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REVIEW

Brain JNK and metabolic disease

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Abstract

Obesity, which has long since reached epidemic proportions worldwide, is associated with long-term stress to a variety of organs and results in diseases including type 2 diabetes. In the brain, overnutrition induces hypothalamic stress associated with the activation of several signalling pathways, together with central insulin and leptin resistance. This central action of nutrient overload appears very rapidly, suggesting that nutrition-induced hypothalamic stress is a major upstream initiator of obesity and associated diseases. The cellular response to nutrient overload includes the activation of the stress-activated c-Jun N-terminal kinases (JNKs) JNK1, JNK2 and JNK3, which are widely expressed in the brain. Here, we review recent findings on the regulation and effects of these kinases, with particular focus on the hypothalamus, a key brain region in the control of energy and glucose homeostasis. JNK1 blocks the hypothalamic–pituitary–thyroid axis, reducing energy expenditure and promoting obesity. Recently, opposing roles have been identified for JNK1 and JNK3 in hypothalamic agouti gene-related protein (AgRP) neurons: while JNK1 activation in AgRP neurons induces feeding and weight gain and impairs insulin and leptin signalling, *JNK3* (also known as *MAPK10*) deletion in the same neuronal population produces very similar effects. The opposing roles of these kinases, and the unknown role of hypothalamic JNK2, reflect the complexity of JNK biology. Future studies should address the specific function of each kinase, not only in different neuronal subsets, but also in non-neuronal cells in the central nervous system. Decoding the puzzle of brain stress kinases will help to define the central stimuli and mechanisms implicated in the control of energy balance.

Keywords CNS · Diabetes · JNK · Kinases · Metabolism · Obesity · Phosphorylation · Review · SAPK · Signalling · Stress

Abbreviations

AgRP	Agouti gene-related protein
ARC	Arcuate nucleus
BAT	Brown adipose tissue
CART	Cocaine- and amphetamine-regulated transcript
CNS	Central nervous system
DIO	Diet-induced obesity
ER	Endoplasmic reticulum
HFD	High-fat diet
IRE1	Inositol-requiring enzyme 1
JIP	c-Jun N-terminal kinase-interacting protein
LC3	Light-chain 3
MAPK	Mitogen-activated protein kinase
MKK	Mitogen-activated protein kinase kinase
NPY	Neuropeptide Y
POMC	Proopiomelanocortin
SAPK	Stress-activated protein kinase
T3	Triiodothyronine
T4	Thyroxine
UPR	Unfolded protein response
VMH	Ventromedial nucleus of the hypothalamus
XBP1	X-box binding protein 1

Supplementary Information The online version of this article (https://doi.org/10.1007/s00125-020-05327-w) contains a slideset of the figures for download.

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The central nervous system and the control of energy homeostasis

The maintenance of body weight represents the balance between the energy derived from food intake and that expended in basal metabolism, thermogenesis and physical activity. Food intake and energy expenditure are both tightly regulated by homeostatic mechanisms involving crosstalk between the brain and peripheral tissues. The brain perceives modifications in body energy state by identifying variations of circulating factors and via vagal afferents. In response to modification of metabolism, specialised neuronal networks in the brain coordinate adaptive changes in food intake and energy expenditure. This coordination requires complex and integrated management whereby peripheral signals activate different neurocircuits located in several brain areas that are essential for regulation of energy homeostasis (see comprehensive reviews [1–4]).

This review focuses on the hypothalamus, the most exhaustively studied brain area regarding metabolic actions. The hypothalamus lies below the thalamus and is organised into multiple neuronal clusters, called nuclei. Among the different nuclei, the arcuate nucleus (ARC) has privileged access to peripheral signals because it is situated on top of the endocrine median eminence, a circumventricular organ devoid of the blood–brain barrier. The ARC thus integrates metabolic signals from the periphery as well as peripheral and brain neuronal inputs to regulate homeostatic pathways. This integration occurs in the two neuronal populations of the ARC: a set of anabolic neurons co-expressing neuropeptide Y (NPY), agouti gene-related protein (AgRP) and γ-aminobutyric acid (GABA); and an adjacent set of catabolic ARC neurons that co-express proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) [1].

