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Review

Central effects of estradiol in the regulation of food intake, body weight, and adiposity☆

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ABSTRACT

In recent years, obesity and its associated health disorders and costs have increased. Accumulation of adipose tissue, or fat, in the intra-abdominal adipose depot is associated with an increased risk of developing cardiovascular problems, type-2 diabetes mellitus, certain cancers, and other disorders like the metabolic syndrome. Males and females differ in terms of how and where their body fat is stored, in their hormonal secretions, and in their neural responses to signals regulating weight and body fat distribution. Men and post-menopausal women accumulate more fat in their intra-abdominal depots than pre-menopausal women, resulting in a greater risk of developing complications associated with obesity. The goal of this review is to discuss the current literature on sexual dimorphisms in body weight regulation, adipose tissue accrual and deposition.

Contents

1. Introduction

Gonadal hormones potently control food intake and body weight. In female animals, the activational effects of estradiol acutely and chronically influence body weight homeostasis [1–3]. In rats and mice, estrogen exerts a tonic inhibitory effect on meal

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size and daily food intake throughout the ovarian cycle and a cyclic inhibitory effect during the peri-ovulatory phase [1,3–5]. Removal of estrogen leads to changes in meal size and duration [6,7], hyperphagia, and obesity. Estrogen has similar effects in humans where it modulates peri-ovulatory decreases in daily food intake [8]. Additionally, reductions in estrogen are associated with changes in body weight and fat distribution in humans, which parallel the findings in animals [8]. Estrogen has the ability to control energy balance, food intake, and body fat distribution and this may be mediated through its interaction with orexigenic and anorexigenic hormones. This review aims to explore these interactions and discuss the link between estrogen and obesity.

1.1. Estrogen regulates adiposity

The accumulation of fat in a central distribution (intra-abdominal) has emerged as a risk factor for the metabolic syndrome [9,10] which includes a higher risk of diabetes, hypertriglyceridemia, hypertension, and cardiovascular disease [11]. Estrogen promotes the accumulation of subcutaneous fat [12], and the loss of estrogen with menopause is associated with an increase in central fat [10,13]. The sexual dimorphism in adipose tissue distribution may partially explain the greater risk for the metabolic syndrome in men compared with pre-menopausal women.

1.2. Estrogen regulates adipose tissue distribution

Visceral fat varies inversely with estrogen levels [14]. When estrogen levels become sufficiently low visceral fat accumulation occurs in females, possibly due to direct effects of estrogen, especially since progesterone and androgen receptors (PR and AR), as well as, estrogen receptor (ER) are expressed in adipose tissues [15]. Subcutaneous adipose tissue has higher concentrations of ER and PR; however, visceral adipose tissue has higher concentrations of AR [16]. Additionally, subcutaneous adipose tissue has few androgen receptors, and estrogen down-regulates AR expression in subcutaneous fat [17]. Adipose tissue-specific AR knock-out mice have increased intra-adipose estradiol levels, which leads to increased subcutaneous obesity and hyperleptinemia [18].

Ovariectomized (OVX) rats gain fat, specifically visceral fat with no change of subcutaneous fat [19]. Peripheral or central administration of estradiol to OVX rats restores central leptin sensitivity and changes their body fat distribution to mirror that of intact females; additionally, altering the sex hormone milieu in males with estradiol administration increases sensitivity to central leptin and increases subcutaneous fat deposition [19]. An important implication from these findings is that estrogen regulates body fat distribution, interacts with the integrated adiposity message conveyed to the brain by leptin, and enhances leptin's action in sympathetic activation to the visceral fat, which facilitates fat mobilization in the visceral depot and fat deposition in the subcutaneous depot.

1.3. Estrogen regulates adiposity through estrogen receptors

Estrogen regulates body adiposity and fat distribution through its receptors, ER alpha (ERα) and beta (ERβ) [20,21]. However, only ERα has been reported to have a major influence on energy homeostasis [22]. ERα is necessary for estradiol's genomic actions on body weight regulation [23] while ERβ functions more as a modulator of estrogen actions [24]. Rapid, non-genomic actions of estradiol also have been described and some of them appear to involve ERα [25].

