The Neurobiology of Sexual Function

Cindy M. Meston, PhD; Penny F. Frohlich, MA

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. *Arch Gen Psychiatry. 2000;57:1012-1030*

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 sildenifil 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 Pfaus[1]). 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 Response*[2] model and Kaplan's[3] 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 Leiblum[4]).

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

From the Department of Psychology, University of Texas, Austin.

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.[5] 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 adrenoceptors 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[6]).

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[7]). 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.[8]

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 thoracolumbar control, seminal fluid is propelled into the bulbar urethra 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 bulbar urethra.[9] 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.[7]

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 Beck[10]).

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 Meston[11]). 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 Gorzalka[12,13]). 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 desynchrony 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 stimulus 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 al[14]).

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 study[18] 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 thoughts[19,20] 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.[9] 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 study[25] 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 cancer[29] and patients with polycystic ovaries[30] 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 levels[32] and may be restored with exogenous administration of supraphysiological levels of testosterone with or without estradiol.[33,34] Consistent with these findings, Sherwin[35] 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.[32,36] Testosterone administration to female-to-male transsexuals and androgen deprivation in male-to-female transsexuals[37] 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[38] noted a relation between midcycle testosterone levels and intercourse frequency. Bancroft et al[39] reported a relationship between testosterone levels and masturbation but not intercourse frequency, and Udry et al[40] 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[41] 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,[31,42] and from studies that show androgen antagonists and oral contraceptives do not consistently suppress libido in women.[43] 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).[43]

With regard to testosterone's affect on sexual arousal, Schreiner-Engel et al[44] 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[45] failed to find menstrual cycle–related changes in physiological sexual arousal, and Schreiner-Engel et al[46] 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[47] and postmenopausal[48] women. Neither study found a significant difference in physiological sexual arousal with acute dehydroepiandrosterone vs placebo administration. The study conducted in postmenopausal women[48] 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.[49-51] In women, some early studies have claimed that estrogen (especially estradiol) is important for normal sexual desire,[52] but most researchers agree that estrogens play only a minimal role in female sexual desire. For example, Schreiner-Engel et al[31] found no significant differences in estrogen levels between women with and without clinically diagnosed hypoactive sexual desire; Dennerstein et al[53] found fluctuations in sexual desire across the menstrual cycle to be unrelated to estrogen levels; Abplanalp et al[54] found no significant relationship between estradiol levels and enjoyment of heterosexual activity or number of heterosexual activities; and an abundance of studies have reported no change in sexual desire secondary to exogenous estrogenic compounds given to women with a variety of gynecological disorders[55-58] (but see also Dennerstein and Burrows[59]and Dennerstein et al[60]). Moreover, while administration of both estrogen and androgen to natural or surgically menopausal women has been shown to restore levels of sexual desire, estrogen treatments alone have generally not shown to be successful.[34,58]

Estrogen deficiency, as occurs with menopause, causes a decrease in genital vasocongestion and lubrication and atrophy of the vaginal epithelium. Such changes not only impair the physiological sexual arousal response in women and may cause dyspareunia (pain during intercourse), but can adversely influence the psychological experience of sexual arousal. Together with changes in mood that frequently accompany estrogen loss, these changes could be expected to indirectly impair sexual desire. In such cases estrogen replacement therapy has been shown to effectively restore vaginal lubrication and consequently enhance sexual desire and satisfaction.[61]

Progesterone

Little research has examined the effects of progesterone on male sexuality. One early study[62] noted a decrease in sexual "libido" in 4 men receiving intramuscular progesterone treatment, and other early studies[63] 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[64-66] (but see also McCullough[67]) as have subfascially implanted progesterone pills that are used to treat various gynecological disorders.[68] However, an early study by Bakke[69] 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[46,70,71] or postmenopausal[32,33,56,72-76] women.

Prolactin

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[77-82] (but see also Franks et al[83] and Koppelman et al[84]). It is unclear whether the reversal of sexual symptoms secondary to bromocriptine treatment is attributable to the lowering of serum prolactin levels, to the correction of hypothalamic dopaminergic dysregulation, or to an interaction between these 2 mechanisms.[85] 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.[86] Such findings could of course 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[79,87] (but see also Waterman et al[88]).

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,[89-92] but has also been described in men with unusually low levels of prolactin,[93] 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[94]). The affect of prolactin on sexual arousal may occur peripherally, centrally (given its ability to enter into cerebrospinal fluid), or via dopaminergic regulation.[95] 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[96]).

A number of studies in human males have found prolactin levels to either decrease immediately following sexual arousal,[97-99] or to remain unchanged after film-induced sexual arousal, masturbation, or coitus.[100-104] 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.[105] In women, Exton et al[95] 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.[106-109] Using a continuous blood sampling technique and anal electromyography, Carmichael et al[107] 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.[110,111] A recent study conducted by Turner et al[112] 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 (ie, periventricular nucleus of the hypothalamus), and shortens the ejaculation latency and postejaculation interval when injected either centrally or peripherally (for review see Carter[113]). In female animals, oxytocin injected either centrally or peripherally has also been shown to facilitate sexual behavior, as measured by increases in lordosis responding.[113] Perhaps the best-known roles of oxytocin are related to maternal behaviors, namely, parturition, milk ejection and lactation, and possibly maternal bonding.[113]

Cortisol

Hypercortisolism, also known as Cushing syndrome, can produce a constellation of symptoms including depression, insomnia, and decreased libido in males and females.[114-117] This syndrome is associated with increased corticotropin levels, and symptom severity is most severe when corticotropin and cortisol levels are high[114] and less severe when cortisol levels are high but corticotropin levels are low.[115] 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.[116-118]

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.[95,100,105,119,120] 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.[121]

Pheromones

Pheromones are substances secreted from glands at the anus, urinary outlet, breasts, and mouth.[122] 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,[123] 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,[124] and menstrual cycle regularity[125-127] and increased estrogen levels during the luteal phase[126,128] have been noted among women with frequent sexual exposure to men. In a recent double-blind, placebo-controlled study, Cutler et al[129] 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 and cGMP produces relaxation of the smooth muscles of the penile arteries and corpus cavernosum resulting in increased blood flow into the penis.[130,131] 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[132] and, with the exception that the clitoris does not contain a subalbugineal layer (which contributes to the rigidity of the penis), the anatomy of the clitoris is similar to that of the penis.[133]

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.[134,135] 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.[136] Numerous well-controlled studies have reported that sildenafil is well tolerated and effective in alleviating erectile dysfunction resulting from organic, psychogenic, and mixed causes.[137-143]

Sildenafil has not yet been approved for women by the Food and Drug Administration. Sildenafil is effective in inhibiting the metabolism of cGMP in clitoral tissue.[144] Preliminary findings from a double-blind, placebo-controlled, 2-way crossover study showed a significant increase in vaginal pulse amplitude (ie, 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.[145] Some studies have found sildenafil treatment reverses antidepressant-induced sexual dysfunction in women.[146-148] 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.[149] 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.[150]

The **Figure** summarizes 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 (eg, monoamine oxidase inhibitors and atypical antipsychotics).[151,152] 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[153]). Indeed, depending on the study, between 2% and 75% of patients prescribed SSRIs report sexual side effects[151,154-158] that are often alleviated by reducing the dosage.[159]

It is not known why SSRIs produce sexual side effects but some evidence suggests that activation of the serotonin$_2$ receptor impairs sexual functioning and stimulation of the serotonin$_{1A}$ receptor facilitates sexual functioning. Cyproheptadine reduces activity at postsynaptic serotonin receptors such as the serotonin$_2$ receptor and has been reported to reduce antidepressant-induced sexual side effects.[160] 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 serotonin$_2$ receptor antagonist[161] and reportedly causes fewer sexual side effects compared with traditional SSRIs.[154,158,162,163] It is believed that nefazodone produces both a reduction in number and a down-regulation of serotonin$_2$ receptors as well as an up-regulation of serotonin$_{1A}$ receptors.[161] Some evidence suggests that the serotonin$_{1A}$ agonist, buspirone, may be useful in reversing SSRI-induced sexual dysfunction[164] although findings as to its effectiveness have been mixed.[165]

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 serotonin$_{1A}$ receptor lowers the threshold for ejaculation and antagonism of the serotonin$_2$ receptor inhibits sexual behaviors (such as mounting), while activation of the serotonin$_{1B}$ and serotonin$_{1C}$ receptors inhibits sexual behaviors.[166]

