Published in final edited form as:

Appetite. 2008 November ; 51(3): 452–455. doi:10.1016/j.appet.2008.06.007.

ENDOCRINE LINKS BETWEEN FOOD REWARD AND CALORIC HOMEOSTASIS

Dianne Figlewicz Lattemann, Ph.D.

VA Puget Sound Health Care System, Seattle WA

University of Washington School of Medicine, Seattle WA

Abstract

Both intrinsic and extrinsic (endocrine) inputs to the CNS modulate motivation for feeding. Endocrine inputs such as insulin and leptin can have very rapid effects, but also the potential for chronic actions to decrease rewarding attributes of food. Future studies should elucidate the neural and cellular mechanisms which underlie these endocrine actions in the CNS.

Keywords

Insulin; leptin; food deprivation

To consider the concept of caloric homeostasis, one must consider the organism as a member of a species. Evolutionary perspective tells us that the “job” of a species is to successfully replicate itself and to that end, an animal must survive long enough to achieve reproductive competence and, at a minimum, mate successfully. In many animal species, survival of a parent to support and nourish a young animal to a state of adequately functional independence is an additional requirement. Presumably with that goal, the homeostasis of food intake, as well as fluid balance, evolved in a physically challenging environment where adequate supply of food (or fluid) could never be assured. Hence, we live as animals with brains constantly monitoring for food, and the avoidance of potential starvation. Highly sensitive and effective neural systems have developed that allow us to find the activity of eating reinforcing and motivating, and to learn and remember very rapidly about stimuli and environments which signal the likely availability of more food. Recent research suggests that the reward value of food is not only assessed by intrinsic central nervous system (CNS) circuitry but can be modified by hormones that signal acute and chronic caloric status to the CNS (Figlewicz, 2003).

It is clear that nutritional status has a dramatic effect upon the rewarding aspect(s) of many stimuli, including food. Specifically, food restriction or food deprivation increase the rewarding attributes of stimuli assessed in several types of behavioral paradigms. This has been documented repeatedly in the drug abuse literature (Carroll & Meisch, 1984). It has been demonstrated, for example, that both drug self-administration (motivated work for a dose of drug) and the propensity to relapse to drug-taking are enhanced in animals that are acutely food

Corresponding Author: Dianne Figlewicz Lattemann, Ph.D., VA Puget Sound Health Care System (151), 1660 So. Columbian Way, Seattle WA 98108, latte@u.washington.edu, 206-768-5240.
Attention: Special Section edited by G.P. Smith and D. Booth

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

restricted or more chronically food deprived (Comer *et al.*, 1995; Shaham *et al.*, 2000). The paradigm of lateral hypothalamic (LH) self-stimulation has been interpreted as a behavioral activity which accesses 'reward circuitry' and brain self-stimulation is significantly increased in association with food deprivation (Margules & Olds, 1962; Carr, 2007). Food as a stimulus is, likewise, more rewarding in food-deprived animals, when evaluated in paradigms that assess reward. The physiological advantage of this is obvious.

From the psychological perspective, one might invoke increased drive; enhanced salience of a food stimulus, or of cues that signal the availability of food; and decision-making that involves increased effort. Numerous behavioral approaches have been used to assess 'food reward'. Thus, self-administration of food (pressing a lever to obtain a small amount of food) (Figlewicz *et al.*, 2006); moving down a runway or maze for food (Salamone *et al.*, 2007); the conditioning of a place preference with a drug (Bell *et al.*, 1997) or with food (Figlewicz *et al.*, 2001; Lepore *et al.*, 1995); the hedonic valuation of food (Levine, 2006); and cue-conditioned overfeeding (Petrovich & Gallagher, 2003) elicit stronger performances when an animal is food-deprived. Performance in these tasks may represent enhanced reinforcing and motivating properties of food, and learned association of being in a location in which food was available. That the tasks evaluate different aspects of reward and motivation is reflected in findings that the CNS circuitry engaged by the different tasks is overlapping but not identical (Ikemoto & Wise, 2004; McBride *et al.*, 1999).

