Leptin and the Control of Body Weight: A Review of Its Diverse Central Targets, Signaling Mechanisms, and Role in the Pathogenesis of Obesity

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The groundbreaking discovery of leptin in 1994 ignited the field of obesity research by providing the first direct evidence for a hormonal system primarily involved in body weight regulation. Advances in this field over the past 15 years have led to a detailed understanding of the central targets and mechanisms of leptin action. Although the arcuate melanocortin pathway is currently the best described target of leptin action, in this article we review recent evidence pointing to a system in which leptin acts at distinct sites and through different mechanisms within the central nervous system (CNS) to mediate energy homeostasis and feeding behavior. It appears that leptin controls feeding not just by providing physiological satiety signal, but also by mediating "synaptic plasticity" as well as modulating the perception of reward associated with feeding. Furthermore, we also review advances in our understanding of leptin resistance, a critical consequence and possible precursor of obesity.

LEPTIN

Leptin is a hormone produced by adipose tissue, acting as a sensor of fat mass in part of a negative feedback loop that maintains a set point for body fat stores. Circulating leptin concentrations closely parallel body fat stores (1), such that a rise in adiposity increases leptin production, hence inhibiting food intake and vice versa. Consequently, both humans and mice with inherited loss of function mutations of the genes encoding either leptin or its receptor display severe early onset obesity (2–6). Leptin deficiency is unique among monogenic obesity syndromes identified so far in that it is amenable to treatment with recombinant leptin (7–9).

Leptin's role in the negative feedback regulation of body weight is well established in rodents, but there remain some unresolved questions regarding its exact role in humans. Notably, most obese individuals have high leptin levels as predicted, but these do not induce the expected loss in fat mass (10–12). Furthermore, despite initial interest in the therapeutic properties of recombinant leptin, administering the hormone to obese individuals does not induce weight loss as predicted, suggesting that obese individuals may be resistant to the effects of leptin (13). A further puzzling finding is that large interindividual variations in serum leptin levels exist, independent of fat mass, in women naturally tending to have higher levels than men (14,15).

These observations would suggest that the primary function of the leptin signal is not to prevent excessive weight gain. In fact, evolutionary pressures have geared this system to favor fat storage over fat consumption. Thus the major physiological role of leptin is not as a "satiety signal" to prevent obesity in times of energy excess, but as a "starvation signal" to maintain adequate fat stores for survival during times of energy deficit (16).

LEPTIN RECEPTOR

Although the range of clinical phenotypes of congenital leptin and leptin receptor deficiency is similar, leptin receptor deficiency in humans results in a less severe phenotype (6). It is also believed to be more prevalent than leptin deficiency, and may account for up to 3% of all cases of extreme early onset obesity. The hypothalamic arcuate nucleus (ARC) is a major site for leptin signaling and leptin resistance (17–19). Within the arcuate, two distinct classes of neurons exist; one class expresses the peptides POMC (proopiomelanocortin) and cocaine and amphetamine–related transcript which reduce food intake, whereas the other expresses two peptides known as NPY (neuropeptide Y) and AgRP (agouti-related protein) which stimulate feeding behavior (20,21). Leptin receptors are highly expressed on the membranes of both types of neurons allowing leptin to reciprocally regulate these two populations.

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The leptin receptor is a single membrane spanning protein which shows structural similarity to the class 1 cytokine receptor family (22,23). Several different alternatively spliced isoforms of the leptin receptor (ObR) exist (22), each with a characteristic intracellular domain. Depending upon the length of the intracellular domain the isoforms are classified as either short or long. The short isoforms (ObRa, ObRb, ObRc, ObRd, ObRe, and ObRf) have limited signaling capacity whereas the long isoform ObRb is believed to be the primary signaling form of the receptor (22,24,25). The ObRa and ObRc are expressed at high levels in the cerebral microvessels which constitute the blood–brain barrier and play key roles in leptin transport into the CNS (26). Leptin transport is markedly impaired in both mice lacking the ObR and in mouse models of diet-induced obesity (26). It is generally assumed that this impairment of transport results from a saturation of the leptin transporter due to the high endogenous leptin levels of these mice. In support of this argument, leptin transport has been shown to be normalized in another rodent model of ObR deficiency, the Koletsky rat, when a perfusion method that negates the effect of serum leptin levels is used. It seems likely, however, that short isoforms of the receptor actually modulate the activity of a separate transporter for leptin, whose identity remains unknown (27).

