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Insulin, leptin, and food reward: update 2008

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Figlewicz DP, Benoit SC. Insulin, leptin, and food reward: update 2008. *Am J Physiol Regul Integr Comp Physiol* 296: R9–R19, 2009. First published October 22, 2008; doi:10.1152/ajpregu.90725.2008.—The hormones insulin and leptin have been demonstrated to act in the central nervous system (CNS) as regulators of energy homeostasis at medial hypothalamic sites. In a previous review, we described new research demonstrating that, in addition to these direct homeostatic actions at the hypothalamus, CNS circuitry that subserves reward and motivation is also a direct and an indirect target for insulin and leptin action. Specifically, insulin and leptin can decrease food reward behaviors and modulate the function of neurotransmitter systems and neural circuitry that mediate food reward, i.e., midbrain dopamine and opioidergic pathways. Here we summarize new behavioral, systems, and cellular evidence in support of this hypothesis and in the context of research into the homeostatic roles of both hormones in the CNS. We discuss some current issues in the field that should provide additional insight into this hypothetical model. The understanding of neuroendocrine modulation of food reward, as well as food reward modulation by diet and obesity, may point to new directions for therapeutic approaches to overeating or eating disorders.

motivation; food intake; dopamine

RECENT DATA SUGGEST that the peripheral regulators of energy balance, leptin and insulin, may play important roles in the occurrence of behaviors typically classified as nonhomeostatic. For example, central insulin and leptin are sufficient to reduce operant responding for palatable foods and to attenuate food-induced conditioned place preferences (CPPs) independent of their effects to regulate energy balance. Since findings such as these have generated much interest in the potential roles of central leptin and insulin signaling in brain reward pathways, we believe it is instructive to begin with a consideration of such findings in a larger historical context. In fact, the observation that energy balance or deprivation state can significantly influence behavioral responses to obtain food or the reward associated with food is many decades old. In one early theoretical conceptualization, Hull et al. (98, 99) proposed that responding or motivation could be explained by $sER = \text{sHr} \times \text{D} \times K$, where *sEr* represents the reaction potential or motivation of a behavior, sHr represents the habit strength or number of experiences, D represents drive or hours of deprivation, and *K* represents the value, reward, or hedonic quality of the food to be obtained. Hull et al. reasoned that the expression of a behavior was a direct function not only of learning and experience but, also, the "need" state and the "value" of the food available. As an example, one might train a rat such that pressing a lever delivers a food pellet. After the rat learns the task, the number of presses on any given trial would be significantly increased by food depriving the rat and/or increasing the incentive and hedonic properties of the pellet (such as would be the case with high-fat high-sugar food pellets). Along these lines, Ferster and Skinner (64) observed that response rates on different schedules of reinforcement in pigeons were significantly increased by restriction of their body weight. In an early series of studies, Ferster and Skinner observed a direct inverse relationship between the birds' body weight and their rates of responding for food pellets.

Food restriction of experimental animals in these and other similar studies was often imposed to increase the occurrence of the behaviors that the experimenters sought to study. In many cases, rats, mice, and other experimental animals are regularly food deprived, so that the behavior, neurobiology, and genetics of learning and memory can be studied using food reward paradigms. In this way, the relationship between energy balance and "reward" or "reinforcement" has been well characterized (31, 34), although for reasons largely unrelated to that which now generates much interest and enthusiasm: the idea that the modern epidemic of obesity may be in part related to reward and hedonic mechanisms and that failure of regulatory systems might be related to dysregulations of reward systems. The historical lesson is that food deprivation or negative energy balance promotes responding for foods and other reinforcements. Coupled with our current knowledge that negative energy balance leads to low levels of circulating leptin and insulin, this leads to the hypothesis that low levels of these hormones might be associated with increased responding to obtain rewards. It also suggests the corollary hypothesis that increased leptin and insulin might be sufficient to attenuate responding for reward. In fact, recent and historical data are consistent with both hypotheses and are summarized below. An intriguing speculation based on the formulation of Hull et al. (98, 99) is that signals that reflect energy balance would be included in the variable of "drive" (D) and, as such, would

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be predicted to act by altering the gain of other factors determining motivation.

