

Metabolic and hormonal control of the desire for food and sex: Implications for obesity and eating disorders

Jill E. Schneider*

Department of Biological Sciences, Lehigh University, 111 Research Drive, Bethlehem, PA 18015, USA

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Abstract

During evolution, the ability to overeat and store the extra energy as glycogen and lipids in specialized tissues must have conferred a reproductive advantage by releasing animals from the need to eat constantly, enabling them to engage in behaviors that improved reproductive success. Mechanisms that inhibited ingestive behavior might have been most adaptive when they caused individuals to stop foraging, hoarding and eating in order to find and court potential mates. Conversely, the ability to abstain from reproductive activities to engage in foraging and eating was probably critical for individual survival during severe energetic challenges because reproductive processes are energetically costly and can be delayed until the energetic conditions improve. The mechanisms that control ingestive behavior most likely evolved under conditions in which both food and mates were available, and thus, our understanding might be limited by our narrow focus on food intake in animals isolated from potential mates, and reproductive behaviors in the absence of food. Our understanding of obesity and eating disorders will be enriched by the study of the choice between ingestive and reproductive behaviors and by a renewed attention to “reproductive” hormones such as gonadal steroids and hypothalamic releasing hormones. Furthermore, leptin and reproductive hormones have both organizational and activational effects on the energy balancing system including those mechanisms that control appetite, body fat content and body fat distribution. Understanding these organizational and activational effects on body fat distribution might lead to a better understanding of sex differences in the propensity to develop obesity, type II diabetes and eating disorders.

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Obesity research has revealed a long list of neuropeptides, peripheral hormones and metabolic events that accompany eating and fasting, and yet, the incidence of obesity is rising throughout the developing world. In parallel with our waistlines, research on obesity and eating disorders has expanded tremendously and yet there is still no consensus on the primary causes and remedies. There is no clear agreement about the relative importance of genetic predisposition, readily available, highly palatable food, food marketing, dietary fat, carbohydrates, artificial sweeteners, sedentary lifestyle, maternal nutrition, sleep deprivation and stress (Clement, 2005; Copinschi, 2005). Public policy debates that pit “will power” and personal responsibility against genetics are more polarizing than constructive. Most research on ingestive behavior starts

with the assumption that internal rheostatic mechanisms naturally limit food intake in order to avoid obesity. An evolutionary perspective, however, suggests that the propensity to overeat and store energy has promoted reproductive success, at least in some environments, during some evolutionary time periods, in some mammalian species. In many species, the ability to stop eating was probably most adaptive when it provided more time and energy to engage in courtship, mating and raising offspring. This perspective has the potential to reveal the key physiological systems that link energy balance to reproductive success.

An evolutionary perspective begins with the idea that most of the traits we see in extant organisms result from a combination of natural selection and random events, such as genetic drift. For those traits that are molded primarily by natural selection, gene frequencies of alleles increase in successive generations if those alleles confer reproductive

* Fax: +1 610 758 4004.

E-mail address: js0v@lehigh.edu.

success (i.e., more offspring are born and raised to sexual maturity). For those of us interested in physiological mechanisms, these evolutionary considerations bring our attention to pleiotropic effects of “obesity” genes on reproductive success.

A survey of all mammalian orders shows that energy availability is the most important environmental factor that controls reproduction (reviewed by Bronson, 1989). Energy is required for all cellular processes, and reproductive processes are among the most energetically expensive, especially in females (reviewed by Bronson, 1989). Energy, however, is not available continuously in most environments. In many species, the hormones of pregnancy are known to increase food intake, energy storage and fuel efficiency in specialized adipose tissue depots in advance of the birth of offspring (Wade and Schneider, 1992). Conversely, the mechanisms that inhibit hunger are most adaptive because they bring a cessation of foraging, hoarding and eating long enough to find and court potential mates and care for offspring. These arguments are dramatically illustrated by examples of mammals, birds and reptiles that fast or dramatically reduce food intake during the breeding season, migration, molting, incubation, or during defense of territories or harems (Mrosovsky and Sherry, 1980). However, similar mechanisms might be at work in most other species, in which the key to reproductive success lies in the moment-to-moment change in behavioral priorities. These brain mechanisms promote the motivation to engage in both reproduction and eating, but each at the appropriate time. In nature, these behaviors occur in an environment in which there is often a choice between foraging and courtship. Perhaps the mechanisms that underlie initiation and termination of eating will be more easily revealed if we study the choice between eating and sex in a seminatural environment in which both food and potential mates are freely available. If the choice between eating and sex serves a purpose related to energetics, it would be predicted that this choice would be sensitive to prior energy balance as well as the so-called orexigenic and anorectic peptides.

