

Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms

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ABSTRACT

Food intake is a complex behavior that can occur or cease to occur for a multitude of reasons. Decisions about where, when, what, and how much to eat are not merely reflexive responses to food-relevant stimuli or to changes in energy status. Rather, feeding behavior is modulated by various contextual factors and by previous experiences. The data reviewed here support the perspective that neurons in multiple hippocampal subregions constitute an important neural substrate linking the external context, the internal context, and mnemonic and cognitive information to control both appetitive and ingestive behavior. Feeding behavior is heavily influenced by hippocampal-dependent mnemonic functions, including episodic meal-related memories and conditional learned associations between food-related stimuli and postingestive consequences. These mnemonic processes are undoubtedly influenced by both external and internal factors relating to food availability, location, and physiological energy status. The afferent and efferent neuroanatomical connectivity of the subregions of the hippocampus is reviewed with regard to the integration of visuospatial and olfactory sensory information (the external context) with endocrine and gastrointestinal interoceptive stimuli (the internal context). Also discussed are recent findings demonstrating that peripherally derived endocrine signals act on receptors in hippocampal neurons to reduce (leptin, glucagon-like peptide-1) or increase (ghrelin) food intake and learned food reward-driven responding, thereby highlighting endocrine and neuropeptidergic signaling in hippocampal neurons as a novel substrate of importance in the higher-order regulation of feeding behavior.

Keywords: Feeding, Learning, Memory, Obesity, Reward, Ventral hippocampus

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The rising prevalence of obesity in the United States is driven, in part, by a linear increase in average daily caloric consumption (1–3). Innovative pharmacologic and other therapies that can reduce excessive food intake are urgently needed, as behavior therapy offers limited success and gastrointestinal bariatric surgery, while effective, has serious adverse consequences (4). Basic science investigation of the systems neuroscience of feeding behavior has historically, and nearly exclusively, focused on neurons in the arcuate hypothalamic nucleus and to a lesser extent on neurons in other hypothalamic nuclei and the caudomedial medulla. Recent studies have expanded focus beyond these common targets, focusing attention on additional hindbrain, midbrain, and forebrain regions, including the parabrachial nucleus (5), ventral tegmental area (VTA) (6,7), medial prefrontal cortex (mPFC) (8,9), amygdala and extended amygdala (10), and nucleus accumbens (11–13). Neuroanatomically interconnected with several of these regions is the hippocampus, a forebrain structure historically associated with mnemonic control. Emerging evidence supports the view developed further here that hippocampal neurons contribute to the anatomically distributed neural control of feeding behavior. Our model proposes that

hippocampal neurons integrate previous learned experience (episodic memories, conditional associative learning, incentive factors) with the external sensory context (visuospatial, olfactory, gustatory cues) and the internal context (interoceptive energy status cues) to influence decisions about when, where, what, and how much to eat. Below, we highlight a diverse range of data that support this model.

HIPPOCAMPAL-DEPENDENT MNEMONIC INFLUENCES ON FEEDING

Episodic Memory

The hippocampus is required for the formation and consolidation of declarative memory, which is composed of semantic memory and episodic memory (14,15). The former represents the conscious recollection of general factual information, whereas the latter represents autobiographical memories of events that can be explicitly recalled. Eating a meal or snack can become an episodic memory that is consolidated to long-term memory and recalled at a later time. The relevance of

hippocampal-dependent episodic memory function to feeding behavior is supported by data showing that both meal initiation and meal size are influenced by the degree to which previous meals can be explicitly recalled. For example, amnesic patients with extensive bilateral hippocampal damage who show deficits in establishing new episodic memories will consume a second or even third meal offered only minutes later (16). Higgs *et al.* (17) expanded these findings by showing that while patients with hippocampal damage persistently consume multiple successive meals, they demonstrate reduced liking of foods that were sampled versus foods presented but not sampled, a phenomenon known as sensory-specific satiety. These findings indicate that sensory-specific hedonic modulation of feeding does not require hippocampal-dependent episodic memory of recent feeding occasions. In healthy human subjects, Higgs (18,19) also demonstrated that priming the explicit recall of a recent meal decreases the amount of food that is consumed at the subsequent meal.

