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Chapter Two

THE ROLE OF THE BRAIN AND NERVOUS SYSTEM

Andrea Bradford and Cindy Meston

It is commonly remarked that the brain is our most vital sexual organ. Indeed, without higher brain functions to contribute to its most salient emotional and perceptual qualities, sexual activity would be a very different experience from what most of us would expect. However, the brain also moderates other important aspects of sexual response. Distinct brain areas appear to be involved in generating sexual motivation or drive, recognizing a potential sexual partner, coordinating movement during sexual activity, inhibiting sexual responses in certain circumstances, and learning sexual preferences. Without coordinated input from one or more of these functional areas of the brain, sexual behavior is markedly altered.

The pathways involved in the neural control of sexual response serve as conduits for sensory, motor, visceral, and regulatory information. Although higher brain areas govern the conscious appreciation of sexual behavior, many of the basic neural pathways involved in genital responses are controlled at the level of the spinal cord. Pelvic nervous function, particularly in men, is at present more thoroughly understood than the higher brain systems that facilitate, inhibit, or activate spinal neural pathways involved in sexual behavior. This chapter will outline the role of the brain and nervous system in sexual function, beginning at the level of the genitals and proceeding into the higher control centers of the brain.

METHODS FOR STUDYING THE BRAIN AND NERVOUS SYSTEM

Much of our knowledge of how sexual behavior is regulated by the nervous system is derived from studies conducted with nonhuman mammals, with rats being the most common species discussed in the recent literature (Goldstein et al., 2004). The advantages of studying sexual behavior in nonhuman species are numerous. Generally speaking, permanent experimental manipulations, such as lesions to parts of the brain or removal of reproductive tissues, do not present the same obvious ethical issues that would arise in humans. Moreover, most small mammals can be easily bred to provide a large study group consisting of both genetically and environmentally homogeneous animals, eliminating many of the sources of variation present in real-world contexts.

Neurons release a variety of chemical signals, or neurotransmitters, depending on their function. The type of neurotransmitter(s) released from a neuron is determined by the genes expressed by that neuron. The rate of neurotransmitter release depends on several factors including genetics, the degree of stimulation that the neuron receives, and patterns of stimulation over time (i.e., neurotransmitter release can be sensitized or desensitized to future stimulation). Although there is much variability in the function of individual neurons, bundles of related neurons often release a common set of neurotransmitters that serve specific functions. One method for studying the nervous system, therefore, is to measures the amount of a given neurotransmitter in the bloodstream or in the tissue surrounding a localized group of neurons. Because neurotransmitters require a receptor at the receiving end of a transmission (either on another neuron or on some other target tissue), it is also possible to understand how a neurotransmitter works by studying the location, distribution, and function of its receptors. Many such studies have been conducted using tissue samples obtained from animals or human cadavers.

Other research on animals has examined sexual behavior and physiological changes in response to direct activation of brain areas or nerves by means of either electrical stimulation or direct injection of neurotransmitters. This research is especially useful for isolating the particular aspects of sexual function governed by a discrete brain structure or group of neurons. However, it is difficult to unequivocally declare one structure the "master" over any given sexual response as neurons do not operate in isolation. The interconnectivity among neural tissues, the potential influence of multiple neurotransmitters at a common site, and the complexity of quantifying some sexual behaviors have complicated the development of an integrated neurological model of sexual response.

Unfortunately, the disadvantages of relying on animal models of sexuality are considerable. Although many regions of the brain are similar across mammalian species, certain higher cognitive abilities, particularly those unique to humans, cannot be modeled precisely in animals. Significant difficulties arise when attempting to compare complex sexual behaviors between humans and other species. This is particularly troublesome in studies designed to elucidate the mechanisms of sexual desire or sexual motivation. For example, sexually

receptive female rats (i.e., female rats in heat) solicit males by wiggling their ears and by darting toward the male and running away, apparently provoking a "chase." When the male attempts to mount, she assumes a mating posture (known as lordosis) by arching the back, elevating the genital region, and deflecting the tail to facilitate copulation. Although these behaviors appear to be motivated and specific to sexual behavior, their human equivalents are often difficult to conceptualize and apply to research findings from animal studies. Thus in understanding some aspects of sexual behavior and sexual function, translating behavior from animals to humans is often problematic.

Most studies in living humans have adopted one of several indirect approaches to studying neurological aspects of sexual function. The administration of drugs that mimic the activity of the body's own neurotransmitters has been a common strategy to study both basic sexual physiology and potential treatments for sexual problems. Another strategy is to examine sexual behavior in people with an illness or injury affecting a part of the brain or nervous system thought to be involved in sexual function. Research involving men and women with spinal cord injury or traumatic brain injury, for example, has contributed to knowledge on the role of nervous system structures in sexual response (Sipski, 2002). Several recent studies have adopted the opposite approach by assessing nervous system function among individuals whose primary clinical concern is sexual dysfunction. Studies examining sensory function (e.g., Connell et al., 2005), activation of key brain areas (e.g., Holstege et al., 2003; Komisaruk et al., 2004), and other aspects of neural function are only beginning to be employed in research on sexual disorders. Neurologically based research has also been conducted to examine differences between men and women and to explore the biological basis of sexual orientation.