Heine et al. [22] reported that male and female mice with total body deletion of ERα, ERα-knock-out (αERKO) mice, have increased adiposity in both male and female mice, suggesting an important role for this estrogen receptor in the regulation of body weight and adiposity. Recently, site-specific knockdown of ERα expression in the VMH, a brain region critical for body weight regulation, demonstrates the role of VMH ERα activity in the regulation of body weight homeostasis [23]. Knockdown of VMH ERα results in obesity due to an anabolic process, with changes in energy expenditure primarily mediating the weight gain [23]. These data are consistent to previous finding in the αERKO mice where it has been demonstrated that the obesity is primarily due to changes in energy expenditure rather than changes in food intake [22,26] and those mice have increased visceral adiposity (unpublished data). These data suggest that estrogen signaling with critical hypothalamic nuclei is responsible for the regulation of body weight via modulating energy expenditure.

Since ERα is expressed in hypothalamic areas that regulate energy homeostasis [27–33], the absence of ERα expression is consistent with changes in body weight. Furthermore, ERα polymorphisms identified in humans have been associated with increased levels of visceral fat.

A ventral medial nucleus (VMN) specific ERα knockdown in both female mice and rats resulted in phenotypes characteristic of a metabolic syndrome [23]. Microinjections of low doses of estradiol directly into the brain were shown to inhibit food intake [19,34,35]. Taken together, these observations suggest that the binding of estradiol to ERα in the hypothalamus, or elsewhere in the brain, may represent a mechanism by which estradiol regulates food intake, body weight, and possibly body fat distribution.

1.4. Estrogen regulates adiposity by decreasing inflammation

Obesity is a state of chronic inflammation, and inflammatory signaling pathways in obesity are linked to insulin resistance [36–38]. Sex differences where females are protected have been reported in diet-induced obesity, insulin resistance and inflammatory response to a high-fat (HF) diet [39–41]. This may be explained in part by the anti-inflammatory properties of estrogen [42]. Recent studies have shown that estradiol may play a role in reducing the inflammatory response in adipose, cardiovascular, and neural systems [43], in addition to being neuroprotective both *in vivo* and *in vitro* [44,45].

ERα (and in some cases ERβ) is expressed in immune and cytokine-producing cells including macrophages and microglia, and *in vitro* studies have shown estradiol-activated ERα decreases the number of pro-inflammatory cytokines [44,45]. The anti-inflammatory properties of estradiol can be partially explained by the ability of ERs to act as transcriptional repressors by inhibiting the activity of nuclear factor kappa B (NFκB) through protein-protein interactions between agonist-bound ERs and activated NFκB subunits [42,46,47]. Estradiol's inhibitory effect on NFκB function is not fully understood and may be target selective [47–49].

Symptoms of a metabolic syndrome increase when animals are maintained on a HF diet or when females have low ovarian hormone levels. Free fatty acids (FFAs), particularly saturated fatty acids, increase inflammation by activating toll-like receptor 4 (TLR4) [50]. Muscle and liver expression of tumor necrosis factor-alpha (TNFα), interleukin-6 (IL-6), and NFκB also increase with HF diets [50]. Estradiol has been shown to be neuroprotective and to increase the expression of growth factors and proteins involved in apoptosis [51,52].

Estradiol signaling pathways are active in monocytes and macrophages, and ERs are expressed by these cells [45,53]. Therefore, the protective effects of estradiol in neurodegenerative diseases can be mediated by inhibiting the inflammatory response, and consequently, hormone withdrawal can increase inflammation [53].

Both in a model of brain inflammation and in primary cultures of microglial cells, estradiol inhibited the synthesis of inflammatory mediators induced by lipopolysaccharide (LPS) [44,45,53,54]. Moreover, hormone loss in OVX mice resulted in increased microglial activation [54], while estradiol replacement decreased microglia activation [53]. These data provide strong evidence that chronic inflammation in the brain can be regulated by estradiol.

2. Estrogen interacts with orexigenic neuropeptides

Estrogen has been proposed to act directly and indirectly to decrease orexigenic peptides and decrease food intake. In this section, we will review the literature and describing the interactions of estrogen and neuropeptides that increase food intake.

2.1. Neuropeptide Y

Neuropeptide Y (NPY) is an important central regulator of energy homeostasis in many hypothalamic neurons [55,56]. NPY is a potent orexigen, which increases feeding behavior in fed and fasted animals [57]. Estrogen acts via the estrogen receptors (ERs) in the hypothalamus to reduce feeding [58], and may mediate its anorectic effects by decreasing NPY expression or release [59]. In addition, estrogen directly affects NPY neurons, however, in which area of the brain or how this effect occurs is still unclear [61].

