Cross-talk between estrogen and leptin signaling in the hypothalamus

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Gao Q, Horvath TL. Cross-talk between estrogen and leptin signaling in the hypothalamus. Am J Physiol Endocrinol Metab 294: E817–E826, 2008. First published March 11, 2008; doi:10.1152/ajpendo.00733.2007.—Obesity, characterized by enhanced food intake (hyperphagia) and reduced energy expenditure that results in the accumulation of body fat, is a major risk factor for various diseases, including diabetes, cardiovascular disease, and cancer. In the United States, more than half of adults are overweight, and this number continues to increase. The adipocyte-secreted hormone leptin and its downstream signaling mediators play crucial roles in the regulation of energy balance. Leptin decreases feeding while increasing energy expenditure and permitting energy-intensive neuroendocrine processes, such as reproduction. Thus, leptin also modulates the neuroendocrine reproductive axis. The gonadal steroid hormone estrogen plays a central role in the regulation of reproduction and also contributes to the regulation of energy balance. Estrogen deficiency promotes feeding and weight gain, and estrogen facilitates, and to some extent mimics, some actions of leptin. In this review, we examine the functions of estrogen and leptin in the brain, with a focus on mechanisms by which leptin and estrogen cooperate in the regulation of energy homeostasis.

Leptin Levels Index the Status of Energy Stores

Leptin was initially characterized as an anti-obesity hormone (121). However, its role is more accurately described as a “fat reporter” (feedback signal) (119); that is, leptin itself has no, or limited direct effect on fat tissues, instead, its anti-obesity effect requires functional “controllers” (neuronal and/or humoral), the machineries directly responsible for reducing food intake and increasing energy expenditure. Mature leptin is a 16-kDa peptide hormone synthesized and secreted by white adipocytes, the major energy pool in the body. Leptin levels in relation to the amount of body fat serves as an index of body energy storage and feeds back to the central nervous system (CNS) to regulate energy homeostasis (68). Thus, energy homeostasis is reached in animals and humans by a mechanism that defines negative energy balance as its default state, unless a negative feedback signal is available upon elevated fat stores, indexed by increased leptin levels. When this feedback mechanism is disrupted (70), the brain continuously “senses” a state of negative energy balance, promotes feeding, and reduces energy expenditure by default.

Obesity Simulates a State of Negative Energy Balance

Although obesity is a state in which a huge amount of excess body energy (fat) is accumulated, the behavior and physiology of obese individuals mirror those promoted during a state of negative energy balance, including hyperphagia and low metabolic rates. Under normal conditions, brain regions involved in long-term energy balance, by definition, must sense the amount of existing fuel in the body and use this knowledge to adjust energy intake and expenditure. That is, energy homeostasis is maintained tightly by surveillance of and responses to alteration in body energy stores: a negative energy balance promotes food intake and restricts energy expenditure, and vice versa. However, body energy levels are not sensed via circulating levels of fuel molecules (i.e., glucose or lipids) under most circumstances but, as described above, via leptin, which indexes the amount of energy (fat) in store. When leptin levels in the circulation are high, neurons in the hypothalamus and elsewhere in the brain interpret a high energy status, and thus inhibit food intake and increase energy expenditure. However, when leptin signaling is disrupted, as in leptin resistance or, in extreme cases, in leptin or leptin receptor deficiencies, the energy homeostatic machineries recognize a state of extreme negative energy balance and initiate various behavioral and physiological responses, regardless of actual body energy (fat) stores. Animals and humans with leptin signaling disrupted are not only hyperphagic but also have extreme difficulty utilizing stored energy (Fig. 1).

Negative Energy Balance Is Associated with Infertility

A characteristic phenotype of negative energy balance is hypothalamic hypogonadism (10, 58). This condition is reversible upon recovery of energy stores. This evolutionary adaptation allows an individual or species to survive when food is scarce (112). It is particularly important to female reproduction; a critical fat mass, greater than 10%, is required for ovulation to occur in women (45). Hypogonadotropic hypogonadism is also a common phenotype in obesity caused by genetic deficiencies in leptin signaling (19). The fact that

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reproductive dysfunction in ob/ob mice can be reversed by leptin treatment indicates that developmental abnormalities in brain structures involved in reproduction caused by leptin deficiency are insufficient to interfere with normal leptin regulation of reproduction (22).