NEURAL ASPECTS OF GENITAL SEXUAL RESPONSE

General Organization of the Peripheral Nervous System

The nervous system can be divided into the central nervous system, consisting of the brain and spinal cord, and the peripheral nervous system (PNS), consisting of the network of nerves that transmit to and from all the other organs and tissues in the body. The PNS supplies the nerve fibers that are directly responsible for transmitting sensory information and inducing muscle activity, although higher coordination from the spinal cord and brain are essential. Although command of many PNS functions is under conscious control, much of the motor control throughout the body is involuntary. For example, the contractions of the heart muscle and of the muscle tissue surrounding the blood vessels (vascular smooth muscle) influence heart rate and blood pressure and are under the control of the *autonomic* branch of the PNS.

Glandular activity and contraction of some muscles in the gut (nonvascular smooth muscle) are also under autonomic control. Not surprisingly, the autonomic nervous system plays a vital role in the control of sexual responses. Erection of the penis, for example, depends on autonomic signals to relax the muscles surrounding the blood vessels and sinus cavities within the penile shaft, allowing for an increase in blood flow. An inhibitory autonomic mechanism is also necessary to terminate the erection when appropriate.

The autonomic nervous system can be further subdivided into parasympathetic and sympathetic branches. With few exceptions, both branches send nerve fibers to various target organs and tissues and in many cases serve opposing functions. In humans the parasympathetic, sympathetic, and sensory nerve fibers involved in sexual response converge in a network of fibers known as the pelvic plexus. Parasympathetic neurons originate at the sacral level of the spinal cord and are connected to the pelvic plexus via the pelvic nerve. Sympathetic neurons originate at the thoracic and lumbar levels of the spinal cord and run through the hypogastric nerve to the genitals. The interactions among sympathetic and parasympathetic nerve fibers in the pelvic plexus are poorly understood. However, it appears unlikely that these systems serve distinct, opposing functions at all times.

Free nerve endings near the body's surface are equipped with specialized receptors that are activated by touch, pressure, pain, or temperature. These receptors vary according to both the type of information they detect and the threshold of stimulation required to become activated; thus a variety of receptors work in concert to provide a multifaceted sensory experience (Martin, 1991). The major conduit for sensory information from the genitals is the pudendal nerve, a bundle of nerve fibers that transmit impulses generated from nerve endings in the external genitalia. Sensory information from the internal genitalia is also transmitted via nerve fibers that run along the pelvic and hypogastric nerves.

Male Sexual Arousal

Provoked by sexual interest, a sexually arousing stimulus, or touch, penile tumescence increases with relaxation of the blood vessels entering the penis. Given adequate sexual stimulation, the penis becomes fully engorged, resulting in erection. The parasympathetic neurons conveyed by the pelvic nerve are primarily responsible for the control of erection. In general, acetylcholine is regarded as the primary neurotransmitter secreted by parasympathetic neurons throughout the body. However, the most prominent effects on erectile function are mediated by the neurotransmitter nitric oxide, which is also released from many parasympathetic neurons. Nitric oxide is released in response to sexual stimulation and activates a metabolic pathway resulting in the production of cyclic guanosine monophosphate (cGMP), which in turn relaxes the vascular smooth muscle of the penis (Burnett, Lowenstein, Bredt, Chang, & Snyder, 1992). Maintenance of the resulting erection depends on the ongoing production of nitric oxide, contingent on continued sexual stimulation. Androgens also seem to be important in facilitating the production of nitric oxide.

Normally, cGMP—the facilitator of erections—is broken down by enzymes known as phosphodiesterases (PDEs). However, this may be circumvented by inhibiting the activity of these enzymes. Sildenafil (Viagra) and other drugs used to treat erectile disorder inhibit PDE type 5. In doing so, these drugs enhance the concentration of cGMP, allowing for greater smooth muscle relaxation and therefore improved erection (for a thorough discussion of PDE-5 inhibitor pharmacology, see Padma-Nathan et al., 2004).

In addition to activating cGMP, nitric oxide also appears to inhibit the action of the sympathetic neurotransmitter norepinephrine (Cellek, 2000). In contrast to nitric oxide, norepinephrine appears to be the major neurotransmitter responsible for *contraction* of the penile smooth muscle, limiting blood flow and thereby maintaining flaccidity of the penis. Although this inhibitory role is important, excessive norepinephrine may be problematic. Typically, the concentration of norepinephrine in the penile blood supply is reduced during erection (Becker et al., 2000, 2002). However, norepinephrine may increase during sexual arousal in men with erectile disorder (Becker et al., 2002). Erectile difficulty may result from the use of drugs, such as some treatments for high blood pressure, that stimulate particular types of norepinephrine receptors (Srilatha, Adaikan, Arulkumaran, & Ng, 1999). Blocking the receptors that respond to norepinephrine, on the other hand, may facilitate erection (Blum, Bahnson, Porter, & Carter, 1985).

