Published in final edited form as:
Pharmacol Biochem Behav. 2010 November ; 97(1): 15–24. doi:10.1016/j.pbb.2010.03.002.

ENERGY REGULATORY SIGNALS AND FOOD REWARD

Dianne P. Figlewicz[1,2] and **Alfred J. Sipols**[3]

[1] VA Puget Sound Health Care System, Seattle Division, Seattle WA 98108

[2] Dept. of Psychiatry and Behavioral Sciences, University of Washington, Seattle WA 98195

[3] Faculty of Medicine, and Institute of Experimental and Clinical Medicine, University of Latvia, Riga, Latvia LV-1586

Abstract

The hormones insulin, leptin, and ghrelin have been demonstrated to act in the central nervous system (CNS) as regulators of energy homeostasis, acting at medial hypothalamic sites. Here, we summarize research demonstrating that, in addition to direct homeostatic actions at the hypothalamus, CNS circuitry that subserves reward and is also a direct and indirect target for the action of these endocrine regulators of energy homeostasis. Specifically, insulin and leptin can decrease food reward behaviors and modulate the function of neurotransmitter systems and neural circuitry that mediate food reward, the midbrain dopamine (DA) and opioidergic pathways. Ghrelin can increase food reward behaviors, and support midbrain DA neuronal function. We summarize discussion of behavioral, systems, and cellular evidence in support of the contributions of reward circuitry to the homeostatic roles of these hormones in the CNS. 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.

Keywords

insulin; leptin; ghrelin; motivation; food intake; reward; dopamine

INTRODUCTION

The causes underlying the modern epidemic of obesity have become an area of research focus across many disciplines evaluating nutrition, ingestive behavior, and metabolism. It has been proposed that the increased rates and severity of obesity may be in part related to the ready availability of highly palatable food. Consumption of palatable food is associated with CNS reward, motivational, and hedonic mechanisms, and simultaneously may be associated with dysregulation of CNS energy-regulatory systems. An early and continued research emphasis in ingestive behaviors has been on the actions of endocrine factors at the medial hypothalamus, which is a key site in the CNS regulation of metabolism, energy balance, and caloric intake in the context of physiological need. Extensive evidence that the hormones leptin and insulin act at the medial hypothalamus to provide negative feedback for food intake and body weight is

Correspondence: Dianne Figlewicz Lattemann, Ph.D., Research Career Scientist, VA Puget Sound Health Care System, Research Professor, Dept of Psychiatry & Behavioral Sciences, University of Washington, Metabolism/Endocrinology (151), VA Puget Sound Health Care System, 1660 So. Columbian Way, Seattle WA 98108, Phone: 206-768-5240, latte@u.washington.edu.

summarized below (and see:Ahima et al., 2001; Barsh and Schwartz, 2002; Baskin et al., 1999; Beck, 2000; Figlewicz, 2003; Horn et al., 1999; Seeley and Schwartz, 1999; Woods et al., 2003). Discussion of more recent evidence, that insulin and leptin also act at reward circuitry in the brain, follows. Finally, the hormone ghrelin has been identified as an endocrine orexigen, that also interacts with both hypothalamic and reward circuitry, and those observations are summarized.

ENERGY REGULATORY HORMONES SIGNAL IN THE CNS

In 1979, it was demonstrated in a primate model that insulin infused into the CNS caused a significant decline in food intake and body weight (Woods et al., 1979), and it was proposed that insulin served as an 'adiposity signal' that completes a negative feedback loop linking the behavior of feeding with size of adipose stores (Porte and Woods, 1981). Many studies since have validated this basic concept (e.g., Air et al., 2002a; Air et al., 2002b; Air et al., 2002c; Brief and Davis, 1984; Chavez et al., 1995; McGowan et al., 1990). In the mid-1990s the candidate energy-regulatory signal and adipose hormone, leptin, was identified (Zhang et al., 1994), and has now been well-characterized as a regulator of energy homeostasis acting in the CNS. Two aspects of this hypothetical model had to be addressed in order to validate a role for energy regulatory signals in modulating any aspect of CNS function.

First, it had to be demonstrated that these circulating signals have access to CNS circuitry. The presence of insulin in the CNS was reported in 1979 (Havrankova et al., 1979), and many studies established that the predominant amount of insulin in the CNS can be accounted for by receptor-mediated transport across the blood-brain barrier into the CNS (Coker et al., 1990; Dernovsek et al., 1984; Dernovsek and Bar, 1985; Giddings et al., 1985; Israel et al., 1993; King and Johnson, 1985; Schwartz et al., 1992; Schwartz et al., 1999). Although intermittent reports have suggested that insulin can be synthesized locally in the developed (adult) CNS, quantities appear to be negligible particularly when compared to the affinity of the receptor for peripherally circulating insulin. The relationship between CNS and plasma levels of insulin is saturable (non-linear), consistent with a receptor-mediated transport process. In the 1990s, when the adipose hormone leptin was identified, evidence rapidly accumulated that it likewise could be transported by multiple mechanisms into the CNS (Banks et al., 2000, Banks et al., 2002; Hileman et al., 2002; Kastin and Pan, 2000; Maness et al., 2000; Maresh et al., 2001; Munzberg, 2008). Relative levels of both leptin and insulin in the CSF are decreased in association with obesity (Banks et al., 1999; Banks et al., 2001; Caro et al., 1996; Kaiyala et al., 2000; Schwartz et al., 1990; Schwartz et al., 1996; Stein et al., 1987). Recent studies from Banks and colleagues have shown increased transport of both insulin and ghrelin, but decreased transport of leptin, by serum triglycerides, suggesting a more complex relationship between nutritional status, obesity status, and transport of these endocrine signals into the CNS (Banks, 2008; Banks et al., 2008; Urayama and Banks, 2008).

Additionally, the presence of functional insulin and leptin receptors in the CNS was established. Receptors for both insulin (Corp et al., 1986; Havrankova and Roth, 1978; Kenner et al., 1995; Unger et al., 1991; Werther et al., 1987; Zahniser et al., 1984) and leptin (Elmquist et al., 1998; Leshan et al., 2006) are widely expressed throughout the CNS. The medial hypothalamus, a key center for the regulation of energy homeostasis and coordination of metabolic events, is a major target for both insulin and leptin action (Baskin et al., 1999; Mirshamsi et al., 2004; Niswender et al., 2004; Seeley and Schwartz, 1999). Other CNS sites and neural systems are targets for insulin and leptin action (Figlewicz et al., 1990; Figlewicz, 2003; Grill et al., 2002; Harvey, 2007; McNay, 2007). Studies utilizing antisense oligonucleotides against the insulin receptor and conditional, localized knockout of the insulin receptor, have elucidated the contribution of the brain insulin receptor to energy homeostasis and glucose homeostasis (Bruning et al., 2000; Koch et al., 2008; Obici et al., 2002; Obici and

Rossetti, 2003). The leptin receptor, likewise 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' (Chua et al., 1996) of the leptin receptor, and recent use of receptor constructs with modifications in signaling capability validate the importance of CNS leptin action in energy homeostasis.

The role of the orexigenic peptide ghrelin in CNS regulation of metabolic processes and energy homeostasis, in contrast to that of insulin and leptin, is at present somewhat more equivocal. Originally isolated in the X/A-like endocrine cells of the oxyntic gastric mucosa (Kojima et al, 1999), which by most accounts are the preponderant source of circulating ghrelin (Ariyasu et al, 2001), expression of this peptide has also been demonstrated in a number of diverse tissues, including the small intestine (Date et al, 2000), pancreas (Volante et al, 2002), kidney (Mori et al, 2000), testis (Tanaka et al, 2001), ovary (Caminos et at, 2003), and CNS (Korbonits et al, 2001). Moreover, the diffuse sites of hypothalamic and extra-hypothalamic expression of ghrelin in the CNS suggest that this "brain-gut" peptide plays a much broader role in brain signaling than just the control of food intake. Since hypothalamic ghrelin is endogenous in origin (Cowley et al, 2003), being locally expressed in numerous axon terminals, its function as a neurotransmitter sets it apart from peripheral peptide hormones arriving at the hypothalamus via specific transport. Nevertheless, the demonstration of ghrelin-containing neurons innervating the arcuate (ARC), ventromedial (VMN), paraventricular (PVN) and dorsomedial nuclei, along with ghrelin expression in arcuate neurons terminating on pro-opiomelanocortin (POMC), neuropeptide Y (NPY) and other ghrelin-producing neurons is consistent with a major role in energy homeostasis.

Ghrelin is a natural ligand of the 1a isoform of the growth hormone secretagogue receptor (GHS-R) (Howard et al, 1996), which is distributed in diverse tissues both peripherally and in the CNS (Gnanapavan et al, 2002). Type 1a GHS-R has been identified in peripheral endocrine tissue such as the adrenal gland, testis, ovary, pancreas, and thyroid, as well as in the stomach, kidney, liver, arteries, heart and adipose tissue (Papotti et al, 2000). CNS distribution of 1a GHS-R is likewise widespread, with marked expression observed in the ARC and VMN of the hypothalamus (Mitchell, 2001). Although extra-hypothalamic sites of expression include the cerebral cortex, dentate gyrus, hippocampus, substantia nigra, ventral tegmental area, nodose ganglion, and dorsal vagal complex of the medulla, it is hypothalamic GHS-R and its co-expression with growth hormone-releasing hormone, NPY, POMC, somatostatin (SS), and tyrosine hydroxylase (TH) that lends further credence to ghrelin signaling comprising a viable component of nutritional homeostasis and metabolism.

The multiple effects of insulin and leptin on energy homeostasis depend upon interaction with key hypothalamic nuclei and peptides to regulate energy balance (Inui, 1999). Among the most extensively studied CNS mediators are NPY (Clark et al., 1984; Schwartz et al., 1992; Sipols et al., 1995; White et al., 1990), POMC and its product α-melanocyte stimulating hormone (α-MSH), and the melanocortin antagonist, AgRP (for reviews, see: Benoit et al., 2000; Morton and Schwartz, 2001; Seeley et al., 1999; Woods et al., 2000). POMC and AgRP are selectively expressed in neurons of the ARC colocalized with receptors for insulin and leptin, and they are endogenous circuitry capable of regulating food intake (Cheung et al., 1997; Mizuno et al., 1999; Mountjoy and Wong, 1997). Leptin and insulin increase expression of the anorexic peptide, α-MSH, and decrease expression of AgRP (see (Benoit et al., 2000) for reviews). Collectively, these data suggest that leptin and insulin act on ARC melanocortin (AgRP and POMC) neurons to regulate food intake and energy balance. It is likely that other endogenous neurotransmitters either directly or indirectly mediate the CNS effects of leptin and insulin. Among these, the orexigenic peptides orexin-A and melanin concentrating hormone (MCH) are expressed in the lateral hypothalamus (Broberger et al., 1998; Mondal et al, 2000; Peyron

et al., 1998). Intriguingly, recent data suggests 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 (e.g., [Clegg et al., 2002]; for reviews see [Boutrel and deLecea, 2008; Hervieu, 2003]).