The choice between food and sex

In female laboratory animals, there is a periovulatory increase in sex behavior (Beach et al., 1982; Christie and Bell, 1971; Ciaccio et al., 1979; Komisaruk and Diakow, 1973), but the females' periovulatory preference for sex over food is only assumed. Despite the extensive neural and hormonal overlap, ingestive behaviors are typically studied separately from reproductive behaviors, with a few notable exceptions (Ammar et al., 2000; Kalra et al., 1988; Kaplan et al., 1992). In our laboratory, we have been studying female hamsters' food intake and sex behavior in a unique apparatus that enables assessment of the females' preference for males versus food. If the preference for males relative to food is a pivotal adaptation to fluctuating energy availability, food deprivation would be predicted to increase the preference for hoarding compared to the preference for courtship, even if this metabolic challenge were not severe enough to inhibit the HPG system and ovulation.

In contrast to the metabolic control of behavioral choice, metabolic control of the HPG system is well documented (reviewed by Schneider, 2004; Wade and Jones, 2004). In rats, hamsters, sheep and monkeys, energetic challenges indirectly prevent the expression of sex behavior by inhibition of the HPG system. Food deprivation inhibits the gonadotropin releasing hormone (GnRH) pulse generator, a diffuse interacting group of GnRH neurons in the hypothalamus (Bronson, 1986, 1999), and this leads to a loss of the pulsatile release of GnRH into the pituitary portal system. Inhibition of GnRH secretion leads to a cascade of inhibitory effects including decreased gonadotropin secretion, cessation of follicle development, decreased synthesis and secretion of gonadal steroids and the absence of steroid-induced reproductive behaviors (reviewed by Schneider, 2004; Wade and Jones, 2004). In addition, energy balance can act directly on the synthesis and secretion of pituitary gonadotropins, estradiol (E), progesterone (P), and, as emphasized in this review, energy balance can change neural responsiveness to E (Wade and Jones, 2004).

In Syrian hamsters, a 48-h period food deprivation on days 1 and 2 of the 4-day estrous cycle inhibits ovulation and sex behavior (expected to occur on day 4). Anestrus and anovulation are induced only if this 48-h period of food deprivation encompasses days 1 and 2 of the estrous cycle, the early follicular phase (Morin, 1986), and only if the hamsters are lean (Schneider and Wade, 1989, 1990). Thus, to test the hypothesis that behavior is more sensitive to energetic challenges than the HPG system, we have been studying the effects of food deprivation on sex and ingestive behavior in fatter hamsters, which would not be expected to show food deprivation-induced anestrus.

The consummatory components of behavior under investigation are those that involve the motor programs involved in eating and copulation (e.g., the amount of food ingested and the lordosis reflex in female rodents), whereas the appetitive components are those initial behaviors that arouse animals and bring them in contact with food or mates (Beach, 1976; Everitt, 1990). Appetitive sex behaviors include the preference for males over food and vaginal scent marking, whereas consummatory sex behavior is represented by lordosis duration. Vaginal scent marking varies predictably over the 4-day estrous cycle, peaking along with increasing concentrations of E on estrous cycle day 3 (Baranczuk and Greenwald, 1973; Takahashi and Lisk, 1983). These marks are attractive to male hamsters (Johnston, 1975), and are distributed in the environment in such a way that they guide the male to the female in time for mating (Takahashi and Lisk, 1983). In contrast to vaginal marking, the lordosis reflex is an immobile posture that represents copulatory performance, and requires proestrus levels of both E and P. The appetitive aspects of ingestive behavior include the preference for food over males, food hoarding and the latency to start eating, whereas food intake represents the consummatory aspect of ingestive behavior.

To examine the choice between food and sex, female hamsters are tested in an apparatus that allows the female one of three free choices; she can either remain in her home cage or

enter one of two tubes. One tube leads to a Food Box containing a measured amount of food. The other tube leads to a Sex Box, a cage that contains a sexually experienced, adult male hamster. Prior to the test, females are acclimated (habituated) to their home cage, which contains food, water and nesting material, and then, they are trained to differentiate between the tube that leads to the male and the tube that leads to the food. These females are either fed ad libitum or food deprived for 48 h beginning at the onset of the dark period on day 1 of the estrous cycle until the same time on day 3, just before the behavioral choice test. Just prior to the start of the preference test, food in the Food Box and in the cage is measured. Females have access to both tubes for 90 min, and all behaviors are recorded by an experimenter every five seconds for the first 15 min of the test. At the end of the 90-min period, all food in all parts of the apparatus are measured to determine the amount of food eaten and hoarded (carried from the Food Box to the home).

