Sex differences in the physiology of eating

Lori Asarian¹ and Nori Geary²

¹Institute of Veterinary Physiology and Center for Integrated Human Physiology, University of Zurich, Zurich, Switzerland; and ²Schwerzenbach, Switzerland

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Asarian L, Geary N. Sex differences in the physiology of eating. Am J Physiol Regul Integr Comp Physiol 305: R1215–R1267, 2013. First published July 31, 2013; doi:10.1152/ajpregu.00446.2012.—Hypothalamic-pituitary-gonadal (HPG) axis function fundamentally affects the physiology of eating. We review sex differences in the physiological and pathophysiological controls of amounts eaten in rats, mice, monkeys, and humans. These controls result from interactions among genetic effects, organizational effects of reproductive hormones (i.e., permanent early developmental effects), and activational effects of these hormones (i.e., effects dependent on hormone levels). Male-female sex differences in the physiology of eating involve both organizational and activational effects of androgens and estrogens. An activational effect of estrogens decreases eating 1) during the periovulatory period of the ovarian cycle in rats, mice, monkeys, and women and 2) tonically between puberty and reproductive senescence or ovariectomy in rats and monkeys, sometimes in mice, and possibly in women. Estrogens acting on estrogen receptor-α (ERα) in the caudal medial nucleus of the solitary tract appear to mediate these effects in rats. Androgens, prolactin, and other reproductive hormones also affect eating in rats. Sex differences in eating are mediated by alterations in orosensory capacity and hedonics, gastric mechanoreception, ghrelin, CCK, glucagon-like peptide-1 (GLP-1), glucagon, insulin, amylin, apolipoprotein A-IV, fatty-acid oxidation, and leptin. The control of eating by central neurochemical signaling via serotonin, MSH, neuropeptide Y, Agouti-related peptide (AgRP), melanin-concentrating hormone, and dopamine is modulated by HPG function. Finally, sex differences in the physiology of eating may contribute to human obesity, anorexia nervosa, and binge eating. The variety and physiological importance of what has been learned so far warrant intensifying basic, translational, and clinical research on sex differences in eating.

SEX DIFFERENCES ARE PERVERSIVE in physiology and medicine (51, 64, 73, 109, 110, 466, 797, 826). The controls of eating and energy homeostasis are no exceptions. It was observed approximately 100 years ago that removal of the ovaries leads to marked accretion of adipose tissue in rats (697), that daily food intake expressed as kilocalories per gram body weight differs between male and female rats (778), and that food intake varies regularly through the ovarian cycle in intact female rats (674, 779). Sex differences in eating have been the subject of physiological research ever since. The clinical relevance of this work is increasingly evident. In the United States, women are approximately threefold more vulnerable than men to psychiatric eating disorders (346, 351) and approximately twofold more vulnerable to severe and morbid obesity (BMI ≥ 35 and 40 kg/m², respectively, mass/height²) (226). Women also appear to suffer more from these disorders in terms of physical and psychological functioning and quality of life (24, 84, 273, 292, 465, 531, 762). The increased obesity burden suffered by women is reflected in the fact that >80% of bariatric surgery patients in the United States are women (568, 630). Obesity also decreases fertility and increases the risks of miscarriage and serious health problems for mother and child during pregnancy and after birth (357). In short, eating and weight management are special challenges for women’s health. In light of this, our goals are to critically review present understanding of sex differences in the physiology of eating, to identify important gaps in current knowledge, and to highlight opportunities for basic and translational research. We focus on eating, that is, the controls of the “consummatory” behavior of meal taking and related measures of the total amount consumed. Except for a few instructive examples, we restrict our review to laboratory rats and mice and to anthropoid primates, i.e., monkeys, apes, and humans (infraorder Simiiformes or Anthropoidea).

We consider both male-female sex differences and sex-specific effects, i.e., effects that occur only in one sex, such as effects related to ovarian cycles, pregnancy, and lactation, as well as effects controlled by gonadal steroid hormones. As reflected in our review, there is much more work on females, especially ovarian-cycle effects and estrogen-mediated effects, than on male-female sex differences or androgen-mediated effects. We focus on biological sex differences, but emphasize at the outset that it is impossible to draw sharp lines between purely biological and nonbiological causes of sex differences in behavior (e.g., 48, 250, 797). We consider food choice only in the context of the total amount eaten. Although we review some
subjective phenomena that are closely connected to eating per se, such as ratings of palatability, we do not review the wide range of subjective and behavioral phenomena integral to a full understanding of eating, for example, foraging and other “appetitive” behaviors (41), cognitive and social controls of eating, and stress- or immune-related controls.

**Neuroendocrine Background**

We begin with an overview of hypothalamic-pituitary-gonadal (HPG) axis function for several reasons. 1) A common source of error is the failure to recognize differences in HPG axis function among women, rats, mice, and other species, a potential problem that is compounded by the ever-increasing understanding of HPG axis physiology. 2) Most of the known HPG mechanisms underlying sex differences in eating involve gonadal steroid hormones. But because the mechanisms of many sex differences in eating remain unclear, it would be premature to assume that other HPG mechanisms are not involved. For example, changing levels of estrogens alone may fully explain changes in eating during the ovarian cycle in mice and rats, but do not do so in women. 3) The many metabolic feedbacks onto the hypothalamic controls of ovarian cycling and ovulation (187, 330, 646, 787, 812) suggest it is likely that hypothalamic reproductive physiology also controls eating, although such controls have not yet been identified. 4) Neuroendocrinology is a vibrant area, and many novel discoveries and concepts are likely to be relevant to the physiology of eating. We also discuss in this section some criteria that we used to select physiologically reasonable methods for hormone treatment and to distinguish apparently aphysiological results.

**Gonadal steroid hormones.** Estrogens, androgens, and progestins (or progestagens) are groups of gondadal steroid hormones, each defined by its biological activity (74). In rats and anthropoid primates, 17β-estradiol (or estradiol) is the most potent estrogen and usually circulates in the highest concentrations (236, 556, 821). For example, rats’ ovaries secrete ~5–8-fold more estradiol than estrone (655), and exogenous estradiol inhibited eating ~10-fold more potently than exogenous estrone in ovariectomized rats (766). Testosterone is the primary androgen, and progesterone is the primary progestin. Gonadal steroid hormones act on cognate receptors, i.e., estrogen receptors (ER), progestin receptors (PR), and androgen receptors (AR). Classical steroid receptors are nuclear receptors, although, as described below, the importance of membrane-mouted steroid receptors is increasingly apparent. For example, the principal ER, ERO, and ERβ, are expressed in tissue-specific patterns both in nuclei and on membranes (470, 479).

Figure 1 schematizes the principal pathways of human gonadal steroidogenesis (for a detailed review, see Ref. 484). Males and females produce both androgens and estrogens, and both have biological effects in each sex. The gonads are the source of almost all circulating androgens in men and of circulating estrogens and progestins in premenopausal women, and these molecules act as hormones. In contrast, most circulating estrogens and progestins in men, a significant amount of circulating androgens in premenopausal women, and all of the gonadal steroids in the plasma of postmenopausal women derive mainly from other tissues, and these molecules appear to have their main biological actions in those tissues before reaching the circulation; i.e., they do not act as classical hormones (411, 448, 669). This is sometimes referred to as intracrine function. Recognition of its importance has fundamentally changed endocrinology in recent decades. In the brain, locally produced steroids are called neurosteroids (240, 477, 478, 611). In anthropoid primates, the adrenal glands are a major source of precursor molecules for local steroid synthesis. In rats and mice, synthesis begins with cholesterol, which cannot pass the blood-brain barrier and is synthesized de novo in the brain, or with gonadal steroid hormones taken up from the circulation. For example, in rat hypothalamic neurons, circulating estrogens regulate the expression of β3-hydroxysteroid dehydrogenase, which controls the synthesis of progesterone from cholesterol, and recent studies indicate that it is this neuroprogesterone, not endocrine progesterone, that initiates the LH surge and ovulation (477, 478). There is a report that another neurosteroid, 17α-estradiol, may affect eating (104). Finally, 2-hydroxyestradiol and 2-hydroxyestrone are catabolic products of estrogens that circulate in the blood and may act in the brain to affect food reward (29) (please see *Physiological Sex Differences in Disordered Eating*).

**Origins of sex differences in brain and behavior.** Biological sex differences derive from two evolutionary forces: natural selection, due to the different biological roles of males and females, and sexual selection, due to competition for mates. The proximal causes of biological sex differences comprise a complex interplay of genetic and endocrine mechanisms (9, 10, 32, 271, 425, 456, 471, 671, 807). In most mammals, the development of phenotypic sex differences is initiated by genes on the X and Y sex chromosomes, with females typically possessing the XX karyotype and males, the XY karyotype. There are relatively few genes on the sex chromosomes (~0.15% of human genes are Y-linked and ~4.5% are X-linked), and their functions are not yet fully understood. At the blastocyst stage of embryological development, corresponding to 70–100 cells in humans, most cells inactivate one or the other X chromosome, according to a random process. In these cells, only one of the two alleles of each gene is active. In humans, however, 15–25% of genes escapes X inactivation. A key sex-determination gene is *Sry* (Sex determining region on Y), whose presence causes the undifferentiated fetal gonad to develop into a testis; in the absence of *Sry*, autosomal or X genes induce ovarian differentiation. De Vries et al. (174) deleted *Sry* from the Y chromosome and inserted it in into an autosome, thus enabling dissociation of sex-chromosome effects from *Sry*-determined effects, i.e., mainly effects mediated by gonadal hormones. Analyses of this “four core-genotype” model indicate that while the majority sex differences in reproductive behaviors and the related brain structures in mice are controlled by *Sry* via gonadal hormones, a variety of other sex differences are controlled more by sex chromosomes than gonadal steroids (425). Two tests of eating in the four core-genotype model were recently reported (please see *Sex differences in eating in rats and mice*).

Relatively permanent effects of gonadal steroid hormones in early development or during puberty are called “organizational effects” (8, 551). Early masculinization and defeminization of male brains results from the surge in androgen secretion by the testes that occurs during the end of the embryonic period through the first postnatal day in rats and mice and between week 10 and 20 of pregnancy in humans (652). In mice and rats, these effects of androgens require their aromatization to
estradiol, which combines with maternal estrogens prenatally; whether this is also so in humans is unclear. Female rat and mouse brains are protected from these processes because there is no perinatal gonadal androgen secretion and because the developing brain is protected from maternal estrogens by H9251-fetoprotein, which binds estrogens to create a complex that does not cross the placenta. The importance of H9251-fetoprotein is underscored by demonstrations by Bakker and her colleagues (33, 279) that 1) the brains and reproductive behavior of female transgenic mice that do not express H9251-fetoprotein were masculinized and defeminized with testosterone treatment, and 2) that the feminine phenotype was rescued by blocking embryonic metabolism of testosterone with an aromatase inhibitor. In humans, α-fetoprotein is abundant, but does not bind estrogens. Sex hormone-binding globulin, rather than α-fetoprotein, may protect the developing human female brain from estrogens (306).

Feminization begins during postnatal week 2 in rats and mice, when the infant ovary begins to secrete estrogens and α-fetoprotein secretion decreases. Further work by Bakker and Baum

Fig. 1. The principal pathways of human gonadal steroid hormone synthesis. Molecules are shown in standard line-angle diagrams, and enzymes are represented as numbered arrows, with the major pathway in adult gonads circled. Steroidogenesis begins with the cleavage of the 6 C side chain from cholesterol (C27H46O) by the mitochondrial cholesterol side-chain cleavage enzyme, otherwise known as P-450scc or CYP11A1 (arrow 1) to yield pregnenolone (C21H32O2). Note that it and other progestins (or progestagens; labeled in blue, with the structure of progesterone, the principal progestin, also in blue) are 21 C molecules. Subsequent steps occur on the smooth endoplasmic reticulum. Progestins are metabolized to androgens (labeled in red, with the principal androgen, testosterone, diagrammed in red), which are 19 C, and to mineralocorticoids and glucocorticoids (not shown), which are 21 C. Androgens are metabolized to estrogens (labeled in green, with the principal estrogen, estradiol, diagrammed in green), which are 18 C. Note that all of these steroids retain the basic 17 C “gonane” structure, consisting of three cyclohexane rings and one cyclopentane ring, but differ in the attached side groups and oxidation states of the rings. An additional estrogen, estriol (not shown), is synthesized in significant amounts only by the placenta and fetal liver. Other labeled enzymes: 2, 17α-hydroxylase; 3, 17, 20-lyase; 4, 17β-hydroxysteroid dehydrogenase; 5, 3β-hydroxysteroid dehydrogenase; 6, 5α-reductase; 7, aromatase; 8, 21-hydroxylase.
(32) on transgenic mice lacking aromatase clearly demonstrated the active role of estrogens in this process. They found, for example, that female mice lacking aromatase failed to develop normal female adult reproductive behavior (34) and that estradiol treatment between postnatal days 15 and 25, but not before day 15, was sufficient to reinstate normal adult behaviors (88).

In contrast to the permanent or “organizational” sex-differentiating effects of gonadal hormones early in development, effects at other life stages are often reversible and are called “activational effects” (8, 551). These occur only in the presence of the hormones involved and, therefore, wax and wane during reproductive life. Often activational sex differences require anatomic substrates generated in early development by sexually differentiated organizational processes.

**HPG function in adults.** The fundamentals of HPG axis function in rats (and presumably in mice, but this has not been as extensively characterized) and humans (understood mainly from studies in monkeys) are similar (236, 556, 821) (134, 289, 290). Gonadotropin-releasing hormone (GnRH; formerly called luteinizing hormone-releasing hormone) is secreted pulsatile from neurons located in the hypothalamic preoptic area in rats and mice and in the arcuate nucleus in monkeys and humans into the hypophyseal-portal circulation. This leads to secretion of follicle-stimulating hormone (or FSH) and luteinizing hormone (or LH) from the anterior pituitary into the general circulation. These stimulate the secretion of gonadal steroids.

Gonadotropin (or LH) from the anterior pituitary into the general circulation. These stimulate the secretion of gonadal steroids. GnRH secretion is also regulated by a pulse generator, which has a constant period of about 2–3 h in men and 60–90 min in women. Both slower and faster frequencies fail to produce normal gonadal steroid levels. Gonadal steroids, LH, and other HPG-axis hormones provide feedback signals to both the pituitary and hypothalamic levels. Feedback is mainly negative in males and contributes to a relatively constant hormone secretion in adult males. The resulting plasma levels of testosterone are ~2–3 ng/ml in mice, ~1–3 ng/ml in rats, ~8–15 ng/ml in cynomolgus monkeys, and ~3–10 ng/ml in men (520). Both positive and negative feedbacks occur in females, leading to changing hormone secretion through the ovarian cycle, as described in the next sections.

**SPONTANEOUS OVARIAN CYCLES.** HPG axis function and the control of ovulation vary widely across mammalian species. Many are seasonal ovulators (454), some are mating-induced ovulators (364), and a few, including rats, mice, and anthropoid primates, display spontaneous cycles. In this latter group, ovulation occurs in spontaneous rhythms, or ovarian cycles, that occur regularly throughout the year between puberty and reproductive senescence, except during pregnancy and lactation. These are known as estrous cycles in rats, mice and several other species and as menstrual cycles in women, monkeys, apes, and a few other species in which the cycle ends with discharge of endometrial tissue.

**Ovulation and behavioral estrus occur in 4–5-day cycles in rats and mice.** Rats’ sexual receptivity is maximal in the middle of the nocturnal phase of estrus and near zero during diestrus (estrus phases are defined in the next section) (72, 825). In contrast, women are sexually receptive throughout their ovarian cycle, although the degree of receptivity apparently varies (247, 295). There is little or no seasonal variation in reproductive function of mice and rats (421). In addition to reproductive behaviors, eating, locomotor activity, nest building, fluid intake, food hoarding, and other behaviors vary rhythmically during the estrous cycle (217, 224, 251, 727). The maxima of these cycles are not all in phase, and a variety of evidence indicates that they are separately controlled. For example, although facilitation of the copulatory behavior lordosis and decreased eating both occur during the night of estrus in rats, facilitation of lordosis requires progestins, as well as estrogens (549), but the estrous decrease in eating does not (15, 259, 766). Ovarian cycle effects are the most researched sex differences in eating, and we review them in detail.

**OVARIAN CYCLE PHASE.** Rat and mouse ovarian cycle phases or days are most frequently categorized by “vaginal cytology” (48, 236) based on Long and Evans’s (440) classical description of the associations among ovulation, reproductive-tract histology, and reproductive behavior, and named as suggested by Heape (321). Vaginal estrus, marked by the cornification of vaginal epithelial cells, begins around the LH surge, which occurs near dark onset, and ends during the subsequent light phase. Thus, vaginal cytology is best sampled in the nocturnal phase or early in the diurnal phase, as indicated by the hatched bar at the bottom of Fig. 2. As mentioned above, behavioral estrus and the estrous decrease in eating are most prominent during the nocturnal phase after the LH surge. In order to have this nocturnal phase occur during the nominal day of estrus, cycle days should not begin at the midpoint of the dark phase, i.e., midnight, as ordinary clock-time days do. Beginning cycle days at the midpoint of the dark and using diurnal vaginal cytology to assign day names leads to the unfortunate consequence that estrous behaviors occur during the day labeled proestrus. This is a major source of confusion in across experiment comparisons. Therefore, here, we begin cycle days at dark onset and assign names based on early light-period vaginal cytology (15). The preovulatory phase of the cycle usually lasts 3 days, labeled diestrus 1 (or metestrus), diestrus 2 (or diestrus), and proestrus.

Women’s cycle days are numbered either J forward from the first day of menses, which is the beginning of the follicular phase, and with day 1, the presumed day of ovulation, dividing the follicular and luteal phases, or 2) backward (follicular stage) and forward (luteal phase) from the LH peak. Detection of the LH peak by assaying plasma or urinary LH is considered the gold standard for ovarian-cycle research (55, 342). If LH is measured, the periovulatory phase is the 4 days around the LH peak (ovulation usually occurs within 1 day of the LH peak).

**NEUROENDOCRINE CONTROL OF THE OVARIAN CYCLE.** The cyclic changes in LH, FSH, estradiol, and progesterone in 4 day-cycling rats and women are shown in Figs. 2 and 3, respectively. Some obvious differences are J) cycle length is much longer in women (~28 days) than in rats and mice (usually 4 or 5 days); 2) absolute levels of estrogen are much higher in women; 3) absolute levels of progesterone are lower in women; and 4) the pattern of hormone secretion after ovulation is very dissimilar in humans and rats (discussed below).

The patterns of LH, FSH, and estrogen secretion are similar in women and rats and mice during the preovulatory phase of the cycle, i.e., during the follicular phase in women and diestrus 1 through early estrus in rats and mice. The preovulatory levels of LH and FSH, although low, are required to increase follicular production of estrogens. LH stimulates pro-
duction of androgens by the theca cells, which express LH
receptors, cholesterol side-chain cleavage enzymes, and 17α-
hydroxylase. FSH stimulates production of estrogens from
these androgens by the granulosa cells, which express FSH
receptors and aromatase. Estrogens act in the hypothalamus
and pituitary to regulate cycle dynamics. During the preovu-
latory phase, estrogens exert mainly positive-feedback effects,
causing progressive increases in the frequency and magnitude
of GnRH pulses and, consequently, of LH pulses, culminating
in a surge of LH that initiates ovulation. Ovulation occurs ~36
h after the surge in women and ~10 h after the LH surge in rats
(i.e., late in the dark phase).

The pattern of progestin secretion during the preovulatory
phase is different in women vs. rats and mice. There is virtually
no progestin secretion during the human preovulatory phase,
whereas in rats and mice, there is a small peak in progestin
secretion during diestrus 2, originating from corpora lutea
formed in the previous cycle (see below), and a larger peak just
after the LH surge, originating from the granulosa cells of the
preovulatory follicle. Plasma testosterone levels also vary through
the menstrual cycle from ~0.5 ng/ml during the follicular phase to
~1.5 ng/ml during the luteal phase (524).

The postovulatory or luteal phase in anthropoid primates is
marked by creation of the corpus luteum, which results from
the transformation of granulosa and theca cells into carotenoid-
concentrating, yellowish luteal cells after ovulation. Connu-

Fig. 2. Plasma levels of LH, FSH, estradiol, and progesterone during the 4-day
ovarian cycle of rats maintained under 12:12-h light-dark cycle. Ovarian cycle
days, labeled on the basis of vaginal cytology and beginning at dark onset, are
diestrus 1 (D1), diestrus 2 (D2), proestrus (P), and estrus (E). Values are
smoothed averages based on several sources (101, 114, 444, 511, 684). Solid
bars along x-axis indicate nocturnal periods. LH levels are presented as fold
increases over basal (= 1) because published proestrous peak concentrations
vary >20-fold. Estradiol’s molecular weight is 272 and progesterone’s is 314.
Hormone concentrations during the additional day in 5 day-cycling rats are
similar to those in diestrus 1 (282). The pattern may vary slightly in rats
maintained under 14:10-h light-dark cycle (90). The hatched rectangle at the
bottom right of the figure indicates the period during which estrous vaginal
smears occur most regularly.

