The melanocortin system as a central integrator of direct and indirect controls of food intake

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The neural control of food intake and body weight is a complex function in which cognitive and emotional variables, as well as long-term signals of metabolic status and fuel storage, are integrated with short-term signals related to individual meals. Several years ago, Smith (20) proposed a useful classification of the myriad signals that influence the amount of food eaten during individual meals: direct controls, which arise from the interaction of ingested stimuli with receptors in the gastrointestinal tract; and indirect controls, which comprise all other controls of food intake, including signals pertaining to the status of body fat stores, such as leptin and insulin. According to this model, indirect controls affect meal size by increasing or decreasing the potency of direct controls. Early support for this concept was supplied by Woods and colleagues (7, 19), who showed that infusion of insulin into the brain increases sensitivity to the gut-derived “satiety factor” cholecystokinin (CCK), and similar interactions between CCK and other indirect controls, including leptin and estrogen, have since been documented (2, 4, 5).

An important strength of this model is the framework it provides for identifying the neural circuits that detect and integrate these direct and indirect signals. It is widely accepted that excitatory gustatory and inhibitory gastrointestinal feedback, major determinants of meal size, are relayed to the brain through cranial nerve nuclei in the caudal brain stem. Taste information supplied by the facial, glossopharyngeal, and vagus nerves is first processed by the nucleus of the solitary tract (NTS) (21), and relevant visceral sensory information, such as gastric and intestinal distension or the release of CCK, is relayed to the central nervous system (CNS) through vagal afferents that synapse in the same hindbrain area (15). Indirect controls of food intake are more diverse and do not enter the brain through a single afferent route. The adipocyte-derived hormone leptin is an important example of an indirect control that communicates information regarding body energy stores to the brain. Leptin circulates at levels proportionate to body fat mass, crosses the blood-brain barrier, binds to its receptors on neurons in key brain areas for food intake control, and in so doing ultimately favors the consumption of smaller meals (8). The concept that leptin action in the forebrain reduces meal size by enhancing the hindbrain response to gastrointestinal satiety signals has recently received direct experimental support (16).

The forebrain melanocortin system, including subsets of neurons that contain either pro-opiomelanocortin (POMC, the melanocortin precursor polypeptide) or agouti-related peptide (AgRP, an endogenous melanocortin receptor antagonist) in the arcuate nucleus of the hypothalamus (ARC), is strongly implicated as a central mediator of the actions of leptin and of other hormonal and nutrient-related indirect controls of food intake (1). These ARC neurons influence feeding behavior and energy expenditure through their effects on melanocortin 3 and 4 receptors (MC3/4-R) in adjacent brain regions, including the hypothalamic paraventricular nucleus and lateral hypothalamic area (3, 9). Neurons in these areas, in turn, project to the caudal brain stem where they can interact with neural circuits that process meal-related signals from the gastrointestinal tract. In addition, both POMC neurons and MC4-R are present in the NTS itself (13, 17, 18), and melanocortin signaling in this hindbrain area is clearly implicated in the control of food intake (25). Since the NTS is also supplied by projections from a subset of POMC neurons in the ARC (18, 26, 27), melanocortin signaling pertinent to the processing of direct controls of meal size can potentially originate from POMC cells in both forebrain and hindbrain.

The existence of a descending ARC-NTS POMC projection was established decades ago though the use of immunohistochemical staining and radioimmunoassays for POMC cleavage products combined with lesions and transections (12, 18, 26). Because POMC is expressed in cell bodies in both the ARC and NTS, these techniques were critical for demonstrating that POMC-derived products in the hindbrain originate from cells located in both brain areas. These early studies also suggested that NTS POMC cells project exclusively within the caudal medulla, while ARC POMC cells project more widely throughout the brain. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Zheng and colleagues (27) provide new insights regarding those POMC cells that project from the ARC to the NTS and expand on earlier evidence for the relevance of hindbrain MC4-R in the control of meal size and energy expenditure (23, 24). These investigators employed the combination of retrograde tracing and immunohistochemical staining to identify a small subpopulation of ARC POMC cells that send axons to the NTS. They also show that fibers containing α-melanocyte-stimulating hormone (α-MSH, a POMC cleavage product and agonist of MC3/4-R) are found in the NTS in close proximity with neurons that are activated (as judged by c-fos staining) by gastrointestinal nutrient infusion, but whether these melanocortinergic fibers originate in the ARC or from within the NTS remains uncertain. In addition, this group performed pharmacological experiments that expand on previous evidence that hindbrain MC-R influence meal size (24), including the demonstration that injection of MTII, a MC3/4-R agonist, directly into the dorsal vagal complex (DVC) decreases meal size, whereas intra-DVC administration of SHU9119, an antagonist at these receptors, exerts the opposite effect. The effect of intra-DVC SHU9119 treatment is especially important in that it confirms a role for endogenous MC3/4-R agonist activity within the NTS in the control of meal size. Taken together, these findings support a model in which a leptin-
sensitive descending ARC-NTS POMC projection can interact with direct controls of meal size as they are transduced in the hindbrain.

Further research is required to determine whether melanocortinergic input to NTS neurons involved in meal termination is supplied by the ARC-NTS POMC projection or from the POMC cells that reside within the NTS. While it seems likely that both populations of POMC cells provide significant stimulation to NTS MC4-R, our understanding of the role played by the hindbrain POMC neuron population in food intake control has lagged behind that of its hypothalamic counterpart, in part because of difficulties inherent in the immunohistochemical identification of these cells (due to a low abundance of POMC-derived peptides and their rapid transport out of the cell body). Mice that express green fluorescent protein exclusively in POMC cells provide a useful new tool for investigating the role of these hindbrain POMC neurons. Using such mice, Fan and colleagues (6) found that a large subset of NTS POMC cells are activated by peripheral CCK treatment, whereas no such response was observed in ARC POMC cells. In addition, they showed that hindbrain ventricular administration of SHU9119 reversed CCK-induced anorexia to a greater degree than did forebrain ventricular treatment. These data suggest a model in which NTS POMC cells and their stimulation of hindbrain MC4-R are part of a circuit that processes direct controls of meal size in the brain. Whether hindbrain POMC cells are responsive to food deprivation, leptin, insulin, or other signals of peripheral metabolic status, as are POMC cells in the ARC, remains an important unanswered question. Although leptin and insulin receptors are present in the NTS (11, 14, 22), and while intra-DVC leptin treatment effectively reduces food intake (11), additional studies are required to determine whether NTS POMC cells respond directly to these hormones and thus serve as a central mediator of indirect controls of meal size.

Available evidence supports the idea that hindbrain MC4-R-bearing neurons receive input from both ARC lepin-responsive POMC cells and NTS CCK-responsive POMC cells, positioning them as true integrators of these indirect and direct controls of meal size. The role of NTS POMC cells in detecting and responding to signals of longer-term metabolic status remains to be clarified, and it is not currently possible to assign a greater importance to one source of MC4-R ligand over the other in the control of meal size. The characterization of the descending POMC projection to the NTS expands the possibilities for feeding-relevant routes of communication between the forebrain and hindbrain and supports the perspective that the CNS control of food intake is broadly distributed, involving multiple levels of the neuraxis (10).

REFERENCES