The sensory information from the penis is transmitted via the dorsal nerve of the penis, a branch of the pudendal nerve. The role of basic sensory capacities in sexual function is still being explored. Sensitivity of the penis to tactile stimulation typically declines with age but is also reduced among men with erectile dysfunction regardless of age (for review, see Rowland, 1998). On the other hand, several studies have investigated the possibility that premature ejaculation might be related to penile *hypersensitivity*, although this hypothesis has not been consistently supported (Rowland, Haensel, Blom, & Slob, 1993; Paick, Jeong, & Park, 1998; Xin et al., 1996).

Considerable speculation has surrounded the effect of circumcision on sexual sensation and enjoyment. Masters and Johnson (1966) first investigated this question with neurological testing of the glans, finding no differences in sensitivity to light touch between circumcised and uncircumcised men. A more recent study examined the ability to perceive pressure, vibration, and temperature changes on the glans of the penis in uncircumcised men and men who had been circumcised as newborns (Bleustein, Fogarty, Eckholdt, Arezzo, & Melman, 2005). After controlling for medical conditions that might affect tactile sensitivity, the authors of the study concluded that there were no differences between circumcised and uncircumcised men on sensory test scores. However, a study conducted on men who were circumcised as *adults* revealed significant declines in penile tactile sensitivity and erectile function from pre- to postcircumcision (Fink, Carson, & DeVellis, 2002). It is possible that negative sexual outcomes of circumcision are mitigated by early age at the time of the surgery. However, this topic remains controversial (American Academy of Pediatrics, 1999).

Female Sexual Arousal

The precise neural mechanisms of female sexual response are less understood than those of males, although many are analogous between the sexes. The physiological changes that occur during sexual response in women are largely the result of increased blood flow to the pelvic region and involuntary muscle contractions, regulated by a complex series of events in the nervous system. The labia, clitoris, and the tissues surrounding the vaginal opening become engorged with blood and swell. The vaginal tissues also become engorged, and the increased pressure in the small blood vessels causes a leakage of fluid that flows through the mucous lining of the vagina and contributes to lubrication (Levin, 1992). Contractions of internal pelvic muscles lift the uterus, cervix, and part of the upper vagina, widening and lengthening the vaginal barrel (Masters & Johnson, 1966; Shafik, 1995). At the peak of sexual excitement, a series of vaginal, uterine, and rectal sphincter contractions occurs during orgasm, along with other physiological changes (Masters & Johnson, 1966). Both autonomic and somatic (voluntary) nerve fibers are intricately involved in the regulation of these responses.

As in men, the parasympathetic nerves are widely implicated in facilitating female sexual response. Animal models indicate that pelvic nerve stimulation (resulting largely in parasympathetic activity) increases vaginal and clitoral blood flow (Giuliano et al., 2001; Min et al., 2001). Vasoactive intestinal peptide (VIP), released from the terminal parasympathetic neurons, has been considered the primary neurotransmitter affecting genital blood flow in women. Early research in human females indicated that VIP levels in the bloodstream rose during sexual arousal (Ottesen et al., 1982). Likewise, intravenous administration of VIP resulted in significant increases in vaginal blood flow and vaginal lubrication in women (Ottesen et al., 1983, 1987). The effect of VIP-enhancing drugs on sexual arousal is currently unknown, although potential pharmaceutical formulations are currently under investigation (e.g., Sethi, Önyüksel, & Rubinstein, 2005).

In addition to VIP, nitric oxide also appears to mediate female sexual arousal. Neurons that release nitric oxide have been found in clitoral and vaginal tissue in anatomical studies. In an animal model, administration of a drug known to block the production of nitric oxide inhibited increases in vaginal blood flow (Kim et al., 2004). Because of its ability to enhance nitric oxide–dependent sexual arousal in men, sildenafil (Viagra) and other PDE-5 inhibitors have also been investigated as potential therapies for women. In one study, healthy women who took sildenafil versus a placebo showed greater increases in vaginal blood flow during sexual arousal (Laan et al., 2002). Other research has found that women taking sildenafil reported improved experience of sexual arousal and orgasm compared to women taking a placebo (Caruso, Intelisano, Farina, Di Mari, & Agnello, 2003). Despite some evidence that PDE-5 inhibitors promote improved genital blood flow, their clinical utility has been limited (Jackson, Gillies, & Osterloh, 2005). This is due in part to wide variability in the degree to which such drugs favorably impact the mental or subjective experience of sexual arousal in women (e.g., Basson, McInnes, Smith, Hodgson, & Koppiker, 2002). Whereas in men, enhanced genital engorgement is highly correlated with self-reported arousal, in women, correlations between genital blood flow and self-reported arousal are highly variable (Chivers, Seto, Lalumiere, Laan, & Grimbos, 2005). Several theorists have speculated that affective and contextual cues may be more important to the mental experience of sexual arousal in women than are feedback cues from genital responses (Prause & Janssen, 2006; Rosen & Beck, 1988).

