3 Neuroendocrinology of Sexual Behavior in the Female

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We begin our study of sexual behavior with females. In many species females display cycles of reproductive function, and behavior is an integral part of that cycle. For example, female rats ovulate about every 4 days and will, for a period of a few hours during that time, allow males to copulate with them. This receptivity on the part of the female occurs at a particular point in the ovulatory cycle that favors fertilization and pregnancy. The receptive behavior is coordinated by the same gonadal hormones that guide ovulation. The close correlation between female receptivity and gonadal hormones has made it possible to discover a good deal about how hormones affect this and other feminine sexual behaviors.

What sexual behaviors do females display, which hormones affect these behaviors, and where do the hormones act to exert these effects? When during the ovulatory cycle will females of various species, including humans, mate, and how do pregnancies affect the probability of mating?

Introduction

As described in chapter 2, steroid hormones may affect behavior either through organizational effects on the developing nervous system or through activational effects in adults. Organizational and activational effects of hormones are not mutually exclusive phenomena. In fact, as will be discussed in this chapter, organizational effects of gonadal hormones on sexual differentiation of the brain may not be manifest in sexually dimorphic behavior in the adult without the additional activational stimulus of specific gonadal hormones.

This chapter will focus on the activational effects of hormones that influence adult female sexual behavior. However, these behavioral actions are dependent upon the previous hormonal experiences of the individual. Early hormone exposure can alter the birth, survival, or death of neurons. In addition, the capacity of a given cell to produce chemicals or respond to subsequent neuroendocrine changes within the body can be regulated during development. Thus, the organizational effects of hormones are thought to produce sex differences in the patterns of neural connections and functions within the brain. By comparison, activational effects of hormones are transient and tend to coordinate behavior with an internal event, such as ovulation or sperm production, or an external event, such as the presence of a sexual partner.

In addition to sex differences, there also are significant species differences in reproductive behaviors. In spite of interspecific variation in the patterns of sexual behavior, it has been possible to compare the behavioral effects of a variety of hormones across species. Most of the available research examining the mechanisms underlying female sexual behavior has been conducted in rodents, such as rats, mice, and hamsters. References to a variety of other species are included here to illustrate other principles relating to behavioral endocrinology.

Definitions Important for Studies of Female Sexual Behavior

For simplicity, feminine sexual behavior can be divided into two components. Precopulatory behaviors, leading to copulation, may be described as courtship behaviors. Copulatory behaviors, usually defined by reflexive postures, are often considered separately from courtship. The reflexive sexual posture, called **lordosis**, is similar across many species (see figure 1.1 in chapter 1 for an illustration of the lordosis posture in the rat). Both courtship and copulatory behaviors may be influenced by hormones. However, courtship behaviors vary across species, and researchers have tended to focus on the more stereotyped components of sexual behavior, such as lordosis.

COURTSHIP BEHAVIORS

Under natural conditions, courtship interactions prior to or associated with sexual behavior function to permit mate selection.[683] Both sexes usually participate in mate selection. However, sex differences in gamete (i.e., egg and sperm) production are associated with sex differences in reproductive strategies. For example, females may ovulate on a periodic or cyclic basis. In contrast, at least during breeding seasons, males maintain a relatively constant supply of sperm. Consequently, females have fewer potential opportunities than do males to produce offspring. It was assumed for many years that females would be more likely to select a single sexual partner, whereas males would be more likely to have several sexual partners. Parentage can be determined by comparing the profile or fingerprint of DNA contained in every cell of an individual. Recent studies using DNA fingerprinting suggest that absolute sexual exclusivity may be rare in both sexes. These studies have indicated that in species in which the female simultaneously rears multiple young it is not uncommon to find litters that are sired by more than one male. This has been found to be true even in species that have been considered to be socially monogamous.[191] Additional discussions of the adaptive significance of courtship behaviors can be found in chapters 6 and 7.

For the female, the hormonal events associated with ovulation promote social affiliation, courtship, and subsequent copulation.[282] Under laboratory conditions in rats, estrogen increases a female's willingness to approach a male and induces sexual solicitations, known as **proceptive behavior**. In the rat there are three components to proceptive behavior: **approach**, **orientation**, and **run-**

away. In the rat, proceptive behaviors include an approach to the male followed by sniffing and grooming (orienting) as well as ear wiggling and hopping and darting. Ear wiggling is an extremely rapid vibration of the head that makes it appear as though the ears are wiggling and usually occurs in response to an approach and contact by the male. Hopping and darting consist of a rapid hop with almost rigid legs combined with fast "darting" movements away from the male (runaway). This sequence of behaviors frequently induces the male rat to chase after the female rat.

McClintock argues that these behaviors are not necessarily always solicitatious behaviors and that they also can serve to pace the rate of mating. Repeated intromissions (insertions of the penis into the vagina) are necessary for ejaculation. During copulation in rats, the male's intromissions trigger progesterone secretion (and other hormonal changes) in the female; this production of progesterone is necessary for successful implantation of fertilized eggs. The optimal number of intromissions and the interval between intromissions necessary to induce the progestational state needed for pregnancy is species specific. In many species pregnancy cannot occur in the absence of an appropriate pattern of vaginal-cervical stimulation. The female can pace the timing of copulations with solicitations of the male.[683]

If the female is permitted to set the pace of intromissions, she will choose a pace that optimizes pregnancy induction. This has been demonstrated in experiments that permit the female to control interactions with a male. If a test apparatus is designed so that the female pushes a lever to open a partition that allows a male to enter or that allows the female to escape from the male, the female will slow the pace of mating. As a result, the female requires fewer intromissions to trigger the progestational state.[683] When animals mate in a large group environment, or when a pair of familiar male and female rats mate, it is the female that initiates copulatory sequences by engaging in solicitatious behavior. Under these circumstances, the female normally sets the pace for mating. Thus, these precopulatory behaviors and the pacing of copulatory events can regulate the female's reproductive success.

In addition to facilitating proceptive behaviors, estrogen can also enhance the attractivity of the female (i.e., her value as a stimulus capable of evoking sexual responses from a male rat).[91] For example, estrogen priming can induce the production of stimuli such as odors, sounds, or physical changes in the female that make her more attractive to the male; concurrently, estrogen promotes proceptive behaviors that are associated with positive responses to a male's physical advances. Prolonged exposure to progesterone, which normally occurs in pregnancy, may inhibit subsequent proceptivity, sexual attractivity, and ovulation.

Thus, for the female, courtship involves behaviors that typically occur when a female is sexually receptive and the concurrent production of specific odors, sounds, and other physical stimuli that signal the female's estrous condition. Specific courtship behaviors vary with the species. Examples of the role of

organizational and activational effects of hormones in the development of courtship are discussed in chapter 7.

COPULATION

Studies of the physiological mechanisms responsible for female sexual behavior have focused most often on the analysis of copulatory reflexes.[282] Sexual receptivity in rodents and a variety of other mammals has been operationally defined by the occurrence of lordosis. Lordosis is usually characterized by immobility on the part of the female and an arching of the back, which in conjunction with hindleg extension elevates the rump and head. In species with a long tail, the female may also deviate the tail to one side. In some cases, lordosis is seen prior to male contact, but most commonly this posture is elicited by male mounting or manual stimulation of the female's flank and hindquarters. In rats it is common to calculate a **lordosis quotient** (LQ). The LQ is the ratio of the number of lordosis postures shown in response to a fixed number of mounts (usually 10) × 100. Thus, if a female shows five lordosis responses to ten mounts she is said to have an LQ of 50 and would be assumed to be moderately receptive.[91] In a number of species, such as voles and hamsters, it is difficult for a male to mount a "nonreceptive" female, preventing the calculation of an LQ. In the latter cases, the sexual receptivity of the female may be indexed by the frequency of lordosis or the duration of the lordosis posture during a fixed test period with a sexually active male.

