Leptin and brain–adipose crosstalks

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Abstract

Interactions between the brain and distinct adipose depots have a key role in maintaining energy balance, thereby promoting survival in response to metabolic challenges such as cold exposure and starvation. Recently, there has been renewed interest in the specific central neuronal circuits that regulate adipose depots. Here, we review anatomical, genetic and pharmacological studies on the neural regulation of adipose function, including lipolysis, non-shivering thermogenesis, browning and leptin secretion. In particular, we emphasize the role of leptin-sensitive neurons and the sympathetic nervous system in modulating the activity of brown, white and beige adipose tissues. We provide an overview of advances in the understanding of the heterogeneity of the brain regulation of adipose tissues and offer a perspective on the challenges and paradoxes that the community is facing regarding the actions of leptin on this system.

The maintenance of energy homeostasis is achieved by sophisticated brain circuits that rigorously maintain energy levels by affecting food intake and energy expenditure. The identification of the leptin gene (*Lep*) in 1994 ushered in the molecular era of obesity research and provided new opportunities to better understand the mechanisms regulating energy homeostasis[1–3]. Despite tremendous efforts to identify the multiple factors that contribute to excessive fat accumulation, the obesity epidemic continues to worsen, with more than one-third of US adults being obese[4]. Adipose tissue has a central role in leptin production and in the management of systemic energy stores. Understanding how the actions of leptin on the CNS influence adipose tissues, and how adipose tissue metabolism in turn is affected by the sympathetic nervous system (SNS), represents a novel opportunity to tackle the obesity problem.

Brown adipose tissue (BAT) and white adipose tissue (WAT) are specialized for non-shivering thermogenesis and lipid storage, respectively[5,6] (FIG. 1). Under specific

physiological conditions, clusters of brown-like adipocytes in white fat ('brite' adipocytes) can also develop through so-called browning or 'beiging' of WAT. The development of beige adipose tissue (BeAT) has an important role in systemic metabolic regulation[6,7] (BOX 1). The activity of adipose cells is tightly regulated by the SNS. In particular, increased SNS outflow promotes fat mobilization[8]. Activation of the SNS stimulates non-shivering thermogenesis[9] and participates in the development of BeAT[7]. Importantly, sympathetic tone is differentially regulated in the adipose depots. For example, in response to fasting, most tissues, including BAT, will experience a decrease in sympathetic tone, whereas sympathetic activity in WAT increases to allow fatty acid mobilization[10] (FIG. 1a). By contrast, cold exposure increases sympathetic outflow to both BAT and WAT to provide substrates for non-shivering thermogenesis[11] (FIG. 1a). This divergence implies that complex and distinct CNS circuits have evolved to coordinate adipose tissue metabolism.

The brain regulates BAT, WAT and BeAT metabolism through efferent pathways; in turn, these tissues relay information to the brain about the status of energy stores through sensory innervation and hormone secretion[8,12,13]. Increased interest in this bidirectional interaction between the brain and adipose depots was catalysed by the cloning of *Lep*[3]. Leptin is an adipokine with multiple functions; for example, it regulates appetite, body weight, the maturation of the reproductive axis and neuroendocrine adaptations to fasting[14,15]. Leptin is also generally acknowledged to act within the brain to regulate glucose homeostasis[16–18]. The confirmation that functional brown adipocytes exist in adult humans[19,20] has also spurred new studies on the neural regulation of BAT. While the role of leptin in regulating energy balance is well known, its role in the neural regulation of BAT, WAT and BeAT is still debated. Many extensive and up-to-date reviews are available on the neural control of adipose tissue or the leptin-sensitive neurons that maintain energy balance[2,9,17,21–24]. However, the two systems are generally separately discussed, when they could instead be considered as one. For instance, leptin contributes to the regulation of the sympathetic tone to BAT, WAT and BeAT; in turn, the transcription and secretion of leptin in adipocytes are controlled by the SNS[25–29]. Therefore, the goal of this Review is to discuss the role of leptin as a key regulator of the sympathetic outflow to adipose tissues. We also take this opportunity to stress the heterogeneity of the innervation of adipose tissue and to discuss the mechanisms by which the SNS regulates the synthesis and release of leptin. Ultimately, this Review is aimed at identifying some of the challenges ahead in the field of energy metabolism and underscoring important notions to consider in understanding obesity and other metabolic complications.

Leptin and adipose functions

The CNS regulates peripheral tissues through the SNS and the parasympathetic nervous system (PNS)[30]. The monoamine noradrenaline is the main neurotransmitter released by the sympathetic nerves, whereas acetylcholine is the main neurotransmitter of the PNS[31]. Sympathetic ganglion cells are innervated by preganglionic fibres that primarily emerge from the intermediolateral column (IML) of the spinal cord. By contrast, parasympathetic ganglion cells receive their preganglionic input from neurons in the brainstem, such as the dorsal nucleus of the vagus nerve[31]. Another distinction between the SNS and PNS is that sympathetic ganglion neuron bodies are located in the `bilateral chain` of sympathetic

ganglia, whereas the `terminal ganglia` of the PNS are very near, or even within, the innervated organ[31].

Adipose tissue receives an SNS innervation; however, the role of the PNS in adipose innervation is unsettled[8,32,33]. The number of fibres expressing choline *O*-acetyltransferase (ChAT; a marker of parasympathetic neurons) present in inguinal WAT is negligible compared with the number of fibres expressing tyrosine hydroxylase (TH; a marker of sympathetic neurons)[8,34]. The SNS regulates the non-shivering thermo genesis function of BAT[9], energy storage and mobilization by WAT and the development of BeAT[7] (FIG. 1). The importance of the sympathetic control of fat mobilization was supported by the early observation that in adrenal demedullated rats, chemical sympathectomy using *N-ortho*-chloro-benzyl-*N'*,*N''*-dimethylguanidine prevents cold-induced lipolysis, an effect that is reversed by treatment with with noradrenaline[35]. Subsequent work showed that `noradrenaline turnover` is increased in adipose tissue in cold-exposed or fasted rodents[36–38]. Moreover, optogenetic nerve stimulation of SNS fibres in mice increased fatty acid release[39]. Below, we discuss how leptin influences the sympathetic regulation of BAT, WAT and BeAT functions in response to metabolic challenges.

Neural control of leptin levels

Leptin is predominantly secreted from visceral white adipocytes in rodents[40] and from subcutaneous adipose tissue in humans[41]. There is a general consensus that leptin levels are tightly correlated with adiposity in both rodents and humans[42]. Although leptin is required for regulating food intake, it is not viewed as a short-term 'satiety' signal, as food consumption takes several hours to influence circulating levels of leptin[43]. The expression and protein levels of leptin are subject to many regulatory factors. For instance, both *Lep* expression and circulating leptin levels show a circadian rhythm; in rats, they peak during the late-dark, active period (`zeitgeber time` 21) and reach their nadir during the late-light, inactive period (zeitgeber time 9)[44]. However, the changes in leptin expression across the circadian cycle are very modest (about 1.5-fold)[44] compared with changes in response to metabolic challenges (such as fasting or cold exposure), which rapidly affect leptin synthesis independent of changes in fat mass[26,40,45] (FIG. 2). For instance, fasting mice for 24 h is sufficient to reduce *Lep* mRNA levels fourfold[40], whereas 4 h of cold exposure reduces *Lep* mRNA levels to undetectable levels[26]. Likewise, fasting reduces circulating levels of leptin (by about 60–70%) in obese and normal-weight human participants[45] and in rats[46]. As discussed below, the SNS has been implicated as a key acute regulator for both leptin synthesis and secretion; other factors that also regulate circulating leptin levels (such as insulin and glucocorticoids) are not discussed here[45,47,48] (FIG. 2).

