

Autonomic Nervous System Influences The Role of the Sympathetic Nervous System in Female Sexual Arousal

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Anatomy of the Sympathetic Nervous System in the Female Genitalia

The autonomic nervous system provides most of the innervation to the internal genital organs and is essential to the sexual response. It has generally been presumed that parasympathetic activity is responsible for achieving sexual arousal through localized vasodilation, resulting in genital swelling and lubrication, while orgasm is mediated through a sympathetic response. However, the interaction of these two systems is complex and remains poorly understood. Innervation of the genitalia in human females runs primarily through a common network of converging autonomic and sensory fibers known as the pelvic plexus. In some nonhuman mammals it has been observed that sympathetic and parasympathetic fibers may actually innervate a few postsynaptic neurons in the pelvic plexus. In addition, sympathetic and parasympathetic neurons in the pelvic plexus may sometimes communicate laterally (Dail, 1996). However, the degree to which different nerve types in the plexus might interact with one another remains speculative. The significance of such interactions is likewise unknown.

Anatomical studies have indicated that the sympathetic nervous system's (SNS) contribution to the pelvic plexus originates from multiple sources. The superior hypogastric plexus gives rise to two sympathetic nerves that run bilaterally into the left and right pelvic plexuses (Donker, 1986; Maas, DeRuiter, Kemter, & Trimboos, 1999). Other inputs stem directly from sympathetic chain ganglia along the thoracolumbar spinal cord (Donker). In addition to these routes, genital tissues may receive innervation from so-called "short" adrenergic fibers that arise from localized ganglia. Owmnan, Rosengren, and Sjöberg (1967) found that such ganglia were particularly abundant in the human vagina. Interestingly, estrogen and other sex steroids may significantly influence sympathetic innervation in the pelvic organs (e.g., Zoubina & Smith, 2001).

Consistent with histochemical studies of human genital tissues (e.g., Owmnan, Rosengren, & Sjöberg, 1967), it is generally accepted that norepinephrine is the dominant neurotransmitter of the SNS. Adrenergic nerve

terminals in the pelvic plexus target both vascular and nonvascular smooth muscle in most, if not all female genital organs. The study of adrenoceptors in the genital tract is therefore extremely important to the understanding of the role of the SNS in physiological sexual arousal. However, this approach is not comprehensive. Studies of adrenoceptors alone cannot address the effects of nonadrenergic-noncholinergic (NANC) neurotransmitters, such as neuropeptide Y and galanin, which are often colocalized within sympathetic nerve fibers. The functional significance of these neuropeptides is only beginning to be understood (for review, see Argiolas, 1999).

Attempts have been made to characterize the distribution of adrenoceptors in genital tissue. Anatomical studies have suggested that mammalian vaginal, cervical, uterine, and clitoral tissues contain both alpha- and beta-adrenoceptors. Beta adrenoceptors are also present in some genital tissues, particularly the uterus, although they have received considerably less attention in studies of sexual function. In humans, both alpha- and beta-adrenoceptors appear to regulate smooth muscle tone in vaginal and clitoral tissue (Min et al., 2001; Traish, Moreland, Huang, Kim, & Goldstein, 2000). Traditionally, it has been thought that alpha-adrenoceptors are located postsynaptically and regulate smooth muscle contractility, while beta-adrenoceptors are located presynaptically and serve an autoregulatory function to inhibit release of norepinephrine and other neurotransmitters (e.g., Iversen, Iversen, & Saper, 2000). However, it is known that the alpha-2 receptor subtype is found both pre- and postsynaptically. A recent study indicates that activation of postsynaptic alpha2 adrenoceptors in the corpus cavernosum induces smooth muscle contraction (Gupta et al., 1998). Therefore, alpha2 adrenoceptors appear to serve opposite ends, depending on their location within the synapse. This somewhat paradoxical conclusion must be approached with caution. Understanding how adrenergic mechanisms influence female sexual arousal is limited by current knowledge of the distribution of adrenergic receptors on the nerves serving the genitalia.

