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The Role of Ovarian Hormones and the Medial Amygdala in Sexual Motivation

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Abstract
Purpose Although research into the neurobiology of sexual desire in women is active, relatively little is understood about the origins of sexual motivation in women. The purpose of our review is to discuss factors that influence a central sexual motivational state and generalized arousal as potential drivers of sexual motivation in women and female rats.
Recent Findings Sexual motivation is the product of interactions of the central motive state and salient sexually relevant cues. Ovarian hormones and generalized arousal influence the central motive state, and endogenous levels of estradiol and progesterone correlate with sexual motivation and behavior in women. The amygdala is a key integratory site for generalized arousal and sexual sensory stimulation, which could then increase sexual motivation through its downstream projections.
Summary Our model of enhanced female sexual motivation suggests that the combined effects of dopamine and progesterone receptor activation in the medial amygdala increase the incentive properties of a sexual stimulus. Further study into the interactions of ovarian hormones and mediators of generalized arousal on the processing of sexually relevant cues informs our understanding of the neurobiology of female sexual motivation and could lead to the development of therapeutics to treat the dysfunctions of sexual desire in women.

Keywords Estradiol · Progesterone · Progesterone receptor · Proceptive behavior · Dopamine receptor · Dopamine

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Introduction

Sexuality in women is a highly complex process that requires the integration of psychological, physiological, and external elements. One key component of sexuality is sexual desire and motivation. A lack of desire or motivation, rather than physical inability, to engage in sexual behaviors is more prevalent in women [1]. While the neurobiology of sexual desire in women is an active and growing field of study, relatively little is understood about the origins of sexual motivation in women. In this review, we discuss the conceptualizations of sexual motivation and desire in women. We next review the top-down, neurobiological mechanisms through which sexual desire may occur, with consideration of the potential neural circuitry that may mediate sexual desire. We then discuss the role of ovarian hormones and generalized arousal as drivers of sexual motivations. Finally, we review data from animal models which suggest that sexual motivation may arise as a convergence of ovarian hormones and dopamine, which may serve to increase the salience of sexually related stimuli.

Historical Views of Sexual Desire in Women

The distinction of sexual dysfunctions from normal healthy sexual functions is based upon cultural norms and ideals, which themselves are influenced by historical mores and biases. For example, excessive female desire, characterized

by the presence of masturbation and insatiable sexual desires, has been the primary concern historically [2]. The dysfunction of "nymphomania" continued well into the Victorian era when medical professionals sought to repurpose sexual activity from pleasure to reproduction and childbearing (reviewed in [3]). The notion that women have a weak sex drive and only engage in sexual behaviors to please their partner or for reproduction continued to dominate norms in the early twentieth century [4].

The publications of *Sexual Behavior in the Human Female* [5] and *Human Sexual Response* [6] ushered in the modern, scientific era of research into sexual motivations and behaviors. These publications led to a reconceptualization of what constitutes normal, healthy sexual behaviors as they discussed previously taboo topics such as masturbation, orgasm, and sexual activity outside of marriage. Low or inhibited sexual desire, characterized as persistent inhibition of sexual desire, emerged first as a dysfunction in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III). This dysfunction was later renamed hyposexual desire disorder (HSDD) and characterized by deficient or absent sexual fantasies and desire of sexual activity. It is important to recognize that a diagnosis of HSDD is only made when this lack of sexual desire is distressful, rather than in cases in which the absence of sexual fantasies or motivation causes no concern (e.g., asexuality). Women diagnosed with sexual dysfunctions, of which the lack of sexual desire predominates [7–10], report significant levels of emotional and psychological distress, reduced general health, and poor quality of life [11, 12].

