

Blessing, Chapter 7: Eating and Metabolism, (part 2)

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The medulla oblongata and the regulation of food intake

Several lines of evidence indicate the importance of lower brainstem regions in the regulation of eating and body weight. The most important *prima facie* evidence is that the medulla oblongata is the region of the brain containing direct connections with afferent and efferent nerves innervating the various abdominal organs. The area postrema has long been recognized as important in mediation of nausea and vomiting. Neoplasms involving the dorsal portion of the medulla oblongata may be associated with early satiety and weight loss (Masdeu and Ross, 1988). The integrative potential of the lower brainstem is evidenced by the increase in blood glucose in response to hypoglycemia, which still occurs after collicular transection (see earlier in this chapter). Finally, as discussed in Chapter 1 and in the introduction to this chapter, rats chronically maintained after collicular transection retain quite complex eating responses, including eating in response to food deprivation and hypoglycemia.

The increase in plasma glucose and the increase in feeding observed after injection of thioglucose into the forebrain lateral ventricle is prevented by occlusion of the aqueduct (Ritter et al., 1981). Both responses remain intact when thioglucose is infused into the fourth ventricle, even if the aqueduct is occluded (Fig. 7.10).

Figure 7.10 **A**, Infusion of 5-thioglucose into the lateral ventricle of rats increases food intake when the aqueduct is patent but not when it is blocked. Infusion of 5-thioglucose into the fourth ventricle increases food intake regardless of whether the aqueduct is patent or blocked. **B**, Blood glucose is affected in a similar manner. The aqueduct must be patent for an intraventricular infusion of 5-thioglucose to increase blood glucose, indicating that the relevant receptors are in the vicinity of the fourth ventricle and therefore probably in the hindbrain. (Modified from Ritter et al., 1981.)

This evidence indicates that it is the lower brainstem rather than the forebrain that contains the neural circuitry mediating the responses to hypoglycemia. The nTS is likely to be part of this circuitry, because it contains neurons responsive to hypoglycemia and because primary vagal afferents from the liver and the gut, also responsive to hypoglycemia, terminate in this region of the medulla (see below). Abdominal vagal section does not prevent the occurrence of feeding in response to systemic 2-deoxyglucose, but lesions of the nTS-area postrema region do prevent this response (Ritter and Taylor, 1990).

Ritter and Dinh (1994) mapped the central distribution of fos-containing neurons after peripheral administration of 2-deoxyglucose. In the brainstem, fos-positive cells were observed in the area postrema, the nTS, the ventrolateral medulla, the lateral parabrachial nucleus, and the locus coeruleus. In the hypothalamus there were positive neurons in paraventricular and supraoptic nuclei. The appearance of fos was not prevented by prior abdominal vagotomy. Since 2-deoxy-D-glucose

activates many physiological systems (e.g., secretion of adrenal medullary catecholamines and gastric acid), it is difficult to know whether any of the fos-containing brainstem neurons are directly sensitive to reduced glucose availability. Nevertheless, it is notable that fos-positive neurons were not observed in the hypothalamus within ventromedial nuclei or in the lateral hypothalamus.

Peripheral receptors for glucose and other nutrients

That hepatic receptors might signal information concerning glucose levels to the brain was first postulated by Russek (1963). Intraportal infusions of glucose were shown to reduce food intake, and similar injections of 2-deoxy-D-glucose stimulated eating more rapidly than similar intrajugular injections (Novin et al., 1973). The effects were blocked by sub-diaphragmatic vagotomy, constituting strong evidence for the existence of hepatic glucose receptors associated with vagal afferents. The suppression of feeding normally observed following total parenteral nutrition in rats is much less marked following anterior sub-diaphragmatic vagotomy, indicating that signals originating in the liver may normally suppress food intake (Yang et al., 1992). Recordings from hepatic vagal afferents documented an inverse relationship between rates of firing and concentrations of glucose in the portal blood. Sectioning the hepatic branch of the vagus nerve abolished reflex responses initiated by the hepatic "glucostat"; decreased portal glucose concentration increased the discharge of adrenal sympathetics and reduced activity in pancreatic vagal efferents, effects still observed in the rat after midpontine transection (Armin and Grant, 1959; Nijima, 1982, 1984).

Glucose-sensitive nTS neurons also receive inputs from hepatoportal vagal afferents that are themselves glucose sensitive (Adachi et al., 1984). Some nTS neurons driven by hepatic vagal afferents decrease their discharge rate in response to hepatic infusion of isotonic glucose (Adachi, 1981). Maintenance of euglycemia in the liver, using a portal infusion of glucose, reduces the secretion of adrenal catecholamines in response to insulin-induced hypoglycemia, emphasizing the physiological importance of hepatic glucoreceptors in initiating the CNS response (Donovan et al., 1991). Hepatic glucose receptors may also affect gastric motility and secretion via an effect on vagal afferents (Sakaguchi, 1995).

Mei (1978) recorded extracellularly from cat nodose ganglion cells and demonstrated that perfusion of the duodenum and the jejunum with glucose solutions and other carbohydrates excited some normally silent cells. The same cells were unresponsive to mechanical stimuli (distention and mucosal stroking) or osmotic stimuli. Intravenous infusion of glucose into the systemic or portal circulation decreased the activity, and subsequent intravenous injection of insulin increased the activity. Intraduodenal infusion of isotonic glucose suppressed feeding in rabbits with continuous access to food, but not in fasted animals (Novin et al., 1974). In contrast, intraportal infusion of isotonic glucose suppressed feeding in the fasted animal. These findings were seen as a potential mechanism for stopping intake when smaller quantities of nutrient are required.

Inhibition of fatty acid oxidation may increase food intake, an effect that appears to depend on vagal afferents, including hepatic afferents (Scharrer and Langhans, 1986; Ritter and Taylor, 1990).

Systemic administration of 2-mercaptoacetate (a fructose analogue used to inhibit fatty acid oxidation)

induces c-fos in neurons in the area postrema, the nTS, and the lateral parabrachial nucleus, an effect that is also abolished by abdominal vagotomy (Ritter and Dinh, 1994; Ritter et al., 1994).

It is thus apparent that many studies attest that portal structures, including the liver, contain nerves that monitor concentrations of nutrient substances, including glucose. The physiological importance of the signals travelling in these afferent nerves is not yet established, but presumably they mediate fine-tuning aspects of metabolic regulation, perhaps acting in concert with other visceral afferents to contribute to the overall control of food intake (Novin et al., 1985). There is no obvious defect in plasma glucose regulation in patients with hepatic transplants.

