This article provides a review of the past and current literature on the neurobiology of sexual function. The influence of endocrine, neurotransmitter, and central nervous system influences on male and female sexual function are discussed for sexual desire, arousal, and orgasm or ejaculation stages of sexual responding. Endocrine factors reviewed include the following: androgens, estrogens, progesterone, prolactin, oxytocin, cortisol, and pheromones. Neurotransmitters and neuropeptides discussed include nitric oxide, serotonin, dopamine, epinephrine, norepinephrine, opioids, acetylcholine, histamine, and γ-aminobutyric acid. Central nervous system influences on sexual function are discussed briefly with reference to brainstem regions, the hypothalamus, and the forebrain.

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Within the past decade, increasing research attention has been paid to the neurobiology of sexual function. This has been fostered, in part, by a growing awareness of the deleterious effects of pharmacological agents on sexual behavior, by an increased recognition of the high incidence of sexual difficulties present in men and women and, most recently, by the enormous success of using sildenafil citrate (Viagra) for the treatment of male erectile dysfunction. In this article, we provide a concise review of the past and current literature on the endocrine, neurotransmitter, and central nervous system (CNS) influences on male and female sexual function. We would like to acknowledge the enormity of the field at the outset, and emphasize that this article is meant as a broad overview of the field. Wherever applicable, within each section, we refer the readers to more in-depth, specialized reviews. While the focus of this article is on human research, in areas such as the brain localization of sexual function where little human data exist, we also briefly summarize the findings from the animal literature (for a more detailed review of the animal literature in this field, see Pfau3). One must, of course, exercise caution when extending animal findings to the complex experience of human sexual function.

Wherever possible in the present review, the effects of endocrine, neurotransmitter, and CNS influences are discussed separately as they pertain to the sexual response phases of desire, arousal, and orgasm (including ejaculation in males). This classification of sexual disorders draws heavily on Masters and Johnson’s Human Sexual Response2 model and Kaplan’s3 triphasic model of sexual response in which desire, arousal, and orgasm are conceptualized as distinct and sequential phases. In actual clinical practice, however, sexual desire, arousal, and orgasm difficulties more often than not coexist—suggesting an integration of phases, and desire does not necessarily precede arousal—arousal responses may also ignite desire (for a review of problems associated with this classification system in women, see Leiblum4).

STAGES OF HUMAN SEXUAL RESPONSE

Sexual desire is commonly defined as the broad interest in sexual objects or experiences. Because there is no objective physiological criterion for desire, it is generally inferred by self-reported frequency of sexual thoughts, fantasies, dreams, wishes, and interest in initiating and/or engaging
in sexual experiences. Definition of this construct is complicated by factors such as attitudes, opportunity and/or partner availability, mood, and health.

Intimately connected with sexual desire, sexual arousal is defined in both subjective (eg, feeling sexually excited) and physiological terms (eg, genital vasocongestion). Physiological sexual arousal in males involves the regulation of penile hemodynamics that is dependent on signal input from central and peripheral nervous systems, and on a complex interplay between neurotransmitters, vasoactive agents, and endocrine factors. Within the penile sinusoidal tissue is a central artery and veins that exit and drain the erectile bodies. The smooth muscles that line the sinusoidal spaces and the central artery are tonically contracted during the flaccid state. Erection begins with smooth muscle relaxation mediated by nonadrenergic-noncholinergic autonomic nerves that, together with the vascular endothelium, release nitric oxide (NO) into the corpus cavernosum of the penis. The second messenger, cyclic guanosine monophosphate (cGMP), mediates the effects of NO that causes smooth muscle relaxation. Smooth muscle relaxation reduces vascular resistance and the erectile bodies fill with blood. Once the erectile bodies become engorged, the emissary veins are compressed under the tough fibroelastic covering and blood is trapped in the penis. Normally, detumescence occurs with the release of catecholamines during orgasm and ejaculation. Activation of the sympathetic adrenergic nerves causes the release of noradrenaline, which acts on adrenergic receptors in the trabecular smooth muscle of the corpus cavernosum and in penile vessels. In addition to mediating detumescence, the sympathetic nervous system may play a role in maintaining a nonerect state. Centrally, penile erection is controlled by centers located in the thoracolumbar and lumbosacral regions of the spinal cord. Erections are elicited in a variety of physiological contexts via information sent from the periphery and supraspinal nuclei to these centers. The locus ceruleus (located in the pons) sends noradrenergic fibers to the forebrain and spinal cord, including those areas controlling erection (for a review of male sexual physiology, see Creed et al").

Physiological sexual arousal in women begins with increased clitoral length and diameter, and vasocongestion of the vagina, vulva, clitoris, uterus, and possibly the urethra. Comparable to the penis, the corpora cavernosa of the clitoris consist of a fibroelastic network and bundles of trabecular smooth muscle. Pelvic nerve stimulation results in clitoral smooth muscle relaxation and arterial smooth muscle dilation. With sexual arousal, there is an increase in clitoral cavernosal artery inflow and an increase in clitoral intracavernous pressure that leads to tumescence and extrusion of the clitoris. Engorgement of the genital vascular network increases pressure inside the vaginal capillaries and results in lubrication of the epithelial surface of the vaginal wall. The neurotransmitters that mediate clitoral and arterial smooth muscle dilation remain undetermined. Recent animal studies suggest that adrenergic nerves induce contraction and α-adrenergic receptors mediate contraction in both clitoral cavernosal and vaginal tissue (for a review of female sexual physiology, see Levin"). Preliminary studies suggest that NO may play an important role in relaxing clitoral corpus cavernosum smooth muscle, and vasoactive intestinal peptide may play an important role in the relaxation of vaginal tissue.

In males and females, orgasm is characterized by a peak in sexual pleasure that is accompanied by rhythmic contractions of the genital and reproductive organs, cardiovascular and respiratory changes, and a release of sexual tension. In men, during the emission stage of orgasm that is believed to be under throracolumbar control, seminal fluid is propelled into the bulbourethra via the release of norepinephrine that acts on α-adrenergic receptors, the smooth muscles of the vas deferens, prostate, and seminal vessels. During the ejaculatory phase, which is mediated by a sacral spinal reflex, semen is released through the urethra via contractions of the striated muscles that surround the bulbourethra. The extent to which central neurophysiological events are related to the intensity or experience of orgasm is unknown. While orgasm is generally the result of both genital and psychological stimulation, evidence suggests central stimulation alone may trigger orgasm.