ESTRUS AND THE ESTROUS CYCLE

The time during a female's reproductive cycle when she is sexually receptive, or willing to mate, is known as estrus. Behavioral estrus is sometimes called heat. The cyclic ovarian events that determine when an animal comes into estrus is known as the estrous cycle. The specific events of the estrous cycle will be described in detail later. In primates, the ovarian cycle is referred to as a menstrual cycle. The menstrual cycle is characterized by uterine bleeding, known as menstruation. Although there is some cyclicity in sexual behavior during the menstrual cycle[1086] (see chapter 5), female primates will mate throughout the menstrual cycle, and a true estrus is not seen in primates. In the estrous cycle of rodents and other nonprimates, menstrual bleeding does not occur, although in a few species, such as dogs, bleeding is associated with ovulation.

Basic Neuroendocrine Functions in the Female

Ovarian Function and Behavioral Receptivity

The gonads have two important functions. They produce ova or sperm (i.e., **gametogenesis**), and they synthesize gonadal steroid hormones (i.e., **steroidogenesis**). Gonadal steroids in turn coordinate neuroendocrine aspects of reproduction, including sexual behavior.

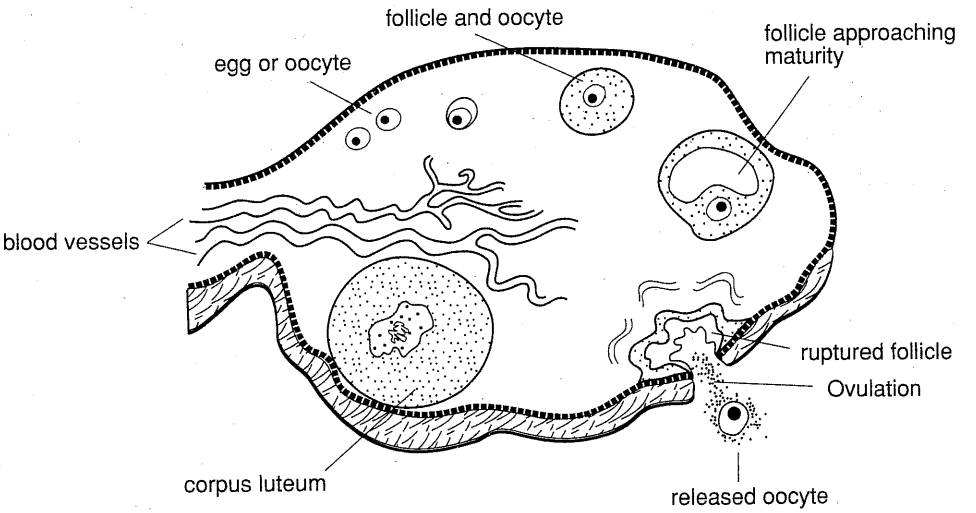

Figure 3.1 Schematic representation of the cycle of follicular development, ovulation, and corpus luteum development in the mammalian ovary. The developing oocyte is nurtured by the follicle, and this is referred to as the follicular phase of the ovarian cycle (depicted as follicle and oocyte; the follicle is approaching maturity). The period around the time when the follicle ruptures, releasing the oocyte (ovulation) is referred to as the periovulatory period. The follicle that remains in the ovary after ovulation becomes the corpus luteum. The phase of the ovarian cycle during which the hormone secretions of the corpus luteum prepare the uterus for implantation of a fertilized egg is called the luteal phase (in species that have an active corpus luteum). See text for additional details.

The primary functional components of the mammalian female gonad (ovary) are the eggs, follicles, and corpus luteum (figure 3.1). Each egg is surrounded by a follicle, which nurtures the developing egg or oocyte, a process called **oogenesis**. The major hormonal function of the follicle is the production of estrogens, including estradiol, estriol, and estrone. When an egg ovulates (is physically expelled) from a follicle, the follicle may be converted into a new structure called a corpus luteum. The corpus luteum is a source of progesterone and other hormones that prepare the uterus for implantation of the fertilized egg.

Mammalian ovarian function involves cycles of follicle development, ovulation (of a small number of follicles), and subsequent corpus luteum formation. In many species, the hypothalamic-pituitary axis regulates ovarian activity, and one or more eggs are produced at regular intervals. However, as described later, not all animals ovulate "spontaneously." There are a number of different patterns of hormone secretion. These patterns in a variety of mammals are reviewed in detail by Feder[342, 343] and Morali and Beyer.[746]

PHASES OF THE OVARIAN CYCLE

In animals that ovulate spontaneously, the duration of an ovarian cycle can vary from approximately 4 days (in mice, rats, and hamsters), to approximately 16 days (in guinea pigs) or longer (in primates). Each phase of the ovarian cycle

is usually referred to by the events that are occurring in the ovary during that phase (figure 3.1).

Follicular Phase The cycle begins with the development of the egg. During this phase, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are released by the pituitary to induce the ovary to begin gametogenesis. The follicle nurtures the egg and also produces estrogen. This phase is referred to as the follicular phase. The follicular phase lasts from 3 days in rodents to 10 to 14 days in humans.

Periovulatory Period As the egg matures, the rate of estrogen secretion increases. A surge of estrogen precedes ovulation and induces the release of a pulse of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which in turn induces a pulse of LH release by the pituitary. The pulse of LH causes the follicle to rupture, resulting in ovulation. This is referred to as the periovulatory period because it describes the sequence of events surrounding ovulation. LH also induces a preovulatory surge of progesterone release from the ovaries. In some animals (e.g., rats and hamsters) the preovulatory surge of progesterone triggers the onset of sexually receptive behavior. The periovulatory period takes about 12 hours in most rodents; in humans it occurs over a period of 1 to 2 days. In rodents, behavioral estrus occurs in association with the periovulatory period.

Luteal Phase The follicle, once it has ruptured and expelled its egg, is transformed into a new endocrine organ known as the corpus luteum (named for the fact that it appears as a "yellow body"). In some animals (e.g., rats and mice) the corpus luteum is not spontaneously retained (i.e., is not "functional"). In such species the corpus luteum is retained only in the event of a pregnancy, signaled by vaginal-cervical stimulation. In turn, progesterone secreted by the corpus luteum plays a major role in the implantation of the egg in the uterine wall and the maintenance of pregnancy. In other species, including primates, the corpus luteum is spontaneously functional. In humans, progesterone and estrogen are secreted by the corpus luteum for a period of about 10 days. This postovulatory period is referred to as the luteal phase. In a nonpregnant female the duration of the luteal phase is determined by the life of the corpus luteum. If an egg is fertilized, implantation in the uterus is facilitated by the luteal phase hormones. The controversial drug RU-486 (the abortion pill) produces its effect by blocking the action of progesterone, thus preventing implantation.

Menstrual Phase In primates, menstruation occurs after the fall in progesterone and estrogen secretion, associated with regression of the corpus luteum. The long (menstrual) cycle of primates results in a build-up of the uterine wall (endometrium), and sloughing of the endometrium results in uterine bleeding. In species such as rodents, which have shorter (estrous) cycles, the endometrial wall is thinner and does not bleed, and there is no event analogous to menstruation.

