

Central Control of Visceral Motor Functions

The caudal part of the nucleus of the solitary tract is a key integrative center for reflexive control of visceral motor function and an important relay for visceral sensory information that reaches other brainstem nuclei and fore-brain structures (Figure 21.7; see also Figure 21.5). The rostral part of this nucleus is a gustatory relay, receiving input from primary taste afferents (cranial nerves VII, IX, and X) and sending projections to the gustatory nucleus in the ventral posterior thalamus (see Chapter 15). The caudal visceral sensory part of the nucleus of the solitary tract provides input to primary visceral motor nuclei, such as the dorsal motor nucleus of the vagus nerve and the nucleus ambiguus. It also projects to premotor autonomic centers in the medullary reticular formation and to higher integrative centers in the amygdala (specifically, the central group of amygdaloid nuclei; see Box 31B) and hypothalamus (see below). In addition, the nucleus of the solitary tract projects to the **parabrachial nucleus** (so named because it envelops the superior cerebellar peduncle, also known by the Latin name *brachium conjunctivum*). The parabrachial nucleus, in turn, relays visceral sensory information to the hypothalamus, amygdala, thalamus, and medial prefrontal and insular cortex (see Figure 21.7; for clarity, the cortical projections of the parabrachial nucleus are omitted).

Although one might argue that the posterior insular cortex is the primary visceral sensory area and the medial prefrontal cortex is the primary visceral motor area, it is more accurate to emphasize the interactions among these cortical areas and related subcortical structures. Taken together, they constitute a **central autonomic network**. This network accounts for the integration of visceral sensory information with input from other sensory modalities and from higher cognitive centers that process emotional experiences. Involuntary visceral reactions such as blushing in response to consciously embarrassing stimuli, vasoconstriction and pallor in response to fear, and autonomic responses to sexual situations are examples of the integrated activity of this network. Indeed, autonomic function is intimately related to emotional processing, as emphasized in Chapter 31.

The hypothalamus is a key component of this central autonomic network that deserves special consideration. The **hypothalamus** is a heterogeneous collection of nuclei in the base of the diencephalon that plays an important role in

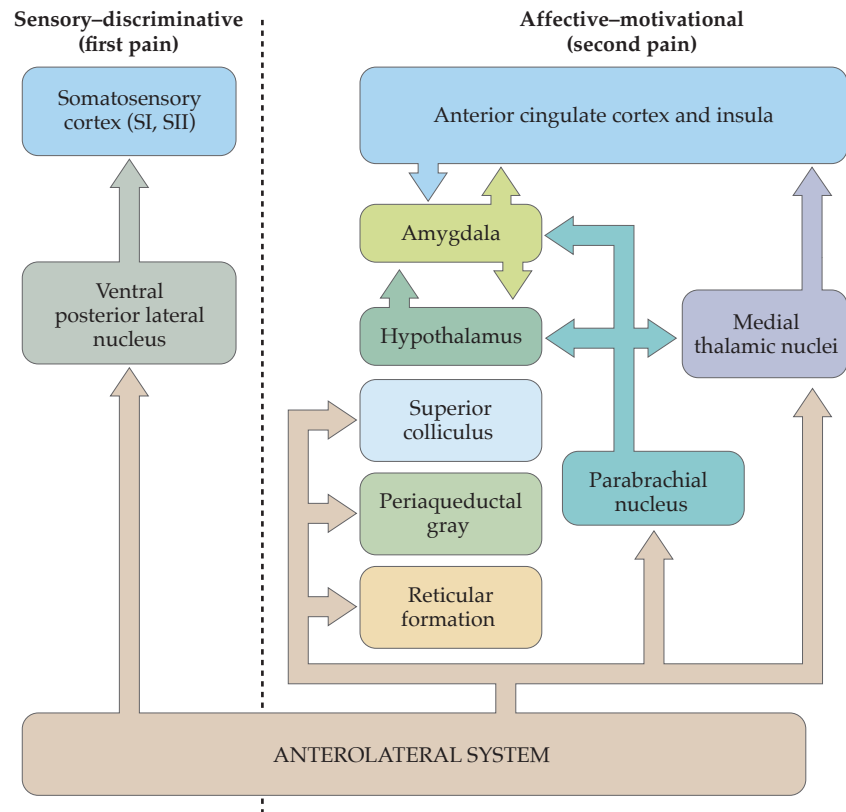


FIGURE 21.7 A central autonomic network for the control of visceral motor function. The distribution of visceral sensory information within this network is illustrated on the right side of the figure; the generation of visceral motor commands is shown on the left. However, extensive interconnections among autonomic centers in the forebrain (e.g., between the amygdala and associated cortical regions or hypothalamus) militate against a strict parsing of this network into afferent and efferent limbs. The hypothalamus, a key structure in this network, integrates visceral sensory input and higher-order visceral motor signals (see Box 21A).