The choice between food and sex, and the appetitive aspects of sex and ingestive behavior (vaginal marking and food hoarding) vary significantly over the estrous cycle in fed animals, and food deprivation significantly decreases the preference for sex and vaginal marking and increases the preference for food and food hoarding (Schneider et al., submitted for publication). Previously food-deprived females that are re-fed after the preference test on day 3 show normal lordosis latency and duration on day 4 that are not significantly different from those of ad libitum fed females on day 4. The same period of food deprivation significantly decreases vaginal marking and the latency to show aggression with no significant effects on plasma E concentrations, and the correlation between vaginal marking and plasma E concentration are not significant.

The adipocyte hormone leptin is a possible candidate hormone for control of the preference for sex, because plasma leptin concentrations decrease rapidly after food deprivation (within 12 h), far more rapidly than changes in body fat content (Schneider et al., 2000), and leptin treatment attenuates food deprivation-induced increases in hoarding in male Syrian hamsters (Buckley and Schneider, 2003). In contrast, treatments that inhibit metabolic fuel oxidation fail to alter hunger motivation in this species (Lazzarini et al., 1988; Schneider et al., 1988) and fail to increase hoarding in Siberian hamsters (Bartness and Clein, 1994). Thus, if the change in preference for sex were mediated by a decrease in leptin secretion, it would be predicted that the effects of food deprivation would be reversed by treatment with leptin. Consistent with this prediction, the food deprivation-induced changes in the preference for the Sex Box, vaginal scent marking and food hoarding are reversed by systemic leptin treatment (Schneider et al., submitted for publication). The number of vaginal marks per unit of time in the Sex Box is significantly increased in leptin treated, food-deprived, compared to vehicle-treated, food-deprived or vehicle-treated, fed females, suggesting that leptin actually enhances appetitive aspects of sex behavior in addition to inhibiting appetitive aspects of ingestive behavior (Schneider et al., submitted for publication).

These data are consistent with the hypothesis that the appetitive, motivational aspects of both sexual and ingestive

behavior are more sensitive to energetic challenges than the underlying neuroendocrine system that controls the estrous cycle and fertility. Whereas other experiments have been able to dissociate the occurrence of estrous behavior from the HPG system (Hansen et al., 1980), these are the first to do so in the context of metabolic control of behavior. In addition, these are the first data to show that leptin actually increases sexual motivation in females, independent of the effects on estrous cyclicity or on food intake because the number of vaginal marks per unit of time in the Sex Box is significantly increased in leptin treated food-deprived, compared to vehicle-treated food-deprived or vehicle-treated, fed females (Schneider et al., submitted for publication).

The food deprivation-induced decrease in E-dependent vaginal marking, in the absence of significant decreases in plasma E concentrations, suggests that food deprivation reduces sensitivity to E. Consistent with this idea, 48 h of food deprivation decreases E-receptor- α (ER α) immunoreactivity in the ventromedial hypothalamus (VMH) along with lordosis duration in ovariectomized (OVX) females treated with E+P (Li et al., 1994). The VMH is one of the brain areas thought to be involved in sexual motivation, including the motivation to engage in vaginal scent marking and lordosis in Syrian hamsters (Takahashi and Lisk, 1987). In addition, food deprivation might influence sexual motivation by enhancing the ability of estrogen-concentrating neurons to affect downstream neurotransmitter/neuropeptide systems such as those for dopamine, serotonin, NPY, agouti-related protein (AgRP), endogenous melanocortin receptor ligands, galanin-like peptide, GnRH-II, kisspeptin, gonadotropin inhibiting hormone or corticotropin releasing hormone (Bentley et al., 2006; Corp et al., 2001; Day et al., 2005; Jones et al., 2002; Keene et al., 2003; Meisel et al., 1996; Michel and Cabanac, 1999; Smith et al., 2006).