Insulin receptors in the brain

Insulin receptors are present in the brain, and peripheral insulin can be transported into the brain, possibly affecting eating and metabolism by a central mechanism (Unger et al., 1991; Schwartz et al., 1993). Emphasis has been placed on insulin receptors in the hypothalamus, but they also occur in the nTS and the area postrema (Unger et al., 1991). Increased CNS levels of insulin are thought to inhibit food intake, leading to weight loss (Chavez et al., 1995). Insulin-mediated activation of the sympathetic nervous system, perhaps via an effect on paraventricular hypothalamic neurons, may increase thermogenesis (Menéndez and Atrens, 1991). Schwartz and colleagues (1993c) suggest that increased hypothalamic insulin decreases hypothalamic neuropeptide Y, thereby affecting food intake and body weight. This interesting area of research may lead to a more explicit understanding of what is meant by "set point", with reference to food intake and body weight.

Leptin and possible brain receptors for this hormone

A brief account of this newly discovered hormone is presented toward the end of this Chapter (7).

Satiety Factors Originating in the Upper Gastrointestinal Tract

Pavlov (1910) noted that esophag-ostomized dogs increase their food intake. Similarly, rats with food drained from the stomach via a gastric cannula eat virtually continuously (Young et al., 1974). Thus the presence of food in the stomach and the upper intestine somehow triggers events that inhibit eating. How this occurs has been an active and fruitful field of research.

Paintal (1954) first demonstrated that gastric distension activates vagal afferents. He hypothesized that this activity might be responsible for the feeling of satiation that follows a meal, thereby inhibiting further eating. The electrophysiological observation has been confirmed in different species (Andrews et al., 1980; Davison and Clarke, 1988). Generalized gastric distension does inhibit eating and drinking in esophagostomized dogs (Janowitz and Grossman, 1949; Towbin, 1949). This inhibition is blocked by vagotomy, but not by sympathectomy (Towbin, 1955), suggesting a role for vagal afferents.

Participation of gastrointestinal hormones in the satiety process was suggested by Gibbs, Young, and Smith (1973) when they hypothesized that cholecystokinin (CCK), secreted from the upper small intestine after a meal, might act as part of the mechanism eliciting postprandial satiety. These investigators found that systemically administered CCK terminated eating in rats with gastric fistulae,

inducing the grooming and sleeping behaviors normally observed in intact rats after natural eating (Fig. 7.11).

Figure 7.11 **A**, Intraperitoneal administration of CCK reduces the increased consumption of food (taken as 100%) in rats with chronic gastric fistulae. (Modified from Gibbs et al., 1973.) **B**, Effect on food consumption in CCK-treated rats with chronic gastric fistulae of selective bilateral sectioning of either the afferent or the efferent medullary rootlets of the vagus nerve. After an afferent lesion, the suppressive effect of CCK is abolished, and rats continue to eat an increased amount. After an efferent lesion the suppressive effect of CCK on food consumption is still present. (Modified from Smith et al., 1985.) **C**, Soybean trypsin inhibitor (STI) releases endogenous CCK from the upper gastrointestinal tract, thereby decreasing food intake, an action reversed by concurrent administration of a CCK_A receptor antagonist. (Modified from Weller et al., 1990.) **D**, Administration of a CCK_A receptor antagonist increases food intake in rhesus monkeys in a dose-dependent manner. (Modified from Moran et al., 1993).

This important observation has proven most robust so that an impressive array of evidence now attests that exogenously administered CCK decreases food intake in many species, including primates and humans (Kissileff et al., 1981; Foltin and Moran, 1989; Silver and Morley, 1990; Smith and Gibbs, 1994). Other peptides, including bombesin (Gibbs et al., 1979; Martin and Gibbs, 1980; Hostetler et al., 1989; Muurahainen et al., 1993), may also act as satiety factors after systemic administration. In this book, emphasis is placed on the CCK experiments.

The blood-brain barrier for peptides precludes a direct action of CCK on the CNS. In the hindbrain, a locally modified blood-brain barrier in subportions of the nTS and the dmX could expose neurons in these nuclei to systemically circulating molecules, including peptides (Gross et al., 1990; 1991; Shaver et al., 1991; Hernandez et al., 1994). The area postrema is a well-characterised circumventricular organ with neuronal cell bodies on the blood side of the barrier and axonal processes projecting widely within the brain (Shapiro and Miselis, 1985a). These local hindbrain windows in the blood-brain barrier could also mediate some of the satiety effects of exogenously administered CCK.

Abdominal vagal inputs to the CNS were shown to be of major importance when the satiety effect of CCK in the gastric-fistula-sham-feeding preparation was shown to be abolished by abdominal vagotomy (Smith et al., 1981; Joyner et al., 1993). Selective section of the sensory roots of the vagus, intracranially, also abolished the satiety effect, demonstrating that afferent vagal fibers are involved (Smith et al., 1985). Systemic capsaicin, which damages unmyelinated afferents, attenuates the satiety effect (Ritter and Ladenheim, 1985; Yox and Ritter, 1988; McCann et al., 1988b), supporting the view that vagal afferents are predominantly involved. The satiety effect of CCK on natural feeding in the intact animal has also been shown to be abolished by sectioning the abdominal vagi (Joyner et al., 1993; Eberle-Wang et al., 1993).

The actions of CCK include relaxation of the stomach and inhibition of gastric emptying, each of which may contribute to gastric distention, a satiety factor in its own right (Debas et al., 1975).

However, vagotomy does not appear to abolish the satiety effect of gastric distension per se (Kraly and Gibbs, 1980). Furthermore, the motor effects of CCK on the stomach are not directly mediated; they also depend substantially on CCK stimulation of afferent vagal terminals (McCann et al., 1988b; Raybould et al., 1987; Raybould and Taché, 1988; Blackshaw and Grundy, 1991; Schwartz et al., 1993), as does CCK-induced pancreatic enzyme secretion (Li and Owyang, 1994). The efferent components of these reflexes, being vagally mediated, are prevented by hexamethonium (Raybould et al., 1987), but this agent does not block the satiety effect. Secretin also inhibits gastric emptying by a capsaicin-sensitive vagal afferent pathway, but secretin is without effect on food intake (Conover et al., 1989; Raybould and Holzer, 1993; Lu and Owyang, 1995).

The satiety and the gastric emptying effects of CCK (also vagally mediated) follow similar dose-response relationships (McCann et al., 1989c), suggesting commonality of the peripheral and central neural pathways mediating these events. Gastric distension and CCK have additive satiety effects, reflecting synergistic effects on vagal afferents in rats (Davison and Clarke, 1988; Schwartz et al., 1991a,b; 1993a,b). As shown in Figure 7.12, infusion of CCK into the celiac artery enhances the vagal afferent response to gastric distension in the rat, even after the vagal activity elicited by the CCK has dissipated.