the coordination and expression of visceral motor activity (see Box 21A). The major outflow from the relevant hypothalamic nuclei is directed toward autonomic centers in the reticular formation; these centers can be thought of as dedicated premotor circuits that coordinate the efferent activity of preganglionic visceral motor neurons. They organize specific visceral functions such as cardiac reflexes, bladder control reflexes, sexual function reflexes, and critical reflexes underlying respiration and vomiting (see Box 17C).

In addition to these important projections to the reticular formation, hypothalamic control of visceral motor function is also exerted more directly by projections to the cranial nerve nuclei that contain parasympathetic preganglionic neurons, and to the sympathetic and parasympathetic preganglionic neurons in the spinal cord. Nevertheless, the autonomic centers of the reticular formation and the preganglionic visceral motor neurons that they control are competent

CLINICAL APPLICATIONS

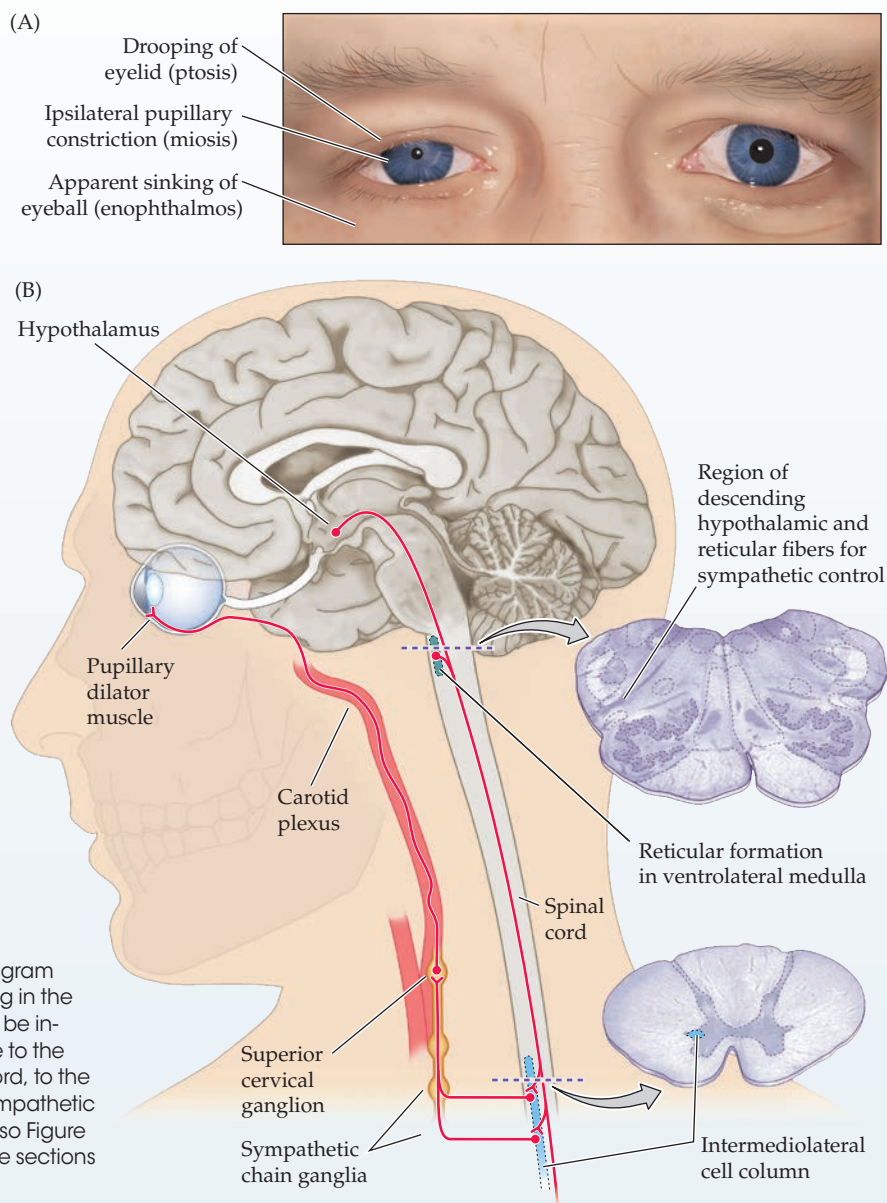
Horner's Syndrome

The characteristic clinical presentation of damage to the pathway that controls the sympathetic division of the visceral motor system to the head and neck is called Horner's syndrome, after the Swiss ophthalmologist who first described this clinical picture in the mid-nineteenth century. The main features, as illustrated in Figure A, are decreased diameter of the pupil on the side of the lesion (*miosis*), a droopy eyelid (*ptosis*), and a sunken appearance of the affected eye (*enophthalmos*). Less obvious signs are decreased sweating, increased skin temperature, and flushing of the skin on the same side of the face and neck.

All these signs are explained by a loss of sympathetic tone due to damage somewhere along the pathway that connects visceral motor centers in the hypothalamus and reticular formation with sympathetic preganglionic neurons in the intermediolateral cell column of the thoracic spinal cord (Figure B). Lesions that interrupt these fibers often spare the descending parasympathetic pathways, which are located more medially in the brainstem and are more diffuse. The sympathetic preganglionic targets that are affected by such lesions include the neurons in the intermediolateral cell column in spinal segments T1–T3 that control the dilator muscle of the iris and the tone in smooth muscles of the eyelid and globe, the paralysis of which leads to miosis, ptosis, and enophthalmos. The flushing and decreased sweating are likewise the result of diminished sympathetic tone, in this case governed by intermediolateral cell column neurons in somewhat lower thoracic segments.

