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CNS targets of adipokines

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Abstract

Our understanding of adipose tissue as an endocrine organ has been transformed over the last twenty years. During this time a number of adipocyte-derived factors or adipokines have been identified. This paper will review evidence for how adipokines acting via the central nervous system (CNS) regulate normal physiology and disease pathology. The reported CNS-mediated effects of adipokines are varied and include the regulation of energy homeostasis, autonomic nervous system activity, the reproductive axis, neurodevelopment, cardiovascular function, and cognition. Due to the wealth of information available and the diversity of their known functions, the archetypal adipokines leptin and adiponectin will be the focused on extensively. Other adipokines with established CNS actions will also be discussed. Due to the difficulties associated with studying CNS function on a molecular level in humans, the majority of our knowledge, and as such the studies described in this paper, comes from work in experimental animal models; however, where possible the relevant data from human studies are also highlighted.

Didactic Synopsis

Major Teaching Points:

1. In addition to storing excess energy as triglyceride, adipose tissue is an important endocrine organ secreting factors called adipokines into the circulation that act on their receptor targets in distant tissues, including the CNS.

2. Leptin is a key adipokine which acts on target receptors throughout the brain to signal how much energy the body has stored.

    a. Obesity (excess adipose tissue) is associated with high levels of circulating leptin.
    b. Reduced circulating leptin is a key signal for the activation of CNS pathways which promote weight gain, including increased food intake and reduced energy expenditure.
    c. Leptin acting in the brain also regulates the activity of other neuroendocrine axes including the reproductive axis and the thyroid hormone axis, and can also regulate cardiovascular function.

3. Other adipokines that act in the CNS to modulate physiological processes include adiponectin, resistin, apelin, visfatin and adipocyte-derived cytokines.

Introduction

In the past twenty years there has been a transformation in our understanding of adipose tissue as an endocrine organ. Numerous adipocyte-derived cell signaling proteins, or adipokines, have been identified that have critical functions in normal physiology and pathophysiology. The goal of this paper is to provide an overview of the site and mechanism of action of some of the key adipokines in the central nervous system (CNS), focusing on those with the most well defined and widespread CNS actions. The sheer diversity and number of adipokines that have been identified means that it would be beyond the scope of this review to feature them all, and any omissions should not be taken as indication that these factors are not considered important but as a reflection of a desire to provide a comprehensive overview of the adipokines that have the most diverse and currently well-characterized CNS actions, specifically leptin and adiponectin. Due to the difficulties associated with studying CNS function on a molecular level in humans, the majority of our knowledge, and as such the studies described in this paper, comes from work in experimental animal models; however, where possible the relevant data from human studies are also highlighted.

A list of abbreviations used in this paper can be found in **table 1**.

Leptin

Leptin is arguably the prototypical adipokine. Originally identified in 1994 as the product of the *obese* (*ob*) gene, leptin is evolutionarily conserved across mammalian and non-mammalian species (637). The white adipose tissue (WAT) expression of the *ob* gene is regulated by energy status, being upregulated by increased adiposity associated with obesity (positive energy balance) (195, 240, 366, 376) and decreased by negative energy balance associated with fasting (195, 569). There is also evidence that leptin (*ob*) gene expression in WAT is diurnally regulated (498). Leptin is secreted into the blood where, in mammals, circulating levels are a reflection of the amount of WAT stored (377): the more WAT stores, the more circulating leptin. Indeed, reduced levels of circulating leptin associated with weight-loss is a key signal for the activation of CNS pathways which promote weight gain, including increased food intake and reduced energy expenditure (313, 475, 489). The discovery of leptin gave great hope for the development of a potential specific therapeutic target for obesity. Indeed, early promising studies demonstrated that exogenous administration of leptin into lean and diet-induced obese (DIO) rodents reduces food intake and body weight (83, 235, 452). However, evidence rapidly emerged that the high circulating levels of leptin associated with obesity were both a cause and consequence of resistance to the effects of the hormone on appetite and metabolism (195).

Even before the cloning of leptin evidence suggested the existence of an adipose-derived circulating factor that could regulate feeding behavior by acting in the brain (121, 278). After the

cloning of leptin, this was supported by data indicating that radiolabeled leptin bound at high-levels in the hypothalamus of the rodent brain and that exogenous leptin treatment normalized the elevated hypothalamic neuropeptide Y (NPY) gene expression in leptin-deficient obese *ob/ob* mice (539). The importance of the hypothalamus as a key site of leptin action was confirmed when the leptin receptor was identified and cloned in 1995 (555).

Due to the critical importance of adequate energy reserves for numerous physiologic processes one of the key integrative roles of leptin, which will be described in more detail in the sections below, is as an indicator of sufficient energy availability/reserves, as the circulating levels of this hormone drop rapidly during fasting which in turn modulates the activity of a number of neuroendocrine axes (8).

Leptin receptor signaling

There are six alternatively spliced forms of the leptin receptor (Ob-Ra-f) that have been identified (345, 592). These are all single transmembrane spanning proteins, with the exception of Ob-Re which is predicted to be a soluble protein (345). Of these the full-length or long-form receptor (Ob-Rb), the only variant with a long intracellular domain sufficient for downstream signaling, is believed to be the principal signaling form (41, 214, 345). Ob-Rb is a type 1 cytokine receptor. Upon leptin binding to the extracellular domain of the receptor dimer, Janus kinase (JAK) 2 is activated, resulting in phosphorylation of the intracellular domain of receptor at three tyrosine residues – Tyr985, Tyr1077 and Tyr1138, each of which mediate distinct downstream signaling events (**figure 1**): 1) Phosphorylation of Tyr985 resulting in recruitment of Src-homology 2 domain-containing phosphatase 2 (SHP2/PTPN1) leading to activation of the extracellular signal-regulated kinases (ERK) signaling cascade (27, 89, 357); 2) Phosphorylation of Tyr1077 resulting in recruitment of the transcription factor signal transducer and activator of transcription (STAT) 5 (219) and 3) Phosphorylation of Tyr1138 resulting in recruitment of the transcription factor STAT3 (27, 357, 579). Indeed, activation/phosphorylation of STAT3 (pSTAT3) is a commonly used experimental marker of leptin receptor activation/activity *in vivo* and *in vitro* (579). Activation of leptin receptor signaling also can result in activation of the phosphatidylinositol 3-kinase (PI3K) pathway via insulin receptor substrate (IRS) proteins (160, 480). In the course of normal homeostasis, negative feedback inhibition of Ob-Rb signaling is provided by suppressor of cytokine signaling (SOCS) 3 (53, 55, 164) binding at Try985 and PTP1B acting at JAK2 (106, 628). Genetic technologies have enabled determination of the relative physiological significance of activation of different signaling pathways downstream of the leptin receptor. These will be addressed in each of the relevant sections below.

In the rest of the document any reference to “leptin receptor is signaling” typically is relating to the full-length or long-form receptor (Ob-Rb) unless stated otherwise.

Leptin receptor expression in the CNS

Within the rodent brain early *in situ* hybridization studies revealed that Ob-Rb mRNA is highly expressed in the hypothalamus (398) and that this receptor is activated by exogenous leptin treatment (579, 609). Subsequent studies have revealed a more widespread distribution of leptin receptors across the CNS (180) fitting with its diverse functions (**table 2**). *In situ* hybridization studies have revealed a distinct CNS distribution of the different leptin receptor isoforms, with Ob-Ra and Ob-Rb being the principal forms expressed in the hypothalamus and OB-Ra, OB-Rc and OB-Rf predominating in the choroid plexus (226). The use of transgenic technologies has enabled animals with fluorescently tagged leptin receptors to be created, which has facilitated detailed studies mapping CNS sites of leptin receptor expression and their downstream targets to be mapped (449, 508).

Although outside of the CNS, of relevance to topics to be discussed later in this review, leptin receptors are also expressed on the nodose (inferior) ganglion of the vagus nerve (76, 79).

Leptin receptors are found on a variety of different neuronal populations in the brain (**table 2**). This widespread distribution contributes to its role as a neuromodulator of numerous neuroendocrine and non-neuroendocrine pathways, which will be described in more detail later in this review. Specific deletion of leptin receptors from different neuronal populations has differential effects on physiology which will be described in the relevant sections below. While the majority of work on CNS targets of leptin has focused on neurons, leptin receptors are also found on non-neuronal cells in the CNS including astrocytes (110, 272, 442), microglia (455), tanycytes (23), endothelial cells (54, 217), and choroid plexus epithelial cells (146, 398).

Leptin entry into the brain

In order to mediate its effects via the centrally expressed receptors leptin needs to enter the CNS. The blood-brain barrier (BBB) functions to protect the brain from fluctuations in the body and helps to maintain the microenvironment in the CNS. Made up of endothelial cells which line the cerebral microvessels, the function of the BBB is regulated by the interaction of endothelial cells with other cellular components of the ‘neurovascular unit’ including astrocytes and neurons (1). The BBB regulates movement of substances including nutrients and hormones, including leptin, in and out of the brain.

Proximal to the cerebral ventricles are circumventricular organs within the brain. Whist there is some debate surrounding the number of circumventricular regions in the mammalian brain, major sites include the median eminence (ME) and adjacent neurohypophysis, organum vasculosum lamina terminalis, subfornical organ (SFO) and the area postrema (AP) (167). In these small regions of the brain, the BBB of cerebral microvessels is more readily permeable, facilitating communication between the brain and cerebrospinal fluid (CSF), and factors circulating in the blood. Evidence suggests that portions of the ME within the hypothalamus lack the normal protein components of the BBB, suggesting an absence of the normal barrier in this area (71, 426). Of significance to the CNS actions of leptin, data indicates that a population of hypothalamic arcuate (ARC) neurons adjacent to the ME project outside of the BBB and are able to rapidly respond to peripherally administered leptin, as assessed by expression of pSTAT3 (185). As such, circumventricular organs are critical sites of entry for adipokines in the brain and are important for their centrally mediated effects (199).

Understandably, due to the importance of the hypothalamus in the regulation of energy homeostasis, the ME has been the focus of most studies examining the entry of leptin into the brain. However, it is important to note that the choroid plexus (146), SFO (528) and AP (250, 400) are also sites at the blood-brain and/or brain-CSF interface that are also directly responsive to leptin and may mediate some of its CNS effects.

The CNS is the principal site of action of leptin mediating many of its known physiological effects. Early studies, shortly after its cloning, tracing the entry of radiolabeled leptin into the brain indicated that 75% of circulating ^{125}I labelled leptin enters the brain (32). Major sites of entry of leptin in to the CNS include the choroid plexus and ME (32, 146). Leptin receptors are expressed on cerebral endothelial cells of both rodents and humans (54, 217). While obesity is associated with increased circulating leptin, leptin transport into the brain and subsequent CSF levels of leptin are not concomitantly increased, suggesting that leptin transport into the brain is saturable (77, 87). This saturable transport mechanism is one proposed cause of leptin-resistance associated with obesity, which will be discussed in greater detail later in this review. In addition to obesity, a number of factors and physiological states have been shown to influence leptin transport into the CNS, shown in **table 3**.

CNS Leptin Resistance

CNS leptin-resistance is characterized by a loss of physiological responsiveness to leptin despite the high circulating levels seen in both obese individuals and animals (without congenital leptin deficiency), and was recognized early after the leptin gene was first cloned (195). While obesity is associated with chronic elevations in circulating leptin (235), it is debated whether leptin

resistance is a cause or consequence of obesity (416), or quite likely both. Within the hypothalamus, there is evidence to suggest that leptin-resistance associated with diet-induced obesity is more pervasive in the ARC than other nuclei, including the ventromedial hypothalamus (VMH), dorsomedial hypothalamus (DMH) and lateral hypothalamic area (LHA) (387, 413), likely due to its proximity to the ME causing this region to be readily exposed to the high circulating levels of leptin and proinflammatory cytokines derived from WAT of obese animals. Interestingly, the ventral tegmental area (VTA), which is a key component of the dopaminergic reward pathway, also shows leptin-resistance in response to diet-induced obesity in rats (387). Improving CNS leptin sensitivity is seen as a potential therapeutic target for metabolic disease, and as such there is extensive interest in understanding the molecular mechanisms behind this phenomenon. A combination of defective leptin signaling and impaired entry of leptin into the CNS are both thought to be contributing factors (170).

Recent evidence suggests that mimicking obesity-associated elevations in circulating leptin by chronically infusing leptin into wild-type lean mice is not sufficient to induce leptin resistance regardless of the nutritional state of the animal (fed/fasting) (476). This indicates that other pathophysiological changes associated with obesity are likely contributing to the development of leptin-resistance. Candidates include inflammation and endoplasmic reticulum (ER) stress.

Diet-induced obesity causes inflammation and ER stress in the brain, with the hypothalamus being the predominantly studied region in this regard (143, 438, 561, 635). Supporting a potential role of ER stress as a causative factor in the development of central leptin-resistance, induction of ER stress using genetic and pharmacologic tools is sufficient to induce leptin-resistance *in vitro* (438) and *in vivo* within the hypothalamus (438, 608) as assessed by a reduction in leptin induced phosphorylation of STAT3. This is supported by the finding that treatment with compounds that enhance ER function, 4-phenyl butyrate (PBA) and tauroursodeoxycholic acid (TUDCA), improves leptin-sensitivity in genetic (*ob/ob*) (438) and diet-induced (608) mouse models of obesity.

In common with inflammatory signaling, induction of hypothalamic ER stress activates the nuclear factor-kappa B (NFκB) signaling pathway and pharmacological inhibition of ER stress reduces high-fat diet-induced hypothalamic activation of the NFκB signaling cascade (635). This suggests that activation of NFκB signaling is an important downstream mediator of ER stress in this context. In the same study, virally mediated activation of NFκB signaling in the hypothalamus was sufficient to induce leptin-resistance in lean mice while inhibition of NFκB signaling, specifically in agouti-related protein (AgRP) neurons of the medial basal hypothalamus, reduced high-fat diet induced weight gain and leptin-resistance (635). Interestingly, in contrast, chronic activation c-Jun N-terminal kinases (JNKs) but not NFκB signaling specifically in AgRP neurons is sufficient to

stimulate obesity and leptin resistance (572), indicating that different hypothalamic neuronal populations may have distinct roles in the response to inflammation. Upstream of NFκB signaling, the adaptor protein MyD88 and its associated receptor toll-like receptor 4 (TLR4) are important for mediating leptin-resistance associated with high-fat feeding by direct central administration of saturated fatty-acids (18, 317).

As described above, in the course of normal homeostatic leptin signaling, negative feedback inhibition of Ob-Rb signaling is provided by SOCS3 (53, 55, 164) and PTP1B binding (106, 628). Obesity is associated with elevated hypothalamic expression of both SOCS3 (53) and PTP1B (629) and genetic deletion of SOCS3 and PTP1B binding from the CNS or specifically from proopiomelanocortin (POMC) neurons in the hypothalamus protects against high-fat diet-induced leptin-resistance (44, 307, 405). Together these findings suggest that SOCS3 and PTP1B may also play a role in the development of obesity associated leptin-resistance. Expression of SOCS3 (536) is induced via transcriptional activation of STAT signaling; however, in the case of obesity leptin induced phosphorylation of STAT3 is decreased (170), which suggests that alternative (non-STAT3 mediated) pathways are likely to be contributing to the upregulation of SOCS3 in this context. Additionally, expression of PTP1B is increased by inflammation (629) and ER stress (443) via the activation of NFκB signaling suggesting a potential mechanistic link between inflammatory signaling and ER stress and the development of CNS leptin-resistance. The potential molecular signaling mechanisms underlying the development of CNS leptin-resistance are summarized in **figure 1**.

One of the challenges in studying mechanisms of leptin-resistance in experimental animal models is that intervention (genetic or pharmacological) associated improvements in leptin resistance are typically associated with weight-loss or a failure to gain weight when exposed to an obesogenic diet; thus, it often is difficult to differentiate whether the reduced leptin-resistance is due to the reduced weight gain or *vice versa.* These challenges are elegantly discussed in a 2010 review by Myers and colleagues (416).

Impaired entry into the brain has been proposed as another potential mechanism underlying CNS leptin resistance (170). As described above, a recent study by Balland and colleagues (23) has demonstrated that intact leptin receptor signaling in tanycytes is critical for leptin entry into the CNS and that this is defective in obese animals (both diet-induced and genetic). This provides a molecular basis linking both underlying tenets of CNS leptin resistance: defective leptin signaling and impaired entry of leptin into the CNS. Whether similar pathological stimuli, namely inflammation and ER stress, impair tanycyte mediated leptin transport into the CNS remains to be fully determined.

Importance of leptin in development of neural circuitry

A number of pieces of evidence support an important role for leptin in the development of neural circuitry. Early studies in obese mice with congenital leptin deficiency (*ob/ob* mice) showed that these animals have fundamental differences in the macrostructure of their brains, including decreased brain weight and volume, and impaired organization of dendrites within the hypothalamus (48, 49). The reduction in brain weight in *ob/ob* mice can be reversed by leptin treatment from 4-weeks (5, 541), suggesting a key role for leptin in brain development. Although rare in humans, congenital leptin deficiency is associated with changes in brain size and structure which can be reversed, at least, in part by leptin treatment (365, 389).

Leptin receptors are expressed in the brain (leptomeninges and choroid plexus) from early in embryonic development [E13.5 in the mouse (262)]. There is a post-natal surge in leptin levels in rodents, independent of adipose mass, starting at post-natal day 4 and peaking at post-natal day 10, which does not concomitantly impact energy homeostasis but is believed to act as a developmental cue (7). In mice, hypothalamic circuitry key for the regulation of energy homeostasis is not fully developed at birth but the intra-hypothalamic and extra-hypothalamic projection develops rapidly becoming mature by around post-natal day 16-18 (65, 66). The development of the intra-hypothalamic projections from the ARC to the paraventricular nucleus of the hypothalamus (PVH) are attenuated in mice with defective leptin signaling [leptin-deficient *ob/ob* mice (66) and *db/db* mice with dysfunctional leptin receptors (65)], which may provide a neuroanatomic basis for many of the neuroendocrine abnormalities seen in these animals. Mimicking the post-natal leptin surge by leptin injection into the leptin-deficient *ob/ob* mice was sufficient to partially restore the ARC to PVH neuronal projections supporting a critical role for the post-natal leptin surge in the development of hypothalamic neuroendocrine circuitry (66). Indeed, *in vitro* experiments in organotypic hypothalamic slices from post-natal brains demonstrated leptin to be a potent neurotrophic factor (66). Administration of leptin in adult animals was not able to restore these critical projections, emphasizing the importance of leptin during this key stage in CNS development. This is further strengthened by data indicating that inhibiting the neonatal leptin surge using a leptin antagonist in wild-type rats alters hypothalamic gene expression of neurotrophic factors and intermediate filament proteins (nestin and vimentin) (367, 395), implicated in growth and survival of neural cells. Interestingly, these effects appear to be sexually dimorphic during the neonatal period and also with respect to their phenotypic manifestations in the adult animal (367, 395).

POMC and AgRP neurons of the ARC, which are critical for the regulation of energy homeostasis (530), send projections to the PVH. In line with previous studies, leptin deficient *ob/ob* mice show reduced AgRP and POMC fiber density (as assessed by α-melanocyte stimulating hormone [αMSH] immunoreactivity) in regions of the PVH containing both neurosecretory and pre-

autonomic neurons (68). Significantly, post-natal leptin treatment in leptin-deficient *ob/ob* mice partially restores ARC to PVH projections of AgRP but not POMC neurons in regions of the PVH containing pre-autonomic neurons (68), pointing to a differential regulation of the development of these important neuronal pathways by leptin. In contrast, perhaps surprisingly, leptin treatment was not able to regulate either POMC or AgRP inputs on to PVH neurosecretory neurons in *ob/ob* mice, indicating a differential role of leptin in the development of hypothalamic autonomic compared with neurosecretory circuitry. Indeed, these anatomical findings are supported by physiological data indicating that *ob/*ob mice treated with leptin from post-natal day 4-14 show a modest improvement in the phenotypic manifestations of their autonomic deficits including a modest reduction in food intake, body weight, adipocyte size and thermogenic response to cold exposure (68). In addition to impacting neurons, recent data suggests that post-natal leptin treatment can also impact the proliferation of hypothalamic astrocytes, which may in turn influence synaptic function and connectivity within the hypothalamus during this critical developmental stage (491).

In the absence of congenital alterations in leptin-signaling, acquired early disruptions in leptin signaling associated with leptin-resistance caused by post-natal over-nutrition [small litter size] (67, 215), or neonatal exposure to obesity or diabetes (537) also impacts development of the hypothalamic circuitry regulating energy homeostasis.

The development of mice with defects in specific signaling pathways downstream of leptin receptor activation has enabled genetic dissection of the leptin receptor signaling pathways mediating the actions of leptin on hypothalamic development. Leptin-induced activation of STAT3 and ERK signaling appear to be important for control of projections from ARC neurons to the PVH (64).

In addition to hypothalamic development there is evidence to suggest that leptin signaling may also be important for the development of other key circuits in the brain including those regulating cognition and emotion. Absence of leptin-signaling in *db/db* or *ob/ob* mice is associated with complex changes in response to neurobehavioral testing characteristic of memory deficits, depression and an altered anxiety profile (361, 516, 616). Alterations in these behavioral paradigms can be representative of alterations in hippocampal function. Indeed, further examination has revealed that *db/db* mice have reduced dendritic spine density in dentate gyrus (544), CA1 and CA3 neurons (147) within the hippocampus which may account for the neurobehavioral deficits seen in these animal models. Furthermore, congenital defects in leptin receptor signaling in both *db/db* mice and Zucker rats cause impaired hippocampal long-term potentiation (LTP) (212, 361). Together these data suggest an important role for leptin in synapse development in the hippocampus which impacts its function. A role for leptin in modulating hippocampal function will be discussed further later in this review.