Similarly, leptin treatment restores gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) secretion and pubertal development in leptin-deficient patients, confirming its critical role in the hypothalamic control of reproduction in humans (42). Leptin pulsatility is positively and strongly correlated with LH and estrogen levels in normal cycling women (66), whereas the mean leptin levels and diurnal leptin rhythm are impaired in women suffering from hypothalamic amenorrhea (61, 69). Leptin also restores reproductive function in food-deprived animals and humans, even though their energy stores are not necessarily improved. Leptin accelerates the onset of sexual maturation in ad libitum-fed postnatal mice (1, 23). More recently, recombinant leptin was reported to increase mean LH levels and LH pulse frequency as well as estrogen levels. It improved reproduction in women with hypothalamic amenorrhea (116). Leptin replacement also restores the pituitary-gonadal axis in lipodystrophic patients (79).

Leptin Signaling: Central Role of STAT3

A single gene in both rodents and humans encodes leptin receptors (LRs) (24, 29, 107), a gp130-like receptor family member of class 1 cytokine receptors, which include the receptors for ciliary neurotropic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), interleukin-6 (IL-6), and granulocyte colony-stimulating factor (G-CSF), etc. These receptors mediate various biological processes through JAK-STAT signaling (104, 107). Six variants of LRs have so far been identified (Fig. 2A), which differ in the COOH terminals of their proteins (26, 48, 108). Leptin receptor-b (LRb), which possesses the longest intracellular domain, is evolutionary conserved among species and solely mediates energy homeostasis. The mice that lack only LRb exhibit a phenotype indistinguishable from that of leptin and leptin receptor deficiencies (25, 26, 30, 62, 107).

LRb is highly expressed in hypothalamic neurons associated with feeding and metabolism (40). Leptin binding to LRb activates the associated JAK2 tyrosine kinase and then activates the STAT3, STAT5, phosphatidylinositol 3'-kinase (PI3K), and MAPK pathways, among others (Fig. 2B) (51, 74). Among these pathways, STAT3 is crucial, since abrogation of LRb-STAT3 signaling, neuronal STAT3, or STAT3 in LRb neurons recapitulates the obesity of db/db animals, including hyperphagia and decreased energy expenditure, to a great degree (6, 46, 84). During leptin signaling, JAK2 phosphorylates LRb on three sites in its intracellular domain: Tyr985, Tyr1077, and Tyr1138. Phosphorylated Tyr1138 (pY1138) recruits STAT3 to the LRb-JAK2 complex (5, 7, 117), where JAK2 phosphorylates it (pY705). The subsequent dimerization and nuclear transport of STAT3 result in the alteration of cell transcription and function (94). For example, STAT3 directly activates proopiomelanocortin (POMC) transcription to promote anorexia and increase energy expenditure.

Phosphorylation of Tyr985 (Y985) of the LRb recruits the SH2 domain containing tyrosine phosphatase-2 (SHP-2) along with the growth factor-bound protein-2 (GRB2) (9), which is crucial for the activation of the MAPK pathway. The suppressor of cytokine signaling-3 (SOCS3), the STAT3 pathway-
induced feedback inhibitor (101), competes with SHP-2 for Y985. SOCS3 is involved in region-specific leptin resistance in diet-induced obese mice (72), and deficiencies of it in the brain suppress diet-induced obesity (71), as does mutation of Tyr985 of LRb (11). These observations suggest that Tyr985 of LRb and SOCS3 contributes to feedback inhibition of leptin action in vivo.

Less is known about the function of Tyr1077 of LRb and STAT5 activation in leptin action. Nevertheless, leptin stimulation of STAT5 phosphorylation and nuclear accumulation in the hypothalamus have recently been reported (51, 73). Furthermore, deletion of STAT5 in the brain results in obesity, although the extent to which this reflects a defect in leptin action remains unclear (63).

