

REVIEWS

Pathways of Sexual Desire

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ABSTRACT

Introduction. Sexual desire is controlled by brain systems involved in sexual excitation and inhibition. Hypoactive sexual desire disorder (HSDD) may result from hypofunctional excitation, hyperfunctional inhibition, or some mix of the two.

Aim. This study aimed to identify neurochemical and neuroanatomical systems involved in sexual excitation and inhibition, their role during normal, and hypoactive sexual expressions.

Methods. A comprehensive review of the human and animal literature is made, and a theory surrounding the ways that HSDD can be manifested and treated is presented.

Main Outcome Measures. Drug effects and neural systems derived largely from rat studies that are involved in the stimulation of sexual desire (excitatory system) vs. the stimulation of sexual reward, sedation, and satiety (inhibitory system).

Results. Brain dopamine systems (incertohypothalamic and mesolimbic) that link the hypothalamus and limbic system appear to form the core of the excitatory system. This system also includes melanocortins, oxytocin, and norepinephrine. Brain opioid, endocannabinoid, and serotonin systems are activated during periods of sexual inhibition, and blunt the ability of excitatory systems to be activated.

Conclusions. Drugs that stimulate the activation of hypothalamic dopamine or that blunt endocannabinoid or serotonin release and/or postsynaptic binding may be effective in stimulating sexual desire in animals and humans. The characterization of how those drugs work will help generate a rational approach to drug development in the treatment of HSDD. Pfaus JG. Pathways of sexual desire. *J Sex Med* 2009;6:1506–1533.

Key Words. Sexual Desire; Hypoactive Sexual Desire Disorder; Neuropharmacology; Treatment; Libido

Introduction

Sexual desire seems a straightforward concept, yet there is no agreed-upon definition of what it is or how it manifests itself. In the Diagnostic and Statistical Manual of the American Psychiatric Association—Edition IV—Text Revision (DSM-IV-TR), the diagnosis of hypoactive sexual desire disorder (HSDD) is given when “desire for and fantasy about sexual activity are chronically or recurrently deficient or absent” [1]. By converse logic, then, sexual desire is the presence of desire for and fantasy about sexual activity. This definition appears coherent but is circular. Many clini-

cians and motivational theorists alike view desire as distinct from arousal in both animals and humans. This is apparent in the DSM’s categorization of arousal disorders distinct from desire disorders, a distinction that generally reflects blood flow to the genitals and erectile tissues vs. a “psychological” sexual interest in which individuals “want” sex (as defined by Robinson and Berridge [2]). In practice, however, desire may well be informed or even confirmed by the presence of autonomic and central responses that define arousal, and there is a growing body of evidence that people regard desire and arousal as parts of one another, despite being given distinct

definitions (e.g., [3,4]). When an individual expresses sexual desire behaviorally, it follows that attention and behavior focus on obtaining some form of positive sexual reinforcement. This can occur alone in fantasies or together with others in goal-directed social and sexual behaviors. Thus, in addition to subjective appraisals of desire, the concept encompasses the effort, including risk, that individuals engage in to obtain sexual rewards, the excitement displayed in anticipation of such rewards, and the strength of the incentive value ascribed to a particular sexual stimulus.

All animals, including humans, manifest sexual desire behaviorally. Desire can be inferred from increased motor output in anticipation of copulation or other sexual behaviors or from the amount of work performed for the opportunity to copulate or to obtain primary or secondary (conditioned) sexual rewards associated with these behaviors. Animals, including humans, also choose between two or more sexual incentives based on the strength of the incentive cues and their own internal drive state. What characterizes those behaviors is that they occur before copulation. Solicitation, courtship, operant responses, conditioned locomotion in anticipation of sex, time spent near a place associated with sexual rewards, and the choices made between two or more incentives can all be considered analogies of sexual desire. The strength of the behavior can be observed as increasing or decreasing or can be tested by increasing the criterion level of responding that animals must attain before they are given access to rewards. Simply put, animals with more "desire" will display more robust behavior than animals with less desire. Desire can also be inferred from certain behaviors that occur during copulation, for example, the amount of solicitation a female rat will perform toward a particular male rat or the degree of chasing behavior a male rat will perform to catch a pacing female rat. A growing body of evidence indicates that these aspects of sexual behavior are controlled by a common set of brain regions and altered in a relatively selective fashion by certain drugs that are known to alter desire in humans [5,6]. This, in turn, allows researchers to construct a neurochemistry and neuroanatomy of sexual desire that have predictive validity for humans and other animals. The elucidation of neurochemical pathways that control sexual desire thus generates a vehicle for the construction of rational approaches to pharmacotherapy to treat desire disorders.

Common Structure of Sexual Behavior

All behaviors have a beginning, a middle, and an end, and all organisms that engage in sexual behavior share a common set of principles and end points that define the behavior, along with particular neural mechanisms that make it successful [6]. We must be able to respond to hormonal and neurochemical changes that signal our own sexual arousal and desire. This ability underlies our moment-to-moment level of attention to sexual cues [7,8] and defines a large part of the internal state that is commonly referred to as "sex drive." The rest requires a complex mix of instinct, learning, and feedback, a neural organization that allows us to initiate and terminate interactions with external sexual incentives. We must be able to identify external stimuli that predict where potential sex partners can be found, to seek out, solicit, court, or otherwise work to obtain sex partners, distinguish external cues and behavioral patterns of potential sex partners from those that are not sexually receptive, and to pursue sex partners once sexual contact has been made. Neural mechanisms that allow sexual responding to become habitual or automated with practice exist, and such processes may underlie the ability of sexually experienced animals to be less affected by treatments that disrupt sexual responding in sexually naive animals. Similarly, neural mechanisms that allow the stimulation received during sexual contact to be perceived as rewarding exist. Such reward contributes to the formation of preferences for salient stimuli associated with positive sexual reinforcement and leads to a state of sexual satiety in which inhibitory neural systems are activated. Those inhibitory systems blunt the reactivation of desire, arousal, and sexual behavior for a period of time that depends critically on the intensity of the reward/satiety state, the context in which sexual arousal occurs, and the expectancy of the individual. In the "normal" human sexual response, this pattern flows from desire and excitement at the prospect of sexual interaction, to its initiation, to a rising "plateau" in which sexual responding is maintained or intensified on its way to an orgasm, and finally to resolution or refractoriness after an orgasm (as in Kaplan [9] and Masters and Johnson [10]). Many aspects of sexual desire are manifested before the opportunity to engage in sexual behavior becomes apparent. Thus, although some appetitive responses made prior to copulation are not specific to sexual behavior (e.g., bar pressing in rats or flower giving in people), they can be

considered “sexual” if they occur in anticipation of a sexual reward.

Homologies and Analogies

Because a substantial portion of knowledge concerning the neurochemistry of sexual behavior has been derived from laboratory animals like rats, it is important to understand how their behavior is similar to our own. Despite being many bred for many generations in laboratory settings, rats maintain individual differences akin to wild rats in sexual response [11], including differences in the ability to display both excitatory and inhibitory conditioning of sexual responses paired with sexual reward and nonreward, respectively [6,12,13]. Indeed, Waldinger and colleagues [14–16] have demonstrated individual differences in male rat ejaculatory latencies that have allowed them to classify male rats as “premature” or “delayed” ejaculators using a similar statistical criterion as that for humans and generated a more rational approach to preclinical studies of pharmacotherapy [14–16].

To understand how animal sexual behavior is homologous or analogous to our own, it has been useful heuristically to separate both animal and human sexual activities into so-called “appetitive” and “consummatory” phases that roughly characterize behaviors animals engaged in prior to or during copulation, respectively [17]. Appetitive human sexual behaviors include solicitations, flirtations, fantasy prior to sexual interactions, and the work or strategies employed to negotiate a successful sexual interaction. Such behaviors have unambiguous animal homologies and analogies [6]. Female rats, for example, control the initiation and rate of copulation through a complex act of solicitation and runaway [6,11,18]. Solicitations can be distal or proximal (e.g., behaviors that Beach [19] referred to as proceptive hops and darts around the male), all of which compel the male to chase and mount the female. Sexual desire can also be inferred from male chasing behavior, which reflects the willingness to work to obtain a mount or penile intromission with the female. Appetitive behaviors in particular have become important preclinical models for sexual “desire” in animals because they reflect the willingness of an animal to initiate and engage in a sexual interaction [20].

Like humans, rats show a high degree of behavioral flexibility during the appetitive phase and can learn to associate a variety of neutral stimuli like odors with sexual rewards [12,13,21–26]. In turn, those stimuli act as primes to stimulate desire and

sexual responding. As noted above, it is easy to see how appetitive behaviors such as bar pressing and flower giving are analogous. The question that arises is how we equate the consummatory behaviors between laboratory animals and humans. However, unlike humans, rats do not engage in a copulatory “lock” in which the partners stay together until an ejaculation or an orgasm(s) is reached. Rather, rats make brief copulatory contact, largely directed by the female (reviewed in Pfaus et al. [6]). Females solicit copulation from males and then run away, forcing the males to chase them. After a runaway, a female rat holds an estrogen-dependent stationary posture called “lordosis,” which is intensified when a male palpates the flanks as he mounts. After mounting with penile intromission into the vagina and pelvic thrusting that stimulates the clitoris, the male dismounts, and the female runs away. She then reinitiates contact with the male and runs away again, whereupon he chases her until she stops to hold another lordosis posture, allowing him to mount and intromit again. This cycle occurs several times until the male ejaculates. The female regulates his behavior by soliciting his mounts and by controlling the temporal pattern in which they occur. Her control of the initiation and rate of copulation is called “pacing” [18], and pacing is the critical factor for sexual rewards in the female rat [22,25], just as ejaculation is the critical factor for sexual rewards in the male rat [13,21,26]. In both cases, a sexual reward reinforces behaviors and cues that come before it, making it possible to pair neutral cues such as odors with sexual reward states, so that desire toward those cues (e.g., increased solicitations by females toward males bearing the conditioned cue, ejaculatory preference by males for females bearing the conditioned cue, or conditioned place preference) can be studied directly.

