Published in final edited form as:

Trends Endocrinol Metab. 2010 February ; 21(2): 68. doi:10.1016/j.tem.2009.08.004.

Insulin, Leptin and Reward

Jon F. Davis, Derrick L. Choi, and Stephen C. Benoit

University of Cincinnati, Department of Psychiatry, Cincinnati OH USA.

Abstract

Feeding for pleasure, or “non-homeostatic feeding”, potentially contributes to the rapid development of obesity worldwide. Obesity is associated with an imbalance of regulatory hormones which normally act to maintain stable energy balance and body weight. The adiposity hormones insulin and leptin are two such signals elevated in obesity with the capacity to dampen feeding behavior through their action on hypothalamic circuits which regulate appetite and metabolism. Recent evidence suggests that both hormones achieve this degree of regulation by inhibiting the rewarding aspects of feeding behavior, perhaps by signaling within midbrain reward circuits. This review describes the capacity of both insulin and leptin to regulate reward-related behavior.

The prevalence of obesity has reached epidemic proportion, and the development of pharmacological treatments continues to challenge current thinking. Over the past several years, key insights have broadened our understanding of how organisms sense and respond to peripheral and central signals to regulate energy homeostasis. However, this increased understanding has not yet led to successful therapies to reduce body weight. Importantly, feeding for pleasure or “non-homeostatic feeding” is presumed in part to underlie the rapid development of obesity worldwide [1]. Recent evidence suggests that non-homeostatic feeding is controlled by mesolimbic circuitry [2], and it is now clear that consumption of palatable foods elicits neuroadaptive changes within brain reward circuitry which may promote continued overfeeding behavior ([3,4]; for review the reader is directed to [5]). Such an association indicates an overlap in the involvement of brain circuitry that regulates reward and metabolism.

The adipose hormones insulin and leptin signal at distinct brain nuclei to regulate energy expenditure and metabolism by decreasing feeding behavior. However, both insulin and leptin are also capable of signaling within brain reward circuits. Hence, the possibility exists that insulin and leptin regulate food intake by inhibiting the rewarding aspects of feeding. Here, we consider the food and drug reward to be identical phenomena occurring through processes originating in the mesolimbic system. This review details the potential of insulin and leptin to regulate food and drug intake through their action on midbrain reward circuits.

Regulation of homeostatic feeding by insulin and leptin

Insulin produced by pancreatic β -cells and leptin derived from adipocytes increase in proportion to fat mass and consequently relay information about peripheral fat stores to central

Corresponding Author(s): Jon F. Davis, PhD, Stephen C. Benoit, PhD, University of Cincinnati, Department of Psychiatry North, Genome Research Institute Building E, Lab 334, 2170 East Galbraith Road Cincinnati, OH 45237 Jon.Davis@uc.edu; Choidl@email.uc.edu; Stephen.Benoit@uc.edu;.

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.

effectors in the hypothalamus to modify food intake and energy expenditure [6-9]. The actions of insulin and leptin on food intake occur in part by convergence on a specific set of neurons within the Arcuate nucleus (ARC) of the hypothalamus [10,11] to regulate feeding in response to stored calories or “homeostatic feeding”. The ARC contains two distinct sets of neurons with opposite effects on feeding behavior that each express insulin and leptin receptors. Through coordinated action on hypothalamic neurons that stimulate or inhibit feeding behavior, insulin and leptin function centrally as satiety signals to decrease food intake when energy levels are met and adipose tissue has been restored. Separate from their expression in hypothalamic centers, the receptors for both insulin and leptin are present in brain reward circuitry [12], suggesting their roles in the rewarding aspects of feeding behavior in addition to their effects on metabolism. Moreover, a collection of recent neuroanatomical, behavioral and functional evidence suggests that these effects on food reward are achieved through signaling within these circuits [12-15].

In the context of reward-related behavior, it is interesting to consider how plasma levels of insulin and leptin might be capable of modulating brain reward circuitry. Although insulin and leptin levels increase in response to high energy meals and stored calories, it is known that they also increase in anticipation of a meal [16-17]. The pre-meal rise in insulin can be achieved through learned associations with environmental cues associated with feeding [18,19]. Leptin normally follows a diurnal pattern of secretion with the largest increases occurring after the onset of the dark period when rodents normally ingest their largest meal [20,21]. However, similar to insulin, leptin can also be entrained to meal patterns [17], raising the possibility that daily rhythm of leptin secretion is subject to alteration by learned responses associated with altered meal patterns.