Fig. 3. Plasma levels of LH, FSH, estradiol, and progesterone during the human
ovarian cycle. Cycle phases, labeled with respect to the LH peak, are
follicular (F), periovulatory (PO), and luteal (L). The follicular phase begins
with menses, and the LH peak and ovulation occur ~14 d later. Longer
menstrual cycles are usually caused by prolonged follicular phases. Values are
smoothed averages based on several sources (97, 617, 638, 735).
Review

ing LH secretion stimulates the corpus luteum to secrete estrogens and progestins; in women, this phase lasts ~10–14 days. Progestins maintain the corpus luteum and stimulate angiogenesis and hypertrophy of the uterine endometrium (the decidual response). Estradiol levels are higher during most of the luteal phase than during the follicular phase, although lower than during the periovulatory phase. The human luteal phase ends with degeneration of the corpus luteum, shedding of the uterine decidua, and menstruation. The drop in secretion of progestins, estrogens, and inhibin releases the hypothalamus and pituitary from inhibition and increases GnRH pulse frequency, thus increasing LH and FSH secretion and initiating the follicular phase of a new cycle. If pregnancy occurs, secretion of chorionic gonadotropin maintains the corpus luteum.

Rats and mice do not provide an adequate model of the human luteal phase. Unlike women, rats and mice lack a prolonged postovulatory phase during which functional corpora lutea maintain high plasma estrogen and progestin levels (236, 313, 314). First, estrogen levels are basal by the time of ovulation and do not increase again until the next cycle. Second, rat corpora lutea begin to develop not after ovulation, as in women, but one or two cycles earlier; thus, two or three generations of corporal lutea are present simultaneously. These reach their maximal size and secretory potential during their final diestrus, which explains the small peak in progestin secretion during diestrus 2, and thereafter begin to degenerate. Another factor that decreases plasma progesterone levels and deciduation is that rat corpora lutea express 20α-dihydroxy-steroid dehydrogenase, which converts progesterone to 20α-hydroxyprogesterone, a less biologically active progestin. A second, larger peak in progesterone occurs simultaneously with the LH surge and ends near ovulation. As already noted, this progesterone originates in the preovulatory follicles, not the corpora lutea. By a few hours after ovulation, progesterone levels are no longer sufficient to maintain the decidual response. Follicular estrogen secretion and the next cycle begin during the light phase after ovulation, after only 6–8 h of recovery of HPG axis and reproductive tract.

Stimulation of the rat uterine cervix during mating causes secretion of pro lactin from the anterior pituitary, which maintains the corpora lutea for about the duration of the human luteal phase after nonfertile mating (“pseudopregnancy”) and throughout pregnancy (usually 21 days) after fertile mating. Pseudopregnancy also occurs spontaneously. Despite the maintenance of the corpora lutea and the similar durations of rat pseudopregnancy and the luteal phase, the endocrine profiles are different. Plasma levels of progesterone increase during pseudopregnancy as in the luteal phase, but plasma estradiol levels are minimal, as in normal pregnancy (249, 728). Inadvertent induction of pseudopregnancy can hamper studies of intact cycling rats.

Kisspeptin and gonadotropin-inhibitory peptide. The recently discovered hypothalamic peptides kisspeptin (268, 283, 377, 552) and gonadotropin-inhibitory peptide (GnIH) or RFamide-related peptide-3 (127, 407, 745) play important roles in HPG axis function. In mice and rats, kisspeptin is expressed most densely in the preoptic area, anteroventral periventricular nucleus (AVPV), and arcuate nucleus (the latter is often called the infundibular nucleus in humans). GnRH neurons are a major target of kisspeptinergic fibers. Kisspeptin is vital for pubertal development. In mice or humans lacking the kisspeptin receptor Kiss1R, GnRH secretion is insufficient to support normal pubertal development (hypogonadotropic hypogonadism). An elegant recent study by Lomniczi et al. (439) indicates that the timing of puberty in female rats depends upon epigenetic silencing of two transcription-repressor genes that suppress kisspeptin expression.

After puberty, kisspeptin is involved in the feedback control of gonadal steroids on GnRH secretion. In both sexes, gonadectomy leads to increased kisspeptin mRNA in the arcuate nucleus and decreased kisspeptin mRNA in the AVPV, suggesting negative and positive feedbacks, respectively (in females, negative feedback predominates in the early and mid-follicular phases, and positive feedback predominates in the late follicular and preovulatory phases; in males the two influences apparently are in tonic balance). Rometo et al. (610) showed that the estrogenic feedback effect also occurs in women by demonstrating 1) that the increases in GnRH secretion that occurs in postmenopausal women and in ovariectomized cynomolgus macaques (Macaca fascicularis) were associated with increased kisspeptin expression in the arcuate nucleus, and 2) that in ovariectomized monkeys estradiol treatment reversed both effects. In another interesting study (682), kisspeptin mRNA expression in the preoptic area and caudal arcuate nucleus and GnIH mRNA expression in the dorsal medial and paraventricular nuclei were higher in the follicular than the luteal phases of rhesus macaques (Macaca mulatta).

Estrogen signaling via ERα mediates kisspeptin function in a complex fashion. For example, conditional knockout of ERα in kisspeptin neurons both advances the onset of puberty and retards subsequent pubertal development in female mice (464). A recent study by Frazao et al. suggests that these disparate effects may be due in part to the different effects of estradiol acting via ERα on the electrophysiological activity of AVPV vs. arcuate kisspeptin neurons (233).

The synchrony of rat and mouse ovarian cycles with the circadian pacemaker, which results in cycle periods that are even multiples of days and which times the LH surge to occur at dusk, depends on kisspeptin neurons in the AVPV (236, 377, 793). In rats, estrogens stimulate these kisspeptin neurons, which, in turn, drive GnRH neurons in the preoptic area to produce the LH surge and ovulation; in contrast, in women, estrogenic positive feedback appears to be mediated by kisspeptin neurons in the arcuate nucleus that project to the mediobasal hypothalamus, with preoptic and circadian inputs not required (236, 793).

GnIH is synthesized by neurons in the dorsomedial nucleus of the hypothalamus in rats and mice (127, 407, 408, 745, 747). In one study, GnIH was found in the arcuate nucleus in women and female cynomolgus macaques (610); in another study, it was found in the intermediate periventricular (which is adjacent to the dorsomedial nucleus) and paraventricular nuclei in female rhesus macaques (746); and in a third study, it was found in the arcuate, dorsomedial and intermediate periventricular nuclei of female rhesus macaques (682). Interestingly, in the latter study, kisspeptin mRNA expression in the preoptic area and arcuate nucleus and GnIH mRNA expression in the dorsomedial and paraventricular nuclei were higher in the follicular phase than in the luteal phase (682). GnIH fibers project to similar areas as the GnRH neurons, as well as several other brain areas (127, 204–208).
407, 745). GnIH is thought to be involved in the negative feedback effects of estrogens early in the follicular phase and to sharpen the control of LH and FSH secretion by acting as a functional antagonist to GnRH.

Kisspeptin and GnIH both appear to affect eating. Central administration of kisspeptin inhibited eating in male mice (692), and central administration of GnIH stimulated eating in male mice, rats, and cynomolgus monkeys (127, 352, 498, 682). In addition, in female rats, knockdown of Arc kisspeptin neurons with saporin conjugated to the neurokinin-3 receptor, which the Arc kisspeptin neurons also express, reduced the effect of ovariectomy to increase body weight; unfortunately food intake was not measured (487). Fu and van der Pol (243) described a potential mechanism for the effects of kisspeptin and GnIH on eating. They found that kisspeptin fibers make excitatory synapses on arcuate nucleus neurons that express proopiomelanocortin, the precursor of the eating-inhibitory neuropeptide α-melanocortin-stimulating hormone (α-MSH), and indirectly inhibit arcuate neurons that express neuropeptide Y (NPY), which stimulates eating (sex differences in the effects of α-MSH and NPY are described below). Furthermore, GnIH inhibited the proopiomelanocortin neurons and reduced the effect of kisspeptin. Clearly, more work directed at analyzing sex differences in the eating effects of kisspeptin and GnIH is called for.

Reproductive senescence. The loss of fertility in aging females has different causes in rats vs. anthropoid primates. In rats, the repeated exposure of the brain to estrogens through reproductive life leads to progressive degeneration and unresponsiveness of the arcuate nucleus, such that cycling ends well before the ovaries are depleted of ova (347). Older female rats retain potentially viable ovaries in a state of arrested follicular development for months, during which time they display vaginal estrus. In contrast to rats, although aging affects numerous facets of HPG function in women, cycling is maintained until the ovaries are depleted (98, 189, 235, 303, 420, 508, 638). Thus, from the perspective of hypothalamic-pituitary function, young ovarioctomized rats provide a better model of human menopause than do older, reproductively senescent rats.

Menopause occurs between 45 and 55 yr of age in ~95% of women (276, 327, 629, 730). The menopausal transition is marked by increasing cycle-length variability, steady increases in basal FSH, and steady decreases in inhibin and anti-Müllerian hormone. Indeed, plasma levels of anti-Müllerian hormone in women 20–50 yr of age predicted the onset of menopause with an mean error of only 6 mo (730). In contrast, average plasma estradiol levels do not change much before menopause. Rather, they remain similar to those in younger women until menopause and then decrease over about a year to a fraction of the premenopausal basal level (98, 99, 303). Postmenopausal plasma estrogens derive mainly from the adipose tissue, and their levels are associated with adiposity (361). Obesity is also associated with slightly later age of menopause [i.e., a median delay of ~1 yr in overweight and obese women in a recent careful study (492)]. The mechanisms for this are not understood (28, 424, 492). Aging also affects HPG function in men, with the result that bioavailable testosterone levels decrease by ~2%/yr after age 40 (220, 308).

Hormone treatment regimens. Gonadectomy and hormone replacement are classic endocrine methods. Because endogenous testosterone levels are relatively constant, mimicking them is simple. Endogenous testosterone levels in adult rats vary according to age, strain, etc., from ~1–7 ng/ml, and near-physiological replacement is usually achieved with constant-release silicone-capsule implants (117, 118, 659). Because reproductive hormone levels cycle in female rats, however, constant-release pellets cannot be considered physiological. Indeed, daily or continuous peripheral administration of low estradiol doses or even single high doses of long-lasting estrogens such as estradiol valerate can disrupt ovarian cycling, induce pseudopregnancy, elicit progressive, aphasisiological changes in several brain neurochemical receptor systems and in behavior, and greatly accelerate the degeneration of the arcuate nucleus (83, 179, 347, 467, 468, 528, 529, 647). In contrast, a weekly cyclic estradiol injection regimen in which 10 μg estradiol benzoate was injected on Tuesdays and Wednesdays and progesterone priming and sexual-receptivity tests were done on Fridays led to stable, normal levels of progestin and oxytocin receptors and in sexual receptivity (647). Plasma estradiol levels in rats maintained on this regimen, however, increased to more than 4 times the proestrous maximum for several days and never decreased below the proestrous maximum (804). Reducing the two estradiol benzoate doses to 2 μg led to a more normal magnitudes of plasma estradiol, but still maintained the proestrous level for an abnormal duration and did not fully reproduce normal patterns of food intake (255). In contrast to these weekly schedules, subcutaneous injection of 2 μg estradiol benzoate once each 4th day produced near-physiological 4-day cycles of plasma estradiol concentration (15, 476) (Fig. 4) and led to normal spontaneous meal patterns, food intake, and body weight (15). Note that because of the rapid rates of esterification of estradiol benzoate in the plasma and clearance of estradiol from the plasma in rats (417, 724), the durations of the estradiol increases in these studies are due mainly to the slow entry of subcutaneously injected estradiol into the circulation.

Doses more than 20 μg estradiol consistently elicit signs of aversion in female rats, such as abnormal latency and duration of the eating-inhibitory effect, abnormal orofacial expressions, and the formation of conditioned taste aversions (253, 254, 333). We do not consider estradiol’s aversive effects to be...
useful in the analysis of its physiological effects on eating and do not consider high-dose studies here.

Subcutaneous injection of 0.5 mg/rat progesterone or 0.5–2 mg/100 g body wt progesterone increased plasma progesterone concentration to about the estrous maximum, although the time course was prolonged compared with estrus (3). Less information is available concerning appropriate doses for mice or for other HPG hormones. Becker et al. (48) provide an excellent discussion of technical and interpretational issues surrounding peripheral gonadal steroid hormone treatment.

Dose is also crucial in interpreting central steroid hormone treatments. Implants of ~3 ng 3H-labeled estradiol, prepared by filling the distal 1 mm of 28-gauge cannulas with 1:300 estradiol:cholesterol mixtures, into the ventromedial hypothalamic area (VMH) produced measurable label within only ~500 μm of the implant site and, in combination with peripheral progesterone injections, were sufficient to increase sexual receptivity in ovariectomized rats (168, 169). A formal mapping study for the inhibition of eating has not been done. Tests performed by Butera and colleagues (103, 108) of intrahypothalamic implants of ~100 ng estradiol in the distal 1 mm of 28-gauge cannulas indicated that estradiol spread <1 mm in amounts sufficient to inhibit eating and did not produce peripheral estrogenic effects, such as increased uterine weight or cornification of vaginal epithelial cells. Intrahypothalamic implants of more concentrated estradiol mixtures, both in the study by Butera and Beikirch (103) and many earlier studies, were sufficient to produce peripheral effects. Because the threshold peripheral estradiol dose for the inhibition of eating seems to be less than that for cornification of vaginal epithelial cells (190), such large doses clearly cannot be used to identify local effects. We (732) demonstrated that doses of ~200 ng 3H-labeled estradiol applied to the surface of the dorsal hind-brain just posterior to the area postrema in 1-mm2 pieces of absorbable surgical fabric produced measurable label only ~200 μm caudally, ~600 μm rostrally, and ~500 μm ventrally and did not lead to detectable amounts of estradiol in the plasma.

Latency of estrogen’s effect on eating. A frequent source of confusion is that in rats and mice, most estrogen-dependent responses occur during the nocturnal phase of estrus, when plasma estrogen levels are low, not high (please see Fig. 2). This timing probably reflects the dependence of the behaviors on transcriptional effects of estrogens, whose downstream consequences require hours or days to complete. This reasoning suggests that events during the ovarian cycle that depend on gene expression are likely to be due to the increases in plasma estrogens during diestrus, i.e., 1–2 days prior to estrus, and not to the peak of estrogen concentration during proestrus. This has been shown to be the case both for the LH surge (236) and for lordosis, a reflexive proceptive behavior characteristic of estrus that depends on increased expression of progestin receptors (549). For example, acute antagonism of estrogenic function during diestrus blocked the proestrus surge of LH and ovulation, whereas the same treatment early in proestrus had no effect (221, 510).

The estrogenic inhibition of eating in ovariectomized mice and rats has a latency that suggests a similar interpretation. Physiological or modest pharmacological peripheral doses of estradiol in a lipid vehicle, such as sesame oil, decrease eating ~24–48 h later in mice and rats, depending on the circadian time of administration (255, 287, 637, 731). Central administration of estradiol inhibited eating with a similar latency in rats (732). These data suggest that endogenous estrogens normally act in diestrus to initiate effects that result in reduced eating during estrus. We consider the typical ~24–48 h latency of the estrogenic inhibition of eating to be a useful criterion for the physiological relevance of estrogenic treatments in rats and mice. That is, if an estrogen or estrogen agonist decreases eating in <24 h in mice or rats, it is unlikely to mimic the physiological action of endogenous estrogens (please see Refs. 203, 286, 333, 731 and Site of ER Controlling Eating for further discussion). Unfortunately, we know of no data on the time course of any estrogenic effect on eating or on HPG axis function in monkeys, apes, or women.

Sex Differences in Eating in Rats and Mice

Male-female differences. Total daily energy intake in male rats exceeds that in females to an extent greater than predicted by their larger lean body mass and metabolic rate (790, 803). Normal “homeostatic” eating also contributes to the maintenance of significantly less body fat content in male than female rats (129). As described below, both organizational and activational effects of estrogens and androgens appear to contribute to these differences. There may be a species difference in how males’ greater intake is expressed in spontaneous meal patterns: the greater total food intake of male than female Long-Evans rats maintained on a palatable liquid diet resulted mainly from larger meals (457), whereas the greater food intake of similarly maintained male than female C57BL/6j mice resulted entirely from more frequent meals (701).

Activational effects of estrogens and androgens contribute to the maintenance of normal levels of food intake in rats, but do so in opposite ways. With few exceptions, ovariectomy increases rats’ daily food intake and body weight by increasing meal size, and estradiol treatment normalizes all three measures; in contrast, orchietomy decreases daily food intake and body weight by decreasing meal frequency, and testosterone treatment normalizes them (15, 18, 77, 102, 115, 191, 202, 203, 267, 726, 764, 776). As we review below, the estrogenic control of eating in rats is the best understood of these phenomena. There are many species differences in the effects of gonadectomy on eating and weight. For example, as discussed below, ovariecotomy often fails to elicit overeating in mice. In addition, in many species orchietomy increases food intake and adiposity (341). This may be the case for monkeys and humans, as we also discuss below.

There is an interesting male-female sex difference in regulatory or homeostatic eating. Male mice that were acutely food-deprived for 24 h (513), chronically food-restricted until they lost about 15% body weight (660), or underwent partial licectomy (660) all compensated by overeating, whereas similarly challenged female mice compensated by decreasing energy expenditure without overeating. A similar sex difference in postdeprivation eating occurred in both rats (751) and humans (820). The developmental origins of this sex difference are reviewed in the next section; whether activational effects also contribute is unknown.

There is also a sex difference in conditioned taste aversion learning in rats. In several tests, males and females acquired taste aversions to unconditioned stimuli such as LiCl similarly,
but females’ taste aversions extinguished faster after acquisition, i.e., began to ingest the conditioned stimulus, typically, a sweet solution, in normal amounts sooner when it was presented repeatedly in the absence of the unconditioned stimulus (160). Activational effects of both estrogens and androgens appear to contribute to this sex difference (116, 819). These findings merit further research because conditioned taste aversions are probably important in the control of eating in humans, especially in certain clinical populations, for example patients undergoing radiation or chemotherapy and patients with bulimia nervosa (65, 86, 641).

Development. Work begun in the 1970s by Wade and colleagues (266, 764) and others (56, 507, 452) demonstrated that neonatal masculinization of female rat pups increased their food intake and decreased their sensitivity to the eating-inhibitory effects of estrogens as adults. The latter effect suggests that, as is the case for numerous sexually differentiated brain functions, activational effects of estrogens in adults require organizational programming of the developing neural substrate. Nohara et al. (513) recently discovered some of this substrate. They found that female mice that were masculinized with neonatal testosterone treatment ate like intact males in that 1) they ate more than intact females at 6 wk of age, as previously described, and 2) unlike intact females, they increased eating following a 24-h fast when tested as adults. Nohara et al. (513) also identified two changes in the physiology of hypothalamic proopiomelanocortin (POMC) circuits that may underlie the sex differences in eating (POMC is the precursor of the neurotransmitters α- and β-melanocyte-stimulating hormone, which are involved in energy homeostasis; please see Sex Differences in Central Controls of Eating). That is, both hypothalamic expression of the POMC gene and the arborization of hypothalamic POMC neurons were reduced in neonatally masculinized females from the intact-female to the intact-male level. Comparison of neonatal treatment with estradiol and 5α-dihydrotestosterone, which cannot be converted to estradiol, verified that these effects were AR-mediated. Masculinization also led to hyperleptinemia and reduced the sensitivity of exogenous leptin to upregulate POMC, decrease eating and prevent adipose-tissue mass accumulation. These effects were estrogen dependent. The changes in plasma leptin concentrations and leptin sensitivity, however, lay outside the normal range, suggesting that the neonatal manipulations were not entirely physiological.

Chen et al. (122, 123) reported the first measurements of eating in the four core-genotype model of HPG axis development (described in The origins of sex differences in brain and behavior). They found that in C57BL/6J mice, both gonadal sex (testes or ovaries) and chromosomal sex (XX or XY) affected eating: 1) gonadal females (i.e., without Sry) ate more than gonadal males (with Sry) during the dark regardless of their chromosomal sex (XX or XY) (Fig. 5), and 2) gonadal and chromosomal females (XX with Sry) ate more than all other groups during the light and had an approximately twofold more fat mass (not shown). Estrogen and androgen treatments were not tested. Chen et al.’s (122, 123) and Nohara et al.’s (513) elegant studies, together with recent translational work on organizational influences on eating disorders (please see Physiological Sex Differences in Disordered Eating), should rekindle interest in the development of sex differences in eating (290).

Puberty involves changes in the secretion of HPG and other hormones, tissue sensitivity, and neuronal architecture (670, 671). Pubertal brain maturation appears to be necessary for the estrogenic inhibition of eating: 1) exogenous estradiol inhibited eating only in postpubertal rats (649, 765, 771), and 2) the amplification of endogenous cholecystokinin satiation by exogenous estradiol began at puberty (please see Cholecystokinin). In contrast, testosterone treatment did increase eating in prepubertal male rats (518), indicating that the maturation of the neural substrate for HPG-control of eating is sex-specific.

An organizational effect of estrogens also appears to be necessary for the stimulation of eating by prolactin treatment that occurs in adult female, but not male, rats (323). That is, prolactin stimulated eating in adult males whose brains were feminized by castration on postnatal day 1, but not in adult females masculinized by neonatal testosterone treatment. This organizational effect may be required for the increased eating that occurs in pregnancy and lactation described below.

