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# Hypothalamic redox balance and leptin signaling - Emerging role of selenoproteins

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## Abstract

The hypothalamus is the central neural site governing food intake and energy expenditure. During the past 25 years, understanding of the hypothalamic cell types, hormones, and circuitry involved in the regulation of energy metabolism has dramatically increased. It is now well established that the adipocyte-derived hormone, leptin, acts upon two distinct groups of hypothalamic neurons that comprise opposing arms of the central melanocortin system. These two cell populations are anorexigenic neurons expressing proopiomelanocortin (POMC) and orexigenic neurons that express agouti-related peptide (AGRP). Several important studies have demonstrated that reactive oxygen species and endoplasmic reticulum stress significantly impact these hypothalamic neuronal populations that regulate global energy metabolism. Reactive oxygen species and redox homeostasis are influenced by selenoproteins, an essential class of proteins that incorporate selenium co-translationally in the form of the 21$^{st}$ amino acid, selenocysteine. Levels of these proteins are regulated by dietary selenium intake and they are widely expressed in the brain. Of additional relevance, selenium supplementation has been linked to metabolic alterations in both animal and human studies. Recent evidence also indicates that hypothalamic selenoproteins are significant modulators of energy metabolism in both neurons and tanycytes, a population of glial-like cells lining the floor of the 3$^{rd}$ ventricle within the hypothalamus. This review article will summarize current understanding of the regulatory influence of redox status on hypothalamic nutrient sensing and highlight recent work revealing the importance of selenoproteins in the hypothalamus.

## Graphical abstract

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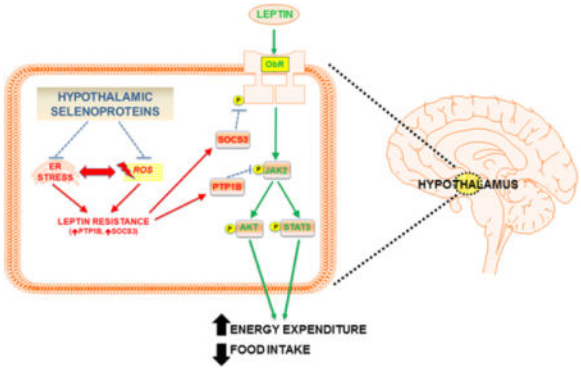


**Keywords**

Selenoprotein; hypothalamus; leptin; energy metabolism; obesity; endoplasmic reticulum stress

## Introduction

Obesity and type 2 diabetes arise from disturbed regulation of energy metabolism and are of rapidly increasing prevalence in developed nations [1]. The central regulator of food intake and energy expenditure is the hypothalamus, a neural structure located on the ventral portion of the brain that is comprised of several distinct nuclei and a vast array of diverse cell types. It is the most important target site for the anorexigenic effects of leptin, as the leptin receptor (ObR) is abundantly expressed. Moreover, recent findings indicate that obesity is associated with hypothalamic damage in both rodents and humans [2]. Additional studies have shown that administration of a high fat diet (HFD) promotes endoplasmic reticulum (ER) stress and inflammation in the hypothalamus, which in turn leads to diminished sensitivity to leptin and insulin [3,4]. Interestingly, in response to a HFD, hypothalamic dysfunction has been reported to precede the development of peripheral symptoms [2]. In sum, a growing body of evidence suggests that hypothalamic impairment may be the root cause of many disturbances related to energy homeostasis.

Over the past decade, it has become increasingly apparent that redox status significantly impacts hypothalamic nutrient sensing. Reactive oxygen species (ROS) are byproducts of oxygen metabolism that include superoxide ion-radical ($O_2^{\bullet -}$), hydrogen peroxide ($H_2O_2$), and hydroxyl radical ($^{\bullet}OH^-$). Within the cell, the primary generator of ROS is the mitochondrial electron transport chain, and other significant producers include NADPH oxidases at the cell membrane, peroxisomes in the cytosol, and protein disulfide isomerases in the ER [5]. Under normal conditions, ROS are important mediators of cell signaling that modify thiol residues in target proteins. However, deleterious effects occur when ROS levels exceed the capacity of endogenous antioxidant defense mechanisms, resulting in oxidative stress. These harmful insults include lipid peroxidation, DNA damage, and protein carbonylation. To curb oxidative stress, cells utilize a variety of enzymatic and non-enzymatic antioxidants. Prominent antioxidant enzymes in brain include the superoxide dismutases, glutathione peroxidases (GPXs), and thioredoxin reductases (TXNRDs).

## Selenium, selenoproteins, and energy metabolism

Both GPXs and TXNRDs fall into the category of selenoproteins, which are characterized by the co-translational incorporation of selenium (Se) as the 21st amino acid, selenocysteine (Sec). The beneficial influence of Se upon antioxidant function is largely mediated by Sec residues present in selenoproteins. Sec is structurally analogous to cysteine (Cys), with the sole difference being that Se is substituted for the sulfur atom normally present in Cys. In comparison to Cys, Sec possesses several noteworthy properties that enhance catalysis of redox reactions, such as greater nucleophilicity and a lower pKa. Interestingly, unlike the other amino acids, the biosynthesis of Sec always occurs on its own selenocysteine-specific tRNA, designated $tRNA^{[Ser]Sec}$ (gene symbol *TRSP*). Sec incorporation during protein synthesis is dependent upon the presence of both a UGA codon in the open reading frame and a selenocysteine insertion sequence in the 3′ untranslated region [6]. Selenoprotein synthesis is required for mammalian life, as demonstrated by the fact that mice with global deficiency for *Trsp* fail to survive early embryogenesis [7]. For a more detailed summary of the mechanisms governing selenoprotein synthesis, we direct our readers to several outstanding reviews on this subject [8 – 10].

Selenoproteins are encoded by 25 distinct human genes; these include the GPXs, TXNRDs, and iodothyronine deiodinases (DIOs) [11]. The GPXs comprise an essential group of enzymes that uses glutathione as a co-factor to catalyze the reduction of hydrogen peroxide and/or phospholipid hydroperoxide. Humans possess eight genes encoding GPX enzymes and five of these are selenoproteins (GPX1-4, GPX6) containing Sec in the active site. The GPXs differ in subcellular localization, tissue-specific expression, and substrate specificity.

The TXNRDs (TXNRD1-3) constitute a fundamental pillar of the thioredoxin (TXN) system, which also requires TXN and NADPH. TXNs are potent oxidoreductases that catalyze disulfide bond formation by means of a dithiol-disulfide exchange mechanism. The two quintessential features of TXNs are: 1) a –CXXC- motif within the active site and 2) a characteristic tertiary structure consisting of four antiparallel beta sheets sandwiched between three alpha helices that is known as a TXN fold. In mammals, there are three isoforms of TXN (TXN1-3) and a host of other proteins that are considered members of the TXN superfamily due to the presence of these characteristic structural features. Some of these are selenoproteins, as will be discussed later. Disulfide bonds in TXNs are reduced by TXNRDs by means of a NADPH-dependent mechanism where electrons are taken from NADPH by TXNRDs and transferred to TXNs.

The DIOs are vital mediators of thyroid metabolism that are encoded by three distinct genes (DIO1-3) in mammals. Thyroid hormone activation is dependent upon conversion of the prohormone thyroxine ($T_4$) to the biologically active form, 3,5,3′-triiodothyronine ($T_3$), which can be catalyzed by either DIO1 or DIO2. In opposition, DIO3 mediates the irreversible inactivation of $T_3$ and $T_4$ to yield the inactive hormones $T_2$ and $rT_3$, respectively.

There is also a contingent of additional selenoproteins lacking clearly established functions that are designated by the root symbol SELENO followed by a letter [12]. Within this group, SELENOP is perhaps the most notable. It is unique in that it possesses multiple Sec residues

and facilitates Se transport between organs. SELENOP-mediated delivery of Se to target tissues occurs upon binding to a lipoprotein receptor-related protein (LRP) and subsequent endocytosis. Both LRP2 (also known as megalin) [13] and LRP8 (also known as ApoER2) [14, 15] have been shown to promote SELENOP uptake into various cell types. Upon endocytosis, the Sec residues present in SELENOP must then be processed in order for the Se to be reutilized for further selenoprotein synthesis. This task is accomplished by the enzyme selenocysteine lyase (SCLY), which decomposes Sec into L-alanine and selenide [16]. The selenide can then be converted to selenophosphate, an essential precursor for Sec biosynthesis. In addition to SELENOP, there is a group of 6 relatively uncharacterized ER-resident selenoproteins with the SELENO root name (SELENOF, SELENOK, SELENOM, SELENON, SELENOS, SELENOT) that have sparked increasing interest in the selenium field. The ER is the primary intracellular reservoir of $Ca^{2+}$ and is also essential for the proper folding and processing of secretory proteins. It has been documented that various ER-resident selenoproteins play significant roles in $Ca^{2+}$ signaling (SELENOK, SELENOM, SELENON, SELENOT), protein folding (SELENOF), and ER-associated degradation (SELENOK, SELENOS) [17]. For example, SELENOK and SELENON regulate $Ca^{2+}$ signaling through interactions with the inositol 1,4,5-triphosphate receptors (IP3Rs) [18] and the SERCA2B pump [19], respectively. It should also be noted that a number of proteins with the SELENO root name have structures containing TXN-folds where Cys residues normally present in the active site motif have been replaced by Sec. These include SELENOF, SELENOH, SELENOM, SELENOO, SELENOP, SELENOT, SELENOV, and SELENOW. It is highly likely that these proteins act in a manner similar to TXNs and therefore contribute to the overall activity of the TXN system.

Against the backdrop of growing rates of obesity and type 2 diabetes, there has been an elevated interest in the metabolic effects of Se supplementation and its potential effects on redox signaling. Documented evidence from *in vitro* [20] and *in vivo* [21] studies conducted in the early 1990s first showed that inorganic Se can act as a potent insulin mimetic. Subsequently, an unanticipated secondary outcome of the Nutritional Prevention of Cancer (NPC) trial was the finding that Se-supplemented patients (200 μg daily as Se-yeast) had an increased likelihood of developing type 2 diabetes in comparison to placebo-assigned controls [22]. Yet, the increased risk of type 2 diabetes was only statistically significant for participants whose baseline plasma Se level was in the top tertile initially. Since publication of these findings, the adverse effect of excess Se supplementation upon energy homeostasis has been corroborated in rodent studies [23, 24]. In line with these results, increased levels of SELENOP and GPX1 have also been linked to metabolic disturbances. Significantly elevated levels of serum SELENOP and hepatic *SELENOP* mRNA were observed in a study of patients with type 2 diabetes [25]. Moreover, the aforementioned report also showed that administration of purified SELENOP disrupted insulin signaling both *in vitro* and *in vivo*. Similarly, overexpression of *Gpx1* in mice promotes the development of insulin resistance and obesity [26]. Finally, whole body knockout of either *Selenop* [25] or *Gpx1* [27] leads to improved glucose tolerance and enhanced insulin sensitivity.

