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The Role of Hypothalamic Estrogen Receptors in Metabolic Regulation

Aaron Frank[2], **Lynda M. Brown**[1], and **Deborah J. Clegg**[2,*]

[1]Food and Nutrition Sciences Program, North Carolina Agricultural and Technical State University, Greensboro, NC 27411-0002, USA

[2]Department of Internal Medicine, Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, TX 75390-8854, USA

Abstract

Estrogens regulate key features of metabolism, including food intake, body weight, energy expenditure, insulin sensitivity, leptin sensitivity, and body fat distribution. There are two ”classical“ estrogen receptors (ERs): estrogen receptor alpha (ERS1) and estrogen receptor beta (ERS2). Human and murine data indicate ERS1 contributes to metabolic regulation more so than ESR2. For example, there are human inactivating mutations of ERS1 which recapitulate aspects of the metabolic syndrome in both men and women. Much of our understanding of the metabolic roles of ERS1 was initially uncovered in estrogen receptor α-null mice ($ERS1^{-/-}$); these mice display aspects of the metabolic syndrome, including increased body weight, increased visceral fat deposition and dysregulated glucose intolerance. Recent data further implicate ERS1 in specific tissues and neuronal populations as being critical for regulating food intake, energy expenditure, body fat distribution and adipose tissue function. This review will focus predominantly on the role of hypothalamic ERs and their critical role in regulating all aspects of energy homeostasis and metabolism.

Keywords

body weight; energy balance; hypothalamus; 17β-estradiol; estrogen receptor alpha (ERS1); estrogen receptor beta (ERS1); G protein-coupled estrogen receptor (GPER); neuropeptides

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*Corresponding Author: Deborah J. Clegg, Department of Internal Medicine, Touchstone Diabetes Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd., K5.252, Dallas, TX 75390-8854 USA, Phone: +1 214-648-3401, Fax: +1 214-648-8720, deborah.clegg@utsouthwestern.edu.

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Disclosures
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1. Introduction

The brain is the central integration site for body weight regulation. Within the brain, the hypothalamus is a complex structure of nuclei, pathways and neurotransmitter systems that controls food intake and energy expenditure [1; 2; 3; 4]. Early interest in the hypothalamus stemmed from findings that lesioning specific hypothalamic nuclei produced dramatic changes in food intake and energy homeostasis. In 1954, Dr. Stellar suggested the hypothalamus was the central neural structure involved in the control of food intake [5]. The so-called “Dual-Center Hypothesis” was based on earlier experiments by Hetherington and Ranson where electrolytic lesions were placed in two brain regions of rats. Lesions of the ventral medial hypothalamus (VMH) increased food intake and induced obesity [6; 7]. It was hypothesized the lesions affected satiety, leading the VMH to be dubbed the ”satiety center“ [8; 9]. In contrast, lesions of the lateral hypothalamic area (LHA) decreased food intake and provoked weight loss [10]; this region became known as the ”hunger center“ [11]. Electrical stimulation of the two hypothalamic centers supported the hypothesis: stimulation of the VMH caused rats to stop eating [12], while stimulation of the LHA caused sated rats to eat [13]. Thus, the Dual-Center Hypothesis became the dominant theory of how the central nervous system (CNS) controls food intake [5; 14; 15]. Recently, elegant studies using viral vector technology and generation of transgenic mice with selective deletions or targets of specific brain regions have substantiated these original findings and clearly demonstrated that the hypothalamus is one of the major brain centers for the regulation of energy homeostasis and food intake.

The hypothalamus exerts its influence on energy homeostasis through regulation of both anabolic and catabolic pathways [16; 17; 18]. Anabolic pathways increase food intake, decrease energy expenditure and consequently increase body weight/adiposity. These pathways are activated when energy stores are low (negative energy balance). Catabolic pathways are activated by positive energy balance. These pathways decrease food intake, increase energy expenditure and decrease body weight/adiposity. The interplay of various hypothalamic nuclei with peripheral hormones, neuropeptides and nuclear receptors represents a critical aspect of hypothalamic regulation of energy metabolism [16; 17; 18].

