Estrogen, Body Weight, and Appetite

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Obesity, commonly defined in Western countries as a body mass index [BMI] exceeding 30 kg/m^2, and overweight, defined as a BMI between 25 and 30 kg/m^2, (NIH, 1998; WHO, 2000) are increasing (Hedley et al., 2004). In the US, the NHANES database demonstrates that adult obesity rates have doubled from 15% (1976-1980) to 30.9% (1999-2000) (Flegal, Graubard, Williamson, & Gail, 2005). Obesity is a significant problem and is increasing worldwide (Popkin & Gordon-Larsen, 2004). In Europe, the obesity rates have been estimated to vary from 11-12% (males-females, Denmark) to 22-35% (males-females, Malta) (IOTF, 2005). Increases in obesity rates are also noted in developing countries (Mendez, Monteiro, & Popkin, 2005) and in the pre-adult years. During the time period of 1980 to 2002, the percentage of overweight children and teens (aged 6-19 years) in the US increased from 5% to 16% (CDC, 2005).

Rising obesity rates have important health consequences. Obesity is linked with increased risk of acute and chronic illness including cardiovascular disease (Krauss, Winston, Fletcher, & Grundy, 1998), several forms of cancer (Calle, Rodriguez, Walker-Thurmond, & Thun, 2003), and type 2 diabetes mellitus (Pi-Sunyer, 1999); it is associated with excess mortality (Flegal et al., 2005). As well, excess body weight causes or exacerbates symptom conditions such as arthritic joint pain (Hochberg et al., 1995), sleep problems including obstructive

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sleep apnea (Namyslowski et al., 2005), and asthma (Shore &Johnston, 2005). Compared to non-obese children, children who are obese are at increased risk for hypertension, dyslipidemias, and diabetes mellitus (Goran, Ball, & Cruz, 2003). Obesity is associated with fewer years of disability-free life (Peeters, Bonneux, Nusselder, DeLaet, & Barendregt, 2004), loss of productivity (Ferraro & Booth, 1999; Narbro et al., 1996), and considerable economic burden (Finkelstein, Fiebkorn, & Wang, 2003).

Many Asian population groups also demonstrate significant and increasing obesity rates (IOTF, 2005). The data are sometimes conflicting, partly because of varying obesity definitions and varying data collection methods. When Asian people are compared with Caucasians of the same BMI, Asian people have a larger percentage of body fat and greater risk for obesity-related health conditions (Ko et al., 2001; Wang et al., 1994). Based on these observations, several countries and a WHO expert panel recommend that a BMI between 23-24.9 kg/m^2 be considered overweight and a BMI greater than 25 kg/m^2 be considered obese for Asian people (Choo, 2002; Kim et al., 2001). Using this standard, a national health and nutrition survey in South Korea noted an increase in the prevalence of adult obesity from 13.9% (in 1995) to 30.6% (in 2001) (Kim, Ahn, & Nam, 2005).

Gender appears linked with obesity, particularly among older age groups, but the data are not consistent. When height and weight are measured, female gender usually emerges as a risk factor for obesity. Recent NHANES data, collected by measuring height and weight, demonstrate that in the US, obesity is more prevalent among women than men, particularly in the older age groups (Hedley et al., 2004). A study using self report data shows that South Korean men reach a peak prevalence of obesity during their 40's; South Korean women continue to increase in body weight until age 70 (Kim et al., 2005). John, Hanke, Grothues and Thyrian (2005), studying a broad cross section of German residents, note that underreporting of BMI is more prevalent among women than men, particularly among women over 50 years of age. Thus, self-report data, at least in some cultures, might underestimate obesity prevalence and age disparityof weight data.

Many factors are likely to contribute to health status, health behaviors, and body weight. Among those factors are age, metabolic rate, physical activity level, stress, cultural factors, socioeconomic status, health status and health literacy, dietary composition, attitudes, and beliefs. Gender affects appetite and body weight indirectly by altering factors which contribute to food choice. However, there is emerging evidence that gender affects appetite and body weight directly, altering the physiological control systems which regulate appetite. This paper reviews evidence that estrogen is linked with altered physiologic regulation of appetite.