Intracellular signaling secondary to insulin and leptin interaction with CNS receptors has been elucidated from studies in the medial hypothalamus. Signaling for the CNS insulin receptor is comparable to post-receptor mechanisms in peripheral target tissues. The receptor is an autophosphorylating tyrosine kinase, and its activation leads not only to tyrosine phosphorylation of other proteins including the key signaling moiety, IRS, but also to a cascade of additional phosphorylation events, including activation of the PI3 kinase pathway (Hadari et al., 1992), and phosphorylation of Akt/PKB (Heidenreich, 1989; Heidenreich, 1993; Kenner and Heidenreich, 1991; Niswender et al., 2003; Shemer et al., 1989). The leptin receptor, upon leptin binding, can likewise initiate IRS phosphorylation, and activation of the PI3 kinase pathway (Niswender et al., 2003). 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 SOCS-3 which provides negative feedback on leptin signaling (Leshan et al., 2006; Robertson et al., 2008). Thus, there are both parallel and unique intracellular pathways by which insulin and leptin can mediate intracellular events related to ingestive behavior and caloric homeostasis (Carvalheira et al., 2001; Carvalheira et al., 2005, Pocai et al., 2005). 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 pathophysiologic state in which either energy regulatory signals are decreased in relative or absolute amount in the CNS; or there is direct CNS resistance to their action (Clegg et al., 2005; DeSouza et al., 2005; Irani et al., 2007; Munzberg et al., 2005; Wang et al., 2001). Collectively, this research has paved the way for studies of endocrine signaling within reward circuitry.

Electrophysiological studies by several investigators (Cowley et al., 2003; Seoane et al., 2003; Zigman et al., 2006) have similarly confirmed the ARC as a major site of ghrelin action in neurons controlling food intake. Although the neuronal expression of ghrelin within several hypothalamic regions has been reported, there has been some controversy regarding this expression, and it is likely that a significant contribution to medial hypothalamic effects comes from peripherally synthesized (i.e., gastric) ghrelin (please see [Sakata et al., 2009] and [Castaneda et al., 2010] for discussion and references). Ghrelin-positive terminals have been reported to innervate a number of different ARC neurons expressing type 1a GHS-R that project mainly to the PVN. In a group of ARC neurons, ghrelin has been shown to directly increase firing of NPY/AgRP neurons, which then inhibit POMC neurons via GABA and NPY release. Given the putative roles of NPY and AgRP as potent orexigens and POMC as an anorexigen, the modulation of neuronal activity by ghrelin is entirely consistent with its hypothesized role in signaling nutritional insufficiency. In a group of medial PVN neurons, ghrelin was found to reduce inhibitory GABAergic input, an effect substantially dependent upon Y1 and Y5 NPY receptor signaling. This effect within the PVN, along with the ability of ghrelin to increase firing of ARC neurons inhibited by leptin (Traebert et al., 2002), further supports a role for ghrelin in maintaining energy balance.

Along with its ability to influence feeding pathways via direct synaptic processes, several studies suggest that ghrelin may also regulate neurotransmission via gene expression. Increased mRNA levels of NPY and AgRP in ARC neurons are associated with intracerebroventricular (ICV) doses of ghrelin that stimulate food intake (Nakazato et al., 2001; Seoane et al., 2003), suggesting an effect on *de novo* neurotransmitter synthesis. Moreover, direct ICV administration of ghrelin in many hypothalamic nuclei involved in feeding resulted in increased neuronal activation, as evidenced by elevated Fos expression (Lawrence et al., 2002),

particularly in many NPY ARC neurons (Wang et al., 2002), a number of orexin neurons in the lateral hypothalamus (Toshinai et al., 2003), and some oxytocin neurons in the PVN (Olszewski et al., 2007). Together with recent observations of type 1 cannabinoid receptor inactivation blocking the ability of ghrelin to increase AMP-activated protein kinase in the hypothalamus (Kola et al., 2008), these findings illustrate the complex interactions of ghrelin with many neurotransmitter systems crucial to the central regulation of feeding and energy homeostasis. An additional aspect regarding ghrelin and food intake, i.e. the motivational aspect, is discussed below.

An overarching question remains as to the origin of ghrelin that may be central to *in vivo* signaling of energy disequilibrium. While there is no dispute that ghrelin functions as a classical neurotransmitter across synapses to influence postsynaptic activity – as demonstrated in many of the above-cited studies – one cannot discount the possibility that circulating gastric ghrelin activates hypothalamic type 1a GHS-R populations via intermediary neurons in circumventricular organs such as the subfornical organ (SFO). As mentioned above, it is now nearly universally agreed that the circulating energy regulatory signals insulin and leptin gain access to their hypothalamic receptors via specific transport mechanisms across the blood-brain barrier (BBB). As a "brain-gut" peptide, the ghrelin pool that influences food intake could at least partly be extra-hypothalamic in origin, given that gastric secretion of ghrelin is many-fold that of hypothalamic release. Importantly, a substantial number (30%) of SFO neurons are responsive to ghrelin *in vitro* by increasing intracellular calcium secretion and number of action potentials (Pulman et al, 2006). Therefore, ghrelin-sensitive SFO neurons that innervate the hypothalamus could well play a crucial role in relaying information about circulating ghrelin concentrations (which, among other humoral signals, reflect the state of energy homeostasis) to the ARC for integration into the neuronal feeding pathways.

ENERGY REGULATORY SIGNALS MODULATE FOOD REWARD

A current focus of energy homeostasis research is the elucidation of how environmental factors such as diet composition interact with the energy regulatory signal-CNS feedback loop to modulate the effectiveness of these signals. For example, putting rats on a high fat diet results in an impairment in the action of insulin to decrease body weight (Arase et al., 1988; Chavez et al., 1996), and a similar observation has been made for leptin (Lin et al., 2001). The extrapolation of these observations is that endogenous energy regulatory signals in the CNS may also become ineffective at providing 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 (Hill et al., 2003; Mokdad et al., 2001), and a high incidence of obesity in the pediatric age group as well (Kim et al., 2006), interpreted as a significant environmental influence over the neural circuitry associated with the physiological maintenance of energy homeostasis. The epidemiologic finding also emphasizes that attention should be focused on additional CNS circuitry which is either directly or indirectly connected with hypothalamic circuitry to modulate feeding behavior.

One obvious target for study is the CNS circuitry which mediates motivation and reward. Midbrain circuits intimately involved in reward signaling have been previously identified using reproductive behavior and drug addiction paradigms. Components of this circuitry are activated with, and contribute to, complex behaviors including food seeking and food intake ((Berridge, 1996; Berridge and Robinson, 1998; Berthoud, 2004) and see below). This circuitry includes specific sub-regions 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 hedonic evaluation of the stimulus and associative learning (Everitt, 1999; Ikemoto, 2007; Ishiwara et al., 2004; Petrovich and Gallagher, 2003; Robbins and Everitt, 1996; Rollins and King, 2009; Will et al., 2004; Wise, 2002). 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 both anatomically and functionally (Berthoud, 2007; Kelley and Berridge, 2002; Kelley et al., 2002; Stratford and Kelley, 1999). Insulin and leptin receptors are expressed throughout the limbic forebrain, including the hippocampus; the amygdala; and the lateral hypothalamic/zona incerta area (Figlewicz et al., 2003; Leinninger and Myers, 2008; Leshan et al., 2006). 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, "non-homeostatic" feeding (Berridge and Robinson, 1998; Berthoud, 2004; Berthoud, 2007). 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 diets that are low in fat, as they are preferentially over-consumed. In humans, individual differences exist in the reinforcing value of food with obese individuals displaying a stronger preference for diets high in fat and carbohydrates relative to non-obese individuals (Drewnowski et al., 1992a; Drewnowski et al., 1992b; Drewnowski and Popkin, 1997).

Berridge and colleagues have provided a conceptual framework for the consideration of reward, proposing that there is 'wanting' of food (or another stimulus) and 'liking' of food. The behavior associated with non-homeostatic feeding is in part regulated by the mesolimbic dopamine system (Berridge and Robinson, 1998), and within this system, the neurotransmitter dopamine plays a substantial role in the regulation of food reward. They have identified nucleus accumbens (NAc) dopamine projections as central to 'wanting'. The NAc represents a functionally specialized subregion of the striatum which is a critical anatomical component of CNS reward circuitry, with the extensive projection of DA neurons from the midbrain ventral tegmental area (VTA) and associated DA cell groups (Ikemoto and Wise, 2004). 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 (Ikemoto and Wise, 2004; Richardson and Gratton, 1996; Schultz, 2002; Smith, 1995). The neural mechanisms of food reward are believed to be similar, if not identical, to drug rewards (Carelli, 2002; Kelley and Berridge, 2002).

DA neuronal activation can be modulated by the experience (e.g., [Bassareo et al., 2002]) or nutritional status of an animal. Wilson and colleagues demonstrated that food-restricted rats trained to drink a palatable liquid food had greater dopamine release in the NAc than free-feeding rats (Wilson et al., 1995). One question, then, is whether these dopamine neurons are a target for neural or endocrine factors that change in association with fasting and food restriction. Indeed, a neuroendocrine milieu exists in fasted animals that would bias them towards enhanced dopaminergic function. Adrenal glucocorticoid levels are elevated with fasting, and Piazza and colleagues have provided evidence that glucocorticoids can facilitate dopamine release and dopamine-mediated behaviors (Marinelli and Piazza, 2002). Additionally, both insulin and leptin levels rapidly decrease in association with food restriction or fasting (Havel, 2002), and both inhibit performance in food reward behavioral tasks that are dopamine-dependent (Figlewicz et al., 2001; Figlewicz et al., 2004; Figlewicz et al., 2007). Conversely, new studies demonstrate that ghrelin—which is increased in association with food deprivation—can increase NAc dopamine levels (Jerlhag et al., 2006) and, acting at the VTA, can stimulate feeding (Abizaid et al., 2006; Naleid et al., 2005) and increase dopamine neuronal activity (Abizaid et al., 2006).