**SEX RESEARCH METHODS**

Insight into the neurobiology of sexual function comes from 3 principal research methods: (1) animal studies, (2) human studies involving laboratory manipulations of sexual responding, and (3) clinical reports of sexual dysfunction secondary to drug treatment or disease. In male mammals, behavioral indexes of sexual initiation, maintenance, efficacy, ejaculation latency and intervals, and reinitiating mating after ejaculation serve as models for sexual interest, arousal, orgasm, and refractory periods, respectively, in human males. In female mammals, the most frequently studied sexual behavior is the lordosis response—a spinal reflex in response to a male’s attempt to mate. It is unclear how lordosis responding might reflect the human female sexual response, and whether it even provides an appropriate model for studying female sexuality. Other measures of sexual behavior in female mammals such as ear wiggling and rejection behaviors all reflect sexual interest or motivation. There is no appropriate animal model for female sexual arousal or orgasm. Also limiting the generalizability of animal studies is the fact that cognitive aspects of sexuality (eg, fantasy) are more likely to play an important role in human sexuality than in other species.

Laboratory studies of sexual responding focus primarily on sexual arousal. In males, erectile responses are most commonly measured in response to visual stimuli using a mechanical strain gauge that measures changes in penile tumescence via an increase in penile circumference. No information is provided regarding the firmness or rigidity of erection with this device. The device consists of 2 arcs of
surgical spring material with a pair of mechanical strain gauges at the junction. Increases in penile circumference cause a flexing of the gauges and a corresponding change in resistance. The device is simple to use, reliable, and relatively unobtrusive (for a review of the techniques used to measure male sexual arousal, see Rosen and Beck10).

Assessment of physiological sexual arousal in women relies primarily on indirect measurement of vaginal blood flow (direct assessment of vasocongestion is too invasive a technique to be used with human subjects) and includes vaginal photoplethysmography, indirect measures of heat dissipation, and pulsed wave Doppler ultrasonography. The most frequently studied of these techniques is vaginal photoplethysmography. The vaginal photoplethysmograph is a clear acrylic, tampon-shaped device that contains either an incandescent light source, or an infrared light-emitting diode as a light source and a photosensitive light detector. The light source illuminates the capillary bed of the vaginal wall, and the photo transistor detects the light that is reflected back from the vaginal wall and the blood circulating within it (for a review of the techniques used to measure female sexual arousal, see Meston11). A recurrent issue with this measurement technique in women is the low correlation between psychophysiological measures and verbal reports of sexual arousal (eg, Meston and Gorzalka12,13). This contrasts findings reported in men that usually indicate a high positive correspondence between penile photoplethysmography and subjective reports of sexual arousal. It is unclear whether this disynchrony between responses in women reflects an inability of women to detect subtle changes in vaginal blood flow, or whether women estimate the degree to which they are subjectively aroused according to standards other than genital blood flow changes. That is, for women, external stimuli information may play a more important role in assessing feelings of sexual arousal than do internal, physiological cues.

Until recently, laboratory studies of centrally mediated sexual behavior were limited by techniques that were either too crude or too invasive for use with humans. Consequently, most of our knowledge in this regard comes from animal studies. Functional brain imaging techniques such as positron emission tomography have only begun to be applied to the field of human sexuality.

Reports on the sexual consequences of pharmacological treatment or disease provide an indirect means for generating hypotheses about the pathways involved in human sexuality. This method is limited by a general lack of controlled inquiry, and the various concerns associated with self-report measures of sexuality (eg, response biases) (for review, see Meston et al14).

ENDOCRINE FACTORS

Androgens

In men, numerous studies have shown that withdrawal of exogenous testosterone in hypogonadal or castrated men causes a rapid and marked decrease in sexual interest and activity that is reinstated in a few weeks with testosterone replacement therapy.15-17 One study18 that differentiated between hypergonadotropic and hypogonadotropic hypogonadal males found long-term testosterone treatment to be more beneficial for enhancing the subjective quality of sexual acts, sexual excitement, and frequency of sexual thoughts among males with hypergonadotropic hypogonadism. In adolescent boys, levels of free testosterone have been shown to predict the frequency of sexual thoughts19,20 and monthly measures of salivary testosterone have been positively correlated with the initiation and rate of sexual intercourse.21 It is possible that in this latter study increased intercourse frequency may have caused the increase in the testosterone level. In normal adult males there exists wide individual variability in circulating testosterone levels that do not seem to be linked in any meaningful way with individual differences in levels of drive or sexual behavior.22 It is believed that the level of testosterone required for sexual interest and activity in adult males is lower than normal males’ circulating levels of testosterone. Consequently, variability in testosterone levels above this threshold level, or exogenously induced testosterone changes above this level, would not be expected to influence sexual interest or behavior.8 In aging males, androgen dehydroepiandrosterone has been publicized to increase sexual and overall well-being. Findings from a recent well-controlled, double-blind study, however, found only minimal beneficial effects on sexual function.23

Testosterone has been shown to restore nocturnal penile tumescence responses in hypogonadal men with impaired nocturnal penile tumescence.24 It is unclear whether testosterone also influences erectile responses to external stimuli. A recent study25 showed testosterone increased sexual arousal and enjoyment among hypogonadal and normal men, and had a positive effect on mood only among men with abnormally low testosterone levels. Other studies have found testosterone does not significantly influence erectile responses to erotic stimuli among hypogonadal men, nor do erectile responses differ significantly between hypogonadal and normal men.16,24,26 Among males with normal testosterone levels, testosterone has not been shown to facilitate erection.27

In an early study of women who had undergone bilateral oophorectomy and adrenalectomy,28 removal of the ovaries decreased sexual desire to a certain extent, but removal of the adrenal glands had an even more deleterious effect on sexual desire. The findings from this and similar studies conducted in patients with cancer29 and patients with polycystic ovaries30 are limited by the unique characteristics of the patients and by the anecdotal and uncontrolled nature of the reports.31 Studies of surgically menopausal women generally indicate that desire drops from presurgery levels32 and may be restored with exogenous administration of supraphysiological levels of testosterone with or without estradiol.33,34 Consistent with these findings, Sherwin35 found that sexual desire, arousal, and fantasies in oophorectomized women were higher among those...
women who had high vs low ratios of total testosterone-sex hormone–binding globulin. With natural menopause, androgen levels are positively correlated with sexual interest. 