Surprisingly, despite thousands of reports published since the 1930“s investigating the role of various hypothalamic nuclei in the regulation of food intake and body weight [19; 20; 21], studies of the effect of sex on the hormonal and neuronal pathways of energy regulation have been sparse. However, recent data demonstrate that males and females do differ in terms of CNS regulation of body weight and homeostasis [22; 23]. Both testosterone and estrogens influence metabolism, energy homeostasis, food intake, and body fat distribution, partially through hormonal receptors which are co-localized with hunger (orexic) and satiety (anorexic)-inducing neuropeptides within the hypothalamus. This review will explore the relationship of estrogens, estrogen receptors (ERs) and peripheral hormones in hypothalamic regulation of energy homeostasis.

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The role of ERs and genomic vs. non-genomic signaling

The ”classical“ nuclear ER was cloned in 1985 [24] and renamed estrogen receptor alpha (ERα/ESR1) when a second nuclear estrogen receptor (estrogen receptor beta (ERβ/ESR2)), was discovered 10 years later [25]. The ER subtypes are expressed differentially throughout the brain [25; 26; 27; 28; 29; 30; 31; 32; 33], and in many cases their distribution differs by sex.

Once thought to function solely as genomic transcription factors [34; 35]; however, ERs have also been shown to participate in non-genomic signaling pathways. “Classical” genomic activity of ERs occurs over the course of hours; ligand binding induces conformational changes of the receptor, allowing it to dissociate from chaperone heat-shock proteins and dimerize with other ERs [36]. The ligand-dimer complex binds either directly to estrogen response elements (ERE) in target gene promoters or indirectly to AP-1 or SP-1 response elements via protein tethering to DNA [37]. The physiologic responses mediated by ERs vary across cell types and depend upon the presence and concentration of ER subtypes, ligands, and co-activator and co-repressor proteins [36; 38]. Interestingly, while highly active estrogens such as 17 beta-estradiol (E2) function as ER ligands, many pharmacological, as well as environmental and food compounds, are capable of binding and promoting ER activity [36]. Once ligand has bound and activated the ER, transcription proceeds in a cyclic fashion, cycling on and off target promoters as long as ligand is present.

Non-genomic steroid/steroid receptor activation of ERs occurs more quickly than the classical pathway, typically over the course of minutes or seconds. Extra nuclear and membrane-associated isoforms of ESR1 and ESR2 localize to plasma membrane caveolae and congregate with signaling molecules, including G proteins, growth factor receptors, tyrosine kinases (Src), linker proteins (MNAR), and orphan GPCRs, facilitating interaction and rapid intracellular signaling in the presence of ligand [39]. For example, the E2/ER complex induces activation of the mitogen-activated protein (MAP) kinase cascade and phosphatidylinositol 3-kinase (PI3K) pathways, causing a rise in intracellular calcium [40; 41]. ERs also activate protein kinase B (PKB/Akt) in neurons [42; 43; 44], and activation of the PI3K/Akt cascade mediates a variety of E2“s central actions, including neuronal excitability, neuro-protection, reductions in inflammation, and neurite outgrowth [45], as well as body weight regulation. While E2 activates G protein-coupled estrogen receptor (GPER; also called GPR30), the role of GPER in body weight regulation still requires validation. In one study of female mice lacking GPER, the obesity phenotype emerged in only one of four GPER mutant mouse lines [46; 47]. Multiple groups have described collaboration between membrane-localized ESR1 and GPER, presumably at the membrane of several E2-sensitive cell lines. GPER also induces the expression of ERS136, a transcriptionally inactive and truncated version of the classical long isoform of ERS1, ERS166 [48]; however, its function with respect to metabolism remains unclear.