The effects of norepinephrine, the dominant neurotransmitter of the sympathetic nervous system, have been less studied in women than in men. Animal studies indicate that stimulation of sympathetic nerves results in decreased vaginal blood flow (Guiliano et al., 2001a), but this can be reversed by drugs that block norepinephrine (Kim, Min, Huang, Goldstein, & Traish, 2002). In humans, one such drug, phentolamine, has shown some efficacy as a treatment for sexual arousal difficulties in women (Rosen, Phillips, Gendrano, & Ferguson, 1999; Rubio-Aurioles et al., 2002). Meston and McCall (2005) found that women with sexual dysfunction had higher levels of plasma norepinephrine, both before and after exposure to an erotic film, than did women without sexual dysfunction, also suggesting a possible role of norepinephrine in the inhibition of women's sexual response.

Interestingly, however, several lines of evidence suggest that sympathetic activity may accompany or even facilitate sexual arousal in women. Women presented with a sexually arousing film have shown elevated norepinephrine levels in urine (Levi, 1969) and blood (Exton et al., 2000). Another study indicated that levels of norepinephrine in the bloodstream increased during sexual intercourse and declined rapidly after orgasm (Wiedeking, Ziegler, & Lake, 1979). In studies of women with spinal cord injury Sipski and colleagues reported that physiological sexual arousal was impaired in women whose injuries were located in the region from which sympathetic nerve pathways to the genitalia emerge (Sipski, Alexander, & Rosen, 1997, 2001). Other research has found enhanced vaginal blood flow responses among women after taking a drug (ephedrine) that mimics the action of norepinephrine (e.g., Meston & Heiman, 1998) and after exercising at levels of intensity known to activate the sympathetic nervous system (Meston & Gorzalka, 1995, 1996). However, findings from a double-blind clinical trial indicated that ephedrine was no more effective than placebo in reversing antidepressant-induced sexual arousal dysfunction (Meston, 2004). Furthermore, some findings have suggested that abnormally high levels of sympathetic activity may inhibit female sexual responding (Meston & Gorzalka, 1996; Rellini & Meston, 2006). Because the roles of the sympathetic and parasympathetic nervous systems in female sexual function remain unclear, it is difficult to draw firm conclusions on the basis of these findings.

The external genitalia receive a rich supply of neurons sensitive to tactile stimulation. The pudendal nerve is the major conduit for sensory information from the clitoris, labia, and other external genitalia. Several studies have examined the possibility that genital sensory deficits may contribute to sexual dysfunction in women. Connell and colleagues (2005) found that thresholds for clitoral tactile sensation were higher on average among women who reported problems with sexual desire and sexual arousal on a questionnaire. The authors speculated that pudendal nerve function may be compromised in women with certain types of sexual disorders. However, a different study reported that tactile sensitivity in the fingertip was also related to sexual arousal difficulties (Frohlich & Meston, 2005). Thus it is unclear whether problems related to lower sexual sensitivity are linked to genital function specifically or to a more general neurological phenomenon.

Although the nature of sensory innervation to the vagina, cervix, and uterus differs from that of the clitoris, introitus, and other external genital structures (Hoyt, 2006), some sensory information from the internal genitalia is transmitted via the hypogastric and pelvic nerves to the spinal cord. Accumulating evidence suggests that sensory information from the genitals may also be transmitted via a nonspinal route. Research on nonspinal sensory pathways has been prompted in part by the observation that women with complete spinal cord injury retain some ability to perceive sexual arousal and orgasm during genital stimulation (e.g., Whipple, Gerdes, & Komisaruk, 1996). Findings from these studies have pointed to the vagus nerve as a conduit for sensory information from the genitals (Komisaruk & Whipple, 2005; Komisurak et al., 2004; Whipple & Komisaruk, 2002). The vagus nerve is a major parasympathetic nerve that connects the brain directly to several major internal organs and serves numerous regulatory functions. Although the vagus nerve appears to serve as an alternative sensory pathway in spinal cord–injured women, its general role in female sexual function remains to be fully understood.

Central Nervous System

The central nervous system consists of the brain and spinal cord. Many of the basic genital functions relevant to sexual behavior are reflexes; that is, they require no input from the brain in order to be executed. The autonomic nerves originating in the spinal cord and projecting to the genitalia are in immediate control of involuntary genital muscles, including those that regulate genital engorgement. In their "default" state, these spinal pathways are inhibited. Thus healthy individuals are in a nonsexually aroused state most of the time. This basic state of inhibition can be modified, however, with the input of sensory information from the genitals. Most sensory information travels via the pudendal nerve from the site of stimulation toward the spinal cord. At the level of the spinal cord, sensory information is further relayed to the brain but may also directly activate spinal autonomic neurons that cause genital responses. Circuits that operate at the level of the spinal cord without necessary mediation from the brain are known as reflexes and are generally mediated by short interneurons that connect spinal sensory and motor (autonomic) pathways.