In 2003, we published a review exploring "a new CNS role for adiposity signals" (65). Since then, a number of studies that *1*) confirm the actions of insulin and leptin to decrease food reward and the motivation to feed and *2*) have begun to explore cellular and central nervous system (CNS) circuitry-related mechanisms have been carried out. Here, we provide an update of the field and critical discussion of newly developing questions. An early and continued research focus has been on the actions of these two hormones at the medial hypothalamus, which historically has been identified as a major player in the CNS regulation of metabolism, energy balance, and caloric intake in terms of physiological need. Because the behavioral, cellular, and molecular actions of insulin and leptin at the medial hypothalamus have been well studied, this material is summarized briefly. We refer the reader to recent reviews, including our 2003 review, which provide more detailed discussion and historical references on this topic (1, 11–13, 65, 96, 167, 194), which has provided the groundwork for studies assessing food reward regulation.

INSULIN AND LEPTIN: ADIPOSITY SIGNALING IN THE CNS

In 1979, it was demonstrated in nonhuman primates that insulin infused into the CNS caused a significant decline in the animals' food intake and body weight (193). This observation was made in the context of a contemporary model: that circulating humoral factors could regulate individual meal size, as well as food intake and body weight over a longer time course (47, 124, 141, 177). Porte and Woods (153) proposed that insulin served as an "adiposity signal" and completes a negative-feedback loop that links the behavior of feeding with the size of adipose stores. Many studies over the intervening decades have essentially validated this basic concept (2–4, 25, 38, 125). In the mid-1990s, the candidate adiposity signal and adipose hormone leptin was identified (197) and has been well characterized as a regulator of energy homeostasis.

As reviewed earlier (65), two critical issues needed to be addressed to argue for a role for adiposity signals in modulating any aspect of CNS function. The first issue is the need for circulating signals to have access to CNS circuitry. The presence of insulin in the CNS was reported in 1979 (88), and many studies established that the predominant amount of insulin in the CNS can be accounted for by receptor-mediated transport into the CNS (46, 52, 53, 79, 106, 115, 164, 165). Although intermittent reports have suggested that insulin can be synthesized locally in the developed CNS, quantities appear to be negligible, particularly compared with the affinity of the receptor for insulin. The relationship between CNS and plasma levels of insulin is saturable (nonlinear), consistent with a receptor-mediated transport process. In the 1990s, the adipose hormone leptin was identified, and knowledge was rapidly acquired that it (similarly) could be transported by multiple mechanisms into the CNS (7, 10, 92, 109, 121, 123, 137). Relative levels of leptin and insulin in the cerebrospinal fluid are decreased in association with obesity (8, 9, 30, 108, 162, 163, 178). The functional implication is that, in circumstances of chronic hyperinsulinemia and hyperleptinemia, such as obesity, less adiposity signaling would be available to the CNS.

The second basic issue relates to the presence of insulin and leptin receptors in the CNS. Receptors for insulin (48, 87, 113, 181, 187, 195) and leptin (60, 119) are widely expressed throughout the CNS. Extensive research has established that the medial hypothalamus, a key center for the regulation of energy homeostasis and coordination of metabolic events, is a major target for insulin and leptin action (12, 127, 142, 167). Other CNS sites and neural systems are targets for insulin and leptin action (73, 81, 86, 126). Studies utilizing antisense oligonucleotides against the insulin receptor or conditional localized knockout of the insulin receptor, aided our understanding of the have to contribution of the brain insulin receptor to energy and glucose homeostasis (27, 116, 145, 146). The leptin receptor, similarly extensively expressed, is present as different splice-variant isoforms in the CNS, with the "signaling" form OBRb having the major role in leptin action. The obese *db/db* mouse and Zucker *fa/fa* rat represent naturally occurring "knockouts" (41) of the leptin receptor, and recent use of receptor constructs with modifications in signaling capability validates the importance of CNS leptin action in energy homeostasis.

Leptin and insulin have multiple effects on energy homeostasis that depend on the activation of key hypothalamic nuclei and peptides to regulate energy balance (103). Among the most extensively studied mediators are neuropeptide Y (42, 43, 166, 173, 188), proopiomelanocortin (POMC) and its product α-melanocyte-stimulating hormone, and the melanocortin antagonist agouti-related peptide (AgRP) (for reviews see Refs. 14, 135, 168, and 194). POMC and AgRP are selectively expressed in neurons of the arcuate nucleus (ARC) colocalized with receptors for insulin and leptin, and they represent endogenous circuitry capable of regulating food intake (40, 128, 136). Genetic deletion of the critical melanocortin-4 receptor recapitulates the obese phenotype of leptin-deficient mice, including obesity (100), and selective ablation of the AgRP neurons in adult mice causes severe starvation and death (82). Leptin and insulin increase expression of the agonist α-melanocyte-stimulating hormone and decrease expression of AgRP (for review see Ref. 14). Collectively, these data suggest that leptin and insulin act on ARC melanocortin (AgRP and POMC) neurons to regulate food intake and energy balance (Fig. 1).