In an attempt to better describe the various mechanisms of estrogenic action, Park *et al.* examined whether E2 regulates body weight homeostasis through the classical or non-classical ER signaling pathways by generating a novel mouse model with a knock-in mutation blocking the DNA binding domain of ESR1[49]. These mice, termed NERKI

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(nuclear ESR1 knock-in mice), were leaner and had normal glucose homeostasis, insulin sensitivity, energy homeostasis, and physical activity when compared with ERα knock-out (ERKO) or wild-type mice. NERKI mice had lower leptin levels than ERKO and enhanced hypothalamus-specific leptin sensitivity as measured by phospho-STAT3 activation. The authors also found an increase in phosphorylated Akt after E2 injections in the ventral medial nucleus. Together this data indicates that non-classical ER signaling plays a critical role in mediating the metabolic effects of estrogens.

Hypothalamic ERs and Metabolic Regulation

ESR1 mediates the anti-obesity effects of estrogens; deletion of the receptor increases adiposity and causes the metabolic syndrome in both male and female mice [50]. ESR2 is less effective in this regard; its deletion does not promote obesity or any of the metabolic consequences associated with obesity [51]. ESR1 is expressed in several different brain regions implicated in regulating energy homeostasis, including the ventrolateral portion of the VMH (VL VMH), the arcuate nucleus (ARC), the medial preoptic area (MPOA), and the paraventricular nuclei (PVN) [26; 27; 28; 29; 30; 52; 53].

Early attempts to determine the influence of E2 and their receptors in regulating food intake and body weight in the CNS were performed by intra-nuclear microinjections of estradiol benzoate (E2) [54]. Due to the difficulty in precisely placing cannulae or producing lesions in small, complex hypothalamic regions, findings obtained from these studies are somewhat controversial. For example, E2 implanted in the PVN decreased food intake and body weight in ovariectomized (OVX) rats in the absence of peripheral estrogenic stimulation. Moreover, the anorexigenic effects of subcutaneous E2 were blunted in rats with PVN lesions [55]. However, subsequent studies failed to reproduce these phenotypes in rats with PVN implants of E2 [56]. Effects of E2 in the MPOA have also been controversial, with only one report showing an anorexigenic response following sight-directed E2 administration [57], whereas several others have demonstrated E2 implanted in this nucleus has no effect on feeding [55]. The ARC and VMH are two hypothalamic nuclei that are relatively small structures/areas which are difficult to selectively target; therefore, earlier microinjection studies were not able to rigorously distinguish these two regions and failed to provide consistent results [55].

Subsequently, we have reported that site-specific reductions of ESR1 in the VL VMH using a small hairpin (sh) interference RNA decreased sensitivity to E2-induced weight loss, as well as decreased energy expenditure and increased visceral fat deposition, implicating VL VMH ESR1 in energy homeostasis [58]. More recently, suppression of ESR1 expression in neurons from the VMH using the steroidogenic factor-1 (SF1) promoter in a transgenic mouse model produced similar results. In this model, bodyweight increased significantly in female but not male transgenic mice. Notably, the female transgenic mice gained a significant amount of perigonadal visceral adipose tissue and manifested dysregulated thermogenesis, likely an effect of reduced sympathetic activity at the level of the brown adipose tissue [58]. These findings show that activity of ESR1, specifically in the VMH, is critical for regulation of energy expenditure in females.

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Estrogens interact with leptin

First described in 1994 [59], leptin has proven to be a key metabolic protein with actions throughout the body. Secreted from adipose tissues in direct proportion to adiposity, leptin crosses the blood-brain barrier and interacts with leptin receptors in the hypothalamus and brainstem to influence food intake and energy expenditure [14; 16; 60; 61; 62; 63; 64; 65; 66; 67; 68]. Specifically, leptin provides a powerful catabolic signal to the brain, inhibiting food intake and increasing energy expenditure [14; 16; 60; 61; 62; 63; 64; 65; 66; 67; 69; 70].