Animal Models of Sympathetic Nervous System Activity and Sexual Arousal

Pharmacological Manipulation of Sexual Behavior

Using pharmacological treatments, a number of studies have demonstrated the influence of adrenergic transmission in the regulation of sexual behavior in females. Most studies of this nature have used ovariectomized animals treated with standardized doses of estradiol and progesterone. This study serves two purposes: first, to elicit sexually receptive behavior from a sexually unreceptive baseline, and second, to control for the potential influence of unequal sex hormone levels on adrenergic transmission. Animal models of female sexual behavior may assess several different mea-

sures of sexual responding: receptivity (lordosis quotient), which is the ratio of the number of spinal reflexes in response to male attempts to mate; proceptivity, which is measured as the number of ear wiggles per minute; and rejection behaviors, which are measured as the number of kicking, boxing, running away, and squealing behaviors in response to a male's attempt to mate. Application of these behaviors to human sexual behavior is obviously limited. Although there is no human equivalent of lordosis, it is considered an analog of sexual arousal in other mammals.

Yanase (1977) found that epinephrine, but not norepinephrine, stimulated lordosis behavior in estradiol-treated, ovariectomized rats. However, other findings have supported the role of norepinephrine in stimulating lordosis. Vincent and Feder (1988) found that injection of either an alpha-2 or alpha-1 adrenergic agonist induced lordosis behavior in a small proportion of guinea pigs, but when used in combination, induced lordosis in 76% of the animals.

Studies examining the effects of adrenergic and antiadrenergic agents are complicated by the fact that some of the drugs used do not act exclusively on adrenergic systems. For example, yohimbine acts as both an alpha-2 adrenoceptor antagonist and a serotonin receptor antagonist (Broadley, 1996, p. 216). In such a case, the study must rule out the effects of different neurotransmitter systems on the phenomenon of interest. Nock and Feder (1979) observed that the dopamine beta-hydroxylase inhibitor U-14,624 abolished lordosis behavior in female guinea pigs. U-14,624 was believed to increase dopamine and serotonin availability while decreasing norepinephrine levels. After both dopamine and serotonin blockade failed to reverse the effects of U-14,624, the authors determined that only concurrent administration of the alpha-2 adrenergic agonist clonidine was able to restore lordosis behavior in animals treated with U-14,624. Thus, the inhibitory effects of U-14,624 on lordosis were concluded to be associated primarily with decreased availability of norepinephrine, rather than increased dopamine or serotonin levels.

Although central mechanisms have usually been implicated in the adrenergic control of lordosis, a peripheral mechanism cannot be ruled out. The facilitatory effect of norepinephrine on lordosis responses may indicate the involvement of the SNS. If so, one would expect drugs that decrease SNS activity might also decrease sexual arousal. To examine this possibility, Meston, Moe, and Gorzalka (1996) conducted a series of studies on sexual behavior in female rats treated with various drugs that inhibit SNS activity. The first study examined the influence of clonidine, an antihypertensive medication, on sexual responding. Clonidine acts centrally and peripherally as an alpha-2 adrenergic agonist, presumably with the effect of decreasing norepinephrine release. In the second and third studies, the effects of drugs guanethidine and naphazoline on sexual responding were examined. Naphazoline also acts as an alpha-2 adrenergic agonist, and guanethidine

is believed to exert effects similar to those of clonidine, but they do not cross the blood-brain barrier. Each study included 15 ovariectomized female rats treated with estrogen and progesterone to induce heat, and each used a repeated measures design in which the animals received either a low, moderate or high dose of the drug.

Clonidine, guanethidine, and naphazoline all suppressed lordosis responses at both moderate and high doses. Clonidine and guanethidine significantly decreased proceptive behavior at both moderate and high doses, and naphazoline significantly decreased proceptivity at moderate doses. Clonidine significantly increased the number of rejection behaviors at both moderate and high doses; guanethidine and naphazoline also increased rejection behaviors, but the results did not reach statistical significance. Although these drugs have potential sedative effects and may have thus suppressed sexual behavior, this explanation alone is inconsistent with the observed increases in active rejection behaviors. Because guanethidine and naphazoline act to selectively inhibit peripheral sympathetic outflow without influencing adrenergic mechanisms at a central level, the results of this study suggest that inhibition of the SNS may inhibit sexual behavior in the female rat.