Ghrelin may also be involved in the expression and maintenance of behaviors exhibited prior to actual ingestion, including, but not limited to, the appetitive aspects of food seeking, selection, memory, and reward (Naleid et al, 2005). Application of nanomolar amounts of

ghrelin to *in vitro* VTA slices resulted in increased action potentials in dopaminergic neurons from normal mice, but not from mice missing the GHS-R gene (Abizaid et al, 2006). Moreover, ghrelin appears to increase excitatory inputs on DA neurons in the VTA, consistent with increased activation of reward systems. Studies of GHS-R and DA receptor co-localization in the VTA of transgenic mice reveal a potentiation effect of ghrelin through the GHS-R on the DA receptor, such that an excess amount of DA is released in the NAc (Jiang et al, 2006). Speculation as to the behavioral correlate of these neurophysiological findings – e.g., increased locomotion in search of food is suggested by a recent study (Blum et al, 2009) in GHS-R knockout mice – at present remains fairly hypothetical. However, it is clear that ghrelin is well positioned to signal not just feeding in a mechanical sense through its hypothalamic receptor populations, but also the antecedent or motivational attributes of feeding behavior through GHS-R populations in the VTA (Abizaid, 2009).

Food restriction or fasting indeed enhance the addictive or reinforcing properties of drugs of abuse, as found in both drug self-administration and relapse to drug-taking paradigms; intraventricular leptin can reverse food deprivation-induced relapse to heroin self-administration (Carroll and Meisch, 1984; Shalev et al., 2001; Shalev et al., 2002). 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 that normally would not support sustained self-stimulation activity at these sites becomes efficacious when animals are maintained on a food-restriction paradigm (Carr, 1996; Carr, 2002). Intraventricular leptin shifts the dose-response curve in food restriction-sensitive perifornical hypothalamic sites to the right (i.e., reverses the effect of food restriction); and administration of insulin into the brain of either food-restricted or *ad libitum* feeding rats increases the threshold for self-stimulation, both reversing the decreased threshold observed with fasting, and elevating the threshold above its 'free-feeding' level (Carr et al., 2000; Fulton et al., 2000). 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.

Several studies implicate insulin and leptin in food reward *per se*. 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 (Davis and Smith, 1002; Schneider et al., 1990); self-administration (Ikemoto and Wise, 2004); and the conditioning of a place preference (Papp, 1988). Figlewicz and colleagues have demonstrated suppression of acute sucrose licking (intraventricular insulin) (Sipols et al., 2000); food-conditioned place preference (intraventricular insulin or leptin) (Figlewicz et al., 2004); and sucrose self-administration (intraventricular insulin or leptin) (Figlewicz et al., 2006) in rats fed *ad libitum* chow. DiLeone and colleagues (Hommel et al., 2006), and Morton and colleagues (Morton et al., 2009), have now demonstrated that direct administration of leptin into the VTA decreases chow intake in *ad lib* feeding rats. Taken together, the results of these different behavioral paradigms—self administration, lick rate task, conditioned place preference (CPP) and free-feeding of the baseline diet, chow—demonstrate that insulin and leptin, across a concentration range from fasting to free-feeding to elevated levels, are able to modify behaviors that reflect acute and learned reward evaluation. Some further resolution of these actions remain, for example, whether the effects of exogenous insulin and leptin reflect a simulation of physiological changes as would occur postprandially. Additionally, whether the rapid and chronic effects of both insulin and leptin are mediated via the same circuitry and the same neural mechanisms remains to be elucidated. There appear to be multiple anatomical loci implicated as targets for insulin- and leptin-induced suppression of food reward, including the lateral hypothalamus (Carr et al., 2000; Fulton et al., 2000; Leinninger and Myers, 2008).

Studies from a number of laboratories have focused on insulin and more recently, leptin, effects on the midbrain DA neurons at both the cellular and the behavioral level. Insulin receptors had historically been identified in the VTA and the striatum, using receptor autoradiography and receptor immunocytochemistry approaches (Unger et al., 1991; Werther et al., 1997), and insulin and leptin receptor mRNA is expressed in the substantia nigra (Elmquist et al., 1998). Figlewicz and colleagues have localized both insulin receptors and leptin receptors on midbrain DA neurons, including those of the VTA, as well as medial and lateral substantia nigra (Figlewicz et al., 2003). The presence of functional receptors has been confirmed by work of Fulton (Fulton et al., 2006) and Hommel (Hommel et al., 2006). Recent studies have identified that insulin and leptin increase PI3kinase activity when given directly into the VTA (Figlewicz et al., 2007). Further, leptin (administered peripherally, intraventricularly, or directly into the VTA) increases Jak-STAT phosphorylation, and this is critical for the effect of leptin in the VTA to decrease chow feeding (Morton et al., 2009). The identification of synaptic or neural mechanisms that underlie insulin and leptin effects on food reward remain to be fully elucidated. Hommel et al. (2006) have reported that leptin decreases DA neuronal action potentials in VTA slices. One potential cellular target for insulin action is the dopamine re-uptake transporter (DAT), which inactivates DA signaling by transporting DA back into the DA nerve terminal from the synapse (Jaber et al., 1997). Both the synthesis, and the activity or synaptic concentrations, of the DAT can be regulated by intracellular signaling systems including PI3kinase (Garcia et al., 2005; Vaughan et al., 1997). Both *in vivo* and *in vitro* effects of insulin (or its lack, in diabetic models) on expression and activity of the DAT (Figlewicz et al., 1994; Patterson et al., 1998; Sevak et al, 2008): Insulin can increase mRNA levels of, and synaptic activity of, the DAT. The functional implication of this would be that increased DAT activity could result in increased 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. Thus, although there have been limited studies of direct insulin and leptin effects, findings to date suggest that, in non-obese animal models insulin and leptin should act overall to decrease DA signaling.

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 (e.g., [Alvaro et al., 1996]) and pharmacological studies have outlined functional roles for these receptors in the modulation of drug-taking behavior. Antagonism of these receptors in NAc inhibits operant responding for cocaine, while central agonism of this system augments amphetamine-induced behaviors (e.g., [Hsu et al., 2005]). Orexin neurons exhibit diverse projections in the CNS to sites including the VTA (e.g., [Fadel and Deutch, 2002]). Orexin-expressing neurons of the LH have mu-opioid receptors; and the molecular physiology of these neurons is altered with morphine administration or withdrawal, emphasizing their role in CNS reward circuitry (Georgescu et al., 2003). Orexinergic projections signal specifically on a majority of dopamine neurons to activate the mesolimbic pathway (Zheng et al., 2007), and VTA neuron populations express both orexin receptor subtypes (Marcus et al., 2001). 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 that an orexin antagonist could block the reinstatement of an extinguished place preference for morphine, and that intra-VTA orexin-A was sufficient to reinstate the place preference, in rats (Harris et al., 2005). Additional evidence comes from studies of genetic models demonstrating the inability of orexin-deficient mice to form morphine-conditioned place preferences (Narita et al., 2006). Orexin action in the LH also appears necessary for the acquisition and expression of morphine-induced CPP (Harris et al., 2007). Finally, Borgland (Borgland et al., 2006) 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 energy

regulatory 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 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 (Figlewicz et al., 2008).

ENERGY REGULATORY SIGNALS MODULATE PALATABILITY

Endogenous opioid neural networks appear to play a role in the regulation of food intake, food hedonics, and food choice in animals (Glass et al., 1999; Levine et al., 2003), and in human subjects (Drewnowski et al., 1992; Drewnowski et al., 1995; Yeomans et al., 1990). Although experimental evidence demonstrates that DA and the opioids play somewhat different roles in the mediation of food reward, the neuroanatomical circuitry that is implicated in opioid effects overlaps significantly with motivational circuitry. Opioids injected into numerous brain regions, including the VTA or the NAc, stimulate food intake (Badiani et al., 1995; Figlewicz et al., 2008; Lamonte et al., 2009; Noel and Wise, 1995); and food-induced DA release in the NAc is dependent upon opioid action in the VTA (Tanda and DiChiara, 1998). Further, activation of opioid receptors in the VTA is reinforcing (McBride et al., 1999); mu opioid recptor-induced inhibition of GABA neurons therein, which impinge on DA neurons, results in disinhibition of these DA neurons and facilitated DA release (Johnson and North, 1992; Cameron et al., 1997; Ford et al., 2006). The relevance of this for feeding resides in the observation of MacDonald et al. (2004) that stimulation of feeding by VTA administration of a mu opioid agonist is dependent upon DA1 receptor activity in the nucleus accumbens. Thus, there is functional crosstalk between opioids and dopamine.

Endogenous opioids and synthetic opiate peptides can enhance food intake (Arjune et al., 1990; Arjune et al., 1991; Carr et al., 1991; Frisina and Sclafani, 2002; Islam and Bodnar, 1990; Levine et al., 1990; Levine et al., 1991; Jarosz and Metzger, 2002; Kirkham and Blundell, 1986; Kirkham and Cooper, 1988a; Kirkham and Cooper, 1988b; Lang et al., 1981; Marks-Kaufman et al., 1984;. Yu et al., 1997; Yu et al., 1999) One ongoing question is whether opioids are responsible for intake of food in general or only of pleasurable food intake. The opioid antagonist naloxone has been shown to decrease preferentially motivation for, and consumption of, a palatable food (vs. rat chow) in non-deprived rats (Barbano and Cador, 2006; Cleary et al., 1996; Giraudo et al., 1993). Thus, opioids appear to signal hedonic value of a food independent from nutritional needs. However, in a study where animals were deprived of food for 24 hours, then given a choice between a preferred diet and a non-preferred diet, the general opioid antagonist, naltrexone, injected into the PVN decreased intake of both diets, but naltrexone injected into the amygdala decreased intake only of each animal's preferred diet (Naleid et al., 2007). Since the PVN plays a larger role in energy homeostasis, and the amygdala mediates portions of the emotional response to feeding, the study concluded that opioids affect different aspects of food intake in different CNS sites. Some have argued that opioids specifically enhance intake of fat. Indeed, many studies support a role for opioids in fat appetite (Glass et al., 1996; Islam and Bodnar, 1990; Kelley et al., 2002; Weldon et al., 1996; Yanovski and Yanovski, 2002; Zhang et al., 1998). Other studies, however, suggest that opioids modulate intake of an animal's preferred food, regardless of nutrient content (Glass et al., 1996; Glass et al., 1997; Gosnell and Krahn, 1992; Levine et al., 2003; Marks-Kaufman et al., 1985; Pomonis et al., 1997). Palatability influences both the amount and type of food that is ingested (Berridge, 1996). For example, it is well known that even non-caloric solutions will elicit drinking behavior in sated rats if they are made to taste sweet (Capaldi et al., 1997). Several hypothalamic peptides project to CNS areas important for taste processing (nucleus of the

solitary tract), and hedonics and reward. With regard to such CNS-intrinsic signals, as reviewed by Olszewski and Levine (Olszewski et al., 2004), the opioid nociceptin may enhance or sustain feeding by interacting with feeding-termination neuropeptide pathways such as a-MSH, oxytocin, or CRH.