Figure 7.12 A, Electrophysiological recording from a representative gastric vagal afferent fiber in response to a 1 ml gastric saline load (top panel), a close arterial infusion of CCK (middle panel), or a combination of both these stimuli (lower panel). **B**, Interaction between CCK and gastric saline load in increasing the number of afferent vagal spikes. (Modified from Schwartz et al., 1993b.)

Effects of CCK on vagal afferent discharge have also been studied in anesthetized ferrets (Blackshaw and Grundy, 1990). Recordings were obtained from single cervical vagal afferents, responding either to mechanical distension of portions of the stomach or the duodenum or to mucosal stimuli (stroking, acidity, hypertonicity). Close intra-arterial infusion of CCK increased vagal afferent discharge in fibers sensitive to mucosal stimulation. Afferents from tension receptors in the stomach did not respond to CCK, but afferents from tension receptors in the duodenum did increase their discharge. The data suggest that in the ferret it is mainly gastrointestinal mucosal receptors that are directly stimulated by CCK.

Before the discoveries of Smith and Gibbs concerning CCK, other agents, such as 5-HT, were known to activate abdominal and cardiopulmonary afferents (e.g., in the Bezold-Jarisch reflex; see Chapters 4 and 5). As discussed later in this chapter, a physiological role for an interaction between 5-HT and abdominal vagal afferents in the initiation of nausea and vomiting is now established. The demonstration that CCK acts on peripheral vagal afferents was an important discovery particularly because CCK was already a well-characterized hormone, already known to be released in response to eating, and already established as a key player in the physiology of digestion.

The idea that a peripheral agent such as CCK being excluded from the CNS by the blood-brain barrier can affect brain function via an action on the distal terminal of a vagal afferent fiber is a most important concept in neurobiology. We readily accept that a cutaneous event, such as an ant bite,

initiates complex events including activation of unmyelinated cutaneous sensory afferents, with consequent pain and altered behavior. The discoveries concerning the peripherally initiated satiety actions of CCK demonstrate that unmyelinated visceral afferents may constitute an important route whereby peripheral agents, in an endocrine or paracrine manner, can produce complex effects on brain function.

CNS Pathways mediating satiety effects of CCK

"Satiety" is a complex concept, encompassing psychological, behavioral, and physiological components. The centrally mediated effects of systemic CCK illustrate this diversity. Apart from its ability to stop rats eating, exogenous CCK causes rats with gastric fistulas to groom for a short period, then sleep (Gibbs et al., 1973). Exploratory behavior is decreased, an effect also abolished by vagotomy (Crawley et al., 1981). As discussed in succeeding sections of this chapter, systemic CCK in large doses may cause visceral discomfort or even frank nausea and vomiting, as well as induce conditioned taste aversions, and may cause neurohypophyseal secretion. It is clear that CCK must affect neuronal function in many regions of the CNS. At present we have only a few windows into these obviously complex central pathways. Since the vagus projects to the nTS, the relevant CNS pathways must be connected with this nucleus.

Extracellular recordings in and near the nTS have identified neurons whose discharge is altered by systemic or intra-arterial injection of CCK close to the celiac axis (Raybould et al., 1985, 1988; Ritter et al., 1989). These recording studies are unable to identify whether the nTS cells are innervated by vagal afferents or whether they are higher order interneurons, possibly even vagal preganglionic cells in the dorsal motor nucleus. Infusion of CCK excites some cells and inhibits others. Gastric distention also affects the discharge rate of neurons and increases uptake of 2-deoxy-D-glucose in the nTS region (Barber and Burks, 1983; Raybould et al., 1985, 1988; Gonzalez et al., 1986). The change in discharge rate following peripheral administration of CCK is capsaicin sensitive, but the change following gastric distention in the rat is apparently resistant to capsaicin (Ritter et al., 1989), a result that is difficult to understand given that gastric distension and CCK infusion excite the same vagal afferents in this species (Schwartz et al., 1991a). Moreover, cervical vagotomy abolishes the changes induced by gastric distension on the discharge rate of nTS neurons (Raybould et al., 1988) and there is a strong positive correlation between the effects of CCK and the effects of gastric distention on the discharge rate of individual neurons (Raybould et al., 1985, 1988; Ritter et al., 1989).

Peripheral administration of CCK causes expression of fos protein in neurons within the area postrema, the nTS, and the ventrolateral medulla oblongata; double-label studies in the rat indicate that both the A2 and the A1 catecholamine neurons are involved in this process (Luckman, 1992). The CCK effect on fos expression in the nTS is prevented by prior administration of CCK antagonists (Fraser and Davison, 1993). The same study reported that meal ingestion also induces fos expression in the nTS, but this expression was not blocked by CCK antagonists, implying that ingestion of a meal also has other, non-CCK-mediated effects that induce fos expression in the nTS.

As expected, nTS lesions block the ability of CCK to reduce feeding (Crawley and Schwaber, 1983; Edwards et al., 1986). The area postrema is usually also damaged by these lesions, and all axons from area postrema neurons either terminate in or traverse the nTS. Selective ablations of the area postrema itself do not block the satiety effects of CCK (Edwards and Ritter, 1981). Indeed, damage to the area postrema, possibly involving the immediately adjacent nTS, causes rats to consume increased amounts of particularly palatable foods and solutions (Edwards and Ritter, 1981). This effect is not seen with sub-diaphragmatic vagotomy (Edwards and Ritter, 1986). The satiety effects of peripherally administered bombesin also depend on the integrity of the area postrema and the nTS (Ladenheim and Ritter, 1993).

Lesion studies of brain regions beyond the nTS have not produced a clear consensus as to the central pathways mediating the satiety actions of intraperitoneal CCK. Grill and Smith (1988) reported that CCK decreases sucrose intake in chronic decerebrate rats, suggesting that lower brainstem neural circuitry can mediate the satiety response. However other evidence suggests the satiation effect of CCK is abolished by dorsal midbrain lesions and by lesions of the PVH, but not by lesions of the amygdala or the bed nucleus of the stria terminalis (Crawley et al., 1984; Crawley and Kiss, 1985), although not all these observations have been confirmed (Flanagan et al., 1992a; Grill and Smith, 1988). Neurons in the ventromedial nucleus of the hypothalamus, the traditional brain "satiety center," do not appear to be involved in the satiety actions of peripherally administered CCK (Kulkosky et al., 1976; Smith et al., 1981; Grill and Smith, 1988).