Research from physiological psychologists and behavioral neuroscientists has been elucidating the neural substrates mediating or modulating the enhanced drive and effort for food, in circumstances of food deprivation. Berridge and colleagues (Berridge, 2004) have presented the differential constructs of 'wanting' food (motivation) and 'liking' food (hedonic valuation) and provided substantial evidence that these may be mediated in the central nervous system (CNS) by somewhat unique circuitries. Nutritional status has been shown to modulate both motivation for food as well as, in certain paradigms, the efficacy of signals relating to food palatability (Barbano & Cador, 2005). Critical for the mediation of motivation for food are the mesolimbic dopamine (DA) neurons, with cell bodies in the ventral tegmental area (VTA) projecting to the prefrontal cortex and to the striatum, including the nucleus accumbens (NAc) (Smith, 1995; Smith, 2004; Wise, 2005). Critical for mediation of palatability and palatability-based food choices are populations of endogenous opioidergic neurons and their receptors (Bodnar, 2004; Glass *et al.*, 1999; Levine, 2006; Olszewski & Levine, 2007; Zhang & Kelley, 2000). Exogenous administration of mu, delta, and kappa opioids has been shown to increase feeding; mu opioids have been studied most extensively, increasing food intake when administered into a number of CNS sites. Synaptic connections between the VTA, NAc, and medial hypothalamus provide the anatomic basis for direct 'crosstalk' between CNS circuitry which assesses energy balance and caloric homeostasis, and the lateral hypothalamus may be a key intermediary site, with reciprocal synaptic connections to all of these regions (Berthoud, 2004; Berthoud, 2007). Little is currently known about intrinsic CNS mechanisms that may mediate the enhanced rewarding value of food in association with caloric deprivation, although both dopaminergic and opioidergic pathways have been implicated (Carr, 2007).

Our focus has been upon the contribution of extrinsic signals to the CNS. Food deprivation and caloric restriction invoke a pattern of well-characterized endocrine changes, which is modified by the duration and severity of calorie deprivation. Key endocrines include the adrenal glucocorticoids and ghrelin, secreted in increased amounts in association with calorie deprivation; and insulin and leptin, which are secreted in association with food intake and increased adipose mass, and conversely, are decreased in the circulation in association with calorie deprivation. The glucocorticoids have been implicated in increased drug taking (Piazza & LeMoal, 1997) but have not been extensively studied in formal paradigms of food reward. Their involvement in stress-associated intake of 'comfort foods' has been recently described

(LaFleur, 2006). Ghrelin, an orexigenic hormone (Cummings, 2006), has been shown to increase feeding when administered directly into the VTA (Naleid *et al.*, 2005), and can increase sucrose self-administration when given into the third cerebroventricle (Overduin, Cummings, and Lattermann, unpublished). The actions of insulin and leptin have been much better characterized and they are implicated in the change of reward behavior in general, and food reward specifically, both in the scenario of the fed vs. calorie-deprived states, and when administered exogenously during the fed state. Both insulin and leptin have been identified as ‘candidate adiposity signals’ which inform the CNS regarding the energy balance of the organism (Baskin *et al.*, 1999; Niswender *et al.*, 2004).

In 1994, we reported that intraventricular (IVT) administration of insulin in the rat increased expression of an important regulatory protein for dopamine (DA) activity, the re-uptake transporter (DAT) in the VTA and substantia nigra compacta (SNc) (Figlewicz *et al.*, 1994). The DATs are expressed on the synaptic membrane of DA neurons, and act to clear DA from the synapse, thus terminating signaling. A great deal has been learned in the intervening fifteen years about the specific neuronal expression, and regulation of both synthesis and activity (Blakely *et al.*, 2005) of the DAT. Our initial observation intrigued us, and we made the subsequent observations that DAT expression was decreased in association with acute food restriction, and further, that activity of the DAT measured by *in vitro* voltammetric uptake of DA was decreased in striatal slices (containing DA nerve terminals) taken from food restricted animals (Patterson *et al.*, 1998; Zhen *et al.*, 2006). However, if insulin was added to the *in vitro* bath, DA uptake by the ‘food restricted’ striatal slices was normalized. Thus, it appears that insulin regulates both synthesis and functional activity of the DAT. The further implication of this is that insulin increases clearance of, and decreases synaptic concentrations of DA, hence DA activity. This line of research has now been extended by Galli and colleagues. Using cultured cells transfected with DATs and expressing insulin receptors, they have shown that the insulin effect is due to enhanced plasma membrane recruitment of DATs, and is dependent upon activation of a PI3 kinase signaling pathway (Garcia *et al.*, 2005). PI3 kinase signaling has been identified as critical for the energy-regulatory actions of insulin at the hypothalamus (Niswender *et al.*, 2003).