Recent work has also elucidated several other key players in the regulation of food intake and body weight that are likely to mediate (directly or indirectly) the effects of leptin and insulin. Among these, orexin-A and melanin-concentrating hormone are expressed in the lateral hypothalamus (LH) (26, 131, 151). Both are orexigenic: in mice lacking either peptide or its key receptors, metabolic rates and ingestive behavior are altered. Intriguingly, recent data suggest that orexin-A may be an important factor in the effects of drugs of abuse. Orexin antagonists blunt the behavioral response to cocaine and other psychostimulants and may be important for the rewarding effects of food as well (44; for reviews see Refs. 24 and 91).

Much has been learned about intracellular signaling by insulin and leptin in the CNS from studies in the medial hypothalamus. Initial studies validated that signaling for the CNS insulin receptor is comparable to postreceptor mechanisms in peripheral target tissues. That is, the receptor is an autophosphorylating tyrosine kinase, and its activation leads not only to tyrosine phosphorylation of other proteins, includ-

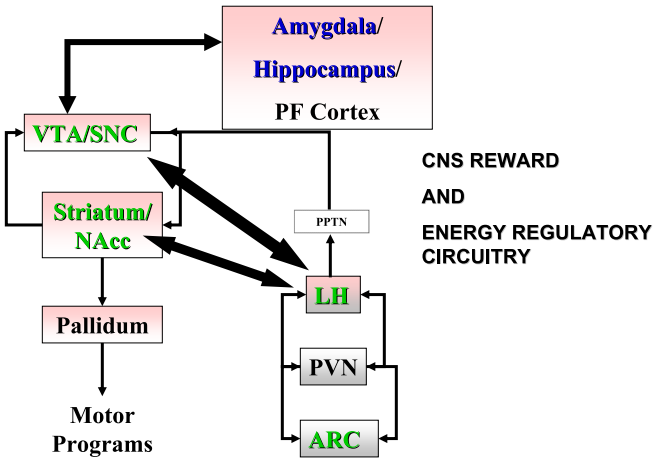

Fig. 1. Energy regulatory (gray) and reward circuitry (rose) and major synaptic connections. Green labels highlight targets of insulin and leptin; blue labels highlight targets of insulin (not determined for leptin). CNS, central nervous system; PPTN, pedunculopontine tegmental nucleus; PVN, paraventricular nucleus; PF, prefrontal; VTA, ventral tegmental area; SNC substantia nigra pars compacta; NAcc, nucleus accumbens; LH, lateral hypothalamus; ARC, arcuate nucleus.

ing the key signaling moiety insulin receptor substrate, but also to a cascade of additional phosphorylation events, including activation of the phosphatidylinositol 3 (PI3)-kinase pathway (83) and phosphorylation of Akt/PKB (89, 90, 112, 143, 171). The leptin receptor, upon leptin binding, can similarly initiate insulin receptor substrate phosphorylation and activation of the PI3-kinase pathway (144). However, the receptor does not have intrinsic tyrosine kinase activity; thus JAK-STAT signaling is a critical initial event, leading to transcriptional events and, ultimately, to the generation of suppressor of cytokine signaling-3, which provides negative feedback on leptin signaling (119, 157). Recently, activation of the mammalian target of rapamycin pathway in medial hypothalamic neurons has been reported, and early studies suggest that activation of this pathway is correlated with anorexigenic and metabolic homeostasis events (49). Collectively, these studies support the concept that insulin and leptin can mediate intracellular events related to ingestive behavior and caloric homeostasis via parallel and unique intracellular pathways (36, 37, 152). They provide correlative or direct evidence of the importance of these signals in mediating in vivo events. A current research emphasis is on differential effects of insulin and leptin, in terms of time course of action, intracellular mechanisms, and effects on glucose homeostasis vs. energy balance, within the hypothalamus. This detailed physiological information will contribute to insights into pathophysiology. For example, in metabolic circumstances in which plasma insulin or leptin levels are low (starvation and reduced adiposity), signaling would be decreased and drive for food intake would be increased. Obesity (excessive adiposity) would represent a pathophysiological state in which adiposity signals are decreased in relative or absolute amount in the CNS or there is direct CNS resistance to their action (35, 45, 54, 104, 138, 184). In summary, 30 years of research have confirmed the overall hypothesis that hormones that reflect the size of adipose and calorie stores can act directly within the CNS to provide negative feedback on food intake and modulate energy utilization. As discussed below, this research has paved the way for studies of insulin and leptin signaling within reward circuitry.