There are several splice variants of the leptin receptor: the long form (leprb) is thought to be critical for regulating energy balance [71]. Leprb"s are localized in several brain areas including the VMH and the ARC, and are co-localized with several other receptors and neuronal pathways believed to be involved in controlling food intake, energy homeostasis and reproduction [72; 73; 74]. Leptin has the ability to activate or inhibit hypothalamic neurons [73; 75; 76]. Importantly with respect to the potential role of estrogens to regulate energy homeostasis, leprb expression in the ARC is co-localized with ESR1 [77], and estrogens have been reported to regulate the expression of leprb in the ARC [78], possibly via an ERE on the leptin receptor gene [79]. Leptin levels are higher in females, even before puberty, when compared with males, and these levels are independent of differences in body composition [80; 81; 82]. After puberty, estrogens increase and testosterone decreases leptin synthesis and secretion via sex steroid receptor-dependent transcriptional mechanisms [83].

Estrogens may promote leptin"s catabolic action in the brain. Higher levels of estrogens have been associated with increased leptin sensitivity [84; 85; 86]; however, some studies have failed to observe direct estrogen-leptin interactions [87; 88; 89]. Although circulating leptin protein levels do not change appreciably during the estrous cycle, ARC leprb expression is highest during estrous and metestrous [78]. In rodents food intake in females varies across the estrus cycle; therefore, shifts in leprb receptor expression and, by extension, leptin sensitivity, may be a potential mechanism for changes in food intake during the cycle. Critically, OVX or removal of endogenous estrogens has been shown to decrease sensitivity to leptin delivered to the brain, while E2 replacement following OVX restored the anorexigenic effects of leptin [23]. Analogously, E2 administration to males increased CNS leptin sensitivity [23]. Additionally, females displayed greater activation of markers of leptin receptor activity as measured by c-Fos (a marker of neuronal activation) and pSTAT3 (a marker of leptin receptor activation) immunoreactivity in the ARC than males following intra-third ventricular (i3vt) leptin administration, suggestive of enhanced leptin sensitivity [23].

Ladyman *et al*. characterized a form of leptin resistance in pregnancy, providing additional evidence of leptin/estrogen interactions in the regulation of metabolism. Leptin treatment in pregnant rats impaired activation of pSTAT3 and reduced leprb mRNA in the VMH when compared to non-pregnant females [90]. Early in pregnancy, there was a reduction in estrogens, supporting the idea that low levels of estrogens are associated with reduced leptin sensitivity. However, there were no changes in leptin activation of pSTAT3 in the ARC of

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pregnant females, nor were there changes in leprb in pregnant versus non-pregnant females, suggesting a possible tissue specific interaction between estrogens/leptin and their receptors.

Estrogens influence insulin sensitivity

In 1953, Kennedy *et al*. hypothesized that adipose tissues produce a hormone that functions as part of a feedback mechanism, informing the brain of the relative amount of adipose tissue in the periphery. He coined this the ‘adiposity theory of body weight regulation’ [91]. Initially, insulin was posited to be this hormone. Subsequently, it has been shown that insulin is not secreted by the adipose tissues *per se*, but is secreted relative to overall adipose tissue mass [92; 93; 94; 95; 96]. Obese animals and humans have higher basal insulin levels and secrete more insulin in response to a meal than lean individuals [94; 97]. Insulin increases during meals and other periods of positive energy balance and decreases during fasting and periods of negative energy balance. Additionally, insulin receptors are distributed in discrete brain areas, including the hypothalamus [98; 99; 100], and activation of hypothalamic insulin receptors decreases food intake and body weight [16; 62; 101; 102; 103]. Manipulation of gonadal steroid levels influences insulin sensitivity [22; 23; 86], suggesting that the relative amount of androgens and E2 are key determinants of the brain“s sensitivity to the catabolic actions of insulin. When there is proportionally less estrogen, CNS insulin sensitivity increases.