Although leptin activates the PI3K pathway in the brain, the molecular details of this regulation remain enigmatic (77, 120). Insulin receptor substrate-2 (IRS-2) may represent one intermediary, as CNS deletion of IRS-2 results in increased adiposity due to hyperphagia with decreased energy expenditure (16, 106, 118). The PI3K pathway also regulates the electrophysiology of hypothalamic neurons (102) and the function of the sympathetic nervous system, which contribute to the reduction of feeding (87).

Estrogen Is a Potent Regulator of Both Energy Balance and Fertility

Like leptin, the gonadal steroid hormone estrogen reduces food intake and body adiposity and increases energy expenditure in animals and humans of both sexes through a hypothalamic mechanism (17, 35, 81). It exerts a profound impact on reproduction both peripherally and centrally. The central effect of estrogen in the regulation of reproduction is directly related to reproductive hormone cycles. In fact, the actions of estrogen on the hypothalamic GnRH neuronal network are required to trigger the episodic release of GnRH that leads to a pulsatile pattern of LH secretion (54) (Fig. 3). The ability of leptin to restore fertility is also achieved by restoring GnRH and LH surges, which in turn, reverse hypogonadotropic hypogonadism. In adult females, circulating estrogen is mainly produced in the ovary. Locally, estrogen can be converted from testosterone and androstenedione by the enzyme cytochrome P-450 aromatase (P450aro). The levels of P450aro in male brains are slightly higher than in females (64, 67, 92); however, aromatase-deficient mice accumulate excess adipose tissue in both sexes (57) and impair male fertility (56, 89). In humans, aromatase deficiency has been associated with hypogonado-
tropic hypogonadism and infertility in both sexes (14, 99),
suggesting that local estrogen is important for homeostasis and
reproduction. Consistent with this, P450aro is highly and
selectively expressed in the regions associated with metabo-
lism, i.e., ventromedial hypothalamus (VMH) and reproduc-
tion, i.e., preoptic area (POA) (76).

Estrogen and Leptin Target Common Neuronal Structures

The primary sites of estrogen receptors (ERs) include the
same areas where LRs are located (82). In fact, estrogen and
leptin receptors are colocalized in neurons within the areas
known to coordinate metabolism and gonadal function, such as
the arcuate nucleus (ARC), VMH, and POA (34) (Fig. 4A).
Physical or chemical lesions to these regions (15, 109, 111)
result in hyperphagia and obesity, whereas expression of leptin
in these regions reduces food intake and body weight (4).
Similarly, estrogen infusions into the VMH, ARC, or paraven-
tricular nucleus (PVN) reduce food intake and body weight
(17, 81). The ARC, VMH, and PVN form the hypothalamic
anorectic center, from which the “antiobesity” effect emanates
in response to leptin stimulation (95). In the ARC, for example,
the anorexigenic POMC neurons (Fig. 4B) act to inhibit food
intake through the release of the POMC cleavage product
α-melanocyte-stimulating hormone (α-MSH). The orexigenic
neuropeptide Y (NPY) neurons act against POMC neurons to
promote feeding; interestingly, these neurons are also impli-
cated in fertility (41, 93). When leptin signaling is diminished,
POMC expression is reduced and NPY expression is increased.
Thus, leptin exerts its antiobesity effect by both activating
POMC neurons and inhibiting NPY neurons, while estrogen
exhibits similar molecular and cellular effects as leptin in these
regions.