Acute treatment with catecholamines (such as noradrenaline) reduces leptin levels through a β_3-adrenergic receptor (β_3-AR)–cAMP-dependent mechanism (FIG. 2). This finding is supported by evidence that β_3-AR agonists (including CL316243 and BRL35153A)[27–29,49–52] and cAMP analogues (for example, dibutyryl-cAMP (DBcAMP)) or activators (such as forskolin)[28,53] suppress *Lep* expression in rodent gonadal adipocytes and leptin levels (FIG. 2). By contrast, sympathetic blockade with the TH inhibitor α-methyl-*p*-tyrosine (AMPT) increases *Lep* expression[51,54] (FIG. 2). Furthermore, chemical

destruction of dopaminergic and noradrenergic neurons with 6-hydroxydopamine (6-OHDA) raises leptin levels (about 15-fold) in rats just 18–20 h after treatment[55]. However, data from pharmacologic sympathectomy studies must be interpreted with caution; for example, such treatments may cause neurotoxic lesions of the midbrain dopamine neurons[56]. Nevertheless, (male) individuals with spinal cord injuries also have inappropriately high leptin levels, even at low body mass index[57], suggesting that sympathetic denervation also impairs leptin regulation in humans. In addition, leptin seems to regulate its own expression by acting on the SNS: exogenous leptin reduces *Lep* expression in gonadal adipose tissue but not in mice lacking dopamine β-hydroxylase (DBH), the enzyme responsible for converting dopamine to noradrenaline[58] (FIG. 2). Newly developed genetic tools that enable targeted manipulations of molecules involved in sympathetic signalling represent a promising way to delineate the tissue-specific regulation of leptin production[59]. Overall, these observations indicate that SNS activity decreases leptin expression independently of adiposity, and most likely through activation of β_3-AR[25–29], although other receptors may also regulate leptin. Notably, the VGF-derived neuropeptide TLQP21, which is involved in energy balance regulation[60], might potentiate β_3-AR-dependent lipolysis through an adipocyte complement 3a receptor 1 (C3aR1)-dependent mechanism[61]; however, whether TLQP21 also affects leptin production requires further investigation.

Less is known about SNS-mediated regulation of *Lep* transcription. Several transcription factors directly regulate leptin expression: the transcription factor AP-2β (TFAP2B) inhibits leptin expression by directly binding to the *Lep* promoter[62], whereas neurofibromin (NF1) and forkhead box protein L2 (FOXL2) both have positive effects on *Lep* expression[63,64]. In addition, the *Lep* promoter contains functional binding sites for CCAAT/enhancer-binding proteins (CEBPs), the transcription factor SP1, the glucocorticoid receptor (GR), cAMP-responsive element-binding protein (CREB) and sterol regulatory element-binding protein 1C (SREBP1C)[65–71]. These transcription factors are unlikely to mediate the SNS-dependent regulation of *Lep* expression, however, as they do not seem to mediate the effects of fasting or feeding on leptin levels[72]. Moreover, the potential transcription factors repressing leptin in response to cold are still unknown. The SNS-dependent regulation of leptin production might also be coupled to a lipid-sensing mechanism[1], although the intracellular factors mediating this have yet to be identified.

Cold exposure and fasting each cause profound, yet reversible, decreases in leptin levels[26,45,73–75], suggesting that the regulation of leptin does not reflect adiposity but, rather, energy demand. As cold exposure and fasting are important modulators of sympathetic tone, regulation of leptin by these metabolic stressors is probably dependent on the SNS[45,75–77]. Supporting this idea, treatment with β-blockers, such as propranolol, attenuates fasting-induced reductions in leptin[51], whereas AMPT increases leptin levels even in fasted animals[51,54] (FIG. 2). Paradoxically, leptin and its receptor seem to be required for the effect of the SNS on leptin expression: 24 h fasting leads to a ~70% decrease in leptin levels in lean *Fa/Fa* rats expressing wild-type leptin receptor but does not affect leptin levels in leptin-receptor-deficient (*fa/fa*) Zucker rats[75,78]. Together, these studies support the model that the nervous system can modulate leptin levels independently of adiposity.

Lipolysis

WAT contributes to energy homeostasis by storing energy (mainly as triglycerides) and by mobilizing free fatty acids when energy is needed[79] through a process known as lipolysis (FIG. 1b). The breakdown of lipids involves a tightly regulated hydrolytic process in which intracellular cAMP activates a well-established molecular cascade involving adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), monoglyceride lipase (MGL) and perilipins[80] (FIG. 1b). Dysregulation of adipose tissue metabolism leads to various complications, including `ectopic lipid accumulation`, lipotoxicity, insulin resistance and obesity[79]. WAT also has an important endocrine function, as it secretes adipokines[79] and microRNAs[81] that can influence systemic metabolism. Evidence suggests that increased visceral WAT (such as gonadal or retroperitoneal WAT) is associated with metabolic dysfunction, whereas increased subcutaneous WAT (for example, inguinal WAT) is protective[79]. The latter notion is supported by the fact that overexpression of adiponectin, which leads to a massive increase in subcutaneous adipose tissue, protects against diet-induced insulin resistance in mice[82]. The notion of healthy versus unhealthy WAT expansion has also recently been carefully reviewed[79]. Investigations are still ongoing to better understand the relative contributions and functions of the different WAT depots to energy homeostasis.

The importance of the SNS in regulating WAT lipolysis is supported by the abundance of adrenergic receptors at the surface of the adipocytes that are upstream of the lipolytic cascade (FIG. 1). Moreover, bilateral adrenal demedullation does not prevent lipolysis[83,84], suggesting that catecholamines originating from SNS neurons are required for the breakdown of lipids. Work conducted primarily in Siberian hamsters suggests that SNS innervation of WAT is both sufficient and necessary for the regulation of WAT lipolysis[8]. Consistent with this was the identification of an anatomic bidirectional connection between postganglionic neurons and WAT that controls lipolysis[8,85,86] (BOX 2). Functional evidence includes early observations that hemiplegic patients mobilize lipids only from their intact leg and that dogs with spinal cord injury do not mobilize lipids[87]. WAT surgical denervation studies in different species, including rodents and cats, were also key in determining the sufficiency of intact nervous input to adipose tissue for lipolysis[87].

Leptin can influence the sympathetic tone to WAT. Central administration of leptin reduces gonadal fat weight independently of changes in food intake[88], decreases lipogenesis in gonadal WAT[89] and increases sympathetic tone towards inguinal WAT[90]. More recently, a leptin-dependent neuro–adipose tissue connection was shown to regulate lipolysis[39]. Using optical projection tomography together with multiphoton microscopy, axon bundles in the inguinal WAT were shown to come into close proximity to adipocytes (FIG. 1a). Importantly, optogenetic activation of these neurons increased levels of noradrenaline and activated HSL, a key enzyme for lipolysis, in inguinal WAT. Furthermore, the effect of leptin on HSL phosphorylation was prevented by surgical denervation of the tissue, suggesting that the local sympathetic innervation of inguinal WAT is required for the lipolysis-stimulating effects of exogenous leptin[39].

Although there are other conflicting findings suggesting that injection of 6-OHDA in adipose tissue does not prevent the effects of leptin on lipolysis[91,92], these studies suggest that leptin influences triglyceride breakdown in WAT through actions on the SNS. Studies in cultured rat adipocytes from different fat pads also indicate that leptin can directly stimulate lipolysis[93–95] (although these effects are very modest when compared with that of noradrenergic signalling). Although these studies relied on high exogenous or pharmacological doses of leptin, they do suggest that leptin-induced lipolysis plays an important part in fine-tuning fuel usage in response to metabolic challenges. However, it remains paradoxical that the physiological decrease in leptin levels observed with fasting is concomitant with elevated lipolytic rates in WAT. Indeed, if the function of leptin is to stimulate lipolysis, why would leptin levels decrease in situations where lipolysis needs to be activated? One possibility is that the effects of leptin on lipolysis depend on insulin levels[96] and on the sympathetic tone.