We next explored the possible *in vivo* or behavioral relevance of our observations with the DAT. Work from Shaham and colleagues (2000) called attention to the well-documented observation, discussed above, that food restriction or deprivation enhanced the addictive and relapse potencies of a number of types of abused drugs (Shalev *et al.*, 2001), and that one key anatomic substrate is the midbrain DA neurons. We speculated that insulin might be one specific factor contributing to this phenomenon. We thus begin to test the hypothesis that insulin would decrease ‘reward’ behavior for food, evaluated in several behavioral paradigms. Coinciding with this, studies of the role of leptin in blunting reward were begun in other labs. Independently, Carr and colleagues (2000), and Fulton and colleagues (2000) reported that IVT insulin and leptin could reverse the enhanced responding for brain electrical stimulation that occurs with food restriction. These studies, along with our work demonstrating insulin and leptin effects on food-conditioned place preference (Figlewicz *et al.*, 2004) and sucrose self-administration (Figlewicz *et al.*, 2006), have provided substantive support for our hypothesis and additionally implicated leptin in this modulatory action.

The observation of decreased food reward with IVT insulin or leptin administration leads to the question of target CNS sites of action. In 2003 we reported the expression of both insulin receptors and leptin receptor immunoreactivity on TH-positive (presumptively, DA) neurons in the VTA and substantia nigra compacta (Figlewicz *et al.*, 2003). Leptin receptor mRNA on TH neurons has been reported by Hommel and colleagues (2006). We have also observed immunoreactivity for both insulin and leptin receptors on TH-negative neurons (presumptively, GABAergic), and we have obtained preliminary evidence for insulin receptor

immunoreactivity on some identified GABA neurons in the VTA. In particular we find co-expression with TH (hence, within DA neurons) at a high level in the anterior VTA. The behavioral relevance of this receptor expression has been demonstrated by a few labs, including our own: insulin and leptin administered directly into the VTA decrease both baseline, and mu opioid-stimulated, feeding (Figlewicz *et al.*, 2007; Fulton *et al.*, 2006; Hommel *et al.*, 2006; Morton *et al.*, 2007).

Several groups have begun to elucidate cell signaling pathways activated by insulin and leptin within the VTA. We have observed increased PIP3 immunoreactivity in response to direct injection of insulin or leptin into the VTA (Figlewicz *et al.*, 2007). DiLeone and colleagues (Hommel *et al.*, 2006) and Fulton and colleagues (2006) have identified activation of the JAK-Stat3 pathway in response to peripheral or local (intra-VTA) leptin administration, and leptin administration and activation of the JAK-Stat pathway is also critical for the decrease in food intake when leptin is injected into the VTA (Morton *et al.*, 2008). Since both leptin and insulin can activate multiple signaling pathways including PI3 kinase (Carvalho *et al.*, 2005; Mirshamsi *et al.*, 2004; Niswender *et al.*, 2004), the connection between cell signaling pathways and behavioral effects will require further exploration. From a broader perspective it is clear that the VTA can serve as a direct anatomical substrate for either leptin or insulin action. Further, although the feeding paradigms used to obtain the results described above do not allow us to state definitively that insulin or leptin are decreasing the rewarding attributes of food, they imply a physiological role for this major component of CNS reward circuitry in feeding.

