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Metabolic Impact Of Sex Hormones On Obesity

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Abstract

Obesity and its associated health disorders and costs are increasing. Men and postmenopausal women have greater risk of developing complications of obesity than younger women. Within the brain, the hypothalamus is an important regulator of energy homeostasis. Two of its sub-areas, the ventrolateral portion of the ventral medial nucleus (VL VMN) and the arcuate (ARC) respond to hormones and other signals to control energy intake and expenditure. When large lesions are made in the hypothalamus which includes both the VL VMN and the ARC, animals eat more, have reduced energy expenditure, and become obese. The ARC and the VL VMN, in addition to other regions in the hypothalamus, have been demonstrated to contain estrogen receptors. There are two estrogen receptors, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). We and others have previously demonstrated that activation of ERα by estrogens reduces food intake and increases body weight. This review focuses on the relative contribution of activation of ERα by estrogens in the ARC and the VL VMN in the regulation of food intake and body weight. Additionally, estrogen receptors have been found in many peripheral tissues including adipose tissue. Estrogens are thought to have direct effects on adipose tissue and estrogens may provide anti-inflammatory properties both in the periphery and the in the central nervous system (CNS) which may protect women from diseases associated with inflammation. Understanding the mechanisms by which estrogens regulate body weight and inflammation will assist in determining potential therapeutic agents for menopausal women to decrease the propensity of diseases associated with obesity.

Keywords

body weight regulation; hypothalamus; inflammation; estrogens; estrogen receptor alpha (ERα); neuropeptides

Introduction

Obesity, resulting from an imbalance between energy intake and expenditure, is now recognized as a serious and global health problem (Steinbaum, 2004; Berthoud and Morrison, 2008). More than 300 million adults worldwide are obese, and in the United

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States, over 30% of the population are considered obese and 60% are overweight (Wang et al., 2008). Obese individuals are at an increased risk for developing type II diabetes, hypertension, coronary heart disease and stroke. In the United States obesity is associated with 300,000 premature deaths every year (Allison et al., 1999). The past decade has been attempting to identifying key hormones and other signals that influence body weight.

Males and females differ in terms of how and where they store body fat, the hormones they secrete in proportion to their fat, and the way their brains respond to signals that regulate food intake and body weight (Clegg et al., 2003; Clegg et al., 2006). The focus of this review is to discuss the potential role of estrogens as determinants mediating the sexual dimorphism in body weight regulation. In women, estrogens may be responsible for body weight homeostasis. Reductions in circulating estrogens, which occurs following ovariectomy (OVX) in experimental rodent models, results in increased body adiposity which can be ameliorated by exogenous estradiol-17β administration (Clegg et al., 2003; Clegg et al., 2006). In women, menopause is has been associated with increased in adiposity and shifts in body fat distribution, which can be altered by exogenous hormone replacement therapy (Samaras et al., 1999; Ryan et al., 2002).

Hypothalamic Control of Body Weight

In an effort to identify targets for therapeutic treatments to reduce food intake and body weight, obesity research has focused on central metabolic and hormonal pathways that control energy homeostasis (Obici, 2009). The hypothalamus is one area within the CNS that has received attention as a region in the brain that controls food intake, energy expenditure and body weight homeostasis. Since the 1930's, several thousand reports have been published investigating the potential role of various hypothalamic nuclei in the regulation of food intake and body weight (York and Bray, 1972; Bray et al., 1982; Bray, 1984). Early interest in the hypothalamus stemmed from findings that dramatic changes in food intake, body weight, and energy homeostasis could be produced by lesioning specific hypothalamic nuclei, such as the ventral medial hypothalamus (VMH) (Hetherington and Ranson, 1940; Rowland et al., 1975; Louis-Sylvestre et al., 1980) or the lateral hypothalamic area (LH) (Anand and Brobeck, 1951; Danguir and Nicolaidis, 1980; Milam et al., 1980). More recently, areas in the hypothalamus such as the ventral medial nucleus (VMN) and arcuate (ARC) nucleus (among others) have been identified as targets for hormonal and neuropeptide signals that can produce marked in energy homeostasis.