Browning

Under specific sustained conditions (for example, with chronic adrenergic stimulation using CL316243 or cold exposure), specific WAT depots, particularly those in the subcutaneous compartment, can develop clusters of brite adipocytes (BOX 1; FIG. 1a) with the characteristics of brown fat cells (including expression of mitochondrial brown fat uncoupling protein 1 (UCP1), `multilocularity` and high mitochondria content)[7]. Development of these brite cells improves insulin sensitivity and systemic metabolism[7], yet the thermogenic potential of BeAT is still controversial[11,97].

It is still unclear whether leptin directly regulates the browning of WAT and how this process might influence the regional synthesis and secretion of leptin. However, there is evidence that central leptin positively influences gonadal WAT browning[98]. Using volume fluorescence-imaging techniques to visualize the neural arborizations in mouse inguinal WAT, it was recently shown that sympathetic fibres are in close apposition to over 90% of adipocytes[34]. Supporting these observations, investigators recently developed an Adipo-Clear model in which fat pads were delipidated to enable 3D whole-tissue imaging and found dense staining of sympathetic fibres in close contact with the majority of adipocytes in inguinal WAT[99]. Interestingly, blocking the outgrowth of neural fibres to inguinal WAT using genetic or pharmacologic tools prevented the sympathetic arborization of the tissue and the ability of cold to promote the development of brite adipocytes[34]. Moreover, genetic deletion of the three β-ARs also prevented cold-induced browning of inguinal WAT[34]. These results confirm that the sympathetic innervation of inguinal WAT is required for cold-induced development of BeAT. Although there is a clear link between the activation of adrenergic receptors and BeAT development in mice[7], the mechanisms by which the SNS positively regulates browning of WAT are still unknown. One way the sympathetic signal propagates among brite adipocytes is through a cell-to-cell connexin 43 gap-junction system[100] (FIG. 1a). It is tempting to speculate that the propagation of a sympathetic neuronal signal in response to SNS activation allows these gap-junction channels to also negatively regulate leptin secretion in BeAT. However, there is not yet any direct evidence that leptin production and BeAT development are inversely related.

Fasting leads to the inhibition of the thermogenic programme (that is, changes in gene expression) in BeAT[101] and preferentially suppresses the browning of retroperitoneal WAT. Similar to leptin regulation, these fasting-induced adipose effects are likely to be mediated by the SNS[51,54]. However, it is also possible that fasting-induced alterations in browning are secondary to hypoglycaemia or hypoinsulinaemia and represent part of an evolutionary mechanism to reduce fuel consumption under low-energy conditions. Notably, changes in sympathetic outflow induced by fasting differ between fat depots[101]: noradrenaline levels are increased in BAT and inguinal WAT, are reduced in retroperitoneal WAT, and are unchanged in gonadal WAT. Interestingly, fasting prevents the ability of cold exposure to promote browning, again suggesting that there may be an evolutionary mechanism to promote energy conservation during fasting[101]. Whether and how the fasting-induced inhibition of browning is linked to the fasting-induced inhibition of leptin is yet to be demonstrated. In addition, the central pathways responsible for driving SNS outflow to WAT, for suppressing browning and leptin secretion and for inducing lipolysis are yet to be determined.

Non-shivering thermogenesis

The ability of brown adipocytes to generate heat, a process referred to as non-shivering thermogenesis, is mediated by UCP1, a mitochondrial protein that has the unique ability to uncouple the process of substrate oxidation from electron transport[5,9] (FIG. 1c). Although several anatomical depots of brown fat have been identified in rodents[102], most of the current knowledge relates to interscapular BAT. The most powerful activator of BAT thermogenesis is undoubtedly cold exposure[103]. Upon cold exposure, BAT takes up and metabolizes different substrates (such as glucose and free fatty acids)[104]. These substrates are then incorporated into lipid vesicles directly, or through de novo lipogenesis, and are ultimately used by mitochondria to generate heat in response to adrenergic stimulation[105].

Brown adipose depots are richly innervated by sympathetic fibres[106]. Retrograde transneuronal viral tracing using pseudorabies virus (PRV) was instrumental in mapping the sympathetic innervation of BAT[107,108]. Sympathetic preganglionic neurons innervating interscapular BAT are located in the IML of the T1–T6 spinal segments[109,110], and the sympathetic postganglionic neurons that project into interscapular BAT are located in the T1–T5 paravertebral ganglia, with a large number in the stellate ganglion[111] (BOX 2). Again, these data must be interpreted with caution, as PRV can infect different neuronal terminals. Furthermore, PRV trans-synaptic transduction means that the tracing is not limited to first-order neurons. The activity of brown fat and its thermogenic capacity (that is, its ability to expand its thermogenic machinery by increasing levels of proteins involved in fat oxidation and thermogenesis) are dependent on noradrenaline[105]. Denervation of interscapular BAT prevents or impairs cold-induced thermogenesis[9], indicating the importance of sympathetic innervation.

Early studies suggested that leptin had a thermogenic effect. For example, many hypothalamic neurons involved in regulating non-shivering thermogenesis are also leptin sensitive[112], and leptin-deficient mice have a lowered core temperature when housed in conditions below `thermoneutrality`[113]. Exogenous hypothalamic leptin also enhances

glucose uptake by BAT and raises BAT temperature[114–117]. Moreover, in rodents, leptin administration exerts a mild `pyrexic` effect[113,118–120] and increases the noradrenaline turnover to BAT[121]; activity in sympathetic nerves innervating BAT[122], kidneys, adrenals and hindlimb[123]; glucose uptake to heart and muscle[117]; glucose turnover in the liver[124]; and arterial pressure[125–127]. Leptin positively regulates *Ucp1* mRNA expression in rodent BAT[121,128–132], and this effect is blocked by sympathetic denervation[128] and in mice lacking DBH[58].

More recent findings, however, suggest that leptin is not a major regulator of non-shivering thermogenesis. In particular, the lowered core temperature of leptin-deficient mice is caused by an increase in heat loss (that is, increased thermal conductance) from these animals rather than by defects in non-shivering thermogenesis[113,133]. Leptin-deficient mice defend a lower body temperature, suggesting that leptin may have pyrexic, rather than thermic, effects[113]. Thus, leptin might affect thermoregulation through vasomotor or thermal conductance mechanisms rather than by directly affecting BAT thermogenesis. Moreover, increasing evidence suggests that the effects of exogenous leptin treatments do not accurately reflect endogenous physiology. For example, animals fed a high-fat diet (HFD) are resistant to exogenous leptin but remain completely sensitive to endogenous leptin[134]. Furthermore, a pegylated leptin receptor antagonist (PLA) that acted as a competitive antagonist of the leptin receptor increased feeding and body weight in both lean and diet-induced obese mice[134]. Moreover, this analogue also blocked signal transducer and activator of transcription 3 (STAT3) signalling, the best-known readout of leptin action, suggesting that, at a minimum, the development of `leptin resistance` could raise the set point for leptin in specific neurons, causing neurons to require a higher concentration of leptin to activate STAT3 signalling. Together, these studies highlight the need for developing new tools aimed at modulating endogenous leptin.