Although there is no human counterpart for the multiple intromission pattern of male rats or the lordosis posture of female rats, copulation in rats can yield clues about motivational and reward states that are altered by pharmacological agents. For example, rats that ejaculate with few or no preceding intromissions (as occurs after injections of the drug 8-OH-DPAT, a serotonergic drug that binds to presynaptic autoreceptors and blocks serotonin release) are said to have a facilitated ejaculation but not a facilitated sexual motivation or desire. In fact, such rats do not show a copulatory-conditioned place preference (see below), indicating that ejaculation that comes too quickly is not rewarding. Conversely, chronic

treatment of male rats with the selective serotonin reuptake inhibitor (SSRI) fluoxetine induces a progressive delay in the ejaculation latency and reduces the number of ejaculations that male rats can achieve in a timed test, along with decreases in measures of sexual desire that are not secondary to decreases in motor ability. Even the lordosis posture can reflect the state of sexual desire in female rats. Female rats that have associated sexual rewards with a male bearing a neutral odor cue not only solicit males bearing the odor selectively but also display higher-magnitude lordosis postures with such males [12,22]. In both male and female rats, the opioid receptor antagonist naloxone blocks the development of appetitive sexual behaviors, high-intensity lordoses, and conditioned place and partner preferences. Thus, by using a rich combination of unconditioned appetitive responses and conditioned copulatory behaviors, a rational psychopharmacology of sexual desire can be constructed by using “models” of sexual desire in rats or other species that are homologous or analogous to human sexual desire.

Structure of Inhibited Desire

The DSM’s description of HSDD [1] as a desire that is chronically or recurrently deficient or absent, taking into account factors that affect sexual functioning, such as age and the context of the person’s life, assumes that its absence occurs in situations that would be appropriate for its expression (the diagnosis should not, for example, be given to someone who loses desire for sex with an abusive partner). To the extent that the desire has a beginning and an end during the normal flow of sexual behavior (or indeed, during *any* motivated behavior), the neural mechanisms underlying its activation and/or inhibition are likely altered in HSDD. This could occur because of hypofunctional excitation and/or hyperfunctional inhibition that leads to a net decrease in ideations or behaviors indicative of desire.

The notion of separate but interactive neural systems for behavioral excitation and inhibition goes back to the work of early neurophysiologists like Sechenov, Sherrington, and Pavlov and more modern psychologists like Gray, who applied the idea to the study of fear and anxiety [27]. It has important implications for motivation in general because it posits that behavior can commence either because of direct excitation or through a process of disinhibition. Bancroft and Janssen advanced this concept further by proposing a theo-

retical model of dual control of male erectile response in which the net expression of sexual behavior is based on the influence of excitatory and inhibitory mechanisms in the brain [28]. Perelman’s “Sexual Tipping Point®” (STP) model expanded those concepts further by postulating a set point or threshold for the expression of all sexual functions or dysfunctions for any individual that varied dynamically within and between any given sexual experience(s) (Figure 1, modified from Perelman [29]). The STP model encompasses the dynamic balancing of excitatory and inhibitory influences on both the body and mind while simultaneously referring to any combination of desire, arousal, orgasm, or resolution response in men and women. All dual control models stress the adaptive nature of excitatory and inhibitory processes. For example, the adaptive nature of sexual excitement would drive individuals to seek out sex partners for reproductive or reward purposes. The adaptive nature of sexual inhibition would guard against situations that threaten the individual, including chronically stressful life events. Bancroft and Janssen viewed sexual excitement or inhibition as an individual tendency: “For the majority, the presence of a fairly typical level of inhibition proneness is adaptive, helping to keep the individual out of trouble. Those whose propensity for central inhibition of sexual response is too high have increased vulnerability to sexual dysfunction. For those whose inhibitory propensity is too low, an increased likelihood of engaging in high risk sexual behavior may result.” (p. 571). Indeed, the study of sexual inhibition is critical if we are to understand how certain events or drugs like alcohol or cocaine may induce sexual disinhibition and the propensity to engage in risky sexual behaviors [30,31].

Responsiveness to inhibition is easy to categorize behaviorally. Individuals either will or will not do something. The presence of inhibition can be inferred if an individual wanted to do something but did not, owing to an obvious unconditional threat or a conditioned cultural proscription against the activity (complete with the possibility of getting caught). This last point, however, raises some interesting issues regarding the arousing nature of stimuli that normally induce inhibition. Central excitation and inhibition both activate the autonomic nervous system. In simple terms, life-threatening stimuli activate the sympathetic arm, increasing blood flow and oxygen uptake to muscles and organs that need it and turning off blood flow to the genitals. However, in response to

Dual Control Model

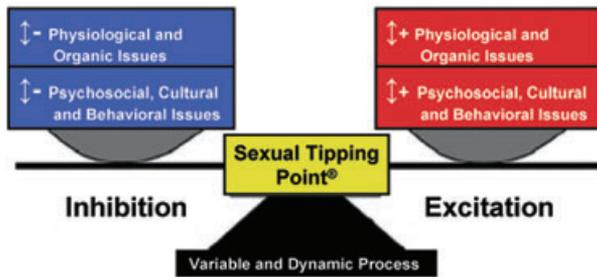


Figure 1 Dual control model of sexual responding that integrates different biopsychosocial influences on sexual function around a Sexual Tipping Point® hypothesized by Perelman [29] to balance the net effect of sexual excitation and inhibition. The interplay between mechanisms of excitation and inhibition generates an individual's level of sexual responsiveness at any given time, and sexual tipping points are thought to exist throughout the phases of the sexual response cycle.

sexual stimuli, both arms of the autonomic nervous system are activated, with the sympathetic system increasing blood flow from the heart and the parasympathetic system increasing blood flow to the genitals. A small degree of stress or threat in humans (e.g., something “naughty” or mildly painful) can be arousing, especially for individuals with low levels of arousability. Translated to a sexual situation, such arousal could be directed into sexual activity, perhaps to the point in some individuals that it becomes a necessary antecedent. Anger, fear, or even short-lived terror can be a prelude to sex specifically because it stirs passion or arousal that leads to an “excitation transfer” into sexual excitement under the right circumstances [32]. However, stimuli that evoke excitation and inhibition may be different for different individuals, such that what inhibits one person may actually excite another.

Mechanisms of Sexual Excitation

Steroid hormones activate mechanisms of sexual excitation by directing the synthesis of enzymes and receptors for several interactive neurochemical systems [5,33]. Those include dopamine (DA), norepinephrine (NE), melanocortin (MC), and oxytocin (OT) systems acting in hypothalamic and limbic regions of the brain to stimulate sexual arousal, attention, and behaviors directed at both

conditioned and unconditioned sexual incentives (Figure 2).

Steroid Hormones

It is generally accepted that steroid hormone actions in the mediobasal hypothalamus and limbic system prime the brain to be selectively responsive to sexual incentives [5,34,35]. Such priming involves molecular actions that result from the binding of androgens, estrogens, and progestins to specific hormone receptor complexes and that lead to the synthesis of different neurotransmitters and transmitter receptors. This creates a neurochemical state in which sexual stimuli are attended to selectively and are more likely to induce sexual responding [5,6,33]. Evidence for this comes from studies showing that natural or surgically induced states of hypogonadism in animals and humans are typically associated with a decreased responsivity to sexual stimuli [36–42] and a loss of appetitive sexual behavior. Indeed, many individuals presenting with decreased sexual desire have concomitant endocrine dysregulation, including decreased

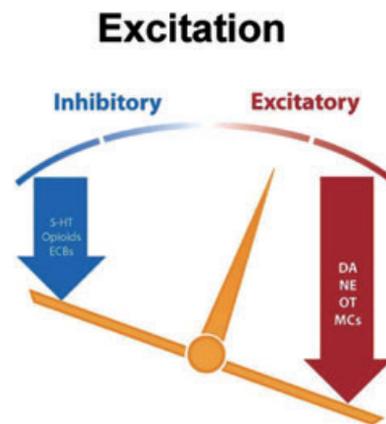


Figure 2 Mechanisms of sexual excitation. Sexual excitation involves the activation of neurotransmitters such as noradrenaline (NE) and oxytocin (OT), which stimulate sexual arousal, and dopamine (DA) and melanocortins (MCs), which stimulate attention and desire, within regions of the hypothalamus and limbic system, in response to sexual cues and stimulation. The activation of those neurochemical systems blunts the influence of inhibitory mechanisms, such as endogenous opioids, which are released in the cortex, limbic system, hypothalamus, and midbrain during an orgasm or sexual reward; endocannabinoids (ECBs), which mediate sedation; and serotonin (5-HT), which is released in those regions to induce refractoriness and sexual satiety. Sexual excitation can be primed internally by steroid hormone actions or externally by sexual incentives or drugs that activate excitatory neurochemical systems.

plasma testosterone and hyperprolactinemia [43]. In castrated male rats, appetitive and consummatory sexual responding is restored by exogenous replacement with testosterone or by placement of testosterone or estradiol in regions of the mediobasal hypothalamus, most notably the medial preoptic area (mPOA) or in midbrain regions such as the ventral tegmental area (VTA) [44–46]. Conversely, gonadally intact male rats that copulate to several ejaculations become sexually exhausted [47,48] and will not display normal patterns of copulation for days afterward. Such males have reduced androgen receptor levels in certain hypothalamic regions such as the mPOA, and limbic regions such as the nucleus accumbens (NAcc) [49]. In castrated female rats, appetitive and consummatory sexual responding is restored by the sequential replacement with estradiol and progesterone [35,50], or estradiol and testosterone [51].

Sexual desire, genital arousal, and the emotional response to sexual stimuli also change across the ovulatory cycle in females. In humans, for example, a number of women report that their sexual desire rises steadily in the week prior to ovulation, and peaks around the time of ovulation, only to be followed by a precipitous decline over the subsequent week [52–54]. Similar findings have been reported in approaches and solicitations made around the time of the midcycle estradiol peak in female rhesus macaques [55] and in female rats on the evening of Proestrus [18,19]. Changes in cognitive ability as a function of the ovulatory cycle have been known for decades [56–59], and increases in subjective sexual arousal and desire induced by an erotic video are reported to be greater during the follicular than luteal phase [60]. Krug et al. examined changes in cortical event-related potentials (ERPs) in premenopausal women during the ovulatory, midfollicular, and menstrual phases of the cycle in response to pictures depicting different activities, including sexually explicit situations [61]. Electrodes were placed across the midline of the skull, and ERPs were sampled from frontal, midparietal, and occipital poles. During the ovulatory phase, the amplitude of the late positive component (LPC) that peaks 550–600 msec after the presentation of a stimulus was larger in response to sexual stimuli than that of the LPCs evoked by the other stimuli (people, babies, or body care products). This did not occur during the other phases of the cycle or when the task required structural processing (determining the number of parallel lines on a screen). The LPC

is thought to reflect deep emotional processing of stimulus valence (e.g., “good” vs. “bad”). Thus, the positive increase in LPC to sexual stimuli suggests a greater valence of those stimuli during the ovulatory phase. Another study used BOLD contrast images taken by functional magnetic resonance imaging to compare brain activation of premenopausal women in midluteal or menstrual phases of the cycle in response to erotic video clips with that in response to neutral video clips [62]. Increased activation by the erotic clips was observed in the anterior cingulate cortex (ACC), left insula, and orbitofrontal cortices during the midluteal phase relative to the menstrual phase. The ability of erotic visual stimuli to activate limbic and cortical structures is reduced after menopause but can be restored to premenopausal levels following combined estradiol and testosterone treatment [63], as can sexual desire and subsequent sexual activity in postmenopausal women who experience its loss [64–66].