Whereas SELENOP and GPX1 obstruct insulin signaling in the periphery, selenoproteins appear to have a positive influence on metabolic signaling in the brain. The importance of selenoproteins to the nervous system is well established, as mice with neuron-specific

ablation of either *Trsp* or *Gpx4* are unable to survive into adulthood [28]. Selenium transport to the brain occurs primarily through LRP8-mediated uptake of SELENOP [14, 29]. LRP8 is highly expressed at the blood-brain barrier and studies by Burk and colleagues have shown that it binds SELENOP in the choroid plexus [29]. Additionally, constitutive deletion of *Selenop* or *Lrp8* results in similar patterns of diminished Se levels in brain and neurological dysfunction [14, 30]. The neurological deficits can largely be mitigated by Se supplementation, indicating that SELENOP is not the sole supplier of Se to the brain [31, 32]. It has been suggested that a small molecule form of Se, most likely selenosugar, also helps distribute Se to the brain [33]. Furthermore, although LRP8 is the principal mediator of SELENOP uptake into the nervous system, LRP2 has been implicated and is also present at the blood-brain barrier [34]. SELENOP from the periphery binds to LRP2 and/or LRP8 at the blood-brain barrier and is transported into the brain by transcytosis or some other undetermined means (Figure 1). Within the brain, SELENOP is predominantly produced by astrocytes, which have been proposed to provide Se to adjacent neurons by secreting SELENOP [29, 33]. This notion is supported by the fact that the expression pattern of *Selenop* is complementary to that of other selenoproteins, as high levels of *Gpx4, Selenof, Selenok, Selenom*, and *Selenow* were reported in neurons of the mouse brain [35]. Furthermore, many of the aforementioned selenoproteins are highly expressed in the hypothalamus and recent evidence suggests that they significantly contribute to leptin signaling and energy homeostasis. These current findings will be discussed in detail following an overview of the proteins, pathways, and circuits involved in hypothalamic leptin signaling.

## The central melanocortin system

Within the hypothalamus reside several discrete nuclei that orchestrate autonomic, neuroendocrine, homeostatic, and limbic responses necessary for energy homeostasis. High expression of the leptin receptor (ObR) is found in many of these, including the arcuate (ARC), paraventricular (PVN), dorsomedial, lateral, and ventromedial nuclei [36]. With respect to leptin signaling, the ARC is the best understood and most important hypothalamic region [37, 38]. It is situated in an ideal position to monitor circulating levels of hormones and nutrients, as it neighbors the median eminence (ME), an area thought to lack the blood-brain barrier (BBB) [39, 40]. The ME contains a high density of fenestrated capillaries, which allows the passage of peptides from the peripheral blood supply. Entry of leptin into the hypothalamus is regulated by tanycytes, a population of glial-like cells that line the floor of the 3$^{rd}$ ventricle. Both LRP2 and ObR have been implicated in leptin transport across the BBB and recent evidence indicates that they together form a complex that promotes receptor binding and endocytosis [41, 42]. Following transport across the ME, leptin acts upon two main populations of neurons in the ARC, which comprise opposing arms of the central melanocortin system (Figure 2). One group consists of orexigenic neurons that co-express agouti-related peptide (AGRP), neuropeptide Y (NPY) [43], and the inhibitory neurotransmitter gamma aminobutyric acid (GABA) [44]. The other population is composed of anorexigenic neurons that contain proopiomelanocortin (POMC)-derived peptides, such as α-melanocyte stimulating hormone (α-MSH) [45]. The effect of leptin upon POMC neurons is stimulatory, whereas in contrast, leptin inhibits AGRP neurons. It is also worth

noting that glucose is believed to be the primary fuel for POMC neurons, as these cells are excited by increasing glucose levels [46]. In opposition, glucose inhibits AGRP neurons [47, 48] and free fatty acids are speculated to serve as their main energy substrate [49]. Both AGRP and POMC cell populations send dense projections to the PVN, which contains high levels of the melanocortin-4 receptor (MC4R) [50]. Here, α-MSH activates the MC4R, whereas these same receptors are inhibited by AGRP [51]. PVN input from the ARC also regulates the synthesis of corticotropin-releasing hormone (CRH) [37] and thyrotropin-releasing hormone (TRH) [52]. Both CRH and TRH are released into the ME and control the hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-thyroid axis, respectively. The PVN also projects to brain stem regions that control satiety and energy expenditure, including the nucleus of the solitary tract, parabrachial nucleus, and dorsal motor nucleus of the vagus. For a more in depth overview of the brain circuitry engaged by leptin, we direct our readers to several excellent review articles on this subject [53 – 55].

The fundamental importance of AGRP and POMC neuronal populations to energy homeostasis has been illustrated in numerous studies using conditional approaches to specifically target each cell type. ObR deletion in POMC neurons results in obesity and altered expression of hypothalamic neuropeptides [56], although the phenotype is much milder than that of mutant mice lacking functional genes for either leptin (*ob/ob*) or the leptin receptor (*db/db*). Likewise, adult-onset obesity and hyperphagia were observed in a mouse model with progressive neurodegeneration of POMC neurons [57]. In contrast, diptheria toxin-induced ablation of AGRP neurons in adult mice results in severe hypophagia, leading to rapid body weight loss and eventual starvation [58]. Conversely, selective activation of AGRP neurons leads to ravenous feeding behavior [59, 60].

## Leptin signaling

The ObR is a single membrane spanning protein that is structurally related to interleukin 6-type cytokine receptors [61]. Although several splice variants of the ObR exist, the full length variant is the primary conveyor of leptin-mediated cell signaling [62]. Leptin binding stimulates receptor dimerization, resulting in phosphorylation of Janus kinase 2 (JAK2). JAK2 then phosphorylates two key tyrosine residues in the cytoplasmic domain of the ObR, $Tyr^{985}$ and $Tyr^{1138}$, which serve as docking sites for SH2-containing tyrosine-specific protein phosphatase (SHP2) and signal transducer and activator of transcription 3 (STAT3), respectively [63]. SHP2 binding at $Tyr^{985}$ promotes activation of the extracellular signal-regulated kinase (ERK) pathway, while STAT3 is subsequently phosphorylated upon attachment at $Tyr^{1138}$. When phosphorylated, STAT3 dimerizes and translocates to the nucleus, where it promotes transcription of multiple downstream targets, including POMC [64], TRH [65], and suppressor of cytokine signaling 3 (SOCS3) [66]. The ObR also activates a parallel pathway involving JAK2, the insulin receptor substrate (IRS), phosphatidylinositol 3-OH kinase (PI3K), and AKT. In this pathway, the SH2B1 adapter protein recruits IRS proteins to interact with JAK2, allowing JAK2 to phosphorylate IRS target proteins, which in turn leads to downstream activation of PI3K and AKT. The current literature indicates that the anorexigenic effects of leptin in the hypothalamus require activation of both the JAK2-STAT3 [67] and IRS-PI3K pathways [68] (Figure 3).

Whereas leptin activates the JAK2-STAT3 pathway in both AGRP and POMC neurons, it exerts distinct effects on these cell types with respect to signaling, $Ca^{2+}$ mobilization, and neuronal firing. Leptin has an excitatory effect on POMC neurons, as it stimulates $Ca^{2+}$ influx [69] and promotes neuronal firing [68, 70]. In contrast to POMC cells, the effects of leptin on AGRP neurons are inhibitory, resulting in hyperpolarization and diminished release of the orexigenic neuropeptides, AGRP and NPY. Leptin-induced hyperpolarization also leads to disinhibition of POMC neurons, as the tonic inhibition normally exerted by AGRP neurons is removed [45]. There is also evidence suggesting that the coupling of the leptin receptor to the PI3K pathway may differ between AGRP and POMC neurons. One particular study reported that leptin stimulated PI3K signaling in POMC neurons, while on the other hand, robust PI3K activation was observed in response to leptin withdrawal in AGRP counterparts [71]. Finally, it has been demonstrated that leptin treatment decreases cytosolic $Ca^{2+}$ levels in AGRP neurons [69].

## Leptin resistance

One of the hallmarks of obesity is leptin resistance, in which increasing leptin levels fail to reduce feeding behavior and stimulate energy metabolism [72]. Rodent studies involving administration of a HFD indicate that hypothalamic leptin resistance arises from two distinct causes: 1) impaired access of extracellular leptin to hypothalamic receptors and 2) an intracellular deficit in cell signaling. This viewpoint is supported by results showing that when animals are subjected to a HFD, the hypothalamus retains partial ability to respond to leptin when given by the intracerebroventricular route, whereas intraperitoneal administration fails to elicit any response [73, 74]. Moreover, human studies have reported that obese subjects exhibit a decreased ratio of cerebrospinal-fluid (CSF) leptin/serum leptin, implying compromised entry of peripheral leptin to the brain. One noteworthy clinical study reported that serum leptin levels were increased by 318% in obese patients while CSF leptin levels were only 30% higher [75]. As noted earlier, a major point of exchange between the peripheral blood supply and CSF is the ME, which lies at the base of the 3$^{rd}$ ventricle. Entry to the 3$^{rd}$ ventricle is protected by a tanycytic barrier that regulates access of proteins and hormones from the fenestrated capillaries of the ME [76]. Recent findings in mice indicate that these tanycytes mediate leptin transport from the blood to the brain and that this transport is impaired by a HFD [77]. The aforementioned study also showed that leptin transport by tanycytes was dependent upon ObR binding and ERK activation, but was not affected by inhibitors of AKT and STAT3 signaling. Of potential relevance, LRP2 has also been shown to promote both leptin transport across the blood-CSF barrier [78] and hypothalamic leptin signaling [41]. Furthermore, it was recently reported that mice with conditional deletion of LRP2 in endothelial cells at the blood-brain barrier exhibit obesity, neuroinflammation, and deficient hypothalamic leptin signaling relative to controls [79]. These findings are particularly interesting from the standpoint of Se metabolism, as LRP2 also mediates SELENOP uptake [13, 34].