The relevance of these latter findings to the control of normal feeding behavior is limited by the fact that individuals are rarely explicitly asked to recall a recent meal. An elegant study by Brunstrom *et al.* (20) provided evidence that episodic meal-related memory influences appetite in neurologically intact subjects using procedures that did not involve specific instructions to recall a recent meal. The experimenters covertly manipulated the perceived versus the actual amount of soup consumed during an experimental meal by refilling or drawing soup from a bowl during consumption. When assessed immediately after such a meal, hunger ratings were influenced more by the actual than by the perceived amount consumed. By contrast, the effect was reversed several hours after consumption; the perceived amount and not the actual amount consumed influenced hunger ratings. Collectively, these results demonstrate that hippocampal-dependent episodic memory influences feeding via two mechanisms: 1) primed episodic recall of a recent meal reduces the amount subsequently consumed; and 2) the perceived amount and not the actual amount of food consumed during a recent meal influences hunger levels reported hours later.

The impact of episodic meal-related mnemonic information on feeding has been modeled indirectly in rodents. Henderson *et al.* (21) recently examined the impact of postprandial inactivation of hippocampal neurons on subsequent feeding behavior. After rats were trained to reliably and rapidly consume a 32% sucrose solution at a scheduled time daily, reversible inactivation of dorsal hippocampal neurons (via parenchymal gamma-aminobutyric acid receptor agonist infusion) immediately following sucrose consumption decreased the latency to initiate feeding and increased the size of the subsequent chow meal. One interpretation of these results consistent with the human literature is that neural inactivation of hippocampal neurons disrupted consolidation for the memory of the meal, thereby decreasing the latency to initiate another meal and increasing the amount of food consumed. An alternative (yet not mutually exclusive) interpretation is that hippocampal inactivation disrupted processing of interoceptive satiation and/or satiety signals. This latter interpretation is discussed in more depth below.

Conditional Associative Learning

Food-related cues (visual, olfactory, and gustatory) become associated with rewarding or negative postingestive consequences, and these learned associations powerfully influence subsequent feeding behavior. The most classic example of this is conditioned flavor avoidance (or aversion) learning, in which animals will avoid (or reject) flavor cues that have been previously associated with visceral malaise (22,23). Neutral flavor cues can also become appetite promoting based on their learned associations with nutritive consequences. For example, in flavor preference learning, nonnutritive orosensory flavors paired with gastric nutrient infusions are subsequently preferred compared with flavors associated with control conditions (24). In addition, taste stimuli such as quinine that evoke aversive taste reactivity responses can evoke ingestive oral responses when associated with a nutritive consequence (25).

The hippocampus is not required for conditioned flavor avoidance (or aversion) learning [except with long-trace delays (26)], nor is it necessary for most types of simple associative appetitive learning, generally speaking (27). Rather, hippocampal neural processing is engaged when learned associations between stimuli and outcomes are conditional (28–32). For instance, rodents with complete hippocampal lesions perform as well as control subjects when learning a Pavlovian discrimination problem in which a discrete auditory cue (tone, or A) signals food reinforcement (A+ trials) and another auditory cue (white noise, or B) does not (B– trials). However, hippocampal lesions severely impair the ability to learn a conditional discrimination problem in which a third cue (light, or X) signals (or sets the occasion for) when the tone will not be reinforced (X– > A– trials) (33).

Davidson, Kanoski, Benoit, and colleagues (34–38) have previously argued that this type of hippocampal-dependent conditional discrimination learning captures the type of mnemonic process that influences many aspects of normal feeding behavior. As indicated above, food-related cues become appetite promoting based on their learned postingestive nutritive outcomes. However, eating in response to these conditioned food cues is not always an appropriate or adaptive behavior, such as in the presence of a predator or during positive energy balance. The decision to eat or not to eat, or how much to eat, at any moment in time is modulated by various external and internal contextual cues, as well as cognitive factors (e.g., incentive motivation) that set the occasion for feeding behavior. Hippocampal-dependent neural integration of contextual and incentive factors and previous food-related experiences (episodic memories) contributes to the timing of eating and the amount consumed. Given its interconnectivity with neurons in various feeding-relevant regions, hippocampal neurons occupy prime neural real estate for the integration of learned incentive factors with the detection and utilization of food-relevant stimuli that inform about both external and internal contextual cues (Figure 1).