An animal's energy state can impact activity of the opioid system and the behaviors mediated by opioids (Levine et al., 1995; Rudski et al., 1994). Food restricted rats show significant reductions in mu- and increases in kappa-opioid receptor binding in several forebrain areas related to food reward and in the hindbrain parabrachial nucleus (Wolinsky et al., 1994; Wolinsky et al., 1996a; Wolinsky et al., 1996b). Conversely, mu-opioid receptor binding is increased in reward-related sites in animals made obese on a high-fat diet (Smith et al., 2002). As described above, leptin and insulin modulate brain self-stimulation (Carr et al., 2000; Fulton et al., 2000), for which CNS opioidergic signaling has been implicated (Carr, 1996). The question of whether energy regulatory signals can blunt palatability-induced feeding has been evaluated to a limited extent. Insulin and leptin decrease intake of sucrose in non-deprived rats, and modulate opioid effects on sucrose intake. Intraventricular insulin decreases sucrose pellet intake stimulated by a kappa opioid agonist, and acts cooperatively with a subthreshold dose of a kappa opioid antagonist to decrease baseline intake of sucrose pellets (Sipols et al, 2002). This would be consistent with an action at the medial hypothalamus, where dynorphin receptors have been localized. Further, sucrose pellet intake stimulated by direct intra-VTA injection of the mu-opioid agonist DAMGO, can be inhibited by concurrent injection of insulin or leptin into the same site (Figlewicz et al., 2007). Since the feeding effect of mu opioids in the VTA is dependent upon dopamine release (MacDonald et al., 2004), one may speculate that insulin and leptin block the DAMGO effect by blocking DA neuronal activity. The observation of Hommel et al. (2006), that leptin can directly modulate DA neuronal activity within the VTA, provides early support for this, however, clearly, further study is warranted. Given the identification in human eating disorders of a role for opioids, particularly mu opioids (Drewnowski et al., 1992), such studies have potential clinical relevance. This is underscored by the recent report that leptin treatment in 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 (Farooqi et al., 2007).

CONCLUSION

The table below summarizes the effects of insulin, leptin, and ghrelin on reward behaviors. Clearly, there is much yet to be learned about ghrelin-related peptide effects on motivation and palatability-driven feeding. However, the generalized effect of food restriction on drug-seeking (Carroll and Meisch, 1984), and the observation of leptin reversal of food restriction-induced heroin relapse (Shalev et al., 2001), suggest that insulin, leptin, and ghrelin may act by modulation of dopaminergic or opioidergic function.

EFFECTS OF INSULIN, LEPTIN, AND GHRELIN ON REWARD BEHAVIORS

Behavior	Insulin	Leptin	Ghrelin
Brain self-stimulation	decrease (ICV)	decrease (ICV)	not determined
Relapse to heroin seeking	not determined	decrease (ICV)	not determined
Acute sucrose licking	decrease (ICV)	not determined	no effect (ICV)*
Food CPP	decrease (ICV)	decrease (ICV, SC)	not determined
Sucrose self-administration	decrease (ICV,ARC)	decrease (ICV)	increase (ICV)*
Chow intake (4–24 hr)	decrease (ICV)	decrease (ICV,VTA)	increase (ICV,VTA)

Behavior	Insulin	Leptin	Ghrelin
Acute sucrose intake	decrease (ICV,VTA)	decrease (VTA)	not determined

* "Ghrelin affects motivational but not hedonic aspects of feeding", J. Overduin and D.E. Cummings, North American Association for the Study of Obesity annual meeting 2007

In conclusion, studies over the past decade have demonstrated that food deprivation- or restriction-induced sensitization of brain reward circuitry and function is due in part to the contributions of insulin, leptin, and ghrelin interactions with major dopaminergic and opioidergic networks in the CNS. These studies serve as a model for the testing of future candidate energy regulatory signals' (endocrine, or endogenous to the CNS) role in the modulation of food reward and palatability. There is also the possibility that dysregulation of those circuits may adversely affect body weight regulation. For example, studies in humans (Wang et al., 2001) and animals (Bina and Cincotta, 2000) suggest that changes in central dopamine may contribute to the development of obesity. Further, some human studies report that obese individuals have a decreased propensity to engage in the use of recreational drugs and a decreased frequency of substance abuse disorders (Simon et al., 2006). One implication of these findings is that obesity is capable of altering processes within the endogenous reward system of the brain. As recent research into animal models of obesity (Davis et al., 2008; Fulton et al., 2006; Hommel et al., 2006) suggests downregulation of dopaminergic pathways, future studies will need to focus on other CNS pathways or networks that may subserve food reward, and may provide appropriate targets for obesity therapeutics.

Acknowledgments

This work is supported by a Career Scientist Award from the Dept. of Veterans Affairs and NIH Grant DK40963 (DPF); and a University of Latvia Grant Y2-ZP84-003 (AJS).

References

Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, Elsworth JD, Roth RH, Sleeman MW, Picciotto MR, Tschöp MH, Gao XB, Horvath TL. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. J Clin Invest 2006;116:3229–39. [PubMed: 17060947]

Abizaid A. Ghrelin and dopamine: new insights on the peripheral regulation of appetite. J Neuroendocrinol 2009;21:787–93. [PubMed: 19523165]

Ahima RS, Osei SY. Molecular regulation of eating behavior: new insights and prospects for therapeutic strategies. Trends Mol Med 2001;7:205–13. [PubMed: 11325632]

Air EL, Benoit SC, Clegg DJ, Seeley RJ, Woods SC. Insulin and leptin combine additively to reduce food intake and body weight in rats. Endocrinology 2002;143:2449–52. [PubMed: 12021212]

Air EL, Benoit SC, Smith KAB, Clegg DJ, Woods SC. Acute third ventricular administration of insulin decreases food intake in two paradigms. Pharmacol Biochem Behav 2002;72:423–29. [PubMed: 11900815]

Air EL, Strowski MZ, Benoit SC, Conarello SL, Salituro GM, Guan XM, Liu K, Woods SC, Zhang BB. Small molecule insulin mimetics reduce food intake and body weight and prevent development of obesity. Nature Medicine 2002;8:179–83.

Alvaro JD, Tatro JB, Quillan JM, Fogliano M, Eisenhard M, Lerner MR, Nestler EJ, Duman RS. Morphine down regulates melanocortin-4 receptor expression in brain regions that mediate opiate addiction. Mol Pharmacol 1996;3:583–91. [PubMed: 8794897]

Arase K, Fisler JS, Shargill NS, York DA, Bray GA. Intracerebroventricular infusions of 3-OHB and insulin in a rat model of dietary obesity. Am J Physiol 1988;255:R974–81. [PubMed: 3059829]

Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosoda K, Akamizu T, Suda M, Koh T, Natsui K, Toyooka S, Shirakami G, Usui T, Shimatsu A, Doi K, Hosoda H, Kojima M, Kangawa K, Nakao K. Stomach

is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. J Clin Endocrinol Metab 2001;86:4753–8. [PubMed: 11600536]

Arjune D, Bowen WD, Bodnar RJ. Ingestive behavior following central [D-Ala2,Leu5,Cys6]-enkephalin (DALCE), a short-acting agonist and long-acting antagonist at the delta opioid receptor. Pharm Biochem Behav 1991;39:429–36.

Arjune D, Standifer KM, Pasternak GW, Bodnar RJ. Reduction by central beta-funaltrexamine of food intake in rats under freely-feeding, deprivation and glucoprivic conditions. Brain Res 1990;535:101–9. [PubMed: 1963340]

Badiani A, Leone P, Noel MB, Stewart J. Ventral tegmental area opioid mechanisms and modulation of ingestive behavior. Brain Res 1995;670:264–76. [PubMed: 7743190]

Banks W, Clever C, Farrell C. Partial saturation and regional variation in the blood-to-brain transport of leptin in normal weight mice. Am J Physiol 2000;278:E1158–65.

Banks W, DiPalma C, Farrell C. Impaired transport of leptin across the blood-brain barrier in obesity. Peptides 1999;20:134145.

Banks W, King B, Rossiter K, Olson R, Olson G, Kastin A. Obesity-inducing lesions of the central nervous system alter leptin uptake by the blood-brain barrier. Life Sciences 2001;69:2765–73. [PubMed: 11720081]

Banks W, Niehoff M, Martin D, Farrell C. Leptin transport across the blood-brain barrier of the Koletsky rat is not mediated by a product of the leptin receptor gene. Brain Research 2002;950:130–36. [PubMed: 12231237]

Banks WA. The blood-brain barrier as a cause of obesity. Curr Pharm Des 2008;14:1606–14. [PubMed: 18673202]

Banks WA, Burney BO, Robinson SM. Effects of triglycerides, obesity, and starvation on ghrelin transport across the blood-brain barrier. Peptides 2008;29:2061–65. [PubMed: 18682266]

Barbano MF, Cador M. Differential regulation of the consummatory, motivational, and anticipatory aspects of feeding behavior by dopaminergic and opioidergic drugs. Neuropsychopharmacology 2006;31:1371–81. [PubMed: 16205784]

Barsh GS, Schwartz MW. Genetic approaches to studying energy balance: perception and integration. Nature Reviews 2002;3:589–600.

Baskin DG, Figlewicz Lattemann 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;848:114–23. [PubMed: 10612703]

Bassareo V, De Luca MA, Di Chiara G. Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. J Neurosci 2002;22:4709–19. [PubMed: 12040078]

Beck B. Neuropeptides and obesity. Nutrition 2000;16:916–23. [PubMed: 11054597]

Benoit SC, Schwartz MW, Baskin DG, Woods SC, Seeley RJ. CNS melanocortin system involvement in the regulation of food intake and body weight. Hormones & Behavior 2000;37:299–308. [PubMed: 10860674]

Berridge KC. Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev 1996;20:1–25. [PubMed: 8622814]

Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 1998;28:309–69. [PubMed: 9858756]

Berthoud HR. Neural control of appetite: cross-talk between homeostatic and non-homeostatic systems. Appetite 2004;43:315–17. [PubMed: 15527935]

Berthoud H-R. Interactions between the “cognitive” and “metabolic” brain in the control of food intake. Physiol Behav 2007;91:486–98. [PubMed: 17307205]

Bina KG, Cincotta AH. Dopaminergic agonists normalize elevated hypothalamic neuropeptide Y and corticotropin-releasing hormone, body weight gain, and hyperglycemia in ob/ob mice. Neuroendocrinol 2000;71:68–78.