Reproduction, on the other hand, is coordinated by the
hypothalamic anteroventral periventricular nucleus (AVPV)
and the POA, where GnRH neurons reside (50, 98) (Fig. 4).
GnRH neurons are the final output of a network that integrates
environmental and hormonal cues to regulate the secretion of
reproductive hormones; they are inhibited by negative energy
balance (37). Both inhibitory and stimulatory actions of estrogen
on GnRH neurons during the cycle are required for establishing a coordinated hormone cycle through distinct pathways (20). The stimulatory effect of estrogen triggers the episodic release of GnRH and induces a pulsatile pattern of LH
secretion (54). In rats, the GnRH neurons located in the rostral
POA were particularly important in triggering a GnRH surge.
The GnRH network requires preexposure to elevated estrogen
and the presence of a circadian input to initiate a cascade of
neural events (65, 115). The nature of these events remains to
be addressed. The induction of progesterone receptors in the
AVPV by estrogen (65) and the synaptic plasticity on GnRH
neurons may be involved (59, 103). Similarly, leptin also
affects the POA and GnRH neurons, albeit indirectly, as GnRH
neurons do not express LRb (114). Leptin pretreatment pre-
vents fasting-induced reduction of the activities of GnRH
neurons (103), suggesting that the knowledge on preexisting of
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Fig. 4. Common hypothalamic nuclei targeted by estrogen and leptin.
A: metabolic nuclei, the arcuate nucleus (ARC) and the ventromedial hypo-
thalamic area (VMH), as well as the reproductive nuclei, the anteroven-
tricular periventricular nucleus (AVPV) and the preoptic area (POA), where the GnRH
neurons reside, are located ventromedially in the brain. The top 2 panels are
coronal sections of mouse hypothalamus; bottom panel is a sagital section of
a mouse brain detailing the anterolateral relationship between the POA and
ARC (yellow), both of which are targeted by estrogen and leptin to control energy
balance and reproduction. B: proopiomelanocortin (POMC) neurons in the
ARC: GFP-labeled POMC neurons of the ARC are encircled by the white line,
whereas neuropeptide Y (NPY) neurons tend to localize within more medial
portion of the ARC (circled in yellow), with a significant degree of overlap
between the 2 populations. ME, median eminence; V3, 3rd ventricle.
each have some distinct actions via some neural populations that respond to one but not the other, leptin and estrogen act in many overlapping hypothalamic regions and neuron populations to regulate energy homeostasis and reproduction.

**Estrogen Mimics Leptin’s Effect on Rewiring of Melanocortin Neurons**

The hypothalamus senses peripheral signals to coordinate body homeostasis through the neuroendocrine axis, and by connecting to various brain structures. Estrogen and leptin both act in overlapping neurons in the hypothalamus to regulate long-term energy balance and fertility. How the two signals are translated to appropriate neuronal adaptations to exert their antiobesity effect is not well addressed. It has recently been uncovered that leptin rapidly rewires the synaptic input on hypothalamic melanocortin neurons, resulting in an increased POMC tone (83) followed by decreased food intake and adiposity. Estrogen also reduces appetite and adiposity (35, 112) and influences synaptology in unidentified cells in the ARC (75). This suggests that synaptic plasticity may be a common regulatory element of estrogen and leptin. Indeed, we found that, like leptin, estrogen triggers robust increases in the number of excitatory inputs on the ARC POMC neurons (47). This leads to a corresponding change in the electronic tone in these cells, measured as an increase in the events of random presynaptic release. Interestingly and informatively, estrogen’s effect on energy regulation is effective in leptin and LR mutant mice. Consistent with this observation, that estrogen triggered effect on energy regulation is effective in leptin and LR mutant mice. Thus, estrogen and leptin signals in regulating energy homeostasis are, in part, translated to the synaptic adaptations in the POMC neurons to induce an antiobese neuronal response. Since both signals are also important for normal reproduction, a similar mechanism underlying hypothalamic control of fertility may be expected.

**Estrogen and Leptin Signaling Interact Via STAT3**

The overlap in function and targeted nuclei between estrogen and leptin are overwhelming. However, whether this implies a direct interaction between the two signals remains to be addressed. At the least, this notion is supported in several ways. First, estrogen sensitizes leptin signaling, whereas estrogen deficiency causes central leptin insensitivity and increased hypothalamic NPY (2). For example, in females, chronic estrogen withdrawal, as in ovariectomy in rodents and postmenopause in humans, causes leptin resistance, whereas estrogen replacement prevents this phenotype (2). More directly, estrogen increases leptin-induced STAT3 phosphorylation in the ARC (28), indicating that estrogen may interact with the leptin pathway at the level of STAT3. Since estrogen’s effect on homeostasis and synaptogenesis is independent of leptin and LRs (35, 52), this suggests that interaction between estrogen and leptin signaling must bypass LRs and directly target the leptin downstream component.