Evidence for endogenous CCK-mediated satiety systems

In the physiological situation, duodenal mucosal cells normally secrete CCK in response to the presence of amino acids and fats in the intestinal lumen. There have been dissenting voices (see below), but there is now reasonable evidence that this intestinally secreted CCK acts as a physiological satiety factor in experimental animals and probably in humans. Ascertaining the effects of exogenous administration of CCK is complicated because different peptide fragments predominate in different species, and the specificity of antibodies used in radioimmunoassay of CCK is obviously crucial in determining endogenous levels of the hormone. Interactions between CCK and other hormones (Le Sauter and Geary, 1987) and between CCK and mechanical gastric factors (Schwartz et al., 1991a) may also be important. It is also important whether the experimental animal is in the fasted or normally fed state when endogenous CCK is secreted (G.P. Smith et al., 1989).

Of relevance also is the precise relationship between afferent vagal terminals and secreted CCK. After intravenous administration of CCK in dogs, the systemic venous concentration required for a satiety effect is 10-fold higher than that normally observed after a meal (Reidelberger et al., 1989).

However, the systemic venous concentration may not be the relevant measure. The hormone could be secreted in a paracrine manner, with high local concentrations later reduced by hepatic uptake and dilutions within the systemic vascular system (Greenberg and Smith, 1988).

The specificity of the satiety effect of CCK has been questioned by critics who consider that induction of nausea is the principal means whereby CCK inhibits eating (Deutsch and Hardy, 1977; Moore and Deutsch, 1985; Morley et al., 1985; Miaskiewicz et al., 1989; Silver and Morley, 1990; Stricker and

Verbalis, 1990). The issue is complex because satiety and nausea are psychologically related and may possibly be on a continuum. Thus it may be that both the nausea and satiety actions of CCK reflect different degrees of activation of the same central pathway. Smith and Gibbs (1992) review the evidence very thoroughly, citing numerous instances in which slow continuous infusion of CCK inhibits food intake in doses that do not produce nausea in humans or markers of abdominal malaise in experimental animals.

Strong evidence that the satiety effect of exogenous CCK is more than a nonspecific nausea-producing action comes from the demonstration that CCK receptor antagonists actually increase food intake in their own right, thereby suggesting that endogenous CCK normally suppresses food intake. Early studies used proglumide, a relatively poor antagonist. As shown in Figure 7.11D, more potent CCK antagonists, particularly type A antagonists, independently increase food intake in various species including rhesus monkeys (Hewson et al., 1988; Weller et al., 1990; Asin et al., 1992; Miesner et al., 1992; Moran et al., 1992, 1993; Murphy et al., 1992; Weatherford et al., 1992). CCK_a antagonists may stimulate food intake independently of their action on abdominal vagal afferents (Reidelberger, 1992). When administered to humans these specific CCK_a antagonists cause increased hunger ratings (Wolkowitz, 1990), but no study has yet demonstrated increased food intake in humans in response to CCK receptor antagonists.

Binding studies have established an appropriate anatomical substrate whereby endogenous, peripherally released CCK could affect the central nervous system. The CCK_a receptor is synthesized by nodose ganglion cells and transported peripherally to subdiaphragmatic branches, as well as centrally to the nTS (Zarbin et al., 1981; Moran et al., 1987, 1990; Ladenheim et al., 1988; Hill et al., 1990; Lin and Miller, 1992). It may be that vagal afferents with CCK_a receptors project principally to the medial nTS, while afferents with type B receptors project to more lateral nTS regions (Corp et al., 1993). Efferent vagal axons do not transport CCK receptors (Moran et al., 1990). Some abdominal vagal afferents do project to the area postrema, but (probably) not those from the stomach (Leslie et al., 1982; Shapiro and Miselis, 1985b). This may account for the failure of vagotomy to affect CCK binding in the area postrema. CCK receptors are also synthesized by certain CNS neurons (Hill et al., 1990), and it is therefore not known whether human nTS CCK receptors (Giampaolo et al., 1989) are in central processes of nodose ganglion cells.

The weight of evidence thus indicates that endogenously secreted CCK is a physiological satiety factor, affecting the CNS via a primary action on the peripheral processes of abdominal vagal afferents. As already mentioned, this demonstration is most important in its own right and also because the mode of action may prove a model for the manner in which other peripheral agents might affect neuronal function in the CNS.

Nausea, Vomiting, and Conditioned Taste Aversions

When nausea and vomiting follow ingestion of toxic agents it is easy to appreciate the adaptive nature of the response. Nausea and vomiting can occur in humans as a "cephalic phase" response to perception of repugnant odors or traumatic sights such as bodily mutilation. Motion-induced emesis is less easy to place in a physiological context. Nausea, one of the most unpleasant sensations, can be

studied only in humans. However, retching, vomiting, and profuse salivation, frequent accompaniments of nausea in human, have been studied in cats, dogs, ferrets, house musk shrews, and nonhuman primates. Neither rats nor rabbits vomit. Since spontaneous vomiting rarely occurs, emetic agents such as intravenous apomorphine (a dopamine receptor agonist), intragastric copper sulfate, lithium chloride, anticancer agents, and total body irradiation are used to induce vomiting in experimental studies.

Toxin detection in the stomach initiates exceedingly complex visceral and somatic responses (Lang, 1990). The proximal stomach relaxes, and there is reverse peristalsis in the small intestine. Pulse and breathing rates increase, and sweating and salivation occur. Neurohypophyseal hormones are secreted, and the subject may become drowsy. A characteristic bodily posture is adopted. Retching involves facial, laryngeal, tongue, pharyngeal, cervical, intercostal, and abdominal muscles. A coordinated retrograde gastric contraction expels the stomach contents. There may be associated diarrhea.

This constellation of behavioral, gastrointestinal, respiratory, somatic, cardiovascular, and neuroendocrine responses is coordinated by the central nervous system. Many somatic motor and visceral premotor nuclei are involved in the various components of the response, and each of these normally participates in functions unrelated to vomiting. Thus, activation of abdominal muscles during vomiting occurs via the caudal ventral medullary expiratory neurons normally involved in respiration (Miller and Nonaka, 1990b). What is distinctive about vomiting is the sequential activation of the various components, suggesting that the control of vomiting might be understood not in terms of a specific emetic center, but in terms of a "pattern generator" (Carpenter, 1990), as has been suggested for complex behaviors such as walking or swimming (Grillner et al., 1995).

Early searches for a CNS emetic center in experimental animals used the traditional electrical stimulation and ablation procedures. Understandably, given the complexity of the vomiting response, the search for electrophysiological correlates did not contribute greatly to the unravelling of the relevant central pathways. Surprisingly, it has not been easy to induce vomiting in anesthetized animals by stimulation of any brainstem, hypothalamic, or forebrain region. Wang and Borison (1950) explored the lower brainstem in the unanesthetized decerebrate cat and demonstrated that vomiting could be elicited by electrical stimulation in the dorsolateral medulla, rostral to the obex. The region was extensive, and the complementary ablation experiments in the dog were necessarily heroic. The stimulation studies have not been confirmed (Miller and Wilson, 1983; Miller et al., 1994), and little of permanent benefit was established in these experiments. Reflex vomiting still occurs in decerebrate, chronically maintained cats and dogs (Siegel et al., 1986; Koga and Fukuda, 1992).