Damage to the descending sympathetic pathway in the brainstem will, of course, affect sweating and vascular tone in the rest of the body on the side of the lesion. However, if the damage is to the upper thoracic outflow (as is more typical), the upper thoracic chain, or the superior

cervical ganglion, then the manifestations of Horner's syndrome will be limited to the head and neck. Typical causes in these sites are stab or gunshot wounds or other traumatic injuries to the head and neck, and tumors of the apex of the lung, thyroid, or cervical lymph nodes.



(A) Major features of Horner's syndrome. (B) Diagram of the descending sympathetic pathways arising in the hypothalamus and reticular formation that can be interrupted to cause Horner's syndrome. Damage to the preganglionic neurons in the upper thoracic cord, to the superior cervical ganglion, or to the cervical sympathetic trunk can also cause Horner's syndrome (see also Figure 21.1). The transverse lines indicate the level of the sections shown at right.

to function autonomously should disease or injury impede the ability of the hypothalamus to govern the many bodily systems that maintain homeostasis. Figure 21.7 summarizes the general organization of this central autonomic control.

Some important clinical manifestations of damage to this descending system are illustrated in Clinical Applications, and Box 21B discusses the relevance of this central control to the feeding system and the problem of obesity.

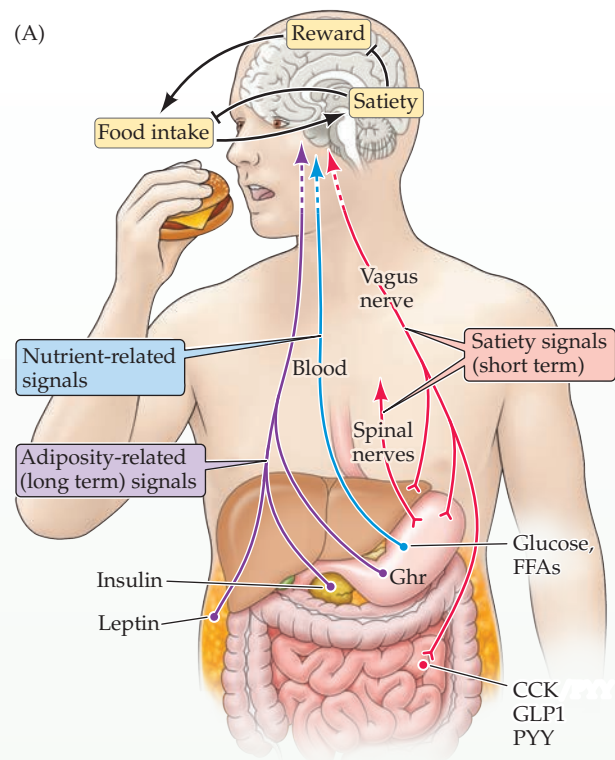
BOX 21B ■ Obesity and the Brain

Obesity—and its relationship to a broad range of diseases, including diabetes, cardiovascular disease, and cancer—has become a major public health concern in most developed countries, particularly the United States. Whereas the signature of obesity is obviously an excess of body fat, the underlying cause or causes are generally thought to lie in abnormal regulation by the brain circuits that control appetite and satiety (the feeling of fullness following a meal). This fact makes weight loss particularly difficult for many obese individuals. Thus, understanding the CNS mechanisms that regulate food intake and metabolism is essential for developing effective strategies to combat this serious health problem.