The long form of the receptor, ObRb is heavily expressed in the hypothalamus in contrast where it mediates the effects of leptin on energy homeostasis (25,28). The membrane expression of the ObRb is in part regulated by the OB-R gene–related protein which controls endocytic internalization (29). A lack of functional ObRb is responsible for the obesity and metabolic syndrome observed in the db/db mouse model (4).

LEPTIN RESISTANCE

Leptin resistance, a term not without controversy, is used to describe the apparent paradox of leptin's action as an anorectic hormone and its elevated levels in the majority of obese individuals. Conceptually, because it has evolved as a trigger of the starvation response, we are designed to respond to low levels of leptin, which occurs when our fat stores are depleted, and not when it is circulating at normal or elevated levels. There are a number of proposed molecular mechanisms used to describe the phenomenon of leptin resistance. These encompass a spectrum of molecular and functional disorders, which can broadly be characterized into: (i) impaired leptin transport across the blood–brain barrier and (ii) impairment of leptin receptor function and signaling. Importantly, compelling evidence suggests that leptin itself may play an important role in the development of resistance to its own effects, so called "leptin-induced leptin resistance." Chronically raised leptin levels which characterize obesity decrease the transport of leptin into the CNS and impair the signaling properties of leptin receptors. The resulting resistance to leptin confers increased susceptibility to diet-induced obesity, which in turn raises leptin levels further and worsens existing leptin resistance leading to a vicious cycle of weight gain. Therefore in addition to being a major cause of obesity, leptin resistance is also an important consequence (30,31).

BLOOD–BRAIN BARRIER

Studies show that the blood–brain barrier is a crucial site for leptin resistance (32–34). At a molecular mass of 16 kDa, leptin is too large to undergo transmembrane diffusion and is transported into the brain by a saturable transport system. Although leptin is widely transported throughout the CNS, the most intensive region of uptake is the hypothalamic ARC. Several factors have been identified to influence the rate of leptin transport into the CNS. α-Adrenergic stimulation for example increases transporter activity (35), whereas hypertriglyceridemia markedly impairs it (36). Hypertriglyceridemia is generally observed during prolonged starvation and it is hypothesized that the ability of triglycerides to inhibit leptin transport may have in part arisen as an evolutionary mechanism to counteract the propagation of anorexic signals during food shortage. Conversely, hypertriglyceridemia is also associated with obesity and may in part be responsible for the impairment of leptin transport that is observed in obese individuals and defines the condition of peripheral leptin resistance (32–34). Peripheral resistance like central resistance is both a cause and a consequence of obesity, meaning that the two types of resistance are likely to co-exist and once established set off a vicious cycle of weight gain (32–34).

LEPTIN RECEPTOR SIGNALING

Activation of the ObRb initiates a cascade of signal transduction pathways, deficits of which may play an important role in the etiology of leptin resistance. Thought to be of particular importance is the JAK/STAT (Janus kinases/signal transducers and activators of transcription) pathway (24,37). The ObRb has no intrinsic tyrosine kinase activity and therefore must recruit cytoplasmic kinases, especially JAK2 which in turn phosphorylate numerous tyrosine residues of the intracellular domain (37). Although the precise mechanisms of JAK2 activation and signaling remain to be elucidated, a growing body of evidence supports a model in which leptin binding triggers ObRb aggregation into oligomers such that their constitutively bound JAK2 molecules are brought within close contact of each other, hence enabling them to autophosphorylate (38–40). It appears that there are three conserved tyrosine residues in the intracellular domain which are phosphorylated and contribute to signaling—Y985, Y1138, and Y1077 (39,41,42) (**Figure 1**). The phosphorylated domains provide highly specific binding sites for src homology 2 (SH2) domain containing proteins such as STATs which are activated and translocated to the nucleus where they behave as transcription factors. STAT3 is known to be crucial to energy homeostasis, and after binding to the ObR becomes the substrate of receptor-associated JAKs and subsequently dissociates from the receptor before forming active dimers (41).