Central resistance to insulin and leptin

Importantly, the ability of insulin and leptin to access central circuits is regulated by their active transport across the blood brain barrier (BBB) [22,23]. As these transport mechanisms are saturable, they are subject to being rendered insensitive when exposed to elevated plasma levels of each hormone such as that seen in obesity [24,25]. It is unclear if leptin insensitivity is present in brain reward circuitry; however, given their active transport into the brain, it is quite possible that resistance also occurs in these regions. One implication of this resistance is that the ability of insulin and leptin to diminish reward is most sensitive in lean individuals. It is also possible that prolonged elevations in insulin and leptin during the development of obesity and prior to resistance produce changes that are manifested during obesity. This could be achieved through over activation of insulin and leptin signaling within brain reward circuitry. Nevertheless, this collection of data suggests that insulin and leptin might affect reward processing at distinct temporal intervals or in a more graded fashion as they both increase as a function of stored adipose tissue. Furthermore, the ability of each hormone to reach and act upon central circuits which mediate reward is most likely compromised in obesity and more sensitive in lean individuals. However, both are capable of entering the brain through circumventricular organs without transport across the BBB, leading to the notion that resistance may occur through de-sensitization of receptor signaling rather than decreased central access [26]. Whereas it is clear that sensitivity to each hormone exists at the level of the hypothalamus, there have been no investigations of insulin or leptin flux within brain reward regions or the sensitivity of these systems in relation to their prolonged elevation as seen in obesity. Moreover, there are no studies to date which examine reward behavior during acute temporal intervals linked to feeding when insulin or leptin are elevated endogenously. It therefore remains possible that insulin and leptin affect reward by direct action or through eliciting long term changes within reward circuitry. Although these possibilities remain to be tested directly, many investigators have examined reward behavior using models in which insulin and leptin are elevated naturally by obesity or prolonged increases in caloric consumption [27-35].

Metabolic status and reward related behaviors

In times of caloric restriction or deprivation, both insulin and leptin levels decrease and generally speaking, this augments reward-related behaviors. Laboratory animals trained to self-administer (SA) a variety of psychostimulant drugs increase their SA behavior after food deprivation, an effect dependent on reduced body weight [36,37]. Caloric restriction represents a less stringent, more prolonged manipulation compared to total food deprivation and restricting the amount of daily consumed calories also enhances the acquisition of drug self-administration and increases the willingness to engage in self-administration behavior [38, 39]. Moreover, caloric restriction increases psychostimulant induced locomotion in DBA/2J mice which are naturally resistant to the behavioral effects of psychomotor drugs [40]. Collectively, these behavioral observations suggest that metabolic perturbations that decrease body weight and hence circulating levels of insulin and leptin, augment the acquisition, expression and locomotor activating properties of psychostimulant drugs. Thus, socioeconomic conditions which limit food availability as well as metabolic interventions such as dieting represent substantial risk factors contributing to disordered eating and addiction [41-43].

Conversely, dietary regimens that increase body weight and hence plasma insulin and leptin, decrease reward-related behaviors. Obesity, defined by a body mass index (BMI) of 30 or greater, is associated with a significantly lower lifetime risk of substance abuse disorders in humans [44]. Indeed, obese individuals abuse nicotine [27] and marijuana [28] significantly less than normal weight subjects, and studies conducted in laboratory animals are consistent with these findings. For example, when exposed to a nutritionally complete high fat diet, obese rats display attenuated acquisition of cocaine self-administration behavior [29]. In addition, both obesity and maintenance on high calorie diets decreased amphetamine induced conditioned place preference and attenuated sucrose responding on schedules that require both low and high work requirements [30]. Similarly, rats rendered obese through exposure to a “supermarket” diet display attenuated operant responding for sucrose [31].

However, obese individuals are sensitive to the rewarding properties of palatable foods. Obese individuals display enhanced neuronal activation of brain reward circuitry when exposed to feeding associated cues [32] and crave energy rich diets to a greater degree than lean individuals [33]. This effect in humans can also be extended to food self-administration, as animals maintained on a variety of energy rich diets display enhanced response for food rewards [34]. Moreover, rats lacking the receptor for the satiety signal cholecystokinin (CCK-1R) self-administer sucrose more than lean controls [35]. Thus, in genetic models predisposed toward becoming obese or during the development of obesity, animals display a high degree of motivation to obtain palatable foods; however, once obese, the motivation to work for palatable foods is decreased below control levels.

In this sense, the process of becoming obese and obesity itself represent dissociable states in relation to motivation, but not reward. This contention is supported by the observation that obese individuals are capable of responding to appetitive stimuli associated with palatable foods, but are unwilling to “work” to obtain either food or drug rewards.