Appetite Regulation

Interrelated neuronal and endocrine systems control feeding behavior. Neuropeptides involved in appetite regulation are classified as anorexigenic (evoke satiety) or orexigenic (cause hunger). Anorexigenic and orexigenic hormones act centrally, primarily in the hypothalamus, to regulate appetite. The arcuate nucleus at the base of the hypothalamus is pivotal. Two populations of neurons in the arcuate nucleus contribute to central appetite regulation. One population expresses neu-

ropeptide Y (NPY) and agouti-related peptide (AgRP). Both NPY and AgRP areorexigenic, associated with hunger and food consumption. The other population co-expresses pro-opiomelanocortin (POMC) and cocaine- and amphetamine- regulated transcript (CART); these are anorexigenic, associated with inhibited food intake. Among anorexigenic peptides, the hypothalamic melanocortin -melanocyte-stimulating hormone (α-MSH, a cleavage product of POMC) is the most strongly implicated in the normal control of food intake. When α-MSH activates two distinct melanocortin receptors (Mc3r & Mc4r, expressed in hypothalamus and other brain regions), anorexia results and food intake is inhibited (Wren et al., 2000). Deficiency of α-MSH or melanocortin receptors causes hyperphagia and obesity (Barsh, Farooqi, & O'Rahilly, 2000).

There are extensive reciprocal connections among the brain areas involved in appetite control. Arcuate nucleus neurons project widely to the medial thalamic nuclei, central gray, dorsal motor nucleus of vagus (DMV), cortex, nucleus of solitary tract, locus coeruleus, spinal cord, and amygdala. Of these, the DMV is critical in central regulation of gut motility, potentially linking appetite with gut function.

Ghrelin.

The recently discovered hormone ghrelin (Wren et al., 2001a) may provide clues about the integration of central and peripheral regulation of gut function and appetite. The 28 amino-acid hormone is secreted primarily by neuroendocrine cells in the stomach and duodenal epithelium of rats and humans (Wren et al., 2001b). Ghrelin is strongly orexigenic, associated with hunger; it is the first circulating hormone demonstrated to stimulate food intake in man; it also decreases energy expenditure. Exogenous ghrelin administration increases food intake in rats (Matsumura, Tsuchihashi, Fuji, Abe, & Iida, 2002) and humans (Furuta, Funabashi, & Kimura, 2001); it increases adiposity and lowers the metabolic rate in rats (Asakawa et al., 2001). In humans, plasma ghrelin levels rise shortly before and fall shortly after meals, a pattern consistent with a role in the urge to eat (Masuda et al., 2000). Intravenous administration stimulates release of pituitary growth hormone (Trudel et al., 2000; Wren et al., 2001a) and gastrin (Tschop et al., 2001). It is tempting to speculate that ghrelin links enteric nutrition with central regulation of food intake, metabolism, and digestion. Both AgRP and NPY are apparent targets of direct ghrelin action (Pelleymounter et al.,1995). Ghrelin-targeted arcuate nucleus neurons may also affect neuroendocrine cells that are responsible for the regulation of pituitary hormone secretions, including gonadotrophs (LH/FSH) (Smedh, Hakansson, Meister, & Uvnas-Moberg, 1998).

Leptin.

Leptin is a hormone with actions opposing ghrelin. Leptin, a larger peptide hormone, is a secretory product of adipocytes, particularly subcutaneous rather than visceral adipocytes. Leptin evokes increased satiety, reduced appetite, and increased energy expenditure. Lack of leptin is associated with hunger, excess food intake, and obesity. Leptin receptors are found in the hypothalamus where leptin binding stimulates α-MSH and inhibits NPY and AgRP. Central and peripheral leptin administration reduces food intake and causesweight loss in mice (Schwartz, Woods, Porte, Seeley, & Baskin, 2000;

Takaya et al., 2000). Leptin administration causes marked curbing of the appetite and weight loss in individuals who are deficit in the hormone, but not in those with normal leptin function. Leptin is critically linked with gonadal hormones and reproductive status. For example, mice lacking the leptin gene are obese and infertile (Lee, Wang, Englander, Kojima, & Greeley, 2002).

Other hormones.

Other hormones involved in regulation of appetite and body weight include insulin, cholecystokinin (CCK), polypeptide Y (PPY), pancreatic polypeptide (PP), and many others. Insulin is secreted from pancreatic β cells in response to plasma glucose levels; it is associated with satiety and increased energy expenditure. Unlike leptin, insulin levels are correlated with visceral rather than subcutaneous fat deposits. Like leptin, insulin stimulates POMC neurons and inhibits NPY neurons. Food evokes CCK release from the duodenum and jejunum, inhibiting food intake and decreasing meal size and duration. CCK receptors are found on the pancreas, vagal afferents, enteric neurons, and in the hypothalamic appetite centers. Vagotomy abolishes the anorectic effect of CCK (Smith, Jerome, Cushin, Eterno, & Simansky, 1981). Hypothalmic Mc4r receptors are involved in CCK-linked satiety. PPY is released into the circulation from the distal intestinal wall following food intake. Release is likely mediated via the vagus and results in satiety. The pancreas releases PP in response to food intake; it also decreases food intake. The anorexogenic hormones PPY and PP are orexigenic when administered centrally. There is some evidence of sexual dimorphism with each of these appetite-linked hormones.