Mice with a targeted mutation is a key intracellular tyrosine residue (Y1138) of the ObR which is essential for STAT3 activation (s/s) are markedly hyperphagic,

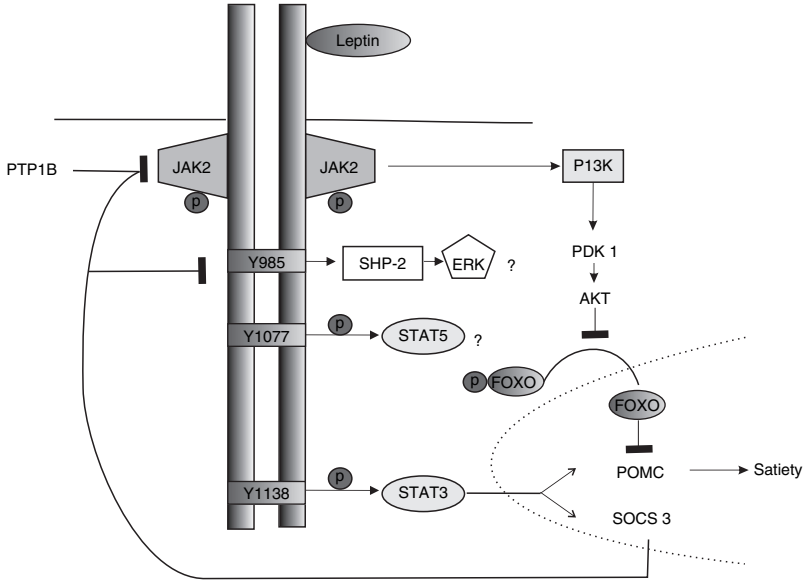

Figure 1 The major signaling pathways activated by the ObR. Ligand binding triggers autophosphorylation of ObR-associated JAK2, which in turn is activated and phosphorylates three critical intracellular tyrosine residues: Y985, Y1077, and Y1138. Phosphorylation of Y985, leads to the activation of extracellular signal–regulated kinase (ERK) signaling, while the phosphorylated Y1077 residue mediates the activation of STAT5. STAT3, which is a transcription factor for proopiomelanocortin (POMC) is activated by Y1138. POMC expression is also increased by signaling through P13K pathway, which inhibits the dephosphorylation of FOXO 1, an inhibitor of POMC transcription. ObR signaling is subject to negative regulation by SOCS3 and protein-tyrosine phosphatase 1B (PTP1B). PDK 1, 3-phosphoinositide-dependent protein kinase 1; STAT, signal transducers and activators of transcription.

obese and at the same time display a suppression of hypothalamic melanocortin activity suggesting that STAT3 may participate in energy homeostasis by regulating the melanocortin gene expression (43). Xu *et al.* using cre recombinase technology elegantly demonstrated that STAT3 is necessary for inducing POMC transcription. Despite this, however, mice lacking STAT3 in POMC-expressing neurons are responsive to the anorexigenic effects of leptin and display no increased sensitivity to a high-fat diet, highlighting that the STAT3/POMC pathway forms only part of the energy homeostatic response to leptin (44).

Current thinking regarding the precise role of the ObR-STAT3 signal in regulating ARC AgRP/NPY-expressing neurons, however, remains unclear. Studies of ARC neuron activity in both db/db and s/s mouse models using c-Fos-like immunoreactivity suggest that the ObR-STAT3 pathway has little, if any, importance in the regulation of orexigenic neurons within the ARC (45). A more recent study, however, specifically targeting STAT3 in AgRP/NPY neurons promotes an important role for this signal in normal energy homeostasis. Mice lacking STAT3 expression in these neurons are hyperphagic, obese, and display increased levels of basal NPY expression although AgRP expression remains relatively constant (46). Whatever the precise role of the STAT3 signal, the significance of other transcription factors including the phosphoinositide 3 kinase (PI3K)-regulated transcription factor of the forkhead-family, FOXO 1 in the regulation of AgRP/NPY neurons cannot be underestimated.