Effects of Direct Stimulation of Nerves and Tissues

In vivo studies of direct nerve stimulation can differentiate genital responses to parasympathetic and sympathetic outflow. Studies of this type have used electrical stimulation of dissected nerves in order to determine specific effects on target tissues. In rats, electrical stimulation of both the pelvic (parasympathetic) and hypogastric (sympathetic) nerves induced contractions of uterine and cervical smooth muscle, which were further enhanced by pretreatment with estrogen (Sato, Hayashi, & Garfield, 1989; Sato, Hotta, Nakayama, & Suzuki, 1996). Pelvic nerve stimulation increased uterine blood flow, while hypogastric nerve stimulation decreased blood flow. The decrease in uterine blood flow following hypogastric stimulation was eliminated with phenoxybenzamine, an alpha-1 adrenergic antagonist (Sato et al., 1996). Similarly, in guinea pigs, stimulation of the hypogastric nerve induced uterine contractions and increased uterine sensitivity to oxytocin; these effects could be blocked with the alpha-1 adrenergic antagonist phentolamine (Marshall & Russe, 1970). Stimulation of the pelvic plexus, which comprises both pelvic and hypogastric nerves, increased uterine and vaginal blood flow in rats (Vachon, Simmerman, Zahran, & Carrier, 2000). However, another study found that direct stimulation of the sympathetic chain countered the increase in vaginal blood flow resulting from pelvic nerve stimulation (Giuliano et al., 2001).

A different strategy used to examine adrenergic influences on genital

tissue function involves electrical stimulation of smooth muscle tissue dissected from genital organs. Subsequent treatment with antiadrenergics and other agents can be used to detect moderating influences of neurotransmitters on tissue responses. In a study of rabbit myometrium and cervical tissue, contractile responses to electrical field stimulation was attenuated by both guanethidine, an antiadrenergic agent, and atropine, an anticholinergic agent, but not by propranolol, a selective beta-adrenergic antagonist (Bulat, Kannan, & Garfield, 1989). Rabbit vaginal tissue contractile responses to electrical stimulation were attenuated by several alpha, and alpha₂, adrenergic antagonists (Kim, Min, Huang, Goldstein, & Traish, 2002).

The above studies suggest that stimulation of the sympathetic nerves supplying the genitalia results in contractions of both nonvascular and vascular smooth muscle, which may in turn limit blood flow to the uterus, vagina, and other tissues. Given that sexual arousal involves a vasoconstrictive response, the contention that arousal is mediated through activity of the SNS is apparently contradictory. To date, this discrepancy has been addressed infrequently in the literature. It has been suggested, however, that the vasoconstrictive effects of norepinephrine are superseded by the effects of other neurotransmitters that act as local vasodilators in the presence of sexual stimulation. If this is the case, then other peripheral effects of SNS activation, such as increased heart rate and blood pressure, may facilitate the vasocongestive response (Kim et al., 2002).

Human Models of SNS Activity and Sexual Arousal

Neuroendocrine Markers of Sympathetic Activity and Sexual Arousal

Indirect evidence for a facilitatory influence of SNS activation on the male sexual arousal is provided by biochemical and physiological research that indicates that diffuse SNS discharge occurs during the later stages of sexual arousal (Jovanovic, 1971) with marked increases in heart rate and blood pressure occurring during orgasm (Fox & Fox, 1969). Significant increases in urinary (Levi, 1969) and plasma (Exton et al., 2000) norepinephrine concentrations have been found in women after viewing a sexually arousing film. Increases in plasma norepinephrine, a sensitive index of SNS activity, have also been shown to accompany increases in sexual arousal during intercourse and to decline rapidly following orgasm (Wiedeking & Ziegler, & Lake, 1979). Bnde, Gertner, Hwang, and Kadi (1988) measured urinary vanillylmandelic acid (VMA) 1 hour before, within an hour after intercourse, and in a 23-hour pooled sample after intercourse in 11 female males. Vanillylmandelic acid is the ultimate metabolic product of epinephrine and norepinephrine in the urine and thus one of the most accurate methods of studying total sympathetic activity. The authors found a significant increase in VMA 1 hour prior to intercourse and 1 hour postintercourse in comparison to preintercourse baseline levels. The pooled 23-hour

sample showed levels of VMA higher than pre- but not postintercourse levels. These findings provide objective evidence for considerable involvement of the SNS during and in anticipation of intercourse.

Spinal Cord Injury Studies

Sexual impairments brought about by spinal cord injury (SCI) provide a novel model of sexual dysfunction with which to investigate the SNS contribution to sexual arousal. The origin of much of the sympathetic innervation to the genitalia can be localized to a discrete region of the thoracolumbar spinal cord. By observing sexual responses in women who have lesions of these areas, the effects of sympathetic disruption can be inferred to some degree. Research in this area has focused on specific arousal phase responses, notably vaginal vasocongestion, among women with varying degrees of SCI. These studies have typically distinguished between "psychogenic" arousal, modeled by genital responses to erotic audiovisual stimuli, and "reflex" responses to tactile stimulation of the genitals. Beabd (1989) studied 15 women with complete and incomplete SCIs at the cervical, thoracic, and lumbar levels. According to their medical records, both reflex and psychogenic vaginal lubrication were absent among women with SCIs between T10 and T12, a region from which genital sympathetic nerves originate. In addition, these women reported an absence of sensations associated with sexual arousal. Only reflex lubrication was preserved in women with injuries above T10, whereas psychogenic lubrication was preserved in women with injuries below T12. The absence of vaginal lubrication and subjective sensation in women with injuries to the lower thoracic spinal cord suggests involvement of the sympathetic nervous system in these responses.

