Brain Stem

Ingestive behaviors are phylogenetically ancient; obviously, all our ancestors ate and drank, or else they died. Therefore, we should expect that the basic ingestive behaviors of chewing and swallowing are programmed by phylogenetically ancient brain circuits. Indeed, studies have shown that these behaviors can be performed by decerebrate rats, whose brains were transected between the diencephalon and the midbrain (Norgren and Grill, 1982; Flynn and Grill, 1983; Grill and Kaplan, 1990). Decerebration disconnects the motor neurons of the brain stem and spinal cord from the neural circuits of the cerebral hemispheres (such as the cerebral cortex and basal ganglia) that normally control them. The only behaviors that decerebrate animals can display are those that are directly controlled by neural circuits located within the brain stem. (See Figure 11.18.)

Decerebrate rats cannot approach and eat food; the experimenters must place food, in liquid form, into their mouths. Decerebrate rats can distinguish between different tastes; they drink and swallow sweet or slightly salty liquids and spit out bitter ones. They even respond to hunger and satiety signals. They drink more sucrose after having been deprived of food for 24 hours, and they drink less of it if some sucrose is first injected directly into their stomachs. They also eat in response to glucoprivation. These studies indicate that the brain stem contains neural circuits that can detect hunger and satiety signals and control at least some aspects of food intake.

Two regions of the medulla, the area postrema and the nucleus of the solitary tract (henceforth referred to as the AP/NST), receive taste information from the tongue and a variety of sensory information from the internal organs, including signals from detectors in the stomach, duodenum, and liver. In addition, this region contains a set of detectors that are sensitive to the brain’s own fuel: glucose. All this information is transmitted to regions of the forebrain that are more directly involved in control of eating and metabolism. Evidence indicates that events that produce hunger increase the activity of neurons in the AP/NST. In addition, lesions of this region abolish both glucoprivic and lipoprivic feeding (Ritter and Taylor, 1990; Ritter, Dinh, and Friedman, 1994).

Hypothalamus

Discoveries made in the 1940s and 1950s focused the attention of researchers interested in ingestive behavior on two regions of the hypothalamus: the lateral area and the ventromedial area. For many years investigators believed that these two regions controlled hunger and satiety, respectively; one was the accelerator, and the other was the brake. The basic findings were these: After the lateral hypothalamus was destroyed, animals stopped eating or drinking (Anand and Brobeck, 1951; Teitelbaum and Stellar, 1954). Electrical stimulation of the same region would produce eating, drinking, or both behaviors. Conversely, lesions of the ventromedial hypothalamus produced overeating that led to gross obesity, whereas electrical stimulation suppressed eating (Hetherington and Ranson, 1942).

ROLE IN HUNGER

Research in the last decade has discovered several peptides produced by neurons in the hypothalamus that play a special role in the control of feeding and metabolism (Arora and Anubhuti, 2006). Two of these peptides, melanin-concentrating hormone (MCH) and orexin, produced by neurons in the lateral hypothalamus, stimulate hunger and decrease metabolic rate, thus increasing and preserving the body’s energy stores.

Melanin-concentrating hormone received its name from its role in regulating changes in skin pigmentation in fish and other nonmammalian vertebrates (Kawauchi et al., 1983). In mammals it serves as a neurotransmitter. Orexin (from the Greek word orexis, “desire, appetite”) was discovered by Sakurai et al. (1998). (This peptide is also known as hypocretin.) As we saw in Chapter 8, degeneration of neurons that secrete orexin is responsible for narcolepsy. Evidence reviewed there indicates that it plays a role in keeping the brain’s sleep-waking switch in the “waking” position.

decerebration A surgical procedure that severes the brain stem, disconnecting the hindbrain from the forebrain.

melanin-concentrating hormone (MCH) One of two peptide neurotransmitters found in a system of lateral hypothalamic neurons that stimulate appetite and reduce metabolic rate.