Ovarian cycle. The initial reports that rats eat least during the periovulatory (estrous) phase of the ovarian cycle and most during diestrus have been replicated countless times in rats (for reviews, see Refs. 18 and 764) and extended to mice (527, 547, 731), humans, and many other species. The estrous minimum in daily food intake is typically ~20% less than the diestrous maximum. Rarely, food intake did not vary across the cycle. For example, Varma et al. (758) reported that Fischer 344 rats, a small, lean strain, did not eat less during estrus, and Petersen (547) reported that mice fed a honey-laced wheat-cereal diet ate more during estrus, although chew-fed fed mice ate less.

Importantly, the estrous decrease in eating in rats is due solely to a decrease in the size of spontaneous meals, with no contribution from a decrease in meal frequency (15, 77, 190, 207, 527, 547). Indeed, meal frequency usually increases during estrus [meal size was also reduced in the Fischer 344 rats mentioned above, but this was fully compensated for by the increase in meal frequency (758)]. These and data reviewed in the next section suggest that these two parameters of spontaneous feeding are controlled separately. The proximal physiological mechanisms for the estrous decrease in eating are discussed.
below. Fessler (222) has advanced an interesting hypothesis concerning its ultimate adaptive meaning.

There are several reports of altered macronutrient selection during the estrous cycle (42, 261, 358, 423, 808). The forms of macronutrients used in these studies and the specific changes in macronutrient selection observed varied widely, however, suggesting that food properties unrelated to macronutrient type caused the results. For example, as reviewed below, cyclic changes in the rewarding effect of sweet taste may contribute to cyclic changes in eating.

The estrous inhibition of eating in rats follows the diestrus increase in plasma levels of estrogens with the time lag discussed above (please see Latency of estrogen’s effect on eating). In contrast, neither the smaller peak in plasma progesterin levels during diestrus 2 nor the larger periovulatory peak is related to changed eating. The estrous inhibition of eating in rats is not secondary: 1) to stimulation of locomotor activity because the former is expressed as a decrease in meal size and the latter causes a decrease in meal frequency (207); 2) to increases in appetitive or consummatory reproductive behavior because both estradiol and progesterone are necessary to normalize most or all reproductive behaviors in ovariectomized rats (242, 549, 690); or 3) to estrogen-dependent changes in water intake (151, 224, 237, 355, 384, 406, 726, 727) because these are not synchronous in intact, cycling rats (maximum water intake occurs on diestrus 1 and decreases on diestrus 2) and because food intake increased ~3 days before water intake increased after ovariectomy (727) [the estrogenic controls of eating and drinking also were dissociated in several tests in guinea pigs (155)]. Nevertheless, it would be useful to determine spontaneous meal patterns in a more naturalistic environment permitting social interactions, reproductive behavior, foraging for food, etc. (for example, Refs. 386 and 473).

Ovariectomy and hormone treatment. Ovariectomy both abolishes the cyclicity of eating, as would be expected by disruption of the ovarian cycle, and increases daily food intake above the diestrous maximum for several weeks, leading to increased body weight and adiposity (15, 77, 130, 589, 662, 726, 764) (Fig. 6A). In contrast to the effect of menopause in women, however, the gain in adipose tissue in rats is mainly in the subcutaneous depots, not intra-abdominal depots, and lean body mass is increased, not decreased (274).

As Drewett (191) originally pointed out, the acyclicity and the increased overall level of eating after ovariectomy suggest that HPG-axis function normally exerts two influences on eating: 1) a tonic inhibition, whose loss after ovariectomy increases the basal level of eating, and 2) a phasic or cyclic inhibition, whose loss leads to acyclicity.

Early demonstrations that estradiol-treated ovariectomized rats ate normal amounts and maintained normal body weight indicated that estrogens are the crucial link between HPG-axis function and eating in rats (191, 589, 726, 764, 766, 771) (for reviews see Refs. 18, 102, 203, and 253). Most importantly, a near-physiological cyclic regimen of estradiol treatment was sufficient to maintain both the tonic and the phasic controls of eating, normal spontaneous meal patterns, and normal body weight in ovariectomized rats (15) (Fig. 6, B and C). In contrast, near-physiological doses of progesterone did not affect eating or body weight in rats, although pharmacological doses may do so (259, 294, 764, 766). The efficacy of estradiol treatment to normalize body weight may depend on when treatment is begun because estradiol was markedly less effective in reversing ovariectomy-induced weight gain than in preventing it (726).

As discussed in the previous section, the cyclic inhibition of eating during estrus is likely to result from the increase in estrogen secretion 24–48 h earlier during diestrus 2. This explanation, however, leaves unclear why the even higher estrogen level during proestrus fails to further decrease eating during diestrus 1. This unexpected pattern may result from the central processing of the estrogenic signal. It does not involve another ovarian control because it occurs in estradiol-treated ovariectomized rats as well (15).

The duration of exogenous estradiol’s eating-inhibitory effect suggests that estrogen secretion during diestrus 2 and proestrus is sufficient to produce the tonic inhibition of eating throughout the cycle: 1) Asarian and Geary (16) observed that in ovariectomized rats maintained on weekly cyclic treatment with 2 µg estradiol benzoate, food intake returned to the level of untreated rats 5 days after estradiol treatment. Because of the rapid esterification of estradiol benzoate to estradiol and the rapid clearance of estradiol from the circulation (417, 724), estradiol levels return to basal within 2 days of injection. 2) Similarly, Gray and Greenwood (287) reported that ovariectomized rats’ food intake was still decreased 7 days after injection of 2 µg estradiol benzoate. 3) Tarttelin and Gorski (727) reported that if rats spontaneously entered pseudopregnancy, during which there is little estrogen secretion, intake increased above the diestrous level after ~5 days. These data suggest that the eating-inhibitory effect of estrogens secreted during diestrus and proestrus persists ~4–7 days, more than long enough to explain the tonic inhibition of eating during the cycle.

GnRH, LH, FSH, and prolactin do not appear to mediate the effects of estradiol on eating because exogenous estradiol still inhibited eating in hypophysectomized rats (771). Hypophysectomy also decreases the secretion of estrogens, however, so the observation that hypophysectomy did not increase eating or body weight in the same study (771) appears paradoxical. It may be that capacity of hypophysectomized rats to gain weight is impaired. Consistent with this idea, a more selective lesion, transgenic deletion of FSH receptors, prevented ovarian follicle development and produced a typical estrogen-deficiency syndrome in female mice, including increased body weight and adiposity; unfortunately eating was not measured (162).

The effects of ovariectomy and of estradiol treatment on eating in rats, like the estrous decrease in eating, are expressed solely as changes in spontaneous meal size; i.e., increases and decreases, respectively (15, 77, 107, 376). Meal frequency usually decreases slowly after ovariectomy and increases with estradiol treatment, but not enough to balance the meal size effects, at least for several weeks after ovariectomy. Female mice also decrease meal size during estrus (547). As reviewed below, this specificity has been a useful clue for investigations of the underlying mechanisms. In contrast, the mechanism for the slowly developing, apparently compensatory decrease in meal frequency that limits the effect of ovariectomy on body adiposity has received no attention.

Finally, there appears to be a species difference in the effect of ovariectomy on eating in mice and rats. In mice, ovariectomy usually (350, 604, 796), but not always (75, 130), increases body weight and adiposity without affecting eating. This is presumably due to the many effects of estrogens on
physical and metabolic energy expenditure, energy metabolism, and adipose tissue physiology (40, 361, 462, 463, 729, 767). It would be interesting to determine whether this species difference is related to one or more of the neural mechanisms underlying the divergent controls of eating and energy expenditure described in male rats (e.g., Refs. 36, 500, 673).

Pregnancy and lactation. As described in Wade and Schneider’s expert reviews (645, 770), animals respond in a variety of ways to the energetic challenges of pregnancy and lactation. Rats and mice eat more and select different micronutrients and macronutrients during pregnancy and lactation (26, 81, 133, 197, 214, 639, 691, 779). The underlying neuroendocrine controls are not well understood. Part of the cause may be simply the release from the estrogenic inhibition of eating, as suggested by the pseudopregnancy and ovariectomy data reviewed above. Other factors must also be involved, however, because rats eat more during the later stages of pregnancy and during lactation than after ovariectomy. Both oral and postigestive factors may contribute. Bowen (80) found an increase in the intake of a sweet food in pregnant rats, suggesting that the phenomenon in pregnant women described below is, at least in part, physiological. The increase in intake of sweet foods may be specific because, in another study (691), pregnant rats increased intakes of a 55% high-fat diet and of

**Fig. 6.** Cyclic estradiol benzoate (EB) treatment models the endogenous cycle and maintains normal patterns of body weight gain, daily food intake, and spontaneous meal size in ovariectomized (OVX) rats. **A:** OVX increased and cyclic estradiol treatment normalized body weight. Data to left of the solid vertical lines are from the last ovarian cycle before OVX (x-axis labels appear in panel B; Preovx; D1, diestrus 1; D2 diestrus 2; P, proestrus; E, estrus), and data to the right of the solid vertical lines are sham-operated intact rats (solid circles), OVX rats treated with EB (triangles), and OVX rats treated with the oil vehicle (open circles); dashed vertical lines divide the numbered 4-day treatment cycles (days 1–4), which are aligned so that the last day of each cycle is the second day after EB injection, the day that models estrus. **B:** OVX increased and cyclic estradiol treatment normalized daily food intake (x-axis labels explained above). Note 1) that OVX elevated, and EB normalized, the basal level of daily food intake (tonic estrogenic inhibition of eating; tested on day 2) and 2) that OVX eliminated, and EB reinstated, the drop in food intake during estrus in intact rats and on cycle day 4 in OVX rats (phasic or cyclic estrogenic inhibition of eating). **C:** OVX increased and cyclic estradiol treatment normalized nocturnal spontaneous meal size. Triangles indicate mean meal sizes during the last cycle Preovx (abbreviations as above); solid circles indicate mean Postovx meal sizes during cycles 2–7 of cyclic EB treatment (injection time indicated by arrow); and open circles indicate mean Postovx meal sizes in control rats treated with the oil vehicle. *Significantly different from intact rats and EB-treated rats on day 2; †Significantly different from diestrus 2 (intact group) or day 2 (OVX group). Meal frequency was not increased by OVX or decreased by EB (data not shown). Reprinted from *Hormones and Behavior*, Cyclic estradiol treatment normalizes body weight and restores physiological patterns of spontaneous feeding and sexual receptivity in ovariectomized rats, 42: 461–471, 2002; republished with permission from Elsevier; from Asarian and Geary (15).
chow similarly. Potential roles for CCK and leptin signaling in the increase in eating during pregnancy are reviewed below (please see subsections Cholecystokinin and Leptin).

Lactational hyperphagia again highlights the primacy of meal size in the HPG control of eating in rats discussed above. That is, rat dams increase spontaneous meal size early in lactation and increase meal frequency only later on and if nursing larger litters (227, 702). Lactational hyperphagia is not dependent on ovarian function because it was not affected by postpartum ovariectomy (227). It may result from increases in NPY in the dorsomedial hypothalamus driven by increased prolactin secretion and by downregulation of an inhibitory αMSH input (119, 802). The reductions in basal insulin and leptin that accompany lactation do not cause the hyperphagia because normalization of insulin and leptin levels did not affect it (811).

Contemporary investigators have not pursued a classical observation by Curt Richter on dietary self-selection by pregnant and lactating rats (251). Richter (590) showed that if rats could obtain certain micronutrients, such as sodium and calcium, from sources other than the source of dietary energy, energy intake during pregnancy and lactation was markedly reduced. Thus, the appetites for micronutrients, not energy, drive much of the hyperphagia in chow-fed rats during pregnancy and lactation. Clearly, the mechanisms underlying these effects should be investigated in situations that permit the rats to regulate micronutrient homeostasis and energy homeostasis separately.

Androgens. Androgens have activational effects on eating in rats in addition to the organizational effects described above. Adult orchietomy decreases rats’ daily food intake and body weight, and androgen treatment, usually with testosterone propionate, normalizes both (115, 266, 402, 516, 518, 622, 764, 767, 776). Testosterone increased eating similarly in one study in mice (546), but not another (495). In both species, the eating effects were due to changes in meal frequencies, with meal size moving in the opposite direction (115, 546). The mechanisms through which orchietomy and androgen treatment affect eating have been studied far less than those of ovariectomy and estrogen treatment. Androgens, like estrogens, have many metabolic effects that can lead to changes in body weight and composition in the absence of changes in eating (40, 361, 462, 463, 625, 729, 767), and orchietomy and androgen treatment seem to affect body weight and body composition more reliably than they do eating. Transgenic mice lacking androgen receptors also increased adiposity without increasing eating (216).

The effects of androgens on eating may be related in part to aromatization to estrogens. In some (288, 519, 664), but not all (199, 266, 622), studies, treatment with relatively high doses of testosterone propionate, which can be aromatized to estrogens, increased eating more potently than similar doses of nonaromatizable androgens, such as of 5-alpha-dihydrotestosterone propionate. It remains unclear, however, whether physiological androgen doses would produce such an effect.

Sex Differences in Eating in Anthropoid Primates

Male-female differences. Although males and females may eat differently from a very young age, most sex differences in human eating do not appear to be physiologically based (171, 188, 234, 565, 605, 783, 788). For example, Wardle et al. (783), in an analysis of data from 23 countries, found that women chose fewer high-fat foods and more fruits and high-fiber foods than men, but that health beliefs explained ~50% of the effects and dieting status as much as 20%. Nevertheless, there are at least four apparently physiological sex differences in human eating. 1) Men, who are generally larger than women, eat more than women and, as in rats, increases in meal size rather than in meal frequency produced this difference (172). 2) Men were more responsive than women to the negative-feedback effects of oral nutrient loads on eating in several situations (170, 544, 605). 3) Men were more responsive than women to the eating-stimulatory effect of food deprivation (820), paralleling the rat and mouse phenomena described above. 4) Finally, again as in rats and mice, normal homeostatic eating maintains a significantly higher body adiposity in women than in men; at a “normal” BMI of 22–23 kg/m², women had 26% more fat as a percent of body weight vs. 13% in men (245).

Understanding the mechanisms underlying this sex difference may have important ramifications for the general understanding of energy homeostasis.

A number of epidemiological studies done in several Western societies that involved different ethnicities and social strata, included adults and children as young as 2–5 yr of age, and assessed intakes of solid foods, carbonated beverages, and fruit juices failed to detect male-female differences in sugar intake, expressed as a percentage of total energy intake (78, 539, 733, 782). Sex differences in food selection did appear, however, in surveys of obese persons. Drewnowski et al. (194) reported that obese men identified high-fat, high-protein foods among their favorites, whereas obese women identified, high-fat, high-carbohydrate foods, especially high-sugar foods, among their favorites. Macdiarmid et al. (451) showed that this difference was reflected in food intake: obese women ate more high-sugar, high-fat foods (median intake ~146 g/day of cakes, chocolate, etc.) than did obese men (~103 g/day), leading to a higher sugar intake (21 vs. 17% of daily energy). Nonobese persons did not show this difference. As discussed below, these differences may result from sex differences in flavor hedonics. It is important to determine whether they develop prior to obesity or are consequences of obesity (e.g., Ref. 696). Finally, recent data suggest that the trend toward overeating in the United States is stronger in women, who increased daily energy intake 22% between 1971 and 2004, than men, who increased only 10% (437). In that overeating appears to be the primary cause of the obesity epidemic (195, 496, 716), this difference could contribute to the sex differences in obesity prevalence mentioned above (226).

Three findings support the view that a physiological sex difference affects sweet preference in anthropoid primates: 1) Among the Hadza of Tanzania, hunter-gatherers who derive >90% of their energy from wild food, although honey was the most preferred food in both sexes, women preferred sweet berries more than meat, whereas men preferred meat more than berries (61). 2) A field study of wild Bornean orangutans (Pongo pygmaeus) indicated that when sweet fruits were in season, males increased their intake about twofold (from 3,800 to 8,400 kcal/day), whereas females increased their intake about four-fold (from 1,800 to 7,400 kcal/day) (401). 3) In a laboratory study in which savanna baboons (Papio cynoceph-
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*alia* were offered 75% sucrose fruit-flavored candy and chow pellets, females ate relatively more sugar than males (228).

**Ovarian cycle. Cyclic Changes in Eating.** We know of three within-subjects studies of women’s eating throughout the ovarian cycle (229, 278, 450). These involved a total of 53 women. Food intake was measured by weighing the food and converting these data to energy equivalents, and cycling was characterized by urinary LH assays and reports of menses. As shown in Fig. 7A, these studies demonstrated that eating decreases through the follicular phase to a minimum during the periovulatory phase and is similarly high during the early-follicular and luteal phases. The weighted mean differences in food intake between the luteal and periovulatory phases was 275 kcal/day, and that between the mid-follicular and luteal phases was 228 kcal/day. Significant differences in food intake between the midfollicular and midluteal phases were detected in 9 of 10 similarly designed studies in which only those two cycle phases were tested (n = 192, mean effect, 218 kcal/day) (38, 353, 431, 436, 458, 544, 558, 561, 725, 809); the negative result occurred in the smallest study (n = 9) (809). Similar cyclic changes in food intake also were found in many studies reviewed by Buffenstein et al. (92) and by Dye and Blundell (198), which used less sensitive methods, such as use of body temperature to monitor cycling and use of food diaries to measure eating (789). Those studies also provided evidence that the cyclic changes in eating do not occur during anovulatory cycles (38, 596).

None of the studies reviewed above determined whether the cyclic changes observed were due to changes in spontaneous meal size, as in rats, or changes in meal number. In two studies involving test meals, however, meal size was significantly less in the midfollicular phase than in the luteal phase (85, 561), consistent with the idea that in women as in rats, cyclic changes in eating are expressed as changes in spontaneous meal size.

Cyclic changes in eating across ovarian cycle similar to that seen in women were found in several studies of rhesus macaques (153, 154, 156, 373, 615) (Fig. 7B) and in both captive and wild chacma baboons (Papio ursinus) (70). The monkey studies demonstrate that eating decreases continuously during the follicular phase and is maintained at a relatively constant high level during the luteal phase. In wild baboons, the cyclic effect was similar in females that were in consort with males and those that were not in consort, indicating that reproductive behavior did not influence eating.

All of these data, together with the apparently similar periovulatory decrease in eating in rats and mice, indicate that cyclic changes in women’s eating are biological sex differences under the control of HPG axis function. The magnitudes of the effects are more than large enough to be relevant to body weight regulation; recent estimates suggest that consistent imbalances of only 50–100 kcal/day are sufficient to cause the gradual development of obesity (437, 496).

**HPG-axis Mediation.** Eating during the follicular phase in anthropoid primates is closely associated with changes in estrogen levels. From a neuroendocrine perspective, the phase of maximal intake in rats, diestrus, better parallels the early-follicular phase than the luteal phase. Thus, if estrogens do inhibit eating during the follicular phase, then food intake should be maximal during the early follicular phase, when estrogen levels are lowest, and then decrease progressively until the periovulatory phase, when estrogen levels are highest. Although this hypothesis has not been investigated quantitatively, the available data in women (229, 278, 450) and rhesus monkeys (154, 156, 756) are consistent with it (Fig. 7).

In contrast, the contribution of gonadal steroids to the control of eating during the luteal phase is problematic. Estrogen levels are higher in the mid-luteal phase than the midfollicular phase, although food intake is less during the midfollicular phase. This pattern is inconsistent with a simple estrogenic inhibitory effect. Progestins do not appear to provide a solution. Progestins are secreted during the luteal phase, and exogenous progesterone can reduce the eating-inhibitory effect of estrogens, but this appears to be a pharmacological

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**Fig. 7.** Daily food intake during the ovarian cycle in women (A) and rhesus macaques (B). Note the progressive decreases in food intake during the follicular phase in both women and monkeys and the high, constant levels of food intake during most of the luteal phase in monkeys (women’s data were averaged across the entire luteal phase). Women’s data (kilocalories eaten per day; values are expressed as means ± SE) are calculated from three studies in which food intake was measured by weighing, and the cycle phase was monitored with urinary LH and reports of menses in a total of 34 women. In each study, data were averaged across the early-follicular (eF; 4 day), midfollicular (mF; ~9 day), periovulatory (PO; 4 day), and luteal (L; ~11 day) phases. *Significantly different from luteal phase. Adapted from Am. J. Clin. Nutr. (1993; 57: 43–46), American Society for Nutrition (229); Am. J. Clin. Nutr. (1989; 49: 252–258), American Society for Nutrition (278); and Am. J. Clin. Nutr. (1989; 49: 1164–1168), American Society for Nutrition (450). Monkey data are plasma LH concentrations (open circles, means ± SE) and daily food intakes (solid bars, means ± SE) averaged across consecutive 3-day intervals relative to the LH peak (day 0) in 7 monkeys. *Significantly different from day −2/0. Reprinted with permission from Human Reproduction Update, Brain imaging studies of appetite in the context of obesity and the menstrual cycle, Dean A. Van Vugt, 16: 276–292, 2010 (756).
rather than a physiological effect in rats (259, 764, 766) and monkeys (70, 154, 372). For example, using estradiol and progesterone doses that led to changes in plasma levels that were within the range occurring during the menstrual cycle, Czaja (154) failed to detect any effect of either acute or chronic progesterone treatment on eating in ovariectomized rhesus macaques. The effect of progestins in the absence of endogenous gonadal steroids has not been studied in women. Pelkman et al. (544), however, failed to detect any effect of depot medroxyprogesterone on food intake in an adequately powered, prospective, placebo-controlled study in cycling women. That result extends an earlier study in which a low-dose estrogen (35 µg/day ethinyl estradiol) together with escalating progesterin doses (0.5–1.0 mg/day norethindrone) failed to detectably affect food intake measured with diet records in cycling women (201). These studies suggest, but do not prove, that some factor other than estrogens and progestins controls eating during the luteal phase. Further work is required to identify that factor.

