

Ovarian hormones and obesity

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BACKGROUND: Obesity is caused by an imbalance between energy intake, i.e. eating and energy expenditure (EE). Severe obesity is more prevalent in women than men worldwide, and obesity pathophysiology and the resultant obesity-related disease risks differ in women and men. The underlying mechanisms are largely unknown. Pre-clinical and clinical research indicate that ovarian hormones may play a major role.

OBJECTIVE AND RATIONALE: We systematically reviewed the clinical and pre-clinical literature on the effects of ovarian hormones on the physiology of adipose tissue (AT) and the regulation of AT mass by energy intake and EE.

SEARCH METHODS: Articles in English indexed in PubMed through January 2016 were searched using keywords related to: (i) reproductive hormones, (ii) weight regulation and (iii) central nervous system. We sought to identify emerging research foci with clinical translational potential rather than to provide a comprehensive review.

OUTCOMES: We find that estrogens play a leading role in the causes and consequences of female obesity. With respect to adiposity, estrogens synergize with AT genes to increase gluteofemoral subcutaneous AT mass and decrease central AT mass in reproductive-age women, which leads to protective cardiometabolic effects. Loss of estrogens after menopause, independent of aging, increases total AT mass and decreases lean body mass, so that there is little net effect on body weight. Menopause also partially reverses women's protective AT distribution. These effects can be counteracted by estrogen treatment. With respect to eating, increasing estrogen levels progressively decrease eating during the follicular and peri-ovulatory phases of the menstrual cycle. Progesterone levels are associated with eating during the

[†]Retired.

luteal phase, but there does not appear to be a causal relationship. Progestins may increase binge eating and eating stimulated by negative emotional states during the luteal phase. Pre-clinical research indicates that one mechanism for the pre-ovulatory decrease in eating is a central action of estrogens to increase the satiating potency of the gastrointestinal hormone cholecystokinin. Another mechanism involves a decrease in the preference for sweet foods during the follicular phase. Genetic defects in brain α -melanocyte-stimulating hormone–melanocortin receptor (melanocortin 4 receptor, MC4R) signaling lead to a syndrome of overeating and obesity that is particularly pronounced in women and in female animals. The syndrome appears around puberty in mice with genetic deletions of MC4R, suggesting a role of ovarian hormones. Emerging functional brain-imaging data indicates that fluctuations in ovarian hormones affect eating by influencing striatal dopaminergic processing of flavor hedonics and lateral prefrontal cortex processing of cognitive inhibitory controls of eating. There is a dearth of research on the neuroendocrine control of eating after menopause. There is also comparatively little research on the effects of ovarian hormones on EE, although changes in ovarian hormone levels during the menstrual cycle do affect resting EE.

WIDER IMPLICATIONS: The markedly greater obesity burden in women makes understanding the diverse effects of ovarian hormones on eating, EE and body adiposity urgent research challenges. A variety of research modalities can be used to investigate these effects in women, and most of the mechanisms reviewed are accessible in animal models. Therefore, human and translational research on the roles of ovarian hormones in women's obesity and its causes should be intensified to gain further mechanistic insights that may ultimately be translated into novel anti-obesity therapies and thereby improve women's health.

Key words: obesity / ovarian hormones / women / adipose tissue / weight regulation / central nervous system / estrogens / progestins / eating / energy expenditure

Introduction

That obesity is pandemic is well known. (Obesity is typically defined as BMI [weight in kg/height in m²] ≥ 30 .) In contrast, the importance of gender as a variable in obesity is less well appreciated. In fact, worldwide, about twice as many women as men suffer from severe obesity (i.e. grades 2 and 3 obesity, BMI ≥ 35 and 40 kg/m^2 , respectively) (Fig. 1). Although social factors, especially gender inequality, certainly contribute to male–female differences in obesity prevalence (Kautzky-Willer *et al.*, 2016), the consistent worldwide disparity in prevalence of severe obesity strongly suggests that biological factors, i.e. physiological sex differences, also contribute. In support of this, pre-clinical and clinical studies have revealed women-specific factors in the two physiological determinants of obesity, the level of energy intake, which is to say eating, and the level of energy expenditure (EE). Furthermore, this work indicates that ovarian hormones, in particular estrogens, influence both eating and EE in women. Finally, data also implicate ovarian hormones in the metabolic function of adipose tissue (AT). In light of these considerations, the goal of this review is to provide a critical update on the roles of ovarian hormones on the principle components of obesity, i.e. eating and EE, and on AT physiology.

Methods

Articles in English indexed in PubMed through January 2016 were searched using the following keywords related to: (i) 'reproductive hormones': estrogen, estradiol, estrone, estriol, estrogen receptors 1 and 2 (ESR1 and ESR2 in humans, Esr1 and Esr2 in mice and rats; formerly known as ER α and ER β , respectively), progesterone, progesterone receptor, androgen and androgen receptors, (ii) 'weight regulation': food intake, AT, adiposity, adipocyte, hunger, flavor hedonics, satiation, satiety, EE, physical activity, resting energy expenditure (REE), diet-induced EE, insulin, leptin, inflammation, ghrelin, cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1) and peptide YY(3–36) and (iii) 'central nervous system (CNS)': neuropeptide Y (NPY), α -melanocyte-stimulating hormone (α -MSH), dopamine, serotonin, melanocortin 3 or 4 receptor (MC3R, MC4R), agouti-related

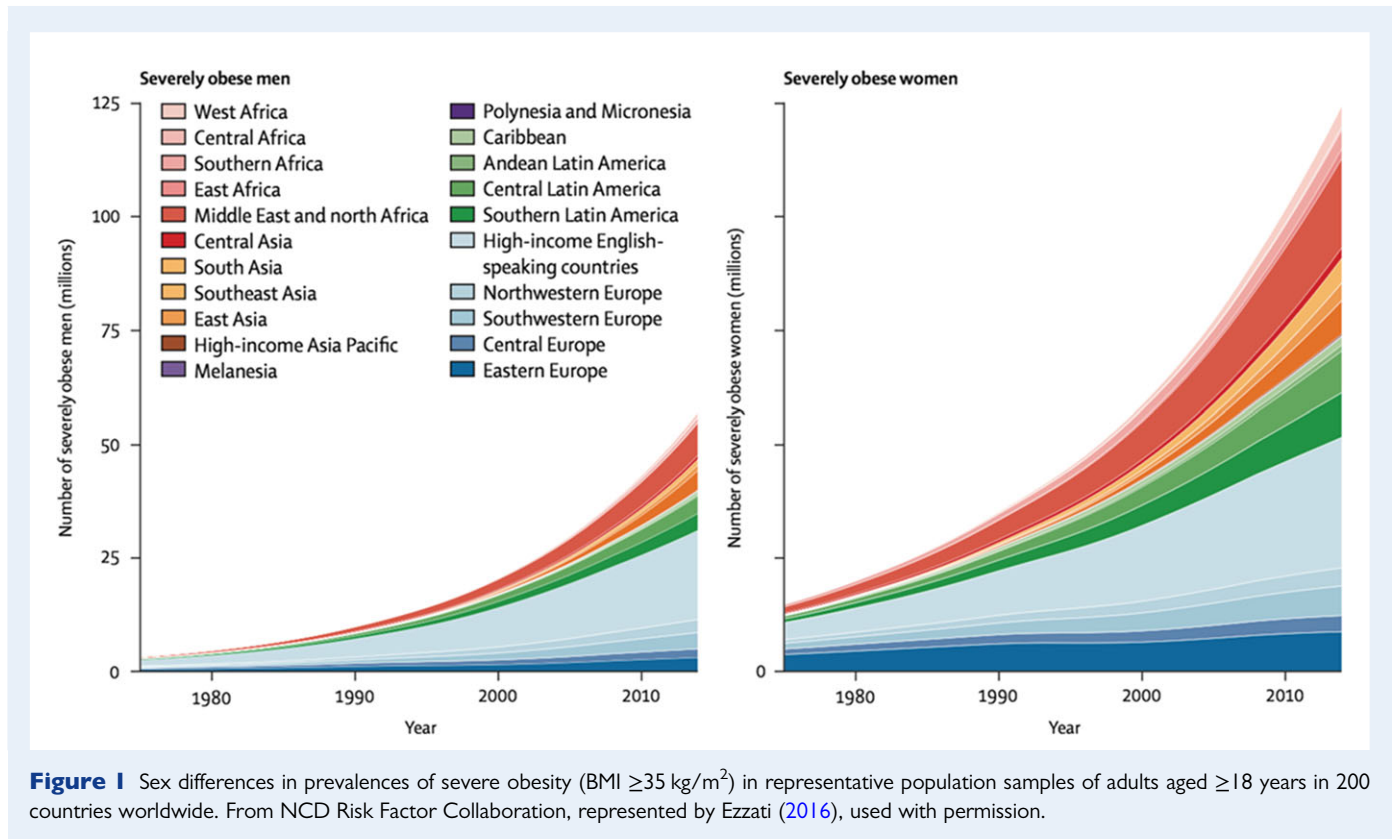
protein (AgRP), nucleus of the solitary tract (NTS), striatum, putamen, nucleus accumbens, caudate nucleus, frontal cortex and functional MRI (fMRI). Searches were of the form: body weight OR obesity AND (a 'reproductive hormone' set element) AND (a 'weight regulation' or 'CNS' set element), where capital letters indicate Boolean connectors. We sought to identify emerging research foci with clinical translational potential rather than to provide a comprehensive review.

Adipose tissue physiology

Measurement of body adiposity

Anthropomorphic adiposity measures, such as BMI, waist circumference (WC) and waist–hip ratio (WHR) are simple and inexpensive, but relatively imprecise measures of body adiposity. Errors are introduced by sex, age, ethnicity and individual differences in body composition, such as muscle mass. For example, in one study, BMI misclassified the adiposity of one-third of young adult female athletes (Ode *et al.*, 2007). Furthermore, BMI systematically over-estimates the adiposity of shorter people and under-estimates the adiposity of taller people. Although both BMI and WC are better predictors of total-visceral AT (defined below) than WHR (Pouliot *et al.*, 1994; Kamel *et al.*, 2000; Koren *et al.*, 2013), in women, WC and WHR predict cardiovascular disease better than BMI (Goh *et al.*, 2014). With respect to clinical practice, however, an expert panel (Klein *et al.*, 2007) concluded that additional anthropomorphic measures are unlikely to affect clinical management if BMI and standard cardiometabolic risk factors are considered (Kiernan and Winkleby, 2000).

Numerous other methods more accurately detect whole-body adiposity. Some, including air displacement plethysmography and hydrostatic weighing (Silver *et al.*, 2010; Moon *et al.*, 2011; Fields *et al.*, 2015), are limited in their ability to measure regional AT differences. Dual-energy X-ray absorptiometry (DEXA) can detect regional fat and bone-mineral density and with the aid of a special algorithm can distinguish intra-abdominal and subcutaneous fat (Kaul *et al.*, 2012), but DEXA does not measure AT volume or distinguish water and



other lean-tissue mass (Santen et al., 2010). MRI and computed tomography (CT) are the best available methods to measure AT volume and regional distribution *in vivo*. Whole-body imaging (i.e. axial images every few cm) is most accurate. Single-level, cross-sectional images are more common, but which abdominal level best estimates central subcutaneous and total-visceral AT is controversial (Kuk et al., 2006; Shen et al., 2012).

