# The Biologic Basis for Libido

*James G. Pfaus, PhD*, and Lisa A.Scepkowski, MA*

**Address**
*Center for Studies in Behavioral Neurobiology,
Department of Psychology, Concordia University,
7141 Sherbrooke West, Montréal QC H4B 1R6, Canada.
E-mail: Jim.Pfaus@concordia.ca

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Libido refers to a fluctuating state of sexual motivation in all organisms. Sexual motivation is altered by internal factors, such as circulating steroid hormone levels and feedback from sexual stimulation; external factors, such as the presence of sexually relevant incentives; and by the cognitive processing of these factors that provides variations in sexual arousability and expectation of sexual reward. Libido thus reflects constant fluctuations in sexual arousal, desire, reward, and inhibition. Recent advances in neurochemical detection, pharmacologic analyses, and brain imaging, have helped identify neuroanatomic and neurochemical systems that regulate these four aspects of sexual function. Another important factor is the activation of central monoamine and neuropeptide systems that link incentive motivation, reward, and inhibition together with autonomic pathways that detect and relay sexual arousal. The activation of these systems by steroid hormones, and modulation by expectancy of sexual reward, are critical features of the neural "state" in which reactivity to sexual incentives is altered.

## Introduction

Libido has always been associated with sexual motivation. Indeed, the Latin root refers specifically to sexual lust, a term that conjures images of highly motivated behavior. Libido is observed in the strength of desire and response toward a sexual incentive. Therefore, it can be regarded as a conscious reflection of sexual motivation, which we define here as the energizing force that generates our level of sexual interest at any given time. It drives our sexual fantasies; compels us to seek out and evaluate sexual incentives; regulates our levels of sexual arousal and desire; and enables us to masturbate, copulate, or engage in other forms of sex play. Sexual motivation is often viewed as an internal process built upon neuroendocrine mechanisms, such as alterations in brain neurochemical function set forth by steroid hormone actions. It is, however, also modulated by experiences and expectations; learned patterns of behavior; and underlying neural activity related to sexual arousal, desire, reward, and inhibition. In turn, these aspects of sexual function feed back on mechanisms of motivation, either to increase (as in the case of arousal, desire, or reward) or decrease (as in the case of reward or inhibition) the expression of sexual interest or libido (Fig. 1). Delineating the neural mechanisms that underlie these aspects of sexual function has been the focus of recent research in both animals and humans.

## Sexual Arousal

Physiologic sexual arousal in all animals can be defined as increased autonomic activation that prepares the body for sexual activity. This includes parasympathetic blood flow to genital and erectile tissues and sympathetic blood flow from the heart to striated and smooth muscles that participate in sexual responses (eg, increased breathing rate, heart rate, pupil dilation). Sexual arousal also includes a central component that increases the psychologic preparedness to respond to sexual incentives.

Increases in general sympathetic outflow produce increases in libido. This can occur following the use of psychomotor stimulant drugs [1] or the ingestion of herbal "aphrodisiacs" that contain psychoactive alkaloids or other substances that stimulate the autonomic nervous system [2]. However, these putative increases in libido are most likely to occur in sexually specific situations, indicating an interaction between autonomic activation and the central processing of sexual incentives in the immediate environment. High sympathetic activation is an important antecedent of premature ejaculation [3], which is often characterized by "high" libido in anticipation of sexual activity. In women, situations such as acute exercise or exposure to stimuli that arouse a sympathetic response can produce increases in physiologic sexual arousal. However, although vaginal pulse amplitude in response to visual erotica can be increased following exercise [4] or ephedrine [5], this does not translate into an increase in subjective sexual arousal. Thus, general stimulation of sympathetic outflow appears to make individuals more aroused in general and may increase libido if the situation contains appropriate sexual cues.

### Penile erection

Erection is stimulated in hypogonadal men and castrated male rats by androgens [6]. Treatments that enhance penile erection in nonhypogonadal men with erectile dysfunction also enhance penile erection in gonadally intact male rats.