The preference data reveal a sharp contrast between the effects of leptin on consummatory and appetitive aspects of sex behavior. Food deprivation decreases lordosis duration in OVX female hamsters treated with E+P, and leptin treatment of food-deprived females exaggerates, rather than reverses, this dysfunction in sexual performance (Wade et al., 1997). The effects of leptin on appetitive sex behavior in hamsters are the exact opposite. Leptin treatment fully reverses the effects of food deprivation on vaginal scent marking and the preference for sex (Schneider et al., submitted for publication).

Similar dissociation between effects of leptin on appetitive and consummatory ingestive behavior are obtained in male rats given a choice between an estrous female and a bottle of sucrose (Ammar et al., 2000). Male rats prefer to visit an estrous female rather than drink from a bottle of sucrose, just as fed female hamsters prefer to visit a male rather than hoard food. Leptin treatment in male rats decreases sucrose consumption but also enhances the number of ejaculations per unit time without proportionally decreasing the number of intromissions per unit time, and this is similar to leptin-induced enhancement of female hamster vaginal marking per unit time in the Sex Box along with increases in time spent in the Sex Box. Treatment of male rats with NPY, in contrast, has little effect on male sex behavior in the absence of food or sucrose, but when NPY-

treated males are provided with a choice between a female and a bottle of sucrose, the males prefer to drink sucrose (Ammar et al., 2000). Finally, in male rats, leptin *increases* and NPY *decreases* passive consumption of sucrose when it is orally infused, a measure of purely consummatory ingestive behavior (Ammar et al., 2000). Together, these results are consistent with the idea that leptin stimulates a preference for sex over food, and are not consistent with the notion of leptin as a satiety hormone. Similarly, NPY is not strictly an 'orexigenic' peptide, but rather a peptide that increases the motivation to choose appetitive aspects of ingestion rather than sex during energetic challenges. Thus, in rats, hamsters, and perhaps other species, the role of these peptides is to rank and prioritize appetitive behaviors under conditions of fluctuating energy availability.

One more result from experiments using the hamster preference apparatus is important. A subset of food-deprived hamsters showed a very high preference for males over food, despite a similar loss of body weight and despite spending the same amount of time eating as those females in which food deprivation reduced preference for sex. This subset of food-deprived hamsters increased their time spent eating, but also visited the male instead of hoarding food. This group of food deprivation-nonresponsive hamsters demonstrates that the hunger for food and sex are not mutually exclusive. Similarly, when male and female rats receive oral infusions of glucose, they show consummatory ingestive behavior while simultaneously engaging in sexual performance (Kaplan et al., 1992). Thus, it appears that ingestive behavior is not the flip side of sex behavior. Animals must prioritize these competing desires and choose to engage in behaviors based on fluctuating environmental variables such as energetic status and the presence or absence of potential mating partners.

Consistent with this point of view, decreases in circulating leptin, increases in circulating ghrelin, and elevated central NPY increase appetitive aspects of ingestive behavior without affecting consummatory ingestive behavior in Siberian and Syrian hamsters. These peptides affect food hoarding more than they affect food intake, whereas drugs that inhibit moment-to-moment fuel oxidation are without effect (Bartness, 1990; Buckley and Schneider, 2003; Day and Bartness, 2001, 2003, 2004; Day et al., 2005; Keen-Rhinehart and Bartness, 2005). Although these hoarding experiments were not conducted in the presence of potential mating partners, the results are consistent with the notion that these peptides affect appetitive rather than consummatory aspects of ingestion.

Other species display these shifts in behavioral priorities, but some are more sensitive to moment-to-moment changes in energy availability and less sensitive to hormones such as leptin. For example, species with a high metabolic rate, such as musk shrews, show reproductive behavior that is highly sensitive to rapid changes in fuel oxidation (Temple et al., 2003). A 48-h period of food restriction eliminates musk shrew sex behavior, which is fully reinstated after only three hours of re-feeding (Temple and Rissman, 2000). Because these animals are extremely lean and unable to rely on body fat stores, it would be predicted that sex and ingestive behaviors in musk shrews

would be less sensitive to endocrine factors that correlate with body fat content, such as leptin and insulin, and more sensitive to rapidly fluctuating changes in fuel availability. Indeed, sex behavior in musk shrews is inhibited by treatment with either inhibitors of free fatty acid or glucose oxidation alone (Temple et al., 2002).

