Cell Metabolism
Review

Hindbrain Neurons as an Essential Hub in the Neuroanatomically Distributed Control of Energy Balance

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This Review highlights the processing and integration performed by hindbrain nuclei, focusing on the inputs received by nucleus tractus solitarius (NTS) neurons. These inputs include vagally mediated gastrointestinal satiation signals, blood-borne energy-related hormonal and nutrient signals, and descending neural signals from the forebrain. We propose that NTS (and hindbrain neurons, more broadly) integrate these multiple energy status signals and issue-output commands controlling the behavioral, autonomic, and endocrine responses that collectively govern energy balance. These hindbrain-mediated controls are neuroanatomically distributed; they involve endemic hindbrain neurons and circuits, hindbrain projections to peripheral circuits, and projections to and from midbrain and forebrain nuclei.

Introduction

The rapid and dramatic increase in obesity prevalence over the last three decades cannot be attributed to "metabolic need" alone. As a result, so-called "need-independent" controls of human eating behavior, such as the feeding triggered by the attraction of food (also known as food reward) or by conditioned, social, and temporal cues to eat are generating renewed attention as an explanation of the chronic hyperphagia that is the hallmark of the obesity "epidemic." At the same time, recent experiments show that the central nervous system (CNS) action of energy status signals such as leptin, ghrelin, glucagon-like peptide-1 (GLP-1), and peptide YY (PYY) affect food preference, the incentive value of food, and other cognitive controls of food intake (Batterham et al., 2007; Kanoski et al., 2011b; Kenny, 2011; Malik et al., 2008; Rosenbaum et al., 2008). These and other data support the view that the brain processes environmental and hedonic information that interacts with the neural processing of energy status signals to determine when we initiate feeding and how much we eat.

This Review addresses the location of the neurons and the neural circuits that comprise the energy balance control system. The Review also considers the anatomical path from input (e.g., energy status signal sensing) to output (response production) and discusses neuroanatomical models of energy balance control. A central theme is that hindbrain neurons make several key contributions to a neuroanatomically distributed energy balance control system—they (1) detect and integrate energy status signals, (2) receive input from neurons in the periphery and from other brain regions that also detect and integrate energy information, (3) project to other brain regions to provide information that is integrated by those neurons to control energy balance, and (4) control responses through their local hindbrain, rostral, and peripheral projections.

The sections that follow discuss contributions of hindbrain neurons to (1) input and integration of energy status signals, (2) output and response control, (3) the integration of descending information arising from forebrain neurons, and (4) the transmission of hindbrain-processed signals to midbrain and forebrain neurons.

I. Input: Hindbrain Neurons Receive and Integrate Energy Status Signals

Among the array of CNS nuclei that contribute to energy balance control, it is arguable that the nucleus of the solitary tract (NTS) receives and processes the greatest amount of neuronally mediated and circulating energy status signals (Figure 1A). This section discusses the NTS processing of energy status signals conveyed via (1) vagal afferent transmissions from the gastrointestinal (GI) tract, (2) blood-borne endocrine signals secreted from peripheral organs (i.e., adipose tissue, pancreas, GI tract), and (3) circulating nutrients (e.g., glucose). We take the perspective that the CNS control of energy balance involves coordinated, multisynaptic processing by anatomically distributed neurons. In this section we highlight accumulating evidence showing that integrated processing of this array of complimentary and antagonizing signals begins within the NTS.

Vagal Mediation of Gastrointestinal Satiation Signals

During meal ingestion, the GI tract senses the chemical, nutritive, osmotic, and volumetric properties of the ingested food via a complex communication system that involves interaction between enteroendocrine cells and vagal and spinal afferents. The proximal location of the stomach within the GI tract and its rich vagal afferent innervatation (Wang and Powley, 2000) provide an early monitoring system for the status of meal ingestion. These gastric intake inhibitory signals involve volumetric-mechanical distension of the organ and not the chemical/nutritive properties of the ingestate (Mathis et al., 1998; Phillips

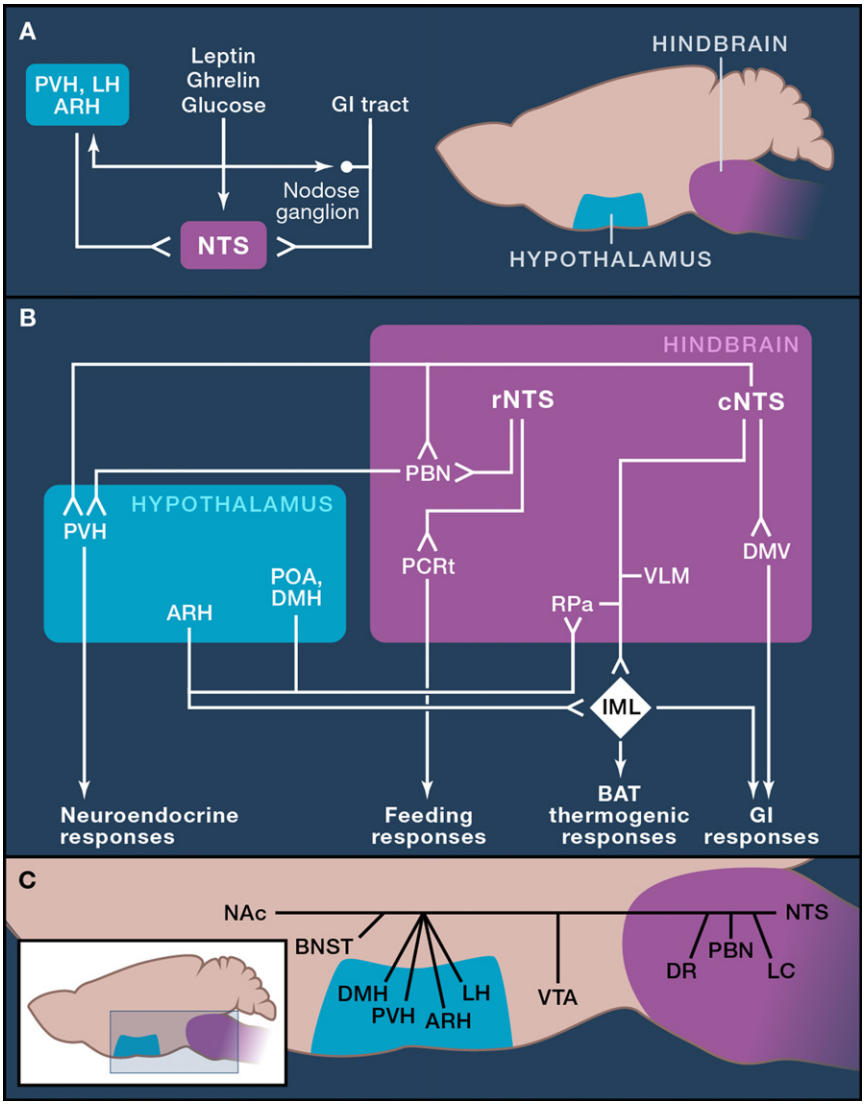

Figure 1. NTS Neurons Are Exquisitely Well Connected to Influence Energy Balance Control