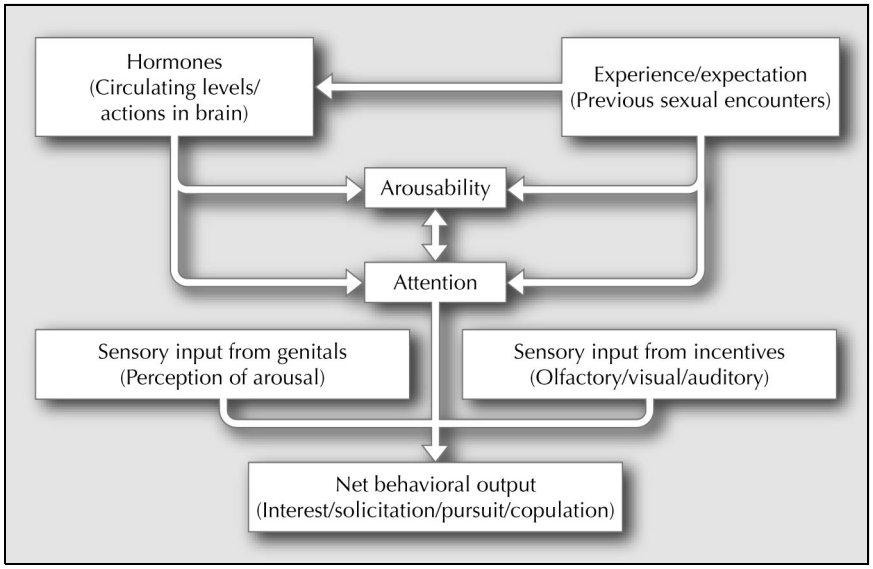


**Figure 1.** Hypothetical relationship of experience, hormonal activation, arousability, attention, and stimulus processing from genital sensations and external incentives on libido. Note that excitatory and inhibitory feedback can occur anywhere in this flow chart to strengthen or reduce responding. Such feedback provides moment-to-moment modulation of libido.

Examples of these treatments include phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil, tadalafil, and vardenafil; dopamine receptor agonists, such as apomorphine; melanocortin agonists, such as PT-141, prostaglandin $E_1$, oxytocin; $\alpha_2$ receptor agonists, such as yohimbine, idazoxan, and imiloxan; and vasodilators that act through nitric oxide substrates, such as nitroglycerine, sodium nitroprusside, and linsidomine [6,7]. It is presumed that these compounds exert their erectogenic actions in the autonomic nervous system, although some of the drugs, such as apomorphine, oxytocin, and the $\alpha_2$ receptor agonists, could exert actions centrally. In fact, apomorphine can induce erectile responses in male rats after infusions to the medial preoptic area (mPOA) of the anterior hypothalamus [8].

Psychogenic erections can be stimulated in men by exposure to visual sexual stimuli. The ease with which men achieve or maintain erection in response to erotic cues can be taken as an index of libido, and latency to, and duration of, full erection can be measured. A recent study of both healthy men and those with erectile dysfunction found that the melanocortin agonist PT-141 induced erections in healthy men and enhanced erection in response to visual sexual stimuli in men with erectile dysfunction [9]. "Noncontact" erections in rats can be provoked by exposure to sexually receptive females or vaginal estrous secretions [10]. Such erections are potentiated by androgens, by drugs that stimulate nitric oxide release in the paraventricular hypothalamus, or by dopamine release in the mPOA [11]. Conversely, dopamine receptor antagonists, such as haloperidol, reduce both physiologic and subjective sexual arousal in men [1] and inhibit erections in male rats [12].