With respect to intracellular signaling, both suppressor of cytokine signaling 3 (SOCS3) [80] and protein tyrosine phosphatase 1B (PTP1B) [81] have been demonstrated to counter the actions of leptin. SOCS3 mediates feedback inhibition of leptin signaling by binding to $Tyr^{985}$ of the leptin receptor, which prevents the association of necessary signaling proteins

at this site [82]. On the other hand, PTP1B dephosphorylates JAK2 and thereby attenuates downstream activation of the leptin signaling pathway [83]. Correspondingly, hypothalamic levels of PTP1B and SOCS3 have been documented to increase in response to both DIO [84, 85] and aging [86, 87]. Further support for the negative influence of these two proteins upon leptin signaling comes from findings that neuron-specific SOCS3 deletion [88] and constitutive knockout of PTP1B [89] attenuate the effects of a HFD in mice.

Recent studies also indicate that development of hypothalamic leptin resistance initially occurs in a population of AGRP neurons residing outside the BBB that directly sense blood-borne metabolic signals. Work conducted by the laboratory of Allison Xu and colleagues demonstrated that the majority (~70%) of AGRP neurons are situated outside the BBB, whereas most (~90%) neighboring POMC neurons are located inside the BBB [90]. Moreover, in response to a HFD, they found that while leptin resistance and SOCS3 upregulation in AGRP neurons occurred within days, it took several weeks for similar alterations to transpire in POMC counterparts. Subsequent studies by this group has shown that AGRP neurons are especially vulnerable to circulating toxins and that damaged AGRP neurons are rapidly replaced by cells derived from post-mitotic cells [91].

## ER stress as a causative factor in leptin resistance

One well established cause of leptin resistance is ER stress. This phenomenon results from the accumulation of misfolded proteins and/or ER $Ca^{2+}$ depletion, which in turn, leads to activation of the unfolded protein response (UPR) in order to restore cellular homeostasis. Moreover, although ROS and ER stress are interrelated, the relationship is complex and varies depending on the context. For example, there is evidence in the literature that ROS promotes ER stress [92, 93] and that the UPR itself can stimulate ROS production [5]. Activation of the UPR is mediated by three parallel signaling pathways that are each initiated by an ER-resident transmembrane sensor [94]. These three sensor proteins are as follows: IRE1 (inositol requiring enzyme 1), PERK (protein kinase PKR-like ER kinase), and ATF6 (Activating transcription factor 6). Phosphorylation of IRE1 unmasks its endonuclease activity and triggers cytosolic splicing of X-box binding protein 1 (XBP1s) mRNA, which then translocates to the nucleus and upregulates UPR target genes [95]. Moreover, activated IRE1 can also stimulate a downstream pathway involving apoptosis signal-regulating kinase (ASK1, also known as MAP3K5) and Jun N-terminal kinase (JNK) [96]. Similar to IRE1, PERK is phosphorylated in response to ER stress. PERK then phosphorylates the α-subunit of the eukaryotic translation initiation factor 2α (eIF2α), thereby inactivating it. This leads to an attenuation of general protein synthesis and diminishes the load of newly synthesized proteins entering the ER. However, this also results in preferential translation of select genes containing internal ribosome entry sites. Paramount among these is activating transcription factor 4 (ATF4), which increases expression of downstream targets containing a C/EBP-ATF response element, such as CHOP [97]. Whereas both IRE1 and PERK are type I transmembrane proteins that oligomerize and autophosphorylate in response to ER stress, ATF6 migrates from the ER to the Golgi and is subsequently proteolyzed. Cleavage of ATF6 allows its N-terminal fragment to enter the nucleus and act as a transcription factor to increase expression of various downstream target genes. The net response to UPR activation is a transient reduction in general translation

coupled with up-regulation of select genes that mediate ER protein folding, lipid biosynthesis, and ER-associated degradation.

ER stress occurs in response to a variety of insults and influences downstream pathways involved in both antioxidant defense and apoptosis. Documented physiological sources of ER stress include lipotoxicity [98, 99], ROS [92], and hypoxia [100]. ER stress can also be induced by a number of chemical agents, which act by depleting ER $Ca^{2+}$ levels (thapsigargin), disrupting N-linked glycosylation (tunicamycin), inhibiting protein transport from the ER to the Golgi apparatus (Brefeldin A), or reducing disulfide bond formation (dithiothreitol) [101 – 104]. The causative role of hypothalamic ER stress upon leptin resistance was demonstrated in a landmark report from the laboratory of Dongsheng Cai and colleagues in 2008 [3]. Here it was shown that a HFD promotes hypothalamic ER stress and inflammation by activating the IKKβ/NF-κB pathway. The hypothalamic inflammation was at least partially due to ER stress, as activation of NF-κB could be suppressed by 3$^{rd}$ ventricle infusion of the ER stress inhibitor, TUDCA. Additional experiments revealed that conditional ablation of IKKβ in AGRP neurons protected against metabolic impairments resulting from a HFD. Finally, this study showed that forced activation of the NF-κB pathway upregulated SOCS3, a negative regulator of leptin signaling [3]. A subsequent paper by Thaler et al. built upon these findings and demonstrated that hypothalamic inflammation precedes changes in body composition and the development of inflammation in peripheral tissues [2]. This report showed that increased hypothalamic inflammatory signaling in rodents was apparent within 3 days of a HFD, prior to any significant change in body weight. Moreover, parallel MRI studies in humans revealed increased gliosis in the hypothalamus of obese humans [2]. Another apparent downstream effect of ER stress is impaired post-translational processing of POMC, which thereby reduces the amount of α-MSH peptide available for activation of downstream anorexigenic pathways [105]. Somewhat paradoxically, evidence also indicates that upregulation of some UPR target genes promotes leptin signaling. Studies conducted by Ozcan et al. demonstrated that leptin signaling could be enhanced *in vitro* by exogenous expression of either spliced XBP1 (XBP1s) or the ATF6 N-terminal region that promotes transcription of UPR target genes [4]. Conversely, this same research group also showed that neuronal-specific ablation of XBP1 increases susceptibility to DIO. Subsequent work has reported that constitutive expression of spliced XBP1 in POMC neurons increases energy expenditure and protects against a HFD in mice [106]. Moreover, in response to ER stress, the aforementioned mice displayed enhanced leptin signaling in conjunction with diminished levels of PTP1B and SOCS3 in POMC neurons relative to controls. Of additional relevance, an earlier study performed microarray analysis on NIH-3T3 fibroblasts with enforced expression of spliced XBP1 to identify genes targeted by XBP1. Among the most upregulated transcripts were SELENOM, LRP8, and several members of the TXN superfamily [107].

With further regard to the TXN system, several recent studies have shown that the thioredoxin interacting protein (TXNIP) is an important player at the crossroads of ER stress, cell survival, and energy metabolism (Figure 4). TXNIP promotes activation of the NLRP3 inflammasome [108] and acts as a negative regulator of TXN [109] and mTOR-dependent pathways [110]. Moreover, in response to severe ER stress, TXNIP is rapidly upregulated through the IRE1 and PERK pathways [111, 112]. Elevated TXNIP levels leads

to activation of the NLRP3 inflammasome, cleavage of procaspase-1, and interleukin 1β secretion [108, 111]. TXNIP expression is also induced by glucotoxicity and this promotes apoptosis of pancreatic β cells [113]. Hypothalamic TXNIP has been implicated in energy metabolism, as levels are increased in mouse models of obesity [114]. In addition, lentiviral-mediated knockdown of hypothalamic TXNIP was shown to protect against metabolic impairments arising from a HFD [114]. Further studies showed that overexpression of TXNIP in AGRP neurons reduces energy expenditure, impairs leptin sensitivity, and promotes diet-induced obesity [115]. In line with these findings, it was recently reported that hypothalamic overexpression of TXN1 is protective in a rodent model of type 1 diabetes [116].

## ROS and hypothalamic nutrient sensing

Within the hypothalamus, a key influence upon ROS production is circulating nutrient levels. Studies in rats demonstrated that intra-carotid glucose administration stimulates ARC neuronal activity and that this increase in activity can be blocked by co-treatment with the $H_2O_2$-degrading enzyme, catalase [117]. Further experiments using *ex vivo* hypothalamic slices showed that a transient increase in glucose concentration triggered a subsequent rise in ROS generation. These results suggest that increasing glucose concentrations stimulate ROS production, and that in turn, the elevation in ROS promotes neuronal activity in the ARC. Similarly, treatment with lipids and/or leptin can augment hypothalamic ROS generation. For example, induction of acute hypertriglyceridemia was shown to elevate ROS production in the ventral hypothalamus [118]. Likewise, leptin treatment was reported to augment ROS levels in both immortalized hypothalamic neurons and ARC-derived primary cultures [119]. Research conducted by the laboratory of Horvath and colleagues has also revealed that ROS generation and responsivity differs between AGRP and POMC cell types in the hypothalamus. In mice fed a standard lab chow diet, significantly higher baseline ROS levels were observed in POMC neurons in comparison to AGRP counterparts [49]. Moreover, ROS has a stimulatory effect on POMC neurons, as indicated by patch–clamp electrophysiological recordings showing that $H_2O_2$ treatment increases the firing rate of POMC neurons [120]. Additional studies on mice fed a HFD showed that central infusion of $H_2O_2$ increased c-fos expression in POMC neurons, diminished feeding behavior, and augmented STAT3 phosphorylation in response to peripheral leptin treatment. Conversely, intracerebroventricular administration of an ROS scavenger greatly attenuated c-fos expression in POMC neurons, while food intake and c-fos levels in AGRP counterparts were significantly elevated. In summary, these findings indicate that ROS significantly regulates the activity of both AGRP and POMC neurons in reciprocal manners (Table 1).

Another important factor modulating mitochondrial ROS generation is the uncoupling proteins (UCP1-5) that reside in the inner mitochondrial membrane and act by uncoupling oxidative phosphorylation from ATP production. Among this protein family, UCP2 exhibits the highest expression in the hypothalamus [121] and has been implicated in neuroprotection, energy metabolism, and synaptic plasticity [122]. UCP2 negatively regulates mitochondrial $H_2O_2$ production [123] and its activity increases in response to superoxide [124] and lipid peroxidation [125]. Although the precise mechanism by which UCP2 influences ROS generation is not entirely clear, it has been found conjugated with

glutathione under resting conditions. As ROS levels increase, UCP2 is deglutathionylated and increased proton leakage across the inner mitochondrial membrane ensues [126]. UCP2 has also been proposed to act as a metabolic switch that promotes oxidation of fatty acid substrates in preference to glucose [49]. Moreover, it is hypothesized that fasting-induced UCP2 activation is triggered by increased ROS generation derived from fatty acid oxidation. Indeed, in AGRP neurons, UCP2 suppresses ROS production in response to treatment with the orexigenic peptide, ghrelin [49]. On the other hand, evidence suggests that UCP2 attenuates glucose sensing in POMC neurons [127].