Pharmacological regulation of reward by insulin and leptin

Brain Stimulation Reward

Electrical stimulation of the lateral hypothalamus (LH) is a potent way to assay reward behavior in laboratory animals. In this model, rats actively seek out stimulation of the LH [36], an effect known as “brain stimulation reward” (BSR). Early studies investigating the effects of metabolic factors on BSR indicated that anorectic doses of insulin caused rats to self-stimulate less

[45]. Over twenty years following this discovery, it was demonstrated that intraventricular (ICV) administration of both insulin and leptin elevated BSR thresholds [46,47], thus decreasing the rewarding properties associated with LH stimulation. These demonstrations were particularly impressive in that 1) both insulin and leptin were administered into the third ventricle of the brain and 2) both decreased BSR for a prolonged period after administration. Thus, insulin and leptin are capable of affecting reward through direct action within the brain.

Intravenous Self-Administration

Studies investigating the effects of insulin and leptin on drug SA are limited; however, a few important studies indicate that both are capable of modulating drug intake. Rats trained to self-administer cocaine display decreased rates of responding when insulin levels are artificially lowered through streptozotocin treatment [48], suggesting that circulating insulin modulates drug taking behavior. In addition, central administration of leptin decreases food deprivation-induced reinstatement of heroin SA [49] indicating that leptin negates the facilitating effects of caloric deprivation on drug SA behavior. Combined with the observation that obese individuals SA abuse drugs less often, these studies underscore the potential for insulin and leptin to modulate drug intake.

Self-Administration of Palatable foods

Similar to drug SA behavior, laboratory animals can be trained to self-administer palatable foods such as sucrose or diets high in fat. Using this mode of reinforcement, ICV delivery of both insulin and leptin decreased responding for sucrose [13] suggesting that similar to their effects on BSR, insulin and leptin act centrally to modulate food reward. A series of behavioral pharmacological manipulations performed by Figlewicz and colleagues determined that the ARC nucleus of the hypothalamus is the sole site responsible for insulin's negative effects on food SA behavior [50], suggesting that insulin signaling within the ARC may synaptically mediate reward through its connections with brain reward circuitry outside the hypothalamus [51]. Although leptin receptors are expressed in brain reward circuits, at this point, it remains unclear where leptin might act to reduce reward behavior; this aspect of leptin signaling will be discussed in greater detail in the following section.

Perhaps more important is the observation that central insulin and leptin signaling can be rendered ineffective through increased caloric consumption prior to increases in body weight [13]. This finding is in agreement with the demonstration that exposure to high fat diets in rodents attenuates food SA and the acquisition of psychostimulant place preferences [30], suggesting that insulin and leptin negatively impact food reward prior to the development of obesity. Thus, due to the modulation of insulin and leptin sensitivity by diet, it is possible that the process contributing to decreased reward behavior in obese individuals occurs during the development of obesity when both are naturally elevated in the blood. Therefore, the changes observed once body weight has increased may be due to plastic changes within reward circuitry brought about by prolonged elevations in insulin and leptin. However, this hypothesis requires further investigation.

Modulation of feeding by insulin and leptin within mesolimbic circuits

Separate from their expression in hypothalamic regions that regulate energy balance, both insulin and leptin receptors are expressed within the mesolimbic system, namely the ventral tegmental area (VTA) (12) (Figure 1). The VTA contains dopaminergic neurons which innervate the nucleus accumbens (NAcc) to comprise the mesolimbic dopamine system (Box 1). Mesolimbic signaling has been hypothesized to play an integral role in mediating the rewarding properties of abused drugs and food [63], thus raising the possibility that insulin and leptin may provide feedback on mesolimbic circuitry to regulate reward-related behavior.

Dopamine signaling within mesolimbic neurons mediates the willingness to engage in rewarding behaviors or “wanting”, while the pleasure associated with a particular reward or “liking” is attributed to mesolimbic opioid action [64]. Although no direct evidence exists in relation to which aspect of motivation is affected by insulin or leptin respectively, or if this process is similar for food and drug reward, anatomically speaking, both are in position to modulate processes regulated by mesolimbic dopamine. It is unclear if insulin signaling within VTA neurons affects drug-related reward, although insulin delivered directly into the VTA does not affect food SA [50]. However, insulin signaling within the VTA is capable of affecting feeding behavior in models known to stimulate consumption of palatable foods. Specifically, direct application of insulin into the VTA also decreases opioid induced sucrose intake in rats [50], suggesting that insulin signaling within VTA neurons negatively regulates the “liking” of palatable foods.

It is unclear if manipulation of leptin signaling within the VTA alter reward-related behaviors. However, systemic doses of leptin are sufficient to decrease the firing threshold of dopaminergic neurons within the VTA [15] and, like insulin, direct administration of leptin into the VTA decreases food intake [15,65]. Furthermore, reducing leptin receptor via central genetic manipulations within VTA neurons augments food intake and acute feeding responses in animals exposed to a palatable high fat diet [15]. This suggests that leptin signaling within this region modulates food intake and potentially the hedonics associated with palatable food consumption.