Brain activation during the presentation of visual sexual stimuli has been studied using positron emission tomography (PET) and functional MRI. These studies have found common regions of activation in men and women, including the anterior cingulate cortex, medial prefrontal cortex, ventral striatum/nucleus accumbens, claustrum, hypothalamus, and amygdala [13–17,18•]. However, the last two structures are activated more in men than in women viewing the same sexual stimuli [17,18•]. Activation of the inferior extrastriate cortex, inferolateral prefrontal cortex, hypothalamus, and midbrain was correlated with subjective sexual arousal in men after viewing an erotic film [15,17,18•], whereas activation of the parietal cortex alone in men viewing erotic pictures was correlated with subjective sexual arousal [16]. However, men with hypoactive sexual desire disorder (HSDD) display an abnormal activation of the medial orbitofrontal cortex, a region previously implicated in the inhibitory control of motivated behavior, relative to control subjects [19•]. In male and female rats, nearly identical regions of the brain are activated by copulatory stimulation, including ejaculation and vaginocervical stimulation. A subset of those regions (nucleus accumbens, hypothalamus, amygdala) is activated by exposure of male rats to sexually arousing estrous odors or neutral odors paired with sexual reward [20].

### Vaginal/clitoral arousal

Relative to our understanding of the mechanisms underlying penile erection, far less is known about the activation of physiologic or psychogenic sexual arousal in females. The nitric oxide-cyclic guanosine monophosphate pathway appears to be critical for vaginal blood flow, as it is for penile blood flow. Treatment with androgens facilitates vaginal nitric oxide synthase activity, along with vaginal smooth muscle relaxation [21]. However, studies testing the efficacy of PDE5 inhibitors to increase vaginal blood flow or pulse amplitude on their own, or to augment genital responses during the presentation of visual sexual stimuli, have generated conflicting results. These results range from no appreciable effects, to increases in subjective arousal, to increases in genital arousal without corresponding increases in subjective arousal [22]. Recently, a signifi-

cant positive effect of sildenafil was shown on both subjective arousal and perception of genital arousal in women with arousal disorder and lower vaginal pulse amplitude [23]. Part of the problem with conducting studies of female arousal is the high degree of variability in physiologic and subjective responses. This may reflect several variables, including differences in placement of a vaginal plethysmograph, exposure to different types of sexual stimuli, and the phase of the ovulatory cycle in which women are tested.

## Sexual Desire

Sexual desire has been extremely difficult to define. No agreed-upon definition exists except that inferred from the definition of HSDD in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) [24]. HSDD is defined as a condition in which "desire for and fantasy about sexual activity are chronically or recurrently deficient or absent." By converse logic, sexual desire would be the presence of desire for, and fantasy about, sexual activity. Desire can be viewed as distinct from arousal in animals and humans, with desire constituting a psychologic interest in sex and behaviors that reflect such interest. Despite the fact that desire and arousal are separate processes, desire may be informed or confirmed by the presence of autonomic or central arousal. In fact, many women and men regard sexual desire and arousal as parts of one another, despite their distinct definitions [25,26]. Thus, desire as it is expressed physically in conscious goal-directed behavior, most closely resembles the "lust" of libido.

Desire can be inferred in animals by their willingness to work for sexual reinforcers or in behavior that reflects the anticipation of sexual activity [27]. Several lines of evidence link the desire for sex to the activation of brain dopamine systems. Microdialysis studies have shown that dopamine release in the mPOA and nucleus accumbens increases in male rats in response to both conditioned and unconditioned incentive cues that predict sexual reward [28]. Dopamine receptor antagonists injected peripherally or centrally to these regions disrupt anticipatory conditioned excitement [29]. Lesions of the basolateral amygdala (a region that sends glutamate afferents to the nucleus accumbens) decrease operant responding for secondary sexual reinforcers. This decrease can be reversed by infusions of amphetamine to the nucleus accumbens [30]. Conditioned partner preferences in rats occur when a neutral stimulus (eg, almond odor) is paired with a sexual reward. In male and female rats, we have shown that presentation of the conditioned stimulus alone induces anticipatory psychomotor stimulation and activates brain regions associated with incentive motivation and attention (eg, nucleus accumbens, ventral tegmentum), sexual behavior (mPOA, basolateral and medial amygdala), and reproductive processes (supraoptic and paraventricular nuclei of the hypothalamus). Such activation does not occur in control animals that receive either no association of the odor with reward or that receive random association of the odor with reward and non-reward [31]. Indeed, we have found selective activation of both oxytocin- and GnRH-containing neurons by the odors in males and females, respectively, indicating that systems for sex and reproduction are being activated selectively. Finally, the melanocortin receptor agonist PT-141 increases rates of solicitation in female rats primed with estrogen and progesterone, or estrogen alone [32•]. In preliminary studies, we found that the dopamine receptor agonist apomorphine also increases rates of solicitation in females primed with estrogen alone. To the extent that solicitation in female rats and anticipatory psychomotor stimulation in male rats are analogies of "sexual desire," the activation of these two neurochemical systems in the brain may form an important part of the pathway that mediates libido. Interestingly, estradiol increases both dopamine and melanocortin synthesis in hypothalamic and limbic structures, and androgens activate nitric oxide pathways that facilitate dopamine release. The increase in female-initiated sexual activity around the time of ovulation [33], and the increase in anticipatory sexual activity in males, may be primed by the activation of these two systems by steroid hormones.