INSULIN, LEPTIN, AND FOOD REWARD

A current extension of this research focuses on how environmental factors such as diet composition can interact with the adiposity signal-CNS feedback loop to modulate the effectiveness of adiposity signals. In 1988, Arase and colleagues (6) observed that a high-fat diet resulted in an impairment in the action of insulin, given directly into the CNS, to decrease body weight in rats. This finding was subsequently replicated (39), and a similar observation was made for leptin (120). Extrapolation of these observations might suggest a loss of the effectiveness of endogenous adiposity signals in the CNS to provide feedback signaling. Data collected by the Centers for Disease Control document a pervasive increase of obesity in adults across the United States in the 1990s and 2000s (93, 129, 130) and a high incidence of obesity in the pediatric age group as well (114), interpreted as a significant environmental influence over the neural circuitry associated with the physiological maintenance of energy homeostasis. The epidemiological finding also emphasizes that attention should be focused on additional CNS circuitry that is directly or indirectly connected with hypothalamic circuitry to modulate feeding behavior.

One obvious target for study is the CNS circuitry that mediates motivation and reward. Components of this circuitry are activated with, and contribute to, complex behaviors such as food seeking and food intake (16, 18, 19; see below). This circuitry includes portions of the cerebral cortex, hippocampus, and amygdala and the striatonigral pathway, which is implicated in transposing motivational aspects of stimuli into motor responses, as well as in hedonic evaluation of the stimulus and associative learning (61, 101, 105, 150, 156, 158, 189, 191). As discussed below, the major neurotransmitter pathways associated with motivation and hedonics are mesolimbic dopamine (DA) and certain CNS opioid pathways. In terms of neural connectivity, the hypothalamus is linked to the "motivational circuitry" of the CNS, and numerous mono- and multisynaptic pathways between different components of the limbic circuitry and the hypothalamus have been identified (19, 20, 179). The anatomic and functional relevance of this circuitry to food intake is discussed in recent reviews (16, 110, 111). Insulin and leptin receptors are expressed throughout the limbic forebrain, including the hippocampus, the amygdala, and the LH/zona incerta area (69, 118, 119). This provides one rationale for exploring the potential that the limbic forebrain may itself be a direct target for insulin or leptin.

Food intake can be driven by energy demands, i.e., "homeostatic" feeding. However, food intake can also be driven by the palatability or pleasure associated with eating a preferred food, "nonhomeostatic" feeding (18–20). The palatability of a particular food source is assumed to be related to the flavor and taste of that food, and high-fat diets are generally considered more palatable than low-fat diets, inasmuch as they are preferentially overconsumed. In humans, individual differences exist in the reinforcing value of food, with a stronger preference for diets high in fat and carbohydrates displayed by obese than by nonobese individuals (57–59).

Berridge and colleagues provided a conceptual framework for the consideration of food reward, proposing that there is

"wanting" of food (or another stimulus) and "liking" of food (16). The behavior associated with nonhomeostatic feeding is in part regulated by the mesolimbic DA system (18), and within this system, the neurotransmitter DA plays a substantial role in the regulation of food reward. They identified nucleus accumbens (NAc) DA projections as central to wanting. The NAc represents a functionally specialized subregion of the striatum, which is a critical anatomic component of CNS reward circuitry, with the extensive projection of DA neurons from the midbrain ventral tegmental area (VTA) and associated DA cell groups (substantia nigra) (101, 102). Activation of these midbrain DA neurons has been implicated in the motivating, rewarding, reinforcing, and incentive salience properties of natural stimuli such as food and water, as well as drugs of abuse (16, 18, 155, 161, 176, 192). The neural mechanisms of food reward are believed to be similar, if not identical, to drug rewards (29, 111). There is also the possibility that dysregulation of those circuits may adversely affect body weight regulation. For example, studies in humans (183) and animals (21) suggest that changes in central DA may contribute to the development of obesity. Furthermore, some human studies report a decreased propensity to engage in the use of recreational drugs and a decreased frequency of substance abuse disorders in obese individuals (172, 185). One implication of these findings is that obesity is capable of altering processes within the endogenous reward system of the brain.

