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MODULATION OF FOOD REWARD BY ADIPOSITY SIGNALS

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Abstract

Extensive historical evidence from the drug abuse literature has provided support for the concept that there is functional communication between central nervous system (CNS) circuitries which subserve reward/motivation, and the regulation of energy homeostasis. This concept is substantiated by recent studies that map anatomical pathways, or which demonstrate that hormones and neurotransmitters associated with energy homeostasis regulation can directly modulate reward and motivation behaviors. Studies from our laboratory have focused specifically on the candidate adiposity hormones, insulin and leptin, and show that these hormones can decrease performance in behavioral paradigms that assess the rewarding or motivating properties of food. Additionally we and others have provided evidence that the ventral tegmental area may be one direct target for these effects, and we are currently exploring other potential anatomical targets. Finally, we are beginning to explore the interaction between adiposity signals, chronic maintenance diet of rats, and different types of food rewards to more closely simulate the current food environments of Westernized societies including the U.S. We propose that future studies of food reward should include a more complex environment in the experimental design that takes into account abundance and variety of rewarding foods, psychological stressors, and choices of reward modalities.

Keywords

insulin; leptin; ventral tegmental area; dopamine; self-administration

Introduction

The ability of nutritional status to modulate performance in behavioral tasks that assess reinforcement, motivation, or reward has been well-appreciated for many decades. Almost exclusively, studies have focused on the generalized outcome that food restriction or food deprivation results in enhanced performance in behavioral paradigms. Although examples of this are too numerous to be described completely here, the reader is directed to recent reviews (1-3). Observations from these studies include increased self-administration of several classes of addictive drugs (cocaine, amphetamine, opioids, etc) (4); enhanced relapse to drug taking (5); decreased threshold for lateral hypothalamic self-stimulation (6,7); and cocaine-conditioned place preference (8). Since each of these behavioral paradigms utilizes a somewhat

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different subset of CNS circuitry, and evaluates different aspects of motivation or reinforcement, such results argue for a very strong interaction between brain reward circuitry, and the CNS circuitry which regulates nutritional status and energy homeostasis. The anatomical and neurochemical correlates of this altered behavioral sensitivity have begun to be elucidated: Increased dopamine release within the nucleus accumbens (Nacc) (9); altered re-uptake of dopamine in the NAcc (a paradigm-dependent observation [10-12]); and downstream sequelae of dopamine receptor activation in the Nacc have been the most intensely investigated possibilities (13). Altered activity in specific brain opiodergic circuitry may be involved as well (14).

Food is a naturally rewarding and motivating stimulus and, perhaps not surprisingly, behavioral performance in tasks where food is the reward is enhanced by food restriction or deprivation. Self-stimulation within certain lateral hypothalamic sites induces an eating response, and self-stimulation-induced feeding is augmented with food restriction (15). Likewise, the ability of food to condition a place preference, or self-administration of food, is increased with food deprivation (16-20). Since peripherally-derived signals of body adiposity or energy homeostasis, i.e., the pancreatic hormone insulin and the adipose-derived hormone leptin, have been shown to act within the CNS (21), their role in mediating the effect of food restriction on motivational behaviors has been investigated (1). Both insulin and leptin administered intracerebroventricularly (ICV) can reverse the shifted threshold of lateral hypothalamic self-stimulation following food restriction (22,23). ICV leptin also reverses food-restriction-enhanced relapse to heroin self-administration (5). Finally, peripheral leptin replacement reverses food-restriction-induced conditioning of place preference by sucrose (24). It should be emphasized that the underlying significance of all of these studies lies not solely in the demonstration that these candidate adiposity signals regulate food reward, but in the generalization that can be derived from these findings: Any neuroendocrine signal, peripherally or centrally derived, may be a candidate for modulation of food reward and this hypothesis can be systematically evaluated by taking advantage of well-characterized behavioral paradigms to start to discern which components of reward and motivation are being affected. The orexigenic peptide ghrelin, for example, can stimulate feeding when administered into the ventral tegmental area (VTA) (25), a major dopaminergic nucleus and critical center of motivational circuitry within the CNS (26).