Ovariectomized (OVX) rats experience a rapid weight gain, which can be reversed by estradiol replacement [6,59] administered either peripherally or centrally [19,62]. Estradiol deficiency results in increased NPY concentrations in the paraventricular nucleus (PVN) of the hypothalamus [63] and elevated NPY mRNA expression in the arcuate nucleus (ARC) of the hypothalamus [64,65]. Bonavera et al. reported that estradiol treatment decreased hypothalamic NPY levels in the PVN of OVX rats [59,63].

NPY neurons in the hypothalamus not only affect feeding, but they also influence reproduction. Therefore, estradiol can modulate both of these neuroendrocrine systems by regulating NPY gene expression. NPY neurons are activated by signals indicating reduced energy availability, such as decreased levels of circulating glucose, leptin or insulin, which increase NPY release in the PVN to stimulate feeding [66]. This may be due to estradiol stimulating NPY [67], NPY Y1 receptor [68] expression and NPY release [59]. In an *ex vivo* hypothalamic neuronal cell line, N-38, estradiol affected the expression of NPY in a biphasic manner, which corresponded to changes in the ERα:ERβ ratio. When the ERα:ERβ ratio was high, NPY transcription was repressed; conversely, when the ratio was low, NPY transcription was stimulated. These results provided evidence that the ratio of ERs expression in the hypothalamus may differentially regulate NPY *in vivo* [61].

2.2. Ghrelin

Ghrelin acts on growth hormone secretagogue receptors (GHSRs) to increase food intake. While mainly synthesized by the stomach, ghrelin is also found in the hypothalamus, pituitary gland, hippocampus, brain cortex, adrenal gland, intestine, and pancreas [69–71]. Exogenous ghrelin is less potent in intact female rats than in male rats or OVX females [72]. Central, intra-third ventricular (i3vt), or peripheral ghrelin administration reliably increased feeding in intact male rats and OVX females [73–79]; however, the threshold for a significant increase in feeding using either administration route was significantly greater in intact females than in males or OVX females [72]. When OVX rats were treated with estradiol, moderate intra-peritoneal (i.p.) or i3vt doses of ghrelin no longer stimulated eating. Together, these data demonstrate that estradiol reduces the orexigenic potency of ghrelin. Lastly, estradiol reduced the eating-stimulatory effect of i3vt ghrelin in male rats, indicating that the estrogenic effect exists in both sexes, which is a point of potential therapeutic relevance [72]. Careful attention to sex differences and gonadal hormone status should be included in the development of any ghrelin-based clinical control for eating behaviors.

The eating-stimulatory effect of ghrelin varies across different phases of the ovarian cycle in intact rats [72]. Administration of i3vt ghrelin had no reliable overall effect when cycle day was not taken into account. However, when the cycle day was considered, i3vt ghrelin increased eating during diestrus 1 and diestrus 2, but not during proestrus or estrus. In addition, in estradiol-treated OVX rats, ghrelin increased food intake on the days that modeled diestrus in intact rats, but not on the days that modeled proestrus or estrus. This indicates that there are cyclic variations in eating in rats and mice, and spontaneous food intake is maximal during diestrus and minimal during estrus. Therefore, the analogous peri-ovulatory decreases in eating in women may be due to changes in estrogenic tone that affect ghrelin's eating-stimulatory action [72]. To assess the importance of ghrelin signaling in OVX'd-induced hyperphagia and obesity, *Ghsr*$^{-/-}$ mice lacking GHSR were OVX'd [72]. The OVX mice, which were similar to wild-type mice in body weight and food intake pre-surgery, showed no increase in food intake or body weight gain after surgery. This indicates that estradiol tonically inhibits endogenous ghrelin signaling in mice and that release from this inhibition is necessary for OVX mice to increase food intake and body weight. This mechanism may account for other sex differences in eating and weight regulation previously reported in *Ghsr*$^{-/-}$ mice. For example, female *Ghsr*$^{-/-}$ mice accumulated less body weight and adiposity when given a HF diet [80]. Also, the magnitude of the differences in adiposity observed between *Ghsr*$^{-/-}$ and wild-type mice were greater in females than in males [80]. Ghrelin signaling appears to be a necessary component of the estrogenic control of eating and weight regulation [72].