MACRONUTRIENT INTAKE. Dye and Blundell (198) reviewed 15 studies in which macronutrient intakes were tabulated across the ovarian cycle; none found a significant effect. Nevertheless, there may be a cyclic change in the intake of sweet foods. Bowen and Grunberg (82) found that women ate more of three sweet test foods during the luteal phase than during the mid-follicular phase, whereas intakes of salty and of bland foods did not vary. Similarly, Fong and Kretch (229) reported that women consumed significantly more sugar-containing carbonated drinks (typically about 0.3 M sucrose) during the luteal phase (417 ± 27 ml/day; mean ± SE) than during the midfollicular, periovulatory, or menses phases (335 ± 31, 359 ± 26, and 370 ± 26 ml/day, respectively). Kemnitz et al. (373), however, failed to find a cyclic change in rhesus macaques’ intake of 0.5 M sucrose that was offered 3 days/ wk, 2 h/day. The possible contributions of cyclic changes in sensory and hedonic processing of sweets is discussed below.

INTERACTION WITH COGNITIVE CONTROLS OF EATING. The follicular and periovulatory decrease in eating can be modulated by non biological factors. For example, the decrease is apparently blunted or absent in women with high levels of dietary restraint (92, 198), a psychological trait related to the ability to limit eating cognitively that is an important control of eating in many young women (322, 328, 794). In an interesting study, Li et al. (431) found that the difference in energy intake between the follicular and luteal phases in a group of university students was ~10% when weekday data were used and ~23% when weekend data were used. This weekend effect was not attributable to changes in alcohol intake, in frequency of restaurant visits, or in the daily level of energy intake, which did not vary significantly across the week. One possibility is that it was due to the relaxation of cognitive restraint on weekends, but this was not measured.

Food cravings, i.e., recurring intense desires for specific foods, are a common and stable aspect of human eating, distinct from the palatability [i.e., craved foods are not simply those an individual finds most palatable (786, 813)]. In both the United States and Spain, women crave sweet foods most frequently, whereas men crave mainly savory foods (543, 623, 823). This sex difference may be related to the sex difference in sweet hedonics discussed below.

Chocolate is the single most craved food among women in the United States, United Kingdom, Canada, and Spain, and many women report cyclic changes in craving, especially for chocolate, with a maximum in the late luteal and menses phases (738, 822). This cyclic effect does not seem to be hormonally based: 1) neither frequency of cravings nor the type of food craved were significantly related to circulating estrogen levels (597); 2) progesterone administration did not affect cravings (480); 3) premenopausal and postmenopausal women who were chocolate cravers had similar frequencies of chocolate craving (338); and 4) there was no cyclic change in chocolate cravings in Spanish women whose chocolate cravings were as intense as those reported by U.S. American women who did crave cyclically (822).

Carbohydrate craving may represent a form of self-medication for dysphoria (137). Early reports linked carbohydrate craving to serotonergic (640) and opioidergic (192, 193) function, but neither lead has been pursued. Carbohydrate craving is often discussed in relation to premenstrual dysphoria and bulimia nervosa, but whether they are, indeed, linked remains controversial (132, 296, 752, 813).

Loss of ovarian function and hormone treatment. Menopause increases adiposity independent of aging (336, 429, 535, 550, 714, 739, 741), and some data indicate that high-estrogen hormone-replacement treatment (HRT) prevents this (297, 312, 419, 628, 686). Whether ovariectomy (or oophorectomy), menopause, or exogenous estrogens affect eating in women, however, remains in doubt, perhaps due to the inadequacies in the designs used so far. For example, Lovejoy et al. (443) had subjects complete 4-day food diaries annually and failed to detect any change in total energy intake between 3 yr premenopause and 2 yr postmenopause. The power of this study, however, was such that changes of >30% were required for significance. We know of three reports in which HRT failed to affect eating (585, 587, 672). None of these studies, however, was strongly designed. For example, in one (587), only a single day’s food intake was estimated by interview, and in another (585), a between-subjects design with only 6 and 9 women was used. In the third study (672), normal-weight women who had natural menopause 0.5–5 yr previously were randomly assigned either an HRT regimen or to placebo in a double-blind design (n = 14 each), and eating was estimated by food diaries for 3-day periods at the onset and after 2 yr of treatment. HRT was associated with a decrease in daily intake of 212 kcal/day (12%), compared with no change in untreated women, but none of the differences was statistically significant. The power of the food diary method to detect differences and the potential influence of the time since menopause were not assessed. In addition, HRT was a relatively high-progestin regimen (6.25 mg/day oral conjugated estrogens plus 2.5 mg/day medroxyprogesterone), which may have masked an effect of estrogens on eating, as occurs in rats (766).

In contrast, experiments with monkeys provide stronger support for the hypothesis that loss of ovarian function increases eating due to release from estrogenic inhibition. Sullivan et al. (705) showed rhesus macaques’ food intake increased 29% and body weight 3% during the first 2 mo after ovariectomy compared with preovariectomy baselines. In a follow-up study (707), they found that 3 mo of treatment with the selective estrogen-receptor modulator GSK232802A decreased body weight 4.6% in a group of ovariectomized rhesus
macaques whose body weights previously increased 4.8% after ovariectomy. GSK232802A decreased food intake ~5–10% during the treatment period, and food intake also correlated negatively ($r = 0.52$) with weight loss during this period. Finally, GSK232802A increased spontaneous physical activity, measured with triaxial accelerometry. Interestingly, the fattest, least active monkeys showed the largest activity increases and weight losses. They also previously reported that spontaneous activity levels, but not food intake levels, were inversely correlated with weight gain over a 3-mo period in intact female rhesus macaques (706). These data, together with Lovejoy et al.’s (443) report that spontaneous activity decreases across the menopausal transition, identify physical activity and eating as important targets for future menopause research.

Pregnancy and lactation. Women increase energy intake during pregnancy and lactation in a way that appears to meet their increased energetic costs (47, 71, 569). Part of the mechanism appears to be related to altered food preferences. Most women increase intake of craved foods during the third through the seventh month of pregnancy (58, 81, 337, 564). Sweet foods, including fruits and fruit juices, dairy foods, and chocolate are most frequently craved. Increased food cravings during pregnancy are also thought to contribute to excessive gestational weight gain, which occurs in about one third of pregnant women and increases a variety of health risks both for mother and child (144, 526, 642, 654). For this reason and because the results of current intervention strategies are inconsistent (721), the physiological controls of increased eating during pregnancy are an important research challenge.

Some women also develop aversions, often to foods that are usually liked. Because food aversions and nausea develop most frequently around the third month of pregnancy, it is possible that they are produced by the increases in human chorionic gonadotropin that occur at this time (244, 540). A moderate degree of nausea and vomiting is considered normal during pregnancy and may improve pregnancy outcomes (244, 540).

Androgens. The role of androgens in eating in anthropoid primates is unknown. In rhesus monkeys, testosterone treatment failed to significantly affect eating despite producing large (~50%) increases in body weight and lean body mass in 7–9 yr-old monkeys that had been orchietomized at 0–3 mo of age (375). The potential influences of the early orchietomy and the long orchietomy-treatment delay on the results were not assessed. We know of no studies of androgens and eating in healthy men. Male hypogonadism has a variety of causes, but often appears as men’s testosterone levels decrease during aging (161, 553, 711). It is associated with increased adiposity. Changes in appetite have not been reported to our knowledge. Hypogonadism is treated with testosterone, which suppresses the HPG axis and leads to infertility, or, if fertility is desired, by stimulating the HPG axis with either gonadotropins or the estrogen-receptor modulator clomiphene citrate, which decrease estrogen negative feedback (161, 553, 711). Thus, hypogonadal men seem to present a potentially interesting model for investigation of androgenic influences on eating.

**ER Mechanisms Controlling Eating**

Two types of nuclear ER, ERα, and ERβ, were identified in the 1990s (178, 512). These are encoded by separate genes, *ESR1* and *ESR2* in humans and *Erα* and *Erβ* in mice. The two genes have overlapping but distinct expression patterns in the brain and periphery, and *Erα* and *Erβ* knockout mice display distinctive phenotypes. The classical mode of action of nuclear ER involves binding to estrogen-response elements (ERE), which, in turn, bind to DNA and affect gene transcription, usually over the course of hours to days (125, 326). More recently, it has been found that ERα and ERβ, as well as a variety of novel ER, are expressed outside the nucleus, usually on cell membranes (428, 475, 548, 602, 759). In addition to genomic effects via non-ERE transcription promoters, membrane ER have rapid (i.e., within seconds) nongenomic effects. These rapid effects are increasingly recognized to be crucial for many neural actions of estrogens.

**ERα in rats and mice.** The phenotypes of transgenic mice with null mutations affecting estrogen signaling via ERα demonstrate a necessary role for ERα role in weight regulation, but do not clearly disclose their role in the control of eating. Heine et al. (324) characterized the obesity phenotype of the original line of *Erα−/−* mice. Both male and female *Erα−/−* mice had excess body weight and body fat, especially intra-abdominal fat, signs of metabolic syndrome, and decreased energy expenditure. Food intake, tested continuously beginning at 60 days of age, was unchanged in male *Erα−/−* mice; again females were not tested. Ohlsson et al. (523) found a similar adiposity phenotype in another line of *Erα−/−* mice, but did not measure eating. Jones et al. (356) tested transgenic aromatase-deficient mice, which cannot synthesize estrogens, and found that food intake was reduced in females beginning before 5 wk of age; males were not tested. Xu et al. (812) reported that female transgenic mice lacking ERα only in the brain ate more than wild-type mice at 7 wk of age, but they did not test other ages. Finally, Park et al. (537) described a strain of *Erα−/−* mice in which non-ERE estrogen signaling was transgenically rescued, *Erα−/−/AA* mice. Eating tests beginning at 3 wk of age failed to reveal any difference between female wild-type mice and either *Erα−/−* or *Erα−/−/AA* mice in intake of chow or of a 45% high-fat diet. We conclude that there is no apparent reason to expect disruption of peripheral ERα signaling to obscure an effect of brain ERα lesion on eating and, therefore, that until Xu et al.’s (812) solitary report of increased eating in transgenic mice with disrupted ERα is extended, the *Erα−/−* phenotype fails to provide clear evidence that ERα signaling is necessary for the normal control of eating. Given the difficulty in interpreting negative transgenic null-mutation data and the many positive indications that ERα is involved in the control of eating that we review below, however, we do not consider this a crucial failure.

To better establish whether activation effects of estrogens control eating and adiposity, Geary et al. (257) tested the effects of estradiol treatment in *Erα−/−* mice that were ovariectomized after puberty. Estradiol reduced daily food intake, weight gain, and fat gain in wild-type, but not *Erα−/−* mice (Fig. 8). Estradiol also increased CCK satiation in wild-type, but not *Erα−/−*, mice (please see Cholecystokinin). Because CCK is involved in the phasic control of eating by estrogens, these data indicate that an activation effect of estrogen signaling via ERα is involved in both the phasic and the tonic estrogenic control of eating. This does not preclude the possibility that organizational effects mediated by ERα are also important for these controls.
In one study of Erα^{-/-} mice, there was a suggestion of a non-ERα contribution to the estrogenic inhibition of eating: Naaez et al. (502) found that food intake was lower in ovariectomized than in nonovariectomized Erα^{-/-} mice during one of three weeks tested. For the following reasons, this report requires replication to be considered as substantial evidence: 1) circulating estrogen levels are ~10-fold elevated in ERα^{-/-} mice (140), so that ovariectomized Erα^{-/-} mice receiving a physiological estrogen treatment would be a better comparison; 2) the difference in food intake between ovariectomized and nonovariectomized mice over the 3-wk test was not significant; and 3) the three individual weeks were tested independently, and the significance level for at least one positive result in three trials is only \( P < 0.14 \).

Pharmacological studies buttress the conclusion that ERα mediates the activational eating-inhibitory actions of estrogens. There are several reports that the selective ERα agonist 4,4,4-(4-propyl-[1H]-pyrazole-1,3,5-triy)-trisphenol inhibits eating in ovariectomized rats and mice (203, 309, 603, 637). This compound, however, inhibits eating much faster than estradiol in ovariectomized rats and mice (257) and prevented the estrous decrease in eating in intact rats. These data indicate that ERα mediates both the cyclic and the tonic activational, eating-inhibitory effects of estrogens.

**ERα in humans.** An epidemiological study of allelic variation at locus rs7757956 in intron 4 of *ESR1*, which encodes human ERα, provides compelling evidence that an activational effect of estrogen signaling via ERα is related to adiposity in girls. Tobias et al. (737) classified a sample of children who were on average 11.8 yr old according to pubertal development, using the Tanner scale (Tanner scores are based on the development of pubic hair and breasts in girls and pubic hair, penis, and testicles in boys; 1 is prepubertal, 2, early, 3 mid-, 4, late, and 5 postpubertal or adult). They found that girls with TT genotype at locus rs7757956 who were in Tanner stages 3–5 had 9% more body fat, as measured by DEXA, than girls with TA or AA genotypes. No such effect was detected in boys. Girls with TT genotype who were in Tanner stages 3–5 also had 18% more height-adjusted body fat than girls with TT genotype who were in Tanner stages 1–2; the comparable difference in girls with TA or AA genotype was significantly less, 7%. As a result, girls with TT genotype who were in Tanner stages 3–5 had a 36% increase in the risk of being overweight, according to UK pediatric norms, whereas girls with TT genotype who were in Tanner stages 1–2 had no increased risk. Interestingly, the TT genotype was the most frequent, occurring in ~75% of boys and girls, suggesting that increased adiposity in women was once adaptive. How this *ESR1* polymorphism affected adiposity is unknown. From our perspective, a crucial question is whether it affected fat mass by reducing estrogens’ eating-inhibitory effect or, for example, by affecting adipose-tissue metabolism directly (178). Other *ESR1* polymorphisms have also been related to increased adiposity (525, 763), but in each case, the findings are inconsistent across populations studied (737, 763).

**ERβ.** The failure of several selective ERβ agonists (309, 603, 637, 731) and one selective ERβ antagonist (635) to affect eating in rats or mice and the failure of null mutation of ERβ to affect the eating and body weight responses to ovariectomy and estradiol treatment in mice (257) indicate that ERβ is not involved in the estrogenic control of eating or energy homeostasis in rats or mice. Two studies, however, suggest that this issue may merit further research. First, Liang et al. (432) reported that the eating-inhibitory effect of intracerebroventricular infusion of estradiol was reduced by simultaneous intracerebroventricular infusion of ERβ-antisense oligonucleotides, but not by ERα-antisense oligonucleotides. Both of these results are anomalous, and the paradigm has not been further tested. It may have been important that a water-soluble estradiol compound was used because water-soluble estradiol produced unusual results in several tests (please see *Hypothalamus*). Second, Yepuru et al. (814) reported that high-fat diet-fed ovariectomized mice chronically treated with a novel selective ERβ agonist ate less and did not gain body weight or fat. Their agonist appeared to function by activating uncoupling protein-1 and blocking peroxisome proliferator-activated receptor-γ in the adipose tissue. No evidence was presented, however, to indicate whether these effects were physiological or purely pharmacological.

**Novel estrogen receptors.** Two novel G protein-coupled ERs may be involved in the estrogenic control of eating. One, GPR30, is expressed on the endoplasmic reticulum of a variety of cell types (503, 588). Haas et al. (298) reported that male and
female mice with null mutations of GPR30 (GPR30<sup>−/−</sup> mice) developed marked intra-abdominal obesity, as well as a number of other abnormalities. The effects of ovarioectomy and estradiol treatment, however, did not differ between wild-type mice and a different strain of GPR30<sup>−/−</sup> mice (795). A second novel ER, Gq-mER, is expressed on the cell membranes of proopiomelanocortin (POMC), dopamine, and GABA neurons in the arcuate nucleus of the hypothalamus (576, 601, 602). Gq-mER reduces the activation of potassium channels on GABA<sub>G</sub> and µ-opioid receptors and affects the expression of NPY and other neuropeptides involved in the control of energy homeostasis. The Gq-mER-selective agonist STX reduced food intake and body weight gain in ovarioctomized guinea pigs under several conditions (576, 599, 600). Importantly, however, doses of STX and estradiol that had similar effects on total food intake had opposite effects on spontaneous meal patterns: estradiol decreased meal frequency, whereas STX decreased mainly meal size (600). This suggests that STX is unlikely to mimic the tonic effects of endogenous estrogens on eating in guinea pigs. Unfortunately, whether the estrous decrease in eating in guinea pigs (156) is produced by changes in meal size or meal frequency is unknown.

More generally, the apparent necessity of ERα for the estrogenic inhibition of eating in rats and mice and the ~2-day latency of this effect both indicate that the rapid actions of novel membrane ER are unlikely to be sufficient for the estrogenic inhibition of eating in these species (12, 731). They may, however, interact with slower, ERα-mediated effects to control eating. Kow and Pfaff (404) described just such an interaction in the control of the lordosis reflex. They found that maximal lordosis was induced by two brief pulses of estradiol, separated by 5 h, delivered into the VMH, and that this occurred even if only one pulse was estradiol and the other pulse was a complex of estradiol bound to albumin complex, which does not penetrate cell membranes and, therefore, activated membrane ER.

**Site of ER Controlling Eating**

Eckel (203) and Rivera and Eckel (592) provided pharmacological evidence that activation of ER in the brain is necessary and sufficient for the estrogenic inhibition of eating by comparing the eating-inhibitory effects of peripheral and central injections of ICI-182,780, a pure antiestrogen that apparently does not cross the blood-brain barrier. Infusion of ICI-182,780 into the lateral ventricle reversed the eating-inhibitory effect of peripheral estradiol injection in ovarioctomized rats, but subcutaneous ICI-182,780 injections did not. Conversely, peripheral, but not central, ICI-182,780 treatment blocked estradiol’s effects on uterine weight and vaginal cytology. Xu et al.’s (812) report that transgenic mice with a brain-specific deletion of ERα are hyperphagic and obese is also consistent with Rivera and Eckel’s (592) data, although a developmental defect appeared to account for most of their effect (i.e., hyperphagia seemed to appear before puberty), and the effects of ovarioectomy and estrogenic stimulation were not tested.

Investigations of brain sites of ER that control eating using local estradiol administration and brain lesions are summarized in Table 1 (studies using central doses greater than ~300 ng are not included for the reasons described in *Hormone treatment regimens*). As Table 1 and the discussion below indicate, there is no consistent evidence for a role of any hypothalamic ER population in the estrogenic control of eating in rats or mice. In contrast, several approaches implicate ERα in the caudal medial nucleus of the solitary tract (cmNTS) in the estrogenic inhibition of eating.

**cmNTS.** The first suggestion that the nucleus of the solitary tract (NTS) might be involved in the estrogenic control of eating came from our finding that the NTS was one of the brain areas in which estradiol treatment increased the number of neurons expressing c-Fos after food ingestion or CCK injection in ovarioctomized rats and mice (205, 206, 257, 688) (the effects of estrogens on CCK satiation are reviewed in *Cholecystokinin*). The next c-Fos finding was more interesting. Estradiol increased the numbers of cells expressing c-Fos in response to intraduodenal infusions of fat only in one brain area, the cmNTS just posterior to the area postrema. The effect was CCK-dependent, and, most importantly, many of the neurons expressing c-Fos also expressed ERα (17). The cmNTS has the densest population of ERα-expressing neurons in the NTS (17, 643, 663, 668, 688, 689, 757).

We then showed that local administration of estradiol to the surface of the hindbrain over the cmNTS was sufficient to reduce eating and to increase the number of ERα-expressing neurons expressing c-Fos. cmNTS neurons also expressed the Gq-mER-selective agonist STX reduced c-Fos immunocytochemistry, in ERα-expressing neurons.