Mitochondria are dynamically regulated by changing environmental conditions and are intrinsically tied to the rate of energy production and ROS generation. One key modulator of mitochondrial dynamics is the mitochondrial-associated membrane (MAM), which is the interface between the mitochondria and endoplasmic reticulum (ER). This site is involved in a number of important cellular processes, including $Ca^{2+}$ signaling [128], lipid biosynthesis [129], and mitochondrial division [130]. Moreover, of particular importance to obesity, it has been shown that administration of a HFD selectively reduces ER-mitochondria contact sites in POMC neurons [131]. ER-mitochondrial interactions are regulated by the mitofusins, a class of mitochondrial dynamin-like GTPase proteins that play a central role in mitochondrial fusion [132]. Reduced expression of mitofusin 2 (MFN2) has been linked to obesity in both humans and rodents [133]. Furthermore, conditional deletion of MFN2 in POMC neurons results in diminished ER-mitochondria contacts, increased ER stress, leptin resistance, reduced energy expenditure, and obesity [131]. In contrast, ablation of either MFN1 or MFN2 in AGRP neurons inhibits mitochondrial fusion in these cells and protects against diet-induced obesity [134].

## Hypothalamic selenoproteins and energy metabolism

Emerging evidence indicates that multiple selenoproteins are abundantly expressed in the hypothalamus and that their expression levels are regulated by nutrient availability [35, 135]. For example, a recent analysis of the transcriptome of AGRP and POMC neurons derived from young adult mice revealed that multiple selenoproteins are abundantly expressed in these two important cell types. In this specific study, relatively high transcript levels (>100 transcripts per million) were reported for *Gpx1, Gpx3, Selenof, Selenok, Selenom, Selenot*, and *Selenow* in both AGRP and POMC neurons [135]. Additionally, data from an earlier study reported that the normal physiological response to leptin within the hypothalamus involves the upregulation of multiple selenoprotein genes. Indeed, microarray analysis of laser-captured PVN tissue determined that four selenoprotein transcripts (*Gpx3, Gpx4, Selenok, Selenom*) were among the top one hundred genes positively regulated by leptin [136]. Conversely, hypothalamic levels of GPX4 have been found to decrease upon administration of a high-fat, high-sucrose diet (HFHS) [137]. Another study reported that $Gpx4^{+/-}$ mice display increased susceptibility to metabolic disturbances when challenged with a HFHS diet [138]. However, whether these alterations were associated with the hypothalamus is unclear, as the brain was not examined in this study of GPX4 haploinsufficiency. With respect to SELENOM, we have observed enriched expression in the ARC and PVN by means of immunohistochemistry [139]. Furthermore, $Selenom^{-/-}$ mice develop obesity in adulthood, which coincides with hypothalamic leptin resistance and

altered regulation of the hypothalamic-pituitary-adrenal axis. Yet, no disturbances in hepatic insulin signaling or glucose tolerance were observed in *Selenom*$^{-/-}$ mice. We have also found that protein levels of several selenoproteins (SELENOM, GPX1, SELENOS) are significantly reduced in hypothalamic samples from mice constitutively lacking *Scly* [140]. It should also be noted that the mice in the aforementioned study were fed Se-adequate lab chow and that hypothalamic levels of the essential selenoproteins, selenophosphate synthetase 2 (SEPHS2) and TXNRD1, were indistinguishable from controls. Metabolic disturbances have been previously documented in *Scly*$^{-/-}$ mice, as these animals develop metabolic syndrome when challenged with a Se-deficient diet [141]. Thus, one of the contributing factors to the metabolic dysfunction apparent in *Scly*$^{-/-}$ mice may be altered hypothalamic redox tone resulting from diminished synthesis of select selenoproteins.

Results stemming from multiple studies also indicate that hypothalamic DIO2 plays an integral role regulating the activity of AGRP neurons. Global deletion of DIO2 leads to significant alterations in energy metabolism, including impaired brown adipose thermogenesis [142] and increased susceptibility to diet-induced obesity [143]. Whereas DIO2 expression is minimal in AGRP and POMC neurons, it is highly expressed in tanycytes of the ARC [144, 145]. Moreover, hypothalamic DIO2 expression is strongly induced by inflammatory stimuli that activate the NF-κB pathway [146]. Furthermore, it has been proposed that DIO2-expressing tanycytes act as ‘gatekeepers’ for the activation of hypothalamic thyroid hormone, as these cells are in direct contact with AGRP neurons [147]. For example, studies conducted by Coppola et al. showed that fasting led to increased levels of DIO2 expression and active T3 in the ARC [148]. These changes promoted downstream elevations in UCP2-dependent mitochondrial uncoupling, mitochondrial proliferation, and neuronal activity within AGRP neurons. It was also shown that feeding behavior following fasting was significantly diminished in both UCP2 and DIO2 knockout mice relative to wild-type controls, providing support for the concept that T3-mediated UCP2 promotes activation of orexigenic AGRP neurons.

The notion that hypothalamic selenoproteins are significant regulators of energy metabolism has been directly assessed in two recently published studies using the Cre/Lox system to conditionally target the hypothalamus. The first study involved conditional deletion of the selenocysteine-specific tRNA (*Trsp*) in cells expressing Cre-recombinase under the control of the rat insulin promoter (*RIP-Cre*) [149]. As RIP is normally expressed in pancreatic β-cells and within cells of the hypothalamus, the resulting mouse model (*Trsp*$^{RIP\text{-}Cre}$) had disrupted selenoprotein synthesis in both the pancreas and hypothalamus. It is also worth noting that the hypothalamic cell types targeted in the *Trsp*$^{RIP\text{-}Cre}$ mouse included mostly neurons, as well as some scattered astrocytes. Moreover, Cre recombinase expression was observed in POMC, but not AGRP neurons. When challenged with a HFD, these mice displayed increased oxidative stress and decreased numbers of POMC neurons within the hypothalamus, along with diminished responsiveness to leptin and insulin relative to controls. Similar deficits were not observed in another mouse model (*Trsp*$^{Ins1\text{-}Cre}$) where ablation of selenoprotein synthesis was restricted to pancreatic β-cells by means of a Cre-recombinase controlled by the insulin 1 promoter (*Ins1-Cre*). From these results, the authors concluded that selenoprotein synthesis within the hypothalamus, but not the pancreas, is necessary for normal sensitivity to leptin and insulin. In a subsequent report, another

research group generated mice where *Gpx4* was conditionally deleted in either AGRP (*Gpx4*$^{Agrp\text{-}Cre}$) or POMC (*Gpx4*$^{POMC\text{-}Cre}$) neurons in order to investigate the contribution of hypothalamic GPX4 to energy homeostasis [137]. Given that GPX4 is an essential enzyme protecting against lipid peroxidation and ferroptosis [150], it was anticipated that hypothalamic-specific deletion would severely impact energy homeostasis. Yet, when challenged with a HFHS diet, *Gpx4*$^{POMC\text{-}Cre}$ mice exhibited no significant changes for any of the metabolic parameters measured in this study. In contrast, male *Gpx4*$^{Agrp\text{-}Cre}$ exhibited increased weight gain, reduced locomotion, and a decreased respiratory quotient. Surprisingly, these parameters were not significantly affected in female *Gpx4*$^{Agrp\text{-}Cre}$ mice. Moreover, glucose tolerance and hypothalamic density of POMC and AGRP neurons were unaffected in both *Gpx4*$^{POMC\text{-}Cre}$ and *Gpx4*$^{Agrp\text{-}Cre}$ mice relative to their respective controls. These results indicate that the influence of GPX4 upon POMC neurons is dispensable, whereas in AGRP neurons, GPX4 exerts a marginal contribution to energy homeostasis. This suggests that GPX4-independent mechanisms of antioxidant defense may be of greater importance to these hypothalamic neuronal populations.

## Concluding remarks

The recent demonstration that conditional ablation of selenoprotein synthesis in RIP-Cre expressing cells leads to an array of metabolic abnormalities alludes to the importance of hypothalamic selenoproteins in energy homeostasis. However, with the exception of the well characterized role of DIO2 in tanycytes, the functional contribution of individual selenoproteins and the specific hypothalamic cell types where they are most essential remains largely unresolved. It is probable that some ER-resident selenoproteins play key roles, given their relative abundance in hypothalamic neurons and the established fact that ER stress impedes leptin signaling. Among this group, present evidence is most suggestive for SELENOM, as *Selenom*$^{-/-}$ mice were previously found to develop obesity and hypothalamic leptin resistance. Yet, both the mechanistic function and the hypothalamic cell type where SELENOM is most influential are currently uncertain.

Another largely unexplored frontier of principal relevance to energy metabolism pertains to the potential influence of selenoproteins at the MAM. These contact sites are of important clinical significance, as MAM abnormalities have been linked to both neurodegenerative and metabolic disorders [151]. The MAM is essential for a variety of cellular processes, including $Ca^{2+}$ homeostasis, energy metabolism, lipid synthesis, and apoptosis. In addition, these ER-mitochondria interactions are dynamically regulated by multiple factors, including $Ca^{2+}$ levels and the cellular redox state [152]. As selenoproteins are implicated in both redox balance and $Ca^{2+}$ signaling, it is plausible that they are significant players at the MAM. Moreover, recent proteomic analyses of MAM samples derived from mouse brain revealed the presence of SELENOF and TXNRD1 in this particular locale [153]. Whether these and/or additional selenoproteins substantially impact mitochondrial function at the MAM merits further investigation.