A previous review of the human and animal literature suggests

Table 1. Endocrine Factors and Sexual Function in Males and Females*

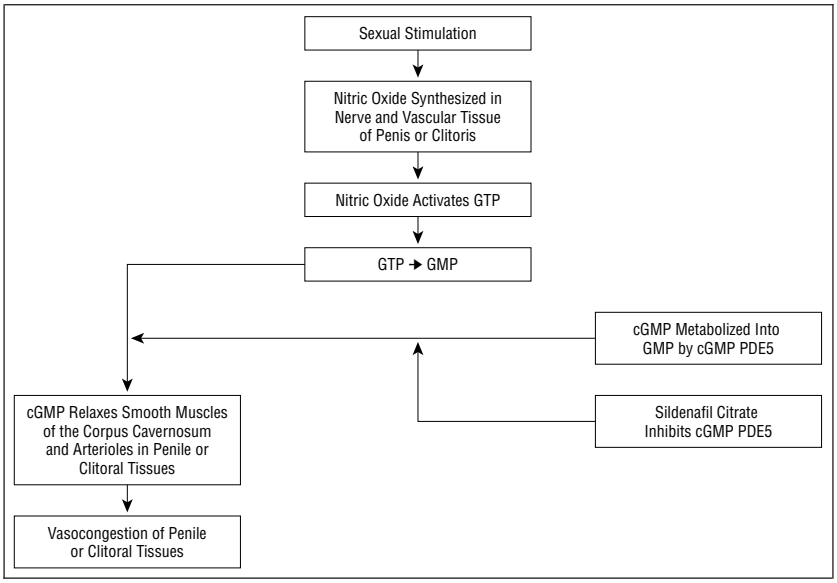
	Males			Females		
Hormone	Change in Hormone Level	Change in Sexual Functioning	Population Sampled/ Study Details	Change in Hormone Level	Change in Sexual Functioning	Population Sampled/ Study Details
Testosterone						
Sexual desire	↑	↑	Transexuals male → female[37]	↑	↑	Naturally menopausal[32,36]
	↑	↑	Hypogonadal or castrated[15-17]	↑	↑	Surgically menopausal[33,34]
	↑	↑	Adolescent boys[19,20]	↑	↑	Intercourse frequency in normal women[38]
	↑	0	Normal range testosterone levels[22]	↑	↑	Initiating intercourse in adolescent females[41]
	↓	↓	Hypogonadal or castrated[15-17]	↑	↑	Masturbation frequency in normal women[39]
	↑ (Chronic)	↑	Hypergonadotropic or hypergonadal[18]	↑	0	Intercourse frequency in normal women[39]
	↑ (DHEA)	0	Aging males[23]	↓	↓	Oophorectomy; adrenalectomy[28,32,35]
				↓	↓	Transexuals male → female[37]
				0	↑↓	Hypoactive sexual desire disorder vs normal no difference in testosterone levels[31,42]
Sexual arousal	↑	↑	Nocturnal penile tumescence—hypogonadal[24]	↑	↑	Vaginal blood flow in normal women[44]
	↑	0	Erotic stimuli—hypogonadal[16,24,26]	↑	↑	Subjective arousal to films with DHEA—postmenopausal[48]
	↑	↑	Erotic stimuli—hypogonadal or normal[25]	↑	0	Subjective arousal to films with DHEA—premenopausal[47]
				↑	0	Physiological arousal to films with DHEA—premenopausal and postmenopausal[47,48]
Estrogen						
Sexual desire	↑	0	Normal males[27]	↑	↑	Normal women[52]
	↑	↓	Sex offenders[49-51]	↑	0	Menopausal women[34,58]
				↑	0	Miscellaneous gynecological disorders[55-58]
				0	↑↓	Hypoactive sexual desire disorder vs normal[31]
Sexual arousal	. . .	. . .	. . .	↓	↓	Menopausal[61]
				↑	↑	HRT—menopausal[61]
Progesterone						
Sexual desire	↑	↓	Intramuscular injections in normal subjects[62]	↑	↓	Subfascially implanted progesterone pill users[68]
	↑	↓	Hyperactive sexual desire[63]	↑	↓	Contraceptive users[64-66]
				↑	↑	Hysterectomized, menopausal[69]
				↑	0	Premenopausal[46,70,71]
				↑	0	Postmenopausal[32,33,56,72-76]
Prolactin						
Sexual desire	↑	↓	Hyperprolactemia[77-82]	↑	↓	Hyperprolactemia[77-82]
	↓	↑	Bromocriptine treatment for hyperprolactemia[77-82]	↑	↓	Sexual activity in hyperprolactemia[94]
				↑	↓	Lactating women[86]
				↓	↑	Bromocriptine treatment for hyperprolactemia[77-82]
Sexual arousal	↑	↓	Hyperprolactemia[89-92]	. . .	. . .	. . .
	↑	↑	During masturbation[105]	. . .	. . .	. . .
	↓	↓	Hypoprolactemia[93]	. . .	. . .	. . .
	↓	↑	Postarousal from masturbation or coitus[97-99]	. . .	. . .	. . .
	0	↑	Postarousal from masturbation or coitus[100-104]	. . .	. . .	. . .
Orgasm	. . .	. . .		↑	↑	Following orgasm in normal women[95]
Oxytocin						
Sexual desire	. . .	. . .	. . .	↑	↑	Breast feeding[110,111]
Sexual arousal	↑	↑	Normal men[106-108]	↑	↑	Normal women[106-108]
				↑	↑	Breast feeding[110,111]
Orgasm	↑	↑	Normal men[106-108]	↑	↑	Normal women[106-108]
	↑	↑	Intensity of orgasm[107]	↑	↑	Intensity of orgasm[107]
Cortisol						
Sexual desire	↑	↓	Cushing syndrome[114-117]	↑	↓	Cushing syndrome[114-117]
Sexual arousal	0	↑	Normal men[100,105,119,120]	0	↑	Normal women[95,119]
	↑	↓	Psychogenic erectile dysfunction, poor responders to ICI[121]			
Orgasm	0	↑	Normal men[120]	0	↑	Normal women[95]
Pheromones						
Sexual attractiveness	↑	↑	Normal men[129]	. . .	. . .	. . .

*↑ *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.[167] 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[168-175] 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.[171] 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.[175]

Side effects such as decreased libido, delayed orgasm, and anorgasmia have been reported with monoamine oxidase inhibitor and SSRI use in women.[151,153,176] Women also experience lower rates of sexual dysfunction when taking nefazodone as compared with more traditional SSRIs such as paroxetine.[154,158,163] Cyproheptadine, a serotonin$_2$ antagonist, has been effective in alleviating antidepressant-induced anorgasmia[160] but can produce a reversal in depressive symptoms.[176] A prospective study examining 344 male and female outpatients found that SSRI-induced sexual dysfunction was more severe in women than in men.[155] Animal studies have conflicting findings with some studies reporting that serotonin antagonists and agonists inhibit lordosis in female rats[177-182] while others report that serotonin agonists facilitate lordosis.[183,184] Endogenous serotonin levels increase during proestrus, the time when female rats become sexually receptive.[185]



Sexual stimulation leads to the production of nitric oxide which in turn stimulates a cascade of events that, providing normal functioning, leads to penile and clitoral tumescence. Erectile dysfunction, and possibly female sexual arousal dysfunction, can be treated with a medication such as sildenafil (Viagra) that facilitates and/or prolongs penile or clitoral tumescence by inhibiting the metabolism of cyclic guanosine monophosphate (cGMP). GTP indicates guanosine triphosphate; PDE, phosphodiesterase; and PDE5, phosphodiesterase type 5.

Dopamine

Antiparkinsonian medications (eg, apomorphine hydrochloride, levodopa) act as dopamine agonists and have been reported to increase sexual desire[186,187] (such cases occur in <1% of patients[188]; for a thorough review of dopamine and sexual behavior, see Melis and Argiolas[189]). Animal studies generally support this notion. Dopamine agonists, such as apomorphine, LY 163502, and RDS-127, increase mounting behavior[190-192] and cause an increase in sexual behavior in sexually satiated male rats.[193]

Several reports indicate that the parkinsonian medication, levodopa, produces erection.[194-196] The D_1 and D_2 dopamine agonist, apomorphine facilitates erection in men with normal erectile capacity.[197-203] 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[204-205] and produce prolonged erections (priapism).[206-209] A dopamine-induced erection was antagonized by the antipsychotic, haloperidol, which antagonizes the D_2 receptor.[210] In male rats, the dopamine agonists apomorphine, LY 163502, and RDS-127, decrease the latency to ejaculation.[190-192] 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.[190,192]

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.[187] 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.[211-213] Findings from animal studies are conflicting with some studies indicating that dopaminergic activity facilitates lordosis responses while other studies reported that it inhibits lordosis.[214] 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 autoreceptor[215] 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 capacity[216] 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 desire[220] 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 erection[222,223] 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 ejaculation[225,226] and did not produce an increase in sexual activity.[226] These effects were reversed by the D_2 antagonist, haloperidol.[226]

Epinephrine

In sexually functional men, the blood plasma epinephrine level shows a nonsignificant increase just prior to masturbation[105] 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. α_1-Adrenergic receptors have been found in human penile tissue and blockade of α_1-adrenergic receptors produces an erection.[6]

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 stimulus 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 Gorzalka[230-232] 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 several minutes of orgasm.[95] Reports of decreased sexual arousal and orgasm in females taking antipsychotic medications (thioridazine and trifluoperazine),[151] which act to suppress α -adrenoreceptors,[233] 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 masturbation and sexual activity and increased up to 12-fold at orgasm.[105,234,235] Kruger et al[105] 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 al[100] 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 effects[151] 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.[227] 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 narcotics[241,242] and agonists and antagonists of naturally occurring opioids such as endorphins, enkephalins, and dynorphins[243] (for a thorough review of opioids and sex, see Pfaus and Gorzalka[244]). Indeed, it is well established that abuse of opioids leads to sexual difficulties.[242] 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.[244] 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 opiate 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 failure[248-250] and naloxone induced a partial erection in 3 of 6 men with normal erectile functioning.[251] Men taking naltrexone did not differ in luetinizing 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.[251]

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.[100,105] One of the studies examined β-endorphin levels during orgasm as well but also noted no significant change.[105] 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 women[95] 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 al[6]). 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 nerves[253] and contains cholinergic receptors[254,255] 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 ejaculation 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 literature[265] cited a handful of case studies in men reporting loss of libido and erectile failure associated with the histamine$_2$ (H_2) 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 H_2 and possibly H_3 receptor may be involved.[266] In one isolated case, a woman experienced loss of libido associated with cimetidine use.[265] The sexual difficulties associated with H_2 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)[267] has been identified as important in male, and possibly female, orgasm.[268] Neurons in this area have been transneuronally labeled following virus injection into the penis[269] 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.[268] 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.[269-272]

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 behavior[275] 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 rats[276] 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.[269-272] 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.[112,281,282] 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,[284,285] 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.[286,287] Right-to-left hemispheric activity asymmetry was also note during nocturnal penile tumescence.[288] A study in right-handed men, using single photon emission computed tomography found an increase in right prefrontal cortex blood flow during orgasm.[289] Hypersexuality has been associated with the bilateral removal of temporal lobes,[290] and following frontal lobotomy.[291] Recently, positron emission tomography was used to identify the brain areas activated in healthy males during visually evoked sexual arousal.[292] 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).[292] 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

Table 2. Neurotransmitter (NT) Influences on Sexual Function in Males and Females

