A potential role for the hippocampus in energy intake and body weight regulation

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Recent research and theory point to the possibility that hippocampal-dependent learning and memory mechanisms translate neurohormonal signals of energy balance into adaptive behavioral outcomes involved with the inhibition of food intake. The present paper summarizes these findings and ideas and considers the hypothesis that excessive caloric intake and obesity may be produced by dietary and other factors that are known to alter hippocampal functioning.

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Much research has been devoted to identifying and understanding the role of inhibitory gut–brain signals in the control of energy intake and body weight [1]. A widely held view is that the arrival of nutrients in the gut gives rise to relatively short-term hormonal (e.g. cholecystokinin (CCK)) meal termination or 'satiety' signals [2]. The effectiveness of these signals is thought to be modulated by circulating adiposity hormones (e.g. leptin and insulin) that provide information about the longer term, as opposed to meal-related status of bodily energy stores [3]. In addition, ghrelin has been identified as a gastric peptide that functions as a physiological meal initiation or 'hunger' cue [4] that is elicited not only as a result of a change in an animal's nutrient status but also as a learned anticipatory response to environmental cues associated with food [5]. Peripherally administered CCK and leptin appear to have interoceptive sensory consequences similar to those produced by a low level (e.g. 1 h) of food deprivation [6], whereas the cue properties of peripherally or centrally administered ghrelin are similar to higher (e.g. 23 h) levels of food deprivation [7,8]. All of these signals are transmitted to the brain where they are thought to be detected primarily by hypothalamic and hindbrain nuclei [2,9].

While the identification of physiological meal-related and adiposity signals has contributed much to our understanding of the control of food intake and body weight regulation, relatively little is known about how the information provided by these cues is translated by the brain into adaptive behavioral outcomes. Although the hypothalamus and hindbrain have been identified as brain substrates that are involved with the detection of satiety, adiposity, and hunger cues, the ultimate decision to eat or to refrain from eating may depend on the processing of these signals at other brain sites involved with the higher order control of behavior.

The hippocampus, a medial temporal lobe structure long regarded as an important substrate for learning and memory [10], has received increasing attention for its potential role in energy regulation. While some have suggested that hippocampal participation in energy homeostasis might not rely exclusively on learning and memory [11,12], findings and theoretical developments encourage the hypothesis that hippocampal-dependent learning and memory mechanisms might contribute directly to the higher order control of food intake. The purpose of this paper is to summarize and integrate some of these findings and ideas.

What does the hippocampus do?

Historically [10], the hippocampus has been identified most closely with (a) encoding and retrieval of spatial relations among objects in the environment (i.e. spatial memory) and (b) the formation and recall of memories about events and facts (i.e. declarative memory). While these conceptualizations are based primarily on studies of human amnesia, other more recent views of hippocampal function are derived from modern associative learning theories. Morris [13] noted that several of these newer accounts converge on the idea that the hippocampus is needed to resolve 'predictable ambiguities' that exist when a single stimulus consistently signals different outcomes dependent on the presence or absence of other cues.

Negative occasion setting is a hippocampal-dependent process involved with learning to resolve predictable ambiguities. Rats with hippocampal lesions exhibit impaired negative occasion setting when they readily

learn to respond to a conditioned stimulus (CS) that is consistently followed by delivery of a food pellet unconditioned stimulus (US) but are impaired at learning that a different cue (i.e. a negative occasion setter) signals when the CS will not be followed by the US. In this problem, although the ambiguity involved with predicting when the CS will be followed by reinforcement or nonreinforcement is resolved by the presentation of the negative occasion setting cue, rats with hippocampal lesions tend to respond to the CS as much on nonreinforced trials when the negative occasion setter is present as on reinforced trials when the CS occurs alone [14].

Removing the hippocampus also interferes with the ability of rats to use context cues (e.g. background, apparatus and temporal cues) to signal that a previously trained CS will no longer be followed by its unconditioned stimulus (US). According to Holland and Bouton [15], negative occasion setting by context cues may be a specialized function of the hippocampus. A recent imaging study [16] supports a similar conclusion. Human subjects were trained in one context with a visual CS that signaled delivery of a mild shock. The CS was subsequently extinguished in a different context. Functional magnetic resonance imagery (fMRI) showed that after extinction, the ventromedial prefrontal cortex (VMPFC) and the hippocampus were activated when the CS was presented in the extinction context, but not when it occurred in the training context. Consistent with a negative occasion setting interpretation, this finding suggests that retrieval of the memory depends on hippocampal-dependent gating of CS outputs to the VMPFC by the extinction context.

To eat or not to eat—a case of predictable ambiguity

When food and stimuli associated with food are encountered, these cues may evoke vigorous appetitive and consummatory responding on some occasions and little or no responding at other times. A common interpretation of this pattern of behavior is that animals engage in appetitive and eating behavior until they become satiated and then refrain from making these responses until satiety wanes [9]. *How does satiety inhibit, and the absence of satiety promote, appetitive responding?* The answer to this question may depend on an animal's ability to resolve a predictable ambiguity by learning that satiety signals predict when food cues will not be followed by an appetitive postingestive US. In other words, just as experimentally programmed negative occasion setters resolve ambiguity by predicting when a CS will not be followed by its US, interoceptive satiety signals may resolve ambiguity by predicting when food cues will not be followed by appetitive postingestive outcomes [17].