orexin One of two peptide neurotransmitters found in a system of lateral hypothalamic neurons that stimulate appetite and reduce metabolic rate. Also called hypocretin.
Researchers refer to MCH and orexin as orexigens, "appetite-inducing chemicals." Injections of either of these peptides into the lateral ventricles or various regions of the brain induce eating. If rats are deprived of food, production of MCH and orexin in the lateral hypothalamus increases (Qu et al., 1996; Sakurai et al., 1998; Dube, Kalra, and Kalra, 1999). Of these two orexigenic hypothalamic peptides, MCH appears to play the more important role in stimulating feeding. Mice with a targeted mutation against the MCH gene or those that receive injections of an MCH receptor antagonist eat less than normal mice and are consequently underweight (Shimada et al., 1998). In addition, genetically engineered mice with increased production of MCH in the hypothalamus overeat and gain weight (Ludwig et al., 2001).

The axons of MCH and orexin neurons travel to a variety of brain structures that are known to be involved in motivation and movement, including the neocortex, periaqueductal gray matter, reticular formation, thalamus, and locus coeruleus. These neurons also have connections with neurons in the spinal cord that control the autonomic nervous system, which explains how they can affect the body's metabolic rate (Sawchenko, 1998; Nambu et al., 1999). Figure 11.19 shows these connections. (See Figure 11.19.)

As we saw earlier, hunger signals caused by an empty stomach or by glucoprivation or lipoprivation arise from detectors in the abdominal cavity and brain stem. How do these signals activate the MCH and orexin neurons of the lateral hypothalamus? Part of the pathway involves a system of neurons that secrete a neurotransmitter called neuropeptide Y (NPY), an extremely potent stimulator of food intake (Clark et al., 1984). Infusion of NPY into the hypothalamus produces ravenous, almost frantic eating.

Yang et al. (2009) found that a genetic manipulation that increased the production of NPY in the hypothalamus increased food intake in rats. In contrast, a manipulation that decreased its production reduced eating, obesity, and diabetes of members of a strain of rats that had been selectively bred to overeat and become obese.

The cell bodies of most of the neurons that secrete NPY are found in the arcuate nucleus, located in the hypothalamus at the base of the third ventricle. The arcuate nucleus also contains neurosecretory cells whose hormones control the secretions of the anterior pituitary gland. (Refer to Figure 11.18.) Neurons that secrete NPY are affected by hunger and satiety signals; Sahu, Kalra, and Kalra (1988) found that hypothalamic levels of NPY are increased by food deprivation and lowered by eating. Glucose-sensitive neurons in the medulla also activate NPY neurons. Sindelar et al. (2004) found that in normal mice, glucoprivation caused an increase in NPY production. They also found that mice with a targeted mutation against the gene for NPY showed a feeding deficit in response to glucoprivation.

As we saw earlier, ghrelin, released by the stomach, provides a potent hunger signal to the brain. Shuto et al. (2002) found that rats with a targeted mutation that prevents ghrelin receptors from being produced in the hypothalamus ate less and gained weight more slowly than normal rats did. Evidence indicates that the ghrelin receptors that stimulate eating are located on NPY neurons (Willesee, Kristensen, and Romer, 1999; Nakazato et al., 2001; Van den Top et al., 2004). Thus, two important hunger signals—glucoprivation and ghrelin—activate the orexigenic NPY neurons.

Through what neural circuits does NPY exert its effects on eating and metabolic functions? NPY neurons of the arcuate nucleus send a projection directly to the MCH and orexin neurons in the lateral hypothalamus that stimulate eating (Broberger et al., 1998; Elias et al., 1998a). In addition, NPY neurons send a projection of axons to the paraventricular nucleus (PVN)—a region of the hypothalamus where infusions of NPY affect metabolic functions (Bai et al., 1985).