The site of the GHSR-mediated effects on eating remains unclear [78,81–83], so estradiol may influence ghrelin and its receptors either centrally or peripherally [72]. In male brains, GHSR have been implicated in ghrelin's eating-stimulatory effect in the ARC, PVN, ventral tegmental area, and dorsal vagal complex [76,83–88]. Since administration of exogenous ghrelin can reach all of these ER-containing sites, each area could mediate the observed sex differences [72]. In contrast, Currie et al. failed to observe any sex difference following direct ghrelin microinjections to the ARC or PVN [89]. However, since ovarian cycling was not monitored, it is possible that the female rats were acyclic, which may have caused an artificial increase in ghrelin-induced eating. It is also possible that estrogenic actions on nucleus tractus solitaries (NTS) neurons contribute to the observed effects. Exogenous estradiol was shown to act on ERα-expressing neurons in the NTS to inhibit eating [90], and ghrelin microinjection into the NTS stimulated eating in male rats [87].

2.3. Melanin-concentrating hormone (MCH)

Since its discovery in hypothalamic neurons [91,92], MCH has been recognized as an important regulator of energy homeostasis [93]. Central administration of MCH promotes feeding [94,95], while genetic ablation of the MCH gene produces a lean phenotype [96,97]. In addition, MCH is upregulated by fasting [94]. MCH neurons in the lateral hypothalamic area (LHA) receive inputs from NPY/AgRP and POMC neurons in the ARC [98–103]. Therefore, MCH neurons are in a position to integrate the feeding response because they have projections from the ARC and to brain structures like the nucleus accumbens [104].

Messina et al. investigated the effect of centrally injected MCH on feeding in estradiol- and vehicle-treated OVX rats and male rats. MCH increased the meal size in all three groups. Addition-

ally, intake increased more in rats in diestrus than rats in estrus, although MCH increased food intake in both groups. Overall, estradiol decreased the orexigenic effect of MCH, leading the authors to hypothesize that the decrease in food intake during estrus was mediated by a decrease in MCH signaling [7]. In a second study, Santollo et al. examined whether the behavioral effects of MCH were sexually dimorphic. They observed a greater increase in food intake, meal size, and water intake following MCH treatment in male rats than in estradiol-treated OVX rats [6]. Additionally, they observed that higher MCH doses were necessary to increase food intake in estradiol-treated OVX rats, suggesting that estradiol reduced MCH sensitivity in female rats [6]. Given that circulating levels of estradiol are lower in males than in females, this sex difference may contribute to the increased sensitivity to MCH in male rats.

There are several ways that estradiol could decrease MCH signaling. By acting on nuclear ERs in the lateral hypothalamus (LH) and zona incerta (ZI) [105], estradiol can alter gene transcription. ERs can modulate gene expression locally by decreasing MCH synthesis. In support of this hypothesis, physiological doses of estradiol decreased pre-pro MCH mRNA expression in the ZI of OVX rats [106] and the LH of obese male rats [107]. In addition, chronic estradiol treatment in male rats blocked increases in LH MCH mRNA expression induced by fasting [107]. In contrast, pharmacological doses of estradiol in male mice increased MCH mRNA within hypothalamic tissue punches [108]. These discrepancies emphasize the need for additional research in intact, cycling rats to determine the role of endogenous estradiol in regulating MCH mRNA expression. It is also possible that estradiol, acting at nuclear ERs in brain regions that express MCH-1 receptors [28,109], can decrease MCH signaling by decreasing the number or binding affinity of MCH-1 receptors. A recent study demonstrated that LH neurons containing MCH-1 receptors and ERs are not coexpressed, but are in close proximity to one another [110].

Several studies evaluated whether MCH affects meal size or number [6,7,111]. The size of the first meal increased following MCH treatment in male and estradiol- or vehicle-treated OVX rats. In male and vehicle-treated OVX rats, MCH increased the average meal size throughout the period of increased food intake. There was no change in meal size in the estradiol-treated OVX rats, and there were no differences in meal number in any group, indicating that MCH increases food intake by increasing meal size in both males and females [6].

3. Estrogen interacts with anorexigenic neuropeptides

Estrogen has been reported to have an inhibitory effect on body weight gain in animal models [4,19,62]. ERα null mice are obese, insulin resistant, and have decreased energy expenditure [22,112]. This model indicates that ERα is critical for the estrogenic control of feeding behaviors and body weight [112]. Estrogen decreases food intake through its direct effects and through its interactions with other compounds that reduce food intake. In this section we will review the literature on estrogen's interactions with anorexigenic hormones.