**Table 1. Status of central ER populations in the control of eating**

<table>
<thead>
<tr>
<th>Site</th>
<th>Sufficient?</th>
<th>Necessary?</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain stem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cmNTS</td>
<td>Yes (732)</td>
<td>Yes (19, 20)</td>
<td>ERα/c-Fos colocalization</td>
</tr>
<tr>
<td>DR</td>
<td>Yes (636)</td>
<td></td>
<td>Latency</td>
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<td></td>
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</tr>
<tr>
<td>VMH</td>
<td>Yes (636)</td>
<td>No (103, 533)</td>
<td></td>
</tr>
<tr>
<td>MPOA</td>
<td>Yes (158, 636)</td>
<td>No (75, 374, 499, 734, 812)</td>
<td></td>
</tr>
<tr>
<td>PVN</td>
<td>Yes (103, 104, 108)</td>
<td>No (381)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No (345)</td>
<td></td>
<td>Latency</td>
</tr>
</tbody>
</table>

Sufficiency is indicated by a decrease in eating following administration of small amounts of estradiol in the brain area indicated in ovarioctomized rats; necessity is indicated by a diminished or absent effect of peripheral estradiol on eating or weight gain following electrolytic, chemical, or molecular lesion of the brain area indicated in ovarioctomized rats or, in the case of the ventromedial hypothalamus (VMH) in mice, VMH data include both the ventromedial nucleus (VMN) and the arcuate nucleus (Arc). References are shown in parentheses. DR, dorsal raphe nucleus; cmNTS, caudal medial nucleus of the solitary tract; MPOA, medial preoptic area; PVN, paraventricular nucleus. “Latency” indicates that the eating-inhibitory effect was much faster (i.e., a few hours) than that of peripherally administered estradiol (i.e., ~2 days), as described in text. “ERα/c-Fos colocalization” indicates that food stimuli elicited neural activity, as indicated by c-Fos immunocytochemistry, in ERα-expressing neurons.
cmNTS neurons that expressed c-Fos after CCK injections (732). Finally, we tested the effects of administration of anti-ERα siRNA into the cmNTS of ovariectomized rats. cmNTS anti-ERα siRNA treatment prevented estradiol treatment from tonically or cyclically decreasing meal size and food intake, 2) from increasing the eating-stimulatory effect of CCK-1 receptor (CCK-1R) antagonism, 3) from increasing CCK-induced c-Fos expression in the NTS or hypothalamus, and 4) from restraining body-weight gain (Fig. 9) (19, 20). These data indicate that cmNTS ERα are necessary for much or all of estrogens’ effects on meal size, food intake, and body weight.

Hypothalamus. Surprisingly, hypothalamic ER and hypothalamic neural networks do not appear to be crucial for the tonic estrogenic inhibition of eating. Some positive results have been reported, but in each case, these are counteracted by convincing negatives or procedural questions. For example, Butera and colleagues (102–104, 106, 108) reported that bilateral implants of ~100–300 ng estradiol into the paraventricular nuclei of ovariectomized rats modestly (in comparison to peripheral estradiol injection) reduced food intake in ovariectomized rats and that subcutaneous injections of estradiol did not inhibit eating in ovariectomized rats with bilateral lesions of the paraventricular nuclei, but, for reasons that remain unclear, others failed to replicate these results (159, 343). For example, Dagnault and Richard (158) found that peripheral estradiol implants inhibited eating through a 26-day test as much in ovariectomized rats with bilateral lesions of the paraventricular nuclei as sham-lesioned rats. This indicates that neither ER in the paraventricular nuclei nor paraventricular neural networks are necessary for the tonic estrogenic inhibition of eating.

The situation is similar for other hypothalamic areas. Dagnault and Richard (158) and Santollo et al. (636) reported that implants of estradiol into the medial preoptic area inhibited eating in ovariectomized rats, but neither Butera and Beikirch (103) nor Hrupka et al. (343) could replicate this. It may have been important that both positive results were obtained with a water-soluble estradiol preparation containing ~5% estradiol and 95% 2-hydroxypropyl-β-cyclodextrin that inhibited eating rapidly, within 2 h (158) or 24 h (636). This is much faster than the normal latency of peripheral estradiol’s eating-inhibitory effect, 24–48 h (please see Latency of estrogen’s effect on eating). These rapid effects may have been mediated by membrane ER, as suggested by reports that estradiol immediately affects electrophysiological activity in the medial preoptic area (370, 371). In addition, peripheral estradiol still reduced eating and body weight in ovariectomized rats with lesions of the medial preoptic area (381). Implants of modest amounts of estradiol into the ventromedial hypothalamus, which would stimulate ER in both the ventromedial and arcuate hypothalamic nuclei, did not inhibit eating (103, 533), and peripheral estradiol still inhibited eating in ovariectomized rats (374, 734) or mice (75) with ventromedial hypothalamic lesions. In addition, administration of anti-ERα siRNA into the ventromedial hypothalamus did not affect the estrogenic inhibition of eating in ovariectomized mice, although it decreased energy expenditure, increased body weight, and prevented the estrogen stimulation of locomotor activity (499). Similarly, transgenic female mice lacking ERα specifically in neurons expressing steroidogenic-factor 1, which are found only in the VMH, were not hyperphagic, although they were hypometabolic and had massive hypertrophy of the gonadal fat pads (812). Santollo et al. (636) recently reported that administration of 250 ng of a water-soluble estradiol preparation into the arcuate nucleus inhibited eating in ovariectomized rats. Again, the inhibition occurred unusually rapidly, in <24 h, suggesting that it did not reflect a normal estrogenic effect. The same is true of their report (636) that showed that administration of water-soluble estradiol into the dorsal raphe nucleus inhibited eating in ovariectomized rats.

Sex Differences in Peripheral Controls of Eating

Eating is controlled by a cascade of peripheral positive- and negative-feedback signals that are sequentially activated by food stimuli from the oropharynx, gastrointestinal system, and postabsorptive compartment (67, 416, 678, 799). Neural feedback signals from the oropharynx follow bites or licks of food by seconds and are present more or less continuously throughout the meal. Neural and endocrine signals arising from gastrointestinal and metabolic food stimuli begin during the meal and are maintained for minutes to hours afterward. Other signals related to postprandial metabolism or to delayed and integrated consequences of eating, notably changes in adiposity, may act tonically. Overall, dozens of peripheral feedback signals are thought to be involved in the control of eating.

![Fig. 9. Estradiol treatment reduced nocturnal spontaneous meal size (A) and body weight gain (B) in ovariectomized control rats, but not in ovariectomized rats that received bilateral injections of adenovirus-vectored anti-ERα siRNA in the caudal medial nucleus of the solitary tract (cmNTS) (ERαKD; control rats received cmNTS injections of antiluciferase siRNA). Rats received subcutaneous injections of 2 μg estradiol benzoate (EB) or the oil vehicle (Oil) each 4th day. Meal sizes are averages of data from the cycle day of the estradiol treatment regimen that modeled estrus, from cycles 5–9; this day should reflect both the cyclic and the tonic effects of estradiol. Body weight gains are from surgery through cycle 9. *Significantly less than oil-treated rats that received the control siRNA (19, 20).](http://ajpregu.physiology.org/doi/10.1152/ajpregu.00446.2012)
Table 2. Summary of sex differences in peripheral controls of eating

<table>
<thead>
<tr>
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<th>Rat, mouse</th>
<th>Human</th>
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<tbody>
<tr>
<td>Orosensory capacity</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Gastric mechanoreception</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
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<tr>
<td>CCK</td>
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<tr>
<td>GLP-1</td>
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<tr>
<td>Apolipoprotein A-IV</td>
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<td>Glucagon</td>
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<tr>
<td>Insulin</td>
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<tr>
<td>Amylin</td>
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<tr>
<td>Fatty acid oxidation</td>
<td>+</td>
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<tr>
<td>Leptin</td>
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+++ , strong evidence of physiological role in mediating a sex difference in eating; +, some evidence; −, no data. Please see text for details.

Eleven of these signals have been reported to display sex differences (Table 2).

Gustation. Sex differences in the contribution of orosensory stimuli to the control of eating can arise from 1) differences in gustatory sensation, reviewed in this section, or 2) differences in central processing of peripheral gustatory and other oral stimuli, in particular, hedonic evaluations made by the brain, reviewed in Orosensory hedonics.

Sex differences in electrophysiological responses to sapid stimuli have been reported at three levels of the gustatory pathway. Stratford et al. (699) found that whole-nerve chorda tympani responses to lingual application of various concentrations of monosodium glutamate (umami taste) and to combinations of lactic acid and monosodium glutamate were greater in male than in female rats, whereas responses to NaCl and NH₄Cl were similar in males and females. These data indicate that there are sex differences in gustatory neurons in the thalamic taste nucleus. These data indicate that there are sex differences in electrophysiological responses of the gustatory system, but do not yet provide a firm basis for the interpretation of behavioral sex differences.

There are sex differences in human gustatory capacity at the most peripheral level—the taste receptors. Women have more fungiform taste papillae on the anterior tongue than men (Fig. 10), and their papillae tend to have more pores leading to the taste buds (46, 573). The density of fungiform papillae is associated with the density of afferent innervation of the tongue by the chorda tympani and trigeminal nerves; in addition, it is significantly correlated with 1) the sensory intensity (independent of hedonic valence) of sweet solutions and foods, 2) tactile acuity on the tongue surface, and 3) the sensory intensity of creaminess of fatty foods (213, 316, 317). As a result, because women generally have more fungiform taste papillae than men, they perceive foods as sweeter and creamier than men. Thus, to paraphrase Linda Bartoshuk (43), men and women live in different taste worlds. There is also evidence that pregnancy alters gustatory sensation (573). For example, in one study (196), women perceived bitter taste stimuli as more intense early in pregnancy, but less intense later in pregnancy, compared with nonpregnant women. The effects of such sensory differences on eating, however, have not yet been extensively investigated. Furthermore, the changes in bitter sensitivity during pregnancy do not offer an obvious potential explanation for the changes in eating observed during pregnancy because the two do not occur at the same time (please see Pregnancy and Lactation).

Gastric mechanoreception. Signals related to gastric mechanoreception, motility, volume, and emptying contribute to the control of eating (166, 167, 339, 360). Although there are sex differences in gastric emptying, there is no direct evidence that these underlie sex differences in the control of eating. We are not aware of reports of male-female sex differences in gastric emptying in rats. Gangula et al. (248) reported a trend for slower emptying in female than male rats 4 h after a meal, suggesting that there may be reliable differences at earlier times after meals.

In female rats, 15 min emptying of an intragastric load was increased by ovariectomy and normalized by estradiol or estradiol-progesterone treatment, but not by progesterone alone (120). CCK contributed to the inhibitory effect of estradiol on gastric emptying because 1) estradiol increased plasma CCK levels after the intragastric load and 2) the CCK1 receptor antagonist devazepide blocked the effect (806). Blaustein and
Wade (76) did not see an effect of estradiol on gastric emptying; whether this was because they tested anesthetized rats or another procedural difference is not clear. Gastric emptying was also increased in lactating rats (121). In one study, neither orchietomy nor testosterone treatment affected gastric emptying in male rats (120).

In contrast to the lack of male-female sex differences in gastric emptying in rats, women empty both solids and liquids from the stomach significantly more slowly than men (60, 163, 349, 399). Differences often appear soon enough (i.e., <30 min) to potentially affect within-meal control of eating. In one study (349), a similar male-female sex difference in gastric emptying of solid food was found for postmenopausal women who took estrogen-progestin hormone treatments, but not for postmenopausal women who did not. Whether the ovarian cycle affects emptying is not clear: 1) Gill et al. (270) found that solid food, but not liquid food, emptied from the stomach faster during follicular phase than the luteal phase; 2) Brennan et al. (85) found that liquid food emptied from the stomach faster during the follicular phase; and 3) Horowitz et al. (340) failed to find cycle differences in emptying of either solid or liquid food. Eating was measured in only one of these tests. Brennan et al. (85) reported that oral loads of 50 g glucose in 300 ml water emptied from the stomach ~15–20% more slowly and that intake during a meal 90 min later was ~700 KJ less during the midfollicular phase than the midluteal phase in normal-weight women. If the food ingested during these meals also emptied more slowly, the decrease in meal size is unlikely to have resulted from feedback effects of postgastric food stimuli. Thus, these data suggest that the potency of satiation signals related to gastric mechanoreception varies during the ovarian cycle in women.

Ghrelin. Ghrelin is unique among gut peptides in that its secretion increases during intermeal intervals and that ghrelin administration increases eating, apparently by acting centrally (383). Clegg et al. (130) reported that both intraperitoneal and intraventricular (third ventricle) ghrelin administration increased intake significantly more in intact male rats and untreated ovariectomized female rats than intact female rats or estradiol-treated ovariectomized rats. Furthermore, the eating-stimulatory effect of both peripheral and central ghrelin administration varied cyclically in both intact, cycling rats and ovariectomized rats cyclically treated with estradiol, such that ghrelin was more efficacious during diestrus 1 and 2 than during proestrus or estrus (Fig. 11). Butera (102) found similar changes in the eating-stimulatory potency of peripheral ghrelin. These data suggest that ghrelin may be necessary for both the tonic and the cyclic estrogenic controls of eating. One aspect of the ghrelin’s effect in ovariectomized rats, however, is inconsistent with this conclusion and requires resolution. Ghrelin’s effects in ovariectomized rats were due to changes in meal frequency, not in meal size (102, 130), whereas estrogens affect meal size, not meal frequency (please see Ovariectomy and hormone treatment).

Sex differences in ghrelin’s eating-stimulatory effect may be mediated by changes in ghrelin secretion, as well as changes in ghrelin sensitivity. Female rat gastric mucosal cells that are immunopositive for ghrelin also express ERα, and ovariectomy temporarily increases both the number of cells immunopositive for ghrelin and plasma ghrelin level (130, 461, 626). The time courses of the postovariectomy increases in plasma ghrelin level and in eating were strikingly similar (130), again consistent with a tonic estrogenic effect of ghrelin on eating in rats. Ghrelin levels have not been determined through the estrous cycle, and no changes in plasma levels of active ghrelin were detected in normally cycling women (157).

How estrogens influence ghrelin’s eating-stimulatory effect in mice is not clear. Clegg et al. (130) reported that ovariectomy did not increase food intake or body weight in transgenic mice with null mutations of the ghrelin receptor, suggesting a necessary role for estrogens. Maletínská et al. (453), however, failed to detect any influence of estradiol treatment on the eating-inhibitory and weight-reducing effects of twice daily subcutaneous injections of the ghrelin antagonist [D-Lys3]GHRP-6 in ovariectomized mice fed chow or high-fat diet. A parsimonious potential resolution of these data is that estrogens act during early development to reduce the eating-stimulatory effect of ghrelin in adult mice.

Ghrelin levels are positively associated with testosterone levels in men and estrogen levels in women, and ghrelin levels increased both in hypogonadal men treated with testosterone (532) and postmenopausal women treated with estrogens (369, 541). These findings, however, have not yet been linked to the control of eating.

Cholecystokinin. CCK is an important controller of meal-ending satiation in animals and humans (52, 416, 591, 677). CCK secretion increases during meals, and premeal administration of CCK-1R antagonists increased meal size in both male rats and men. CCK-1R antagonism also reduces or eliminates the satiating action of intraduodenal infusions of several nutrients, including, in male rats, fats, proteins, and some carbohydrates and, in humans, fats. CCK acts locally in the abdomen to initiate a vagal afferent signal that is transmitted to the NTS.

RATS AND MICE. There is extensive evidence that an activation of the ghrelin receptor eliminates the ghrelin’s effect in ovariectomized rats, estradiol treatment increases meal size in both male rats and men. CCK-1R agonism also reduces or eliminates the satiating action of intraduodenal infusions of several nutrients, including, in male rats, fats, proteins, and some carbohydrates and, in humans, fats. CCK acts locally in the abdomen to initiate a vagal afferent signal that is transmitted to the NTS.

Fig. 11. Cyclic changes in the eating-stimulatory effect of ghrelin in rats. The estrous cycle was monitored in intact rats (D1, diestrus 1; D2, diestrus 2; P, proestrus; E, estrus), and third cerebroventricular injections of 0.1 nmol of ghrelin or saline were tested on each cycle day. Ghrelin stimulated eating only on D1 and D2. *Significantly different from saline, same cycle day. Reprinted with permission from the American Diabetes Association from Diabetes, Deborah J. Clegg, Lynda M. Brown, Jeffrey M. Zigman, Christopher J. Kemp, April D. Strader, Stephen C. Benoit, Stephen C. Woods, Michela Mangiaracina, and Nori Geary, 56: April 2007; from Clegg et al. (130).
intraperitoneal CCK injection and 4) increased the desatiating effect of CCK-1R antagonism, with the effect in each case larger on the day modeling estrus than on the day modeling diestrus. 5) Estradiol treatment also increased the satiating effect of intraduodenal infusions of small amounts of fat in ovariectomized rats, and this was reversed by CCK-1R antagonism. Some of these data are shown in Fig. 12. [Wager-Srdar et al. (774) failed to see some of these effects, perhaps because of their use of high doses of CCK and estradiol.]

Estrogens act via ERα to increase CCK satiation. Estradiol treatment did not increase the desatiating effect of CCK-1R antagonism in ovariectomized ERO−/− mice (257) or in ovariectomized rats in which ERα in the NTS were silenced by treatment with anti-ERα siRNA (20).

Modulation of CCK satiation may also contribute to the hyperphagia of pregnancy and lactation. The eating-inhibitory potency of intraperitoneal injection of CCK was less on day 14 of pregnancy than in rats tested during diestrus and decreased progressively during lactation (775). The mediating mecha-

nism is unknown, but apparently does not require elevated prolactin (775).

In contrast to the involvement of CCK in the estrogenic control of eating, CCK does not appear to be involved in either the organizational or activational effects of androgens on eating. Shimizu et al. (661) reported that the effects of orchiectomy and testosterone treatment tended to be increased, not decreased, in Otsuka Long-Evans Tokushima Fatty (OLETF) rats, in which meal size, daily food intake, and body weight are increased due to a CCK-1R-null mutation (719). It is important to note that both peripheral and central CCK-1R signaling are disrupted in OLETF rats and that as a result of the latter, they also overexpress neuropeptide Y in the dorsomedial hypothalamus (490). Thus, Shimizu et al.’s (661) data suggest that androgens do not interact with any of these eating-control mechanisms.

HUMANS. The evidence for a sex difference in the satiating effect of CCK in humans is mixed. Burton-Freeman et al. (100) reported that there were close relationships between subjective hunger and fullness, rated on 100-mm visual-analog scales, and plasma CCK concentration after various 30% fat test meals in both men and women, but that the relationships differed between the sexes. For example, in women, but not in men, meals with almonds as the main fat source produced less CCK secretion and less fullness than the other meals. Overall, subjective fullness increased more in women, ~3.7 mm for each 1 pmol/l change in plasma CCK concentration vs. only ~1.5 mm/pmol/l CCK in men. Under different conditions, however, Nolan et al. (514) detected no sex differences in hunger or satiety ratings despite that postprandial CCK concentrations were elevated markedly more in women than in men 5 min after a test meal and were consistently, although nonsignificantly, elevated more in women throughout the following hour. Kissileff et al. (385) found that intravenous infusion of 112 ng/min CCK-8 significantly reduced meal size.
in women (~120 g), but not in men (~70 g) but, again, the sex difference was not significant. It is possible that the apparent sex difference in this study was due to differential effects of the CCK infusions on plasma CCK levels because identical doses were given to all subjects, although women weighed less (59 vs. 72 kg). Unfortunately, none of these three studies monitored menstrual cycling, which, as the studies discussed below suggest, may have added significant variability to the results.

Two attempts to detect cyclic changes in endogenous CCK satiation in women produced encouraging data. Pohle-Krauza et al. (561) had women ingest 10 g L-phenylalanine, which is a potent CCK secretagogue in humans (although not in rats), 20 min prior to lunch and dinner buffet meals in the midfollicular and the midluteal phases. In 11 subjects with low rigid-restraint [i.e., scores of 0 or 1 in the rigid-restraint subscale of the three-factor eating questionnaire (703)], L-phenylalanine reduced total daily food intake significantly more in the follicular phase than in the luteal phase. Surprisingly, just the opposite occurred in the 9 women with high rigid-restraint scores. These data suggest that CCK, ovarian cycling, and cognitive restraint may interact in the control of eating in women. Whether these effects were related to differences in CCK secretion was not determined. Brennan et al. (85), in the study reviewed just above (please see Gastric mechanoreception), found no cyclic change in postprandial CCK levels after a test meal. As gastric emptying was significantly reduced during the follicular phase, however, it is possible that intraintestinal nutrient stimuli stimulated CCK secretion more effectively during the follicular phase.

VAGAL MECHANISMS. That estradiol increases the satiating potency of exogenous CCK in ovariectomized rats (105, 259) indicates that estrogens change the neural processing of CCK afferent signaling to modulate CCK satiation rather than increasing CCK secretion. Such altered processing could occur due to changes in CCK-1 receptor function in vagal afferent terminals in the abdomen. Because most CCK receptors in the NTS are expressed on the central terminals of vagal afferents (136, 491), we estimated changes in abdominal vagal CCK-1 receptor function by measuring estradiol’s effects on CCK-1 receptor function in the NTS (258). Neither CCK-1 receptor number nor affinity was altered. Thus, estrogen signaling apparently either 1) increases transduction of CCK-1 receptor activation into a vagal afferent signal (hypothesis 1) or 2) modulates processing of this signal in the NTS or further downstream (hypothesis 2). The findings that female rats have ~50% more myelinated vagal afferent fibers than males due to the presence of a specific low-threshold fiber type and that the excitability of these fibers is estrogen-dependent (430, 575) are consistent with hypothesis 1. On the other hand, the necessity of ERα expression in the NTS for the estrogenic modulation of CCK satiation (please see cmNTS) strongly supports hypothesis 2. Perhaps both mechanisms contribute.

Because lesion of abdominal vagal afferents eliminates the satiating actions of exogenous and endogenous CCK in male rats, vagotomy should also interfere with the estrogenic inhibition of eating. This has been tested once, and the result was negative. That is, ovariectomy still increased body weight, and subsequent estradiol treatment still decreased body weight, in rats with total subdiaphragmatic vagotomies (212) The reason for this apparent discrepancy is unclear. It may have been important that neither meal patterns nor food intake was measured in this study or that, because of the debilitating effects of total vagotomy (405), all the vagotomized rats maintained body weights well below those of control rats. It is also possible that the apparent discrepancy is due to compensatory effects of other estrogen-related but vagally independent signals.

