Hypothalamic-Brainstem Circuits Controlling Eating

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Abstract

It is now axiomatic that neurons in the hypothalamic arcuate nucleus have a primary role in responding to changes in circulating levels of leptin and transmitting signals to downstream circuits that influence eating and energy expenditure. Signals generated from the gastrointestinal tract during meals reach the brainstem, via the vagus nerve and other routes, and impinge on neural circuits that influence the timing and size of meals and amount of food consumed. One of the mechanisms by which leptin exerts its anorexic effects is by increasing the effectiveness of intestinal signals that cause satiation during a meal. It is clear that the effects of gut satiation signals such as CCK can be amplified by leptin acting in the CNS, and in the arcuate nucleus in particular. The present article describes the state of our knowledge about specific neural circuits between the hypothalamus and brainstem that play a role in the interaction of leptin and meal-control signals to control food intake.

Many years of research have established that energy homeostasis is regulated by the central nervous system (CNS) through the control of eating and energy expenditure. This process involves the integration of very different types of sensory information. One type, 'meal-control signals, involves afferent information arising in relation to eating that affect meal timing and size. A prototypical example is cholecystokinin (CCK), a gut peptide that is released from the intestines during meals and acts to produce meal-ending satiation. The CCK satiation signal and many other meal-control signals reach the nucleus tractus solitarius (NTS) in the caudal brainstem, via the vagus nerve and other routes. In contrast to meal-control signals, 'adiposity signals' are humoral signals generated in proportion to adipose tissue mass that directly affect CNS neurons and circuits that regulate energy homeostasis. The best researched examples of these are leptin and insulin. Each of these hormones is thought to act via receptors in the hypothalamic arcuate nucleus (Arc) to affect eating and energy expenditure over the longer term. The identity of the neurons in the CNS circuits processing meal-control and adiposity signaling has been the subject of intense research in recent years, and the literature in this area has been reviewed in this volume [1, 2] and elsewhere [3, 4].

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Clearly, for adiposity signals to control eating, they must interact in the CNS with the neural representations of meal-control signals. It is now axiomatic, first, that Arc neurons have a primary role in responding to changes in circulating levels of leptin, insulin, and other metabolic and endocrine adiposity signals related to energy homeostasis and transmitting signals to downstream circuits that influence eating and energy expenditure and, second, that one of the mechanisms by which adiposity signals exert their anorexic effects is by increasing the effectiveness of gastrointestinal meal-control signals that cause satiation or satiety. Only recently, however, have details about the neural circuits mediating this interaction begun to emerge [3–6]. Therefore, in the present chapter we describe the state of our knowledge of the specific hypothalamic-brainstem neural circuits that mediate the interaction between meal-control and adiposity signals to control eating and energy homeostasis. We focus on CCK and leptin, the signals for which the most information regarding neural processing is available.

Functional Interactions of Adiposity and Satiation Signals

Several lines of evidence indicate that adiposity signals increase the potency of CCK and other meal-control signals. Exogenous leptin increased the ability of gastric loads or exogenous CCK-8 to inhibit eating [5, 6] and to enhance brainstem neuronal activation, as measured by c-Fos expression [5–8]. Leptin also enhanced the food intake and brainstem c-Fos responses to bombesin [9] (an anuran homolog to the mammalian brain-gut peptides gastrin-releasing peptide and neuromedin B), as well as the eating responses to PYY(3–36) [10] and GLP-1 [11]. Likewise, in transgenic rats with impaired leptin signaling, restoration of leptin signaling specifically to the Arc was sufficient to enhance the satiating potency and the c-Fos response to CCK-8 [12]. A similar decrease in CCK-8's satiating potency as in leptin receptor-deficient rats occurred in fasting rats, in which endogenous leptin levels are very low [13].

Other data indicate that hypothalamic-brainstem connections may be sufficient, but are not necessary, for CCK to inhibit eating. First, the eating-inhibitory effect of CCK-8 in neonatal rats was accompanied by c-Fos induction in the brainstem, but not the hypothalamus, suggesting that a neural connection between the forebrain and brainstem is not essential in order to respond to CCK [14]. Second, decerebrate rats, in which all neural connections between hypothalamus and brainstem are severed, also had intact eating responses to CCK and other short-term meal-related stimuli, but they are not able to mount a normal compensatory response to fasting-induced energy deficits by increasing food intake [15].