Attention has remained focused on the emetic role of the brainstem, especially the nTS since vagal afferents terminate there and in the nearby area postrema. In 1889, Openchowski established that the emetic action of intragastric copper sulfate depends on the integrity of the abdominal vagus, an observation appreciated by Cajal (1909), confirmed early this century by Miller (1910), and demonstrated for other emetic agents including whole body irradiation, cytotoxic drugs, and bacterial enterotoxins. In 1891, Thumas demonstrated that the vomiting response to apomorphine in the dog

depends on the integrity of midline structures in the region of the obex, presumably reflecting the importance of the area postrema and the nTS (Wang and Borison, 1950). Subsequent studies, especially those by Borison and his colleagues, established the area postrema as a "chemoreceptive trigger zone" critical for the occurrence of vomiting induced by apomorphine. Useful reviews of the area postrema have been written by Borison (1989) and by Miller and Leslie (1994). The role of abdominal vagal afferents in the emetic action of these agents and the production of emesis by electrical stimulation of these afferents are discussed by Andrews and colleagues (1990). Foerster observed that electrical stimulation of the vagus under local anesthesia produces nausea and vomiting in humans (see Alvarez, 1948), although more recent studies using cervical vagal stimulation as a treatment for epilepsy have not verified this (Landy et al., 1993; Uthman et al., 1993).

Area postrema lesions prevent the emetic actions of apomorphine whether it is administered systemically or into the cerebral ventricles (Share et al., 1965). Similarly, the emetic actions of the cardiac glycosides and the opioids, agents that readily cross the blood-brain barrier, also depend on the integrity of either the area postrema or the abdominal vagus (Gaitonde et al., 1965; Share et al., 1965; Borison, 1989). The nausea and vomiting produced when L-dopa is first administered to patients with Parkinson's disease can be reduced by including a peripherally acting dopa-decarboxylase inhibitor with the preparation. This indicates that when L-dopa crosses into the brain and is converted into dopamine it does not cause nausea or vomiting by a central action. Ablation of the area postrema prevents L-dopa emesis in animals (Bieger et al., 1978). Metaclopramide, a peripherally acting dopamine antagonist, is an effective anti-nausea agent in humans. In experimental animals, lesions of the area postrema do not prevent motion sickness (Kohl and MacDonald, 1991). Borison (1989) emphasized that the central emetic control system has proven peculiarly difficult to excite by direct intracerebral application of chemical agents or by focal electrical stimulation of the brain in experimental animals. Similarly in humans, nausea and vomiting are rare symptoms of epileptic discharge; nor are they common with focal cerebral electrical stimulation of forebrain regions (Penfield and Boldrey, 1937). In the animal studies, the result is somewhat puzzling in view of the importance of labyrinthine and vestibular factors in producing nausea and vomiting. One might imagine that stimulation of the central connections of these organs would also cause emesis.

Nausea and vomiting are very common in conditions associated with ischemia or infarction of the medulla, pons, or cerebellum. When the cerebral hemispheres are damaged (as in tumor, abscess, or hemorrhage) the associated vomiting probably reflects brain swelling, with secondary pressure on brainstem structures. Raised intracranial pressure commonly causes vomiting, especially when the posterior fossa is affected. Migraine and cluster headache are also notable for the associated nausea and vomiting. Whether all these conditions somehow affect the area postrema is currently unknown. Clinical examples of vomiting caused by tumors and other conditions affecting the area postrema in humans are discussed in Chapter 8 (see Fig. 8.9 for MRI).

Presumably the efferent projections of area postrema neurons should provide clues as to the central pathways mediating the emetic response, but so far anatomical studies have not specifically focused on this question. The area postrema may also be involved in nausea and vomiting induced by vagal afferents. Activation of gastric vagal afferents excites neurons in the area postrema (Yuan and Barber,

1993). Fos immunohistochemical studies suggest that abdominal vagal afferent impulses reach the nTS, especially the subnucleus gelatinous just below the area postrema, the area postrema itself and the ventrolateral medulla (Reynolds et al., 1991; Gieroba and Blessing, 1994b; Boissonade et al., 1994). Fos studies in cats after administration of emetic agents acting at the area postrema and via afferent vagal pathways demonstrate activation of neurons in similar medullary regions (Miller and Ruggiero, 1994). Motoneurons mediating the somatic act of vomiting include those in the nucleus ambiguus. Nearby neurons have discharge characteristics consistent with their function as an emetic pattern generator, possibly activated by vagally driven nTS neurons (Koga and Fukuda, 1992; Fukuda and Koga, 1992).

Conditioned taste aversions

Animals surviving after ingestion of toxins that cause vomiting or abdominal malaise acquire avoidance responses in a remarkably efficient manner, even though several hours may have elapsed between ingestion and illness. This "bait shyness" occurs only with poisons that cause malaise, not with those, such as the poison used to kill rats, that gradually deplete clotting factors and cause death by hemorrhage.

Garcia and colleagues (1955, 1968, 1974) studied the conditions under which bait shyness occurs. A single ingestion of a particularly flavored substance together with a toxin, or together with an illness-inducing dose of radiation, caused the animal to avoid the substance, even though it might previously have been a preferred food. In contrast, even after many trials, rats did not learn to avoid a particular place in which the radiation or the toxin was administered. Acquisition of these "conditioned taste aversions" is extremely robust, probably representing a genetically favored form of learning, with obvious survival value. Garcia and Ervin (1968) summarize the situation as follows:

The rat acts as if it has a hypothesis "it might have been something I ate which made me ill." Humans behave in the same way in spite of their elegant cortical development. When they become seasick they may "intellectually know" that the rocking motion of the boat has made them ill, but they "intuitively feel" that if they had not eaten that particular food before sailing or if the boat had not smelled of paint and fuel oil they would not have been so ill. For a long time afterward, these tastes and smells may elicit a feeling of nausea as if true stimulus substitution had occurred. Rarely, if ever, do they complain of such malaise when looking at a boat. On the contrary they may hang seascapes on their walls and intellectually long for the sea.

Accounts of the occurrence of conditioned taste aversions in humans have been presented by Garb and Stunkard (1974) and by Bernstein (1978).

The acquisition of taste aversions in association with agents that cause nausea and vomiting suggests that the vagus nerve or the area postrema may be involved. Sub-diaphragmatic vagotomy was found to disrupt a taste aversion conditioned with intragastric copper sulfate, with much less effect when this agent was administered intravenously (Coil et al., 1978). Lesions of the area postrema also

prevent conditioning of taste aversions to agents whose emetic action is dependent on the area postrema, but not to D-amphetamine, which suppresses food intake centrally without causing nausea or vomiting (Harris et al., 1947; Berger et al., 1973; Ritter et al., 1980; Rabin et al., 1983; Bernstein et al., 1992).