Effects of leptin on energy and glucose homeostasis

The most well described physiologic roles of leptin are in the regulation of energy homeostasis. Leptin impacts energy homeostasis on multiple levels including regulating food intake, energy expenditure, thermogenesis and glucose homeostasis. Loss of leptin-signaling in rodents (122, 211, 285, 570, 571) and humans (404) results in profound dysregulation of energy homeostasis characterized by obesity, increased food intake, insulin resistance and altered energy expenditure including impaired thermoregulation. Genetic dissection of the leptin-signaling pathways critical for glucose and energy homeostasis has revealed a key role for a number of proteins including STAT3 (37-39), STAT5 (450), PI3K (423, 638). Moreover, loss of inhibition of leptin signaling through modulation of SOCS3 binding site (Tyr985) results in mice which are leaner than their wild-type littermates (56).

AMP-activated protein kinase (AMPK) is key cellular mediator of energy homeostasis found in both neurons and glia in the CNS (for review see (385)). AMPK activity is increased in times of energy deficit, acting to conserve cellular energy by switching off unnecessary energy consuming pathways and promote ATP production (244). *In vivo* leptin treatment decreases AMPK activity in both the hypothalamus (403) and caudal brainstem (249). Furthermore, genetic or pharmacological stimulation of AMPK activity in the hypothalamus or brainstem is sufficient to attenuate the inhibitory effects of leptin on food intake (249, 403, 554) suggesting that suppression of AMPK activity is a key downstream cellular mediator of leptin-signaling in the CNS. In addition to modulating food intake, AMPK has also been implicated in mediating leptin-induced sympathetic nerve activation (554) suggesting that AMPK action may also impact the effects of leptin on thermogenesis, cardiovascular and renal function.

The roles of different discrete neuropeptides in mediating the downstream effect of leptin on energy homeostasis have been studied extensively using both genetic and pharmacologic studies in rodents, and will be discussed further below. However, as these neuropeptides typically have restricted distribution these studies have resulted in elucidation of discrete leptin-regulated circuits in the CNS and the potentially functional overlap/redundancy between these circuits is not always clear. Other studies have taken a different approach and have sought to determine the broader common critical downstream consequences of leptin signaling that are critical for the regulation of energy homeostasis. Taking a wider overview, the work of Vong and colleagues examined the role of excitatory compared with inhibitory neurotransmission in mediating the effects of leptin on energy homeostasis (587). To do this they created transgenic mice with loss of leptin-signaling in glutamatergic (VGlut2; excitatory) or GABAergic (VGat; inhibitory) neurons. They found that predominantly inhibitory GABAergic signaling was important for mediating the downstream effects of leptin on energy homeostasis, while the contribution of excitatory

glutamatergic neurons was relatively small. GABAergic neurons that are directly responsive to leptin (as indicated by leptin-induced pSTAT3 immunoreactivity) were found in the ARC, DMH and LHA.

While the hypothalamus has been the main area of the brain that has been studied with respect to the role of leptin in the regulation of energy homeostasis, other brain regions including nuclei of the hindbrain and components of the mesolimbic dopamine system have also been investigated (see **figure 2**).

Leptin-mediated effects on energy homeostasis via the hypothalamus

Perhaps the best known and well characterized CNS targets of leptin are the hypothalamic neurons involved in the modulation of energy homeostasis. Early studies indicated that in addition to reducing food intake, hyperglycemia and hyperinsulinemia, chronic leptin treatment in mice reduced hypothalamic NPY mRNA in *ob/ob* mice, suggesting that NPY neurons of the hypothalamus were key mediators of the effects of leptin on food intake and glucose homeostasis (539). Importantly, the effects of leptin on regulating hypothalamic NPY mRNA levels in this model are a direct consequence of leptin treatment and not merely a side effect of weight-loss, as vehicle-treated *ob/ob* animals which were pair-fed to the leptin-treated *ob/ob* group showed a similar degree of weight-loss with no associated reduction in hypothalamic NPY mRNA levels (506). Another key observation in this important study was the finding that leptin-treated *ob/ob* mice showed a greater reduction in serum glucose and insulin than pair-fed vehicle-treated *ob/ob* mice*,* which lost similar amounts of body weight, providing an early indication of a key role of leptin in regulating glucose homeostasis independent of its impact on body weight (506). The ability of leptin to regulate hypothalamic NPY mRNA was also replicated in wild-type animals where leptin treatment can reverse fasting-induced reductions in expression of this gene (506). A key role for NPY in mediating the effects on leptin on energy homeostasis was reinforced by additional studies demonstrating that leptin receptors are localized in NPY neurons of the rodent brain (397) and these neurons express SOCS3 and STAT3 after peripheral administration of leptin (174, 234). Furthermore, genetic deletion of NPY in *ob/ob* mice partially reverses their obesity phenotype (183).

The finding that loss of NPY-signaling attenuated but did not completely reverse the obesity phenotype in *ob/ob* mice (183) suggested there were other important downstream targets of leptin's effects on energy homeostasis that remained to be discovered. Like the *ob/ob* mouse, the phenotype of the obese yellow (A^y) mouse had been described in the 1940's (150) but in the late 1990's when the mechanisms of leptin's actions on energy homeostasis were beginning to be elucidated the underlying molecular basis of the obesity in this model was also undetermined. It

was known that genetic mutations in the A^y mouse and the phenotypically-related viable-yellow (Av^y) mouse both resulted in ectopic over-expression of the agouti protein which was known to be important in regulating pigmentation in hair follicles via its action on melanocortin-1 receptors (MC1R) (369). As mice that lack MC1R are not obese (484) the obesity phenotype of the A^y mouse could only be due to the action of agouti at an alternative receptor. Being expressed in a number of key hypothalamic sites important for the regulation of energy homeostasis (and other neuroendocrine and autonomic functions) (412) the melanocortin-4 receptor (MC4R) was a key candidate. In 1997 the MC4R-null mouse was generated and found to have an obesity syndrome highly similar to that of the A^y mouse, but without the associated coat color phenotype (284). Shortly thereafter, leptin receptors were found to be expressed on ARC POMC-neurons (the major source of endogenous melanocortin receptor agonists in the brain) (108) and administration of a synthetic antagonist for the MC3R and MC4R (SHU9119) into the brain was able to attenuate the ability of peripherally administered leptin to reduce food intake (510). These studies indicated an important role for the central melanocortin system in mediating the downstream effects of leptin on energy homeostasis. However, crossing A^y and *ob/ob* mouse strains together indicates that while central melanocortin signaling is important for mediating the effects of leptin, it can also exert effects on energy homeostasis (and indeed other neuroendocrine pathways) independent of leptin signaling (61).

In 1997, a homologue of agouti was cloned and discovered to be a selective endogenous antagonist of the melanocortin receptors expressed in the brain (MC3R and MC4R) (433). Named AgRP, its mRNA was found to be expressed in the ARC and ME and to be down regulated in obese *ob/ob* mice but highly upregulated by fasting (233, 433, 520). Transgenic overexpression of AgRP under the control of the β-actin promotor resulted in a similar phenotype to the mice with transgenic overexpression of Agouti, however, without the alterations in pigmentation (433). A single injection of AgRP directly into the brain robustly increases food intake (169) an effect that persists for several days (232). Soon after its discovery, AgRP was shown to co-localize with NPY in the ARC in neurons with close proximity to POMC neurons (233) and suggested that a presence of a critical leptin-sensitive neuronal circuit regulating energy homeostasis within the hypothalamus. ARC POMC neurons have also been shown to co-express cocaine- and amphetamine-regulated transcript (CART), another neuropeptide which reduces food intake and whose expression is regulated by nutritional status and leptin (330). The leptin-sensitive melanocortin circuit in the ARC made up of anorexigenic POMC/CART neurons and orexigenic NPY/AgRP neurons, which inhibit and stimulate food intake respectively, plays a pivotal role in energy homeostasis via MC4R expressed at downstream sites, including the PVH, has been extensively studied and recently comprehensively reviewed elsewhere (547) (summarized in inset box of **figure 2**). This central melanocortin circuit has also been shown to be critical for mediating the effects of other key hormones involved in regulating energy homeostasis including

adiponectin (464), ghrelin (573, 593) and insulin (45), and as such the modulatory activation of leptin on this circuit can in turn modulate the efficacy of these key metabolic hormones (113, 256, 564).

The importance of ARC leptin signaling in the regulation of energy homeostasis is indicated by a study showing that introduction of functional leptin receptors in the ARC of Koletsky rats, which have defective leptin-signaling, using an adenoviral mediated gene delivery approach attenuates the obesity phenotype in this model (409). In genetically modified mice which are obese due to the presence of a transcriptional blocker inhibiting leptin receptor expression, site-specific reactivation of leptin receptor expression in ARC neurons alone is sufficient to improve the obesity, hyperinsulinemia, hyperglycemia and hypoactivity (129). Modulations in energy homeostasis are also seen in a number of other studies in mice looking at modulating leptin-signaling specifically in POMC (24, 152, 257, 307, 459, 581) and AgRP neurons (581). Collectively these studies reveal subtle differences in the role of different elements of ARC leptin signaling in regulating body weight and glucose homeostasis, but importantly demonstrate that the ARC is not the sole site mediating the effects of leptin on energy balance.

Detailed mapping studies indicate that while the ARC is one of the hypothalamic sites with the highest level of cell bodies expressing leptin receptor significant numbers were also found in the ventral premammillary nucleus (vPMN) and the DMH, while neuronal projections of leptin receptor expressing neurons were enriched in the PVH, anteroventral periventricular nucleus and the central nucleus of the amygdala (449). These findings are supported by studies mapping of pSTAT3 immunoreactivity after peripheral leptin-treatment (413). The widespread expression of leptin receptors/leptin-responsive neurons in different hypothalamic nuclei highlights that the modulatory actions of leptin on energy homeostasis circuits are complex and diverse and extend far beyond the ARC (417).

The LHA is important for regulating feeding behavior, wakefulness and arousal (59). Importantly, the LHA is also critical for mediating reward behavior and is a key gateway between the hypothalamus and the mesolimbic dopamine system (151, 246, 305). Neurons of the LHA express leptin receptors (180, 352) and are directly responsive to leptin as indicated by leptin-induced expression on pSTAT3 immunoreactivity and changes in electrical activity (352). Indeed, different populations of LHA neurons were either depolarized or hyperpolarized by leptin suggesting that leptin may exert differential effects via the modulation of neuronal activity in this brain region. In addition to direct regulation, the LHA can also be indirectly regulated by leptin via ARC NPY and POMC neurons which project to the LHA (174, 177). Direct administration of leptin into the LHA decreases food intake and body weight in rats (352) supporting a role for the LHA in mediating the homeostatic effects of leptin. This is further supported by data indicating that disruption of leptin-signaling in the LHA increases food intake and body weight (139).

Within the LHA leptin receptor neurons are GABAergic (352, 587) and a subpopulation(s) of these also express the neuropeptides neurotensin (353) and galanin (339). Interestingly, despite their known role in regulating energy homeostasis (497, 518) - both are implicated in stimulating feeding - neither orexin nor melanin concentrating hormone (MCH) neurons in the LHA contain leptin receptors (352). However, leptin can exert an indirect inhibitory effect on LHA orexin (but not MCH) neurons via adjacent neurotensin (216, 368) and galanin neurons (338). Genetic-deletion of leptin receptors from neurotensin neurons results in animals with early-onset obesity associated with elevated food intake and reduced locomotor activity (353). In contrast, leptin receptor deletion from galanin neurons results in late onset obesity and an increased preference for sucrose over fat (338). Although galanin and neurotensin extensively colocalize in the LHA (339), the differential effects of loss of leptin-signaling in galanin compared with neurotensin neurons may potentially be explained by the fact that while both neuronal populations innervate orexin neurons within the LHA, galanin neurons in this region project to the locus coeruleus (338) and neurotensin neurons project to the VTA (353). The differences in phenotype between the two models may also be explained by the fact that both neurotensin and galanin are expressed in neurons at sites outside of the LHA (321, 525). Myers and colleagues have proposed a model in which leptin receptor expressing neurons in the LHA tonically inhibit local orexin neurons and that reductions in leptin-signaling, associated with negative energy balance *e.g.* fasting or starvation, remove this inhibition leading to increased activity of orexin neurons resulting in increased food intake, arousal, and locomotor activity (216).

The DMH is another key hypothalamic site mediating the effects of leptin on energy homeostasis. Indeed, diet-induced obesity in rodents is associated with induction of NPY expression in this region, which is not evident under normal weight animals (227). These diet-induced obesity associated DMH NPY neurons coexpress CART, and leptin directly induces depolarization and increased firing activity in these cells (348) indicating a potential role for leptin in regulating their activity. Leptin-action in the DMH has been shown in a series of independent studies to be critical for the regulation of energy expenditure/thermogenesis. Leptin-deficient *ob/ob* mice have profound deficits in their ability to regulate brown adipose tissue (BAT) activity and adjust to cold temperatures (260, 570, 571) indicating a key role for leptin in regulating this key physiological adaptation. Furthermore, the ability of leptin to reduce body weight in mice is partially dependent on thermogenesis in BAT (126).

A central circuit encompassing projections between the median preoptic area (mPOA), DMH and rostral raphe pallidus (rPA) (84, 623) regulates sympathetic output to BAT during cold exposure. Retrograde labeling studies in mice have demonstrated that a subpopulation leptin receptor expressing neurons in the DMH project to BAT and are activated (as assessed by expression of c-FOS immunoreactivity) by cold-exposure (636). These anatomical findings were supported by physiological studies published around the same time by an independent group which indicate

that intra-DMH administration of a leptin receptor antagonist in mice was sufficient to attenuate the thermogenic effect of peripherally administered leptin (182). Intra-DMH leptin administration can also reverse the low body temperature (hypothermia) that is a physiological characteristic of leptin-deficient *ob/ob* mice (483). Interestingly, the hyperthermic effect of leptin is intact in diet-induced obese mice, which is in contrast to leptin's effects on food intake which are attenuated by obesity (182).

Activation of DMH leptin receptor cells using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) induces weight-loss associated with increased energy expenditure (BAT thermogenesis and locomotor activity) but not changes in food intake (483). The same study indicates that virally mediated genetic deletion of leptin receptors from DMH neurons in mice produces the opposite effect, namely increased body weight associated with reduced energy expenditure and locomotor activity (483). A complementary study by the same group also demonstrated an important role for leptin receptors in the mPOA in mediating body temperature, further reinforcing a key role for leptin in modulating the tone of the central circuit regulating thermogenesis (625). Within the DMH prolactin-releasing peptide (PrRP) neurons are responsive to leptin and deletion of leptin receptors from these cells attenuates the thermogenic effects of leptin indicating that DMH PrRP neurons are key mediators of leptin's effect on thermogenesis (155).

The VMH has long been known to be a key site in the regulation of energy homeostasis. Early studies indicated that lesioning the VMH region in rodents leads to profound obesity (254) and furthermore, mice which lack the transcription factor steroidogenic factor-1 (SF-1) have defective VMH development and are obese (378). The VMH has populations of glucose-sensing neurons (for review see (492)). Critically, VMH neurons also expresses leptin receptors (180) and are directly responsive to leptin, as indicated by the expression of nuclear localization of STAT3 after leptin treatment (275). Direct injection of leptin in to the VMH is sufficient to reduce food intake (290, 501) and stimulate sympathetic nervous system activation in rodents (243, 502). Interestingly, pregnancy is associated with a reduction in leptin receptor mRNA and a concomitant reduction in leptin-induced pSTAT3 in the VMH but not the ARC, suggesting that the VMH may be a critical site mediating pregnancy-induced leptin-resistance (336).

Neurons in the medial VMH send excitatory inputs to ARC POMC neurons (542), providing evidence for a functional regulatory interaction between these two leptin-sensitive areas. Loss of leptin receptor signaling in SF-1 neurons of the VMH results in obesity and impaired glucose tolerance on standard chow and also enhanced weight gain on a high-fat diet (52, 149). In support of a potential role for VMH leptin signaling in sympathetic nervous system activation, mice with loss of leptin receptor signaling in SF-1 neurons display a defect in diet-induced thermogenesis (149). Activation of PI3K signaling is one of the pathways downstream of leptin

receptor activation (423, 638). PI3K signaling in VMH SF-1 neurons leads to enhanced diet-induced obesity and a defect in diet-induced thermogenesis, suggesting the PI3K may be one of the key signaling pathways mediating the effects of leptin in VMH neurons (613). Furthermore, the effect of VMH leptin signaling on tissue glucose utilization and insulin-sensitivity appear to be mediated via ERK signaling (565). Enhancing leptin signaling in VMH SF-1 neurons by specific deletion of SOCS3 increased the efficacy of leptin in reducing food intake and also resulted in improved glucose homeostasis in both standard chow and high-fat fed mice (634). Preventing PTP1B mediated inhibition of leptin signaling in VMH SF-1 neurons (SF-1 PTP1B null mice) also enhances leptin-sensitivity but surprisingly resulted in increased body weight in high-fat fed female mice, which was associated with reduced energy expenditure and sympathetic nervous system activity (111). As PTP1B also regulates insulin signaling, it is has been proposed that enhanced insulin signaling in the SF-1 PTP1B null mice counteract the effects of improved leptin-sensitivity in these animals when exposed to a high-fat obesogenic diet (111). The neurochemical identity of leptin responsive neurons in the VMH remains to be fully determined, but candidates include pituitary adenylate cyclase-activating polypeptide (PACAP) (248) and dynorphin (175).

Within the hypothalamus multiple distinct nuclei are sensitive to leptin and have been implicated in mediating the effects of the adipokine on energy homeostasis. While some overlapping actions/ redundancy exist it is likely that we have yet to uncover the true integrative and coordinated action of these site in the regulation of this complex physiologic process.

Extra-hypothalamic effects of leptin on energy homeostasis

While the hypothalamic effects of leptin in regulating energy homeostasis have been the most extensively studied (see preceding section), deletion of leptin receptors from various hypothalamic neuronal populations (described above (24, 52, 149, 152, 257, 307, 338, 353, 459, 581)) does not fully recapitulate the metabolic phenotype of the animals with congenital leptin-signaling defects (122, 211, 285, 570, 571). This indicates that leptin signaling in extra-hypothalamic areas is also critical for the normal regulation of energy homeostasis.

Leptin-mediated effects on energy homeostasis via the hindbrain

In animal models, leptin receptor expression has been reported in a number of hindbrain sites relevant to the regulation of energy homeostasis including the area postrema, nucleus of the solitary tract (NTS), dorsomotor nucleus of the vagus (DMX), lateral parabrachial nucleus (lPB), and ventrolateral medulla (VLM) (225, 399, 400). However, variation in distribution and abundance has been reported between mammalian species (399, 400). Early studies indicated

that administration of leptin in rodents induces c-FOS immunoreactivity in the NTS and lPB in the brainstem (179); yet, subsequent studies reported low levels of activation in the NTS (175, 591), suggestive of a failure of leptin to activate neurons in this region. As c-FOS is thought to principally be a marker of neuronal activation, the failure of leptin to induce c-FOS in the NTS may be explained by the finding that leptin has been found to inhibit excitability of NTS neurons (604). Mapping of leptin-induced expression of phosphorylated STAT3 confirms that the NTS, DMX and lPB are direct targets for the action of leptin (79, 178, 209, 225, 266, 281). Neurochemical characterization indicates that cholecystokinin (CCK) neurons in the lPB and NTS are leptin-responsive (175, 209). Additionally, in the NTS preproglucagon (a precursor for glucagon like peptide-1 [GLP-1]) and POMC neurons are direct targets for leptin (178, 209, 281), while cholinergic neurons are a target of leptin in the DMX (79).

The functional significance of these anatomical studies has been verified by numerous independent groups. Administration of leptin into the fourth ventricle or dorsal vagal complex (DVC; a region of the brainstem encompassing the NTS, area postrema and DMX) reduces 24 h food intake and induces weight-loss over the same period (225). In a subsequent study the viral-mediated knock-down of leptin receptor expression in the DVC in rats caused modest but chronic hyperphagia leading to body weight gain (250) indicating a role for endogenous leptin signaling in the homeostatic regulation of food intake. Loss of leptin receptors from hindbrain preproglucagon/GLP-1 neurons in mice led to a similar phenotype of modest hyperphagia and weight gain (509) , although phenotypic differences were seen in the animals between the two studies which the authors propose may be related to differences in brain stem expression of leptin receptors in mice and rats (282).

One of the mechanisms by which brainstem leptin-signaling has been proposed to modulate energy homeostasis is via modulation of gut-brain communication. An early study indicated that injection of leptin into the fourth ventricle was sufficient to inhibit gastric emptying (526) supporting a role for leptin in modulating gastrointestinal (GI) function, likely via modulation of vagal efferent tone. This early work was followed on by subsequent studies indicating that peripheral leptin treatment enhanced NTS neuron activity in response to gastric distention (505) and nutrient preloading (181), thus providing a neurophysiologic mechanism for how leptin may act to reduce meal size.