A second CNS site which has already been recognized as an important anatomical substrate for the energy regulatory actions of insulin and leptin is the arcuate nucleus (ARC). We have followed our initial observation that intraventricular insulin (and leptin) decreases sucrose self-administration, with a study to determine the anatomical locus(oci) mediating this effect. Insulin was administered directly into the NAc, paraventricular nucleus of the hypothalamus (PVN), VTA, and ARC. We observed an anatomically-specific effect of insulin to decrease sucrose self-administration given into the ARC, which quantitatively accounts for the effect of insulin given IVT (Figlewicz *et al.*, 2008). This result suggests that endocrine input at the medial hypothalamus must then be relayed to the brain reward circuitry to modulate sucrose self-administration. It should be emphasized that this effect occurs at a dose of insulin which does not have chronic effects to decrease 24-hr food intake or body weight. Thus, the effect of insulin on motivation or effort for food may be a contributing mechanism to, and not a consequence or correlate of, the well-defined effect of insulin to regulate body weight and adiposity.

The ability of energy regulatory signals to restrain body weight and adiposity can be modified under a number of circumstances. Similarly, the ability of energy regulatory signals to restrain food reward can also be modified. We have observed that feeding rats a high fat baseline diet (chow with 30% or more fat) results in both an increase in baseline responding for sucrose, and prevention of the ability of IVT insulin and leptin to decrease responding (Figlewicz *et al.*, 2006). A parallel impairment of the energy-regulatory action of insulin and leptin at the medial hypothalamus had been made by several laboratories (Clegg *et al.*, 2005; Munzberg & Myers, 2005). Recent studies suggest that impaired intracellular signaling may underlie or contribute to this impairment. Since we have determined that the effect of insulin to decrease sucrose self-administration is likewise mediated through the medial hypothalamic ARC, it is possible that similar changes of cell signaling modify insulin effects on both food reward and caloric homeostasis. Alternatively, downstream or independent changes may occur in brain reward circuitry as a result of different baseline diet composition or its perceived hedonic value. Given the propensity of Westernized diets to be high in fat (e.g., >30% of daily caloric intake),

further mechanistic insight into the interaction between high(er) fat diets and motivation for food treats is warranted.

Persuasive as the collective evidence with exogenous insulin and leptin is, before we conclude more definitively that very acute effects of these adiposity signals to decrease food reward are physiological, and are a component of their more chronic effect to decrease food intake and body weight, the parameters of their efficacy need to be addressed and defined more clearly. This has already been done in the work of Fulton (2000) and Carr (2000) and their respective colleagues, in which food restriction-induced increases of lateral hypothalamic self-stimulation are reversed to baseline levels by intraventricular leptin or insulin. Comparable studies specifically testing food reward paradigms have not been carried out. Note that the effects of insulin or leptin given IVT or into specific brain regions usually occur within 10–30 minutes.

The goal of our studies has been to simulate a ‘dessert’ or ‘between meal snack’ neuroendocrine milieu. Data on transport kinetics have suggested that elevations of plasma insulin or leptin are associated with increased CNS levels in a 20–30 minute timeframe (Banks & Kastin, 1998; Figlewicz, 2003). Theoretically, a rise of insulin at the onset of a meal would result in elevated brain levels by ‘dessert time’ in a reasonably paced meal, that could provide a brake on reward value of dessert. The onset of leptin action is less easy to fit into a behavioral framework as leptin levels show a circadian pattern associated with the taking of meals (Kalsbeek *et al.*, 2003) but leptin secretion is not tied to the ingestive bout in the way that insulin is. Intriguingly Morton and colleagues (2007) have found that intra-VTA leptin enhances the ability of the meal-regulatory peptide cholecystokinin to decrease size of acute feeding bouts, and thus in the context of normal circadian behaviors this may be a truly physiological role for leptin. Another possibility to be explored is that leptin in the CNS sets a ‘tone’ and the shorter-timeframe, meal-related, excursions of insulin can amplify that tone or perhaps require it, for insulin efficacy. This potential synergy remains to be explored.