Extensive research has focused on the action of peripheral signals on the central nervous system (CNS), including the effects of hormones and nutrients on these neuronal populations (see comprehensive reviews [5–7]). When circulating factors penetrate the ARC, these neurons can directly sense changes in circulating factors and initiate appropriate pathways to regulate food intake and/or energy expenditure. The two ARC neuronal populations show a clear response to exogenously administered circulating factors. This response can occur, for example, via activation of hormone receptors, which are abundantly expressed in both POMC and AgRP/NPY neurons [6]. The basic model of feeding regulation by these neuronal populations is that signals circulating at higher levels during states of negative energy balance (e.g., the hormone ghrelin) stimulate the activity of AgRP and decrease the activity of POMC neurons. Conversely, signals providing information of positive energy balance (e.g. the hormone leptin) reduce the activity of AgRP neurons and stimulate POMC neurons (see comprehensive reviews [5–7]).

The link between hypothalamic stress and metabolic dysfunction

One of the most challenging aspects of this homeostatic maintenance is understanding how these neuronal networks respond to nutritional stress, caused either by nutrient excess or deficiency. A large body of evidence accumulated in recent years indicates that important stress-related biological processes exert effects within the hypothalamus that coordinately act to modify feeding and energy expenditure.

ER stress One important manifestation of stress is protein misfolding, through which amino acid chains acquire incorrect native three-dimensional conformations. Impaired protein folding results from the failure of the endoplasmic reticulum (ER) to cope with the excessive folding demand in response to heightened rate of protein synthesis and/or flux through the secretory pathway. Recent evidence indicates the existence of a causal link between hypothalamic ER stress (a response triggered by unfolded and/or misfolded protein accumulation) and the development of obesity [8], and genetic and diet-induced obesity (DIO) models have revealed enhanced expression of ER stress markers in the hypothalamus [9–14]. More specifically, the hypothalamus of rodents rendered obese by being fed a high-fat diet (HFD) expresses elevated levels of ER stress markers such as inositol-requiring enzyme 1 (IRE1) and protein kinase R-like endoplasmic reticulum kinase (PERK) phosphorylation, spliced X-box binding protein 1 (XBP1) and C/EBP homologous protein (CHOP) [12, 14]. Saturated fatty acids such as palmitate activate ER stress in hypothalamic neurons, suggesting that dietary composition is an important factor in the induction of hypothalamic ER stress [9–11].

Pharmacological studies support the link between hypothalamic ER stress and metabolic dysfunction. Injection of ER stress inducers into rodent brains stimulates food intake and body-weight gain, whereas the administration of ER stress inhibitors reduces obesity [12–16]. In addition, genetic studies have shown that the unfolded protein response (UPR) in hypothalamic AgRP and POMC neurons plays a key role in the regulation of energy balance. Unexpectedly, induction of the UPR transcription factor XBP1 in POMC neurons protects against diet-induced obesity, improves hepatic insulin sensitivity and suppresses endogenous glucose production [9]. In line with this finding, the inhibition of IRE1 in POMC neurons accelerates diet-induced obesity, concomitant with a decrease in energy expenditure and impaired insulin sensitivity [17]. However, targeted overexpression in the ventromedial nucleus of the hypothalamus (VMH) of GRP78, an ER-located chaperone that facilitates protein folding upstream of the ER UPR, was sufficient to alleviate ER stress and to revert the obese and metabolic phenotype [16].

Autophagy Another key factor in homeostasis mechanisms in the hypothalamus is the important role of autophagy in hormetic reactions. Hormesis is the phenomenon through which exposure of cells, organs or organisms to a mild stress prepares them to mount an adaptive response that allows them to tolerate a subsequent stronger and potentially lethal exposure to the same stress. Studies in vitro and in vivo have shown that starvation induces autophagy in the hypothalamus [18]. Removal of serum from hypothalamic GT1-7 cells triggered an increase in protein levels of the lipid-conjugated form of the autophagosome marker light-chain 3 (LC3)-II, an effect reversed by serum refeeding [18]. Another study showed that autophagy was also induced in hypothalamic cell lines subjected to low glucose availability by 2-deoxy-D-glucose-induced glucoprivation or glucose deprivation [19]. In line with this, mice subjected to 6 h of food restriction showed increased LC3-II protein levels in the mediobasal hypothalamus, and this effect was reversed by refeeding [18]. The induction of autophagy during starvation seems to be mediated by the lack of nutrients, since LC3-II protein levels decrease when serum-starved hypothalamic cells are supplemented with alternative energy sources such as methylpyruvate and methylsuccinate [18].