3.1. Insulin

Kennedy [113] hypothesized that fat stores produce a hormone that functions as a negative feedback control for adiposity, and one early suggestion was that hormone was insulin [114,115]. Plasma insulin levels directly correlate with body weight and adiposity [116–118]. Obese animals and humans have higher basal insulin levels and secrete more insulin in response to a meal than lean individuals [116,119]. Insulin increases during meals and other periods of positive energy balance and decreases during fasting and other periods of negative energy balance.

Insulin receptors are distributed in discrete brain areas, including the hypothalamus [120–122]. Hypothalamic insulin receptors are thought to mediate food intake and body weight regulation via mechanisms similar to leptin [102,123–126].

Hormones provide important regulatory signals to the brain. Manipulation of gonadal steroid levels can influence leptin and insulin sensitivities and body fat distribution [19]. This implies that the relative amounts of androgen and estradiol are key determinants of the brain's sensitivity to the catabolic actions of insulin. When there is proportionally less estrogen, this favors insulin sensitivity.

3.2. Leptin

First described in 1994 [127], leptin has proven to be a key metabolic hormone with actions throughout the body. Analogous to insulin, plasma leptin levels are directly correlated with adiposity. Circulating leptin is transported into the brain, where leptin receptors exist in many areas, including the ARC [128,129]. Leptin has many actions within the brain, including reducing food intake and increasing energy expenditure.

Male and female rats differentially respond to centrally administered leptin [62,130]. In females, estradiol alters the sensitivity to centrally administered leptin and changes the body fat distribution [19]. Peripheral or central administration of estradiol to OVX females restores their central leptin sensitivity and changes their body fat distribution to be more similar to intact females. Additionally, administering estradiol to males increases the sensitivity to central leptin and increases subcutaneous fat deposition [19]. These findings indicate that gonadal steroids mediate body fat distribution and interact with the integrated adiposity message conveyed to the brain by leptin, which results in differential sensitivities of this signal in males and females.

Leptin provides a powerful catabolic signal to the brain, resulting in inhibition of food intake [99,102,123,131–136]. Leptin levels are higher in females, even before puberty, compared with males, and these levels are independent of differences in body composition [137–139]. After puberty, estrogen and testosterone further modulate leptin synthesis and secretion via sex steroid receptor-dependent transcriptional mechanisms [140]. Leptin is secreted from adipose tissue in direct proportion to fat content, and it penetrates the blood–brain barrier to interact with leptin receptors in the hypothalamus and brainstem [99,123,131,134,141–143]. Although several splice variants of the leptin receptor are known, OB-Rb is the critical variant for regulating energy balance [144].

ERs are also expressed in the brain, including the hypothalamic regions that regulate food intake and body weight [21,27,28,30–32,105,145]. OB-Rb expression has been colocalized with ERα in the ARC [146], and estrogen has been reported to regulate the expression of OB-Rb mRNA [147], possibly via an estrogen-responsive element on the leptin receptor gene [148]. The extensive hypothalamic colocalization of these two receptors suggests there is a closely coupled interaction for regulating the behavioral and neuroendrocrine mechanisms. Studies indicate that when estrogen levels are low, central leptin sensitivity is reduced, as in OVX females [63] and intact males. Conversely, when estrogen levels are relatively high, as in intact females, and in both estradiol-treated OVX females and males, leptin sensitivity is high [62,149].

OB-Rb leptin receptors colocalize with several neuropeptides believed to be involved in controlling food intake and reproduction. Leptin has the ability to activate or inhibit hypothalamic neurons [150–152]. Thus, leptin is ideally situated to link metabolic status and brain function. Diano et al. reported colocalization of leptin and estrogen receptors [146]. Animals with higher estrogen levels

have higher plasma leptin and higher hypothalamic OB-Rb expression levels [19]. There is an inverse relationship between plasma leptin and hypothalamic OB-Rb mRNA, which is not correlated with estrogen status [19]. Additionally, hypothalamic OB-Rb mRNA expression was greater in OVX animals than in intact females, consistent with previous findings [153]. These results were in contrast with one study that observed no difference in hypothalamic OB-Rb mRNA expression between sham and OVX rats [63] and a second that reported decreased OB-Rb expression in OVX rats in comparison to sham-operated females [154]. Kimura et al. [154] detected no change in plasma leptin levels in OVX females, despite observing that the OVX rats weighed significantly more than the sham-operated females. In contrast, in other studies, a significant increase in plasma leptin was observed following the weight gain associated with OVX [19,63]. These varying results indicate that the assay time may be critical for understanding the physiological roles of estrogen and leptin in regulating body weight. Additionally, since only OB-Rb mRNA expression has been measured, it is unknown how estrogen may impact the OB-Rb protein and signaling.