	Males			Females		
Neurotransmitter	Change in NT Level	Change in Sexual Functioning	Population Sampled/ Study Details	Change in NT Level	Change in Sexual Functioning	Population Sampled/ Study Details
Serotonin						
Sexual arousal	↑	↓	MAOI, SSRI, antipsychotic users[151-158]	↑	↓	MAOI, SSRI users[151,153]
	↓	↑	Cyproheptadine hydrochloride with antidepressants[160]			
Sexual arousal	↑	↓	Antipsychotic users[151,152]			
Orgasm	↑	↓	MAOI, SSRI, antipsychotic users[151,158]	↑	↓	MAOI, SSRI users[151,153]
	↓	↑	Cyproheptadine with antidepressants[160]	↑	↑	Cyproheptadine with antidepressants[160]
	↑	↓	SSRIs as a treatment for premature ejaculation[168-175]	. . .	. . .	. . .
Dopamine						
Sexual desire	↑	↑	Apomorphine hydrochloride/levodopa—patients with Parkinson disease[186-188]	↑	↑	Levodopa/carbidopa—patients with Parkinson disease (case study)[187]
Sexual arousal	↑	↑	Apomorphine/levodopa—Parkinson disease[194-196]	. . .	. . .	. . .
	↑	↑	Apomorphine treatment—erectile failure[202-203]	. . .	. . .	. . .
	↓	↑	Antipsychotic medication users[206-209]	. . .	. . .	. . .
	↓	↓	Antipsychotic medication users[204-205]	. . .	. . .	. . .
	↑	↓	Chronic cocaine user[216]	. . .	. . .	. . .
Orgasm	↑	↓	High doses and chronic cocaine user[216]	↑	↓	Antipsychotic medication users[211-213]
Adrenaline						
Sexual desire	. . .	. . .	. . .	↑	↑	Normal[95]
Sexual arousal	↑	↓	Sexually functional[6]	↑	↑	Normal[95,227,228]
	0	↑	Viewing an erotic film[100]	↑	↓	Heightened nervous system arousal—(normal and HSDD)[230-232]
				↑	↓	Heightened nervous system arousal—(anorgasmic women)[232]
				↑	↓	Heightened nervous system arousal[232]
				↓	↓	Clonidine user with heightened nervous system arousal[229]
				↓	↓	Antipsychotic treatment[151]
Orgasm	. . .	. . .	. . .	↑	↑	Normal[95]
				↓	↓	Antipsychotic treatment[151]
Norepinephrine						
Sexual drive	. . .	. . .	. . .	↑	0	Hypoactive sexual desire disorder[240]
Sexual arousal	↑	↑	Normal[105,234,235]	↑	↑	Normal[95,235]
	↑	↑	Yohimbine treatment for ED[237-239]			
Orgasm	↑	↑	Normal[105,234,235]	↑	↑	Normal[95,235]
	↑	↑	Yohimbine treatment for anorgasmia[237-239]			
Acetylcholine						
Sexual arousal	↑	↑	Precontracted corpus cavernosum tissue[256]	↓	0	Atropine administration to normal women[263]
	↑	0	Corpus cavernosum of men with diabetes mellitus[257]			
	↑	↑	Bethanechol for antidepressant induced erectile dysfunction[258,259]			
Orgasm	↑	↑	Bethanechol chloride for antidepressant-induced ED[258,259]	↓	0	Atropine administration to normal women[263]
Histamine						
Sexual desire	↓	↓	Cimetidine and ranitidine users[265]	↓	↓	Cimetidine user (case study)[265]
Sexual arousal	↑	↑	Injection into corpus cavernosum—psychogenic impotence[266]	. . .	. . .	
	↓	↓	Cimetidine and ranitidine users[265]	. . .	. . .	. . .

(Continued)

Table 2. Neurotransmitter (NT) Influences on Sexual Function in Males and Females (cont)

	Males			Females		
Neurotransmitter	Change in NT Level	Change in Sexual Functioning	Population Sampled/ Study Details	Change in NT Level	Change in Sexual Functioning	Population Sampled/ Study Details
Opioids						
Sexual desire	↑	↓	Long-term opiod users[244]	↑	↓	Long-term opiod users[244]
	↑	↓	Intraspinal injections[245]	↑	↑	Long-term opiod users[244]
	↓	↑	Withdrawal from opiate addiction[244]	↓	↓	Withdrawal from opiate addiction[244]
				↓	↑	Naloxone hydrochloride users (1 in 4 women)[251]
Sexual arousal	↑	↓	Long-term opiod users[244]	↓	0	Naloxone users[251]
	↑	↓	Intraspinal injections[245]	↓	0	Naloxone treatment for arousal disorder[252]
	↓	↑	Withdrawal from opiate addiction[244]	0	↑	Blood plasma level while viewing an erotic film[95]
	↓	↓	Withdrawal from opiate addiction[244]	. . .	. . .	. . .
	↓	↑	Naltrexone treatment[247]	. . .	. . .	. . .
	↓	↑	Naltrexone treatment for erectile failure[248-250]	. . .	. . .	. . .
	↓	↑	Naloxone in men with normal erectile functioning[251]	. . .	. . .	. . .
	0	↑	Blood plasma level while viewing an erotic film[100,105]	. . .	. . .	. . .
Orgasm	↑	↓	Long-term opiod users[244]	↑	↓	Long-term opiod users[244]
	↓	↑	Withdrawal from opiate addiction[244]	0	↑	Blood plasma level while viewing an erotic film[95]
	↓	↓	Withdrawal from opiate addiction[244]	. . .	. . .	. . .
	0	↑	Blood plasma level while viewing an erotic film[105]	. . .	. . .	. . .

*↑ *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 serotonin$_2$ 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 α_1-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 H_2 and pos-

sibly H_3 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 neuroanatomical 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.[293] Similarly, increased prolactin activity results in decreased dopamine activity in the medial preoptic area[294] and it has been suggested that prolactin antagonism of dopamine may be responsible for the refractory period in males.[295] Serotonin administration to the lateral hypothalamic area produces a suppression of normal dopamine release in the nucleus accumbens of the male rat.[296] A previous review of the male rat literature suggests contradictory evidence that gonodal hormones and serotonin interact to affect sexual functioning.[166] Previous reviews of the female rat literature suggest that all lordosis-facilitating agents (eg, α_1-adrenergic agonists) require initial estrogen priming to effectively produce the lordosis response and estrogen affects noradrenaline and serotonin turnover.[297,298] To our knowledge, no studies have been published in the human literature examining the interaction between hormones, neurotransmitters, and neuropeptides.

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Corresponding author: Cindy M. Meston, PhD, University of Texas at Austin, Department of Psychology, Mezes Hall 330, Austin, TX 78712.

REFERENCES

1. Pfaus JG. Neurobiology of sexual behavior. *Curr Opin Neurobiol.* 1999;9:751-758.
2. Masters WH, Johnson VE. *Human Sexual Response.* Boston, Mass: Little Brown & Co Inc; 1966.
3. Kaplan HS. *Disorders of Sexual Desire.* New York, NY: Brunner/Mazel Inc; 1979.
4. Leiblum SR. Definition and classification of female sexual disorders. *Int J Impot Res.* 1998; 10(suppl 2):S104-S106.
5. Kloner RA, Jarow JP. Erectile dysfunction and sildenafil citrate and cardiologists. *Am J Cardiol.* 1999;83:576-582.
6. Creed KE, Carati CJ, Keogh EJ. The physiology of penile erection. *Rev Reprod Biol.* 1991;13: 73-95.
7. Levin RJ. The mechanisms of human female sexual arousal. *Annu Rev Sex Res.* 1992;3:1-48.
8. Kim N. Regulation of smooth muscle contractility: organ bath studies. Paper presented at: Boston University School of Medicine and the Department of Urology Conference: New Perspectives in the Management of Female Sexual Dysfunction; October 23, 1998; Burlington, Mass.
9. Schiavi RC, Segraves RT. The biology of sexual function. *Psychiatr Clin North Am.* 1995;18:7-23.
10. Rosen RC, Beck JG. *Patterns of Sexual Arousal: Psychophysiological Processes and Clinical Applications.* New York, NY: Guilford Press; 1988.
11. Meston CM. The psychophysiological assessment of female sexual function. *J Sex Educ Ther.* 2000;25:6-16.
12. Meston CM, Gorzalka BB. The effects of sympathetic activation on physiological and subjective sexual arousal in women. *Behav Res Ther.* 1995;33:651-664.
13. Meston CM, Gorzalka BB. The differential effects of sympathetic activation on sexual arousal in sexually functional and dysfunctional women. *J Abnorm Psychol.* 1996;105:582-591.
14. Meston CM, Heiman JR, Trapnell PD, Paulhus DL. Socially desirable responding and sexuality self-reports. *J Sex Res.* 1998;35:148-157.
15. Davidson JM, Kwan M, Greenleaf WJ. Hormonal replacement and sexuality. *Clin Endocrinol Metab.* 1982;11:599-623.
16. Kwan M, Greenleaf WJ, Mann J, Crapo L, Davidson JM. The nature of androgen action on male sexuality: a combined laboratory/self-report study on hypogonadal men. *Clin Endocrinol Metab.* 1983;57:557-562.
17. Skakkeoaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonodal men: a double-blind controlled study. *Clin Endocrinol.* 1981;14:49-61.
18. Gooren L. Hypogonadotropic hypogonadal men respond less well to androgen substitution treatment than hypergonadotropic hypogonadal men. *Arch Sex Behav.* 1988;17:265-270.
19. Halpern CT, Udry JR, Campbell B, Suchindran C, Mason GA. Testosterone and religiosity as predictors of sexual attitudes and activity among adolescent males: a biosocial model. *J Biosoc Sci.* 1994;26:217-234.
20. Udry JR, Billy JO, Morris NM, Groff TR, Raj MH. Serum androgenic hormones motivate sexual behavior in adolescent boys. *Fertil Steril.* 1985;43: 90-94.
21. Halpern CR, Udry JR, Suchindran C. Monthly measures of salivary testosterone predict sexual activity in adolescent males. *Arch Sex Behav.* 1998;27:445-465.
22. Schiavi RC, White D. Androgen and male sexual function: A review of human studies. *J Sex Marital Ther.* 1976;2:214-228.
23. Flynn MA, Weaver-Osterholtz D, Sharpe-Timms KL, Allen S, Krause G. Dehydroepiandrosterone replacement in aging humans. *J Clin Endocrinol Metab.* 1999;84:1527-1533.
24. O'Carroll R, Shapiro C, Bancroft J. Androgens, behavior and nocturnal erection in hypogonadal men: the effects of varying the replacement dose. *Clin Endocrinol.* 1985;23:527-538.
25. Alexander GM, Swerdloff RS, Wang CW, Davidson T. Androgen-behavior correlations in hypogonadal men and eugonadal men, I: mood and response to auditory sexual stimuli. *Horm Behav.* 1997;31:110-119.
26. Bancroft J, Wu FCW. Changes in erectile responsiveness during androgen replacement therapy. *Arch Sex Behav.* 1983;12:59-66.
27. O'Carroll RE, Bancroft J. Testosterone therapy for low sexual interest and erectile dysfunction in men: a controlled study. *Br J Psychiatry.* 1984; 145:146-151.
28. Waxenberg SE, Drellich MG, Sutherland AM. The role of hormones in human behavior, I: changes in female sexuality after adrenalectomy. *J Clin Endocrinol.* 1959;19:193-202.
29. Drellich MG, Waxenberg SE. Erotic and affectional components of female sexuality. In: Masserman J, ed. *Science and Psychoanalysis.* New York, NY: Grune & Stratton Inc; 1966:192-217.
30. Gorzynski G, Katz JL. The polycystic ovary syndrome: psychosexual correlates. *Arch Sex Behav.* 1977;6:215-222.
31. Schreiner-Engel P, Schiavi RC, White D, Ghizzani A. Low sexual desire in women: the role of reproductive hormones. *Horm Behav.* 1989;23: 221-234.
32. Leiblum S, Bachmann G, Kemmann E, Colburn D, Schwartzman L. Vaginal atrophy in the postmenopausal woman: the importance of sexual activity and hormones. *JAMA.* 1983;249:2195-2198.
33. Sherwin BB. Changes in sexual behavioral as a function of plasma sex steroid levels in postmenopausal women. *Maturitas.* 1985;7:225-233.
34. Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. *Psychosom Med.* 1985;47:339-351.
35. Sherwin BB. The free testosterone index as a predictor of sexual behavior in postmenopausal women receiving hormone replacement therapy [abstract]. In: Program and abstracts of the Seventh Conference of the Society for Menstrual Cycle Research; 1987; Ann Arbor, Mich. Abstract.
36. McCoy N, Davidson JM. A longitudinal study of the effects of menopause on sexuality. *Maturitas.* 1985;7:203-210.
37. Van Goozen SHM, Frijda NH, Wiegant VM, Endert E, Van de Poll NE. The premenstrual phase and reactions to aversive events: a study of hormonal influences on emotionality. *Psychoneuroendocrinology.* 1996;21:479-497.