Using vaginal photoplethysmography, Sipski, Alexander, and Rosen (1997) studied vaginal pulse amplitude (VPA) responses to erotic stimulation in women with SCIs affecting sensation to the T11-L2 dermatomes. The authors reasoned that women with damage to sensory neurons at these levels would also have impaired SNS outflow from those regions, given the close proximity of the sympathetic and somatosensory neurons within the spinal cord. The authors compared women with SCI who had varying degrees of pinprick sensation in the T11-L2 dermatomes to women who had lost all sensation in these areas. Each woman was examined under two conditions: audiovisual erotic stimulation alone and audiovisual erotic stimulation with manual clitoral stimulation. Both groups showed increases in subjective sexual arousal under the two conditions. Whereas women with some preserved dermatomal sensation showed intact VPA responses to audiovisual stimuli, women with absent sensation showed no vaginal response. When manual stimulation was added to the audiovisual stimulation, the groups showed similar increases in VPA responses. However, heart rate and respiration rate were significantly

greater among women with preserved sensation during the combined stimulation condition.

A second study by Sipski, Alexander & Rosen (2001) used a similar methodology to compare VPA responses of a control group of 21 able-bodied women to those of 68 SCI women under conditions of audiovisual stimulation alone and audiovisual plus manual stimulation. Consistent with previous findings, women with impaired sensation at the T11-L2 dermatomes showed decreased physiological sexual arousal compared to able-bodied women. Further, the degree of sensory impairment resulting from injury to the T11-L2 region was predictive of the intensity of the vasodilatory response, with less impaired women responding more like able-bodied women. When compared to women with injuries at different levels of the spinal cord, this pattern was unique to women with injuries between T11 and L2.

Effects of Physiologically Induced SNS Activation on Sexual Arousal

The above studies suggest an active role of the SNS during sexual arousal in women. Whether or not activation or inhibition of the SNS influences subsequent sexual arousal is a related but different question. Hoon, Wincez, and Hoon (1977) were the first to report that vaginal blood volume (VBV) responses were increased when women viewed an anxiety-evoking film prior to an erotic film versus a neutral travel film prior to an erotic film. Palace and Gorzalka (1990) replicated these findings in both sexually functional and dysfunctional women. To the extent that anxiety-evoking films increase SNS arousal, these findings support a facilitatory role of SNS activation on sexual arousal in women. However, it should be noted that heart rate, an indirect indicator of SNS activity, was either not measured or failed to increase significantly with exposure to the anxiety films. Hence, assumptions about SNS activation in these studies are highly speculative. Wolpe (1978) offered an alternative explanation for these findings. He described the finding as an "anxiety relief" phenomenon by which the anxiety films were so aversive that, by contrast, the erotic films were so much more appealing that they consequently facilitated sexual responding strictly via cognitive processes.

Meston and colleagues examined the effects of SNS activation on sexual arousal using intense, acute exercise as a means of eliciting SNS activity. Exercise was chosen based on numerous pharmacological and physiological studies that indicate that moderate to high intensities of exercise are accompanied by significant SNS activity (for review, see DiCarlo & Bishop, 1999). In the first of this series of studies (Meston & Gorzalka, 1995), 35 sexually functional women between the ages of 18 and 34 participated in two counterbalanced sessions during which they viewed a neutral film followed immediately by an erotic film. In one of the sessions, subjects engaged in 20 minutes of intense stationary cycling before view-

ing the films. Prior to engaging in the two experimental sessions, the women were given a submaximal bicycle ergometer fitness test in order to estimate their maximum volume of oxygen uptake (VO_2 max), an indicator of cardiovascular fitness. This allowed the workload and cycle speed to be set so that all participants exercised at a constant 70% of their VO_2 max. Behaving women exercise at relative workloads, differences in physiological responses resulting from variations in fitness levels are minimized (Grossman & Moretti, 1986). Sexual arousal was measured subjectively using a self-report questionnaire adapted from Heiman and Rowland (1983) and physiologically using a vaginal photoplethysmograph (Simschak & Geer, 1975). Both VPA and VBV were used as indices of sexual arousal. Heart rate was used as an indirect indicator of SNS activation.