The existence of sexual reflexes has been supported by studies in animals and humans with spinal cord injuries that block the transmission of sensory information to the brain via spinal pathways. The bulbocavernous reflex is the best known example and is present in both sexes. Stimulation of the glans (either of the penis or clitoris) causes a contraction in the bulbocavernous muscle. In clinical examination, this appears as a contraction of the anus. A more complicated response is ejaculation, which can be provoked in animals with complete spinal lesions (e.g., McKenna, Chung, & McVary, 1991). Ejaculation is a coordinated event during which a sympathetic reflex contracts the prostate, epididymis, and vas deferens to cause the emission of semen from the lower genital tract, while a parasympathetic reflex provokes the genital and pelvic floor muscle contractions needed for ejection of semen (McMahon et al., 2004). Similar muscle contraction reflexes have been observed in female animals with spinal cord lesions, suggesting that female orgasm may also be mediated through a reflex pathway (McKenna et al., 1991) Although these responses may be executed without input from the brain, moderation of genital reflex pathways from higher control centers is integral to normal sexual function, as will be discussed shortly.

Although tactile stimulation can affect certain physiological responses more or less automatically, more complex processing at the level of the brain is necessary for the richer sensory experience of sexual stimulation. Touch cannot be perceived *consciously* until impulses from sensory neurons reach the brain. Once sensory information is transmitted from the genitals, it is relayed to the brain through the spinal cord or sensory vagus nerves. Neurons involved in the transmission of sensory information ultimately reach the thalamus, which modifies the signals and relays them to the cerebral cortex for higher processing. In the cerebral cortex the information is integrated with signals from other sensory pathways converging on the thalamus (e.g., touch, hearing). In addition, the human brain is capable of generating its own imagery and other conscious thoughts that may comprise sexual fantasy. These various inputs, in conjunction with hormonal and other neurological factors, may influence the activity of brain areas that send signals to inhibit, facilitate, or activate spinal pathways involved in sexual response. In effect, the brain can be viewed as a master control center for sexual function, receiving and integrating information while simultaneously sending input to modify the activity of the spinal nerves that project to the genitals. Several of the most important brain regions involved in regulating sexual responses will be reviewed here.

Regulation of Sexual Arousal and Orgasm

The hypothalamus is one of the most important brain structures in the regulation of sexual behavior. Multiple regions of the hypothalamus appear to be activated in sexual contexts, influencing different aspects of sexual behavior. The paraventricular nucleus of the hypothalamus (PVN) is a center thought to be influential in the control of sexual arousal and orgasm. Neurons from this region project directly to autonomic nerves in the spinal cord that control genital responses (Veronneau-Longueville et al., 1999). The PVN is also connected to several brain areas outside the hypothalamus, including some that are considered vital to learning and memory. Oxytocin is the major neurotransmitter released from these neurons. Oxytocin is often associated with childbirth as it is one of the dominant neurotransmitters responsible for stimulating uterine contractions during labor. Interestingly, sexual intercourse has been discussed as a method of promoting labor (Kavanagh, Kelly, & Thomas, 2001) since oxytocin is also released from the brain during sexual activity.

Animal studies indicate that oxytocin plays a role in the generation of sexual arousal. Oxytocin administration stimulates erection (Giuliano, Bernabe, McKenna, Longueville, & Rampin, 2001b; Martino et al., in press). Drugs that block oxytocin, on the other hand, inhibit "noncontact" erections, that is, erections due to stimulation other than direct genital contact (Melis, Spano, Succu, & Argiolas, 1999). Less is known about the potential implications for oxytocin in human sexual arousal. Salonia and colleagues (2005) reported an association between oxytocin levels and women's self-reported ability to achieve and maintain vaginal lubrication during sexual activity. However, much remains unknown about the importance of oxytocin for normal sexual arousal. Most human studies concerning the impact of oxytocin on sexual response have examined its role in orgasm. These studies have noted substantial elevations in oxytocin over baseline levels in both men and women following orgasm (Blaicher et al., 1999; Carmichael et al., 1987; Kruger et al., 2003; Murphy, Seckl, Burton, Checkley, & Lightman, 1987). In one of these studies, women who showed greater releases of oxytocin tended to rate their orgasms as more intense (Carmichael et al., 1987).

The neurons of the PVN are sensitive to several neurotransmitters that may either promote or inhibit their release of oxytocin. Dopamine stimulates activity of these neurons, thereby indirectly promoting sexual arousal. Drugs that mimic the action of dopamine have been shown to promote increased genital blood flow, and it is thought that this results from stimulation of neurons that release oxytocin (e.g., Melis, Succu, Mascia, & Argiolas, 2005). Likewise, blockage of dopamine inhibits oxytocin-mediated erection (Martino et al., in press). The class of neurotransmitters known as opioids (including drugs such as morphine and codeine as well as endogenous substances such as endorphins) inhibit secretion of oxytocin from PVN neurons (Ingram, Kavadas, Thomas, & Threapleton, 1996). Studies in male rats indicate that increased opioid production in the PVN is associated with reduced levels of oxytocin and erectile failure (Arletti et al., 1997). This is a likely mechanism for the well-known detrimental effects of long-term opioid use on sexual function in both men and women (Pfaus & Gorzalka, 1987). Gamma-aminobutyric acid is a common inhibitory neurotransmitter throughout the brain and also appears to block transmission of oxytocin from PVN neurons, inhibiting sexual responses (Melis, Succu, Mascia, & Argiolas, 2001).