38. Persky H, Lief HI, Strauss D, Miller WR, O'Brien CP. Plasma testosterone level and sexual behavior in couples. *Arch Sex Behav.* 1978;7:157-173.
39. Bancroft J, Sanders D, Davidson D, Warner P. Mood, sexuality, hormones, and the menstrual cycle; III: sexuality and the role of androgens. *Psychosom Med.* 1983;45:509-516.
40. Udry JR, Talbert LM, Morris NM. Biosocial foundations for adolescent female sexuality. *Demography.* 1986;23:217-230.
41. Halpern CT, Udry JR, Suchindran C. Testosterone predicts initiation of coitus in adolescent females. *Psychosom Med.* 1997;59:161-171.
42. Stuart FM, Hammond DC, Pett MA. Inhibited sexual desire in women. *Arch Sex Behav.* 1987; 16:91-106.
43. Redmond G. Testosterone and female sexual dysfunction. Paper presented at: Boston University School of Medicine and the Department of Urology Conference: New Perspectives in the Management of Female Sexual Dysfunction; October 23, 1998; Burlington, Mass.
44. Schreiner-Engel P, Schiavi RC, Smith H, White D. Sexology: sexual biology, behavior and therapy. In: Hoch Z and Lief HI, eds. *Selected Papers Of The Fifth World Congress Of Sexology.* Amsterdam, the Netherlands: Exerpta Medica; 1982:88-92. 1982:165.
45. Meuwissen I, Over R. Sexual arousal across phases of the human menstrual cycle. *Arch Sex Behav.* 1992;21:101-119.
46. Schreiner-Engel P, Schiavi RC, Smith J, White D. Sexual arousability and the menstrual cycle. *Psychosom Med.* 1981;43:199-214.
47. Meston CM, Heiman JR. Acute DHEA effects on sexual arousal in premenopausal women. *J Sex Marital Ther.* In press.
48. Hackbert L, Heiman JR, Meston CM. The effects of DHEA on sexual arousal in postmenopausal women. Paper presented at: Annual Meeting of the International Academy of Sex Research; June 24, 1998; Stony Brook, NY.
49. Bancroft J, Tennent G, Loucas K, Cass J. The control of deviant sexual behavior by drugs, I: behavioral changes following oestrogens and antiandrogens. *Br J Psychiatry.* 1974;125:310-315.
50. Cooper AJ. Progestogen in the treatment of male sex offenders: a review. *Can J Psychiatry.* 1986; 31:73-79.
51. Field LH, Williams M. The hormonal treatment of sexual offenders. *Med Sci Law.* 1970;10:27-34.
52. Benedek T, Rubenstein BB. The correlations between ovarian activity and psychodynamic processes, II: the menstrual phase. *Psychosom Med.* 1939;1:461-485.
53. Dennerstein L, Gotts G, Brown JB, Morse CA, Farley TM, Pinol A. The relationship between the menstrual cycle and female sexual interest in women with PMS complaints and volunteers. *Psychoneuroendocrinology.* 1994;19:293-304.
54. Abplanalp JM, Rose RM, Donnelly AF, Livingstone-Vaughan L. Psycho-endocrinology of the menstrual cycle, II: the relationship between enjoyment of activities, moods and reproductive hormones. *Psychosom Med.* 1979;41:605-615.
55. Burger HG, Hailes J, Menelaus M, Nelson J, Hudson B, Balazs N. The management of persistent menopausal symptoms with oestradiol-testosterone implants: clinical, lipid and hormonal results. *Maturitas.* 1984;6:351-358.
56. Furuhjelm M, Karlgren E, Carlstrom K. The effect of estrogen therapy on somatic and psychical symptoms in postmenopausal women. *Acta Obstet Gynecol Scand.* 1984;63:655-661.
57. Nathorst-Boos J, von Schoultz B, Carlstrom K. Elective ovarian removal and estrogen replacement therapy: effects on sexual life, psychological well-being and androgen status. *J Psychosom Obstet Gynaecol.* 1993;14:283-293.
58. Salmon UJ, Geist SH. Effect of androgens upon libido in women. *J Clin Endocrinol.* 1943;3:235-238.
59. Dennerstein L, Burrows GD. Hormone replacement therapy and sexuality in women. *Clin Endocrinol Metab.* 1982;11:661-679.
60. Dennerstein L, Burrows GD, Wood C, Hyman G. The effect of estrogen and progestogen. *Obstet Gynecol.* 1980;56:316-322.
61. Sherwin B. The psychoendocrinology of aging and female sexuality. *Annu Rev Sex Res.* 1991; 2:181-198.
62. Heller CG, Laidlaw WM, Harvey HT, Nelson WO. Effects of progestational compounds on the reproductive processes of the human male. *Ann N Y Acad Sci.* 1958;71:649-665.
63. Money J. Use of an androgen-depleting hormone in the treatment of male sex offenders. *J Sex Res.* 1970;6:165-172.
64. Huffer V, Levin L, Aronson H. Oral contraceptives: depression and frigidity. *J Nerv Ment Dis.* 1970;151:35-41.
65. Kane FJ, Lipton MA, Ewing JA. Hormonal influences in female sexual response. *Arch Gen Psychiatry.* 1979;20:202-209.
66. Warner P, Bancroft J. Mood, sexuality, oral contraceptives and the menstrual cycle. *J Psychosom Res.* 1988;32:417-427.
67. McCullough RC. Rhythms of sexual desire and sexual activity in the human female [abstract]. *Dissertation Abstracts Int.* 1974;34:4669B-4670B.
68. Greenblatt RB, Mortara F, Torpin R. Sexual libido in the female. *Am J Obstet Gynecol.* 1942; 44:658-663.
69. Bakke J. A double-blind study of a progestin-estrogen combination in the management of the menopause. *Pacific Med Surg.* 1965;73:200-205.
70. Persky J, O'Brien CP, Kahn MA. Reproductive hormone levels, sexual activity and moods during the menstrual cycle. *Psychosom Med.* 1976; 38:62-63.
71. Persky H, Charney N, Lief HL, O'Brien CP, Miller WR, Strauss D. The relationship of plasma estradiol level to sexual behavior in young women. *Psychosom Med.* 1978;40:523-535.
72. Utian WH. The true clinical features of postmenopause and oophorectomy and their response to oestrogen therapy. *S Afr Med J.* 1972; 46:732-737.
73. Campbell S. Double-blind psychometric studies on the effects of natural estrogens on postmenopausal women. In: Campbell S, ed. *The Management of the Menopausal and Post-Menopausal Years.* Baltimore, Md: University Park Press; 1976:149-158.
74. Coope J. Double-blind cross-over study of estrogen replacement. In: Campbell S, ed. *The Management of the Menopausal and Post-Menopausal Years.* Baltimore, Md: University Park Press; 1976:159-168.
75. Campbell S, Whitehead M. Oestrogen therapy and the menopausal syndrome. *Clin Obstet Gynecol.* 1977;4:31-47.
76. Studd JWW, Collins WP, Chakravarti S, Newton JR, Oram D, Parsons A. Oestradiol and testosterone implants in the treatment of psychosexual problems in the postmenopausal woman. *Br J Obstet Gynaecol.* 1977;84:314-315.
77. Bancroft J. Hormones and human sexual behavior. *J Sex Martial Ther.* 1984;10:3-21.
78. Bancroft J, O'Carroll R, McNeilly A, Shaw R. The effects of bromocriptine on the sexual behavior of a hyperprolactinaemic man: a controlled case study. *Br J Psychiatry.* 1984;21:131-137.
79. Buckman MT, Kellner R. Reduction of distress in hyperprolactinemia with bromocriptine. *Am J Psychiatry.* 1984;6:351-358.
80. Dornan WA, Malsbury CW. Neuropeptides and male sexual behavior. *Neurosci Biobehav Rev.* 1989;13:1-15.
81. Muller P, Musch K, Wolf AS. Prolactin: variables of personality and sexual behavior. In: Zichella L, Pancheri P, eds. *Psychoneuroendocrinology in Reproduction.* Amsterdam, the Netherlands: Elsevier/North Holland Biomedical Press; 1979:357-372.
82. Schwartz MF, Bauman JE, Masters WH. Hyperprolactinemia and sexual disorders in men. *Biol Psychiatry.* 1982;17:861-876.
83. Franks S, Jacobs HS, Martin N, Nabarro JDN. Hyperprolactinaemia and impotence. *Clin Endocrinol.* 1978;8:277-287.
84. Koppelman MCS, Parry BL, Hamilton JA, Alagna SW, Loriaux DL. Effect of bromocriptine on mood, affect and libido in hyperprolactinemia. *Am J Psychiatry.* 1987;144:1037-1041.
85. Gooren L. Preliminary evidence that not prolactin itself, but the underlying dopaminergic dysregulation causes male sexual dysfunction in the cases of hyperprolactinemia. Paper presented at: International Academy of Sex Research, August 16, 1986; Amsterdam, the Netherlands.
86. Kayner CE, Zager JA. Breast-feeding and sexual response. *J Fam Pract.* 1983;17:69-73.
87. Fava GA, Fava M, Kellner R, Serafini E, Mastrogiacomo I. Depression, hostility and anxiety in hyperprolactinemic amenorrhea. *Psychother Psychosom.* 1981;36:122-128.
88. Waterman GS, Dahl RE, Birmaher B, Ambrosini P, Rabinovich H, Williamson D, Novacenko H, Nelson B, Puig-Antich J, Ryan ND. The 24-hour pattern of prolactin secretion in depressed and normal adolescents. *Biol Psychiatry.* 1994;35: 440-445.
89. Besser GM, Thorner MO. Prolactin and gonadal function. *Pathol Biol (Paris).* 1975;23:779-794.
90. Buvat J, Ashour M, Buvat-Heraut M, Fossati P. Prolactin and human sexual behavior. In: Rubin C, Harter M,eds. *Progress in Prolactin Physiology and Pathology.* Amsterdam, the Netherlands: Elsevier/North Holland Biomedical Press; 1978:258-264.
91. Horrobin DF. Prolactin and mental illness. *Br J Psychol.* 1974;124:456-458.
92. Legros J, Mormot C, Servalis J. A psychoendocrine study of erectile psychogenic impotence: a comparison between normal patients and patients with abnormal glucose tolerance test. In: Carenza L, Pancheri P, Zichella L, eds. *Clinical Psychoneuroendocrinology and Reproduction.* New York, NY: Academic Press Inc; 1992:301-319.
93. Deutsch S, Sherman L. Hypoprolactinaemia in men with secondary sexual impotence and men with premature ejaculation [abstract]. In: *Endocrinology Society Meeting Abstracts.* New York, NY: Endocrinology Society; 1979:350.
94. Muller P, Musch K, Wolf AS. Prolactin variables in personality and sexual behavior. In: Zichella L, Pancheri P, eds. *Psychoneuroendocrinology in Reproduction.* Amsterdam, the Netherlands: Elsevier/North-Holland Biomedical Press; 1979: 359-372.