The hypothalamus and pituitary should not be forgotten in the energy balance equation. For example, the hypothalamic neurohormones, GnRH-I and -II have important effects on both sex and ingestive behavior in addition to their pivotal role in controlling fertility. The special role of GnRH-II in sex behavior and, in particular, the metabolic control of sex behavior was discovered in musk shrews. In females of this species, sexual receptivity is inhibited by a 48-h period of food restriction. GnRH-II, originally isolated in chickens, has more recently been found in marsupials, musk shrews, tree shrews, capybaras, monkeys and humans (Temple et al., 2003). Treatment with GnRH-II has little or no effect on LH secretion in fed animals; however, it reverses the effects of food restriction on sex behavior in musk shrews (Temple et al., 2003). Consistent with the reciprocal link between energy balance and reproduction, treatment with GnRH-II, but not GnRH-I decreases food intake and also reverses the effects of food deprivation on ingestive and sex behavior in female musk shrews (Temple et al., 2003) and ingestive behavior in mice (Kauffman and Rissman, 2004). It will be interesting to learn whether GnRH-II plays a role in the choice between food and sex and other motivated behaviors in a wide array of species.

Relevance to human beings

The relationship between reproduction and energy balance might be important for understanding human obesity and eating disorders. The health consequences of obesity and eating disorders are well documented and publicized, and yet these problems persist. Why has natural selection failed to eliminate these aversive, unhealthy and unfashionable conditions? One explanation is that alleles encoding traits that compromise the health of the individual will be favored by natural selection if those traits confer a net increase in reproductive success (Williams, 1957). For example, if a gene decreases the lifespan but increases the ability to produce offspring and raise them to sexual maturity, then that gene will be selected (Williams, 1957). Pleiotropic gene effects might explain the persistence of obesity even though it carries co-morbidities such as heart disease and type II diabetes. Genes that increase the propensity to eat and store energy might be closely associated with reproductive success, and if this reproductive advantage offsets the associated decrease in lifespan, then the propensity for obesity will persist in the population. Genetics studies have demonstrated a relatively high heritability of body mass and body fat distribution in humans (Allison et al., 1994; Bouchard, 1997). Furthermore, obese mothers tend to have significantly more children and give birth to offspring that are likely to eventually develop obesity (Ellis and Haman, 2004). Under these circumstances, obesity would be expected to increase in subsequent generations as long as the decrease in lifespan did

not negate the increase in reproductive success (Ellis and Haman, 2004).

It would be helpful to understand the exact physiological and behavioral mechanisms that lead to this differential reproductive success of obese mothers. Decreases in reproductive success in rural subsistence agricultural populations during seasons of low food availability are thought to be primarily due to decreases in embryo implantation after fertilization, rather than decreases in the frequency of sexual intercourse (Becker, 1994). However, the mechanisms that explain the higher number of offspring of obese, compared to medium-weight mothers in western industrialized societies have not been identified to the best of my knowledge.

Alternatively, or in addition, other adaptive consequences of the obese genotype might offset the morbidity and mortality of type II diabetes. Those individuals with the genetic predisposition to develop type II diabetes in modern societies (in which energy availability is high and demand for energy expenditure low), might have had reproductive and survival advantages during the times in evolutionary history when energy availability was low and the demand for energy expenditure was high (Neel, 1962). Specific genetic examples have been reported in mice that are heterozygous for the genes that confer the propensity to develop type II diabetes. For example, heterozygotes for the *ob* or *db* gene are better able to survive a long period of food deprivation compared the wild-type mice that do not develop obesity and diabetes (Coleman, 1979). Thus, genes that cause obesity in the homozygous state confer survival, and possible reproductive, advantages in the heterozygous state. This situation might be illustrated by those human populations with the highest prevalence of type II diabetes and obesity, the Nauru Islanders, Arizona Pima Indians and urban Wigela people of Papua New Guinea, which are currently experiencing food abundance and low demand for energy expenditure typical of our modern western lifestyle. These populations all share a past history of dramatic fluctuations in energy supply and demand due to drought and famine. The current rise in obesity compared to earlier time periods is consistent with the idea that genes coding for type II diabetes and obesity might have conferred survival, and possibly reproductive advantage during times of low food availability and high energy expenditure (Diamond, 2003). The specific mechanisms that underlie these reproductive advantages might be elucidated by studying a variety of mammals in natural or seminatural environments in which both food and mates are available.