SHP-2 is another SH2 domain containing protein which binds to an intracellular tyrosine (Y985) residue phosphorylated by JAK2 and activates the extracellular signal–regulated kinase pathway (47,48). Other pathways known to be activated in response to ObRb activation include the STAT5 (49,50), mitogen-activated protein kinase (24,41), 5′-AMP-activated protein kinase (51), and PI3K (52) pathways. Our understanding of the importance of these individual pathways to the neuroendocrine functions of leptin, however, still remains superficial. The mitogen-activated protein kinase pathway may play a role in the regulation of linear growth and reproductive function whereas PI3K signaling is believed to contribute to energy homeostasis (43).

Leptin receptor stimulation mediates the tyrosine phosphorylation of insulin receptor substrate proteins by JAK2, independently of tyrosine phosphorylation sites on the ObRb (53). Insulin receptor substrate in turn recruits, phosphorylates, and activates PI3K, leading to an accumulation of its product phosphatidylinositol 3,4,5-triphosphate. Phosphatidylinositol 3,4,5-triphosphate activation leads to sequential activation of 3-phosphoinositide-dependent protein kinase 1 and AKT culminating in the inhibition of FOXO 1, which is known to inhibit POMC expression. Evidence supporting the role of PI3K signaling in energy homeostasis includes the following observations: (i) mice lacking insulin receptor substrate 2 are hyperphagic and obese (54), (ii) pharmacological blockade of PI3K activity blocks the anorectic effect of leptin (53), (iii) chronic activation of the P13K pathway, by the deletion of an inhibitory regulator PTEN leads to diet-induced obesity (55), and (iv) mice lacking 3-phosphoinositide-dependent protein kinase 1 in POMC-expressing neurons display an obese phenotype which can be reverted by inhibiting FOXO 1 activation (56). A role for PI3K signaling has also been proposed in leptin-mediated stimulation of sympathetic outflow (57). Importantly, the PI3K pathway is also the major intracellular pathway activated by insulin receptor signaling, making this a crucial stage at which leptin and insulin may coordinately act to control energy homeostasis. The insulin–P13K pathway hyperpolarizes POMC neurons via adenosine triphosphate sensitive K^+ channels, thereby reducing their sensitivity to leptin (55). This may be an important mechanism by which overfeeding leads to impaired leptin sensitivity.

CELLULAR LEPTIN RESISTANCE

The JAK/STAT pathway is subject to negative feedback regulation by the SOCS family of proteins (58–60). In particular,

leptin signaling via Y1138 and STAT3 induces the expression of SOCS3 mRNA in the hypothalamus, which has been shown to inhibit the phosphorylation and activation of JAK2 and Y985 (61–63). In fact, over expression or over activation of SOCS3 is a proposed mechanism for leptin resistance, particularly in diet-induced obese states (64). In other words, adiposity and increased levels of leptin in obesity enhance SOCS3 expression which serves to dampen leptin receptor signaling, resulting in a nonlinear relationship between leptin concentration and signaling response.

Reducing SOCS3 activity in mice either by neuron-specific conditional knockouts or heterozygous global knockouts enhances both STAT3 expression and the weight reducing effects of peripherally administered leptin (65,66). Furthermore, genetically engineered mice (l/l), with a mutation in a key tyrosine residue (Y985) responsible for the activation and recruitment of both SOCS3 and SHP-2 display reduced feeding and adiposity, increased STAT3 activation and increased sensitivity to leptin (41,67). Although the loss of SHP-2 recruitment in these mice may reduce anorectic effect, it is believed that this is more than compensated by the loss of the inhibitory signal from SOCS3 hence resulting in a net anorectic effect. Nevertheless, there is conflicting evidence regarding the exact role of SOCS3 as its mRNA levels have been found to be similar in both l/l and wild-type mice, leading to the presumption that SOCS3 alone cannot mediate the entirety of the inhibitory effects of the Y985 residue. Interestingly, the s/s mouse described earlier also displays some unique features compared to wild types and db/db mice, including enhanced immune function, increased linear growth, and reduced attenuation of JAK2 and STAT3 signaling in response to prolonged receptor stimulation (43,68–70). This is possible by virtue of the loss of the inhibitory signal from SOCS3.