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## Abbreviations

| | |
|---|---|
| **α-MSH** | α-melanocyte stimulating hormone |
| **AGRP** | agouti related protein |
| **ARC** | arcuate nucleus of hypothalamus |
| **ATF** | activating transcription factor |
| **BBB** | blood-brain barrier |
| **CRH** | corticotropin-releasing hormone |
| **CSF** | cerebrospinal fluid |
| **Cys** | cysteine |
| **DIO** | iodothyronine deiodinase |
| **ER** | endoplasmic reticulum |
| **ERK** | extracellular signal-regulated kinase |
| **GABA** | gamma aminobutyric acid |
| **GPX** | glutathione peroxidase |
| **HFD** | high fat diet |
| **HFHS** | high-fat, high-sucrose diet |
| **IRE1** | inositol requiring enzyme 1 |
| **IRS** | insulin receptor substrate |
| **JAK2** | janus kinase 2 |
| **LRP** | lipoprotein receptor-related protein |
| **MAM** | mitochondria-associated membrane |
| **MC4R** | melanocortin-4 receptor |
| **ME** | median eminence |
| **MFN** | mitofusin |
| **NPY** | neuropeptide Y |
| **ObR** | leptin receptor |
| **PERK** | protein kinase PKR-like ER kinase |
| **PI3K** | phosphatidylinositol 3-OH kinase |
| **POMC** | proopiomelanocortin |

| | |
|---|---|
| **PTP1B** | protein tyrosine phosphate 1B |
| **PVN** | paraventricular nucleus of hypothalamus |
| **ROS** | reactive oxygen species |
| **SCLY** | selenocysteine lyase |
| **Se** | selenium |
| **Sec** | selenocysteine |
| **SOCS3** | suppressor of cytokine signaling 3 |
| **STAT3** | signal transducer and activator of transcription 3 |
| **TRH** | thyrotropin-releasing hormone |
| **$tRNA^{[Ser]Sec}$** | selenocysteine-specific tRNA |
| **TXN** | thioredoxin |
| **TXNIP** | thioredoxin-interacting protein |
| **TXNRD** | thioredoxin reductase |
| **UCP** | uncoupling protein |
| **UPR** | unfolded protein response |
| **XBP1** | X-box binding protein 1 |

## References


1. Mokdad AH, et al. The spread of the obesity epidemic in the United States, 1991-1998. JAMA. 1999; 282:1519–22. [PubMed: 10546690]
2. Thaler JP, et al. Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest. 2012; 122:153–62. [PubMed: 22201683]
3. Zhang X, et al. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell. 2008; 135:61–73. [PubMed: 18854155]
4. Ozcan L, et al. Endoplasmic reticulum stress plays a central role in development of leptin resistance. Cell Metab. 2009; 9:35–51. [PubMed: 19117545]
5. Eletto D, Chevet E, Argon Y, Appenzeller-Herzog C. Redox controls UPR to control redox. J Cell Sci. 2014; 127:3649–58. [PubMed: 25107370]
6. Berry MJ, et al. Recognition of UGA as a selenocysteine codon in type I deiodinase requires sequences in the 3′ untranslated region. Nature. 1991; 353:273–6. [PubMed: 1832744]
7. Bosl MR, Takaku K, Oshima M, Nishimura S, Taketo MM. Early embryonic lethality caused by targeted disruption of the mouse selenocysteine tRNA gene (Trsp). Proc Natl Acad Sci U S A. 1997; 94:5531–4. [PubMed: 9159106]
8. Hatfield DL, Gladyshev VN. How selenium has altered our understanding of the genetic code. Mol Cell Biol. 2002; 22:3565–76. [PubMed: 11997494]
9. Driscoll DM, Copeland PR. Mechanism and regulation of selenoprotein synthesis. Annu Rev Nutr. 2003; 23:17–40. [PubMed: 12524431]
10. Papp LV, Lu J, Holmgren A, Khanna KK. From selenium to selenoproteins: synthesis, identity, and their role in human health. Antioxid Redox Signal. 2007; 9:775–806. [PubMed: 17508906]

11. Labunskyy VM, Hatfield DL, Gladyshev VN. Selenoproteins: molecular pathways and physiological roles. Physiol Rev. 2014; 94:739–77. [PubMed: 24987004]
12. Gladyshev VN, et al. Selenoprotein Gene Nomenclature. J Biol Chem. 2016; 291:24036–24040. [PubMed: 27645994]
13. Olson GE, Winfrey VP, Hill KE, Burk RF. Megalin mediates selenoprotein P uptake by kidney proximal tubule epithelial cells. J Biol Chem. 2008; 283:6854–60. [PubMed: 18174160]
14. Burk RF, et al. Deletion of apolipoprotein E receptor-2 in mice lowers brain selenium and causes severe neurological dysfunction and death when a low-selenium diet is fed. J Neurosci. 2007; 27:6207–11. [PubMed: 17553992]
15. Olson GE, Winfrey VP, Nagdas SK, Hill KE, Burk RF. Apolipoprotein E receptor-2 (ApoER2) mediates selenium uptake from selenoprotein P by the mouse testis. J Biol Chem. 2007; 282:12290–7. [PubMed: 17314095]
16. Esaki N, et al. Enzymatic synthesis of selenocysteine in rat liver. Biochemistry. 1981; 20:4492–6. [PubMed: 6456763]
17. Pitts MW, Hoffmann PR. Endoplasmic reticulum-resident selenoproteins as regulators of calcium signaling and homeostasis. Cell Calcium. 2017
18. Fredericks GJ, et al. Stable expression and function of the inositol 1,4,5-triphosphate receptor requires palmitoylation by a DHHC6/selenoprotein K complex. Proc Natl Acad Sci U S A. 2014; 111:16478–83. [PubMed: 25368151]
19. Marino M, et al. SEPN1, an endoplasmic reticulum-localized selenoprotein linked to skeletal muscle pathology, counteracts hyperoxidation by means of redox-regulating SERCA2 pump activity. Hum Mol Genet. 2015; 24:1843–55. [PubMed: 25452428]
20. Ezaki O. The insulin-like effects of selenate in rat adipocytes. J Biol Chem. 1990; 265:1124–8. [PubMed: 2153102]
21. McNeill JH, Delgatty HL, Battell ML. Insulinlike effects of sodium selenate in streptozocin-induced diabetic rats. Diabetes. 1991; 40:1675–8. [PubMed: 1756907]
22. Stranges S, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. Ann Intern Med. 2007; 147:217–23. [PubMed: 17620655]
23. Labunskyy VM, et al. Both maximal expression of selenoproteins and selenoprotein deficiency can promote development of type 2 diabetes-like phenotype in mice. Antioxid Redox Signal. 2011; 14:2327–36. [PubMed: 21194350]
24. Zeng MS, et al. A high-selenium diet induces insulin resistance in gestating rats and their offspring. Free Radic Biol Med. 2012; 52:1335–42. [PubMed: 22342560]
25. Misu H, et al. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. Cell Metab. 2010; 12:483–95. [PubMed: 21035759]
26. McClung JP, et al. Development of insulin resistance and obesity in mice overexpressing cellular glutathione peroxidase. Proc Natl Acad Sci U S A. 2004; 101:8852–7. [PubMed: 15184668]
27. Loh K, et al. Reactive oxygen species enhance insulin sensitivity. Cell Metab. 2009; 10:260–72. [PubMed: 19808019]
28. Wirth EK, et al. Neuronal selenoprotein expression is required for interneuron development and prevents seizures and neurodegeneration. FASEB J. 2010; 24:844–52. [PubMed: 19890015]
29. Burk RF, et al. Selenoprotein P and apolipoprotein E receptor-2 interact at the blood-brain barrier and also within the brain to maintain an essential selenium pool that protects against neurodegeneration. FASEB J. 2014; 28:3579–88. [PubMed: 24760755]
30. Hill KE, et al. Deletion of selenoprotein P alters distribution of selenium in the mouse. J Biol Chem. 2003; 278:13640–6. [PubMed: 12574155]
31. Hill KE, Zhou J, McMahan WJ, Motley AK, Burk RF. Neurological dysfunction occurs in mice with targeted deletion of the selenoprotein P gene. J Nutr. 2004; 134:157–61. [PubMed: 14704310]
32. Peters MM, Hill KE, Burk RF, Weeber EJ. Altered hippocampus synaptic function in selenoprotein P deficient mice. Mol Neurodegener. 2006; 1:12. [PubMed: 16984644]
33. Burk RF, Hill KE. Regulation of Selenium Metabolism and Transport. Annu Rev Nutr. 2015; 35:109–34. [PubMed: 25974694]

34. Chiu-Ugalde J, et al. Mutation of megalin leads to urinary loss of selenoprotein P and selenium deficiency in serum, liver, kidneys and brain. Biochem J. 2010; 431:103–11. [PubMed: 20653565]
35. Zhang Y, et al. Comparative analysis of selenocysteine machinery and selenoproteome gene expression in mouse brain identifies neurons as key functional sites of selenium in mammals. J Biol Chem. 2008; 283:2427–38. [PubMed: 18032379]
36. Scott MM, et al. Leptin targets in the mouse brain. J Comp Neurol. 2009; 514:518–32. [PubMed: 19350671]
37. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest. 1996; 98:1101–6. [PubMed: 8787671]
38. Satoh N, et al. The arcuate nucleus as a primary site of satiety effect of leptin in rats. Neurosci Lett. 1997; 224:149–52. [PubMed: 9131658]
39. Broadwell RD, Brightman MW. Entry of peroxidase into neurons of the central and peripheral nervous systems from extracerebral and cerebral blood. J Comp Neurol. 1976; 166:257–83. [PubMed: 57126]
40. Merchenthaler I. Neurons with access to the general circulation in the central nervous system of the rat: a retrograde tracing study with fluoro-gold. Neuroscience. 1991; 44:655–62. [PubMed: 1721686]
41. Gil SY, et al. Clusterin and LRP2 are critical components of the hypothalamic feeding regulatory pathway. Nat Commun. 2013; 4:1862. [PubMed: 23673647]
42. Byun K, et al. Clusterin/ApoJ enhances central leptin signaling through Lrp2-mediated endocytosis. EMBO Rep. 2014; 15:801–8. [PubMed: 24825475]
43. Hahn TM, Breininger JF, Baskin DG, Schwartz MW. Coexpression of Agrp and NPY in fasting-activated hypothalamic neurons. Nat Neurosci. 1998; 1:271–2. [PubMed: 10195157]
44. Horvath TL, Bechmann I, Naftolin F, Kalra SP, Leranth C. Heterogeneity in the neuropeptide Y-containing neurons of the rat arcuate nucleus: GABAergic and non-GABAergic subpopulations. Brain Res. 1997; 756:283–6. [PubMed: 9187344]
45. Cowley MA, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature. 2001; 411:480–4. [PubMed: 11373681]
46. Ibrahim N, et al. Hypothalamic proopiomelanocortin neurons are glucose responsive and express K(ATP) channels. Endocrinology. 2003; 144:1331–40. [PubMed: 12639916]
47. Mountjoy PD, Bailey SJ, Rutter GA. Inhibition by glucose or leptin of hypothalamic neurons expressing neuropeptide Y requires changes in AMP-activated protein kinase activity. Diabetologia. 2007; 50:168–77. [PubMed: 17093945]
48. Chalmers JA, Jang JJ, Belsham DD. Glucose sensing mechanisms in hypothalamic cell models: glucose inhibition of AgRP synthesis and secretion. Mol Cell Endocrinol. 2014; 382:262–70. [PubMed: 24145125]
49. Andrews ZB, et al. UCP2 mediates ghrelin's action on NPY/AgRP neurons by lowering free radicals. Nature. 2008; 454:846–51. [PubMed: 18668043]
50. Mountjoy KG, Mortrud MT, Low MJ, Simerly RB, Cone RD. Localization of the melanocortin-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain. Mol Endocrinol. 1994; 8:1298–308. [PubMed: 7854347]
51. Ollmann MM, et al. Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. Science. 1997; 278:135–8. [PubMed: 9311920]
52. Diano S, Naftolin F, Goglia F, Csernus V, Horvath TL. Monosynaptic pathway between the arcuate nucleus expressing glial type II iodothyronine 5′-deiodinase mRNA and the median eminence-projective TRH cells of the rat paraventricular nucleus. J Neuroendocrinol. 1998; 10:731–42. [PubMed: 9792325]
53. Dietrich MO, Horvath TL. Feeding signals and brain circuitry. Eur J Neurosci. 2009; 30:1688–96. [PubMed: 19878280]
54. Flak JN, Myers MG Jr. Minireview: CNS Mechanisms of Leptin Action. Mol Endocrinol. 2016; 30:3–12. [PubMed: 26484582]
55. Sutton AK, Myers MG Jr, Olson DP. The Role of PVH Circuits in Leptin Action and Energy Balance. Annu Rev Physiol. 2016; 78:207–21. [PubMed: 26863324]