## Sexual Reward

An emerging idea from animal studies is that desire is linked to an expectation of reward and that such expectation fluctuates over time given the actual level of reward experienced. Sexual reward is inferred in animals by the strength of operant or instrumental responding toward a particular sexual reinforcer and by the strength of copulatory responding (ie, behaviors that typically denote desire). Contextual factors, such as settings, are also important components of positive sexual experiences for both men and women. Recent work using the conditioned place preference (CPP) paradigm has been particularly useful in delineating the behaviors and neurochemical systems necessary for sexual reward in rats [34,35]. For male rats, ejaculation is critical in the formation of CPP, whereas for female rats, the ability to control the initiation and rate of copulation (pacing) is critical. If one distinctive side of a CPP apparatus is paired with a rewarding sexual experience and the other side is paired with a less rewarding sexual experience (eg, copulation but not ejaculation in males; nonpaced copulation in females), both male and female rats will spend significantly more time in the side associated with reward. This indicates a preference for contextual cues associated with reward. Systemic administration of the opioid receptor antagonist naloxone during rewarded training trials blocks the induction of sexual CPP in both males and females. This suggests that the release of endogenous opioids is a critical factor in the sexual reward induced by ejaculation in males and pacing in females. Interestingly, treatment with dopamine receptor antago-

nists does not block the induction of sexual CPP, indicating that dopamine activation is not a necessary component of sexual reward [36]. However, dopamine is required for animals to display conditioned appetitive responses and may be necessary for smaller, more appetitive types of reward when animals attempt to gain access to sex partners and solicit sex. Systemic administration of opioid agonists disrupts the initiation of sexual behavior in both male and female rats [37], and opioid agonists infused directly into the mPOA have similar inhibitory effects in male rats. Dopamine release decreases abruptly in the nucleus accumbens and in the mPOA when male rats ejaculate, and the incentive salience of females is diminished during the absolute refractory period. The decrease in dopamine release in the nucleus accumbens may be due to an activation of serotonin release in the lateral hypothalamus by ejaculation [38]. Lesion studies suggest that the nucleus accumbens plays an excitatory role in sexual arousal, whereas the lateral hypothalamus plays an inhibitory role in sexual arousal but an excitatory role in the regulation of ejaculation [39].

Activation of oxytocin and vasopressin pathways by sexual reward may be a critical component of future social bonding. Monogamous prairie voles bond with their first sex partner for life and share parental duties [40]. Polygamous montane voles do not and neither do rats. Monogamous bonding in female prairie voles can be disrupted by injections of an oxytocin antagonist, whereas bonding in male prairie voles is disrupted by injections of a vasopressin antagonist [41]. Male prairie voles have a greater density of the vasopressin type 1a (V1a) receptor in the ventral pallidum compared with male montane voles, and viral gene transfection of the V1a receptor to the ventral pallidum of male montane voles renders them behaviorally monogamous [42••]. Polygamous male and female rats can be conditioned to display a partner preference based on odors or other cues associated with sexual reward [43,44], and we have recently found that such cues activate oxytocin and vasopressin neurons, in addition to dopamine release. Thus, a consequence of early sexual reward is bonding to cues that predict the reward, cues that become highly arousing and desired. In humans, this process may play an important role in the formation of preferences for cues that we find attractive at a distance.