Another molecule which has attracted interest for its role in the negative regulation of leptin signaling by dephosphorylating JAK2 is protein-tyrosine phosphatase 1B (PTP1B) (71–73). Although studies have confirmed that neuron-specific or global PTP1B knockouts increase leanness and leptin sensitivity, PTP1B expression and activity remain independent of leptin or body fat mass, highlighting that this molecule may not directly contribute to perturbations of leptin signaling observed in obesity (71,73–75).

It appears, therefore, that leptin-responsive neurons implement rather complex mechanisms of controlling their own sensitivity to leptin. But what is the physiological and evolutionary function of this? Interestingly it has been suggested that leptin resistance may be a mechanism of helping to detect energy flux (the rate of energy expenditure) rather than the current energy stores alone. The determination of energy flux is a more accurate indicator of the true energy balance and the future energy requirements of an organism. For example an organism may still be in negative energy balance despite having high energy/fat stores during pregnancy, illness, or intensive exercise. A system which dampens leptin responses in high energy states is more sensitive to negative energy flux as it is less likely to be potentially disastrously overwhelmed by strong anorexic signals.

The concept of reversing central leptin resistance using pharmacological agents which target the negative regulators of leptin signaling is promising. However, there exists a difficulty in these molecules that are ubiquitously expressed both centrally and peripherally and play important roles in a number of signaling processes. Any drug designed to target either SOCS3 or PTP1B for in order to enhance STAT3 activation in hypothalamic centers concerned with energy homeostasis will disrupt many other signaling properties of these proteins unless it acts highly specific. The critical importance of SOCS3 for example is confirmed by the finding that homozygous SOCS3 knockout mice die *in utero* (76). Similarly, although PTP1B knockout mice are lean and resistant to diet-induced obesity, the enzyme is believed to carry important roles in cell cycle regulation, integrin and epidermal growth factor receptor signaling, and responses to cell stress (77). Another potential means of increasing leptin sensitivity is to enhance the membrane expression of its receptors. As earlier mentioned surface OB-R expression is negatively regulated by the OB-R gene–related protein. Silencing of this transcript enhances both hypothalamic OB-R expression and signaling as well as conferring resistance to diet-induced obesity. Interestingly, despite the overall change in membrane expression of the OB-R, silencing of the OB-GRP predominantly influences STAT3 expression without having an effect on P13K expression. Consequently, targeting this pathway may not necessarily alleviate deranged glucose homeostasis (29).

LEPTIN AND SYNAPTIC PLASTICITY

It is becoming clear that in addition to engaging classical "neuropeptide/receptor" systems within the brain, leptin also rapidly modifies synaptic connections between neurons. Pinto *et al*. elegantly demonstrated that leptin can induce changes in the balance of excitatory and inhibitory synapses to both POMC- and NPY-expressing neurons (78). In this study, a whole cell patch clamp technique was used to demonstrate that ob/ob mice have increased inhibitory postsynaptic currents on POMC-expressing neurons and increased excitatory postsynaptic currents on NPY-expressing neurons compared to their wild-type littermates. These differences correlated with morphologic differences of the ratios of inhibitory and excitatory synapses projecting to the two groups of neurons. Astonishingly, leptin treatment of ob/ob mice induced a rapid normalization of the balance of synaptic inputs to these two groups of neurons within just 6 h. Although this re-wring of synaptic inputs occurs over a much shorter time course than the observed change in feeding behavior, its importance to normal energy homeostasis is highlighted by the fact that another appetite regulatory hormone, ghrelin, has a similar effect (79).

In addition to its role in synaptic plasticity, leptin has also been implicated as a neurotrophin, and may be responsible for the development during the neonatal period of specific circuitry both

within the arcuate and between the arcuate and other hypothalamic centers involved in energy homeostasis including the paraventricular nucleus (PVN), lateral hypothalamic area, and dorsomedial hypothalamic nucleus. Perturbed arcuate connectivity can be reversed in ob/ob mice by administering leptin perinatally, but not in adulthood (80). These data support the idea that a perinatal leptin surge acts as a developmental signal to promote arcuate connectivity and the formation of pathways which control energy homeostasis. Beyond its role in the hypothalamus, leptin is also proposed to play an important role in long-term potentiation, which underlies learning and memory within the hippocampus (81,82).