Neurochemical and Neuroanatomical Systems

Insights into the neurochemistry of sexual desire can be gleaned from a variety of anecdotal and historical accounts of substances that “enhance libido.” However, such enhancement can mean anything from the stimulation of erection in individuals with some degree of erectile difficulty (e.g., yohimbine) to a stimulation of desire in individuals with “low” desire (e.g., apomorphine) to a disinhibitory effect on individuals with “normal” but perhaps suppressed desire (e.g., alcohol). The use of animal models has advanced the study of both the neurochemistry and neuroanatomy of sexual behavior considerably, and specific neurochemical substrates in different brain regions have been studied in detail.

Dopamine

The major systems for sexual excitement center around mesolimbic, nigrostriatal, and hypothalamic DA (Figure 3), which control general attention to incentive stimuli (especially stimuli of learned significance), concomitant responses made toward those stimuli, and autonomic outflow that controls sympathetic activation in some tissues (such as the heart) and parasympathetic activation of genital blood flow, respectively [67]. Cell bodies of the mesolimbic DA system arise in the VTA and project diffusely to different limbic and cortical structures, including several amygdala nuclei, NAcc, olfactory tubercle and piriform cortex, lateral septum, and the ACC. The mesocortical

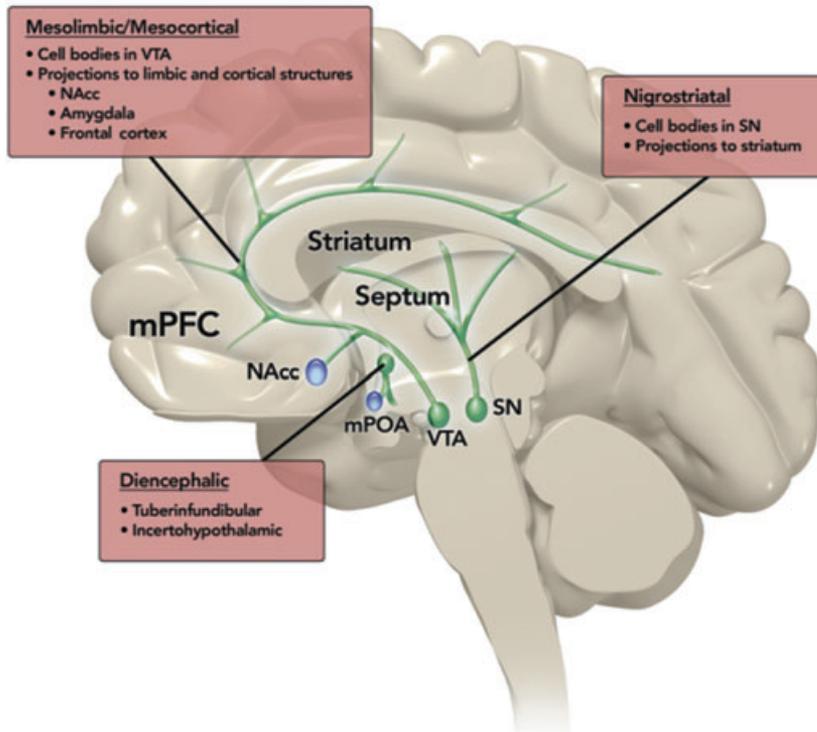


Figure 3 Brain dopamine (DA) systems. Three major systems contribute to sexual arousal and desire, including the diencephalic incertohypothalamic DA system, with terminals in the mPOA of the anterior hypothalamus, the mesolimbic and mesocortical DA system, with terminals in the NAcc (and other limbic regions) and mPFC, respectively, and the nigrostriatal system, with terminals in the striatum (caudate and putamen). These systems control attention and incentive motivation and link sexual stimuli to autonomic outflow. The tuberoinfundibular DA system controls hormone release from the anterior pituitary gland. VTA = ventral tegmental area; mPFC = medial prefrontal cortex; SN = substantia nigra; mPOA = medial preoptic area; NAcc = nucleus accumbens.

arm projects DA fibers largely to the medial prefrontal cortex (mPFC), a region implicated in executive control and inhibition [68]. Cell bodies of the nigrostriatal system arise in the substantia nigra and project to the caudate and putamen, known collectively as the striatum. DA projections to the mPOA arise from the zona incerta under the thalamus [69]. Those latter projections are independent of the systems in the midbrain, although output from the mPOA to the VTA links them together such that DA release patterns in the mPOA and NAcc of male rats during copulation are virtually identical [70]. Lesions of the mPOA disrupt certain appetitive behaviors, such as solicitation in female rats or sexually rewarded maze learning in male rats, and abolish the initiation of copulation in male rats and the timing of pacing and lordosis in female rats [71,72]. Lesions of the NAcc disrupt the ability of distal sexual cues to elicit sexual arousal in male rats [23,73] and disrupt approach behavior in female rats [74]. Finally, general noradrenergic tone in the forebrain is important for the control of arousal and in the autonomic nervous system for the control of genital blood flow. Accordingly, these systems can be viewed as excitatory “targets” in the development of pharmacologically based therapies to treat HSDD. Notably, direct-acting general DA agonists have been studied in this regard in men and

women, as have drugs that act indirectly to increased DA transmission selectively in the mPOA [20,67,75].

A well-documented side-effect of the treatment of Parkinson’s disease with 3,4-dihydroxy-*L*-phenylalanine (*L*-DOPA) is enhanced libido [76]. Subsequent work showed that *L*-DOPA stimulated both appetitive and consummatory sexual behaviors in sexually sluggish or castrated male rats [77,78] and that those effects were blocked by the DA receptor antagonist pimozide. It is now generally acknowledged that DA agonists stimulate sexual excitement and arousal in both rats and humans, especially in circumstances where the expression of these appetitive behaviors is endogenously low. Although the general DA receptor agonist apomorphine stimulates penile erection in normally functioning male rats and men with erectile dysfunction [79,80], it has not been reported to affect measures of sexual desire in normally functional rats. However, the D2-selective agonist quinlorane activated copulation in sexually inactive male rats and reduced the ejaculatory threshold in males who copulated [81]. Conversely, DA antagonists, which are used clinically as major tranquilizers and antipsychotic drugs, disrupt appetitive sexual behaviors and delay the initiation of copulation in normally functioning male rats [82–84] and abolish appetitive sexual behaviors in

castrated female rats primed fully with estradiol and progesterone [85]. Estradiol facilitates DA release, and testosterone potentiates the synthesis of nitric oxide that controls DA release in rats [86–88]. Thus, steroid hormones appear to set the stage for increased DA synthesis and release during periods in which sexual responding might be enhanced.

Like humans, male and female rats display increased motor output in anticipation of sexual rewards (e.g., increased wheel running or level changing in bilevel chambers). These measures of anticipatory excitement can be increased by treatments that increase the incentive salience of the sex partner (e.g., ovariectomized female rats given hormone replacement with estradiol benzoate alone, rendering them moderately sexually receptive, vs. estradiol benzoate and progesterone, rendering them fully sexually receptive and proceptive), and by DA agonist drugs or other psychomotor stimulant drugs (e.g., low doses of amphetamine or cocaine). These measures can be reduced by systemic treatment with DA antagonists or by direct microinjection of a DA antagonist into the mPOA or NAcc.

All animals will work to obtain sexual rewards, and such behavior can be viewed as analogous to desire. Sexual rewards may come in the form of primary reinforcers (e.g., orgasm in humans, ejaculation in male rats, or the ability to regulate or “pace” copulation in female rats) or secondary reinforcers, such as stimuli associated with sexual gratification (e.g., certain facial features, clothes, or smells in humans; certain odors or place cues in rats [89]). In male rats, these behaviors have included performance in obstruction boxes, straight-alley running, maze learning, crossing of electrified grids, nose pokes, and other attempts to “get to” a potential sex partner behind a wire-mesh screen, digging through sand, bar pressing for a sex partner, or responding for cues associated with the arrival of a sex partner. Indeed, to gain access to receptive females, male guinea pigs will learn to run an alley, male pigeons will learn to peck keys, and male stickleback fish will learn to swim through rings (reviewed in Pfaus et al. [6,89]).

Some appetitive instrumental sexual responses are expressed easily, without much prior experience (e.g., nose pokes, digging, obstruction box performance, crossing electrified grids), whereas others require some degree of training (maze learning, bar pressing) [6,36,89]. Those behaviors can be reduced following castration, indicating that gonadal steroid actions in the brain are

necessary for their development and/or maintenance, or following lesions of certain steroid-concentrating brain regions, for example, basolateral amygdala. They can also be reduced after a devaluation of the reward offered by the incentive the male is working for (e.g., switching from receptive female to no female, an extinction procedure) or following infusions of DA antagonists to the NAcc [36]. Restoration of bar pressing in male rats with lesions of the basolateral amygdala can be made following infusions of amphetamine to the NAcc, indicating that mesolimbic DA release is critical for the expression of that behavior and suggesting that the extensive glutamate projections from basolateral amygdala to the NAcc modulate DA release. DA antagonists administered systemically to male rats reduce running speed in a runway that leads to a goal box containing a sexually receptive female, and microinjections to the mPOA disrupt maze learning for sexual reinforcement in male rats. It is likely that different DA terminal regions play a role in different types of unconditioned and conditioned sexual activities. Female rats will bar-press for access to gonadally intact, sexually active males, and access to intromissions from a male that was made contingent on poking a lever with the nose increased the incidents of nose poking in sexually receptive female rats. However, contingent access to male odors alone did not support increases in behavior, indicating that the copulatory stimulation was rewarding. As noted above, paradigms that allow females to control or “pace” the rate of copulation result in sexual rewards. Any imposition of an operant prior to copulatory stimulation, therefore, allows females to pace copulation at their own preferred rate. Although copulation in general increases DA release in the mPOA, NAcc, and striatum of male and female rats, such operant “pacing” of copulation increases DA release more in the striatum than unpaced copulation does. Consistent with this, lesions of the striatum reduce the efficiency of females to pace the copulatory interactions, whereas lesions of the NAcc result in females that avoided sexual contact.