NEUROANATOMICAL CONNECTIVITY

External Sensory Food-Relevant Information

Visuospatial, olfactory, and gustatory cues arising from the external environment influences feeding behavior by 1) facilitating

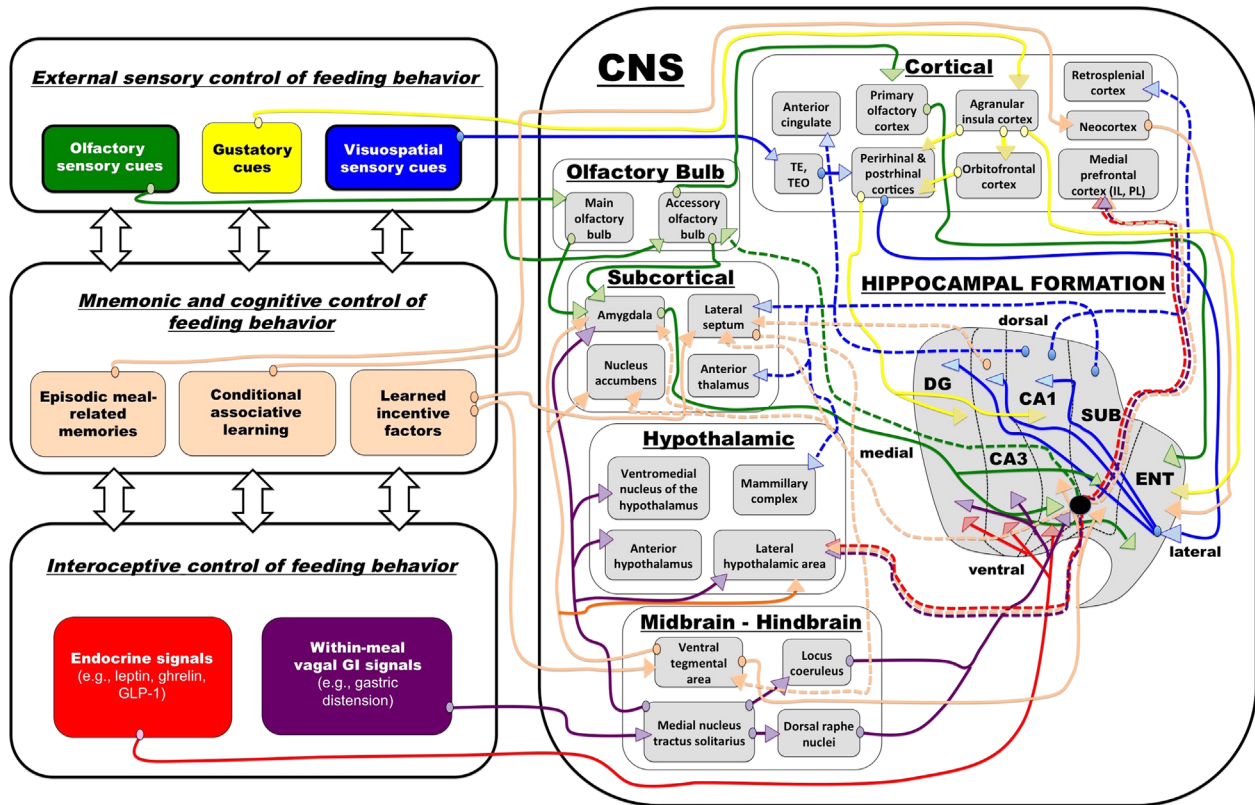


Figure 1. Model for the central integration of information related to energy balance and its convergence within the hippocampal formation. Extrinsic energy balance related connections of the hippocampal formation are represented by colored lines (solid lines = inputs, dashed lines = outputs, arrows = afferent targets, ovals = connection origin; color coded to represent different categories of information). The flat-map representation of the hippocampal formation depicts an unfolded rat hippocampus. The black disk indicates the position of ventral CA1/subiculum containing glutamatergic output neurons that process and transmit energy balance relevant signals. CA1/3, field 1/3 of Ammon’s horn; CNS, central nervous system; DG, dentate gyrus; ENT, entorhinal areas; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; IL, infralimbic; PL, prelimbic; SUB, subiculum. [Adapted with permission from Petrovich *et al.* (40).]