Estrogens interact with the melanocortin system

The arcuate nucleus (ARC) has been demonstrated to be a key site of leptin and insulin receptor activation and activity [3; 68]. Leprb/insulin receptors reside predominately in two populations of ARC neurons: those expressing pro-opiomelanocortin (POMC) [104; 105] and those expressing neuropeptide Y (NPY) and agouti-related peptide (NPY/AgRP) neurons [106]. Central administration of NPY potently increases food intake and decreases energy expenditure and fat oxidation [107; 108; 109; 110]. AgRP is an antagonist at melanocortin-3 and melanocortin-4 (MC3/MC4) receptors, and its administration increases food intake. Both leptin and insulin administration decrease NPY/AgRP mRNA, demonstrating leptin/insulin are critical determinants of ARC NPY activity [106]. POMC neurons release cleaved products such as α-melanocyte stimulating hormone (αMSH), which acts in the PVN and lateral hypothalamus on MC3/MC4 receptors to reduce food intake and increase energy expenditure [14; 63; 76; 111]. Chronic administration of αMSH reduces body weight and adiposity [112]. Leptin/insulin facilitates POMC neuronal release of αMSH [113; 114]; this is one of the mechanisms by which leptin/insulin reduces food intake and increases energy expenditure. Consequently, within the ARC, leptin/insulin elicits a powerful catabolic affect by activating αMSH and simultaneously inhibiting anabolic NPY/AgRP release [14].

Importantly, with respect to estrogenic regulation of these neuronal populations in the ARC, ESR1 is not co-localized or expressed on NPY/AgRP neurons [115]; however, we and others have found POMC neurons do express ESR1 [4; 116; 117]. POMC levels are also responsive to gonadal steroids; POMC mRNA fluctuates over the course of the estrous cycle, with the most dramatic changes during proestrus when plasma E2 peaks [114; 118;

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119; 120]. OVX with concomitant reductions in circultating E2 decreases POMC mRNA, an effect reversed by E2 replacement [121]. Lower POMC levels are also observed in ESR1 knockout mice [122].

E2 activates POMC neurons partly via PI3K-mediated mechanisms [123; 124]. Additionally, E2 administration rapidly increases activity at incoming excitatory synapses of POMC neurons, enhancing miniature excitatory postsynaptic current recorded from POMC green fluorescent protein neurons [125]. These synaptic rearrangements in POMC neurons tightly parallel the effects of E2 on food intake, energy expenditure and body weight [125]. Collectively, these findings suggest that ESR1 functions in POMC neurons to influence energy homeostasis and may provide a mechanism for the anorexigenic effects of E2. Recently, we reported that knock down of ESR1 from POMC neurons in female mice caused significant increases in food intake and body weight gain; however, these effects did not occur in male knockdown mice [4]. Female knockdown mice also had increased plasma E2 levels, suggesting the POMC neuronal population is an important area for regulation of the negative feedback loop and the hypothalamic pituitary gonadal axis (HPG).

In an additional experiment, ESR1 knockdown in *both* POMC and SF1 neurons exacerbated both previously described phenotypes: female mice had significantly greater overall body weight gain due to both increased food intake and reductions in energy expenditure, as well as increased visceral adiposity in the perigonadal depot [4]. Hart-Unger and Korach summarized these findings [126], indicating that E2 acts on hypothalamic POMC neurons to suppress food intake and maintain the negative feedback loop. In SF1 neurons of the VMH, E2 increases energy expenditure through activation of the sympathetic nervous system in brown adipose tissue (BAT) as well as regulates the deposition of fat within the visceral depot.

Furthermore, E2 opposes the orexigenic effect of certain neuropeptides. For example, while NPY promotes food intake and body weight gain [110], E2 suppresses NPY release. NPY increases following OVX with concomitant reduction of E2, and administration of E2 to the ARC reverses this increase [84; 127]. Similarly, increased NYP resulting from food deprivation can be reversed by administration of E2 in OVX mice. Lastly, chronic E2 treatment decreases NPY levels and its release in the PVN [128]. These important findings show that E2 strongly impacts the CNS to regulate food intake, energy expenditure, body fat distribution, and the reproductive axis.