Testosterone administration to female-to-male transsexuals and androgen deprivation in male-to-female transsexuals also support the notion that androgenic hormones play an important role in the sexual desire of males and females.

Studies on the relation between testosterone level and sexual desire in premenopausal, healthy women have rendered somewhat inconsistent results. Persky et al noted a relation between midcycle testosterone levels and intercourse frequency. Bancroft et al reported a relationship between testosterone levels and masturbation but not intercourse frequency, and Udry et al reported a relationship between testosterone levels and sexual interest among adolescents but found that peer relationships were a more important determinant of sexual behavior. Halpern et al also reported a significant relationship between adolescent females’ testosterone levels and initiation of coitus. While sexual desire is influenced by androgen levels in women, androgens alone are not sufficient for the experience of sexual desire. This is evident from studies that have failed to find significant differences in testosterone levels between women with and without clinically diagnosed hypoactive sexual desire disorder, and from studies that show androgen antagonists and oral contraceptives do not consistently suppress libido in women.

Testosterone treatment seems to be useful in facilitating sexual desire in a subset of women with hypoactive sexual desire, but it requires safety monitoring for potential lipoprotein changes, cardiovascular effects, and androgenic skin changes (eg, acne, hirsutism, or androgenic alopecia). With regard to testosterone’s affect on sexual arousal, Schreiner-Engel et al found higher levels of vaginal blood flow responses to erotic stimuli among women with high vs lower levels of circulating testosterone. Also using psychophysiological techniques, Meuwissen and Over failed to find menstrual cycle–related changes in physiological sexual arousal, and Schreiner-Engel et al found menstrual cycle–related changes in physiological sexual arousal unrelated to gonadal hormone variations. Two recent psychophysiological studies examined the effects of exogenous dehydroepiandrosterone administration on subjective and vaginal blood flow measures of sexual arousal in premenopausal and postmenopausal women. Neither study found a significant difference in physiological sexual arousal with acute dehydroepiandrosterone vs placebo administration. The study conducted in postmenopausal women did, however, note a significant increase in subjective ratings of sexual arousal with dehydroepiandrosterone administration.

**Estrogens**

Most research suggests that estrogens have little direct influence on sexual desire in either males or females. In men, relatively high levels of exogenous estrogen have been somewhat effective in inhibiting sexual desire among sex offenders and men who experience uncontrollable sexual urges. In women, some early studies have claimed that estrogen (especially estradiol) is important for normal sexual desire, but most researchers agree that estrogens play only a minimal role in female sexual desire. For example, Schreiner-Engel et al found no significant differences in estrogen levels between women with and without clinically diagnosed hypoactive sexual desire; Dennerstein et al found fluctuations in sexual desire across the menstrual cycle to be unrelated to estrogen levels; Alplanalp et al found no significant differences in estrogen levels between women with and without clinically diagnosed hypoactive sexual desire; Dennerstein et al found no significant differences in estrogen levels between women with and without clinically diagnosed hypoactive sexual desire; and consequently enhance sexual desire and satisfaction. Little research has examined the effects of progesterone on male sexuality. One early study noted a decrease in sexual “libido” in 4 men receiving intramuscular progesterone treatment, and other early studies have used progesterone treatment to reduce excessive sexual desire in men. To our knowledge, no controlled studies have been conducted on the relation between progesterone treatment and sexual desire in men.

Certain oral contraceptives that increase progesterone levels throughout the female cycle have been associated with decreased sexual interest and desire (but see also McCulloch et al) as have subfascially implanted progesterone pills that are used to treat various gynecological disorders. However, an early study by Bakke found estrogen and progesterone treatment enhanced sexual desire among hysterectomized, menopausal women to a greater extent than did estrogen alone. It is generally agreed on, however, that progesterone treatment does not have a substantial influence on the sexual desire of either premenopausal or postmenopausal women.

**Progesterone**

Men and women with abnormally high levels of prolactin frequently re-
port a decrease in sexual interest that is restored with bromocriptine treatment, a dopamine agonist that lowers prolactin levels. Other evidence for an inhibitory influence of prolactin on sexual desire in women comes from a limited number of studies that have found lactating women (who have naturally increased levels of prolactin) report decreased sexual desire compared with prepregnancy levels. Such findings could be the result of numerous other psychological factors associated with postpartum changes. Indeed, a number of studies have associated high levels of prolactin with mood disturbances including anxiety and depression (but see also Waterman and colleagues).

Prolactin's effect on other aspects of human sexual behavior remains equivocal. Erectile dysfunction has been described in men with abnormally high levels of prolactin, but has also been described in men with unusually low levels of prolactin, suggesting more than a simple inhibitory role of prolactin on erectile ability. In women, abnormally high levels of prolactin have been associated with amenorrhea, infertility, and decreased sexual activity (for review, see Muller et al). The affect of prolactin on sexual arousal may occur peripherally, centrally (given its ability to enter into cerebrospinal fluid), or via dopaminergic regulation. Animal studies indicate that prolactin has an overall inhibitory influence on male and, although less well documented, female sexual behavior, although short-term hyperprolactinemia seems to facilitate some aspects of sexual behavior in male rats (for review, see Drago).

A number of studies in human males have found prolactin levels to either decrease immediately following sexual arousal or to remain unchanged after film-induced sexual arousal, masturbation, or coitus. A number of methodological differences between studies such as the sexual stimuli used and the time point at which blood assays were taken could possibly explain these discrepant findings. Using a more precise continuous blood sampling and endocrine assessment technique, the prolactin level was shown to substantially increase during masturbation-induced sexual arousal in men. In women, Exton et al reported a significant and 2-fold increase in prolactin levels in women following orgasm that remained elevated when measured 60 minutes after sexual arousal.