Neurons in the nTS, and possibly in the area postrema, are presumably necessary to detect the malaise-inducing agents that function as the unconditioned stimulus in the acquisition of the taste aversion. In rabbits, the robust conditioned taste aversion established by the contingent pairing of sucrose-water with intraperitoneal cisplatin depends more on abdominal vagal afferents than on the area postrema (Messenger and Blessing, 1994). Electrophysiological studies in rats have identified area postrema neurons that discharge in response both to excessive gastric distention and to local application of lithium chloride or apomorphine (Tsukamoto and Adachi, 1994). When saccharine is given to animals made sick with intraperitoneal lithium chloride, there is an increase in the discharge of nTS neurons in response to the conditioned stimulus, a hypersensitivity possibly relevant to the subsequent avoidance of saccharine (Chang and Scott, 1984).

When sucrose is contingently paired with lithium chloride so as to establish a conditioned taste aversion, subsequent exposure to sucrose results in appearance of fos in neurons within the nTS in regions just rostral to the obex (Haupt et al., 1994; Swank et al., 1995), but not in more caudal and more rostral nTS regions that contain fos-positive cells after exposure to the unconditioned stimulus (amphetamine lithium chloride). Possibly the fos-containing cells in the intermediate nTS have a role in integrating more rostral gustatory and more caudal visceral inputs to the nTS. Alternatively, it might be that exposure to the conditioned stimulus causes some cardiovascular or visceral response that secondarily activates neurons in the intermediate region of the nTS.

Central pathways beyond the nTS must be involved in the expression of taste aversions. As documented earlier in this chapter, neural circuitry sufficient for basic discriminative responses to gustatory stimuli is present in the lower brainstem in rats. However, decerebrate rats can neither acquire nor retain a conditioned taste aversion (Grill and Norgren, 1978a). Regions rostral to the midbrain are therefore essential for the integration of taste and visceral cues and for the establishment of the aversion. The relevant circuitry is not yet established; some ascending information is likely to be relayed via the parabrachial nucleus; the amygdala may be important (Bermudez-Rattoni et al., 1986; Yamamoto and Fujimoto, 1991; Hatfield et al., 1992; Kesner et al., 1992; Yamamoto et al., 1995).

Vasopressin and oxytocin secretion during nausea and vomiting

Nausea and vomiting are frequently associated with secretion of neurohypophyseal hormones, a relationship first noted for vasopressin in dogs treated with intragastric copper sulfate or subcutaneous morphine (Andersson and Larsson, 1954). Similar stimuli, including lithium chloride, also cause secretion of vasopressin in monkeys (Verbalis et al., 1987) and oxytocin in rats (Verbalis et al., 1986b). Plasma vasopressin increases in humans made nauseous by intravenous ethanol, by subcutaneous apomorphine, by water loading, and by illusory self motion, but not by ingestion of ipecacuana (Coutinho, 1969; Eversman et al., 1978; Rowe et al., 1979; Nussey et al., 1988; Koch et

al., 1990). In humans both nausea and secretion of vasopressin in response to subcutaneous morphine are prevented by pretreatment with haloperidol, a dopamine antagonist (Rowe et al., 1979). The neurohypophyseal hormones almost certainly do not cause nausea and vomiting. Their secretion may have adaptive physiological effects, such as decreased absorption of toxin following vasoconstriction of upper gastrointestinal blood vessels in response to increased circulating levels of vasopressin.

In both monkeys and humans systemic bolus administration of CCK may cause nausea, vomiting, and secretion of vasopressin, which in humans is proportional to the degree of nausea produced (Verbalis et al., 1987; Miaskiewicz et al., 1989). In ferrets, stimulation of the abdominal vagus causes vomiting as well as secretion of vasopressin (Hawthorn et al., 1988). Some of the experimental findings are illustrated in Figure 7.13.

Figure 7.13 **A**, Effect of emetic agents on vasopressin secretion in the dog. (Modified from Andersson and Larsson, 1954.) **B**, Plasma vasopressin after administration of apomorphine in human subjects. (Modified from Rowe et al., 1979.) **C**, Plasma vasopressin after electrical stimulation of the afferent abdominal vagus nerve in anesthetized ferrets. (Modified from Hawthorn et al., 1988.)

The afferent abdominal vagus and the area postrema function as windows through which malaise-inducing stimuli interact with central neural pathways regulating the neurohypophysis. Electrical stimulation of the afferent abdominal vagus promptly causes emesis together with secretion of vasopressin in the ferret and vasopressin secretion without emesis in the rabbit (Hawthorn et al., 1988; Gieroba and Blessing, 1994a). Rabbits do not vomit, but development of abdominal malaise in this species is suggested by their robust conditioned taste aversions to anticancer agents, such as cisplatin, which cause vigorous vomiting and increased vasopressin secretion in humans (Fisher et al., 1982; Messenger and Blessing, 1994). Similarly, although rats do not vomit, the malaise-inducing action of agents that cause secretion of oxytocin can be inferred by their parallel ability to produce conditioned taste aversions in this species (Verbalis et al., 1986a,b). In rats, oxytocin secretion may be triggered by normal feeding as well as by CCK, suggesting that neurohypophyseal activation may reflect both satiety and nausea-producing actions of this hormone (Verbalis et al., 1986a). Pathways mediating the neurohypophyseal responses to CCK include the afferent vagus, the nTS, and the paraventricular and supraoptic nuclei (Verbalis et al., 1986a,b; Nink et al., 1991). Conditioned taste aversions may themselves depend on a vagal action of the malaise-inducing unconditioned stimulus (Coil et al., 1978; Martin et al., 1978; Messenger and Blessing, 1994), and it may be that the same afferent input to the nTS mediates the conditioned taste aversion, the nausea and vomiting, and the secretion of neurohypophyseal hormones. The A1 noradrenaline neurons in the caudal ventrolateral medulla may be involved in CCK-induced secretion of neurohypophyseal hormones in the rat (Blackburn and Leng, 1990; Luckman, 1992) and in the hormonal response to abdominal vagal stimulation in the rabbit (Gieroba and Blessing, 1993, 1994a). Direct nTS-hypothalamic pathways may also be important in secretion of oxytocin in the rat (Day and

Sibbald, 1988a; Raby and Renaud, 1989a). Discharge of oxytocin neurons, but not vasopressin neurons, in the rat magnocellular nuclei is affected by peripheral CCK and by gastric distension (Renaud et al., 1987).