VTA neurons are activated in part by the hypothalamic orexin system [59,60]. Importantly, orexin neurons are activated in response to both food and drug related cues, and orexin signaling within VTA neurons regulates non-homeostatic feeding behavior [58,61]. Interestingly, central leptin administration is capable of downregulating prepro-orexin and orexin-1 receptor mRNA in the hypothalamus [62], suggesting that in addition to modulating VTA neuronal function directly, leptin can also mediate activation of this circuitry (Figure 1). When considering these findings collectively, it is intriguing to speculate that leptin regulates feeding through its actions on hypothalamic orexin neurons and reward-related behaviors through VTA signaling mechanisms that ultimately affect dopamine tone; however these hypotheses remain to be tested.

Molecular regulation of reward by insulin and leptin

Both insulin and leptin signal through the tyrosine kinase family of receptors [66-68]. Typically, tyrosine kinase mediated signaling occurs through autophosphorylation of adjacent receptors or through recruitment of signaling molecules to phosphorylated tyrosine residues in the receptor tail [69]. A critical difference in insulin and leptin mediated signaling lies in the method of activation upon ligand binding -- the insulin receptor has intrinsic activity in that insulin binding stimulates auto-phosphorylation and activation of downstream signaling targets, whereas leptin receptor requires Jak-STAT binding for full activation [67,68]. Once activated, both insulin and leptin activate insulin receptor substrate (IRS) [68,69] and its downstream targets (Figure 2). Interestingly, IRS signaling within mesolimbic neurons regulates several aspects of psychostimulant exposure. Apart from being a downstream mediator of insulin and leptin signaling, IRS is a neurotrophic factor which mediates the effects of morphine on mesolimbic cellular morphology [70], an effect implicated in the addictive process. In addition, IRS overexpression in the VTA augments the rewarding and psychomotor activating effects of cocaine, while blocking IRS signaling attenuates these behaviors [71]. Although IRS is capable of binding many intracellular signaling proteins, the majority of its binding sites activate the phosphatidylinositol triphosphate (PI3-K) pathway [26]. Consistent with the effects of IRS on cocaine reward, modulation of PI3-K regulates the expression of behavioral sensitization to cocaine [72], suggesting that IRS-PI3-K signaling within

mesolimbic circuits modulates drug reward behaviors. A recent study by Morton and colleagues report that the ability of leptin to reduce food intake when administered into the VTA is dependent on Jak-STAT signaling but not IRS activation [65] which may represent a level of molecular specificity in relation to the regulation of food intake and food reward. When viewed collectively, these results suggest that manipulation of effector proteins linked to insulin and leptin receptor activation are capable of altering drug reward as well as food intake. However, at this point there is no functional evidence available suggesting that insulin or leptin signal through these effectors to modulate reward.

Summary and perspectives

In this review, we discuss evidence that the adiposity hormones insulin and leptin negatively impact reward behavior. A critical aspect of this regulation is the temporal component of insulin and leptin resistance which suggests that increased caloric consumption alone is capable of negatively influencing reward, an effect independent of body weight gain. Importantly, both hormones are capable of signaling within brain reward circuitry, and perturbations of their signaling mechanisms in these regions decrease feeding behavior and consumption of palatable foods. Insulin signaling in mesolimbic regions has been associated with decreases in opioid driven behaviors while leptin action in mesolimbic neurons negatively regulates dopamine tone. Due to the dissociation of overall reward into “liking” an opioid driven phenomenon and “wanting” a dopaminergic dependent process, it is possible to hypothesize that the ability of each hormone to affect reward is also dissociated. In this way, insulin action in mesolimbic neurons might affect the pleasure associated with palatable food consumption while leptin signaling in this region negatively regulates the motivation necessary to obtain a food reward. It is also possible that the effects of insulin and leptin on reward occur independent of opioid signaling. Both insulin and leptin inhibit food self-administration in laboratory rodents, a process dependent on intact dopamine function.

In either case, it is important to note that at this point these hypotheses are highly speculative and require further testing to be validated. Nevertheless, the emergence of genetic tools which selectively alter insulin and leptin receptor expression/signaling within discrete mesolimbic nuclei make it possible to now test these hypotheses directly. Through the utilization of these techniques and others, the exact nature of the ability of insulin and leptin to negate reward behavior will undoubtedly be further refined.