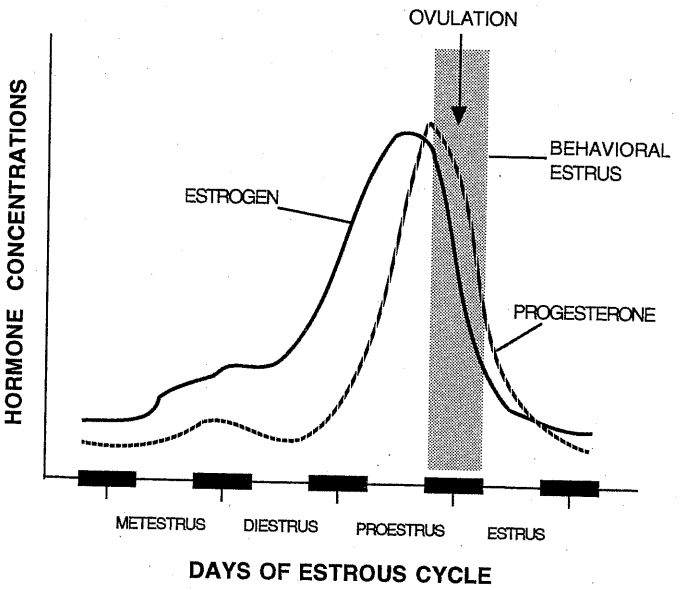

Figure 3.2 Relative concentrations of estradiol and progesterone in serum during the estrous cycle of a female rat. The days of the 4-day estrous cycle (metestrus, diestrus, proestrus, and estrus) are determined from examination of the vaginal epitheleum (slides containing cells from the walls of the vagina are examined under a microscope). Nights are represented by the dark bars on the X axis. Behavioral estrus (dark hatched column) usually begins on the night of proestrus. In the absence of mating, behavioral estrus can persist for 12 hours or more.

ASSOCIATION BETWEEN THE OVARIAN CYCLE, REPRODUCTIVE BEHAVIOR, AND OTHER NEURAL AND PERIPHERAL SYSTEMS IN RODENTS

Ovarian hormones coordinate sexual receptivity, mating, and sperm availability with ovulation. In many species female copulatory behaviors are tightly regulated by ovarian hormones. The 4-day estrous cycle of the rat is an example of the tight regulation that exists between hormones and behavior.

In rats the 4 days of the cycle are usually described relative to the day of ovulation (figure 3.2). **Metestrus** is a day of reduced hormonal and behavioral activity and is the day following ovulation. **Diestrus** is the day associated with the onset of follicular activity and estrogen secretion. **Proestrus** is the day before estrus and includes the major hormonal events that induce behavioral estrus. The GnRH and LH surges that trigger eventual ovulation usually occur on the evening of proestrus. Behavioral estrus and copulatory behavior are first seen on proestrus. **Estrus** describes the day of the estrous cycle on which ovulation actually occurs.

The ovary (possibly with assistance from the adrenal) produces pulses of estrogens, some androgens (testosterone or others), and a surge of progesterone and other progestins on proestrus. These hormones enter the general circulation and act sequentially throughout the body to prime the nervous system,

pituitary, uterus, vagina, mammary glands, and other tissues for behavioral estrus and subsequent ovulation, pregnancy, and lactation.

The lordosis posture results from a cascade of spinal reflexes that are modulated by specific brain regions and neurochemicals that will be described below. Lordosis can be elicited at the level of the spinal cord by strong somatosensory (i.e., tactile) stimuli. However, in tests with males, lordosis is infrequent in prepubertal females or in adult females following removal of the ovary (ovariectomy or spaying). Thus, in many mammals,[309, 1086] ovarian secretions acting on the nervous system are essential for the normal expression of female sexual behavior.

OTHER CONSIDERATIONS

Sexual behavior in females is clearly influenced by ovarian function. However, it is also important to remember that many aspects of reproduction are regulated by environmental stimuli such as photoperiod, food, and water. Environmental regulators produce seasonal variations in sexual activity in many species. In addition, reproductive old age or senescence can limit reproduction. In small rodents, spontaneous ovulation may occur under optimal environmental conditions to permit frequent pregnancies. In large mammals such as some primates and ungulates, spontaneous ovulation is regulated by seasonal factors to ensure the birth of young during a period of resource availability (such as spring in the northern hemisphere). Thus, sheep have an 8-month gestational period, and their breeding season begins during times of decreasing day length (fall in the northern hemisphere), so that the young are born in spring, when food is available. The importance of biological rhythms in the regulation of endocrine systems and cycles will be discussed in greater detail in chapter 16.

Variation in Mechanisms Mediating Ovulation

Ovulation may either be timed by endogenous stimuli, as described above, or *induced* by exogenous stimuli. In some animals sexual receptivity occurs in spontaneous cycles, but ovulation does not occur without copulation (**induced ovulation**). In other species both behavioral estrus and ovulation are induced by specific stimuli (**induced estrus and ovulation**).

INDUCED OVULATION

Induced ovulation usually relies on the presence of copulatory stimuli from the male to provide the surge of hypothalamic-pituitary hormones required to trigger egg release. This is considered an opportunistic reproductive strategy. In induced ovulators (such as rabbits, cats, and ferrets) the ovary may produce waves of follicles during the reproductive season and remain quiescent at other times. These animals come into a period of behavioral estrus, during which follicles are activated to produce mature eggs. The follicle does not rupture and ovulation does not occur, however, unless the animal mates during this period.

In cats, ferrets, and rabbits, as the waves of ovarian follicles mature, the ovary secretes estrogen. Estrogen in turn induces, within a day or more, behavioral estrus leading to mating. In these species, copulatory stimuli from the male (usually vaginal-cervical stimuli) are essential for the induction of ovulation. Copulation activates a neural response that results in hypothalamic release of GnRH, which in turn induces pituitary release of LH to induce rupture of the follicle and ovulation. Progesterone is probably not essential to trigger female receptivity in induced ovulators, but it may play a role in the termination of estrus.[190, 343]

INDUCED ESTRUS AND OVULATION

In some animals (such as prairie voles) both estrus and ovulation are induced. These animals may remain reproductively inactive until stimuli from a male are present. Thus, the stimuli from the male can regulate the reproductive condition of the female, guaranteeing that a male partner will be present when the female becomes sexually active.

This pattern of induced reproductive condition is typical of highly social mammals, including prairie voles. These animals are thought to rely on chemical signals, biologically active odors or pheromones, from the male to activate ovarian estrogen secretion. Prairie voles show no indication of cyclic ovarian activity, and, in the absence of male-related stimuli, female prairie voles do not show behavioral estrus. After an initial exposure to a male or male pheromones, estrogen is secreted, which primes the female. After a day or more of male exposure, sexual receptivity is usually observed, and ovulation is induced by about 10 to 12 hours following coitus. Progesterone secretion follows ovulation by a day or more in this species. In this case, progesterone probably functions primarily to inhibit receptivity in prairie voles.[190]

The musk shrew also relies on social stimuli for the induction of lordosis. Virgin female musk shrews are not receptive but begin to show sexual behavior within 1 hour of male exposure.[857] It was originally believed that this species was capable of steroid-independent sexual receptivity.[309] Female musk shrews will mate while the ovary is hormonally quiescent. In addition, ovarian estrogen or exogenous estrogen at doses that mimic those found in intact females are not effective in inducing sexual receptivity. However, recent studies by Rissman and her associates[857] have revealed that the ovary is involved in sexual receptivity, apparently through the use of androgens.

Doses of androgens near the physiological range are capable of inducing receptivity in the musk shrew. Thus, like males of many species, female shrews may utilize androgens to regulate sexual activity. It appears that these androgens are behaviorally most effective following conversion (aromatization) into estrogens.[857] Enzymes capable of aromatizing androgens to estrogens exist within the brain, suggesting the possibility that androgens enter the brain in that form and are converted within brain tissue to estrogens. The musk shrew is a tropical species and is found in breeding condition throughout the

year. Rissman and associates[857] suggest that this mechanism would allow year-round breeding while minimizing the systemic exposure of the female to estrogen, which is potentially toxic.