Histological or plasma assays may soon provide suitably accurate and clinically practical measures of specific AT depots. For example, L e et al. (2011) found that the degree of macrophage infiltration in subcutaneous AT biopsies predicted total-visceral AT volume, intrahepatic lipid content and several plasma markers of cardiometabolic-disease risk. Therefore, such methods may provide safe and cost effective ways to measure AT compartments relevant for health in the future.

General aspects of AT

Energy is stored for long periods as intracellular droplets of triacylglycerol within adipocytes, which are mostly organized in discrete AT depots (Rosen and Spiegelman, 2014). Preadipocytes are pluripotent cells that can differentiate into white or brown adipocytes, macrophages, or muscle and bone progenitors (Tchkonia et al., 2013). The differentiation of adipocytes from preadipocytes is controlled by insulin-like growth factor, glucocorticoids, and other growth factors and hormones (Cristancho and Lazar, 2011; Tang and Lane, 2012). Although the roles of gonadal hormones in this process remain obscure, the important role of estrogens is indicated by the effect of estrogenic endocrine disruptors, such as bisphenol, which disrupt normal pre-adipocyte differentiation *in vitro* and by their association

with obesity (Vom Saal et al., 2012; Boucher et al., 2014; Ohlstein et al., 2014).

The traditional view was that AT is a passive storage depot. AT energy storage is indeed long term; the half-life of individual triacylglycerol molecules in the subcutaneous AT of healthy humans is 1.6 years, which is orders of magnitude more than that of any other energy metabolite (Amer et al., 2011). Nevertheless, contemporary research clearly indicates, first, that AT is a dynamic organ that contributes to metabolic homeostasis in multiple ways, and, second, that in obesity, AT becomes dysfunctional and contributes to whole-body pathophysiology and health risk. These pathophysiological processes are mediated both by free fatty acids (FFA) and other metabolites released by AT and by signaling molecules secreted by adipocytes, called adipokines, which have local (paracrine) and endocrine signaling functions (Lee et al., 2013; Tchkonia et al., 2013). Additional signaling molecules are secreted by AT endothelial cells and AT-resident immune cells.

A rough categorization of human AT includes five major depots (Shen et al., 2003). (i) Subcutaneous AT can be found from the head to foot in obese individuals. Subcutaneous AT includes superficial and deep sections separated by a fascial plane (Scarpa's fascia) in the lower trunk and gluteofemoral areas. As described below, the different components of subcutaneous AT are separately regulated. (ii) Visceral or intraperitoneal AT includes the omental (attached to the stomach), mesenteric (attached to the small intestine) and epiploic (attached to the large intestine) depots. These depots contain numerous lymph nodes and are especially prone to infiltration by macrophages during hypertrophy (Gabrielsson et al., 2003; Lee et al., 2013; Tchkonia et al., 2013). In addition, mesenteric AT is exposed to absorbed lipids as they drain through the lymphatics. Finally, the vasculature of visceral

AT drains into the hepatic-portal vein, exposing the liver to increased levels of the FFA, adipokines and immune mediators that it releases. (iii) Retroperitoneal and pelvic AT are separate depots, but are often categorized together with visceral AT because they cannot be easily distinguished with imaging; we refer to this sum as 'total-visceral AT'. (iv) Intra- and extra-pericardial AT are found around the heart and great vessels. (v) Intramuscular AT lies between the muscle fascicles. Subcutaneous and visceral AT have received the most research attention and are the focus of this review. Visceral fat is associated with impaired health, while other AT compartments contribute to a lower degree or may even have a protective effect (Després and Lemieux, 2006).

Vague (1947) first noted that, compared with men, women tend to have relatively more gluteofemoral AT and relatively less centrally located AT, i.e. abdominal subcutaneous and total-visceral AT. More recent studies have confirmed this notion and indicate that these effects are evident across a wide range of BMI (Gallagher et al., 2005). Nevertheless, there is substantial individual variation in obesity habitus. Indeed, some obese women have a male-typical, central AT distribution (Karpe and Pinnick, 2015).

Female-typical adiposity

Puberty and young adulthood

The typical female pattern of regional AT distribution emerges during puberty (Shen et al., 2009; Taylor et al., 2010). In healthy weight females, the greater absolute AT mass becomes obvious only after puberty (healthy weight is BMI 18.5–24.9 kg/m²). As a result, a normative young adult woman in the USA (height 1.6 m, BMI 22.5 kg/m²) has ~18 kg body fat (~30% of body weight), of which only ~5% is total-visceral AT (Gallagher et al., 1996; Shen et al., 2009; Camhi et al., 2011), whereas a normative male (height 1.8 m) has ~12 kg body fat (~15% body weight), of which ~11% is total-visceral AT.

Female-typical AT results from differences among the AT depots in the balance of uptake and release of FFA (Santosa and Jensen, 2015). FFA uptake and triacylglyceride synthesis are greater in women's gluteofemoral than abdominal subcutaneous AT, and lipolysis rates are lower, thus selectively increasing the relative size of the gluteofemoral depot. These processes are controlled by complex interactions of genes and ovarian hormones that are only beginning to be understood, for example, through recent studies of differential AT gene expression (Gesta et al., 2006; Fried et al., 2015; Friedl et al., 2015; Karpe and Pinnick, 2015). One study (Karastergiou et al., 2013) found that of 284 genes that were differentially expressed in gluteofemoral compared with abdominal subcutaneous AT in overweight (mean BMI, 27 kg/m²) adults, 159 were differentially expressed only in women. Furthermore, many of the genes were homeobox-family (*HOX*) genes, which are involved in cell differentiation. Thus, a parsimonious hypothesis is that increased levels of estrogens or other reproductive hormones during puberty differentially activate *HOX* and other genes to determine regional AT distribution and physiology.

Mouse models provide further evidence that abdominal and gluteofemoral subcutaneous adipocytes differentiate in a sex-dependent, cell-autonomous fashion (Fried et al., 2015). For example, *Esr1* was necessary for establishing the identity of mouse white-adipocyte progenitor cells (Lapid et al., 2014), and female transgenic mice lacking

Esr1 selectively in adipocytes became obese due to expansion of gonadal AT, whereas additional knockout of *Esr2* had no effect (Davis et al., 2013). Although this result cannot be translated simply to humans because humans do not have gonadal AT depots, the similar gene-expression patterns of mouse gonadal AT and human omental AT (Gesta et al., 2006) encourages the view that estrogen-ESR1 signaling contributes similarly to the development of human visceral AT. Finally, when the testes-determining *Sry* gene was transplanted from the Y chromosome to an autosome in order to yield XX or XY mice with either male or female gonads, XX mice had twice as much AT as XY mice independent of gonadal status, indicating an important contribution of sex-linked genes to the sex difference in total body fat (Chen et al., 2012). Ongoing research is translating these kinds of data into human AT physiology (Karastergiou et al., 2013).

The search for genes mediating the high heritability of human obesity and regional AT distribution has not yet been successful. The failure of most studies to take into account the age of onset of obesity, in particular pubertal development, may contribute to this lack of success. A recent large ($n = 224\,459$) genome-wide association study identified 49 single-nucleotide DNA polymorphisms (SNP) related to WHR phenotypes, with 19 expressed more in women (Shungin et al., 2015). Overall, most SNP were in or near genes expressed by adipocytes or related to insulin resistance, suggesting that their analysis might lead to a better understanding of regional fat distribution and related pathophysiology. None was apparently related to *ESR1*, *ESR2*, androgen receptor or synthesis of estrogens or androgens, which might be expected to be especially important in the development of obesity during puberty. Interestingly, however, SNPs associated with fat distribution had little overlap with those found in a similar analysis to be associated with BMI, which were predominately expressed in the brain (Locke et al., 2015). This suggests that different biological processes underlie the accumulation and distribution of excess body fat (Lee and Mattson, 2014; Fu et al., 2015). Moreover, epigenetic regulatory mechanisms, which are not revealed in SNP analyses, are also involved in the development of obesity (Dalgaard et al., 2016).

Other methods have revealed some genes apparently involved in the estrogenic regulation of total adiposity. A study of SNP rs7757956 in intron 4 of *ESR1* indicated that an activational effect of estrogen signaling via ESR1 influences the development of obesity in pubertal girls (Tobias et al., 2007). Girls, but not boys, on average 12 years old, who were in Tanner stages 3–5 and bore a TT genotype at rs7757956 had 9% more body fat, as measured by DEXA, than TA- or AA-genotype girls. They also had 18% more height-adjusted body fat than TT-genotype girls in Tanner stages 1–2. As the TT genotype is common (75%), this may be an important contributor to female obesity. The influence of this SNP at later ages remains to be investigated.

Studies of hormonal contraception have failed to reveal significant effects on body weight. Gallo et al. (2014) screened 734 English-language reports of effects of combination oral hormonal contraceptives or combination skin patches on body weight in healthy reproductive-age women and found 49 that met their quality criteria (inclusion of at least three cycles, inclusion of effect means and variabilities, etc.). These failed to show any consistent effect of combination contraceptive use or its discontinuation on body weight, although the amount and quality of data were not judged to be of the highest quality. For example, only four studies included placebo-treated or no-intervention groups. A similar

review of the effects of progestin-only contraceptives on body weight identified only 15 studies, most of moderate to low quality (Lopez et al., 2013). Of these, 12 failed to detect weight changes, but in three studies there were weight gains of ~2 kg/y. Percent body AT was also increased in two studies in which body composition was measured. Thus, progestin-only contraception may slightly increase body weight and adiposity, but the available evidence does not establish this unambiguously.

Gonadotropin-releasing hormone (GnRH) agonists are often used to treat early or precocious puberty. Studies of the effect of GnRH-agonist treatment on weight gain are mixed, with some studies suggesting a small increase (Aguiar et al., 2006; Wolters et al., 2012), some showing a decrease (van der Sluis et al., 2002) and others indicating no effect (Glab et al., 2009; Ko et al., 2011). Interestingly, weight increase seems to occur only in girls who are healthy-weight when initiating treatment, but not in girls who are already overweight (Wolters et al., 2012). GnRH agonists are also used in the treatment of endometriosis, but this is rarely done for more than 6 months in adult women due to deleterious effects on bone metabolism. Unfortunately, to the best of our knowledge, none of the studies investigating the use of GnRH agonists in women with endometriosis have described effects on body weight.

Menopause and hormone therapy

Aging *per se* increases adiposity, which complicates the estimation of the effects of menopause. Age and menopause are best segregated with multiple regression or similar statistical analyses, and therefore we consider only such studies. Table 1 shows data from five such cross-sectional studies, four in which DEXA was used to estimate whole-body lean and fat masses (Ley et al., 1992; Svendsen et al., 1995; Panotopoulos et al., 1996; Trémollières et al., 1996) and one in which whole-body MRI was used (Phillips et al., 2008). Strikingly, these studies indicate that in both healthy-weight and mildly obese women, menopause increases body fat by ~5% of body weight and decreases fat-free body mass by a slightly smaller amount. These opposing changes explain why menopause has no marked effect on

body weight or BMI in most studies. The obvious clinical implication of these data is that women should be advised to lose several kilograms of body fat during the menopausal transition in order to maintain cardiometabolic health.

