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Central Neural Pathways and Integration in the Control of Food Intake and Energy Balance

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The transmission of gut neural signals related to the controls of food intake, such as gastric volume and gastrointestinal nutrient exposure, is primarily mediated by the afferent vagus nerves supplying the gut. Complete surgical transection of these gut afferent vagal nerves chronically increases meal size in rodent models, yet does not promote increases in body weight, because decreased meal number compensates for the additional caloric intake in each larger meal. Gut vagal afferents project first to central nervous system caudal brainstem sites important in the control of meal size, including the nucleus of the solitary tract (NTS) and area postrema (AP), then via distinct pathways to the brainstem lateral parabrachial nucleus (lPBN) and forebrain limbic and hypothalamic regions, including the amygdala, bed nucleus of the stria terminalis, and the lateral and paraventricular nuclei of the hypothalamus (PVN).

The Melanocortin Pathway

The PVN is a neuroanatomical crossroads between ascending control feeding signals arising from the brainstem, and feeding excitatory and inhibitory neuropeptide signals from hypothalamic arcuate nucleus (ARC) projection neurons, located within the base of the brain abutting the third intracerebral ventricle. ARC neurons include neurochemically distinct populations of feeding-stimulatory (orexigenic) agouti-related peptide (AgRP)/neuropeptide Y (NPY), and feeding-inhibitory (anorexigenic) pro-opiomelanocortinergic (POMC) neurons. AgRP acts as a melanocortin receptor 3/4 (MC3/4R) antagonist in PVN neurons to promote food intake and body weight gain, while the POMC product alpha-melanocyte-stimulating hormone (alpha-MSH) acts as an agonist at PVN MC3/4R to reduce feeding and adiposity.

Results from molecular genetic studies support the relevance of brain melanocortin receptor signaling in obesity and food intake. Mutations in the *MC4R* gene, occurring

in the obese population at approximately 6%, are the most common known cause of monogenic human obesity, characterized by early onset hyperphagia and increased meal size. Mice lacking *MC4R* demonstrate a similar profile of hyperphagia early in development that promotes obesity in adulthood, and mice unable to synthesize the endogenous *MC4R* agonist alpha-MSH are hyperphagic and obese. Furthermore, hypothalamic PVN and brainstem administration of *MC4R* agonists reduce food intake by limiting meal size, resulting in decreased body weight. In contrast, parenchymal administration of *MC4R* antagonists in these sites increases food intake, body weight, and adiposity.

Distinct brainstem projecting populations of MC3/4R neurons in the PVN produce glutamate and oxytocin, two neurochemicals with important feeding modulatory actions at caudal brainstem neurons that receive feeding control signals. Stimulation of glutamatergic projections from the PVN to neurons in the lPBN inhibits feeding, while oxytocinergic nerve projections from the PVN innervate NTS neurons that are activated by feeding inhibitory doses of the gut satiety peptide cholecystokinin (CCK), a negative feedback control of food intake. Brainstem application of oxytocin receptor (OR) antagonists blocks the ability of CCK to inhibit food intake, and brainstem administration of OR antagonists alone markedly increases meal size. In addition to the feeding modulatory PVN hypothalamic glutamatergic and oxytocinergic projections to the brainstem, alpha-MSH fibers arising from the ARC project directly to the NTS, where pharmacological activation of MCR3/4R reduces feeding and body weight. Together, these findings identify reciprocal functional connections between brainstem (NTS and lPBN) and hypothalamus (PVN, ARC) that can drive a recurrent loop to limit feeding by forebrain modulation of gut-derived control signals acting in the brainstem.

The relevance of AgRP for the control of body weight and feeding is highlighted by the consequences of selective stimulation or inhibition of AgRP neurons; neurochemically specific photo- or chemostimulation of AgRP neurons inhibits PVN oxytocin neurons and rapidly increases meal size, while photostimulation of ARC POMC neurons reduces feeding and body weight. Ablation of AgRP/NPY neurons in adult mice results in profound anorexia and starvation, accompanied by hyperactivation of lPBN neurons. Stimulation of inhibitory lPBN gamma-aminobutyric acid (GABA) A receptors prevents the anorexia produced by AgRP neuronal ablation, suggesting a descending hypothalamic modulatory pathway to limit the activation of the lPBN, a brainstem relay that processes negative feedback controls of ingestion.

Brainstem integration of peripheral meal-related controls and central feeding modulatory neurochemical signals is supported by the neuroanatomical convergence of gut feeding controls and central melanocortin action: alpha-MSH projections to the brainstem terminate on gut-sensitive, CCK-responsive NTS neurons, and brainstem application of *MC4R* antagonists block the satiety actions of peripheral feeding inhibitory doses of CCK. Taken together with the previously discussed consequences of hypothalamic melanocortin pathway activation, these data demonstrate that central melanocortins have neuroanatomically distributed, redundant effects that are important for the control of feeding behavior and energy balance.