Oxytocin

Circulating levels of the neuropeptide hormone oxytocin increase during sexual arousal and orgasm in both men and women. Using a continuous blood sampling technique and anal electromyography, Carmichael et al reported a positive correlation between oxytocin levels and the intensity, but not duration, of orgasmic contractions in males and females. For multiorgasmic women, the amount of oxytocin level increase also correlated positively with subjective reports of orgasm intensity. In a few case reports a synthetic form of oxytocin used to facilitate breastfeeding was linked to increased sexual desire and vaginal lubrication. A recent study conducted by Turner et al found a positive relationship between plasma oxytocin levels and measures of positive affect. To the extent that positive mood and sexual interest may be related, oxytocin may play an indirect role in sexual desire.

Most of what we know about the influence of oxytocin on sexual behavior, however, is based on animal studies. In male animals, oxytocin facilitates penile erections when injected into specific areas of the brain (e.g., periventricular nucleus of the hypothalamus), and shortens the ejaculation latency and postejaculation interval when injected either centrally or peripherally (for review see Carter). In female animals, oxytocin injected either centrally or peripherally has also been shown to facilitate sexual behavior, as measured by increases in lordosis responding. Perhaps the best-known roles of oxytocin are related to maternal behaviors, namely, parturition, milk ejection and lactation, and possibly maternal bonding.

Cortisol

Hypercortisolism, also known as Cushing syndrome, can produce a constellation of symptoms including depression, insomnia, and decreased libido in males and females. This syndrome is associated with increased corticotropin levels, and symptom severity is most severe when corticotropin and cortisol levels are high and less severe when cortisol levels are high but corticotropin levels are low. Some evidence suggests that this pattern of abnormal regulation of corticotropin and cortisol levels, and the resulting symptoms, may be the result of hypersecretion of corticotropin-releasing hormone. Depression, like Cushing syndrome, is associated with both overactivity of cortisol and loss of libido.

Blood cortisol levels, drawn continuously while subjects viewed an erotic film, did not significantly change in male and female subjects during either arousal or orgasm. Cortisol levels were higher in men with psychogenic erectile dysfunction who demonstrated a poor response to intracavernosal injection of a smooth muscle relaxant. These men also scored higher on measures of anxiety.

Pheromones

Pheromones are substances secreted from glands at the anus, urinary outlet, breasts, and mouth. In nonhuman mammals, a specialized olfactory structure, the vomeronasal organ, acts as the anatomic locus for pheromonal signals. The vomeronasal organ has been identified in humans, but, to date, there have been no human studies linking behavioral change and stimulation of vomeronasal organ receptors. Most of the research on pheromones and sexuality in hu-
mans has centered on female reproductive cycle influences. For example, menstrual synchrony has been demonstrated among women living together, and menstrual cycle regularity and increased estrogen levels during the luteal phase have been noted among women with frequent sexual exposure to men. In a recent double-blind, placebo-controlled study, Cutler et al reported that men exposed to a synthesized human male pheromone reported higher levels of sexual intercourse, sleeping with a romantic partner, and petting/affection/kissing, but no change in masturbation frequency. The authors interpreted these findings as evidence for male pheromones increasing the sexual attractiveness of men to women.

Table 1 summarizes the endocrine factors and sexual function in males and females.

NEUROTRANSMITTERS AND NEUROPEPTIDES

Nitric Oxide

Nitric oxide is an essential component in the production of penile, and possibly, clitoral vasocongestion and tumescence. Sexual stimulation leads to NO production that in turn stimulates the release of guanylate cyclase. Guanylate cyclase converts guanosine triphosphate to cGMP, which produces relaxation of the smooth muscles of the penile arteries and corpus cavernosum resulting in increased blood flow into the penis. Some evidence suggests that this may also occur in the clitoris. Immunohistochemical evaluation of the human clitoris revealed that NO is produced in this tissue and, with the exception that the clitoris does not contain a subalbuginal layer (which contributes to the rigidity of the penis), the anatomy of the clitoris is similar to that of the penis.

Normally, cGMP is metabolized by cyclic nucleotide phosphodiesterase isozymes into guanosine 5′-monophosphate. As long as sexual stimulation continues, cGMP production and metabolism remain balanced and penile or clitoral tumescence is sustained. Erectile dysfunction can result when this process is not working normally or when it is partially or completely disrupted. Sildenafil, a drug designed to treat erectile difficulties, prolongs the action of cGMP by inhibiting the metabolism of cGMP by phosphodiesterase type 5. Numerous well-controlled studies have reported that sildenafil is well tolerated and effective in alleviating erectile dysfunction resulting from organic, psychogenic, and mixed causes.

Sildenafil has not yet been approved for women by the Food and Drug Administration. Sildenafil is effective in inhibiting the metabolism of cGMP in clitorial tissue. Preliminary findings from a double-blind, placebo-controlled, 2-way crossover study showed a significant increase in vaginal pulse amplitude (i.e., a measure of moment-to-moment changes in vasocongestion) with a single dose of sildenafil citrate (50 mg) among 12 sexually functional women. Subjective reports of sexual arousal were not significantly altered with sildenafil treatment in this study. Some studies have found sildenafil treatment reverses antidepressant-induced sexual dysfunction in women. A recent 12-week study conducted internationally in 577 primarily premenopausal women with female sexual arousal dysfunction found 30% to 50% of the women taking sildenafil reported an increase in sexual function compared with 43% of the women who received placebo. In an open-label, nonrandomized 12-week study conducted among 33 sexually dysfunctional, postmenopausal women, receiving sildenafil showed a significant therapeutic response in only 6 women.

The Figure summarizes the process that leads to penile and clitoral tumescence.

Serotonin

A variety of psychoactive medications that affect serotonin activity produce sexual side effects, but many of these drugs are not specific to serotonin (e.g., monoamine oxidase inhibitors and atypical antipsychotics). Selective serotonin reuptake inhibitors (SSRIs), as the name indicates, act to specifically increase serotonin activity and they are also associated with sexual side effects such as decreased libido and impaired ejaculation (for review, see Rosen et al). Indeed, depending on the study, between 2% and 75% of patients prescribed SSRIs report sexual side effects that are often alleviated by reducing the dosage.