Hull and colleagues have argued that the desire/ejaculation (D1/D2) receptor ratio in the mPOA of male rats is critical for the stimulation of sexual arousal and D1 and D2 through integrated control of behavior and autonomic processes [67,75]. This makes the coordinated activation of mPOA and NAcc critical in the stimulation of sexual excitement. Interestingly, ejaculation decreases DA

release precipitously in the mPOA and NAcc, but not in striatum, of male rats [70]. This decline lasts through the absolute refractory period and is followed by a progressive increase during the relative refractory period, when arousing stimuli can activate copulation in male rats [90]. Interestingly, in males that copulate to sexual exhaustion, DA in the NAcc reduces to precopulatory baseline levels [91]. Removal and reintroduction of the familiar female do not increase DA release, but placement of a new receptive female in with the male results in a small increase. However, this increase is not of sufficient magnitude to induce a full copulatory response.

Norepinephrine

Central noradrenergic systems play a vital role in general arousal and in the control of autonomic outflow. Cell bodies arise in the locus coeruleus at the border of the midbrain and brain stem and project to virtually all forebrain regions, including the hypothalamus, limbic and motor systems, and cortex (Figure 4) [92]. Norepinephrine release in different regions of the brain controls different aspects of motivation with an “inverted U-shaped curve,” in which an optimal level of norepineph-

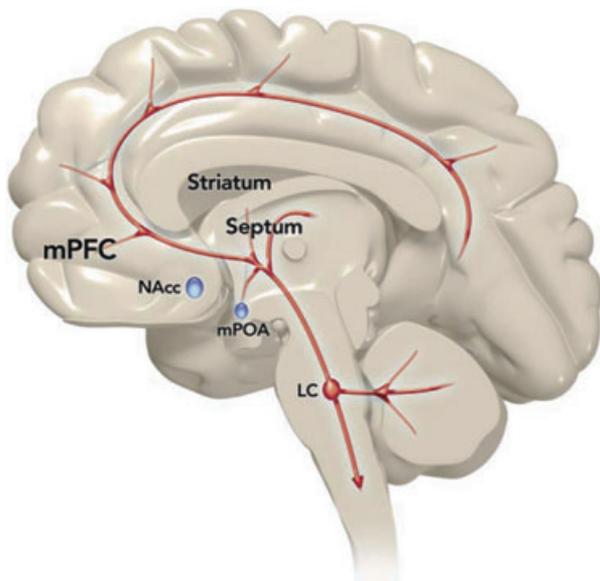


Figure 4 Brain norepinephrine system. This system arises in the locus coeruleus (LC) and projects caudally to the cerebellum and brain stem and rostrally to the hypothalamic, limbic, motor, and cortical systems in the forebrain. This system controls a variety of arousal mechanisms through response selection and autonomic activation. mPOA = medial preoptic area; NAcc = nucleus accumbens; mPFC = medial prefrontal cortex.

rine transmission supports an optimal level of behavior but in which a high amount of transmission disrupts behavior by producing a generalized fear response [93]. Norepinephrine binds to two classes of receptor, classically termed “ α ” and “ β ,” respectively, and differentiated according to whether the receptor stimulates (β) or inhibits (α) the stimulation of the second messenger adenylate cyclase [94]. The α receptors are further classified into α_1 and α_2 subtypes, which are found either postsynaptically or presynaptically, respectively. Thus, actions of norepinephrine at α_1 receptors result in a postsynaptic effect, whereas actions at presynaptic α_2 receptors serve as a short-loop inhibitory feedback mechanism that reduces norepinephrine release. Drugs such as clonidine that act as α_2 agonists reduce norepinephrine release and lead to less sympathetic tone and sedation, whereas drugs such as yohimbine that act as α_2 antagonists block the ability of endogenous norepinephrine to induce inhibitory feedback and thus result in sustained noradrenergic tone.

Estradiol increases norepinephrine synthesis in the brains of female rats [95], and norepinephrine transmission in the ventromedial hypothalamus potentiates lordosis in female rats [33,96]. Estradiol also suppresses α_1 noradrenergic receptor densities in the mPOA of female rats [97], although infusions of an α_1 antagonist to the mPOA have little effect on castrated females primed with estradiol and progesterone [98]. Although systemic administration of the α_2 agonist clonidine to sexually inactive, castrated male rats does not stimulate copulation [99], it decreases the proportion of gonadally intact, sexually active male rats that achieve ejaculation [100]. In women, clonidine reduces the vaginal response to erotic stimuli [101]. Administration of the α_2 antagonist yohimbine stimulates penile erection in male rats and men via autonomic activation [102] and can reverse the sexual inhibition that follows sexual exhaustion in male rats [103]. Yohimbine increased the rate of mounting in male rats [104] except at high doses where it inhibited mounting altogether. Conversely, lesions of noradrenergic cells in the locus coeruleus increase the postejaculatory refractory period of male rats, and administration of norepinephrine synthesis inhibitors like sodium diethyldithiocarbamate increases the mount and intromission latencies, suggesting a decrement in sexual desire [105]. Such a decrement could be explained by sluggish arousal induced by diminished norepinephrine transmission. It is likely that decreased noradrenergic tone

could easily account for decreases in sexual desire owing to insufficient general arousal. This may play a role in the manifestation of decreased sexual desire in generally hypoarousable individuals.

Melanocortins

Neuropeptides derived from Pro-opiomelanocortin (POMC) include β -endorphin, adrenocorticotrophic hormone (ACTH), and α -melanocyte stimulating hormone (α -MSH). The latter two bind to different melanocortin receptors (MCRs) of which at least five types exist [106]. Of those, the MC3 and MC4 subtypes exist in hypothalamic and limbic regions of the mammalian brain [107]. Cell bodies of this system arise in the arcuate and periarculate nuclei near the base of the third ventricle in the hypothalamus and project axons diffusely to the hypothalamus, limbic system, midbrain, and brain stem (Figure 5) [108,109]. Estradiol increases α -MSH levels in the mediobasal hypothalamus of female rats [110,111], suggesting that α -MSH release may be one of several intermediaries of estrogen action.

Recently, two MC agonists, melanotan-II (MT-II) and its metabolite bremelanotide (formerly PT-141), have been reported to stimulate both

sexual arousal and desire in humans and rats following intranasal, intravenous, and subcutaneous administration. Both MT-II and bremelanotide stimulate erection in sexually functional men and rats, and in men with erectile dysfunction [112–114]. Bremelanotide also stimulates appetitive level changing in male rats (unpublished observations). In women [114,115] and female rats [116,117], MT-II and bremelanotide increase measures of sexual desire, including solicitations and hops and darts in rats and subjective measures of desire in women. The effectiveness of systemic MT-II and bremelanotide to stimulate sexual desire in female rats has been replicated following infusions to the lateral ventricles of the brain (indicating a central mechanism of action) and following infusions directly to the mPOA [20]. Interestingly, systemic administration of bremelanotide stimulates DA release selectively in the mPOA, and its effect on solicitations is blocked by coadministration of a selective MC4 antagonist or D1 antagonist [20]. This suggests that MCs act presynaptically to increase DA release in the mPOA and that such release acts on D1 receptors there to facilitate sexual desire. It is not yet known whether this mechanism also controls the induction of penile erection and increases the level changes in male rats.

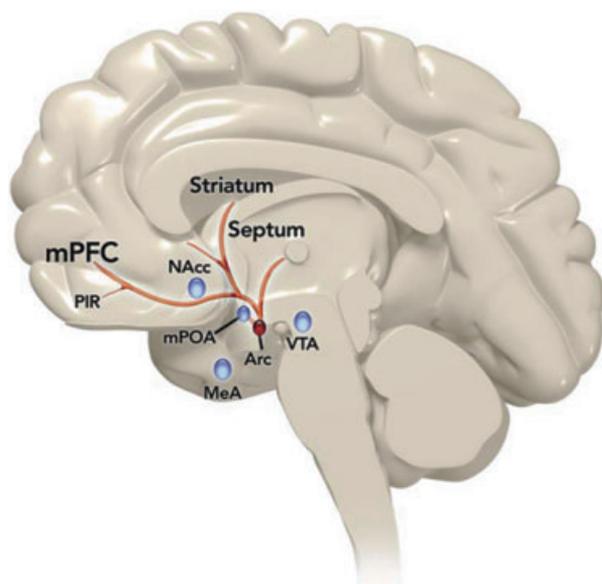


Figure 5 Brain melanocortin system. This system arises in the arcuate nucleus of the hypothalamus (Arc) and projects rostrally to hypothalamic and limbic forebrain regions. This system potentiates sexual desire through an interaction with DA release in the mPOA. DA = dopamine; mPOA = medial preoptic area; NAcc = nucleus accumbens; mPFC = medial prefrontal cortex; VTA = ventral tegmental area; MeA = medial amygdala; PIR = piriform cortex.