Inhibition of Sexual Responses

The nucleus paragigantocellularis is located in the brain stem. It receives sensory information from the genitals and, in turn, sends neurons directly back to the spinal cord (Marson & McKenna, 1990). The primary function of the nucleus paragigantocellularis is inhibitory; in normal, non–sexually aroused states, it hinders spinal reflexes that produce genital engorgement and orgasmic responses. The primary neurotransmitter released from the neurons of the nucleus paragigantocellularis is serotonin. Thus drugs that increase levels of serotonin in the brain may be expected to result in even greater inhibition of sexual responses. Accordingly, antidepressants that raise serotonin levels in the brain are frequently associated with sexual complaints, including inhibited orgasm (for review, see Meston & Gorzalka, 1992). Lesions to the nucleus paragigantocellularis have the opposite effect. The loss of this inhibitory influence from the brain can lower the threshold of stimulation required to activate sexual responses (Marson, List, & McKenna, 1992; Yells, Hendricks, & Prendergast, 1992) and moderate the inhibitory effects of serotonin on sexual behavior (Yells, Pendergast, Hendricks, & Nakamura, 1994).

Sexual Motivation

It has long been recognized that most humans possess some degree of innate drive for sexual activity. Like hunger, thirst, and sleep, sexual motivation varies between individuals and is influenced by a complex interaction of physiological and psychological factors. Although conscious thought may clearly contribute to or diminish one's motivation for sexual activity, some aspects of sexual motivation are not under obvious voluntary control.

The medial preoptic area (MPOA) of the anterior hypothalamus is thought to play a role in sexual motivation in mammals. It is connected to the multiple brain areas involved in sexual behavior, including others within the hypothalamus (Marson & Foley, 2004; Simerly & Swanson, 1988). The MPOA is activated during male (e.g., Baum & Everitt, 1992) and female (e.g., Kato & Sakuma, 2000) sexual behavior in animals, and direct stimulation of the MPOA has been associated with increased genital blood flow (Giuliano et al., 1996) and activation of mating behavior (van Dis & Larsson, 1971). Numerous studies indicate that, as in the paraventricular nucleus of the hypothalamus, dopamine is the major neurotransmitter that stimulates MPOA neurons involved in sexual activity (for review, see Melis & Argiolas, 1995). These observations have prompted interest in the potential clinical usefulness of drugs that mimic the action of dopamine in the central nervous system (e.g., Caruso et al., 2004).

Several lines of research have aimed to understand the unique contributions of the MPOA to sexual behavior by examining the effects of its absence. Lesions to the MPOA abolished mating behavior in male rats (Szechtman, Caggiula, & Wulkan, 1978), monkeys (Slimp, Hart, & Goy, 1978), and other species. However, this does not point to a role for the MPOA in genital responding as other findings indicated that MPOA lesions did not inhibit masturbation (Slimp et al., 1978) or erections during sleep (Schmidt, Valatx, Sakai, Fort, & Jouvet, 2000). A study in female rats revealed that MPOA lesions caused the rats to avoid potential male sexual partners but did not eliminate displays of sexual receptivity (Whitney, 1986). On the basis of these studies, it has been hypothesized that the MPOA is critical to identifying sexual mates but not necessarily to sexual drive per se (McKenna, 1999).

Human brains have an anterior hypothalamic region that appears to be analogous to the MPOA in other mammals, although function of this structure remains unclear. Several intriguing characteristics of this structure are worthy of further investigation. Given the presumed role of the MPOA in mate selection, it is not surprising that this area of the hypothalamus is among the brain regions that differentiate males and females. In humans, four small groups

of cells near this region (called the interstitial nuclei of the anterior hypothalamus; INAH 1–4) have been investigated for potential sex differences. Multiple studies have confirmed that INAH 3, and possibly other nuclei, are significantly larger in men than in women (Allen, Hines, Shryne, & Gorski, 1989; Byne et al., 2001; LeVay, 1991). Interestingly, some findings have also suggested that INAH 3 is smaller in volume among homosexual men compared to heterosexual men (Byne et al., 2001; LeVay, 1991). Although it is tempting to draw conclusions on the basis of anatomical findings, the functional significance of these differences is not yet understood. However, imaging studies of the hypothalamus during sexual stimulation are consistent with anatomical sex differences, showing greater activation in males than in females (e.g., Karama et al., 2002).