Blum ID, Patterson Z, Khazall R, Lamont EW, Sleeman MW, Horvath TL, Abizaid A. Reduced anticipatory locomotor responses to scheduled meals in ghrelin receptor deficient mice. Neuroscience 2009;164:351–9. [PubMed: 19666088]

Borgland SL, Taha SA, Sarti G, 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]

Boutrel B, de Lecea L. Addiction and arousal: the hypocretin connection. Physiol Behav 2008;93:947–51. [PubMed: 18262574]

Brief DJ, Davis JD. Reduction of food intake and body weight by chronic intraventricular insulin infusion. Brain Res Bull 1984;12:571–75. [PubMed: 6380652]

Broberger C, deLecea L, Sutcliffe JG, Hokfelt T. Hypocretin/orexin- and melanin-concentrating hormone-expressing cells form distinct populations in the rodent lateral hypothalamus: relationship to the neuropeptide Y and agouti gene-related protein systems. J Comp Neurol 1998;402:460–74. [PubMed: 9862321]

Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Muller-Wieland D, Kahn CR. Role of brain insulin receptor in control of body weight and reproduction. Science 2000;289:2122–25. [PubMed: 11000114]

Cameron DL, Wessendorf MW, Williams JT. A subset of ventral tegmental area neurons is inhibited by dopamine, 5-hydroxytryptamine and opioids. Neuroscience 1997;77:155–166. [PubMed: 9044383]

Caminos JE, Tena-Sempere M, Gaytan F, Sanchez-Criado JE, Barreiro ML, Nogueiras R, Casanueva FF, Aguilar E, Dieguez C. Expression of ghrelin in the cyclic and pregnant rat ovary. Endocrinology 2003;144:1594–602. [PubMed: 12639944]

Capaldi ED, Hunter MJ, Lyn SA. Conditioning with taste as the CS in conditioned flavor preference learning. Animal Learning and Behavior 1997;25:427–36.

Carelli RM. Nucleus accumbens cell firing during goal-directed behaviors for cocaine vs. 'natural' reinforcement. Physiol Behav 2002;76:379–87. [PubMed: 12117574]

Caro J, Kolaczynski J, Nyce M, Ohannesian J, Opentanova I, Goldman W, Lynn R, Zhang P, Sinha M, Considine R. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet 1996;348:159–61. [PubMed: 8684156]

Carr KD. Augmentation of drug reward by chronic food restriction: Behavioral evidence and underlying mechanisms. Physiology and Behavior 2002;76:353–64. [PubMed: 12117572]

Carr KD. Feeding, drug abuse, and the sensitization of reward by metabolic need. Neurochem Res 1996;21:1455–67. [PubMed: 8947935]

Carr KD, Aleman DO, Bak TH, Simon EJ. Effects of parabrachial opioid antagonism on stimulation-induced feeding. Brain Res 1991;545:283–6. [PubMed: 1650277]

Carr KD, Kim G-Y, Cabeza de Vaca S. Hypoinsulinemia may mediate the lowering of self-stimulation thresholds by food restriction and streptozotocin-induced diabetes. Brain Research 2000;863:160–8. [PubMed: 10773204]

Carroll ME, Meisch RA. Increased drug-reinforced behavior due to food deprivation. Adv Behav Pharmacol 1984;4:47–88.

Carvalheira 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]

Carvalheira JBC, Siloto RMP, Ignacchitti I, Brenelli SL, Carvalho CRO, Leite A, Velloso LA, Gontijo JAR, Saad MJA. Insulin modulates leptin-induced STAT3 activation in rat hypothalamus. FEBS Letters 2001;500:119–24. [PubMed: 11445068]

Castaneda TR, Tong J, Datta R, Culler M, Tschop MH. Ghrelin in the regulation of body weight and metabolism. Front Neuroendo 2010;31:44–60.

Chavez M, Kaiyala K, Madden LJ, Schwartz MW, Woods SC. Intraventricular insulin and the level of maintained body weight in rats. Behav Neurosci 1995;109:528–31. [PubMed: 7662162]

Chavez M, Riedy CA, Van Dijk GV, Woods SC. Central insulin and macronutrient intake in the rat. Am J Physiol 1996;271:R727–31. [PubMed: 8853397]

Cheung CC, Clifton DK, Steiner RA. Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. Endocrinology 1997;138:4489–92. [PubMed: 9322969]

Chua SC Jr, Chung WK, Wu-Peng XS, Zhang Y, Liu SM, Tartaglia L, Leibel RL. Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. Science 1996;271:994–6. [PubMed: 8584938]

Clark JT, Kalra PS, Crowley WR, Kalra SP. Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. Endocrinology 1984;115:427–8. [PubMed: 6547387]

Cleary J, Weldon DT, O'Hare E, Billington C, Levine AS. Naloxone effects on sucrose-motivated behavior. Psychopharmacology 1996;126:110–4. [PubMed: 8856829]

Clegg DJ, Air EL, Woods SC, Seeley RJ. Eating elicited by orexin-A, but not melanin-concentrating hormone, is opioid mediated. Endocrinology 2002;143:2995–3000. [PubMed: 12130565]

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. Am J Physiol 2005;288:R981–6.

Coker GT, Studelska D, Harmon S, Burke W, O'Malley KL. Analysis of tyrosine hydroxylase and insulin transcripts in human neuroendocrine tissues. Mol Brain Res 1990;8:93–8. [PubMed: 1976199]

Corp ES, Woods SC, Porte D Jr, Dorsa DM, Figlewicz DP, Baskin DG. Localization of 125I-insulin binding sites in the rat hypothalamus by quantitative autoradiography. Neurosci Lett 1986;70:17–22. [PubMed: 3534636]

Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL, Strasburger CJ, Bidlingmaier M, Esterman M, Heiman ML, Garcia-Segura LM, Nillni EA, Mendez P, Low MJ, Sotonyi P, Friedman JM, Liu H, Pinto S, Colmers WF, Cone RD, Horvath TL. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 2003;37:649–61. [PubMed: 12597862]

Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, Nakazato M. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology 2000;141:4255–61. [PubMed: 11089560]

Davis JD, Smith GP. Analysis of the rhythmic tongue movements of rats ingesting maltose and sucrose solutions. Behav Neurosci 1992;106:217–28. [PubMed: 1554433]

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 DA turnover in the rat. Behav Neurosci 2008;122:1257–63. [PubMed: 19045945]

Dernovsek K, Bar R, Ginsberg B, Lioubin M. Processing of cell-bound insulin by capillary and macrovascular endothelial cells in culture. J Clin Endo Metab 1984;58:761–763.

Dernovsek KD, Bar BS. Rapid transport of biologically intact insulin through cultured endothelial cells. Am J Physiol 1985;248:E244–251. [PubMed: 3881990]

De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollner RL, Boschero AC, Saad MJ, Velloso LA. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 2005;146:4192–9. [PubMed: 16002529]

Drewnowski A, Krahn DD, Demitrack MA, Nairn K, Gosnell BA. Taste responses and preferences for sweet high-fat foods: evidence for opioid involvement. Physiol Behav 1992;51:371–9. [PubMed: 1313591]

Drewnowski A, Krahn DD, Demitrack MA, Nairn K, Gosnell BA. Naloxone, an opiate blocker, reduces the consumption of sweet high fat foods in obese and lean female binge eaters. Am J Clin Nutr 1995;61:1206–12. [PubMed: 7762518]

Drewnowski A, Kurth C, Holden-Wiltse J, Saari J. Food preferences in human obesity: carbohydrates versus fats. Appetite 1992;18:207–21. [PubMed: 1510463]

Drewnowski A, Popkin BM. The nutrition transition: New trends in the global diet. Nutr Rev 1997;55:31–43. [PubMed: 9155216]

Elmquist JK, Bjorbaek C, Ahima RS, Flier JS, Saper CB. Distribution of leptin receptor mRNA isoforms in the rat brain. J Comp Neurol 1998;395:535–47. [PubMed: 9619505]

Everitt BJ, Parkinson JA, Olmstead MC, Arroyo M, Robledo P, Robbins TW. Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. Ann N Y Acad Sci 1999;877:412–38. [PubMed: 10415662]

Fadel J, Deutch AY. Anatomical substrates of orexin-dopamine interactions: lateral hypothalamic projections to the ventral tegmental area. Neuroscience 2002;111:379–87. [PubMed: 11983323]

Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Leptin regulates striatal regions and human eating behavior. Science 2007;317:1355. [PubMed: 17690262]

Figlewicz DP. Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. Am J Physiology 2003;284:R882–92.

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;118:479–87. [PubMed: 15174925]

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. Am J Physiol 2008;295:R388–94.

Figlewicz DP, Bennett JL, Naleid AM, Davis C, Grimm JW. Intraventricular insulin and leptin decrease sucrose self-administration in rats. Physiol Behav 2006;89:611–6. [PubMed: 17045623]

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 Research 2003;964:107–15. [PubMed: 12573518]

Figlewicz DP, Higgins MS, Ng-Evans SB, Havel PJ. Leptin reverses sucrose-conditioned place preference in food-restricted rats. Physiol Behav 2001;73:229–34. [PubMed: 11399316]

Figlewicz DP, Naleid AM, Sipols AJ. Modulation of food reward by adiposity signals. Physiology & Behavior 2007;91:473–78. [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;644:331–4. [PubMed: 8050044]

Figlewicz D, Szot P, Greenwood MRC. Insulin stimulates inositol incorporation in hippocampus of lean but not obese Zucker rats. Physiology and Behavior 1990;47:325–30. [PubMed: 2159162]

Ford CP, Mark GP, Williams JT. Properties and opioid inhibition of mesolimbic dopamine neurons vary according to target location. J Neurosci 2006;26:2788–2797. [PubMed: 16525058]

Frisina PG, Sclafani A. Naltrexone suppresses the late but not early licking response to a palatable sweet solution: opioid hedonic hypothesis reconsidered. Pharm Biochem Behav 2002;74:163–72.

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;51:811–22. [PubMed: 16982425]

Fulton S, Woodside B, Shizgal P. Modulation of brain reward circuitry by leptin. Science 2000;287:125–8. [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;68:102–9. [PubMed: 15795321]

Georgescu D, Zachariou V, Barrot M, Mieda M, Willie JT, Eisch AJ, Yanagisawa M, Nestler EJ, DiLeone RJ. Involvement of the lateral hypothalamic peptide orexin in morphine dependence and withdrawal. J Neuroscience 2003;23:3106–11.

Giddings SJ, Chirgwin J, Permutt M. Evaluation of rat insulin messenger RNA in pancreatic and extrapancreatic tissues. Diabetologia 1985;27:343–7. [PubMed: 2412922]

Giraudo SQ, Grace MK, Welch CC, Billington CJ, Levine AS. Naloxone's anorectic effect is dependent upon the relative palatability of food. Pharm Biochem Behav 1993;46:917–21.

Glass MJ, Billington CJ, Levine AS. Opioids and food intake: distributed functional neural pathways? Neuropeptides 1999;33:360–8. [PubMed: 10657513]

Glass MJ, Billington CJ, Levine AS. Naltrexone administered to central nucleus of amygdala or PVN: neural dissociation of diet and energy. Am J Physiol 2000;279:R86–92.