As Verbalis and colleagues (1986a) suggest, it appears that elevated levels of neurohypophyseal hormones are a marker of disinclination to eat, with higher levels indicating the presence of malaise rather than satiety. In rats, peak oxytocin levels occur when the animal stops eating. However, oxytocin does not, of itself, have a satiety action, nor does it cause learned taste aversions (Verbalis et al., 1986a,b; McCann et al., 1989c). Presumably, secretion of oxytocin or vasopressin in response to peripheral malaise and satiety-inducing stimuli has some physiological role. Both hormones are secreted in amounts that cause vigorous contraction of smooth muscle. There could be effects on gastrointestinal motility and blood flow, thereby decreasing toxin absorption.

Presence of 5-HT₃ receptors on gastrointestinal vagal afferents and their role in vomiting

Systemic administration of 5-HT has many physiological consequences, including production of nausea and vomiting, an effect now recognized to be due to stimulation of 5-HT₃ receptors (Torii et al., 1991). Many of the gastrointestinal effects of phenyl-biguanide occur because this agent is a relatively selective 5-HT₃ receptor agonist (Miller and Nonaka, 1992). The ferret has been used as an animal model for studying the relationship between 5-HT and emesis, especially in relation to the effects of anticancer chemotherapeutic agents such as cisplatin. The work of Andrews and colleagues (1990) is especially important. The emetogenic action of the anticancer agent cisplatin depends on the release of 5-HT from entero-chromaffin cells in the mucosal villi of the upper intestine (Schwörer et al., 1991). Other chemotherapeutic agents, and radiation, presumably also release this agent. The 5-HT then stimulates 5-HT₃ receptors on the distal terminals of afferent vagal fibers (Andrews et al., 1990; Miller and Nonaka, 1992; Kamato et al., 1993). Injection of 5-HT into the celiac arterial trunk of anesthetized ferrets causes vagal afferents to discharge, an effect prevented by 5-HT₃ receptor antagonists (Blackshaw and Grundy, 1993). Arterial injections of 5-HT also altered the discharge rate of single-fiber vagal efferents, with the effect once again prevented by 5-HT₃ receptor antagonists (Blackshaw, 1994). The same study found that gastric or esophageal distention also affected the discharge of many vagal efferent fibers, but this effect was not prevented by 5-HT₃ receptor antagonists, suggesting that the afferents sensitive to 5-HT are mucosal receptors rather than mechanoreceptors.

The emetic effect of both cisplatin and 5-HT agents is substantially reduced by vagotomy and by 5-HT₃ receptor antagonists, but not by hexamethonium or atropine (Torii et al., 1991; Fukui et al., 1993; Kamato et al., 1993; Rudd and Naylor, 1994). Interestingly, no studies have so far determined whether stimulation of 5-HT₃ receptors on vagal afferents also causes neurohypophyseal secretion. The introduction of 5-HT₃ receptor antagonists has reduced the incidence of nausea and vomiting consequent upon anticancer chemotherapy or whole body radiation in humans (Cubeddu et al., 1990; Grunberg and Hesketh, 1993).

Relationship between CCK and 5-HT

Both 5-HT and CCK can cause nausea and vomiting by activating receptors on the peripheral ends of gastrointestinal vagal afferents. Particular investigators have studied either CCK or 5-HT, and so far there are few studies of the interaction of these compounds. The satiating action of CCK may involve an interaction with 5-HT₁ but not 5-HT₃ receptors (Poeschla et al., 1993). In pigs, CCK-induced secretion of vasopressin and inhibition of feeding is not blocked by 5-HT₃ receptor antagonists (Parrott et al., 1992). Injection of CCK into the gastric artery discharges vagal afferents in ferrets, and this response is blocked by 5-HT₃ receptor antagonists (Blackshaw and Grundy, 1993). A summary diagram illustrating the role of CCK, 5-HT, vagal afferents, and the area postrema in secretion of vasopressin and oxytocin is shown in Figure 7.14.

Figure 7.14 Pathways for secretion of neurohypophyseal hormones in response to gastrointestinal stimuli, including 5-HT and CCK. The A1 and A2 groups of catecholamine neurons are indicated. Abbreviations listed on pages xiii-xiv.

Mechanism of action of traditional anti-emetic agents

This subject has been reviewed by Leslie and colleagues (1990). What is remarkable is the paucity of evidence for a primary brain action of any anti-emetic agent and the general lack of information concerning the mechanism of action of most anti-emetics.

Antihistamines and dopamine antagonists probably work by blocking receptors on area postrema neurons, outside the blood-brain barrier. Muscarinic cholinergic agents also probably act peripherally, possibly on labyrinthine end organs. These agents could also block the effect of efferent vagal impulses, thereby interfering with some event that secondarily stimulates vagal afferents. Such a mechanism suggests that 5-HT₃ antagonists could be effective in motion sickness. Further studies are required concerning this maker.

Regulation of Metabolism, Temperature, and Body Weight: Interactions with Vasomotor Activity

Ingested food is digested, absorbed, and stored as glycogen or as adipose tissue before being metabolized, either aerobically or anaerobically, to produce the adenosine triphosphate (ATP) required for bodily function. The ATP is expended in both internal (maintaining cellular function) and external (somatic movements) work. Heat is produced according to the efficiency of the chemical reactions involved and the amount of work performed. Conservation or dissipation of this heat is achieved largely via sympathetic and parasympathetic vasomotor mechanisms so that core body temperature (especially brain temperature) remains close to a set point. Thus vasomotor-regulatory neural circuitry in the hypothalamus and lower brainstem could be linked to CNS pathways controlling the behavioral and metabolic interplay responsible for maintenance of body weight.

Figure 7.15 Possible metabolic and body temperature interrelationships that could involve sympathetic nerve activity in the regulation of body weight.

Much debate has centered on the existence and physiological importance of a so-called shunt pathway in mammals, especially in humans (Fig. 7.15), representing a potential means whereby body mass could be regulated independently of food intake or external work. Perhaps by altering the efficiency of metabolism or by selectively diverting carbohydrates or fats into the shunt pathway body mass could be reduced via increased heat production, with thermal stability maintained by increased heat loss. Alternatively, primary activation of heat loss mechanisms (via modulation of appropriate sympathetic and parasympathetic activity) could, by reducing body temperature, lead to secondary activation of heat-producing metabolic pathways, perhaps including shunt pathways, so that body weight is reduced to maintain body temperature. According to this manner of thinking, the weight conscious can "burn off fat."