(A) Afferent input to NTS neurons. The figure highlights input to medial NTS neurons from the following: (1) blood-borne energy-status signals such as leptin, ghrelin, and glucose; (2) the gastrointestinal tract (via the vagus nerve) that process sensory signals of gastrointestinal origin and respond to leptin and other energy-status signals; and (3) hypothalamic neurons (PVH, LH and ARH) that themselves are responsive to energy-status signals. For clarity, inputs to medial NTS neurons from other parts of the brain and inputs to neurons in other regions of the NTS that receive cranial nerve input of oral (gustatory) and thoracic origin are not included.

(B) Output from NTS neurons. NTS neurons from caudal regions (cNTS) project to vagal efferent neurons in DMV to control parasympathetic gastrointestinal responses including insulin secretion and gastric emptying, to the intermediolateral cell column of the spinal cord along with projections from neurons in other regions of the hindbrain (RPa, VLM, PBN) and hypothalamus (POA, DMH, ARH) to control sympathetic efferent responses of relevance to energy expenditure and gastrointestinal responses, and to PVH neurons to influence neuroendocrine responses. Neurons from rostral regions of NTS (rNTS) and PBN neurons project to the parvocellular reticular formation (PCRt) to control ingestive consummatory (licking, chewing, swallowing, rejection) response. For clarity, input to these response pathways from other brain regions, not highlighted in text, are not included.

(C) Rostral projections of NTS neurons. The labeled structures receive monosynaptic projections from neurons located in different regions of the NTS. For clarity, other projections of NTS neurons to sites within the hindbrain and to the periphery are not shown.

and Powley, 1996, Powley and Phillips, 2004; Seeley et al., 1995). The vagal sensory endings responsive to stretch and/or tension appear to include both intraganglionic laminar endings (IGLEs) and intramuscular arrays (IMAs) (for Review, see Ritter, 2004). Tension and stretch detection of the gastric wall by IGLEs and IMAs results in glutamatergic neuronal transmission from vagal axon projections to NTS neurons. However, serotonin (5-HT) secreted from gastric enterochromaffin (EC) cells provides the principal intake inhibitory secretion signal following volumetric distension. This satiating response following gastric distension-derived serotonergic excitation of the vagus is principally mediated by 5-HT type-3 receptors (5-HT3R) expressed on peripheral dendritic terminals of vagal afferents innervating the stomach (Glatzle et al., 2002; Hayes et al., 2004, 2006; Hayes and Covasa, 2006; Mazda et al., 2004). Thus, in addition to vagal-glutamatergic transmission to the NTS, gastric distension results in vagal axon serotonergic signaling to caudal NTS neurons (Berthoud et al., 2004; Ritter, 2004).

The chemical and nutritive properties of the ingested food stimulate the release of a number of gut peptides and neurotransmitters from the small intestine. A non-comprehensive list of the prominent intestinally derived *satiation signals* (i.e., intake inhibitory signal arising during the meal and influencing its course) includes cholecystokinin (CCK), 5-HT, PYY, glutamate, enterostatin, and GLP-1 (Chaudhri et al., 2006). While receptors for many of these satiation signals are expressed in the brain, under normal physiological conditions, the available circulating levels of these chemical signals appear to not be elevated in sufficient quantity to have direct action within the brain. Instead, the majority of GI-derived satiation signaling is communicated to the brain via a paracrine-like activation of specific receptors expressed on the dendritic terminals of vagal afferent neurons whose cell bodies are found in the *nodose ganglion* (Hayes et al., 2010a; Moran, 2006; Ritter, 2004; Smith, 1996). Support for vagal afferent mediation of many GI-derived satiation signals comes from studies that chemically or surgically lesion the vagus, revealing that in the absence of vagal afferent transmission the intake inhibitory response to peripherally administered satiation signals is blocked or reduced (e.g., CCK, GLP-1, gastric distension,

PYY) (Kanoski et al., 2011a; Mazda et al., 2004; Neary et al., 2005; Smith et al., 1985).

Vagal processing and integration: Given that many gut peptides signal for a reduction in feeding, a fundamentally simple question with a complex answer is, how does the brain distinguish its response to one vagally mediated gut peptide (e.g., GLP-1) from another (e.g., CCK)? While a multitude of possible explanations exist by which the vagus and brain partition and simultaneously integrate an array of anorectic signals, the solution likely involves a combination of the following hypotheses: (1) selective branches of vagal afferents are more or less responsive to different neuropeptides as a result of varying receptor expression patterns along the GI tract and supporting organs; (2) the type of vagal afferents activated (i.e, myelinated [type-A] and/or unmyelinated [type-C]) produces a unique transmission pattern to the NTS (Ritter, 2004); (3) the specific vagal neurotransmitter(s) (i.e., 5-HT and/or glutamate) engaged by specific gut peptides may differentially encode signals to the NTS; and (4) the intensity, frequency, and duration of neuronal excitation by each gut peptide on the vagus is also likely different for each hormone.

An important example of vagal integration of satiation signals is that of CCK and gastric distension. Schwartz and Moran (Schwartz et al., 1993; Schwartz and Moran, 1996) show that single vagal afferent fibers are responsive to both CCK and gastric distension, and when these two GI satiation signals are applied in combination the firing rate and total spike number increase in a dose- and volume-dependent fashion. Indeed, this vagal integration is postulated to contribute to the enhanced behavioral suppression of food intake when CCK and gastric distension are combined (Moran et al., 2001; Ritter, 2004; Schwartz and Moran, 1996). Under normal physiological conditions, activation of CCK-1 receptors suppresses gastric emptying, thereby temporally enhancing gastric distension (Bozkurt et al., 1999; Moran and McHugh, 1982; Schwartz et al., 1991). Importantly, however, CCK-1 receptors do not mediate gastric-distension-induced neuronal signaling (van de Wall et al., 2005; Yoshida-Yoneda et al., 1996). Therefore, the vagal interactions between CCK and gastric distension likely involve participation of *other* GI-derived satiating signals, such as 5-HT, which is both released in response to gastric distension (Mazda et al., 2004) and interacts with CCK to reduce food intake (Hayes and Covasa, 2005). Indeed, blockade of 5-HT3R attenuates suppression of food intake by CCK (Daughters et al., 2001; Hayes et al., 2004), intraduodenal nutrients (Burton-Freeman et al., 1999; Savastano et al., 2005), and gastric distension (Hayes et al., 2006; Hayes and Covasa, 2006). The interaction and processing of the intake inhibitory signaling of CCK and gastric distension by the vagus nerve is but one example of many interactions that occur between various GI-derived satiation signals.