Menopause appears to preferentially increase total-visceral AT, although the magnitude of the effect is uncertain. In two studies (Kanaley et al., 2001; Franklin et al., 2009) in which several axial MRI scans were made between the head of the femur and the kidneys in white US American women, both abdominal subcutaneous and total-visceral AT increased after menopause, with a slightly greater relative increase in total-visceral AT. In another MRI study (Phillips et al., 2008), however, the relative increase in total-visceral AT was twice that of total AT. Several studies using DEXA confirmed a correlation between postmenopausal status and increased total-visceral AT (Svendsen et al., 1995; Trémollières et al., 1996; Gambacciani et al., 1999; Lovejoy et al., 2008). Even in non-obese women, significant increases in total-visceral fat (Abdulnour et al., 2012) and percent body lipid (Ho et al., 2010) occurred during the menopausal transition. Moreover, in BMI-matched (~25 kg/m²) pre- and postmenopausal women, percent visceral AT was significantly lower in the premenopausal group, whereas no association of age and total-visceral AT was detected (Kanaley et al., 2001).

We are not aware of imaging studies on the effects of surgical menopause by ovariectomy on AT. Although results have to be interpreted with caution due to methodological limitations, such as lack of control for the indications for surgery or for hysterectomy versus ovariectomy, the available data support an association between surgical menopause and increased weight gain (Sowers et al., 1996; Matthews et al., 2001; Tom et al., 2012), in line with the importance of ovarian hormones for obesity.

In younger postmenopausal women (age 50–59 y), estrogenic hormone therapy (HT) reduces fat mass, improves bone-mineral density, appears to preserve fat-free mass (FFM), reduces the risk of type-2 diabetes mellitus, retards atherosclerosis and reduces all-cause mortality (Santen et al., 2010; Manson et al., 2013; Manson and Kaunitz, 2016).

Table 1 Menopause-associated increases in adiposity, measured with DEXA or CT and dissociated from the effect of aging with multiple-regression analysis.

Study	Lean mass (kg)		Fat mass (kg)		% Fat	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
Panotopoulos et al. (1996)	43	41*	30	31*	~41	~44*
Ley et al. (1992)	38 ± 3	38 ± 3	19 ± 6	23 ± 5*	32	36*
Trémollières et al. (1996)	36 ± 3	36 ± 3 ^a 35 ± 3 ^{b*}	18 ± 5	18 ± 5 ^a 20 ± 5 ^{b*}	32	32 ^a 35 ^{b*}
Phillips et al. (2008)	41	37	22 ± 1	32 ± 2*	~35	~46
Svendsen et al. (1995)	Δ = -4.0*		Δ = 3.1*		Δ = 5.4 ± 1.6*	

Data are means ± SEM; lean mass does not include bone; ~ indicates estimated from data given. Subject characteristics (mean ± SD) were: Panotopoulos et al. (1996): French women, 26 premenopausal, aged 43 ± 4 y, BMI 31 ± 3 kg/m², and 73 postmenopausal, aged 54 ± 4 y, BMI 31 ± 4 kg/m²; data are sums of arms, trunk and legs, not whole body; variabilities of sums not given; Ley et al. (1992): British women, 61 premenopausal, aged 32 ± 6 y, BMI 22 ± 2 kg/m², and 70 postmenopausal, aged 53 ± 5 y, BMI 24 ± 2 kg/m²; (Trémollières et al., 1996): French women, 68 premenopausal, aged 49 ± 3 y, BMI 22 ± 2 kg/m²; (Phillips et al., 2008): US American women, 58 premenopausal, aged 39 ± 1 y, BMI 24 ± 1 kg/m², and 20 postmenopausal, aged 61 ± 2 y, BMI 28 ± 1 kg/m², not all variability or statistics reported; (Svendsen et al., 1995): Swedish women collated by age decade; overall n = 407, age range 18–80 y, mean BMI per decade, ~22–25 kg/m²; data are estimated menopause effect (Δ). *Significant menopause effect. DEXA, dual-energy X-ray absorptiometry; CT, computerized tomography.

^aIn total, 100 younger postmenopausal, aged 54 ± 3 y, BMI 22 ± 2 kg/m².

^bIn total, 37 older postmenopausal, aged 64 ± 4 y, BMI 23 ± 2 kg/m².

At least in the case of atherosclerosis, benefits occur only if estrogenic HT is begun within less than ~6 y of menopause (Hodis *et al.*, 2016). In addition, estradiol treatment, but not progestin or testosterone treatment, was shown to lower plasma very low-density lipoprotein-triglyceride concentrations by ~30% in healthy postmenopausal women by increasing their plasma clearance (Smith *et al.*, 2014).

Santen and colleagues reviewed 13 placebo-controlled DEXA or CT studies in which unopposed estrogen HT or estrogen plus progestin HT reduced body fat. HT with progestins alone increased adiposity (Clark *et al.*, 2005; Dal'Ava *et al.*, 2014), indicating that the effects of HT on adiposity loss are purely estrogenic. Santen *et al.* (2010) also reviewed eight studies in which estrogenic HT reduced the tendency of postmenopausal women to develop more central obesity, versus two in which this was not the case, consistent with the data reviewed above indicating that estrogens contribute to the determination of regional adiposity distribution.

That observation that estrogen levels are higher in non-obese than obese premenopausal women also supports a role of estrogens in restraining AT. Age-corrected early-follicular estradiol levels were 40 pg/ml in healthy-weight women versus 33 pg/ml in obese women, with no overlap in 95% confidence intervals (95% CI) (Freeman *et al.*, 2010). In contrast, after menopause estradiol levels were lower overall, although higher in obese than in non-obese women (21 vs 12 pg/ml, no overlap in 95% CI). After menopause, estradiol originates mainly in the AT and appears to have no endocrine function.

It is important to emphasize that as a result of the opposite effects of HT on adiposity and FFM, HT leads to little or no change in total body weight. According to a Cochrane meta-analysis (Norman *et al.*, 2000), unopposed estrogen treatment had no significant effect on total weight (nine randomized controlled trials [RCTs], mean difference vs no HT, 0.0 kg, 95% CI: -0.6 to 0.7 kg) or BMI (two RCTs, mean difference -0.1 kg, 95% CI: -0.4 to 0.1 kg); similarly, estrogen plus progestin treatment had no significant effect on weight (10 RCTs, mean difference, 0.0 kg, 95% CI: -0.4 to 0.5 kg) or BMI (10 RCTs, mean difference -0.1 kg, 95% CI: -0.3 to 0.1 kg). Thus, the fear of some women that estrogenic HT leads to weight gain (Légaré *et al.*, 2000) is unfounded. Rather, the likelihood of beneficial changes in body composition and metabolic health with estrogenic HT should be considered by women deciding on postmenopausal HT.

Obesity pathophysiology

Simple obesity

Obesity causes progressive cardiometabolic dysfunction (Lumeng *et al.*, 2007; Mauvais-Jarvis *et al.*, 2013; Tchkonja *et al.*, 2013). Expanded AT depots release more FFA, which increase insulin secretion, decrease insulin sensitivity and increase hepatic production of very low-density lipoproteins. In addition, hypertrophic adipocytes attract macrophages into the AT, which induces a sterile inflammation-like state characterized by secretion of numerous proinflammatory cytokines and adipokines. Finally, AT vasculature often fails to expand sufficiently in obesity, leading to local hypoxia that exacerbates the inflammatory state (Pasarica *et al.*, 2009; Sun *et al.*, 2013).

These processes are influenced importantly by ovarian hormones. For example, in rats, ovariectomy increases immune-cell infiltration into the AT and increases insulin resistance even if adiposity is controlled

(Rogers *et al.*, 2009; Vieira Potter *et al.*, 2012). Increases in circulating adipokines and immune factors in postmenopausal women suggest similar effects contribute to increased risk of cardiometabolic disease in these women (Pfeilschifter *et al.*, 2002; Polotsky and Polotsky, 2010). Conversely, in younger postmenopausal women, HT reduces or delays these pathological processes (Santen *et al.*, 2010; Manson *et al.*, 2013; Manson and Kaunitz, 2016). Thus, studies of the roles of estrogens are an emerging theme in obesity-related cardiometabolic disease (DeClercq *et al.*, 2008; Monteiro *et al.*, 2014; Blenck *et al.*, 2016).

An additional potential mechanism through which estrogens improve AT function is related to the 'browning' of white adipocytes (Palmer and Clegg, 2015), i.e. increased expression of uncoupling protein-1 (UCP-1), which generates heat without synthesizing ATP, thus increasing EE, and reduces cardiometabolic risk (Rosen and Spiegelman, 2014). Estrogens may induce browning in two ways. First, estrogens act in the heart to increase the secretion of cardiac natriuretic peptides (Jankowski *et al.*, 2001; Wang *et al.*, 2002), which in turn act in the AT to increase browning (Collins, 2014). Second, estrogens may increase hypothalamic expression of brain-derived neurotrophic factor, which increases sympathetic outflow to the AT and increases browning (Cao *et al.*, 2011; Palmer and Clegg, 2015).

Different AT depots are differentially predisposed to obesity-related pathophysiology (Lee *et al.*, 2013; Tchkonja *et al.*, 2013; Fried *et al.*, 2015; Karpe and Pinnick, 2015) (Fig. 2). Centrally located AT, especially visceral AT, brings the greatest health risk (Wang *et al.*, 2005; Després and Lemieux, 2006; Pischon *et al.*, 2008). A variety of data indicate that this is related to the direct delivery of FFA and proinflammatory immune mediators to the liver (Bergman *et al.*, 2006; Rytko *et al.*, 2011; Item and Konrad, 2012). Indeed, omental AT resection added further metabolic benefits to Roux-en-Y gastric bypass surgery (Dillard *et al.*, 2013). Mesenteric AT appears to be even more toxic, as in comparison to subcutaneous or omental AT, it is more densely innervated by sympathetic efferents, expresses more glucocorticoid receptors and is more prone to macrophage migration (Tchkonja *et al.*, 2013). Abdominal subcutaneous AT also has adverse metabolic characteristics (Tchkonja *et al.*, 2013), especially deep abdominal subcutaneous AT (Smith *et al.*, 2001; Koster *et al.*, 2010).

In contrast to all other AT depots, superficial gluteofemoral subcutaneous AT actually reduces cardiometabolic-disease risk (Snijder *et al.*, 2004; Yusuf *et al.*, 2005; Koster *et al.*, 2010; Lee *et al.*, 2013). Indeed, women with marked gluteofemoral obesity often remain metabolically healthy (Karpe and Pinnick, 2015). Many factors appear to contribute to the development of larger gluteofemoral subcutaneous AT depots in women and to this depot's protective nature (Santosa *et al.*, 2008; Lee *et al.*, 2013; Tchkonja *et al.*, 2013; Karpe and Pinnick, 2015). Gluteofemoral subcutaneous AT releases more of the insulin-sensitizing adipokine palmitoleate than abdominal subcutaneous AT (Pinnick *et al.*, 2012). Adipocytes in gluteofemoral subcutaneous AT also have greater lipoprotein-lipase (LPL) activity in women than men, indicating that they more effectively clear triacylglyceride after meals (Votruba and Jensen, 2007). Moreover, uptake of plasma FFA, lipogenesis and triacylglycerol re-esterification is greater in women's gluteofemoral subcutaneous AT than in their abdominal subcutaneous AT, whereas the opposite is true in men (Koutsari *et al.*, 2011; Søndergaard *et al.*, 2012). Together, these characteristics of women's gluteofemoral subcutaneous AT contribute to the greater size of this depot, the greater stability of stored triacylglycerol, and the lower plasma FFA levels.