Estrogen Receptors and Body Weight Regulation

The classical nuclear estrogen receptor (ER) was cloned in 1985 (Green et al., 1986) and renamed estrogen receptor alpha (ERα) when a second nuclear estrogen receptor (estrogen receptor beta (ERβ)), was discovered 10 years later (Kuiper et al., 1996). Both ERs are also expressed in the brain (Simerly et al., 1990; Kuiper et al., 1996; Shughrue et al., 1997; Simonian and Herbison, 1997; Voisin et al., 1997; Osterlund et al., 1998; Mitra et al., 2003; Merchenthaler et al., 2004). Stimulation of ERs engages both genomic and non-genomic events that may mediate distinct functions of estrogens. Little is known about the critical intracellular signals that mediate the anorexigenic effects of estrogens. Genomic activation of ERs results from estrogens binding to estrogen response elements (EREs) in promoter regions of target genes (Pappas et al., 1995; Razandi et al., 1999). Additionally, estrogens can also initiate rapid signaling events within minutes via non-genomic mechanisms (Kelly and Levin, 2001). ERs in the plasma membrane are able to activate the MAP-kinase cascade and PI3K pathway, causing a rise in intracellular calcium (Balthazart et al., 2001; Sutter-Dub, 2002). ERs also activate protein kinase B (PKB/Akt) in neurons (Singh, 2001; Ivanova et al., 2002; Wilson et al., 2002). The PI3K/Akt cascade mediates a variety of estrogens'

central actions, including neuronal excitability, neuroprotection, reductions in inflammation, and neurite outgrowth (Vasudevan and Pfaff, 2008), and potentially body weight regulation. Estrogens' activation of ERs results in a range of biological effects which will be described in more detail below.

Male and female mice with a targeted deletion in the ERα gene (ERαKO) have increased adiposity (Heine et al,. 2000). The cause of the obesity is unclear; however, overeating does not appear to be essential (Shughrue et al., 1997; Shughrue et al., 1997; Heine et al., 2000; Ohlsson et al., 2000; Vidal et al., 2000; Geary et al., 2001), and the increased adiposity in ERαKO mice is attributed primarily to decreased energy expenditure (Heine et al., 2000; Ohlsson et al., 2000). While estradiol-17β replacement prevents OVX wildtype mice from developing hyperphagia and obesity, such protective effects are blocked in OVX ERαKO mice (Geary et al., 2001).

Additionally, both estrogen receptors (ERs) are expressed in peripheral tissues, such as adipose tissue, where they may influence adiposity and inflammation. Further supporting a role for ERα in the regulation of body weight, are the findings that increased visceral adiposity has been associated with the Xbal polymorphism of the human ERα gene, in which guanidine is substituted for adenine in exon one (Speer et al., 2001; Yamada et al., 2002; Okura et al., 2003). A study of over two thousand Japanese women reported that there was increased fat mass and waist-hip ratios (an index of visceral adiposity) in pre-menopausal women that had the polymorphism compared to the control cohort of women with the normal genotype (Yamada et al., 2002; Okura et al., 2003; Okura et al., 2003). The polymorphism did not affect adiposity in postmenopausal women or in men. Thus, polymorphisms of the human ERα gene may impair estrogen signaling and lead to increased visceral adiposity and its attendant health risks.

CNS ERs and Body Weight Regulation

Due to the findings that targeted deletion in the ERα gene (ERαKO) have increased adiposity (Heine et al., 2000), ERα may be important in the regulation of body weight. ERα is ubiquitously expressed in rodent brains, but the physiologically relevant sites of ERα in the regulation of food intake and energy expenditure have not been identified. ERα is expressed in the ventrolateral portion of the VMN, the ARC, the medial preoptic area (MPOA), and the paraventricular nuclei (PVN) (Simerly et al., 1990; Simonian and Herbison, 1997; Voisin et al., 1997; Osterlund et al., 1998; Wilkinson et al., 2002; Shima et al., 2003; Merchenthaler et al., 2004). ERβ is found in the same hypothalamic nuclei as ERα, but ERβ expression is significantly reduced relative to ERα.