Integrations performed by vagal afferent neurons are not limited to those involving GI-derived satiation signals but also include the processing of circulating signals of energy availability (i.e., leptin). Given that gastric chief cells and some mucosal cells secrete leptin in response to nutrient ingestion (Bado et al., 1998), and that leptin receptors (LepRb) are expressed on cell bodies of vagal afferent neurons in the *nodose ganglion* (Burdyga et al., 2002; Buyse et al., 2001), experiments by Peters and colleagues examined the hypotheses that gastric leptin acts as a satiation signal by activating LepRb-expressing terminals of vagal afferent neurons in a paracrine-like fashion (Peters et al., 2005a) and that the vagus integrates leptin's anorectic signal with other vagally mediated satiation signals (e.g., CCK) (Peters et al., 2005b). When combined, IP CCK and intraceliac infusion of low doses of leptin (resulting in GI-specific elevations in leptin) interact to suppress food intake and augment neural activity in nodose neurons. Therefore, it is worth examining whether this type of enhanced nodose electrophysiological response can result in enhanced NTS signaling and subsequently augmented food intake suppression.

Blood-borne Energy Status Signals

Leptin receptor: LepRb are expressed in three caudal brainstem nuclei: the parabrachial nucleus, the area postrema (AP), and the NTS (Patterson et al., 2011; Scott et al., 2009). The functional effects of leptin signaling in the parabrachial nucleus are not well investigated. Direct injection of leptin to the AP parenchyma in rats failed to reveal functional effects of AP leptin signaling (Kanoski et al., 2012; see also Patterson et al., 2011). By contrast, a variety of evidence shows that NTS leptin signaling is an important contributor to energy balance control. Parenchymal NTS leptin injection reduces food intake and body weight (Grill et al., 2002; Kanoski et al., 2012). NTS LepRb positive neurons are among a variety of neurons labeled by the transynaptic effects of pseudorabies viral injection of BAT, indicating their potential role in thermogenic control (Zhang et al., 2011). In fact, low doses of leptin injected into the caudal fourth ventricle, whose effect is confined to the dorsal hindbrain (Hayes et al., 2009b), elevates core temperature and heart rate (Skibicka and Grill, 2009a). When medial NTS LepRb expression is reduced by 40% through virally mediated RNAi LepRb knockdown (KD), rats are hyperphagic (on chow as well as palatable diets), obese, and do not respond to the intake inhibitory effect of CCK (Hayes et al., 2010b; see also complementary behavioral pharmacology data in Huo et al. [2007] and Kanoski et al. [2012]) and electrophysiologic data indicate that mNTS neurons are depolarized by both leptin and vagal GI afferent input (Hisadome et al., 2010). Collectively, these findings support the hypothesis that endogenous NTS leptin signaling is necessary for body-weight control through its effects on food intake and that hindbrain leptin signaling results in intake inhibition via a process that amplifies the intake inhibitory effect of GI satiation signals.

Hindbrain glucose sensors: Neurophysiologic, behavioral, and neuroendocrine data support the idea first proposed by Mayer (Mayer, 1953) that variations in plasma glucose (or correlates of CNS energy availability) alter the neural excitability of specialized neurons that participate in the neural control of energy balance. Glucose-sensitive neurons are found in hindbrain and hypothalamus and—as discussed below—these neurons, through connections to effector circuits, play a critical role in regulating glucose and energy homeostasis by controlling endocrine pancreas secretions, hepatic glucose production, feeding behavior, and energy expenditure. The mechanisms mediating the detection of glycemic changes (and/or the consequences of cytoglucopenia) that are coupled to alterations in the excitability of these glucose-sensitive neurons are still under investigation (Thorens, 2010). It is already clear, however, that this

glucose-sensing process in CNS neurons avails of some of the same proteins that contribute to glucose sensing in pancreatic β cells.

A variety of studies have evaluated the role of the low-affinity glucose transporter type 2 (GLUT2), glucokinase, and the K_{ATP} channel subunit SUR1, SUR2, and Kir6.2 in central glucose sensing (see reviews Jordan et al., 2010; Levin, 2006; Marty et al., 2007). GLUT2 KO mice are hyperphagic and fail to increase or decrease feeding in response to intracerebroventricular (icv) 2-deoxyglucose or glucose, respectively (Bady et al., 2006). Examination of fluorescent reporter genes that label GLUT2-expressing cells reveals a high concentration of hindbrain neurons with this genotype in the NTS, dorsal motor nucleus of the vagus nerve (DMV) and ventrolateral medulla (VLM) (Arluison et al., 2004; Mounien et al., 2010). Astrocytes in the DVC also express GLUT2 (Marty et al., 2005), and glial activation of neurons may play a role in this system, as glial-to-neuron communication/activation has been documented for other functions involving NTS neurons (Hermann et al., 2009; McDougal et al., 2011). These GLUT2-expressing hindbrain neurons are coextensive with the location of hindbrain neurons that are (1) neurophysiologically responsive to changes in plasma glucose or to local glucose levels (Dallaporta et al., 1999; Mizuno and Oomura, 1984; Yettefti et al., 1997), and (2) part of a circuit that drives counterregulatory responses to control glucose homeostasis (Ritter et al., 2000, 2011). Hindbrain neuron involvement in counterregulation response production is discussed below.

Ghrelin. Ghrelin, a gastric secreted peptide whose endogenous levels are inhibited by ingested food (Overduin et al., 2005), stimulates feeding by its action on the growth hormone secretogue receptor (GHSR). GHSR is broadly distributed in the CNS including expression in the NTS and other hindbrain neurons (Zigman et al., 2006). Direct NTS injection of low doses of ghrelin increases food intake (Faulconbridge et al., 2003). One mechanism that may contribute to NTS ghrelin-stimulated feeding involves attenuating the neural activity in NTS neurons driven by vagal afferent GI satiation signals. Indeed, the tyrosine hydroxylase (TH) expressing A2/C2 neurons in the mNTS that are activated by electrical stimulation of the solitary tract (visceral afferent stimulation) (Appleyard et al., 2007; Sumal et al., 1983) are inhibited by bath application of ghrelin (Cui et al., 2011).