The results indicated a significant increase in both VPA and VBV responses to the erotic films after exercise. Heart rate significantly increased with exercise (70 bpm vs. 90 bpm); there were no significant changes in heart rate between the neutral and erotic films. There were no significant differences in self-report measures of sexual arousal, positive affect, or negative affect with exercise, and correlations between subjective and physiological indices were not significant.

Meston and Gorzalka (1996a) used the same methodology to examine the indirect effects of SNS activation in women with sexual difficulties. Twelve participants were sexually functional, 12 reported low sexual desire, and 12 were anorgasmic. There were no significant differences in VPA or VBV responses between the subject groups during the no-exercise condition. With exercise, however, there were significant increases in VPA and VBV among sexually functional women, a significant increase in VPA and VBV responses among women with low sexual desire, and a significant decrease in VPA and a nonsignificant decrease in VBV with exercise among anorgasmic subjects. Heart rate significantly increased with exercise among all subject groups. There were no significant effects of exercise on subjective ratings of sexual arousal, positive affect, negative affect, or anxiety, and no significant differences between groups on these measures.

A follow-up study conducted by Meston and Gorzalka (1995) examined whether the exercise-induced increases in VPA and VBV responses were in fact the result of other potential "nonsexual" consequences of exercise or, alternatively, of the passage of time postexercise given that the presentation of the erotic films consistently followed that of the neutral films. Ten sexually functional women between the ages of 19 and 34 participated in a repeated-measures design study in which they engaged in two counterbalanced sessions where they viewed either a neutral film followed by an erotic film or two consecutive neutral films (Meston & Gorzalka, 1995). In both sessions, subjects engaged in 20 minutes of stationary cycling at 70% of their VO_2 max. Vaginal pulse amplitude and VBV were significantly increased with the presentation of an erotic film, but showed

no change with the presentation of a second neutral film. The results of this experiment suggest that exercise per se does not simply increase VPA and VPA responses but, rather, exercise in the presence of an erotic stimulus enhances genital engorgement.

In the exercise studies noted above, approximately 15 minutes had passed from the cessation of exercise to the onset of the erotic stimulus. Although research indicates that SNS influences remain significantly elevated for approximately 30–40 minutes following intense exercise, at 15 minutes postexercise heart rate had declined considerably from levels during and immediately following exercise. This leads one to question whether exercise would have an even greater facilitatory influence on physiological sexual responses if measured immediately following exercise, and whether the level of SNS activation is in some way related to the level of physiological sexual arousal. Thirty-six sexually functional women between the ages of 18 and 45 participated in a study designed identically to the original exercise study with the following exception: Sexual arousal was measured at either 5 minutes, 15 minutes, or 30 minutes postexercise in an effort to examine the approximate influences of high, moderate, and low levels of SNS activation on sexual responding (Meston & Gorzalka, 1996b). Vaginal pulse amplitude responses were significantly decreased at 5 minutes, significantly increased at 15 minutes (a replication of the original study), and marginally increased at 30 minutes postexercise. Vaginal blood volume findings showed a similar pattern to the VPA results, but did not reach statistical significance. Heart rate significantly increased with exercise in each of the conditions (97, 87, 80 bpm at 5, 15, and 30 minutes postexercise, respectively), and there were no significant effects of exercise on subjective ratings of sexual arousal or positive or negative affect. One interpretation of these findings is that there may be an optimal level of SNS activation for physiological sexual arousal below and beyond which SNS activation may have less of a facilitatory influence or even an inhibitory influence on physiological sexual arousal.

Interpretation of the above studies that used exercise to increase SNS activity is confounded by the potential role of hormones. In addition to creating SNS dominance, exercise at the intensity used in the above studies has been shown to influence the secretion of hormones such as estrogen, testosterone, cortisol, and prolactin (e.g., Keizer, Kuipers, de Haan, Beckers, & Habers, 1987). To date, research has not adequately addressed whether short-term changes in these hormones influence sexual arousal in women.

