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## Learned and Cognitive Controls of Food Intake

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### Abstract

While much has been elucidated about the hypothalamic controls of energy balance, the epidemic of obesity continues to escalate. Recent work has suggested that extra-hypothalamic central nervous system structures may play a previously un-appreciated role in the control of ingestive behavior and body weight regulation. Because animals can and do learn about food and food-related stimuli, as well as the consequences of eating, we and others have sought to understand the cognitive process that underlie that learning. Additionally, we have begun to investigate the neuro-anatomical bases for complex learning about food and food-cues. Here we review some evidence for learning about food as well as evidence that the hippocampus may play a critical role in the brain's ability to regulate body weight through such learning processes.

### Introduction

The regulation of body weight is controlled by a complex integration of peripheral signals and central effector mechanisms. In its simplest form, the regulation of body weight was assumed to involve a negative feedback loop. According to this conceptualization, peripheral signals of energy balance, including hormones and nutrients, are detected directly or indirectly by central (e.g., hypothalamic nucleus) effector systems to produce behavioral and physiological outputs that regulate food intake and energy expenditure. Much recent evidence demonstrates that animals are capable of learning about these signals as well as the about the feedback produced as a consequence of food ingestion. Further, evidence demonstrates that these learned relationships can exert control over subsequent eating behaviors. It is now recognized that this learned control of eating is part of the regulation of feeding, and under certain circumstances these learned controls may be able to override physiological regulatory mechanisms

### Pre-ingestive mechanisms

For an animal to learn about signals associated with energy balance, one must assume that the presence or absence of energy stores are associated with detectable, interoceptive sensory cues. In fact, the initiation of food seeking and ingestion is often considered to result from homeostatic signals that accumulate over the interval since food was last consumed. Specifically, food deprivation is thought to generate homeostatic signals related to the gradual depletion of energy stores (e.g., Woods et al, 2000), and these signals may make

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animals more likely to engage in appetitive behaviors that ultimately lead to food consumption. Similarly, food intake can produce various energy repletion or “satiety” signals that are thought to prevent positive energy balance by suppressing eating and appetitive behavior. The first requirement for changes in physiological systems related to food deprivation to be able to affect food-seeking and other pre-ingestive behaviors is that animals must be able to detect these changes. In fact, there is compelling evidence, using Pavlovian conditioning techniques, demonstrating that animals can learn to respond to the presence or absence of these internal signals.

We have extensively used a paradigm for assessing a “deprivation-discrimination” process (e.g., Seeley, et al., 1995; Davidson et al., 1992) In this procedure, rats are trained such that one level of food deprivation (e.g., 24 hr) is always associated with the delivery of a specific unconditioned stimulus (US), while another level of deprivation (e.g., 0 hr) is not. Physiological cues arising from 24-hr food deprivation then become discriminative signals for the subsequent presentation of the US. Thus, these animals come to anticipate reinforcement when they are 24-hr food deprived, but not when they are 0-hr deprived. Importantly, in these experiments, another group of rats receives the reverse contingency between deprivation and reinforcement (i.e., the US is presented when 0-hr food deprived, but not when 24-hr food deprived). Discrimination is evident to the extent that an animal makes more anticipatory responses (i.e., behaviors appropriate for preparing for the US) when under their reinforced compared to their non-reinforced level of food deprivation.

Using both appetitive (peanut oil, sucrose pellets) and aversive USs (foot-shock), we have found that rats readily solve this discrimination (e.g., Davidson et al., 1993; Davidson et al., 1988; Davidson et al., 1996; Seeley et al., 1995). There are two important implications of this. The first is that food deprivation (or its absence) produces reliable internal signals that the animal can detect and use to influence its behavior. The second is that once rats have been trained to respond differentially to these signals, they can then be assessed for generalization to pharmacological manipulations that influence food intake.