spatial navigation to procure food; 2) indicating the presence and location of nonfood factors (e.g., social, life threatening) that influence the likelihood of engaging in feeding vs. alternative behaviors; and/or 3) determining the safety or nutritive content of orally ingested foods. Within the hippocampus proper (cornu ammonis [CA] fields/Ammon’s horn), external contextual visuospatial information is primarily processed in the dorsal (septal and anterior) subregion in rodents (analogous to caudal hippocampus in primates). Visuospatial information is communicated to dorsal hippocampus (dHP) neurons via cortical pathways involving communication from inferior temporal visual areas TEO and TE to the perirhinal and postrhinal cortices (39) and then to the caudolateral entorhinal cortex, which innervates all components of the hippocampal formation (CA fields, dentate gyrus, subiculum) (40–42). Visuospatial information is represented within the hippocampus primarily by the activity of pyramidal place cell CA1 and CA3 neurons that possess spatially selective firing fields to reflect the animal’s current spatial location. Place cell neurons are located across the dorsoventral hippocampal axis; however, the breadth of spatial representation increases linearly in rodents from less than 1 meter at the dorsal pole to ~10 meters at the ventral pole (43).

Consistent with dHP specialization for neural processing of fine-tuned spatial representation, dHP damage or inactivation typically produces greater deficits in spatial learning compared with ventral regions (temporal and posterior; anterior in primates) (44–46). However, ventral hippocampus (vHP) neurons also contribute to visuospatial navigation and external contextual learning (10,38,47–50). The functional distinction between dorsal and ventral hippocampal regions with regard to visuospatial learning is controversial and has been reviewed elsewhere (41,51,52).

Food-relevant visuospatial information is likely transmitted from dorsal CA1 (dCA1) neurons directly (and polysynaptically through dorsal subiculum [dSub]) via efferent projections to the anterior cingulate and retrosplenial cortices (53), two cortical regions that integrate visuospatial and mnemonic information to influence navigation and reward-based decision making. Visuospatial information is also processed downstream of the hippocampus in the lateral septum, mammillary complex, and anterior thalamus, primarily via dSub efferent pathways (54). The importance of these dCA1 and dSub efferent pathways to cognitive processing of external visuospatial contextual features is exemplified by the fact that lesions or temporary inactivation to any of these individual

output regions produces deficits in spatial or contextual learning that are comparable with hippocampal lesions (50,55–60).

Olfactory cues also have a critical role in food procurement by providing information about the location of food and nonfood factors (e.g., predator, potential mate) that affect the likelihood of foraging or feeding. Olfactory information reaches the hippocampal formation through direct projections from the primary olfactory cortex to the medial band of the entorhinal cortex, which then projects to vHP neurons (41). Olfactory input from the main olfactory bulb also reaches the lateral entorhinal cortex and ventral CA1 (vCA1) and ventral subiculum (vSub) via an indirect pathway relayed through the posterior amygdala (40). Efferent pathways arising from the vCA1 and vSub directly innervate the accessory olfactory bulb (61), suggesting a bidirectional modulation of olfactory processing in vHP neurons. Consistent with the preferential olfactory innervation of vHP versus dHP, vCA1 neurons respond more strongly to aversive/avoided olfactory contextual cues compared with dCA1 neurons (49).

Taste-relevant information is relayed to hippocampal neurons from the agranular insular gustatory cortex through perirhinal and lateral entorhinal cortices (62). Orbitofrontal cortical neurons also transmit taste-relevant information to parahippocampal regions through the rostral perirhinal and postrhinal cortices (63). There is also evidence that CA1 and dentate gyrus neurons are critical for learning the context specificity of taste–postingestive associations (64). However, much remains to be understood about the precise neuro-anatomical pathways relaying gustatory information to the hippocampus and their functional significance.

Interoceptive Energy-Relevant Information

The hippocampus, particularly the vHP, processes visceral energy status-relevant information and utilizes this information to control learned appetitive behavior. Consistent with this notion, a human amnesic with bilateral hippocampal damage will consistently rate his or her hunger levels in the middle of the magnitude scale, regardless of when food was last consumed (16,17). In rats, hippocampal lesions impair learning (or retaining) a discrimination problem in which different levels of food restriction (24 hours vs. 1 hour) are discriminative stimuli signaling a forthcoming food reinforcement (65).