95. Exton MS, Bindert A, Kruger T, Scheller F, Hartmann U, Schedlowski M. Cardiovascular and endocrine alterations after masturbation-induced orgasm in women. *Psychosom Med.* 1999;61: 280-289.
96. Drago F. Prolactin and sexual behavior: a review. *Neurosci Biobehav Rev.* 1984;8:433-439.
97. Rowland DL, Heiman JR, Gladue BA, Hatch JP, Doering CH, Weiler SJ. Endocrine, psychological, and genital response to sexual arousal in men. *Psychoneuroendocrinology.* 1987;12:149-158.
98. La Ferla J, Anderson D, Schalch D. Psychoendocrine response to sexual arousal in human males. *Psychosom Med.* 1978;40:166-172.
99. Stoleru SG, Ennaji A, Counot A, Spira A. LH pulsatile secretion and testosterone blood levels are influenced by sexual arousal in human males. *Psychoneuroendocrinology.* 1993;18:205-218.
100. Carani C, Bancroft J, Del Rio G, Granata ARM, Facchinetti F, Marrama P. The endocrine effects of visual erotic stimuli in normal men. *Psychoneuroendocrinology.* 1990;15:207-216.
101. Purvis K, Landgren B, Cekan Z, Diczfalusy E. Endocrine effects of masturbation in men. *J Endocrinol.* 1976;70:439-444.
102. Brown WA, Heninger G. Cortisol, growth hormone, free fatty acids, and experimentally evoked affective arousal. *Am J Psychol.* 1975;132:1172-1176.
103. Lee R, Jaffe R, Midgley A. Lack of alteration of serum gonadotropins in men and women following sexual intercourse. *Am J Obstet Gynecol.* 1974;120:985-987.
104. Lincoln G. Luteinizing hormone and testosterone in man. *Nature.* 1974;252:232-233.
105. Kruger T, Exton MS, Pawlak C, von zur Muhlen A, Hartmann U, Schedlowski M. Neuroendocrine and cardiovascular response to sexual arousal and orgasm in men. *Psychoneuroendocrinology.* 1998;23:401-411.
106. Carmichael MS, Humbert R, Dixen J, Palmisano G, Greenleaf W, Davidson JM. Plasma oxytocin increases in the human sexual response. *J Endocrinol Metab.* 1987;64:27-31.
107. Carmichael MS, Warburton VL, Dixen J, Davidson JM. Relationships among cardiovascular, muscular, and oxytocin responses during human sexual activity. *Arch Sex Behav.* 1994;23:59-77.
108. Murphy MR, Seckl JR, Burton S, Checkley SA, Lightman SL. Chances in oxytocin and vasopressin secretion during sexual activity in men. *J Clin Endocrinol.* 1987;65:738-741.
109. Blaicher W, Gruber D, Bieglmayer C, Blaicher AM, Knogler W, Huber JC. The role of oxytocin in relation to female sexual arousal. *Gynecol Obstet Invest.* 1999;47:125-126.
110. Anderson-Hunt M, Dennerstein L. Increased female sexual response after oxytocine [editorial]. *BMJ.* 1994;309:929.
111. Anderson-Hunt M, Dennerstein L. Oxytocin and female sexuality. *Gynecol Obstet Invest.* 1995; 40:217-221.
112. Turner RA, Altemus M, Enos T, Cooper B, McGuinnesss T. Preliminary research on plasma oxytocin in normal cycling women: investigating emotion and interpersonal distress. *Psychiatry.* 1999;62:97-112.
113. Carter CS. Oxytocin and sexual behavior. *Neurosci Biobehav Rev.* 1992;16:131-144.
114. Starkman MN, Schteingart DE, Schork MA. Depressed mood and other psychiatric manifestations of Cushing's syndrome: relationship to hormone levels. *Psychosom Med.* 1981;43:3-18.
115. Starkman MN, Schteingart DE. Neuropsychiatric manifestations of patients with Cushing's syndrome: relationship to cortisol and adrenocorticotropic hormone levels. *Arch Intern Med.* 1981; 141:215-219.
116. Gold PW, Kling MA, Khan I, Calabrese JR, Kalogeras K, Post RM, Avgerinos PC, Loriaux DL, Chrousos GP. Corticotropin-releasing hormone: relevance to normal physiology and to the pathophysiology and differential diagnosis of hypercortisolism and adrenal insufficiency. *Adv Biochem Psychopharmacol.* 1987;43:183-200.
117. Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, Merriam GR, Bardin CW, Loriaux DL. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab.* 1985;61:536-540.
118. Kennedy SH, Dickens SE, Eisfeld BS, Bagby RM. Sexual dysfunction before antidepressant therapy in major depression. *J Affect Disord.* 1999;56: 201-208.
119. Exton NG, Truong TC, Exton MS, Wingenfeld SA, Leygraf N, Saller B, Hartmann, U, Schedlowski M. Neuroendocrine response to film-induced sexual arousal in men and women. *Psychoneuroendocrinology.* 2000;25:187-199.
120. Ismail AAA, Davidson DW, Loraine JA, Fox CA. Relationship between plasma cortisol and human sexual activity. *Nature.* 1972;237:288-289.
121. Granata A, Bancroft J, Del Rio G. Stress and the erectile response to intracavernosal prostaglandin E_1 in men with erectile dysfunction. *Psychosom Med.* 1995;57:336-344.
122. Cohn BA. In search of human skin pheromones [a review]. *Arch Dermatol.* 1994;130:1048-1051.
123. Garcia-Welasco J, Mondragon M. The incidence of the vomeronasal organ in 1000 human subjects and its possible clinical significance. *J Steroid Biochem Mol Biol.* 1991;39: 561-563.
124. McClintock, MK. Menstrual synchrony and suppression. *Nature.* 1971;229:244-245.
125. Cutler WB, Garcia CR, Krieger AM. Sexual behavior frequency and menstrual cycle length in mature premenopausal women. *Psychoneuroendocrinology.* 1979;4:297-309.
126. Cutler WB, McCoy N, Davidson JM. Sexual behavior, steroids and hot flashes are associated during the perimenopause [letter]. *Neuroendocrinol Lett.* 1983;5:185.
127. Cutler WB, Preti G, Huggins GR, Erickson B, Garcia CR. Sexual behavior frequency and biphasic ovulatory-type menstrual cycles. *Physiol Behav.* 1985;34:805-810.
128. McCoy N, Cutler W, Davidson JM. Relationships among sexual behavior, hot flashes, and hormone levels in perimenopausal women. *Arch Sex Behav.* 1985;14:385-394.
129. Cutler WB, Friedmann E, McCoy NL. Pheromonal influences on sociosexual behavior in men. *Arch Sex Behav.* 1998;27:1-13.
130. Burnett AL. Role of nitric oxide in the physiology of erection. *Biol Reprod.* 1995;52:485-489.
131. Burnett AL. Nitric oxide in the penis: physiology and pathology. *J Urol.* 1997;157:320-324.
132. Burnett AL, Calvin DC, Silver RI, Peppas DS, Docimo SG. Immunohistochemical description of nitric oxide synthase isoforms in human clitoris. *J Urol.* 1997;158:75-78.
133. Toesca A, Stolfi VM, Cocchia D. Immunohistochemical study of the corpora cavernosa of the human clitoris. *J Anat.* 1996;188(Pt 3):513-520.
134. Beavo JA. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. *Physiol Rev.* 1995;75:725-748.
135. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol.* 1998;159: 2164-2171.
136. Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, Osterloh IH, Gengell JC. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res.* 1996;8:47-52.
137. Montorsi F, McDermott TE, Morgan R, Olsson A, Schultz A, Kirkeby HJ, Osterloh IH. Efficacy and safety of fixed-dose oral Sildenafil in the treatment of erectile dysfunction of various etiologies. *Urology.* 1999;53:1011-1018.
138. Dinsmore WW, Hodges M, Hargreaves C, Osterloh IH, Smith MD, Rosen RC. Sildenafil citrate (Viagra) in erectile dysfunction: near normalization in men with broad-spectrum erectile dysfunction compared with age-matched healthy control subjects. *Urology.* 1999;53:800-805.
139. Marks LS, Duda C, Dorey FJ, Macairan ML, Santos PB. Treatment of erectile dysfunction with sildenafil. *Urology.* 1999;53:19-24.
140. Padma-Nathan H, Steers WD, Wicker PA. Efficacy and safety of oral sildenafil in the treatment of erectile dysfunction: a double-blind, placebo-controlled study of 329 patients. *Int J Clin Pract.* 1998;52:375-379.
141. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med.* 1998; 338:1397-1404.
142. Derry FA, Dinsmore WW, Fraser M, Gardner BP, Glass CA, Maytom MC, Smith MD. Efficacy and safety of oral sildenafil (Viagra) in men with erectile dysfunction caused by spinal cord injury. Neurology. 1998;51:1629-1633.
143. Giuliano F, Hultling C, El Masry WS, Smith MD, Osterloh IH, Orr H, Maytom M. Randomized trial of sildenafil for treatment of erectile dysfunction in spinal cord injury. *Ann Neurol.* 1999;46:15-21.
144. Park K, Moreland RB, Goldstein I, Atala A, Traish A. Sildenafil inhibits phosphodiesterase type 5 in human clitoral corpus cavernosum smooth muscle. *Biochem Biophys Res Comm.* 1998; 249:612-617.
145. Laan E, van Lunsen RHW, Everaerd W, Heiman JR, Hackbert L. The effects of sildenafil on women's genital and subjective sexual response. Paper presented at: 26th Annual Meeting of the International Academy of Sex Research; Paris, France; June 23, 2000.
146. Ashton AK. Sildenafil treatment of paroxetine-induced anorgasmia in woman [letter]. *Am J Psychiatry.* 1999;156:800.
147. Ashton AK, Bennett RG. Sildenafil treatment of serotonin reuptake inhibitor-induced sexual dysfunction [letter]. *J Clin Psychiatry.* 1999;60:194-195.
148. Nurnberg HG, Hensley PL, Lauriello J, Parker LM, Keith SJ. Sildenafil for women patients with antidepressant-induced sexual dysfunction. *Psychiatr Serv.* 1999;50:1076-1078.
149. Basson R, McKinnis R, Smith M, Hodgson G, Spain T, Koppiker N. Efficacy and safety of sildenafil in estrogenized women with sexual dysfunction associated with female sexual arousal disorder. Abstract presented at: Annual Meeting of the American College of Obstetrics and Gynecologists; San Fransisco, Calif; May 23, 2000.
150. Kaplan SA, Reis RB, Kohn IJ, Ikeguchi EF, Laor E, Te AE, Martins AC. Safety and efficacy of sil-