An important question is whether or not administration of exogenous compounds that change food intake will elicit patterns of responding similar to those seen after periods of food deprivation or food repletion. That is, we have sought to assess whether peptides or hormones might play a role in the production of interoceptive sensory stimuli that underlie the states of “hunger” and “satiety” and contribute to the altered behavioral responses to food and food-related stimuli. In other words, does a peptide, hormone or compound that changes food intake also elicit sensory consequences like those following “hunger” or “satiety?” In this respect, we have defined “hunger” and “satiety” 1) operationally as periods of 24- and 0-hr food deprivation, respectively, and 2) functionally as the consequent physiological events of different degrees of food deprivation (e.g., associated changes in peripheral signals like leptin, insulin, and glucose, as well as central neuropeptides such as NPY or a-MSH [see Woods, 2000 for review]). The use of behavioral techniques unrelated to food intake per se is important because 1) we seek to understand what physiological systems underlie specific psychological states such as hunger or satiety, and 2) because they help reduce the potential confounds encountered when tests rely solely on measures of food intake (see Davidson et al., 1993). For example, differentiate behavioral control by deprivation intensity stimuli from the potential effects of deprivation manipulations on the taste and postingestive consequences of eating, learning about deprivation intensity cues can be evaluated when eating, food, and in some studies, external cues related to food, are absent from the test situation.

Employing this type of deprivation-discrimination in a previous experiment, we observed that following intracerebroventricular administration of melanocortin agonists rats respond

as if they were 0-hr food deprived and, conversely, that melanocortin antagonists elicit responding like that following 24-hr food deprivation. Additionally, we have also demonstrated that the orexigenic stomach-derived hormone ghrelin elicits conditioned responding like that observed following a period food deprivation and that the gut peptide cholecystokinin and the adipocyte hormone leptin, both of which act to reduce food intake, generalize to a state of 0-hr food deprivation (e.g., Davidson et al., 2005; Kanoski et al., 2007b; Kissileff and Van Itallie, 1982; Woods et al., 2000). On the other hand, administration of NPY does not elicit behavior similar to 24-hr food deprivation in this paradigm, suggesting that this peptide acts via mechanisms other than inducing an interoceptive state of “hunger” or by abolishing “satiety” cues (e.g., Jewett et al., 1991; Seeley et al., 1995). These findings collectively suggest that while many exogenous factors have been reported to significantly affect food intake in rats, not all may do so by mimicking the effects of differing degrees of food deprivation or by eliciting what would experientially be called “hunger” or “satiety.”

## Post-ingestive mechanisms

After an animal has consumed food and is operationally “sated,” post-ingestive processes are thought to be engaged which influence subsequent food intake. It is well known that animals learn about these post-ingestive consequences of eating (e.g., Drucker et al., 1994; Elizade and Sclafani, 1990; Lucas and Sclafani, 1989; Sclafani, 1991). One early example of post-ingestive learning is the conditioned taste aversion. When rats experience visceral illness after ingestion of a novel flavor, they will readily avoid that flavor in the future (e.g., Garcia and Koelling, 1966). Thus, an animal in this situation has learned that the post-ingestive consequences of eating a particularly flavored food are negative. Importantly, the avoidance of the illness-induced flavor can be independent of physiological states. For example, water-deprived rats will readily avoid saccharin-flavored water if the saccharin has been associated with illness. That is, the rats will avoid repleting water balance to avoid the anticipated negative post-ingestive outcome.