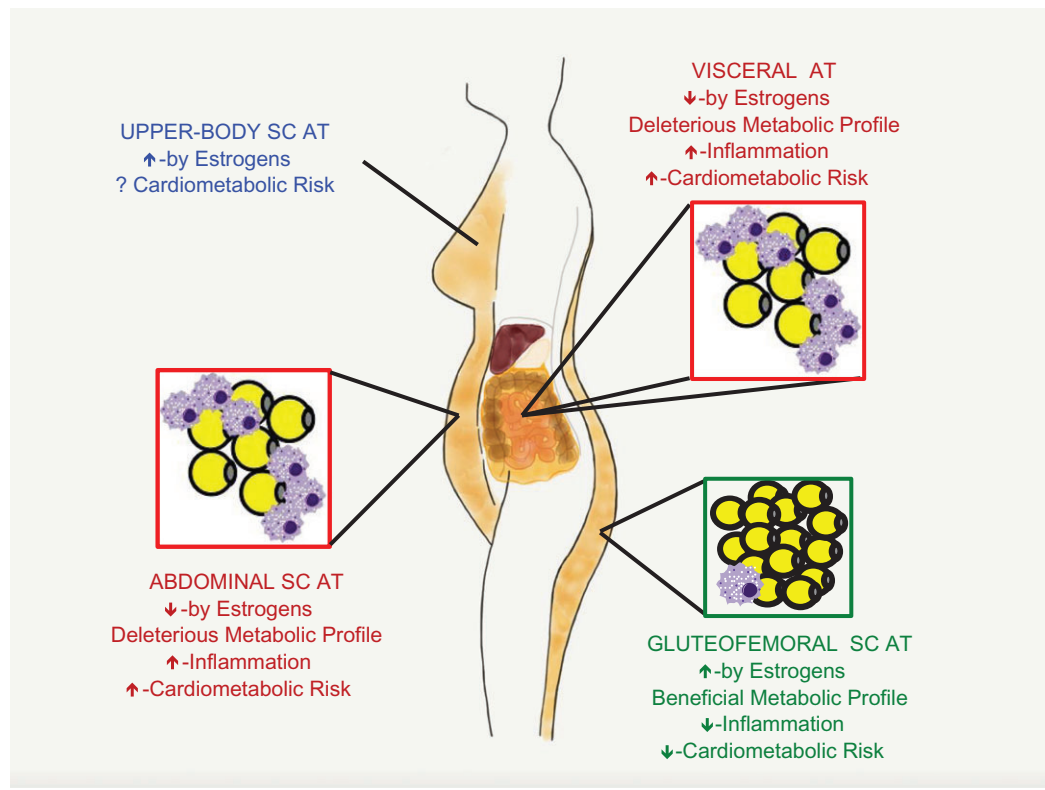


Figure 2 Female-typical adiposity and associated cardiometabolic risk. Following puberty, girls and women (F) tend to deposit excess triacylglycerol as gluteofemoral SC AT, whereas males (M) tend to deposit it as abdominal SC AT; males also have more visceral AT, i.e. AT whose vasculature enters the portal vein and liver. Gluteofemoral AT is cardiometabolically benign (green) because it traps triacylglycerol, so contributes little to plasma lipid levels, and because it is resistant to inflammation. In contrast, abdominal SC AT and visceral AT are cardiometabolically toxic (red) because they have higher relative rates of lipolysis, which increases plasma lipids, and because they are prone to inflammation, which leads to increased levels of circulating proinflammatory molecules. The relative amounts of upper-body SC AT are variable, and its cardiometabolic consequences are poorly understood (blue). For further explanation, see text. SC AT, subcutaneous adipose tissue.

Another factor relevant to sex differences in AT function is the greater proliferative potential of preadipocytes in subcutaneous versus visceral AT. For example, Tchoukalova et al. (2010) overfed healthy-weight men and women (mean BMI, 22.1 kg/m²) for 8 weeks, leading to a gain of 3.8 kg fat mass and an increase in mean BMI to 23.6 kg/m². Strikingly, women displayed greater AT hyperplasia, so that their average adipocyte size decreased with weight gain. This was most evident in femoral fat samples and was associated with relatively greater expansion of gluteofemoral than central AT. In addition, women with larger baseline abdominal subcutaneous adipocytes also displayed marked hyperplasia in that depot. This suggests that as AT expands in obesity, the larger number of gluteofemoral adipocytes in women permits them to store more triacylglycerol before reaching dysfunctional degrees of hypertrophy (Tchkonina et al., 2013). Unfortunately, the specific effects of ovarian hormones on AT cell biology have not yet been intensively researched. This is a major challenge facing women's health research.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, chronic anovulation and polycystic ovaries (Dumesic et al., 2015;

McCartney and Marshall, 2016). One of the primary pathological changes thought to lead to PCOS is increased ovarian androgen secretion. Indeed, increased androgen production occurs even in theca cells cultured from women with PCOS (Nelson et al., 1999). This pathology may be caused in some women by polymorphisms of *DENND1A*, which encodes a protein affecting the placement of cell-surface receptors (McAllister et al., 2014).

Although the prevalence of PCOS is similar in healthy-weight, overweight and obese women (Yildiz et al., 2008), about 40–50% of PCOS patients are obese (Carmina et al., 2009; Teede et al., 2010). Some studies suggest that PCOS is associated with greater abdominal obesity (Carmina et al., 2007), but this is controversial (Barber et al., 2008). Although obesity pathophysiology related to PCOS is poorly understood, several results support key roles of increased estrogen and androgen secretion. Androgens can lead to dyslipidemia indirectly by exacerbating insulin resistance, leading to altered lipid metabolism and body composition, and directly, through effects in the AT (Diamanti-Kandarakis, 2007). Whether AT dysfunction is primary or secondary to hyperandrogenism or other abnormalities in PCOS, however, remains unknown (Villa and Pratley, 2011). Women with

PCOS have lower LPL expression in subcutaneous AT than healthy women (Mannerås-Holm *et al.*, 2014). Both androgens and estrogens inhibit AT LPL activity (Pedersen *et al.*, 2004; Blouin *et al.*, 2010), and even after controlling for BMI, expression of LPL in the subcutaneous AT correlated negatively with plasma estradiol (Mannerås-Holm *et al.*, 2014). Excessive visceral-fat distribution (Diamanti-Kandarakis, 2007; Escobar-Morreale and San Millán, 2007) and disturbed adipokine release seem to influence PCOS development (Torres-Leal *et al.*, 2010; Villa and Pratley, 2011). For example, in women with PCOS, leptin expression was reduced in the subcutaneous AT, adiponectin expression was reduced in both subcutaneous and omental AT and adiponectin receptor-2 expression was reduced in subcutaneous AT (Carmina *et al.*, 2008; Mannerås-Holm *et al.*, 2014). These and other adipokines may modulate the hypothalamic-pituitary-gonadal axis through receptors in pituitary FSH, LH and TSH cells (Sone *et al.*, 2001; Taheri *et al.*, 2002; Psilopanagiotti *et al.*, 2009) so as to increase ovarian hormone secretion in patients with PCOS (Olszanecka-Glinianowicz *et al.*, 2011, 2013). In addition, some adipokines may directly influence ovarian steroidogenesis (Tersigni *et al.*, 2011). Consistent with a link between decreased adipokines and increased ovarian hormone secretion, plasma estradiol levels were found to be negatively correlated with adiponectin receptor-1 in the subcutaneous AT of women with PCOS independent of BMI; testosterone levels, however, were not significantly correlated with adiponectin receptor-1 (Mannerås-Holm *et al.*, 2014). Interestingly, although AT inflammation was not different in women with PCOS and BMI-matched control women (Lindholm *et al.*, 2011), adiponectin release in response to the proinflammatory cytokine tumor necrosis factor- α was decreased in adipocytes obtained from overweight or obese women with PCOS (Chazenbalk *et al.*, 2010).

Eating

General aspects of the control of eating

The intake of metabolic energy occurs mainly in the form of meals (including snacks). Meals and the surrounding affective and cognitive processes are the products of a widely distributed information-processing network in the brain, described below, that produces conscious and unconscious responses that underlie planning to obtain food, motivational urges to eat, eating *per se*, the pleasurable, or hedonic, aspects of eating, satiation and the effects of nutrient repletion on learning.

The primary internal stimuli controlling eating include the subjective value assigned to food and neural and endocrine feedbacks from the gastrointestinal (GI) tract, from AT, and from metabolic processes. 'Food value' in this context refers to reinforcement, i.e. the ability of food stimuli to support learning, to generate approach behavior and to elicit emotional responses, including flavor hedonics (Schultz, 2015). Beyond these, there are several secondary or modulatory internal factors, ranging from circadian rhythm to psychological factors and motivators such as stress, emotional state, cognitive control, etc. As reviewed below, reproductive hormones importantly modulate these physiological controls of eating (Asarian and Geary, 2013; Mauvais-Jarvis *et al.*, 2013; López and Tena-Sempere, 2015). External stimuli, in particular stimuli with learned cognitive and affective meanings, also play important modulatory roles in eating (French *et al.*, 2012;

Higgs *et al.*, 2012). There is a dearth of research on the influence of reproductive hormones on these controls of eating. This is unfortunate because, for example, estrogens and their lack after menopause can influence affective (Joffe *et al.*, 2011; Schmidt *et al.*, 2015) and cognitive (Hara *et al.*, 2015) functions in women.

Roles of ovarian hormones

The best-established effect of ovarian hormones on eating is the progressive decrease in eating during the follicular phase of the menstrual cycle. In healthy-weight cycling women, food intake decreases ~200–300 kcal/d from the luteal maximum to the peri-ovulatory minimum (Fig. 3), an amount relevant to body-weight regulation (Hall *et al.*, 2011; Asarian and Geary, 2013). Available data indicate that eating does not decrease during anovulatory cycles (Barr *et al.*, 1995; Rock *et al.*, 1996), and that the decrease in ovulatory cycles is due to decreased meal size rather than decreased meal frequency (Pohle-Krauza *et al.*, 2008; Brennan *et al.*, 2009) and is related to a decrease in the intake of sweet foods (Bowen and Grunberg, 1990; Fong and Kretsch, 1993). Old-world monkeys and apes (Parvorder *Catarrhini*), which have ovarian cycles similar to those of women (Zeleznik and Pohl, 2006), as well as mice, rats and many other species, display comparable cyclic decreases in meal size and food intake. Loss of

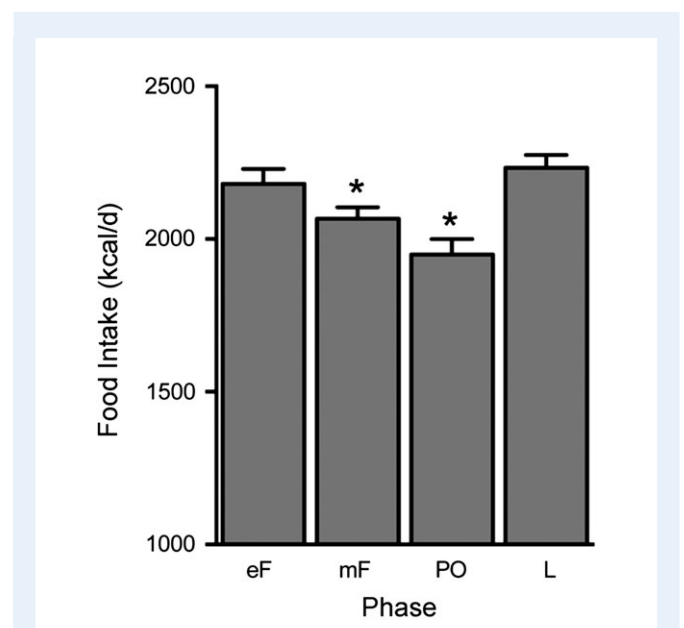


Figure 3 Daily food intake during the ovarian cycle in women. Note the progressive decrease in energy intake during the follicular phase, the nadir around ovulation and the high level during most of the luteal phase. Data are amounts eaten per day (kcal, means and standard errors of the mean) calculated from three studies in which food intake was measured by weighing and the cycle phase was monitored with urinary luteinizing hormone tests and reports of menses in a total of 34 women. In each study, data were averaged across the early-follicular (eF; 4 d), midfollicular (mF; ~9 d), peri-ovulatory (PO; 4 d) and luteal (L; ~11 d) phases. *Significantly different from luteal phase. Original data are from Fong and Kretsch (1993), Gong *et al.* (1989) and Lyons *et al.* (1989), and the figure is reprinted from Asarian and Geary (2013); used with permission.

estrogens after ovariectomy increases meal size, food intake and body weight in old-world monkeys, rats and mice (Bellino and Wise, 2003; Sullivan et al., 2005; Asarian and Geary, 2013), suggesting that increased eating contributes to the increase in AT after menopause in women, but whether this is true is unknown.