The terminals of hypothalamic NPY neurons release another orexigenic peptide in addition to neuropeptide Y: agouti-related peptide, otherwise known as AGRP (Hahn et al., 1998). The two hormones appear to act together. AGRP, like NPY, is a potent and extremely long-lasting neuropeptide Y (NPY) A peptide neurotransmitter found in a system of neurons of the arcuate nucleus that stimulate feeding, insulin and glucocorticoid secretion; decrease the breakdown of triglycerides; and decrease body temperature.

arcuate nucleus A nucleus in the base of the hypothalamus that controls secretions of the anterior pituitary gland; contains NPY-secreting neurons involved in feeding and control of metabolism. paraventricular nucleus (PVN) A nucleus of the hypothalamus located adjacent to the dorsal third ventricle; contains neurons involved in the control of the autonomic nervous system and the posterior pituitary gland.

agouti-related protein (AGRP) A neuropeptide that acts as an antagonist at MC-4 receptors and increases eating.
OREXIGEN. Infusion of a very small amount of this peptide into the third ventricle of rats produces an increase in food intake that lasts for six days (Lu et al., 2001).

I should briefly mention one other category of orexigenic compounds: the endocannabinoids. (See Di Marzo and Mattia, 2005, and Belloccio, 2010, for reviews of the evidence cited in this paragraph.) One of the effects of the THC contained in marijuana is an increase in appetite—especially for highly palatable foods. The endocannabinoids, whose actions are mimicked by THC, stimulate eating, apparently by increasing the release of MCH and orexin. (As you will recall from Chapter 4, cannabinoid receptors are found on terminal buttons, where they regulate the release of other neurotransmitters.) Levels of endocannabinoids are highest during fasting and lowest during feeding. A genetic mutation that disrupts the production of the enzyme that destroys the endocannabinoids after they have been released causes overweight and obesity. Cannabinoid agonists have been used to increase the appetite of cancer patients, and until adverse side effects were discovered, cannabinoid antagonists were used as an aid to weight reduction. (I will discuss this use later in this chapter, in the section on obesity.)

In summary, activity of MCH and orexin neurons of the lateral hypothalamus increases food intake and decreases metabolic rate. These neurons are activated by NPY/AGRP-secreting neurons of the arcuate nucleus, which also project to the paraventricular nucleus, which plays a role in control of insulin secretion and metabolism. The endocannabinoids stimulate appetite by increasing the release of MCH and orexin. (See Figure 11.20.)

ROLE IN SATIETY

As we saw earlier in this chapter, leptin, a hormone secreted by well-fed adipose tissue, suppresses eating and raises the animal's metabolic rate. The interactions of this long-term satiety signal with neural circuits involved in hunger are now being discovered. Leptin produces its behavioral and metabolic effects by binding with receptors in the brain—in particular, on neurons that secrete the orexigenic peptides NPY and AGRP.

Activation of leptin receptors on NPY/AGRP-secreting neurons in the arcuate nucleus has an inhibitory effect on these neurons (Glaum et al., 1996; Jobst, Enriori, and Cowley, 2004). Because NPY/AGRP neurons normally activate orexin and MCH neurons, the presence of leptin in the arcuate nucleus decreases the release of these orexigens. Leptin appears to suppress animals' sensitivity to both olfactory and gustatory stimuli associated with food. Getchell et al. (2006) found that ob mice, who lack the leptin gene, found buried food much faster than normal mice did. An injection of leptin into the mutant mice increased their time to find food. In addition, Kawai et al. (2000) found that leptin decreased the sensitivity of gustatory sweet receptors to the taste of sucrose and saccharine.

The arcuate nucleus contains two other systems of peptide-secreting neurons, both of which serve as anorexigens ("appetite-suppressing chemicals"). Douglass, McKinzie, and Couceyro (1995) discovered a peptide that is now called CART (for cocaine- and amphetamine-regulated transcript). When cocaine or amphetamine is administered to an animal, levels of this peptide increase, which may have something to do with the fact that these drugs suppress appetite. CART neurons appear to play an important role in satiety. If animals are deprived of food, levels of CART decrease. Injection of CART into their cerebral ventricles inhibits feeding, including the feeding stimulated by NPY, whereas infusion of a CART antibody, which destroys molecules of CART, increases feeding (Kristensen et al., 1998).

CART neurons are located in the arcuate nucleus and send their axons to a variety of locations (Koylu et al., 1998). In the context of the present topic the most important connections are probably those with the paraventricular nucleus and those with the MCH and orexin neurons.