Oxytocin

OT is a neuropeptide that has been identified as a “bonding hormone” in both sexual and parental behavior [118,119]. OT cell bodies are found in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus. Large, magnocellular neurons in those regions project to the posterior pituitary whereas small, parvocellular neurons project diffusely throughout the hypothalamus and limbic system (Figure 6). Infusions of OT to the mPOA or ventromedial hypothalamus facilitates lordosis behavior in female rats [120,121], whereas infusions to the PVN of male rats stimulates penile erection [122]. Systemic administration of OT facilitates ejaculation in male rats treated chronically with the SSRI fluoxetine [14,123] and facilitates the acquisition of a sexually conditioned partner preference in male rats (unpublished observations). Conversely, infusion of an OT receptor antagonist blocks bonding. Sexual incentives activate OT release in the brain of male rats [124], and neutral odors associated with sexual rewards activate parvocellular OT neurons selectively in the PVN of male rats [125]. Interestingly, stimulation of D2 receptors in the PVN stimulates

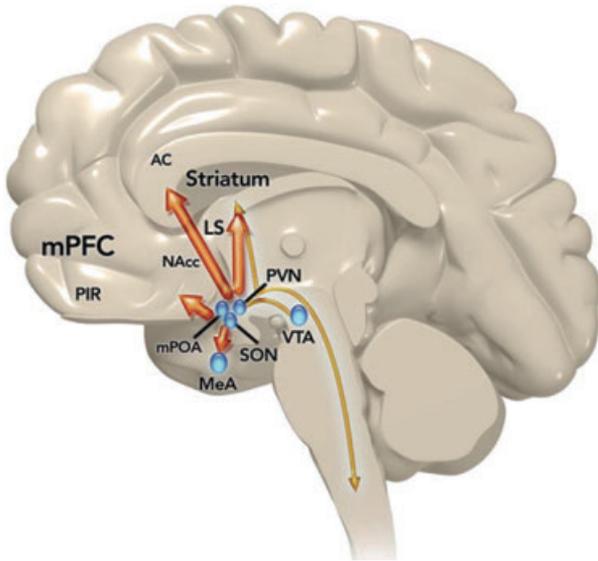


Figure 6 Brain oxytocin (OT) system. Cells arise in two hypothalamic regions: the paraventricular nucleus (PVN) and the supraoptic nucleus (SON). Large (magnocellular) neurons in those regions project to the posterior pituitary gland, where OT is released directly into the bloodstream. Smaller (parvocellular) neurons project to other regions of the hypothalamus and the limbic system. This system is involved in the stimulation of genital blood flow during sexual arousal and in linking sexual rewards to bonding. AC = anterior cingulate gyrus; mPOA = medial preoptic area; NAcc = nucleus accumbens; mPFC = medial prefrontal cortex; VTA = ventral tegmental area; MeA = medial amygdala; PIR = piriform cortex.

OT release and increases extracellular DA levels in the NAcc [126], suggesting another mechanism by which hypothalamic DA can integrate with mesolimbic DA through an OT intermediary. It is also notable that the PVN receives a substantial neural projection from the mPOA [127], raising the possibility that the activation of the mPOA can lead in sequence to the activation of the PVN.

Mechanisms of Sexual Inhibition

Relative to sexual excitation, far less is understood about mechanisms of sexual inhibition. It is assumed that sexual inhibition is an adaptive response that serves both reproductive and social end points, for example, to keep individuals out of trouble or to allow a sufficient amount of sexual reward to induce a restorative state of sexual satiety that presents as a “refractory phase.” Kinsey et al. [128] hypothesized that sexual refractoriness in males occurs after ejaculation to allow time to generate more sperm for a subsequent ejaculation. Bancroft and Janssen [28] argued that a normal

amount of sexual inhibition keeps individuals from engaging in risky or inappropriate sexual behaviors, which a lack of inhibition would promote (as occurs in individuals with KluverBucy Syndrome, dementia, or frontotemporal cortical and amygdala damage sustained after head trauma) [93,129–132]. Conversely, too much central inhibition was viewed as increasing the risk of sexual dysfunction, including inhibited arousal, desire, and/or a diminished capacity to achieve sexual gratification. Excessive inhibition may thus lead to a numbing of intimacy and disruption of bonding between partners, to the point that sexual activity, if it is engaged in at all, becomes a routine of “going through the motions” rather than an enriching and rewarding experience.

The concept of inhibition is further related to that of “executive function,” in which the individual has to choose among several possibilities and create hierarchies based on expectancies, planned actions, and calculations. Cognitive psychologists view executive functions as the role of the prefrontal cortex [133,134], which must inhibit a complex and ongoing interplay of motor tendencies to arrive at planned and sustained actions. People or rats with disrupted prefrontal function,

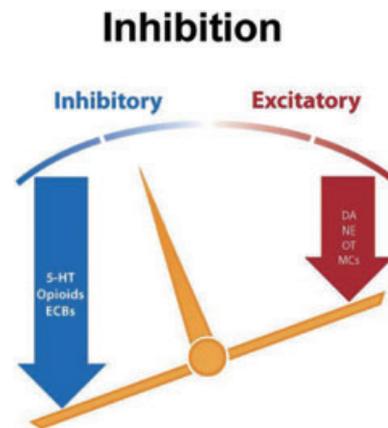


Figure 7 Mechanisms of sexual inhibition. Brain opioid, endocannabinoid, and serotonin systems blunt the action of excitatory mechanisms. This occurs normally at the end of the sexual response cycle during a period of “sexual satiety” or refractoriness (e.g., after one or many orgasms). However, it can also occur if the endogenous inhibitory mechanism(s) is (are) tonically activated by situational variables such as stress or by drugs that augment their actions (e.g., SSRIs). They can also be overly activated when sexual excitatory mechanisms are endogenously blunted, as may occur in hypogonadal individuals or those taking drugs that diminish excitatory influences directly (e.g., major tranquilizers). SSRI = selective serotonin reuptake inhibitor; DA = dopamine; NE = noradrenaline; OT = oxytocin; MC = melanocortin; ECB = endocannabinoid.

either because of lesions or neurochemical imbalance, have great difficulty focusing attention on tasks, are unable to inhibit competing responses, and experience retroactive and proactive interference [133–137]. With regard to sexual behavior, it is assumed that cultures superimpose a moral value of “right” and “wrong” on the hierarchies so that some behaviors that feel good are “right” and can be experienced without guilt, whereas others are “wrong” and carry the weight of guilt and/or rule of law against them. This type of inhibition represents an “approach-avoidance” conflict, where the expectation of reward drives the desire, but the inhibition imposed by the real or perceived aversive consequences of engaging in sexual activity blunts the initiation of behavior. Finally, sexual inhibition can also be induced by sexual nonreward. This type of inhibition overlays itself on desire components directly to suppress them. Accordingly, the “prosexual” nature of drugs such as alcohol or cocaine may be a function of their ability to disinhibit such suppressed sexual responding. For example, sexually active male rats have to learn to inhibit their sexual advances toward sexually nonreceptive females [138]. Once learned, this inhibition can be disinhibited by low doses of alcohol.

To the extent that a blunting of attention toward sexual incentives and the inhibition of sexual responses are observed naturally during the sexual refractory state, it can be speculated that inhibitory systems exist in the brain that are activated by mechanisms of sexual reward and satiety (Figure 7). These systems inhibit the activation of excitatory mechanisms reviewed above and possibly shift attention and behavior to nonsexual stimuli or situations. At least three neurochemical systems may do this simultaneously in the brain: opioids, which mediate sexual reward states; endocannabinoids, which induce sedation; and serotonin, which induces satiety.

Opioids and Reward

Sexual desire is inextricably linked to sexual rewards. However, it is difficult to know exactly what is rewarding for any person or within a culture, and sexual behavior can occur for reasons that have nothing to do with sexual gratification per se. But sexual reward as a general concept has a more pervasive problem: its association in psychology with positive reinforcement. Positive reinforcers are traditionally considered events or stimuli that increase the probability of ongoing behavior (e.g., [139]). Small food pellets to a

hungry rat are positive reinforcers because they increase responding for them. Playing with one’s hair or sideways glances during a bout of flirting would also be considered positive reinforcers if they increase the degree of responding between the flirting pair [140]. However, large rewards, such as one or more orgasms that induce satiety, force the theory to become curvilinear because such mechanisms place negative feedback on behavior by activating inhibitory neural pathways. Satiety mechanisms are absolutely critical for any regulatory behavior [141]. But is satiety rewarding?

In any motivational system, rewards should be considered a dynamic function with an inverted U-shaped relationship to ongoing behavior: Low rewards do not sustain behavior, moderate to ideal rewards do, and high rewards induce the inhibitory feedback that characterizes satiety. With regard to sexual behavior, rewards that sustain sexual arousal and desire might be considered low to moderate, whereas high rewards like orgasm(s) might be those that induce a period of sexual refractoriness. The reward value of satiety may also depend on the time frame. Although sexual satiety decreases sexual responding in the short term, the reward associated with it in male and female rats is necessary for the conditioning of sexual preferences and heightened anticipation for sex in the long term. A final note of caution: In the study of feeding, satiety lies on a continuum to aversion where continued food ingestion after one is full leads to emesis. Likewise, continued genital stimulation after an orgasm can be experienced as aversive in both men and women [10], although the nature of the sensation is obviously different.

Opiates like heroin produce a rush of euphoria followed by a prolonged period of relaxation [142], a state that has been referred to as a “pharmacogenic orgasm” [143]. This opioid reward state induces a dramatic decline in sexual arousal and desire in both men and women and inhibits the ability to achieve an orgasm in those who are able to generate enough sexual arousal to sustain sexual intercourse [142]. A “natural” version of this state is induced by an orgasm (e.g., [144]) and by certain copulatory behaviors in rats. For example, ejaculation in male rats induces the release of endogenous opioids [145] and is the critical component of sexual reward that supports the induction of conditioned place and partner preferences [13,21]. This reward state is dependent on opioid transmission because the administration of naloxone