The brain regulates appetite and satiety via the neural activity that is modulated by chemical signals. These chemical signals are secreted into the circulation by fat-storing adipose tissues throughout the body. This feedback loop entails some of the central components of the visceral motor system, in addition to endocrine mechanisms via insulin, growth hormone, and a growing list of factors that signal metabolic state, adiposity (amount of body fat), and nutrient balance.

The peptide **ghrelin** is secreted by the stomach prior to feeding, presumably as a signal of hunger; adipocytes (the cells that concentrate lipids in fatty tissues) increase their secretion of **leptin** into the circulation following feeding, presumably one of several signals for satiety (Figure A). The receptors for these peptides are concentrated in small groups of neurons in the ventrolateral and anterior hypothalamus (see Box 21A), which interact with additional hypothalamic neurons in the arcuate region. These ghrelin- and leptin-sensitive cells modulate the activity of neurons expressing the opiomelanocortin propeptide (POMC) and the subsequent secretion of α -melanocyte secreting hormone (α -MSH), one of the peptides encoded by the POMC transcript. This hormone evidently regulates appetite and satiety by acting on specific receptors (particularly the melanocortin receptor subtype called MCR-4) located on additional populations of hypothalamic and brainstem neurons (particularly those in the nucleus of the solitary tract), as well as by endocrine mechanisms that remain poorly understood.

(A) Body-brain dynamics in energy homeostasis. The CNS integrates longer-term, state-dependent signals (leptin, ghrelin [Ghr], insulin) and shorter-term, feeding-dependent signals related to nutrient content (glucose, free fatty acids [FFAs]), satiety (peptide YY [PYY], glucagon-like peptide 1 [GLP1], cholecystokinin [CCK]), and visceral motor activity of the gut. Central integration of such signals regulates food intake and energy expenditure. (After Marx, 2003; Morton et al., 2014.)

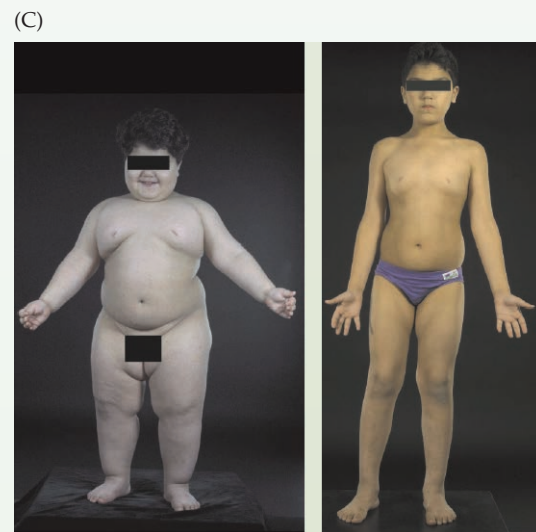


The interactions of leptin, ghrelin, α -MSH, and MCR-4 were determined in animal models. Two recessive mutations in mice—obese (*ob/ob*) and diabetic (*db/db*)—were identified based on excessive body weight and failure to regulate food intake, respectively. When each mutation was cloned, the

mutant gene in *ob* mice turned out to be the gene for leptin, and the *db* gene that for the leptin receptor. Mutations in the *POMC* (Figure B) and *MCR4* genes also lead to obesity in mice. The results of inactivation of the *ghrelin* gene are less clear; however, pharmacological and physiological studies



(B) A *POMC* knockout mouse (left) and a wild-type littermate (right).
(C) The effect of leptin treatment in a human. At age 3 years, the child weighed 42 kg (left); at age 7 years, following treatment, the same child weighed 32 kg (right). (B from Yaswen et al., 1999; C from O'Rahilly et al., 2003.)



BOX 21B ■ (continued)

associate changes in ghrelin levels with altered feeding patterns and weight loss. Studies in mice have thus provided a solid framework for examining the physiological mechanisms regulating food intake in humans. Nonetheless, the relevance of the mice studies to morbid human obesity remained unclear until recently.