Hindbrain integration and processing of vagal- and blood-borne energy-status signals. Complementing the processing and integration performed by the vagus nerve, the encoding, differentiation, and integration of the array of vagally or blood-borne energy-status signals also involves processing by NTS neurons. The following hypothesized mechanisms may explain distinct neuronal, behavioral, and physiological responses to gut peptides and/or circulating hormones and nutrients. These NTS-mediated processing-mechanisms would include, but are not limited to the (1) neuroanatomical pattern and percent of NTS neurons activated (see Peters et al. [2011] for example); (2) intensity, frequency, and duration of neuronal activation; (3) phenotype(s) of NTS neurons activated, and (4) vagally mediated neurotransmitter(s) that activates NTS neurons. Many of these mechanistic roles in NTS processing of energy-balance signals has been reviewed elsewhere (see Berthoud, 2004; Grill, 2010; Moran and Ladenheim, 2011; Powley, 2000; Rinaman, 2010; Ritter, 2004; Schwartz, 2010 for review). Here, we review select cellular signaling mechanisms that occur *within* individual NTS neurons in response to vagal and/or blood-borne energy-status signals that may account for integration of multiple energy-status signals. Below, we also review the role that descending projections from forebrain structures have on NTS-mediated processes for energy balance control.

Intracellular signaling pathways as a point of convergence for NTS-mediated anorectic signals: Recent evidence suggests that the intracellular signaling pathways within NTS neurons provide points of convergence and antagonism for various vagally mediated satiation signals and for blood-borne signals of energy availability. One mechanism hypothesized to account for interactions between different energy-status signals is that activation of separate receptors expressed on a given neuron could lead to an enhanced response via converging intracellular signaling pathways (Berthoud et al., 2006; Daniels et al., 2005; Hayes et al., 2011). It is also possible that activation of a single receptor expressed on a neuron may produce long-term changes in gene transcription and protein synthesis that could potentiate the intake inhibitory effects of other anorectic systems that also act upon the same neurons. Indeed, NTS mediation of the intake inhibitory responses of a number of anorectic signals (e.g., CCK, melanocortin, leptin, amylin, GLP-1) involves some of the same intracellular signaling pathways (e.g., PKA, MAPK, AMPK) (Boyle et al., 2011; Hayes et al., 2009b, 2010b, 2011; Sutton et al., 2004, 2005).

NTS integration of LepRb signaling and GI-derived satiation signals provides an instructive example. Neuropharmacological studies show hindbrain-delivered leptin amplifies the food intake-suppressive effect of gastric distention (Huo et al., 2007). Complementing these findings are results showing that mNTS/AP-targeted RNAi-mediated knockdown of LepRb (LepRb KD) abolished the potent food intake-suppressive effects of CCK (Hayes et al., 2010b) and reduced the intake suppression following intraduodenal nutrient infusion (Kanoski et al., 2012). Recent findings from our laboratory also show that the hyperphagia induced by mNTS/AP LepRb KD results primarily from an increase in meal size (Kanoski et al., 2012). This result is consistent with the explanation of the hyperphagia associated with global LepRb deficiency in rats (Koletsky [fa^k / fa^k]) (Castonguay et al., 1982; Morton et al., 2005) and leptin deficiency in mice (*ob*/*ob*) (Ho and Chin, 1988). In both cases the obese phenotype is driven by hyperphagia associated with increased meal size and not by increased meal frequency. Thus, the LepRb processing in the mNTS appears to be a critical mediator of this meal size-regulatory effect.

In addition to the required endogenous role of LepRb signaling in the mNTS to energy-balance regulation (Hayes et al., 2010b), GLP-1Rs expressed on NTS neurons are also critically involved in food intake regulation (Hayes et al., 2009a, 2011). Recent data, using various dose combinations of leptin and the GLP-1R agonist exendin-4, show that hindbrain GLP-1R and LepRb signaling interact in control of food intake and body weight in at least an additive fashion (Zhao et al., 2012). Moreover, blockade of hindbrain GLP-1R attenuated the intake inhibitory effects of hindbrain leptin. Together with previous reports (Hayes et al., 2009a, 2010b), these findings suggest that the interaction between hindbrain LepRb and GLP-1R signaling may be physiologically relevant for the normal control of food intake.

Common intracellular signaling pathways contribute to the intake suppression produced by CNS LepRb or GLP-1R activation, including the mitogen-activated protein kinase (MAPK) (Bjørbaek et al., 2001; Hayes et al., 2011) and AMPK (Gao et al., 2007; Hayes et al., 2009b, 2010b; Minokoshi et al., 2004). The role of reduced AMPK signaling in mediating the intake inhibitory response to mNTS LepRb signaling is established as a required pathway using conventional pharmacological activators (i.e., AICAR) and inhibitors (i.e., compound C) (Hayes et al., 2009b, 2010b), and also through selective mNTS LepR knockdown (Hayes et al., 2010b). Similarly, mNTS GLP-1R signaling potently suppresses food intake and does so in part through an AMPK-dependent pathway. That is, mNTS GLP-1R activation suppresses food intake via a coordinated PKA-dependent activation of the p44/42MAPK pathway and simultaneous inhibition of the AMPK pathway. It is hypothesized that the combined activation of common intracellular signaling pathways (e.g., AMPK), putatively within the same NTS neuron contributes to the aforementioned additive suppression of food intake by hindbrain leptin and GLP-1R signaling. Such an effect may also increase the sensitivity of NTS neurons to other satiation signals (e.g., amylin, CCK, and gastric distension) whose intake suppressive effect may also involve these same intracellular signaling pathways (see Berthoud et al., 2006; Grill, 2010; Hayes et al., 2010a; Potes and Lutz, 2010 for review).

II. Output: Hindbrain Neurons Are Critical Contributors to Response Control

The contribution of hindbrain neurons to many aspects of energy-balance response control is discussed in the following subsection. The source of the input engaging hindbrain output-related neurons differs for the various types of responses (See Figure 1B). For some responses, like gastric emptying control, incretin effects or taste-driven oral motor feeding responses, the response-driving input arises from cranial afferents such as vagal afferents or cranial nerve innervation of the taste receptor cells. For other responses, like brown fat thermogenesis, the inputs to hindbrain premotor neurons arise from many sources including but not limited to forebrain neurons and spinal thermoreceptors.

