy expenditure is constant, we need two mechanisms to maintain a relatively constant body weight. One mechanism must increase our motivation to eat if our long-term nutrient reservoir is becoming depleted, and another mechanism must restrain our food intake if we begin to take in more calories than we need. Unfortunately, the first mechanism is more effective than the second one.

Signals from the Environment

The environment of our ancestors shaped the evolution of these regulatory mechanisms. In the past, starvation was a much greater threat to survival than overeating was. In fact, a tendency to overeat in times of plenty provided a reserve that could be drawn upon if food became scarce again—which it often did. A feast-or-famine environment favored the evolution of mechanisms that were quick to detect losses from the long-term reservoir and provide a strong signal to seek and eat food. Natural selection for mechanisms that detected weight gain and suppressed overeating was much less significant.

The answer to the question posed by the title of this section, "What starts a meal?" is not simple. Most people, if they were asked why they eat, would say that they do so because they get hungry. By that they probably mean that something happens inside their body that provides a sensation that makes them want to eat. But if this is true, just what is happening inside our bodies? The factors that motivate us to eat when food is readily available are very different from those that motivate us when food is scarce. When food is plentiful, we tend to eat when our stomach and upper intestine are empty. This emptiness provides a hunger signal—a message to our brain that indicates that we should begin to eat. The time it takes for food to leave our stomach would seem to encourage the establishment of a pattern of eating three meals a day. In addition, our ancestors undoubtedly found it most practical to prepare food for a group of people and have everyone eat at the same time. Most modern-day work schedules follow this routine as well.

Although an empty stomach is an important signal, many factors start a meal, including the sight of a plate of food, the smell of food cooking in the kitchen, the presence of other people sitting around the table, or the words "It's time to eat!" As I write this in the late afternoon, I am anticipating a tasty meal this evening and look forward to eating it. I don't feel particularly hungry, but I like good food and expect to enjoy my dinner. My short-term and long-term nutrient reservoirs are well stocked, so my motivation to eat will not be based upon a physiological need for nourishment.

Signals from the Stomach

As we just saw, an empty stomach and upper intestine provide an important signal to the brain that it is time to start thinking about finding something to eat. Recently, researchers discovered one of the ways this signal may be communicated to the brain. The gastrointestinal system (especially the stomach) releases a peptide hormone called ghrelin (Kojima et al., 1999). The
name ghrelin is a contraction of GH releasIn, which reflects the fact that this peptide is also involved in controlling the release of growth hormone, usually abbreviated as GH. Researchers have discovered that blood levels of this peptide increase with fasting and are reduced after a meal. In humans, blood levels of ghrelin increase shortly before each meal, which suggests that this peptide is involved in the initiation of a meal. (See Figure 11.12.) Ghrelin is a potent stimulator of food intake, and it even stimulates thoughts about food. Schmid et al. (2005) found that a single intravenous injection of ghrelin not only enhanced appetite in normal subjects, it also elicited vivid images of foods that the subjects liked to eat. Subcutaneous injection or infusion of ghrelin into the cerebral ventricles of laboratory animals causes weight gain by increasing food intake and decreasing the metabolism of fats (Tschöp, Smiley, and Heiman, 2000; Ariyasu et al., 2001; Bagnasco et al., 2003).

What controls ghrelin secretion? Secretion of this hormone is suppressed when an animal eats or when an experimenter infuses food into the animal’s stomach. Injections of nutrients into the blood do not suppress ghrelin secretion, so the release of the hormone is controlled by the contents of the digestive system and not by the availability of nutrients in the blood (Schaller et al., 2003). In fact, the entry of food into the upper part of the small intestine—the duodenum—suppresses ghrelin secretion (Overduin et al., 2005). Thus, although the stomach secretes ghrelin, the secretion of this hormone appears to be controlled by receptors present in the upper part of the small intestine, not in the stomach itself. (If you’re interested, the original Greek name for the duodenum was dodekadalaktolon, or “twelve fingers long.” More precisely, the duodenum is twelve finger widths long.)

Although ghrelin is an important short-term hunger signal, it clearly cannot be the only one. For example, people with successful gastric bypass surgery have almost negligible levels of ghrelin in the blood. Although they eat less and lose weight, they certainly do not stop eating. In addition, mice with a targeted mutation against the ghrelin gene or the ghrelin receptor have normal food intake and body weight (Sun, Ahmed, and Smith, 2003; Sun et al., 2004). However, Zigman et al. (2005) found that this mutation protected mice from overeating and gaining weight when fed a tasty high-fat diet that induced obesity in normal mice. Thus, alternative mechanisms can stimulate feeding which, given the vital importance of food, is not surprising. In fact, one of the factors that complicates research on ingestive behavior is the presence of redundant systems.