Experiments in rats and mice indicate that estrogens signaling via *Esr1* mediate the cyclic change in eating in those species. This cyclic effect appears to correspond to the decrease in eating during the human follicular and peri-ovulatory phases (Asarian and Geary, 2013). Rats and mice do not have luteal phases, however, and the control of eating in this phase of the menstrual cycle is less well understood. Although it is reasonable to hypothesize that progestins oppose the inhibitory effects of estrogens during the luteal phase, data fail to support this. Physiological doses of estradiol were shown to inhibit eating in ovariectomized rhesus macaques, and this was not affected by progesterone treatment (Czaja, 1978). Similarly, estrogen together with escalating progestin doses failed to affect eating in women (Eck et al., 1997), although the experiment was limited because the participants were cycling, so that the treatment effects may have been obscured by the effects of endogenous hormones, and because diet records, rather than measure of actual eating, were used. Yet in addition, depot medroxyprogesterone failed to affect food intake in an adequately powered, prospective, placebo-controlled study in cycling women (Pelkman et al., 2001).

Binge eating, referring to eating an abnormally large amount of food on a single occasion with a feeling of loss of control overeating, is a dysregulated form of eating especially prevalent in girls and women (Reichborn-Kjennerud et al., 2003; Hilbert et al., 2012). Binge eating is prodromal to bulimia nervosa, binge-eating disorder and obesity. It is also highly heritable (Davis, 2015). Female rats are much more prone than male rats to develop binge-like eating (Klump et al., 2013). Related to binge eating is emotional eating, i.e. eating in response to negative emotions, and this is also more prevalent in girls and women.

Binge eating develops most often during puberty, in association with higher estrogen levels (Klump et al., 2010). In addition, binge and emotional eating vary through the menstrual cycle, with lower rates in the late-luteal through the peri-ovulatory phases and higher rates during the mid-luteal phase (Culbert et al., 2016). A time-series analysis of binge tendencies and ovarian hormone levels through the cycle suggested that estrogens inhibit emotional and binge eating and progestins oppose this effect of estrogens, i.e. indirectly stimulate emotional and binge eating (Klump et al., 2014). This is the strongest indication that progestins are clinically important in dysregulated eating in human females. Estradiol, but not progesterone, was shown to reduce amounts eaten during binge-like episodes in rats (Yu et al., 2011), but whether this is a useful model of binge size or frequency in women is not known.

Peripheral mechanisms

Taste. Although the perception of sweet and creaminess differs in men and women (Bartoshuk et al., 1994; Hayes and Duffy, 2008) and women's intake of sweet food increases during the luteal phase (Bowen and Grunberg, 1990) and during pregnancy (Belzer et al., 2010), the roles of ovarian hormones in these phenomena have not been carefully investigated (Asarian and Geary, 2013).

GI signals. A variety of GI neural and endocrine signals are candidate meal-control mechanisms (Camilleri, 2015; Steinert et al., 2016). Unfortunately, research on their operation in women remains sparse (Asarian and Geary, 2013). Ghrelin, a hormone secreted by the stomach, stimulates meal initiation and increases meal size. In rats, there was an estradiol-dependent increase in ghrelin's eating-stimulatory effect during the first 2 days of the 4-day ovarian cycle (ovulation occurs on the last night), and ghrelin levels increased after ovariectomy in parallel to the increase in eating (Clegg et al., 2007). The small-intestinal hormone CCK reduces meal size by hastening meal termination, i.e. by producing satiation. CCK is the only endocrine meal-control signal that can be considered to have a proven normal or 'physiological' role in humans. That is, intravenous infusion of CCK in amounts that mimic prandial changes in plasma levels is sufficient to reduce meal size; CCK-receptor antagonists reduce the satiating potency of intraduodenal fat infusions and CCK-receptor antagonists administered alone increase meal size (Steinert et al., 2016). In rats, estrogens act via *Esr1* in the caudal medial NTS (cmNTS) to increase CCK's satiating action (see below). Unfortunately, whether estrogens affect CCK satiation in women is unknown. The intestinal hormones GLP-1 and peptide YY (3-36) are also candidate eating-inhibitory signals, and estradiol increases the GLP-1 satiating action in ovariectomized rats (Asarian and Geary, 2013).

Leptin. Endocrine signals related to AT mass, notably leptin and insulin, contribute to the control of eating (Levin et al., 2011; Le Foll et al., 2014). Leptin is secreted by white adipocytes, and basal (fasting) plasma leptin levels are highly correlated with AT mass. Interestingly, for a given level of fat mass, leptin levels are higher in women than men, and this difference decreases after menopause. Estrogen levels and differences in intra-abdominal and subcutaneous AT distribution contribute to these effects (Rosenbaum and Leibel, 1999; Rosenbaum et al., 2001). Originally hypothesized to be the crucial link between body adiposity and the controls of eating and EE, leptin is now considered to defend only against reductions in body weight, not against weight increases (Ravussin et al., 2014). Whether estrogens interact with leptin to control eating are controversial. In ovariectomized rats, estradiol increased the eating-inhibitory potency of acute leptin injections (Clegg et al., 2003), but not that of chronic leptin treatment (Chen and Heiman, 2001). Furthermore, food intake was not correlated to plasma leptin levels in cycling women (Paolisso et al., 1999). None of these studies, however, was done in the weight-reduced state, when leptin's contribution to eating is greatest.

The brain mechanisms mediating potential interactive effects of leptin and estrogens on eating are also uncertain. In mice and rats, *Esr1* is expressed in ~10% of neurons that express the signaling leptin receptor (*Leprb*) in the arcuate nucleus of the hypothalamus (ARC), the cmNTS and several other areas thought to mediate the control of eating (Asarian, unpublished data; Kim et al., 2016). *Esr1/Leprb* co-expression is much higher, ~80%, in the preoptic area (Kim et al., 2016), one of the brain sites containing the GnRH neurons that control FSH and LH secretion (Herbison, 2006). Kim et al. (2016) reported that although food intake was increased in transgenic mice lacking *Esr1* in *Leprb* neurons globally, estradiol treatment did not activate *Leprb* neurons in the ARC of ovariectomized mice, suggesting that estrogens and leptin do not affect ARC *Esr1/Leprb* neurons to inhibit eating. In contrast, Asarian (unpublished data) found that

knockdown of *Leprb* neurons in the mNTS with RNA interference increased eating and completely prevented estradiol from inhibiting food intake in ovariectomized rats, suggesting that an *Esr1/Leprb* interaction in the mNTS is necessary for the normal control of eating.

Insulin. Basal plasma levels of insulin also correlate with body fat mass, and insulin may act in the brain to control eating and EE. Estrogens appear to regulate the effects of insulin on eating. Central administration of insulin was found to inhibit eating more in ovariectomized than in intact rats, and this was reversed by central estradiol administration (Clegg *et al.*, 2006). These effects do not occur in peripubertal rats (Keen-Rhinehart *et al.*, 2009), further suggesting an activation role of estradiol. Interestingly, female, but not male, transgenic mice with brain-specific null mutations of the insulin receptor are hyperphagic, which in females was related to profound reductions of LH and signs of defective ovarian follicle maturation, indicating a role for neural insulin receptors in the normal function of the hypothalamic-pituitary-gonadal axis (Brüning *et al.*, 2000).

Intra-nasal insulin delivery has been used to selectively stimulate brain insulin receptors in humans. Similar to the rat studies, intra-nasal insulin before meals decreased eating more in men than in reproductive-age women (Benedict *et al.*, 2008). In apparent contrast to the findings of Clegg *et al.* (2006) in rats described above, premeal intra-nasal insulin failed to inhibit eating in postmenopausal women (Krug *et al.*, 2010). In contrast, intra-nasal insulin given after meals reduced subsequent intake of preferred snack foods in young women taking high-estrogen contraceptives, suggesting that insulin increases postprandial satiety in women (Hallschmid *et al.*, 2012). These data suggest that central insulin-based pharmacotherapy might be an effective obesity treatment in women.

Central mechanisms

A widely distributed central neural network controls eating (Berthoud, 2002; Shin *et al.*, 2009; Grill and Hayes, 2012; Castro and Berridge, 2014; Schultz, 2015; Val-Laillet *et al.*, 2015; Farr *et al.*, 2016; Geary and Moran, 2016). Local circuits in the caudal brainstem integrate a variety of sensory inputs, including gustatory, vagal afferent, spinal-visceral afferent and many GI-hormone signals, and also produce the consummatory behaviors of eating. Animal studies indicate that the hypothalamus plays the leading role in homeostatic eating, i.e. eating stimulated by nutrient depletion. Additional cerebral regions involved in eating include primary and secondary gustatory regions (insula and orbitofrontal cortex, OFC) as well as regions involved in memory (hippocampus) and cognitive control (dorsolateral prefrontal cortex, inferior frontal cortex and cingulate cortex). Neuropharmacological and molecular-genetic studies in animals and fMRI studies in humans indicate that the striatum (which consists of the nucleus accumbens, caudate nucleus and putamen), the OFC, the amygdala and the midbrain dopamine neurons perform neural computation of the subjective value of food stimuli ('value' was defined above). Estrogens and other gonadal steroids diffuse freely through the blood-brain barrier (Pardridge *et al.*, 1980), act on cognate receptors in several of these areas and through them affect eating-related neural information processing in these areas and in areas linked to them via neural projections (López and Tena-Sempere, 2015) (Fig. 4).