Feeding Behavior

Craig (1918) distinguishes between a contact or *consummatory* phase for feeding behavior that is preceded by a search or *appetitive* phase. Hindbrain neurons are central to the control of the *ingestive consummatory behaviors* that are driven by oral contact with food. Both the primary motor neurons that control movements of the tongue, jaw, pharynx, and facial muscles and the premotor neurons that constitute the central pattern generators for patterned rhythmic oral motor behaviors such as licking, chewing, swallowing, and food rejection are located in the hindbrain (see Blessing [1997] for details and illustrations). Work of Travers and colleagues identify neurons in the intermediate and parvocellular regions of the lateral medullary reticular formation (RF), subjacent to the rostral nucleus of the solitary tract (rNTS), as the site of the premotor neurons that govern the production of patterned ingestion and rejection responses and the transition between ingestion and rejection (Chen and Travers, 2003; Chen et al., 2001; Venugopal et al., 2010). This hindbrain substrate for premotor control of food ingestion and rejection response is the target of descending projections from hypothalamic and other forebrain nuclei whose neurons respond to energy status signals (Gutierrez et al., 2006; Sawchenko, 1998).

Input to the ingestive premotor neurons also arises from caudal brainstem (midbrain and hindbrain) neurons. The importance of caudal brainstem input to hindbrain ingestive premotor neurons is highlighted by procedures that eliminate all forebrain-caudal brainstem bidirectional communication. Such studies reveal that the taste-elicited, oral motor responses of chronically maintained *decerebrate* rats are comparable to those of intact brain control rats (Grill and Norgren, 1978; Kaplan and Grill, 1989). Additional support for the conclusion that caudal brainstem neural circuits are sufficient for the food contact-driven ingestive consummatory behavior comes from clinical data showing that taste-elicited ingestion and rejection responses of anencephalic human neonates (e.g., brains not developed beyond the midbrain) are identical to those of normal neonates (Steiner, 1973). While data from these special cases (decerebrate rats, anencephalic neonates) provide conclusive support for the sufficiency of caudal brainstem circuits in ingestive consummatory response control, they do not speak to a potentially powerful contribution of descending projections from forebrain neurons in the control of feeding behavior in normal animals (see section III, below). Defining which energy balance relevant forebrain neurons connect directly or indirectly to lateral medullary RF neurons or to other hindbrain neurons contributing to response control will be useful in this regard. A later section of the Review highlights functional links between hypothalamic (e.g., lateral hypothalamic [LH] and paraventricular hypothalamic [PVH]) axons and NTS neurons.

Nutrient Transit, Absorption, Partitioning, Storage, and Mobilization

Once ingested, food is transported from the mouth to the stomach and from the stomach to the intestine, the principal site of nutrient absorption. The premotor neurons that contribute to the control of nutrient partitioning, storage, and mobilization by modulating the rate of gastric emptying and influencing nutrient absorption are found in the DMV containing parasympathetic vagal efferent neurons, and also in aspects of the sympathetic nervous system (e.g., Ahrén, 2000). DMV neurons located in the dorsomedial medulla just ventral to the NTS provide vagal efferent output that controls gastric emptying rates, pancreatic and intestinal enzymatic secretions, and intestinal motility rates. Together, manipulation of these physiological responses influences the exposure of the chemical and nutritive properties of the ingested food to the enteroendocrine cells of the intestine affecting the pattern and magnitude of gastrointestinal and pancreatic hormone secretion (Berthoud, 2008; Reimann et al., 2008). Using ultrastructural analysis, Rinaman et al. (1989) described a monosynaptic gastric vago-vagal circuit that provides an anatomical substrate for the relay of gastric afferent information directly to gastric vagal motor neurons. Such *vago-vagal reflexes* consist of three components: sensory vagal afferents, second-order integrative neurons of the NTS, and efferent vagal neurons of the DMV. Travagli et al. (2003) describe CNS modulation of vago-vagal reflexes via hindbrain thyrotropin-releasing hormone input to the NTS. Abdominal GLP-1R-driven incretin and gastric emptying effects are mediated by the

paracrine action of released GLP-1 on vagal afferent neurons (Holst, 2007). NTS neurons process this information and relay it to a variety of CNS sites including hindbrain neurons that contribute to the food intake and gastric emptying effects of peripheral GLP-1R stimulation (Hayes et al., 2008). Vagal efferent stimulation of pancreatic islet cells results in insulin secretion and thereby provides another source of nutrient storage control (Ahrén, 2000). Many anatomically distributed CNS sites can directly modulate DMV-mediated parasympathetic output controlling for gastric emptying rates and pancreatic projecting signals modulating counterregulatory hormone secretions, e.g., (Jiang et al., 2003; Rinaman et al., 1989; Rogers et al., 1980; Zheng et al., 2005).

Taste and other cephalic sensory stimuli contribute to normal glucose tolerance via a neurally mediated, cephalic phase of insulin secretion that involves the vagal efferent input to the β cell (Ahrén, 2000; Siegel et al., 1980). Caudal brainstem neuronal projections to DMV neurons are sufficient to mediate taste-driven cephalic insulin secretion when descending forebrain projections are surgically eliminated (Flynn et al., 1986). A cephalic phase regulation of glucagon secretion has also been found in a variety of species (Teff and Engelman, 1996) and can be triggered by glucopenia (Havel and Taborsky, 1989) directed to the dorsomedial medulla in intact rats (Andrew et al., 2007). Identifying additional sources of forebrain input to the DMV neurons that provide CNS control of nutrient absorption, storage, and mobilization is necessary for a more complete picture of neural control of energy balance.

Glucose Homeostasis

Glucose is the primary energy substrate for CNS neurons. Claude Bernard's (Bernard, 1855) report of hyperglycemia induced by probing the medulla suggests that the CNS contributes to the control of blood glucose via stimulation of the sympathetic outflow (Feldberg et al., 1985), an idea that is still widely accepted today (Jordan et al., 2010; Marty et al., 2007). This section reviews findings that link hindbrain neurons to the control of sympathetic and behavioral responses that mediate hepatic glucose production and counterregulation. The related topic, the sensing of blood glucose itself or of correlates of cellular energy availability, was discussed in the section on hindbrain energy status signal processing above.