Estrogen, Food Intake, and Body Weight

Studies demonstrate that estrogen treatment is often associated with decreased appetite, decreased food intake, and decreased body weight gain. In rats, food intake varies with the estrus cycle, with lowest consumption occurring during estrus immediately after estrogen levels have peaked (Toth, Poehlman, Matthews, Tchernof, & MacCross, 2001). Following ovariectomy, rats consume more food and gain more weight than pre-ovariectomy (Bond, Heitkemper, & Jarrett, 1994; Toth et al., 2001). Chronic estrogen administration to ovariectomized rats reduces the weight gain to or below pre-ovariectomy levels (Bond et al., 1994; Toth et al., 2001). Estradiol administered to ovariectomized rats in cyclic physiologic doses (every fourth day, mimicking the estrus cycle) is similarly associated with cyclic variation in voluntary food intake, with the lowest food intake being on the day of the estradiol injection; ovariectomized rats with cyclic estradiol injection gain less weight than non-injected ovariectomized rats (Asarian & Geary, 2002).

Butera and Czaja (1984) report that in guinea pigs, estrogen evokes appetite suppression centrally. Ovariectomized guinea pigs were implanted with bilateral guide cannulae aimed at either the ventromedial hypothalamus, paraventricular nucleus (PVN), or preoptic area the animals were then injected unilaterally with cholesterol or estradiol 17-beta. Estradiol implants in the ventromedial-arcuate nucleus region and PVN significantly reduced food intake and body weight gain relative to cholesterol implants in the same brain region, even when the doses were too low to induce systemic (vaginal) effects.

Estrogen suppresses appetite in some non-human primate models. Several investigators have

reported that spontaneous feeding is diminished during the early follicular phase of non-human primates compared with the luteal phase, with cycle phase deduced based on visual inspection and signs of menstruation (Czaja, 1978; Rosenblatt, Dyrenfurth, Ferin, & vande Wiele, 1980). Ovariectomized primates demonstrated increased food intake and body weight gain, an effect reduced by administration of estrogen (Kemnitz, Gibber, Lindsay, & Eisele, 1989). Interestingly, when food delivery was a reward for behavior, only 1 of 4 female monkeys demonstrated a menstrual cycle-linked variation in motivational feeding (Roth, Negue, Knudson, Burgess, & Mello, 2005)

There is some evidence of estrogen-linked appetite suppression in humans. Many reports note that women eat less food during the peri-ovulatory phase of the menstrual cycle (time of rising estrogen level) compared with other phases, although the effect is subtle (Davit, 1981; Gong, Garrel, & Calloway, 1989; Lyons, Truswell, Mira, Vizzard, & Abraham, 1989; Reimer, Debert, House, & Poulin, 2005). Barr, Janelle, and Prior (1995), using temperature spike as an indicator of ovulation, noted that women lacking a mid-cycle temperature spike (thus assumed to be anovulatory) did not vary their diet intake.

Reduced calories during the peri-ovulatory phase is generally accounted for by reduced fat and/or carbohydrate intake. In a small study of menstruating women over three consecutive menstrual cycles, higher estradiol levels were associated with a tendency for lower energy intake, primarily accounted for by a decrease in carbohydrate intake (Alberti-Fidanza,Fruttini, & Servili, 1998). Reimer, Debert, House, and colleagues (2005) reported that the luteal phase was characterized by increased caloric intake and increased intake of fat calories. Li, Tsang, and Lui (1999) studying young Chinese women with confirmed ovulatory cycles (by documenting a surge of luteinizing hormone), noted increased caloric intake in the luteal phase, accounted for primarily by an increase in fat calories, but also by increased dietary carbohydrate calories.

Interestingly, findings during menopause are not consistent. Post menopausal status is associated with increased weight gain compared to pre-menopausal rates. However, a Cochrane Review meta analysis concludes that there is no evidence that estrogen, taken alone or in combination with progesterone, alters body weight gain in post menopausal women (Norman, Flight, & Rees, 2000).