Box 1

Neuroanatomical regulation of mesolimbic signaling by Insulin and Leptin

A large body of evidence supports a role for mesolimbic dopamine signaling in both food and drug reward paradigms. Research in this area has benefited from the use of a variety of manipulations to study this concept including genetic, functional, and pharmacological approaches. For instance, mice unable to synthesize dopamine display drastically reduced food intake and body weight, and require exogenous dopamine to prevent starvation [52]. Ablation of dopamine neurons using 6-OHDA leads to decreased food hoarding behavior [53], as well as decreased feeding efficiency [54]. A prominent theory of midbrain dopaminergic signaling ascribes that DA neurons report errors in predicted expectancies of reward [55,56]. In this way, dopamine initially associated with reward consummation is over time, converted and used as a signal that predicts the emergence or availability of a rewarding stimulus. In support of this hypothetical framework, studies utilizing in vivo microdialysis and voltammetric techniques to monitor sub-second fluctuations of dopamine during operant conditioning experiments have confirmed this idea. In these studies, animals trained to lever press for sucrose reliably displayed an increase in dopamine release immediately prior to pressing the lever to receive a sucrose reward. However, this dopamine

surge returned to baseline levels upon consummation of the reward itself [56,57]. Recent evidence indicates that the orexin system, the brain's endogenous arousal system, is capable of activating the mesolimbic system and modifying dopamine dependent behaviors [58, 59]. Pharmacological blockade of orexin receptors within ventral tegmental area (VTA) neurons attenuates both food and drug reward [60,61]. Interestingly, leptin receptors are expressed in the brain region that produces orexin, the lateral hypothalamus (LH). Centrally administered leptin is capable of downregulating orexin expression in the LH [62], and insulin and leptin are capable of modulating feeding behavior through their direct action on VTA neurons. Thus, it is possible that leptin and insulin act at two distinct regions within this circuitry to mediate reward related to food and drug intake.

References

- Berthoud HR. Brain, appetite and obesity. *Physiol Behav* 2005;85:1–2. [PubMed: 15924902]
- Zheng H, Lenard NR, Shin AC, Berthoud HR. Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals. *Int J Obes (Lond)* 2009;33(Suppl 2):S8–13. [PubMed: 19528982]
- Teegarden SL, Nestler EJ, Bale TL. Delta FosB-mediated alterations in dopamine signaling are normalized by a palatable high-fat diet. *Biol Psychiatry* 2008;64:941–950. [PubMed: 18657800]
- Olausson P, Jentsch JD, Tronson N, Neve RL, Nestler EJ, Taylor JR. DeltaFosB in the nucleus accumbens regulates food-reinforced instrumental behavior and motivation. *J Neurosci* 2006;26:11809–10.
- Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr* 2009;139:629–632. [PubMed: 19176746]
- Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 1995;269:543–546. [PubMed: 7624777]
- Frederich RC, Hamann A, Anderson S, Lollmann B, Lowell BB, Flier JS. Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nat Med* 1995;1:1311–1314. [PubMed: 7489415]
- Panksepp J, Nance DM. Insulin, glucose and hypothalamic regulation of feeding. *Physiol Behav* 1972;9:447–451. [PubMed: 4658589]
- Woods SC, Porte D Jr. Neural control of the endocrine pancreas. *Physiol Rev* 1974;3:596–619. [PubMed: 4601624]
- Abizaid A, Horvath TL. Brain circuits regulating energy homeostasis. *Regul Pept* 2008;149:3–10. [PubMed: 18514925]
- Elmqvist JK, Bjorbaek C, Ahima RS, Flier JS, Saper CB. Distributions of leptin receptor mRNA isoforms in the rat brain. *J Comp Neurol* 1998;395:535–547. [PubMed: 9619505]
- Figlewicz DP, Evans SB, Murphy J, Hoen M, Baskin DG. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat. *Brain Res* 2003;964:107–115. [PubMed: 12573518]
- Figlewicz DP, Bennett JL, Naleid AM, Davis C, Grimm JW. Intraventricular insulin and leptin decrease sucrose self-administration in rats. *Physiol Behav* 2006;89:611–616. [PubMed: 17045623]
- 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]
- 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]
- Reiser S, Hallfrisch J. Insulin sensitivity and adipose tissue weight of rats fed starch or sucrose diets ad libitum or in meals. *J Nutr* 1977;1:147–55. [PubMed: 833676]