Socially induced estrus and ovulation are primary modes of reproductive activation in some species and also may be alternative modes of reproduction in animals that are usually characterized as having spontaneous or cyclic ovulation. Under suboptimal environmental conditions, such as irregular light cycles or limited availability of food or water, even species that usually show cyclic patterns of spontaneous estrus and ovulation can revert to socially induced reproductive activation. Such flexibility in patterns of reproduction is especially characteristic of rodents, such as mice and rats, that inhabit highly variable environments.

SYNCHRONY OF OVARIAN CYCLES

Another consequence of the influence of social stimuli on ovarian cycles is the phenomenon of estrous synchrony. When female rats or mice are housed together, "cycles change in length until estrus is synchronized within the social group; as a consequence, females tend to come into heat and ovulate on the same day."[683]

McClintock[683] has demonstrated that this coordination of estrous cycles in rats is modulated by airborne chemicals. If rats are housed in separate cages but have a common air supply, estrous synchrony develops. The synchrony of cycles involves the coordination of at least two different chemosignals or pheromones. These two pheromones have opposing effects, one shortening the estrous cycle and enhancing the probability of the female coming into estrus and ovulating and the other lengthening the cycle while suppressing estrus and ovulation.

A similar phenomenon has been reported in human females. Female coeds living together in a residential women's college have been reported to show menstrual cycle synchrony after a period of 4 to 7 months.[682] A second study investigating menstrual synchrony in college-age women found that the amount of time women spent together, not just the sharing of common living quarters, determined whether two women would become synchronous. Over a 4-month period, women who identified each other as close friends became synchronous for the onset of menstruation.[435] The mechanisms mediating this effect in humans are unknown.

Pregnancy and the Ovarian Cycle

Pregnancy inhibits ovarian cycles. However, on the day of birth (parturition) or shortly thereafter, females of some species come into estrus. This is referred to as postpartum estrus. In addition, in some instances reproductive cycles are suspended during lactation. Thus, there is a complex interaction between pregnancy, lactation, and the ovarian cycle.

POSTPARTUM ESTRUS

Once a female rodent has successfully mated, the physiology of pregnancy suspends the ovarian cycle. However, in many species, females show behavioral receptivity in the period just prior to or following parturition, and ovulation also follows birth. Postpartum estrus is similar but not identical to a cyclic estrus. The duration of mating during the postpartum period is typically less extended than that in cyclic estrus.[683] Postpartum estrus seems to maximize the reproductive potential of a female; litters conceived in postpartum estrus are born at approximately the time that the older litter is weaned (21 to 23 days after the birth of the older litter).

In addition, in monogamous or pair-bonding species such as prairie voles, females in postpartum estrus may be very selective in their choice of a sexual partner. Monogamous females usually mate preferentially with their familiar partner and often will attack unfamiliar males.[191] Thus, in species with a monogamous mating system, partner familiarity can play a particularly important role in the expression of sexual activity in the postpartum period.

The endocrinology of postpartum estrus is not well documented. However, it is likely that female rodents come into estrus as a result of exposure to estrogen that is secreted during pregnancy or during the peripartum. Even in species like rats that rely on sequential exposure to estrogen and progesterone for cyclic estrus induction, females can respond to estrogen alone if the hormone is present over an extended period of days. In most mammals the progesterone level is elevated throughout pregnancy and falls rapidly just before parturition. Progesterone relaxes the smooth muscle of the uterus, and a decline in progesterone may be necessary for the uterine contractions associated with delivery. There also may be a surge of progesterone during the postpartum period in some species.

In rats there is evidence that oxytocin, which promotes parturition, also can facilitate female sexual behavior in estrogen-primed females.[179] Thus, prolonged exposure to estrogen and progesterone during pregnancy and the subsequent decline in progesterone would set the stage for postpartum estrus. In some cases a second surge of progesterone and a parturitional surge of oxytocin also may be components of the timing mechanisms that link postpartum estrus and parturition.

LACTATIONAL INHIBITION OF FEMALE SEXUAL BEHAVIOR

After a brief period of postpartum estrus, females that nurse their young may experience an inhibition of ovarian cycles and female sexual receptivity. Follicular maturation and ovarian steroid production often are inhibited during lactation. The absence of appropriate steroid hormone priming presumably results in the absence of female sexual behavior. However, lactational acyclity is not absolute, and, especially when food is plentiful, females may resume cycling and ovulate before lactation ceases. Prolonged exposure to the two major hormones of lactation, prolactin and oxytocin[1109] or the endogenous opiates[976] also may inhibit sexual behavior.

Reproductive Inhibition

Both spontaneous and induced ovulators can fail to cycle or show sexual behavior in the presence of other females. This reproductive inhibition may occur in young females, resulting in a delay in the onset of ovarian activity (puberty).[1062] In addition, reproductive inhibition has been described in adult, cycling, or postpartum estrous females.[158, 308] In highly social species, including monogamous mammals such as prairie voles,[190] small social primates known as marmosets, and even female-only parthenogenic lizards (see chapter 6), it is common for only the oldest or dominant female within a group or family to reproduce. A particularly extreme case of reproductive inhibition occurs in the naked mole rat, in which only one female within a colony of hundreds is cycling or capable of reproduction.[940]

Reproductive inhibition or delay can be adaptive. Inhibited females may assume other functions within the family or gain benefits by waiting to reproduce.[1090] In addition, although they delay their own reproduction, such females may indirectly enhance their reproductive fitness by increasing the probability that a larger portion of the family (carrying at least some of their own genes) will survive. Group living may be generally stressful, and stress can inhibit reproduction[22] (see also chapter 10). However, it also has been shown in a variety of mammals that females can emit chemical signals or pheromones that inhibit or delay the reproduction of other members of their group.[158, 308, 683, 1062]

Expression of Feminine Sexual Behavior in Adulthood

Physiological Mechanisms Regulating Female Sexual Behavior in Rodents

In ovary-intact female rodents, lordosis is rare during the metestrous and diestrous phases of the female's estrous cycle. Female rats with a 4-day cycle usually show lordosis during the evening of proestrus and, if unmated, remain sexually receptive through the day of estrus. These effects can be shown to be hormone dependent.

ESTROGEN

The actions of various endocrine factors in sexual behavior are species specific. However, the most consistent element regulating female reproductive behavior is the steroid hormone estrogen. Estrogen plays the major coordinating role in female reproduction through its ability to stimulate or regulate various target organs including the nervous system.

The presence or absence of a given receptor can allow or prevent the cellular actions of a given hormone.[644, 812] Estrogen receptors are distributed in particular regions of the brain and spinal cord (figure 3.3) and show remarkable consistency in their location across a variety of vertebrate species. Regulation of receptors can occur through changes in the number of receptors or through

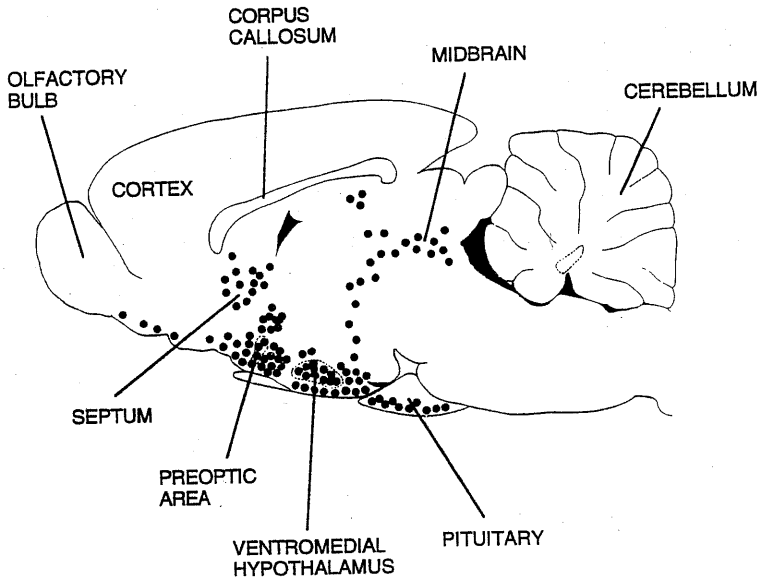

Figure 3.3 Sagittal (lateral) section of a female rat brain showing the relative distribution of estradiol-concentrating cells. Areas of highest concentration are represented by dots. Highest concentrations are found in the preoptic area, hypothalamus (especially the ventromedial hypothalamus), amygdala (not shown), septum, and midbrain central gray (Pfaff and Schwartz-Giblin, 1988). These distributions were determined by examining autoradiograms of brain slices. Radioactively labeled estradiol is injected into an ovariectomized rat. After the radioactively labeled estradiol has circulated throughout the body for a few hours, it will be selectively retained by cells that contain estrogen receptors. The brain can then be sliced and the location of the estrogen receptors determined.