Neural Connections between the Hypothalamus and NTS

Descending Arc-NTS Projections

How does hypothalamic leptin signaling communicate with brainstem NTS neurons that respond to satiation signals, such as CCK? We address this question with a discussion of some of the known descending forebrain-brainstem neuronal circuits likely involved with transmitting hypothalamic leptin signaling to brainstem neurons sensitive to satiation signals. Studies have shown that α-melanocyte-stimulating hormone (α-MSH) projections originating from proopiomelanocortin (POMC) neurons in the Arc terminate in close

anatomical proximity to neurons in the NTS that are sensitive to gastric distension [16], confirming that α-MSH projections from the Arc to the NTS exist. Moreover, endogenous melanocortin signaling in the brainstem contributes to the eating-inhibitory response to CCK-8 [17]. Together, these findings raise the possibility that melanocortin input from the Arc-NTS pathway containing α-MSH is an important mechanism to explain how leptin signaling in the hypothalamus communicates with key neurons in the brainstem sensitive to CCK.

Descending Paraventricular Nucleus-NTS Projections

Several findings support a role for oxytocin and corticotrophin-releasing factor (CRF) neurons in the paraventricular nucleus (PVN) in the control of eating and regulation of body weight. These peptides each inhibit eating when injected intracerebroventricularly (ICV) [18, 19]. Oxytocin gene expression is decreased in *Sim1* haploinsufficient mice, a condition accompanied by hyperphagia and obesity [20]. Both oxytocin and CRF peptides induce c-Fos in brainstem areas involved in controlling eating and receptors for both peptides are found in the NTS [21, 22].

Leptin-induced activation of melanocortin-sensing circuits in the PVN may explain how hypothalamic leptin signaling communicates with PVN neurons that project to brainstem neurons sensitive to CCK and other meal-control signals. PVN neurons express melanocortin receptors (MC3R and MC4R) and the PVN is an important site for the action of melanocortins on eating [23]. Subsets of neurons in the PVN that project to the NTS express MC4R mRNA [24] and/or oxytocin, and these oxytocin neurons increase c-Fos expression in response to leptin [7]. Oxytocin fibers in the medial NTS are distributed in close anatomical proximity to neurons that are activated to express c-Fos by exogenous administration of CCK-8 [25]. Central administration of an oxytocin receptor antagonist attenuates the ability of leptin to enhance this neuronal response to CCK-8 in the medial NTS [7]. Oxytocin fibers in the NTS also are found in close anatomical proximity to GLP-1 neurons in the NTS [26]. Furthermore, ICV administration of oxytocin induces c-Fos expression in GLP-1 neurons in the NTS, whereas ICV administration of a GLP-1R receptor antagonist blocks the effects of ICV oxytocin to inhibit eating [27], a finding that supports the existence of a PVN-NTS oxytocin projection linking hypothalamic leptin signaling with brainstem neurons that control food intake. Taken together, these findings raise the possibility that a leptin-sensitive melanocortin projection to the PVN activates oxytocin neurons that project to brainstem neurons that are sensitive to meal-control signals.

Leptin may also influence brainstem satiation circuitries through PVN CRF neurons [28]. MC3R/MC4Rs are found on CRF neurons in the PVN [29], and PVN CRF neurons have direct projections to the NTS [30, 31]. Leptin activation of STAT3 phosphorylation, a marker of direct leptin action, has also been shown to increase thyroid releasing hormone (TRH) mRNA levels in a subpopulation of PVN neurons [32], consistent with a putative role for TRH in the control of eating and energy metabolism [33]. It is not known, however, whether the leptin responsive TRH neurons in the PVN contribute to the TRH present in the NTS [34]. Finally although leptin activates c-Fos expression in a subpopulation of oxytocin PVN neurons that project to the NTS [7] and immunocytochemical evidence for leptin receptor

expression in the PVN has been reported [35], it remains to be demonstrated whether PVN oxytocin neurons are activated directly by leptin or indirectly downstream of primary leptin action in the Arc or elsewhere.

Descending Lateral Hypothalamus-NTS Projections

Leptin-sensitive POMC and NPY neurons in the Arc innervate melanin-concentrating hormone (MCH) and orexin neurons in the lateral hypothalamus (LH) [36]. Descending projections from the LH to the NTS contain orexin [37] and MCH, and these MCH fibers innervate neurons in the NTS activated by gastric nutrient loads [38]. Thus, it is possible that leptin signaling to the Arc could be relayed to NTS neurons that are sensitive to meal-control signals via MCH and orexin neurons in the LH. Leptin may also directly inhibit descending LH-NTS projections, as LH leptin administration decreases food intake [39] and leptin receptors are expressed by MCH and orexin neurons [40, 41].

