

Review

Biology of Sexual Dysfunction

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Abstract:

Sexual activity is a multifaceted activity, involving complex interactions between the nervous system, the endocrine system, the vascular system and a variety of structures that are instrumental in sexual excitement, intercourse and satisfaction. Sexual function has three components i.e., desire, arousal and orgasm. Many sexual dysfunctions can be categorized according to the phase of sexual response that is affected. In actual clinical practice however, sexual desire, arousal and orgasmic difficulties more often than not coexist, suggesting an integration of phases. Sexual dysfunction can result from a wide variety of psychological and physiological causes including derangements in the levels of sex hormones and neurotransmitters. This review deals with the biology of different phases of sexual function as well as implications of hormones and neurotransmitters in sexual dysfunction

Key Words: Sexual dysfunction, Hormones, Neurotransmitters

Introduction:

Sexual activity is a multifaceted activity, involving complex interactions between the nervous system the endocrine system, the vascular system and a variety of structures that are instrumental in sexual excitement, intercourse and satisfaction.(1) Sexual function is our physiological capacity to experience desire, arousal and orgasm. Normal sexual function requires the integrity of the genitalia, the reliable co-ordination of blood flow, the activation of various smooth and skeletal muscles and the stimulation of local secretions. This is linked with cognitive processes attending to the sexual meaning of what is happening. Problem anywhere in the entire sequence may lead to sexual dysfunction. Sexual dysfunction can result from a wide variety of psychological and physical causes. Pathophysiology of sexual dysfunction involves derangements in the levels of sex hormones and neurotransmitters.

Sexual Response Cycle:

As defined by Kaplan, this consists of three phases- desire, arousal (excitement) and orgasm.(2) However, the division is arbitrary and it only helps to organize clinical and research oriented problems involving sexuality. In clinical practice sexual desire, arousal and orgasmic difficulties more often than not coexist, suggesting an integration of phases.

1. Desire (Libido)

It is a complex construct involving physiologic, cognitive, behavioural, developmental and cultural components,(3) which are thought of as the broad interest in sexual experiences including thoughts, fantasies, dreams and wishes along with an interest in initiating or engaging in sexual activity and frustration due to lack of opportunity for sexual expression.(1) This stage is hypothetically a dopaminergic phenomenon mediated by mesolimbic dopaminergic "reward centre" including medial preoptic area (MPA) and anterior hypothalamus. The reward centre receives inputs from serotonergic and noradrenergic neurons and contains dopaminergic cell bodies.(4) Other contributing factors include testosterone and oxytocin, as well as personality characteristics and psychosocial context.

2. Arousal

Sexual arousal is characterized by a subjective sense of sexual excitement associated with observable physiological changes such as penile tumescence in men and pelvic vasocongestion, vaginal lubrication and swelling of external genitalia in women. These responses may be accompanied in both sexes by other bodily changes like skin flushing, tachycardia etc.(5)

Psychogenic penile erections are mediated by impulses descending from the cerebral cortex and limbic system to reach thoracolumbar sympathetic ganglia (inferior hypogastric plexus) and sacral parasympathetic ganglion. (6) Baseline non-erect state is maintained by tonic

adrenergic stimulation of μ_1 and μ_2 adrenoceptors.(7)

The sacral plexus via the pudendal and perineal nerves, initiates tactile reflexogenic erections. Hypogastric plexus mediates psychogenic penile erections. Efferent impulses from the parasympathetic vasodilator fibers in sacral plexus initiate vasodilatory mechanism for penile erection.(8)

Psychological sexual arousal in women begins with increased clitoral length and diameter, and vasocongestion of the vagina, vulva, clitoris, uterus, and possibly the urethra. Pelvic nerve stimulation results in clitoral smooth muscle relaxation and arterial smooth muscle dilation. With sexual arousal, there is an increase in clitoral cavernosal artery inflow and an increase in clitoral intracavernous pressure that leads to tumescence and extrusion of the clitoris. Engorgement of the genital vascular network increases pressure inside the vaginal capillaries and results in lubrication of the epithelial surface of the vaginal wall. The neurotransmitters that mediate clitoral and arterial smooth muscle dilation remain undetermined.(9)

3. Orgasm

Orgasm in both sexes is characterized by climax of sexual pleasure associated with rhythmic contractions of perineal muscles, cardiovascular and respiratory changes and a release of sexual tension.(3)

In men, there are two physiological stages of orgasm – (i) Emission, (ii) Ejaculation

Emission involves the propulsion of seminal fluid to the bulbar urethra by the contraction of the smooth muscles of the vas deferens, prostate and seminal vesicles. This process is thought to be under the control of thoracolumbar sympathetic nerves which release norepinephrine on to alpha receptors. After emission, the external sphincter is opened to allow release of fluid. In the second stage, a local, parasympathetic, sacral spinal reflex activates the striated muscles surrounding the bulbar urethra, producing ejaculation. The rhythmic contraction of these muscles propels the semen outward. It is unclear to what degree the occurrence and intensity of orgasm are shaped by central neurochemical and cognitive processes.(5) Smooth muscle controlled emission and striated muscle determined ejaculation involve separate nerve inputs and can be pharmacologically distinguished.