Insulin, leptin, and food reward

Of particular interest to us is the phenomenon of palatable food intake in the face of caloric repletion. In “Westernized” societies caloric intake is chronically excessive, and this is due in part to the unlimited availability of inexpensive, highly palatable, highly calorically dense food (27). Thus, while it is possible that the enhanced rewarding or motivating values of food with food restriction or deprivation may reflect what happens during dietary cycling and bingeing, we consider it important to understand what drives non-regulated feeding that occurs in the physiological setting of caloric repletion, and how, if at all, such drives can be modulated. Accordingly, we have focused on the effects of insulin (and leptin) to modify performance in food reward tasks in food-replete rats. We have chosen to administer insulin and leptin ICV at doses which, in our lab, do not cause a change of 24-h body weight, hence defined as subthreshold. Thus, the effects we have observed cannot be secondary to the well-defined energy regulatory effects of insulin and leptin, but may in fact contribute to the energy regulatory effects, as we discuss further below. We have demonstrated that ICV insulin synergizes with a subthreshold dose of the D2 receptor antagonist raclopride to decrease activity in a 5-min sucrose lick rate task (28). This task, developed and validated by Smith and Davis (29), represents a ‘pure hedonic’ response of the animal to a solution, and, because of its very acute timing, does not involve any post-ingestive feedback. Smith and Davis further demonstrated the dopaminergic dependence of this task since performance is decreased with

the administration of a D2 receptor antagonist (30). This suggested to us that insulin could decrease the primary rewarding value of sucrose solutions; could do so on a very acute basis, as it was administered 15 min prior to the lick rate task; and might act in whole or part through modulation of brain dopaminergic pathways.

To pursue this further we evaluated the ability of insulin or leptin to prevent the conditioning of a place preference (CPP) to a food reward. This task is likewise dependent on intact dopaminergic signaling in the CNS (16,24), however it evaluates a different aspect of reward. Rather than directly evaluating the hedonic value of a food, it evaluates the strength of an association between a rewarding experience (food reward, administration of an addictive drug) and the place in which it is experienced (31). Thus, learning is implicated in this behavioral task. We observed that a high-fat food treat available within the CPP chamber could condition a place preference, and this could be completely blocked by ICV administration of subthreshold doses of insulin or leptin (32). Initially, insulin or leptin were infused continuously during the training period and on the test day itself (when no food reward is actually available). Subsequently, we tested whether insulin or leptin blocked the acquisition or the expression, or both, of the conditioned place preference by administering insulin and leptin chronically during the training period only, or injected acutely on the test day itself. We observed that insulin and leptin specifically blocked the expression, but not the learning of the place preference. The mechanistic implication of this finding is discussed below; as with the lickometer study the CPP study suggests that insulin and leptin can act very acutely (within minutes of ICV administration) to block food reward.

Finally, we have evaluated the ability of ICV insulin or leptin to decrease self-administration of a sucrose solution (33). This task evaluates motivation to work for a rewarding substance. As with the other behavioral tasks described above, we administered insulin or leptin immediately prior to a session in which a rat needs to work progressively harder (press a lever an increasing number of times) to obtain a sucrose reward. Both insulin and leptin decreased the number of presses on the lever that would lead to reward (active lever), but did not change the number of presses on a lever that does not result in any reward but reflects non-specific activity on the part of the rat. This latter finding is consistent with one measure in the CPP study: acute administration of insulin or leptin had no effect on overall locomotor activity of the rats. Taken together these studies emphasize the ability of insulin or leptin to acutely decrease multiple aspects of food reward: hedonics, place preference (the seeking of a place associated with a reward), and motivation to work for a food reward. Whether these effects generalize to all types of food reward or whether, for example, there are differential effects of insulin and leptin on sweet vs. fat food reward remains to be systematically investigated.