Broto and Gorzalka (2002) examined sexual responses in pre- and postmenopausal women using laboratory-induced hyperventilation as a means of increasing SNS activity. The authors did not measure heart rate or any other indicator of SNS activity, but cited research that this technique induces sympathetic dominance for approximately 7 minutes (Achenbach,

1960; Mavroudakis, Chiappa, & Kiers, 1994). Twenty-five young premenopausal women, 25 postmenopausal women, and 25 premenopausal women age-matched to the menopausal group participated in two counterbalanced sessions in which VPA and subjective sexual arousal was measured either during baseline or following the hyperventilation procedure. The authors found that SNS activation increased VPA responses compared to baseline only among the young premenopausal women. Using the same hyperventilation procedure to induce SNS activity, Broto (unpublished manuscript) found that SNS activation significantly increased VPA responses among sexually healthy women, but significantly decreased VPA responses among women with sexual arousal difficulties that were psychological in nature. Women with sexual arousal difficulties that were physical in nature showed a marginal but nonsignificant increase in VPA with heightened SNS activity. In both studies, SNS activation using a hyperventilation technique had no significant impact on subjective sexual arousal.

Effect of Adrenergic Agonists on Sexual Arousal

Meston and Heitman (1998) examined the effects of ephedrine, an alpha-adrenergic agonist, on VPA responses. Twenty sexually functional women participated in two counterbalanced conditions in which they received either placebo or ephedrine (50 mg) using a double-blind protocol. Ephedrine significantly increased VPA responses to an erotic, but not neutral, film and had no significant effect on subjective ratings of sexual arousal or on measures of positive or negative affect. The finding that when subjects viewed a nonsexual travel film there were no significant differences in VPA responses between the ephedrine and placebo conditions parallels the finding that exercise significantly increased VPA responses to erotic but not neutral stimuli. As with exercise, this suggests that ephedrine did not simply facilitate physiological responses through a general increase in peripheral resistance but, rather, acted in some way that selectively prepared the body for genital response. While ephedrine substantially increases peripheral sympathetic outflow, interpretation of this study findings is limited by the fact that ephedrine also has centrally acting properties that potentially would account for the results.

In a recent follow-up study, Meston (2004) examined whether ephedrine would be effective in reversing sexual dysfunction induced by selective serotonin reuptake inhibitors (SSRIs). Given that treatment for SSRIs inhibited sexual side effects using centrally acting serotonergic agents may diminish the antidepressant's therapeutic effectiveness (e.g., Gillin, 1994), it was hypothesized that targeting peripheral rather than central mechanisms may be a more viable treatment approach. Presumably, this would circumvent the reversal of antidepressant's therapeutic effects on depression that are presumably centrally mediated. Nineteen sexually dysfunctional women receiving either fluoxetine, sertraline, or paroxetine partic-

pared in an 8-week, double-blind, placebo-controlled, crossover study of the effects of ephedrine (50 mg) on self-report measures of sexual desire, arousal, orgasm, and sexual satisfaction. While there were significant improvements relative to baseline in sexual desire and orgasm intensity, pleasure on 50-mg ephedrine 1 hour prior to sexual activity, significant improvements in these measures as well as in sexual arousal and orgasmic ability were also noted with placebo. Whether or not the women in the study experienced an increase in genital vasocongestion was not assessed; thus assertions regarding the indirect impact of SNS activation on physiological sexual arousal cannot be made. As was the case in the laboratory study noted above, ephedrine did not substantially impact the women's psychological experience of sexual arousal.

Two studies examined the effects of moderate doses of clonidine, a selective alpha₂ adrenergic agonist, on subjective and plethysmograph indices of sexual arousal (Meston, Gorzalka, & Wright, 1997). In the first study, 11 sexually functional women, ages 18–42, participated in two sessions in which they viewed a neutral film followed immediately by an erotic film. In one session the women received a placebo and in one session they received 0.2 mg clonidine 1 hour prior to viewing the films. The study was conducted using a double-blind, placebo-controlled, repeated-measures, protocol. The second study followed the identical procedure with the exception of the following: In both sessions, subjects engaged in 20 minutes of intense stationary cycling 1 hour following either placebo or clonidine administration but prior to viewing the films.