Related studies have demonstrated that leptin is able to impact food intake via modulation of the action of gut released peptides at hindbrain sites. CCK released from the GI tract acts as a satiety factor reducing meal size via its action on receptors located on vagal afferents which are relayed to the DVC in the brainstem and also forward on to higher centers regulating food intake (154). Multiple independent groups have demonstrated that in rodents the injection of sub-threshold doses of leptin and CCK, which alone do not influence feeding behavior, can produce reductions

in food intake indicative of a synergistic action of the two peptides (10, 35, 390, 603). This effect was seen when leptin was administered peripherally (10, 35) or into brain via cerebroventricular injection (390, 603). The inter-relationship between leptin- and CCK-signaling is further strengthened by the finding that absence of intact leptin signaling in Koleysky (408) or Zucker (401) rats is associated with increased meal-size and relative insensitivity to the effects of CCK on food intake, although interpretation of these findings may be complicated by the profound obesity in these models that likely impacts numerous parameters. However, the importance of leptin in modulating the actions of CCK on food intake in a physiological context are further supported by the data indicating that fasting-induced reductions in circulating leptin also impair the ability of CCK to reduce food intake, an effect that can be reversed by restoration of leptin levels by exogenous administration of leptin (393). Leptin receptors in the NTS are critical for mediating the effects of CCK on food intake as adenoviral mediated knockdown of leptin receptors in this brain region attenuates the satiating effect of exogenously administered CCK and also leads to an increased meal size, indicative of a disruption of the normal satiety pathways (250).

In addition to NTS leptin-signaling forebrain sites have also been implicated as being important in mediating the synergetic interaction between leptin and CCK. Co-administration of leptin and CCK leads to an amplification of neuronal activation in the PVH, as assessed by c-FOS immunoreactivity, compared with that seen following either peptide alone, suggesting that the PVH may be an important site of functional convergence of both peptides (35, 181). Indeed, surgical transection of the connectivity between forebrain and hindbrain in rats prevented the inhibition of food intake associated with co-administration of leptin and CCK, indicating that connectivity between the two areas is critical for mediating the synergetic action of these two peptides (10). Descending oxytocin pathways from the PVH to the NTS have been implicated as potential key mediators (57). Interestingly, in Koletsky rats restoration of leptin-signaling in the ARC, a brain region with direct connectivity to the PVH, using viral-mediated gene delivery was sufficient to reduce average meal-size to that seen in wild-type animals and also restore sensitivity to the satiating effects of exogenously administered CCK (408). Together, these data suggest that hypothalamic leptin-signaling can modulate the activity of CCK via descending neuronal pathways from the PVH to the NTS. Interestingly, a recent study has demonstrated that CCK-neurons of the NTS, that are known to be leptin responsive (209), project to the PVH and play an important role in regulating satiety (133).

In common with CCK, leptin has also been shown to act synergistically with GLP-1 to reduce food intake; indeed the interaction between GLP-1 and leptin in the regulation of energy homeostasis bears a lot of similarities to the interaction with CCK described above. GLP-1 like CCK is a peptide released from the GI tract that has been shown to mediate satiety and is also expressed in neurons of the NTS of the brain stem (568). Peripherally secreted GLP-1 is also an incretin

hormone. It is not clear whether peripherally derived GLP-1 enters the brain and/or whether the interaction between leptin and GLP-1 signaling in the CNS is largely mediated downstream of CNS derived GLP-1 (568). As described above, leptin receptors are found on GLP-1 neurons in the NTS (218) and are directly responsive to leptin-treatment in mice as indicated by expression of pSTAT3 immunoreactivity (209, 281). Electrophysiologic studies indicate that GLP-1/preproglucagon neurons of the NTS are depolarized by leptin and receive direct input from vagal afferent fibers (261). Intracerebroventricular administration of a GLP-1 antagonist [extendin 9-39] at a dose that had no effect when administered alone, is sufficient to attenuate the effect of leptin on food intake (218, 639), implicating GLP-1 signaling in mediating some of the downstream effects of leptin on food intake. Furthermore, co-administration of leptin and a GLP-1 agonist [exendin-4] into the fourth cerebroventricle in rats had an additive inhibitory effect on food intake. In rats, peripheral leptin administration can attenuate fasting-induced reductions in NTS GLP-1 mRNA (281) an effect that is not seen in mice, indicating that there may be important differences between the two species. NTS GLP-1 neurons send projections to the hypothalamus as well as a number of other brain sites (340). As with CCK, intact hypothalamus-brainstem connectivity appears to be required for the interaction between leptin and GLP-1 signaling in the regulation of energy homeostasis, as the additive effect on food intake is attenuated in midbrain transected rats (11). Loss of leptin receptors from GLP-1 neurons in the NTS is sufficient to impact food intake and induce a modest increase in body weight in animals fed standard laboratory chow indicating that endogenous GLP-1 neurons are important downstream mediators of endogenous leptin signaling (509). These animals are, however, capable of reducing their food intake and body weight in response to exogenous peripheral leptin infusion over the course of a week, indicating that in this context leptin receptors on GLP-1 neurons are not required for the effect on food intake and body weight, likely due to a compensation by other leptin activated pathways.

In addition to the caudal brainstem nuclei (NTS, AP, VLM and DMX) another direct target of leptin in the hindbrain is the lPB (79, 178, 209, 225, 266, 281). The parabrachial nucleus (PBN) is a key intermediary site linking the hypothalamus to the caudal brainstem including the NTS and VLM (500). Within the PBN, leptin receptors are expressed in CCK neurons which project to the VMH (194). Leptin receptor expressing neurons in the PBN are inhibited by leptin but activated by low glucose levels indicating that they may be a key regulatory node for low-glucose sensing linking the hypothalamus and brainstem (194). Deletion of leptin receptors from CCK neurons resulted in mice with an exaggerated counter-regulatory response (CRR) to low-glucose characterized by a reduced glucose infusion rate in a hypoglycemic clamp (194). The same study nicely demonstrated using chemogenetic technologies (DREADDs) that inhibition of the activity specifically of PBN leptin receptor containing neurons blunted the CRR while activation of these neurons enhanced it, in a process that could be inhibited by the CCK-receptor antagonist

proglumide. While mice with deletion of leptin receptors from all CCK neurons including those found in the PBN show normal food intake and body weight, an independent study demonstrated that direct injection of leptin into the PBN reduces food intake and meal size in rats leading to a reduction in body weight (13). This suggests that the effect of intra-PBN leptin on food intake is mediated by neurons in the PBN that do not contain CCK or alternatively, that other pathways adapt to maintain normal energy homeostasis in mice with leptin receptors deleted from their CCK neurons.

Role for non-neuronal targets of leptin in the regulation of energy homeostasis

Within the CNS the majority of work examining the role of leptin in regulating energy homeostasis has focused on neuronal signaling; however recent work has begun to explore the contribution of non-neuronal cells as targets for leptin's actions, in particular the potential role of astrocytes. Leptin receptors are expressed in astrocytes (110, 271, 272, 442). Indeed, astrocytes have been shown to be directly responsive to leptin as indicated by increased translocation of STAT5 to the nucleus of astrocytes following systemic leptin treatment *in vivo* in rats (415). Additionally, studies show that leptin treatment can induce both pSTAT3 and pSTAT5 in astrocytes *in vitro*, with pSTAT5 showing more pronounced regulation (60) indicating that it may be the predominant signaling pathway downstream of leptin receptor activation in astrocytes; however, further work needs to be done in this area. *In vitro*, leptin induces an increase in intracellular calcium in astrocytes, providing further evidence of a functional effect of leptin on downstream signaling in astrocytes (272).

In obese animal models, both monogenic and diet-induced, leptin receptor expression is upregulated in hypothalamic astrocytes, suggestive of a potential role of astrocytic leptin-signaling in the regulation of energy homeostasis (272, 442). This expression data is supported by mechanistic studies indicating that leptin treatment regulates both the structure and function of hypothalamic astrocytes; including levels of hypothalamic glial-fibrillary acidic protein (GFAP) and vimentin, key structural proteins (207), as well as the expression of glucose and glutamate transporters found in astrocytes (202). Conditional deletion of leptin receptors from GFAP-expressing astrocytes in adult mice reduces astrocytic coverage of melanocortin neurons (POMC and AgRP) in the ARC resulting in an increase in synapse number and a change in the neurophysiological activity of these neuronal populations (310). While there were no notable differences in feeding behavior in these animals under normal husbandry conditions (freely available standard chow), the animals' demonstrated altered physiological responses when experimentally challenged. Conditional deletion of leptin receptors from GFAP-expressing astrocytes in mice resulted in an enhanced response to manipulations that typically increase food intake, fasting or ghrelin treatment, and attenuation of the ability of leptin to reduce food intake

(310). Together these data point to a role for leptin in regulating the astrocytic modulation of synaptic activity in ARC melanocortin neurons. The importance of astrocytes in mediating the effects of leptin on energy homeostasis was supported by a subsequent study demonstrating that chemogenetic activation of astrocytes using DREADDs enhanced the reduction in food intake associated with leptin-treatment, while inhibition of astrocytes attenuated it (618). Of note, germ-line deletion of leptin receptors from GFAP-expressing cells does not lead to any overt changes in body weight or feeding behavior on standard chow, but a modest and complex difference in their response to high-fat feeding that requires further study (293).

Effects of leptin on the modulation of CNS reward pathways

In addition to increasing food-seeking behavior, negative energy balance associated with food restriction/fasting increases other motivated behaviors including drug-seeking and rewarding brain self-stimulation via electrodes implanted into the brain (435). As such, food-restriction is often used as an experimental context in neurobehavioral studies in rodents as a motivational tool. Early functional *in vivo* studies indicated that intracerebroventricular treatment with leptin can attenuate the ability of food-restriction to increase rewarding brain self-stimulation, via electrodes implanted in the LHA, providing evidence for a role of leptin in modulating reward pathways (206).

The dopaminergic reward pathways are critical for the regulation of motivated behaviors including food-seeking (606). Leptin receptors are expressed on dopaminergic (191, 264) and GABAergic neurons of the VTA which project to the nucleus accumbens (205) suggestive of a role of leptin in modulating the critical mesoaccumbens dopamine pathway. *Ex vivo*, leptin decreases the frequency of excitatory postsynaptic currents in VTA dopaminergic neurons, providing a neurophysiological evidence for a role of leptin in modulating the activity of this pathway (563). This is supported by studies which demonstrate that absence of leptin-signaling in leptin deficient *ob/ob* mice is associated with reduced levels of tyrosine hydroxylase, the rate limiting enzyme in dopamine synthesis, in the VTA and a deficit in amphetamine-induced motivated behavior (205), both of which can be reversed by systemic leptin treatment. Leptin acting directly in reward centers of the brain has also been shown to modulate feeding. Administration of leptin directly into the VTA reduces food intake in rodents while knock-down of leptin receptors in this region increases food intake and preference for palatable foods (sucrose and high-fat) (264). The effect of intra-VTA administered leptin on food intake appears to be dependent on JAK2 signaling but not PI3K or mechanistic target of rapomycin (mTOR), which is in contrast to the effects of intra-hypothalamic leptin (407).

In addition to mediating important aspects of the leptin effect on food intake, VTA leptin signaling is also important for energy expenditure as loss of STAT3 signaling in dopamine neurons is

associated with an increase in the rewarding effect of voluntary activity (running) in mice (189), an effect that can be reverse by intra-VTA administration of leptin. Leptin receptor expressing neurotensin neurons of the LHA innervate the VTA and intra-LHA administration of leptin into leptin deficient *ob/ob* mice was sufficient to increase VTA tyrosine hydroxylase gene expression and nucleus accumbens dopamine levels, indicating a functional anatomic link between LHA and the mesoaccumbens dopamine system (352, 353). Like the hypothalamic nuclei, the VTA neurons also show cellular leptin resistance in response to diet-induced obesity (387).

Leptin in the modulation of other neuroendocrine axes

Reproduction

Reproduction is energetically demanding, particularly for female animals. As such, having sufficient energy reserves in the form of stored body fat is essential for the health of the mother and the offspring. Circulating leptin levels play a key role in communicating information on body fat stores to the CNS, with a drop in circulating leptin levels being a key mediator of the neuroendocrine deficits triggered by the reduction in energy availability associated with fasting (8). Leptin has been shown in numerous studies to have a key role in modulating multiple aspects of reproductive function from puberty to lactation (98).

Before the cloning of leptin it was known that both male and female obese *ob/ob* mice had severe reproductive deficits with the homozygous female animals being sterile and the male animals only capable of reproducing when their excess body weight was curtailed by food restriction (127). Detailed characterization of these animals revealed an absence of ovulation due to reduced levels of reproductive hormones associated with dysfunction at the hypothalamic-pituitary level (40, 493-495, 549); ovaries from female *ob/ob* mice were functional when transplanted into lean mice (279). The reduced levels of reproductive hormones in *ob/ob* mice cause immaturity/atrophy of the reproductive organs (550). Breeding of homozygous *ob/ob* animals is typically achieved through pairing heterozygous *ob/+* animals.

After the cloning of the *Ob* gene and identification of the hormone leptin in 1994, early studies explored whether leptin replacement in *ob/ob* animals was sufficient to reverse the reproductive deficits. Continuous peripheral leptin-treatment in adult female *ob/ob* mice was able to restore the ability of the animals to become pregnant, deliver and nurse healthy pups (99). While the leptin-treatment in female *ob/ob* mice caused a reduction in body mass, weight-loss in control *ob/ob* mice caused by food restriction alone was not sufficient to restore reproductive capacity indicating that the absence of leptin signaling and not just obesity was the principal cause of sterility in the

mice. Continuous leptin treatment was required to restore fertility in *ob/ob* mice as subsequent withdrawal of treatment post-partum prevented subsequent pregnancies (99). A complementary study of Barash and colleagues, published in the same year, indicated that two-weeks' of peripheral leptin treatment in both male and female *ob/ob* mice caused an increase in gonad weight, and began to normalize some of the notable histologic differences in the seminal vessels (males), ovaries and uterus (females), compared with control animals. Serum levels of key reproductive hormones were also regulated in *ob/ob* mice by leptin treatment; females showed elevated serum luteinizing hormone (LH) and males elevated serum follicle–stimulating hormone (FSH) (33). As with the study of Chehab and colleagues, these effects were found to be independent of leptin's effect on body-weight. Together these early studies pointed to a critical role for leptin in the control of the reproductive system. Intriguingly, the genetic background of the *ob/ob* mice is a critical factor determining the severity of the loss of leptin signaling on reproductive function, with *ob/ob* mice on a C57BL6 background being largely sterile while animals which carry with the same mutation of the BALB/cJ background are capable of reproducing despite profound obesity (184) suggesting the existence a strain dependent genetic modifiers of leptin's effect on reproduction.

In addition to animal models, intact leptin signaling has also been shown to be critical for reproductive function in humans. Although rare in humans, in agreement with the data from mice, genetic defects in the *ob* gene cause severe obesity and individuals do not undergo puberty unless treated with leptin (186, 404). However, leptin has also been shown to be critical for reproductive function in humans without genetic alterations in leptin signaling. Amenorrhea is seen in female patients with very low leptin levels caused by the presence of low body fat including athletes (341), patients with anorexia nervosa (252, 324) or lipodystrophy (583). This has been shown to be reversible by leptin treatment in athletes and others with hypothalamic amenorrhea (114, 599).

Puberty

Body fat level is associated with the onset of puberty with low levels such as those seen in female athletes being associated with delayed onset (197) while high levels of body fat associated with obesity are linked to early onset (12, 140). In boys and girls increased serum leptin levels have been shown to be associated with the onset of puberty (117, 208, 380). Studies in wild-type female mice indicate that peripheral administration of leptin causes earlier onset of puberty and maturation of the reproductive tract (6, 100); however other studies suggest that in the rodent the role of leptin is more permissive, necessary for the onset of puberty but not sufficient to trigger it (109).

CNS pathways mediating leptin's effects on the reproductive axis

Pulsatile gonadotrophin-releasing hormone (GnRH) secretion and the subsequent surge of LH prior to ovulation is critical for reproduction in female mammals. Leptin receptors are expressed in the pituitary gland (168, 630) and also hypothalamic neuroendocrine neurons (**table 2**) which are key components of the reproductive axes. Loss of leptin receptors specifically in neurons is sufficient to reduce plasma estradiol levels in female mice indicating a key role of centrally acting leptin in mediating female sex hormone secretion (120). Interestingly, in the same study, plasma testosterone levels were unchanged by neuronal leptin receptor deletion, suggesting sexual dimorphism in how leptin impacts reproduction. In a complementary study, reintroduction of functional leptin receptors into neurons in *db/db* mice (which have defective leptin signaling) is sufficient to restore fertility in both male and female animals (490) reinforcing the critical role of neuronal leptin signaling for fertility.

In male and female rats, sheep, cows and rhesus monkeys peripheral leptin treatment is sufficient to reverse the fasting-induced reduction in pulsatile LH secretion (193, 322, 373, 418, 596) providing evidence for a role of leptin in the nutritional regulation of reproductive hormone secretion across multiple species. Administration of a leptin anti-serum also decreases LH pulsatility in normally fed female rats providing further evidence of a role of leptin in the modulation of LH secretion in the absence of a nutritional stress (90). The effects of leptin on LH secretion can be prevented by antagonism of central MC4R (596) indicating a potential role of the central melanocortin system in mediating the effects of leptin on secretion of reproductive hormones. The absence of leptin receptor expression on GnRH neurons (193) indicates an indirect effect of leptin in modulating this pathway. An indirect effect of leptin in modulating GnRH neurons was supported by a robust study in mice which demonstrated that leptin administration into the brain failed to induce STAT3 signaling in GnRH neurons and genetic deletion of leptin receptors specifically from GnRH neurons in mice had no impact on fertility (467).

A number of CNS pathways have been implicated in mediating the effect of leptin on reproduction. It has been argued that the redundancy within this pathway is understandable from an evolutionary context given the importance of reproduction for survival of a species (98). The kisspeptin pathway, peptides encoded by the *Kiss1* gene acting via the Kiss1-receptor/GPR54, is a key regulator of puberty and reproduction in humans and rodents (142, 513) acting via modulation of GnRH neurons. Kiss-1 and GPR54 are nutritionally regulated showing a reduction in response to calorie restriction (421) and obesity associated with a high-fat diet or leptin-deficiency in *ob/ob* mice (188); all states in which leptin signaling is reduced. Leptin administration in leptin-deficient *ob/ob* mice increases *Kiss-1* gene expression and induces sexual maturation (527). These findings led to the hypothesis that the kisspeptin pathway may be

a key functional link between leptin and the regulation of the reproductive axis. However, in common with GnRH neurons, Kiss-1 neurons do not appear to be directly activated by leptin (188, 421). There is also conflicting evidence as to whether ARC Kiss-1 neurons express leptin receptors, with some studies suggesting up to 40% colocalization (527) and others indicating that only a very limited number of kisspeptin neurons (<6% in the ARC and none in the anteroventral periventricular nucleus) express leptin receptors (311). Kiss1 expression in the brain is increased during pubertal development (512). A detailed analysis in the change in Kiss-1 and leptin receptor expression over time (94) indicates that in prepubertal female mice there are low levels of leptin receptor expression in Kiss-1 neurons and accordingly at this age few Kiss-1 neurons are activated (as assessed by pSTAT3, c-FOS or pSTAT5 immunoreactivity) by leptin treatment. After sexual maturation 10-15% of ARC Kiss-1 neurons expressed leptin receptors. This anatomic evidence is supported by genetic studies in mice that demonstrate the deletion of leptin receptors from hypothalamic Kiss-1 neurons has no impact on puberty (157). Furthermore, re-expression of endogenous leptin receptors in Kiss-1 neurons of leptin receptor null animals using cre-mediated removal of a transcriptional blocking cassette also failed to restore normal reproductive function to the leptin receptor null animals (94). Together these studies indicate that the kisspeptin pathway is not directly mediating the effects of leptin signaling on the onset of puberty. But an indirect/downstream role of kisspeptin in mediating leptin's effects on reproduction and the potential role of leptin in direct modulation of Kiss-1 neurons in adult animals has not yet been clarified.

The central melanocortin system has also been implicated in mediating leptin's effects on reproduction. Melanocortin neurons of the ARC, both POMC and AgRP, express leptin receptors (108, 397) and have been shown to innervate both GnRH and Kisspeptin neurons (432, 516, 607). A subpopulation of Kiss-1 neurons of the mPOA and ARC both express MC4R (516). These data provide a potential anatomical basis for a role for the central melanocortin system in mediating the effects of leptin on reproduction. Indeed, pharmacologic studies indicate that inhibiting MC4R attenuates leptin's ability to induce LH release in fasted female rats (596). However, others have shown that while antagonism of central melanocortin receptors (MC3R/MC4R) using SHU9119 attenuates leptin's ability to reduce food intake in *ob/ob* mice, it does not prevent leptin induced stimulation of reproductive function in these animals (616). While leptin receptors in POMC or AgRP neurons are not necessary for the onset of puberty and fertility in mice (283, 453), loss of AgRP signaling or heterozygosity of MC4R is sufficient to restore reproductive capacity (onset of puberty, fertility and lactation) in female *db/db* mice without any significant changes in body weight (288). Together these data suggest a complex interaction between the leptin and melanocortin systems in the regulation of reproductive function, the study of which may be complicated by redundancy in the system and developmental compensation in

knockout mouse models. Future studies utilizing inducible transgenic models may help to provide more clarity.

Genetic deletion of leptin receptors from GABAergic but not glutamatergic neurons (384) in female mice leads to reproductive deficits characterized by a disrupted estrous cycle and reduced ovarian and uterine weight. This suggests an important role for inhibitory GABAergic tone in mediating leptin's effects on reproduction. Kiss-1 neurons receive GABAergic inputs which are regulated by both time of day and estradiol (144). GABAergic signaling has also been shown to regulate GnRH neuron activity (595). This suggests that a leptin→GABA→Kisspeptin/GnRH pathway may be one mechanism by which leptin may be able to indirectly modulate the reproductive axis. Critically, AgRP neurons in the ARC are GABAergic, whereas POMC neurons are both GABAergic and glutamatergic (607) providing a functional anatomical link between the leptin and melanocortin systems that may provide further insights into how these systems interact in the regulation of reproduction.