Behavioral paradigms evaluating reward and food reward provide evidence for a significant effect of metabolic status on performance in these paradigms and support the idea that insulin and leptin may play a role in modulating reward function in the CNS (74). Food restriction or fasting paradigms (in which endogenous insulin and leptin are decreased) enhance the addictive or reinforcing properties of drugs of abuse, as found in drug self-administration and relapse to drug-taking paradigms; intraventricular leptin can reverse food deprivation-induced relapse to heroin self-administration (34, 169, 170). Measurement of DA levels in NAc interstitial fluid has shown a greater DA response to food reward in food-deprived than in ad libitum-fed rats (190). Data from the experimental approach of brain self-stimulation have shown that food restriction shifts the dose-response curve for self-stimulation in some perifornical hypothalamus sites to the left, such that weaker electrical current, which normally would not support sustained self-stimulation activity at these sites, becomes efficacious when animals are maintained on a food-restriction paradigm (31, 32). Intraventricular leptin administration shifts the dose-response curve for self-stimulation in food restriction-sensitive perifornical hypothalamic sites to the right (i.e., reverses the effect of food restriction), and comparable data demonstrate that administration of insulin into the brain of food-restricted or ad libitum-feeding rats increases the threshold current needed to sustain LH self-stimulation, reversing the decreased threshold observed with fasting and elevating the threshold above its "free-feeding" level (33, 76). This evidence, although limited, suggests that insulin and leptin may play a major role in mediating the effects of altered metabolic status on reward paradigms in general.

Additionally, several studies implicate insulin and leptin in food reward. In addition to normal feeding, DA activity has been implicated in behavioral paradigms that evaluate different aspects of reward or motivation: acute licking of palatable solutions (50, 160), self-administration (102), and CPP (148). Sipols and colleagues (175) demonstrated suppression of acute sucrose licking (intraventricular insulin) and Figlewicz et al. demonstrated decreased food-CPP (intraventricular insulin or leptin) (66) and sucrose self-administration (intraventricular insulin or leptin) (68) in rats fed chow ad libitum. In these studies, doses of insulin and leptin were subthreshold for effects on chronic food intake or body weight and effects were observed very acutely (within minutes). Hommel and colleagues (95) and Morton and colleagues (134) demonstrated that direct administration of leptin into the VTA decreases chow intake in ad libitum-feeding rats. Taken together, the results of these four different types of behavioral paradigms—self-administration, lick rate task, CPP, and free feeding of the baseline chow diet—demonstrate that insulin and leptin, across a concentration range from fasting to free-feeding to elevated (as would occur postprandially) levels, are able to modify behaviors that reflect acute and learned reward evaluation independent of their action(s) to regulate body adiposity. Whether the rapid and chronic effects of insulin and leptin are mediated via the same circuitry and the same neural mechanisms remains to be elucidated. Furthermore, different anatomic loci, including the LH, appear to be targets for insulin- and leptin-induced suppression of food reward (33, 76, 118).

Studies from Figlewicz and colleagues focused on insulin and, more recently, leptin effects on the midbrain DA neurons at the cellular and behavioral levels. Insulin receptors have been identified in the VTA and the striatum in previous anatomic studies using receptor autoradiography and receptor immunocytochemistry approaches (181, 187), and expression of insulin and leptin receptor mRNA in the substantia nigra has been reported (60). We have localized insulin and leptin receptors on midbrain DA neurons, including those of the VTA, as well as medial and lateral substantia nigra (69). The presence of functional receptors has been confirmed by Fulton et al. (75) and Hommel et al. (95). Thus this critical motivational circuitry has the potential to serve as a direct target for adiposity signals. Recent studies have shown that administration of insulin and leptin directly into the VTA increases PI3-kinase activity (71). Furthermore, leptin (administered peripherally, intraventricularly, or directly into the VTA) results in an increase in JAK-STAT phosphorylation, which is critical for the effect of leptin in the VTA to decrease chow feeding (134). The synaptic or neural mechanisms that underlie insulin and leptin effects on food reward remain to be elucidated. We identified one potential cellular target for insulin action, the DA reuptake transporter (DAT), which inactivates DA signaling by transporting DA back into the DA nerve terminal from the synapse (107). The synthesis and the activity or synaptic concentrations of the DAT can be regulated by intracellular signaling systems, including PI3-kinase (77, 182). We have observed in vivo and in vitro effects of insulin on expression and activity of the DAT (72, 149). Insulin can increase mRNA levels and synaptic activity of the DAT. The functional implication of this increased DAT activity could be an increase in clearance of DA from the synapse and, hence, decreased DA signaling. This would be consistent with an action of insulin to decrease the rewarding aspect of food. Comparable cellular studies to identify regulatory proteins in DA neurons that are targets of leptin have not been done,