Data regarding clinical conditions is consistent with the view that estrogen suppresses appetite. Although many women with bulimia nervosa have irregular or absent menstrual cycles, several studies suggest that among cycling women with bulimia nervosa, there is increased frequency of binging during the late luteal-premenstrual phase (Gladis & Walsh, 1987; Lester, 2003).

Estrogen and Appetite Regulation

The mechanisms underlying the association between estrogen and appetite are not fully explained. Estrogen is known to evoke effects via genomic (i.e., stimulates chromosomes to activate protein synthesis) and non-genomic (independent of protein synthesis) mechanisms. It is unclear whether the effects on appetite and energy consumption are genomic, non-genomic, or both. There is some evidence that estrogen alters the levels of and/or sensitivity to appetite-related hormones.

Estrogen and leptin.

If the anorexogenic effects of estrogen were mediated by leptin, one would predict that plasma leptin levels and/or leptin sensitivity would be higher in conjunction with estrogen. There is some evidence this is the case. There is a sex-related difference in circulating leptin levels, with females having higher levels than males. This is true in rats (Woods, Gotoh, & Clegg, 2003); women have 2- to 3- fold higher leptin levels than men (Considine et al., 1996). Thomas et al. (2000) studied leptin, sex-steroids, and body composition (DEXA) in adult men, premenopausal women, and post menopausal women with and without hormone replacement therapy (HRT). Serum leptin levels were related to body composition, and to circulating sex steroid and insulin levels. Women had a larger fat mass than men, but after adjusting for the larger fat mass, leptin levels remained significantly higher in women compared to men. Serum leptin levels correlated positively with bioavailable estrogen (estradiol plus estrone) in the post-menopausal women who not taking HRT. Others have found that leptin levels remain higher in women compared to men, after correcting for absolute fat mass (Rosenbaum et al., 1996). Circulating leptin levels are better correlated with subcutaneous fat than with intra-abdominal fat. Possibly because premenopausal females have more subcutaneous fat than males; plasma leptin levels correlate better with body fat content in women than in men(Woods, Gotoh, & Clegg, 2003). Similarly, female rats carry more subcutaneous fat than male rats they secrete more leptin than males (Clegg, Riedy, Smith, Beniot, & Woods, 2003).

The female brain is relatively more sensitive to leptin than the male brain. Leptin administered into the third ventricle caused diminished food intake and reduced body weight in both male and female rats, but the effect was more pronounced and more prolonged in the females (Clegg et al., 2003).

Estrogen and Ghrelin.

If the anorexogenic effects of estrogen were mediated by ghrelin, then one would predict that plasma ghrelin levels and/or ghrelin sensitivity would be lower in conjunction with estrogen. There is evidence of interaction between ghrelin and estrogen, but relationships are complex and the data are conflicting. Animal studies show that estrogen contributes to regulation of ghrelin secretion. Matsubara, Sakata, Wada, and colleagues (2004) report that estrogen administration in ovariectomized rats reduces the number of ghrelin-producing cells and ghrelin mRNA in the stomach, and reduces plasma ghrelin levels, consistent with the prediction. However, Barken, Dimaraki, Jessup, and colleagues (2003) compared men versus women in late follicular phase (when estrogen levels are high); they found that the women had significantly higher plasma ghrelin concentrations. There are half-sites for estrogen on the human ghrelin gene, suggesting that estrogen may regulate ghrelin gene expression (Kojima & Kangawa, 2005). Puri et al. (2006) studied the trigeminal ganglia of female mice and noted that ghrelin mRNA was present, and that the levels varied in synchrony with the estrus cycle, being highest at the high estrogen phases of the cycle. Interestingly, the reverse pattern was observed in the ovary, where high estrogen phases of the estrus cycle were associated with the lowest expression of ghrelin mRNA (Caminos et al., 2003).

Plasma ghrelin levels vary significantly with body weight, nutritional status, and age. Plasma ghrelin levels are lower with obesity and higher

during starvation, consistent with energy homeostasis. Administration of estrogen to postmenopausal women who were normal to overweight was associated with increased plasma ghrelin levels (Kellokoski et al., 2005). In a study of 60 adult (primarily overweight) men and women of varying ages, there was no gender difference found in plasma ghrelin levels, nor was there a difference in plasma ghrelin levels between pre menopausal (menstrual cycle phase not reported) versus post menopausal status, nor between postmenopausal women with versus without HRT (Purnell, Weigle, Breen, & Cummings, 2003). Lebenthal, Gat-Yablonski, Shtaif, and colleagues (2006) report that when estrogen is administered to peri-pubescent short stature girls (aged 8-12.5 years old), there was no group difference in plasma ghrelin levels. The same study showed that testosterone administration to peri-pubescent short stature boys, plasma ghrelin levels significantly declined.