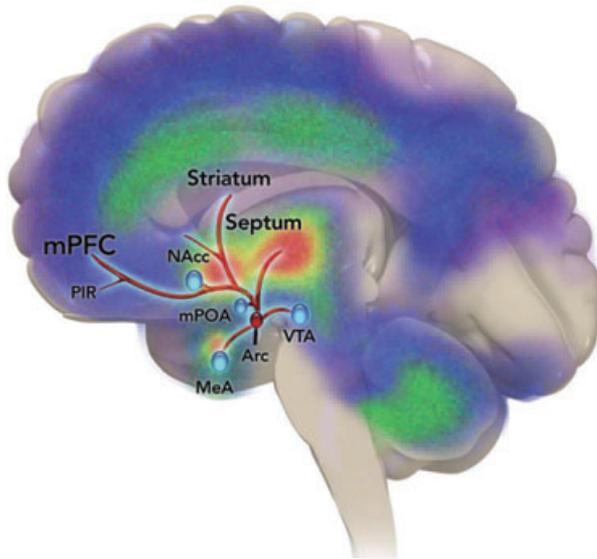


Figure 8 Brain opioid systems overlaid on opioid binding regions (high density of receptors indicated by red to yellow, lower density in green to blue). Three systems exist: the pro-opiomelanocortin (POMC)-derived opioids such as β -endorphin, which arise from the same population of projection neurons that produce the melanocortins; the interneurons in the cortex, limbic system, hypothalamus, and brain stem, which produce enkephalins and dynorphins; and the intrinsic hypothalamic fibers, which contain endomorphins. These systems are activated at orgasm in humans, at ejaculation in male rats, and during paced copulation in female rats. They shut down hypothalamic regions associated with sexual arousal and desire, thereby inducing refractoriness. However, opioids are also released in the VTA during phases of sexual arousal and desire and help to disinhibit DA neurons and, thereby increasing DA release in mesolimbic terminals. This is an important mechanism by which experience with sexual rewards sensitizes sexual excitement once the inhibitory effects of refractoriness and satiety wear off. VTA = ventral tegmental area; DA = dopamine; mPOA = medial preoptic area; mPFC = medial prefrontal cortex; NAcc = nucleus accumbens; PIR = piriform cortex; MeA = medial amygdala.

during training blocks the development of the preferences [21]. Injections of the nonselective opioid receptor antagonists naloxone or naltrexone also reverse the sexual inhibition displayed by male rats after reaching sexual exhaustion [146]. Similarly, in female rats, the ability to control or “pace” the initiation and rate of copulation supports the conditioning of place and partner preferences that are blocked if naloxone is administered during training [12,22–25]. In female rats, the expectation of sexual nonreward (induced by naloxone during their first few sexual experiences with males) creates a state in which solicitations are inhibited, despite full priming with steroid hormones [12]. Interestingly, in males, the reward

state also requires a critical level of arousal prior to ejaculation to support the conditioned preferences [147], suggesting an interaction between the intensity of sexual activity prior to an ejaculation or an orgasm and the degree of reward experienced from it.

Opioid peptides are derived not only from POMC (β -endorphin) but also from pro-enkephalin (Met⁵- and Leu⁵-enkephalin) and prodynorphin (DYN-A, DYN-B), which bind differentially to the three classes of opioid receptors: μ , δ , and κ [148]. Opioid neurons exist as projection neurons from POMC-rich periaruate fields (the same neurons that give rise to α -MSH) and as interneurons in forebrain and midbrain regions of the VTA, NAcc, striatum, ACC, and cortex (Figure 8) [109]. Infusions of μ opioid receptor agonists to the mPOA inhibit sexual behavior in male rats [149–151], and infusions to the mPOA or VMH inhibit sexual behavior in female rats [152]. Conversely, μ opioid receptors are activated in the mPOA following copulation in male rats [153], and infusions of a μ antagonist to the mPOA, but not NAcc, block sexually conditioned place preference [154]. Enkephalin levels

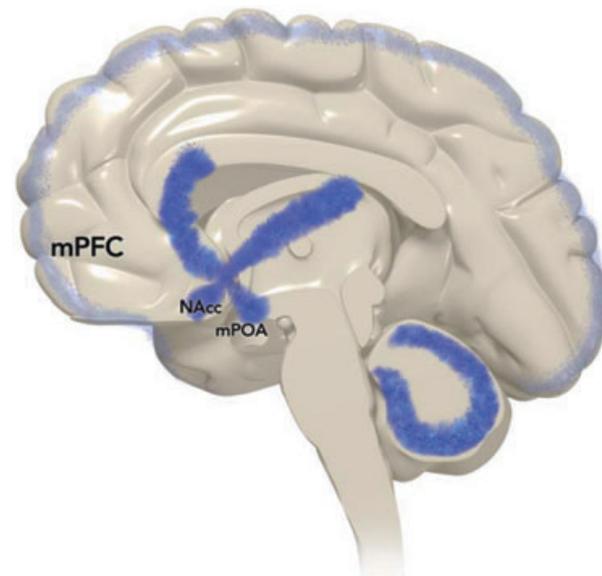


Figure 9 Brain endocannabinoid systems. Cortical, limbic, hypothalamic, and motor regions contain medium to high density of CB1 receptors (in blue), and cells that make endocannabinoids (e.g., anandamide) are intrinsic to those regions. This system induces a natural anxiolytic and sedative effect that counteracts stress activation through the modulation of DA and NE release. It is itself modulated by brain opioid and serotonin release. CB1 = cannabinoid; DA = dopamine; NE = noradrenaline; NAcc = nucleus accumbens; mPOA = medial preoptic area.

are also elevated in the frontal cortex, hypothalamus, and midbrain of sexually exhausted or inactive male rats [155]. These data suggest that opioid release in the hypothalamus, and in particular the mPOA, produces a reward state and is a major factor in sexual refractoriness.

In contrast to the induction of sexual refractoriness in the mPOA, opioids in the VTA stimulate sexual activity in sexually sluggish male rats. For example, infusions of morphine or dynorphin 1-13 to the VTA stimulated female-directed behavior and mounting in male rats, and repeated administration of morphine to this region sensitized DA release in the NAcc [156]. Interestingly, repeated exposure of male rats to sexually receptive females also sensitized DA release in the NAcc, an effect that was attenuated by pretreatment with naloxone [157]. Naloxone infusions to the VTA also block the development of anticipatory level changing in bilevel chambers [158]. Opioids in the VTA stimulate DA release in the NAcc [159,160]. This occurs by opioid-induced inhibition of γ -aminobutyric acid (GABA) interneurons, which normally place a tonic block on the stimulation of DA cell bodies in the VTA [161]. Thus, opioid release in the VTA appears to sensitize responses to sexual incentive stimuli. However, opioid release also occurs in the VTA in response to sexual incentive stimuli prior to copulation.

Finally, infusion of δ receptor agonists to the lateral ventricles or VMH facilitates sexual behavior in female rats [162,163], whereas infusion to the mPOA inhibits female sexual behavior [164]. A similar effect has been reported for GABA A agonists in the VMH and mPOA of female rats [165]. Local effects of opioids in different hypothalamic regions may modulate the overall electrophysiological responsiveness of neurons to change the way that sexual stimuli are processed or responded to [166], and estrogens may set this up by stimulating the synthesis of enkephalin in the VMH [167]. Interestingly, in the mPOA, estrogen causes the internalization of μ opioid receptors (a signature of activation), but progesterone decreases this internalization, suggesting a mechanism by which the pattern of estrogen and progesterone actions could "time" sexual behavior to coincide with ovulation in the rat [168].

Endocannabinoids and Sedation

Engaging in sexual activity to ejaculation or orgasm(s) induces a state of sedation in which individuals and animals are less responsive to anxiety-

provoking or stressful stimuli [169]. The sedative effects of cannabinoids have been known for centuries [170]. The discovery of the cannabinoid type 1 (CB1) receptor in motor, limbic, and hypothalamic regions of the mammalian brain (Figure 9), and endogenous ligands for those receptors in diffuse populations of neurons and glial cells, has generated a flurry of research into their endogenous function [171]. It has become clear that a variety of emotional and regulatory functions, such as pain, anxiety, feeding, and sexual desire, are mediated by endocannabinoids. In addition, endocannabinoids appear to "cross-talk" with hormone receptor-induced changes in second-messenger actions in the hypothalamus to generate changes in behavior [172]. Several cannabinoid agonists and antagonists have been suggested for clinical use in the treatment of pain, inflammation, feeding, and sexual disorders [173].

Sexually, cannabinoid agonists such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC) have not only effects similar to alcohol, with disinhibited sexual desire in putatively inhibited individuals but also a blunting of somatosensory awareness that leads to an increase in erection and ejaculation latencies [174]. Similar effects have been reported in male rats with both THC and the endogenous cannabinoid agonist anadamide [175,176]. Antagonists of the CB1 receptor, such as SR141716A or AM251, facilitate erection and ejaculation [177-179]. However, sexual motivation in presumably noninhibited male rats is impaired by THC treatment [176]. In that study, approach of a male toward a sexually receptive female was impaired by THC treatment. Although THC facilitates lordosis in female rats [172,180], CB1 agonists can inhibit both lordosis and proximal solicitations (proceptive hops and darts) [181]. Conversely, treatment of estrogen-primed female rats with the CB1 antagonist AM251 increases both lordosis and solicitation behaviors [182]. As in male rats, appetitive sexual motivation (speed in a runway where a male is in the goal box) can be enhanced by CB1 antagonists, suggesting that a state of endocannabinoid activation may carry with it a concomitant inhibition of sexual desire [182]. Interestingly, extracellular concentrations of endocannabinoids in the hypothalamus are highest in female rats during diestrus, a period of sexual inhibition, and decrease toward proestrus and estrus, when females are at their peak of sexual responsiveness [183,184]. Although the study of endocannabinoids is relatively new, the powerful effect of drugs acting as CB1 agonists or antago-

nists is stimulating a rapid assessment of their use in clinical medicine. Antagonists may well be developed for use in the stimulation of desire that has been inhibited by hyperstimulation of endocannabinoid release.

Serotonin and Satiety

Serotonin neurons arise in the Raphe nuclei of the midbrain and send extensive axonal projections to brainstem, midbrain, and forebrain sites, including the hypothalamus, limbic system, hippocampus, and cortex, and down the spinal cord to lower lumbar and sacral regions that control genital reflexes (Figure 10). The idea that brain serotonin induces satiety comes from the feeding literature, in which serotonin transmission in certain hypothalamic regions decreases appetite [185]. This notion linked nicely to those put forth in the 1960s by Meyerson [186] that brain serotonin was responsible for sexual inhibition and that serotonin and DA systems were interconnected and mutually inhibitory with regard to sexual behavior. In his view, treatments that stimulated serotonin release and postsynaptic binding decreased sexual behavior, whereas treatments that inhibited sero-

tonin synthesis, release, or receptor binding facilitated sexual behavior. Evidence for an inhibitory effect of serotonin on sexual behavior came initially from studies using treatments that inhibited serotonin neurotransmission. For example, systemic treatment with the serotonin synthesis inhibitor parachlorophenylalanine (PCPA) facilitates sexual behavior in sexually sluggish, gonadally intact or castrated male rats [45,187]. Electrolytic or neurotoxic lesions of serotonin neurons or systemic PCPA treatment of sexually vigorous male rats produces a dramatic reduction in the length of the postejaculatory refractory period [188], suggesting that serotonergic transmission inhibits the resumption of sexual behavior after ejaculation. Neurotoxic lesions of descending serotonin pathways to the spinal cord facilitate penile reflexes in rats [189], suggesting that they are under tonic inhibition by descending serotonin action. Conversely, delayed or inhibited ejaculation and anorgasmia are common side effects of SSRIs used for the treatment of depression [174]. Similar effects occur in male rats treated chronically with fluoxetine or other SSRIs [15,122], and these effects lead to a decrease in sexual motivation and desire [118,190]. These effects have led to the idea that serotonin mediates sexual inhibition during periods of “sexual satiety” (e.g., after ejaculation, when sexual exhaustion has been reached, or in females with subthreshold hormone priming) [66,191]. Steroid hormones do not produce consistent effects on this system, suggesting that it operates relatively independently of hormonal modulation [191,192].