Granted that these issues are addressed, and we arrive at the conclusion that endocrine signals, such as insulin and leptin, can serve to restrain any of the aspects of food reward (motivation, effort-based decision making, hedonic valuation, reinforcement), we still are left with the question of why it is advantageous for a homeostatic system to evolve such mechanisms. Perhaps the answer lies in the need of an organism to engage in other behaviors, in order to survive and reproduce, and hence once an animal has eaten enough to generate signals of plenty (insulin being relevant for shorter-term repletion and leptin being relevant for longer-term calorie storage), food becomes a less relevant stimulus, and the animal turns to other critical behaviors: drinking, for fluid homeostasis; social or affiliative behaviors as species-appropriate; mating behaviors as appropriate; or even seeking a safe and quiet place to rest to allow the body an opportunity to digest and assimilate calories. The ‘setpoint’ of the CNS, as currently evolved, to strongly bias humans to eat whenever food is available pushes modern man to a new and somewhat maladaptive homeostasis from the perspective of being longer-lived. Understanding the brain reward system and its modulation may lead us to design behavioral strategies (the diversion of other activities that are as engaging and rewarding as eating) in addition to the currently limited medical approaches to curb eating. Respect for ‘the wisdom of the body’, rather than denial, should guide our future basic and translational research on food reward contributions to caloric homeostasis.

Acknowledgments

The author is a Research Career Scientist (DVA) and is supported by a Merit Review Program (DVA) and NIH grant RO1-DK40963. The editorial input of Dr. Gerard P. Smith is gratefully acknowledged.

References

- Banks WA, Kastin AJ. Differential permeability of the blood-brain barrier to two pancreatic peptides: insulin and amylin. *Peptides* 1998;19:883–889. [PubMed: 9663454]
- Barbano MF, Cador M. Various aspects of feeding behavior can be partially dissociated in the rat by the incentive properties of food and the physiological state. *Behavioral Neuroscience* 2005;119:1244–1253. [PubMed: 16300432]
- Baskin DG, Figlewicz Lattermann D, Seeley RJ, Woods SC, Porte D Jr, Schwartz MW. Insulin and leptin: dual adiposity signals to the brain for the regulation of food intake and body weight. *Brain Research* 1999;848:114–123. [PubMed: 10612703]
- Bell SM, Steward RB, Thompson SC, Meisch RA. Food deprivation increases cocaine-induced conditioned place preference and locomotor activity in rats. *Psychopharmacology* 1997;131:1–8. [PubMed: 9181629]
- Berridge KC. Motivation concepts in behavioral neuroscience. *Physiology & Behavior* 2004;81:179–209. [PubMed: 15159167]
- Berthoud HR. Neural control of appetite: cross-talk between homeostatic and non-homeostatic systems. *Appetite* 2004;43:315–317. [PubMed: 15527935]
- Berthoud H-R. Interactions between the “cognitive” and “metabolic” brain in the control of food intake. *Physiology & Behavior* 2007;91:486–498. [PubMed: 17307205]
- Blakely RD, Defelice LJ, Galli A. Biogenic amine neurotransmitter transporters: just when you thought you knew them. *Physiology* 2005;20:225–231. [PubMed: 16024510]
- Bodnar RJ. Endogenous opioids and feeding behavior: a 30-year historical perspective. *Peptides* 2004;25:697–725. [PubMed: 15165728]
- Carr KD. Chronic food restriction: Enhancing effects on drug reward and striatal cell signaling. *Physiology & Behavior* 2007;91:459–472. [PubMed: 17081571]
- Carr KD, Kim GY, Cabeza de Vaca S. Hypoinsulinemia may mediate the lowering of self-stimulation thresholds by food restriction and streptozotocin-induced diabetes. *Brain Research* 2000;863:160–168. [PubMed: 10773204]
- Carroll ME, Meisch RA. Increased drug-reinforced behavior due to food deprivation. *Advances in Behavioral Pharmacology* 1984;4:47–88.
- Carvalho JB, Torsoni MA, Ueno M, Amaral ME, Araujo EP, Velloso LA, Gontijo JA, Saad MJ. Cross-talk between the insulin and leptin signaling systems in hypothalamus. *Obesity Research* 2005;13:48–57. [PubMed: 15761162]
- Clegg DJ, Benoit SC, Reed JA, Woods SC, Dunn-Meynell A, Levin BE. Reduced anorexic effects of insulin in obesity-prone rats fed a moderate-fat diet. *American Journal of Physiology* 2005;288:R981–R986. [PubMed: 15604298]
- Comer SD, Lac ST, Wyvell CL, Curtis LK, Carroll ME. Food deprivation affects extinction and reinstatement of responding in rats. *Psychopharmacology* 1995;121:150–157. [PubMed: 8545519]
- Cummings DE. Ghrelin and the short- and long-term regulation of appetite and body weight. *Physiology & Behavior* 2006;89:71–84. [PubMed: 16859720]
- Figlewicz DP. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. *American Journal of Physiology* 2003;284:R882–R892. [PubMed: 12626355]
- Figlewicz DP, Bennett JL, Aliakbari S, Zavosh A, Sipols AJ. Insulin acts at different CNS sites to decrease acute sucrose intake and sucrose self-administration in rats. *American Journal of Physiology*. 2008In press, available on-line
- Figlewicz DP, Bennett J, Evans SB, Kaiyala K, Sipols AJ, Benoit SC. Intraventricular insulin and leptin reverse place preference conditioned with high fat diet in rats. *Behavioral Neuroscience* 2004;118:479–487. [PubMed: 15174925]
- Figlewicz DP, Bennett JL, Naleid AM, Davis C, Grimm JW. Intraventricular insulin and leptin decrease sucrose self-administration in rats. *Physiology & Behavior* 2006;89:611–616. [PubMed: 17045623]
- Figlewicz DP, Evans SB, Murphy J, Hoen M, Myers M, Baskin DG. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. *Brain Research* 2003;964:107–115. [PubMed: 12573518]