In vivo studies have shown that autophagy is suppressed by knockdown of 5′ AMP-activated protein kinase (AMPK) in the ARC, which triggers downregulation of the expression and the stimulation of POMC neurons, resulting in inhibition of food intake and reduced body weight [19]. Several reports have demonstrated that the deletion of autophagy-related genes in specific hypothalamic neurons alters energy balance. Deletion of the essential autophagy gene *Atg7* in AgRP neurons reduces body weight and adiposity and results in failed AgRP upregulation in response to starvation [18]. Autophagy is also important in POMC neurons, where the lack of *Atg7* promotes adiposity, impairing lipolysis and altering glucose homeostasis [20, 21]. Similar results were found in mice lacking *Atg12* in POMC neurons; these mice showed accelerated weight gain, adiposity and glucose intolerance associated with increased food intake and reduced ambulation [22].

Inflammation One of the most frequent physiological responses to stress is inflammation, and chronic overnutrition is known to activate inflammatory pathways both systemically and centrally [23]. This inflammatory response, unlike the classical inflammatory response to pathogens, is relatively low grade. Inflammation in the brain, particularly in the hypothalamus, can provoke dysfunction of neurohormone- and neurotransmitter-mediated pathways that regulate energy balance, leading to obesity and related disorders [24, 25]. Diet-induced metabolic inflammation in the hypothalamus can happen rapidly, in a body-weight-independent manner that precedes the development of obesity. This hypothalamic inflammation has broad effects on peripheral tissues. It is associated with impaired insulin release by pancreatic beta cells, weaker insulin action on target tissues, the development of renovascular dysfunction leading to hypertension, and reduced thermogenesis. For more detailed information on hypothalamic inflammation and metabolic dysfunction, see [26, 27].

Lipotoxicity Another important stressor is inappropriate lipid deposition in organs other than adipose tissue, which causes adverse effects on cellular metabolism, known as lipotoxicity [28, 29]. Reactive lipid species, such as diglycerides, non-esterified fatty acids, free cholesterol and ceramides, can be more toxic than other lipid species such as triacylglycerols. Their accumulation is a feature of insulin resistance, type 2 diabetes, liver disease and CVD. Lipotoxicity occurs through inflammation and ER stress [30–32]. Hypothalamic lipotoxicity has been shown to induce insulin resistance, dysregulation of glucose homeostasis and a dysfunction in energy balance [33]. The central administration of ceramides increases ER stress in the mediobasal hypothalamus, which contains the ARC and the VMH, and induces a marked feeding-independent weight gain, which is associated with decreased mRNA expression of thermogenic markers in brown adipose tissue (BAT) [34].

Stress kinases and energy metabolism

Although there are different types of cellular stress, a large part of the cellular response to toxins, physical stresses and inflammatory cytokines occurs through stress-activated protein kinase (SAPK) signalling via the c-Jun N-terminal kinase (JNK) and p38 pathways [35]. Protein phosphorylation regulates the transduction, amplification and integration of many intracellular and intercellular processes [36], and protein kinases are central players in almost every signalling pathway involved in normal development and disease, including the regulation of whole-body energy homeostasis.

The stress kinases p38 and JNK are mitogen-activated protein kinases (MAPKs), principally activated by stress such as cytokines, excess of non-esterified fatty acids, inflammation and ER stress [37, 38]. These serine/threonine kinases are evolutionarily conserved in all eukaryotes. They regulate cellular adaptation and participate extensively in the control of cell fate decisions such as proliferation, differentiation and death, as well as in the regulation of stress responses [39, 40]. Stress kinases are activated by triple kinase pathways that include a MAPK kinase kinase (MKKK), a MAPK kinase (MKK) and the terminal MAPK. This organisation promotes signal amplification and fidelity [41]. Tight regulation of the pathway is further ensured by scaffolding proteins that cluster specific MAPK cascade components with their substrates at discrete subcellular sites [42]. While MKK4 and MKK7 are the main activators of JNKs, the p38 pathway is triggered primarily by