Counterregulation: Support for the conclusion that hindbrain neurons play an important role in engaging the sympathoadrenal, glucagon, and corticosterone elements of counterregulation comes from a variety of laboratories. Using the induction of cellular glucopenia via direct parenchymal application of glucose analogs (e.g., 5-thioglucose [5TG]), S. Ritter and colleagues show that it is the catecholaminergic (CA) neurons in the medulla that are key trigger zones for sympathoadrenal hyperglycemia, glucagon, and corticosterone secretion, and for food intake responses driven by glucopenia or hypoglycemia. Given the historical focus on hypothalamic energy sensing (e.g., Mayer, 1953), it is interesting to note that careful mapping of a broad range of hypothalamic nuclei with targeted glucopenia fails to trigger any counterregulatory responses other than corticosterone (Berthoud and Mogenson, 1977; Ritter et al., 2000; cf, Borg et al., 1995). Using immunohistochemical detection of systemically injected 2-deoxyglucose (2DG)-induced c-Fos activation colocalized with the enzymes TH and phenethanolamine-N-transferase as markers for adrenergic and noradrenergic neurons, respectively, the same group concludes that it is primarily adrenergic neurons located in C2 (NTS) and C3 cell groups of the dorsal medulla, as well as the A1/C1 neurons of the (VLM), that are the targets of activation by systemic glucopenia (Ritter et al., 1998). These neurons could be considered key elements in the CNS circuit controlling glucose homeostasis.

To identify the neurons receiving the axonal projections of these hindbrain CA neurons, these investigators utilized a toxin-antibody complex: saporin conjugated to dopamine beta hydroxylase (DSAP). Injection of DSAP into the PVH would presumably lesion those hindbrain CA neurons with PVH projecting axons, whereas DSAP injected into the interomediolateral cell column in the spinal cord would lesion hindbrain CA that, based on their spinal projection, could be considered sympathetic premotor neurons (Ritter et al., 2001, 2003, 2006). Two studies employing PVH DSAP injections conclude that PVH projecting hindbrain CA neurons are required for the glucopenia triggered feeding response (Hudson and Ritter, 2004; Ritter et al., 2001). Importantly, however, other data are inconsistent with this conclusion. Two studies show that cytoglucopenia (systemic 2DG) or hypoglycemia (systemic insulin) increases the intake of an orally infused diet, relative to a control treatment, in decerebrate rats whose forebrain projecting axons were surgically severed; intact control rats performed similarly (Darling and Ritter, 2009; Flynn and Grill, 1983). These results and other data suggest that (1) axons of individual hindbrain CA neurons implicated in the control of counterregulation project to multiple targets (e.g., Banihashemi and Rinaman, 2006) and (2) despite severing of forebrain projecting axons of such multitarget CA neurons (i.e., decerebration), their axon projections within the caudal brainstem sustain function (see Rinaman [2003] for discussion). These findings specify the intracaudal brainstem projection targets of hindbrain CA neurons as critical elements for feeding response controls. One potentially relevant intrahindbrain target of these glucopenia responsive hindbrain CA neuron are the medullary RF ingestive consummatory premotor neurons (Day et al., 1997). The contribution of hindbrain CA neurons to the neuroendocrine response aspects of counterregulation (e.g., corticosterone secretion) is discussed next.

Excitation of the HPA axis arises from distinct neuron populations including several in the hindbrain and amygdala (Herman and Cullinan, 1997). Notable among these are hindbrain CA neurons in A2/C2 (NTS) and A1 (VLM) that project directly to corticotrophin releasing factor (CRF)-containing PVH neurons (Cunningham and Sawchenko, 1988). Hindbrain CA projections are functionally relevant for HPA hormonal response to various stimuli including hemorrhage/hypotension, respiratory distress, immune challenge, and counterregulation triggered by hypoglycemia/glucopenia. CA deafferentation markedly reduces corticosterone release triggered by insulin or 2-DG treatment (but not the release by circadian control or by the forced-swim stressor) and prevents 2-DG from elevating PVH CRH expression (Ritter et al., 2003). Hypothalamically projecting hindbrain CA neurons express a variety of chemical signals (epinephrine, norepinephrine [NE], neuropeptide Y, or galanin); direct PVH injection of NE mimics the PVH neuroendocrine responses to

glycemic challenge (Khan et al., 2007). Interestingly, PVH neurons send reciprocal connections to A1/C1 VLM neurons and to mNTS neurons including A2 neurons (Geerling et al., 2010).

Hepatic glucose production: There is accumulating evidence that the vagal efferent innervation of the liver, with premotor neurons located in hindbrain DMV, contributes to the control of glucose homeostasis and of energy balance more broadly. A variety of recent reports indicate that stimulation of CNS nutrient sensors by various correlates of energy repletion, such as long chain coenzyme A, glucose, insulin, and leptin reduce hepatic glucose production through a neural pathway involving vagal efferent transmission. For example, hepatic glucose production is reduced following ventricular infusion of oleic acid (Obici et al., 2002) and involves a mechanism that includes changes in fatty acid β-oxidation, the activation of CNS K_{ATP} channels, and hepatic vagal efferent signaling (Lam et al., 2005; Obici et al., 2003; Pocai et al., 2005). The functional inputs to hindbrain DMV neurons that engage hepatic vagal efferent traffic likely include input from so-called nutrient sensors located in the hypothalamus e.g., (Spanswick et al., 1997) and elsewhere, including the hindbrain itself (Ritter et al., 2011).

Energy Expenditure

Brown adipose tissue (BAT) thermogenesis, a major thermogenic effector for energy balance control and for thermoregulation, is controlled by CNS sympathetic premotor neurons and adrenergic receptors on brown adipocytes (Bachman et al., 2002; Morrison, 2011). Exciting new data demonstrate the presence of BAT and its energetic function in adult humans (e.g., Ouellet et al. [2011]). In animal models, pseudorabies virus transynaptic tracer injections in BAT label a broad network of CNS sites participating in the sympathetic efferent control of BAT thermogenesis (Bamshad et al., 1999). Various studies prominently highlight the critical role for the hindbrain sympathetic premotor neurons located in the raphe pallidus (RPa) and their modulation by axonal projections arising from several neuronal groups in the hypothalamus (medial preoptic nucleus, dorsomedial nucleus) and the medulla (NTS, VLM) (Cao et al., 2010; Morrison, 2011). Data from decerebrate rats lacking forebrain- caudal brainstem communication show elevated BAT temperature in response to RPa injection of melanocortin receptor agonist (Skibicka and Grill, 2008); decerebrate rats maintain core temperature in response to most cold environments (Nautiyal et al., 2008). These findings support the hypothesis that caudal brainstem integrators and endemic effector circuits contribute to energy expenditure function to some degree.