Analogously, animals can also learn about the positive post-ingestive consequences of food intake. For example, rats can learn to associate foods or tastes with specific nutrient or caloric content (Drucker et al., 1994; Friedman et al., 1983; Lucas and Sclafani, 1999; Perez et al., 1999; Tordoff and Tepper, 1987). This kind of learning can then influence subsequent food choice decisions. Generally, flavors paired with more calories will be preferred relative to those paired with fewer calories (Ackroff and Sclafani, 2006). However, particularly high levels of nutrient density will reduce intake of an associated flavor, a phenomenon known as conditioned satiety (e.g., Booth, 1972). Deprivation state can also affect these flavor preferences, with preferences for flavors paired with more caloric foods enhanced by food deprivation and depressed under states of satiety (e.g., Fedorchak and Bolles, 1987; Yin et al., 2005). Finally, rats can be trained to increase caloric-intake and/or meal-size by anticipating an energy deficit. When placed on a meal-feeding schedule, rats may have access to food for a only a limited time each day. Across days, the amount of food consumed increases, until near that exhibited by an ad-lib fed control group. Under these circumstances, the rat is thought to anticipate the subsequent absence of food and mount a learned response that enables increased consumption in a short period of time (e.g., Drazen et al., 2006; Woods, 2009).

One way in which learning about the post-ingestive effects of particular foods has been conceptualized is termed “incentive value”. According to this view, the magnitude of the positive post-ingestive consequences of ingestion is a function of deprivation state. Therefore, animals assign incentive values to specific foods based upon the degree of food deprivation present when the foods are consumed (e.g., Balleine, 1992; Balleine, 1994;

Dickinson and Balleine, 1994; Dickinson and Balleine, 1995). During fasting, consumption of foods, particularly novel foods, will lead to assignment of a higher incentive value for that food than when the same food is consumed when an animal is sated. Over time, multiple experiences with foods under a variety of deprivation conditions will ultimately allow an animal to modulate their intake of a variety of foods based on the anticipated post-ingestive effects, or the incentive value they have assigned, given their deprivation level at a particular eating occasion. However, if an animal encounters a particular food only when food deprived, that food will maintain a consistently higher incentive value than foods that are sampled under both low and high deprivation. A higher incentive value, even in the absence of food deprivation, can subsequently elicit both increased food intake and increased appetitive approach behaviors (e.g., Balleine, 1992).

Based on this notion, we developed an experimental paradigm designed to assess the effects of hypothalamic peptides on the learning of these flavor → post-ingestive relationships (e.g., Benoit et al., 2001). In this paradigm, animals are trained to associate a cue with a specific food (e.g., sucrose) under one deprivation condition. Animals are then exposed to this same food under either the same deprivation condition, a novel condition, or after being treated with a peptide of interest. They can then be tested for responding to the food-paired cue under the novel deprivation condition. Having been previously exposed to the food under this condition can alter the animals responding during the test, relative to those animals that always received the food in the same deprivation condition. This is because the former group has had the opportunity to acquire new information about the post-ingestive effects of the food under this state. Importantly, responding of the group treated with the peptide of interest (in the original deprivation condition) can then be compared to the animals in both groups to determine the effect of this peptide to alter what is learned about the post-ingestive consequences of the food (e.g., Benoit et al., 2000; Benoit et al., 2001).

Because of its strong effects on food intake behaviors, the hypothalamic melanocortin peptide, alpha-melanocyte stimulating hormone ( $\alpha$ -MSH), seemed an obvious candidate assess for post-ingestive consequences. With respect to learning about post-ingestive consequences, we observed that the  $\alpha$ -MSH analogue MTII (which potently reduces food intake) was unable to support post-ingestive learning like that following the ingestion of food in a sated state (Benoit et al., 2001). These data suggest: 1) That the processes underlying consumption of food and learning about the post-ingestive effects of food intake may be separable and 2) That specific neuropeptide systems might be involved in one, but not another of the processes.

Collectively, these studies suggest that animals can learn about their internal states by detecting interoceptive sensory stimuli and associating those stimuli with consequences of eating. Likewise, they can anticipate the consequences of food intake and adjust their responses to external food cues appropriately. In this way, animals, including humans, are not thermostats per se, in that they do not detect levels of energy availability to initiate or terminate a meal on a moment to moment basis. Rather, we argue they integrate previous experience to anticipate future outcomes. From this perspective the control appetitive behaviors relies on an animal's knowledge about the relationship between energy state signals, food cues, and the likely post-ingestive consequences of eating, rather than solely on signals related to its immediate needs. In fact, Woods (Woods, 1991; Woods, 2009) has similarly proposed that the role of leaning in the control of food intake is precisely to prevent disturbances from physiological imbalance.