changes in the affinity of a receptor for the hormone. A molecule that binds to a receptor is called a ligand, and when a ligand has a weak affinity for a receptor, it does not bind very tightly to the receptor. Very high concentrations may therefore be required to elicit a biological response.

During periods of hormone deprivation the sensitivity to estrogen decreases. This is thought to be primarily due to a decrease in the number of estrogen receptors. If hormone treatment is initiated, estrogen receptors are self-nduced over a period of hours or days. It is generally assumed that the induction of estrogen receptors is essential for centrally mediated female sexual receptivity.

A number of other hormones may influence behavior through their interactions with estrogen and its receptors. In general, receptors may respond to a variety of molecules with similar structures; however, the binding affinity may be weaker for some structures than others. Therefore, other hormones or neurotransmitters can influence the effect of estrogen by competing with estrogen for the receptor.

The behavioral effects of estrogen usually require at least 24 hours to be expressed, and the hormone is most effective if given in discontinuous pulses.[210, 812] Endogenous hormone secretion is often pulsatile, and these pulses may be necessary for normal hormonal action. Uninterrupted, pro-

longed exposure to estrogen can result in a relative insensitivity to its behavioral effects, probably caused by a decrease in the number of receptors.

Pulsatile estrogen treatment produces rapid (within minutes) and long-lasting effects that eventually result in polypeptide or protein synthesis in neurons containing estrogen receptors.[812] Injection of protein synthesis inhibitors disrupts the ability of steroids to facilitate female sexual behavior. Various neurochemicals or receptors also may be synthesized under the influence of estrogen or progesterone. Of importance to female sexual behavior in the rat is the estrogen-dependent induction of receptors for progesterone.[931] Progestin receptors are probably essential to permit a normal behavioral response to the endogenous preovulatory surge of progesterone that triggers the onset of lordosis.

PROGESTERONE

In estrogen-primed female rats progesterone clearly enhances lordosis behavior.[88] However, progesterone is not effective in inducing lordosis in ovariectomized females that have not received estrogen. Because progestin receptors are induced by estrogen, estrogen indirectly regulates the behavioral effects of progesterone. In addition, under conditions in which estrogen, without progesterone, induces lordosis it is possible that estrogen acts in part through stimulation of progestin receptors.[931] Species that do not depend on progesterone for the induction of estrus such as prairie voles[190, 216] and ferrets[80] nonetheless have progestin receptors in their brains; the function of these receptors is unknown at present.

ANDROGENS

In female rats androgens released during mating may pace patterns of female sexual behavior by inhibiting receptivity.[330] Mating-timed inhibitions of receptivity are probably adaptive in reducing risks, such as predation, associated with sexual behavior. From the male's perspective, turning off the female's receptivity would help to protect his copulatory "investment" in the female.

Androgens also have been implicated in the induction of female sexual behavior in a variety of species (reviewed in Rissman[857]).[941] However, at least in rodents, androgens are probably not normally essential for estrus induction. As discussed earlier, the female musk shrew may rely on androgens as a prohormone from which brain tissues can produce estrogens. Androgens may be important for the motivational components of female sexual behavior in humans and other primates.[942, 1086] The latter hypothesis will be discussed in chapter 5.

Interactions Between Sexual Behavior and Gonadal Steroid Hormones

The onset of sexual receptivity and lordosis usually follows within 1 to 4 hours after the preovulatory surge of progesterone. By this time, the female also has been exposed to increasing concentrations of follicular estrogen. Without

estrogen priming progesterone does not induce the onset of sexual receptivity. The onset of lordosis precedes ovulation by about 10 to 12 hours, and this timing provides an opportunity for mating to occur and sperm to reach the ovary prior to or immediately following ovulation.[19, 20, 683]

The priming of progesterone receptors by estrogen is functionally important, at least in female rats. As discussed in chapter 1, steroid hormones characteristically induce the production of their own receptors. In addition, estrogen also induces the production of progesterone receptors. Thus, estrogen priming results in the induction of progesterone receptors, reducing the amount of progesterone required to induce sexually receptive behavior. Through this mechanism, estrogen acts to regulate directly the effect of progesterone on female sexual receptivity.

The duration and termination of sexual receptivity also may be regulated in part by the same hormones that induce estrus. If estrogen is withdrawn, receptivity is lost within a matter of hours. In addition, prolonged exposure to progesterone inhibits subsequent sexual receptivity, even in species that rely on progesterone for estrus induction.[343] The ability of progesterone to initially facilitate and later inhibit receptivity is termed the biphasic effect of progesterone. Within a given estrous cycle, the duration of behavioral estrus is probably regulated by declining concentrations of estrogen and long-term exposure to progesterone. Furthermore, once the hypothalamus has been exposed to progesterone, there is a down-regulation of progesterone receptors and therefore a refractory period. Thus, unlike the initial effect of estrogen described earlier, progesterone does *not* induce an increase in the number of its receptors but actually *causes a decrease* in receptor availability. A period of a relatively low hormone level followed by reexposure to estrogen to induce progesterone receptors and then to progesterone to activate the receptor response is usually necessary to reinstate sexually receptive behavior.

Copulatory stimuli play a major role in inhibiting subsequent female sexual receptivity and thus in inducing sexual satiety. Copulatory stimulation releases progesterone and other neurochemicals, which may combine with prolonged exposure to progesterone to terminate the sexual receptivity of a recently mated female.[20, 187]

Species vary in the amount of time spent in copulatory activities. Female guinea pigs may become unreceptive after experiencing a single ejaculation, whereas rats may mate for several hours,[20, 683] and female prairie voles remain behaviorally receptive for a day or longer.[190] Different patterns of postcopulatory progesterone release[191] or species differences in sensitivity to progesterone's inhibitory effects may contribute to species differences in patterns of sexual behavior.

Neural Regulation of Feminine Sexual Behavior

Pfaff and Schwartz-Giblin[812] offer a schematic description of the nervous system based in part on the embryology of neural development. Using this model,

they have divided the nervous system into functional modules or subdivisions that include the forebrain, hypothalamus, midbrain, lower brainstem, and spinal cord.

FOREBRAIN

As far as we know, no part of the forebrain is essential for the appearance of lordosis, and, in fact, the forebrain may inhibit the lordosis reflex. Within the forebrain, lesions in adult animals of the cerebral cortex, septum, preoptic area, and olfactory bulb do not eliminate female sexual receptivity. When tested in confined cages with highly motivated males, lesioned females have high lordosis quotients and may even respond more easily or show lordosis postures of a longer duration than those seen in nonlesioned females.[812] These findings are complicated by the disruption of various sensory systems that occur with such lesions and may indicate that females have less fear of the males or are interpreting differently other sensory experiences such as genital stimulation. In addition, female rats that have been decorticated as infants do not show an enhanced lordosis response and are less responsive to males when tested under conditions of low estrogen.[192] In general, the presence or absence of a particular neural tissue may affect behavior in more than one way, depending on the age at which the lesion occurs and the conditions of behavioral testing.