It is not known why SSRIs produce sexual side effects but some evidence suggests that activation of the serotonin2 receptor impairs sexual functioning and stimulation of the serotonin1A receptor facilitates sexual functioning. Cyproheptadine reduces activity at postsynaptic serotonin receptors such as the serotonin1 receptor and has been reported to reduce antidepressant-induced sexual side effects. Cyproheptadine also affects the activity of the other monoamines making it difficult to determine whether the reversal of sexual side effects results from activity on the serotonin receptors or on the receptors of other monoamines. Nefazodone is a selective serotonin reuptake inhibitor as well as a serotonin2 receptor antagonist and reportedly causes fewer sexual side effects compared with traditional SSRIs. It is believed that nefazodone produces both a reduction in number and a down-regulation of serotonin2 receptors as well as an up-regulation of serotonin1A receptors. Some evidence suggests that the serotonin1A agonist, buspirone, may be useful in reversing SSRIs-induced sexual dysfunction although findings as to its effectiveness have been mixed.

Studies conducted on male rats suggest that activation of some serotonin receptor subtypes facilitates sexual behavior while activation of other receptor subtypes inhibits sexual behavior. Specifically, activation of the serotonin1A receptor lowers the threshold for ejaculation and antagonism of the serotonin1B receptor inhibits sexual behaviors (such as mounting), while activation of the serotonin1B and serotonin1C receptors inhibits sexual behaviors.

A previous review of the human and animal literature suggests
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*Indicates increase; ↓, decrease; 0, no change; DHEA, dehydroepiandrosterone; ellipsis, not applicable; HRT, hormone replacement therapy; and ICI, intracavernous injection.
that some sexual side effects of SSRIs may result from serotonin’s actions in the periphery of the body rather than the CNS. Approximately 95% of serotonin receptors are located in the periphery of the body and peripheral serotonin acts on the smooth muscles of the vascular system to produce vasodilation and vasoconstriction, acts on the smooth muscles in the genitals, and is active in peripheral nerve functions including those of the sexual organs.

Recent studies indicate that SSRIs may be a useful treatment for premature ejaculation. Paroxetine, sertraline, and fluoxetine have all been found effective in increasing the latency to orgasm from less than 1 minute to between 2 and 6 minutes. The increase in ejaculation latency is dose dependent although at higher doses the likelihood of an ejaculation also increases. A study comparing men with ejaculation latencies of less than 1 minute to men with ejaculation latencies of greater than 1 minute found that paroxetine treatment increased the ejaculation latency 420% and 480%, respectively, suggesting that the paroxetine-induced delay in ejaculation is a function of baseline latency.

Side effects such as decreased libido, delayed orgasm, and anorgasmia have been reported with monoamine oxidase inhibitor and SSRI use in women. Women also experience lower rates of sexual dysfunction when taking nefazodone as compared with more traditional SSRIs such as paroxetine. Cyproheptadine, a serotonin, antagonist, has been effective in alleviating antidepressant-induced anorgasmia but can produce a reversal in depressive symptoms. A prospective study examining 344 male and female outpatients found that SSRI-induced sexual dysfunction was more severe in women than in men. Animal studies have conflicting findings with some studies reporting that serotonin antagonists and agonists inhibit lordosis in female rats but others report that serotonin agonists facilitate lordosis. Endogenous serotonin levels increase during proestrus, the time when female rats become sexually receptive.

**Dopamine**

Antiparkinsonian medications (eg, apomorphine hydrochloride, levodopa) act as dopamine agonists and have been reported to increase sexual desire (such cases occur in <1% of patients; for a thorough review of dopamine and sexual behavior, see Melis and Argiolas). Animal studies generally support this notion. Dopamine agonists, such as apomorphine, LY 163502, and RDS-127, increase mounting behavior and cause an increase in sexual behavior in sexually satiated male rats.

Several reports indicate that the parkinsonian medication, levodopa, produces erection. The D1 and D2 dopamine agonist, apomorphine facilitates erection in men with normal erectile capacity. As noted earlier, bromocriptine, which decreases prolactin levels and is also a long-acting dopamine agonist, facilitates erectile functioning. Antipsychotic medications, which tend to decrease dopaminergic activity, have been reported to both impair erection and produce prolonged erections (priapism). A dopamine-induced erection was antagonized by the antipsychotic, haloperidol, which antagonizes the D2 receptor. In male rats, the dopamine agonists apomorphine, LY 163502, and RDS-127, decrease the latency to ejaculation. The degree to which dopamine agonists affect sexual behavior seems to be dependent on both drug dose and the amount of time between drug introduction and behavioral observation, although small doses of dopamine agonists have been reported to delay ejaculation.

Few articles have reported the role of dopamine in female sexuality. An increase in sexual behavior has been noted in one isolated case report of a woman receiving a combination of levodopa and carbidopa treatment that increased dopamine activity. Delayed or inhibited orgasm in women has been associated with antipsychotic medications that decrease dopamine activity such as trifluoperazine hydrochloride, fluphenazine hydrochloride, and thioridazine hydrochloride. Findings from animal studies are conflicting with some studies indicating that dopaminergic activity facilitates lordosis responses while other studies reported that it inhibits lordosis. The contradictory findings could be explained by the fact that female rats differ in their response to dopamine depending on...
their degree of receptivity prior to manipulation of dopamine activity. That is, low doses of dopamine agonists facilitate receptivity in females with low receptivity while high doses inhibit receptivity in females exhibiting high receptivity.214

Cocaine enhances dopamine activity by blocking the presynaptic autoreceptor215 and cocaine is commonly believed to enhance sexual pleasure. Low doses of cocaine may enhance sexual enjoyment by stimulating the limbic system and by delaying ejaculation.216 Studies of cocaine addicts suggest that chronic cocaine use may impair sexual functioning. Thirty percent of male cocaine abusers reported that cocaine impaired ejaculation and 80% of female abusers reported that it reduced sexual enjoyment.217,218 High doses of cocaine may impair erectile capacity216 possibly as a result of the vasoconstrictive effects of cocaine.219 High doses of cocaine can produce anorgasmia and high doses and long-term use may also produce a reduction in sexual desire.216 Withdrawal from cocaine use can produce a temporary reduction in sexual desire220 that may be restored after 3 weeks of abstinence.221