In the first study, 9 out of 15 and 7 out of 15 subjects showed a decrease in VPA and VBV, respectively, with clonidine, but the results did not reach statistical significance. In the second study, which involved heightened SNS activation, there was a significant decrease in both VPA and VBV with clonidine administration during the erotic films. Heart rate was significantly decreased with clonidine during the second (heightened SNS) study only. Subjective ratings of sexual arousal were marginally decreased in the first study and significantly decreased in the second (heightened SNS) study. Because clonidine has both central and peripheral properties, it is unclear at which level clonidine acted to influence sexual responding. Centrally, clonidine may have suppressed sexual responses indirectly via changes in neurohypophysial hormone release or directly by activating central sites responsible for the inhibition of sexual reflexes (Riley, 1995). Peripherally, clonidine may have suppressed sexual arousal by decreasing norepinephrine release from sympathetic nerve terminals. Support for the latter notion is provided by the finding that clonidine inhibited sexual responding only when subjects were in a state of heightened SNS activity. The fact that clonidine has been reported to significantly inhibit SNS, but not hormonal, responses to exercise (Engelman et al., 1989) is consistent with the suggestion that clonidine acted to inhibit sexual responding and

suppress SNS activity. However, given that the role of the alpha₂ adrenoceptor in female sexual function has not been clearly elucidated, the potential that clonidine inhibits SNS outflow to the genitalia is tentative.

Effects of Adrenergic Antagonists on Sexual Arousal

Several studies have examined adrenergic blocking drugs on sexual arousal in women. Rosen, Phillips, Gendrano, and Ferguson (1999) found a facilitatory effect of the nonselective alpha-adrenergic antagonist phentolamine mesylate (40 mg administered orally) on VPA and subjective sexual arousal responses in six postmenopausal women with female sexual arousal disorder (FSAD). A facilitatory influence of phentolamine mesylate on VPA responses was also noted in a larger sample of postmenopausal women in a FSAD-receiving hormone replacement therapy (HRT; Rubio-Auriedes et al., 2002). The study was conducted using a double-blind, placebo-controlled, randomized, four-way crossover design in which postmenopausal women either on ($n = 19$) or not on ($n = 22$) HRT received placebo (vaginal solution or oral tablet), 5-mg and 40-mg phentolamine vaginal solution, and 40-mg oral phentolamine. Physiological sexual responses were significantly greater than placebo with 40-mg phentolamine vaginal solution during the HRT, but not among the non-HRT women. Subjective sexual arousal was increased with 40-mg phentolamine oral tablet and to a lesser degree with 40-mg phentolamine vaginal solution only among the women receiving HRT. Because phentolamine crosses the blood-brain barrier, it is not known whether these effects are attributable to a central or peripheral mechanism, or both.

Meston and Worcel (2002) examined the effects of the alpha₂ adrenoceptor antagonist yohimbine, either alone or in combination with the nitric oxide precursor L-arginine, on subjective and physiological responses to erotic stimuli in postmenopausal women with FSAD. Twenty-four women participated in three treatment sessions in which subjective and VPA sexual responses to erotic stimuli were measured following administration of either L-arginine glutamate (6 g) plus yohimbine HCl (6 mg), yohimbine alone (6 mg), or placebo, using a randomized, double-blind, three-way crossover design. Sexual responses were measured at approximately 30, 60, and 90 minutes post-drug administration. The combined oral administration of L-arginine glutamate and yohimbine increased VPA responses at 60 minutes post-drug administration, compared with placebo. VPA responses at 30 and 90 minutes post-drug administration were increased compared to placebo but did not reach significance. Yohimbine alone had no significant impact on VPA responses at any of the time periods. There were no significant increases in subjective measures of sexual arousal in any of the experimental conditions. These findings are limited by the fact that the study design was unable to control for potential central nervous system effects of yohimbine.

Conclusion

The traditional model of the female sexual response holds that the arousal phase is mediated by parasympathetic activity, with sympathetic impulses predominating at orgasm. However, several lines of evidence suggest that increased sympathetic nervous system activity is a prominent feature of sexual arousal. Lacking sufficient knowledge about the function and distribution of sympathetic nerves, as well as ethical and accurate means of directly manipulating SNS outflow, investigators have been limited to conclusions drawn from indirect observations of SNS activation and inhibition in humans. Studies of women before and after exposure to sexually arousing stimuli have shown that concentrations of norepinephrine and its metabolites are elevated immediately following sexual arousal, and search conducted on women with spinal cord injuries suggests that damage to the spinal cord at the level of sympathetic innervation significantly impairs the sexual response. Physical exercise at intensities that are thought to increase SNS outflow has been shown to enhance sexual arousal responses in women. Based on putative pharmacological manipulations of SNS outflow, several studies suggest that sexual arousal may be enhanced or inhibited by adrenergic potentiation or blockade, respectively. These findings are supported by observations in animal models suggesting that adrenergic agonists increase, and adrenergic antagonists decrease, sexual behavior. However, these findings do not positively establish SNS activation as a mediator of sexual arousal. At least one well-controlled pharmacological study has demonstrated that adrenergic blockade, an analog of SNS inhibition, enhances sexual arousal responses in some women.