HYPOTHALAMUS

The hypothalamus has long been viewed as a critical component of the circuitry needed for female sexual behavior. Of particular importance within the hypothalamus is the ventromedial hypothalamic (VMH) nucleus (see figure 3.3 and chapter 1). This small concentration of cells plays a critical role in lordosis behavior. Lesions of the VMH usually disrupt lordosis behavior, particularly if the female is tested under conditions in which she cannot escape male mounting. However, smaller VMH lesions are less effective than large lesions, and small lesions may not inhibit lordosis under test conditions in which the female regulates the copulatory interactions. Under the latter conditions, females with small VMH lesions exhibit lordosis behavior but spend more time than normal females in areas of the test cage that cannot be reached by the males. Thus, it has been suggested that, following the lesion, stimuli from the male have become more aversive. Conversely, it can be argued that under normal conditions hypothalamic neurons regulate the interpretation of somatosensory input as either aversive or not.[931]

Estrogen, progesterone, and other neurochemicals may interact within the VMH to facilitate or inhibit the expression of female sexual behavior. One of the brain areas that concentrates steroid hormones is the basal hypothalamus. Facilitative effects on lordosis in ovariectomized female rats can be measured following small implants of estrogen and progesterone,[886] and these effects are selectively localized in the VMH. Hormonal effects within the VMH may be mediated by modulation of the intensity or interpretation of sensory inputs such as tactile stimuli. Such modulation could then alter the probability that

the female would remain in the presence of the male or would show lordosis if mounted.

MIDBRAIN

Estrogen receptors also are localized within the midbrain central gray. Neurons from the ventromedial hypothalamus send axons to the midbrain central gray, as do neurons in the spinal cord receiving information from sensory systems that are important for lordosis. This connection may be important, therefore, in the activation of lordosis behavior.[866] Destruction of this area reduces lordosis in female rats, while electrical stimulation in the midbrain can facilitate lordosis.

LOWER BRAINSTEM AND SPINAL CORD

Fibers from the brainstem descend to the spinal cord through the vestibulospinal and reticulospinal tracts.[812] Reticulospinal pathways in particular are believed to be hormone dependent. Postural adjustments associated with lordosis are presumably integrated in these areas. Complete spinal transections eliminate lordosis, but relatively large lesions may have little effect on this behavior as long as the lateral funiculus, containing the above mentioned tracts, is intact.

The Neural Circuit Mediating the Lordosis Reflex

Using the units of the brain described earlier, Pfaff and Schwartz-Giblin[812] have proposed a model for the neural circuits regulating the lordosis reflex in the rat (figure 3.4). The lordosis reflex in the rat begins in response to sensory stimuli applied by the male during mounting. Sensory input is relayed from the sensory receptors into the spinal cord, where input converges on interneurons. Activation of these interneurons can trigger lordosis. If the spinal cord is isolated from the brain, however, females do not exhibit lordosis. It is concluded, therefore, that additional neural circuitry is normally necessary for initiation of lordosis.

Stimuli received from mounting are relayed from the spinal interneurons to ascending fibers that project to the reticular formation in the medulla and the midbrain central gray. This circuit is activated whenever a female is mounted by a male, even if she is not behaviorally receptive. It is the activation of hypothalamic neural centers by estrogen and, in some cases, progesterone that determines whether this sensory input will trigger lordosis. These hormones also influence the attractiveness of the rat, so a female that is not receptive is also not as attractive to a male rat and is less likely to be mounted in the first place.

Estrogen and progesterone act in the VMH to promote lordosis. This has been demonstrated in a number of ways. First, as discussed earlier, the VMH contains neurons that accumulate estrogen and progesterone, indicating that the appropriate receptors are found in the area. Local implants of estrogen into

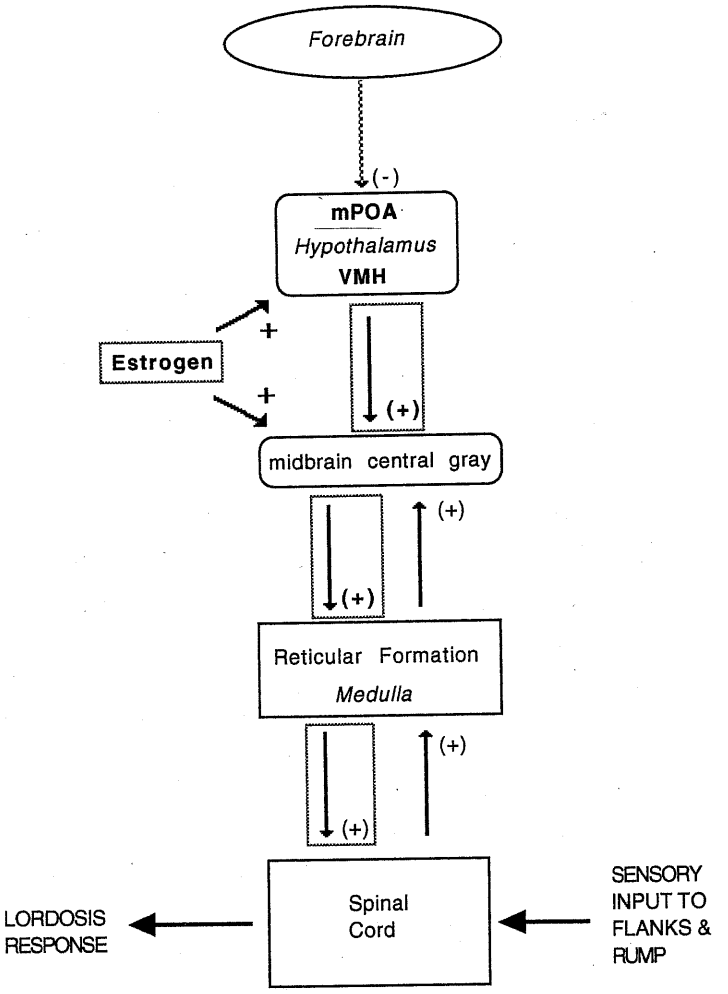

Figure 3.4 Schematic representation of the neural circuit mediating the lordosis reflex in the rat. Sensory input on the rump and flanks from the male mounting the female is received at the spinal cord. This sensory information is relayed to ascending fibers that project to the medullary reticular formation and the midbrain central gray. This circuit is activated by sensory input whenever it is received. The lordosis reflex is triggered, however, only if the female rat has been previously exposed to estrogen (indicated by the hatched boxes around the descending arrows). strogen acts in the medial preoptic area (mPOA) and the ventromedial hypothalamus (VMH) regions of the hypothalamus and in the midbrain central gray (indicated by the arrows with +) to enhance the excitability of midbrain target neurons, so that the lordosis reflex is triggered in response to mounting by a male rat. The forebrain can inhibit the lordosis reflex when conditions are not favorable for mating. Large arrows at bottom indicate sensory input and motor output. Smaller vertical arrows indicate the direction of information flow and whether the stimulus is excitatory (solid arrows with [+]) or inhibitory (stippled arrow with [−]). (Adapted from Pfaff and Schwartz-Giblin, 1988.[812])

the VMH will facilitate lordosis, whereas estrogen implants elsewhere have little effect. Implants of antiestrogens in the VMH inhibit behavior. Other experiments have demonstrated specific effects of estrogen on electrical activity and gene expression in neurons located within or near the VMH.