The often used “thrifty” gene hypothesis (Neel, 1962) illustrates the hypothetical adaptive value of energy efficiency during evolution, but this particular terminology is misleading in the context of the many genes that contribute to body weight, body fat content and body fat distribution. In the majority of cases, neither obesity nor eating disorders can be explained by any one major dysfunction controlled by a gene or small group of genes. Body weight and adiposity are quantitative traits and the most common forms of obesity are polygenic (Boutin and Froguel, 2001). Molecular analysis of quantitative trait loci has estimated that there are many independent loci that influence

body weight in mice, and thus there are likely to be many genes in which allelic variation can account for body weight differences in human beings (Barsh et al., 2000). It is not surprising then that single gene mutations account for less than 5% of the overweight and obese population (Boutin and Froguel, 2001). It is unlikely that any one gene, thrifty or not, will explain human obesity. Furthermore, environmental factors acting throughout development of the individual interact with these genetic factors. The wide range of variation in body weight and adiposity and the relatively high degree of additive genetic variance in body weight and adiposity suggests that natural selection has not acted intensely on any one particular morphological type, either lean or obese. Our species can and does survive and reproduce at a wide range of body weights and adiposity levels and thus, selection has allowed for a great deal of additive genetic variation in this trait. It is not surprising then that we have not yet found a natural mechanism that controls food intake for the express purpose of constraining body weight and adiposity within a fashionable and healthy range that maximizes life expectancy in the face of calorie-dense, readily available food. Such a “healthy,” fashionable phenotype is observed, but it is not “normal” by evolutionary standards. This phenotype is simply part of a continuum of variation in adiposity that has been tolerated by natural selection during human evolution, and body types on the extreme ends of the frequency distribution might have been critical for population survival during certain periods of our evolutionary history. The array of alleles that influence food intake have allowed organisms to engage in activities necessary for perpetuation of the species in the habitats in which these organisms evolved. In our species, it is likely that these habitats contained dramatic fluctuations in energy availability, exacerbated by the energetic demands for migration, predator avoidance, hunting and agriculture (Wells, 2006). Future research must start with the notion that the mechanisms that inhibit food intake evolved to optimize reproductive success under conditions in which the availability of and demands for metabolic fuels fluctuate.

Reproductive hormones and the rise in obesity and eating disorders

All of the above considerations together suggest that reproductive neuroendocrinology might hold the key to understanding obesity and eating disorders. Energy availability affects responsiveness to steroids (as described earlier in this review), but also, steroids influence energy balance and body fat distribution in adulthood and during early development.

Depending on the species, a pre- or neonatal rise in either androgens or estradiol masculinizes the external genitalia and the brain mechanisms that control male-typical behavior, so that, at puberty the full-blown male-typical morphology and behavior are expressed upon the increase in peripubertal androgens (Cooke et al., 1998). The longlasting, prenatal effects of steroids are termed “organizational,” whereas the more acute effects in adulthood are sometimes termed “activational.” Energy balance and body fat distribution are part of the sexual dimorphism in many mammalian species

including our own, and gonadal steroids have important effects on body size, body fat content and body fat distribution (Nilsson et al., 1998). Human beings are strongly sexually dimorphic for body size and fat distribution with profound health consequences. These sexual dimorphisms often arise pre- or neonatally through the activational and organizational effects of steroids on the brain and periphery (Nilsson et al., 1998).

First, consistent with our view that metabolic signals and hormones change sensitivity to E or downstream effects of E, there are sex differences in the effects of the metabolic hormones leptin and insulin. Female mice are more sensitive than males to the anorectic effects of leptin treatment, whereas males are more sensitive than females to the anorectic effects of the pancreatic hormone insulin (Clegg et al., 2006). These results are consistent with the notion that E and leptin interact to control the choice between food and mating in females (discussed earlier in this review).