In women less is known about the neural mechanisms of orgasm and the process is assumed to be largely similar to that in the male. Women are capable of experiencing multiple orgasms in rapid succession, without the more prolonged refractory periods. Mechanisms that make this possible are not clear, although it is hypothesized that women are less sensitive to the post-orgasmic secretion of prolactin that is hypothesized to produce a refractory period in men and women.(10)

Some women ejaculate fluid from the urethra with orgasm. Chemical analysis of this fluid confirms that while it may be mixed with small amounts of urine, it is predominantly a secretion from the paraurethral glands, thought to be a vestigial equivalent of the prostate. But this goes unrecognized when it occurs in a retrograde direction.(11)

Role of pituitary, adrenal and sex hormones in Sexual function:

Testosterone, estrogen, progesterone, prolactin oxytocin, cortisol, pheromones are the various hormones implicated in sexual function.

Testosterone

Testosterone has been shown to restore nocturnal penile tumescence responses in hypogonadal men, in whom this is impaired.(12) A recent study showed testosterone increased sexual arousal and enjoyment among hypogonadal and normal men, and had a positive effect on mood only among men with abnormally low testosterone levels.(13) In normal adult males, there exists wide individual variability in circulating testosterone levels that do not seem to be linked in any meaningful, way with individual differences in levels of drive or sexual behavior.(14) It is believed that the level of testosterone required for sexual interest and activity in adult males is lower than normal males' circulating levels of testosterone. Among males with normal testosterone levels, testosterone has not been shown to facilitate erection.(15)

In an earlier study of women who had undergone bilateral oophorectomy and adrenalectomy, removal of the ovaries decreased sexual desire to a certain extent, but removal of the adrenal glands had an even more deleterious effect on desire.(16) Studies of surgically menopausal women generally indicate that desire drops from presurgery level and may be restored with exogenous administration of suprphysiological levels of testosterone with or without estradiol.(17)

Estrogens

Most research suggests that estrogens have little direct influence on sexual desire in either males or females. In men, relatively high levels of exogenous estrogen have been somewhat effective in inhibiting sexual desire among sex offenders and men who experience uncontrollable sexual urges.(18,19) In women, some early studies have claimed that estrogen (especially estradiol) is important for normal sexual desire, but most current researches agree that estrogens play only a minimal role in female sexual desire.(20,21)

Estrogen deficiency, as occurs with menopause, causes a decrease in genital vasocongestion, lubrication and atrophy of the vaginal epithelium. Such changes not only impair the physiological sexual arousal response in women and may cause dyspareunia (painful intercourse), but can adversely influence the psychological experience

of sexual arousal. These changes could be expected to indirectly impair sexual desire.(22)

Progesterone

Early studies have revealed a decrease in sexual desire in men receiving intramuscular injections of progesterone. (23,24) No controlled studies have been conducted on the relationship between progesterone treatment and sexual desire in men.

Certain oral contraceptives that increase progesterone levels throughout the menstrual cycle in female have been associated with decreased sexual interest and desire.(25,26) It is generally agreed on, however, that progesterone treatment does not have a substantial influence on the sexual desire of either premenopausal or postmenopausal women.(17,27,28)

Prolactin

Men and women with abnormally high levels of prolactin report a decrease in sexual interest that is restored with bromocriptine treatment.(29) It is unclear whether the reversal of sexual symptoms secondary to bromocriptine treatment is attributable to the lowering of serum prolactin levels, to the correction of hypothalamic dopaminergic dysregulation, or to an interaction between these two mechanisms.(30)

Prolactin's effect on other aspects of human sexual behaviour remains equivocal. Erectile dysfunction has been described in men with abnormally high levels of prolactin, (31) but has also been described in men with unusually low levels of prolactin, (32) suggesting more than a simple inhibitory role of prolactin on erectile ability. In women, abnormally high levels of prolactin have been associated with amenorrhoea, infertility and decreased sexual ability.(33)

Oxytocin

Circulating levels of oxytocin increase during sexual arousal and orgasm in both men and women.(34) Using a continuous blood sampling technique and electromyography, it was reported to have a positive correlation between oxytocin levels and the intensity, but not the duration of orgasmic contraction in males and females.(35) Most of what we know about the influence of oxytocin on sexual behaviour however is based on animal studies.