56. Balthasar N, et al. Leptin receptor signaling in POMC neurons is required for normal body weight homeostasis. Neuron. 2004; 42:983–91. [PubMed: 15207242]
57. Xu AW, et al. Effects of hypothalamic neurodegeneration on energy balance. PLoS Biol. 2005; 3:e415. [PubMed: 16296893]
58. Luquet S, Perez FA, Hnasko TS, Palmiter RD. NPY/AgRP neurons are essential for feeding in adult mice but can be ablated in neonates. Science. 2005; 310:683–5. [PubMed: 16254186]
59. Aponte Y, Atasoy D, Sternson SM. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. Nat Neurosci. 2011; 14:351–5. [PubMed: 21209617]
60. Krashes MJ, et al. Rapid, reversible activation of AgRP neurons drives feeding behavior in mice. J Clin Invest. 2011; 121:1424–8. [PubMed: 21364278]
61. Baumann H, et al. The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors. Proc Natl Acad Sci U S A. 1996; 93:8374–8. [PubMed: 8710878]
62. Bjorbaek C, Uotani S, da Silva B, Flier JS. Divergent signaling capacities of the long and short isoforms of the leptin receptor. J Biol Chem. 1997; 272:32686–95. [PubMed: 9405487]
63. Morris DL, Rui L. Recent advances in understanding leptin signaling and leptin resistance. Am J Physiol Endocrinol Metab. 2009; 297:E1247–59. [PubMed: 19724019]
64. Munzberg H, Huo L, Nillni EA, Hollenberg AN, Bjorbaek C. Role of signal transducer and activator of transcription 3 in regulation of hypothalamic proopiomelanocortin gene expression by leptin. Endocrinology. 2003; 144:2121–31. [PubMed: 12697721]
65. Harris M, et al. Transcriptional regulation of the thyrotropin-releasing hormone gene by leptin and melanocortin signaling. J Clin Invest. 2001; 107:111–20. [PubMed: 11134186]
66. Banks AS, Davis SM, Bates SH, Myers MG Jr. Activation of downstream signals by the long form of the leptin receptor. J Biol Chem. 2000; 275:14563–72. [PubMed: 10799542]
67. Bates SH, et al. STAT3 signalling is required for leptin regulation of energy balance but not reproduction. Nature. 2003; 421:856–9. [PubMed: 12594516]
68. Hill JW, et al. Acute effects of leptin require PI3K signaling in hypothalamic proopiomelanocortin neurons in mice. J Clin Invest. 2008; 118:1796–805. [PubMed: 18382766]
69. Muroya S, et al. Orexins (hypocretins) directly interact with neuropeptide Y, POMC and glucose-responsive neurons to regulate Ca 2+ signaling in a reciprocal manner to leptin: orexigenic neuronal pathways in the mediobasal hypothalamus. Eur J Neurosci. 2004; 19:1524–34. [PubMed: 15066149]
70. Wang JH, et al. Leptin regulated calcium channels of neuropeptide Y and proopiomelanocortin neurons by activation of different signal pathways. Neuroscience. 2008; 156:89–98. [PubMed: 18588949]
71. Xu AW, et al. PI3K integrates the action of insulin and leptin on hypothalamic neurons. J Clin Invest. 2005; 115:951–8. [PubMed: 15761497]
72. Cui H, Lopez M, Rahmouni K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. Nat Rev Endocrinol. 2017; 13:338–351. [PubMed: 28232667]
73. Van Heek M, et al. Diet-induced obese mice develop peripheral, but not central, resistance to leptin. J Clin Invest. 1997; 99:385–90. [PubMed: 9022070]
74. El-Haschimi K, Pierroz DD, Hileman SM, Bjorbaek C, Flier JS. Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. J Clin Invest. 2000; 105:1827–32. [PubMed: 10862798]
75. Caro JF, et al. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet. 1996; 348:159–61. [PubMed: 8684156]
76. Mullier A, Bouret SG, Prevot V, Dehouck B. Differential distribution of tight junction proteins suggests a role for tanycytes in blood-hypothalamus barrier regulation in the adult mouse brain. J Comp Neurol. 2010; 518:943–62. [PubMed: 20127760]
77. Balland E, et al. Hypothalamic tanycytes are an ERK-gated conduit for leptin into the brain. Cell Metab. 2014; 19:293–301. [PubMed: 24506870]
78. Dietrich MO, et al. Megalin mediates the transport of leptin across the blood-CSF barrier. Neurobiol Aging. 2008; 29:902–12. [PubMed: 17324488]

79. Bartolome F, et al. Obesity and neuroinflammatory phenotype in mice lacking endothelial megalin. J Neuroinflammation. 2017; 14:26. [PubMed: 28143489]
80. Bjorbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS. Identification of SOCS-3 as a potential mediator of central leptin resistance. Mol Cell. 1998; 1:619–25. [PubMed: 9660946]
81. Cheng A, et al. Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B. Dev Cell. 2002; 2:497–503. [PubMed: 11970899]
82. Bjorbaek C, El-Haschimi K, Frantz JD, Flier JS. The role of SOCS-3 in leptin signaling and leptin resistance. J Biol Chem. 1999; 274:30059–65. [PubMed: 10514492]
83. Myers MP, et al. TYK2 and JAK2 are substrates of protein-tyrosine phosphatase 1B. J Biol Chem. 2001; 276:47771–4. [PubMed: 11694501]
84. Munzberg H, Flier JS, Bjorbaek C. Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. Endocrinology. 2004; 145:4880–9. [PubMed: 15271881]
85. White CL, et al. HF diets increase hypothalamic PTP1B and induce leptin resistance through both leptin-dependent and -independent mechanisms. Am J Physiol Endocrinol Metab. 2009; 296:E291–9. [PubMed: 19017730]
86. Peralta S, Carrascosa JM, Gallardo N, Ros M, Arribas C. Ageing increases SOCS-3 expression in rat hypothalamus: effects of food restriction. Biochem Biophys Res Commun. 2002; 296:425–8. [PubMed: 12163036]
87. Morrison CD, et al. Increased hypothalamic protein tyrosine phosphatase 1B contributes to leptin resistance with age. Endocrinology. 2007; 148:433–40. [PubMed: 17038557]
88. Pedroso JA, et al. Inactivation of SOCS3 in leptin receptor-expressing cells protects mice from diet-induced insulin resistance but does not prevent obesity. Mol Metab. 2014; 3:608–18. [PubMed: 25161884]
89. Zabolotny JM, et al. PTP1B regulates leptin signal transduction in vivo. Dev Cell. 2002; 2:489–95. [PubMed: 11970898]
90. Olofsson LE, Unger EK, Cheung CC, Xu AW. Modulation of AgRP-neuronal function by SOCS3 as an initiating event in diet-induced hypothalamic leptin resistance. Proc Natl Acad Sci U S A. 2013; 110:E697–706. [PubMed: 23386726]
91. Yulyaningsih E, et al. Acute Lesioning and Rapid Repair of Hypothalamic Neurons outside the Blood-Brain Barrier. Cell Rep. 2017; 19:2257–2271. [PubMed: 28614713]
92. Xue X, et al. Tumor necrosis factor alpha (TNFalpha) induces the unfolded protein response (UPR) in a reactive oxygen species (ROS)-dependent fashion, and the UPR counteracts ROS accumulation by TNFalpha. J Biol Chem. 2005; 280:33917–25. [PubMed: 16107336]
93. Kuwabara WM, et al. NADPH oxidase-dependent production of reactive oxygen species induces endoplasmatic reticulum stress in neutrophil-like HL60 cells. PLoS One. 2015; 10:e0116410. [PubMed: 25668518]
94. Tabas I, Ron D. Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. Nat Cell Biol. 2011; 13:184–90. [PubMed: 21364565]
95. Lee K, et al. IRE1-mediated unconventional mRNA splicing and S2P-mediated ATF6 cleavage merge to regulate XBP1 in signaling the unfolded protein response. Genes Dev. 2002; 16:452–66. [PubMed: 11850408]
96. Urano F, et al. Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. Science. 2000; 287:664–6. [PubMed: 10650002]
97. Averous J, et al. Induction of CHOP expression by amino acid limitation requires both ATF4 expression and ATF2 phosphorylation. J Biol Chem. 2004; 279:5288–97. [PubMed: 14630918]
98. Milanski M, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci. 2009; 29:359–70. [PubMed: 19144836]
99. Contreras C, et al. Central ceramide-induced hypothalamic lipotoxicity and ER stress regulate energy balance. Cell Rep. 2014; 9:366–77. [PubMed: 25284795]
100. Pereira ER, Frudd K, Awad W, Hendershot LM. Endoplasmic reticulum (ER) stress and hypoxia response pathways interact to potentiate hypoxia-inducible factor 1 (HIF-1) transcriptional activity on targets like vascular endothelial growth factor (VEGF). J Biol Chem. 2014; 289:3352–64. [PubMed: 24347168]