STAT3 as a target of estrogen signaling in cells has been reported (12, 97). Distinct activation mechanisms by which estrogen activates STAT3 have been observed (Fig. 5), which may explain divergent effects of estrogen on STAT3 function (positive or negative) in transcription. These mechanisms provide “shortcut” pathways bypassing membrane-associated receptors. For example, STAT3 is phosphorylated and activated in response to estrogen in cells involving multiple intracellular signal pathways that include MAPK, Src kinase, and PI3K (12, 18) and/or direct physical association between ERs and STAT3 (27). In the animals, it was observed that estrogen activates STAT3 in the hypothalamus in a signal-transducing fashion. Peripheral (ip) administrations of estrogen induced tyrosine phosphorylation of STAT3 in the hypothalamus in less than 30 min. This effect of estrogen on STAT3 tyrosine phosphorylation is JAK independent but may involve the Src kinase pathway (Ref. 47 and Nie Y, unpublished data), and is effective in obese mutant, e.g., db/db mice. This is consistent with the fact that estrogen reduces food intake and body weight. It also regulates synaptology in hypothalamic melanocortin feeding circuits in wild-type, ob/ob, and db/db mutant mice. Finally, with a neural STAT3 knockout (STAT3N-/-) mouse model, which exhibits obesity and infertility, a phenotype highly resembling leptin deficiency (46), estrogen exhibited no

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**Fig. 5.** Estrogen (E2) receptors (ERs) activate STAT3 to promote gene expression in the hypothalamus. Agonist-bound ERs activate STAT3 (tyrosine phosphorylation) independently of LRb-mediated mechanism by direct binding or via other signal transduction pathways such as MAPK, PI3K, and Src kinase (Src-K). Activated STAT3 alters gene transcription cellular function in corresponding hypothalamic neurons. LRb-mediated STAT3 activation is not illustrated here (see Fig. 2).
effect on reducing body weight. These observations strongly suggest that STAT3 proteins are positioned downstream of estrogen signaling in neurons and are required for estrogen’s antiobesity effect.

**STAT3 in Reproduction and Metabolism**

A variety of rodent models have been employed to probe the importance of STAT3 to leptin action and reproductive function. In the first two of these, it was noted that mutation of the STAT3 binding site on LRb promoted dramatic obesity, with only modest impairment of fertility (6). In contrast, brain-wide deletion of STAT3 resulted in obesity and infertility, suggesting that STAT3 is crucial for the regulation of reproduction as well as metabolism (46). Indeed, this is to be expected given that estrogen acts in part via STAT3. A role for STAT3 in reproduction is also supported by the finding that STAT3 inhibitors, when injected into the hypothalamus, block the LH surge (13). Thus, although STAT3 signaling by leptin may not be essential for the regulation of reproduction, STAT3 itself is required, presumably due to its importance in the estrogen response. Recent findings in which deletion of STAT3 from all LRb neurons resulted in obesity but not infertility suggest that the role for STAT3 in reproduction may be due to estrogen effects in non-LRb neurons (84).

**ER(s) Involved in Cross-Talk with STAT3**

The cross-talk between estrogen and STAT3 is done, at least in part, through classic ERs, the ligand-dependent nuclear transcription factors, which sensitively respond to 17β-estradiol. The potential roles for recently uncovered membrane ERs (86) in this matter may not be ruled out; however, they require more studies. The agonist-bound ERα and ERβ activate STAT3 to stimulate a STAT-regulated promoter in cells. This correlates with cytoplasmic sublocalization of ERs and is independent of DNA-binding domains of ERs, suggesting a nongenomic mechanism of ERs (12, 97). Other interactive mechanisms between ERs and STAT3 include direct physical coupling between the two. For example, in the human neuroblastoma cell line SK-N-BE, ERα blocks the mitogenic effect of TGF-α signaling and induces differentiation independently of ERα’s DNA binding activity but requires a transcriptionally active STAT3. In this process, ERα directly binds to STAT3 (27). It is also true that ERs and STAT3 are both known to be able to associate coregulators, such as CREB, CBP/P300, and NcoA/SRC1a (38, 90). Thus, the interaction between ERs and STAT3 may involve coregulators. The binding between ERs and STAT3 in general does not alter the binding specificity of STAT3 to DNA and does not involve estrogen response elements. Finally, STAT3 also enhances the transactivation function of ERs (33, 21), suggesting that ERs and STAT3 may act mutually as coactivators to facilitate signaling.