In earlier attempts to determine the effects of estrogens on food intake and body weight in hypothalamic regions, intranuclear microinjections of estradiol benzoate were performed (Wade and Zucker 1970). However, due to the difficulty in precisely placing cannulae or producing lesions in small but complex hypothalamic regions, findings obtained from these studies are somewhat controversial. For example, earlier studies showed that estradiol-17β implanted in the PVN decreases food intake and body weight in OVX rats (Butera and Beikirch, 1989) in the absence of any signs of peripheral estrogenic stimulation. Additionally, the anorexigenic effects of subcutaneous estradiol-17β are blunted in rats with PVN lesions (Butera et al., 1992). However, the subsequent studies failed to reproduce these phenotypes in rats with PVN implants (Hrupka et al., 2002). Effects of estrogen in the MPOA are also controversial, with only one report showing an anorexigenic response of estradiol-17β (Dagnault and Richard, 1997), whereas several other groups showed that estradiol-17β implanted in this nucleus has no effect on feeding (Butera and Beikirch, 1989). The ARC and VMH are nearby structures in the ventral hypothalamus. Earlier

microinjection studies may not have been able to rigorously distinguish these two regions, and therefore failed to provide consistent results (Butera and Beikirch, 1989). However, we have reported that site-specific reductions of ERα in the VL VMN result in increased adiposity, no change in food intake, and suppression of energy expenditure, implicating VL VMN ERα in energy homeostasis (Musatov et al., 2007). Additionally, the hindbrain (caudal NTS) might be another site of estrogens' regulation of food intake due to the recent findings of Thammacharoen where they placed an estradiol-containing haemostatic cloth which decreased food intake in OVX rats (Thammacharoen et al., 2008).

Following OVX, the oft-observed consequence is that a rat becomes transiently hyperphagic and gains weight, mainly as fat (Wade, 1972; Drewett, 1973; Leshner and Collier, 1973; Blaustein and Wade, 1976; Wade and Gray, 1979; Wade et al., 1985; Kemnitz et al., 1989; Wallen et al., 2001). However, an important but often forgotten aspect of OVX is that there is not an obligatory increase of food intake. OVX rats that are pair-fed to estradiol-17β-treated rats, however, increase body weight, gaining as much as *ad libitum*-fed OVX rats (Mueller and Hsiao, 1980). Additionally, if a female rat is fattened prior to removal of the ovaries, she simply remains fat after the operation without the necessity of overeating; i.e., the OVX (and presumably lack of estrogens) dictated that the rat carry more fat, but did not dictate that the rat become hyperphagic (Bartness and Waldbillig, 1984).

Estrogens Interact with Leptin

First described in 1994 (Zhang et al., 1994), leptin has proven to be a key metabolic protein with actions throughout the body. Leptin provides a powerful catabolic signal to the brain, resulting in inhibition of food intake and increasing energy expenditure (Ahima et al., 1999; Elias et al., 1999; Elmquist et al., 1999; Schwartz et al., 2000; Woods et al., 2000; Morton et al., 2003; Seeley and Woods, 2003; Balthasar et al., 2004; Schwartz and Porte, 2005). Leptin is secreted from adipose tissue in direct proportion to fat content, and it crosses the blood-brain barrier to interact with leptin receptors in the hypothalamus and brainstem (Tartaglia et al., 1995; Ahima et al., 1996; Seeley et al., 1996; Ahima et al., 1999; Elias et al., 1999; Morton et al., 2003; Schwartz and Porte, 2005). Although there are several splice variants of the leptin receptor, the long form (termed leprb) is the critical variant for regulating energy balance (Chen et al., 1996). Leprb are localized in several brain areas including the VMN and the ARC, and leprb are colocalized with several neuropeptides believed to be involved in controlling food intake and reproduction (Van Dijk et al., 1996; Elmquist et al., 1997; Elmquist et al., 1998). Leptin has the ability to activate or inhibit hypothalamic neurons (Elmquist et al., 1998; Elmquist et al., 1998; Elmquist et al., 1998). Thus, leptin is ideally situated to link metabolic status and brain function. It has been reported that leprb expression in the ARC is co-localized with ERα (Diano et al., 1998), and estrogens have been reported to regulate the expression of leprb mRNA in the ARC (Bennett et al., 1999), possibly via an ERE on the leptin receptor gene (Lindell et al., 2001). The extensive hypothalamic co-localization of these two receptors suggests a closely coupled interaction between these peripheral signals in the regulation of energy homeostasis.

