What Stops a Meal?

There are two primary sources of satiety signals—the signals that stop a meal. Short-term satiety signals come from the immediate effects of eating a particular meal, which begin long before the food is digested. To search for these signals, we will follow the pathway traveled by ingested food: the stomach, the small intestine, and the liver. Each of these locations can potentially provide a signal to the brain that indicates that food has been ingested and is progressing on the way toward absorption. Long-term satiety signals arise in the adipose tissue, which contains the long-term nutrient reservoir. These signals do not control the beginning and end of a particular meal, but they do, in the long run, control the intake of calories by modulating the sensitivity of brain mechanisms to the hunger and satiety signals that they receive.

Gastric Factors

The stomach apparently contains receptors that can detect the presence of nutrients. Deutsch and Gonzalez (1980) found that when they removed food from the stomach of a rat that had just eaten all it wanted, the animal would immediately eat just enough food to replace what had been removed—even if the experimenters replaced the food with a nonnutritive saline solution. Obviously, the rats did not do so simply by measuring the volume of the food in their stomachs, because they were not fooled by the infusion of a saline solution. Of course, this study indicates only that the stomach contains nutrient receptors; it does not prove that there are not detectors in the intestines as well.

Intestinal Factors

Indeed, the intestines do contain nutrient detectors. Studies with rats have shown that afferent axons arising from the duodenum are sensitive to the presence of glucose, amino acids, and fatty acids (Ritter et al., 1992). In fact, some of the chemoreceptors found in the duodenum are also found in the tongue. These axons may transmit a satiety signal to the brain.

Feinle, Grundy, and Read (1997) had people swallow an inflatable bag attached to the end of a thin, flexible tube. When the stomach and duodenum were empty, the subjects reported that they simply felt bloated when the bag was inflated, filling the stomach. However, when fats or carbohydrates were infused into the duodenum while the bag was being inflated, the people reported sensations of fullness like those experienced after eating a meal. Thus, stomach and intestinal satiety factors can interact. That’s not surprising, given the fact that by the time we finish a normal meal, our stomachs are full and a small quantity of nutrients has been received by the duodenum.

After food reaches the stomach, it is mixed with hydrochloric acid and pepsin, an enzyme that breaks proteins into their constituent amino acids. As digestion proceeds, food is gradually introduced from the stomach into the duodenum. There, the food is mixed with bile and pancreatic enzymes, which continue the digestive process. The duodenum controls the rate of stomach emptying by secreting a peptide hormone called cholecystokinin (CCK). This hormone receives its name from the fact that it causes the gallbladder (cholecyst) to contract, injecting bile into the duodenum. (Bile breaks fats down into small particles so that they can be absorbed from the intestines.) CCK is secreted in response to the presence of fats, which are detected by receptors in the walls of the duodenum. In addition to stimulating contraction of the gallbladder, CCK causes the pylorus to constrict and inhibits gastric contractions, thus keeping the stomach from giving the duodenum more food.

Obviously, the blood level of CCK is related to the amount of nutrients (particularly fats) that the duodenum receives from the stomach. Thus, this hormone could potentially provide a satiety signal to the brain, telling it that the duodenum was receiving food from the stomach. Many studies have indeed found that injections of CCK suppress eating. However, mice with a targeted mutation against the gene responsible for the production of CCK ate normal amounts of food and did not become obese. Presumably, compensatory mechanisms such as the secretion of PYY prevented the animals from overeating. CCK does not act directly on the brain; instead, it acts on receptors located in the junction between the stomach and the duodenum (Moran et al., 1989).

Investigators have discovered another chemical produced by cells in the gastrointestinal tract that serves as an additional satiety signal. This chemical, peptide YY₃₋₃₆ (let’s just call it PYY), is
released by the small intestine after a meal in amounts proportional to the calories that were just ingested (Pedersen-Bjergaard et al., 1996). Only nutrients caused PYY to be secreted; a large drink of water had no effect. Injections of PYY significantly decreased the size of meals eaten by members of several species, including rats and both lean and obese humans (Batterham et al., 2007; Schloegl et al., 2011). In addition, Stoeckel et al. (2008) found that the amount of PYY released after a meal correlates positively with people's ratings of satiety. (See Figure 11.15.)

Liver Factors

Satiety produced by gastric factors and duodenal factors is anticipatory; that is, these factors predict that the food in the digestive system will, when absorbed, eventually restore the system variables that cause hunger. Not until nutrients are absorbed from the intestines can they be used to nourish the cells of the body and replenish the body's nutrient reservoirs. The last stage of satiety appears to occur in the liver, which is the first organ to learn that food is finally being received from the intestines.

Evidence that nutrient detectors in the liver play a role in satiety comes from several sources. For example, Tordoff and Friedman (1988) infused small amounts of two nutrients, glucose and fructose, into the hepatic portal vein. The amounts they used were similar to those that are produced when a meal is being digested. The infusions "fooled" the liver; both nutrients reduced the amount of food that the rats ate. Fructose cannot cross the blood–brain barrier and is metabolized very poorly by cells in the rest of the body, but it can readily be metabolized by the liver. Therefore, the signal from this nutrient must have originated in the liver. These results strongly suggest that when the liver receives nutrients from the intestines, it sends a signal to the brain that produces satiety. More accurately, the signal continues the satiety that was already started by signals arising from the stomach and upper intestine.