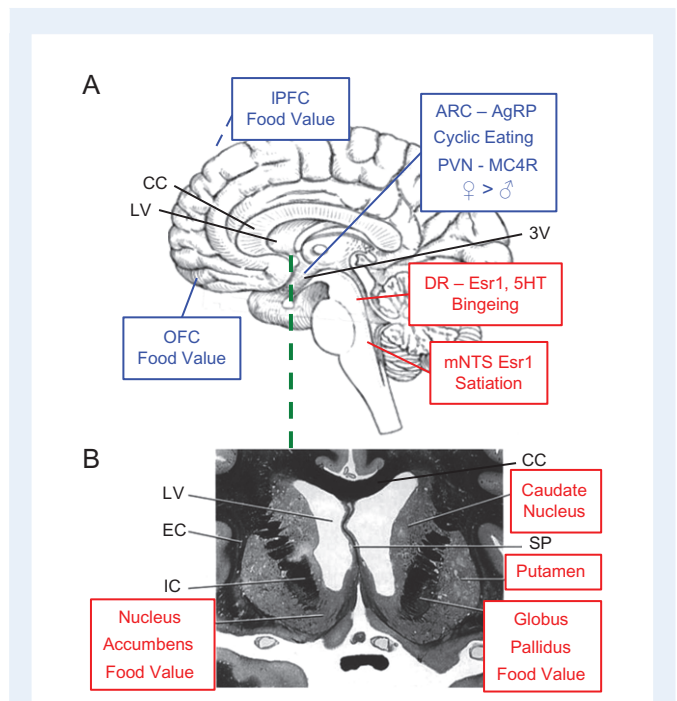


Figure 4 Some brain areas where estrogens affect the control of eating, based on animal (A) and human (B) research. Shown in red are brain areas where estrogens act directly via estrogen receptor 1 (*Esr1*) to affect eating; in blue are areas where estrogen may affect neural processing directly or indirectly through actions in other brain areas. (A) A schematic mid-sagittal section of the human brain highlighting areas in which estrogens affect eating. In the cmNTS, estrogen actions on *Esr1* reduce meal size, in part by increasing the satiating potency of CCK; in the dorsal raphe nucleus (DR), estrogens bind to *Esr1* to change serotonergic (5HT) neurotransmission so as to reduce binge-like eating. In the ARC (just lateral to the third ventricle, 3V) estrogens affect the activity of neurons expressing AgRP to reduce food intake during the early phase of the ovarian cycle. In the paraventricular nucleus of the hypothalamus (just lateral to the 3V), estrogens affect the activity of neurons expressing MC4R to reduce food intake in females (♀) more than in males (♂). Numerous fMRI studies implicate the OFC and IPFC (out of sight on the lateral surface of the cerebral hemisphere) in the neural computation of the value of food stimuli, which, as explained in the text, includes reinforcement, approach generation and affect. Ovarian hormones influence these processes. For example, visual food stimuli elicited larger responses in the IPFC in sated than in hungry women when tested during the late follicular phase, but not when tested during the early-follicular phase. (B) A schematic frontal section of the ventromedial area of the frontal lobes at the level shown by the green line in A. fMRI studies implicate the dorsal striatum (which consists of the head of the caudate and the putamen), the nucleus accumbens and the globus pallidus in the neural computation of food value. Again, ovarian hormones influence these processes; for example, pictures of high energy-foods elicited larger responses in women tested during the peri-ovulatory phase than during the luteal phase. See text for details. Abbreviations: LV, lateral ventricle; CC, corpus callosum; EC, extreme capsule; IC, internal capsule; SP, septum pellucidum; ARC, arcuate nucleus of the hypothalamus; CCK, cholecystokinin; IPFC, lateral prefrontal cortex; fMRI, functional MRI. Brain schematics are from <http://www.clker.com/clipart-90953.html>; the frontal lobe section was originally published in Haines (2012); used with permission.

Studies in rats indicate that estrogen-Esr1 signaling in neurons in the cmNTS in the caudal brainstem controls the estrogenic inhibition of normal eating (Asarian and Geary, 2013). That is, knockdown of cmNTS Esr1 with RNA interference increases eating and body weight and completely blocks the usual eating-inhibitory effect of estradiol in ovariectomized rats. No other brain site has been similarly linked to the estrogenic control of eating (e.g. ARC data were discussed in the leptin sections) (Asarian and Geary, 2013). The network effects of cmNTS estrogen stimulation, of course, may involve the hypothalamus and other forebrain sites. For example, expression of the neurotransmitter AgRP in ARC neurons changes across the ovarian cycle in mice, and transgenic lesions of AgRP neurons prevent the cyclic decrease in eating; these neurons do not express Esr1, however, indicating that these effects are functionally downstream of estrogens' neural actions (Olofsson et al., 2009).

AgRP neurons appear to be selectively involved in the aversive, homeostatic hunger produced by prolonged food deprivation, in contrast to the incentive-state like hunger that is more operative in spontaneous eating (Betley et al., 2015). AgRP neurons secrete the neurotransmitters NPY and glutamate as well as AgRP, and these molecules appear to make temporally distinct contributions to hunger (Krashes et al., 2013). Unfortunately, the roles of ovarian hormones in these effects have not yet been tested. It is important to note in this regard that specific aspects of eating are likely to involve Esr in different sites. For example, binge-like eating in mice apparently depends on estrogen-Esr1 signaling in serotonergic neurons in the dorsal raphe nuclei (Cao et al., 2014). This is especially interesting because women with bulimia nervosa have reduced serotonin-transporter binding in the dorsal raphe both during active bulimia nervosa and after recovery (Pichika et al., 2012).

Pro-opiomelanocortin neurons, which release the neurotransmitters α -MSH and β -endorphin, also may be involved in the estrogenic inhibition of eating. Brain α -MSH neurons signal mainly via MC3R in the ARC and via MC4R in the paraventricular nucleus of the hypothalamus (Biebermann et al., 2012), and loss-of-function polymorphisms of human MC4R lead to voracious appetite and obesity (Dempfle et al., 2004; Stutzmann et al., 2008; Valette et al., 2013). MC4R defects have a prevalence of ~2–5% in obese Europeans, making it one of the commonest of all genetic diseases (O'Rahilly and Farooqi, 2006; Tao, 2010). Importantly, weight gain is about twice as much in women as in men, ~8–9 kg/m² versus ~4–5 kg/m². Mice with null mutations of this gene (*Mc4r*^{-/-} mice) show a similar syndrome, again with a marked sex difference that begins around puberty, suggestive of activational effects of reproductive hormones (Huszar et al., 1997). In contrast, obesity was already present in pre-pubertal boys and girls with either of two MC4R polymorphisms (Vogel et al., 2011). Separate analyses of just one of these, SNP rs17782313, however, unveiled a pronounced sex difference. In women bearing this SNP, but not in men, there were increases in the eating traits disinhibition and emotional eating as well as differences in gray-matter volume in eating-related areas including the right amygdala, right hippocampus and medial OFC (Horstmann et al., 2013). The effects of estrogens on pro-opiomelanocortin (POMC) neurons may be mediated by both Esr1 (Xu et al., 2011) and the recently discovered Gq-coupled membrane estrogen-receptor (Smith et al., 2013). Whether estrogens act directly or indirectly on POMC neurons and the sites involved, however, are unknown.

Human functional neuroimaging studies converge with animal studies in identifying subcortical and cortical brain structures that are involved in the control of eating. Typically, these studies localize regions that respond differently to food and non-food stimuli, to hunger and satiety, and in obese and normal-weight women (Morris and Dolan, 2001; Wang et al., 2004; Small and Prescott, 2005; Stoeckel et al., 2008; Schur et al., 2009; Salem and Dhillo, 2015). Both animal and human receptor expression studies suggest that reproductive hormones may affect the function of these regions. For example, in humans, ESRI are abundant in the hypothalamus, amygdala, hippocampus, nucleus accumbens and several cortical regions (Hara et al., 2015). Importantly, this includes membrane estrogen receptors, which mediate rapid effects on neural activity, as well as classical nuclear estrogen receptors (Almey et al., 2015). Furthermore, estrogens are required to maintain dopamine innervation of the striatum, and estrogen and/or progesterone replacement can rescue ovariectomy-induced reductions in caudate dopamine (Kritzer et al., 2003). Progesterone receptors are also expressed in food-related regions beyond the hypothalamus, including the caudate (Zhu et al., 2003), amygdala, hippocampus and frontal cortex (Brinton et al., 2008). Although the exact role of hormones in many of these regions is not entirely clear, the widespread distribution of their receptors in areas mediating hedonics, motivation and cognition reinforces the notion of their involvement in non-reproductive neural functions, particularly in the control of normal and dysregulated eating.

There are sex-related structural differences in brain areas involved in processing food-related information (Ruigrok et al., 2014); for example, women compared with men express relative increases in regional gray-matter volume or density in frontal cortex, dorsal striatum and right insula, but relative reductions in ventral striatum, amygdala, hippocampus and left insula. Sex modulates the functional activation of these regions in a corresponding way. Obese women show different neural responses to pictures of high energy-food than lean women or obese men. For example, dorsal-striatal activity to high energy-food pictures is enhanced in obese women (Rothmund et al., 2007; Geliebter et al., 2013). Rodent research implicates the dorsal striatum in the development of inflexible, habitual control of eating (Furlong et al., 2014). Accordingly, eating habits may be particularly inflexible in obese women.

Changes in neural responses to food pictures through the menstrual cycle suggest a role of ovarian hormones in processing food-related information. Accordingly, the reduced food intake in the peri-ovulatory phase of the menstrual cycle is reflected in changes in the responses of eating-related regions. Specifically, the ventral striatum shows enhanced activity to high versus low energy-food pictures during the peri-ovulatory compared with the luteal phase (Frank et al., 2010), in line with the notion of enhanced dopaminergic reward activity during the peri-ovulatory phase (Dreher et al., 2007; Frank et al., 2010). In a separate group of subjects, these neural effects were mirrored by reduced appeal of high energy-food pictures during the peri-ovulatory phase compared with the luteal phase, with unchanged appeal of low energy-food pictures. Thus, the meal size-limiting effects of estrogens during the peri-ovulatory phase are mediated by increased ventral striatal responses to high-calorie food, reflecting increased reward sensitivity induced by higher levels of estrogens. Indeed, separate research showed a positive correlation between estradiol levels and amphetamine-induced euphoria in women during

the follicular, but not the luteal, phase, suggesting that estrogens make women more sensitive to (striatal) dopamine (Justice and de Wit, 1999). These findings converge with reports of reduced reward sensitivity and dopamine release in obesity and therefore conceptualize increased food intake as an attempt to compensate for reduced reward value of food (for review, see Val-Laillet *et al.*, 2015).

Moreover, neural responses to food pictures reflect interactions between prandial state and menstrual-cycle phase. Specifically, responses to food pictures in the lateral prefrontal cortex (IPFC) are enhanced in the fed compared with the hungry state during the late-follicular (high-estrogen), but not the early-follicular (low-estrogen), phase (Alonso-Alonso *et al.*, 2011). Thus, estrogens may act in the prefrontal cortex to facilitate cognitive control over appetite in the fed state, i.e. reduce the tendency to 'eat in the absence of hunger,' a trait associated with increased obesity risk (French *et al.*, 2012). In line with this notion, the IPFC is less activated after meals in obese women than in healthy-weight or formerly obese women (Le *et al.*, 2007). Furthermore, stronger lateral prefrontal responses to food pictures predict reduced subsequent energy intake (Cornier *et al.*, 2010), and these responses are smaller in obese compared with healthy-weight individuals (Batterink *et al.*, 2010).

Although converging evidence from human neuroimaging studies identifies regions involved in mediating the influence of ovarian hormones on processing food-related stimuli, there is a dearth of studies that directly investigate the effects of sex and ovarian hormones on precisely defined components of neural processing related to eating. Addressing this gap would involve using real food rather than pictures and using paradigms established in the fields of reinforcement learning, affective neuroscience and decision neuroscience. For example, it would be interesting to directly test the effects of estrogens on the neural mechanisms underlying Pavlovian and goal-directed aspects of eating. One hypothesis would be that estrogens act in the striatum to make eating behavior flexible and goal-directed.