Glass MJ, Cleary JP, Billington CJ, Levine AS. Role of carbohydrate type on diet selection in neuropeptide Y-stimulated rats. Am J Physiol 1997;273:R2040–5. [PubMed: 9435659]

Glass MJ, Grace M, Cleary JP, Billington CJ, Levine AS. Potency of naloxone's anorectic effect in rats is dependent on diet preference. Am J Physiol 1996;271:R217–21. [PubMed: 8760223]

Gosnell BA, Krahn DD. The effects of continuous naltrexone infusions on diet preferences are modulated by adaption to the diets. Physiol Behav 1992;51:239–44. [PubMed: 1313587]

Grill HJ, Schwartz MW, Kaplan JM, Foxhall JS, Breininger J, Baskin DG. Evidence that the caudal brainstem is a target for the inhibitory effect of leptin on food intake. Endocrinology 2002;143:239–46. [PubMed: 11751615]

Gnanapavan S, Kola B, Bustin SA, Morris DG, McGee P, Fairclough P, Bhattacharya S, Carpenter R, Grossman AB, Korbonits M. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. J Clin Endocrinol Metab 2002;87:2988–91. [PubMed: 12050285]

Hadari YR, Tzahar E, Nadiv O, Rothenberg P, Roberts C Jr, LeRoith D, Yarden Y, Zick Y. Insulin and insulinomimetic agents induce activation of phosphatidylinositol 3′-kinase upon its association with pp 185 (IRS-1) in intact rat livers. J Biol Chem 1992;267:17483–6. [PubMed: 1381348]

Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. Nature 2005;437:556–9. [PubMed: 16100511]

Harris GC, Wimmer M, Randall-Thompson JF, Aston-Jones G. Lateral hypothalamic orexin neurons are critically involved in learning to associate an environment with morphine reward. Behav Brain Res 2007;183:43–51. [PubMed: 17599478]

Havel PJ. Role of adipose tissue in body-weight regulation: mechanisms regulating leptin production and energy balance. Proc Nutr Soc 2000;59:359–71. [PubMed: 10997652]

Harvey J. Leptin regulation of neuronal excitability and cognitive function. Curr Opin Pharm 2007;7:643–7.

Havrankova J, Roth J. Insulin receptors are widely distributed in the central nervous system of the rat. Nature 1978;272:827–9. [PubMed: 205798]

Havrankova J, Roth J, Brownstein M. Concentrations of insulin and of insulin receptors in the brain are independent of peripheral insulin levels: studies of obese and streptozotocin-treated rodents. J Clin Invest 1979;64:636–42. [PubMed: 156737]

Heidenreich KA. Insulin and IGF-I receptor signaling in cultured neurons. Ann NY Acad Sci 1993;692:72–88. [PubMed: 8215046]

Heidenreich KA. Insulin receptors mediate growth effects in cultured fetal neurons. II. Activation of a protein kinase that phosphorylates ribosomal protein S6. Endocrinology 1989;125:1458–63. [PubMed: 2667959]

Hervieu G. Melanin-concentrating hormone functions in the nervous system: food intake and stress. Expert Opin Ther Targets 2003;7:495–511. [PubMed: 12885269]

Hileman S, Pierroz D, Masuzaki H, Bjorbaek C, El-Haschimi K, Banks W, Flier J. Characterization of short isoforms of the leptin receptor in rat cerebral microvessels and of brain uptake of leptin in mouse models of obesity. Endocrinology 2002;143:775–83. [PubMed: 11861497]

Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? Science 2003;299:853–5. [PubMed: 12574618]

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;51:801–10. [PubMed: 16982424]

Horn CC, Addis A, Friedman MI. Neural substrate for an integrated metabolic control of feeding behavior. Am J Physiol 1999;276:R113–9. [PubMed: 9887184]

Howard AD, Feighner SD, Cully DF, Arena JP, Liberator PA, Rosenblum CI, Hamelin M, Hreniuk DL, Palyha OC, Anderson J, Paress PS, Diaz C, Chou M, Liu KK, McKee KK, Pong SS, Chaung LY, Elbrecht A, Dashkevicz M, Heavens R, Rigby M, Sirinathsinghji DJ, Dean DC, Melillo DG, Patchett AA, Nargund R, Griffin PR, DeMartino JA, Gupta SK, Schaeffer JM, Smith RG, Van der Ploeg LH. A receptor in pituitary and hypothalamus that functions in growth hormone release. Science 1996;273:974–7. [PubMed: 8688086]

Hsu R, Taylor JR, Newton SS, Alvaro JD, Haile C, Han G, Hruby VJ, Nestler EJ, Duman RS. Blockade of melanocortin transmission inhibits cocaine reward. Eur J Neurosci 2005;8:2233–42. [PubMed: 15869520]

Ikemoto S. Dopamine reward circuitry: Two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. Brain Research Reviews 2007;56:27–78. [PubMed: 17574681]

Ikemoto S, Wise RA. Mapping of chemical trigger zones for reward. Neuropharmacology 2004;47:190–201. [PubMed: 15464137]

Inui A. Feeding and body-weight regulation by hypothalamic neuropeptides--mediation of the actions of leptin. Trends Neurosci 1999;22:62–7. [PubMed: 10092045]

Irani BG, Dunn-Meynell AA, Levin BE. Altered hypothalamic leptin, insulin, and melanocortin binding associated with moderate-fat diet and predisposition to obesity. Endocrinol 2007;148:310–6.

Ishiwari K, Weber SM, Mingote S, Correa M, Salamone JD. Accumbens dopamine and the regulation of effort in food-seeking behavior: modulation of work output by different ratio or force requirements. Behavioural Brain Research 2004;151:83–91. [PubMed: 15084424]

Islam AK, Bodnar RJ. Selective opioid receptor antagonist effects upon intake of a high-fat diet in rats. Brain Res 1990;508:293–6. [PubMed: 2155039]

Israel PA, Park CR, Schwartz MW, Green PK, Sipols AJ, Woods SC, Porte D Jr, Figlewicz DP. Effect of diet-induced obesity and experimental hyperinsulinemia on insulin uptake into CSF of the rat. Brain Res Bull 1993;30:571–5. [PubMed: 8457906]

Jaber M, Jones S, Giros B, Caron MG. The dopamine transporter: a crucial component regulating dopamine transmission. Mov Disord 1997;12:629–33. [PubMed: 9380041]

Jarosz PA, Metzger BL. The effect of opioid antagonism on food intake behavior and body weight in a biobehavioral model of obese binge eating. Biol Res Nurs 2002;3:198–209. [PubMed: 12184663]

Jerlhag E, Egecioglu E, Dickson SL, Andersson M, Svensson L, Engel JA. Ghrelin stimulates locomotor activity and accumbal dopamine-overflow via central cholinergic systems in mice: implications for its involvement in brain reward. Addiction Biology 2006;11:45–54. [PubMed: 16759336]

Jiang H, Betancourt L, Smith RG. Ghrelin amplifies dopamine signaling by cross talk involving formation of growth hormone secretagogue receptor/dopamine receptor subtype 1 heterodimers. Mol Endocrinol 2006;20:1772–85. [PubMed: 16601073]

Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci 1992;12:483–488. [PubMed: 1346804]

Kaiyala KJ, Prigeon RL, Kahn SE, Woods SC, Schwartz MW. Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. Diabetes 2000;49:1525–33. [PubMed: 10969837]

Kastin A, Pan W. Dynamic regulation of leptin entry into brain by the blood-brain barrier. Regulatory Peptides 2000;92:37–43. [PubMed: 11024563]

Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M. Opioid modulation of taste hedonics within the ventral striatum. Physiology and Behavior 2002;76:365–77. [PubMed: 12117573]

Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci 2002;22:3306–11. [PubMed: 11978804]

Kenner KA, Heidenreich KA. Insulin and insulin-like growth factors stimulate in vivo receptor autophosphorylation and tyrosine phosphorylation of a 70K substrate in cultured fetal chick neurons. Endocrinology 1991;129:301–11. [PubMed: 1711464]

Kim J, Petersen KE, Scanlon KS, Fitzmaurice GM, Must A, Oken E, Rifas-Shiman SL, Rich-Edwards JW, Gillman MW. Trends in overweight from 1980 through 2001 among preschool-aged children enrolled in a health maintenance organization. Obesity 2006;14:1107–12. [PubMed: 16899790]

King GL, Johnson S. Receptor-mediated transport of insulin across endothelial cells. Science 1985;227:1583–6. [PubMed: 3883490]

Kirkham TC, Blundell JE. Effect of naloxone and naltrexone on the development of satiation measured in the runway: comparisons with d-amphetamine and d-fenfluramine. Pharm Biochem Behav 1986;25:123–8.

Kirkham TC, Cooper SJ. Attenuation of sham feeding by naloxone is stereospecific: evidence for opioid mediation of orosensory reward. Physiol Behav 1988;43:845–7. [PubMed: 2853375]

Kirkham TC, Cooper SJ. Naloxone attenuation of sham feeding is modified by manipulation of sucrose concentration. Physiol Behav 1988;44:491–4. [PubMed: 2853384]

Koch L, Wunderlich FT, Seibler J, Konner AC, Hampel B, Irlenbusch S, Brabant G, Kahn CR, Schwenk F, Bruning JC. Central insulin action regulates peripheral glucose and fat metabolism in mice. J Clin Invest 2008;118:2132–47. [PubMed: 18451994]

Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999;402:656–60. [PubMed: 10604470]

Kola B, Farkas I, Christ-Crain M, Wittmann G, Lolli F, Amin F, Harvey-White J, Liposits Z, Kunos G, Grossman AB, Fekete C, Korbonits M. The orexigenic effect of ghrelin is mediated through central activation of the endogenous cannabinoid system. PLoS ONE 2008;12:1797.

Korbonits M, Bustin SA, Kojima M, Jordan S, Adams EF, Lowe DG, Kangawa K, Grossman AB. The expression of the growth hormone secretagogue receptor ligand ghrelin in normal and abnormal human pituitary and other neuroendocrine tumors. J Clin Endocrinol Metab 2001;86:881–7. [PubMed: 11158061]

Lamonte N, Echo JA, Ackerman TF, Christian G, Bodnar RJ. Analysis of opioid receptor subtype antagonist effects upon mu opioid agonist-induced feeding elicited from the ventral tegmental area of rats. Brain Res 2009;929:96–100. [PubMed: 11852035]

Lang IM, Strahlendorf JC, Strahlendorf HK, Barnes CD. Effects of chronic administration of naltrexone on appetitive behaviors of rats. Prog Clin Biol Res 1981;68:197–207. [PubMed: 7301882]

Lawrence CB, Snape AC, Baudoin FM, Luckman SM. Acute central ghrelin and GH secretagogues induce feeding and activate brain appetite centers. Endocrinology 2002;143:155–62. [PubMed: 11751604]

Leinninger GM, Myers MG Jr. LRb signals act within a distributed network of leptin-responsive neurones to mediate leptin action. Acta Physiol 2008;192:49–59.