- Figlewicz DP, Higgins MS, Ng-Evans SB, Havel PJ. Leptin reverses sucrose-conditioned place preference in food-restricted rats. *Physiology & Behavior* 2001;73:229–234. [PubMed: 11399316]
- Figlewicz DP, Naleid AM, Sipols AJ. Modulation of food reward by adiposity signals. *Physiology & Behavior* 2007;91:473–478. [PubMed: 17137609]
- Figlewicz DP, Szot P, Chavez M, Woods SC, Veith RC. Intraventricular insulin increases dopaminergic transporter mRNA in rat VTA/substantia nigra. *Brain Research* 1994;644:331–334. [PubMed: 8050044]
- Fulton S, Pissios P, Manchon RP, Stiles L, Frank L, Pothos EN, Maratos-Flier E, Flier JS. Leptin regulation of the mesoaccumbens dopamine pathway. *Neuron* 2006;51:811–822. [PubMed: 16982425]
- Fulton S, Woodside B, Shizgal P. Modulation of brain reward circuitry by leptin. *Science* 2000;287:125–128. [PubMed: 10615045]
- Garcia BG, Wei Y, Moron JA, Lin RZ, Javitch JA, Galli A. Akt is essential for insulin modulation of amphetamine-induced human dopamine transporter cell-surface distribution. *Molecular Pharmacology* 2005;68:102–109. [PubMed: 15795321]
- Glass MJ, Billington CJ, Levine AS. Opioids and food intake: distributed functional neural pathways? *Neuropeptides* 1999;33:360–368. [PubMed: 10657513]
- Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, Thurmon JJ, Marinelli M, DiLeone RJ. Leptin receptor signaling in midbrain dopamine neurons regulates feeding. *Neuron* 2006;51:801–810. [PubMed: 16982424]
- Ikemoto S, Wise RA. Mapping of chemical trigger zones for reward. *Neuropharmacology* 2004;47:190–201. [PubMed: 15464137]
- Kalsbeek A, Ruiter M, la Fleur SE, Van Heijningen C, Buijs RM. The diurnal modulation of hormonal responses in the rat varies with different stimuli. *Journal of Neuroendocrinology* 2003;15:1144–1155. [PubMed: 14636176]
- LaFleur SE. The effects of glucocorticoids on feeding behavior in rats. *Physiology & Behavior* 2006;89:110–114. [PubMed: 16540130]
- Lepore M, Vorel SR, Lowinson J, Gardner EL. Conditioned place preference induced by delta9-tetrahydrocannabinol: comparison with cocaine, morphine, and food reward. *Life Sciences* 1995;56:2073–2080. [PubMed: 7776834]
- Levine AS. The animal model in food intake regulation: examples from the opioid literature. *Physiology & Behavior* 2006;89:71–84. [PubMed: 16859720]
- Margules DL, Olds J. Identical ‘feeding’ and ‘rewarding’ systems in the lateral hypothalamus of rats. *Science* 1962;135:374–375. [PubMed: 14469788]
- McBride WJ, Murphy JM, Ikemoto S. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. *Behavioural Brain Research* 1999;101:129–152. [PubMed: 10372570]
- Mirshamsi S, Laidlaw HA, Ning K, Anderson E, Burgess LA, Gray A, Sutherland C, Ashford ML. Leptin and insulin stimulation of signaling pathways in arcuate nucleus neurons: PI3K dependent actin reorganization and KATP channel activation. *BMC Neuroscience* 2004;5:54. [PubMed: 15581426]
- Morton GJ, Matsen M, Figlewicz D, Schwartz MW. Leptin signaling in the ventral tegmental area enhances the satiety response to cholecystokinin. *Diabetes* 2007;56:A403.
- Morton GJ, Matsen M, Kim F, Schwartz MW, Figlewicz DP. Leptin action in the ventral tegmental area reduces food intake via mechanisms independent of IRS-PI3K and mTOR signaling. *Diabetes* 2008;57:A435.
- Munzber H, Myers MG Jr. Molecular and anatomical determinants of central leptin resistance. *Nature Neuroscience* 2005;8:566–570.
- Naleid AM, Grace MK, Cummings DE, Levine AS. Ghrelin induces feeding in the mesolimbic reward pathway between the ventral tegmental area and the nucleus accumbens. *Peptides* 2005;26:2274–2279. [PubMed: 16137788]
- Niswender KD, Morrison CD, Clegg DJ, Olson R, Baskin DG, Myers MG Jr, Seeley RJ, Schwartz MW. Insulin activation of phosphatidylinositol-3-kinase in the hypothalamic arcuate nucleus: a key mediator of insulin-induced anorexia. *Diabetes* 2003;52:227–231. [PubMed: 12540590]