The differences in leptin sensitivity caused by the presence or absence of estrogen must occur downstream of OB-Rb transcription and translation [19]. Additionally, females have greater c-Fos and pSTAT3 immunoreactivity in the ARC than males following i3vt leptin (unpublished data), which suggests that despite having fewer hypothalamic OB-Rbs, females have greater leptin signaling in this brain region. Therefore, there may be an estrogen threshold required to enhance the central sensitivity to leptin.

3.3. Serotonin

Estradiol decreases food intake by selectively influencing the neural controls of meal size, which may require the serotonergic system [155]. Estradiol heightens the anorexia induced by increased serotonergic neurotransmission [156] and decreases the hyperphagia induced by decreased serotonergic neurotransmission [157,158]. Estradiol was reported to increase the expression of the serotonin transporter (5-HTT) in the dorsal and median raphe nuclei [159]. Other labs reported that acute injection of estradiol increased 5-HTT mRNA levels in the dorsal raphe nuclei (DRV) of OVX rats [160,161]. The DRV has reciprocal connections with the hypothalamus and parabrachial nucleus [162,163] putting the DRV in a position to directly regulate part of the neural network controlling food intake [159]. The estradiol/serotonin interaction may also have a clinical relevance, since human 5-HTT promoter polymorphisms are associated with anorexia nervosa, an eating disorder that primarily affects women [164,165].

3.4. Cholecystokinin (CCK)

Cholecystokinin (CCK) is synthesized and released from cells of the upper intestine and acts on abdominal CCK-A receptors. It plays a variety of roles in the digestive process, including slowing gastric emptying and intestinal motility (see review [166]). CCK exerts its satiety action primarily by activating subdiaphragmatic vagal afferent neurons [1,167–169]. Administration of CCK antagonists increases food intake by increasing meal size [170]. Several experiments highlighted the interactions between estrogen and CCK. CCK-A antagonists decreased food intake to a greater extent when intact female or estradiol-treated OVX rats were in estrus, and this effect was lessened in diestrus rats [171–174].

Because CCK satiation depends on vagal afferents [175–177], up-regulation of CCK receptors in the terminals of vagal afferent fibers may account for the increased CCK sensitivity. To investigate this hypothesis, *in vitro* quantitative autoradiography was used to measure the effects of estradiol 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 [177], and in two interconnected areas, the area postrema (AP) and the VMN. Estradiol treatment in OVX animals did not alter the number or affinity of CCK receptors [178], suggesting that the up-regulation of CCK receptors does not mediate the increased sensitivity to CCK following estradiol treatment. Estrogen increased the potency of CCK by increasing the sensitivity of vagal CCK-A receptors, but did not increase CCK secretion or the number of CCK-A receptors [178–181].

CCK's effects on meal size have been characterized in male rats by examining the pattern of c-Fos expression after consumption [182–187] or injection of CCK [188–192]. Estradiol treatment in OVX rats increased the number of feeding- and CCK-induced c-Fos-positive cells within the NTS, PVN, and the central nucleus of the amygdala [183,193]. These data suggest that exogenous estradiol may decrease meal size by selectively increasing neuronal activity in multiple brain areas that control meal size. It is currently unknown whether a similar mechanism underlies the decrease in meal size or increase in CCK satiation, which occurs during estrus in cycling rats.

Although there is solid evidence that estradiol increases the potency by which CCK exerts its direct, inhibitory control over meal size, such an interaction does not completely account for the decrease in food intake during estrus in gonadally intact rats or following estradiol treatment in OVX rats. For example, blocking the release of CCK during a meal attenuated, but did not block, the phasic inhibitory decrease in meal size, observed during estrus in gonadally intact rats [174]. Additionally, endogenous CCK does not appear to play a role in the tonic inhibitory action of estradiol [172,174]. Thus, estradiol must modulate the potency of other stimuli that directly generate negative feedback during a meal.

4. Summary

This review focused on the literature describing estrogen's interactions with orexigenic and anorexigenic neuropeptides and how these interactions affect food intake and adiposity. In addition, estrogen's steroid structure imparts anti-inflammatory effects that may explain how intact females on HF diets decrease inflammation. Understanding the neurophysiology of estrogen may lead to possible interventions for post-menopausal women, who are at an increased risk for the metabolic syndrome.

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