17. Schoeller DA, Cella LK, Sinha MK, Caro JF. Entrainment of the diurnal rhythm of plasma leptin to meal timing. *J Clin Invest* 1997;7:1882–87. [PubMed: 9312190]
18. Drazen DL, Vahl TP, D'Alessio DA, Seeley RJ, Woods SC. Effects of a fixed meal pattern on ghrelin secretion: evidence for a learned response independent of nutrient status. *Endocrinology* 2006;147:23–30. [PubMed: 16179409]
19. Woods SC, Vasseli JR, Kaestner E, Szakmary GA, Milburn P, Vitiello MV. Conditioned insulin secretion and meal feeding in rats. *J Comp Physiol Psychol* 1977;1:128–33. [PubMed: 838910]
20. Cuesta M, Clesse D, Pevet P, Challet E. From daily behavior to hormonal and neurotransmitters rhythms: comparison between diurnal and nocturnal rat species. *Horm Behav* 2009;55:338–347. [PubMed: 19027018]
21. Kalsbeek A, Fliers E, Romijn JA, La Fleur SE, Wortel J, Bakker O, Endert E, Buijs RM. The suprachiasmatic nucleus generates the diurnal changes in plasma leptin levels. *Endocrinology* 2001;142:2677–2685. [PubMed: 11356719]
22. Banks WA, Kastin AJ, Huang W, Jaspan JB, Maness LM. Leptin enters the brain by a saturable system independent of insulin. *Peptides* 1996;2:305–11. [PubMed: 8801538]
23. Duffy K, Pardridge WM. Blood-brain barrier transcytosis of insulin in developing rabbits. *Brain Res* 1987;420:32–8. [PubMed: 3315116]
24. Schwartz M, Niswender K. Adiposity signaling and biological defense against weight gain: absence of protection or central hormone resistance? *J Clin Endocrinol Metab* 2004;89:5889–97. [PubMed: 15579732]
25. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000;106:171–6. [PubMed: 10903330]
26. Myers MG Jr. Leptin receptor signaling and the regulation of mammalian physiology. *Recent Prog Horm Res* 2004;59:287–304. [PubMed: 14749507]
27. Blendy JA, Strasser A, Walters CL, Perkins KA, Patterson F, Berkowitz R, Lerman C. Reduced nicotine reward in obesity: cross-comparison in human and mouse. *Psychopharmacology (Berl)* 2005;180:306–315. [PubMed: 15719224]
28. Warren M, Frost-Pineda K, Gold M. Body mass index and marijuana use. *J Addict Dis* 2005;24:95–100. [PubMed: 16186086]
29. Wellman PJ, Nation JR, Davis KW. Impairment of acquisition of cocaine self administration in rats maintained on a high fat diet. *Pharmacol Biochem Behav* 2005;1:89–93.
30. Davis JF, Tracy AL, Schurdak JD, Tschop MH, Lipton JW, Clegg DJ, Benoit SC. Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat. *Behav Neurosci* 2008;122:1257–1263. [PubMed: 19045945]
31. Scalfani A, Springer D. Dietary obesity in adult rats: similarities to hypothalamic and human obesity syndromes. *Physiol Behav* 1976;3:461–71. [PubMed: 1013192]
32. Volkow ND, Wang GJ, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philos Trans R Soc Lond B Biol Sci* 2008;363:3191–3200. [PubMed: 18640912]
33. Drewnoski A, Kurth C, Holden-Wiltse J, Saari J. Food preferences in human obesity: carbohydrates versus fats. *Appetite* 1992;3:207–21.
34. la Fleur SE, Vandershuren LJ, Luijendijk MC, Kloeze BM, Tiesjema B, Adan RA. A reciprocal interaction between food-motivated behavior and diet-induced obesity. *Int J Obes* 2007;8:1286–94.
35. Hajnal A, Acharya NK, Grigson PS, Covasa M, Twining RC. Obese OTLEF rats exhibit increased operant performance for palatable sucrose solutions and differential sensitivity to D2 receptor agonism. *Am J Physiol Regul Integr Comp Physiol* 2007;5:R1846–54. [PubMed: 17804583]
36. Carroll ME, Meisch RA. Oral phencyclidine (PCP) self-administration in rhesus monkeys: effects of feeding conditions. *J Pharmacol Exp Ther* 1980a;214:339–346. [PubMed: 6771393]
37. Carroll ME, Meisch RA. The effects of feeding conditions on drug-reinforced behavior: maintenance at reduced body weight versus availability of food. *Psychopharmacology (Berl)* 1980b;68:121–124. [PubMed: 6107944]
38. Carroll ME, Stotz DC, Kliner DJ, Meisch RA. Self-administration of orally-delivered methohexital in rhesus monkeys with phencyclidine or pentobarbital histories: effects of food deprivation and satiation. *Pharmacol Biochem Behav* 1984;20:145–151. [PubMed: 6694994]