Second, E and ER are also implicated in the sexual dimorphism in body fat distribution. Males tend to have abdominal obesity and accumulate fat in the viscera, whereas females tend to store more fat subcutaneously, particularly in the gluteofemoral regions (hips and thighs), and it is now well established that body fat distribution is far more critical to long-term cardiovascular health and glucose homeostasis than overall body fat content or body mass index (Bjorntorp, 1988; Despres, 1993; Gillum, 1987; Macor et al., 1997; Marin and Bjorntorp, 1993; Van Gaal et al., 1988). There is speculation that male humans have an innate attraction to female figures with a low waist-to-hip ratio because this morphological type is associated with higher fertility and cardiovascular health (Singh, 1993, 1994a,b,c). Cardiovascular disease, insulin resistance and type II diabetes are more prevalent in men than in women, and men tend to have a higher waist-to-hip ratio. In women, a masculinized, high waist-to-hip ratio predicts the negative cardiovascular and glycemic side effects of obesity, whereas there are no known health risks associated with obesity when the waist-to-hip ratio is below 0.7 for women and 0.9 for men (Singh, 1993; Van Pelt et al., 2002, 2005). In fact, it has been suggested that a high percentage of gluteofemoral fat is actually cardioprotective, either directly, or because it is an excellent predictor of low visceral fat levels (Van Pelt et al., 2005). Plasma levels of insulin and leptin are correlated with body fat content; however, insulin levels are more closely correlated with visceral fat content, whereas leptin levels are more closely correlated with subcutaneous fat content. The female-typical body fat distribution is characterized by more subcutaneous than visceral body fat, and total body fat is more closely correlated with plasma leptin concentrations than with plasma insulin concentrations in females (Woods et al., 2003). The male-typical body fat distribution is characterized by more visceral than subcutaneous body fat, and total body fat is more closely correlated with plasma insulin concentrations than with plasma leptin concentration in males (Woods et al., 2003). It is conceivable that higher levels of E in adult females account for this sex difference in leptin and insulin sensitivity. In addition, E and its action on ER α and ER β are implicated in control of body fat content and distribution. For example, mice without the

functional estrogen receptor, ER α knockout (ER-KO) mice, are obese (Heine et al., 2000; Naaz et al., 2002).

Third, it is possible that estrogens or ER-binding molecules alter the development of the fetus, resulting in permanent changes to the adipocytes and cellular metabolism, and these, in turn, lead to excess visceral body fat, cardiovascular disease and type II diabetes in adulthood. One might predict that pre- or neonatal steroids or steroid-like molecules would increase visceral fat accumulation in both males and females.

What might be causing the overexposure of the developing fetus to estrogen or ER-binding molecules? Excessive exposure to molecules that bind to steroid receptors or receptors for other endogenous ligands is an increasing concern. Endocrine disruptors are molecules that bind to endogenous hormone or neuropeptide receptors and mimic or block the action of endogenous ligands for those receptors (Baillie-Hamilton, 2002). For example, many natural and synthetic molecules are known to bind to estrogen receptors, either mimicking or blocking estrogen action. Accumulating evidence suggests that estrogen exposure in humans and other animals might be increasing due to various aspects of modern life, including a wide array of ER-binding molecules from pesticides, industrial effluent, meat and dairy products, soy products, plastics and paints (Baillie-Hamilton, 2002). The role of ER in natural body weight regulation and body fat distribution might be central to the rise in obesity (Heindel, 2003; Oken and Gillman, 2003), given the fact that our species might be exposed to these endocrine disrupting agents. Some evidence for the link between endocrine disruptors and obesity is surfacing. For example, neonatal treatment with the synthetic estrogen, diethylstilbestrol (DES), the soy isoflavone, genistein, or the ER-binding molecule known to leach from plastics and paints, bisphenol A, all cause significant increases in body weight and body fat content, have significant influences on differentiation of adipocytes, or disrupt glucose homeostasis, in effect, leading to obesity and insulin resistance in rodents (Masuno et al., 2002; Newbold et al., 2005; Sakurai et al., 2004). Given the known masculinizing effects of neonatal estrogens on the developing reproductive system, including brain and behavior (Cooke et al., 1998), and the presence of ER on adipocytes (Mizutani et al., 1994), one would predict that these estrogen-binding compounds would also masculinize body fat distribution and increase the incidence of abdominal obesity, cardiovascular disease and type II diabetes. This might shed light on some of the causal relationships between obesity and disease. The demonstrated effects of bisphenol A, DES and genistein on body weight, body fat, adipocyte development and glucose homeostasis suggest that at least some of the well-known correlation between obesity and disease, such as prostate and breast cancer, might be due, at least in part, to neonatal or prenatal exposure to these ER-binding molecules rather than to direct effects of obesity per se. Developmental effects of endocrine disruptors on sexual differentiation of the reproductive and immune systems have been documented to some degree (Damstra, 2002), and the picture that emerges is that low doses of these ER-binding molecules during fetal and neonatal development permanently masculinize the nervous, repro-

ductive and immune systems. In addition, there is a sex difference in the incidence of eating disorders, with far more eating disorders reported in women (e.g., Sodersten and Bergh, this issue). As with obesity, recent evidence suggests that the prevalence of eating disorders might stem from early developmental effects on the brain that change neural sensitivity to E. In this case, one would expect prenatal masculinization of the brain (presumably by androgens or their metabolites) to decrease the sensitivity to the anorectic effects of E after puberty, whereas one would expect feminization (perhaps due to a lack of prenatal androgens) to do the reverse (Klump et al., 2006). There are only a few studies so far on the role of these estrogenic and anti-estrogenic compounds on energy balance, but it seems plausible that a part of the worldwide increase in obesity might be traced to these endocrine disruptors.