Defining Sexual Motivation

To discuss sexual motivation, it is important to first define and distinguish the terms sexual desire, sexual arousal, and sexual motivation. *Sexual desire* has been hypothesized to comprise three forces: (i) "drive," the neurobiological component, which is influenced by neurochemical and neuroendocrine status; (ii) "motivation," the emotional/psychosocial component influenced by both personal affective states and interpersonal relationship; and (iii) "wish," the cognitive component, which is influenced by internalized cultural values, meanings, and rules about sexual expression and by previous sexual experiences and outcomes [13]. All three of these components are integrated into a singular, central state that has the potential to change the probability of response to some stimulus (e.g., a sexual partner) based on incentive characteristics of that stimulus [14••]. Therefore, *sexual motivation* is the hypothetical, internal willingness to engage in sexual behaviors. *Sexual arousal*, in contrast, is defined as the physiological responses of the genitals. In summary, sexual motivation is a mental state of interest in sexual activities and sexual arousal is being physically ready to engage in these sexual behaviors [15, 16].

Models of Sexual Motivation and Arousal

Sexual arousal is the basis for the human sexual response cycle as described by Masters and Johnson [6]. In their model, sexual motivation, the innate drive to engage in sexual behavior, precedes sexual arousal and is measured in terms of spontaneous thoughts and fantasies and the initiation of sexual activities either alone or with a partner [6, 17]. Women, however, often report that sexual desire does not necessarily precede, and often occurs simultaneously with, sexual arousal, such that behavioral and physiological sexual responses in women are circular, rather than linear [18, 19]. While many women do not differentiate sexual desire from sexual arousal, they tend to consider sexual desire as a mental state and sexual arousal as a physical state, corresponding to our definitions of sexual motivation and sexual arousal [15, 16]. The ability of sexual arousal to increase sexual motivation is consistent with incentive motivation hypothesis discussed previously. The presence of appropriate incentive stimuli (e.g., a sexual partner and sensory stimulation) increases the central motive state's activity [14••]. Irrespective of whether sexual motivation occurs spontaneously or through the activation of sexual arousal [20], sexual motivation exists as a distinct concept as is demonstrated by the sexual dysfunctions experienced by women.

The circular relationship between sexual arousal and sexual motivation provides the basis of the current controversy in the classification of low sexual desire, or dysfunction in sexual motivation in women. The fifth revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) created sexual interest and arousal disorder (SIAD) by merging HSDD and female sexual arousal disorder (FSAD) following the circular model in which sexual desire and sexual arousal co-occur [21]. In contrast, the International Society for the Study of Women's Sexual Health (ISSWSH) maintains HSDD as a diagnosis distinct from FSAD [22, 23, 24•]. In support of the separate diagnoses, a cluster analysis of sexual difficulties and characteristics reported by women revealed four distinct clusters: healthy sexual desire and arousal, HSDD characterized by low desire, FSAD characterized by low genital arousal with a sexual partner, and HSDD/FSAD characterized by "combined low desire/arousal" [25•]. Women with HSDD and HSDD/FSAD report significantly less subjective sexual arousal when watching erotic videos even though the genital responses are no different from those of healthy controls [26•]. Sexual thoughts or fantasies and the motivation or desire to engage in sexual activity may not always co-occur in these studies. These findings could potentially reflect syndrome severity, separate neural processes for

fantasies and motivation, and/or distinctions between partnered versus solitary sexual expressions [25].

The central motive state can be influenced by psychosocial factors (e.g., a woman's relationship with her partner and past sexual experiences [27–29]), emotional factors (e.g., positive emotional well-being and self-image), and neurobiological factors (e.g., reward from pleasure and orgasm [13]). All behavioral expressions ultimately depend upon the activities of the brain and the nervous systems. Both excitatory and inhibitory neurobiological factors influence sexual motivation (reviewed in [10, 30]); however, this report will focus on the neurobiological factors that increase motivation for sexual behaviors. One such influence on sexual motivation is nonspecific or generalized arousal, which sets the general level of activity in the brain and can influence specific sexual motivations [14••, 31••]. Indeed, this process may explain how sexual arousal increases subjective sexual desire. Another important neurobiological factor that increases sexual motivation is ovarian hormones.