Hippocampal neurons are activated by gastrointestinal satiation signals such as gastric distension (66) and vagus nerve electrical stimulation (67), and hippocampal neural processing directly contributes to meal size control (21,68). Vagally mediated satiation signals are likely transmitted to hippocampal neurons via yet unidentified polysynaptic pathways, given that there are no known monosynaptic pathways between medial nucleus of the solitary tract (mNTS) and hippocampal neurons (68,69). Two putative hindbrain relays connecting vagal input with vHP neurons are the locus coeruleus and dorsal raphe nuclei. Noradrenergic input from locus coeruleus (70,71) and serotonergic input from dorsal raphe nuclei (70) monosynaptically innervate ventral dentate gyrus and vCA1, and these projections have been identified as potentially relaying information from mNTS neurons (72).

The hippocampus also receives neural input communicating food reward-relevant incentive information. Receptors for

dopamine (DA) (D1 receptors and D2 receptors), a key neurotransmitter that encodes the positive affective value of food and food-related stimuli, are expressed throughout the hippocampal formation (73,74). Approximately 15% to 18% of DA neurons in the VTA innervate the vCA1 and vSub, while only half as many DA neurons innervate dHP neurons (75,76). Hippocampal neurons also receive emotion-relevant and other visceral-relevant information from the amygdala, with the posterior basal medial, medial, and central regions heavily innervating the ventral and dorsal dentate gyrus (77) and the lateral amygdala innervating vSub and vCA1 (40).

Hippocampal neurons likely transmit gastrointestinal and other interoceptive feeding-related information to other brain regions primarily via glutamatergic projections arising from vHP neurons. One important efferent pathway from vHP projects to the lateral hypothalamic area (LHA). LHA neurons express feeding-relevant neuropeptides (melanin-concentrating hormone, orexin, neurotensin) (78,79) and LHA lesions produce aphagia and weight loss (80), whereas electrical stimulation of LHA neurons induces robust feeding (81,82). The juxtadorsomedial and juxtaparaventricular LHA subregions receive extensive input from vCA1 and vSub pyramidal neurons (83,84). Neurons in other feeding-relevant hypothalamic nuclei, including the anterior and ventromedial nuclei, also receive direct projections from vCA1 and vSub neurons, albeit to a lesser extent than the LHA (84).

Extensive direct projections are also observed from the vCA1 and vSub neurons to the mPFC (infralimbic and prelimbic subregions) (53,85), which has recently been linked to reward-driven feeding via D1 receptor (8) and opioid receptor signaling (9). Nucleus accumbens core and shell neurons, other key targets of VTA dopamine signaling, receive substantial innervation from the vSub (86–88). The lateral septum, recently associated with the control of gastric motility (89,90) and sucrose hyperphagia (91), is another potential feeding-relevant efferent pathway arising from vSub (92,93) and dorsal CA3 neurons (94). We hypothesize that these monosynaptic outputs from the hippocampus to hypothalamic, striatal, prefrontal cortical, and septal outputs are critical downstream targets for hippocampal neural processing of interoceptive feeding-relevant information.

ENDOCRINE COMMUNICATION

Various endocrine signals secreted from the periphery act on neurons throughout the brain to regulate food intake and body weight. The receptors for many of these signals are expressed in hippocampal neurons, including (but not limited to) cholecystokinin, insulin (95,96), leptin (97), ghrelin (98), glucagon-like peptide-1 (GLP-1) (99), motilin (100), and amylin (101). Similarly, hippocampal neurons express receptors for several central nervous system (CNS)-derived neuropeptides whose release potently modulates feeding, including Y1 receptor (102), melanocortin-4 receptor (103), orexin receptor 1 (104), and melanin-concentrating hormone 1 receptor (105). The role of these hippocampus-expressed endocrine and neuropeptidergic receptors in feeding behavior remains largely unexplored. By contrast, in what follows, data are reviewed for three endocrine signals (leptin, ghrelin, and GLP-1) recently shown to regulate food intake through action on hippocampal

receptors. Interestingly, in addition to regulating food intake, each of these hormonal signals upregulates dynamic structural changes in hippocampal neurons that are purported to contribute to the formation and maintenance of new memories, including synaptic plasticity and neurogenesis (106–108). The neurotrophic functions of these endocrine signals have been reviewed elsewhere (109). Here, we focus on the neural and behavioral mechanisms through which leptin, ghrelin, and GLP-1 communicate interoceptive energy-relevant signals to vHP neurons to influence feeding behavior.