39. Campbell UC, Carroll ME. Acquisition of drug self-administration: environmental and pharmacological interventions. *Exp Clin Psychopharmacol* 2000;8:312–325. [PubMed: 10975619]
40. Cabib S, Orsini C, Le Moal M, Piazza PV. Abolition and reversal of strain differences in behavioral responses to drugs of abuse after a brief experience. *Science* 2000;289:463–465. [PubMed: 10903209]
41. Polivy J, Herman CP. Dieting and Bingeing: a causal analysis. *Am Psych* 1985;40:193–201.
42. Wiederman MW, Pryor T. Substance abuse and impulsive behaviors among adolescents with eating disorders. *Addict Behav* 1996;21:269–272. [PubMed: 8730530]
43. Corwin RL. Bingeing Rats: A model of intermittent excessive behavior? *Appetite* 2006;46:11–15. [PubMed: 16188345]
44. Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry* 2006;63:824–830. [PubMed: 16818872]
45. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 1954;47:419–427. [PubMed: 13233369]
46. Hoebel BG. Hypothalamic self-stimulation and stimulation escape in relation to feeding and mating. *Fed Proc* 1979;38:2454–2461. [PubMed: 385351]
47. Carr KD, Kim GY, de Vaca S Cabeza. Hypoinsulinemia may mediate the lowering of self stimulation thresholds by food restriction and streptozotocin-induced diabetes. *Brain Res* 2000;863:160–8. [PubMed: 10773204]
48. Galici R, Galli A, Jones DJ, Sanchez TA, Saunders C, Frazer A, Gould GG, Lin RZ, France CP. Selective decreases in amphetamine self-administration and regulation of dopamine transporter function in diabetic rats. *Neuroendocrinology* 2003;77:132–140. [PubMed: 12624535]
49. Shalev U, Yap J, Shaham Y. Leptin attenuates acute food deprivation-induced relapse to heroin seeking. *J Neurosci* 2001;21:RC129. [PubMed: 11160414]
50. Figlewicz DP, Bennet JL, Aliakbari S, Zavosh A, Sipols AJ. Insulin acts at different CNS sites to decrease acute sucrose intake and sucrose self-administration in rats. *Am Jour Phys Regul Integr Comp Physiol* 2008;2:R388–94.
51. Kampe J, Tschop M, Hollis J, Oldfield B. An anatomic basis for the communication of hypothalamic cortical and mesolimbic circuitry in the regulation of energy balance. *Eur J Neurosci* 2009;1–16.
52. Zhou QY, Palmiter RD. Dopamine- deficient mice are severely hypoactive, adipsic and aphagic. *Cell* 1995;83:1197–209. [PubMed: 8548806]
53. Kelley AE, Stinus L. Dissaperance of hoarding behavior after 6-hydroxydopamine lesions of the mesolimbic dopamine neurons and its reinstatement with L-Dopa. *Behav Neurosci* 1985;99:531–45. [PubMed: 3939664]
54. Salamone, JD.; Zigmond, MJ.; Stricker, EM. Characterization of impaired feeding behavior in rats given haloperidol or dopmaine-depleting brain lesions; 1990. p. 17-24.
55. Schultz W. Dopamine neurons and their role in reward mechanisms. *Curr Opin Neurobiol* 1997;7:191–197. [PubMed: 9142754]
56. Schultz W, Tremblay L, Hollerman JR. Reward prediction in primate basal ganglia and frontal cortex. *Neuropharmacology* 1998;37:421–429. [PubMed: 9704983]
57. Kiyatkin EA, Gratton A. Electrochemical monitoring of extracellular dopamine in the nucleus accumbens of rats lever pressing for food. *Brain Res* 1994;652:225–34. [PubMed: 7953734]
58. Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. *Nature* 2005;437:556–559. [PubMed: 16100511]
59. Korotkova TM, Sergeeva OA, Eriksson KS, Haas HL, Brown RE. Excitation of ventral tegmental area dopaminergic and nondopaminergic neurons by orexins/hypocretins. *J Neurosci* 2003;23:7–11. [PubMed: 12514194]
60. Borgland SL, Taha SA, Sarti F, Fields HL, Bonci A. Orexin A in the VTA is critical for the induction of synaptic plasticity and behavioral sensitization to cocaine. *Neuron* 2006;49:589–601. [PubMed: 16476667]