The hypothalamic ventral premammillary nucleus (PMv) has emerged as a key site mediating the effects of leptin on the reproductive axis. Anatomical tracing studies in mice reveal that PMv neurons, including those known to express leptin receptors, directly innervate GnRH neurons (157, 288, 355) and lesioning of the PMv in *ob/ob* mice attenuates the ability of exogenous leptin treatment to induce puberty in these animals (157). Reintroduction of leptin receptors into the PMv of leptin receptor null mice was sufficient to induce puberty and positively impact fertility in the absence of any notable effect on the body weight of the animals, which remained obese (157). These studies revealed an anatomical dissociation between the brain regions mediating the effects of leptin on reproduction and energy homeostasis. The neurotransmitter(s) mediating the modulation of GnRH neurons downstream of leptin-induced activation of PMv neurons are not fully elucidated but glutamate and nitric oxide have been implicated (157, 355, 595).

In addition to the importance of leptin receptor expression in different brain regions, specific modulation of different signaling pathways downstream of the leptin receptor has been shown to differentially modulate reproductive function. Genetic modulation of leptin-induced STAT3 signaling either through specific deletion of STAT3 in leptin receptor expressing cells (213) or by genetic introduction of leptin receptors that are unable to couple through STAT3, due to replacement of the Tyrosine residue at 1138 (247), is sufficient to cause an increase in body weight but has no impact on the onset of puberty or fertility. Specific deletion of STAT5 in leptin receptor expressing cells (213) also fails to impact reproductive function. This is perhaps surprising given that preventing leptin-induced phosphorylation of the leptin receptor at Tyr1077 (450), the site that is thought to be important for STAT5 recruitment (219), causes impairments in the estrous cycle of female mice. Together these data indicate that another (as yet

underdetermined) leptin-induced signaling cascade dependent on phosphorylation of Tyr1077 may be important for mediating leptin's effects on reproduction in female mice.

Thyroid hormone axis

The hypothalamus-pituitary-thyroid (HPT) axis regulates the secretion of thyroid hormone which has critical functions including modulation of whole organism and cellular metabolism, cardiovascular function, growth, and development. Absence of leptin signaling is associated with hypothyroidism in *ob/ob* and *db/db* mice (37, 432). In rodents and humans calorie-restriction/fasting leads to downregulation of the HPT axis as a compensatory mechanism to reduce energy expenditure in order to conserve resources during the absence of food (127, 490). Following the cloning of leptin, it was found that treatment with peripheral administration of leptin was sufficient to partially reverse the starvation/fasting-induced reductions in circulating triiodothyronine (T3) and thyroxine (T4) levels in mice, providing evidence of a physiologic role for leptin in wild-type animals in the integration of metabolic cues and the function of the thyroid hormone axis (8, 349). Leptin treatment could also reverse the fall in circulating T3 and T4 levels associated with calorie-restriction induced weight-loss in humans (490).

Within the brain, leptin treatment in rodents reverses the fasting-induced reduction in pro-thyrotropin-releasing hormone (proTRH) mRNA levels in neurons of the PVH, which are key regulators of thyroid-stimulating hormone (TSH) modulating its release from the pituitary. Subsequent studies by multiple independent groups have demonstrated that while leptin can directly activate thyroid releasing hormone (TRH) neurons within the PVH (247, 283), an indirect pathway via the ARC→PVH melanocortin circuitry is also a critical mediator of the effects on leptin on nutritional regulation of the HPT axis (188, 247, 311, 421). This has been confirmed by electrophysiologic studies indicating that both leptin and α-MSH can induce firing activity of PVH TRH neurons (213). In diet-induced obesity it has been proposed that leptin-resistance in the ARC leads to underactivity of the indirect melanocortin mediated pathway and that the function of the HPT axis in the obese state is maintained principally by the direct action of leptin on PVH TRH neurons (453). Mutation of Tyr1138 in the leptin receptor is sufficient to impact the HPT axis indicating that activation of STAT3 downstream of the leptin receptor is a key transcriptional event in mediating leptin's effects on the HPT axis (37).

In addition to modulating the HPT axis at the level of the TRH neurons, leptin can also modulate the activity of the enzyme deiodinase type II (D2; the enzyme which converts T4 to T3) within the brain (80), including the hypothalamus. D2 has been proposed to play a role in regulating the activity of ARC melanocortin neurons via modulation of uncoupling protein 2 (UCP2)(130); as such, modulation of hypothalamic D2 activity may represent another mechanism by which leptin

exerts its effects on whole organism metabolism, although this is an area that requires further study.

CNS mediated effects of leptin on cardiovascular and renal function

Cardiovascular disease is one of the key comorbidities associated with obesity, with elevations in blood pressure believed to be one of the key underlying factors (166, 460). Over the years, hyperinsulinemia (236), endothelial dysfunction (511), inflammation (238, 274), alterations in fluid homeostasis (237) and changes in sympathetic function (153) have all been implicated in mediating obesity-associated cardiovascular pathology. As the focus of this review is CNS targets of leptin, we will focus on how centrally acting leptin may modulate cardiovascular function; but leptin may also impact cardiovascular function *via* direct action on the heart and kidney as leptin receptors are known to be expressed in these organs (345, 592) .

Obesity-associated increases in sympathetic nervous system activity in animals and humans has been implicated in mediating hypertension (486, 534, 624). The link between the sympathetic nervous system and obesity-associated hypertension was further supported by early mechanistic studies in animal models indicating that renal denervation prevented high-fat diet induced increases in arterial pressure and alterations in sodium retention (299).

The importance of leptin in modulating sympathetic nervous system activity was discovered soon after its initial cloning. In rodents, peripheral administration of leptin increased norepinephrine turnover in BAT (123) and sympathetic nerve activity in BAT, kidneys and adrenal glands (251). In conscious non-obese rats, chronic peripheral infusion of leptin increases arterial blood pressure (517), an effect that can be blocked by administration of adrenergic receptor blockers (86). These experiments directly implicated leptin-mediated activation of the sympathetic nervous system in the modulation of the cardiovascular system. The effects of leptin on blood pressure in non-obese animals can also be seen following direct administration into the CNS via cerebroventricular infusion (93, 131, 162); these effects were attenuated by central administration of a melanocortin receptor antagonist implicating the central melanocortin system in mediating, at least in part, the CNS-mediated cardiovascular effects of leptin (134, 163).

Despite profound obesity mice with defective leptin signaling, leptin-deficient *ob/ob* mice and *db/db* mice with defective leptin receptors, fail to show the predicted increase in blood pressure seen in diet-induced obese animals with comparable body weight (382, 522). This is in contrast to the obese agouti yellow mouse with defects in central melanocortin signaling which has the predicted obesity-associated increase in blood pressure (9, 382). This further suggests that leptin exerts important effects on cardiovascular function independent of the central melanocortin system. Surprisingly, leptin-replacement in *ob/ob* mice (leading to serum levels comparable to

those seen in diet-induced obese mice) causes an increase in heart rate and blood-pressure despite a reduction in body weight (522). This was not due to an increase in physical activity as the leptin-treated *ob/ob* animals remained hypoactive compared with their lean and diet-induced obese wild-type counterparts. In agreement with what was seen in the animal models, genetically mediated loss of leptin-signaling (either lack of leptin or defective receptor function), although rare in humans, is also associated with lower blood-pressure compared with age and body-mass index (BMI) matched controls (522).

Within the CNS a number of brain regions have been implicated in mediating the cardiovascular effects of leptin. In anaesthetized rats, direct administration of leptin into the hypothalamus, specifically the ARC (469) or VMH (383), significantly increased arterial blood pressure and renal sympathetic nerve activity but had no impact on heart rate. In contrast, direct injection of leptin into the DMH failed to impact renal sympathetic nerve activity while increasing arterial blood pressure and heart rate (383). This is further supported by studies indicating that loss of leptin signaling specifically in the DMH of mice (via either antibody-mediated or viral-induced knockdown of leptin receptors) is sufficient to attenuate diet-induced obesity associated increases in heart rate and blood pressure (522). Perhaps surprisingly given its role in mediating renal sympathetic outflow (640), injection of leptin directly into the PVH of the hypothalamus did not impact any of the parameters measured (383). Together these data implicate discrete hypothalamic nuclei in mediating the cardiovascular effects of leptin.

The SFO is a circumventricular site which is important in the regulation of autonomic functions including those associated with the cardiovascular system. The long-form of the leptin receptor is expressed in the SFO (528) and direct inject of leptin into the SFO of lean rats dose dependently decreased blood pressure but not heart rate, an effect that is absent in obese animals (529). Specific viral-mediated deletion of leptin receptors from the SFO prevents leptin induced increases in renal sympathetic nerve activity but has no impact on leptin-induced changes in food intake, body weight or sympathetic nerve activity in brown adipose tissue, suggesting that the functional role of leptin-signaling in the SFO is highly specialized (528).

The baroreceptor reflex is a rapid homeostatic mechanism for the maintenance of blood pressure via the regulation of cardiac parameters including heart rate. Within the CNS, autonomic regulatory neurons in the brainstem found in the NTS and VLM, are key in mediating this critical homeostatic feedback loop (137); these are key sites of leptin receptor expression in the rodent brainstem (400). Microinjection of leptin in to the NTS of anaesthetized rats attenuates the reduction in heart rate associated with increased arterial pressure induced by intravenous administration of the α1-adrenergic receptor agonist phenylephrine, indicative of a negative effect of leptin on baroreflex sensitivity (15). In contrast, in the same study NTS leptin administration failed to impact the compensatory increase in heart rate associated with intravenous sodium

nitroprusside-induced decreases in arterial pressure, or acutely impact resting arterial pressure or heart rate. Together these data suggest that NTS leptin may specifically modulate the parasympathetic arm of the baroreflex (15); however, further data also exist that suggests that forebrain and not brainstem sites are important in modulating leptin's effects on the baroreflex (356). In addition to modulating parasympathetic activity, data suggests that administration of leptin into the caudal (but not rostral) NTS increases sympathetic nerve activity in the kidney, yet not BAT (381) implying regional differences in the actions on leptin on cardiovascular parameters within the NTS.

In addition to the NTS, the RVLM is an important site for regulation of sympathetic nervous system control of cardiovascular functions (137). Retrograde tracing studies indicate that leptin receptor expressing cells of the RVLM innervate the kidney and microinjection of leptin directly into the RVLM increases arterial pressure and renal sympathetic nerve activity in anaesthetized rats (34) supporting a role for this brainstem nucleus in mediating the effects of leptin on cardiovascular function.

Leptin receptors utilize a number of different signaling pathways to exert their downstream effects. Interestingly, while diet-induced obesity in rodents is associated with an attenuated response to the effects of leptin on food intake and sympathetic nerve activity in BAT (indicative of leptin resistance) the leptin-induced increase in renal sympathetic nerve activity remains intact (470). This suggests that different pathways are responsible for mediating the leptin-mediated effects on sympathetic activity to different organs.

Pharmacological and transgenic technologies have enabled the dissection of the relative contribution of different CNS leptin signaling pathways in cardiovascular physiology. Loss of endogenous homeostatic modulation of leptin signaling by SOCS3 (which itself inhibits leptin signaling) and SHP-2 (which enhances ERK mediated leptin signaling) following genetic mutation in Tyrosine985 of leptin receptors in mice [$Lepr^{L985}$ (*l/l*) mice] results in animals with elevated blood pressure and heart rate compared to littermate controls, without any notable impact on body weight (245). Leptin treatment in the *l/l* mice further elevated their blood pressure, heart rate and renal sympathetic activity compared to controls. In contrast, the leptin-induced increase in BAT sympathetic nerve activity is attenuated in *l/l* mice *f*urther emphasizing the divergent pathways regulating leptin induced control of renal- and BAT-sympathetic nerve activity (245). Complementary studies indicate that pharmacological inhibition of CNS ERK1/2 signaling has no effect on leptin induced increases in sympathetic activity in the kidney and adrenal gland but abolishes the leptin-induced increase in sympathetic activity in BAT (471). Together these studies indicate that endogenous negative feedback on the leptin signaling mediated via SOCS3 is necessary for normal cardiovascular regulation, while leptin receptor induced activation or ERK1/2 signaling is a key pathway regulating BAT but not renal sympathetic nerve activity.

Further work in the same area indicates that leptin-induced increases in sympathetic activity in the kidney, but not the adrenal gland and BAT, are inhibited by pharmacological CNS blockade of PI3K (468, 471), suggesting that this signaling pathway may be more critical in mediating the leptin-induced modulation of sympathetic activity which modulates cardiovascular function.

While less widely studied, in addition to (or likely upstream of) modulation of the autonomic nervous system, leptin has also been shown to modulate the activity of neuroendocrine systems regulating cardiovascular function (237). The renin-angiotensin system (RAS) has been implicated in mediating obesity-associated hypertension (238). Exogenous leptin treatment regulates gene expression of key elements of the RAS system in the rodent brain and periphery (258, 259). Notably in the CNS, intracerebroventricular administration of leptin increases gene expression of angiotensin-receptor 1a ($AT_{1a}R$) and angiotensin-converting enzyme (ACE) mRNA in the SFO and $AT_{1a}R$ mRNA in the ARC (259). Additionally, in the same study it was shown that pharmacological inhibition of RAS centrally using intracerebroventricular administration of losartan or captopril attenuated leptin induced increases in renal and BAT sympathetic nerve activity (259), an effect also seen in $AT_{1a}R$-deficient mice. Central administration of leptin enhances the hypertensive effect of Angiotensin-II treatment, likely through enhancing CNS RAS signaling (615), and may represent an underlying mechanism for the enhanced hypertensive effect of Angiotensin-II treatment associated with diet-induced obesity in rats (614).

Evidence for a role of leptin in modulating cognitive function

Obesity is associated with altered cognitive function in both adults and children (for review see (543)). Numerous studies have demonstrated a correlative relationship between circulating leptin levels and altered cognitive function in humans (69, 263, 335, 553) but this is not consistently the case across all studies (431, 553, 560) and causation has yet to be definitively proven.

The hippocampus is a key site for modulating emotion, learning and memory formation and is known to express leptin receptors (398). As discussed earlier in this review, there is evidence for changes in hippocampal structure and function in animals with congenital leptin-signaling defects (147, 212, 361, 544) providing evidence for a role of leptin in mediating functional hippocampal development. However, evidence also indicates a potential role for leptin in enhancing cognition *via* modulation of hippocampal function in animals without congenital leptin-deficiency (287). Both *in vivo* (597) and *in vitro* experiments (the latter performed in hippocampal slices) showed that exogenous leptin induces LTP, likely via glutamatergic [N-methyl-D-aspartate (NMDA)] receptor dependent mechanisms (372, 434, 515). Additional modulatory actions of leptin that support a role of leptin in modulating hippocampal synaptic plasticity include reversal of evoked LTP (411) and induction of long-term depression (LTD) in recording conditions that promote enhanced

excitability (165). *In vitro,* leptin can stimulate filopodial density and motility, and ultimately synapse formation in cultured hippocampal neurons (429), providing a mechanistic basis for the enhanced LTP seen following leptin administration. At the molecular level, leptin-induced dendritic spine formation in the hippocampus appears to require activation of the calcium/calmodulin-dependent protein kinase II (CaMKII) signaling cascade and transient receptor potential cation (TRPC) channels (147, 434). These molecular and neurophysiologic changes are reflected in an ability of peripherally administered leptin to enhance the performance of rodents in hippocampal-dependent spatial learning tasks, such as the Morris water maze (434).

Based on its ability to enhance cognitive function (434) and enhance hippocampal synapse formation in animal models (148, 429, 434), leptin has also been explored as a potential therapeutic agent in neurodegenerative diseases such as Alzheimer's disease (AD) in which loss of hippocampal function is a key pathologic feature. *In vitro,* in neuronal cultures and mouse brain extracts, leptin can reduce amyloid-beta (Aβ) secretion (190, 223) and tau-phosphorylation (156, 222-224), which are believed to play a key role in AD pathogenesis. Functionally, leptin can prevent the negative effects of Aβ on LTP *in vitro* and reduce Aβ-induced neuronal cell death *via* a STAT3 mediated mechanism (156). The functional relevance of these *in vitro* studies are confirmed by *in vivo* work that demonstrates that chronic exogenous peripheral leptin treatment is able to reduce pathologic features and enhance cognitive performance in a transgenic mouse model of AD (221, 222). These effects have also been recapitulated in a distinct animal model of AD by an independent research team using a viral-gene delivery approach to enhance leptin levels directly in the brain (454). In normal rats, chronic intracerebroventricular leptin is able to attenuate the impairments in both spatial memory and hippocampal LTP induced by a single acute intracerebroventricular injection of $A\beta_{1-42}$ peptide (566). These animal studies are promising, but further work is needed to determine how these findings may translate to humans.

Adiponectin

Adiponectin is a 244 amino acid protein secreted by adipose tissue (273) which circulates in human plasma at ~1.9-17.0 mg/ml in the form of homomultimers of trimers, hexamers and high molecular weight multimers (HMW) (14, 419, 588). The protein has an N-terminal domain containing collagen repeats whereas the C-terminal has a globular structure which, when cleaved from the mature protein by leukocyte elastase released by monocytes/neutrophils (589), produces globular adiponectin (gAd). The gAd has distinct pharmacological properties from the HMW (3, 198). Mutations within the gene alter the formation of di-sulfide bonds, which impact the ability of adiponectin to form larger HMW. For example, human mutations G90S and G84R prevent adiponectin from forming HMW (588) and are associated with diabetes (584). Moreover,

adiponectin is also post-translationally modified at a number of leucine residues within the globular domain (specifically, residues 68, 71, 80 and 104) and mutation of these residues to arginine, prevents hydroxylation and glycosylation, which abrogates the formation of HMW (594). Importantly, prevention of lysine modification of adiponectin reduces the ability of adiponectin to stimulate AMPK in the liver. Furthermore, treatment of obese *db/db* mice with non-post-translationally modifiable adiponectin (at lysine residues 68, 71, 80 and 104) severely diminishes the ability of adiponectin to reduce hyperglycemia, hyperlipidemia and insulin resistance, suggesting that hydroxylation and glycosylation of adiponectin plays an important role in the insulin-sensitizing function of adiponectin (594). Mutations in the gene have also been reported to alter adiponectin secretion. A mutation resulting in an isoleucine to threonine change at position 164 (I164T) alters the secretion of adiponectin from adipocytes and is associated with the presence of metabolic syndrome (312).

Generally, plasma levels of adiponectin are higher in females than males (124, 440) and circulating levels are significantly lower in people with type-2 diabetes (T2D) (268) and obesity (14), but higher in those with type-1 diabetes (T1D) (379). Adiponectin mRNA expression and secretion from mouse 3T3-L1 adipocytes *in vitro* is downregulated by proinflammatory stimuli such as IL-6 and tumor necrosis factor (TNF) α (73, 187) through a mechanism partly dependent on intact p42/44 MAPK signaling (187). Adiponectin secretion can be increased following weight loss (73), suggesting that changes in adiponectin expression and secretion are sensitive to and respond to the inflammatory stimuli associated with diet-induced obesity. Moreover, adiponectin expression is enhanced by thiazolidinedione (TZD) treatment, in a peroxisome proliferator-activated receptor (PPAR) γ2-dependent manner (230, 375) in insulin-resistant humans and rodents (375).

Adiponectin-deficient mice were generated in 2002; heterozygote mice were reported to be mildly insulin-resistant, whereas the homozygote knockout animals were moderately insulin resistant and glucose intolerant (332, 420), overall, suggesting a critical role for adiponectin in the maintenance of glucose homeostasis. The defects in glucose homeostasis in null animals are exacerbated by high-fat feeding (420), an effect which may be related to elevated plasma TNFα and reduced free fatty acid clearance (374). Nawrocki et al., (2006) also demonstrated that induction of muscle and liver AMPK activity by TZDs was absent in adiponectin null animals, indicating that at least in part, the therapeutic benefit of TZDs is dependent on intact adiponectin-AMPK signaling. This is further strengthened by the observation that pioglitazone-induced improvement in hepatic insulin resistance in *ob/ob* mice is ablated in adiponectin null *ob/ob* mice (331).

Adiponectin knockout animals are resistant to high-fat diet-induced obesity, primarily mediated by increased leptin sensitivity (333). In addition to having alterations in glucose homeostasis,

adiponectin-null animals have increased vascular damage following external vascular cuff injury, supporting a role for adiponectin in maintaining vascular health (332).

Adiponectin entry into the brain

The origin of adiponectin that activates CNS receptors is debated. Adiponectin is found in the CSF from humans and mice; however, the CSF:plasma ratio varies between species. For example, in mice the CSF concentration of adiponectin is approximately 1-4% of plasma (464) whereas in humans, the CSF concentration of adiponectin is lower, at approximately 0.1% of plasma (325, 334); although it should be noted that not all studies have detected adiponectin in the CSF of humans (535).

Recent evidence suggests that adiponectin can directly permeate the BBB. In adiponectin null animals' adiponectin was detected in CSF samples taken three hours after injection of trimeric adiponectin, indicating that the low molecular weight adiponectin can directly enter into the CNS from the circulation (621).

Adiponectin receptors

Adiponectin has two receptors termed AdipoR1 and AdipoR2, which were cloned in 2003 (588). AdipoR1 in humans and mice share 96.8% homology and the AdipoR2 shares 95.2% identity (617). While not G-protein coupled, both receptors have 7 transmembrane domains and have proteins with predicted molecular masses of 42.4 kDa and 35.4 kDa for mouse AdipoR1 and AdipoR2, respectively. AdipoR1 is relatively ubiquitously expressed, with the highest expression seen in skeletal muscle, whereas AdipoR2 is most abundantly expressed in mouse liver (617).