If eating is not merely a reflexive response to physiological deficits cues, it is unlikely that the learned control of energy regulation can be accounted for with reference to the formation of simple direct associations between interoceptive deficit cues and consummatory

responses or postingestive outcomes. Rather cues produced by departures from energy balance are more likely to influence eating behavior by signaling when food and cues related to food will be followed by appetitive postingestive outcomes. In this role physiological signals that correspond to hunger and satiety modulate the ability of food-related cues to evoke ingestive behaviors, by enabling animals to anticipate what the postingestive consequences are associated with those cues. Previously, we proposed that the mechanism which underlies this type of modulatory control is based on the operation of a higher-order Pavlovian conditioning process known as negative occasion (e.g., Davidson et al., 2007).

## Centers of integration

Given the data suggestive that animals learn about the signals preceding food intake, as well as the consequences of eating, one would reason that central structures important for learning processes are likely involved. Some of the key sites that may play important roles in these processes would include the hippocampus, amygdala and prefrontal cortex. In fact, amnesic humans with brain damage that includes the hippocampus have been reported to exhibit insensitivity to signals of hunger and satiety (Hebben et al., 1985; Rozin et al., 1998), an effect that has also been observed in rats with highly selective lesions that are confined to the hippocampus (e.g., Davidson and Jarrard, 1993).

In humans, other reports demonstrate that amnesic patients will consume a test meal, even though have had recently consumed a full meal, suggesting that not only do they not remember consuming the food, they do not adequately detect internal signals arising from the previously consumed foods or utilize these cues to suppress eating (Hebben et al., 1985; Rozin et al., 1998). Recently, Higgs (Higgs, 2005) suggested that the memory of a recent meal may help attenuate the intake of a second meal. Therefore, amnesic patients may be less able to inhibit the intake of a second meal because of the absence of the recent meal memory. These results also suggest that hippocampal damage might interfere with satiety signaling by both interoceptive and exteroceptive cues. Likewise, rats with selective lesions of the hippocampus have been found to exhibit increased appetitive responding for food and increased appetitive behavior, relative to intact controls (Clifton et al., 1998; Davidson and Jarrard, 1993; Davidson et al., 2009; Schmelzeis and Mittleman, 1996). This failure to inhibit responding includes attenuated ability to inhibit responding to food cues when food is no longer being delivered (Chan et al., 2001; Tracy et al., 2001) and an attenuation in their ability to inhibit responding based on internal signals of energy balance (Davidson and Jarrard, 1993; Davidson et al., 2005; Davidson 2009).

Collectively, the findings suggest that the (a) the hippocampus plays a role in the detection of interoceptive signals of energy balance and (b) the hippocampus is necessary for animals to learn about these signals. If this is true, one might also conclude that damage to the hippocampus might impair the regulation of body weight and may promote increased energy balance (or obesity) given the relative failure of hippocampal lesioned rats to inhibit appetitive responding and food intake.

In fact only a few previous studies had assessed the effects of hippocampal lesions on body weight regulation, with mixed results. For example, King et al (King et al., 1996) reported that rats with hippocampal lesions consumed significantly more food than controls but did not gain additional body weight. Forloni et al (Forloni et al., 1986) reported that hippocampal lesions were accompanied by both increased food intake and body weight over a much longer period, but only in female rats. Unfortunately, both of these studies used nonselective lesions which produced damage to extrahippocampal structures, fibers of passage or to and underlying vasculature. Recently, we have addressed these confounding factors by using a highly selective ibotenate lesioning technique (e.g., Jarrard, 1989; Jarrard,

2002) to produce hippocampal damage. In several experiments, we have observed that selective IBO lesions of the hippocampus cause a significant increase in food intake and body-weight gain in male rats over 2–3 months, compared to intact and sham controls (Davidson, et al, 2009; Davidson et al., 2010).