Indirect studies of the effects of SNS stimulation have substantial limitations. Although experimental manipulations designed to increase sympathetic activity are informed by previous physiological research, their effectiveness cannot be verified directly. Further, the impact of these manipulations is generally not limited to the SNS, making it difficult to rule out effects due to hormonal or other nervous system changes. By using more reductive animal model, several recent studies have been able to examine the effects of sympathetic and adrenergic stimulation on genital tissue with greater specificity. Using techniques to directly stimulate autonomic nerve branches in the pelvic region, these studies have supported the conclusion that sympathetic impulses cause genital vascular and non-vascular smooth muscle to contract, limiting blood flow and preventing a full vasocongestive response. However, it is not known to what degree the effects of experimentally induced nerve impulses in isolation resemble physiological processes in natural behavior.

In summary, studies of the role of the SNS in sexual arousal have reached seemingly contradictory conclusions. Although putative markers of

increased SNS activity have been associated with enhanced sexual arousal, this is not in accord with physiological research suggesting that sympathetic outflow limits genital responses necessary for physiological sexual arousal. It is possible that indirect approaches to studying the SNS in sexual arousal are not measuring the effects of sympathetic activity, but rather the effects of some other physiological process. For example, pharmacological effects have not typically controlled for the central nervous system effects of the agents used, and exercise studies have not assessed the contribution of hormonal changes that accompany physical activity. On the other hand, it is possible that sympathetic activity may have a facilitatory effect on sexual arousal in the context of other processes. The localized effects of SNS activation on genital blood flow may be overridden by opposing activity of the parasympathetic nervous system, while the systemic effects of SNS activity, such as increased blood pressure, may facilitate genital engorgement (Kim et al., 2002). If this is the case, discrepancies among study findings may be attributable to the fact that some experiments, particularly animal models, manipulate sympathetic outflow in relative isolation. However, these explanations are hypothetical, as the interaction of the parasympathetic and sympathetic systems during sexual arousal remains largely unknown. Better knowledge of the autonomic innervation to the genitalia and autonomic pharmacology is needed to facilitate the understanding of the processes involved in female sexual arousal.

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Neuroendocrine Processes during Sexual Arousal and Orgasm

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Neuroendocrine Response to Acute Sexual Arousal

Despite investigation now spanning well over 30 years, little consensus has been reached regarding the endocrine control of sexual arousal in healthy humans. Historically, the approach to this question has been to measure the endocrine response to various modes of sexual stimulation. This undertaking allows an examination of hormones that may be involved in the up- or down-regulation of a sexual response, depending on the timing and magnitude of such changes. Numerous studies conducted during the past three decades have shown a high level of agreement in regard to cardiovascular responses to sexual activity (Carmichael, Warburton, Dixon, & Davidson, 1994; Littler, Honour, & Sleight, 1974; Neme, Mansfield, & Kennedy, 1976; Whipple, Ogden, & Komisaruk, 1992). In contrast, studies that examined the responses of sympathetic, pituitary, and gonadal hormones have been notable for lack of consistency in their conclusions (Blancher et al., 1999; Brown & Heninger, 1975; Carani et al., 1990; Carmichael et al., 1994; pp. 10-20; Fox, Ismail, Love, Kirham, & Loraine, 1972; Helman, Rowland, Hatch, & Gladue, 1991; La Ferla, Anderson, & Schacht, 1977; Bee-Staffe, & Midgley, 1974; Levi, 1969; Lincoln, 1974; Pike, Kockotte, & Dittmar, 1974; Purvis, Landgren, Cekan, & Diczfalussy, 1976; Rowland et al., 1987; Stoléru, Ennaji, Counot, & Spira, 1993; Wiedeking, Lake, Ziegler, Kowarski, & Money, 1977). Nevertheless, we must be cognizant that technical advances, combined with the use of a number of very different methodological approaches, contribute significantly to the variance between differences in the data from different experiments.

Inconsistent Methodology

Studies examining the neuroendocrine response to sexual arousal and orgasm have employed a number of different methodologies, thus making general interpretations difficult. One potential confound involves the differences in the methods employed for the induction of sexual arousal. Researchers have employed the viewing of stimulating films, imagery of fantasies, masturbation, and coitus. These methods clearly demonstrate different