Leshan RL, Bjornholm M, Munzberg H, Myers MG Jr. Leptin receptor signaling and action in the central nervous system. Obesity 2006;14 (Suppl):208S–212S. [PubMed: 17021368]

Levine AS, Grace M, Billington CJ. Beta-funaltrexamine (beta-FNA) decreases deprivation and opioid-induced feeding. Brain Res 1991;562:281–4. [PubMed: 1663414]

Levine AS, Grace M, Billington CJ, Portoghese PS. Nor-binaltorphimine decreases deprivation and opioid-induced feeding. Brain Res 1990;534:60–4. [PubMed: 1963567]

Levine AS, Kotz CM, Gosnell BA. Sugars and fats: the neurobiology of preference. J Nutr 2003;133:831S–834S. [PubMed: 12612162]

Levine AS, Weldon DT, Grace M, Cleary JP, Billington CJ. Naloxone blocks that portion of feeding driven by sweet taste in food-restricted rats. Am J Physiol 1995;268:R248–52. [PubMed: 7840328]

Lin L, Martin R, Schaffhauser AO, York DA. Acute changes in the response to peripheral leptin with alteration in the diet composition. Am J Physiol 2001;280:R504–9.

MacDonald AF, Billington CJ, Levine AS. Alterations in food intake by opioid and dopamine signaling pathways between the ventral tegmental area and the shell of the nucleus accumbens. Brain Research 2004;1018:78–85. [PubMed: 15262208]

Maness L, Banks W, Kastin A. Persistence of blood-to-brain transport of leptin in obese leptin-deficient and leptin receptor-deficient mice. Brain Research 2000;873:165–7. [PubMed: 10915826]

Marcus JN, Aschkenasi CJ, Lee CE, Chemelli RM, Saper CB, Yanigasawa M, Elmquist JK. Differential expression of orexin receptors 1 and 2 in the rat brain. J Comp Neurol 2001;435:6–25. [PubMed: 11370008]

Maresh G, Maness L, Zadina J, Kastin A. In vitro demonstration of a saturable transport system for leptin across the blood-brain barrier. Life Sciences 2001;69:67–73. [PubMed: 11411806]

Marinelli M, Piazza PV. Interaction between glucocorticoid hormones, stress, and psychostimulant drugs. Eur J Neurosci 2002;16:387–94. [PubMed: 12193179]

Marks-Kaufman R, Balmagiya T, Gross E. Modifications in food intake and energy metabolism in rats as a function of chronic naltrexone infusions. Pharm Biochem Behav 1984;20:911–6.

Marks-Kaufman R, Plager A, Kanarek RB. Central and peripheral contributions of endogenous opioid systems to nutrient selection in rats. Psychopharmacology 1985;85:414–8. [PubMed: 3927336]

McBride WJ, Murphy JM, Ikemoto S. Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav Brain Res 1999;101:129–52. [PubMed: 10372570]

McGowan MK, Andrews KM, Kelly J, Grossman SP. Effects of chronic intrahypothalamic infusion of insulin on food intake and diurnal meal patterning in the rat. Behav Neurosci 1990;104:373–85. [PubMed: 2189441]

McNay EC. Insulin and ghrelin: peripheral hormones modulating memory and hippocampal function. Curr Opin Pharmacol 2007;7:628–32. [PubMed: 18023257]

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 Neurosci 2004;5:54. [PubMed: 15581426]

Mitchell V, Bouret S, Beauvillain JC, Schilling A, Perret M, Kordon C, Epelbaum J. Comparative distribution of mRNA encoding the growth hormone secretagogue-receptor (GHS-R) in Microcebus murinus (Primate, lemurian) and rat forebrain and pituitary. J Comp Neurol 2001;429:469–89. [PubMed: 11116232]

Mizuno TM, Makimura H, Silverstein J, Roberts JL, Lopingco T, Mobbs CV. Fasting regulates hypothalamic neuropeptide Y, agouti-related peptide, and proopiomelanocortin in diabetic mice independent of changes in leptin or insulin. Endocrinol 1999;140:4551–7.

Mondal MS, Nakazato M, Matsukura S. Orexins (hypocretins): novel hypothalamic peptides with divergent functions. Biochem Cell Biol 2000;78:299–305. [PubMed: 10949081]

Mori K, Yoshimoto A, Takaya K, Hosoda K, Ariyasu H, Yahata K, Mukoyama M, Sugawara A, Hosoda H, Kojima M, Kangawa K, Nakao K. Kidney produces a novel acylated peptide, ghrelin. FEBS Lett 2000;486:213–6. [PubMed: 11119706]

Morton GJ, Blevins JE, Kim F, Matsen M, Nguyen HT, Figlewicz DP. Leptin action in the ventral tegmental area reduces food intake via mechanisms independent of IRS-PI3K and mTOR signaling. American Journal of Physiology 2009;297:E202–E210. [PubMed: 19435852]

Morton GJ, Schwartz MW. The NPY/AgRP neuron and energy homeostasis. Int J Obes Relat Metab Disord 2001;25 (Suppl 5):S56–S62. [PubMed: 11840217]

Mountjoy KG, Wong J. Obesity, diabetes and functions for proopiomelanocortin-derived peptides. Mol Cell Endocrinol 1997;128:171–7. [PubMed: 9140088]

Munzberg H. Differential leptin access into the brain--A hierarchical organization of hypothalamic leptin target sites? Physiol Behav 2008;94:664–9. [PubMed: 18502454]

Munzberg H, Flier JS, Bjorbaek C. Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. Endocrinology 2004;145:4880–9. [PubMed: 15271881]

Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, Matsukura S. A role for ghrelin in the central regulation of feeding. Nature 2001;409:194–8. [PubMed: 11196643]

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;26:2274–9. [PubMed: 16137788]

Naleid AM, Grace MK, Chimukangara M, Billington CJ, Levine AS. Paraventricular opioids alter intake of high-fat but not high-sucrose diet depending on diet preference in a binge model of feeding. Am J Physiol 2007;293:R99–R105.

Narita M, Nagumo Y, Hashimoto S, Narita M, Khotib J, Miyatake M, Sakurai T, Yanagisawa M, Nakamachi T, Shioda S, Suzuki T. Direct involvement of orexinergic systems in the activation of the mesolimbic dopamine pathway and related behaviors induced by morphine. J Neurosci 2006;26:398–405. [PubMed: 16407535]

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;52:227–31. [PubMed: 12540590]

Niswender KD, Morton GJ, Stearns WH, Rhodes CJ, Myers MG Jr, Schwartz MW. Key enzyme in leptin-induced anorexia. Nature 2001;413:794–5. [PubMed: 11677594]

Noel MB, Wise RA. Ventral tegmental injections of a selective mu or delta opioid enhance feeding in food-deprived rats. Brain Res 1995;673:304–12. [PubMed: 7606445]

Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. Nat Neurosci 2002;5:566–72. [PubMed: 12021765]

Obici S, Rossetti L. Minireview: nutrient sensing and the regulation of insulin action and energy balance. Endocrinol 2003;144:5172–8.

Olszewski PK, Levine AS. Minireview: characterization of influence of central nociceptin/orphanin FQ on consummatory behavior. Endocrinology 2004;145:2627–32. [PubMed: 15044361]

Olszewski PK, Bomberg EM, Martell A, Grace MK, Levine AS. Intraventricular ghrelin activates oxytocin neurons: implications in feeding behavior. Neuroreport 2007;18:499–503. [PubMed: 17496811]

Papotti M, Ghe C, Cassoni P, Catapano F, Deghenghi R, Ghigo E, Muccioli G. Growth hormone secretagogue binding sites in peripheral human tissues. J Clin Endocrinol Metab 2000;85:3803–7. [PubMed: 11061542]

Papp M. Different effects of short- and long-term treatment with imipramine on the apomorphine- and food-induced place preference conditioning in rats. Pharmacol Biochem Behav 1988;52:889–93. [PubMed: 3227037]

Patterson T, Brot MD, Zavosh A, Schenk JO, Szot P, Figlewicz DP. Fasting 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. Ann New York Acad Sci 2003;985:251–62. [PubMed: 12724163]

Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, Kilduff TS. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 1998;18:9996–10015. [PubMed: 9822755]

Pocai A, Morgan K, Buettner C, Gutierrez-Juarez R, Obici S, Rossetti L. Central leptin acutely reverses diet-induced hepatic insulin resistance. Diabetes 2005;54:3182–9. [PubMed: 16249443]

Pomonis JD, Levine AS, Billington CJ. Interaction of the hypothalamic paraventricular nucleus and central nucleus of the amygdala in naloxone blockade of neuropeptide Y-induced feeding revealed by c-fos expression. J Neurosci 1997;17:5175–82. [PubMed: 9185555]

Porte D Jr, Woods SC. Regulation of food intake and body weight by insulin. Diabetologia 1981;20 (Suppl):274–280. [PubMed: 7014326]

Pulman KJ, Fry WM, Cottrell GT, Ferguson AV. The subfornical organ: a central target for circulating feeding signals. J Neurosci 2006;26:2022–30. [PubMed: 16481435]

Richardson NR, Gratton A. Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study. J Neurosci 1996;16:8160–9. [PubMed: 8987841]

Robbins TW, Everitt BJ. Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol 1996;6:228–36. [PubMed: 8725965]

Robertson SA, Leinninger GM, Myers MJ Jr. Molecular and nueral mediators of leptin action. Physiol Behav 2008;94:637–42. [PubMed: 18501391]

Rollins BL, King BM. Amygdala-lesion obesity: what is the role of the various amygdaloid nuclei? Am J Physiol 2000;279:R1348–56.

Rudski JM, Billington CJ, Levine AS. Naloxone's effects on operant responding depend upon level of deprivation. Pharm Biochem Behav 1994;49:377–83.

Sakata I, Nakano Y, Osborne-Lawrence S, Rovinsky SA, Lee CE, Perello M, Anderson JG, Coppari R, Xiao G, Lowell BB, Elmquist JK, Zigman JM. Characterization of a novel ghrelin cell reporter mouse. Reg Peptides 2009;155:91–98.

Schneider LH, Davis JD, Watson CA, Smith GP. Similar effect of raclopride and reduced sucrose concentration on the microstructure of sucrose sham feeding. Eur J Pharmacol 1990;186:61–70. [PubMed: 2282936]

Schultz W. Getting formal with dopamine and reward. Neuron 2002;36:241–63. [PubMed: 12383780]

Schwartz M, Figlewicz D, Kahn S, Baskin D, Greenwood M, Porte D Jr. Insulin binding to brain capillaries is reduced in genetically obese, hyperinsulinemic Zucker rats. Peptides 1990;11:467–72. [PubMed: 2199946]

Schwartz M, Peskind E, Raskind M, Boyko E, Porte D Jr. Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans. Nature Medicine 1996;2:589–93.