Leptin and neural control of adipose

Some of the neurons within the central pathways that are connected to adipose depots express leptin receptors. PRV studies have identified brain regions that are polysynaptically connected to interscapular BAT and different WAT depots[86,110,135–138]; these brain regions include brainstem nuclei (specifically, the nucleus of the solitary tract (NTS) and raphe nuclei, such as the raphe pallidus nucleus (RPa)), midbrain nuclei (such as the periaqueductal grey (PAG)) and forebrain nuclei (such as the arcuate nucleus (ARC), dorsomedial hypothalamus (DMH), lateral nucleus (LH), paraventricular nucleus (PVH), suprachiasmatic nucleus (SCN) and the preoptic area (POA) of the hypothalamus) (FIG. 3). Importantly, these structures contain neurons that express considerable levels of leptin receptors[139–141].

Although we now have a better appreciation of the brain circuits involved in WAT regulation, traditionally most of the understanding was based on neuroanatomical studies in Siberian hamsters and, to a lesser extent, in rats. Whether mice and humans also show similar circuitry in terms of innervation is largely unknown. Here, we discuss the different leptin-sensitive brain circuits potentially involved in modulating BAT thermogenesis, WAT lipolysis and BeAT development and metabolism.

Melanocortin system

Recent work has revealed the importance of the leptin–melanocortin system in WAT, BeAT and BAT metabolism. The central melanocortin system includes pro-opiomelanocortin (POMC) neurons producing melanocortins such as α-melanocyte-stimulating hormone (α-MSH). POMC neurons are primarily located in the ARC but can also be found in the NTS[142]. A distinct population of adjacent neurons expresses agouti-related protein (AGRP) in the ARC[143]. These subsets of melanocortin neurons are important targets of leptin and express leptin receptors[144,145]. They act on melanocortin receptor 4 (MC4R) and MC3R, which are widely expressed in the brain[146–148]. In particular, MC4Rs are highly expressed in the PVH, where they control energy balance through a well-described ARC–PVH melanocortin circuit[149–151] (FIG. 3).

The first demonstration of an interaction between the melanocortin system and BAT thermogenesis was made in the late 1990s[152,153]. Central administration of the synthetic melanocortin receptor antagonist SHU9119 completely blocked leptin-induced increases in BAT *Ucp1* mRNA expression in rats[116]. Moreover, central administration of the MC4R agonist MTII increased BAT *Ucp1* mRNA expression — an effect that was blocked by surgical sympathetic denervation[154]. Transgenic mouse models further clarified the role of the leptin–melanocortin system in BAT thermogenesis. For example, compared with wild-type mice, mice lacking MC4R showed a smaller upregulation of BAT *Ucp1* in response to HFD or cold exposure (stressors that affect leptin production)[155]. However, whether leptin directly acts on the melanocortin circuit to regulate BAT activity needs further validation. Interestingly, MC3R and/or MC4R are required for exogenous leptin-induced increases in renal, but not BAT, sympathetic nerve activity in anaesthetized rats[153].

Many MC4R-expressing neurons in the PVH are polysynaptically connected to BAT[138]; however, conditional re-expression of MC4R specifically in the PVH of otherwise MC4R-null mice did not restore impaired energy expenditure in these animals, as assessed by indirect `calorimetry`[156]. Subsequent studies found that MC4R expression in sympathetic, but not parasympathetic, autonomic preganglionic neurons is important for regulating thermogenesis in mice[157] (FIG. 3). Deletion of *Mc4r* in the sympathetic preganglionic neurons using ChAT– Cre mice impaired HFD-induced and cold-induced thermogenesis in BAT and reduced the development of BeAT[157]. These findings support the idea that cholinergic preganglionic neurons might be involved in the effects of leptin and melanocortin on BAT metabolism.

Although the specific MC4R-expressing neuronal populations that regulate BAT thermogenesis are unknown, recent work has suggested a role for ARC neurons. As mentioned, the ARC is a heterogeneous region of the hypothalamus in which melanocortin neurons with opposing functions reside in close proximity to one another[158,159] (FIG. 3). Overexpression of X-box binding protein 1 (XBP1), an important molecule in the endoplasmic reticulum (ER) stress response, in POMC neurons is sufficient to increase thermogenesis in BAT and browning of inguinal WAT[160] (FIG. 3). Thus, XBP1 in POMC neurons may regulate the development of BeAT and hence contribute to improvements in whole-body metabolism. Interestingly, blocking the connexin 43 gap-junction system in

WAT prevents the ability of neuronal POMC XBP1 to affect BeAT development, suggesting that the effects of the melanocortin system on BeAT metabolism require an intact adipocyte gap-junction system[100]. Furthermore, insulin and leptin act together on POMC neurons to promote BeAT formation[161]. Deletion of the tyrosine-protein phosphatases, PTP1B and T cell protein-tyrosine phosphatase (TCPTP; also known as PTPN2), which regulate insulin signalling, in POMC neurons prevents HFD-induced obesity by increasing BeAT development and energy expenditure[161] (FIG. 3). Together, these studies indicate that POMC neurons are important for regulating BAT, WAT and BeAT metabolism.

Deletion of `O-GlcNAc transferase` (OGT) specifically from AGRP-expressing neurons reduces the excitability of these neurons (by inhibiting the activity of voltage-dependent potassium channels) and promotes the development of BeAT[101] (FIG. 3). By contrast, acute chemogenetic activation of AGRP-expressing neurons reduces energy expenditure by suppressing the browning of retroperitoneal and inguinal WAT without affecting the thermogenic programme in BAT[101]. These observations further demonstrate that the process of WAT browning is highly dynamic and specific to different fat depots. Mice lacking synaptic GABA release from hypothalamic neurons expressing rat insulin promoter (RIP), which include AGRP-expressing neurons, also show reduced energy expenditure[162] (FIG. 3). Importantly, the ability of exogenous leptin to increase energy dissipation was attenuated in these mice, suggesting that GABAergic transmission from hypothalamic RIP-expressing neurons is required for exogenous leptin to regulate energy expenditure. Deletion of TCPTP in AGRP-expressing neurons prevented HFD-induced obesity and increased energy expenditure and BeAT development in mice[163] (FIG. 3). Interestingly, deletion of TCPTP from the AGRP-expressing neurons of obese mice restored a lean metabolic phenotype[163]. Although still preliminary, taken together, these studies suggest that leptin has an important role in the melanocortin-dependent regulation of adipose function. Nevertheless, the direct role of leptin signalling in these circuits remains to be addressed.

Thermoregulatory circuits

The preoptic area (POA) of the hypothalamus contains neurons responsible for thermoregulation, including those that regulate BAT thermogenesis[23], through direct connections with the DMH[164] and the RPa[165] (FIG. 3). The fact that leptin-deficient mice are `hypothermic` (or `anapyrexic`[113]) and are unable to defend their body temperature during an acute cold exposure[166,167], together with the observation of high levels of leptin receptors within the POA[140,168], suggests that leptin might influence body temperature by directly acting on POA neurons. Indeed, leptin does affect sympathetic outputs to BAT, as determined by increased BAT temperature and energy expenditure, through GABAergic and glutamatergic neurons of the POA[168,169]. Leptin receptors also play a part in the thermic effect of systemic inflammatory stressors such as `lipopolysaccharide` administration[170]. More recently, however, pharmacogenetic activation of leptin-receptor-expressing POA neurons in mice was reported to induce hypothermia and to reduce energy expenditure through a glutamatergic, but not GABAergic, mechanism[112]. This involvement of glutamate is further supported by the observation that deleting vesicular glutamate transporter 2 (VGLUT2), which is needed for glutamate transmission, from leptin-receptor-expressing neurons in mice drastically reduces energy expenditure and body temperature[171]. As

discussed above, the ultimate thermoregulatory effects of leptin are more likely to involve vasomotor mechanisms than BAT thermogenesis. Additional work is needed to better understand the direct implication of endogenous leptin on the POA–BAT axis.