Glucagon-like peptide-1. Glucagon-like peptide-1 (GLP-1) acting in peripheral paracrine or endocrine and central neurocrine modes appears to contribute to the physiological control of meal size in rats and humans (39, 53, 318, 319, 791). Estradiol increased both the satiating potency of intraperitoneal injections of GLP-1 (Asarian, L., unpublished data) and the desatiating potency of intraperitoneal injections of the GLP-1 receptor-antagonist exendin-9 in ovariectomized rats (13). We assume that this is related to the satiating action of peripheral GLP-1 because, although central GLP-1 neurons are located in the cmNTS, they do not express ERα and do not express c-Fos in response to intraduodenal infusions of Intralipid (Asarian, L., unpublished data). As GLP-1 agonists are attractive candidates for obesity therapy (21, 798), these initial findings certainly merit pursuit.

Apolipoprotein A-IV. Apolipoprotein A-IV is synthesized in the brain, as well as in the intestines, and appears to act physiologically to inhibit eating (744). A study by Shen et al. (657) indicates that apolipoprotein A-IV signaling in the NTS may contribute to the estrogenic inhibition of eating: 1) ovariectomy increased eating and weight gain more in mice with null mutations of the apolipoprotein A-IV gene than in wild-type mice; 2) cyclic estradiol treatment increased the eating-inhibitory effect of an acute injection of apolipoprotein A-IV into the fourth cerebral ventricle of ovariectomized rats; and 3) ovariectomy decreased expression of apolipoprotein A-IV mRNA in the NTS of rats. In addition, apolipoprotein A-IV appeared to interact with CCK signaling to produce satiation in male rats (438), suggesting the interesting hypothesis that the same NTS estrogen-signaling pathway may modulate both CCK and apolipoprotein A-IV satiation.

Glucagon. Glucagon is released from the pancreas during meals, apparently largely due to cephalic phase reflexes, and contributes to the physiological control of meal size in rats and perhaps in humans (300, 801). In ovariectomized rats, estradiol treatment increased both the satiating potency of intrameal hepatic portal infusions of glucagon and the desatiating potency of antagonism of endogenous glucagon by hepatic portal infusion of glucagon antibodies (256). Whether this reflected a cyclic or a tonic effect of estradiol, and whether similar phenomena occur in cycling rats was not determined. There is also a sex difference in glucagon secretion in humans that may be relevant to eating. Both basal plasma glucagon concentration and prandial glucagon concentrations were approximately twofold higher in normal-weight or obese men than in normal-weight or obese women (112). These data indicate that the renewed interest in glucagon as a pharmacological tool in the treatment of obesity (300) should include studies of sex differences in its eating-inhibitory actions.

Insulin. Basal plasma levels of insulin correlate with body fat mass, and tonic insulin signaling is hypothesized to act as a negative-feedback signal linking adiposity to the central nervous system control of energy homeostasis, i.e., to be an adiposity signal (91, 801), although the hypothesis is increasingly controversial (275, 311, 331, 799).
RATS AND MICE. Clegg et al. (129, 131) reported a malefemale sex difference in the eating-inhibitory effect of insulin; i.e., that injection of 1 or 4 mIU insulin into the third cerebral ventricle inhibited eating more in male rats than in age- or weight-matched females. Keen-Rhinehart et al. (368), however, saw no such sex difference in tests of peripubertal male and female rats, which they speculated may have been due to lower endogenous estrogen levels in the young rats. To add to the uncertainty, Brüning et al. (91) reported that female, but not male, transgenic mice with brain-specific-null mutations of the insulin receptor were hyperphagic. This effect may have been secondary to different degrees of disruptions of the HPG axis: female knockout mice had a ~90% reduction in plasma LH concentration, vs. a ~40% reduction in males.

Clegg et al. (129) also reported that both central (20 ng estradiol benzoate once each 4th day into the third ventricle) and subcutaneous (2 µg estradiol benzoate once each 4th day) estradiol treatments decreased the inhibition of eating produced by central injection of 8 mIU insulin in ovarietomized rats. These surprising data suggest that an activational influence of estrogens dampens insulin’s anorexic potency; i.e., that insulin opposes the physiological estrogenic inhibition of eating. Where in the brain the injected hormones acted was not determined.

HUMANS. Hallschmid and colleagues (59, 305) reported a male-female sex difference in insulin’s effects in humans similar to that reported by Clegg et al. (129, 131) in rats. In one study (59), normal-weight (mean BMI, ~21–23) subjects self-administered 160 IU regular human insulin or the vehicle intranasally before eating a buffet breakfast; women used estrogen-dominant contraceptives and were tested with an interval of 28 days to control for cyclic effects on eating. In women, insulin significantly increased energy intake in men, from 1,351 ± 105 to 1,159 ± 96 kcal, but not in women, increasing from 769 ± 44 to 787 ± 41 kcal, and the sex difference was significant. Interestingly, performance in a memory task was improved by insulin in women but not in men. This was followed by an 8 wk, placebo-controlled trial of four daily intranasal insulin treatments, once each meal and again before bedtime (305). Insulin significantly reduced body fat mass, estimated by bioelectric impedance, ~1.4 kg in men and had no detectable effect in women. A variety of neuroendocrine, cardiovascular, metabolic, and subjective measures suggested that these effects were not secondary to deleterious side effects, that the subjects could not detect whether they had received insulin or placebo, and that insulin selectively reduced premeal hunger. A similarly designed trial in obese men indicated that although chronic insulin treatment had the same cognitive effects in obese men as had been found in the normal-weight men, it failed to reduce body weight, suggesting that obesity may induce a kind of insulin resistance in the neural networks regulating body weight (304).

Amylin. Amylin, a peptide cosecreted with insulin from the pancreatic β-cells, has a physiological eating-inhibitory action, and amylin agonists are promising antiobesity agents (446, 447, 618, 619, 801). Two tests of the estrogenic modulation of amylin’s eating-inhibitory effects produced opposite results. Trevaskis et al. (742) reported that cyclic estradiol treatment markedly reduced the potency of chronic subcutaneous infusion of 50 µg·kg⁻¹·day⁻¹ amylin to reduce eating and body weight in ovarietomized rats. On the other hand, Asarian et al. (14) found that in acute eating tests, estradiol cyclically increased the satiating potency of exogenous amylin and the desatiating potency of amylin antagonism. Estradiol also increased the number of dopamine β-hydroxylase-positive cells in the area postrema that expressed c-Fos after amylin injection, consistent with the catecholaminergic mediation of amylin’s satiating effect. Especially in view of amylin’s physiological role and therapeutic potential, it is important to resolve the contrasting outcomes of these studies.

Metabolic signals. A distributed network of metabolite- and hormone-sensing neurons in the brain and periphery contributes to energy homeostasis, in part via the control of eating (69, 416, 427). A relatively small amount of data suggests that there are sex differences in the metabolic control of eating. Wade and Gray (767) proposed in 1979 that estrogens control eating indirectly by increasing the flux of energy metabolites from the adipose tissue into the circulation, from which they reach hepatic or brain metabolic receptors. Attempts to provide experimental support for this hypothesis failed (287, 517, 533, 582, 583), however, and they soon abandoned it (768). More recent experiments with metabolic inhibitors have produced inconsistent results. Swithers et al. (717, 718) found that mercaptoacetate, which antagonizes fatty-acid oxidation, increased eating in male rats, but not females, whereas Sandoval et al. (632) found that mercaptoacetate was more effective in females than males. The cause for this discrepancy is unclear. Sandoval et al. (632) also found a sex difference related to glucose metabolism: 2-deoxy-o-glucose (2DG), which inhibits glycolysis, elicited more eating in male than female rats. Unexpectedly, both estradiol-treated and untreated ovarietomized females were more sensitive to 2DG than intact females (632), which contrasts with an earlier report (469) that estradiol treatment decreased the eating-stimulatory effect of 2DG in ovarietomized rats. Thus, more research is required to determine whether there are sex differences in metabolic controls of eating, and if so, whether they are estrogen-regulated.

Leptin. Basal plasma levels of leptin, like those of insulin, are tightly correlated with body fat mass and are thought to signal adiposity status to the brain and to initiate compensatory changes in eating and energy expenditure, especially in the case of reduced adiposity (218, 239, 422, 501). Dissecting the normal role of endogenous leptin in energy homeostasis has been far more difficult than was expected on the basis of the exaggerated obesity phenotype exhibited by mice, rats or humans with null mutations in the genes encoding leptin or its signaling receptor, leptin receptor-b (252, 331, 799). Nevertheless, there are now several lines of evidence that leptin tonically inhibits eating in mice, rats, and humans (1, 301, 310, 400, 418, 459, 614, 755, 824). It does not appear that this control is sexually differentiated. Although there are clear sex differences in leptin secretion, there is little evidence that these are related to sex differences in eating.

Leptin secretion. Basal plasma leptin levels are linearly related to fat mass in both men and women, with obese and never-obese persons falling on the same line (612, 613). Men and women have different relationships, however, with plasma concentrations of leptin per kilogram body fat mass markedly higher in women. Postmenopausal women have less basal plasma leptin per kilogram fat mass than premenopausal women, but more than men. Genetic differences, differences in androgen and estrogen levels, and regional fat distribution all
appear to contribute to these sex differences in basal plasma leptin levels, with no single factor alone sufficient (488, 598, 612, 613).

Basal plasma leptin concentration is correlated with fat mass in rats as well, but in contrast to humans, postpubertal male rats have higher basal plasma leptin levels than postpubertal females (415, 497, 683). The implication of this for leptin signaling is not clear, however, because plasma concentration of the soluble leptin receptor-e, which acts as a plasma binding protein that reduces leptin signaling, also is much higher in postpubertal male rats than postpubertal female rats (681).

LEPTIN AND SEX DIFFERENCES IN EATING. No role for the sex differences in basal plasma leptin concentration described above in eating has been established. Acute injections of leptin into the third cerebral ventricle, however, inhibited eating more in female rats than male rats (2, 129, 131). This sex difference may be related to activational effects of gonadal steroids. In ovariectomized rats, estradiol treatment increased leptin’s eating-inhibitory potency (2, 129, 131) and upregulated leptin receptor-b, the signaling form, in the hypothalamus (474, 595). The physiological relevance of these effects for leptin’s normal tonic eating-inhibitory effect, however, is uncertain. 1) Plasma estradiol levels did not influence the effect of chronic leptin treatment on body fat mass in female mice (545) or rats (124). 2) The eating-inhibitory potency of chronic leptin treatment did not vary over the ovarian cycle in intact rats (208). 3) Normal-weight women ate less during the periovulatory phase than during the luteal phase, but leptin levels were higher in the luteal phase and were not correlated with eating during any phase (536).

Androgens may affect leptin’s eating-inhibitory potency in the opposite manner as estrogens. This is because exogenous leptin had smaller effects on eating and on nuclear translocation of leptin-signal transducer and activator of transcription 3 in Arc neurons in transgenic mice lacking AR than in male wild-type mice (215). Basal levels of food intake in the AR-knockout and in wild-type mice, however, were not different (215).

Pregnant and lactating rats are both hyperleptinemic and, in terms of the inhibition of eating, leptin resistant. This resistance may be due to increased prolactin levels (412, 743); i.e., release from the tonic inhibitory effect of leptin on eating may increase food intake during pregnancy and lactation. In support of this, Grattan and colleagues (25, 26, 285, 412, 413) showed that 1) pregnancy-induced leptin resistance was associated with elevated neuropeptide Y mRNA and decreased POMC mRNA in the arcuate nucleus during pregnancy, 2) leptin receptor mRNA and leptin-induced phosphorylated-signal transducer and activator of transcription-3 protein decreased in the VMH during pregnancy, and 3) injection of leptin into the third cerebral ventricle that reduced daily food intake by ~20% in nonpregnant rats had no effect in pregnant rats or in pseudo-pregnant rats after intracerebroventricular infusions of prolactin that were designed to mimic the pattern of placental lactogen secretion that occurs during pregnancy. The development of leptin resistance during lactation and lack of effect of leptin on eating during lactation were recently replicated by Suzuki et al. (713). A useful further step would be to verify that progressive decreases in endogenous leptin signaling are necessary for the progressively increased food intake during pregnancy and lactation, as could be done, for example, using leptin antagonism (459, 824). Changes in NPY and melanocortin signaling in the dorsomedial hypothalamus were also implicated in pregnancy-induced hyperphagia (119).

Finally, the many physiological interactions between leptin and gonadal steroids, for example, in the early development of neural architecture controlling adult behavior (493, 667, 805), in pubertal development (187, 563), and in nutritional infertility (645, 769, 787), certainly justify further investigation of their interactions in the control of normal eating and adiposity (see Ref. 567 for further discussion).

Sex Differences in Central Mechanisms Controlling Eating

Neurochemical controls of eating. Neuropharmacological studies, including molecular genetic manipulations of neurochemicals, implicate several brain signaling molecules in sex differences in eating. We review some of the most interesting data. An unfortunate aspect of this literature is that, as yet, no concrete links have been forged between the neurochemical findings reviewed here and the progress in identifying either the sites of ER or the peripheral mechanisms mediating sex differences in eating reviewed above.

SEROTONIN (5-HYDROXYTRYPTAMINE, 5HT). Serotonergic neurotransmission plays integral roles in both satiation and food reward (302, 315, 414, 416). Whether there are male-female differences in the serotonergic control of eating is not clear. In one study, fenfluramine inhibited eating in female rats more than in male rats (209), whereas in another study, it did not (150). In contrast, there are several indications that estrogens affect serotonin-induced eating. Eckel et al. (209) found that the eating-inhibitory effect of the 5HT agonist fenfluramine was larger in intact, cycling rats during estrus than during diestrus and 2) increased by estradiol treatment in ovariectomized rats (593). In addition, they found that intraperitoneal and lateral cerebroventricular injections of meta-chlorophenylpiperazine, a selective antagonist of 5HT2C receptors, increased eating more in estradiol-treated than control ovariectomized rats (594). Souquet and Rowland (687), however, found no difference in the effect of chronic fenfluramine treatment in estradiol-treated than control ovariec-tomized rats. Taken together, these data suggest that 5HT-5HT2C receptor signaling is involved in estrogens’ cyclic, periovulatory eating-inhibitory effect, but not its tonic eating-inhibitory effect. The role of 5HT in the estrogenic control of eating may also be diet-specific because cyclic variations in the eating-inhibitory effect of 5HT were not detected when rats were fed more palatable foods or offered different macronutrient sources (325, 538).

5HT1A autoreceptors also may be involved in the periovulatory decrease in eating because 8-hydroxy-2-9(di-n-propylamino)tetralin (8-OH-DPAT), which decreases 5HT signaling by stimulating 5HT1A autoreceptors, stimulated eating less in estradiol-treated than in control ovariectomized rats (627), 2) in intact females rats than in ovariectomized rats (150), and 3) during proestrus and estrus than during diestrus in cycling rats (749).

Some of this estrogen-serotonin interaction may involve the amygdala. This is because 1) Eckel et al. (205, 206) found that estradiol increased eating and CCK-induced expression of c-Fos in the central nucleus of the amygdala (205, 206), and 2) Parker et al. (538) reported there were cyclic changes in the eating-stimulatory effect of injections of the 5HT2A/2C recep-
tor-antagonist metergoline into the posterior basolateral amygdala. King et al. (379, 380) reported that female rats ate more than male rats following amygdala lesions, but because ovariectomy has similar effects in intact and amygdala-lesioned rats, these data are difficult to relate to those of Eckel et al. (205, 206) and Parker et al. (538).

Rivera et al. (594) reported that estradiol treatment increased 5HT3C receptor content in the dorsal one-third of the caudal brain stem (−10–14.6 mm caudal to bregma), but not in the hypothalamus, suggesting that estradiol increases 5HT signaling by increasing the numbers of 5HT3C receptors in the caudal brain stem. It is important to determine the relationship between these neurons and the cmNTS ERα neurons mediating some of estradiol’s eating-inhibitory and weight-regulatory effects (please see cmNTS). In addition, because the satiating effect of CCK in male rats and mice is mediated in part by 5HT-5HT2C signaling (11, 559, 560), it is important to determine whether 5HT-5HT2C signaling mediates the sex differences in CCK satiation (please see CCK).

MELANOCYTE-STIMULATING HORMONES AND MELANOCORTIN RECEPTORS. α- and β-MSH signaling via MC3 and MC4 receptors contribute crucially to the control of energy homeostasis, with MC4 receptor mechanisms apparently more linked to the control of eating and MC3 receptor mechanisms to the control of metabolism (54, 722, 723). Although MC4 receptors are widely expressed in the brain, populations in the arcuate and paraventricular nuclei of the hypothalamus and caudal brain stem have been most strongly implicated in its eating effects.

There is a striking male-female sex difference in the effect of transgenic null mutations of the MC4 receptor gene in mice (Mc4r−/− mice): female Mc4r−/− mice increased food intake and body weight vs. female wild-type mice markedly more than male Mc4r−/− mice (348, 712) (Fig. 13). In one study (348), excess body weight began to accumulate around puberty in both sexes, suggesting activational effects of gonadal steroid hormones influence MSH-MC4 receptor signaling. There is also a male-female sex difference in the effects of loss of function polymorphisms of the human MC4 receptor gene, such that affected women acrrete twice as much excess BMI as men, ~8–9 kg/m² vs. ~4–5 kg/m² (177, 704). In addition, in a laboratory test-meal study, children of either sex with MC4 receptor polymorphisms ate more than twice as much as control children (219). MC4 receptor defects comprise the commonest form of human monogenic obesity, with a prevalence of ~2–5% in obese Europeans (521, 722, 723). Thus, mutations of the MC4 receptor represent an important sex difference in human eating and weight regulation that is accessible to study in mice.

In contrast to Mc4r−/− mice, transgenic mice with null mutations of the MC3 receptor did not increase intake of either low- or high-fat diet (712). Mutants of both sexes gained excess weight, apparently due to a variety of metabolic defects.

Neuropharmacological studies to date have not recapitulated the sex difference in eating shown by Mc4r−/− mice. 1) Lateral ventricular injections of the broad-spectrum MC receptor agonist MTII affected eating similarly in male and female rats (131). 2) Lateral ventricular injections of MTII affected eating similarly in estradiol-treated and control ovariectomized rats (562). 3) Lateral ventricular injections of the MC3/4 receptor antagonist SHU9119 affected eating similarly in estradiol-treated and control ovariectomized rats (562). Some have
claimed that following SHU9119 treatment in this study (562), the estrogenic inhibition of eating was “not detected” [(599), p 7] or estradiol was “unable to induce anorexia” [(463), p 5]. This is incorrect. SHU9119 did not change the effect of estradiol in tests when it occurred. For example, estradiol decreased 24-h food intake ∼5 g both in rats treated with 500 pmol SHU9119 and in untreated rats [Fig. 1 in (562)].

One possible explanation for the apparent discrepancy between the transgenic and neuropharmacological data is that Mc4r−/− mutation might disrupt early development of the HPG axis and that females may be relatively more sensitive to the disruption than males. A recent study, however, seems inconsistent with this hypothesis. That is, Xu et al. (812) found that female transgenic mice in which ERα was deleted from neurons expressing Pomp, the gene encoding MSH, became hyperphagic beginning around puberty, suggestive of disruption of an activational rather than an organizational effect of estrogens. In this study, however, the weight gain was limited to lean body mass, with no effect on fat mass. Because ovariectomy increases fat mass more than lean mass, the significance of these data for the normal estrogenic regulation of eating and energy homeostasis is unclear.

Agouti-related peptide and neuropeptide Y. Neurons expressing Agouti-related peptide (AgRP), an inverse agonist of MC4 receptors, coexpress neuropeptide Y (NPY) and are found solely in the arcuate nucleus of the hypothalamus; NPY neurons are more widespread (87, 416). NPY and AgRP/NPY neurons project to a variety of forebrain and brain stem sites involved in the control of eating and body weight, and central administration of either peptide potently stimulates eating (22, 87, 416, 693). Although transgenic deletion of the Npy gene or the Agrp gene or silencing them in early development did not affect adult eating or body weight, silencing them in adulthood led to pronounced anorexia (293, 445, 534, 574). Whether there were sex differences in these effects was not reported. Central injections of AgRP elicited similar effects on food intake and body weight in intact and gonadectomized male and female rats (131, 281), however, suggesting that the male-female sex difference in the effect of MC4 receptor mutations described above is not related to AgRP function.

A study by Olofsson et al. (527) indicates that AgRP/NPY neurons play a selective role in the periovulatory decrease in eating in mice. They reported that 1) hypothalamic Agrp and Npy gene expression decreased during estrus and 2) mice with massive degeneration of AgRP/NPY neurons due to transgenic deletion of mitochondrial transcription factor-A in AgRP neurons did not reduce food intake during estrus (Fig. 14), although they were fertile and vaginal estrous cycling was normal. AgRP/NPY neuron-deficient mice displayed normal average levels of food intake and normal body weight, indicating that these neurons selectively control the cyclic, but not the tonic, eating-inhibitory effect of estrogens. This effect was indirect in that hypothalamic AgRP/NPY neurons did not express ERα. The authors also investigated the effects of estradiol treatment, but these data are difficult to interpret physiologically because of the high doses used (2 μg centrally and 150 μg peripherally, please see Hormone treatment regimens). Whether AgRP/NPY neurons are involved in the periovulatory decrease in eating in other species has not been tested, although ovariectomy increased hypothalamic NPY and AgRP mRNA contents in rats (130) and estradiol reduced the concentration of AgRP in the cerebrospinal fluid of ovariolectomized rhesus monkeys (810). Central injections of AgRP had similar effects in estradiol-treated and control ovariolectomized rats (562, 633), which, together with Olofsson et al.’s (527) data, suggests that estrogens may modulate AgRP synthesis and release rather than MC4 receptor function or downstream mechanisms. In contrast to the lack of effect of estradiol on AgRP’s eating-stimulatory effect, estradiol did increase NPY-induced eating in one study (633), suggesting that estrogens may modulate NPY receptor function.