Leptin

The adiposity signal leptin has been importantly implicated in both forebrain and brainstem control of food intake and body weight through both melanocortin-dependent and

independent mechanisms. In very rare cases of human genetic leptin deficiency accompanied by severe obesity, pharmacological administration of leptin eliminates hyperphagia and normalizes body weight and adiposity. A central action of leptin in these effects is suggested by the dense distribution of leptin receptors in hypothalamic ARC POMC and AgRP neurons, as well as in brainstem NTS/AP neurons. Each of these populations is localized near circumventricular organs, characterized by a relatively porous blood–brain barrier that permits enhanced brain access to peripherally circulating factors. Leptin reaches hypothalamic ARC neurons via a highly selective transport system mediated by tanycytes, specialized glial cells lining the third ventricle. Hypothalamic leptin uptake is disrupted in both diet-induced obesity and genetic obesity in *db/db* mice lacking the leptin receptor. Given the morphological similarities shared among circumventricular organs, it is likely that leptin access to the brainstem relies on transport processes similar to those in the hypothalamic ARC.

Leptin injections into the ARC produce long-lasting suppression of meal size and total chow intake, and rats prone to develop diet-induced obesity have defective projections arising from ARC neurons, accompanied by reduced leptin signaling that persists into adulthood. The ability of ARC leptin signaling to reduce feeding is significantly blunted by brainstem injection of *MC4R* antagonists, suggesting a leptin-activated ARC–PVN–NTS melanocortin circuit. Genetically obese (*fa(k)/fa(k)*) rats lack functional leptin receptors and are consequently obese and hyperphagic; their hyperphagia is characterized by increased meal size and reduced feeding inhibitory actions of CCK. Selective restoration of leptin receptors confined to the ARC restores the ability of peripherally administered CCK to both activate brainstem NTS/AP neurons and to limit food intake by a reduction in meal size. Thus, neuroanatomical connectivity between leptin sensitive hypothalamic sites and the caudal brainstem is an important determinant of the brainstem processing of satiety signals.

The metabolic context provided by central signals of adiposity such as leptin also determines the magnitude of the neural response to gut negative feedback signals and their ability to reduce meal size. Gut-sensitive neurons in the NTS are dose-dependently activated by increasing gastric volume stimuli, and central leptin administration increases the neurophysiological potency of such stimuli. Thus, NTS neurons integrate central adiposity signals with peripheral controls of feeding. Such integration occurs not only at the level of the individual neuron but also at a population level, as central leptin also increases the number of NTS cells activated by gastric loads. From a behavioral standpoint, ventricular, lPBN, and NTS leptin administration reduces food intake and body weight in rats, and increases the degree of feeding suppression produced by gastric loads and duodenal nutrient infusions. Conversely, molecular genetic knockdown of brainstem leptin receptors increases food intake by increasing the size of spontaneous meals, increases body weight and adiposity, and blunts the feeding inhibitory effects of CCK. Taken together, these demonstrate the ability of leptin acting at both the brainstem and hypothalamus to modulate the brainstem control of food intake, meal size, body weight, and adiposity.

However, the metabolic milieu determined by either dietary or genetic obesity does not strictly limit the inhibitory potency of all feeding and body weight regulatory stimuli. For example, the ability of oxytocin to (1) reduce food intake and body weight and (2) activate brainstem NTS and AP is preserved in hyperleptinemic, leptin-resistant rats with diet-induced obesity and in Koletsky *fa/fa* rats lacking leptin receptors. In this way, leptin- and obesity-independent determinants of feeding and body weight may also engage brainstem sites that process direct control signals.

Nutrient Sensing

Finally, nutrient sensing by neuronal populations in hypothalamic–brainstem circuits provides another avenue for the integrated and distributed central controls of food intake and body weight. Feeding or gastrointestinal infusion of the essential branched-chain amino acid leucine rapidly elevates its appearance in cerebrospinal fluid, hypothalamus, and brainstem, and hypothalamic activation of leucine signaling pathways, either by leucine itself or downstream mediators, reduces food intake, meal size, and body weight gain. Several genes involved in branched-chain amino acid metabolism have been suggested as candidate genes in human obesity. Furthermore, in humans, single-nucleotide polymorphisms in leucine transporters have been associated with body mass index, and mice with deficient leucine transporter expression have reduced leucine-inhibited food intake and weight gain during high-fat diet maintenance. Leucine directly activates hypothalamic POMC neurons that express oxytocin, and the ability of hypothalamic leucine to reduce feeding is blocked by brainstem administration of oxytocin receptor antagonists, demonstrating that hypothalamic nutrient sensing engages oxytocin brainstem pathways important in the control of meal size. Leucine sensing also appears to be redundantly expressed, as direct brainstem application of leucine and its downstream signaling mediators also reduce food intake, meal size, and body weight gain.