Leptin may also regulate thermoregulation through direct actions on the DMH[23,172–174] (FIG. 3). Disinhibition of the DMH, through unilateral microinjection of bicuculline methiodide (a GABA type A receptor antagonist), evokes non-shivering thermogenesis[172,173], whereas inhibition of DMH neurons prevents BAT thermogenesis[175]. Leptin receptor-expressing DMH neurons project to areas involved in the SNS regulation of body temperature, including the PVH, PAG and RPa[168,176] (FIG. 3). Exogenous leptin activates many DMH neurons[177,178], and intra-DMH injections of leptin increase body temperature[169,179] in both lean and obese mice[180]. Similarly, chemogenetic activation of leptin receptor-expressing neurons in the DMH stimulates BAT thermogenesis and energy expenditure[169]. Interestingly, these effects are blunted or reduced by β_3-AR antagonists[169,180]. Recently, a subpopulation of DMH neurons that co-express leptin receptors and prolactin-releasing peptide (PrRP) was also shown to mediate the effects of leptin on BAT sympathetic nerve activity and temperature in mice[120] (FIG. 3). However, this is unlikely to occur in rats, as PrRP is only weakly expressed in the rat DMH[181]. Leptin may also influence the activity of the RPa. Pharmacological activation of the serotonin receptor 1A (5-HT$_{1A}$ receptor) in the RPa using the specific agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) inhibits leptin-evoked stimulation of BAT sympathetic nerve activity[122] (FIG. 3). However, these effects do not suggest that leptin acts directly on RPa serotonergic cells, as these neurons are not leptin sensitive[182].

Steroidogenic-factor-1-expressing neurons of the ventromedial hypothalamus

The role of the ventromedial hypothalamus (VMH) in regulating non-shivering thermogenesis was unclear for many years. Early studies showed that manipulations of the VMH altered temperature and noradrenaline turnover in BAT[183,184] and fat utilization in WAT[185–188]; however, there was no evidence of direct connections between the VMH and BAT[108]. However, a recent study using PRV tract tracing from BAT shows a substantial percentage of PRV-labelled neurons in the VMH[109], helping to account for earlier works showing a functional connection between the VMH and BAT[185–188].

Leptin microinjection into the VMH increases glucose uptake in different tissues, including BAT — an effect that is blunted by sympathetic denervation[117,189,190]. Furthermore, administration of leptin in the VMH, but not the ARC, PVH or DMH, increases circulating levels of catecholamines, and this effect is abrogated in VMH-lesioned rats[116]. Leptin receptors are expressed throughout the VMH and are especially enriched in the dorsomedial division[178], where steroidogenic factor 1 (SF1)-expressing neurons reside in adult mice[191] (FIG. 3). Genetic deletion of leptin receptors in the dorsomedial VMH using SF1–Cre mice impaired HFD-induced thermogenesis and BAT *Ucp1* expression in mice[192–194]. In particular, SF1 in the VMH is required for thermogenic responses after HFD exposure[194]. Whether leptin also acts through these neurons to regulate WAT lipolysis and BeAT development remains to be determined.

Peripheral afferent neurons

Although fairly preliminary and controversial, there is evidence that peripheral afferent neurons innervate adipose tissues (FIG. 4). The sensory-neuron markers substance P and calcitonin gene-related peptide (CGRP)[195] are expressed in neural fibres innervating BAT[196,197] and WAT[198], and anterograde labelling experiments using both traditional dye and viral tracers show innervation of WAT by afferent neurons in the dorsal root ganglia (DRG)[13,199]. However, the function of this afferent innervation is still unclear. Injection of leptin into one gonadal WAT pad in rats was shown to increase the sympathetic nerve activity of the contralateral epididymal WAT pad within seconds[200,201]. Interestingly, intra-inguinal WAT injection of leptin also increases the electrophysiological activity of afferent neurons in WAT[202]. This suggests the presence of a leptin-sensitive afferent pathway that mediates SNS outflow to WAT to regulate adipocyte function, including lipolysis[203]. It is also possible that sensory innervation carries a negative feedback signal to regulate lipid mobilization[86]. Together, these studies suggest the presence of a leptin-regulated adipose–afferent reflex.

Conclusions and future directions

In this Review, we have highlighted the inherent complexities of the CNS regulatory circuits coordinating adipose tissue function. We have also briefly discussed some controversies and paradoxes that the neuroscience community is facing in regard to leptin and the neural regulation of WAT, BAT and BeAT.

Although our knowledge of the sympathetic regulation of adipose metabolism is ever expanding, many challenges remain (BOX 3), including how to translate findings in rodents to the clinic. Although there are many similarities between rodent and human WAT depots, important differences also exist. For example, there is no omental WAT in rodents and no perigonadal WAT in humans, and there are important differences in the distribution of subcutaneous WAT between rodents and humans[8]. The molecular profile of adipocytes also differs across species. For instance, whereas rodent adipocytes express high levels of β_3-AR, human adipocytes express very few β-ARs and instead express high levels of α_2-ARs[204]. Moreover, the highest levels of leptin are found in the visceral WAT of rodents and subcutaneous WAT in humans[40,41,205]. Our understanding of leptin and the neural control of adipose metabolism must take these interspecies differences into account[206].

Another important challenge is to identify the mechanisms by which the SNS differentially regulates adipose metabolism across different metabolic challenges. Many studies have focused on understanding how high-energy availability (for example, with HFDs) affects adipose metabolism. Although these studies were fundamental in defining important aspects of the pathophysiology of obesity, we believe that we now need to put more emphasis on examining the impact of other metabolic challenges, including states of negative energy balance, such as fasting, exercise, cachexia and cold exposure. Clearly, the physiological functions of leptin also need to be reconsidered in non-obese settings[1,15,207].

Lastly, more studies are warranted on the neural control of various fat depots. The sympathetic activity of adipose tissue is unique compared with that of other tissues, as

evidenced by the fact that fasting decreases the sympathetic tone to most tissues, including BAT, but increases the sympathetic activity towards WAT[10]. Adding to the complexity of adipose physiology, WAT can undergo adipose-depot-specific browning upon SNS activation[7]. Therefore, it is imperative to identify how the CNS differentially regulates each of the fat depots. In the future, it would be useful to develop genetic tools enabling the selective manipulation of the SNS outflow to specific adipose depots. The identification of genes uniquely expressed in stellate or thoracolumbar ganglia could represent a first step in developing such tools. As so aptly described by the late Timothy Bartness, "the trafficking of sympathetic outflow to peripheral tissues remains one of the great mysteries of regulatory biology" (REF.[10]). Thus, developing these genetic tools represents a promising avenue to better understand the regional functions of the sympathetic outflow to adipose tissues.