Recent accounts propose that (a) environmental food cues will tend to evoke eating until that behavior is inhibited by biological control mechanisms and (b) obesity may be more prevalent because these biological control mechanisms are failing (e.g., Berthoud, 2004; Prentice, 2005). What these control mechanisms might be, and why they they fail are two questions fundamental to understanding, and ultimately controlling, the continuing trends toward increased body weight and obesity in the human population. Much previous work aimed at addressing these questions has focused on hypothalamic control mechanisms and on identifying changes in what could be called the “direct effects” (Smith, 2000) of regulatory neuropeptides (e.g., leptin, CCK, ghrelin, etc.) on these mechanisms that could account for increased intake and body weight. By showing that damage to the hippocampus, a brain structure considered to be an important substrate for learning and memory, interferes with the control of food intake and body weight, the present findings encourage us to think about energy dysregulation, not solely as a deficit in some type of hypothalamic signaling system, but as a type of “learning disorder” (Davidson et al., 2007).

Given the fact that the hippocampus appears to play an important role in the regulation of food intake, including learning about internal signals and the association between internal and external stimuli thought to underlie the learning process, we are faced with the same question that has plagued a hypothalamo-centric view of body weight regulation: Why is the incidence of obesity increasing, even in the face of exquisite biological controls? One common answer to that question, at least with respect to the hypothalamus, is that something in the diet (e.g., dietary fat) may help impart “resistance” to signals that normally regulate food intake and body weight. That is, elevated dietary fat, either directly or indirectly confers an insensitivity to hormones or peptides that would otherwise reduce body weight (e.g., Benoit et al., 2009, Clegg et al, 2005). Under those conditions, the obese animal (or human) would continue to consume food even in the presence of elevated energy stores because the brain had become resistant to the effects of inhibitory mechanisms. These ideas also lead us to question whether or not dietary factors may similarly affect the function of the hippocampus, which in turn would lead to decreased hippocampal controls over energy balance.

## Dietary fat and hippocampus

In fact, several recent studies have demonstrated reduced hippocampal function and plasticity in rats maintained on diets high in fat and sugar. One recent study found rats that had been maintained for 90 days on a diet high in saturated fat exhibited both impaired reversal learning and reduced levels of brain-derived neurotrophic factor (BDNF) in both the ventral (but not dorsal) hippocampus and the medial prefrontal cortex (Kanoski et al., 2007a). Importantly, several other reports have linked reductions in BDNF and/or exposure to high-fat diets to interference with hippocampal learning and memory processes (e.g., Liu et al., 2004; Molteni et al., 2002; Monteggia et al., 2004; Wu et al., 2003; Yamada and Nabeshima, 2003).

If we assume that the function of hippocampus in learning about signals of energy balance is similar to the processes underlying learning about complex relationships such as those involved with negative occasion setting one could see how damage to the hippocampus caused by the intake of dietary fats could lead to a failure to appropriately integrate information about energy balance. Under these circumstances, diets high in fat would

promote obesity in part, by disrupting hippocampal function and thereby attenuating the animals' ability to inhibit responding in the presence of stimuli associated with food (for full discussion of this hypothesis, see: Davidson et al., 2007).

## Conclusions

In summary, much previous data demonstrates that animals can and do learn about their own internal state signals and associate those signals with external food cues. They then use that information to guide or coordinate ingestive behaviors. Studies in humans and rats suggest that the hippocampus is an important structure for the detection and integration of internal signals into learned responses that in turn play a role in the regulation of food intake behaviors. Damage to the hippocampus impairs an animal's ability to inhibit responding to food-related cues, even in the absence of signals of energy depletion. Because diets high in fat can impair the function of the hippocampus and results in attenuated performance of hippocampal-dependent tasks, we propose that the consumption of dietary fat leads to obesity, in part, because of attenuated hippocampal-dependent learning processes.

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