Leptin levels are higher in females, even before puberty, compared with males, and these levels are independent of differences in body composition (Shimizu et al., 1997; Demerath et al., 1999; Wu-Peng et al., 1999). After puberty, estrogens and testosterone further modulate leptin synthesis and secretion via sex steroid receptor-dependent transcriptional mechanisms (Machinal et al., 1999).

Estrogens may be modulators of leptin's catabolic action in the brain. Higher levels of estrogens have been associated with increased leptin sensitivity (Ainslie et al., 2001; Clegg et al., 2003; Clegg et al., 2006). Although circulating leptin levels do not change appreciably

during the estrous cycle, ARC leprb expression is highest during estrous and metestrous and is inversely correlated with neuropeptide Y (NPY) mRNA expression (Bennett et al., 1999). OVX lowers sensitivity to central leptin when compared to intact females, and this can be restored by estradiol-17β replacement (Clegg et al., 2006). Analogously, exogenous estradiol-17β administration to male rats will increase sensitivity to central leptin (Clegg et al., 2006). The differences in leptin sensitivity caused by the presence or absence of estrogens may occur downstream of leprb transcription and translation. Additionally, females have greater c-Fos (a marker of neuronal activaton) and pSTAT3 (a marker of leptin receptor activation) immunoreactivity in the ARC than males following intra-third ventricular leptin (unpublished data), which suggests that enhanced leptin sensitivity. Therefore, there may be a threshold for estrogens required to enhance the central sensitivity to leptin.

It should be noted that OVX greatly reduces, but does not eliminate the most physiologically active estrogen, estradiol-17β, since adrenal androgens and other steroids can be aromatized to estrogens in fat and other tissue. Additionally, there is a second form of estradiol, estradiol-17α, which can be synthesized in peripheral tissue (Finkelstein et al., 1981) and in some brain areas (MacLusky et al., 1994) from aromatization of epitestosterone by cytochrome P450 aromatase. Recent reports demonstrated that estradiol-17α has binding affinity for the ERα receptor and that levels increase in the hypothalamus of OVX females (Toran-Allerand, 2005; Toran-Allerand et al., 2005). Peripheral and central administration estradiol-17α decreases food intake and body weight of OVX rats (Donohoe et al., 1984; Butera et al., 1990). These findings suggest that estradiol-17α may modulate estrogen regulation of energy balance and, further, that even following OVX, estradiol-17α may activate ERα.

Leptin resistance may also occur in other states such as pregnancy (Ladyman and Grattan, 2005). These authors demonstrated that pregnant rats treated with leptin had impaired activation of pSTAT3 and reduced leprb mRNA in the VMH when compared to non-pregnant females. However, there were no changes in leptin activation of pSTAT3 in the ARC of pregnant females, nor were there changes in leprb in pregnant versus non-pregnant females. Pregnancy is a state of relative deficiency of estrogens, and these data may support the idea that low levels of estrogens is associated with reduced leptin sensitivity.

Estrogen interacts with the Melanocortin System

The ARC has been well-investigated with regard to central leptin action (Woods and Seeley, 2000; Williams et al., 2001). Leprb is expressed by two populations of ARC neurons, those expressing proopiomelanocortin (POMC) (Cheung et al., 1997; Thornton et al., 1997) and those expressing NPY and agouti-related peptide (NPY/AgRP neurons) (Baskin et al., 1999). NPY is an effective anabolic peptide. Central administration of NPY potently increases food intake and decreases energy expenditure and fat oxidation (Chavez et al., 1995; Levin, 1999; Cone et al., 2001; Herzog, 2003). ARC neurons co-express NPY mRNA and leprb protein. Leptin administration decreases, while lack of leptin or leptin signaling increases, NPY (and AgRP) mRNA, demonstrating that leptin is a critical determinant of ARC NPY functioning (Baskin et al., 1999). POMC neurons secrete the catabolic melanocortin neuropeptide, α melanocyte stimulating hormone (αMSH), which acts in the PVN and lateral hypothalamus on melanocortin 3 and melanocortin 4 (MC3/MC4) receptors to produce a profound catabolic effect by reducing food intake and increasing energy expenditure (Elmquist et al., 1998; Elias et al., 1999; Elmquist et al., 1999; Elias et al., 2000). If administered chronically, MC3/4 agonists reduce body weight and adiposity (Pierroz et al., 2002). Leptin stimulates POMC neurons to synthesize and release αMSH (Seeley et al., 1997; Korner et al., 1999). AgRP is an antagonist at MC3/MC4 receptors, and

