Gender Differences in the Control of Energy Homeostasis

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The world is experiencing an epidemic of obesity and its concomitant health problems. One implication is that the normally robust negative feedback system that controls energy homeostasis must be responding to different inputs than in the past. In this review we discuss the influence of gender on the efficacy of adiposity hormones as they interact with food intake control systems in the brain. Specifically, the levels of insulin and leptin in the blood are correlated with body fat, insulin being related mainly to visceral fat and leptin to subcutaneous fat. Since females carry more fat subcutaneously and males carry more fat viscerally, leptin correlates better with total body fat in females and insulin correlates better in males. High visceral fat and plasma insulin are also risk factors for the complications of obesity, including type-2 diabetes, cardiovascular problems, and certain cancers, and these are more prevalent in males. Consistent with these systemic differences, the brains of females are more sensitive to the catabolic actions of low doses of leptin whereas the brains of males are more sensitive to the catabolic action of low doses of insulin. The implications of this are discussed. Exp Biol Med 228:1175–1180, 2003

Key words: gender difference; obesity; leptin; visceral fat; subcutaneous fat

According to every survey taken, the incidence of overweight and obesity continues to rise in the United States and throughout the world (1–3). Current estimates are that around 60% of Americans have a body mass index (BMI) over 25, indicating that they are "overweight." Of particular importance, the incidence of overweight and obesity is also rising in children (4). While there is considerable debate and controversy as to the cause of this epidemic of obesity, it is generally believed that some combination of readily available and highly palatable foods that have both a high fat content and a high caloric density, and a general reduction in the amount of physical work or exercise practiced by the prototypical adult, are implicated (5, 6).

The list of problems faced by the obese is long, including personal and social stigma and a relatively high incidence of depression and other behavioral disorders. Of particular concern is that the risk for developing numerous serious health problems also increases as one's BMI increases. These health problems include, in addition to premature mortality, an increased incidence and severity of hypertension, diabetes mellitus, several cancers, other cardiovascular disorders, and many more (7–9). A weight gain of 11 to 18 pounds increases a person's risk of developing type-2 diabetes to twice that of individuals who have not gained weight. Over 80% of people with diabetes are overweight or obese. The obese individual is at 50% to 100% increased risk of dying prematurely, compared with individuals at normal weight. Because of these associated disorders, obesity has been called the number one behavioral disorder in the United States (5).

The Paradox

In spite of the fact that the incidence of obesity continues to rise, the regulatory control over body weight is often touted as being a highly precise, negative-feedback homeostatic system (10–13). The term homeostasis refers to the body's normal controls over a number of critical physiological variables whose levels must be maintained within a strict range for the individual to survive (14). For most of these parameters, the continuously ongoing process of homeostasis is a highly complex set of reflexes that monitors the levels of key variables (e.g., blood volume, oxygen delivery to tissues, or body temperature) and initiates corrective responses when their levels reach or approach undesirable levels or thresholds. If insufficient oxygen is reaching the brain, this is detected and several responses are initiated that include increasing heart rate and blood pressure as well as respiratory rate. When applied to body fat, homeostasis refers to those processes that are continuously monitoring body fat and making compensatory adjustments in effector systems such as energy intake and expenditure as needed (11, 13). The activity of this negative feedback system is in turn being constantly influenced by myriad environmental factors such as average food palatability, total daily exer-

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cise, and stress (15, 16). Superimposed on this are factors based on experience such as the time of day that has been associated with food in the past, the social situation, and so on (17). As a consequence, energy homeostasis is a complex ongoing integral of multiple factors that ultimately determine when and how much food is eaten. Viewed in this light, the epidemic of obesity must be considered the result of an altered environment.

In this article, we focus upon the sensory mechanism that informs the brain as to how much fat is present in the body, how this information is translated into behavior, and how gender influences overall body fat and health in general. It has long been recognized that some circulating factor(s) functions as an adiposity signal to the brain (18). That is, whereas direct neural connections between the brain and body fat stores could serve this function, such nerves have not been described. In contrast, there is considerable compelling information that hormones meet the criteria to be adiposity signals. Both leptin, which is secreted from fat cells, and insulin, which is secreted from pancreatic B cells, are secreted and circulate in direct proportion to body fat. That is, obese individuals have higher levels of circulating leptin and insulin than lean individuals. Several reviews of this are available (11, 13, 19–22).