61. Zheng H, Patterson LM, Berthoud HR. Orexin signaling in the ventral tegmental area is required for high-fat appetite induced by opioid stimulation of the nucleus accumbens. *J Neurosci* 2007;27:11075–11082. [PubMed: 17928449]
62. Lopez M, Seoane L, Garcia M Carmen, Lago F, Casanueva F, Senaris R, Dieguez C. Leptin regulation of Prepro-orexin and orexin receptor mRNA levels in the hypothalamus. *Bioch Biophys Res Com* 2000;269:41–45.
63. Saper CB, Chou TC, Elmquist JK. The need to feed: homeostatic and hedonic control of eating. *Neuron* 2002;36:199–211. [PubMed: 12383777]
64. Berridge KC. Food reward: brain substrates of wanting and liking. *Neurosci Biobehav Rev* 1996;20:1–25. [PubMed: 8622814]
65. Morton GJ, Blevins JE, Kim F, Matsen M, Figlewicz DP. The Action of Leptin in the Ventral Tegmental Area to Decrease Food Intake is Dependent on Jak-2 Signaling. *Am J Physiol Endocrinol Metab* 2009;297:E202–10. [PubMed: 19435852]
66. Hadari YR, Tzahar E, Nadiv O, Rothenberg P, Roberts CT Jr, LeRoith D, Yarden Y, Zick Y. Insulin and insulinomimetic agents induce activation of phosphatidylinositol 3'-kinase upon its association with pp185 (IRS-1) in intact rat livers. *J Biol Chem* 1992;267:17483–17486. [PubMed: 1381348]
67. Baumann H, Morella KK, White DW, Dembski M, Bailon PS, Kim H, Lai CF, Tartaglia LA. The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors. *Proc Natl Acad Sci U S A* 1996;93:8374–8378. [PubMed: 8710878]
68. Tartaglia LA. The leptin receptor. *J Biol Chem* 1997;272:6093–6096. [PubMed: 9102398]
69. Koch CA, Anderson D, Moran MF, Ellis C, Pawson T. SH2 and SH3 domains: elements that control interactions of cytoplasmic signaling proteins. *Science* 1991;252:668–674. [PubMed: 1708916]
70. Russo SJ, Bolanos CA, Theobald DE, DeCarolis NA, Renthall W, Kumar A, Winstanley CA, Renthall NE, Wiley MD, Self DW, Russell DS, Neve RL, Eisch AJ, Nestler EJ. IRS2-Akt pathway in midbrain dopamine neurons regulates behavioral and cellular responses to opiates. *Nat Neurosci* 2007;10:93–99. [PubMed: 17143271]
71. Iniguez SD, Warren BL, Neve RL, Nestler EJ, Russo SJ, Bolanos-Guzman CA. Insulin receptor substrate-2 in the ventral tegmental area regulates behavioral responses to cocaine. *Behav Neurosci* 2008;122:1172–1177. [PubMed: 18823173]
72. Izzo E, Martin-Fardon R, Koob G, Weiss F, Sanna P. Neural plasticity and addiction: PI3-kinase and behavioral sensitization. *Nature Neurosci* 2002;5:1263–1264. [PubMed: 12436114]

Figure 1.

The ability of insulin and leptin to reduce reward related behaviors could occur through action at two distinct regions that modulate mesolimbic activity. Tyrosine hydroxylase (TH) neurons in the (VTA) promote feeding and drug taking behavior; these neurons receive a direct connection from orexin neurons located in the lateral hypothalamus (LH) which activates VTA neurons through signaling at the orexin-1 receptor, as indicated by the vertical black lines. This circuit mediates non-homeostatic food consumption and drug relapse behavior. Leptin receptors are present on LH neurons and leptin negatively regulates orexin and orexin-1-receptor gene expression within LH neurons. Moreover, insulin and leptin act upon VTA neurons to negatively regulate dopamine tone and over-consumption of palatable foods as indicated by the green arrows. It is unclear if leptin acting within LH neurons affects arousal, feeding or anticipation of rewards; likewise it is unclear if leptin signaling within VTA neurons affects reward related behaviors. Thus, insulin and leptin may act at two distinct brain regions to modulate mesolimbic signaling and reward related behaviors. VTA: ventral tegmental area, LH: Lateral Hypothalamus.

Figure 2.

The ability of insulin and leptin to mediate reward behavior at the molecular level might occur through the activation of insulin receptor substrate (IRS-2) in ventral tegmental area (VTA) neurons. Both insulin and leptin receptors are present on VTA neurons and upon activation, both activate intracellular signaling cascades that ultimately affect gene transcription. Intracellular signaling from both the insulin and leptin receptor converges at IRS-2. IRS-2 signaling regulates the psychostimulant mediated plasticity and reward. Thus, it is possible for insulin and leptin to regulate reward behaviors through their action on IRS-2 in the VTA. It is unclear if insulin and leptin signaling within VTA neurons elicits IRS-2 activation; however, the ability of leptin to negatively regulate food intake behavior is mediated by Jak-2 (Jak-STAT) signaling within VTA neurons. IRS-2: Insulin receptor substrate, VTA: ventral tegmental area, Jak-2: Janus kinase, Jak-STAT: Janus kinase signal transducers and activators of transcription, TH: Tyrosine hydroxylase.