its administration increases food intake. Hence, within the ARC, leptin elicits a powerful catabolic affect by activating αMSH and simultaneously inhibiting anabolic NPY/AgRP production and release. This produces reduced feeding and increased energy expenditure (Elmquist et al., 1999). Recently, NPY neurons in the ARC where not found to co-express ERα (Olofsson et al., 2009); whereas we and others have found that POMC neurons do co-express ERα (Simonian et al., 1999). Because the leprb gene contains an ERE (Lindell et al., 2001), this provides a critical potential mechanistic link between estrogens' activity and that of leptin on ARC POMC neurons.

A wealth of data support a role for NPY in the regulation of food intake and body weight, e.g., (Herzog, 2003). Consistent with a role of estrogens in the regulation of food intake and body weight, estrogen suppresses NPY release. OVX increases and estradiol-17β treatment decreases levels of NPY mRNA in the ARC (Baskin et al., 1995; Ainslie et al., 2001). Additionally, food deprivation increases ARC NPY mRNA levels less in estradiol-17β treated OVX rats than in vehicle-treated OVX rats (Baskin et al., 1995). Lastly, chronic estradiol-17β treatment decreases NPY levels and NPY release in the PVN (Bonavera et al., 1994).

POMC levels are also responsive to gonadal steroids. POMC mRNA levels fluctuate over the course of the estrous cycle, with the most dramatic changes on the day of proestrus (Wise et al., 1990; Bohler et al., 1991; Korner et al., 1999; Slamberova et al., 2004). POMC neurons express ERα, and OVX decreases POMC mRNA, which is reversed by estradiol-17β replacement (Pelletier et al., 2007). Lower POMC levels are also observed in ERα knockout mice (Hirosawa et al., 2008). Estrogens activate POMC neurons partly via PI3K-mediated mechanisms (Qiu et al., 2003; Malyala et al., 2008). Estradiol-17β administration rapidly increases activity at incoming excitatory synapses onto POMC neurons, enhancing miniature excitatory postsynaptic current recorded from POMC-GFP neurons (Gao et al., 2007). These synaptic rearrangements in POMC neurons tightly parallel the effects of estrogens on food intake, energy expenditure and body weight (Gao et al., 2007). Collectively, these findings suggest that ERα in POMC neurons may contribute to energy homeostasis and the effects of estrogens.

Estrogen Regulates Adiposity

The accumulation of fat centrally (intra-abdominal/visceral adipose tissue) has emerged as a risk factor for the metabolic syndrome (Kannel et al., 1991; Lee et al., 2009). Estrogens promote the accumulation of subcutaneous fat (Krotkiewski et al., 1983); however, visceral fat varies inversely with levels of estrogens (Bouchard et al., 1993). The loss of estrogens with menopause is associated with an increase in intra-abdominal fat accrual (Poehlman et al., 1995; Lee et al., 2009). OVX rats gain fat, specifically visceral fat with no change of subcutaneous fat (Clegg et al., 2006). Furthermore, peripheral or central administration of estradiol-17β to OVX rats changes their body fat distribution to mirror that of intact females. Altering the sex hormone milieu in males with estradiol-17β administration increases subcutaneous fat deposition (Clegg et al., 2006). An important implication from these findings is that estrogens may be critical determinates of body fat distribution.