101. Booth C, Koch GL. Perturbation of cellular calcium induces secretion of luminal ER proteins. Cell. 1989; 59:729–37. [PubMed: 2510935]
102. Lippincott-Schwartz J, Yuan LC, Bonifacino JS, Klausner RD. Rapid redistribution of Golgi proteins into the ER in cells treated with brefeldin A: evidence for membrane cycling from Golgi to ER. Cell. 1989; 56:801–13. [PubMed: 2647301]
103. Dorner AJ, et al. The stress response in Chinese hamster ovary cells. Regulation of ERp72 and protein disulfide isomerase expression and secretion. J Biol Chem. 1990; 265:22029–34. [PubMed: 2254345]
104. DuRose JB, Tam AB, Niwa M. Intrinsic capacities of molecular sensors of the unfolded protein response to sense alternate forms of endoplasmic reticulum stress. Mol Biol Cell. 2006; 17:3095–107. [PubMed: 16672378]
105. Cakir I, et al. Obesity induces hypothalamic endoplasmic reticulum stress and impairs proopiomelanocortin (POMC) post-translational processing. J Biol Chem. 2013; 288:17675–88. [PubMed: 23640886]
106. Williams KW, et al. Xbp1s in Pomc neurons connects ER stress with energy balance and glucose homeostasis. Cell Metab. 2014; 20:471–82. [PubMed: 25017942]
107. Sriburi R, et al. Coordinate regulation of phospholipid biosynthesis and secretory pathway gene expression in XBP-1(S)-induced endoplasmic reticulum biogenesis. J Biol Chem. 2007; 282:7024–34. [PubMed: 17213183]
108. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. Nat Immunol. 2010; 11:136–40. [PubMed: 20023662]
109. Nishiyama A, et al. Identification of thioredoxin-binding protein-2/vitamin D(3) up-regulated protein 1 as a negative regulator of thioredoxin function and expression. J Biol Chem. 1999; 274:21645–50. [PubMed: 10419473]
110. Jin HO, et al. TXNIP potentiates Redd1-induced mTOR suppression through stabilization of Redd1. Oncogene. 2011; 30:3792–801. [PubMed: 21460850]
111. Lerner AG, et al. IRE1alpha induces thioredoxin-interacting protein to activate the NLRP3 inflammasome and promote programmed cell death under irremediable ER stress. Cell Metab. 2012; 16:250–64. [PubMed: 22883233]
112. Oslowski CM, et al. Thioredoxin-interacting protein mediates ER stress-induced beta cell death through initiation of the inflammasome. Cell Metab. 2012; 16:265–73. [PubMed: 22883234]
113. Chen J, Saxena G, Mungrue IN, Lusis AJ, Shalev A. Thioredoxin-interacting protein: a critical link between glucose toxicity and beta-cell apoptosis. Diabetes. 2008; 57:938–44. [PubMed: 18171713]
114. Blouet C, Schwartz GJ. Nutrient-sensing hypothalamic TXNIP links nutrient excess to energy imbalance in mice. J Neurosci. 2011; 31:6019–27. [PubMed: 21508227]
115. Blouet C, Liu SM, Jo YH, Chua S, Schwartz GJ. TXNIP in Agrp neurons regulates adiposity, energy expenditure, and central leptin sensitivity. J Neurosci. 2012; 32:9870–7. [PubMed: 22815502]
116. Zhou C, Routh VH. Thioredoxin-1 Overexpression in the Ventromedial Nucleus of the Hypothalamus Preserves the Counterregulatory Response to Hypoglycemia During Type 1 Diabetes in Male Rats. Diabetes. 2018; 67:120–130. [PubMed: 29079703]
117. Leloup C, et al. Mitochondrial reactive oxygen species are required for hypothalamic glucose sensing. Diabetes. 2006; 55:2084–90. [PubMed: 16804079]
118. Benani A, et al. Role for mitochondrial reactive oxygen species in brain lipid sensing: redox regulation of food intake. Diabetes. 2007; 56:152–60. [PubMed: 17192477]
119. Palomba L, et al. Negative Regulation of Leptin-induced Reactive Oxygen Species (ROS) Formation by Cannabinoid CB1 Receptor Activation in Hypothalamic Neurons. J Biol Chem. 2015; 290:13669–77. [PubMed: 25869131]
120. Diano S, et al. Peroxisome proliferation-associated control of reactive oxygen species sets melanocortin tone and feeding in diet-induced obesity. Nat Med. 2011; 17:1121–7. [PubMed: 21873987]

121. Richard D, et al. Distribution of the uncoupling protein 2 mRNA in the mouse brain. J Comp Neurol. 1998; 397:549–60. [PubMed: 9699915]
122. Toda C, Diano S. Mitochondrial UCP2 in the central regulation of metabolism. Best Pract Res Clin Endocrinol Metab. 2014; 28:757–64. [PubMed: 25256770]
123. Negre-Salvayre A, et al. A role for uncoupling protein-2 as a regulator of mitochondrial hydrogen peroxide generation. FASEB J. 1997; 11:809–15. [PubMed: 9271366]
124. Echtay KS, et al. Superoxide activates mitochondrial uncoupling proteins. Nature. 2002; 415:96–9. [PubMed: 11780125]
125. Echtay KS, et al. A signalling role for 4-hydroxy-2-nonenal in regulation of mitochondrial uncoupling. EMBO J. 2003; 22:4103–10. [PubMed: 12912909]
126. Mailloux RJ, et al. Glutathionylation acts as a control switch for uncoupling proteins UCP2 and UCP3. J Biol Chem. 2011; 286:21865–75. [PubMed: 21515686]
127. Parton LE, et al. Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity. Nature. 2007; 449:228–32. [PubMed: 17728716]
128. Rizzuto R, et al. Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca2+ responses. Science. 1998; 280:1763–6. [PubMed: 9624056]
129. Vance JE. Phospholipid synthesis in a membrane fraction associated with mitochondria. J Biol Chem. 1990; 265:7248–56. [PubMed: 2332429]
130. Friedman JR, et al. ER tubules mark sites of mitochondrial division. Science. 2011; 334:358–62. [PubMed: 21885730]
131. Schneeberger M, et al. Mitofusin 2 in POMC neurons connects ER stress with leptin resistance and energy imbalance. Cell. 2013; 155:172–87. [PubMed: 24074867]
132. de Brito OM, Scorrano L. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature. 2008; 456:605–10. [PubMed: 19052620]
133. Bach D, et al. Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism. A novel regulatory mechanism altered in obesity. J Biol Chem. 2003; 278:17190–7. [PubMed: 12598526]
134. Dietrich MO, Liu ZW, Horvath TL. Mitochondrial dynamics controlled by mitofusins regulate Agrp neuronal activity and diet-induced obesity. Cell. 2013; 155:188–99. [PubMed: 24074868]
135. Henry FE, Sugino K, Tozer A, Branco T, Sternson SM. Cell type-specific transcriptomics of hypothalamic energy-sensing neuron responses to weight-loss. Elife. 2015; 4
136. Tung YC, et al. Novel leptin-regulated genes revealed by transcriptional profiling of the hypothalamic paraventricular nucleus. J Neurosci. 2008; 28:12419–26. [PubMed: 19020034]
137. Schriever SC, et al. Alterations in neuronal control of body weight and anxiety behavior by glutathione peroxidase 4 deficiency. Neuroscience. 2017; 357:241–254. [PubMed: 28627418]
138. Katunga LA, et al. Obesity in a model of gpx4 haploinsufficiency uncovers a causal role for lipid-derived aldehydes in human metabolic disease and cardiomyopathy. Mol Metab. 2015; 4:493–506. [PubMed: 26042203]
139. Pitts MW, et al. Deletion of selenoprotein M leads to obesity without cognitive deficits. J Biol Chem. 2013; 288:26121–34. [PubMed: 23880772]
140. Ogawa-Wong AN, et al. Sexual dimorphism in the selenocysteine lyase knockout mouse. Nutrients. 2018 in press.
141. Seale LA, et al. Disruption of the selenocysteine lyase-mediated selenium recycling pathway leads to metabolic syndrome in mice. Mol Cell Biol. 2012; 32:4141–54. [PubMed: 22890841]
142. de Jesus LA, et al. The type 2 iodothyronine deiodinase is essential for adaptive thermogenesis in brown adipose tissue. J Clin Invest. 2001; 108:1379–85. [PubMed: 11696583]
143. Marsili A, et al. Mice with a targeted deletion of the type 2 deiodinase are insulin resistant and susceptible to diet induced obesity. PLoS One. 2011; 6:e20832. [PubMed: 21698184]
144. Guadano-Ferraz A, Obregon MJ, St Germain DL, Bernal J. The type 2 iodothyronine deiodinase is expressed primarily in glial cells in the neonatal rat brain. Proc Natl Acad Sci U S A. 1997; 94:10391–6. [PubMed: 9294221]

145. Tu HM, et al. Regional distribution of type 2 thyroxine deiodinase messenger ribonucleic acid in rat hypothalamus and pituitary and its regulation by thyroid hormone. Endocrinology. 1997; 138:3359–68. [PubMed: 9231788]

146. Zeold A, et al. Characterization of the nuclear factor-kappa B responsiveness of the human dio2 gene. Endocrinology. 2006; 147:4419–29. [PubMed: 16728495]

147. Barrett P, et al. Hypothalamic thyroid hormone catabolism acts as a gatekeeper for the seasonal control of body weight and reproduction. Endocrinology. 2007; 148:3608–17. [PubMed: 17478556]

148. Coppola A, et al. A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T3 and UCP2. Cell Metab. 2007; 5:21–33. [PubMed: 17189204]

149. Yagishita Y, et al. Nrf2 Improves Leptin and Insulin Resistance Provoked by Hypothalamic Oxidative Stress. Cell Rep. 2017; 18:2030–2044. [PubMed: 28228267]

150. Friedmann Angeli JP, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. Nat Cell Biol. 2014; 16:1180–91. [PubMed: 25402683]

151. Zorzano A, Claret M. Implications of mitochondrial dynamics on neurodegeneration and on hypothalamic dysfunction. Front Aging Neurosci. 2015; 7:101. [PubMed: 26113818]

152. Raturi A, Simmen T. Where the endoplasmic reticulum and the mitochondrion tie the knot: the mitochondria-associated membrane (MAM). Biochim Biophys Acta. 2013; 1833:213–24. [PubMed: 22575682]

153. Poston CN, Krishnan SC, Bazemore-Walker CR. In-depth proteomic analysis of mammalian mitochondria-associated membranes (MAM). J Proteomics. 2013; 79:219–30. [PubMed: 23313214]