III. Hindbrain Neurons Receive and Integrate Descending Information Arising from Rostral Neural Sites that Contribute to Response Control

In addition to the integrations performed by hindbrain neurons involving direct action of energy-status signals (vagal and blood borne), these neurons receive and process input (axonal projections) from neurons in other parts of the brain that also receive and process energy status signals (see Figures 1A and 1B). Some examples are considered here in which descending forebrain/hypothalamic inputs to NTS neurons contribute to the control of feeding behavior.

LH Orexinergic Projections to NTS

Orexin/hypocretin-containing neurons, uniquely expressed in the LH, project throughout the neuraxis and participate in the control of a variety of functions including the sleep/wake cycle, autonomic control, and energy balance. As many as one quarter of these neurons project to the hindbrain nuclei (NTS, caudal raphe, and VLM) (Ciriello et al., 2003; Zheng et al., 2005). Orexin-immunoreactive (ir) fibers are in close apposition to TH-positive neurons in the A2/C2 region (Zheng et al., 2005), and electron microscopy confirms synaptic junctions between orexin fibers and CA-expressing NTS neurons (Puskás et al., 2010). Zheng et al. (2005) also show that varicose orexin-ir fibers are in close apposition to mNTS neurons that express c-Fos following gastric nutrient infusion and that hindbrain orexin A delivery increases intake (see also Parise et al., 2011). Given the established literature showing that electrical or chemical stimulation of LH neurons elicits feeding behavior in satiated rats (Berthoud and Münzberg, 2011; Coons et al., 1965), this anatomical arrangement suggests a possible mediating mechanism for LH-stimulated feeding— orexin acting on NTS neurons or on their vagal afferent presynaptic terminals attenuates processing of vagally mediated GI satiation signals. The concept is supported, in principal, by results showing that LH electrical stimulation (not unique to orexin neurons) inhibits mNTS neurons and that the excitatory response of intestinal or gastric distension on mNTS neurons is reversed by concurrent LH stimulation (electrical or glutamate) stimulation (Jiang et al., 2003).

ARH Melanocortinergic Projections to NTS

The central melanocortin (MC) system is critical to energy-balance control as humans and mice with MC4-R mutation are hyperphagic and obese (Hinney et al., 1999; Huszar et al., 1997). NTS and DMV are among the neurons with the densest MC4-R expression (Kishi et al., 2003). These hindbrain nuclei receive MC agonist ligands (e.g., αMSH) from ARH and from endemic NTS proopiomelanocrotin (POMC) neurons (Zheng et al., 2010), as well as antagonist from other ARH neurons (Broberger et al., 1998). NTS delivery of MC4-R agonist reduces food intake and elevates core temperature and heart rate, whereas antagonist delivery has opposite effects (Skibicka and Grill, 2009b; Williams et al., 2000). Interestingly, the effect of hindbrain MC4-R ligand delivery on meal patterning mirrors effects of GI satiation signals like CCK. Specifically, meal size is reduced by hindbrain delivery of a MC3/4-R agonist whereas hindbrain delivery of a MC3/4-R antagonist increases meal size (Sutton et al., 2005), suggesting to some that hindbrain MC4-R are downstream mediators of CCK-induced intake suppression (Fan et al., 2004). However, others have reported that diminished sensitivity to GI-derived satiation signals (e.g., CCK, bombesin, nutrient preload) is not responsible for mediating the chronic hyperphagia of MC4-R knockout mice (Vaughan et al., 2006).

ARH-NTS melanocortinergic circuits contribute to the food intake suppressive effect of ARH leptin signaling: NTS projecting ARH MC axons appear to be one contributor to the neural circuit mediating the intake suppressive effect of hypothalamic leptin signaling, as MC4-R antagonist injected into NTS attenuates the intake suppressive effect of leptin delivery to ARH (Zheng et al., 2010). Similarly, hindbrain MC4-R signaling is downstream of the effects of hindbrain leptin signaling; a dose of hindbrain

MC4-R antagonist without effects of its own reverses the food intake and the thermogenic effects of hindbrain leptin delivery (Skibicka and Grill, 2009a). ARH POMC neurons appear to make another contribution to the intake inhibitory effect of ARH leptin signaling that involves projections to PVH neurons than in turn project to the NTS. ARH melanocortinergic neurons project to MC4-R bearing PVH neurons that express a variety of hormones including oxytocin (OT) (Liu et al., 2003). A large percentage of the OT-expressing neurons send axons to the hindbrain (Rinaman, 1998).

PVH Oxytocinergic Projections to NTS

The axons of OT-expressing parvocellular PVH (pPVH) hypothalamic neurons project throughout the neuraxis (Rinaman, 1998; Sawchenko and Swanson, 1982). OT axons are in close apposition to mNTS neurons that express Fos-ir in response to CCK injection (Blevins et al., 2003). A functional relationship between OT and GI satiation signaling is suggested by the attenuation of the intake suppressive action of systemic CCK following hindbrain microinjection of OT receptor antagonist (Blevins et al., 2003; Olson et al., 1991). The intake inhibitory effect of oleoylethanolamide (OEA), another vagally mediated gut signal, is also attenuated by hindbrain OT antagonist (Gaetani et al., 2010). Recent data (Peters et al., 2008) suggest a cellular mechanism for the influence of NTS OT signaling on the intake inhibition of NTS processed GI vagal signals. NTS neurons were neurophysiologically identified by glutamate-driven excitatory postsynaptic currents (EPSCs) induced by solitary tract (axons of vagal afferents) stimulation. OT application to the slice increased the frequency of miniature EPSCs in approximately half of the NTS neurons examined. Analysis of the solitary tract-evoked EPSCs indicates that OT increased the release of glutamate from the vagal afferents terminating on the NTS neurons. The findings suggest that OT release acts on a subset of mNTS neurons to enhance visceral afferent transmission via presynaptic and postsynaptic mechanisms.

OT projections to NTS contribute to hypothalamic energy-status signaling effects on feeding: Blevins et al. (2004) investigate the hypothesis that the intake suppressive effect of hypothalamic leptin signaling involves an ARH POMC-to pPVH OT-to NTS circuit. They show that 3rd icv leptin induces c-Fos in PVH OT neurons that are labeled by NTS tracer injection, and that OT antagonist (forebrain ventricle; hindbrain delivery not described) attenuates leptin-induced anorexia. Other hormones expressed by PVH neurons may also contribute to hypothalamic leptin signaling induced feeding inhibition via their projections to NTS, including but not limited to thyrotropin releasing hormone and CRF (Ahima et al., 1996; Harris et al., 2001; Uehara et al., 1998). The intake inhibitory effect of hypothalamic leucine infusion is attenuated by hindbrain icv OT antagonist (Blouet et al., 2009). Similarly, the food intake suppressive effects of nesfatin-1, a food intake suppressing peptide localized to pPVH neurons that also express OT, is reversed by hindbrain icv OT antagonist delivery (Maejima et al., 2009). Collectively, these findings suggest a mechanism by which hindbrain (NTS) processing is required to mediate the intake inhibitory effects of various hypothalamic energy status signals, and that the conduit of such communication involves descending OT communication. More work is required to substantiate this hypothesis.