AdipoR1 and R2 can interact with the adaptor protein APPL1 and in neurons adiponectin can stimulate a number of signaling pathways (**figure 3**) including the insulin receptor substrate1/2 (IRS1/2) pathway leading to increased Akt (serine 473) and ERK (threonine 202/tyrosine 204) phosphorylation (128). Adiponectin can also stimulate the JAK2-STAT3 pathway (128), increasing tyrosine 705 phosphorylation, which is required for transcriptional activation. The adipokine can also activate the AMPK pathway (333), increasing threonine 172 phosphorylation, which greatly enhances kinase activity. In some cell types, particularly vascular endothelial cells, adiponectin can increase eNOS (serine 1177) phosphorylation via the AMPK pathway (422), leading to increased nitric oxide production. This is a neuroprotective pathway and is discussed in more detail below.

Adiponectin receptors in the CNS

Within the CNS, both AdipoR1 and AdipoR2 are found in the hypothalamus in post-mortem human tissue; although, AdipoR1 is expressed throughout the hypothalamus, whereas AdipoR2 is restricted to the PVH (325). In mouse, AdipoR1 is found in the cortex, hippocampus, striatum, thalamus and hypothalamus (**table 4**). Within the hypothalamus, AdipoR1 is localized within the supraoptic nucleus (SON), PVH and ARC (229). AdipoR2 expression is less widespread, being limited to regions of the cortex, hippocampus, amygdala, thalamus and anterior cingulate cortex (ACC) (316) (**table 5**). Within the hypothalamus, AdipoR2-expressing cells are found within the anterior hypothalamic area (AHA) and LHA, perifornical region, SON, PVH and ARC. Within the mouse hypothalamus, AdipoR1 and AdipoR2 are located on both NPY and POMC neurons (229) and on warm-sensitive neurons of the POA, that control the regulation of core body temperature (316).

The expression of both receptor types in the CNS is predominately neuronal although AdipoR1 and AdipoR2 expression is found on GFAP-positive cells, on ependymal cells and tanycytes lining the third ventricle (229). Adiponectin receptors are also expressed within the endothelial cells of the BBB (535), suggesting that some of the metabolic effects of adiponectin may be mediated by altered signaling in brain microvascular endothelial cells.

Adiponectin in neurodevelopment and neurogenesis

High-fat feeding is known to reduce hippocampal neurogenesis in rats (362) and mice (446), with neurogenesis within the dentate gyrus being particularly sensitive to alterations in metabolic state. Moreover, exercise is a known stimulator of neurogenesis in the dentate gyrus (582). Yau and colleagues (2014) investigated whether the exercise-induced changes in hippocampal neurogenesis were dependent on intact adiponectin signaling. They found that after running, hippocampal levels of adiponectin were significantly elevated, in the absence of any changes in AdipoR1, AdipoR2 or the downstream adaptor protein APPL1. Moreover, adiponectin-null animals had diminished running-induced hippocampal neurogenesis, in the absence of any changes in baseline neurogenesis, suggesting that adiponectin specifically regulates exercise-induced neural cell proliferation (621). This work was complemented by another study indicating that adiponectin application can increase the proliferation of cultured hippocampal neural stem cells/progenitors isolated from adult rats. In these cells, adiponectin activated both AMPK and p38 MAPK, however, only p38 MAPK signaling was involved in adiponectin-induced proliferation, as inhibition of this kinase using SB203580 blocked the effect of adiponectin, whereas inhibition of AMPK using compound C was without effect on proliferation (632).

In addition to neural stem cell proliferation, data suggests that adiponectin may also exert trophic effects on neuronal outgrowth. Loss of adiponectin results in decreased dendritic length, reduced

branching and spine density in hippocampal dentate gyrus granule neurons, whereas infusion of adiponectin increased dendritic spine density (633).

Adiponectin and regulation of food intake

As described above, AdipoR1 and AdipoR2 are expressed within the hypothalamus. Specifically, both receptors are expressed in NPY and POMC neurons within the ARC (229). Intravenous administration of adiponectin increases food intake in mice (333) and stimulates the activity of hypothalamic AMPK, a known driver to food intake (403). Interestingly, adiponectin-induced increases in food intake are dependent on AdipoR1-mediated activation of AMPK. Knockdown of AdipoR1 prevents adiponectin-induced increases in hypothalamic AMPK, whereas knockdown of AMPK prevents adiponectin-induced increases in food intake (333). Adiponectin-null animals have significantly reduced basal AMPK phosphorylation in the hypothalamus, suggesting a constitutive role for adiponectin in stimulating hypothalamic AMPK activity.

In contrast, another study has suggested that adiponectin action in the hypothalamus decreases, rather than increases food intake (128). In this study, adiponectin was administered directly into the cerebroventricular system in the brain (intracerebroventricular) as opposed to the intravenous injection utilized by Kubota and colleagues (333). The central administration study by Coope et al (128) went on to demonstrate that adiponectin predominantly utilizes AdipoR1 to alter metabolism and that activation of this receptor recapitulated key features of insulin and leptin-induced signaling pathways, namely activation of the IRS-Akt-forkhead box protein 01 (FOXO1) pathway and the JAK2-STAT3 pathway (128). A 2016 study by Sun et al demonstrated that adiponectin and the small molecular AdipoR agonist AdipoRon excited ARC POMC-expressing neurons (545). This study also showed that adiponectin could directly inhibit ARC NPY/AgRP neurons via the activation of the ATP-sensitive K^+ channel (K_{ATP}). Therefore suggesting that adiponectin could inhibit feeding via direct activation of POMC neurons and simultaneous inhibition of NPY/AgRP neurons, thus reducing inhibitory synaptic input onto POMC neurons (545). The discrepancies in the effect of central compared with peripheral administration of adiponectin on food intake may be dependent on ambient glucose concentrations. During fasting, intracerebroventricular injection of adiponectin significantly decreases food intake; however, co-injection of glucose with adiponectin stimulated food intake (548). This divergence may be explained by differential regulation of ARC POMC neurons at differing glucose concentrations. Using *ex vivo* slice patch clamp experiments in POMC-hrGFP mice, application of adiponectin in the presence of high glucose (10 mM) induced hyperpolarization of POMC neurons, in an AMPK dependent manner. Whereas, during lower glucose (euglycemic; 5 mM), adiponectin depolarized POMC neurons in a PI3K-dependent manner. It should also be noted that the study by Sun et al 2016, also noted adiponectin-induced depolarization of POMC-expressing neurons, however, further lowering of extracellular glucose

over the physiological range (0.5-5 mM) failed to modify the adiponectin response (545). This suggests that supraphysiological glucose levels, where AMPK is sufficiently inhibited, may modify the adiponectin response.

Adiponectin may also play a role in treatment-induced changes in body weight in T2D. For example, while TZDs are anti-hyperglycemic drugs, they can promote weight gain. One mechanism by which this is believed to occur is via the action of TZDs as agonists of PPARγ, leading to lipogenesis, fluid retention and increased appetite. TZDs are also known activators of AMPK signaling in the periphery (201, 496) and in the brain (466), and recent evidence suggests that the TZD pioglitazone (PIO) increases food intake, adiposity, body weight and reduces energy expenditure via a mechanism requiring ARC AdipoR1-mediated activation of AMPK (466). Following PIO treatment, animals had increased serum levels of adiponectin and, despite weight gain observed in PIO-treated animals, hypothalamic leptin and insulin-sensitivity were improved as indicated by the restoration of insulin-induced Akt phosphorylation and leptin-induced pSTAT3 in high-fat fed animals. This improved leptin and insulin sensitivity was also reflected in a restoration of leptin and insulin-induced decrease in acute food intake in PIO-treated mice (466).

Adiponectin and thermogenesis

In addition to impacting energy homeostasis by modulating food intake, recent evidence suggests that adiponectin may play a role in modulating energy expenditure/adaptive thermogenesis. Hui and colleagues (2015) demonstrated that adiponectin expression is significantly increased in the subcutaneous WAT (scWAT) of mice exposed to chronic cold (277). Moreover, this accumulation of adiponectin in scWAT was associated with increased browning of WAT, driven by an enhancement of anti-inflammatory M2 macrophage accumulation in this tissue. Treatment of mature adipocytes with adiponectin increased the expression of uncoupling protein 1 (UCP1), a marker of brown adipose tissue, which was blocked by the AMPK inhibitor Compound C. Moreover, the accumulation of adiponectin was not dependent on AdipoR1 or AdipoR2, but instead the effect was mediated by T-cadherin, which was predominantly expressed on M2 macrophages (277). Taken together, these data suggest that adiponectin drives browning of scWAT.

Further indirect evidence for a role for adiponectin in regulating thermogenesis comes from the study by Kolumam et al (323). This group used an antibody to activate the fibroblast growth factor 1 (FGF1)/βKlotho complex, which when administered produced a variety of beneficial effects in both mice and monkeys, including increased energy expenditure, browning of WAT, weight loss and improved glucose and lipid homeostasis. Importantly, the levels of HMW adiponectin were significantly increased in animals treated with the FGF1/βKlotho-activating antibody and loss of

adiponectin partially reduced the beneficial metabolic effects. The authors propose that the later beneficial effects of the antibody are mediated by adiponectin-dependent browning of WAT. In this study however, it should be noted that the effect of FGF1/βKlotho antibody on insulin-sensitization was independent of adiponectin (323). Further indirect evidence suggests that adiponectin may promote thermogenesis as the study by Hou et al (269) determined that treatment of mice on a high fat diet with irisin, a myokine released from exercising muscle, increased circulating adiponectin and increased markers of browning on WAT, UCP1 and Cidea (269). Although this study did not determine whether browning of WAT by irisin required adiponectin, but it does suggest that adiponectin may be involved. A central effect of adiponectin, may at least in part, contribute to the regulation of heat production as AdipoR1 and AdipoR2 expression has been detected on warm-sensitive neurons within the POA of the hypothalamus, which is involved in thermoregulation. Moreover, central adiponectin injection into the POA increases core body temperature with a concomitant decrease in respiratory exchange ratio (RER), indicating increased lipid oxidation (316). This study demonstrated that both AdipoR1 and AdipoR2 contributed to heat production as knockout of either receptor blunted the adiponectin-induced changes in core body temperature. Interestingly, only loss of AdipoR1 altered the decrease in RER, suggesting that AdipoR1-expressing POA neurons are involved in regulating lipid oxidation/activation of brown adipose tissue, whereas AdipoR2-expressing neurons do not (316).

These studies are in contrast to the study by Qiao and colleagues who demonstrated a suppressive role for adiponectin in browning of adipose tissue (465). In this study, adiponectin knockout animals displayed a higher core body temperature than wild-type mice suggesting a repressive role for adiponectin on browning of adipose tissue during cold exposure. Moreover, viral overexpression of adiponectin in wild-type mice suppressed UCP1 expression in brown adipose tissue, which occurred without a change in mitochondrial DNA copy number (465). This study also demonstrated that adiponectin overexpression reduced β3 adrenergic receptor-mediated lipolysis and thermogenesis. Clearly, further research is required to determine the role of adiponectin in regulating browning of WAT/thermogenesis and under which conditions this adipokine may play a positive or negative role in promoting thermogenesis.

Adiponectin and reproduction

Adiponectin levels increase from birth to adulthood in mice, with the increase larger in female than male mice (124). Moreover, during pregnancy the levels of adiponectin decrease from the 2nd trimester onwards in mice, correlating with the change in circulating prolactin. Direct infusion of prolactin in female mice has also been shown to decrease circulating adiponectin levels (124).

In humans, adiponectin levels also decline during pregnancy, reaching a nadir during lactation (19), moreover, direct application of prolactin to primary cultures of adipocytes decreased adiponectin expression and secretion, suggesting that prolactin drives down adiponectin expression during lactation to promote the storage of fat.

Adiponectin and AdipoR2 are expressed in the human placenta, specifically localized to cytotrophoblast and syncytiotrophoblast cells (82). Treatment of human placental tissue with gAd has been reported to paradoxically increase the release of proinflammatory cytokines IL-1β, IL-6, TNFα and prostaglandins E2 and F2α in an ERK1/2 dependent manner (337). Moreover, the adiponectin expressed in human placenta is secreted and can stimulate ERK1/2 and p38 MAPK signaling when conditioned media from human placental tissue is added to HEK292 cells expressing AdipoR1 (102). The placental expression of adiponectin is decreased in gestational diabetes (102), correlating with the decreased circulating levels seen in women with gestational diabetes (481, 605). The decreased placental production of adiponectin is likely driven by proinflammatory cytokines directly, as application of TNFα, interferon (IFN)-γ and IL-6 all acutely decrease adiponectin secretion from this tissue (102).

In mice, transgenic overexpression of adiponectin produces female mice that are infertile (125). Moreover, women with T1D are subfertile compared to the general population (295) and have been shown to have higher circulating adiponectin levels (379), including throughout the gestational period (474). Importantly, the pituitary gland expresses adiponectin and both AdipoR1 and AdipoR2 (462), specifically within the growth hormone (GH), FSH-, LH- and TSH-producing cells. Using LβT2 pituitary gonadotropic cells, Lu and colleagues demonstrated a functional role for adiponectin in regulating LH secretion. This study showed that LβT2 cells expressed both AdipoR1 and AdipoR2 and treatment with adiponectin led to increased AMPK activation, which was accompanied by decreased LH secretion (which could be mimicked by pharmacological or genetic activation of AMPK). This indicates that the suppression of LH is directly mediated through activation of the AMPK pathway (370).

There is also evidence to suggest that adiponectin may influence the hypothalamic-pituitary-gonadal (HPG) axis at the level of the hypothalamus. Adiponectin has been reported to inhibit GnRH release from cultured hypothalamic GT1-7 cells and in primary mouse hypothalamic cultures in an AMPK-dependent manner (107, 320, 601). As described in the section on leptin and reproduction above, kisspeptin is the peptide hormone encoded by the Kiss1 gene responsible for initiating GnRH release at puberty. Adiponectin inhibits Kiss1 mRNA production in GT1-7 cells, also via an AMPK-dependent pathway (600). Together, these data suggest that increased adiponectin levels associated with starvation/negative energy balance, decrease fertility and puberty via a mechanism involving the suppression of GnRH and LH secretion in the

hypothalamus and pituitary, respectively. Indeed, increased adiponectin levels may explain reduced fertility and the delayed onset of puberty seen in T1D (364).

Bone, energy homeostasis and adiponectin

Osteoblasts and osteoclasts are bone-specific cells that have recently been described as playing a role in maintenance of energy metabolism. Interestingly, mice genetically engineered with loss of osteotesticular protein tyrosine phosphatase (OST-PTP) specifically in osteoblasts are lean, protected from high fat diet-induced obesity and are hypoglycemic (347). This is mediated by hyperinsulinemia due to increased β-cell proliferation combined with increase insulin sensitivity. These animals also display specific hyperadiponectinemia without changes in other circulating adipokines (347). Moreover, co-culture osteoblasts with adipocytes, increased adiponectin expression and loss of OST-PTP further enhanced adiponectin expression, suggesting that a molecule secreted from osteoblasts mediated this response. Furthermore, the hyperinsulinemic/hypoglycemic phenotype of OST-PTP deficient mice could be rescued by deletion of a single copy of osteocalcin, a molecule specifically secreted from osteoblasts, suggesting that osteocalcin directly regulates adiponectin production and β-cell proliferation (347). Interestingly, the link between bone and adiponectin levels may be reciprocal since adiponectin knockout mice have a higher than normal bone density at 6 weeks of age, whereas adiponectin-overexpressing mice have decreased bone mass (297). However, older adiponectin knockout mice develop low bone mass mediated by decreased proliferation of osteoblasts. This led Kajimura and colleagues to speculate that perhaps loss of adiponectin at older ages led to increased sympathetic nervous system activation, which is a stimulator of bone reabsorption (173). This group partially reduced sympathetic tone by removing one copy of dopamine β-hydroxylase (an enzyme involved in catecholamine synthesis), in mice and crossed these with adiponectin-null mice. The resulting offspring showed maintained bone mass at later stages of life, mediated by increased osteoblast proliferation and increased bone mass (297). Taken together, these studies suggest a complex interplay between the peripheral and central effects of adiponectin on bone formation and metabolism.

Adiponectin and mood disorders

Adiponectin has been proposed to have anti-depressive/anxiolytic actions in the CNS. For example, correlative data indicates that plasma adiponectin levels are decreased in patients with major depressive disorder (350, 354) and bipolar depression (280), independently of effects on body weight. A potential mechanism of action of the anti-depressive effects of adiponectin is via an anti-inflammatory action. For example, direct injection of adiponectin into the CNS decreases

pro-inflammatory cytokine expression in microglia from chronically stressed mice (95). Furthermore, the ability of environmental enrichment to reduce stress and the elevations in CNS proinflammatory cytokines (IL-1β, IL-6 and TNFα) in the hippocampus and hypothalamus associated with the chronic administration of corticosterone in mice is lost in adiponectin-null mice (95). Together these data suggests that adiponectin signaling may modulate microglial activation and neuroinflammation in the CNS, which in turn could influence behavior.

Patients with schizophrenia treated with antipsychotic drugs have been reported to present with low serum adiponectin, due to increased adiposity driven by the drug treatment (318, 319). Moreover, the alteration in adiponectin levels is drug specific. In humans, a prospective study found that plasma adiponectin levels were decreased in schizophrenic patients treated with olanzapine, but not those taking risperidone. Although both patient groups gained weight, the decreased adiponectin levels seen in the olanzapine group were associated with the most pronounced weight gain; however, the olanzapine-associated decrease in adiponectin levels were still significant after adjusting for BMI. Recent data suggests that individuals taking clozapine and olanzapine have significantly lower plasma adiponectin that those taking risperidone (36) and that low serum adiponectin levels in male patients is a specific marker for weight gain on clozapine treatment (319). These metabolic side-effects of second generation anti-psychotics have a significant impact of patient welfare, leading to emotional issues related to weight gain and in some cases poor compliance with the treatment (576).

CNS mediated effects of adiponectin on cardiovascular physiology

A major component of the metabolic syndrome is the increased risk of cardiovascular disease, predominately driven by hypertension. Several studies have explored the links between low adiponectin levels and hypertension (2, 289, 304). The current data suggests that lower adiponectin levels correlate with higher blood pressure in both men and women (2, 304). A potential role for adiponectin in modulating cardiovascular physiology is further supported by studies which indicate that polymorphisms in adiponectin itself may underlie blood pressure responses to dietary salt intake. Single nucleotide polymorphisms (SNPs) at rs16861205 and rs822394 in the adiponectin gene were associated with diastolic blood pressure (DBP) response to low salt loading, with the latter SNP also being associated with mean arterial pressure in the Chinese Han population (115). These same SNPs were also associated with the DBP response to high salt loading.

With the CNS the brainstem is an important integratory site for cardiovascular and autonomic sensory afferents, specifically the NTS, which is involved in the baroreceptor reflex which maintains blood pressure homeostasis. Neurons in the NTS express both the AdipoR1 and

AdipoR2 and infusion of adiponectin directly into the NTS in rodents has been reported to decrease blood pressure (270). This is mediated by modulation of the electrical activity of NTS neurons, with the majority of NTS neurons being excited by adiponectin and a proportion being inhibited. In single cell RT-PCR analysis, the majority of the cells depolarized by adiponectin were found to be NPY- and glutamic acid decarboxylase 67 (GAD67)-positive, suggesting that adiponectin acts on the AdipoR1 to depolarize NPY-containing neurons, thereby increasing GABAergic neurotransmission (270).

An independent study also demonstrated that the electrical activity of neurons within the AP, which project to the NTS, are regulated by adiponectin. Neurons within the AP express both AdipoR1 and AdipoR2, and stratifying neuronal responses based on AdipoR expression, indicating that only the neurons which expressed both AdipoR1 and AdipoR2 tended to be electrically altered by adiponectin. In contrast to the work in the NTS (270), this study, demonstrated that adiponectin injection directly into the AP increased, rather than decreased, blood pressure (200). This suggests that the downstream regulation of blood pressure may require the integration of signals from a number of different brain nuclei and further work remains to be done to elucidate the CNS mediated effects of adiponectin signaling on cardiovascular physiology.

Neuroprotective actions of adiponectin

Adiponectin may play a role in protecting neurons during ischemic stroke. Recent data suggests that polymorphisms in both AdipoR1 and AdipoR1 are associated with an increased risk of ischemic stroke in a Chinese population (241, 626). This is supported by animal studies indicating that adiponectin-null animals have a larger infarct area following medial cerebral artery occlusion (MCAO) injury (an experimental model of ischemic stroke) compared to wild-type animals (422). This study also showed that adiponectin protein was localized to the endothelial compartment during transient ischemia, suggesting that adiponectin can accumulate at the site of injury, possibly entering via areas where the BBB is damaged. Moreover, administration of adiponectin using a viral approach could reduce infarct size in both wild type and adiponectin-null animals, an effect that was associated with the increased phosphorylation of endothelial nitric oxide synthase (eNOS). In this study, adiponectin-null mice also displayed reduced cerebral blood flow suggesting that adiponectin-induced activation of eNOS increases perfusion to reduce neuronal damage/death (422). A more recent study found that obesity caused by a Western diet (known to reduce circulating plasma adiponectin levels) in rats, increased MCAO injury and symptom scores of neurological deficits (610). The cellular damage in the hippocampus, striatum and frontal cortex and the neurological deficits could be partially rescued by viral transfer of adiponectin (610).