denafil in postmenopausal women with sexual dysfunction. *Urology.* 1999;53:481-486.
151. Meston CM, Gorzalka BB. Psychoactive drugs and human sexual behavior: the role of serotonergic activity. *J Psychoactive Drugs.* 1992;24:1-40.
152. Aizenberg D, Zemishlany Z, Dorfman-Etrog P, Weizman A. Sexual dysfunction in male schizophrenic patients. *Clin Psychiatry.* 1995;56:4:137-141.
153. Rosen R, Lane R, Menza M. Effects of SSRIs on sexual function: a critical review. *Clin Psychopharmacol.* 1999;19:67-85.
154. Feiger A, Kiev A, Shrivastava RK, Wisselink PG, Wilcox CS. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry.* 1996;57 (suppl 2):53-62.
155. Montejo-Gonzalez AL, Llorca G, Izquierdo JA, Ledesma A, Buosono M, Calcedo A, Carrasco JL, Ciudad J, Daniel E, De La Gandara J, Derecho J, Franco M, Gomez MJ, Macias JA, Martin T, Perez V, Sanchez JM, Sanchez S, Vicens E. SSRI-Induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther.* 1997;23:176-193.
156. Patterson WM. Fluoxetine-induced sexual dysfunction [letter]. *J Clin Psychiatry.* 1993;54:71.
157. Pearlstein TB, Stone AB. Long-term fluoxetine treatment of late luteal phase dysphoric disorder. *J Clin Psychiatry.* 1994;55:332-335.
158. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry.* 1995;56(suppl 6):12-21.
159. Gitlin MJ. Psychotropic medications and their effects on sexual function: diagnosis, biology, and treatment approaches. *J Clin Psychiatry.* 1994;55:406-413.
160. Woodrum ST, Brown CS. Management of SSRI-induced sexual dysfunction. *Ann Pharmacother.* 1998;32:1209-1215.
161. Eison AS, Eison MS, Torrente JR, Wright RN, Yocca FD. Nefazodone: preclinical pharmacology of a new antidepressant. *Psychopharmacol Bull.* 1990;26:311-315.
162. Cyr M, Brown CS. Nefazodone: its place among antidepressants. *Ann Pharmacother.* 1996;30:1006-1012.
163. Robinson DS, Roberts DL, Smith JM, Stringfellow JC, Kaplita SB, Seminara JA, Marcus RN. The safety profile of nefazodone. *J Clin Psychiatry.* 1996;57(suppl 2):31-38.
164. Landen M, Eriksson E, Agren H, Fahlen T. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol.* 1999;19:268-271.
165. Michelson D, Bancroft J, Targum S, Kim Y, Tepner R. Female sexual dysfunction associated with antidepressant administration: a randomized, placebo-controlled study of pharmacologic intervention. *Am J Psychiatry.* 2000;157:239-243.
166. Bitran D, Hull EM. Pharmacological analysis of male rat sexual behavior. *Neurosci Biobehav Rev.* 1987;11:365-389.
167. Frohlich PF, Meston CM. Evidence that serotonin affects female sexual functioning via peripheral mechanisms. *Physiol Behav.* In press.
168. Waldinger MD, Hengeveld MW, Zwinderman AH. Ejaculation-retarding properties of paroxetine in patients with primary premature ejaculation: a double-blind, randomized, dose-response study. *Br J Urol.* 1997;79:592-595.
169. Ludovico GM, Corvasce A, Pagliarulo G, Cirillo-Marucco E, Marano A, Pagliarulo A. Paroxetine in the treatment of premature ejaculation. *Br J Urol.* 1996;77:881-882.
170. McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. *J Urol.* 1999;161:1826-1830.
171. McMahon CG. Treatment of premature ejaculation with sertraline hydrochloride: a single-blind placebo controlled crossover study. *J Urol.* 1998;159:1935-1938.
172. Biri H, Isen K, Sinik, Z, Onaran M, Kupeli B, Bozkirli I. Sertraline in the treatment of premature ejaculation: a double-blind, placebo controlled study. *Int Urol Nephrol.* 1998;30:611-615.
173. Kim SW, Paick JS. Short-term analysis of the effects of as needed use of sertraline at 5 pm for the treatment of premature ejaculation. *Urology.* 1999;54:544-547.
174. Kara H, Aydin S, Yucel M, Agargun MY, Odabas O, Yilmaz Y. The efficacy of fluoxetine in the treatment of premature ejaculation: a double-blind placebo controlled study. *J Urol.* 1996;156:1631-1632.
175. Waldinger MD, Hengeveld, MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol.* 1998;18:274-281.
176. Goldbloom DS, Kennedy SH. Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. *J Clin Psychiatry.* 1991;52:261-262.
177. Uphouse L, Andrade M, Caldarola-Pastuszka M, Jackson A. 5-HT_{1A} receptor antagonists and lordosis behavior. *Neuropharmacology.* 1996;35:489-495.
178. Uphouse L, Andrade M, Caldarola-Pastuszka M, Maswood S. Hypothalamic infusion of the 5-$HT_{2/1C}$ agonist, DOI, prevents the inhibitory actions of the 5-HT_{1A} agonist, 8-OH-DPAT, on lordosis behavior. *Pharmacol Biochem Behav.* 1994;47:467-470.
179. Uphouse L, Caldarola-Pastuszka M. Female sexual behavior following intracerebral infusion of the 5-HT_{1A} agonist, 8-OH-DPAT, into the medial preoptic area. *Brain Res.* 1993;601:203-208.
180. Uphouse L, Caldarola-Pastuszka M, Maswood S, Andrade M, Moore N. Estrogen-progesterone and 8-OH-DPAT attenuate the lordosis-inhibiting effects of the 5-HT_{1A} agonist in the VMN. *Brain Res.* 1994;637:173-180.
181. Uphouse L, Caldarola-Pastuszka M, Moore N. Inhibitory effects of the 5-$HT1_A$ agonists, 5-hydroxy- and 5-methoxy-(3-(DI-*n*-propylamino) chroman), on female lordosis behavior. *Neuropharmacology.* 1993;32:641-651.
182. Uphouse L, Colon L, Cox A, Caldarola-Pastuszka M, Wolf A. Effects of mianserin and ketanserin on lordosis behavior after systemic treatment or infusion into the ventromedial nucleus of the hypothalamus. *Brain Res.* 1996;718:46-52.
183. Aiello-Zaldivar M, Luine V, Frankfurt M. 5,7-DHT facilitated lordosis: effects of 5-HT agonists. *Neuroreport.* 1992;3:542-544.
184. Gorzalka BB, Mendelson SD, Watson NV. Serotonin receptor subtypes and sexual behavior. *Ann N Y Acad Sci.* 1990;600:435-444.
185. Luine V. Serotonin, catecholamines and metabolites in discrete brain areas in relation to lordotic responding on proestrus. *Neuroendocrinology.* 1993;57:946-954.
186. Courty E, Durif F, Zenut M, Courty P, Lavarenne J. Psychiatric and sexual disorders induced by apomorphine in parkinson's disease. *Clin Neuropharmacol.* 1997;20:140-147.
187. Uitti RJ, Tanner CM, Rajput AH, Goetz CG, Klawans HL, Thiessen B. Hypersexuality with antiparkinsonian therapy. *Clin Neuropharmacol.* 1989;12:375-383.
188. Goodwin FK. Psychiatric side effects of levodopa in man. *JAMA.* 1971;218:1915-1920.
189. Melis MR, Argiolas A. Dopamine and sexual behavior. *Neurosc Biobehav Rev.* 1995;19:19-38.
190. Clark JT, Stefanick ML, Smith ER, Davidson JM. Further studies on alterations in male rat copulatory behavior induced by the dopamine-receptor agonists RDS-127. *Pharmacol Biochem Behav.* 1983;19:781-786.
191. Foreman MM, Hall JL. Effects of D_2-dopaminergic receptor stimulation on male rat sexual behavior. *J Neural Transm.* 1987;68:153-170.
192. Hull EM, Bitran D, Pehek EA, Warner RK, Band LC, Holmes GM. Dopaminergic control of male sex behavior in rats: effects of an intracerebrally-infused agonist. *Brain Res.* 1986;370:73-81.
193. Mas M, Fumero B, Perez-Rodriquez I. Induction of mating behavior by apomorphine in sexually sated rats. *Eur J Pharmacol.* 1995;280:331-334.
194. Bowers MB, Woert MV, Davis L. Sexual behavior during L-dopa treatment for parkinsonism. *Am J Psychiatry.* 1971;127:1691-1693.
195. Hyyppa M, Rinne OK, Sonnine V. The activating effect of L-dopa treatment on sexual functions and its experimental background. *Acta Neurol Scand Suppl.* 1970;43(suppl 46):223-224.
196. O'Brien CP, DiGiacomo JN, Fahn S, Schwarz GA. Mental effects of high-dosage levodopa. *Arch Gen Psychiatry.* 1971;24:61-64.
197. Danjou P, Alexandre L, Warot D, Lacomblez L, Puech AJ. Assessment of erectogenic properties of apomorphine and yohimbine in man. *Br J Clin Pharmacol.* 1988;26:733-739.
198. Danjou P, Lacomblez L, Warot D, Peuch AJ. Assessment of erectogenic drugs by numeric plethysmography. *J Pharmacol Methods.* 1989;21:61-69.
199. Lal S, Ackman D, Thavundayil JX, Kiely ME, Etienne P. Effect of apomorphine, a dopamine receptor agonist, on penile tumescence in normal subjects. *Prog Neuropsychopharmacol Biol Psychiatry.* 1984;8:695-699.
200. O'Sullivan JD, Hughes AJ. Apomorphine-induced penile erections in Parkinson's disease. *Mov Disord.* 1998;13:536-539.
201. Segraves RT, Bari M, Segraves K, Spirnak P. Effect of apomorphine on penile tumescence in men with psychogenic impotence. *J Urol.* 1991;145:1174-1175.
202. Lal S, Laryea E, Thavundayil JX, Nair NPV, Negrete J, Ackman D, Blundell P, Gardiner RJ. Apomorphine-induced penile tumescence in impotent patients - preliminary findings. *Prog Neuropsychopharmacol Biol Psychiatry.* 1987;11:235-242.
203. Lal S, Tesfaye Y, Thavundayil JX, Thompson TR, Kiely ME, Nair NPV, Grassino A, Dubrovsky B. Apomorphine: clinical studies on erectile impotence and yawning. *Prog Neuropsychopharmacol Biol Psychiatry.* 1989;13:329-339.
204. Aizenberg D, Zemishlany Z, Dorfman-Etrog P, Weizman A. Sexual dysfunction in male schizophrenic patients. *J Clin Psychiatry.* 1995;56:137-141.

205. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry.* 1994; 151:825-835.
206. Chan J, Alldredge BK, Baskin LS. Perphenazine-induced priapism. *DICP.* 1990;24:246-249.
207. Jackson SC, Walker JS. Self-administered intraurethral chlorpromazine: an unusual cause of priapism. *Am J Emerg Med.* 1991;9:171-175.
208. Merkin TE. Priapism as a sequela of chlorpromazine therapy. *JACEP.* 1977;6:367-368.
209. Mutlu N, Ozkurkcugil C, Culha M, Turkan S, Gokalp A. Priapism induced by chlorpromazine. *Int J Clin Pract.* 1999;53:152-153.
210. Gower AJ, Berendsen HG, Princen MM, Broekkamp CL. The yawning-penile erection syndrome as a model for putative dopamine autoreceptor activity. *Eur J Pharmacol.* 1984;103: 81-89.
211. Ghadirian AM, Chouinard G, Annable L. Sexual dysfunction and plasma prolactin levels in neuroleptic treated schizophrenic outpatients. *J Nerv Mental Dis.* 1982;170:463-467.
212. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med.* 1983;28:497-499.
213. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a five-year, updated, clinical review. *J Reprod Med.* 1990;35: 11-14.
214. Melis MR, Argiolas A. Dopamine and sexual behavior. *Neurosci Biobehav Rev.* 1995;19:19-38.
215. Julien RM. *A Primer of Drug Action: A Concise, Nontechnical Guide to the Actions, Uses, and Side Effects of Psychoactive Drugs.* 7th ed. New York, NY: WH Freeman & Co; 1995.
216. Miller NS, Gold MS. The human sexual response and alcohol and drugs. *J Subst Abuse Treat.* 1988;5:171-177.
217. Smith DE, Wesson DR, Apter-Marsh M. Cocaine and alcohol-induced sexual dysfunction in patients with addictive disease. *J Psychoactive Drugs.* 1984;16:359-361.
218. Gay GR, Newmeyer J, Ellison R, et al. Drug-sex practices in Haight-Ashbury of the "sensuous hippie." In: Sandler M, Gessa DL, eds. *Sexual Behavior: Pharmacology and Biochemistry.* New York, NY: Raven Press; 1975.
219. Cohen S. Cocaine. *JAMA.* 1975;231:74-75.
220. Cocores JA, Dackis CA, Gold MS. Sexual dysfunction secondary to cocaine abuse in two patients. *J Clin Psychiatry.* 1986;47:384-385.
221. Cocores JA, Miller NS, Pottash AC, Gold MS. Sexual dysfunction in abusers of cocaine and alcohol. *Am J Drug Alcohol Abuse.* 1988;14:169-173.
222. Chang AYW, Kuo TBJ, Chan JYH, Chan SHH. Concurrent elicitation of electroencephalographic desynchronization and penile erection by cocaine in the rat. *Synapse.* 1996;24:233-239.
223. Ferrari F, Guiliani D. Influence of eticlopride on cocaine- and DA D_2 agonist-induced behavioral effects in rats. *Pharmacol Biochem Behav.* 1996; 53:525-530.
224. Ferrari F, Guiliani D. Involvement of dopamine D_2 receptors in the effect of cocaine on sexual behaviour and stretching-yawning of male rats. *Neuropharmacology.* 1997;36:769-777.
225. Pomerantz SM, Hepner BC, Wertz JM. Impairment of male copulatory behavior in rhesus monkeys following acute administration of cocaine. *Life Sci.* 1994;54:917-925.
226. Linnankoski I, Gronroos M, Carlson S, Pertovaara A. Effect of cocaine on sexual behaviour in male stumptail macaques. *Pharmacol Biochem Behav.* 1995;52:11-216.
227. Ende N, Gertner SB, Hwang SG, Kadi RS. Measurement of postcoital sympathetic activity in females by means of vanillylmandelic acid. *Horm Behav.* 1989;23:150-156.
228. Meston CM, Heiman JR. Ephedrine-activated sexual arousal in women. *Arch Gen Psychiatry.* 1998;55:652-656.
229. Meston CM, Gorzalka BB, Wright JM. Inhibition of subjective and physiological sexual arousal in women by clonidine. *J Psychosom Med.* 1997; 59:399-407.
230. Meston CM, Gorzalka BB. The effects of sympathetic activation on physiological and subjective sexual arousal in women. *Behav Res Ther.* 1995;33:651-664.
231. Meston CM, Gorzalka BB. The effects of immediate, delayed, and residual sympathetic activation on sexual arousal in women. *Behav Res Ther.* 1996;34:143-148.
232. Meston CM, Gorzalka BB. The differential effects of sympathetic activation on sexual arousal in sexually functional and dysfunctional women. *J Abnorm Psychol.* 1996;105:582-591.
233. Sleight AJ, Koek W, Bigg DCH. Binding of antipsychotic drugs at α_1- and α_{1B}-adrenoceptors: risperidone is selective for the α_{1B}-adrenoceptors. *Eur J Pharmacol.* 1993;238:407-410.
234. Wiedeking C, Lake R, Ziegler M, Kowarski A, Money J. Plasma noradrenaline and dopamine–beta-hydroxylase during sexual activity. *Psychosom Med.* 1977;39:143-148.
235. Wiedeking C, Ziegler MG, Lake CR. Plasma noradrenaline and dopamine–beta-hydroxylase during human sexual activity. *J Psychiatr Res.* 1979; 15:139-145.
236. Stimmel GL, Dopheide JA, Stahl SM. Mirtazapine: an antidepressant with noradrenergic and specific serotonergic effects. *Pharmacotherapy.* 1997;17:10-21.
237. Morales A, Condra M, Owen JA, Surridge DH, Fenemore J, Harris C. Is yohimbine effective in the treatment of organic impotence? results of a controlled trial. *J Urol.* 1987;137:1168-1172.
238. Price J, Grunhaus LJ. Treatment of clomipramine-induced anorgasmia with yohimbine: a case report. *J Clin Psychiatry.* 1990;51:32-33.
239. Reid K, Morales A, Harris C, Surridge DH, Condra M, Owen J, Fenemore J. Double-blind trial of yohimbine in treatment of psychogenic impotence. *Lancet.* 1987;2:421-423.
240. Piletz JE, Segraves KB, Feng Y, Maguire E, Dunger B, Halaris A. Plasma MHPG response to yohimbine: treatment in women with hypoactive sexual desire. *J Sex Martial Ther.* 1998;24:43-54.
241. Stimmel B. Historical perspective. In: Stimmel B, ed. *Heroin Dependency.* New York, NY: Stratton International Medical Book Corp; 1975:1-8.
242. Wikler A. Drug dependence. In: Baker A, ed. *Clinical Neurology.* New York, NY: Harper & Row; 1971.
243. Bloom FE, Rossier J, Battenberg EL, Banyon A, French E, Henricksen SJ, Siggins GR, Segal D, Brown R, Ling N, Guillemin R. Beta-endorphin: cellular localization, electrophysiological and behavioral effects. In: Costa E, Trabucchi M, eds. *Advances in Biochemical Psychopharmacology.* New York, NY: Raven Press; 1978:89-109.
244. Pfaus JG, Gorzalka BB. Opioids and sexual behavior. *Neurosci Biobehav Rev.* 1987;11:1-34.
245. Paice JA, Penn RD, Ryan WG. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. *J Pain Symptom Manage.* 1994;9:126-131.
246. Mirin SM, Meyer RE, Mendelson JH, Ellingboe J. Opiate use and sexual function. *Am J Psychiatry.* 1980;137:909-915.
247. Sandyk R. Naltrexone suppresses abnormal sexual behavior in Tourette's syndrome. *Int J Neurosci.* 1988;43:107-110.
248. Brennemann W, Stitz B, van Ahlen H, Brensing KA, Klingmuller D. Treatment of idiopathic erectile dysfunction in men with the opiate antagonist naltrexone: a double-blind study. *J Androl.* 1993;14:407-410.
249. Fabbri A, Jannini EA, Gnessi L, Moretti C, Ulisse S, Franzese A, Lazzari R, Fraioli F, Frajese G, Isidori A. Endorphins in male impotence: evidence for naltrexone stimulation of erectile activity in patient therapy. *Psychoneuroendocrinology.* 1989;14:103-111.
250. van Ahlen H, Piechota HJ, Kias HJ, Brennemann W, Klingmuller D. Opiate antagonists in erectile dysfunction: a possible new treatment option? *Eur Urol.* 1995;28:246-250.
251. Charney DS, Heninger GR. β_2–Adrenergic and opiate receptor blockade. *Arch Gen Psychiatry.* 1986;43:1037-1041.
252. Brady JP, Bianco F. Endorphins: naloxone failure to increase sexual arousal in sexually unresponsive women: a preliminary report. *Biol Psychiatry.* 1980;15:627-631.
253. Blanco R, Saenz de Tejada I, Goldstein I, Krane RJ, Wotiz HH, Cohen RA. Cholinergic neurotransmission in human corpus cavernosum, II: acetylcholine synthesis. *Am J Physiol.* 1988; 254:H468-H472.
254. Adaikan PG, Karim SMM, Kottegoda SR, Ratnam SS. Cholinoreceptors in the corpus cavernosum of the human penis. *J Auton Pharmacol.* 1983;3:107-111.
255. Godec CJ, Bates H. Cholinergic receptors in corpus cavernosa. *Urology.* 1984;24:31-33.
256. Saenz de Tejada I, Blanco R, Goldstein I, Azadzoi K, de las Morenas A, Krane RJ, Cohen RA. Cholinergic neurotransmission in human corpus cavernosum, I: responses of isolated tissue. *Am J Physiol.* 1988;254:H459-H467.
257. Saenz de Tejada I, Goldstein I, Azadzoi K, Krane RJ, Cohen RA. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. *N Engl J Med.* 1989;320:1026-1030.
258. Segraves RT. Bethanechol reversal of imipramine-induced ejaculatory dysfunction [letter]. *Am J Psychiatry.* 1987;144:1243.
259. Yager J. Bethanechol chloride can reverse erectile and ejaculatory dysfunction induced by tricyclic antidepressants and mazindol: case report. *J Clin Psychiatry.* 1986;47:210-211.
260. Hull EM, Bitran D, Pehek EA, Holmes GM, Warner RK, Band LC, Clemens LG. Brain localization of cholinergic influence on male sex behavior in rats: agonists. *Pharmacol Biochem Behav.* 1988;31: 169-174.
261. Hull EM, Pehek EA, Bitran D, Holmes GM, Warner RK, Band LC, Bazzett T, Clemens LG. Brain localization of cholinergic influence on male sex behavior in rats: antagonists. *Pharmacol Biochem Behav.* 1988;31:175-178.
262. Giuliano FA, Rampin O, Benoit G, Jardin A. Neurological control of penile erection. *Urol Clin North Am.* 1995;22:747-766.
263. Wagner G, Levin RJ. Effect of atropine and methylatropine on human vaginal blood flow, sexual arousal, and climax. *Acta Pharmacol Toxicol.* 1980;46:321-325.
264. Riley AJ, Riley EJ. Cholinergic and adrenergic control mechanisms in human sexual response. In: WheatleyD, ed. *Psychopharmacology of Sexual Dysfunction.* Oxford, England: Oxford University Press; 1983:125-137.