Summary

In summary, brainstem and hypothalamic neuronal interconnections form the basis for a distributed and redundant set of pathways to modulate the control of feeding and body weight (see Figure 1.1). Meal-related sensorineural signals generated by the presence of nutrients along the gastrointestinal tract project to a circuit of brainstem and hypothalamic neurons localized in brain regions with preferred access to circulating factors, including individual nutrients, as well as hormones whose circulating levels reflect the availability of stored nutrients (the adiposity hormones leptin and insulin) and the availability of gastrointestinal nutrients (e.g., ghrelin). Each of these signals of nutrient availability, the gastrointestinal presence of nutrients, circulating nutrients, adiposity hormones, and gut peptides determines the activity of neurons in gut-recipient brainstem and hypothalamic sites, and such activation is strongly associated with the control of food intake and body weight. The unknown functions of the redundant sensitivity to these stimuli in hypothalamic and brainstem sites represent an important gap in our understanding of the neurobiology of energy balance. In physiologically relevant settings, none of these factors acts on feeding or body weight control in isolation; the neurobiological environment of these neuronal populations is characterized by distinct levels of each class of stimuli at any given time. The biological responses of brainstem and hypothalamic neurons to nutritionally relevant stimuli are determined by the metabolic context or milieu in which a stimulus occurs. Accordingly, both neuronal populations also have the capacity to respond to combinations of sensorineural, hormonal, and nutrient stimuli in an integrative fashion. This integrative capacity within and across gut-sensitive neurons appears to be an important index of the feeding and body weight consequences of these interactions. Neuroanatomical connectivity and communication among brainstem and hypothalamic sites suggest that they work in a coordinated fashion to determine energy balance. Progress will depend on the identification of the ways in which physiologically relevant constellations of nutrient-related signals jointly determine the activity

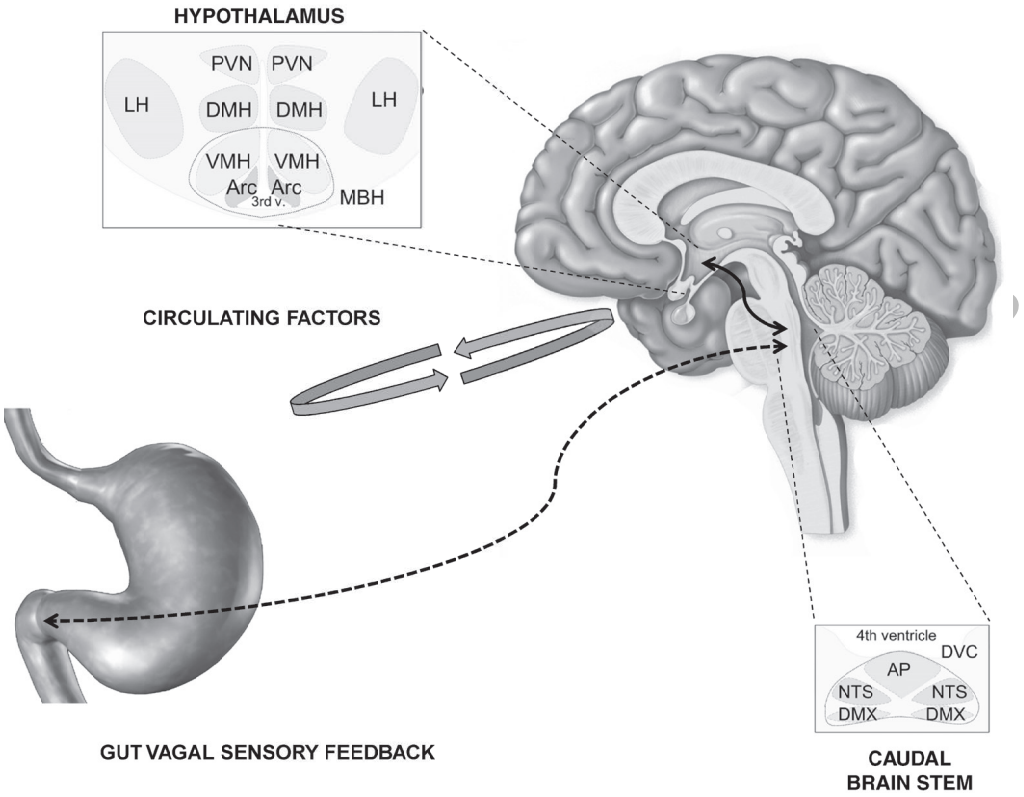

FIGURE 1.1. Schematic of discussed hypothalamic–brain stem circuits involved in controlling energy balance. The diagram depicts a subset of the neuronal connections reported to influence feeding and body weight. Sensory meal-related signals are transmitted via gut sensory vagal afferent projections to the brain stem–hypothalamic axis. Humoral factors, including circulating nutrients, adiposity hormones, and gut peptides also impinge on this axis. Note that the black dashed arrows reflect connectivity between hypothalamic and brain stem regions, and not any specific anatomical pathway. MBH, medibasal hypothalamus; PVN, paraventricular nucleus of the hypothalamus; ARC, arcuate nucleus of the hypothalamus; AP, area postrema; NTS nucleus of the solitary tract.

of hypothalamic and brainstem neuronal circuits in the service of food intake and body weight control.

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