Sexual Pleasure, Learning, and Conditioning

Over the life span, humans develop sexual preferences, desires, and memories that shape future sexual behavior. Although considerable work has been devoted to the potential for instinctive or universal preferences in humans (e.g., Buss, 2000), there is no doubt that individual variability in sexual expression is shaped in part by past experiences. The forebrain includes a number of structures that contribute to motivation and learning. Collectively, these structures are known as the limbic system, which also includes the hypothalamus. The amygdala, a structure also known to play a role in emotional and sensory memories, is involved in sexual motivation. It is connected to the medial preoptic area of the hypothalamus as well as other structures in the limbic system. Experimental evidence suggests that the amygdala is involved in the recognition and processing of sexual stimuli (e.g., De Jonge, Oldenburger, Louwerse, & Van De Poll, 1992). Lesions to the amygdala have been found to decrease motivated sexual behavior (e.g., Rasmussen, Kaada, & Bruland, 1960). Studies in humans indicated that the amygdala was activated while viewing a sexually arousing stimulus (Hamann, Herman, Nolan, & Wallen, 2004; Karama et al., 2002), although to a greater extent in men than in women (Hamann et al., 2004). The amygdala is connected to the hippocampus, a structure critical to the formation of new memories, as well as to areas of the cerebral cortex that are involved in learning and cognition. Recent imaging studies in humans (although almost exclusively in men) reveal that numerous other areas of the forebrain and multiple regions of the cerebral cortex are activated in response to sexual stimulation. The striatum, cingulate cortex, frontal cortex, and other areas appear to play a vital role in integrating sensory information from multiple sources and generating movement and other complex behavior (Arnow et al., 2002; Mouras et al., 2003; Karama et al., 2002; Redouté et al., 2005).

Orgasm is a point of peak sexual stimulation and is highly rewarding in both animals and humans. Adaptive behaviors, including reproductive behaviors, appear to be reinforced through impulses in a region of the brain known as the ventral tegmental area (VTA), which is connected with other structures of the limbic system. Opioids, such as those generated from the hypothalamus, stimulate this area. Activation of the VTA causes a release of dopamine to the amygdala and nucleus accumbens, which in turn connects the VTA to the hippocampus in what can be described as a "learning circuit." Activation of the VTA, and subsequent activation of the nucleus accumbens, is also associated with the experience of reward or reinforcement for behaviors (for a detailed overview of this network, see Le Moal & Simon, 1991). The nucleus accumbens appears to be particularly involved in generating action toward some reward (Salamone & Correa, 2002). Using positron emission tomography to detect changes in blood flow to areas of the brain, Holstege and colleagues (2003) observed that activation of the VTA occurred at the point of orgasm and ejaculation in men. The authors likened this experience to a "heroin rush," noting that similar VTA activation is associated with cocaine and heroin use. Interestingly, however, the abuse of heroin, morphine, and other opiates stimulates the VTA to the point that subsequent activity may be suppressed. In effect, sexual drive is depressed (Holstege et al., 2003).

There are several important ramifications for a rewarding experience of copulation. From an evolutionary perspective, a species that has developed an innate system for reinforcing mating behavior should have greater reproductive success than a species that lacks such a system. On the individual level the animal is able to learn about the context in which the rewarding experience occurs so that these conditions can be sought again. In experimental settings many animals can easily be trained to prefer, for instance, a particular location in their habitat (e.g., Everitt, 1990; Paredes & Alonso, 1997) or a special odor (e.g., Kippin & Pfaus, 2001) associated with access to a mate. Animals can also be motivated to learn to press a lever, run a maze, and even endure electrical shock for the promise of a reward (a sexual partner) at the end of the task or obstacle (for review, see Pfaus, Kippin, & Centeno, 2001). Animal studies have supported the role of the ventral tegmental area in such sexually motivated behavior. In one such study an opioid-blocking drug was administered into the VTA of male rats to suppress VTA activation during copulation with a sexually receptive female. After four such trials, and compared to rats that did not receive these injections, rats that received the opioid-blocking drug did not show normal increases in anticipatory behavior toward the sexually receptive female (van Furth & van Ree, 1996). Whereas anticipatory behavior (e.g., increased motor behavior) would be expected to increase after exposure to a rewarding stimulus, the suppression of the VTA appeared in this case to inhibit such behavioral activation. Another study found that manipulation of the VTA's normal signaling slowed the rate of mating behavior in male rats (Hull, Bazzett, Warner, Eeaton, & Thompson, 1990).

Reinforcement and conditioning of sexual behavior is known to occur in humans as well as animals. In a famous experiment Rachman (1966) "trained" adult males to show genital responses to an image of boots by repeatedly pairing this image with pictures of nude women. Later, more carefully controlled studies confirmed the ability to condition men to respond to nonsexual stimuli through careful and repeated pairing with sexually arousing stimuli (e.g., Hoffman, Janssen, & Turner, 2004; Rachman & Hodgson, 1968), although results of similar tests in women have been inconclusive (Hoffman et al., 2004; Letourneau & O'Donohue, 1997; Meston & Rachman, 1994). Conditioning has been theorized to be important in the development of sexual fetishes (e.g., Rachman, 1966), although this theory is inadequate to explain alone the range of paraphilic sexual behavior. However, several techniques have been developed to use principles of conditioning to *reduce* problematic sexual thoughts or behaviors, particularly among sex offenders but also for individuals with various paraphilic sexual interests (e.g., Wolfe, 1992). Aversion therapy, for instance, involves delivering an unpleasant stimulus (such as an electric shock) in combination with a sexually arousing stimulus until the sexual stimulus no longer elicits a response. Although there is some evidence to support the effectiveness of this treatment, high relapse rates have limited the use of aversion therapy over time (Kilman, Sabalis, Gearing, Bukstel, & Scovern, 1982; Rice, Quinsey, & Harris, 1991). More recent work has examined covert sensitization, a variant of aversive conditioning (e.g., McKibben, Proulx, & Lussier, 2001; Plaud & Gaither, 1997). An alternative technique is a form of "reconditioning," in which the individual masturbates to the unwanted sexual stimulus just to the point of orgasm, at which time the fantasy is turned to a more appropriate or acceptable target of sexual stimulation (such as a spouse or partner). Relatively little research has been done to examine the effectiveness of this and similar techniques (Laws & Marshall, 1991).