The development of selective serotonin receptor agonists and antagonists, and the molecular cloning of serotonin receptors generated a baffling number of morphologically and physiologically distinct receptor subtypes. These were reclassified a decade ago into four main receptor classes (5-HT₁, 5-HT₂, 5-HT₃, and 5-HT₄) that contain seven functional receptor subtypes and four recombinant receptors (5-HT_{1D} α , 5-HT_{1D} β , 5-ht1E and 5-ht1F), along with four additional recombinant receptors (5-ht5A, 5-ht5B, 5-ht6 and 5-ht7) [193]. Drugs selective for those receptors have aided researchers in elucidating the role played by serotonin in sexual behavior. For example, systemic treatment of male rats with the 5-HT_{1A} autoreceptor agonist 8-OH-DPAT (which decreases serotonin release presynaptically) dramatically facilitates ejaculation [194–196]. However, far from facilitating sexual behavior, the drug delays the initiation of copulation, and, when

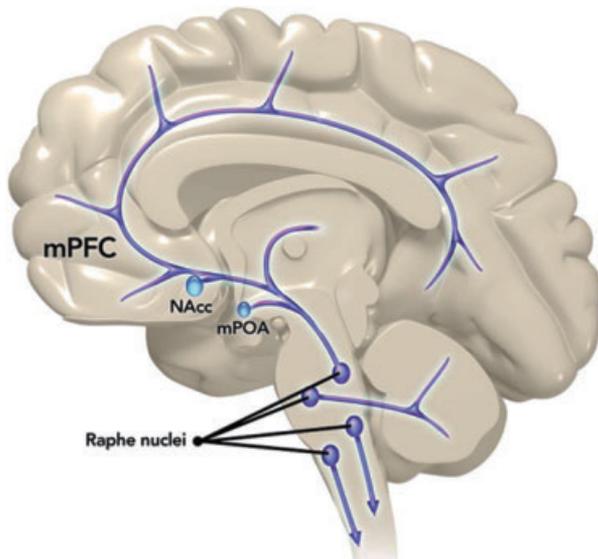


Figure 10 Brain serotonin system. Cells arise from the Raphe nuclei in the brainstem and project caudally to the brainstem and spinal cord and rostrally to the midbrain, hypothalamus, limbic, motor, and cortical regions. In contrast to the euphoria of opioid reward, the activation of this system produces a general sense of satiety, relaxation, and fulfillment. This system appears to inhibit mesolimbic and incertohypothalamic DA release mechanisms in limbic and preoptic terminals by the modulation of descending inhibition from the prefrontal cortex. DA = dopamine.

male rats finally mount, most ejaculate during the first or second intromission. Indeed, the experience of ejaculation under the influence of 8-OH-DPAT does not induce a conditioned place preference [197], further reinforcing the idea that ejaculation needs to ride on a sufficient level of arousal to induce a sufficient intensity of sexual rewards that supports conditioned preferences. However, in male rats made sexually exhausted, 8-OH-DPAT can facilitate mounting behavior [198,199]. Systemic administration of the 5-HT₂/5-HT_{1C} agonist DOI suppressed sexual activity in male rats [200,201], an effect that was antagonized by co-treatment with different selective 5-HT₂ receptor antagonists, all at doses that did not by themselves affect sexual activity. Similarly, administration of the 5-HT_{1B/2C} agonist TFMPP abolished copulation in male rabbits [202]. As mentioned above, the delay in ejaculatory threshold induced by SSRIs can be reversed by systemic administration of OT [14,123] or 8-OH-DPAT [15] or by lesions of the nucleus paragigantocellularis [203], a region of the rostral medulla that contains a large density of serotonin neurons that project to other brain stem and midbrain regions [204].

Infusions of serotonin or TFMPP into the mPOA or NAcc of male rats increased the number of mounts and delayed ejaculation in male rats [205], whereas infusions of 8-OH-DPAT into these brain areas facilitated ejaculation. Indeed, reverse-dialysis of 8-OH-DPAT to the mPOA increased extracellular concentrations of both DA and serotonin there [206]. Levels of the serotonin metabolite 5-hydroxyindoleacetic acid increase in the NAcc during multiple ejaculatory copulations [207]. Serotonin is released in the anterior lateral hypothalamus (LHAA) at the time of ejaculation, and infusions of SSRIs there delay the onset of copulation and delay ejaculation after copulation begins [208]. Interestingly, serotonin release in the LHAA is associated with a decrease in DA release in the NAcc [209], suggesting that ejaculation-induced serotonin release there contributes to the abrupt decrease in NAcc DA following ejaculation.

Although much of the literature on the role played by serotonin in female sexual behavior comes from studies of lordosis, there are occasional hints at effects on female desire. Chronic treatment of female rats with SSRIs reduces lordosis and the amount of time females spend near males [210,211], although tolerance appears to accrue to those effects. However, serotonin

appears to inhibit or facilitate lordosis, depending on the type of serotonin receptor activated [191]. For example, systemic treatment with 8-OH-DPAT inhibits lordosis [212], whereas treatment with 5-HT₂ antagonists facilitates this behavior [213]. The neural mechanisms that generate the stationary spinal dorsiflexion that characterizes lordosis are likely not those that underlie the active headwise orientation and runaway that characterizes full solicitations or the hops and darts that characterize partial solicitations in the female rat [6]. In fact, like mPOA lesions, major tranquilizers that act as both DA and 5-HT₂ receptor antagonists (e.g., haloperidol) typically enhance lordosis while concomitantly abolishing solicitations [85], suggesting that lordosis and solicitations are mutually exclusive behavioral patterns. However, it is also the case that high-intensity lordosis postures are almost always observed in females that engage in a high degree of solicitation of preferred partners [12,21], indicating a positive relationship between those separate neural systems. Systemic treatment with the monoamine oxidase inhibitor pargyline inhibits lordosis and induces a concomitant increase in serotonin levels in the mPOA [214]. Infusions of 8-OH-DPAT to the mPOA inhibit lordosis, especially in a mid-rostrocaudal section of the region [215]. Interestingly, in that study, a majority of females displayed a “frenzied” pattern of hops and darts following 8-OH-DPAT infusions to the same region that suppressed lordosis, suggesting that 5-HT_{1A} receptors in the mPOA play a role in several components of female sexual behavior and perhaps as a mechanism that allows the switching between solicitations and lordosis.

Finally, serotonin appears to exert control over executive function in the prefrontal cortex. Ascending serotonin fibers innervate the prefrontal cortex [216] and modulate descending outputs to a variety of limbic, thalamic, hypothalamic, and midbrain regions, including the mPOA, NAcc, and DA neurons in the VTA [217,218]. The prefrontal cortex contains a high density of 5-HT₁ and 2 receptors, which play a role in inhibiting or facilitating the activity of glutamatergic pyramidal neurons, respectively [219,220]. 5-HT₃ receptors in prefrontal cortex also appear to modulate the ability of fluoxetine to increase DA release there (which in turn produces inhibitory feedback onto mesolimbic DA neurons) [221]. Outputs from prefrontal cortex are excitatory but can stimulate or inhibit DA transmission, depending on whether they innervate DA neurons directly or stimulate

inhibitory GABA interneurons. In this way, ascending serotonin fibers exert finely tuned control over the inhibitory mechanisms of executive function reviewed above. Activation of 5-HT_{1A} and/or blockade of 5-HT_{2A} receptors in the prefrontal cortex enhances the activity of VTA DA neurons that project to the cortex and increases mesocortical DA release [222,223], suggesting an indirect inhibition of mesolimbic DA transmission by serotonin. Interestingly, 5-HT_{2C} receptors are found in GABA interneurons of the prefrontal cortex and appear to modulate their ability to inhibit descending pyramidal neurons [224]. In general, however, activation of 5-HT_{1A}, 1B, 2A, 3, and 4 receptors facilitates DA release, whereas activation of 5-HT_{2C} receptors inhibits release [225]. Moreover, binding of serotonin to 5-HT₂ receptors increases the release of endocannabinoids [226], suggesting that orgasm(s) may result in sexual satiety and a blunting of sexual motivation through multiple neurochemical events that ultimately change the focus of motivational attention and action to nonsexual incentives. The picture that emerges is of serotonin inputs focusing the behavioral inhibition that characterizes executive function by a complex action on multiple 5-HT receptors in prefrontal cortex. The inhibition occurs in part because of inhibitory actions on mesolimbic and hypothalamic systems involved in general and specific attention toward external incentives. Therefore, in cases where serotonergic transmission in this system is overactive, as would occur in individuals on SSRIs, the level of behavioral inhibition should be greater. Add to this the refractory-like state that serotonin can induce on sexual behavior directly through actions in the mPOA and NAcc, and a pattern reminiscent of the one proposed by Bancroft and Janssen [28] emerges of overactive inhibitory systems inducing a propensity for sexual dysfunction, in this case, a propensity for sexual excitement to be suppressed by hyperfunctional serotonin activity in the brain. Interestingly, SSRIs are used to help manage paraphilias [227] and to treat premature ejaculation [228,229], both of which may result from a hyperactive excitatory or arousal systems.