MKK3 and MKK6 [43]. There are three JNK kinases (JNK1, JNK2 and JNK3 [44]), whereas p38 isoforms consist of p38α, p38β, p38γ/SAPK3 and p38δ/SAPK4 [43] (Fig. 1). The distinct p38 and JNK family members are encoded by different genes [38]. Although all p38 family members are widely expressed, p38γ expression is especially high in skeletal muscle and BAT [38, 45], and p38δ is mainly found in testis, pancreas, kidney, lung, small intestine and neutrophils [38]. JNK1 and JNK2 are expressed ubiquitously, whereas JNK3 is restricted to brain, heart, beta cells and testis [38]. The complexity of JNK signalling is increased by alternative splicing to generate a total of ten JNK isoforms [46, 47].

The role of JNKs in the regulation of whole-body energy balance and obesity-related diseases has been intensely studied in relation to peripheral metabolic tissues, in which JNK activation is associated with chronic obesity. In contrast, the roles of JNKs in the brain are less well studied. In adipose tissue, JNK1 controls IL-6 expression and, in consequence, under obese conditions it increases liver lipid content [48]. However, lack of JNK1 in muscle increases liver steatosis while protecting against muscle insulin resistance [49]. Moreover, liver steatosis is also produced by *Jnk1* (also known as *Mapk8*) depletion in liver, suggesting an important physiological role for this kinase in hepatocytes [50].