Leptin

Leptin is a hormone produced principally from white adipocytes (110). Increased CNS leptin receptor (LepRb) signaling potently reduces food intake and body weight, while eliminating leptin signaling through mutation of leptin or LepRb results in hyperphagia and extreme obesity in both humans and rodents [(111) for review]. Leptin reaches the brain through blood-brain barrier transport from the peripheral circulation, with the highest transport observed in the hypothalamus and hippocampus (112). The effects of CNS LepRb signaling on energy balance control were initially thought to be mediated almost exclusively by LepRb signaling in the hypothalamic arcuate nucleus (113); however, subsequent research revealed that mNTS LepRb signaling plays an important endogenous role in food intake regulation (114–116). In addition, LepRb activation in the VTA reduces feeding and mesoaccumbens dopamine signaling (6,117). Our recent data show that activation of hippocampal LepRbs also reduces food intake. Microinjections of leptin delivered to the dHP or vHP reduced 24-hour food intake in rats, with more potent effects observed following ventral than dorsal delivery (38). Collectively, these findings support the view that leptin reduces food intake through a distributed circuitry involving engagement of LepRbs in multiple brain regions (118,119), including the hippocampus.

In addition to reducing home cage chow intake, vHP LepRb activation also reduced learned appetitive, reward-related feeding behaviors (38). vHP leptin administration reduced food seeking in an environment that had been associated with consuming a palatable meal when tested in the absence of food. Moreover, vHP LepRb activation reduced the latency to obtain palatable food in an operant runway procedure and blocked memory consolidation for the spatial location of food. These data suggest that hippocampal leptin signaling modulates memory formation and retrieval in a manner that actively inhibits food-related features in the environment in favor of nonfood features, resulting in reduced appetitive responding in the presence of environmental food-associated cues.

GLP-1

GLP-1 is an incretin hormone produced in the distal small intestines and in the hindbrain (nucleus of the solitary tract [NTS] and reticular formation). Activation of peripheral or central GLP-1 receptors stimulates glucose-dependent insulin release and reduces food intake and body weight (120). Unlike leptin, which is a signal for longer-term energy status, GLP-1 acts primarily as a shorter-term, prandial satiation signal (121–123). GLP-1R activation in the hypothalamus

(paraventricular nucleus or LHA) (124,125) or in the mNTS (126–128) reduces food intake. Recently, the anorectic effects of CNS GLP-1R activation were shown to involve action in the mesolimbic dopaminergic circuitry as well (129–131). GLP-1Rs are also expressed in hippocampal neurons, with the most dense expression patterns observed in the vCA1 and ventral CA3 pyramidal layers (99). Hsu *et al.* (68) have recently shown that vHP GLP-1R activation potently reduced food intake in rats, with ~40% reduction in 24-hour chow intake and ~50% reduction in 24-hour Western diet intake. These intake-reducing effects are physiologically relevant to normal feeding, as vHP administration of the selective GLP-1R antagonist, exendin-(9–39), increased food intake.

In contrast to leptin, the anorectic effects of vHP GLP-1R signaling do not involve blocking incentive aspects of feeding but rather require prandial and/or postprandial mechanisms. For example, vHP GLP-1R activation reduced food intake via a specific effect on meal size without altering meal frequency and also reduced motivated lever-press responding for palatable food under testing conditions that allowed for periodic food consumption, whereas no effects were observed on the expression of conditioned place preference for palatable food when tested without food access. Thus, these data are consistent with the hypothesis that longer-term energy status cues are communicated to hippocampal neurons, in part, through the adipose-derived hormone leptin, thereby reducing appetitive food-seeking/foraging behavior. On the other hand, shorter-term prandial and/or postprandial satiation cues are communicated to the hippocampus, in part, via GLP-1, thereby reducing meal size and appetitive responding during or immediately following food consumption. Interestingly, despite the fact that GLP-1Rs are robustly expressed on hippocampal neurons, NTS GLP-1 neurons do not innervate the hippocampus (68,132), suggesting that under physiological conditions, GLP-1 (of either peripheral or NTS origin) communicates to the hippocampus via humoral volume transmission through the cerebrospinal fluid and/or vasculature. Indeed, active levels of GLP-1 peptides are present in both the cerebrospinal fluid and vHP under physiological conditions (68), although the source (peripheral vs. central) is unclear.