Controlled studies of rats and nonhuman primates suggest that cocaine affects sexual functioning differently after short- vs long-term use. Acute cocaine administration in rats facilitates erection222,223 but also increases the number of mounts needed to ejaculate.224 After long-term (eg, 5 days) cocaine administration, cocaine no longer facilitated erection even after 1 week after termination of the drug.223,224 Short-term cocaine administration in nonhuman primates produced a dose-dependent delay in initiation of copulation and ejaculation225,226 and did not produce an increase in sexual activity.226 These effects were reversed by the D2 antagonist, haloperidol.226

### Epinephrine

In sexually functional men, the blood plasma epinephrine level shows a nonsignificant increase just prior to masturbation105 and urine levels of epinephrine remain unchanged after viewing an erotic film.100 Adrenergic activity plays a role in maintaining the penis in a flaccid state and in producing detumescence. α1-Adrenergic receptors have been found in human penile tissue and blockade of α1-adrenergic receptors produces an erection.9 Adrenergic systems are active in women as they become sexually aroused. The epinephrine and norepinephrine metabolite, vanillylmandelic acid, increases prior to intercourse and continues to be elevated over baseline up to 23 hours following sexual activity.227 Ephedrine, an α- and β-adrenergic agonist, has been shown to significantly increase vaginal pulse amplitude responses to an erotic videotape compared with placebo.228 Consistent with this finding, clonidine, an antihypertensive medication that blocks sympathetic nervous system (SNS) activation, significantly diminishes vaginal pulse amplitude responses to erotic stimuli compared with placebo under conditions of SNS arousal.229 Intense acute exercise known to significantly increase SNS activity, significantly increases vaginal pulse amplitude and vaginal blood volume responses to erotic stimuli in sexually functional women and women with hypoactive sexual desire disorder.230-232 Anorgasmic women showed an inhibition in physiological sexual arousal under conditions of SNS activation.232 Meston and Gorzalka230-232 suggested that there may be an optimal level of SNS activation for facilitation of female sexual arousal. Blood plasma levels of epinephrine have been shown to increase prior to viewing an erotic film, slowly increase during masturbation, peak at orgasm, and returned to baseline levels within 23 hours following sexual stimulation.233 Reports of decreased sexual arousal and orgasm in females taking antipsychotic medications (thioridazine and trifluoperazine),152 which act to suppress α1-adrenergic receptors,234 also provide evidence for a facilitatory influence of adrenergic activity in female sexual responding.

### Norepinephrine

Several studies examining blood plasma levels of norepinephrine (NE) indicate that NE levels increase during sexual activity. In men, blood plasma NE levels were positively correlated with arousal and erection during coitus and sexual activity and increased up to 12-fold at orgasm.235,236,237 Kruger et al238 reported that NE levels declined to baseline levels within 2 minutes of reaching orgasm. In contrast, NE urine levels did not significantly differ in 8 males 4 hours before and 4 hours after viewing a sexually explicit film.100 Given that Carani et al100 did not measure NE levels until 4 hours following sexual stimulation, it is feasible that NE levels did increase during sexual stimulation but were no longer detectable.

Studies reporting the effects of drugs that act on NE receptors further indicate that NE is important in sexual activity in men. As noted earlier, antidepressants such as SSRIs produce a whole host of sexual side effects151 and newer classes of antidepressants that act on NE neurotransmission have been found to produce fewer sexual side effects. For example, mirtazapine is a newly developed antidepressant that increases both serotonergic and noradrenergic activity and early reports suggest that rates of sexual dysfunction with mirtazapine are lower than placebo.236 Similarly, some evidence suggests that yohimbine, a drug that increases NE activity, may be useful in treating erectile dysfunction and anorgasmia.237-239

Studies suggest that NE is also active during the sexual response cycles of women. Blood plasma levels of NE increased during masturbation, peaked at orgasm, and slowly declined following orgasm in normally functioning women.95,235 This finding is consistent with that of a similar study that found that the levels of NE and epinephrine metabolite, vanillylmandelic acid, were elevated 1 hour prior to intercourse and continued to be elevated up to 23 hours after intercourse. Given that vanillylmandelic acid is a metabolite of both NE and epinephrine, it is unclear whether the elevations found resulted from increases in NE, epinephrine, or both.225 Yohimbine produced an increase in NE activity (as measured by levels of the NE metabolite 3-methoxy-4-hydroxyphenylglycol) in women...
with hypoactive sexual desire disorder, but did not significantly alter sexual drive. Furthermore, compared with normally functioning women, women with hypoactive sexual desire disorder did not differ in 3-methoxy-4-hydroxyphenylglycol levels.240

Opioids

Much of what is known about opioids’ role in the sexual response cycle comes from research on the effects of narcotics241,242 and agonists and antagonists of naturally occurring opioids such as endorphins, enkephalins, and dynorphins243 (for a thorough review of opioids and sex, see Pfaus and Gorzalka244). Indeed, it is well established that abuse of opioids leads to sexual difficulties.246 In men, long-term opioid use leads to loss of libido, erectile dysfunction, and when erection is present, inability to achieve orgasm. Long-term opioid use produces a decline in sexual functioning that typically follows a course from mild problems (eg, loss of interest in sex although performance is not impaired when sexual activity occurs) to complete loss of sexual functioning.246 One study examining the effects of intraspinal administration of opioids found that within 1 month of treatment initiation subjects experienced a reduction in libido and erectile difficulties.245 Withdrawal from opioid addiction is characterized by increased frequency of morning erections, spontaneous ejaculation (in the absence of sexual stimuli), and a slow return of sexual drive. Some men, however, experience a complete loss of ability to achieve erection and orgasm.244 Although the mechanism by which opiates affect sexual functioning is unclear, some evidence suggests that increased opioid activity produces a decrease in the levels of circulating hormones, such as luteinizing hormone and testosterone, and that it is the reduction in hormones that leads to sexual dysfunction.245,246

Opioid antagonists such as naloxone and naltrexone hydrochloride have been used to treat erectile dysfunction, but 2 case reports suggest that they may also be used to treat unwanted spontaneous erections.247 Naltrexone vs placebo significantly increased spontaneous erections, morning erections, and coitus in men with erectile failure248-250 and naloxone induced a partial erection in 3 of 6 men with normal erectile functioning.251 Men taking naltrexone did not differ in luteinizing hormone, follicle-stimulating hormone, prolactin, or testosterone.248,250 Some evidence suggests that naloxone administration may reduce the subjective pleasure experienced during arousal and orgasm.231