The ability of regulatory hormones to modulate the strength of appetitive behavior may also depend on their effects on hippocampal-dependent learning and memory processes. The hippocampus is densely populated with both leptin and insulin receptors [12], and administration of each of these peptides has been shown to enhance both hippocampal-dependent spatial memory and hippocampal long-term potentiation (LTP) [18–20], a reported cellular basis for learning and memory [21]. Furthermore, mutant rats lacking CCK receptors not only become obese but also exhibit impaired hippocampal-dependent learning [22,23]. Recent neuroanatomical findings also directly link the hippocampal CA1 cell field to hypothalamic nuclei and other brain circuits thought to underlie energy regulation [24]. Other data point more directly to the hippocampus as a processor of satiety information. Using fMRI, Wang *et al.* [25] reported that, in obese people, the hippocampus is the site of greatest activation following gastric stimulation known to have effects on intake, stomach distention, hormonal, and vagal activity similar to those produced by eating a large meal. In addition, fMRI showed that consuming a liquid meal to satiation decreased hippocampal blood flow for people who were obese or were formerly obese, but not for people who had never been obese ([26], also see reference [27]). In sum, these results indicate that (a) the hippocampus is sensitive to satiety signals; (b) at least some of these signals induce changes in hippocampal activity that are thought to facilitate learning and memory; (c) the hippocampus is part of a neural circuit whereby the information provided by satiety signals could be transmitted from the gut to the hippocampus and from the hippocampus to forebrain circuits involved with energy regulation; and (d) sensitivity of the hippocampus to these signals may be altered in people who have a history of energy dysregulation.

Also, there is evidence that the inhibitory control of food intake and appetitive behavior depends on the structural integrity of the hippocampus. For example, after eating a full meal densely amnesic human patients with hippocampal damage will eat a full second meal that is offered only minutes later [28,29]. Higgs [30] demonstrated that for neurologically intact humans, memories of a prior meal help to inhibit subsequent intake. Densely amnesic patients may be less able to inhibit intake because their access to these memories is very limited. The results also suggest that hippocampal damage might interfere with satiety signaling by both interoceptive and exteroceptive cues.

Food sated rats with highly selective neurotoxic lesions confined to the hippocampus show increased appetitive behavior (e.g. food cup approach, bar pressing) relative to intact controls [31–33] and are impaired in using interoceptive cues arising from low (e.g. 1 h) and high (e.g. 23 h) levels of food deprivation as discriminative stimuli ([32,34] also see reference [35]). Consistent with a role for the hippocampus in negative occasion setting, in these

latter problems, lesioned rats were impaired at using deprivation state cues to inhibit their behavior on non-reinforced trials. Furthermore, when intake suppression during recovery from surgery is accounted for, hippocampal-lesioned rats also show increased food intake and body weight gain [17]. These results suggest that the behavioral inhibition by energy state signals depends on the hippocampus.

Obesity—a hippocampal-dependent phenomenon

Recent findings indicate dietary factors that promote excessive food intake and weight gain can also interfere with hippocampal functioning. For example, epidemiological data associate intake of diets high in saturated fat with weight gain [36,45] and memory deficits [37]. It may be that cognitive deficits are secondary to effects of high-fat diets on the development of insulin resistance. Rats and humans with diabetes mellitus show age-related performance impairments on memory tasks [38], and recent findings from rats indicate that these effects may be accompanied by changes in hippocampal insulin sensitivity [39].

The detrimental effects of high-fat diets on learning and memory may also be related to decreased expression of hippocampal brain-derived neurotrophic factor (BDNF), which is known to play an important role in activity-dependent synaptic plasticity in the adult brain [40,41]. In rodents, administration of exogenous BDNF decreases food intake, whereas genetic models with deficient BDNF signaling exhibit hyperphagia and obesity related primarily to marked increases in meal frequency, but not meal-size or duration [40,42]. This meal pattern suggests that, like rats with selective hippocampal lesions, BDNF-deficient mice may be impaired at inhibiting responding to pre-oral and oral food cues that evoke learned appetitive responses [31,32]. Impaired performance on hippocampal-dependent learning and memory tasks and reduced hippocampal BDNF is also found in rats that have been maintained on a high-fat diet [43,44]. In humans, obese children and adolescents exhibit reduced serum BDNF levels relative to their normal weight counterparts, when variability due to age, gender, race, pubertal status, and platelet count is accounted for ([45] but see reference [46]). Furthermore, in what appears to be the only study of its kind with humans, an eight-year-old female with haploinsufficiency for BDNF exhibited hyperphagia, severe obesity, and cognitive impairments [47].

Current research and theory has tended to treat the effects of BDNF on energy regulation and on cognitive functioning as largely independent phenomena, which involve distinct (e.g. hypothalamic and hippocampal, respectively) neural substrates [40,48]. A question of interest is whether changes in BDNF or other physiological signals (e.g. leptin and insulin) could contribute to energy dysregulation and obesity as a primary consequence of impairing hippocampal functioning. For example, if intake of high-fat (or other) diets disrupts hippocampal functioning, and if one hippocampal function is to inhibit the ability cues associated with those diets to evoke appetitive and consummatory behaviors, this weakening of inhibitory control could promote obesity as part of a 'vicious circle' of increasing fat intake, more severe disruption of hippocampal functioning, and further weakening of the inhibitory control [17]. Although direct tests are needed, much of the data presented in this brief review seem consistent with this general type of working hypothesis.

Conclusions

Researchers have identified a number of contact points between physiological signals and circuits involved with energy regulation and the hippocampus, a brain structure involved with learning and memory. On the basis of these findings, now may be the time to begin connecting these points within a more integrative conceptual framework. In addition to providing a more complete account of how animals maintain energy balance, this framework may lead to new therapeutic approaches to the problems of obesity and cognitive decline.

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