CNS sites of action for adiposity signal modulation of food reward

We have begun to explore the specific CNS location(s) whereby insulin and leptin may decrease food reward, based on our studies of ICV administration. A minimum set of criteria for identifying target sites would have to include the expression of receptors for insulin or leptin, and functional activity of these receptors demonstrated at both the cellular and behavioral level. We have obtained evidence which suggests that the VTA may serve as a direct target for insulin and leptin action. Using fluorescence immunocytochemistry we identified neurons positive for insulin receptors or leptin receptors in the VTA, and some in the adjacent substantia nigra (34). In the medial hypothalamus, a well-characterized target for insulin and leptin effects in the CNS (35), insulin and leptin activate the intracellular PI3 kinase cascade (as initially identified in classic peripheral target tissues), which results in the generation of the signaling molecule PIP3 (36-39). As shown in Figure 1, acute administration of insulin or leptin (approximately fifteen min prior to brain excision) directly into the VTA likewise results in enhanced PIP3 immunoexpression relative to artificial cerebrospinal fluid (CSF)-injected

controls. DiLeone and colleagues have subsequently demonstrated mRNA expression of the leptin receptor, and have demonstrated phosphorylation of STAT3, another downstream marker of leptin action, within the VTA following IP leptin administration (40).

In addition to the demonstration of activation of a cell-signalling pathway, we have identified a critical regulatory protein in dopaminergic neurons which is a target for insulin action, the dopamine re-uptake transporter (DAT). Synaptically released dopamine is retro-transported into dopaminergic nerve terminals where it is re-packaged or degraded and this function of the DAT represents the major mechanism whereby dopamine signaling is terminated within the CNS (41). We have demonstrated that ICV insulin increases DAT mRNA (42), and that *in vitro* insulin reverses the effect of acute, *in vivo*, food restriction to decrease DA re-uptake (i.e., insulin stimulates DAT function) (10). Subsequent studies in cellular systems have demonstrated that this action of insulin is caused by enhanced recruitment of DATs to the cell membrane and is dependent on insulin-stimulation of the PI3 kinase pathway (43). This collective set of evidence strongly suggests that the DAT is likely a physiological target of insulin action. To date, comparable studies have not been carried out for leptin. The functional significance of increased DAT numbers or activity is that released dopamine should be cleared from the synapse more effectively, hence dopamine signaling will be decreased.

Direct acute injection of insulin or leptin unilaterally into the VTA blocks VTA-initiated feeding (Figure 2). Feeding can be stimulated by the administration of a mu-opioid agonist into the VTA such as DAMGO, and this feeding is dopamine-dependent (44). We used a two-day paradigm where rats had *ad libitum* access to sucrose pellets and were tested in the sated condition. On the first day all rats received a CSF injection and baseline sucrose pellet intake was recorded. On the second day, rats received either a second CSF injection (vehicle control); an injection of DAMGO; an injection of insulin or leptin alone; or a combined injection of DAMGO with either leptin or insulin. The data shown in Figure 2 represent the within-subjects' response of each rat relative to its baseline intake, which was approximately fifty sucrose pellets. Injection of DAMGO stimulated pellet intake and this was reversed when insulin or leptin were co-administered. Insulin and leptin alone did not change baseline sucrose intake, and a speculative interpretation of this is that insulin and leptin effects on food reward may only be relevant when there is adequate stimulation or drive within the VTA.

Other candidate CNS sites are beginning to be evaluated as mediators of the ICV actions of insulin and leptin to blunt food reward. Because insulin or leptin signals at the medial hypothalamus are relayed to the lateral hypothalamus (45), which may serve as an integrating site for signals from reward/motivational circuitry (46), we are beginning to test the ability of insulin or leptin administered directly into the arcuate nucleus to decrease performance in food reward paradigms such as those described above. Additionally, we are beginning to explore the possibility that the amygdala (either central or basolateral nucleus) may be an important anatomical mediator of some aspects of food reward. This somewhat speculative hypothesis is based upon the observations that the amygdala is implicated in the expression (but not the learning) of place preference conditioning (47); its important role in cue-conditioned feeding (48) and its important role in the circuitry of nucleus accumbens-stimulated feeding of palatable food (49). This is a limited body of evidence gathered from laboratories that are asking different types of questions; however it seems clear that the amygdala is a good candidate for the systematic evaluation of its role in food reward/motivation paradigms. We are beginning such studies and have preliminary evidence of the expression of insulin receptors in both central and basolateral regions of the amygdala.