The role of endogenous opiates in normal sexual functioning is unclear. Two studies that compared blood plasma levels of β-endorphins in men as they viewed an erotic film vs a neutral film failed to find a statistically significant difference. In both studies, the β-endorphin levels were lower during the erotic film than during the neutral film.200,205 One of the studies examined β-endorphin levels during orgasm as well but also noted no significant change.205 A previous review of the literature examining male laboratory animals (eg, mice, rats, rabbits, dogs, monkeys, and chimpanzees) suggests that endogenous opiate levels may increase during sexual activity.244

Women who become addicted to narcotics, such as heroin, experience changes in sexual functioning including decreased libido, increased libido, anorgasmia, and a loss of libido during heroin withdrawal.244 In one isolated study, short-term administration of the opiate antagonist, naloxone, increased sexual desire in 1 of 4 women but did not affect vaginal lubrication in any of the subjects.251 Blood plasma levels of β-endorphins have not been shown to change during sexual arousal and orgasm in women95 and naloxone vs saline solution has not been effective in altering sexual arousal among women with sexual arousal disorder.252

Acetylcholine

Acetylcholine, together with vasoactive intestinal peptide, has been implicated in penile erection (for review, see Creed et al16). Erection occurs when the smooth muscles of the corpus cavernosum relax permitting increased blood flow into the penile tissue. The human corpus cavernosum is innervated by cholinergic nerves253 and contains cholinergic receptors254,255 suggesting endogenous cholinergic activity in the penile tissue. Furthermore, administration of exogenous acetylcholine chloride to precontracted corpus cavernosum tissue results in a relaxation of the smooth muscles.256 An in vitro study of the corpus cavernosal tissue of men with diabetes mellitus, a condition commonly associated with erectile dysfunction, suggests that acetylcholine-induced relaxation may be impaired in this group.257 The cholinergic agent bethanechol has been reported to be useful in reversing antidepressant-induced erectile and ejaculatory difficulties.258,259 In male rats, cholinergic agonists and antagonists reduced sexual activity while increased cholinergic activity led to more rapid ejaculation.260,261 Although cholinergic fibers may be present in the peripheral nervous system, evidence suggests that penile erection is controlled at the level of the brain and spinal cord.262

There is little mention in the literature of cholinergic involvement in vaginal vasocongestion. In 2 studies, atropine, an acetylcholine antagonist, was administered to women and no change was found in vasocongestion or orgasm.263,264

Histamine

A previous review of the literature265 cited a handful of case studies in men reporting loss of libido and erectile failure associated with the histamine2 (H2) antagonists, cimetidine hydrochloride and ranitidine hydrochloride. When histamine was injected into the corpus cavernosum, it produced full or partial erections in 74% of men with psychogenic impotence. Work with in vitro preparations suggests that the H2 and possibly H1 receptor may be involved.266 In one isolated case, a woman experienced loss of libido associated with cimetidine use.267 The sexual difficulties associated with H2 antagonists may result from a reduction in the uptake of testosterone.265

γ-Aminobutyric Acid

A previous review of the animal literature suggests that γ-aminobutyric acid (GABA) activity inhibits
male rat sexual behaviors including mounting, intromitting, erection, and ejaculation.166 As human males also engage in analogous behaviors, it is possible that GABA inhibits these behaviors in human males as well. To our knowledge, no studies have been published indicating the direct effects of GABA on human sexual behavior, or female rat sexual behavior (Table 2).

THE CNS

Brainstem Regions

The nucleus paragigantocellularis that projects directly to pelvic efferent neurons and interneurons in the lumbosacral spinal cord (the region whereby sexual afferents enter the spinal cord)207 has been identified as important in male, and possibly female, orgasm.208 Neurons in this area have been transneuronally labeled following virus injection into the penis269 and clitoris,270 and lesions to this area suppress a tonic inhibition of the climax-like response.267 Evidence suggests that this region may also play a role in SSRI-induced anorgasmia in males and females.268 The raphe nuclei pallidus, the magnus and parapyramidal region, and the locus ceruleus all project to the lumbosacral spinal cord and may play a role in sexual function. The periaqueductal gray area of the midbrain acts as a relay center for sexually relevant stimuli. Neurons in this region are labeled following viral injection into the penis, penile muscles, clitoris, and uterus.209-272

Hypothalamus

Animal studies indicate that lesions to the medial preoptic area, an area that has widespread connections to the limbic system and brainstem,273,274 significantly impairs male copulatory behavior275 by impairing the animal’s ability to recognize a sexual partner.268 In females, lesions to this area increase lordosis behavior but also increase avoidance of male partners, suggesting a role in mate selection rather than sexual motivation.268 Neurons in the paraventricular nucleus are activated during copulation in female rats276 and following genital stimulation in male rats;277 and electrical stimulation of the paraventricular nucleus elicits penile erections.278 The paraventricular nucleus is labeled after pseudorabies virus injection into the penis, penile muscles, clitoris, and uterus.260-272 During sexual arousal and orgasm, oxytocin from the paraventricular nucleus is secreted from the posterior pituitary into the blood stream in both sexes.279,280 As noted earlier, oxytocin injected into the CNS activates penile erections.113

Forebrain

Using Fos staining in copulatory tests, the medial amygdala and the bed nucleus of the stria terminalis have been identified as playing a role in female sexual behavior. The medial amygdala is believed to play a role in the control of sexual motivation in the male.275,283 Electrical stimulation of the hippocampus has been reported to elicit penile erections, and stimulation of the septal region has been associated with reports of orgasm. Interpretation of such findings are limited by the fact that patients were experiencing severe neurological and psychiatric conditions.