Adiposity Signals

Leptin and insulin are somewhat unique among peripheral hormones related to metabolism in that although they are not made in the brain, the brain nonetheless contains specific receptors for each of them. Further, they are able to reach the brain because each is transported from the blood, through the blood-brain barrier, by a receptor-mediated mechanism (23–28). Hence, biologically active leptin and insulin are delivered into the brain interstitial fluid where they can interact with receptors on neurons. Although receptors for each are located in several discrete areas within the brain, the arcuate nucleus of the hypothalamus has particularly high concentrations of each (11, 29, 30).

Hypothalamic Controls

As depicted in Figure 1, when either exogenous insulin or leptin is administered into the brain near the arcuate nucleus, there is a net catabolic response (11, 30). Animals eat less food and have increased energy expenditure, and this is accomplished because of the reciprocal activity of 2 populations of neurons within the arcuate nucleus, both of which have receptors for both insulin and leptin. One group of neurons synthesizes the peptide known as proopiomelanocorticotropin (POMC). Several tissues synthesize POMC and cleave it into one or several active smaller peptides that are secreted from the cells. Arcuate neurons cleave POMC into α-melanocyte stimulating hormone (αMSH) and release αMSH from axon terminals in several hypothalamic regions including the paraventricular nuclei (PVN) and the lateral hypothalamus (LH) (Fig. 1). Exogenous αMSH

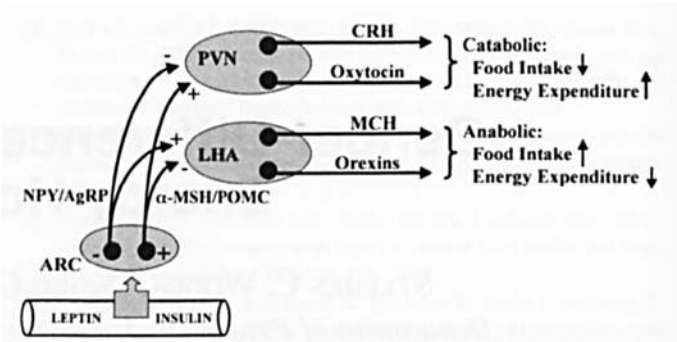

Figure 1. The adiposity hormones, leptin and insulin, enter the hypothalamic arcuate nucleus (ARC) by passing through the blood-brain barrier. In the ARC they stimulate POMC neurons that release α-MSH in the paraventricular nuclei (PVN) and lateral hypothalamic area (LHA); they also inhibit NPY/AgRP neurons in the ARC that also project to the PVN and LHA. Stimulation of the PVN (and/or inhibition of the LHA) has a net catabolic effect, whereas stimulation of the LHA (and/or inhibition of the PVN) has a net anabolic effect. The catabolic effect is mediated in part by corticotropin releasing hormone (CRH) and oxytocin neurons of the PVN neurons and the anabolic effect is mediated in part by melanin concentrating hormone (MCH) and orexin neurons of the LHA. Hence, leptin and insulin collectively activate catabolic pathways while inhibiting anabolic pathways.

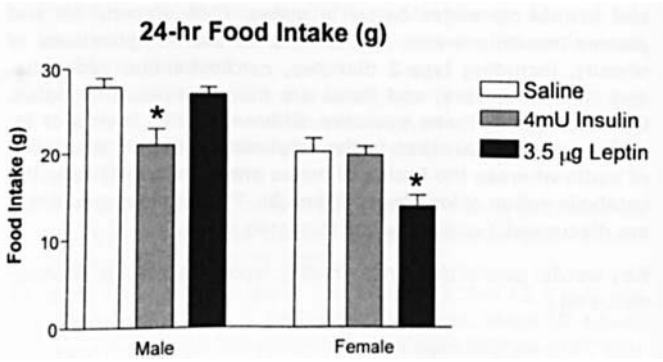

Figure 2. Mean 24-hr food intake in male and female Long Evans rats following the third ventricular administration of either insulin or leptin. The males ate significantly less food ($P < 0.05$) following insulin relative to either saline or leptin. The females ate significantly less food ($P < 0.05$) following leptin relative to either saline or insulin. (* Represents conditions significantly different from saline.)