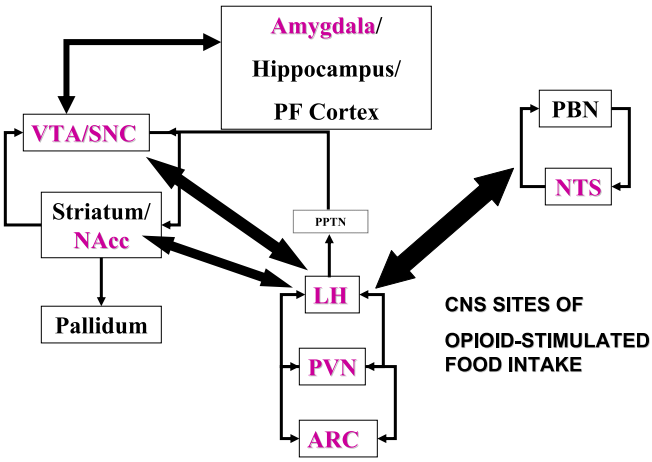

Fig. 2. Food intake, energy regulatory, and reward circuitry. Magenta labels highlight CNS sites in which opioid administration stimulates food intake. PBN, parabrachial nucleus; NTS, solitary tract nucleus.

although there is evidence that leptin regulates DA release and the electrical activity of DA neurons (95).

As mentioned above with respect to energy homeostasis, some effects of insulin and leptin are mediated through secondary hypothalamic peptide effector systems, including melanocortins and orexin-A. For example, melanocortin receptors (MC3R and MC4R) are also expressed in brain regions implicated in addictive behavior (5), and pharmacological studies have outlined functional roles for these receptors in the modulation of drug-taking behavior. Antagonism of these receptors in the NAc inhibits operant responding for cocaine, whereas central agonism of this system augments amphetamine-induced behaviors (97). As discussed elsewhere, orexin neurons exhibit diverse projections in the CNS to sites including the VTA (62). Orexin-expressing neurons of the LH have μ-opioid receptors, and the molecular physiology of these neurons is altered with morphine administration or withdrawal, emphasizing their role in CNS reward circuitry (78). Orexinergic projections signal specifically on a majority of DA neurons to activate the mesolimbic pathway (198), and VTA neuron populations express both orexin receptor subtypes (122). Exogenous orexin can increase VTA dopaminergic neuron firing rates. A specific role for endogenous orexin action in the VTA on reward-seeking behavior is implied in the findings in rats that *1*) an orexin antagonist could block the reinstatement of an extinguished place preference for morphine and *2*) intra-VTA orexin-A was sufficient to reinstate the place preference (84). Additional evidence from studies of genetic models demonstrates the inability of orexin-deficient mice to form morphine-CPPs (140). Orexin action in the LH also appears necessary for the acquisition and expression of morphine-induced CPP (85). Finally, Borgland et al. (23) reported that intra-VTA administration of an orexin antagonist effectively prevents behavioral sensitization and neurophysiological changes that typify chronic cocaine use. The important point is that, to the degree that peripheral adiposity signals may affect reward function, they are likely to do so in part through these critical effector peptides. One important consequence of this could be that neither insulin nor leptin would have to act directly on VTA or NAc cells to exert regulatory control. Rather, as an additional mechanism, they could activate (or inactivate) effector systems in hypothalamic neurons that, in turn, project to the reward circuitry. This notion is supported by a recent study evaluating the specific CNS targets of intraventricular insulin to suppress food reward: the effect of insulin to decrease sucrose self-administration was found to be due to action at the ARC (67).

INSULIN, LEPTIN, AND PALATABILITY

Palatability influences the amount and the type of food that is ingested (15–17). For example, it is well known that even noncaloric solutions, if they are made to taste sweet, will elicit drinking behavior in sated rats (28). Several hypothalamic peptides project to CNS areas important for taste processing (nucleus of the solitary tract) and hedonics and reward, including the VTA, NAc, and substantia nigra. As discussed above, this system is a direct target of insulin and leptin and suggests one mechanism whereby adiposity signals might modulate palatability. Berridge and colleagues (16–18) suggested that "liking" of foods is mediated in the CNS by endogenous opioids. Leptin and insulin, which simulate a state of satiation, have been found to regulate the hedonic qualities of brain self-stimulation (76), for which CNS opioidergic signaling has been implicated (32). Glass and colleagues (80) and others documented the role for opioid peptides to preferentially enhance intake of palatable food over less palatable food (rat chow), although this is somewhat dependent on the opioid receptor populations being targeted. Thus some opioid-receptive sites appear linked predominantly to palatability and some to caloric homeostasis (22, 147, 196). Whether adiposity signals can blunt palatability-induced feeding has been evaluated to a limited extent. Sipols and colleagues (174) reported that intraventricular insulin could blunt the ability of dynorphin to stimulate sucrose pellet intake and also synergize with a subthreshold dose of the dynorphin antagonist nor-binaltorphimine to decrease baseline intake of sucrose pellets (Fig. 2). This would be consistent with an action at the medial hypothalamus, where dynorphin receptors have been localized. Additionally, Figlewicz et al. (71) reported a direct action of insulin and leptin at the VTA to reverse μ-opioid-stimulated sucrose feeding. Although this study did not evaluate palatability per se, rats were tested immediately after feeding, and thus sucrose intake would not reflect caloric need but, it is presumed, would be correlated with liking of the sucrose. Given the identification in human eating disorders of a role for μ-opioids (57), such studies have potential clinical relevance.