Acknowledgments

Glossary

SNS outflow

The release of neurotransmitters derived from sympathetic neurons in peripheral tissues

Fat mobilization

A process, in response to signals for energy, in which fatty acids are released from triglyceride stores in fat cells and delivered to organs

Dermomyotome

The epithelial cell layer constituting the dorsal part of the somite lying under the ectoderm. It gives rise to the dorsal dermis and to the skeletal muscle of the myotome

Bilateral chain

A symmetric chain of sympathetic ganglia located just ventral and lateral to the spinal cord

Terminal ganglia

Parasympathetic ganglia situated within or close to an innervated organ and the site where preganglionic nerve fibres terminate

Noradrenaline turnover

A surrogate index of changes in sympathetic activation, based on the assumption that tissue levels of noradrenaline decline at a rate proportional to initial noradrenaline concentrations. Increased noradrenaline turnover implies increased sympathetic activation

Zeitgeber time

A quantification of time based on the period of a zeitgeber. Under standard light–dark cycles, the time at lights-on is usually defined as zeitgeber time 0 for diurnal organisms, and the time at lights-off is defined as zeitgeber time 12 for nocturnal animals

β-Blockers

β-Adrenergic blocking agents that prevent the effects of the hormone adrenaline

Ectopic lipid accumulation

An accumulation of lipids in lean tissues such as kidneys, liver, muscle and heart that results in lipotoxicity and metabolic diseases

Lipotoxicity

The accumulation of lipid intermediates in non-adipose tissue, leading to cellular dysfunction and death

Multilocularity

The appearance of cytoplasmic lipids arranged in numerous small droplets

Thoracolumbar ganglia

Ganglia arising from the thoracolumbar (T1–L2) regions of the spinal cord

Fluoro-gold

A fluorescent retrograde axonal tracer

Thermoneutrality

The state of thermal balance at which an organism does not need to generate heat in order to maintain a normal core temperature

Pyrexic

Relating to factors that raise body temperature above normal

Leptin resistance

Reduced sensitivity with respect to the metabolic responses to exogenously administered leptin

Calorimetry

The process of measuring the amount of energy as heat released, or absorbed, by an organism

O-GlcNAc transferase

(OGT). An enzyme that catalyses the addition of an N-acetylglucosamine group in O-glycosidic linkage to serine or threonine residues of intracellular proteins

Hypothermic

A condition that leads to a decrease in body core temperature — be that regulated, accidental or forced — when the body dissipates more heat than it generates

Anapyrexic

Relating to decreases in body temperature below normal

Lipopolysaccharide

Large molecules found in the outer membrane of Gram-negative bacteria. They elicit strong immune responses

Omental

Adipose tissue located in the omentum, a layer of peritoneum that surrounds abdominal organs

Cachexia

A syndrome characterized by uncontrolled weight loss, muscle atrophy, fatigue and weakness

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Box 1

What is a 'brite' adipocyte?

In rodents, classic brown adipocytes are located in specific areas, including the interscapular region. Under specific physiological conditions, brown-like adipocytes can also develop within white adipose tissue (WAT). These brown-like adipocytes are generally referred to as recruitable, beige or 'brite' adipocytes. When a WAT depot shelters these brite cells, it becomes labelled as a beige adipose tissue (BeAT), owing to its colour. The process by which these cells develop is called browning or 'beiging'. There is not yet a consensus on the required number of brite cells that need to be present in a specific depot to make it beige. The sole presence of mitochondrial brown fat uncoupling protein 1 (UCP1)-positive cells is generally sufficient to define the development of BeAT.

Classic brown and brite adipocytes share similar properties upon stimulation with adrenergic agonists. However, in contrast to classic brown adipocytes, brite adipocytes are not derived from myogenic factor 5 (MTF5)-positive progenitor cells and homeobox protein engrailed 1 (EN1)-expressing cells of the central dermomyotome. As such, brite adipocytes might be at once both, and neither, brown and white. It has been proposed that these cells are derived from different precursors, differentiate from a white adipocytic precursor or transdifferentiate from an existing mature white adipocyte. It has also been shown that brite adipocytes exhibit a distinct molecular signature that is not shared by either classic brown or white fat cells. Overall, brite adipocytes seem to be recruitable brown cells within WAT and therefore might participate in systemic energy homeostasis.

Box 2

Sympathetic and sensory innervation of adipose tissues

Adipose tissues are richly innervated by the sympathetic nervous system (SNS). The understanding of the innervation patterns of the different fat depots is still evolving, and more studies are needed to better characterize and map how the brain and adipose tissues communicate with each other. Using a combination of fluorescent tract tracers and retrograde labelling (using pseudorabies virus (PRV)), sympathetic thoracolumbar ganglia were observed to project to both gonadal white adipose tissue (WAT) and inguinal WAT in Siberian hamsters and rats[109,208] (FIG. 4). However, anatomical studies also demonstrated that different subsets of sympathetic neurons regulate lipolysis in visceral versus subcutaneous fat pads (FIG. 4). Moreover, the pattern of SNS innervation of fat pads differs in mice, with minimal fibres projecting to gonadal WAT compared with inguinal WAT[99]. The regional specificity of SNS innervation is further emphasized by functional changes (reflected by differences in noradrenaline turnover) observed following treatment with various stimuli. For example, in Siberian hamsters, cold exposure, but not fasting, increases noradrenaline turnover to retroperitoneal WAT, whereas central administration of the melanocortin receptor agonist melanotan II (MTII) increases noradrenaline turnover only to subcutaneous WAT[209]. Fluorogold studies have suggested that neurons in ganglia thoracic spinal segment 13 (T13)– lumbar spinal segment 3 (L3) project to both gonadal and inguinal WAT[210]. However, it is difficult to determine whether these ganglia are part of the SNS, owing to the lack of tyrosine hydroxylase (TH) counterstaining in these studies. Sympathetic thoracic chain ganglia innervating WAT were recently described in mice using TH-specific antibody staining[211]. Thus, coupling tract tracers and retrograde labelling to TH immunostaining will be useful to further determine the nature of the SNS ganglia projection to adipose tissues. Interestingly, the SNS ganglia that innervate inguinal WAT are similar to those innervating brown adipose tissue (BAT) (at T1–T3 and T12–L3 vertebral levels)[109], whereas the SNS ganglia that innervate mesenteric and inguinal WAT were shown to exhibit some regional differences throughout the T5–L13 sympathetic chain levels[208] (FIG. 4). However, there is a caveat associated with PRV tracing studies: glial or phagocytic cells of the immune compartment might accumulate PRV particles, populate the SNS ganglia and be incorrectly interpreted as neurons[211]. Moreover, studies in rats failed to identify innervation of inguinal BAT from ganglion cells in the T13 and the L1– L3 ganglia[110], again reinforcing the need for further investigations into species-specific innervation differences. Although PRV retrograde tracing experiments should be interpreted with caution, the tracing studies nevertheless provide an anatomical picture supporting the differential central sympathetic regulation of different WAT depots. This regional specificity highlights the importance of considering each fat depot as a unique organ in terms of SNS regulation and function. As recently emphasized[212], mice and humans share topological similarity of adipose tissues; however, the pattern of SNS innervation of these fat depots is largely unknown. The differences in innervation may also contribute to differences in leptin expression and regulation between visceral fat and subcutaneous fat, with leptin being predominantly produced by visceral fat in rodents[40].

Box 3

Key outstanding questions

Throughout this Review, we highlight how leptin plays an important role in brain–adipose crosstalk. However, there are many questions that still require attention:

- What are the differences in adipose innervation between males and females? Could differences in sympathetic outflow explain the differences in fat distribution between sexes?

- What are the intracellular mechanisms through which activation of adrenergic receptors regulates leptin expression? How do increased levels of cAMP lead to inhibition of leptin expression and secretion?

- Can we develop genetic tools to neuromodulate specific adipose tissues? This would first require the development of more comprehensive maps of the sympathetic innervation of brown adipose tissue (BAT), beige adipose tissue (BeAT) and white adipose tissue (WAT).

- How similar are the afferent innervations of adipose tissue between Siberian hamsters, rats, mice and humans? It is imperative to fully characterize the innervation patterns in mice to enable the use of the available and expanding library of transgenic tools.

- Is there a similar neural circuit regulating adipose tissue in humans? The fact that there are differences in the expression of adrenergic receptors between rodents and humans suggests that alternative mechanisms for BAT, BeAT and WAT regulation might exist in humans.