Metabolic rate and body temperature do vary in relation to meals, partially because of the energy cost of chemically processing the meal, but also because of complex interactions between metabolism and ingestive behavior (Woods and Strubbe, 1994). When hyperthyroidism occurs, body weight decreases in spite of increased food intake. The mechanism is not fully established, but increased metabolic rate, with increased heat production and dissipation, suggests that "shunt" pathways can occur in humans. Hyperthyroidism usually reflects dysfunction of the thyroid gland or of the posterior pituitary, but occasional cases of excessive secretion of the relevant releasing factor from the median eminence emphasize the capacity of the brain to produce a hyperthyroid state. Increased CNS drive of thyroid secretion could also occur via the sympathetic innervation of the thyroid gland, possibly contributing to bodily adjustment to seasonal changes in ambient temperature. Similar sympathetically driven mechanisms presumably underlie seasonal changes in body fur density, although this is not well established.

This somewhat speculative discussion emphasizes the possibility of significant variability and flexibility in the relationship between food intake, metabolism, body mass, and autonomic nerve activity. Major metabolically mediated changes in body mass are prominent in certain small mammals, particularly rodents, in which energy is stored in brown adipose tissue, especially in the interscapular region. This tissue is densely innervated by sympathetic nerve fibers and is also responsive to β -adrenergic receptor stimulation. Exposure to cold activates sympathetic neural mechanisms, leading to selective metabolism of brown adipose tissue, with increased heat production and maintenance of body temperature. Thermogenesis, which follows food intake in rodents, is also partially mediated by metabolism of brown adipose tissue (Rothwell and Stock, 1979).

Whether such metabolically induced variation in body mass actually occurs in adult humans is not yet proven. Body mass, particularly adipose mass, is a carefully controlled variable. When actual mass deviates from the "set point" the individual compensates mainly by altering food intake and/or external work rather than by altering the efficiency of body metabolism (Leibel et al., 1995; Bennett, 1995). The high correlation between body mass in familial members presumably reflects similar genetic contributions to the regulation of food intake and metabolic rate (Bogardus et al., 1986). Obesity is common in humans and domestic animals, but uncommon in wild animals. This de-emphasizes the role of genetic factors. In the wild, however, opportunities for over-eating and under-exercising are

rare. This reflects competition from other animals, including predators, together with the occurrence of competing behaviors that interfere with immediate food intake. The squirrel gathers abundant nuts just before winter, but genetically determined behavioral programs ensure that most effort goes into storage rather than immediate ingestion.

Although there is no evidence that the brain directly monitors body mass, it could be that a circulating factor signals the amount of body fat, contributing to the regulation of food intake, a theory first advanced by Coleman (1973). Insulin has been postulated to be one such factor, and the newly discovered hormone leptin (see below) is also a candidate hormone for the regulation of food intake. As discussed earlier in this chapter, insulin is transported across the blood-brain barrier, binding to specific receptors in certain brain areas. Activation of insulin receptors in the hypothalamus is thought to inhibit food intake and to increase sympathetic activity and heat production, with resultant loss of body mass, perhaps by somehow inhibiting the actions of neuropeptide Y (Schwartz et al., 1993c). Most attention has been paid to forebrain insulin receptors, but they are also present in the nTS and the area postrema.

Leptin and the brain

Discovery of an obesity coding gene in the mouse led to the identification of a circulating protein (produced by adipose tissue) that is absent in genetically obese mice (Zhang et al., 1994a). The protein has been named leptin, and its administration to obese mice causes loss of weight. In obese humans, plasma levels of the protein are high rather than low, suggesting that an end organ resistance to the normal action of leptin may be related to overeating and obesity (see references in Rohner-Jeanrenaud and Jeanrenaud, 1996). Receptors for leptin have been identified; in mice they are present in the choroid plexus, possibly as part of a system by which leptin is transported into the brain (Tartaglia et al., 1995). Future studies will no doubt localize receptors for leptin in various brain regions. One might predict that the initial search will focus on the hypothalamus. However, given the importance of the lower brainstem in various functions relating to metabolism and food intake, examination of the area postrema and the nTS may also prove rewarding.

Carbohydrate metabolism and vasomotor activity

As would be expected from clinical observations, hypoglycemia activates CNS pathways other than those regulating adrenaline secretion from the adrenal medulla. Hilsted and colleagues (1984) used intravenous insulin to induce hypoglycemia in healthy adult humans, documenting cardiovascular changes that commenced approximately 30 min after insulin administration. Arterial pressure increased. Cardiac output also increased due to increases in stroke volume and heart rate; total peripheral vascular resistance, including lower extremity vascular resistance, decreased. Hepato-splanchnic vascular resistance was unaffected. Plasma concentrations of both noradrenaline and adrenaline increased. Young and colleagues (1984) suggested that increased plasma catecholamines during hypoglycemia reflected increased adrenomedullary secretion, without activation of nonadrenal sympathetic nerves. However, hypoglycemia still increases plasma noradrenaline after adrenal medullectomy in rats (Levin and Sullivan, 1987), and muscle sympathetic activity, directly recorded,

does increase during hypoglycemia in humans (Fagius et al., 1986). The increase could reflect a direct drive from the central nervous system or a reflex baroreceptor effect, triggered by the decreased plasma volume that occurs in hypoglycemia. However, the latter alternative is unlikely, given the rise in arterial pressure usually observed during hypoglycemia.

Increases in plasma glucose, particularly those occurring when insulin levels are also elevated, have complex effects on cardiovascular parameters, mediated by effects on sympathetic vasomotor activity. In rats, moderate doses of glucose increase plasma norepinephrine without changing plasma epinephrine, indicative of increases in nonadrenal sympathetic activity (Levin and Sullivan, 1987; Levin, 1991). Simultaneous administration of both glucose and insulin increases arterial blood pressure and urinary norepinephrine in rats (Young and Landsberg, 1977b; Brands et al., 1991; Meehan et al., 1994), but not in dogs (Hall et al., 1992). Epidemiological evidence emphasizes the relationship between hyperinsulinemia (insulin resistance), obesity, and hypertension in humans (Slater, 1991; Troisi et al., 1991; Istfan et al., 1992; Julius et al., 1992; Landsberg, 1992). The hypertension could occur as a "by-product" of an insulin-mediated increase in sympathetic activity, which, in turn increases metabolic rate to restore energy balance (Landsberg, 1992). This hypothesis invokes the shunt pathway depicted in Figure 7.15. At present there is insufficient evidence to conclude that obesity-associated hypertension is mediated by this form of sympathetic activation. The hypothesis assumes that activation of "the sympathetic nervous system" is global rather than specifically patterned. Anderson and colleagues (1991, 1992) showed in both normotensive and borderline hypertensive humans that euglycemic insulin infusion increased muscle sympathetic nerve activity. However, forearm muscle blood flow actually increased, without a significant change in blood pressure. A muscle vasodilating effect for insulin, dependent on endothelial factors (presumably nitric oxide), has been proposed by Baron (1994).