Table 1. *Effects of insulin or leptin on reward behaviors*

Behavior	Insulin (Route)	Leptin (Route)	Reference No.
Brain self-stimulation	Decrease (icv)	Decrease (icv)	33, 76
Relapse to heroin seeking	Not determined	Decrease (icv)	170
Acute sucrose licking	Decrease (icv)	Not determined	175
Food-conditioned place preference	Decrease (icv)	Decrease (icv, sc)	66, 70
Sucrose self-administration	Decrease (icv, ARC)	Decrease (icv)	67, 68
Acute chow intake (4–24 h)	Decrease (icv)	Decrease (icv, VTA)	2, 3, 75, 95, 134
Opioid-stimulated sucrose intake	Decrease (icv, VTA)	Decrease (VTA)	67, 174

ARC, arcuate nucleus; icv, intracerebroventricularly; sc, subcutaneously; VTA, ventral tegmental area.

This is underscored by the recent report that leptin treatment of two obese leptin-deficient patients was sufficient to reduce food intake, reduce self-report ratings of preference for images of food, and reduce neural activity in the striatum (63).

Table 1 summarizes the effects of insulin and leptin on reward behaviors. Studies that have focused specifically on reward behavior linked with food or feeding stimulated within reward circuitry have not evaluated the possible generalization of insulin or leptin effects on other types of reward (e.g., drugs of abuse). However, the generalized effect of food restriction on drug seeking (34) and the study of Shalev et al. (170) demonstrating leptin reversal of food restriction-induced heroin relapse suggest that insulin, leptin, and other signals of metabolic status (e.g., ghrelin) may act by modulating dopaminergic or opioidergic function.

Finally, there are extremely acute effects (within minutes) and longer-acting effects, such as, the effect of intra-VTA leptin on 24-h chow intake (not yet examined for insulin). This is consistent with observations of acute and chronic leptin action on energy-regulatory circuitry and its function. The very acute effects of insulin, whether observed in fasted/food-restricted or free-feeding rats, support the possibility that, within the context of a meal or eating bout of, for example, 30-min duration (which would correspond to increased insulin access to the CNS), prandial insulin elevation may curtail meal size by impacting on the rewarding aspects of food. There are no data evaluating interaction or synergy of insulin and leptin on food reward, and such studies seem warranted.

INSULIN, LEPTIN, AND FOOD REWARD IN MODELS OF RESISTANCE OR OBESITY

Although the data described above were obtained from studies of nonobese rats and, for the most part, rats eating a conventional (low-fat) chow diet ad libitum, recent studies evaluating reward function and circuitry in animals that are significantly food restricted, chronically maintained on a high-fat diet, or obese suggest that disordered energy homeostasis has a significant impact on the regulation of food reward and CNS DA activity. For example, duration and severity of food restriction have opposite effects on DA release and DA turnover within the NAc (154, 190). Similarly, in the genetically obese *ob/ob* mouse, which lacks functional leptin, DA turnover in the NAc is decreased (75), and releasable DA stores are decreased (159) as well. In contrast, intraventricular leptin has been shown to decrease basal and food-stimulated DA release in the NAc in nonobese rats (117) and directly decrease DA neuronal activation (95). In terms of behavior, 5 wk of exposure to a moderately high-fat diet that did not induce frank obesity has been shown to increase sucrose self-administration and block the ability of intraventricular insulin or leptin to suppress it (68). In contrast, rats fed a high-fat diet for an extended period of time display decreased sucrose self-administration (51). In that series of studies, rats were maintained on a high-fat diet for ~3 mo before undergoing training for sucrose self-administration: one group was fed the high-fat diet ad libitum, and a separate control group was pair fed the high-fat diet to match the kilocalories consumed by a low-fat control-fed group. The pair-fed group did not exhibit a significant increase in body mass or adiposity, but both groups of rats consuming the high-fat diet had elevated plasma (and presumptively, CNS) levels of leptin, and both groups exhibited attenuated sucrose self-administration relative to controls. One obvious interpretation of this finding is that the rats compared high-fat diets and sucrose, and, in effect, access to the high-fat diet in the home cage decreased the perceived reward value of sucrose. To assess whether this difference in responding was due solely to such a "contrast effect" for food, conditioned responding for amphetamine was also assessed. Amphetamine injection conditioned a place preference only in rats maintained on a low-fat diet. Consistent with this, DA turnover in the NAc was substantially decreased in rats maintained on a high-fat, relative to a low-fat, diet. Thus it appears that additional mechanism(s) for an interaction between chronic access to a high-fat diet and brain reward circuitry must be invoked. It seems reasonable to propose that impaired DA release underlies the altered reward behaviors in rats fed a high-fat diet, a hypothesis that can be readily evaluated experimentally.