In sepsis, endothelial dysfunction is a major factor in organ damage, including damage to the brain. Sepsis increases platelet and leukocyte-adhesion in the cerebral microcirculation and this is augmented by the loss of adiponectin. These effects were accompanied by increased BBB dysfunction in these mice (578). Moreover, in obese mice, sepsis induced neuroinflammation, microvascular dysfunction and brain function are impacted more severely than reported in lean animals. Given that obesity is associated with lower adiponectin levels and the evidence suggesting obese individuals have an increased mortality during sepsis, it is plausible that the increased sepsis-associated mortality as seen in obesity may in part, be due to hypoadiponectinemia.

Further evidence for a potential neuroprotective effect of adiponectin comes from animal models of epilepsy. In an experimental model of kainic acid (KA)-induced seizure activity, serum adiponectin levels decreased following KA treatment. This was accompanied by an increase in AdipoR1 expression in the hippocampus, without altering AdipoR2 expression (294). KA also significantly increased markers of cell death including TUNEL and caspase-3, which were all significantly reduced by pre-treatment with adiponectin for 24 hours (294). This study also demonstrated that KA-induced neuroinflammation (as measured by NFκB immunoreactivity) was also diminished by adiponectin, further demonstrating an anti-inflammatory role of adiponectin. Adiponectin also protects against glutamate-induced excitotoxicity in hippocampal neurons. For example, exposure of mouse hippocampal HT22 neurons to glutamate increases cleavage caspase-3, Bax/Bcl2 ratio and TUNEL staining, which is reversed by adiponectin treatment. This occurs by rescue of glutamate-induced decreases in SIRT1 and PGC1α (627).

Adiponectin and neurodegeneration

Obesity and diabetes are linked with increased risk for developing dementia (406), including AD (351, 371), with people with diabetes having an odds ratio of approximately 1.6 for risk of developing dementia. As mentioned above, adiponectin levels are decreased in obesity and diabetes and similarly, adiponectin levels have been reported as decreased in elderly people with mild cognitive impairment (MCI) and AD when compared to cognitively healthy age-matched controls (558). Moreover, in patients with T2D, those with MCI have significantly lower adiponectin compared to control individuals (T2D without MCI) (220). As mentioned above in AD, a key hallmark is the presence of Aβ-plaques. In a cell based study, adiponectin can protect against Aβ-induced cytotoxicity during H_2O_2-induced oxidative stress (96). Furthermore, osmotin, which is a plant-based protein homolog of adiponectin, can improve neurological deficits in a mouse and cell model of AD (514). Treatment of Aβ-overproducing SH-SY5Y cells with osmotin reduced Aβ production via a mechanism requiring activation of AdipoR1, AMPK, SIRT1 and

inhibition of sterol-regulatory element binding protein 2 (SREBP2). The activation of AMPK and increased SIRT1 expression following osmotin treatment was also observed in mice with mutant amyloid precursor protein/presenilin 1 (APP/PS1) and this correlated with the improved performance in hippocampal-dependent memory tests (Morris Water Maze and Y-maze tests) (514).

However, not all studies have found an association between circulating adiponectin levels and dementia. For example, in a Japanese population, Kitagawa and colleagues demonstrated that serum HMW adiponectin was not changed in patients with AD, vascular dementia (VAD) or other types of dementia (314). Similarly, Dukic and colleagues found no association between circulating adiponectin levels and AD, VAD or MCI (161). Conversely, two studies have identified positive correlations between adiponectin levels and MCI (306, 575). Clearly the relationship between circulating/CSF adiponectin and dementia is complex. This is likely complicated by changes in appetite and weight with dementia progression, caused by eating disturbances and altered appetitive and swallowing capabilities (296). Indeed, weight-loss *per se* has been reported to increase circulating adiponectin levels (63, 329, 620).

Adiponectin and glia

Little is known about the role of adiponectin in regulating the function of glial cells within the brain. However, both AdipoR1 and AdiporR2 are present on human U373 astrocytoma cells and cultured human primary astrocytes (590). Furthermore, AdipoR1 is present on GFAP-positive cells within the rat ARC (229), suggesting that adiponectin may play a role in regulating glial cell function. *In vitro* data from human astrocyte cells has shown adiponectin to have a potential proinflammatory role, increasing the mRNA expression of IL-6, MCP-1, IL-1β and IL-8 and also increasing the secretion of IL-6 and MCP-1 (590). However, another study demonstrated that adiponectin injection into the brain promoted an anti-inflammatory phenotype in microglia and brain macrophages in a mouse model of depression (induced by chronic corticosterone administration) (95). It is not clear whether this anti-inflammatory effect is direct on the microglial cells, or by changes in astrocyte-microglia or neuron-microglial signals. Moreover, there is currently no data indicating that microglia or oligodendrocytes express adiponectin receptors. However, adiponectin-null mice treated with KA in order to induce seizes display microglial hypertrophy and clustering in the hippocampus, providing evidence of excessive gliosis, compared to wild-type mice (344). The potential role for adiponectin signaling in glial cell functions requires further study.

Other adipokines

Excluding leptin and adiponectin, numerous adipokines have been identified that have been shown in experimental studies to exert physiologic actions via the CNS. One limitation of many of these studies is that some of these "adipokines" have themselves subsequently been found to be expressed in the CNS, making it challenging to differentiate the CNS-mediated effects of the peripherally-derived protein compared with those of the protein found in the brain. While this does not necessarily indicate that when these are proteins secreted from adipocytes they do not exert CNS-mediated effects which are functionally relevant, it does however complicate our understanding of the underlying mechanisms. Furthermore, while some adipokines have been shown to have physiological effects when injected directly into the CNS, evidence for their transport across the BBB may not have been conclusively proven making the physiological significance of some of the findings unclear; at least under non-pathologic conditions when the BBB is fully intact and functioning normally.

In the following sections we will encounter some of these issues as we review the literature around the CNS targets of some other adipokines that have been shown to have CNS-mediated effects on physiology. Much of this section will be focused on the CNS-mediated effects of these other adipokines on glucose and energy homeostasis, as this has been the main focus of much of the published work; however, other important physiological and pathological are also likely to be regulated by these proteins.

Resistin

Resistin, so-called due to its ability to induce insulin resistance, is a 12.5 kDa cysteine-rich polypeptide hormone (of the resistin-like molecule family) which was discovered as part of a study to identify adipose-derived factors that are regulated by TZD anti-diabetic drugs (540). Resistin is synthesized (during adipogenesis) and secreted from white adipocytes in rodents (540); however, in humans monocytes and macrophages are believed to be the main source (448, 503), highlighting important species differences. Elevated levels of resistin are reported in diet-induced and genetically obese mice (540) with insulin and glucose both proposed to mediate the nutritional regulation of resistin mRNA in WAT and circulating serum levels in rodents (473). In obese humans, resistin serum levels display a positive correlation with alterations in BMI, body fat, circulating insulin and mean glucose amongst others (21, 473). However, it should be stated that a minority of studies have failed to identify a relationship between resistin and known markers of insulin resistance in humans and as such it remains controversial (291, 346, 577). Of interest, in rodents resistin mRNA has also been detected in BAT, pancreatic β-cells, skeletal muscle tissue, kidney (424) and brain (47, 602).

CNS-mediated effects of resistin on glucose and energy homeostasis

Resistin is hypothesized to play a role in obesity-induced insulin resistance and T2D (119, 519) as immunoneutralization of endogenous resistin *in vivo* enhances insulin-stimulated glucose uptake and improves insulin sensitivity in high-fat diet-induced obese mice (540). In contrast, in lean mice, intraperitoneal administration of recombinant resistin results in glucose intolerance and insulin resistance (540). These findings are further supported by work in mice indicating that genetic deletion of resistin in both wild-type and leptin-deficient *ob/ob* animals improves glucose homeostasis (463), while transgenic overexpression of resistin in adipose tissue induces insulin-resistance (445).

How resistin mediates obesity-induced insulin resistance is not well understood, in part due to the fact that the target receptor has not yet been identified (22, 113). However, evidence suggests that central administration of leptin is sufficient to decrease WAT resistin mRNA levels and improve insulin sensitivity in *ob/ob* mice (20) providing a potential functional link between the two adipokines. Resistin-associated impairment in insulin sensitivity occurs primarily in the liver via modulation of hepatic gluconeogenesis (26, 472). Evidence suggests that this effect of may be mediated, at least in part, via the CNS. Hepatic insulin resistance can be induced by acute central infusion of resistin and is linked to glycogenolysis, and induction of cytokine and SOCS3 expression in the liver. These effects are thought to be mediated via the hypothalamus and depend on intact NPY Y1 signaling (414, 523). In rodents, chronic central infusion of resistin promotes inflammation and insulin resistance through hypothalamic TLR4 signal transduction *in vivo*, leading to activation of JNK and p38/MAPK signaling pathways, which upregulates IL-6, SOCS3 and PTP1B (47). This finding indicates that inflammation is a key mechanistic event mediating resistin-induced insulin resistance. Evidence also suggests that chronic central infusion of resistin is sufficient to down impair adiponectin and fibroblast growth factor 21 (FGF21) signaling in the brain and periphery but this appears to be secondary to the inflammatory effects on chronic central infusion of resistin as the effect is lost following inhibition of TL4R signaling (46).

In addition to having an effect on glucose homeostasis, evidence exists for an effect of centrally administered resistin on energy homeostasis in rodents. Intracerebroventricular administration of 10μg resistin acutely suppresses fasting-induced and typical day-time food intake in fed rats (567, 585). In this study, intracerebroventricular resistin was found to induce c-FOS and SOCS3 in the ARC suggesting a hypothalamic site of action. Indeed, centrally administered resistin prevents fasting-induced increases in orexigenic AgRP and NPY mRNA expression, whilst also decreasing anorexigenic CART mRNA expression in the ARC (585). Interestingly, chronic intracerebroventricular infusion of resistin into diabetic rats (that had undergone pancreatectomy) has little effect on food intake or body weight; however, resistin is able to attenuate the effects of

leptin on these parameters when the two were co-infused providing further evidence supporting a potential functional interaction between the two peptides (447). Central administration of resistin has also been shown to impact energy expenditure via modulation of sympathetic nerve activity: increasing skeletal muscle (lumbar) and decreasing brown adipose tissue sympathetic nerve activity (as first demonstrated in rats) potentially implicating resistin, via its effects on sympathetic nerve activity, in metabolic dysfunction seen in obesity and diabetes (328).

Other CNS-mediated effects of resistin on physiology

In addition to impacting glucose and energy homeostasis, other CNS-mediated effects of resistin have also been reported in animal models. These include a role for resistin in regulating pituitary somatotrope cell functions (487), and obesity-induced hypertension, as central resistin was found to enhance renal sympathetic nerve activity (327); thus, impacting salt and water balance (22).

Intriguingly, in contrast to mice, in human-derived adipocytes resistin is barely detectable, with mRNA levels actually reported to be higher in monocytes and macrophages (448, 503). Of note, high concentrations of leptin and insulin upregulate resistin mRNA and protein secretion in human-derived peripheral blood monocyte-enriched mononuclear cells *in vitro* (574). In human obesity, the main source of resistin appears to originate from infiltrating macrophages found in visceral WAT (132). Indeed, a role for resistin in inflammation in immune cells has been proposed, as resistin stimulates proinflammatory TNFα and IL-6 expression in human blood monocyte-enriched mononuclear cells and in both human and mouse macrophages, the latter via NFκB signaling (58, 521, 574).

Resistin has also been implicated in the pathology of a number of conditions characterized by inflammation. For example, people suffering from acute inflammatory disease display higher serum resistin levels (538) and others have suggested a pathological role of resistin in traumatic brain injury (72). Resistin could also potentially be an etiological factor in cardiovascular disease (78, 479), as exogenous resistin has been demonstrated to activate vascular endothelial cells (586) and promote the proliferation of smooth muscle cells (81).

Challenges in understanding the biology of resistin

Overall, our current understanding of the role of resistin in glucose homeostasis, inflammation and vascular disease is complicated by several findings: 1) resistin mRNA levels do not always complement the changes observed in serum resistin levels in models of obesity/T2D; 2) the expression of resistin appears to be differentially regulated both between species (humans vs. rodents) and within tissues (with respect to distribution profiles) (448, 503, 540), and 3) the

receptor mediating the physiological effects of resistin remains to be determined. Studies on resistin demonstrate its ability to activate a variety of signaling cascades; thus, it may potentially interact with one than one receptor, depending on target tissue and cell type (47, 81, 326, 327, 487).

Resistin mRNA is detected in rodent brain, in hypothalamic nuclei such as the ARC, which could be a site of endogenous resistin production (47, 602). In humans resistin has been detected in CSF (325), which may originate from within the brain or from peripheral resistin crossing the through the BBB. The finding of a CNS source of resistin means that many of the CNS-mediated effects of resistin described above could be as a result of the centrally-derived and not WAT-derived peptide pool. This further complicates our current understanding of the physiological role of this adipokine. Further studies examining the effect of selective loss of CNS compared with peripheral resistin pools could help elucidate this.

Apelin

The peptide apelin is an endogenous ligand of the class A G protein-coupled APJ receptor (556), which is reported to share most homology (~30-40%) with the angiotensin II receptor (428). Apelin and the APJ receptor are widely expressed both in the periphery and CNS in humans and rodents (342, 392, 394, 461), including in adipocytes (62). Apelin is obtained from a 77 amino acid preproprotein (preproapelin), enzymatically cleaved to produce bio-active endogenous C-terminal fragments including, apelin-13 (and its pyroglutamylated form, pGlu-apelin-13), apelin-17, apelin-36 and “synthetic” apelin-12 (141, 172, 231). The species-specific distribution of long (apelin-36) and short (for example, apelin-13) forms of apelin has been shown to vary in different tissues ((303), for review see (457)). Recently, another endogenous peptide, Toddler/ELABELA, was also found to activate the APJ receptor and was shown to be important for embryonic development in zebrafish (112, 451). Collectively, apelin-APJ signaling is relatively diverse, as various molecular forms of apelin can bind to and activate APJ receptors, recruiting different G proteins associated with a variety of intracellular cascades in a tissue- and cell-specific manner (427). Masri et al., (386) have demonstrated that the APJ receptor is differentially desensitized as a result of preferential G-protein coupling by apelin fragments.

CNS-mediated physiologic effects of apelin on energy homeostasis

Due to the widespread mRNA expression of mammalian apelin and the APJ receptor, associated functional effects have been demonstrated in the periphery and CNS (88). In 2005, apelin was identified as an adipokine, shown to be expressed and secreted from human and mouse cultured adipocytes, with increased expression seen during adipocyte differentiation (62). Nutritional

status exerts an important influence on apelin expression in adipocytes, with fasting resulting in a strong inhibition, whilst refeeding reversed this effect *in vivo*; in fact, apelin expression is directly regulated by insulin through PI3K, protein kinase C (PKC) and MAPK stimulation, with elevated apelin plasma levels and increased apelin mRNA expression reported in adipocytes from obese hyperinsulinemic mice (62). Importantly, upregulation of adipocyte apelin levels in obesity is only seen when the obesity is associated with hyperinsulinemia, indicative of insulin, rather than obesity *per se*, being a potent regulator of apelin expression (62, 92). Of interest, TNFα has also been shown to induce the expression of apelin in adipose tissue via PI3K, JNK and MAPK1/2 signaling (138). Overall, apelin appears to exert a direct anti-diabetic effect, playing an important role in glucose homeostasis (91, 97). In humans, elevated levels of plasma apelin were reported in morbidly obese and/or in type 2 diabetic subjects (253, 360), although not all studies report a positive correlation between circulating levels of apelin and BMI, highlighting once more that obesity alone does not determine circulating apelin levels (51, 91). More recently, it was shown that the intracerebroventricular injection of a high dose of pGlu-apelin-13 was capable of controlling hepatic glucose metabolism via activation of the sympathetic nervous system, the effect of which was dependent on the elevated production of hypothalamic reactive oxygen species (ROS) by apelin (158). Importantly, these authors concluded that increased levels of central apelin in obese/diabetic mice appears to actually contribute to a type 2 diabetic state, as chronic blockade of central apelin with the APJ receptor antagonist F13A, resulted in an improvement in the regulation of glucose homeostasis during the diabetic state in high-fat fed mice.

A controversial role of apelin and the APJ receptor in the central regulation of food intake exists. The intracerebroventricular administration of pGlu-apelin-13 in fed rats was shown to have no effect on food intake, with a significant increase in food intake seen during the subjective day in fasted rats only at the highest dose tested (551). In another study, it was reported that intravenous injection of apelin-13 did not alter food intake in fed or fasted rats; however, a decrease in food intake was shown after intracerebroventricular infusion of apelin-13 in fed and fasted rats (546). In addition, the central administration of apelin-12 was found to reduce food intake during the subjective night period in rats (2-4 hours post-infusion) and actually stimulated feeding in fed rats during the subjective day, but only at the highest dose and only in some rats (430). Thus, the effectiveness of apelin may depend on the level of satiety of the animal, the time of day, the dose and route of administration, and the apelin form used. The link between body weight and responsiveness to apelin was explored by Clark et al., (116), who showed that intracerebroventricular infusion of apelin-13 (at the end of the subjective day) decreased food intake in diet-induced obese rats fed a control diet, but this effect was absent in diet-induced obese rats fed a high-fat diet. This insensitivity to apelin was associated with the downregulated mRNA expression of hypothalamic APJ receptors by apelin in specifically the diet-induced obese

rats fed a high-fat diet. Of interest, the chronic (10 day) infusion of apelin-13 into the third ventricle in mice resulted in an increase in several parameters measured, including food intake and body weight (these effects were indistinguishable from saline-treated controls after day 8), with secondary effects noted such as increased locomotor activity, especially during the animal's active phase, which was accompanied by an increase in body temperature during this period (580). Higuchi et al., (255) demonstrated that chronic (14 day) intraperitoneal injection of apelin-13 in normal and high-fat fed mice resulted in a decrease in weight of white adipose tissue, with no apparent effect on food intake. This apelin-induced decrease in body adiposity was proposed to be mediated by an increase in energy expenditure, as apelin treatment was associated with the increased mRNA and protein expression of UCP1 and UCP3 in brown adipose tissue and skeletal muscle respectively (255). Furthermore, it is hard to exclude central regulation of energy expenditure by apelin as brain areas, such as the hypothalamus and sympathetic nerve activity are known to regulate UCP1 in brown adipose tissue (25, 504). Indeed, recent evidence has implicated apelin-APJ signaling in the enhancement of brown adipogenesis and adipose tissue browning, involving PI3K/Akt and AMPK signaling and relief from the known inhibitory effects of TNFα on brown adipogenesis (562). The recent report by Drougard et al., (159) showed that chronic intracerebroventricular injection of a high dose of apelin-13 in normal mice was enough to induce the hypothalamic upregulation of proinflammatory markers, in accordance with the previously reported effect of apelin *in vitro,* in microglial BV2 cells (103). In addition, this treatment in mice was associated with no change in either body weight or food intake, yet a decrease in thermogenic capacity and energy expenditure was reported and found to be associated with the decreased mRNA expression of peroxisome proliferator-activated receptor 1 alpha (PGC1α), PR domain containing 16 (Prdm16) and UCP1 in brown adipose tissue (159). These latter findings are suggestive of decreased mitochondrial biogenesis and attenuated activity and function of brown adipose tissue. Of note, the application of apelin-13 in hypothalamic slices was found to stimulate hypothalamic POMC-positive neurons *in vitro* (159), Intriguingly, within the arcuate nucleus of the hypothalamus, ~90% of apelin-positive neurons appear to be POMC-positive, with APJ receptors found to be expressed in ~50% of POMC-positive neurons (477). In line with these findings, Lee et al., (343) previously demonstrated that the application of apelin-13 in hypothalamic slices containing the arcuate nucleus enhanced the intrinsic excitability of identified POMC-EGFP neurons through Gβγ activation of phospholipase C (PLC) -β signaling and inhibition of M-currents via the downstream inactivation of KCNQ channels. It is interesting that Drougard et al., (159) saw no effect of apelin on food intake, yet also reported an enhancement of POMC activity by apelin. Such findings highlight the proposed functional heterogeneity of hypothalamic POMC neurons, with distinct subpopulations responsible for different aspects related to the regulation of food intake and energy metabolism (531).

Apelin and cognitive function

A role for apelin-13 in anxiety (559) and cognition has recently been addressed. With respect to cognition, post-training intracerebroventricular infusion of apelin-13 in mice trained in the novel object recognition memory task was shown to induce impairments in both the formation of short-term memory and consolidation of long-term memory, with no apparent impairment seen in acquisition of the memory *per se* (242). Such findings are in line with the known expression of apelin and the APJ receptor in brain regions associated with learning and memory processing (394). However, apelin and the APJ receptor are also expressed in brain areas related to the stress response (427). Indeed, apelin plays a role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, as central administration of pGlu-apelin-13 increased plasma adrenocorticotropic hormone (ACTH) and corticosterone levels, with findings from hypothalamic extracts demonstrating that this effect of apelin could be mediated through apelin stimulated release of arginine vasopressin (AVP) and corticotrophin releasing hormone (CRH) (551). Furthermore, the recent report by Li et al., (358) demonstrated that in stressed rats which displayed depressive-like and cognitive impairments, the repeated intracerebroventricular infusion of apelin-13 resulted in an anti-depressant-like phenotype, as evaluated in the forced swim and learned helplessness tests. In addition to this, apelin-13 was able to reverse the memory impairment seen in the novel object recognition test in stressed rats, the mechanism of which involved PI3K and MAPK1/2 activation. Thus, apelin-APJ signaling may prove to be a useful target for the treatment of depression.