New directions: Modulation of food reward and reinforcement by baseline diet experience, age, and type of food reward

As we and others have begun to establish that adiposity signals and other CNS energy-regulatory signals may modulate food reward, it is becoming important to put these effects within the context of normal events within daily life and the life cycle. We base this perspective on both studies within obesity research which have clearly demonstrated that diet composition, concomitant with or independent of consequent obesity, can impact on the efficacy of insulin and leptin energy-regulatory effects (50); and on human data demonstrating the extension of significant obesity and onset of type 2 diabetes into younger and younger populations, such that there is a major increase in both pathologies within pediatric and adolescent populations in the U.S. and Westernized societies (51,52). Therefore, we are beginning systematic studies of the effect of changing baseline diet in adult and post-weanling rats prior to testing for motivated work for food rewards (self-administration). We have fed adult rats a higher fat diet (HFD; 31% fat) for five weeks prior to the onset of self-administration training. This baseline diet protocol does not result in significant divergence of weight between HFD- and chow-fed rats but rats demonstrate greater caloric efficiency, at both adult and juvenile ages. In adults, motivated performance for sucrose is increased following the diet intervention; this is observed specifically for 'progressive ratios' self-administration, that is, when the rat presses an increasing number of times on the lever between sucrose rewards. Further, ICV insulin and leptin are ineffective at decreasing sucrose self-administration in these rats (33). This pair of observations suggests that high fat diet experience, independent of overt obesity, can modulate the rewarding or reinforcing value of palatable foods, perhaps by inducing CNS resistance to the effects of adiposity signals. Additionally, we are comparing progressive ratios responding for 5% sucrose or Chocolate Ensure, which is more reinforcing than sucrose solutions. Both chow-fed and HFD-fed rats exhibit increased progressive ratios responding when they are tested with Ensure vs. sucrose. However, as shown in Figure 3, responding for Ensure is significantly more enhanced in the group that had been fed the HFD: The within-subjects' difference between lever presses for Ensure and lever presses for sucrose is greater in rats with a prior history of HFD. This suggests that interactions may occur between the baseline diet experience, and the reinforcing value of highly palatable foods.

Future directions for food reward research

An important challenge awaits investigators of food reward and its potential regulation or modulation. While we are gaining ground on understanding some basic aspects of food reward within a defined physiological context, we need to simultaneously be aware of the greater complexities which may arise in real life situations for people, if we hope to utilize our knowledge for any sort of helpful therapeutic direction (i.e, pharmaceutical or behavioral intervention). For example, food reward is generally evaluated in current laboratory models as a respond/don't respond option. In real life, different modalities of reward may be simultaneously present, and the question then becomes, what is the basis for choice among multiple rewards (e.g., the dinner party: food; water; or a reinforcing AND caloric drug, the alcoholic beverage)? If therapies are developed to blunt the rewarding or reinforcing aspects of food, how will specificity be conferred such that other natural reinforcers such as water, or sex, will remain rewarding? These issues have been addressed conceptually to a limited extent (e.g. [53]) but have not really been tackled at the level of experimental design. Finally, it will be important to continue simulating the conditions of Westernized society that are associated with increased or excessive consumption of high energy density, highly palatable foods. Although most citizens in Westernized societies currently face little stress in the form of predators or chronic adverse physical conditions, psychological stressors are common in U.S. and European society (54) and thus the addition of a chronic or semi-chronic psychological stress component to studies of food reward should provide valuable new insight into

modulation of food reward and reinforcement (55). These studies may be more technically difficult but they will be critical for true translation from what is learned in the laboratory regarding 'food reward', into potentially relevant insights for therapeutic application to the feeding habits and patterns of societies confronted with an obesity epidemic.

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Figure 1.

PIP3-positive neurons were identified by fluorescence immunocytochemistry following acute injection of CSF (upper), 5 mU insulin (middle), or 2.5 μ g leptin (lower) directly into the VTA (2 μ l/10 min). PIP3 immunofluorescence was assayed in 14 micron sections according to the method of Niswender and colleagues (56).

Figure 2. Unilateral DAMGO (3 nmol) administration stimulates 60-min sucrose intake in sated rats, which is reversed by co-administration of 5 mU insulin or 0.2 μ g leptin.

Figure 3.

Differential progressive ratios responding for sucrose vs. chocolate Ensure in sated adult rats with prior history of 5 wk HFD (vs. chow-fed). Data represent the within-subjects' difference of (active lever presses for chocolate Ensure) – (active lever presses for sucrose). See [33] for details of self-administration methodology.