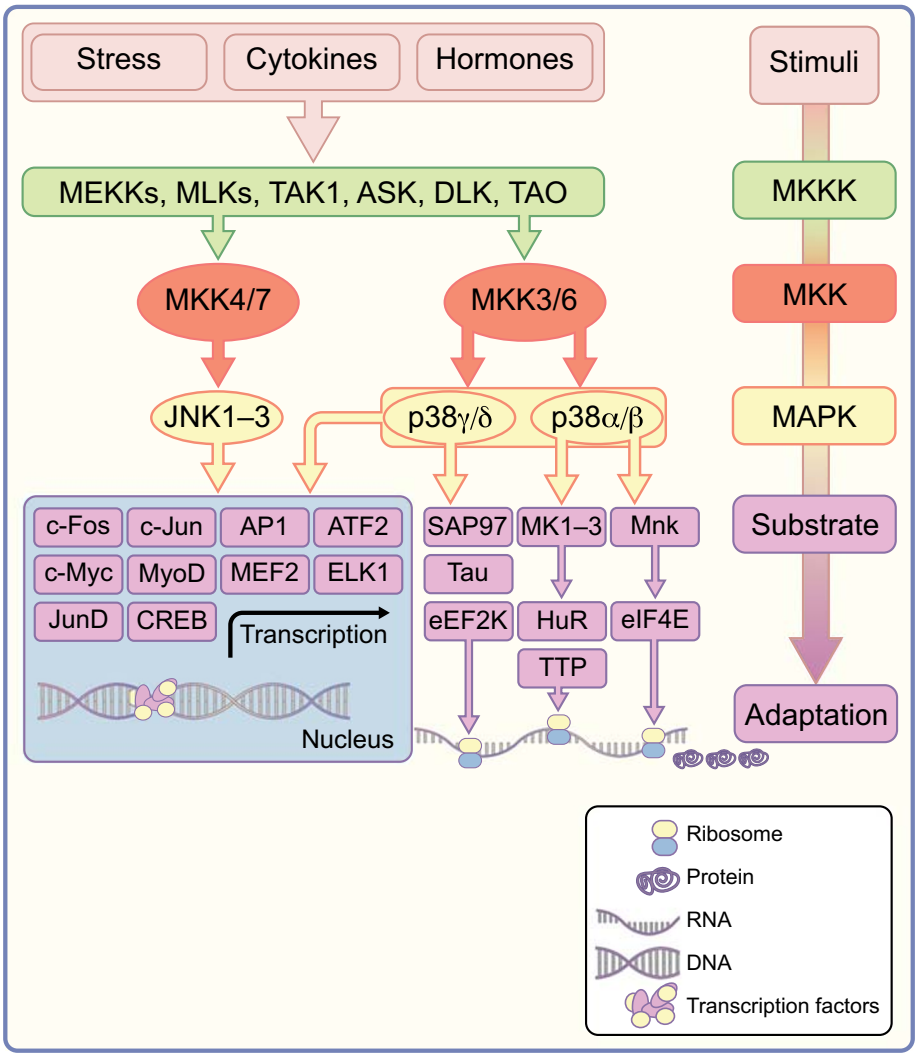

Fig. 1 SAPK pathways. Stress (e.g. NEFAs, reactive oxygen species and ultraviolet exposure), cytokines and hormones are examples of stimuli that lead to activation of SAPK pathways. These stimuli (pink boxes) activate MAPK kinase kinase (MKKK; green boxes), which, in turn, activate MKKs (red boxes) that go on to activate SAPKs (also known as MAPKs; yellow boxes) via phosphorylation. Once activated, SAPKs mediate cell adaptation to stress by phosphorylating several substrates (purple boxes), including other kinases, transcription factors, scaffold proteins, and elongation and initiation factors. AP1, activator protein 1; ASK, apoptosis signal-regulating kinase; ATF2, activating transcription factor 2; CREB, cAMP response element-binding protein; DLK, dual leucine zipper kinase; eEF2K, eukaryotic elongation factor-2 kinase; eIF4E, eukaryotic translation initiation factor 4E; ELK1, ETS like-1 protein; HuR, human antigen R; MEF2, myocyte enhancer factor-2; MEKK, MAPK kinase kinase; MK1–3, MAPK-activated protein kinase 1–3; MLK, mixed lineage kinase; Mnk, MAPK interacting kinase 1; MyoD, myoblast determination protein 1; SAP97, synapse-associated protein 97; TAK1, MAPK kinase kinase 7; TAO, thousand-and-one amino acids protein kinase; TTP, tristetraprolin. This figure is available as part of a downloadable slideset

Surprisingly, depletion of both JNK1 and JNK2 protects against insulin resistance and glucose intolerance [51]. The emerging picture is that JNK family members have tissue-specific actions and appear to participate in organ cross-talk.

Less is known about the role of the p38 pathway in energy homeostasis and the development of obesity-induced changes that lead to disease. Moreover, the function of the different p38 family members in the hypothalamus during this process remains undefined. In peripheral tissues, Ricci and co-workers identified p38δ as a key regulator of insulin secretion and pancreatic beta cell survival [52]. We and others found that levels are elevated in peripheral organs of individuals with type 2 diabetes or obesity [53, 54–56], suggesting that some p38 responses may be important for the pathogenesis of type 2 diabetes and its complications. In line with this view, deletion of *p38γ* and *p38δ* in myeloid cells protects against diet-induced liver steatosis and insulin resistance by eliminating p38γ/δ-mediated neutrophil infiltration of the liver [53]. While the role of p38s in the control of metabolism in peripheral tissues is beginning to be addressed, the function of these kinases in the control of metabolism in the CNS will require in-depth analysis with conditional animal models.

Hypothalamic JNK and energy metabolism

JNK family members are activated in the CNS by several obesity-triggered stimuli, including low-grade inflammation, ER stress and lipotoxicity [57–60]. Several studies have therefore tried to uncover the function of these kinases in the hypothalamus during HFD-induced obesity. The most studied family member in this context is JNK1, the ablation of which protects mice against obesity, glucose intolerance and insulin resistance [57, 61]. In contrast, lack of JNK3 in AgRP neurons triggers obesity [58]. JNK2 is the least studied family member, and very little information is available. A recent study showed that an HFD in the context of whole-body *Jnk2* (also known as *Mapk9*) deletion in mice alters cognitive activity by modulating the insulin receptor, and that depletion of JNK2 results in increased JNK activity in the hippocampus, correlating with increased ER stress and reduced insulin receptor signalling [62]. JNK2 has also been shown to control thyroid hormone levels through cooperation with JNK1 in the pituitary [63].