Insulin

As you will recall, the absorptive phase of metabolism is accompanied by an increased level of insulin in the blood. Insulin permits organs other than the brain to metabolize glucose, and it promotes the entry of nutrients into fat cells where they are converted into triglycerides. You will also recall that cells in the brain do not need insulin to metabolize glucose. Nevertheless, the brain contains insulin receptors (Unger et al., 1989). What purpose do these insulin receptors serve? The answer is that they appear to detect insulin present in the blood, which tells the brain that the body is probably in the absorptive phase of metabolism. Thus, insulin may serve as a satiety signal.

Insulin is a peptide and would not normally be admitted to the brain. However, a transport mechanism delivers it through the blood–brain barrier, and it reaches neurons in the hypothalamus that are involved in regulation of hunger and satiety. Infusion of insulin into the third ventricle inhibits eating and causes a loss of body weight (Woods et al., 1979). In addition, Brüning et al. (2000) prepared a targeted mutation in mice that blocked the production of insulin receptors in the brain without affecting their production elsewhere in the body. The mice became obese, especially when they were fed a tasty, high-fat diet, which would be expected if one of the factors that promotes satiety was absent.

Long-Term Satiety: Signals from Adipose Tissue

So far, I have discussed short-term satiety factors—those arising from a single meal. But in most people, body weight appears to be regulated over a long-term basis. If an animal is force-fed so that it becomes fatter than normal, it will reduce its food intake once it is permitted to choose how much to eat (Wilson et al., 1990). (See Figure 11.16.) Similar studies have shown that an animal will adjust its food intake appropriately if
it is given a high-calorie or low-calorie diet. And if an animal is put on
a diet that reduces its body weight, short-term satiety factors become
much less effective (Cabanac and Lafargue, 1991). Thus, signals arising
from the long-term nutrient reservoir may alter the brain’s sensitivity to
hunger signals or short-term satiety signals.

What exactly is the system variable that permits the body weight of
most organisms to remain relatively stable? It seems highly unlikely that
body weight itself is regulated; this variable would have to be measured
by detectors in the soles of our feet or (for those of us who are sedentary)
the skin of our buttocks. What is more likely is that some variable related
to body fat is regulated. The basic difference between obese and nonobese
people is the amount of fat stored in their adipose tissue. Perhaps fat tis-
sue provides a signal to the brain that indicates how much of it there is.

The discovery of a long-term satiety signal from fat tissue came after
years of study with a strain of genetically obese mice. The ob mouse (as
this strain is called) has a low metabolism, overeats, and gets exceedingly
fat. It also develops diabetes in adulthood, just as many obese people do.
Researchers in several laboratories reported the discovery of the cause
of the obesity (Campfield et al., 1995; Halaas et al., 1995; Pellemounter
et al., 1995). A particular gene, called OB, normally produces a peptide hormone that has been given
the name leptin (from the Greek word leptos, “thin”). Leptin is normally secreted by well-nourished
fat cells. Because of a genetic mutation, the fat cells of ob mice are unable to produce leptin.

Leptin has profound effects on metabolism and eating, acting as an antiobesity hormone. If
ob mice are given daily injections of leptin, their metabolic rate increases, their body tempera-
ture rises, they become more active, and they eat less. As a result, their weight returns to normal.
Figure 11.17 shows a picture of an untreated ob mouse and an ob mouse that has received injec-
tions of leptin. (See Figure 11.17.)

**SECTION SUMMARY**

**What Stops a Meal?**

Short-term satiety signals control the size of a meal. These signals
include feedback from gastric factors that are activated by the entry of
food into the stomach, from intestinal factors that are activated by the
passage of food from the stomach into the duodenum, and from liver
factors that are activated by the presence of newly digested nutrients in
the blood carried by the hepatic portal artery.

The signals from the stomach include information about the volume
and chemical nature of the food it contains. A satiety signal from the in-
testine is provided by CCK, which is secreted by the duodenum when it
receives fat-rich food from the stomach. Information about the secretion
of CCK is transmitted to the brain through the afferent axons of the vagus
nerve. PYY, a peptide secreted after a meal by the intestines, also acts as a
satiety signal. Another satiety signal comes from the liver, which detects
nutrients being received from the intestines through the hepatic portal
vein. Finally, moderately high levels of insulin in the blood, associated with
the absorptive phase of metabolism, provide a satiety signal to the brain.

Signals arising from fat tissue affect food intake on a long-term
basis, apparently by modulating the effectiveness of short-term hun-
ger and satiety signals. Force-feeding facilitates satiety, and starvation
inhibits it. Studies of the ob mouse led to the discovery of leptin, a pep-
tide hormone secreted by well-nourished adipose tissue that increases
an animal’s metabolic rate and decreases food intake.

**Thought Questions**

1. Do you find hunger unpleasant? I find that when I’m looking forward
to a meal I particularly like, I don’t mind being hungry, knowing that
I’ll enjoy the meal that much more. But then, I’ve never gone without
eating for several days.

2. The drive-reduction hypothesis of motivation and reinforcement
says that drives are aversive and satiety is pleasurable. Clearly, sati-
ifying hunger is pleasurable, but what about satiety? Which do you
prefer, eating a meal while you are hungry or feeling full afterward?

**Brain Mechanisms**

Although hunger and satiety signals originate in the digestive system and in the body’s nutrient
reservoirs, the target of these signals is the brain. This section looks at some of the research on the
brain mechanisms that control food intake and metabolism.