Ovarian Hormones and Sexual Motivation

Ovarian hormones do not drive sexual behavior as with rodent models (see subsequent), but they can influence sexual motivation and behavior in women. For example, sexual fantasies, desire, and the initiation of sexual activity by women peak around the time of ovulation [32–34]. In addition, women increase the use of cosmetics and ornamentation such as jewelry during the periovulatory period [35], perhaps in an unconscious attempt to attract a sexual partner, as women have a greater interest in meeting men and in engaging in flirtation behaviors during this phase of the reproductive cycle [36]. While much of this research has been conducted in heterosexual women, recent studies indicate that lesbians also show increased sexual motivation during the ovulatory period [37]. In fact, there are peaks in sexual activities and orgasm during this periovulatory phase in lesbian couples [38].

The increase in sexual motivation around the time of ovulation is most likely influenced by increased hormone levels. Sexual activity in premenopausal women is correlated with elevated concentrations of estrogens, luteal progesterone, and luteinizing hormone (LH), but not testosterone or follicular-stimulating hormone (FSH) [39]. Testosterone concentrations also fail to correlate with increases in sexual motivation among naturally cycling women [40••]. Moreover, postmenopausal women receiving hormone replacement therapies also report no increase in sexual motivation following treatment with physiologically relevant levels of testosterone. These women do, however, report increases in sexual desire following administration of estrogens or administration of supraphysiological testosterone in conjunction with estrogens [41]. Taken together, these data suggest that testosterone does not increase sexual motivation in women, leaving estrogens, particularly estradiol, and progestins as the potential drivers of sexual motivation.

Although it seems likely that the periovulatory peak in sexual motivation is due to ovarian hormones, recent studies have begun to elucidate the relationship between women's endogenous, circulating levels of steroid hormones and their motivation for sexual activities. In one such study, naturally cycling women provided daily saliva samples and ratings of sexual desire and activity for one to two menstrual cycles. These daily changes in ovarian hormones were then correlated with these self-reported ratings of sexual desire for a given day and on 1 and 2 days immediately preceding that same day. Salivary estradiol positively predicted sexual desire measured 2 days later. High levels of progesterone, however, predicted reduced sexual motivation for all days analyzed [40••]. These data suggest that the increase in periovulatory sexual motivation is due to increased levels of estradiol, an observation consistent with much of the literature in non-human primates [42].

Women, however, engage in sexual activity at all points of their menstrual cycle, and they initiate sexual activity during luteal phase, potentially as a means to maintain strong partner bonds and relationships [43]. The increase in sexual activity specifically with a romantic partner correlates positivity with luteal progesterone levels, whereas, estradiol levels correlate with interest in sexual activities with a man who is not their romantic partner [44•]. In fact, extra-pair sexual attractions may reflect the increased salience of features consistent with high-fitness genes during ovulation [45, 46]. However, in a follow-up study, Roney and Simmons found no partner-specific desire and that progesterone levels negatively correlated with sexual motivation for sexual activities with a romantic partner or with another man [47•]. Although discrepancies for the role of progestins on sexual motivation in women remain, these data collectively suggest that ovarian hormones contribute to the central motive state for sexual behavior.

Neurobiology of Sexual Motivation

Functional magnetic resonance imaging (fMRI) studies have identified areas of the brain that are activated during and in response to sexually explicit imagery, typically erotic videos. One important limitation of these studies is that neuronal activation may reflect either sexual motivation or sexual arousal. Moreover, these studies also use images of strangers, eliminating any emotional components of sexual motivation. Nonetheless, sexual stimuli reliably activate the visual processing system (e.g., the primary and extended visual cortical areas) and the limbic system regions such as the amygdala, extended amygdala, ventral striatum or nucleus accumbens,

basal ganglia, orbitofrontal cortex, anterior cingulate cortex, hippocampus, mediodorsal thalamic nucleus, and hypothalamus (reviewed in [48, 49]). Of particular interest is the amygdala, the part of the limbic system that processes both positive and negative emotions [50–52]. The amygdala has extensive reciprocal connections between the visual cortex [53]; receives dopamine projections from the ventral tegmental area, a key brainstem nucleus for general motivation and reward [54–58]; and projects to areas such as the hypothalamus, the ventral striatum/ nucleus accumbens, and the mediodorsal thalamus (reviewed in [59–64]). Therefore, the amygdala could integrate sexually relevant visual stimuli with salient, rewarding factors to increase sexual motivation.