Studies in several animal models of nutritional stress have demonstrated the activation of JNK in the hypothalamus. In mice, hypothalamic JNK and inflammation were increased at postnatal day 21 in the offspring of mothers that consumed an HFD during gestation and lactation, which had the effect of accelerating body-weight and body-fat gain and impairing glucose tolerance [64]. Moreover, HFD-fed adult rats had increased total hypothalamic JNK activity, and intracerebroventricular treatment with a specific JNK inhibitor (SP600125) restored insulin signalling and reduced energy intake and weight loss [65]. Similar results were obtained with the pan-JNK (JNK1/2/3) inhibitor SR-3306, which has brain-penetrating properties. Intraperitoneal or intracerebroventricular administration of SR-3306 reduced food intake and body weight in lean mice, and peripheral administration decreased food intake and obesity in mice fed an HFD [66]. This latter effect likely results from an enhanced anorectic effect of leptin due to an increase in its ability to activate signal transducer and activator of transcription 3 (STAT3) in the hypothalamus [66].

JNK1

In addition to the pharmacological approaches described above, JNK1 actions in the CNS have been investigated in mice lacking JNK1 in the brain (brainJnk1^{KO}), generated by crossing *Jnk1*LoxP/LoxP mice with nestin-Cre mice. Nestin is highly expressed in neural stem cells and neuronal progenitor cells, and therefore nestin-Cre transgenic mice have been widely used to direct recombination in the CNS. However, the nestin-Cre model does not provide neuronal resolution, and these studies did not identify the neuronal subsets in which JNK1 plays an important role. In one study, brainJnk1^{KO} mice had lower HFD-induced body-weight gain than wild-type control mice [57], due to lower food intake, higher physical activity and higher energy expenditure [57]. Moreover, HFD-fed brainJnk1^{KO} mice had better insulin sensitivity and beta cell function than wild-type mice on the same diet [57]. BrainJnk1^{KO} mice have higher body temperature, upregulated expression of thyroid hormone-induced genes and elevated circulating levels of thyroxine (T4) and triiodothyronine (T3), indicating that the increased energy expenditure in these mice is in part mediated by activation of the hypothalamic–pituitary–thyroid axis [57] (Fig. 2). Moreover, the protection of brainJnk1^{KO} mice against DIO was abolished by pharmacological inhibition of thyroid hormone production [57]. Another study showed similar findings, with brainJnk1^{KO} mice gaining less weight than controls on an HFD, having better insulin sensitivity and glucose metabolism, and showing increased thyroid axis activity and protection against hepatic steatosis [57]. However, nestin-Cre mice may have nonspecific deletion and metabolic problems [67] and therefore corroboration of these results will require further research into hypothalamic JNK1 function in POMC-Cre or AgRP-Cre mouse models.

A recent study investigated the specific role of JNK1 and JNK2 in the anterior pituitary. While lack of JNK1 or JNK2 alone had no effect, ablation of both isoforms protected against DIO [63], suggesting redundant roles for JNK1 and JNK2 in the anterior pituitary. In agreement with previous studies [57, 61], glucose metabolism was also improved in