Metabolic Signals

Most of the time, we begin a meal a few hours after the previous one, so our nutrient reservoirs are seldom in serious need of replenishment. But if we skip several meals, we get hungrier and hungrier, presumably because of physiological signals indicating that we have been withdrawing nutrients from our long-term reservoir. What happens to the level of nutrients in our body as time passes after a meal? As you learned earlier in this chapter, during the absorptive phase of metabolism we live on food that is being absorbed from the digestive tract. After that we start drawing on our nutrient reservoirs: The brain lives on glucose, and the rest of the body lives on fatty acids. Although the metabolic needs of the body’s cells are being met, we are taking fuel out of our long-term reservoir—making withdrawals rather than deposits. Clearly, this is the time to start thinking about our next meal.

A fall in blood glucose level (a condition known as hypoglycemia) is a potent stimulus for hunger. Hypoglycemia can be produced experimentally by giving an animal a large injection of insulin, which causes cells in the liver, muscles, and adipose tissue to take up glucose and store it away. We can also deprive cells of glucose by injecting an animal with a drug that interferes with the metabolism of glucose. Both of these treatments cause glucoprivation; that is, they deprive cells of glucose. And glucoprivation, whatever its cause, stimulates eating. Hunger can also be produced by causing lipoprivation—depriving cells of lipids. More precisely, they are deprived of the ability to metabolize fatty acids through injection of a drug that interferes with this process.

duodenum The first portion of the small intestine, attached directly to the stomach.

glucoprivation A dramatic fall in the level of glucose available to cells; can be caused by a fall in the blood level of glucose or by drugs that inhibit glucose metabolism.

lipoprivation A dramatic fall in the level of fatty acids available to cells; usually caused by drugs that inhibit fatty acid metabolism.
The brain cannot metabolize fatty acids; receptors detect only glucose levels.

The liver can metabolize glucose and fatty acids; receptors detect levels of both nutrients.

**FIGURE 11.14 Nutrient Receptors.** The figure shows the probable location of nutrient receptors responsible for hunger signals.

What is the nature of the detectors that monitor the level of metabolic fuels, and where are these detectors located? The evidence that has been gathered so far indicates that there are two sets of detectors: one set located in the brain and the other set located in the liver.

Let's first review the evidence for the detectors in the liver. A study by Novin, VanderWeele, and Rezek (1973) suggested that receptors in the liver can stimulate glucoprivic hunger; when these neurons are deprived of nutrients, they cause eating. The investigators infused 2-DG into the hepatic portal vein. This vein brings blood from the intestines to the liver; thus, an injection of a drug into this vein (an *intraportal* infusion) delivers it directly to the liver. (See **Figure 11.13**.) The investigators found that the infusion of a drug that interferes with glucose metabolism into the hepatic portal vein caused immediate eating. When they cut the vagus nerve, which connects the liver with the brain, the infusions no longer stimulated eating. Thus, the brain receives the hunger signal from the liver through the vagus nerve.

Now let's look at some of the evidence that indicates that the brain has its own nutrient detectors. Because the brain can use only glucose, it would make sense that these detectors respond to glucoprivation—and, indeed, they do. For example, Ritter, Dinh, and Zhang (2000) found that injecting a drug that interferes with glucose metabolism into the medulla induced eating. The medulla's role in control of food intake and metabolism is discussed later in this chapter.

Lipoprivic hunger appears to be stimulated by receptors in the liver. Ritter and Taylor (1990) induced lipoprivic hunger and found that cutting the vagus nerve abolished this hunger. Thus, the liver appears to contain receptors that detect low availability of glucose or fatty acids (glucoprivation or lipoprivation) and send this information to the brain through the vagus nerve (Friedman, Horn, and Ji, 2005).

To summarize: The brain contains detectors that monitor the availability of glucose (its only fuel) inside the blood–brain barrier, and the liver contains detectors that monitor the availability of nutrients (glucose and fatty acids) outside the blood–brain barrier. (See **Figure 11.14**.)

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**SECTION SUMMARY**

**What Starts a Meal?**

Many stimuli, environmental and physiological, can initiate a meal. Natural selection has endowed us with strong mechanisms to encourage eating but weaker ones to prevent overeating and weight gain. Stimuli associated with eating—such as clocks indicating lunchtime or dinnertime, the smell or sight of food, or an empty stomach—increase appetite. Ghrelin, a peptide hormone released by the stomach when it and the upper intestine are empty, is a potent stimulator of food intake. Studies with inhibitors of the metabolism of glucose and fatty acids indicate that low levels of both of these nutrients are involved in hunger; that is, animals will eat in response to both glucoprivation and lipoprivation. These signals are normally present only after more than one meal has been missed. Receptors in the liver detect both glucoprivation and lipoprivation and transmit this information to the brain through sensory axons of the vagus nerve. Glucoprivic eating can also be stimulated by interfering with glucose metabolism in the medulla; thus, the brain stem contains its own glucose-sensitive detectors.