Axons from neurons in the VMH project to the midbrain central gray. Activation of VMH neurons by estrogen results in an increase in the electrical excitability of midbrain target neurons. This in turn activates descending projections that control the motor neurons involved in the lordosis reflex. According to this model, when a female is mounted by a male, if estrogen has potentiated neural activity in the VMH, the output circuitry is excited, and the lordosis reflex is initiated.

This is, of course, a highly simplified summary of the lordosis reflex. Other input to neurons in this circuit (e.g., from the forebrain) can also modulate neuronal activity, thus affecting the probability of lordosis. In addition, there are hormonal effects on neurons in the midbrain central gray as well as on sensory receptors that also affect responsiveness within the circuit. For additional details, the reader is referred again to the review of Pfaff and Schwartz-Giblin.[812]

Neurohormone and Neurotransmitter Regulation of Feminine Sexual Behavior

Neurohormones and neurotransmitters capable of influencing other aspects of reproduction such as ovulation, maternal behavior [573](see also chapter 8), and lactation[473] can also influence female sexual behavior. Knowledge of a species' reproductive strategy and mating system may provide powerful clues about those agents that will be most likely to influence behavior within that species.

A given neurotransmitter or neurohormone may have different actions when present at different sites in the brain. It is also possible and in fact common for a neurohormone or neurotransmitter to facilitate a behavior at one time and inhibit it at another time. These phenomena may be due to differences in receptor physiology or to changes in the circulating hormonal milieu that can alter the neural substrate(s) upon which the neurohormone or neurotransmitter must act. The following is an attempt to synthesize and simplify the roles of a number of neuroactive agents thought to play a role in female sexual behavior.

GnRH

GnRH neurons have their cell bodies in the preoptic area of the hypothalamus with axons that project primarily to the median eminence. Terminals in the median eminence release GnRH into hypophyseal portal vessels. A surge of GnRH carried from the hypothalamus to the pituitary triggers the release of FSH and LH from the pituitary gland. FSH and LH in turn circulate to the ovary and induce ovulation.

Of potential importance to behavior is the fact that GnRH axons also project to the midbrain central gray. Thus, GnRH may also be released in the brain to

influence the probability that lordosis will occur. GnRH administered locally to the midbrain central gray potentiates lordosis behavior. Conversely, antisera to GnRH in the central gray can block lordosis. In spontaneous ovulators, such as rats, GnRH that is endogenously released into the central gray prior to ovulation may help to ensure that female sexual receptivity is synchronized with ovulation.[812]

OXYTOCIN

Oxytocin has traditionally been studied as a posterior pituitary hormone with peripheral actions in birth and lactation. However, it is now known that oxytocinergic neurons (in the paraventricular nucleus of the hypothalamus) release oxytocin into the brain as well as into the bloodstream. Receptors for oxytocin are widespread in the nervous system as well as in the breasts and uterus. The possible role for oxytocin in sexual behavior is particularly interesting because of the unique neuroanatomy of the cells that manufacture this hormone.[473] Oxytocinergic cells are usually separated by glia, but these glia can be retracted within a matter of minutes. This leaves the oxytocin neurons electrically coupled to each other with the potential for synchronous, pulsatile release of hormone.

Peripheral stimuli, such as touch or cervical stimulation, during copulation can trigger the release of oxytocin. Injections of oxytocin stimulate sexual behavior in female rats that are primed with subthreshold doses of estrogen and/or progesterone.[34, 179, 801] In fact, estrogen induces an increase in oxytocin receptors in the VMH. Thus, during estrus, copulatory stimulation that triggers the release of oxytocin could provide a cascade of events that eventually leads to a surge of oxytocin and an enhanced receptor response (reviewed by Carter[188]).

Implantation of oxytocin within the VMH in estrous female rats did not affect lordosis quotients, but females showed reduced aggression and increased physical contact with the male. Since oxytocin is normally released as a result of copulation and not prior to coitus, the normal role of oxytocin may be important for sexual satiety and pair-bonding.[188, 1109]

Centrally released oxytocin also may play a role in the autonomic events (e.g., changes in heart rate) that accompany sexual behavior. Synchronous release of oxytocin into the peripheral circulation could enhance uterine contractility and thus sperm transport. Finally, exposure to long-term or high concentrations of oxytocin may contribute to the sexual satiety that follows extended mating and to the lactational inhibition characteristics of female sexual behavior.[188, 1109]

PROLACTIN

A second lactational hormone, prolactin, also may play a role in female sexual behavior. Prolactin-containing cells are found primarily in the anterior pituitary but also have been identified in the arcuate nucleus of the hypothalamus (near but not within the VMH). Axons from these neurons project throughout

the brain. In particular, there is a projection to the midbrain central gray. Infusions of prolactin into the midbrain central gray can facilitate lordosis in female rats pretreated with low doses of estrogen.[812] The functional significance of prolactin in female sexual behavior is not well understood. However, like oxytocin, prolactin is released in the postpartum period and might synergize with estrogen to time the onset or duration of postpartum estrus.

CATECHOLAMINES

Two catecholamines, dopamine and norepinephrine, also have been implicated in female sexual behavior. The neurochemical events that precede the release of GnRH and oxytocin may also facilitate female sexual receptivity. For example, norepinephrine turnover in the hypothalamus has been correlated with GnRH and oxytocin release, which in turn can facilitate lordosis.

A direct facilitative effect of norepinephrine on lordosis is thought to be due to the activation of a specific class of norepinephrine receptors called α_1-adrenergic receptors found within the VMH. Infusion of norepinephrine into the medial preoptic area or VMH can activate lordosis in animals treated with estrogen. Drugs that block α_1-adrenergic receptors (α_1-antagonists) reduce lordosis. If the axons from the norepinephrine cell bodies in the locus coeruleus that project to the hypothalamus are severed, lordosis is blocked.[812]

Norepinephrine may in part induce these effects on lordosis by modulating progestin binding. Treatment with α_1-adrenergic antagonists can prevent the estrogen-induced increase in progesterone receptors.[744] Norepinephrine, therefore, could facilitate lordosis directly through its effects on adrenergic receptors in the VMH or preoptic area, or indirectly by regulating the release of oxytocin and GnRH.

The catecholamine dopamine may be important for promoting proceptive motor behaviors, including general movement as well as ear wiggling, hopping, and darting. The ascending dopamine projection from the midbrain to the basal ganglia is typically associated with the execution of stereotyped movements (movements that are always done in the same way) and increased sensorimotor responsiveness. Gonadal hormone-induced activation of dopamine activity, therefore, may promote responsiveness of the female to stimulation by the male as well as the exhibition of proceptive behaviors. Some of these ideas will be discussed in chapter 11. This dopamine system, therefore, may participate in the fine-tuning of motor patterns in female sexual behavior, but it is probably not directly involved in the lordosis reflex. There are also dopaminergic neurons contained within the hypothalamus (the incertohypothalamic dopamine neurons). These dopaminergic neurons are implicated in male sexual behavior (see chapter 4), but their role in female sexual behavior has not been demonstrated.

ACETYLCHOLINE

Acetylcholine is a neurotransmitter with widespread neural activity. Acetylcholine cell bodies in the basal forebrain project to the medial basal hypotha-

lamus. Estrogen can increase the activity of choline acetyltransferase, an enzyme necessary for acetylcholine synthesis, and increase the number of acetylcholine receptors in the VMH. These effects were found in female rats but not male rats. The estrogen-induced increase in acetylcholine receptors in the VMH increases the number of cells that respond electrophysiologically to acetylcholine. Clemens and associates[212, 214] have shown that drugs that stimulate acetylcholine receptors can facilitate lordosis in female rats, and drugs that specifically inhibit acetylcholine receptors inhibit lordosis. By applying cholinergic agonists and antagonists locally at specific sites in the brain, they have found that acetylcholine facilitates lordosis when applied to the medial preoptic area, VMH, or midbrain central gray but not when applied to the reticular formation or frontal cortex. Maximum cholinergic facilitation required estrogen pretreatment of animals. Thus, acetylcholine terminals in the hypothalamus are thought to participate in the estrogen-induced facilitation of lordosis behavior.