Electroencephalographic studies have shown a pattern of right temporal activation in right-handed men presented with visual sexual stimuli. Right-to-left hemispheric activity asymmetry was also noted during nocturnal penile tumescence. A study in right-handed men, using single photon emission computed tomography found an increase in right prefrontal cortex blood flow during orgasm. Hypersexuality has been associated with the bilateral removal of temporal lobes, and following frontal lobotomy. Recently, positron emission tomography was used to identify the brain areas activated in healthy males during visually evoked sexual arousal. Results indicated a 3-fold pattern of activation: the bilateral activation of the inferior temporal cortex (a visual association area), the activation of the right insula and right inferior frontal cortex (paralimbic areas relating highly processed sensory information with motivational states), and the activation of the left anterior cingulate cortex (a paralimbic area known to control autonomic and neuroendocrine function). To date, no similar studies have been conducted in females. For a recent and more in-depth review of the CNS control of sexual behavior, see McKenna.268

CONCLUSIONS

We attempted to provide a concise overview of the endocrine, neurotransmitter, and CNS influences on sexual desire, arousal, and orgasm in males and females. Because of an overall scarcity of human studies in this field, and the widely varying methodological quality of those studies available, in many areas of this review the evidence presented appears conflicting and/or incomplete, and we are able to generate only tentative hypotheses. While being cognizant of these limitations, we summarize the findings as follows.

A certain level of testosterone is necessary for sexual desire in males above which testosterone levels are unrelated to levels of sexual drive. Administration of testosterone above this level is ineffective in treating hypoactive sexual desire in men. Testosterone plays a role in nocturnal penile tumescence; whether it influences erectile responses to external stimuli is unclear. Testosterone is related to sexual desire in women but the relationship is not straightforward. Many women with hypoactive sexual desire have normal testosterone levels, some women with low testosterone levels have normal sexual drive, and a higher testosterone level is not usually associated with high libido. Exogenous testosterone treatment is effective for treating a subset of women with low libido—most of the research to this regard has focused on surgically menopausal women. Laboratory studies and studies of menstrual cycle changes have not consistently linked testosterone levels with sexual arousal in women. Estrogens and progesterone do not seem to play a significant role in sexual desire for either males or females. Estrogen deficiency impairs genital
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(Continued)
Table 2. Neurotransmitter (NT) Influences on Sexual Function in Males and Females (cont)

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<tr>
<th>Neurotransmitter</th>
<th>Males</th>
<th>Females</th>
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<td>Opioids</td>
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<td>Sexual desire</td>
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<td>Sexual arousal</td>
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*↑ indicates increase; ↓ decrease; ellipsis, not applicable; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; 0, no change; HSDD, hypoactive sexual desire disorder; and ED, erectile dysfunction.

Vasocongestion and lubrication in females and this may adversely influence sexual arousal and desire. Findings from uncontrolled studies and animal studies tentatively suggest prolactin may have an inhibitory influence on drive in males and females. Controlled human studies suggest the levels of prolactin and oxytocin increase during sexual arousal in men and women. Abnormally high levels of cortisol decrease sexual drive in men and women possibly owing to increased corticotropin-releasing hormone. Minimal research on pheromones and sexual response suggest a facilitatory influence on sexual attractiveness in men.

Nitric oxide (via the conversion of guanosine triphosphate to cGMP) is essential for penile and possibly clitoral vasocongestion. Sildenafil prolongs the action of cGMP and is effective in treating erectile dysfunction of organic, psychogenic, and mixed causes. Research on the effectiveness of sildenafil treatment for female sexual arousal disorder is under way. Findings from animal studies suggest serotonin may facilitate, inhibit, or have no effect on sexual behavior depending on which serotonin receptor subtype is involved. Studies on the effects of antidepressants on human sexual function suggest activation of the serotonin1 receptor impairs all stages of the sexual response in males and females. Case reports in males showing a facilitatory influence of antiparkinsonian medications (which enhance dopamine activity) and an inhibitory influence of antipsychotic medications (which suppress dopamine activity) on desire and erection argue for a facilitatory influence of dopamine on male sexual behavior. Research in male rats indicating dopamine facilitates sexual drive, erection, and ejaculation corroborates these human findings. Limited research conducted in females suggests a facilitatory role of dopamine on sexual desire and orgasm. Adrenergic activity (ephedrine) inhibits erectile responding in men and blockade of α1 receptors produces erection. In women, by contrast, adrenergic activation facilitates vasocongestion and suppression of adrenergic activity impairs sexual arousal and orgasm. Norepinephrine levels increase during sexual arousal in men and women. Minimal research suggests increasing the level of NE may facilitate erectile responding in men; comparable studies have not been conducted in women. Long-term opioid use impairs erection in men possibly via suppression of circulating hormones such as testosterone. Case reports indicate opioid antagonists may restore erectile functioning in dysfunctional men. Limited studies suggest opioids have an analogous effect in women. Acetylcholine facilitates penile erection via the relaxation of smooth muscles of the corpus cavernosum. The role of acetylcholine in female vasocongestion is unknown. Case studies suggest histamine facilitates erection in men with erectile failure. One comparable case study has been reported in women. The H2 and pos-
ibly H₂ receptors have been implicated. Animal studies indicate an inhibitory influence of GABA on male sexual responding. Studies examining the effects of GABA on human sexual behavior have not been conducted.

To date, only one study of neu-roanatomical activation in human brains following laboratory-evoked sexual arousal has been conducted. This study found sexual arousal in males to be associated with bilateral activation of the inferior temporal cortex, the right insular and inferior frontal cortex, and the left anterior cingulate cortex.

This review focused on the independent influences of endocrine, neurotransmitter, and CNS factors on sexual function. However, these systems also interact with one another to affect sexual functioning. For example, when the level of testosterone is increased in the medial preoptic area, it increases NO release that, in turn, facilitates dopamine release. If testosterone or NO release is disrupted, normal sexual behavior, resulting from dopamine release, is impaired in male rats. Similarly, increased prolactin activity results in decreased dopamine activity in the medial preoptic area and it has been suggested that prolactin antagonism of dopamine may be responsible for the refractory period in males. Serotonin administration to the lateral hypothalamic area produces a suppression of normal dopamine release in the nucleus accumbens of the male rat. A previous review of the male rat literature suggests contradictory evidence that gonadal hormones and serotonin interact to affect sexual functioning. Previous reviews of the female rat literature suggest that all lordosis-facilitating agents (e.g., α₁-adrenergic agonists) require initial estrogen priming to effectively produce the lordosis response and estrogen affects noradrenaline and serotonin turnover. To our knowledge, no studies have been published in the human literature examining the interaction between hormones, neurotransmitters, and neuropeptides.

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