- Niswender KD, Baskin DG, Schwartz MW. Insulin and its evolving partnership with leptin in the hypothalamic control of energy homeostasis. *Trends in Endocrinology and Metabolism* 2004;15:362–369. [PubMed: 15380807]
- Olszewski PK, Levine AS. Central opioids and consumption of sweet tastants: when reward outweighs homeostasis. *Physiology & Behavior* 2007;91:506–512. [PubMed: 17316713]
- Patterson TA, Brot MD, Zavosh A, Schenk JO, Szot P, Figlewicz DP. Food deprivation decreases mRNA and activity of the rat dopamine transporter. *Neuroendocrinology* 1998;68:11–20. [PubMed: 9695934]
- Petrovich GD, Gallagher M. Amygdala subsystems and control of feeding behavior by learned cues. *Annals of the New York Academy of Science* 2003;985:251–262.
- Piazza PV, LeMoal M. Glucocorticoids as a biological substrate of reward: physiological and pathophysiological implications. *Brain Research. Brain Research. Reviews* 1997;25:359–372. [PubMed: 9495563]
- Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology* 2007;191:461–482. [PubMed: 17225164]
- Shaham Y, Erb S, Stewart J. Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Research. Brain Research. Reviews* 2000;33:13–33.
- Shalev U, Yap J, Shaham Y. Leptin attenuates food deprivation-induced relapse to heroin seeking. *Journal of Neuroscience* 2001;21:RC129. [PubMed: 11160414]
- Smith GP. Dopamine and food reward. *Progress in Psychobiology and Physiological Psychology* 1995;16:83–143.
- Smith GP. The CNS physiology of food reward: current insights and future directions. *Handbook of Behavioral Neurobiology* 2004;14:15–42.
- Wise RA. Forebrain substrates of reward and motivation. *Journal of Comparative Neurology* 2005;493:115–121. [PubMed: 16254990]
- Zhen J, Reith ME, Carr KD. Chronic food restriction and dopamine transporter function in rat striatum. *Brain Research* 2006;1082:98–101. [PubMed: 16516172]