- What are the central neural circuits regulating BAT, BeAT and WAT? Is leptin required for the differential effects of metabolic stresses such as fasting and cold on adipose tissues?
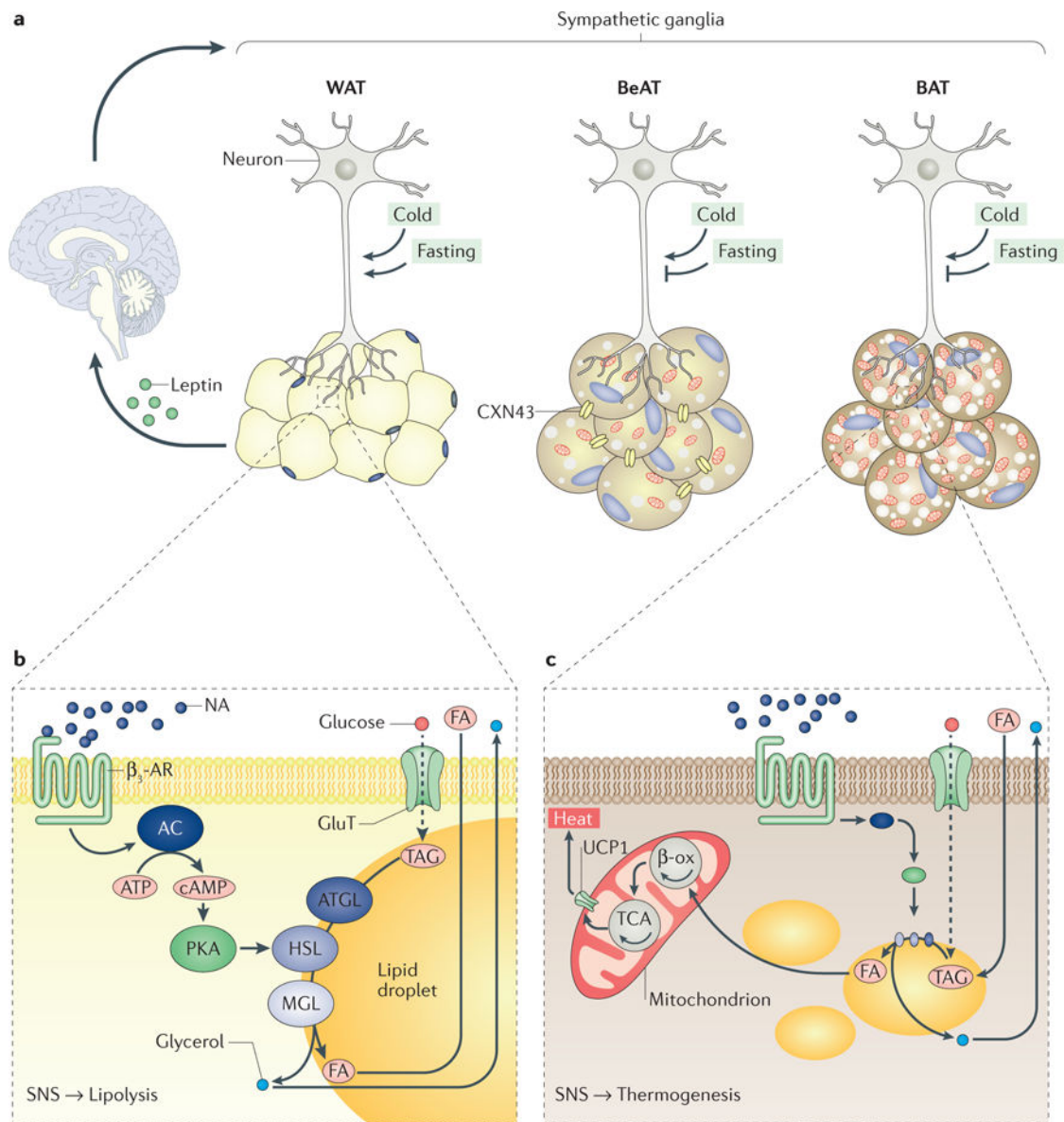
Figure 1. Sympathetic regulation of white, brown and beige adipose tissues
a Innervation of white adipose tissue (WAT), beige adipose tissue (BeAT) and brown adipose tissue (BAT). Neurons of the sympathetic nervous system (SNS) project (via their axons) to different fat depots and establish contacts with adipocytes. A cell-to-cell connexin 43 (CXN43) gap-junction system facilitates the propagation of the sympathetic signal among 'brite' adipocytes. Whether this system is also important for lipolysis is unknown. Leptin, which is secreted from WAT, also affects the SNS outflow via actions in the brain. Cold and fasting differently affect the sympathetic tone to different adipose tissues. **b** SNS-dependent WAT regulation. The SNS regulates WAT energy storage and mobilization. Evidence indicates the existence of a leptin-dependent neuro–adipose tissue connection that plays an important part in fine-tuning fuel usage. The neurons release noradrenaline (NA), which signals to β_3-adrenoceptors (β_3-ARs) located on adipocytes. This signalling promotes a well-characterized cascade of molecular events that trigger lipolysis (lipid breakdown).

Briefly, the accumulation of cAMP promotes protein kinase A (PKA)-dependent activation of a well-established molecular cascade involving adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL) and monoglyceride lipase (MGL), which generate fatty acids (FAs) and glycerol. Glucose can also be incorporated into triacylglycerol (TAG) through de novo lipogenesis and subsequently catabolized to generate FAs and glycerol. cAMP also reduces leptin production (see FIG. 2). In white adipocytes, FA and glycerol are released into the circulation, whereas in brite adipocytes, FA can be used as a substrate for oxidative metabolism in mitochondria. **c** SNS-dependent BAT regulation. The SNS regulates BAT non-shivering thermogenesis. As in WAT, NA signals to β_3-ARs and stimulates lipolysis. Lipolysis in BAT activates mitochondrial uncoupling protein 1 (UCP1) and thermogenesis following oxidation of FAs (via β-oxidation (β-ox) and the tricarboxylic acid cycle (TCA)). As for BeAT, it is assumed that brite adipocytes share features of WAT and BAT; that is, adrenergic stimulation leads to both increased lipolysis and thermogenesis in BeAT. Circulating glucose can also be used by brown adipocytes to generate heat after de novo lipogenesis. AC, adenylyl cyclase; GluT, glucose transporter.
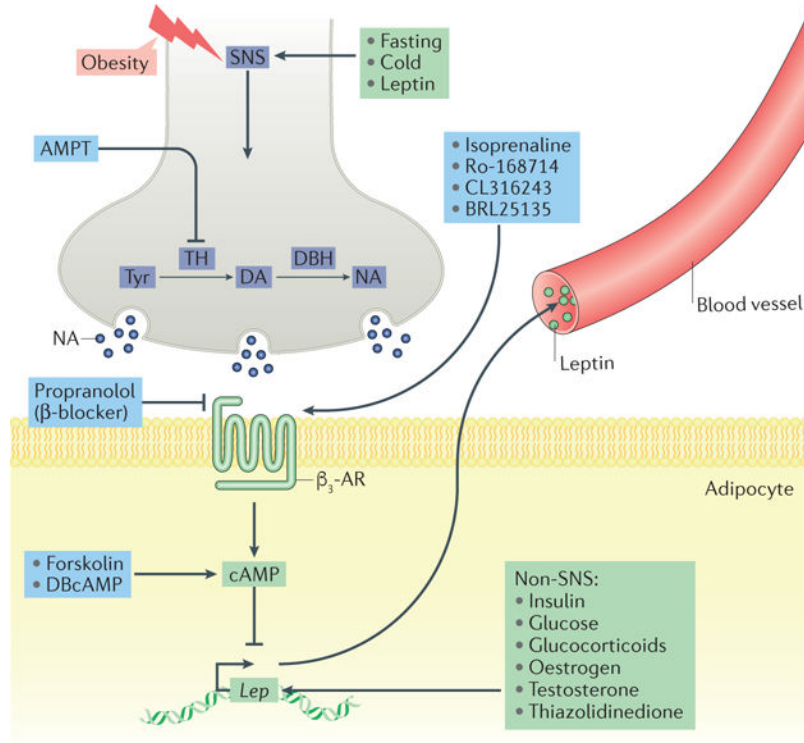
Figure 2. Sympathetic regulation of leptin production