Melanin-concentrating hormone. Melanin-concentrating hormone (MCH) is a hypothalamic neuropeptide that stimulates eating and may contribute to sex differences in eating. Santollo and Eckel (634) reported that the eating-stimulatory effect of lateral cerebroventricular injections of MCH was 1) greater during diestrus than during estrus, 2) reduced by estradiol treatment in ovariolectomized rats, and 3) greater in male rats than in estradiol-treated ovariolectomized females.

Orosensory hedonics. Orosensory hedonic or palatability responses result from evaluative processes in the brain that produce subjective experiences (pleasure, surfeit, disgust, etc.) and controls of eating related to them (66, 68, 416, 607). A variety of data suggest that there are important physiological sex differences in these processes.

Rats. The hedonic control of eating can be assessed behaviorally in animals in situations that minimize the postoropharyngeal effects of food. This can be done by measuring lick rates or intake at just the onset of the meal, in brief-access tests, or in sham-eating tests, during which open gastric cannulas prevent ingested food from accumulating in the stomach or entering the intestines (679). An elegant apparatus for brief-access tests offers animals repeated 10-s exposures to as many as eight different test fluids in random order in the same session, so that the postoropharyngeal food stimuli that develop during the session do not differ for the different test fluids (680). Using this method, Curtis et al. (152) found that 1) male rats licked approximately twofold more 0.025 or 0.05 M sucrose than did females, 2) males and females licked similarly during exposure to 0.1–0.4 M sucrose (Fig. 15A) and...
male rats licked less than females during exposure to mixtures of 0.05 M sucrose and 0.05–0.5 M NaCl. The relative preference of male rats for dilute sucrose may be an organizational effect because licking was similar in untreated and estradiol-treated ovariectomized rats. This palatability difference appeared to be sufficient to control total amount eaten because when offered 0.025 M sucrose and water overnight, males drank approximately twofold more sucrose per gram body weight than either estradiol-treated or untreated ovariectomized females (Fig. 15B). This interpretation is tentative, however, because the postoropharyngeal effects of sucrose were not controlled. The salt preference appears to mirror a sex difference in “need-free” intake of 3% NaCl reported by Chow et al. (126), who also demonstrated that this sex difference is an organizational effect of neonatal androgenization of the brain. Male-female sex differences have also been reported for some other fluids, including glucose-saccharine mixtures (750) and polysaccharides (650). As rats appear unusually reactive to these tastants, the translational relevance of these phenomena is uncertain.

The palatability of dilute sucrose solutions may vary during the ovarian cycle. Atchley et al. (23) reported that rats licked less 0.025 M sucrose during 10-s exposures during estrus than during diestrus 2, but no differences were obtained for more concentrated sucrose solutions (Fig. 15C). This cyclic change in palatability of 0.025 M sucrose did not appear to control amount eaten because there was no cyclic difference in overnight intake of 0.025 M sucrose. 5HT appeared to contribute to the palatability of 0.025 M sucrose during diestrus 2 because fenfluramine decreased 0.025 M brief-access sucrose licking during diestrus 2, but did not affect brief access licking during estrus or overnight (23).

If estrogen treatment decreases the palatability of sweet fluids in ovariectomized rats, the phenomenon must be subtle: 1) The change in brief-access licking of 0.025 M sucrose reported by Atchley et al. (23) did not occur in tests of 0.05–0.4 M sucrose. 2) Curtis et al. (152) reported that twice weekly treatment with 10 μg estradiol benzoate decreased 10-s intakes of 0.05 M sucrose, but not of higher or lower sucrose concentrations. 3) We found that an estradiol treatment regimen that did not affect 0.8 M sucrose intake in sham-eating tests decreased it during real-eating tests (260). Lick records revealed how rapidly postoropharyngeal effects of estradiol can appear: in real-eating tests, neither ovariectomy nor estradiol treatment affected lick rate during the first minute of sucrose access, but ovariectomy increased lick rate during minutes 2–4 compared with intact rats, and estradiol treatment decreased lick rate during minutes 2–4 compared with untreated ovariectomized rats (344).

Sex differences in the hedonics of fat flavor have not been extensively tested in rats. Stratford et al. (699) found that in male, but not female, rats, the addition of 88 μM linoleic acid increased the relative selection of a mixture of 40 mM monosodium glutamate and 5 μM ethanol in 10-min simultaneous-access tests. The addition of 88 μM linoleic acid, however, increased the relative selection of a 100 mM monosodium glutamate-5 μM ethanol solution in both sexes. They concluded that there is a sex difference in the ability of linoleic acid to increase the intensity and palatability of low concentrations of monosodium glutamate. Finally, as for sucrose, there appears to be no activational effect of estradiol on the palatability of fat flavor. We found that corn-oil emulsions elicited a concentration-dependent stimulation of sham eating in ovariectomized female rats, as reported earlier for male rats (485), but we failed to detect any effect of estradiol treatment on sham eating, despite that estradiol significantly decreased real eating of the same solutions (Asarian L, Mangiaracina M, and Geary N, unpublished data; Fig. 15D).
HUMANS: PSYCHOPHYSICS. Determination of sex differences in flavor hedonics in humans requires comparisons of psycho-
physical ratings between different types of subjects, which is a
classical problem in psychophysics. The general labeled-magni-
tude scale is the most valid tool available for this and is
reshaping understanding of the relationships among hedonics,
sex, and obesity (44, 45, 685). For example, Hayes and Duffy
(316) reported a complex interaction between the density of
fungiform papillae on the tongue and the pleasantness of
sucrose-cream mixtures. As described above (please see Gus-
tation), greater densities of fungiform papillae on the tongue
are associated with increases in the perceived intensity of
sweetness and creaminess of food, independent of the hedonic
valence of the stimuli. In this study, Hayes and Duffy (316)
found a sex difference in the relationship between fungiform
papillae density and hedonic ratings. Women with fewer fun-
giform papillae and men with more fungiform papillae found
most pleasant high-creamy, high-sweet flavors, whereas
women with more fungiform papillae and men with fewer
fungiform papillae found most pleasant medium-creamy, me-
dium-sweet flavors. The effects were large: women and men
who preferred most high-creamy, high-sweet flavors endorsed
absolute intensities of liking that were approximately twofold
larger than men and women who preferred most medium-
creamy, medium-sweet flavors (Fig. 16). Given that absolute
liking ratings of the most-preferred foods are positively corre-
lated with BMI (45) and that obese women prefer high-fat,
high-sugar foods (194, 451), these data suggest that a relative
lack of fungiform papillae would increase a woman’s risk for
obesity. How the data relate to obesity risk in men is more
difficult to predict, given that obese men prefer high-fat,
high-protein foods to high-fat, high-sugar foods (194, 451).

The complexity of interactions of sensory and hedonic flavor
responses undoubtedly contributes to the variable findings on
changes in food preferences over the menstrual cycle (e.g.,
241, 359, 472) and in functional brain imaging studies (next
section).

HUMAN FUNCTIONAL BRAIN IMAGING: INTRODUCTION. The neu-
ral bases of normal and disordered human eating, eating-
related behavior, cognition, and affect can now be investigated
with functional brain imaging, which indirectly measures lev-
els of neuronal activity in circumscribed brain areas (111, 141,
173, 230, 410, 509, 753, 756). Progress in this exciting area is
difficult for a number of reasons: 1) Images of brain responses
related to cognition and affect are extraordinarily sensitive to
within- and between-subjects variations in arousal, mood, habi-
ts, life experiences, food-related memories, social context, and
other difficult-to-control factors. 2) Images of brain responses
are only indirect measures of actual neural activity. They are
based on indirect detection of cerebral glucose metabolism
(positronemission tomography) or, more frequently, indirect
detection of cerebral blood flow (functional magnetic reso-
nance imaging). Such measures cannot distinguish inhibition
from excitation. Changes in blood flow or metabolism may
arise from excitatory or inhibitory neural activation. In addi-
tion, differences in response intensity across regions might
have more to do with differences in the neural architecture of
microcircuits within the regions than with differential involve-
ment in processing the stimuli tested. 3) Detection of brain
activation depends both on the physical sensitivity of the
imaging machinery and the information-processing algorithms
used. For example, the present limit of spatial resolution of
brief scans is not sufficient to differentiate activity in adjacent
hypothalamic areas that have different functions. In addition,
the temporal resolution is too poor to enable inferences about
the sequence of information processing. 4) Images of larger
telencephalic areas often differentiate activity within subareas
for which no functional differences are known. 5) Psychological
functions cannot be assigned unambiguously to brain areas.
For example, the orbital frontal cortex (OFC), which
many data suggest is the most important telencephalic node in
the neural network mediating food hedonics, is clearly also
involved in cognitive processes, such as decision making, risk
evaluation, and expectation (66, 403, 409, 410, 530, 609).
Furthermore, there are sex differences in some of these cogni-
tive processes (403, 530).

Despite these difficulties, pictures of foods and tasting food
reliably increase brain activation in a number of areas (111,
173, 410, 509, 753, 754, 756). Increased flavor intensity,
independent of hedonic evaluation, usually increases activation
in the middle insular cortex, cerebellum, and amygdala. In-
creased hedonic intensity usually increases activation in the
OFC, anteroventral striatum, and nucleus accumbens (NAc),
anterior insular cortex (AIC), and anterior cingulate cortex
(ACC). The dorsolateral prefrontal (dLPFC) and parietal corti-
ces are also often activated, which is usually interpreted to be
associated with cognitive or “executive-control” aspects of the
experience. These areas tend to be more activated in people
with higher levels of dietary restraint (dietary restraint is
discussed in Interaction with cognitive controls of eating).
When the stimuli are pictures of foods, the fusiform gyrus, a
higher-order visual processing area, is usually activated.

The involvement of the amygdala and NAc in human hedon-
ics, as well as studies of the involvement of dopaminergic
neurotransmission that we did not review (694, 695), parallel
studies of flavor reward in rats (35, 515, 651). Similarly,
studies of the responses of individual neurons in both subcor-
tical and cortical brain areas in rhesus macaques to taste stimuli
suggest that there is substantial overlap in the neural structures
mediating flavor hedonics in monkeys and in humans (284,
606, 608). Thus, in addition to providing unique insights about
human hedonics, neuroimaging data also support the use of
animal models. Nevertheless, some species differences are to
be expected. For example, neuroimaging and clinical data
indicate that the AIC is necessary for normal affect related to
bodily states, if not for all affect, and monkeys and rodents do
not have a homologous structure (142, 143).

An important discovery is that food stimuli affect brain
activation differently in normal-weight and obese persons
(111, 173, 410, 509, 694, 753, 756). For example, obese
persons typically display greater differential activation in re-
sponse to pictures of high vs. low energy-density foods in the
NAc, AIC, ACC, and OFC, suggesting that increased hedonic
evaluation of food may contribute to the pathophysiology of
obesity. A study by Stice et al. (696) supported this hypothesis.
They found that palatable food and monetary rewards in-
creased brain activation in several brain areas associated with
hedonic evaluations in normal-weight children at high familial
risk for obesity (by virtue of having two overweight or obese
parents) compared with low-risk children (two normal-weight
parents).
Fig. 16. Sex and the density of fungiform papillae (FP) on the tongue interact to determine human hedonic responses to sweet-creamy flavor mixtures. Combinations of sugar solutions and cream were rated using the general labeled-magnitude-estimation scale, which enables valid comparisons of measurements of subjective experience between groups (e.g., between sexes). Men and women with low and high FP densities were analyzed separately. The x-axes are the sensory intensities (i.e., not hedonic intensities) of the sweetness of the stimuli, and the y-axes are the sensory intensities of their creaminess (0 = no sensation; 100 = the strongest imaginable sensation of any kind); note that the sensory intensities of the stimuli tested ranged from 0 to 90. The pleasantness of the stimuli (−100 = strongest imaginable disliking, 0 = neutral; 100 = strongest imaginable liking) are displayed as isohedonic contours; that is, each line indicates the various sweet-creamy combinations that were judged to have a particular pleasantness, the values of which are given on the contours. Insets on the graphs indicate the range of intensities of pleasantness observed. For example, men who had low FP density found the hedonic intensity of the stimuli to range from approximately −5 to −20, with maximum liking (smallest contour area) for stimuli with sensory intensity −50 sweet and −50 creamy. Note that men with low FP densities and women with high FP densities liked best intermediate sweet-creamy intensities best (maximum liking for men, −50 sweet, −50 creamy and for women, −30 sweet, and −40 creamy), but that their degrees of liking were moderate (<25 for men, <20 for women). In contrast, men with high FP densities and women with low FP densities liked higher sweet-creamy intensities best (90 sweet, 90 creamy were most liked by both sexes) and endorsed higher degrees of liking (>30 for men, >40 for women). Note also that flavor mixtures that women with low FP densities liked most (upper right part of graph) were disliked by women with high FP densities. Reprinted from Physiology and Behavior, Oral sensory phenotype identifies level of sugar and fat required for maximal liking, John E. Hayes and Valerie B. Duffy, 95: 77–87, 2008; republished with permission from Elsevier; from Hayes and Duffy (316).
HUMAN FUNCTIONAL BRAIN IMAGING: SEX DIFFERENCES. Male-female sex differences in brain activation in response to the flavors of normal foods (176, 675), to pure tastes (299), and to pictures of food (135, 231, 264, 378, 748) have been reported. In a recent review of this literature, Geliebter et al. (264) concluded that if brain areas are classed by their predominate functions, as described above, pictures of food stimuli elicit more activation in areas related to planning and executing behaviors in men and more activation in areas related to cognitive and affective processes in women. This conclusion, although certainly generally correct, belies the complexity of the data obtained in these studies.

The complex effects of sex on imaging responses is clearly reflected in Geliebter et al.’s (264) study. Subjects were weight-stable, healthy obese men and women. They ate a 1,000 kcal dinner, fasted 12 h, then ate either 750 ml liquid diet (∼740 kcal, fed state) or 750 ml water (fasted state), and were tested 95 min later. The difference in response between high and low energy-density foods was larger in men than women during the fed state in five brain areas and during the fasted state in five different brain areas. The high-low difference was larger in women than in five brain areas during the fed state and during the fasted state in four different areas, as well as two of the same areas, the insula and the dlPFC. The insula responses occurred on the left side in both men and women, but not in similar subregions [Montreal Neurological Institute standard brain coordinates (right-left, anterior-posterior, superior-inferior) −32, −34, 20 and −28, 0, 30, respectively]. In the dlPFC, differences were detected in similar subregions, but occurred in the right hemisphere during the fed state and in the left hemisphere during the fasted state (coordinates 30, 40, 34, and −34, 38, and 32, respectively). Furthermore, in two other parts of the dlPFC, women showed smaller rather than larger responses than men in the fed state (coordinates 42, 34, 16, and 30, 22, 34). The only other area in which brain responses occurred in more than one condition was the right fusiform gyrus, where the high-low difference was larger in men than women in the fed state and larger in women than men in the fasted state. Aside from the lack of menstrual-cycle phase data, this is a well-planned and analyzed study. Nevertheless, current understanding of human brain function simply does not permit a coherent interpretation of most of the effects obtained.

It is possible that studies of brain responses to receipt of food might lead to simpler patterns of data. As far as we know, however, only two such studies have appeared. Haase at al. (299) studied brain responses to intraoral infusions of 0.3 ml 0.04 M caffeine (bitter), 0.01 M citric acid (sour), 0.64 M sucrose (sweet) or 0.16 M NaCl (salty) in normal-weight men and women during fed and fasted states [using a method similar to that of Geliebter et al. (264) described above]. Indeed, only two sex differences in brain responses to sucrose between the fed and fasted states were detected—the differential responses were larger in men than women in the insula and cerebellum (sex differences for other tastes occurred in several other areas). Smeets et al. (675) did a more naturalistic study. Brain responses to chocolate-flavored milk, administered in small amounts by an undescribed method, were tested in normal-weight men and women, first in a fasted state and then after eating solid bittersweet chocolate and water to satiety. Sex differences in the effect of satiation were detected only in three areas: men showed greater increases in activation in the ventral striatum and greater decreases in the medial PFC, while women showed greater decreases in the hypothalamus.

We are aware of two reports that women’s brain activation in response to pictures of foods varies across the menstrual cycle. Frank et al. (232) reported that the differential effect of pictures of high energy-density foods vs. nonfoods was larger in the follicular phase than in the luteal phase in the NAc, amygdala, and hippocampus; the effect of low energy-density foods vs. nonfoods was significant only in the hippocampus. Alonso-Alonso et al. (4) tested the effects of pictures of food before and after a standard meal designed to contain 20% of their daily energy need; this was done once early (days 3–6 after the onset of menstruation) and once late (days 10–13) in the follicular phase of the menstrual cycle. The differential effect of fed vs. fasted states of activation in response to pictures of food was greater in the late vs. the early follicular phase in the inferior frontal gyrus and fusiform gyrus. The inferior frontal gyrus is considered to be an “executive-control” area and, as mentioned above, the fusiform gyrus is a higher-order visual-processing area; thus, neither is likely to be directly involved in the control of eating. Nevertheless, it is intriguing that, unique among cortical areas, the volume of the fusiform gyrus-parahippocampal gyrus area, as well as performance on hippocampal-dependent memory tasks, varied throughout the menstrual cycle (557, 572).

Physiological Sex Differences in Disordered Human Eating

Psychiatric eating disorders. The current view is that the psychiatric eating disorders anorexia nervosa, bulimia nervosa, binge-eating disorder, and “eating disorders not otherwise specified” (which accounts for about half of eating-disorder patients) are caused by complex interactions among cultural, social, familial, and biological factors (5, 30, 365, 387, 460, 740, 777). Perhaps the strongest evidence that biological factors are important in psychiatric eating disorders is their high heritability (heritability is the fraction of phenotypic variance accounted for by genetic variation). Twin studies, for example, suggest that genetic variability accounts for 50–80% of the risks for anorexia nervosa and bulimia nervosa (365, 736, 740).

The various influences on psychiatric eating disorders are thought to interact dynamically, so that precipitating vulnerabilities spiral into vicious cycles involving increasing numbers of causal factors. Sex is clearly an important variable. The lifetime prevalence of psychiatric eating disorders (346, 351) and various symptoms of disordered eating (700) are about three-fold higher in women than in men in community samples, and these differences emerge around the onset of puberty (27, 631, 715). Subclinical symptoms of disordered eating are also more prevalent in females than males (329, 700) and were highly heritable in pubertal and postpubertal girls, but not in prepubertal girls (148). In addition, recovery from eating disorders is slower in women than in men, and rates of remission are higher (698).

That the pathogenesis of eating disorders involves biological factors naturally encourages studies of potential biological bases of these sex differences, but as our review reflects, few human studies have done so. Similarly, although the utility of animal models of disordered eating is increasingly emphasized (113, 138, 139, 362, 363, 665, 676), the contributions of
physiological sex differences are not a major component of these research efforts.

Eating disorders affect gonadal-steroid hormone levels. Women who are acutely ill with anorexia nervosa have abnormally low gonadotropin, estrogen and progestin levels and usually amenorrhea, and women with bulimia nervosa frequently report menstrual dysfunction (30, 332, 334, 483, 566). In addition, testosterone levels are decreased in symptomatic women with anorexia nervosa and increased in symptomatic women with bulimia nervosa (30, 504, 709). Changes in gonadal steroid hormone levels, however, are consequences of weight loss and extreme dieting rather than being causes of disordered eating (7, 30, 277, 483, 586). Nevertheless, pharmacological treatments that affect gonadal hormone levels may be useful in the treatment of disordered eating, as least in selected patients (30, 63, 334, 366, 483, 504). For example, initial results suggest that antianrogenic treatment may reduce binge eating in women with bulimia nervosa (504, 710).

ANOREXIA NERVOSA: HUMAN STUDIES. Twin studies indicate that genetic factors account for up to 74 (395) to 88% (96) of the variance in anorexia nervosa. The genes accounting for this high heritability and their contribution to sex differences in anorexia nervosa are unknown. One potential clue comes from a family-based association study involving 321 French families (761) that suggested that polymorphisms in ESR1, the gene encoding ERα, may contribute. In this study, over-transmission of three ESR1 single-nucleotide polymorphisms (rs726281, rs3798577, and rs2295193), as well as a haplotype of ESR1 involving these and five additional single-nucleotide polymorphisms were associated with restricting-type anorexia nervosa (i.e., energy intake controlled by dieting rather than purging). This study (761) also failed to detect the previously reported (200, 616) association between the single nucleotide polymorphism rs1256049 in ESR2, which encodes ERβ, and anorexia nervosa. Further work is required to determine whether these effects can be replicated and extended to other populations. This has not yet succeeded. Rather, genome-wide association studies to date, although yielding some candidates for further research, have not identified genome-wide significance for variants in ESR1 or any other genes in anorexia nervosa (128, 354, 773, 781).