Recent imaging studies show increases in areas of the amygdala activity during the viewing of sexual imagery, reflecting a potential role in sexual arousal [65–68]. As previously discussed, sexual motivation can be influenced by emotional states, so in order to disambiguate specific sexual-related signals from general emotional processing, Wehrum and colleagues used sexual images, neutral images (e.g., pictures of conversations), positive emotional images (e.g., pictures of sport/adventures), and negative emotional images (e.g., pictures of mutilated bodies) to control for subjective arousal and emotional valiance. In this study, areas of the amygdala showed increased activation following sexual imagery compared to neutral and positive images, but not negative images. However, other studies have reported activation in the amygdala following the presentation of negative images or aversive olfactory stimuli (see for example [69–71]). Methodological differences, laterality differences (the left or right amygdala), or subregion specificity may account for the variation between studies and the activation of the amygdala by negative emotions. Nonetheless, these data suggest that areas of the amygdala activation could be involved in the general emotional or the generalized arousal component of the central motive state as opposed to specific sexual arousal [65, 72].

Areas of the amygdala may also be a key component of the excitatory influence of sexual motivation. Women without HSDD demonstrated increased left amygdala activation during viewing of sexual videos, but this activation did not occur in women with HSDD [68]. In addition, sexual fantasies or imagined stimulation of the clitoris and nipple increase activation of the amygdala, the sensory cortex, and the nucleus accumbens [73•]. There is no difference in the amygdala activation between heterosexual and homosexual women, nor are there differences based upon the type of stimuli (preferred sex versus non-preferred sex) [67•]. This is not to suggest that sexual preference does not influence brain activation in response to sexual stimuli as the mediodorsal thalamic nuclei and the hypothalamus, areas that receive input from the amygdala, exhibit a small but reliable reduction of activation in response to the non-preferred stimuli [67•]. The left anterior hypothalamus shows significant increases in activation following sexual stimuli, compared to neutral and positive images, and the right anterior hypothalamus shows greater activation of the sexual images compared to negative ones [65]. Taken together, these data suggest that the amygdala may mediate general sexual motivation with the specific sexual expressions shaped by regions downstream of the amygdala, such as the hypothalamus.

Hormonal Modulation of Sexual Neurobiology

Recent studies have begun to examine whether the menstrual cycle also influences the neural response to erotic stimuli. During the ovulatory phase, women had increased activation of the anterior cingulate, the left insula, and left orbitofrontal cortex than during menstruation, but other areas such as the hypothalamus, thalamus, and amygdala show no differences in activation based upon the cycle phase [74]. The women also reported less subjective arousal during menstruation, suggesting that the activation of the anterior cingulate, left insula, and left orbitofrontal cortex may reflect sexual arousal, rather than sexual motivation. This study determined the ovulatory period based upon the date of menstruation, rather than measuring hormones, so that increases in activation by hormones may have been missed. Zhu and colleagues measured brain activation evoked by sexual imagery during ovulation, as determined by LH levels, menstruation, and during another point not during menstruation, and at least 3 days from ovulation, during the cycle. Activation of several cortical areas (e.g., inferior frontal gyrus, superior parietal lobe) decreased during ovulation as compared to menstruation, but the activation of subcortical, limbic areas (e.g., amygdala, hypothalamus, and thalamus) did not change [75]. It is possible that this decrease in cortical areas during ovulation reflects a reduction in cognitive or attentional processes that could be inhibitory to sexual behaviors, representing a release from chronic inhibition of sexual behavior. Moreover, when sexual images are presented during the periovulatory peak of estradiol, women showed an increased interest in these images, suggesting that estradiol may alter the emotional valiance of sexual stimuli [76]. Ovarian hormones, specifically estradiol, may increase excitatory and reduce inhibitory influence on sexual motivation, leading to an overall enhanced activation of the central motive state and an increase in sexual behaviors.