Energy expenditure

General aspects of human EE

EE is energy lost in work or heat (urinary nitrogen and glucose losses can also contribute in pathological situations). Total EE includes REE, the postprandial increase in EE due to digestive and metabolic handling of ingesta (known as diet-induced thermogenesis (DIT) or the thermic effect of food), thermoregulatory responses, weight-regulatory EE responses and physical-activity EE. REE is also known as the resting or basal metabolic rate and is sometimes subdivided into sleeping and awake, resting components. In moderately active individuals in a thermoneutral environment, REE usually accounts for ~60–70% of total EE (Levine, 2004), DIT for ~10–15% (D'Alessio *et al.*, 1988; Reed and Hill, 1996) and physical activity for the rest. Physical-activity EE can be further subdivided into exercise or sports activities (including walking for exercise) and non-exercise-activity thermogenesis, which is the energetic cost of occupational physical activity and incidental daily activities, such as sitting, talking, standing, fidgeting, etc.

REE is strongly correlated with FMM ($r^2 \sim 0.6\text{--}0.7$), with no sex difference (Johnstone *et al.*, 2005; Blundell *et al.*, 2010). Individuals with lower REE/FFM values are at increased risk for weight gain (Ravussin *et al.*, 1988), suggesting that genetic differences in the cellular components of

REE may contribute to individual differences in obesity risk (Konarzewski and Książek, 2013). About half of REE is due to membrane processes, mainly Na^+/K^+ -ATPase and UCP-mediated mitochondrial-proton leak (Hulbert and Else, 2005). A decline in UCP activity may explain the decrease in REE with aging (St-Onge and Gallagher, 2010; Saito, 2013) which, as reviewed below, complicates studies of menopausal effects on REE.

The much lower requirement for physical-activity EE in developed societies is thought to contribute to the obesity epidemic and to disease risk (Woolf *et al.*, 2008). Physical activity not only directly increases EE, but also increases REE (Gilliat-Wimberly *et al.*, 2001; Van Pelt *et al.*, 2001). Physical-activity EE can be expressed as metabolic-energy equivalents (MET), the ratio of the rate of EE during the activity and a standard rate, which was originally based on EE while sitting quietly (ASHRAE standard 55, 2016). Only a few physical laborers or athletes regularly exceed a daily average level of 2 MET (Levine, 2004). The recommended minimal level of physical activity for good health in the USA is 500 MET-min/wk (ODPHP, 2016). As moderate-intensity activity, such as walking at ~5 km/h, expends ~3.3 MET and vigorous-intensity activity, such as jogging at ~8 km/h, expends ~6 MET, this recommendation can be met by walking for ~150 min/wk or jogging for ~75 min/wk. Epidemiological data indicate that any level of physical activity reduces adult all-cause mortality risk and that exceeding the MET recommendation 2-fold or more reduces it by ~30–40% (Arem *et al.*, 2015b). Only 40% of US Americans, however, meet this recommendation.

Increased physical-activity EE improves cardiovascular fitness and reduces all-cause mortality independent of BMI (Barry *et al.*, 2014). Furthermore, higher levels of physical-activity EE predict success in maintaining diet-induced weight loss (Phelan *et al.*, 2006). Thus, women should be encouraged to increase physical-activity EE, especially after menopause and in societies in which they tend to be less active (Ford *et al.*, 1991; Livingstone *et al.*, 2001; Sadarangani *et al.*, 2014). The physiological mechanisms mediating these mortality effects are not known. Unfortunately, the substantial error in available methods for measuring habitual physical-activity EE (Arem *et al.*, 2015a; Lim *et al.*, 2015) impedes research progress in this area.

Finally, alterations in total EE contribute to body-weight regulation (Leibel *et al.*, 1995; Hall *et al.*, 2011; Dhurandhar *et al.*, 2015). If body weight decreases, total EE decreases markedly more than predicted by the lower body mass, thus strongly resisting further weight loss. This adaptive reduction in EE is one reason that weight loss is so difficult. For example, a reduction in habitual intake by 200 kcal/d will lead to 19 kg weight loss in 3 y, versus a predicted weight loss of 78 kg if there were no adaptation in EE (Hall *et al.*, 2011). The underlying mechanisms are not fully understood. Changes in the amount or efficiency of physical-activity EE (Leibel *et al.*, 1995; Levine *et al.*, 1999; Levine, 2004) and in UCP-1 expression in brown AT (Fromme and Klingenspor, 2011; Morrison *et al.*, 2014) appear to contribute.

Roles of ovarian hormones

Resting energy expenditure

REE per kg body mass is lower in women due to their higher percent AT, but REE per kg FFM does not appear to differ between the sexes (Buchholz *et al.*, 2001; Johnstone *et al.*, 2005). This deserves more

research, however, with more accurate measurement methods; in the studies cited, residual variability was ~25% of REE, i.e. ~300–400 kcal/d (Wang et al., 2011). Interestingly, women's AT is more metabolically active and ~10 fold more variable than men's (Buchholz et al., 2001). This is due in part to a 5-fold higher expression of UCP-1 in women's brown adipocytes (Nookaew et al., 2013).

REE varies over the menstrual cycle, from a minimum in the early-follicular phase to a maximum ~50–100 kcal/d more in the luteal phase (Day et al., 2005). Administration of a GnRH antagonist during the mid-luteal phase reduced REE to the early-follicular level, indicating a role of ovarian hormones (Day et al., 2005). Progestins seem not to be involved because high-progestin contraceptives have little effect on REE (Pelkman et al., 2001). Estrogens may be the cause because transdermal estrogen treatment increases REE in premenopausal women in whom endogenous ovarian hormones are suppressed by GnRH antagonism for either 6 days or 5 months (Day et al., 2005; Melanson et al., 2015; Van Pelt et al., 2015).

The effect of menopause on REE has not received much investigation. In one 4-year longitudinal study beginning with regularly cycling women at least 43 years of age, sleeping REE decreased by 7.9% in the women who became postmenopausal during the study compared with 5.3% in those who remained premenopausal, but the difference was not statistically significant (Lovejoy et al., 2008). In a 2-week study of postmenopausal women, estrogen treatment did not affect REE (Bessesen et al., 2015). Three-month treatment with a selective estrogen-receptor agonist also failed to increase REE in ovariectomized old-world monkeys (Sullivan et al., 2012). In contrast, estrogens clearly increase REE in laboratory rodents (Rogers et al., 2009), and REE is decreased in *Esr1* knockout mice of both sexes, although not in *Esr2* knockouts (reviewed in Mauvais-Jarvis, 2011; Van Pelt et al., 2015).

Dietary-induced thermogenesis

Studies of reproductive hormonal effects on DIT are contradictory. DIT has been found to increase, decrease or not to change in the luteal phase of the menstrual cycle compared with the follicular phase (Piers et al., 1995; Melanson et al., 1996; Tai et al., 1997; Li et al., 1999). Estrogen treatment did not affect DIT in premenopausal women in whom endogenous ovarian hormones were suppressed by GnRH antagonism (Melanson et al., 1996). We know of no studies of DIT across menopause.

Physical-activity EE

Estrogens increase physical activity in rats, mice and monkeys, but whether this is so in humans is unknown (Asarian and Geary, 2013). One study found that healthy-weight and overweight women walked ~1600 more steps/day (~100–200 kcal/d) during the early-follicular phase compared with the mid-luteal phase (Day et al., 2005). It is interesting to note that physical-activity EE decreased during the luteal phase, whereas REE increased. Estrogen treatment, however, did not affect physical-activity EE in premenopausal women in whom endogenous ovarian hormones were acutely suppressed by GnRH antagonists (Melanson et al., 1996). Around the age of menopause, physical-activity EE tends to decrease substantially, but similarly in women who become postmenopausal and those who do not (30% and 39%, respectively)

(Lovejoy et al., 2008). Even if menopause is not the cause, the magnitude of the average decrease in physical-activity EE in aging women is clearly clinically relevant (Woolf et al., 2008).

Surprisingly, most studies indicate that acute physical activity results in negative energy balance, i.e. energy intake either does not change or is reduced following increased physical activity (King et al., 2011; Deighton et al., 2013; Howe et al., 2014; Blundell et al., 2015). This was recently confirmed in a study in which participants expended ~1.3 MET for two consecutive days with no change in food intake (Douglas et al., 2015). Obviously, at some point regular moderate or high intensity physical activity EE must lead to increase energy intake to avoid weight loss, but how this occurs is also unknown (Stensel, 2010).

Central mechanisms

REE. Genetic and physiological studies in mice and rats indicate that estrogens acting via *Esr1* in the ventromedial nucleus of the hypothalamus increase EE by increasing hypothalamic sympathetic outflow, resulting in increased brown-AT UCP-1 activity (Musatov et al., 2007; Xu et al., 2011; Martínez de Morentin et al., 2014). Because the animals were maintained below thermoneutrality in these studies, however, it is difficult to distinguish REE from thermoregulatory EE. Pronounced species differences also complicate EE research. For example, glucocorticoids decrease brown-AT UCP-1 activity in mice, but stimulate it in humans (Ramage et al., 2016).

Physical-activity EE. Female rats and mice are much more spontaneously active than their male conspecifics. Estrogens appear to act in at least three brain areas to stimulate physical activity in mice and rats. First, Fahrbach et al. (1985) found that estradiol injections into the medial preoptic area increase physical activity in rats. Second, Musatov et al. (2007) found that knockdown of *Esr1* in the VMH reduces physical activity in female rats. Using complementary site-specific knockout and pharmacogenetic stimulation of *Esr1*, Correa et al. (2015) demonstrated that VMH *Esr1* neurons stimulate physical activity in female, but not in male, mice and are a distinct subpopulation not involved in controlling eating, brown-AT activation or fertility, as indicated by the maturation of corpora lutea. Finally, using site-specific *Esr1* knockout or knockdown, Xu et al. (2015) found that *Esr1* neurons in the medial nucleus of the amygdala also control physical activity, but do so similarly in male and female mice.

Physical activity-induced increases in EE affect activity of reward regions of the brain in humans. For example, an escalating 6-month daily treadmill regimen reduced insula responses to highly valued food pictures (vs non-food) in overweight and obese subjects in the fasted state, and this reduction in insula activation correlated with reduction in fat mass and body weight (Comier et al., 2012; McFadden et al., 2013). Moreover, after an acute 60-minute exercise, normal-weight subjects showed increased dorsolateral prefrontal activity and reduced insula, putamen, orbitofrontal and hippocampal activity to pictures of high-calorie food (vs non-food) (Evero et al., 2012; Crabtree et al., 2014). These data suggest that exercise down-regulates the food-related responses of cortical and subcortical reward regions and upregulates the responses of prefrontal control regions. How ovarian hormones influence the relation between exercise and central food processing, however, remains largely unknown.

Discussion

Obesity results from tonically greater energy intake than EE. This simple truth belies the facts that the controls of eating and EE, the development of obesity, and the cardiometabolic consequences of the amount and distribution of AT are each multifactorial processes involving genetic, epigenetic, metabolic, endocrine, psychological, social and cultural factors, most of which are poorly understood. Because obesity remediation is a worldwide health challenge and because current strategies for weight reduction, other than bariatric surgery, have limited efficacy, there is an urgent need for research aimed at developing, first, further preventive and therapeutic strategies to achieve and maintain healthy levels of adiposity, and second, to minimize cardiometabolic and other risks of increased adiposity. Physiological sex differences are important variables in these processes. This should be clear from the marked sex differences in obesity prevalence, especially prevalence of severe obesity ($\text{BMI} \geq 35 \text{ kg/m}^2$).