The sympathetic nervous system (SNS) is a key acute regulator of leptin production. Metabolic challenges affect leptin production through a β_3-adrenergic receptor (β_3-AR)– cAMP-dependent mechanism. Leptin regulates its own expression through a negative feedback loop from adipose tissue to the brain. Other non-SNS-related factors — exogenous and endogenous — also increase or decrease *Lep* expression. AMPT, α-methyl-*p*-tyrosine; DA, dopamine; DBcAMP, dibutyryl-cAMP; DBH, dopamine β-hydroxylase; NA, noradrenaline; TH, tyrosine hydroxylase; Tyr, tyrosine.
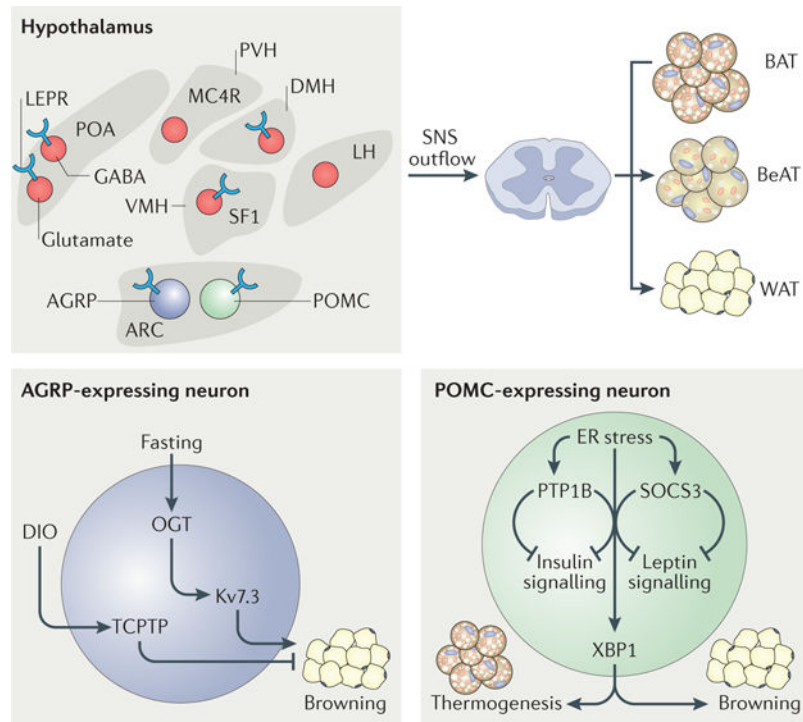
Figure 3. Leptin-sensitive neurons regulating adipose depots

Neurons in several hypothalamic nuclei express leptin receptors, and many of these nuclei are in turn involved in adipose regulation. The arcuate nucleus (ARC)–paraventricular nucleus (PVH) melanocortin system, the thermoregulatory circuit (the preoptic area (POA)–dorsomedial hypothalamus (DMH)–raphe pallidus nucleus) and the steroidogenic factor 1 (SF1)-expressing neurons (of the ventromedial hypothalamus (VMH)) all have roles in regulating the sympathetic nervous system (SNS) outflow to white adipose tissue (WAT), brown adipose tissue (BAT) and beige adipose tissue (BeAT). O-GlcNAc transferase (OGT) and T cell protein-tyrosine phosphatase (TCPTP) expressed in the neuropeptide Y or agouti-related protein (AGRP)-expressing neurons of the ARC are key regulators of BeAT development and are influenced by fasting and diet-induced obesity (DIO). The endoplasmic reticulum (ER) stress response factor X-box binding protein 1 (XBP1) expressed in the pro-opiomelanocortin (POMC)-expressing neurons of the ARC is a key regulator of non-shivering thermogenesis in BAT and BeAT development. LEPR, leptin receptor; LH, lateral hypothalamus; Kv7.3, voltage-gated Kv7.3 channel; MC4R, melanocortin receptor 4; PTP1B, protein-tyrosine phosphatase 1B; SOCS3, suppressor of cytokine signalling 3.
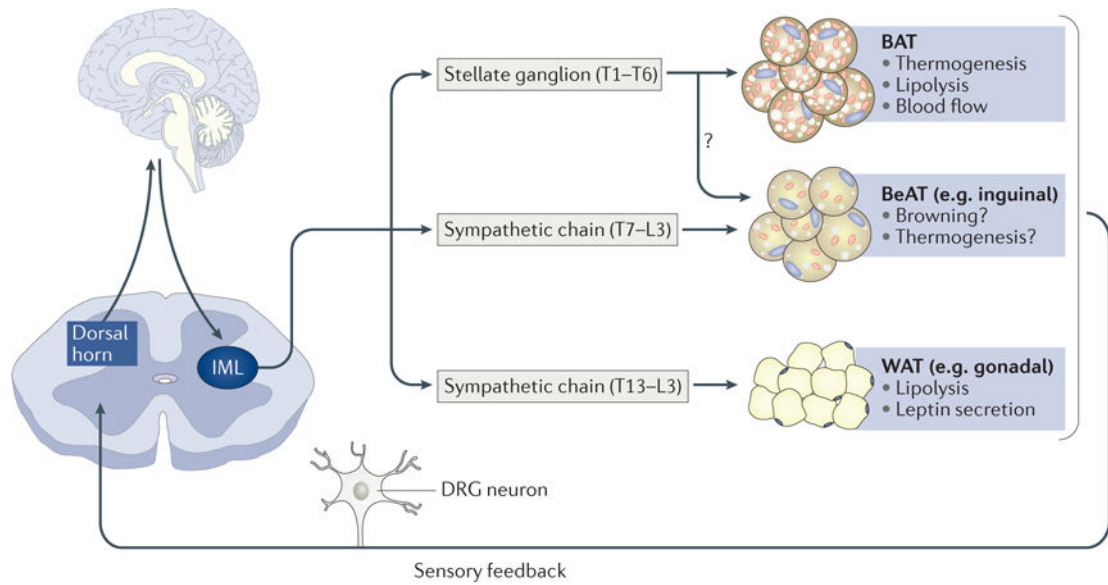
Figure 4. Sympathetic and sensory innervation of adipose tissues
Sympathetic innervations of brown adipose tissue (BAT) originate from the stellate ganglion (T1–T6). Although still debated (owing to divergence in the species studied), sympathetic thoracolumbar ganglia (T7–L3) project to gonadal and inguinal white adipose tissue (WAT) (which is the most characterized inducible beige adipose tissue (BeAT) depot). It is also suggested that there are similarities between inguinal WAT and BAT innervation (with BAT-innervating and WAT-innervating neurons possibly residing in T1–T3 ganglia). Sensory feedback from adipose tissues via the dorsal root ganglion (DRG) to the brain regulates WAT lipolysis and leptin secretion and BAT non-shivering thermogenesis. Additional studies are needed to validate these afferent innervations in mice. IML, intermediolateral column of spinal cord; L, lumbar spinal segment; T, thoracic spinal segment.