A likely postsynaptic model for leptin action is it stimulates POMC and cocaine and amphetamine–related transcript neurons by depolarization through a cation channel, while simultaneously inhibiting NPY- and AgRP-producing neurons (83). Inhibitory GABAergic synapses project from NPY to POMC neurons, such that POMC neurons are also in part activated through disinhibition. A recent electrophysiological study has demonstrated reciprocal effects of leptin on voltage-gated calcium currents in POMC- and NPY-expressing neurons. Leptin signaling increases the maximal current in POMC-expressing neurons while reducing the maximal current in NPY neurons. Furthermore, it appears that these effects may be dependent on JAK2–mitogen-activated protein kinase pathways in NPY neurons and on JAK2–PI3K pathways in POMC neurons (84).

LEPTIN ACTION BEYOND THE ARCUATE

Although the evidence implicating the arcuate as a first-order mediator of leptin's actions is both compelling and substantial, it by no means contributes to the totality of leptin's effects on energy homeostasis. Targeted deletion of the leptin receptor in POMC neurons or its restoration in the arcuate of db/db animals only modestly affects body weight and is not sufficient to alone explain the obesity of POMC-deficient or db/db animals (85,86). Similarly, although s/s mice are markedly obese and hyperphagic, targeted deletions of STAT3 from arcuate POMC and AgRP/NPY neurons only result in a mild obese phenotype (43,44,87). It, therefore, seems likely that leptin acts to control energy homeostasis through discrete populations of ObRb-expressing neurons, the precise functions of many of which remain to be fully characterized. Among the hypothalamic targets of leptin are the ventromedial nucleus, dorsomedial nucleus, lateral hypothalamus, and the PVN (18,28). Although our understanding of the individual functions of each of these areas, however, remains patchy two areas which have attracted recent interest for their roles are the ventromedial nucleus (VMH) and PVN.

It has been known for some time that lesions of the VMH in mice promote hyperphagia and obesity. More recently it has been demonstrated that a population of ObR-expressing neurons in the VMH contributes to satiety via excitatory projections to the arcuate, the density of these projections being dynamically regulated by leptin concentration, demonstrating the exquisite sensitivity of the VMH to leptin (88). In 2006, the importance to normal energy homeostasis of a subpopulation of VMH ObR-expressing neurons co-expressing the transcription factor SF-1 was demonstrated by the observation of obesity in mice following selective deletion of the LRb in these neurons using cre/lox technology (89). The JAK/STAT pathway is probably an important mediator of leptin's actions in these neurons, as targeted deletions of SOCS3 improve both leptin sensitivity and glucose homeostasis (90).

Similarly, lesions of the PVN or the deletion of a single allele of Sim 1, a gene encoding a transcription factor necessary for the normal development of the PVN, produce obesity in both mice and humans (91–93). Perhaps more interestingly, the isolated restoration of the MC4R in the PVN of MC4R null mice completely corrects their hyperphagia and obesity despite the lack of the MC4R within the arcuate (94). In addition to containing a neuronal population expressing the ObR, the PVN also receives dense projections from ObRb-expressing neurons within the arcuate hence allowing for direct and indirect regulation by leptin. A transcriptional profiling study of laser-captured PVN in ad libitum fed mice and fasted mice receiving either leptin or sham treatment has revealed a number of genes which may be regulated by leptin at this site (95). Given leptin's role in synaptic plasticity, it is interesting that among the top 15 genes positively regulated by leptin, 5 were shown to be implicated in synaptic function or plasticity, 4 of which are implicated in synaptic maintenance and development (Basign, Gap43, ApoE, and Gabrap) whereas the final gene, Bsg may coordinate synaptic compartmentalization and strength.

Furthermore, pathway analysis, to reveal groups of functionally related genes, revealed that >9% of the genes positively regulated by leptin play important roles in protein synthesis which is an integral part of synaptic function and remodeling. Moreover, this analysis also revealed genes encoding proteins involved in oxidative phosphorylation, particularly complex 1 proteins regulating ubiquinone biosynthesis, to be the predominant gene set positively regulated by leptin (95). These data suggest that leptin may influence both synaptic function and cellular metabolism, such that fasting produces a switch from oxidative to nonoxidative metabolism which is reversed by leptin. As numerous studies have reported decreased oxidative phosphorylation gene expression in the skeletal muscle of patients with type 2 diabetes, a condition that is associated with obesity, the possibility arises that oxidative phosphorylation may be a unifying central and peripheral mechanism for controlling body weight (96,97). Similarly derangements of oxidative phosphorylation gene expression may contribute both to obesity and diabetes.