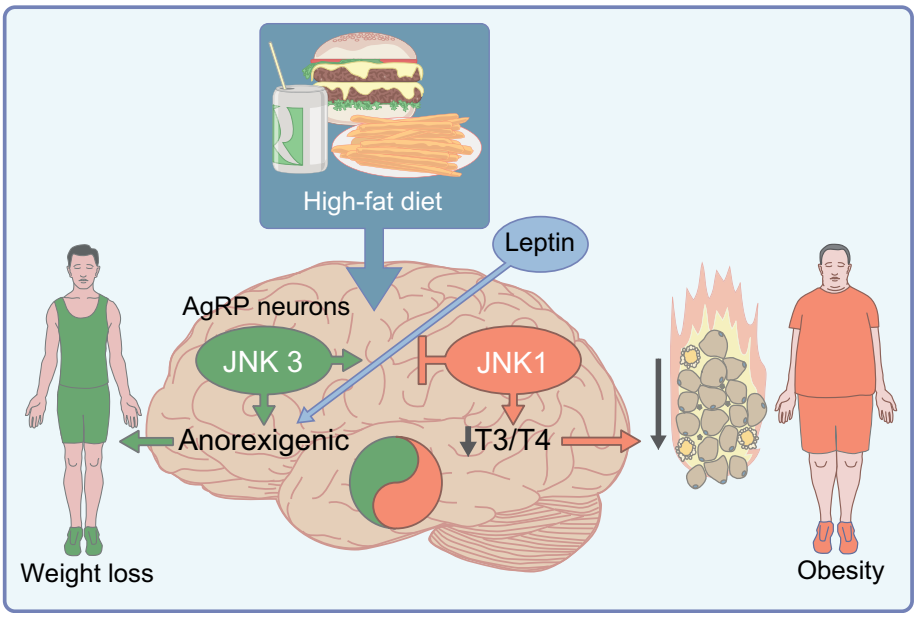

Fig. 2 Opposing roles of JNK1 and JNK3 in the hypothalamus. Activation of JNK1 contributes to diet-induced obesity by affecting the thyroid hormone (T3 and T4) axis, whereas JNK3 is activated by leptin in AgRP neurons and has a protective effect by decreasing food intake. Thus, in the CNS, JNK plays a 'yin-yang' role in that JNK1 activation is obesogenic while JNK3 activation protects against obesity. This figure is available as part of a downloadable slideset

the double-knockout mice, which had elevated circulating levels of thyroid hormones and thyroid-stimulating hormone. The study also showed that JNK controlled the expression of type 2 iodothyronine deiodinase (Dio2), required for T4 conversion to T3.

In another study, overexpression of activated JNK1 in AgRP neurons demonstrated the existence of at least one neuronal population in which JNK1 controls metabolic and endocrine functions [68]. The specific activation of JNK1 signalling in AgRP neurons stimulated their electrical activity relative to control littermates. Consistent with the orexigenic role of this neuronal population, these mice displayed hyperphagia and developed obesity, which was associated with leptin resistance (Fig. 2) [68]. These results are consistent with the reduced food intake observed in brainJnk1^{KO} mice [57].

Another function of JNK1 in AgRP neurons is to regulate the metabolic actions of hypothalamic p53. Lack of p53 in AgRP neurons increases susceptibility to DIO, and these mice have increased levels of phosphorylated JNK [69]. Central treatment of mice lacking p53 in AgRP neurons with the c-Jun inhibitor SP-600125 reduced body weight. In agreement with this result, the increased sensitivity of JNK1-deficient mice to HFD was abolished by p53 knockdown in the mediobasal hypothalamus [69].

In addition to its role in AgRP neurons, JNK1 also mediates the effects of thyroid hormones through its actions within the VMH [70]. Hyperthyroid rats have elevated levels of phosphorylated JNK in the VMH. Among their multiple actions, thyroid hormones promote de novo lipogenesis in the liver; moreover, treatment with SP600125 can reverse the central actions of thyroid hormones in the liver, resulting in decreased hepatic lipid content. Consistent with this finding, central administration of thyroid hormones did not alter lipid metabolism in the livers of JNK1-deficient mice [70]. Thus, even though knowledge of hypothalamic JNK1 is still in its infancy, it is clear that JNK1 acts in the control of the hypothalamic–pituitary–thyroid axis. It appears to have orexigenic functions and may integrate the response to peripheral signals and mediate their systemic effects.

JNK3

JNK3 is selectively expressed in the brain, where its first identified function was the induction of apoptosis in response to neuronal stress [71]. This led to JNK3 being considered as a potential target for treating the neurodegenerative symptoms of Alzheimer's disease [72]. While JNK1 is constitutively activated and localised in axons and dendrites [73, 74] where it regulates axon and dendrite morphology [75], JNK3 has low basal activity and is activated in the nuclei of neurons exposed to stress, being required for stress-induced c-Jun phosphorylation and activator protein 1 (AP-1) activation [71]. These differences in subcellular localisation might imply access to different substrates, and hence distinct functional effects. The implication of brain JNK3 in the regulation of energy balance was recently addressed in a well-designed study using whole-body JNK3-deficient mice or mice with conditional *Jnk3* (also known as *Mapk10*) deletion in POMC or AgRP hypothalamic neurons [58]. The authors found that high-fat feeding induced JNK3 activation in the hypothalamus; however, while JNK3 deficiency in POMC neurons did not affect feeding behaviour, lack of JNK3 in AgRP neurons resulted in HFD-induced hyperphagia [58] (Fig. 2). The authors showed that JNK3 is activated by leptin and regulates excitatory transmission in AgRP neurons [76]. This function of JNK3 might mediate

the actions of leptin in AgRP neurons of mice fed an HFD. JNK1 and JNK3 thus have opposing roles in the CNS: while JNK1 activation in the CNS promotes becoming overweight [57, 61], JNK3 activation protects against obesity [58]. Further research is needed to determine how the action of the three JNK kinases is coordinated in the CNS, including definition of the action of JNK2 and the various JNK splice variants.