SEROTONIN

Among the other neurotransmitters that are implicated in female (and male) sexual behavior is serotonin (5-hydroxytryptamine, 5-HT). Drugs that inhibit serotonin facilitate lordosis in several species including rats[600, 715] and hamsters.[189] Excess serotonin is associated with hyperreactivity to stimuli such as touch; thus, reduced serotoninergic activity might synergize with specific opiates (see later discussion) to modulate the reactivity of the estrous female to painful or aversive stimuli. In addition, serotonin receptors are regulated by estrogen. We can speculate that serotonin, if released during mating, could also play a role in inhibiting further sexual behavior and thus inducing sexual satiety.

GAMMA-AMINOBUTYRIC ACID (GABA)

GABA is generally viewed as an inhibitory neurotransmitter and may also regulate lordosis. Drugs that block GABA can facilitate lordosis, and drugs that stimulate GABA receptors usually inhibit sexual behavior. Schwartz-Giblin and colleagues[931] postulate that estrogen-dependent inhibitions of GABA may act to increase synaptic efficiency (possibly in the spinal cord). Blocking GABA is thought to increase sensitivity to light somatosensory stimuli and thus regulate lordosis behavior at the spinal cord level. GABA neurons are widespread throughout the nervous system and play an important role in the regulation of other processes, including the release of oxytocin.[573] Thus, GABA could have indirect effects on sexual behavior through its actions on other systems.

ENDOGENOUS OPIATES: β-ENDORPHINS AND ENKEPHALINS

In addition to modulating her behavioral arousal, the estrous female must be selectively sensitive or insensitive to contact behaviors, including copulatory stimuli, that might otherwise be aversive.[809] The endogenous opiates, including the β-endorphins and enkephalins, are generally associated with reducing

pain perception but probably also have a role in the modulation of female sexual and social behavior.[22, 976, 1101]

In general, high concentrations of opiates have been associated with the inhibition of sexual behavior and other aspects of reproduction.[813] Opiate treatment reduces GnRH release, and opiate antagonists such as naloxone increase GnRH release. Opiate antagonists facilitate some components of female sexual behavior, possibly through secondary actions on the release of GnRH.[22, 961] High concentrations of opiates, including β-endorphins released during stress, may serve to prevent sexual activity at times when the environment is inappropriate. Opiate release during mating also could inhibit subsequent sexual behavior and thus may be part of the mechanism responsible for sexual satiety. Other possible functions of endogenous opiates in reproduction have been extensively reviewed elsewhere.[22, 813, 976, 1101]

Injections of naloxone or other β-endorphin antagonists into the midbrain central gray facilitate lordosis. This raises the possibility that somatosensory inputs, pain inhibition, autonomic functions, and other fundamental behavioral components of sexual behavior are regulated in the midbrain.[812]

Another class of endogenous opiates, the enkephalins, may have effects that are opposite to those of β-endorphins and thus facilitate female sexual behavior. Enkephalins act on different receptors and in different brain regions than the β-endorphins. Enkephalins are thought to modulate the effects of more arousing hormones and to induce a level of analgesia. Analgesia, especially of the peripheral tissues, is thought to be necessary to allow the female to cope with aversive or painful stimuli encountered during sexual behavior.[809, 931] In spite of its length, the above list of neurohormones and neurotransmitters capable of influencing female sexual behavior is not exhaustive. As new biologically active substances are discovered within the nervous system, they are usually tested for their effects on lordosis, and many prove to be behaviorally active. New neurochemicals remain to be discovered, and many behavioral functions of the well established hormones and neurotransmitters remain to be explored.

Summary

1. In general, at least in rodents, estrogen-priming must occur first if other hormones or neurotransmitters are to facilitate female sexual behavior.

2. In spontaneous ovulators with short estrous cycles, progesterone is the major ovarian hormone that times the onset of female sexual receptivity as measured by lordosis. However, other neurochemicals can "substitute" for or synergize with progesterone in estrus induction. Substances that are released prior to ovulation, including norepinephrine, GnRH, oxytocin, prolactin, enkephalins, and acetylcholine, are all capable of inducing or facilitating female sexual behavior.

3. Chemicals that are released during or as a consequence of mating are most likely to inhibit or abbreviate behavioral estrus. Progesterone, dopamine,

oxytocin, prolactin, serotonin, GABA, and β-endorphins, under certain conditions, inhibit female sexual receptivity. Inhibitory processes are needed to produce cyclic patterns of reproduction. At least some of the neurochemicals that inhibit female sexual behavior also may be involved in postcopulatory sexual satiety.

General Summary and Conclusions

1. Feminine sexual behavior consists of proceptive or courtship behaviors and sexual receptivity or copulatory behaviors. Both of these components are influenced by estrogen and progesterone in most mammals, with the exception of primates. In addition to bringing a male and female together, proceptive behaviors may serve to optimize the pace of the mating sequence for promotion of pregnancy. Copulation requires that a female exhibit a characteristic posture known as lordosis in response to mounting by a male. Females exhibit this reflex when they are sexually receptive during estrus.

2. The phases of the ovarian cycle in spontaneous ovulators are the follicular phase, periovulatory phase, and luteal phase. Not all animals have a luteal phase because, in the absence of copulation, the corpus luteum may not be functional (e.g., in rats, hamsters, and mice). Primates additionally have a menstrual phase. The follicle develops during the follicular phase. The egg is released and animals become sexually receptive during the periovulatory phase. The remaining follicle becomes the corpus luteum in animals with a luteal phase, releasing progesterone and estrogen to prepare the uterus for implantation. In animals with a menstrual phase, the demise of the corpus luteum results in the sloughing off of the uterine lining.

3. In induced ovulators, the ovary produces follicles, and the animals become sexually receptive, but ovulation occurs only if the animal copulates. In other animals, the presence of a male is required to induce both behavioral estrus and ovulation.

4. Estrogen primes progesterone receptors. Therefore, without pretreatment with estrogen, progesterone does not induce sexual receptivity. These hormones also mediate the termination of sexual receptivity. When estrogen is withdrawn, receptivity is lost within hours. Progesterone has a biphasic effect. In the initial phase, progesterone stimulates sexually receptive behavior. However, if progesterone is continuously present for a period of time (as happens as a result of copulation, during the luteal phase, or during pregnancy), receptivity is inhibited.

5. The lordosis reflex is initiated in the rat when, following exposure to estrogen and progesterone, mounting by a male triggers specific sensory input to the midbrain central gray. When converging input from the hypothalamus (and in particular the VMH) and other forebrain structures facilitates neural activity in the midbrain neurons, the sensory input triggers the lordosis reflex.

6. Our understanding of how the lordosis response is modulated by other neural systems is still quite rudimentary compared with our understanding of the basic neural circuit. However, we know that estrogen influences neuro-

transmitter and neurohormone activity in a number of systems that project to the VMH or the midbrain. These systems are, therefore, implicated in modulation of lordosis behavior. Such systems include the norepinephrine and acetylcholine systems as well as GABA, enkephalin, GnRH, oxytocin, and prolactin-releasing neurons. Studies of neuroendocrine correlates of female sexual behavior have focused on the analysis of relatively simple behaviors like lordosis in laboratory rodents. This approach has been productive. However, there is increasing awareness that sexual behaviors occur within social and ecological constraints.[158] More modern approaches to the analysis of female sexual behaviors include this broader perspective and take advantage of species diversity to understand the physiology of female behavior.

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