154. Elias CF, et al. Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. Neuron. 1999; 23:775–86. [PubMed: 10482243]

155. Kuo DY, et al. Role of reactive oxygen species-related enzymes in neuropeptide y and proopiomelanocortin-mediated appetite control: a study using atypical protein kinase C knockdown. Antioxid Redox Signal. 2011; 15:2147–59. [PubMed: 21453188]

## Highlights

- Selenoproteins are key regulators of redox signaling and energy metabolism
- Cellular redox status modulates hypothalamic nutrient sensing
- Hypothalamic selenoproteins promote leptin signaling and energy homeostasis

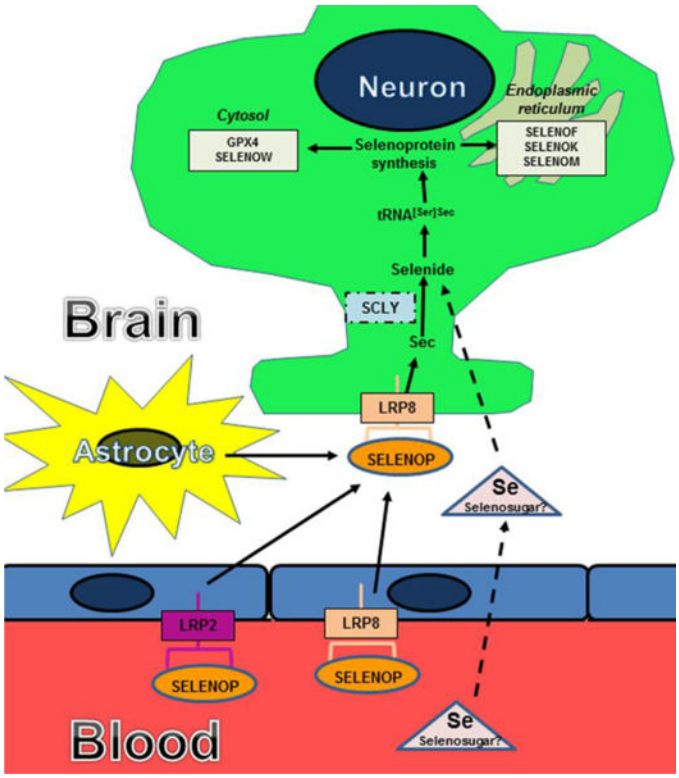


**Figure 1. Overview of Selenium Metabolism and Transport in the Brain**

SELENOP is transported across the blood-brain barrier upon binding to LRP2 or LRP8. Evidence suggests that a small molecule form of Se, presumably selenosugar, can also enter the brain. Within the brain, SELENOP is produced by astrocytes and these cells provide Se to adjacent neurons by secreting SELENOP. LRP8-mediated uptake of SELENOP is the principal route of Se supply to neurons, although alternative pathways exist. The Sec residues present in SELENOP are decomposed into selenide by SCLY. Selenide can then be reutilized for additional selenoprotein synthesis. Also shown are the selenoproteins most widely expressed in neurons, along with their subcellular localization.

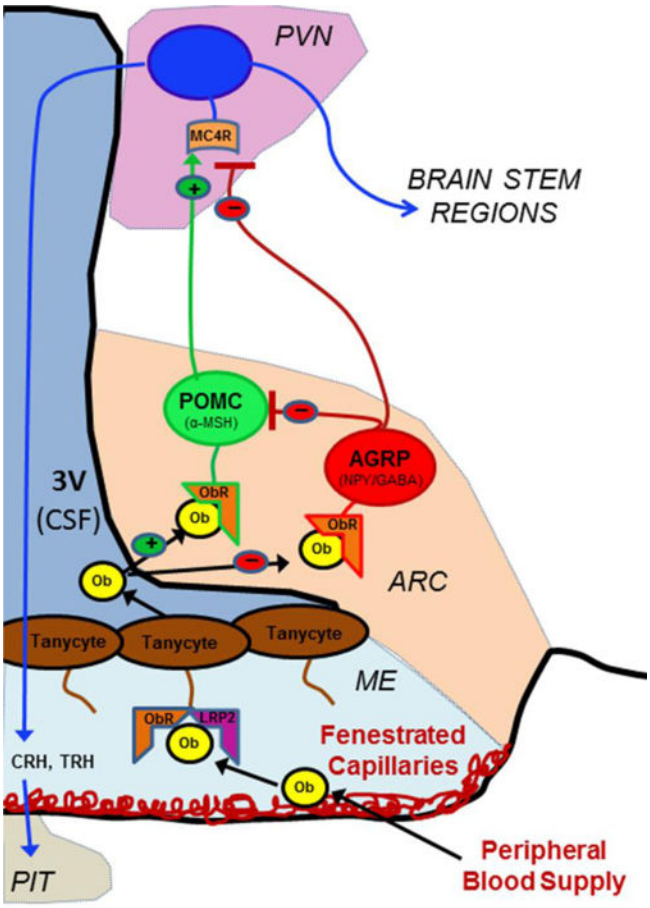


**Figure 2. Influence of Leptin on the Central Melanocortin System**

Circulating leptin enters the median eminence (ME) via the fenestrated capillaries, is transported into the CSF by ObR-expressing tanycytes, and then acts upon AGRP and POMC neurons in the ARC. The effect of leptin upon POMC neurons is stimulatory, whereas it inhibits AGRP neurons. Activation of POMC neurons stimulates release of α-MSH in PVN, which in turn, acts upon the MC4R. The MC4R promotes anorexigenic responses, such as activation of downstream brain stem regions and secretion of CRH and TRH into the ME.

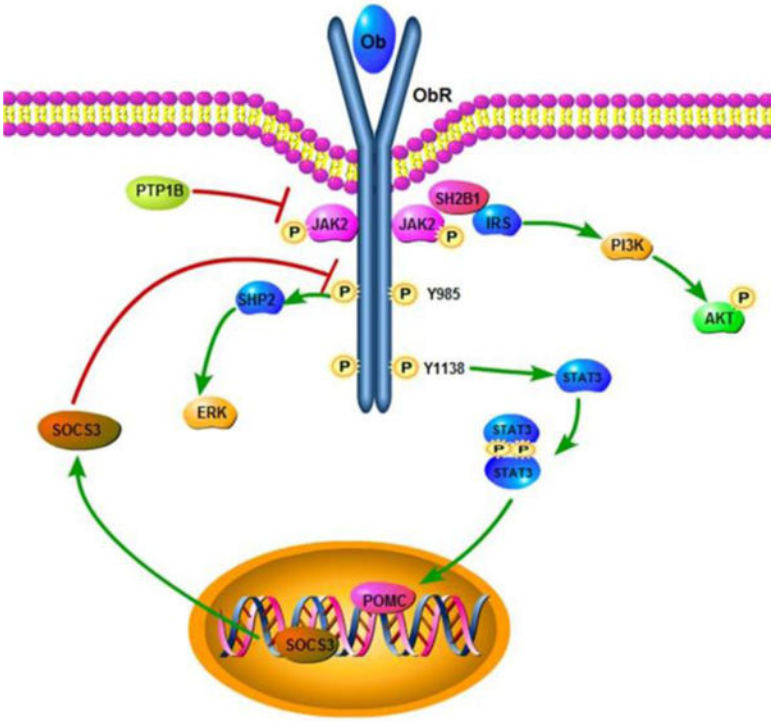


**Figure 3. Summary of Leptin Signaling Pathways**

Upon leptin (Ob) binding to the leptin receptor (ObR), JAK2 is phosphorylated. In turn, JAK2 phosphorylates two key tyrosine residues on the ObR that serve as docking sites for SHP2 (Tyr985) and STAT3 (Tyr1138), which leads to activation of the ERK and STAT3 pathways. Moreover, JAK2 also activates a parallel pathway involving IRS, PI3K, and AKT. When phosphorylated, STAT3 dimerizes and translocates to the nucleus, where it upregulates specific target genes, such as POMC and SOCS3. SOCS3 exerts negative feedback on leptin signaling by binding to Tyr985 of the ObR. Also shown is PTP1B, another negative regulator of leptin signaling that dephosphorylates JAK2.

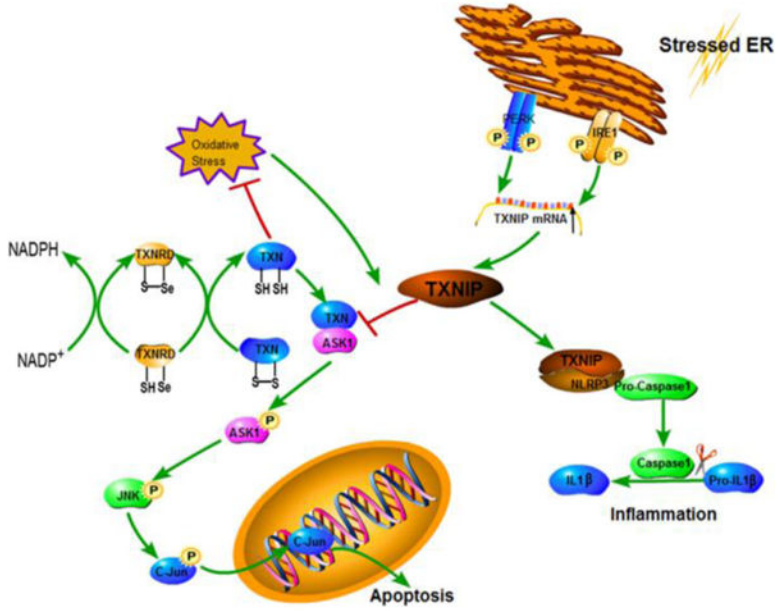


**Figure 4. TXNIP is a Focal Point for Crosstalk between ER Stress Signaling and the Thioredoxin System**

ER stress-mediated activation of IRE1 and PERK leads to increased TXNIP mRNA levels. TXNIP promotes activation of the NLRP3 inflammasome and downstream secretion of IL1β. In parallel, TXNIP negatively regulates TXN and thereby promotes activation of an ASK1-JNK-c-Jun pro-apoptotic pathway. Also shown are TXNRD and NADPH, which are essential components of the TXN system that regenerate reduced TXN from its oxidized form.

**Table 1**

List of various factors and their known effects on AGRP and POMC neuron activity.

| Stimulus | AGRP | POMC | References |
|---|---|---|---|
| Leptin | − | + | [45, 154] |
| Glucose | − | + | [46, 47] |
| ROS | − | + | [120, 155] |
| ER Stress | + | − | [3, 4, 106] |

+ denotes activation, − denotes inhibition.