Consistent with these in vitro data, ERα has been suggested as the main ER that mediates estrogen’s antiobesity effect in both sexes (49, 91). When knocked out, it causes obesity and infertility in both males and females (55, 53). ERα-null animals develop obesity with a more than 100% increase of their fat tissue compared with controls, whereas ERβ-null mice are lean. In the ARC, ERα is the dominant ER, and levels of ERβ are negligible (80). Notably, levels of circulating estrogen in obese ERα-null animals are 10 times higher than those in their wild-type littermates (32), revealing estrogen resistance in these mice. Additional administration of estrogen in ERα-null animals does not reduce either food intake or body weight (49). Finally, ERα-null mutants abolished the effect of estrogen to reorganize the synaptology on POMC perikarya (47). Moreover, although both ERα and ERβ affect fertility, ERα is not required for follicle growth but is indispensable for ovulation, suggesting a hypothalamic effect (36). Thus, it is reasonable to suggest that estradiol’s effect on feeding, metabolism, synaptic plasticity, and fertility is mediated by the ERs and potentially involves STAT3. The function of estrogen and leptin in metabolism and reproduction seem to overlap.

**Questions to Be Assessed**

From signal cross-talk between gonadal hormone estrogen and adipo-hormone leptin point of view, several key questions remain to be assessed:

*Where do estrogen and leptin signaling meet?* Whether STAT3 activation by estrogen occurs in LRb-expressing neurons, and if so, which subpopulation(s) of those neurons in the hypothalamus may be involved has not yet been assessed. Since ERα is found only in a subset of LRb-expressing neurons in the hypothalamic nuclei associated with feeding and metabolism, and estrogen’s effect on homeostasis is less potent than leptin, it is possible that estrogen only activates STAT3 in a subset of leptin-sensitive neurons in the hypothalamus. Similarly, estrogen may activate STAT3 in non-LRb neurons as well. This question is also related to the issue of whether estrogen signaling–STAT3 interaction is indeed occurring in the same cells, which is supported by cell culture studies, or whether it is a secondary effect.

*How do ERs trigger STAT3 phosphorylation in cells?* Even if estrogen signaling and STAT3 directly interact (as acute phosphorylation of STAT3 by estrogen was observed both in cells and in the hypothalamus), it is not known how this process is accomplished in cells. Because ERs themselves are transcription factors possessing no tyrosine kinase activity, a tyrosine kinase must be activated upon estrogen administration. It was suggested that MAPK, Src kinase, and PI3K pathways were required for estrogen activation of STAT3 in cultured cells, but it is not clear how estrogen via ERs triggers these pathways. We found that, in the hypothalamus, estrogen acutely activates Src kinase but does not affect JAKs and other tyrosine kinases that are known to phosphorylate STAT3 (Nie Y, unpublished data). Src kinase is a potent tyrosine kinase known to directly bind to and phosphorylate STAT3. This raised the possibility that Src kinase may be the downstream effector of estrogen signaling in STAT3 phosphorylation. However, how does estrogen activate Src kinase through ERs?

*How might estrogen and leptin regulate synaptology?* One possibility is that both leptin and estrogen regulate genes involving synaptogenesis. Candidate genes such as postsynaptic density-95 (PSD-95), which regulates the balance between excitatory and inhibitory synapses in the primary neuronal cultures prepared from hippocampi of embryonic day (E)18/19 (85), and brain-derived neurotrophic factor (BDNF), a neurotropin that regulates synaptic formation and function and has an antiobesity effect (88). Both genes are regulated by estrogen in vivo (3, 8, 100). PSD-95 is a protein that recruits the...


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CONGENITAL LEPTIN DEFICIENCY AND THE REGULATION OF GONADOTROPIN SECRETION IN THE RAT


Congenital leptin deficiency is associated with severe early-onset hypothalamic amenorrhea: the effects of body composition reduction subjects.