Summarizing, it is clear that there are interactions between ghrelin and estrogen, but the relationships are complex and not fully characterized. At this time, the data relating estrogen and ghrelin are not consistent. Additional study is needed.

Estrogen and other appetite related hormones.

There are relationships among gender, estrogen levels, and some of the other appetite related hormones. Compared with female rats, male rats secrete more insulin; insulin is a better correlate of body fat in male versus female rats. Woods, Gotoh, and Clegg (2003) injected insulin into the third ventricle of the rat brain. They noted that the male rat brain was relatively more sensitive to insulin than the female, evoking diminished food intake in both male and female rats, but at lower doses and for aprolonged time period in the male rats. There are interrelations between leptin and insulin, further complicating observations relating to estrogen and insulin.

Estrogen is a powerful regulator of CCK; estrogen may evoke release of CCK from the intestine and elsewhere, but studies are needed to validate this hypothesis. Estrogen is also linked to PP. Hypoglycemia evoked decrease epinephrine, PP, and leptin release responses in postmenopausal women taking estrogen replacement compared with age- and weight-matched postmenopausal women not taking estrogen replacement and/or compared with male subjects (Sandoval, Ertl, Richardson, Tate, & Davis, 2003). Puri et al. (2006) note that NPY is expressed in the trigeminal ganglia of the female mouse, and that the level increases, like ghrelin, at the high estrogen phases of the cycle.

ANS, CNS, gender/gonadal hormone state, and stress also modify appetite, food intake, and weight gain, but the mechanisms of their interactions are not well delineated. The interactions of ovarian hormone status, diet, stress-related hormones, and gut motility have been the investigator's research focus.

Summary and Conclusions

Summarizing, there is evidence that women more commonly demonstrate overweight and obesity, particularly in the post-menopausal years. There is consistent evidence that estrogen influences appetite and body weight, generally suppressing appetite, diminishing body weight and body weight gain, and favoring deposition of subcutaneous over intra-abdominal fat. Female gender, pre-menopausal status, and estrogen are associated with increased

plasma leptin levels, increased correlation between body fat and plasma leptin levels, and increased central sensitivity to leptin. Leptin evokes increased release of the arcuate nucleus satiety hormones and diminished release of arcuate nucleus orexigenic hormones, likely contributing to diminished food intake and lower weight gain. Data regarding ghrelin and other appetite related peptides are less clear, the evidence inconsistent. It is likely that estrogen blunts appetite and weight gain during the premenopausal years. Interestingly, the major male-female differences in body weight emerge following menopause, when estrogen is diminished or absent. Following menopause in women, estrogen does not appear to have the same efficacy in reducing appetite and body weight gain. Much additional work is needed to clarify the mechanisms underlying women's postmenopausal risk of overweight and obesity.

These observations of sex-differences in appetite regulation suggest that therapeutic approaches to body weight reduction could be tailored to gender and hormonal state. Nurses, seeking to promote health and enhance quality of life, provide clinical advisement related to diet and weight control. Understanding the physiological basis of interactions among estrogen and appetite-related neuropeptides will enhance nursing therapeutics.

Much remains to be explicated in the regulation of body weight. Gender differences are likely to affect appetite and body weight regulation indirectly, for instance, via gender effects on physical activity, sleep, stress responses, or socioeconomic status.

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Abstract

Estrogen, Body Weight, and Appetite

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Obesity rates are increasing worldwide, associated with excess acute and chronic disease risk. In most countries, obesity rates among women exceed rates in men, particularly during the post menopausal years. Many factors affect body weight and appetite, including age, metabolic rate, physical activity level, stress, cultural factors, socioeconomic status, health status and health literacy, diet composition, attitudes,and beliefs. Gender affects appetite and body weight indirectly by altering factors contributingto food choice. However, there is emerging evidence that gender affects appetite and body weight directly, altering the physiological control systems regulating appetite. The follicular menstrual cycle phase (estrogen-rich) is associated with relative suppression of appetite. Lower estrogen levels are associated with increased food intake, body weight gain, and altered body fat distributionin humans and animals. This paper reviews the linkages between estrogen and appetite regulation. While relationships among appetite, body weight, and gender-linked hormones are complex, research elucidating these interrelationships could lead to development of gender-specific treatment approaches for obesity and appetite dysregulation.

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