Progesterone and androgen receptors (PR and AR) as well as ERs are expressed in adipose tissues (Crandall et al., 1998). Subcutaneous adipose tissue has higher concentrations of ERs and PR; however, visceral adipose tissue has higher concentrations of AR (Lu et al., 1998). Additionally, subcutaneous adipose tissue has few AR, and estrogens down-regulates AR expression in subcutaneous fat (Bjorntorp, 1997). Adipose tissue-specific AR knockout mice have increased intra-adipose estrogens, which leads to increased subcutaneous obesity and hyperleptinemia (Yu et al., 2008). The sexual dimorphism in adipose tissue distribution may

partially explain the greater risk for the metabolic syndrome in men compared with premenopausal women.

Estrogen Decreases Inflammation

Obesity is now recognized as a global health problem as previously mentioned, and it may be a result of increased consumption of high fat (HF) diets. Free fatty acids (FFAs), particularly saturated fatty acids, increase inflammation by activating toll-like receptor 4 (TLR4) (Shi et al., 2006). It is increasingly evident that chronic activation of pro-inflammatory pathways may be at least partly responsible for obesity-induced insulin resistance and diabetes (Kahn and Flier, 2000; Wellen and Hotamisligil, 2003; Wellen and Hotamisligil, 2005). For example, the pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNFα), interleukin-6 (IL-6) and C-reactive protein are elevated in individuals with insulin resistance and diabetes (Shoelson et al., 2007; de Luca and Olefsky, 2008; Wang et al., 2008), and elevated in muscle and liver with HF diets (Shi et al., 2006). Suppression of pro-inflammatory responses represents a promising strategy to combat obesity and associated disorders. ERs are expressed in monocytes and macrophages, and estrogens activate these cells (Vegeto et al., 2001; Pozzi et al., 2006). Female rats and mice are relatively protected from HF-induced obesity, insulin resistance and inflammatory responses (Dhar et al., 2004; Gallou-Kabani et al., 2007; Payette et al., 2009). Recent studies have shown that estradiol-17β may play a role in reducing the inflammatory response in adipose, cardiovascular, and neural systems (Turgeon et al., 2006; (hisletti et al., 2005).

In vitro studies have demonstrated estradiol-17β -activated ERα decreases the number of pro-inflammatory cytokines (Vegeto et al., 2001; Vegeto et al., 2003). The anti-inflammatory properties of estradiol-17β 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 (Stein and Yang, 1995; Ghisletti et al., 2005; Kalaitzidis and Gilmore, 2005). Estrogens' inhibitory effect on NFκB function is not fully understood and may be target selective (Harris et al., 2003; Chadwick et al., 2005; Kalaitzidis and Gilmore, 2005; Wise et al., 2009). The PI3K pathway is also implicated in the anti-inflammatory effects of estrogens. For example, estradiol-17β blocks LPS-induced NFκB nuclear translocation in macrophages, an effect that involves the activation of PI3K (Ghisletti et al., 2005). Similarly, estradiol-17β decreases vascular leukocyte accumulation after an ischemia-reperfusion injury (Simoncini et al., 2000). These effects are blocked by PI3K inhibitors (Simoncini et al., 2000).

Conclusion

When women enter menopause, they have a dramatically increased risk for developing obesity, type II diabetes and the metabolic syndrome. Hormone replacement therapy (HRT) could be seen as a way to reduce these risks and, in fact, recent data suggest that pharmacological estrogens can reverse the progression of metabolic diseases. However, due to ubiquitous expression of ERs, especially in peripheral tissues, and to complex intracellular events coupled to ERs (“genomic” and “non-genomic” actions), the metabolic benefits provided by HRT are often associated with increased risk of heart disease and breast cancer. Obviously, one solution to this dilemma would be to target only the ERs involved in energy balance and to develop estrogen-like drugs that only initiate intracellular events that produce metabolic benefits without unwanted side effects. Therefore, future research should focus on identifying the critical brain sites where ERs regulate body weight homeostasis and delineate the intracellular signaling pathways that are required for estrogens' actions. Additionally, understanding the functional role of ERs in the periphery

may reveal new pharmacological targets for the beneficial actions of therapeutic estrogens without the deleterious side effects.

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