Review

Biological Psychiatry

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

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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