If GnRH-II effects on sex and ingestive behavior are sensitive to steroid feedback (as discussed earlier in this review), they also will be susceptible to the action of the ubiquitous endocrine disruptors because releasing hormones are responsive to steroid feedback. If this is true in humans as well, the hypothalamic hormone, GnRH-II, might turn out to be a major factor in obesity by virtue of its inhibitory effects on appetite. In contrast to the gonadal steroids and the hypothalamic neurohormones, the pituitary gonadotropins are largely unexplored with regard to their direct effects on energy balance, to the best of my knowledge. More research on effects all of these so-called “reproductive” hormones on energy balance is in order.

In addition, the list of hormones with organizational effects on the brain with long lasting effects on adult brain behavior now includes the adipocyte hormone leptin. Neonatal surges in leptin organize the neural connections between the arcuate nucleus and other brain areas that mediate the effects of leptin on energy balance (Simerly, 2005). Hormones of the hypothalamic–pituitary–adrenal (HPA) system are also relevant to this discussion because they influence body fat distribution; there are sex differences in responsiveness to adrenal hormones; and disorders of the HPA system often lead to increased exposure to steroids (Dobson and Smith, 2000; Tilbrook et al., 2000, 2002; Peeke and Chrousos, 1995; Loucks and Redman, 2004; Bjorntorp, 1993; Dallman et al., 2005; Slijper, 1984; Gohil et al., 2001; Stikkelbroeck et al., 2003). Together these considerations suggest that we should seek to understand the role of the HPG and HPA systems in control of energy balance and sexual differentiation of the energy balancing system.

Summary and conclusions

It has become increasingly apparent that the study of ingestive behavior can be facilitated by attention to the methodologies and theoretical considerations from the field of reproduction and vice versa, as first suggested by Kennedy (1953) and Kennedy and Mitra (1963) and further elucidated by Wade and Schneider (1992). The link between energy balance and reproduction lies at the core of evolutionary adaptation, and if ingestive and reproductive behaviors were molded by natural

selection, these behaviors occurred in an environment in which there was often a choice between foraging and courtship.

The link between energy balance and reproduction is relevant to understanding medical problems associated with “disregulation” of energy balance. The mechanisms that prioritize feeding and reproduction have been successful for the perpetuation of species including our own, but these mechanisms have been less successful at preventing obesity in modern times. The mean body weight and the incidence of obesity increased in most human populations when these populations were provided with ad libitum availability of highly palatable, calorically dense foods and were released from energetic challenges, such as the need for physical work to obtain food (Wells, 2006). Knowledge of the adaptive significance of leptin, NPY, melanocortin and other circuits and the effects of these circuits on energy efficiency, reproductive behavior and fecundity will suggest realistic and testable hypotheses about the mechanisms that partition energy and prioritize behavioral options. This knowledge might also lead to plausible, testable hypotheses to explain the obesity epidemic and the increase in eating disorders. For example, the biological, evolutionary perspective redirects our attention to the role of reproductive hormones and reproductive neuropeptides on energy balance, ingestive behavior and sexual motivation. There are clear sexual dimorphisms in body fat content and adipose tissue distribution, and these dimorphisms might be brought about by hormone action during a critical period of development. In parallel with the increase in obesity and eating disorders, there has been an increase in presence of molecules that bind to steroid receptors in the environments of western industrialized nations. We need more research on the early developmental effects of synthetic, xenobiotic and phytoestrogens on sexual motivation, fertility and body fat distribution. For behavioral neuroendocrinologists, this perspective suggests a variety of testable hypotheses concerning the mechanisms that control energy balance and reproduction. More progress will be made if we keep in mind that these factors control the motivation to engage in ingestive and sex behaviors instead of or in addition to affecting the ability to perform these behaviors. Finally, we can better understand energy balance and reproduction by studying many diverse species under natural or seminatural circumstances.

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