Other CNS mediated effects of apelin

Functionally, apelin has been shown to be important in cardiovascular functions, regulating both blood pressure and vascular tone via nitric oxide signaling (292, 342, 557) and it also displays angiogenic properties (298). A pathophysiological role of apelin-APJ signaling has been described in human cardiovascular disease (458); however, neuroprotective effects of apelin-APJ have also been described in a model of ischemic/reperfusion injury in rats (631). In line with this, in the CNS, the intracerebroventricular infusion of apelin-13 was found to be neuroprotective suppressing neuroinflammation in an experimental rat model of ischemic stroke (612). In addition, apelin has been shown to play a role in the central control of body fluid homeostasis, involving modulation of AVP release by apelin at the level of the hypothalamus (141, 478, 485).

Does adipocyte-derived apelin exert physiological effects via the CNS?

Although, peripheral administration of apelin-12 increased c-FOS immunoreactivity in a number of brain areas including the PVH, LHA, LPB, NTS and DMX (552), it should, however, be noted that

apelin transport across the BBB has not as of yet been conclusively demonstrated (619). As such, it is unclear whether adipocyte-derived apelin exerts any CNS mediated effects on physiological processes, particularly in the context of obesity /hyperinsulinemia when adipose tissue levels are elevated (62). Further study examining the relative impact of CNS compared with adipose apelin deficiency on normal physiology and pathology may help to address this question.

Visfatin

Visfatin, a 52 kDa protein, first identified as an adipokine in 2005 was shown to be predominately produced and secreted by human and mouse abdominal visceral fat, with plasma levels positively correlating with both the amount of visceral (but not subcutaneous) fat in humans and the development of obesity in mice (204). Visfatin was found to correspond to pre-B-cell colony-enhancing factor (PBEF) (204), a protein with cytokine activity mainly expressed in lymphocytes and other cells found in human bone marrow, muscle and liver (499), also recognized for its nicotinamide phosphoribosyltransferase (NAMPT) activity (488). For clarity, visfatin, PBEF and NAMPT are acknowledged as the same protein (135, 276, 532). Visfatin/NAMPT exists in 2 forms in mammals: the intracellular form which is accepted to have nicotinamide adenine dinucleotide (NAD^+) biosynthetic enzyme function in cellular redox reactions, and an extracellular form the function of which remains controversial, with various attributed roles including as an insulin-mimetic adipokine, proinflammatory cytokine and NAD biosynthetic enzyme (210), all of which will be discussed below. A potentially important role of visfatin in physiology and/or development is supported by the finding that germ-line deletion of the visfatin gene results in embryonic lethality in homozygous deficient animals (204).

Effects of visfatin on glucose and energy homeostasis

Initial findings by Fukuhara et al., (204) demonstrated a glucose-lowering (insulin-mimetic) effect of visfatin through the acute intravenous injection of recombinant visfatin in wild type mice, insulin-resistant obese (KKAy) mice and in streptozotocin-induced models of diabetes in mice. Indeed, chronic administration of recombinant visfatin via adenoviral vector delivery in wild type and KKAy mice also resulted in a lowering of plasma glucose (and insulin) levels. Although animals homozygous for a deletion in visfatin (visfatin$^{-/-}$ mice) died during embryogenesis, animals heterozygous for the deletion (visfatin$^{+/-}$ mice) showed a seemingly normal metabolic phenotype (including body weight and growth rate) except for mild elevations in circulating glucose and slightly impaired glucose clearance in a glucose tolerance test (204). Furthermore, in *in vitro* studies in 3T3-L1 adipocytes and L6 myocytes, visfatin (like insulin) was found to stimulate glucose uptake, whilst also suppressing glucose release in H4IIEC3 hepatocytes (204).

Visfatin was found to bind the insulin receptor (at a different site to that of insulin) and activate downstream insulin signaling, involving the phosphorylation of the insulin receptor, IRS-1 and IRS-2 and activation of PI3K/Akt and MAPK signaling in cultured adipocytes, myocytes and hepatocytes (204). Yet, the binding of visfatin to the insulin receptor was later discovered to be batch-dependent (of purified recombinant visfatin protein preparation), resulting in the subsequent retraction of the original article (203). Nonetheless, findings from other groups reported similar insulin mimetic effects of visfatin in cultured osteoblasts (611) and a possible interaction between visfatin and the insulin receptor to induce glucose uptake in cultured kidney mesangial cells (533). In contrast, a study by Revollo et al., (482) provide strong evidence against an insulin-mimetic action of visfatin instead proposing that the effects of visfatin on glucose homeostasis are mediated by impacting NAD^+ biosynthesis and subsequent regulation of insulin secretion from pancreatic β-cells.

Elevated plasma visfatin levels have been reported in obese and non-obese patients with T2D (104, 171) and in both overweight and obese patients associated with MetS (192). However, the relationship between visfatin and metabolic disorders remains controversial (50, 286, 439), for review see (210)). A potential role for visfatin in the pathogenesis of cardiovascular disease associated with obesity and T2D has been proposed based on evidence of effects of visfatin on vascular inflammation (4, 136). Indeed, visfatin levels and/or mRNA expression in humans appear to be elevated in several other inflammation-associated conditions including, chronic obstructive pulmonary disease (363), rheumatoid arthritis (70, 391, 436) and osteoarthritis (105, 391).

The presence of visfatin in the CNS of rats was first demonstrated in 2003 (315) and some years later visfatin was also identified in human CSF (239). First, the previous observation that elevated plasma visfatin levels were associated with increasing BMI and body fat mass in human subjects was also confirmed by Hallschmid et al., (239); second, they reported the presence of visfatin in human CSF (at ~10% to that of plasma levels); third, a decrease in CSF visfatin levels was found to be related to the incremental rise in several factors including, plasma visfatin levels, BMI, body fat mass and insulin resistance in humans subjects. The authors concluded that since only body fat mass (adiposity) was independently associated with CSF visfatin levels, the decrease in CSF visfatin levels observed may reflect an impaired transport of visfatin across the BBB in obesity and/or may contribute to obesity-related pathologies (239). To date, the direct action of visfatin at the level of the BBB has not yet been explored yet given its impact of vascular endothelial cells (described above) (4, 136) a potential proinflammatory effect on BBB endothelial cells could reasonably be postulated.

It is currently unknown whether circulating visfatin can enter the CNS and moreover, whether or not it can be directly secreted from specialized CNS sites. Nevertheless, a possible role for

visfatin in the central regulation of food intake has been indicated by a study performed in chicks. Intracerebroventricular infusion of recombinant human visfatin in chicks induced an increase in food intake, with associated changes in neuronal activity (as reflected by increased c-FOS expression) in the lateral hypothalamus (118). Recent work in mammals has demonstrated that chronic central infusion of visfatin in diabetic rats improves hypothalamic insulin (but not leptin) signaling through Akt phosphorylation, with no other long-term effects observed with regards to body weight, visceral fat accumulation or energy expenditure (309). This improvement in glucose homeostasis in diabetic rats was found to involve the potentiation of glucose-stimulated insulin secretion, rather than an improvement in insulin sensitivity *per se* and was associated with increased pancreatic β-cell mass (309). The authors proposed a CNS-to-periphery signaling mechanism of visfatin, transmitted via the autonomic nervous system, since the chronic infusion of central visfatin did not alter serum visfatin levels. Recently, it was demonstrated that the NAD^+-dependent deacetylase sirtuin-1 (SIRT1) could promote the release of the extracellular form of NAMPT (visfatin) by deacetylating intracellular NAMPT at lysine 53 in adipocytes, in turn, enhancing the activity of extracellular NAMPT (622). In addition, this peripherally-derived NAMPT was shown to influence hypothalamic NAD^+-SIRT1 signaling and physical activity in mice, suggestive of the important role of adipose tissue in modulating systemic NAD^+ biosynthesis which may be key in the maintenance of metabolic homeostasis (622).

Adipocyte-derived cytokines

As adipocyte-derived cytokines may not be adipokines in the purest sense of the definition, a conscious decision has been made to keep this section brief. Additionally, due to the highly heterogeneous nature of adipose tissue: a mixture of adipocytes, preadipocytes, mesenchymal stem cells, fibroblasts, endothelial and immune cells; it can be experimentally challenging to accurately identify which cell type(s) within adipose tissue are producing cytokines (and in what proportions) under basal and pathological conditions. However, as adipocytes produce cytokines which undoubtedly have critical roles in physiology and pathology, it was felt that they should not be completely omitted.

Proinflammatory cytokines and CNS regulation of energy homeostasis

Obesity is now well accepted to be a state of chronic low-grade inflammation, characterized by the synthesis of proinflammatory cytokines, such as TNFα and IL-6, from both adipocytes and immune cells found within adipose tissue (196, 267, 598). The immunological changes in adipose tissue associated with obesity are diverse and wide-ranging with changes in immune cell populations in adipose tissue from both the innate and adaptive branches of the immune system

(388). The dysregulation of pro- versus anti-inflammatory cytokine production in obese adipose tissue contributes to various aspects of the metabolic syndrome (145, 437). Indeed, obesity-related inflammation is associated with both peripheral and central leptin and insulin resistance (43, 196).

In addition to inducing inflammation in adipose tissue, obesity also leads to elevations in proinflammatory cytokines (143, 561) and activation of glial cells (75, 265, 561) in the CNS. While the hypothalamus is the area of the brain predominantly studied in this regard (75, 265, 561) evidence also indicates that other brain sites including the hippocampus are impacted (75, 228, 456). Indeed, in neurons and astrocytes the NFκB pathway, which is known to be critical in mediating inflammatory signaling, is important for the central regulation of energy homeostasis (74, 635). Furthermore, in a rodent model of obesity, inhibition of TNFα signaling in the hypothalamus by infusion of a neutralizing antibody is sufficient to improve peripheral insulin sensitivity (17, 402) and the thermogenic capacity of BAT (17); thus, demonstrating that modulation of inflammatory signaling in the CNS can induce changes in the function of peripheral organs and potentially contribute to the pathology of the disease. It is important to note that in these studies it is not known whether inhibiting inflammatory signalling in the CNS alters physiology solely by impacting obesity-associated CNS-derived inflammation, CNS-actions of adipocyte/adipose tissue-derived cytokines or a combination of both.

The cellular origin of the proinflammatory cytokines produced in the CNS associated with obesity remains to be fully determined, but is likely to be a combination of glial (astrocytes, tanycytes, and microglia) and neuronal sources. Regardless of the cell(s) producing them, proinflammatory cytokines likely mediate their downstream effects via autocrine and paracrine actions on different cell types. CNS-derived cytokines have extensive roles in modulation of physiology and pathophysiology but as the focus of this article is the CNS actions of adipokines (which may include cytokines derived from adipocytes) we feel a discussion of this is beyond the remit of this article and has recently been extensively reviewed elsewhere (42).

The dissection of central *versus* peripheral actions of adipocyte-derived cytokines is a critical one for our understanding of their physiological actions, particularly in relation to the pathophysiology of obesity-associated inflammation. What currently is not clear is the relative time course of CNS and adipose tissue inflammation in response to obesogenic stimuli such as high-calorie diets: does adipose tissue inflammation promote CNS inflammation via the action of adipose-derived cytokines in the CNS or does CNS inflammation promote inflammatory changes in WAT? Alternatively, do they arise simultaneously in response to common stimuli? Research in rodent models indicates that hypothalamic inflammation arises after only 24h of exposure to an obesogenic high-fat diet (74, 561), which in the 2012 study of Thaler and colleagues (561) was found to be prior to the onset of adipose tissue inflammation. This suggests that hypothalamic

inflammation may be part of a homeostatic response to help restore energy homeostasis via modulation of the hypothalamic neuronal circuitry. Indeed, this is supported by data indicating that inhibition of NFκB signaling in astrocytes (a type of glial cell) was sufficient to acutely alter the feeding response to a high-fat diet (74) suggesting that inflammatory signaling in the brain is important for homeostatic regulation in this context.

Regardless of which arises first, CNS or WAT inflammation, it is highly likely that in obesity the presence of inflammation in both these organs perpetuates the inflammatory state in the other by promoting dysregulation of normal physiological mechanisms within these tissues. However, further work is required to fully clarify the relative contribution of each. In a 2010 review, Banks & Erikson summarized a number of potential mechanisms by which a circulating cytokine can influence CNS function: 1) vagal or other afferent nerve stimulation; 2) release from immune cell transport; 3) stimulation through circumventricular organs; 4) direct passage; and 5) self-stimulated release from CNS pools (31). Importantly, the CNS itself can act as an endocrine organ (28), secreting bio-active substances including centrally-derived TNFα and IL-6 which can cross the BBB to enter the blood (101). Furthermore, the BBB itself is also capable of secreting neuroimmune-related substances, both constitutively and when induced to do so by CNS or peripheral signals (31).

The BBB is critical for CNS function and protects the brain from acute changes in the periphery including infectious agents, toxins and acute nutritional variations (1). Under physiological conditions, some peripheral factors cross the BBB (depending on their polarity and size) in a regulated manner; however, when BBB integrity is disrupted by damage, inflammation and/or oxidative stress (444) this regulation is impacted. Indeed, a positive correlation between obesity/diabetes and increased risk of developing dementia, cognitive impairments and/or neurodegenerative diseases has been established and adipokine dysregulation may play a key role in the development of such disorders (16, 308, 396, 444).

Conclusion

The discovery of adipokines has fundamentally changed our understanding of endocrinology. Through their actions in the CNS, adipokines can influence numerous aspects of physiology as diverse as cognition, reproduction and cardiovascular function. In particular, leptin, with its widespread receptor distribution in the CNS has a neuromodulatory effect on many key neural pathways, including autonomic, mesolimbic dopamine, neuroendocrine, and vagal circuits. A challenge in studying CNS targets of adipokines is that much of the work to date has been carried out in animals (principally rodents) and its transferability to humans is not easily determined. Perhaps by virtue of being the first to be discovered, leptin has been shown to have the most

wide-ranging functions of all adipokines. However, as new adipokines are continuously being identified, our understanding is constantly developing. Recent work has highlighted that in addition to neurons, non-neuronal cells are also important targets for the actions of adipokines (23, 272, 310) and this remains an emerging area of study, as indeed is the role of non-neuronal cells in the regulation of physiological processes.

Despite our growing knowledge and appreciation of the importance of adipokines in modulating a range of physiological functions, to date, this large body of work has only led to the development of one novel Food and Drug Administration (FDA) approved therapeutic application in human disease: the use of a leptin analog to treat generalized lipodystrophy (524). Perhaps the Holy Grail of pharmacological therapies would be the development of the elusive brain permeable leptin-sensitizing agent that could help fight obesity by increasing CNS sensitivity to the patient's high circulating levels of the hormone. Currently, our understanding of how leptin and other adipokines enter the CNS to exert their effects is somewhat incomplete. Investigating this further, whilst advancing our fundamental knowledge of the actions of adipokines in the CNS, will undoubtedly lead to the development of novel therapeutic agents to tackle human disease.

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Tables

Table 1: List of abbreviations

Abbreviation	Definition
Aβ	Amyloid beta
ACC	Anterior cingulate cortex
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
AgRP	Agouti-related protein
AHA	Anterior hypothalamic area
AMPK	AMP-activated protein kinase
α-MSH	Alpha melanocyte stimulating hormone
AP	Area postrema
APP/PS1	Amyloid precursor protein/presenilin 1
ARC	Arcuate nucleus of the hypothalamus
ATP	Adenosine triphosphate
AVP	Arginine vasopressin
BAT	Brown adipose tissue
BBB	Blood brain barrier
BMI	Body mass index
CamKII	Calcium calmodulin-dependent protein kinase II
CART	Cocaine- and amphetamine-regulated transcript
CCK	Cholecystokinin
CNS	Central Nervous System
CRH	Corticotrophin releasing hormone
CRR	Counter-regulatory response
CSF	Cerebral-Spinal Fluid
D2	Deiodinase type II
DBP	Diastolic blood pressure
DMH	Dorsomedial nucleus of the hypothalamus
DMX	Dorsomotor nucleus of the vagus
DREADDs	Designer Receptors Exclusively Activated by Designer Drugs
DVC	Dorsal vagal complex
EGFP	Engineered green fluorescent protein
eNOS	Endothelial nitric oxide synthase
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinases
FDA	Food and Drug Administration
FGF1	Fibroblast growth factor 1
FGF21	Fibroblast growth factor 21

FOXO1	IRS-Akt-forkhead box protein 01
FSH	Follicle–stimulating hormone
GABA	Gamma-aminobutyric acid
GFAP	Glial-fibrillary acidic protein
GH	Growth Hormone
GI	Gastrointestinal
GLP-1	Glucagon like peptide-1
GAD67	Glutamic acid decarboxylase 67
GnRH	Gonadotrophin-releasing hormone
HMW	High molecular weight multimers
HPA	Hypothalamic-pituitary-adrenal
HPG	Hypothalamic-pituitary-gonadal
HPT	Hypothalamus pituitary thyroid
ICV	Intracerebroventricular
IRS	Insulin receptor substrate
Jak	Janus kinase
JNK	c-Jun N-terminal kinase
KA	Kainic Acid
LH	Luteinizing hormone
LHA	Lateral hypothalamic area
lPB	Lateral parabrachial nucleus
IFN	Interferon
LTD	Long-term depression
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
MC3R	Melanocortin-3 receptor
MC4R	Melanocortin-4 receptor
MCAO	Medial cerebral artery occlusion
ME	Median eminence
MCH	Melanin-concentrating hormone
MCI	Mild cognitive impairment
NAMPT	Nicotinamide phosphoribosyltransferase
NAD	Nicotinamide adenine dinucleotide
mPOA	Median preoptic area
mTOR	Mechanistic target of rapomycin
NFkB	Nuclear factor kappa B
NMDA	N-methyl-D-aspartate
NPY	Neuropeptide Y
NTS	Nucleus of the solitary tract
ob	Obese gene
Ob-R	Leptin receptor

OST-PTP	Osteotesticular protein tyrosine phosphatase
PACAP	Pituitary adenylate cyclase-activating polypeptide
PBA	4-phenyl butyrate
PBEF	pre-B-cell colony-enhancing factor
PBN	Parabrachial Nucleus
PGC1α	Peroxisome proliferator-activated receptor 1 alpha
PI3K	Phosphoinositide 3-kinase
PIO	Pioglitazone
PKC	Protein kinase C
PLC	Phospholipase C
POA	Preoptic area
POMC	Proopiomelanocortin
PPAR	Peroxisome proliferator-activated receptor
PMv	Ventral premammillary nucleus
PrRP	Prolactin-releasing peptide
proTRH	Pro-thyrotropin-releasing hormone
pSTAT	Phosphoylated signal transducer and activator of transcription
PTP1B	Protein-tyrosine phosphatase 1B
PVH	Paraventricular nucleus of the hypothalamus
RAS	Renin-angiotensin system
RER	Respiratory exchange ratio
ROS	Reactive oxygen species
rPA	Rostral raphe pallidus
RVLM	Rostral ventrolateral medulla
scWAT	Subcutaneous white adipose tissue
SF-1	Steroidogenic factor 1
SFO	Subfornical organ
SIRT1	Sirtuin-1
SHP2	Src-homology 2 domain-containing phosphatase 2
SHP2	Src-homology 2 domain-containing phosphatase 2
SNP	Single nucleotide polymorphisms
SOCS	Suppressor of cytokine signalling
SON	Supraoptic nucleus
SREBP2	Sterol-regulatory element binding protein 2
STAT	Signal transducer and activator of transcription
T1D	Type-1 diabetes
T2D	Type-2 diabetes
T3	Triiodothyronine
T4	Thyroxine
TH	Tyrosine hydroxylase
TLR4	Toll-like receptor 4

TNFα	Tumor necrosis factor alpha
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone
TUDCA	Tauroursodeoxycholic acid
Tyr	Tyrosine
TZD	Thiazolidinedione
UCP1	Uncoupling protein 1
UCP2	Uncoupling protein 2
VAD	Vascular dementia
VLM	Ventrolateral medulla
VMH	Ventromedial nucleus of the hypothalamus
VTA	Ventral tegmental area
WAT	White adipose tissue

Table 2: Mammalian CNS Leptin Receptor Distribution

CNS expression site	Reference	Cell type
Hypothalamus -Arcuate Nucleus (ARC) -Dorsal Medial (DMH) - Lateral Hypothalamic area (LHA) -Median Eminence (ME) -Paraventricular Nucleus (PVH) -Ventromedial Nucleus (VMH) -Ventral Premammillary Nucleus (PMv) -Median preoptic area (mPOA)	Mercer et al., 1996 (398) Schwartz et al., 1996 (507) Guan et al., 1997 (226) Elmquist et al., 1998 (180) Patternson et al., 2011 (449)	POMC neurons (108) NPY/AgRP neurons (397) Neurotensin neurons (353) CART neurons (176) Galanin neurons (339) TRH neurons (247) Astrocytes (272) Tanycytes (23) GABAergic neurons (587) Prolactin-releasing peptide neurons (PrRP) (155)
Cortex	Mercer et al., 1996 (398)	
Hippocampus	Mercer et al., 1996 (398)	
Thalamus	Mercer et al., 1996 (398) Emlquist et al., 1998 (180)	
Substantia Nigra	Guan et al., 1997 (226) Figlewicz et al., 2003 (191)	Tyrosine hydroxylase (TH) neurons (191)
Ventral tegmental area (VTA)	Figlewicz et al., 2003 (191)	TH neurons (191)
Cerebellum	Guan et al 1997., (226) Emlquist et al., 1998 (180)	
Hindbrain - Area postrema (AP) - Dorsal motor nucleus of the vagus (DMV) - Lateral parabrachial nucleus (lPB) - Nucleus of the solitary tract (NTS) -Spinal trigeminal tract - Spinal trigeminal nucleus	Mercer et al., 1998 (400)	CCK neurons (194, 209) GLP-1 (proglucagon) neurons (209) POMC neurons* (209)
Choroid Plexus & Leptomeninges	Mercer et al 1996 (398)	

*In POMC-EGFP mice

Table 3: Factors which influence leptin transport into the brain

Increase	Decrease
Epinephrine (29)	Obesity (77, 87)
Glucose* (301)	Fasting (300)
Insulin* (301)	Ovariectomy (302)
Alcohol (441)	Triglycerides (30)
CCK-8 (85)	Lipopolysaccharide (425)
Epidermal Growth Factor (23)	c-reactive protein [CRP] (359)

*Non-obese wild-type mice

Table 4: Mammalian CNS AdipoR1 Distribution.