Estrogens interact with cholecystokinin (CCK)

As chyme passes from the stomach to the duodenum, duodeonal I cells synthesize and release the peptide cholecystokinin (CCK). CCK slows gastric emptying and intestinal motility [129], as well as increases satiation by activating subdiaphragmatic vagal afferent neurons [130; 131]. CCK antagonists increase food intake by increasing meal size [132]. Several experiments have highlighted the interactions between E2 and CCK. CCK-A antagonists decreased food intake to a greater extent in E2-treated OVX mice and intact females in proestrus, and this effect was lessened in rats with low E2 levels [133; 134; 135; 136].

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CCK satiation relies on vagal afferents [137; 138; 139], and upregulation of CCK receptors in terminals of vagal afferent fibers increases CCK sensitivity. Evidence for this comes from *in vitro* quantitative autoradiography which measured the effects of E2 on the binding characteristics of CCK receptors in the nucleus of the solitary tract (NTS), a brain area that receives terminal projections of abdominal vagal afferent fibers [137], as well as in two interconnected areas, the area postrema and the VMH. Other evidence suggests E2 increases the sensitivity of vagal CCK-A receptors [140; 141; 142], providing another plausible explanation for the anorexigenic effect of E2.

Estrogens interact with ghrelin

Ghrelin is produced in the stomach and acts on growth hormone secretagogue receptors (GHSRs) in the hypothalamus to increase food intake. While mainly synthesized by the stomach, ghrelin is also found in the hypothalamus and several other brain areas [143; 144; 145]. E2 influences ghrelin efficacy. Exogenous ghrelin stimulated food intake less strongly in intact females than in males or OVX female rats [146]. Peripheral or CNS-delivered ghrelin increased feeding in intact male and OVX females rats [147; 148; 149; 150; 151; 152; 153]; however, the same hyperphagic levels were not achieved when administered to the intact/proestrus phase females [146]. In further support of a potential inhibitory effect of estrogens on ghrelin activation, OVX rats treated with E2 no longer had ghrelin-induced hyperphagia. Furthermore, E2 reduced the orexigenic effects of ghrelin delivered directly into the ARC in male rats, suggesting that E2 suppresses ghrelin-induced hyperphagia [146].

To further explore the ghrelin/E2 interaction, mice lacking GHSR (*Ghsr*$^{-/-}$) received bilateral OVX. While the control/wild type mice increased food intake following the surgery, the *Ghsr*$^{-/-}$ mice did not, suggesting E2 tonically inhibits endogenous ghrelin signaling [146]. Additionally, female *Ghsr*$^{-/-}$ mice were leaner than males, and accumulated less body weight and adiposity following exposure to an obesigenic high-fat diet [154]. In contrast, Currie *et al.* failed to observe any sex difference following direct ghrelin microinjections into the ARC or PVN [155]; however, in these experiments ovarian cycling was not monitored, negating any potential hormonal influence and its impact on ghrelin activity.

Estrogens interact with melanin-concentrating hormone (MCH)

MCH is an orexigenic hormone and important regulator of energy homeostasis [156]. Central administration of MCH promotes feeding [157; 158], while genetic ablation of the *Mch* gene produces a lean phenotype [159; 160]. In addition, *Mch* is upregulated by fasting [158], and MCH neurons in the lateral hypothalamic area (LHA) receive inputs from NPY/AgRP neurons in the ARC [16; 63; 161; 162; 163; 164]. Estrogens influence food intake through their interactions with MCH activity as demonstrated by Messina *et al.* [165]. Central injection of MCH in E2 or vehicle-treated OVX and male rats suppressed MCH-induced feeding following E2 treatments regardless of sex. When endogenous estrogens were monitored in intact females, MCH induced food intake when estrogens were lower. Overall, E2 decreased the orexigenic effect of MCH, leading the authors to speculate that changes in food intake across the estrus cycle may be mediated by changing MCH signaling