Animal Models of Sexual Behavior

As many mechanistic studies cannot be performed in women, animal models can inform the physiological processes underlying sexual motivation in women. Rats are the most frequently used animals in the study of sexual behavior [77, 78].

Sexual behavior in the rat is characterized by a receptive component and a motivational component. The receptive component is lordosis, a reflexive dorsoflexion of the spine that allows for male mounting and intromission (reviewed in [79]). The motivational component is characterized by approach and solicitation behaviors, which serve to initiate sexual contact with a male [77, 79, 80]. Proceptive behaviors such as ear wiggling, hopping, and darting are a type of sexually motivated behavior typically displayed by a female rat in the presence of a male rat [81]. For example, females that display more proceptive behaviors are pursued more frequently by males [82]. These proceptive behaviors precede the first lordosis during the period of sexual receptivity, and the numbers of proceptive events increase in the minute preceding lordosis [83]. Indeed, nearly all male sexual behaviors are preceded by proceptive behaviors [84]. Other sexually motivated behaviors include solicitations, a head-wise orientation to the male followed by running away; approach behaviors, such as those displayed during paced mating; or presentation behaviors, a prelordotic crouch [77]. These sexually motivated behaviors communicate a female rat's willingness to engage in sexual behavior; therefore, they are the most analogous rat model of sexual motivation in women [33, 77].

The period of sexual receptivity in rats is limited to a few hours prior to the onset of ovulation [85, 86]. Several classic studies have demonstrated the role of both estradiol and progesterone in triggering both proceptive and receptive sexual behaviors in the rat [87]. These hormones strongly affect the responses to sexually relevant stimuli, with modest effects on generalized arousal [31••]. The neural circuitry for lordosis, particularly the role of the ventrolateral portion of the ventromedial hypothalamus (vlVMN), has been well established [88, 89]; however, the neural circuitry underlying sexual motivation in the female has not been as well elucidated.

Animal Models of Enhanced Sexual Motivation

We created a model of enhanced sexual motivation in the female rat by using repeated administration of methamphetamine (METH), a drug of abuse that elicits increased sexual drives, desires, and sexual activities in women [90, 91]. Studies from several laboratories, including our own, have demonstrated that METH facilitates sexual motivation in hormonally primed female rodents [92••, 93••, 94•]. METH more than doubles the frequency of sexually motivated behaviors [92••, 93••]. METH increases proceptive behaviors toward males that present with androgen-mediated cues [95••], suggesting that this increase in sexually motivated behaviors is due to an increase in salience of relevant sensory stimulation. This role for more intense processing of sexually relevant sensory stimuli is reflective of the increased activation of areas of the amygdala by erotic visual stimuli in women. The METH-induced increase in sexually motivated behaviors depends upon estradiol and progesterone, which suggest a convergence of ovarian steroids and METH actions to enhance the salience of sexual cues and increase sexual motivation.

The METH-induced increase in sexual motivation depends upon the actions of both catecholamines and ovarian hormones, leading to neuronal activation and neuroplasticity of posterodorsal medial amygdala (MePD) [92••, 93••]. In addition, the administration of ovarian hormones increases tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine synthesis, in the MePD [92••]. The MePD is necessary for the METH-induced enhancements of proceptive behaviors [96••] and the display of "super-solicitational" behaviors such as the mounting of the male rat in a naturally occurring variant of Long-Evans rats [97]. Furthermore, within the MePD, specific populations of neurons capable of responding to both METH and ovarian hormones mediate the heightened, but not baseline, sexually motivated behaviors [98••]. Based on its projections from the visual and olfactory systems, the MePD is poised to imbue sensory stimuli with sexual relevance, or increases the incentive properties of a stimulus, rather than a direct control of the motor output. Consistent with this role of enhancing the incentive salience, neurons of the MePD encode the intensity of the sexual stimulus in a graded manner [99, 100]. In addition, lesions of the MePD do not abolish proceptive behaviors or approach behaviors in a paced-mating paradigm [96••, 101].