Ghrelin

Ghrelin, a peptide hormone secreted from the stomach (133), communicates to the CNS to increase food intake and food-motivated behavior and is the only known circulating hormone with orexigenic properties. Like leptin and GLP-1, ghrelin receptors [growth hormone secretagogue receptor 1-A (GHSR1A)] are expressed throughout the brain and activation of GHSR1As in multiple different brain nuclei increases feeding, including the hypothalamus (134), VTA (7,135), and mNTS (136). GHSR1As are expressed in hippocampal neurons with the most dense expression patterns observed in the vHP (137). We recently observed that activation of GHSR1As in vHP neurons approximately doubled food intake, whereas ghrelin delivered to the dHP had no effect on feeding (138).

Several of our findings suggest that vHP ghrelin receptor signaling increases both appetitive and consummatory aspects of feeding. First, vHP ghrelin increased feeding in rats by elevating both meal frequency and size (138). In further

support of a role in appetitive control, vHP GHSR1A activation increased the frequency of meal initiation in response to discrete auditory cues that were previously conditioned to signal the availability of palatable food (138). In support of a role in consummatory control, a dose of ghrelin subthreshold for intake effects when administered to vHP alone attenuated the reduction in food intake following peripheral administration of the gut-derived satiation hormone cholecystokinin (S.E. Kanoski, Ph.D., unpublished data, 2015).

Collectively, these findings indicate that vHP endocrine receptor signaling both stimulates and reduces feeding-relevant behaviors, with the direction of feeding effects being modulated by signals that inform about either positive (leptin, GLP-1) or negative (ghrelin) energy status.

CONCLUSIONS

Feeding is not always an appropriate or feasible behavior, even when animals are faced with severe nutrient deficiency. On the other hand, feeding can often occur in the absence of metabolic need based on incentive factors and/or exposure to conditioned reward-related cues. In addition to features in the external environment that influence feeding, interoceptive and cognitive factors, such as visceral malaise, satiation, or fear, will decrease the likelihood of feeding or foraging, whereas other interoceptive or cognitive factors, such as hunger arising from food deprivation (negative energy balance) or learned incentive motivation (often associated with positive energy balance) have the opposite effect. Importantly, the relationship between external sensory factors, internal states, and ingestive behavior is dynamic and can be modified with experience. Our model proposes that hippocampal neurons integrate 1) episodic meal-related memories and food-relevant learned associations and incentives; 2) the external sensory food environment; and 3) interoceptive energy status-relevant cues (i.e., the internal context) to regulate decisions about when, where, what, and how much to eat. Visuospatial sensory information relating to food location is communicated primarily to dHP neurons, whereas olfactory cues are communicated primarily to vHP neurons. External contextual information is then transmitted to cortical regions that integrate visuospatial, olfactory, gustatory, and mnemonic information to influence navigation and reward-based decision making. We speculate that the entorhinal cortex is a key site of neural integration of external contextual and episodic mnemonic information, as this region relays visuospatial, olfactory, and gustatory information to hippocampal neurons (40–42,62) and is considered to be an important interface linking the neocortex and hippocampus to control for episodic memory formation and retrieval (139,140).

Gastrointestinal and other visceral information is polysynaptically transmitted to vHP neurons (and dHP to a lesser extent) from hindbrain regions. Hippocampal neurons also receive energy balance relevant information from circulating endocrine signals, such as leptin, GLP-1, and ghrelin, and activation of their receptors in vHP neurons potently decreases (leptin, GLP-1) or increases (ghrelin) food intake and food reward driven appetitive behaviors. We posit that the LHA, mPFC, nucleus accumbens, and the lateral septum are key efferent targets of vHP neurons that process interoceptive

energy balance relevant information downstream of the hippocampus, although these hypotheses remain to be tested.

In conclusion, data reviewed here support the perspective that hippocampal neurons (particularly vHP) are an important neural substrate linking the external context, the internal context, and mnemonic and cognitive information to control both appetitive and ingestive behavior. Hippocampal endocrine and neuropeptidergic signaling is likely to attract considerably more attention as the field expands the scope of the neuroanatomical bases of energy balance beyond hypothalamic substrates.

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