A growing body of evidence also supports a role for extrahypothalamic areas, including brainstem nuclei such as the nucleus tractus solitari (NTS) as target sites for leptin signaling (20,21). The nucleus tractus solitari contains ObR-expressing neurons and also integrates

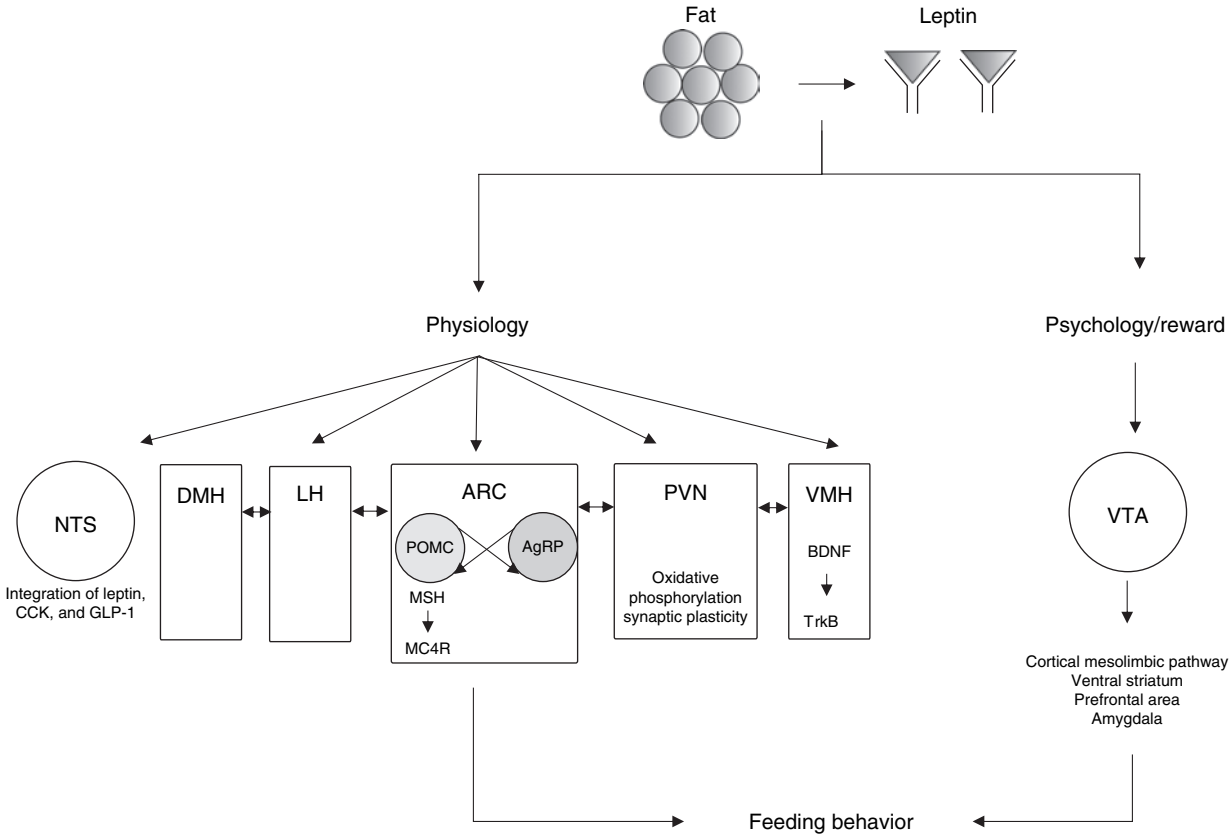

Figure 2 A summary of the physiological and psychological mechanisms by which leptin influences satiety and feeding behavior. Leptin determines the physiological drive to eat predominantly at hypothalamic sites including the paraventricular nucleus (PVN), arcuate nucleus (ARC), dorsomedial hypothalamic nucleus (DMH), lateral hypothalamus (LH), and the ventromedial nucleus (VMH). The brainstem nucleus tractus solitari (NTS) plays an important role as an integrator of hormonal signals including leptin, CCK, and glucagon-like peptide-1 (GLP-1). Leptins effects on reward occur through the mesolimbic dopaminergic pathway, beginning at the ventral tegmental area (VTA) of the brainstem. AgRP, agouti-related protein; POMC, proopiomelanocortin.