Genetic analysis of individuals in human pedigrees with extreme obesity (determined via measured body mass indices and weight/height ratios) has revealed mutations in one or more of the leptin, leptin receptor, or *MCR4* genes.

As a result, these individuals have little sense of satiety after eating and thus fail to regulate food intake based on signals other than gastric distension, pain, and plasma osmolality. How this pathophysiology is related to less extreme degrees of obesity is not yet known, but it is being intensely studied because of its implications for normal weight control.

The emerging understanding of body weight regulation by hypothalamic circuits that are modulated by feedback elicited by hormonal signals from fat tissues has provided new ways of thinking about pharmacological thera-

pies for weight control. Although leptin mimetics have proven generally ineffective, leptin administration in people with leptin deficiencies does reduce food intake and obesity (Figure C). Currently, there is great interest in drugs that modulate α -MSH signaling via MCR-4. Although no effective pharmacological therapies presently exist, clinical investigators hope that such drugs, when combined with behavioral changes in dietary practices and physical activity, will effectively combat this often intractable and increasingly common health problem.

Neurotransmission in the Visceral Motor System

The neurotransmitters used by the visceral motor system are of enormous importance in clinical practice, and drugs that act on the autonomic system are among the most important in the clinical armamentarium. Moreover, autonomic transmitters have played a major role in the history of efforts to understand synaptic function.

Acetylcholine is the primary neurotransmitter of both sympathetic and parasympathetic preganglionic neurons. Nicotinic receptors on autonomic ganglion cells are ligand-gated ion channels that mediate a fast EPSP (much like nicotinic receptors at the neuromuscular junction). In contrast, muscarinic acetylcholine receptors on ganglion cells are members of the 7-transmembrane G-protein-coupled receptor family (see Chapters 6 and 7), and they mediate slower synaptic responses. The primary action of muscarinic receptors in autonomic ganglion cells is to close K^+ channels, making the neurons more excitable and generating a prolonged EPSP. Acting in concert with the muscarinic activities are neuropeptides that serve as co-neurotransmitters at the ganglionic synapses. As described in Chapter 6, peptide neurotransmitters also tend to exert slowly developing but long-lasting effects on postsynaptic neurons. As a result of these two acetylcholine receptor types and a rich repertoire of neuropeptide transmitters, ganglionic synapses mediate both rapid excitation and a slower modulation of autonomic ganglion cell activity.

The postganglionic effects of autonomic ganglion cells on their smooth muscle, cardiac muscle, or glandular targets are mediated by two primary neurotransmitters: norepinephrine (NE) and acetylcholine (ACh). For the most part, sympathetic ganglion cells release norepinephrine onto their targets (a notable exception is the cholinergic sympathetic innervation of sweat glands), whereas parasympathetic ganglion cells typically release acetylcholine.

As might be expected from the foregoing account, these two neurotransmitters usually have opposing effects on their target tissue—contraction versus relaxation of smooth muscle, for example.

As described in Chapters 6 and 7, the specific effects of ACh and NE are determined by the type of receptor expressed in the target tissue and the downstream signaling pathways to which these receptors are linked. Peripheral sympathetic targets generally have two subclasses of noradrenergic receptors in their cell membranes, referred to as α and β receptors. Like muscarinic ACh receptors, both α and β receptors and their subtypes belong to the 7-transmembrane G-protein-coupled class of cell surface receptors. The different distribution of these receptors in sympathetic targets allows for a variety of postsynaptic effects mediated by norepinephrine released from postganglionic sympathetic nerve endings (Table 21.2).

The effects of acetylcholine released by parasympathetic ganglion cells onto smooth muscles, cardiac muscle, and glandular cells also vary according to the subtypes of muscarinic cholinergic receptors found in the peripheral target (Table 21.3). The two major subtypes are known as M_1 and M_2 receptors, M_1 receptors being found primarily in the gut and M_2 receptors in the cardiovascular system. Another subclass of muscarinic receptor, M_3 , occurs in both smooth muscle and glandular tissues. Muscarinic receptors are coupled to a variety of intracellular signal transduction mechanisms that modify K^+ and Ca^{2+} channel conductances. They can also activate nitric oxide synthase, which promotes the local release of nitric oxide in some parasympathetic target tissues (see, for example, the section later in this chapter that discusses autonomic control of sexual function).

In contrast to the relatively restricted responses generated by norepinephrine and acetylcholine released by sympathetic and parasympathetic ganglion cells, respectively, neurons of the enteric nervous system achieve an enormous diversity of effects by virtue of many different