Descending Arc-Parabrachial Nucleus Projections

Recent studies have demonstrated a critical role in the control of food intake for a projection containing agouti-related peptide (AGRP)/gamma-amino butyric acid (GABA) from the Arc to the parabrachial nucleus (PBN) [42]. Lesions of the lateral PBN attenuate conditioned taste aversions [43], as well as the eating-inhibitory effects of amylin and CCK-8 [44]. Whether these lesions alter CCK-8-elicited satiation through interruptions of ascending CCK-8-ergic projections from the PBN to the ventromedial hypothalamus [45] or whether they impair the input of descending Arc-PBN pathways remain to be determined.

Ascending NTS-PVN Projections

Ascending NTS-PVN projections containing norepinephrine [46], neuropeptide Y (NPY) [47], and GLP-1 [48] are implicated in the control of eating. Intra-PVN administration of the cellular toxin saporin that is conjugated to a monoclonal antibody against dopamine β-hydroxylase destroys catecholamine (norepinephrine/epinephrine) neuronal projections from brainstem catecholamine neurons to the PVN, including those in the A1/C1 of the ventrolateral medulla and in the A2/C2 region of the caudal medial NTS [49]. NPY is coexpressed in a subset of these catecholaminergic projections to the PVN, including A1/C1 and C2 [47].

CCK-8 activates catecholamine neurons and NPY neurons in the NTS [50], and many of the CCK-8-activated catecholamine neurons project from the A2 cell group in the NTS to the PVN and amygdala [51]. Selective lesions of the catecholamine neurons in the NTS result in decreased c-Fos induction in oxytocin neurons in the PVN and an attenuated eating-inhibitory response to CCK-8 but did not alter c-Fos expression in the PBN or the central nucleus of the amygdala [52]. Thus, while reciprocal catecholamine connections appear to exist between the hypothalamus and NTS, the circuitry is not well understood and other connections are likely to be important in the control of eating. For example, CCK-8 activates PVN oxytocin neurons that project back to the NTS and nearby nuclei [53]. In addition, CCK-8 activates GLP-1 neurons in the NTS with ascending projections to the PVN [48]. These findings indicate that activation of ascending noradrenergic (and possibly GLP-1)

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projections from the NTS and subsequent activation of PVN oxytocin neurons that project to the NTS are associated with the satiating effect of CCK-8.

Earlier findings indicate that leptin (or gastric load) in combination with CCK-8 result in more c-Fos expression in the PVN compared to either treatment alone [6, 8, 9]. Another potential mechanism to explain how leptin enhances CCK-8-elicited satiation may involve dual activation of oxytocin neurons in the PVN by, first, activation of CCK-sensitive ascending NTS-PVN noradrenergic projections onto PVN oxytocin neurons containing alpha1 adrenergic receptors [54] and, second, leptin-induced activation of Arc projections to PVN oxytocin neurons [2–4, 7]; a population of these dually activated oxytocin neurons projects to the NTS to control eating. Indeed, leptin administration enhances CCK-8-elicited c-Fos induction and c-Fos mRNA expression in tyrosine hydroxylase-immunoreactive catecholamine neurons in the A2/C2 region of the caudal medial NTS [8]. Thus, evidence indicates that a subpopulation of CCK-sensitive catecholamine neurons in the A2/C2 region of the NTS with ascending projections to the PVN (either directly from the NTS or indirectly from the ventrolateral medulla), may contribute to the ability of leptin to enhance the satiety response to CCK-8.

Conclusion

The control of eating and regulation of body weight involves complex CNS neuronal circuits. This review has focused mainly on the controls exerted by the adiposity signal leptin and the meal-control signal CCK. Intact reciprocal neuronal connections between brainstem (especially NTS, PBN) and hypothalamic (especially Arc, PVN and LH) areas are required for the coordinate control of eating by leptin, and perhaps other adiposity signals, and CCK, and perhaps other meal-control signals. This view of the link between homeostatic and meal-control signals is becoming more complicated, however, as new information emerges concerning, for example, the potential role of leptin signaling to ventral telencephalic reward systems. The mechanisms that integrate neuronal crosstalk among the hypothalamus, brainstem, telencephalic reward systems and other brain regions provide a fertile ground for future research.

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