IV. . Ascending Hindbrain Projections to Midbrain/Forebrain Neurons Are Essential for the Neural Control of Food Intake

The literature on the neurobiology of food reward focuses appropriately on gustatory signaling from the oral cavity and its synaptic connections to mesolimbic structures associated with reward processing (MRS) (see Norgren et al., 2006 for review). The ascending central gustatory communication begins with neurons in the *rostral* NTS that receive cranial nerve afferents that innervate taste receptor cells. In the rodent, these neurons project in turn to the parabrachial nucleus (PBN). PBN axons then convey gustatory afferent activity to the medial extension of the thalamic trigeminal relay, or along a separate pathway to the LH, central nucleus of the amygdala (CeA), and the bed nucleus of the stria terminalis (BNST) (Norgren, 1976, 1978; Norgren et al., 2006). The gustatory region of PBN projects to limbic structures—CeA and BNST—that are considered to be primarily responsible for subsequently engaging the nucleus accumbens (NAc) to modulate dopamine signaling (Norgren et al., 2006). While these discoveries define the feed-forward neural circuitry that promotes food intake, largely unexplored are the intake inhibitory feedback signals that accumulate as consumption of a meal progresses and affect MRS neural processing. It is likely that these inhibitory signals are communicated via a CNS relay between GI-derived vagally mediated satiation signals and nuclei of the MRS. The recent discovery of monosynaptic connections from the *caudal* NTS to the ventral tegmental area (VTA) and NAc (Alhadeff et al., 2011; Dossat et al., 2011; Rinaman, 2010) provides such a conduit.

The processing and integration of gastric- and intestinal-inhibitory signals beginning within the NTS in turn counteracts the intake stimulatory gustatory signals from the oral cavity. The notion that postingestive signals modulate gustatory reward has been established for some time (Babcock et al., 1985; Carr and Simon, 1984; Sclafani and Ackroff, 2004); however, the mediating systems and neuronal pathways remain poorly characterized. One possibility is that the neuronal circuitry required for GI inhibitory control of feeding is endemic to the caudal brainstem. Evidence for this hypothesis comes from studies using chronic decerebrate rats showing that the intake inhibitory response to gastric nutrient preloads, as well as intestinally derived satiation signals is equivalent in neurologically intact rats and in rats with neural processing restricted to the isolated caudal brainstem (Grill and Smith, 1988; Hayes et al., 2008; Seeley et al., 1994). As decerebrate rats are unable to engage in appetitive feeding, these findings establish a forebrain-independent neural circuitry that mediates the intake inhibitory effects on GI satiation signals on consummatory phase of feeding control. These data do not address, however, neural control of the appetitive phase of feeding, but they do offer a foundation for an additional hypothesis to explain how GI-derived satiation signals may modulate gustatory reward: namely, that processing and integration of GI satiation signals *within the NTS* (or hindbrain more broadly), modulate the higher-order cognitive centers of the brain involved in the appetitive control of feeding.

The idea that GI-derived vagally mediated satiation signals can modulate the rewarding value of food via direct NTS-relayed monosynaptic projections to nuclei of the MRS (i.e., VTA and

NAc) is novel and provides a rapid temporal modulation of within-meal food intake control (see Figure 1C). Monosynaptic connections from the caudal NTS to the MRS are established (Alhadeff et al., 2011; Dossat et al., 2011; Ricardo and Koh, 1978; Rinaman, 2010). Among the possible phenotypes of NTS neurons considered, GLP-1 synthesizing preproglucagon (PPG; precursor peptide for GLP-1) neurons stand out as an intriguing possibility for a number of reasons, including that these NTS PPG neurons are physiologically required for the normal control of food intake and body weight (Barrera et al., 2011). While immunocytochemisty and in situ hybridization confirm the presence of GLP-1R mRNA and GLP-1 immunopositive fibers, respectively, in both the VTA and NAc (Merchenthaler et al., 1999; Rinaman, 2010), only recently have two, independent labs provided direct evidence that NTS PPG neurons are in fact projecting monosynaptically to the MRS (Alhadeff et al., 2011; Dossat et al., 2011). Double IHC for retrograde tracers injected in the VTA, NAc core, or NAc shell together with PPG-expressing neurons in the caudal NTS provide a previously unidentified mechanism by which central GLP-1 can regulate food intake. Moreover, these NTS GLP-1-to-MRS projections are physiologically relevant for food intake control, as blockade of GLP-1R in the VTA (Alhadeff et al., 2011) or NAc core (Alhadeff et al., 2011; Dossat et al., 2011) increased food intake. The GLP-1R signaling in either the VTA or NAc was shown to preferentially reduce intake of palatable foods and did so in the absence of nausea (Alhadeff et al., 2011). Given that within-meal vagally mediated satiation signals (i.e., CCK and gastric distension) activate NTS PPG neurons (Hayes et al., 2009a; Hisadome et al., 2011; Vrang et al., 2003), these findings provide a mechanism by which hindbrain processing of satiation signals could communicate with higher-order regions of the forebrain, and subsequently modulate food intake by decreasing the rewarding value of the ongoing meal. Of course, PPG neurons are not the sole phenotype of NTS neuron that project to reward processing-associated structures. Indeed, work from Aston-Jones' laboratory has concluded that the primary source of noradrenergic afferents to the NAc originates in the A2 region of the NTS (Delfs et al., 1998). Further identification of NTS neuron phenotypes whose axons project to forebrain nuclei will be useful in better characterizing the mechanisms by which hindbrain processing of energy-status signals modulates appetitive processes of food-intake control.

Conclusions

The case is made that hindbrain nuclei perform integrations that are essential to the control of behavioral, autonomic, and endocrine responses that are marshaled to collectively control energy balance. These hindbrain-mediated response controls involve endemic hindbrain circuits, as well as the participation of midbrain and forebrain nuclei and peripheral circuits. Thus, the hindbrain is viewed here as one key element in the multisite, neuroanatomically distributed control of energy balance function.

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