The central state of sexual motivation is influenced by increased generalized arousal, either from METH or another source. Catecholamines, like dopamine and norephinephrine, are key candidates that may mediate METH's actions. The MePD neurons express dopamine type 1 receptors (D_1R) and α_1 noradrenergic receptors [102–104]. Increased activation of D_1R, in the MePD, increases proceptive behaviors by 2.4-fold, similar to that displayed by animals that receive METH [96••]. Activation of either dopamine type 2 (D_2R) receptors or α_1 receptors fails to increase proceptive behaviors. Ovarian hormones are also critical to increase the central sexual motivational state, and the combination of METH and ovarian hormones increases progestin receptors (PR) in the MePD [96••]. Activation of these PRs in the MePD is also necessary for the METH-induced heightened sexual motivation [96••]. Taken together, these data suggest that the MePD is a key region in a central state influenced by non-specific, or generalized, arousal and ovarian hormones that leads to increased sexual motivation.

Current State of Therapies

Sexual desire and motivation may ultimately result from the interplay of a central state, which is influenced by generalized arousal, with a specific sexual drive and the incentive

properties of a sexual stimulus such as a partner [105, 106]. Steroid hormones play a role in this central state, as reflected in the increased sexual motivation during the periovulatory period [31••, 33]. Moreover, these hormones also increase the incentive properties of sexual stimuli with high levels of estradiol increasing emotional valence to erotic imagery and interest in subsequent images [76]. Although testosterone is currently prescribed off-label for female sexual dysfunction, current clinical evidence indicates that treatments that recapitulate circulating estradiol levels increase sexual motivation in peri- and postmenopausal women, and it is unclear whether testosterone is efficacious at increasing sexual motivation in naturally cycling women (reviewed in [41]).

Drugs targeting the central motivate state, particularly non-specific, or generalized, arousal, could be effective treatments for HSDD. Currently flibanserin, a mixed serotonin agonist and antagonist, is the only non-hormonal medication approved to treat HSDD in premenopausal women [107]. Serotonin seems to play a dual role in sexual behavior: activation of the 5-HT_2-R receptor leads to an attenuation of lordosis [108, 109] and 5-HT_1-R activation facilitates both proceptive and receptive sexual behaviors [110]. Flibanserin fits this dual role in that it inhibits 5-HT_{2A}-R and activates 5-HT_{1A}-R [111]. In addition, buproprion, which inhibits the reuptake of both dopamine and norepinephrine, increases sexual satisfaction and orgasms in women diagnosed with HSDD [112]. Finally, apomorphine, a non-selective dopamine receptor agonist, also shows potential as a therapeutic as it increases several aspects of sexual activity including sexual desire, arousal, orgasm, and enjoyment [113]. Similar to METH, all three of these drugs lead to an increase dopaminergic activity either by an extracellular dopamine and norepinephrine levels or by direct activation of dopamine receptors. While METH itself is not a viable treatment for HSDD, future treatments may be developed by identifying and targeting some of the actions of METH while preventing the adverse consequences of METH use such as drug addiction, unplanned pregnancies, and increased rates of sexually transmitted infections.

Conclusions

While the explicit reasons for engaging in sexual behavior are numerous, ultimately, sexual motivation derives from the integrated activities of a central state and incentive properties of a sexual stimulus. Based on the combined effects of activation of the D1 receptor and PR in the MePD to enhance sexual behavior, we propose that the amygdala at large and the MePD specifically should be the focus of further study as a key area in modulating sexual motivation. Furthermore, the effects of ovarian hormones and generalized arousal on the sexually relevant sensory information in this area are important to further elucidate. A more thorough understanding of the basic drivers of sexual motivation in female rats may result in better therapeutics to treat the dysfunctions of sexual desire in women.

Compliance with Ethical Standards

Conflict of Interest Mary K. Holder reports grants from National Institute on Drug Addiction during the conduct of the study.

Jessica A. Mong reports grants from National Institute on Drug Abuse during the conduct of the study.

Human and Animals Rights and Informed Consent All of the reported experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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