causes animals to eat less food and lose weight when it acts on melanocortin-4 (MC4) receptors in the PVN (31). The leptin/insulin to POMC to αMSH to PVN pathway is highly important to the maintenance of low body weights since when it is interrupted at any point animals tend to eat more food and gain weight (32, 33). This is true whether there is a deficiency of leptin, a deficiency of functional leptin receptors, insufficient αMSH, or else a deficiency of MC4 receptors. Further, humans who are deficient at any of these same points due to an inheritable mutation are also hyperphagic and obese (34, 35). A deficiency of insulin, such as occurs in type 1 diabetes mellitus, is also associated with hyperphagia but the individuals cannot become obese because they cannot store fat in the absence of insulin. Restoring leptin or insulin or αMSH into the brain of individuals lacking them reverses the obesity (36, 37). Recent reviews are available (38, 39).

The second category of arcuate neurons synthesizes neuropeptide Y (NPY) and also projects to the PVN and LH (Fig. 1). When NPY is administered into the brain animals eat more food and burn less energy, and they gain weight when this is repeated over days (40–42). Like POMC neurons, NPY neurons in the arcuate nucleus express both leptin and insulin receptors. However, whereas both leptin and insulin stimulate POMC neurons, they inhibit NPY neurons; and when leptin and insulin levels are low, as after a fast or after weight loss, NPY mRNA is upregulated in the arcuate nucleus (43, 44). Hence, both anabolic (NPY) and catabolic (POMC/αMSH) neurons exist in the arcuate nucleus and are sensitive to the adiposity hormones, leptin and insulin.

There is another level of complexity in that arcuate NPY neurons also synthesize a second neuropeptide called agouti-related peptide or AgRP. AgRP is an endogenous antagonist at MC4 receptors, and its action opposes that of αMSH (45–47). A single administration of AgRP into the brain can stimulate food intake and body weight for up to 7 days (48, 49). Therefore, anabolic arcuate neurons synthesize one peptide (NPY) that stimulates food intake and inhibits energy expenditure directly, and another peptide that blocks the catabolic action of αMSH. It is the balance between these anabolic and catabolic neurons in the brain that determines the level of body fat that is maintained over time.

Differences between Adiposity Hormones

Although both leptin and insulin can be considered as "adiposity" hormones, there are important differences between them in this regard. Leptin is secreted directly from adipose cells in proportion to their metabolic activity. Insulin is secreted from pancreatic B cells in response to increases of circulating glucose. Both are increased in direct proportion to the amount of body fat. Leptin is a much more stable signal in that its half-life in the plasma is around 45 minutes; insulin is a much more short-lived signal in that its plasma half-life is only around 2 to 3 min.

The levels of the 2 hormones also differ with regard to which fat depots they best reflect. More leptin is secreted from subcutaneous fat (50, 51) than from visceral fat, such that circulating leptin correlates better with total subcutaneous fat than with total body fat (52–58). Insulin secretion on the other hand is better correlated with visceral fat such that its levels better reflect visceral than total body fat. This difference has important consequences since it is visceral and not subcutaneous fat that provides the risk factor for the metabolic syndrome as adiposity increases (59–61). Further, there is a major sex difference with regard to the distribution of body fat. As a general rule, females carry more fat subcutaneously (62–66) whereas males carry more fat viscerally (67). This is generally regarded as the reason that men are more prone to develop the metabolic syndrome as adiposity increases than are women (68, 69). Intraabdominal fat is relatively insensitive to insulin (70–73), and insulin action is markedly impaired in individuals with visceral obesity (74, 75). Another point is that plasma leptin correlates better with body fat in women, and plasma insulin correlates better with body fat in men, and plasma insulin is a risk factor for the metabolic syndrome.