A common factor among these models—chronic food restriction, diet-induced obesity, and genetic obesity—is an absence of normal leptin and insulin action. Even short-term access to a high-fat diet can inhibit central leptin or insulin signaling in the CNS. For example, previous research has suggested that access to a high-fat diet for as few as 3 days is sufficient to attenuate the central effects of insulin and leptin on food intake and glucose homeostasis (104, 132, 137, 139, 152, 184). These findings suggest that dietary dysregulation of leptin and insulin effects on reward would not be solely due to hedonic contrast, in general, or food reward, specifically. Intriguingly, studies from other model systems suggest that insulin (133, 180) and leptin (186) may have trophic effects on DA neurons; hence, models of extreme starvation, insulin and leptin resistance, or obesity may result in impaired DA neuronal function and signaling. Studies in the DA-deficient mouse model suggest that other CNS circuitry may be recruited to mediate reward function, in the absence of functional DA

circuitry; for example, Hnasko and colleagues (94) demonstrated that serotonergic pathways mediate cocaine reward in this model. Although the limitations and specific parameters of the models cited here need to be taken into account, it nonetheless should be considered that states of very low insulin and leptin action would result in a low, or anhedonic, mood and decreased motivation. We suggest that insulin and leptin effects on reward circuitry and function would be bimodal, such that low "permissive" concentrations of insulin and leptin sustain dopaminergic neuronal viability and intermediate physiological levels suppress reward function but elevated levels, linked to resistance and metabolic pathophysiology, lead to impaired dopaminergic function. Whether other CNS systems could take over reward function in the context of this pathophysiology is purely conjecture. Careful evaluation of this theory might provide links between obesity and common psychiatric disorders such as eating disorders, depression, and drug addiction. It also has implications for the possible efficacy, or lack thereof, of CNS-targeted therapeutics for obesity. Thus, in Hull's equation, if the variable D has a dopaminergic component that is blunted in obese conditions, then evaluation of the regulation of the variable "habit strength" and its neuropharmacological underpinnings may prove a more fruitful line of research for therapeutic approaches.

CONCLUSION

Studies over the past decade confirm and extend the historic finding that food deprivation or restriction sensitizes brain reward circuitry and function. This review has focused on studies of insulin and leptin function. Newer studies, not reviewed here, suggest that the "hormone of need" ghrelin has predictably opposing effects. Studies in models of pathophysiology are also revealing new dimensions to the modulation of reward function. Understanding of new findings should shed considerable light on the contribution of nonhomeostatic feeding to obesity in contemporary societies that offer abundant, affordable, highly palatable foods (55, 56). Regardless of the specific outcomes of future studies, it seems reasonably clear that the neurobiological controls of eating (especially nonhomeostatic food intake) are tightly linked to the well-established circuits underlying other kinds of reward. Additionally, elucidation of the roles of leptin and insulin in the regulation of these systems may offer key insights into the evolution and function of these circuits and their control of behavior. Finally, a clearer understanding of the function of these circuits may, in fact, help us answer difficult theoretical questions: What exactly is reward? What makes something rewarding? Identification of the precise neural mechanisms would (and will) allow us to abandon the hypothetical constructs to nostalgia and, instead, formulate predictive descriptions of behavior based on specific physiological variables, essentially redefining Hull's equation. This understanding may have broad impact on the development of pharmacotherapies for obesity, as well as treatments for psychiatric disorders and drug abuse.

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