Brain imaging studies have also been conducted in men and women during manual genital stimulation to orgasm [45•,46•]. In men stimulated to ejaculation, PET revealed an increased activation of the cerebellum and midbrain regions, including the ventral tegmental area, zona incerta, subparafascicular nucleus, intralaminar thalamus, lateral putamen, and claustrum. No increased activation was observed in hypothalamic regions, and decreased activation was observed in the amygdala and surrounding entorhinal cortex. Most of these regions are activated by ejaculation in male rats, although the general activation patterns offered by PET do not have the fine-grained spatial resolution of the neuronal markers typically used in rat brain sections (eg, induction of nuclear Fos protein). It is possible that small hypothalamic regions may still have been activated but undetected. In women with complete spinal cord injury who still experienced orgasm from masturbation, fMRI revealed an activation of hypothalamic structures including the paraventricular nucleus; the medial amygdala; the anterior cingulate; the frontal, parietal, and insular cortices; and the cerebellum. Because of the spinal damage, it was concluded that the stimulation of orgasm traveled through the Vagus nerve to activate the brain.

## Sexual Inhibition

Sexual inhibition can be induced by stressful life events or after high sexual rewards (ie, during a refractory period in which reproductive capacity needs to be regenerated before resumption of copulation) [47]. In either case, the activation of inhibitory pathways for sexual arousal and desire generates a state of reduced libido.

Activation of opioid and serotonin release during sexual reward is associated with inhibition of ongoing sexual behavior. This has been studied in male rats following sexual exhaustion. Male rats allowed to copulate to sexual exhaustion with multiple ejaculations do not respond to female solicitations for a period of 24 to 72 hours. This inhibition can be reversed by the 5-HT1A agonist 8-OH-DPAT (an autoreceptor agonist that inhibits serotonin release), the $\alpha_2$ receptor agonist yohimbine, and the opioid receptor antagonist naloxone [48]. Thus, blockade of opioid or serotonin transmission, or activation of parasympathetic pathways involved in erection, can overcome the state of inhibition induced by sexual exhaustion. Activation of opioid transmission by stress may also play a role in sexual inhibition. Male rats find novel environments stressful. In fact, males that are not desensitized to the environment in which they have their first sexual experiences often will never copulate. Pre-exposure to the environment, or treatment with naloxone, increases the proportion of males that copulate on their first trial [49]. Interestingly, sexually naïve males sensitized to amphetamine do not show inhibition during their first exposure to females in a novel environment, despite the drug exposure happening weeks before [50]. Although sexually experienced males show signs of fear (eg, freezing) in novel environments, they do not show subsequent sexual inhibition if a receptive female is placed into the environment. Together, these data suggest that sensitized dopamine systems, produced either by sexual experience, amphetamine preexposure, or blockade of opioid transmission, can overcome the stress-induced inhibition of sexual responding in males.

## Conclusions

Libido reflects our level of sexual interest at any given time. It is determined by the interaction of neural systems that

underlie sexual arousal, desire, reward, and inhibition, processes that are highly influenced by steroid hormone actions. This is especially true for brain dopamine systems that modulate attention toward external sexual incentives and help generate appropriate motor responses. The neuroanatomical and neurochemical mechanisms that influence this process, and are influenced by it, are only beginning to be understood. Likewise, studies concerning the nature of sexual reward; its translation into pleasure, bonding, and sexual inhibition; and the mechanisms that underlie them, have only begun. We have understood libido for centuries at a behavioral level. Studying its biologic basis will help us identify mechanisms of sexual function and dysfunction, and it will perhaps allow us to better understand how function and dysfunction, and also desire and inhibition, are integrated into the experience of all individuals.

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LAS is currently at the Center for Anxiety and Related Disorders, Department of Psychology, Boston University, 648 Beacon Street, 6th Floor, Boston, MA 02215, USA. E-mail: lisasc@bu.edu.

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