Gender and the Regulation of Body Fat

In a recent series of experiments, we asked whether this sex difference is also apparent in an animal model, the laboratory rat. We therefore measured plasma insulin and leptin in adult Long Evans rats and correlated them with body fat. Like humans, female rats have more total fat and higher plasma leptin than males (D.J. Clegg, S.C. Benoit, and S.C. Woods, unpublished data). We then asked whether the brains of males and females are differentially sensitive to insulin and leptin.

For these experiments, we used 1 group of male rats and 2 groups of female rats, one of which had the same age as the males, the other having the same weight as the males but being older. In every experiment, both the age-matched and the weight-matched females performed comparably, such that only male–female differences were observed. We administered a series of doses of insulin or leptin individually into the third cerebral ventricle (i3vt) of male and female rats and measured food intake and body weight. Although both genders had a net catabolic response to each peptide at higher i3vt doses, there were significant differences in the response to lower doses. Relative to a vehicle injection, male rats reduced their food intake beginning at 2 hr and lasting for 24 hr to doses of i3vt insulin of 1 mU and higher, and body weight was reduced after 24 hr. Females, on the other hand, had no change of food intake or body weight at doses up to 4 mU, although the variance increased at the highest dose. In contrast, when low doses of leptin (1 μg) were administered i3vt, both genders had reduced food intake after 2 hr, but the effect was gone by 24 hr in the males. Females, on the other hand, continue to eat less after 24 hr and had reduced body weight as well. Thus, the brains of males are more sensitive to low doses of insulin whereas the brains of females are more sensitive to lower doses of leptin (55) (Fig. 2).

Since, as discussed above, a major site of action of leptin and insulin is the arcuate nucleus, and since both NPY/AgRP and POMC/αMSH neurons project to the PVN and LH (20), we performed a second experiment to determine if MC4 receptors are differentially sensitive in males and females. When MT-II, a synthetic MC4 agonist, was administered i3vt to males and females over a wide range of doses, no sex difference was observed; that is, both genders had a dose-dependent reduction of food intake and body weight (55). This result implies that the sex difference is manifest in the arcuate and not in the PVN. Hence, females are more reliant on leptin as an adiposity signal and males are more reliant on insulin. Females carry more subcutaneous fat and secrete more leptin, leptin is a better correlate of total body fat in females, and female brains are relatively

sensitive to leptin as an adiposity negative feedback signal. Males, on the other hand, carry more fat viscerally and secrete more insulin, insulin is a better correlate of total body fat in males, and the brains of males are more sensitive to the catabolic actions of insulin (55). These observations, besides having fundamental importance for the regulation of energy balance, imply that strategies for reducing body weight in males and females might differ.

We are now considering a possible role of ovarian hormones in determining the sex differences in the sensitivity of the brain to adiposity hormones. Premenopausal women have relatively more subcutaneous fat, and they gain weight in the visceral depot postmenopausally (76, 77). Estrogen insufficiency is thought to be responsible for this redistribution since postmenopausal women who receive estrogen replacement therapy do not display the characteristic visceral weight gain pattern associated with menopause (78–80). Lack of estrogen and the associated increase in visceral adipose tissue in postmenopausal women increases the risk for insulin-resistant diabetes, cardiovascular disease, and breast cancer (81, 82). As discussed above, we have found that females are more sensitive to the anorexigenic effects of leptin than males, and in future experiments we will determine if these differences reflect differences in body fat distribution. That is, we anticipate finding functional neuronal relationships between levels of estrogen and body fat distribution.

In summary, although a robust and highly efficient negative feedback system normally maintains body fat at a relatively constant level, there are extrinsic factors that can have a major impact on the process. While we have focused upon gender differences in this review, it is clear that many other factors can have a major influence as well, including physical activity (83) and the amount of fat in the diet (84, 85).

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