CNS expression site	Reference	Cell type
Hypothalamus -Arcuate Nucleus - Lateral Hypothalamus -Paraventricular Nucleus - Supraoptic Nucleus - Preoptic area	Guillod-Maximin et al., 2009(229)	NPY/POMC neurons; astrocytes; ependymal cells (229) Warm sensitive neurons (316)
Cortex	Guillod-Maximin et al., 2009(229)	
Hippocampus	Guillod-Maximin et al., 2009(229)	
Thalamus	Guillod-Maximin et al., 2009(229)	
Striatum	Guillod-Maximin et al., 2009(229)	
Pituitary	Psilopanagioti et al., 2009 (462)	GH, FSH, LH and TSH neurons
Brainstem - Area postrema - Nucleus of the solitary tract	Fry et al., 2006 (200) Hoyda et al., 2009 (270)	

Table 5: Mammalian CNS AdipoR2 Distribution

CNS expression site	Reference	Cell type
Hypothalamus -Arcuate Nucleus - Lateral Hypothalamus -Paraventricular Nucleus - Supraoptic Nucleus - Preoptic area Perifornical region	Guillod-Maximin et al., 2009 (229) Klein et al., 2011 (316)	NPY/POMC neurons; astrocytes (229) Warm sensitive neurons (316)
Cortex	Guillod-Maximin et al., 2009 (229)	
Hippocampus	Guillod-Maximin et al., 2009 (229)	
Thalamus	Guillod-Maximin et al., 2009 (229)	
Striatum	Guillod-Maximin et al., 2009 (229)	
Pituitary	Psilopanagioti et al., 2009 (462)	GH, FSH, LH and TSH neurons
Brainstem - Area postrema - Nucleus of the solitary tract	Fry et al., 2006 (200) Hoyda et al., 2009 (270)	

Figure Legends

Figure 1: Leptin-signaling in leptin-sensitive compared with leptin-resistant conditions

Leptin-sensitive: Upon leptin binding to the extracellular domain of the receptor dimer, Janus kinase (JAK) 2 is activated resulting in phosphorylation of the intracellular domain of receptor at three tyrosine residues: 1) Phosphorylation of Tyr985 resulting in recruitment of Src-homology 2 domain-containing phosphatase 2 (SHP2/PTPN1) leading to activation of the extracellular signal-regulated kinases (ERK) signaling cascade (27, 89, 357); 2) Phosphorylation of Tyr1077 resulting in recruitment of the transcription factor Signal transducer and activator of transcription (STAT) 5 (219) and 3) Phosphorylation of Tyr1138 resulting in recruitment of the transcription factor STAT3 (27, 357, 579). Activation of Ob-Rb signaling also can result in activation of the phosphatidylinositol 3-kinase (PI3K) pathway via insulin receptor substrate (IRS) proteins (160, 480). Negative feedback inhibition of Ob-Rb signaling is provided by suppressor of cytokine signaling (SOCS) 3 (53, 55, 164) binding at Try985 and PTP1B acting at Jak2 (106, 628).

Leptin-resistant: Diet-induced obesity causes inflammation and ER stress in the brain (143, 438, 561, 635). Obesity-associated inflammation and ER stress activate the nuclear factor-kappa B (NFκB) signaling pathway and c-Jun N-terminal kinase (JNK) in the brain (635). JNK inhibits IRS signaling. In the course of normal homeostatic leptin signaling, negative feedback inhibition of Ob-Rb signaling is provided by SOCS3 (53, 55, 164) and PTP1B binding (106, 628). Obesity is associated with elevated hypothalamic expression of both SOCS3 (53) and PTP1B (629). Expression of PTP1B is increased by inflammation (629) and ER stress (443) via the activation NFκB signaling suggesting providing a further link potential mechanistic link between inflammatory signaling and ER stress and the development of CNS leptin resistance.

Solid blue arrows indicate activation; Dashed blue arrows indicate nuclear translocation; Red lines indicate an inhibitory action.

Figure 1: Teaching Points

Leptin signals through a tyrosine kinase linked receptor. The signaling mechanism is described in the formal figure legend. Phosphorylation of different tyrosine residues on the intracellular domain of the leptin receptor results in the activation of different downstream signaling pathways including kinases and transcription factors. These subsequently mediate a number of different downstream physiological events including modulation of neuroendocrine and autonomic pathways. Feedback inhibition of leptin receptor signaling is mediated via SOCS 3 and PTP1B.

When leptin levels are chronically elevated during obesity leptin signaling becomes less effective: a state known as leptin resistance. On a molecular level inflammation and ER stress associated with obesity lead to an enhancement of the inherent mechanisms inhibiting leptin signaling (SOCS3 and PTP1B) and also stimulation of JNK which inhibits leptin signaling via the IRS/PI3K pathway.

Figure 2: Simplified diagram of CNS neurocircuits regulating energy and glucose homeostasis.

A number of hypothalamic and extrahypothalamic sites have been implicated in the action of leptin in the regulation energy and glucose homeostasis. Due to the extensive neuronal interconnectivity between the brain nuclei in the diagram, for clarity, the neural projections between each site have not been indicated. The hypothalamic ARC contains neuropeptide Y and agouti-related peptide (NPY/AgRP) neurons that stimulate food intake and are inhibited by leptin, and proopiomelanocortin (POMC) neurons that reduce food intake and are stimulated by leptin. NPY/AgRP neurons also inhibit POMC neurons via synaptic release of the neurotransmitter GABA. POMC and AgRP neurons exert their effects on food intake via melanocortin 4 receptors (MC4R) expressed on downstream target neurons.

ARC, arcuate nucleus; LepRb, leptin receptor; Mc3r/Mc4r, melanocortin-3/4 receptor; VMH, ventromedial hypothalamus; LHA, lateral hypothalamic area; PVN, paraventricular nucleus; DMH, dorsomedial hypothalamus; VTA, ventral tegmental area; NTS, nucleus of the solitary tract. Reprinted with permission from (410).

Figure 2: Teaching points

Leptin receptors are found in many different areas of the brain and important in regulating the regulation of food intake and body weight (energy homeostasis), and the control of blood glucose levels. This includes a number of areas within the hypothalamus but also non-hypothalamic areas of the brain including sites in the midbrain (VTA) and brainstem (NTS). The most well characterized and understood effects of leptin on glucose and energy homeostasis occur via its receptors expressed in the hypothalamus. In an area of the hypothalamus called the arcuate nucleus (ARC) neurons containing neuropeptide Y and agouti-related peptide [(NPY/AgRP) that stimulate food intake], and neurons containing proopiomelanocortin [(POMC) that reduce food intake]; both express leptin receptors. Leptin acts to decrease food intake by inhibiting the activity of NPY/AgRP neurons and increasing the activity of POMC neurons. Melanocortin 4 receptors

(MC4R) are important for mediating the downstream effects of POMC and NPY/AgRP neurons on food intake. In humans and animals, mutations in the POMC or MC4R gene cause profound obesity.

Figure 3: Simplified schematic of adiponectin receptor signaling.

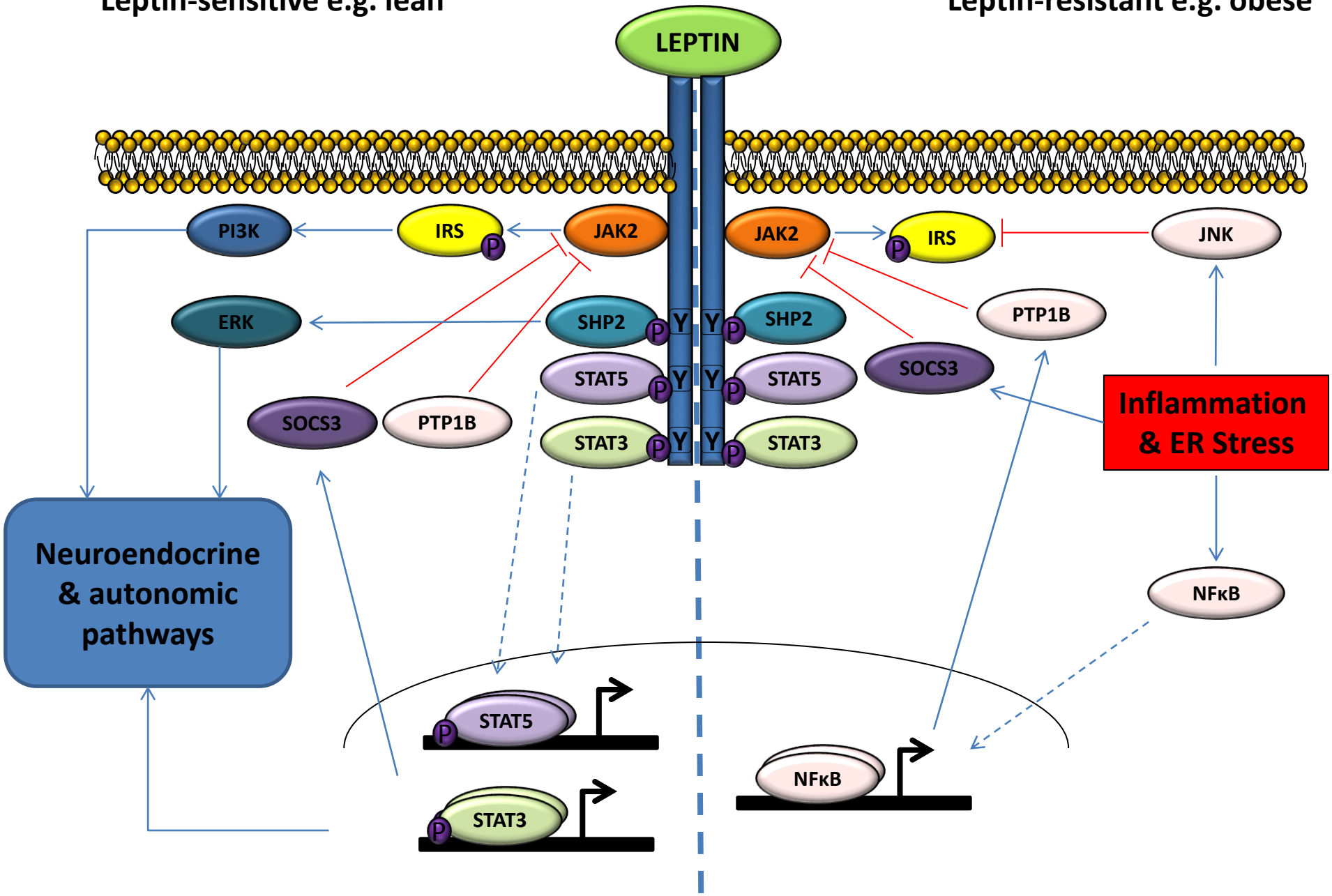
AdipoR1/2 interacts with the adaptor protein APPL1 stimulating the insulin receptor substrate 1/2 (IRS1/2) pathway leading to increased Akt (serine 473), Foxo1 (serine 256) and ERK (threonine 202/tyrosine 204) phosphorylation. Activation of the receptor can also stimulate the JAK2-STAT3 pathway, increasing STAT3 tyrosine 705 phosphorylation, translocation of dimerized STAT3 to the nucleus and activation of transcription. The adipokine can also activate the AMP-activated protein kinase (AMPK) via increasing intracellular calcium levels, leading to activation of calmodulin-dependent kinase kinase β (CamKKβ). Phosphorylation of AMPK (threonine 172) by CamKKβ, increases kinase activity and subsequent leads to phosphorylation of endothelial nitric oxide synthase (eNOS) at serine 1177 by AMPK. Adiponectin can also stimulate the stress activated MAP kinase pathway by stimulating phosphorylation of p38 MAPK.

Figure 3: Teaching points

Adiponectin receptors (AdipoR1/2) are seven transmembrane receptors but are not G-protein coupled. Activation of adiponectin receptors by adiponectin can lead to the activation of a number downstream signaling pathways, as described in the main figure legend. This includes kinases and transcription factors. AMPK, which is activated downstream of adiponectin receptors is a critical enzyme in the modulation of cellular energy levels regulating fatty acid uptake and β-oxidation.

Cross-References

Adiponectin function and regulation
Leptin function and regulation
Autonomic nervous system and adipose tissue
Hormonal influence on reward mechanisms
Leptin and the control of food intake


Leptin-sensitive e.g. lean
Leptin-resistant e.g. obese
LEPTIN
PI3K
IRS
P
JAK2
JAK2
IRS
P
JNK
ERK
SHP2
P
Y
Y
P
SHP2
PTP1B
STAT5
P
Y
Y
P
STAT5
SOCS3
SOCS3
PTP1B
STAT3
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Y
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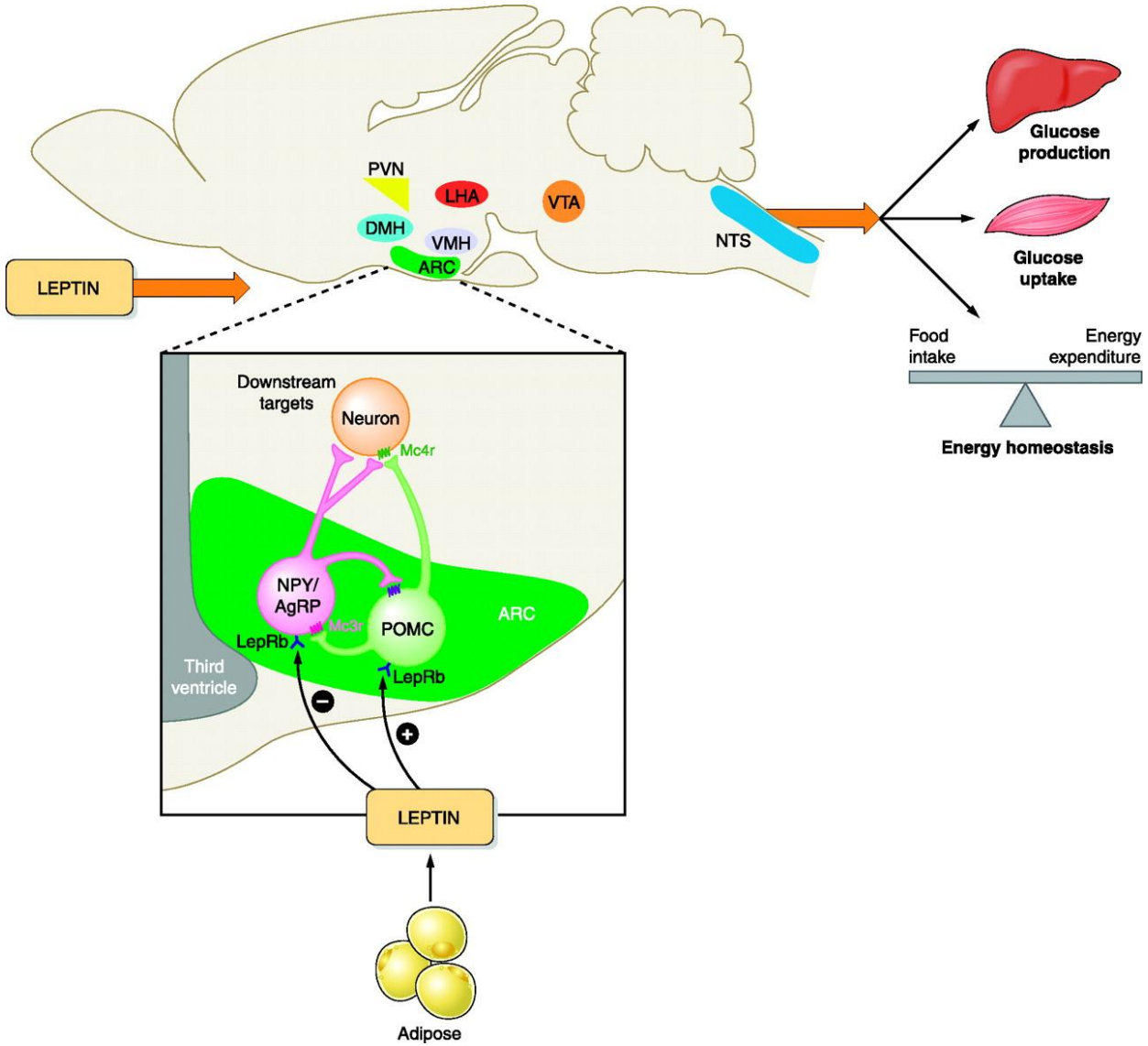
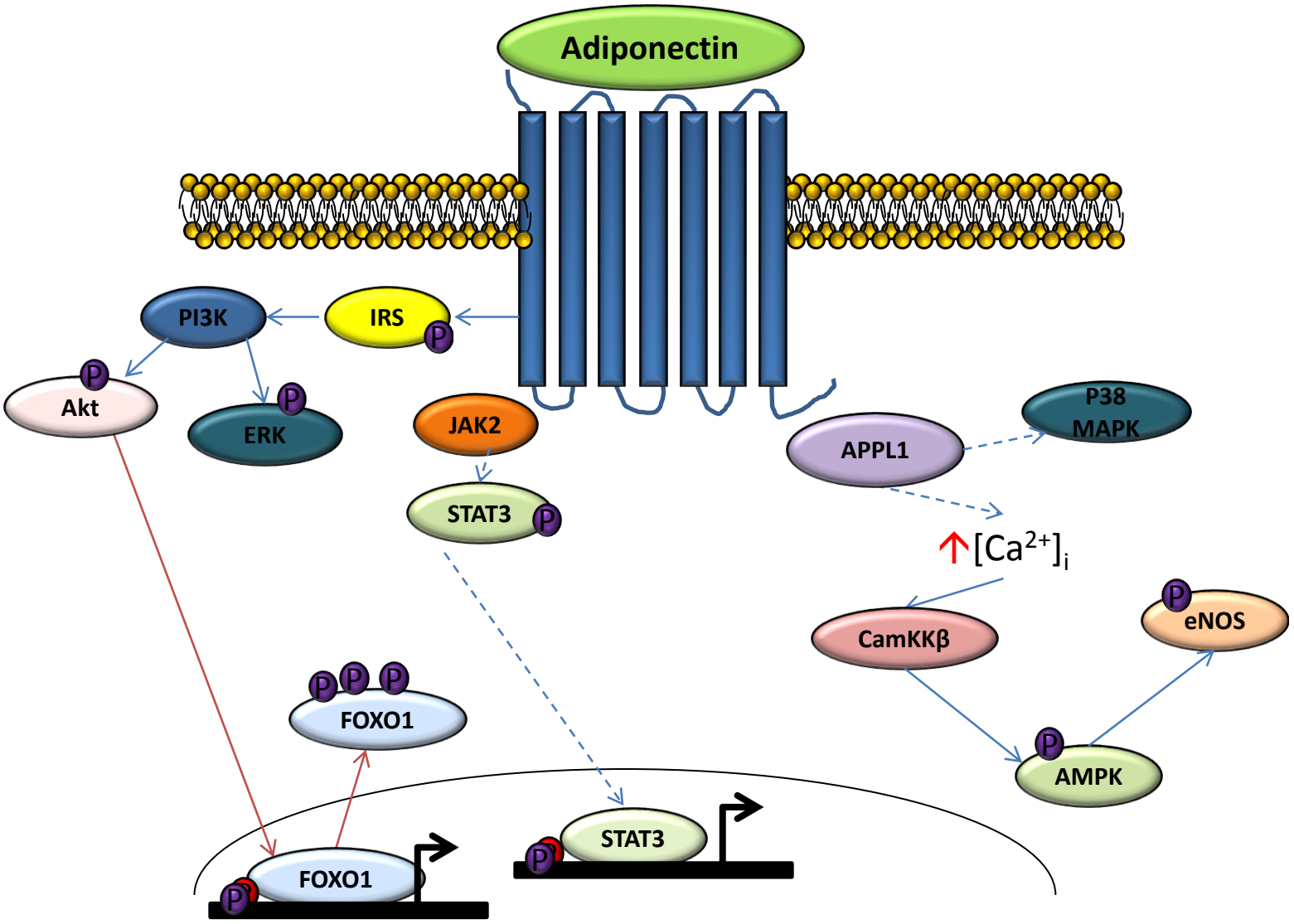
STAT3
Inflammation & ER Stress
Neuroendocrine & autonomic pathways
NFκB
STAT5
P
NFκB
STAT3
P


PVN
LHA
VTA
DMH
VMH
ARC
NTS
LEPTIN
Glucose production
Glucose uptake
Food intake
Energy expenditure
Energy homeostasis
Downstream targets
Neuron
Mc4r
NPY/ AgRP
Mc3r
POMC
ARC
LepRb
LepRb
Third ventricle
LEPTIN
Adipose



Regulation of food intake, reproduction, neuroprotection