Klump and colleagues (146, 389) presented two lines of support for their hypothesis that disordered human eating is influenced by early organizational effects of gonadal steroid hormones similar to those discovered in animals (please see Development). 1) In normal-weight women with either male or female twins, higher ratios of the lengths of the second and fourth fingers, indicative of less prenatal androgen exposure, were significantly correlated with increased scores on a questionnaire measuring subclinical disordered-eating symptoms (389). 2) Disordered-eating scores were significantly higher in girls with female twins than girls with male twins, who presumably had greater prenatal androgen exposure (146). Furthermore, this difference in disordered eating scores emerged during mid-late puberty (147), suggesting that the developmental effect forms a substrate for a later activational effect of gonadal steroids (as described below). These associations, however, were detected in only one (577) of several (31, 95, 449, 571, 581) subsequent studies involving patients with eating disorders. Thus, Klump’s organizational hypothesis requires further research.

The increased incidence of anorexia nervosa around puberty suggests that an activational effect of estrogens may cause anorexia nervosa, as originally hypothesized by Young (815, 816). Reports (389, 579) of significant correlations between salivary estradiol levels and subclinical eating-disorder symptoms across the menstrual cycle are consistent with this hypothesis. Whether any of these women progressed to anorexia nervosa, however, was not established. Misra et al. (486) performed a randomized, double-blind study in which female patients with anorexia nervosa (n = 110; mean age, 16 yr; mean BMI, 17.4 kg/m²; minimum duration of amenorrhea, 3 mo) received either placebo or a physiological regimen of estrogen treatment in addition to their ongoing treatment regimens. Estrogen treatment consisted of a fixed dose of estradiol in older patients and an escalating dose schedule that was designed to mimic peripubertal plasma estradiol levels in younger patients. After 18 mo, estradiol did not significantly affect body weight gain (4.6 ± 1.0 kg in estradiol-treated vs. 4.2 ± 1.0 kg in control patients) or BMI gain (1.6 ± 0.4 kg/m² vs. 1.5 ± 0.4 kg/m²) but did significantly improve spine and hip bone mineral densities. These data suggest that estrogens did not exacerbate the symptoms of anorexia nervosa in these patients, but because eating was not measured and may have been too low in these patients to detect decreases, they are not conclusive.

ANOREXIA NERVOSA: ANIMAL MODELS. The most popular animal model of anorexia nervosa is Routenberg’s (620, 621) activity-based anorexia model, which is self-starvation brought about in mice and rats by providing ad libitum access to an activity wheel and limiting food access to ~1–2 h/day. Few activity-based anorexia studies involve females. Doerries et al. (186) found that female Holtzman Sprague-Dawley rats ran more than weight-matched males, but ate more and lost weight slower. Female rats may not develop activity-based anorexia as reliably as males; in one study, females did not increase activity (79) and in another they increased activity but did not decrease eating (185).

Activity-based anorexia rapidly suppresses ovarian cycling in rats, paralleling the endocrine disturbances of anorexia nervosa (554) and other situations of insufficient energy intake (441, 442, 645, 770, 792). This activity-based-anorexia effect is due to an interaction of high activity and reduced food intake because neither alone was sufficient for it (184, 185, 784). A similar synergistic effect on ovarian cycling occurred in response to combinations of food restriction and psychosocial stress in cynomolgus monkeys (792). Increased activity and decreased eating combine to inhibit kisspeptin or GnRH neurons in the hypothalamus, which leads to reductions in LH and estrogens (175, 456, 666). Whether the reduced estrogen secretion is related to the weaker anorectic effect in female rats compared with male rats (185) is unknown.

There may also be a sex difference in the development of vulnerability to activity-based anorexia in rats. Hancock and Grant (307) reported that early, acute, maternal separation led to greater increases in activity and more profound anorexia in females than males when tested as adolescents, but more in males than females when tested as adults. These data suggest both 1) that early-life stress has complex effects on susceptibility to activity-based anorexia later in life and 2) that sex may affect the susceptibility to activity-based anorexia indirectly.
via effects on stress reactivity, rather than by directly affecting physiological controls of eating.

Kas and colleagues (362, 363) suggest that the high heritability of anorexia nervosa can be fruitfully analyzed by studying genes implicated in the human syndrome that lead to phenotypic variations in animals. They point out that spontaneous activity is an excellent candidate phenotype because marked increases in physical activity frequently accompany anorexia nervosa and the propensity for spontaneous activity is highly heritable in mice. Given that estrogens control physical activity in female mice and rats and that female rodents normally display much higher levels of spontaneous activity than males (251, 433), this phenotype also seems to be a good choice for the investigation of sex differences. Such work, however, may have to be done outside the context of activity-based anorexia, however, because 1) activity-based-anorexia rats display high levels of activity in the absence of LH and estrogens and 2) estradiol treatment reduced activity in weight-reduced rats (656).

**Binge Eating.** Binge eating, defined as repeated episodes of eating abnormally large amounts of food together with the perception of loss of control over eating, is a core diagnostic criterion of bulimia nervosa and binge-eating disorder (5). The lifetime prevalence for bulimia nervosa is approximately three-fold higher in females than males, and that for binge eating disorder is about twice as high (346, 351). Binge eating also occurs outside these disorders, and a recent community sample estimated that 24% of women fall in this category (382). Importantly, the prevalence of binge eating considered as a separate symptom is also ~2–6-fold higher in females than males (145, 196, 223, 320, 329, 584).

The heritability of bulimia nervosa is estimated in twin studies to account for 59 (772) to 95% (94) of the variance. The heritability of binge eating per se is nearly as high (35–85%) (93, 94, 394, 584, 708). This underscores the biological component of binge eating. As for anorexia nervosa, however, the genes underlying this high heritability remain unknown. Work by Davis et al. (164, 165) suggests that it may be related, in part, to gain-of-function polymorphisms in the dopamine D2-receptor and opioid μ-receptor genes. The authors hypothesized that these polymorphisms may predispose people to hedonically based or emotional eating and thus increase their risk for binge-eating disorder. It is important to replicate these findings and determine whether they can be extended to bulimia nervosa. Finally, further evidence that there is a biological component in the sex difference in binge-eating prevalence comes from fascinating recent rat studies indicating that female rats are more prone to display binge eating-like behavior than are male rats (29, 396) (Fig. 17).

Klump et al. (388), as well as others (27, 631, 715) have also investigated the biological contributions to the sharp increases in the incidences of bulimia nervosa and binge-eating disorder that occur in girls at the onset of puberty (~8–10 yr of age). In the Klump et al. study (388), they found 1) no detectable heritability of disordered eating in prepubertal girls; 2) heritability of ~0.5 in girls during and after puberty; and 3) heritability of ~0.5 in boys at all times. In another study (393), they found significant heritability for disordered eating in 10–15-yr-old girls with higher plasma estradiol levels, but not in girls with lower estradiol levels. Pursuing these effects in a rat model, they found that a binge-eating trait emerged in vulnerable rats during puberty (398), but that ovariectomizing these rats increased binge size rather than eliminating binges (397). Taken together, these data suggest that 1) an organizational effect of estrogens at puberty acts on a genetically determined vulnerability to facilitate the development of bingeing in girls and 2) an activational effect of estrogens thereafter may limit binging (please see Ref. 149 for a review).

The estradiol metabolite 2-hydroxy-estradiol may mediate another activational effect of estrogens on bingeing. Catabolism of 2-hydroxy-estradiol, like catabolism of dopamine, is catalyzed by catechol-O-methyltransferase, and loss-of-function polymorphisms in the catechol-O-methyltransferase gene were linked to increased risk for anorexia nervosa and bulimia nervosa (481). Because increased plasma levels of estrogens, leading to increases in 2-hydroxy-estradiol, may competitively inhibit dopamine catabolism and increase synaptic dopamine and because altered dopaminergic mechanisms of food reward may contribute to binge eating (89, 780), catechol-O-methyltransferase could link estrogens to the propensity to binge. In support of this hypothesis, Babbs et al. (29) demonstrated that peripheral injections of 2-hydroxy-estradiol increased eating under binge conditions, but not under normal conditions, in a rat model.

There are several reports that binge frequency and disordered-eating symptoms are higher during the luteal and menstrual phases of the cycle than during the follicular phase (210, 272, 391, 426, 570, 578). Furthermore, within-subject analyses indicate that both binge frequency in patients (210, 391) and

![Fig. 17. Male-female sex difference in rats’ propensities to binge eat. Thirty male and 30 female rats were offered standard chow ad libitum and a palatable commercial cake frosting 3 days/wk for 2 wk, a procedure that leads to increased palatable food intake in comparison to ad libitum access to the same food (138, 139). Four-hour palatable food intakes in each of the six tests were ranked across all rats, and individual differences in binge-eating propensity were scored. Data are percentages of male and female rats that were binge-eating prone (i.e., scored in the highest tertile of palatable food intake in 3 or more of the 6 tests and never scored in the lowest tertile) or binge-eating resistant (i.e., scored in the lowest tertile of palatable food intake in three or more of the six tests and never scored in the lowest tertile). *Significant sex difference, two-proportion z-test, P < 0.001. Adapted from International Journal of Eating Disorders, Sex differences in binge eating patterns in male and female adult rats, Kelly L. Klump, Sarah Racine, Britny Hildebrandt, and Cheryl L. Sisk, 95: 77–87, 2008; republished with permission from John Wiley and Sons; from Klump et al. (396).](http://ajpregu.physiology.org/doi/10.1210/jc.2017-16622.7.60)
disordered-eating symptoms in community samples (390, 392, 578, 580) are positively correlated with preceding progesterone levels and negatively correlated with preceding estradiol levels, suggesting possibly causal relationships. Furthermore, the correlations between estradiol and progesterone levels and disordered eating were evident across a range of patient BMI, levels of dietary restraint, and levels of impulsivity (390, 580). Clearly, mechanistic work on the relationships between activational effects of estrogens and pregestins and binge eating is warranted. Two issues that require further research in this context are whether binge size, in addition to frequency, varies across the cycle and whether cyclic effects on bingeing are related to the cyclic changes in normal eating (please see Ovarian cycle).

The hormonal control of binge size, but not of binge frequency, has been investigated in rat binge-eating models based on intermittent access to palatable food (138, 139). Binge size 1) did not vary across the ovarian cycle in intact rats (57), 2) was tonically, but not cyclically, decreased during a cyclic estradiol treatment regimen that both tonically and cyclically decreased normal eating in ovariectomized rats (817, 818), and 3) was not affected by cyclic treatment with a near-physiological pregestosterone dose, either alone or in combination with estradiol (817). Thus, how closely cyclic changes in binge frequency in women can be modeled in rats is not yet clear.

Finally, test-meal studies indicate that patients who binge eat display decreased perceived satiation together with decreased gastric emptying or increased gastric capacity (180, 263, 265), decreased postprandial plasma ghrelin drops (262), decreased postprandial plasma CCK increases (180, 269, 367, 555), and decreased postprandial plasma GLP-1 increases (506). Whether these are adaptations to binge eating or contribute causally to binge size is not certain. Nevertheless, in view of the sex differences in these mechanisms reviewed above, they merit testing as potential sources of sex differences in binge eating.

Obesity. As reviewed above, the effects of loss of ovarian function and estrogen treatment on adiposity are clearly linked to changes in eating in mice and rats and may be so in women. Here, we discuss two further links among HPG function, eating, and obesity.

POLYCYSTIC OVARY SYNDROME. Polycystic ovary syndrome is an endocrine disorder that includes abnormal ovarian morphology, hyperandrogenism (e.g., hirsutism) and oligomenorrhea or amenorrhea after puberty (211, 280, 334, 785). It affects ~10% of reproductive-aged women. The majority of women with polycystic ovary syndrome are also obese, with atypical regional adipose-tissue distribution, i.e., predominately abdominal rather than gluteo-femoral adiposity. Because obesity, especially abdominal obesity, disrupts ovarian cycling and leads to signs of hyperandrogenism, obesity is presumed to cause or exacerbate polycystic ovary disorder (37, 211, 785). Progressive development of insulin resistance, hyperinsulinemia, and insulin-mediated inhibition of estrogen secretion may also release eating from estrogenic inhibition. In addition, some eating abnormalities that are associated with polycystic ovary syndrome are similar to those of bulimia nervosa, suggesting that increased androgen levels may underlie both (334, 335, 434, 505).

Meal-related gastrointestinal-hormone secretion is disordered in polycystic ovary syndrome: test meals decreased plasma ghrelin levels less (489) and increased plasma CCK level less (335) in patients with polycystic ovary syndrome than in weight-matched control women. Basal ghrelin secretion is also reduced in women with polycystic ovary syndrome, and increased during antiandrogen therapy in one small study (246). More work is required to determine the causes of these changes and whether they are related to disordered eating.

BARIATRIC SURGERY. The most effective treatment for obesity is bariatric surgery. Because prevalence of morbid obesity in the USA is approximately twofold higher in women than men (226) and because women appear to suffer more from these disorders in terms of quality of life (24, 84, 273, 531, 762), >80% of bariatric surgery patients in the United States are women (568, 630). Both animal and human data suggest that physiological sex differences affect bariatric surgery outcome. 1) A retrospective analysis of >1,300 obese women who underwent either Roux-en-Y gastric bypass surgery or gastric banding indicated that presumptively premenopausal women (i.e., women age 20–45 yr) lost significantly more weight than presumptively postmenopausal women (i.e., age 55–65 yr of age) (522). This is consistent with the hypothesis that estrogens affect weight even in women in whom bariatric surgery has massively altered gastrointestinal food handling. 2) Estradiol treatment further decreased eating and body weight after Roux-en-Y gastric bypass surgery in ovariectomized rats (13) (Fig. 18). Thus, physiological sex differences in eating may be important issues in the surgical treatment of obesity.

Conclusions

We reviewed the variety and complexity of physiological sex differences in eating in rats, mice and anthropoid primates, including phenomenology, peripheral and central neuroendocrine mechanisms, and pathophysiology. We discussed physiological sex differences in early development, puberty, and reproductive adulthood and senescence. The prominence and variety of physiological sex differences in rats, mice, and anthropoid primates with potential relevance for understanding normal and disordered human eating convince us of the importance of this area. For example 1) the physiological sex difference in intake of sweets that occurs in animals and women has clear potential implications for the development of countermeasures for worldwide epidemic of overeating and obesity, and 2) evidence for sex-linked physiological contributions to the vulnerability to psychiatric eating disorders may facilitate development of more efficacious treatment of these disorders. Furthermore, the numerous mechanistic approaches that already have been brought to bear on these and other sex differences in eating that we reviewed underscore their tractability to physiological and molecular analyses in humans, as well as in animals. Finally, powerful new methods are likely to accelerate progress in several aspects of physiological sex differences in eating. This is reflected, for example, in work under way on 1) the development of HPG-axis controls of eating, 2) links between gene variations and eating, and 3) functional brain imaging.

The greatest amount of data presently available concerns the activational effects of estrogens on eating in rats and mice. On the basis of these data, as well as the more limited results in anthropoid primates, we hypothesize that the population of ERα-expressing neurons in the cmNTS is an essential component of a local neuronal network that integrates a variety of peripheral afferent signals, as well as descending diencephalic.
and telencephalic influences to control meal size, food intake, and body weight in rats and mice, and probably in women. Fig. 19 diagrams this hypothesis and emphasizes its speculative nature. For example, we conclude that at present 1) CCK, ghrelin, and gustation are firmly established estrogen-sensitive peripheral controls, and, of these, only CCK satiation is certain to be influenced by cmNTS ERα, and 2) 5HT, AgRP, and orosensory hedonics are firmly established estrogen-sensitive central controls, and whether they are affected by cmNTS ERα or provide descending inputs to the local neuronal networks in which cmNTS ERα reside, is wholly speculative. As we also reviewed, however, these disparate data suggest several potential toeholds for efforts to test this and related hypotheses. For example, the apparent similarity of the roles of CCK, 5HT, and AgRP on the phasic estrogenic inhibition of eating during the ovarian cycle presents one such opportunity. Figure 19 also makes clear that there is an androgenic control of meal size, food intake, and body weight and that nothing is known about the central mechanisms mediating it. Finally, available data indicate that progestins do not contribute to the control of eating.

We emphasize that the hypothesis that physiological sex differences in the controls of eating play causal roles in both normal and disordered human eating does not imply either 1) that physiological sex differences in eating alone are sufficient to cause disordered eating or 2) that physiological sex differences not directly involved in eating are not important in disordered eating, for example, variants in ESRI that are related to personality differences in women (482). Rather, our view is that disordered eating results from dynamic interactions among numerous cultural, social, familial, and biological factors to which physiological sex differences, including sex differences in the physiology of eating, may contribute. Furthermore, we believe that physiological sex differences may be relevant to the treatment of disordered eating even if they are not causal. For example, a particular physiologically based therapy may be more or less efficacious in various states of HPG function, such as in premenopausal or postmenopausal women.

Despite the significant progress being made on the study of sex differences in the physiology of eating, many aspects of the problem remain nearly untouched. Examples of such specific issues include 1) how eating is released from estrogenic inhibition during the luteal phase in anthropoid primates, 2) how the activational effects of androgens on eating are mediated, 3) whether and how puberty and reproductive senescence affect eating, and 4) how basic physiological controls of eating contribute to disordered human eating.

In addition to these relatively specific issues, our review also indicates that more integrative approaches are called for. There are opportunities for integrative sex-difference studies of at least five kinds. 1) Almost no studies to date have addressed the neuroendocrine integration of peripheral and central eating-control mechanisms, such as the integration of brain stem and telencephalic neural mechanisms. This type of integration comprises one of the most exciting frontiers in the contemporary physiology of eating (291, 416, 494, 648, 800) and is an unfortunate lacuna in sex-difference research. 2) How hypothalamic and pituitary HPG-axis mechanisms, such as those mediated by kisspeptin or GnIH, are integrated with controls of HPG function, such as in premenopausal or postmenopausal women. Despite the significant progress being made on the study of sex differences in the physiology of eating, many aspects of the problem remain nearly untouched. Examples of such specific issues include 1) how eating is released from estrogenic inhibition during the luteal phase in anthropoid primates, 2) how the activational effects of androgens on eating are mediated, 3) whether and how puberty and reproductive senescence affect eating, and 4) how basic physiological controls of eating contribute to disordered human eating.

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cognitions and affect. These processes also display a variety of sex differences, and there are well-developed methods to assess them in animals and humans (6, 49, 50, 62, 183, 225, 238, 542, 624, 644, 653, 658, 703, 720). The study of interactions among such psychological processes and physiological sex differences in eating seem to us to be profitable avenues of investigation.

All of the problems outlined above have to be tackled to create an integrative regulatory physiology of HPG influences on eating. Viewed from the perspective of these challenges, what has been accomplished seems uneven and fragmentary. Sex is inappropriately neglected in the physiology of eating, as it is in most other branches of physiology and medicine (51, 64, 73, 109, 110, 466, 797, 826). Our review will have succeeded in unknown sites increase meal frequency, food intake, and body weight (green arrows and text boxes). In contrast, progestins appear not to have physiological effects on eating (blue, dashed text box). Challenges for future mechanistic studies of sex differences in eating include 1) establishing the physiological and pathophysiological roles of the estrogeneric mechanisms shown and 2) identifying the androgenic mechanisms affecting eating.

Fig. 19. Schematic summary of the activational effects of gonadal steroid hormones on eating, emphasizing hypothesized neural mechanisms and their integration. The diagram is based on our review of rat, mouse, and anthropoid primate, including human, data. It is superimposed on a schematic midsagittal section of a rat brain, although most named structures are lateral to the midline. Red arrows and text boxes indicate estrogenic mechanisms; question marks and black font identify less well-established mechanisms. Estrogens acting on ERα neurons in the cmNTS (filled oval) affect the neural processing of peripheral CCK signals (solid red arrow) so as to reduce meal size, food intake, and body weight; the same ERα neurons are hypothesized to be involved in the processing of a variety of other peripheral signals, especially ghrelin and gustatory signals, which are apparently affected by estrogens (dashed red arrows). ERα in the dorsal raphe and several hypothalamic areas are not strongly implicated in the control of eating (open red oval). A number of forebrain signaling molecules, especially 5HT and AgRP, as well as flavor hedonics contribute to the estrogeneric control of eating, probably via hypothalamic and telencephalic mechanisms (dashed red arrows). Neural processing in these areas is presumably linked bidirectionally to the cmNTS and other brain stem areas (double-headed dashed red arrow), so that cmNTS ERα may also mediate these effects; non-ERα-expressing AgRP neurons in the Arc are the strongest candidates. Androgens acting on AR in unknown sites increase meal frequency, food intake, and body weight (green arrows and text boxes). In contrast, progestins appear not to have physiological effects on eating (blue, dashed text box). Challenges for future mechanistic studies of sex differences in eating include 1) establishing the physiological and pathophysiological roles of the estrogeneric mechanisms shown and 2) identifying the androgenic mechanisms affecting eating.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: L.A. and N.G. conception and design of research; L.A. and N.G. interpreted results of experiments; L.A. and N.G. prepared figures; L.A. and N.G. edited and revised manuscript; L.A. and N.G. approved final version of manuscript; N.G. drafted manuscript.

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