Hypothalamic JNKs in non-neuronal cells

Despite studies assessing the role in energy homeostasis of JNK1 and JNK3 expressed in specific hypothalamic neurons, roles for JNKs cannot be excluded in non-neuronal cells given the near ubiquitous expression of at least JNK1. This is an important consideration because cells such as astrocytes, microglia and tanycytes play essential roles in the control of systemic energy metabolism through their capacity to modulate hypothalamic neuronal–glial networks in response to metabolic cues [77].

A possible role of JNK in non-neuronal cells was reported in tanycytes, a specialised glial cell type that controls the secretion of neuropeptides by hypothalamic neurons. Tanycytes regulate blood–brain and blood–cerebrospinal fluid exchanges, thereby playing an active role in the shuttling of circulating metabolic signals to hypothalamic neurons that control food intake [78]. Cultured tanycytes respond to inflammatory stimulation with bacterial lipopolysaccharides by increasing protein levels of phosphorylated JNK1 [79], suggesting that JNK1 may play a role in the cellular stress response in different brain cell types. Moreover, whole-body *Jnk1*-knockout mice are protected against HFD-induced hippocampal cognitive impairment and reduced astrocyte and microglial reactivity [80]. Many other non-metabolic actions have been found for JNK isoforms in the brain, including hippocampal neurogenesis [81], depression and anxiety [82].

Conclusions and future directions

The role of the JNK pathway in the regulation of energy metabolism has received intense attention, and its pivotal role in controlling energy expenditure and food intake in the CNS is now better understood. However, further work is needed to define how this signalling pathway is regulated in neurons and to determine which scaffold proteins participate in its activation. The scaffolding protein JNK-interacting protein (JIP)1 is essential for obesity-induced JNK activation, since ablation of this protein results in protection against obesity, insulin resistance and steatosis [83]. This suggests that peptide inhibitors that block JNK activation by disrupting the binding of JNK to JIPs [84] offer an attractive strategy for the treatment of the metabolic syndrome [83]. These peptides have been developed and tested in clinical trials [85]. While they are so far not specific for individual JNK isoforms, they can be fused to a nuclear export or a nuclear localisation sequence, thus targeting JNK activation blockade to a specific cell compartment. This strategy might be particularly helpful given the different subcellular localisations of JNK3 and JNK1/2. Indeed, this approach has been successful in studies investigating neurodegenerative disorders, where inhibition of nuclear JNK proved to be neuroprotective, whereas inhibition of cytoplasmic JNK was not [86]. These peptides have also targeted to mitochondria, were JNK localises in response to certain types of stress; peptide targeting to mitochondria resulted in less ischaemia-induced damage [87]. Similar strategies might be used to direct these JNK peptide inhibitors to specific brain cell types.

In recent years, major efforts have been directed at developing specific JNK inhibitors for each family member. JNK3 would be the target of choice for treating CNS disorders because this JNK family member is a key player in these diseases. The complexity produced by the existence of three JNK family members is increased further by the generation of ten splice variants that were recently shown to be differentially expressed in distinct cell types and to have unique functions [88]. The relevance of these splice variants to the CNS is totally unknown and needs to be addressed. It is also unclear which upstream signals regulate these splice variants and which scaffold proteins mediate their activation. More studies are, therefore, needed to define the roles and activation stimuli of the different JNK family members and splice isoforms in the hypothalamus.

In conclusion, opposing roles have been identified for JNK isoforms in the hypothalamus, with JNK1/2 triggering obesity via the inhibition of thyroid hormones and promoting food intake, whereas JNK3 in AgRP hypothalamic neurons protects against obesity by inhibiting hyperphagia. These opposing actions of JNK family members show that specific JNK1/2 inhibitors [75, 89] will be required for the treatment of metabolic disorders in order to avoid the anticipated obesogenic effects of JNK3 inhibition. However, the most effective inhibitors to date have been pain inhibitors of all JNK isoforms, which inhibit neuroinflammation and improve neurological function during ischaemic brain injury [90, 91]. Thus, more specific therapeutic JNK1/2-based options are needed to unambiguously address the potential of these inhibitors in the treatment of obesity and related diseases.

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