We find that sex-specific physiological mechanisms, especially estrogen-mediated effects, play significant roles in the development of obesity in women as well as in its pathophysiological consequences. Table II summarizes well-established and probable female-specific obesity-related mechanisms, based on a wide variety of human and animal research. Estrogens act in the brain, in the AT and in other peripheral sites to affect: (i) the proximal causes of obesity, i.e. relative increases in eating and decreases in EE, (ii) the amount and regional distribution of AT and (iii) AT depot-specific pathophysiological changes that lead to morbidity. As a result, estrogens contribute both to male–female sex differences in obesity and obesity co-morbidities and to changes in obesity and obesity co-morbidities throughout women's lives (Fig. 5). Therefore, understanding the full impact of AT on women's health will require consideration of hormonal status on each of these processes. Currently astonishingly few data are available to address the normal physiology of these

processes, much less the effects of surgical and hormonal treatments on female overweight and obesity or the pathophysiology of endocrine disorders with obesity as a frequent co-morbidity.

Many of the effects described in Table II may appear to be small. For example, changes in food intake and EE through the menstrual cycle are on average only a few hundred kcal/d. It should be realized, however, that regular small changes in energy balance can lead to substantial differences in body weight and, therefore, be of considerable physiological relevance. The best available estimates indicate that an average increase of only 240 kcal/d in energy intake over EE is sufficient to produce the mean increase in average body weight that underlies the obesity epidemic in the USA (Hall *et al.*, 2011). Thus, the phenomena reviewed here are medically relevant and worthy of increased basic and clinical research.

It is also clear that obesity-related physiological characteristics vary widely across individual women. For example, as reviewed above, although most obese women display the female-typical pattern of relatively more gluteofemoral AT than central AT, some women have male-typical, central AT distribution (Karpe and Pinnick, 2015). The effects of menstrual cycle on flavor preferences also display great inter-subject variability (Bartoshuk *et al.*, 1994, 2006). Such variability may arise for many reasons, ranging from psychological, social and cultural influences on one side to genetic and epigenetic effects on the other side (Shepard *et al.*, 2009). Inter-subject variability together with the modest effect sizes mentioned above is a great challenge for research and an impediment to translation of research data into clinical practice. Research can meet this challenge in a variety of ways. Sample sizes should be based on power calculations taking effect size and variability into account. In addition, special care is required in sex research to consider subject characteristics, including age, race, alcohol use, stress levels or 'allostatic load', psychological traits such as tendencies for emotional or binge eating, etc., that can alter the sex-specific influences on AT physiology, eating and EE. In such cases,

Table II Sex differences and effects of estrogens on adiposity, eating and EE in women.

Adiposity

- ◆ Beginning at puberty, positive energy balance leads to female-typical AT distribution, i.e. greater accretion of gluteofemoral subcutaneous AT and less accretion of visceral AT.
- ◇ Estrogens and adipocyte genes synergize to produce female-typical AT distribution.
- ◇ Loss of estrogens after menopause increases total adiposity and decreases lean body mass, and estrogenic HRT prevents this.
- ◇ Loss of estrogens after menopause partially reverses female-typical regional AT distribution, and estrogenic HRT prevents this.

Eating

- ◆ Increasing estrogen secretion through the follicular phase progressively reduces daily food intake.
- Estrogens act on *Esr1*-expressing neurons in the cmNTS to increase CCK-mediated satiation; several other meal-control mechanisms may participate.
- ◇ Sex differences in gustatory sensory function affect eating.
- ◆ Genetic defects in brain α -MSH–MC4R signaling lead to a more marked overeating and obesity syndrome in females than males.
- ◇ Neuroimaging studies indicate that estrogens increase the activity of striatal dopaminergic neurons that processing of flavor hedonics.
- ◇ Neuroimaging studies indicate that estrogens increase IPFC processing of cognitive controls inhibiting eating.

EE

- ◇ Estrogens increase REE during the luteal phase.
- Estrogens act in several brain sites to increase physical-activity EE in rats and mice.

Note: ◆ indicates well-established effects in humans with proven or likely clinical relevance, as reviewed in text; ○ indicates effects apparent effects in humans with as yet uncertain clinical relevance; ◇ indicates effects established in animal research. Abbreviations: α -MSH, α -melanocyte-stimulating hormone; MC4R, melanocortin 4 receptor; IPFC, lateral pre-frontal cortex; REE, resting energy expenditure; CCK, cholecystokinin; cmNTS, caudal medial nucleus of the solitary tract.

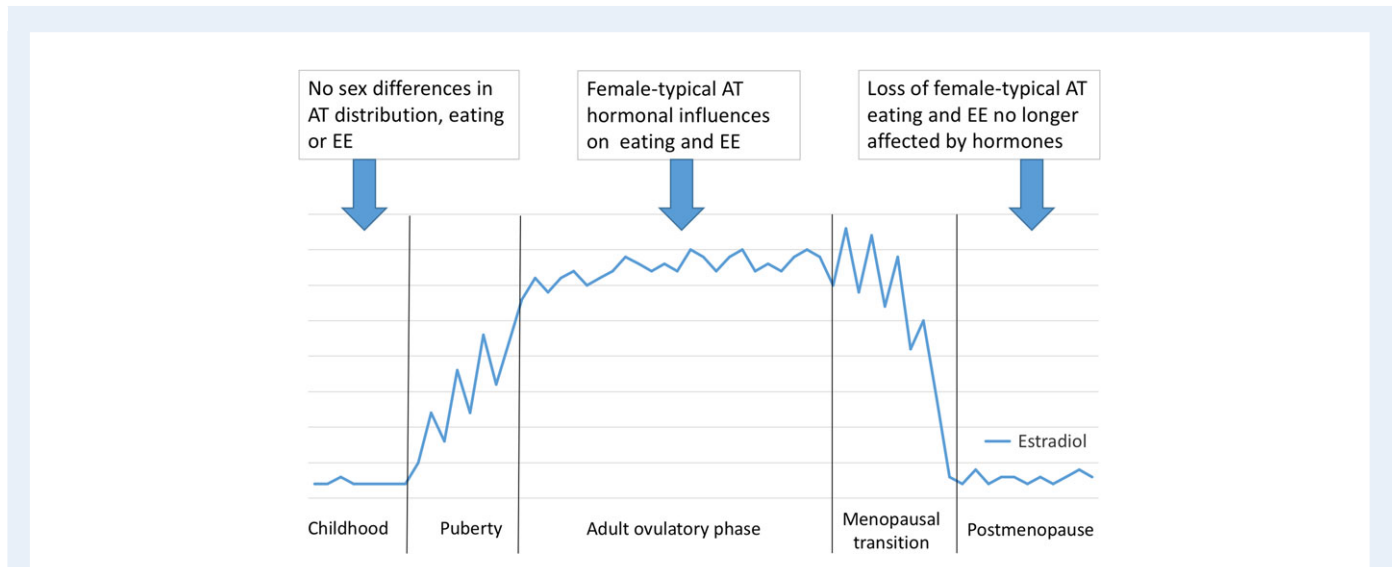


Figure 5 Summary of the principal effects of estrogens, represented by relative estradiol concentrations, on eating, EE and AT through women's life cycles. Note: Estradiol concentrations and durations of epochs are not to scale. See text for details. EE, energy expenditure; AT, adipose tissue.

appropriate statistical tools are helpful; for example, the multiple-regression analyses described above that parse the separate effects of aging and menopause on AT. Finally, researchers should avail themselves of the many methodological improvements that can increase the efficiency and meaning of pre-clinical and clinical sex-related research (Rubinow and Schmidt, 2002; Keitt et al., 2003; Becker et al., 2005; Greenspan et al., 2007; McCarthy et al., 2012).

The homogeneity of study groups with respect to reproductive physiology status itself is another important issue that is often overlooked, in part because findings in one domain fail to reach researchers in other domains. This is one of many reasons that inter-disciplinary investigator groups should be facilitated. Thus, postmenopausal study participants should be characterized, menstrual cycles should be evaluated more accurately in both obese and non-obese women, and effects of the type and duration of HT, including the interval between menopause and beginning HT, should be assessed. In women with surgical menopause, the indication for ovariectomy and whether hysterectomy was also done should be considered. In addition, as it is likely that indications for gynecological surgery differ in obese and non-obese women, due, for example to the higher prevalence of endometrial cancer and disturbed bleeding patterns in obese women (Madsen et al., 2013; Crujeiras and Casanueva, 2015), associations between surgical menopause and adiposity and AT distribution need to be explored. A related issue is that reproductive physiology, in particular estrogens, also may influence experimental outcomes via 'off-target' physiological functions. For example, pharmacological data in women may be influenced by differences in the bioactivity of many drugs due to sex differences in cytochrome p450 enzyme activity, effects of estrogens on hepatic drug metabolism and effects of estrogens on plasma levels of sex-hormone binding globulin and other globulins (Soldin and Mattison, 2009; Spoletini et al., 2012).

We acknowledge weaknesses of the review. We focused on the classical AT depots, although excess adiposity is also associated with increased hepatic, intramuscular and cardiovascular fat, which are

independently associated with cardiometabolic risk and appear to be affected by hormonal status in women (Oosthuyse and Bosch, 2012; El Khoudary et al., 2015; Marino and Jornayvaz, 2015). We focused mainly on pre-clinical whole-body mechanistic studies, at the expense of detailed reviews of cell- and tissue-level studies, genome-wide gene association studies and epidemiological studies, despite the many plausible mechanistic hypotheses that these suggest. We did not consider pregnancy, although postpartum weight gain is an important obesity risk (Gore et al., 2003). We did not consider tissue-specific synthesis of estrogens in the brain or AT or production of neurally active estrogen metabolites or other neurosteroids (Azcoitia et al., 2011; Do Rego et al., 2012; Porcu et al., 2016).

In conclusion, current human and animal research supports significant roles of ovarian hormones, especially estrogens, in the regulation of female AT. These involve influences on eating, EE, AT amount, regional AT distribution and the physiological function of adipocytes in the various AT depots. In the coming years, improvements in research design and analyses and the development of additional powerful methodologies should lead to important progress across the range of diverse influences of female physiology on adiposity. Continued animal research should better characterize, for example, the site and nature of estrogen receptors in the brain that affect eating and EE. Animal research should also lead the way to identifying the downstream molecular mechanisms responding to the activation of estrogen response elements in the DNA, which contribute the hormone's effects on gluteofemoral AT and on most, if not all, of its neural effects. A pressing issue in this connection is the better understanding of the interaction of estrogenic and genetic controls leading to the protective cardiometabolic effects of gluteofemoral AT. Similarly, improvements in the design of fMRI studies should help specify the neural information-processing mechanisms underlying sex-related hedonic and cognitive controls of eating. Progress in these and other research directions described here should lead to better understanding of female obesity, including clinically challenging syndromes such as

PCOS, and, ultimately, to better strategies to maintain and improve women's health in the face of the obesity epidemic.

Authors' roles

All authors contributed to the identification and critical evaluation of the relevant literature and to drafting the manuscript, and all authors approved the final version of the manuscript. B.L. conceived of the theme, prepared the proposal, and contributed clinical and scientific expertise as a gynecological endocrinologist. N.G. contributed expertise in adipose-tissue physiology, exercise physiology and the neuroendocrine regulation of eating and body weight. P.N.T. contributed expertise in functional neuroimaging and cognitive neuroscience. L.A. prepared the proposal and contributed expertise in adipose-tissue physiology and the neuroendocrine regulation of eating and body weight.

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Conflict of interest

None of the authors has any conflict of interest.

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