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[165]. E2 could decrease MCH signaling in the LHA and zona incerta (ZI) [31]. In support of this hypothesis, physiological doses of E2 decreased pre-pro MCH mRNA expression in the ZI of OVX rats [166] and the LHA of obese male rats [167]. In addition, chronic E2 treatment in male rats blocked increases in LH MCH mRNA expression induced by fasting [167]. In contrast, pharmacological doses of E2 in male mice increased MCH mRNA within hypothalamic tissue punches [168]. These discrepancies emphasize the need for additional research to resolve the role of endogenous E2 in regulating MCH expression. E2 may affect the expression of MCH-1 receptors [26; 169], an idea supported by work demonstrating LHA neurons containing MCH-1 receptors have ERs in close proximity [170].

Concluding Remarks

The pace of research on metabolism has been extraordinary over the last decade. The explosion in our knowledge has been driven in part by the multitude of new tools available to investigators and by the overwhelming clinical need to address the epidemic of obesity that confronts the developed world. To address this, we not only have to understand the neuroscience of how food intake and energy expenditure are controlled, but how the body weight regulatory system interfaces with other critical functions such as arousal, reward, sensation, emotion and memory. The important point is that the control of energy balance is not an isolated function but rather an integrated part of how an animal survives.

Another key challenge is to accurately model how sex hormones influence metabolism. This review has begun to address the issue; however, we must cultivate a more nuanced understanding. Taken together, the evidence that ERs and estrogens mediate significant metabolic effects *in vivo* is substantial; however, the fact that men and women differ with respect to metabolism and energy homeostasis is often underappreciated in biological research. Failure to take into account sexual differences in metabolism hinders the correct design and interpretation of metabolic experiments. By better incorporating the effect of sex in our designs, we will generate experimental models with higher physiologic fidelity, thus leading to treatment modalities with a greater impact.

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Highlights

- ERs regulate key features of metabolism
- ERS1 mutations recapitulate aspects of the metabolic syndrome
- ERS1 in female SF1 neurons regulates energy expenditure and fat distribution
- ERS1 in female POMC neurons regulates food intake and negative feedback
- What remains is dissecting the contribution of brain-specific ERs

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Table 1

Table of Abbreviations

AgRP	agouti-related peptide
Akt/PKB	protein kinase B
ARC	arcuate nucleus
CCK	cholecystokinin
CNS	central nervous system
E2	17β-estradiol
ER	estrogen receptor
ERE	estrogen response element
ERS1	ER alpha
$ERS1^{-/-}$	ER alpha null mouse
ERKO	ER knock-out mouse
ERαKO	ER alpha knockout mouse
ERS2	ER beta
HPG	hypothalamic pituitary gonadal axis
$Ghsr^{-/-}$	GHSR null mice
GHSRs	growth hormone secretagogue receptors
GPCR	G protein-coupled receptor
GPER	G protein-coupled ER
i3vt	intra-third ventricular
leprb	long form of the leptin receptor
LHA	lateral hypothalamic area
αMSH	alpha melanocyte stimulating hormone
MAP	mitogen-activated protein
MC3/MC4	melanocortin-3, -4 receptors
MCH	melanin-concentrating hormone
MNAR	modulator of nongenomic activity of ER
MPOA	medial preoptic area
NERKI	nuclear ERα knock-in mouse
NPY	neuropeptide Y
NTS	nucleus of the solitary tract
OVX	ovariectomy
PI3K	phosphatidylinositol 3-kinase
POMC	pro-opiomelanocortin
PVN	paraventricular nucleus
SF1	steroidogenic factor-1
sh	short hairpin
VMH	ventromedial hypothalamus

ZI	zona incerta

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