265. White JM, Rumbold GR. Behavioral effects of histamine and its antagonists: a review. *Psychopharmacology.* 1988;95:1-14.
266. Cara AM, Lopes-Martins RAB, Antunes E, Nahoum CRD, Nucci DE. The role of histamine in human penile erection. *Br J Urol.* 1995;75:220-224.
267. Marson L, McKenna KE. The identification of a brainstem site controlling spinal sexual reflexes in male rats. *Brain Res.* 1990;515:303-308.
268. McKenna K. The brain is the master organ in sexual function: central nervous system control of male and female sexual function. *Int J Impot Res.* 1999;11(suppl 1):S48-S55.
269. Marson L, Platt KB, McKenna KE. Central nervous system innervation of the penis as revealed by the transneuronal transport of pseudorabies virus. *Neuroscience.* 1993;55:263-280.
270. Marson L, McKenna KE. CNS cell groups involved in the control of the ischiocavernosus and bulbospongiosus muscles: a transneuronal tracing study using pseudorabies virus. *J Comp Neurol.* 1996;374:161-179.
271. Marson L. Central nervous system neurons identified after injection of pseudorabies virus into the rat clitoris. *Neurosci Lett.* 1995;190:41-44.
272. Papka RE, Williams S, Miller KE, Copelin T, Puri P. CNS location of uterine-related neurons revealed by trans-synaptic tracing with pseudorabies virus and their relation to estrogen receptor-immunoreactive neurons. *Neuroscience.* 1998; 84:935-952.
273. Simerly RB, Swanson LW. The organization of neural inputs to the medial preoptic nucleus of the rat. *J Comp Neurol.* 1986;246:312-342.
274. Simerly RB, Swanson LW. Projections of the medical preoptic nucleus: *Phaseolus vulgaris* leucoagglutinin anterograde tract-tracing study in the rat. *J Comp Neurol.* 1988;270:209-242.
275. Meisell RL, Sachs BD. The physiology of male sexual behavior. In: Knobil E, Neill JD, eds. *The Physiology of Reproduction.* New York, NY: Raven Press Ltd; 1994:3-105.
276. Flanagan-Cato LM, McEwen BS. Patterns of Fos and Jun expression in the female rat forebrain after sexual behavior. *Brain Res.* 1995;673:53-60.
277. Yanagimoto M, Honda K, Goto Y, Negoro H. Afferents originating from the dorsal penile nerve excite oxytocin cells in the hypothalamic paraventricular nucleus of the rat. *Brain Res.* 1996; 733:292-296.
278. Chen KK, Chan SHH, Chang LS, Chan JYH. Participation of paraventricular nucleus of hypothalamus in central regulation of penile erection in the rat. *J Urol.*1997;158:238-244.
279. Carmichael MS, Humbert R, Dixen JH, Palmisano G, Greenleaf W, Davidson JM. Plasma oxytocin increases in the human sexual response. *J Clin Endocrinol Metab.* 1987;64: 27-31.
280. Carmichael MS, Warburton VL, Dixen JH, Davidson JM. Relationships among cardiovascular, muscular, and oxytocin responses during human sexual activity. *Arch Sex Behav.* 1994;23: 59-79.
281. Tetel MJ, Getzinger MJ, Blaustein JD. Fos expression in the rat brain following vaginal-cervical stimulation by mating and manual probing. *J Neuroendocrinol.* 1993;5:397-404.
282. Erskine MS. Mating-induced increases in Fos protein in preoptic area and medial amygdala of cycling female rats. *Brain Res Bull.* 1993;32:447-451.
283. Everitt BJ, Cador M, Robbins TW. Interactions between the amygdala and ventral striatum in stimulus-reward associations: studies using a second-order schedule of sexual reinforcement. *Neuroscience.* 1989;30:63-75.
284. MacLean PD. Brain mechanisms of primal sexual function. In: Sandler M, Gessa, GL, eds. *Sexual Behavior, Pharmacology and Biochemistry.* New York, NY: Raven Press; 1975:5-7.
285. Chen KK, Chan JY, Chang LS, Chen MT, Chan SH. Elicitation of penile erection following activation of the hippocampal formation in the rat. *Neurosci Lett.* 1992141:218-222.
286. Cohen AS, Rosen RC, Goldstein L. EEG hemispheric asymmetry during sexual arousal: psychophysiological patterns in responsive, unresponsive, and dysfunctional men. *J Abnorm Psychol.* 1985;94:580-590.
287. Tucker DM, Dawson SL. Asymmetric EEG changes as method actors generated emotions. *Biol Psychol.* 1984;19:63-75.
288. Rosen RC, Goldstein L, Scoles V, Lazarus C. Psychophysiologic correlates of nocturnal penile tumescence in normal males. *Psychosom Med.* 1986;48:423-429.
289. Tiihonen F, Kuikka J, Kupila J, Partanen K, Vainio P, Airaksinen J, Eronen M, Hallikainen T, Paanila J, Kinnunen I, Huttunen J. Increase in cerebral blood flow of right prefrontal cortex in man during orgasm. *Neurosci Lett.* 1994;170:241-243.
290. Terzian H, Dalle Ore G. Syndrome of Kluver and Bucy reproduced in man by bilateral removal of temporal lobes. *Neurology.* 1955;5:373-380.
291. Freeman W. Sexual behavior and fertility after frontal lobotomy. *Biol Psychiatry.* 1973;6:97-104.
292. Stoleru S, Gregoire M, Gerard D, Decety J, Lafarge E, Cinotti L, Lavenne F, le Bars D, Vernet-Maury E, Rada H, Collet C, Mazoyer B, Forest MG, Magnin F, Spira A, Comar D. Neuroanatomical correlates of visually evoked sexual arousal in human males. *Arch Sex Behav.* 1999:28:1-21.
293. Hull EM, Du J, Lorrain DS, Matuszewich W. Testosterone, preoptic dopamine, and copulation in male rats. *Brain Res Bull.* 1997;44:327-333.
294. Lookingland KJ, Moore KE. Effects of estradiol and prolactin on incertohypothalamic dopaminergic neurons in the male rat. *Brain Res.* 1984; 323:83-91.
295. Mas M, Fumero B, Gonzales-Mora JL. Voltammetric and microdialysis monitoring of brain monoamine neurotransmitter release during sociosexual interactions. *Behav Brain Res.* 1995; 71:69-79.
296. Lorrain DS, Riolo JV, Matuszewich L, Hull EM. Lateral hypothalamic serotonin inhibits nucleus accumbens dopamine: implications for sexual satiety. *J Neurol.* 1999;19:7648-7652.
297. Everitt BJ, Fuxe K, Hokfelt T, Jonsson G. Role of monoamines in the control by hormones of sexual receptivity in the female rat. *J Comp Physiol Psychol.* 1975;89:556-572.
298. Kow LM, Mobbs CV, Pfaff DW. Roles of second-messenber systems and neuronal activity in the regulation of lordosis by neurotransmitter, neuropeptides, and estrogen: a review. *Neurosci Biobehav Rev.* 1994;18(2): 251-268.