Summary

The central nervous system exerts both direct and indirect control of genital responses and behaviors. Some of the most basic functions of the intact central nervous system are inhibitory; suppression of sexual responses is governed in part by the nucleus paragigantocellularis. Other areas of the brain promote sexual arousal; indeed, without the activity of the paraventricular nucleus and other brain regions that control spinal autonomic nerves, sexual responses could not be generated through psychological arousal alone. The anterior hypothalamus, the amygdala, and other structures of the limbic system seem to be involved in recognizing and responding to sexual stimuli, whereas the ventral tegmental area, nucleus accumbens, and related structures are associated with the rewarding aspects of sexual behavior. These are broad generalizations and are far from complete explanations of the sexual brain; much remains to be learned about how the brain regulates and generates sexual thoughts, reactions, inhibitions, and deviations from typical behavior. Although much of the brain research pertaining to sexuality has been conducted in men, the information available on women's sexual behavior to date indicates that there are key sex differences that may underlie many of the distinctions we commonly make between male- and female-typical patterns of sexual behavior.

SEX DIFFERENCES: THE MAKING OF A MALE OR FEMALE BRAIN

What, exactly, defines an individual as male or female? Although identifying an individual's sex is usually unambiguous, it is has become increasingly clear that sexual differentiation is not an all-or-none process. The most basic criterion for defining sex is the individual's genetic makeup. At typical conception the human egg contributes one X chromosome, and the sperm cell may contribute either an X or Y chromosome. Females develop from a fertilized egg with two X chromosomes (XX), and males develop from a fertilized egg with an X and Y chromosome (XY). Regardless of external appearance or behavior, an individual's *chromosomal sex* is defined by these rules.

It has been observed that developing human embryos are female "by default" and must undergo a series of changes in order to become male. This representation is not completely accurate because embryos do not become male after having been female; rather, they progress from an undifferentiated state to become one sex or the other. However, it is true that becoming male requires several developmental steps that are not required in order to become female. Masculinization of the male embryo is dependent on the normal expression of genes on the Y chromosome that promote the development of the testes. Newly developed testes are able to secrete testosterone, which in turn influences the development of brain structures. Failure to develop functional testes, or an abnormally low responsiveness to testosterone, will result in a female-typical pattern of development. These and other conditions may result in variations in the degree to which the brain is masculinized. Previous studies in animals indicate that prenatal masculinization shapes brain structures that are known to differ between males and females, including the hypothalamus, amygdala, and other areas of the limbic system (for review, see Keefe, 2002).

In contrast to the organizational effects of hormones (i.e., those that result in permanent developmental changes), circulating hormones continue to modify brain and nervous system pathways in reversible, temporary ways. These *activational* effects occur at every level of neural control of sexual function. Receptors for androgens and estrogens are located on the peripheral autonomic nerves, on nerves within the spinal cord, and in multiple structures in the brain. In both males and females, sex hormones play a substantial role in regulating genital sexual function (Giuliano & Rampin, 2004; Min et al., 2003) and may also play a role in cognition and emotion associated with sexual behavior (e.g., Anderson, Bancroft, & Wu, 1992; O'Connor, Archer, & Wu, 2004; Redouté et al., 2005). Activational effects of hormones are of particular interest in women, who experience both cyclical fluctuations in sex hormone levels throughout early to middle adulthood and a relatively abrupt decline in hormone levels following menopause. Effects of the menstrual cycle (e.g., Wilcox et al., 2004) and menopause (Bachmann & Leiblum, 2004) on sexual arousability and sexual behavior seem to be primarily related to changes in estrogen levels, although the impact of androgens has also received considerable study and speculation (Bancroft, 2002).

CONCLUSION

The brain and nervous system act in concert to motivate, coordinate, and execute sexual behaviors and genital responses. Basic genital functions are dependent on the integration of sensory input and autonomic output, much of which is mediated by reflexes at the level of the spinal cord. However, control centers in the brain serve to potentiate or suppress spinal genital pathways, and sexual function is altered substantially without these higher inputs. Sexual arousal and orgasm are therefore the result of multiple events throughout the nervous system, some of which are stimulatory, but also some of which are disinhibitory. Further regulation of sexual behavior by circulating hormones occurs at the level of the genitals, spinal cord, and brain. Sex hormones are important not only to sexual differentiation during development, but to the ongoing regulation of nervous system pathways governing sexual function. Although these elaborate control systems may give the appearance of a built-in or instinctive sexual system, the role of learning and past experience, particularly in humans, cannot be overstated. Indeed, the inherent plasticity of the nervous system is partly responsible for the diversity of sexual expression in men and women.

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