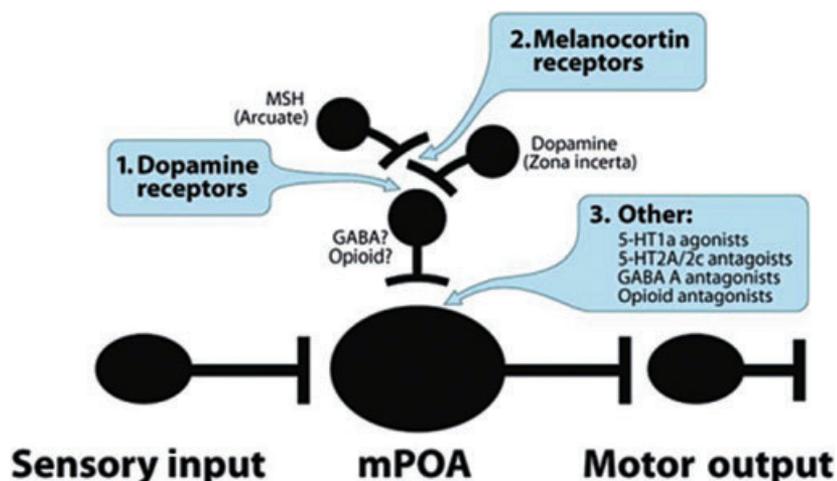
Rational Drug Targets

To the extent that both physiological and psychological “causes” of HSDD involve a hypofunctional excitatory system, a hyperfunctional inhibitory system, or some mix of the two, rational

drug therapies can be envisioned to target one or both of those systems. However, that is easier said than done. Amplification of brain DA transmission carries a risk of drug dependence, addiction, obsessive-compulsive or hypomanic episodes, anxiety, and a sensitization of psychosis, as has been reported for drugs like cocaine [2,230,231]. Inhibition of brain opioid, endocannabinoid, or serotonin systems carries a risk of anxiety, dysphoria, or depression [232,233]. Much of “drug discovery” is serendipitous, and sexual effects are often not recognized until enough subjects in clinical trials or treatment offer the information (e.g., as occurred with fluoxetine [234] and the phosphodiesterase type 5 (PDE-5) inhibitor sildenafil [235]).

Several compounds have been tested in the treatment of HSDD. Although the DA agonist apomorphine induces reliable penile erection in rats and men [79,80,236], its induction of emesis [237] and lack of effect on desire [238] limit its utility. Other drugs have proven more successful. The first to receive peer-reviewed, published clinical findings were the MC analogs MT-II and its metabolite bremelanotide. As mentioned above, both drugs stimulated erections in men and male rats and solicitations in female rats, which prompted successful clinical trials in men as an erection enhancer [112,113] and in women as a promoter of sexual arousal and desire [115]. In the latter case, intranasal bremelanotide was successful in the stimulation of desire in women with decreased libido, and its side effects (nausea, increased systolic blood pressure) were transient and well tolerated in most individuals. The increase in systolic blood pressure in some men, however, was severe enough for the U.S. Food and Drug Administration to demand further safety trials, which effectively ended clinical development of the drug for the treatment of sexual arousal or desire disorders. Systemic administration of bremelanotide activates the mPOA and PVN in both male and female rats and stimulates incerto-hypothalamic DA release selectively in female rats [20]. Bremelanotide stimulated solicitations in female rats following bilateral infusions to the mPOA, but not VMH, and its systemic ability to do this was blocked by infusions of a selective MC-4 antagonist [20]. Interestingly, the ability of systemic administration of bremelanotide to stimulate solicitations in female rats was blocked by infusions of a DA D₁ receptor antagonist to the mPOA, suggesting strongly that the stimulation of DA release in the mPOA and the subsequent activation

Figure 11 Putative neurochemical “targets” in the mPOA that modulate sexual arousal and desire through the activation of incertohypothalamic DA transmission (melanocortins that stimulate DA release or DA agonists that stimulate DA receptors) or the inhibition of γ -aminobutyric acid (GABA), opioid, or serotonin transmission. Endocannabinoids may act here as well. Modified from Hull et al. [67]. MSH = melanocyte-stimulating hormone; DA = dopamine; mPOA = medial pre-optic area.



of D1 receptors there are a critical mechanism of action in the stimulation of solicitations. Systemic administration of bremelanotide also activates the PVN, NAcc, and VTA, an effect that may result secondarily from the activation of the mPOA and its efferents to those regions. Thus, the first targets for the stimulation of desire may well be DA release in the mPOA, its binding to D1 receptors, and intracellular events downstream of D1 binding in postsynaptic neurons that lead to the stimulation of its outputs to the VTA. These in turn may facilitate the stimulation of mesolimbic DA transmission to bring the specific activation of sexual desire in synchrony with general incentive attention. This pathway may form an important “core” of the excitatory system.

The second drug to enter clinical trials for the treatment of HSDD has been flibanserin. This drug works as a mixed 5-HT1A agonist and 5-HT2A antagonist [239,240] and is capable of lowering serotonin levels and increasing DA and NE levels in rat prefrontal cortex [241]. Flibanserin is able to counter the inhibitory effects of stress on behavior but does not induce a conditioned place preference in rats [242]. The unique pharmacological profile of this drug appears to place two “brakes” on the inhibitory serotonergic system: the first to diminish serotonin release by 5-HT1A agonism and the second to inhibit binding to the 5-HT2A receptor involved in inhibitory cortical outflow. To the extent that such outflow inhibits the activation of incertohypothalamic and mesolimbic DA release, this drug should be able to counteract a hyperactive inhibitory system by restoring a more “normal” level of DA and noradrenergic function, in addition to toning down inhibitory serotonergic function. Thus,

the second target for drug development may be the inactivation of inhibitory serotonin inputs to the excitatory system.

A critical feature of both bremelanotide and flibanserin is that they do not stimulate brain DA systems through direct receptor activation, nor do they block the reuptake mechanisms for DA that characterizes psychomotor stimulants like cocaine and amphetamine. Rather, bremelanotide stimulates DA release presynaptically in the mPOA, whereas flibanserin may contribute to its stimulation by blocking inhibitory serotonergic outflow in the prefrontal cortex, lateral hypothalamus, and/or mPOA (Figure 11). This may yield important safety benefits, in that it would be highly unlikely that either drug would contribute to the development of addiction or dependence. Indeed, neither drug alone induces conditioned place preference [116,242]. It is also important that neither drug alters the opioid release that underlies sexual reward, which may reduce the likelihood of “hypersexualization” of patients using these compounds. Should flibanserin and related compounds prove successful in the treatment of low sexual desire in a number of different populations (e.g., premenopausal women with low desire or contraceptive-induced loss of desire, postmenopausal women with low desire, individuals treated with SSRIs), then the theoretical question of whether the sexual excitatory and inhibitory systems operate independently can be answered. This will allow researchers to focus on how the two systems are connected neurologically and how they inhibit one another during the normal expression of sexual behavior. From the studies of Rodríguez-Manzo and Fernández-Guasti on sexual exhaustion in male rats, it would appear that

inhibition is more potent than excitation. In those studies, male rats are allowed copulate to sexual exhaustion, which typically prevents males from responding to females the following day. As noted above, copulatory behaviors (mostly mounts and intromissions) in exhausted males can be stimulated by treatment with the opioid receptor antagonist naloxone or naltrexone, the α_2 adrenergic antagonist yohimbine, or the 5-HT_{1A} agonist 8-OH-DPAT, but not following electrical stimulation of the mPOA [192]. Thus, as with the absolute vs. relative refractory phases, sexual exhaustion as a model of sexual inhibition may possess absolute and relative mechanisms that can be overcome efficiently with treatments that target inhibitory serotonin systems selectively.

Conclusions

Brain pathways for sexual excitation involve the activation of incertohypothalamic and mesolimbic DA transmission in the mPOA and NAcc that focuses attention on incentive sexual stimuli and engages motor patterns of approach and consummation. Collectively, the behavioral patterns stimulated by those systems and the subjective feelings that accompany them constitute the epiphenomenon referred to as sexual desire or, when mixed with genital and sympathetic arousal, "libido." The core of this pathway includes the mPOA and its outputs to the VTA, which contain DA cell bodies that project to various limbic and cortical regions, such as the prefrontal cortex, olfactory tubercle, NAcc, ACC, lateral septum, and corticomedial amygdala. Brain pathways for sexual inhibition involve the activation of inhibitory opioid, endocannabinoid, and serotonergic feedback to various levels of the excitatory pathway. Collectively, the behavioral patterns stimulated by those actions, including sexual reward, satiety, refractoriness, and exhaustion, and the subjective feelings that accompany them constitute the epiphenomenon referred to as inhibited sexual desire. The excitatory pathway is stimulated hormonally and conditionally by the expectancy of sexual rewards. The inhibitory pathway is activated by sexual stimulation that reaches critical thresholds for sexual reward, sedation, and satiety. Both steroid hormones and external incentive stimuli can act as occasion setters for the excitatory system, especially if sufficient time has elapsed since sexual reward or other inhibitory actions were engaged.

As a general rule, inhibition appears to be more "powerful" than direct excitation in the nervous system (e.g., phenomena such as lateral inhibition in the visual system [243]), and "disinhibition" is a common mechanism by which focused activation of neural pathways and behavior is accomplished. Sexual inhibition produces a normal end to sexual behavior; however, its hyperstimulation either from endogenous causes or in response to environmental challenges, such as sexual nonreward and psychiatric treatments that amplify opioid, cannabinoid, or serotonin transmission, leads to a propensity for sexual dysfunction, including disorders of arousal, desire, and/or orgasm [28]. It is not yet known if stressors or experience with sexual nonreward comes to activate inhibitory mechanisms globally or situationally or whether heightened serotonin activity in the frontal cortex, NAcc, lateral hypothalamus, mPOA, or VTA is associated with sexual inhibition. Several behavioral paradigms exist in rats that render them sexually inhibited, and there is a growing body of evidence that this can be overcome by treatments that inhibit the inhibition, thus bringing those systems back to a normal level of functioning [14,15,123]. Bancroft and Janssen [28] developed a Sexual Excitation Scale (SES) and two Sexual Inhibition Scales (SIS1 and SIS2) for men and women, and it will be interesting to see how responses on those scales match predictions made about sexual activity and whether they can track the ability of drugs to improve sexual functioning in inhibited individuals. The pathways reviewed here are by no means exhaustive. Our understanding of the brain is still unfolding, and new mechanisms of extracellular, intracellular, and molecular processings are being discovered in different brain or spinal regions. It is hoped that the ideas put forth here will help guide the development of pharmacotherapy for HSDD and, in turn, help basic researchers and clinicians alike understand that sexual desire and its inhibition are indeed, "all in the head."

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