Schwartz MW, Figlewicz DP, Baskin DG, Woods SC, Porte D Jr. Insulin in the brain: a hormonal regulator of energy balance. Endo Rev 1992;13:387–414.

Schwartz MW, Sipols AJ, Kahn SE, Lattemann DF, Taborsky G Jr, Bergman RN, Woods SC, Porte D Jr. Kinetics and specificity of insulin uptake from plasma to cerebrospinal fluid. Am J Physiol 1990;259:E378–83. [PubMed: 2205107]

Schwartz MW, Sipols AJ, Marks JL, Sanacora G, White JD, Scheurink A, Kahn SE, Baskin DG, Woods SC, Figlewicz DP, Porte D Jr. Inhibition of hypothalamic neuropeptide Y gene expression by insulin. Endocrinology 1992;130:3608–16. [PubMed: 1597158]

Seeley RJ, Schwartz MW. Neuroendocrine regulation of food intake. Acta Paediatr 1999;88(Suppl):58–618.

Seeley RJ, Yagaloff KA, Fisher SL, Burn P, Thiele TE, van Dijk G, Baskin DG, Schwartz MW. Melanocortin receptors in leptin effects. Nature 1999;390:349. [PubMed: 9389472]

Seoane LM, López M, Tovar S, Casanueva FF, Señarís R, Diéguez C. Agouti-related peptide, neuropeptide Y, and somatostatin-producing neurons are targets for ghrelin actions in the rat hypothalamus. Endocrinology 2003;144:544–51. [PubMed: 12538615]

Sevak RJ, Koek W, Daws LC, Owens WA, Galli A, France CP. Behavioral effects of amphetamine in streptozotocin-treated rats. Eur J Pharmacol 2008;581:105–12. [PubMed: 18155695]

Shalev U, Grimm JW, Shaham Y. Neurobiology of relapse to heroin and cocaine seeking: a review. Pharm Reviews 2002;54:1–42.

Shalev U, Yap J, Shaham Y. Leptin attenuates food deprivation-induced relapse to heroin seeking. J Neurosci 2001;21:RC129. [PubMed: 11160414]

Shemer J, Adamo M, Raizada MK, Heffez D, Zick Y, LeRoith D. Insulin and IGF-I stimulate phosphorylation of their respective receptors in intact neuronal and glial cells in primary culture. J Mol Neurosci 1989;1:3–8. [PubMed: 2561992]

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 Psych 2006;63:824–30.

Sipols AJ, Baskin DG, Schwartz MW. Effect of intracerebroventricular insulin infusion on diabetic hyperphagia and hypothalamic neuropeptide gene expression. Diabetes 1995;44:147–51. [PubMed: 7859932]

Sipols AJ, Stuber GD, Klein SN, Higgins MS, Figlewicz DP. Insulin and raclopride combine to decrease short-term intake of sucrose solutions. Peptides 2000;21:1361–7. [PubMed: 11072123]

Smith GP. Dopamine and food reward. Prog Psychobiol Physiol Psychol 1995;16:83–143.

Smith SL, Harrold JA, Williams G. Diet-induced obesity increases mu opioid receptor binding in specific regions of the rat brain. Brain Res 2002;953:215–22. [PubMed: 12384255]

Stein LJ, Dorsa DM, Baskin DG, Figlewicz DP, Porte D Jr, Woods SC. Reduced effect of experimental peripheral hyperinsulinemia to elevate cerebrospinal fluid insulin concentrations of obese Zucker rats. Endocrinology 1987;121:1611–5. [PubMed: 3311715]

Stratford TR, Kelley AE. Evidence of a functional relationship between the nucleus accumbens shell and lateral hypothalamus subserving the control of feeding behavior. J Neurosci 1999;19:11040–8. [PubMed: 10594084]

Tanaka M, Hayashida Y, Nakao N, Nakai N, Nakashima K. Testis-specific and developmentally induced expression of a ghrelin gene-derived transcript that encodes a novel polypeptide in the mouse. Biochim Biophys Acta 2001;1522:62–5. [PubMed: 11718902]

Tanda G, DiChiara G. A dopamine-mu 1 opioid link in the rat ventral tegmentum shared by palatable food (Fonzies) and non-psychostimulant drugs of abuse. Eur J Neurosci 1998;10:1179–87. [PubMed: 9753186]

Toshinai K, Date Y, Murakami N, Shimada M, Mondal MS, Shimbara T, Guan JL, Wang QP, Funahashi H, Sakurai T, Shioda S, Matsukura S, Kangawa K, Nakazato M. Ghrelin-induced food intake is mediated via the orexin pathway. Endocrinology 2003;144:1506–12. [PubMed: 12639935]

Traebert M, Riediger T, Whitebread S, Scharrer E, Schmid HA. Ghrelin acts on leptin-responsive neurones in the rat arcuate nucleus. J Neuroendocrinol 2002;14:580–6. [PubMed: 12121496]

Unger J, Livingston JN, Moss AM. Insulin receptors in the central nervous system: localization, signaling mechanisms and functional aspects. Prog Neurobiol 1991;36:343–62. [PubMed: 1887067]

Urayama A, Banks WA. Starvation and triglycerides reverse the obesity-induced impairment of insulin transport at the blood-brain barrier. Endocrinology 2008;149:3592–97. [PubMed: 18403490]

Vaughan RA, Huff RA, Uhl GR, Kuhar MJ. Protein kinase C-mediated phosphorylation and functional regulation of dopamine transporters in striatal synaptosomes. J Biol Chem 1997;272:15541–6. [PubMed: 9182590]

Volante M, Allia E, Gugliotta P, Funaro A, Broglio F, Deghenghi R, Muccioli G, Ghigo E, Papotti M. Expression of ghrelin and of the GH secretagogue receptor by pancreatic islet cells and related endocrine tumors. J Clin Endocrinol Metab 2002;87:1300–8. [PubMed: 11889202]

Wang G, Lee HM, Englander E, Greeley GH Jr. Ghrelin--not just another stomach hormone. Regul Pept 2002;105:75–81. [PubMed: 11891007]

Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Brain dopamine and obesity. Lancet 2001;357:354–7. [PubMed: 11210998]

Wang J, Obici S, Morgan K, Barzilai N, Feng Z, Rossetti L. Overfeeding rapidly induces leptin and insulin resistance. Diabetes 2001;50:2786–91. [PubMed: 11723062]

Warren M, Frost-Pineda K, Gold M. Body mass index and marijuana use. J Addict Dis 2005;24:95–100. [PubMed: 16186086]

Weldon DT, O'Hare E, Cleary J, Billington CJ, Levine AS. Effect of naloxone on intake of cornstarch, sucrose, and polycose diets in restricted and non-restricted rats. Am J Physiol 1996;270:R1183–8. [PubMed: 8764280]

Werther GA, Hogg A, Oldfield BJ, McKinley MJ, Figdor R, Allen AM, Mendelsohn FAO. Localization and characterization of insulin receptors in rat brain and pituitary gland using in vitro autoradiography and computerized densitometry. Endocrinology 1987;121:1562–70. [PubMed: 3653038]

White JD, Olchovsky D, Kershaw M, Berelowitz M. Increased hypothalamic content of preproneuropeptide-Y messenger ribonucleic acid in streptozotocin-diabetic rats. Endocrinology 1990;126:765–72. [PubMed: 2404748]

Will MJ, Franzblau EB, Kelley AE. The amygdala is critical for opioid-mediated binge eating of fat. Neuroreport 2004;15:1857–60. [PubMed: 15305124]

Wilson C, Nomikos GG, Collu M, Fibiger HC. Dopaminergic correlates of motivated behavior: importance of drive. J Neurosci 1995;15:5169–78. [PubMed: 7623143]

Wise RA. Brain reward circuitry: insights from unsensed incentives. Neuron 2002;36:229–40. [PubMed: 12383779]

Wise RA, Rompre P-P. Brain dopamine and reward. Ann Rev Psychol 1989;40:191–225. [PubMed: 2648975]

Wolinsky TD, Abrahamsen GC, Carr KD. Diabetes alters mu and kappa opioid binding in rat brain regions: comparison with effects of food restriction. Brain Res 1996;738:167–71. [PubMed: 8949943]

Wolinsky TD, Carr KD, Hiller JM, Simon EJ. Effects of chronic food restriction on mu and kappa opioid bidning in rat forebrain: a quantitative autoradiographic study. Brain Res 1994;656:274–80. [PubMed: 7820587]

Wolinsky TD, Carr KD, Hiller JM, Simon EJ. Chronic food restriction alters mu and kappa opioid receptor binding in the parabrachial nucleus of the rat: a quantitative autoradiographic study. Brain Res 1996;706:333–6. [PubMed: 8822378]

Woods SC, Lotter EC, McKay LD, Porte D Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. Nature 1979;282:503–5. [PubMed: 116135]

Woods SC, Schwartz MW, Baskin DG, Seeley RJ. Food intake and the regulation of body weight. Annu Rev Psychol 2000;51:255–77. [PubMed: 10751972]

Yanovski SZ, Yanovski JA. Obesity. New Engl J Med 2002;346:591–602. [PubMed: 11856799]

Yeomans MR, Wright P, Macleod HA, Critchley JA. Effect of nalmefene on feeding in humans. Dissociation of hunger and palatability. Psychopharmacology 1990;100:426–32. [PubMed: 2315439]

Yu WZ, Ruegg H, Bodnar RJ. Delta and kappa opioid receptor subtypes and ingestion: antagonist and glucoprivic effects. Pharm Biochem Behav 1997;56:353–61.

Yu WZ, Sclafani A, Delamater AR, Bodnar RJ. Pharmacology of flavor preference conditioning in sham-feeding rats: effects of naltrexone. Pharm Biochem Behav 1999;64:573–84.

Zahniser NR, Goens MB, Hanaway PJ, Vinych JV. Characterization and regulation of insulin receptors in rat brain. J Neurochem 1984;42:1354–62. [PubMed: 6323631]

Zhang M, Gosnell BA, Kelley AE. Intake of high-fat food is selectively enhanced by mu opioid receptor stimulation within the nucleus accumbens. J Pharm Exp Ther 1998;284:908–14.

Zhang Y, Proenca R, Maffie M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425–32. [PubMed: 7984236]

Zheng H, Patterson LM, Berthoud H-R. Orexin signaling in the ventral tegmental area is required for high-fat appetite induced by opioid stimulation of the nucleus accumbens. J Neurosci 2007;27:110–82.

Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK. Expression of ghrelin receptor mRNA in the rat and the mouse brain. J Comp Neurol 2006;494:528–48. [PubMed: 16320257]