multiple inputs from the gut including vagal afferents, CCK, and glucagon-like peptide-1. The actions of leptin at the brainstem are also proposed to contribute to the perception of reward (Figure 2).

LEPTIN AND REWARD

The decision of whether or not to eat is a very complex process that is governed not only by physiological signals, but also by a multiplicity of other factors including the psychological forces that determine reward (98). This is easily illustrated by the all too familiar paradigm of overindulging on particularly appetizing food, despite feeling full.

In fact, recent evidence highlights that in addition to its role in influencing the physiological component of satiety leptin, it may also regulate the hedonic component of satiety by determining the perception of reward associated with feeding. This action of leptin probably occurs at the level of the mesolimbic dopaminergic system, which appears to operate independently of connectivity with the arcuate. Perhaps this system may explain the weight gain commonly induced by antipsychotic drugs, which act as mixed dopamine receptor antagonists (99). Leptin receptors are highly expressed on dopaminergic neurons within the VTA of the brainstem which project to brain areas including the striatum, amygdala, and prefrontal cortex (98,100–102). Interestingly, the lateral hypothalamus is likely to be an important regulator of this pathway as it contains groups of orexin- and melanocyte-concentrating hormone containing neurons modulated by leptin signaling which project to the ventral tegmental area and the striatum, respectively (103,104). Leptin inhibits the activity of orexin neurons while simultaneously inhibiting the expression of melanocyte-concentrating hormone, the combined effect of which may be to modulate the mesolimbic dopamine signal and reduce food intake (101,105). In support of leptin's inhibitory effect on reward seeking behavior, leptin administration has been shown to decrease the rate of rewarding self-stimulation in the perifornical area of the lateral hypothalamus in nutritionally deficient states (106). Furthermore, the lateral hypothalamus has also been shown to comprise a population of ObR-expressing neurons which project to the ventral tegmental area, allowing leptin to both directly and indirectly modulate this area (107).

Functional imaging studies have also implicated an important role for leptin in the modulation of striatal activity. The activity of the accumbens and caudate nuclei (ventral striatum) measured using functional magnetic resonance

imaging and correlated with subjective measures of food liking in the leptin-deficient fed and fasted states. When these individuals were treated with leptin, food liking ratings were globally reduced, and correlated with striatal activity in only the fasted and not the fed state. These data support a role for leptin in dampening the salience or reward associated with feeding (108). Similar functional magnetic resonance imaging studies have also highlighted the potential for gut hormones such as ghrelin and peptide YY to regulate feeding reward through the mesolimbic system (109,110). Interestingly, in contrast to leptin's effects predominantly on the ventral striatum, ghrelin tended to influence predominantly dorsal striatal regions indicating possible differential sites of action.

The existence of a physiological system for modulating feeding behavior based on perceived reward is puzzling but may provide an adaptive advantage in times of food shortage, allowing excessive food consumption, and energy storage beyond satiety. In the current global obesity pandemic, however, it seems that the ability of leptin and other appetite regulatory hormones to dampen reward is overwhelmed by the excessive availability of highly rewarding food. Reward may therefore be important factor in the inception of obesity.

SUMMARY

Although we have alluded to the fact that a vast number of peripheral and central signals contribute to energy homeostasis, in this article we focus specifically on the leptin signal as an exemplary model of body weight control. We review the evidence challenging the classic view that leptin acts primarily at the ARC to control satiety through the melanocortin pathway. Instead an updated picture is presented whereby leptin acts through a distributed network of intercommunicating neurons to control both the physiological and hedonic determinants of satiety.

DISCLOSURE

The authors declared no conflict of interest.

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