Cortisol

Hypercortisolism (Cushing syndrome) can produce a constellation of symptoms including depression, insomnia and decreased libido in males and females. Cortisol levels were higher in men with psychogenic erectile dysfunction who demonstrated a poor response to intracavernosal injection of a smooth muscle relaxant.(36)

Pheromones

Pheromones are substances secreted from glands at the anus, urinary outlet, breasts and mouth. In a recent double blind, placebo-controlled study, it was reported

that women exposed to a synthesized human male pheromone reported higher levels of sexual intercourse, sleeping with a romantic partner, but no change in masturbation frequency. The authors interpreted these findings as evidence for male pheromones increasing the sexual attractiveness of men to women.(37)

Role of neurotransmitters in sexual function

Nitric oxide, serotonin, dopamine, epinephrine, norepinephrine, acetylcholine, histamine, GABA are all implicated to have roles in sexual function. Neurotransmitters act both within the brain and in peripheral organs, and therefore may play complex and interacting roles in promoting and facilitating sexual functioning.

(a) Nitric oxide (endothelial relaxing factor)

Nitric oxide (NO) is an essential component in the production of penile, and possibly, clitoral vasocongestion and tumescence. The release of NO by cholinergic and non-cholinergic nerves appears to be the major contribution of the parasympathetic nervous system.(38) As described above, NO is now understood to be the most significant mediator of vascular smooth muscle relaxation, responsible for engorgement of erectile tissue in men and women.

Sexual stimulation leads to NO production that in turn stimulates the release of guanylate cyclase. Guanylate cyclase converts guanosine triphosphate to cGMP and cGMP produces relaxation of the smooth muscles of the penile arteries and corpus cavernosum resulting in increased blood flow into the penis.(39) Some evidence suggests that this may also occur in the clitoris.(40)

Normally, cGMP is metabolized by cyclic nucleotide phosphodiesterase isozymes into guanosine 5'-monophosphate. As long as sexual stimulation continues, cGMP production and metabolism remain balanced and penile or clitoral tumescence is sustained.(41) Erectile dysfunction can result when this process is not working normally or when it is partially or completely disrupted. (5)

(b) Vasoactive Intestinal Polypeptide (VIP)

VIP has been less well understood but is shown to co-localize with NO in nerves to genital blood vessels and smooth muscle. In women, systemic administration and local subepithelial injection of VIP result in increased vaginal blood flow and lubrication.(9) In addition, sexual arousal raises the level of VIP found in the plasma. In men VIP also co-localizes with NO and has been shown to play an important role in erection.(5)

(c) Serotonin

Serotonin acts at both central and peripheral receptors in the mediation of sexual function. (5)

Centrally, serotonin appears to downregulate and diminish levels of mesolimbic dopaminergic activity and to elevate prolactin, resulting in decreased libido.(42,43)

In addition, serotonergic activation of different receptor subtypes has differential effects on sexual functioning. Activation of receptor subtype 1_A lowers the threshold for ejaculations, while activation of 2_A , 1_B or 1_C inhibits sexual behaviours and stimulation of 2_C facilitates behaviour in animal models.(44)

Peripherally, at spinal or end-organ receptors, serotonin has inhibitory effects on ejaculation in animals.(45) Also serotonin tends to cause problems with orgasm and desire more than arousal itself. Serotonin even acts on the smooth muscles of the genitals possibly inhibiting the muscular contractions that characterize orgasm.(5) Further, serotonin acts at peripheral nerves, where it appears to affect the flow of genital sensory information. Lastly, serotonin may delay orgasm through pre-synaptic inhibition of adrenergic transmission.(45)

(d) Dopamine

All the four major dopaminergic CNS pathways are proposed to play a role in sexual behavior. The incertohypothalamic pathway stimulation increases all phases of male rat sexual behaviour and induces penile erection. In female rats it induces sexually receptive posture called lardosis. The mesolimbic pathway is involved in the anticipatory phase of sexual activity associated with motivation and sexual reward. The nigrostriatal pathway is important in the motor behaviour required for consummatory sexual activity in male rats. Lastly the tubero infundibular pathway appears to play a role in baseline sexual interest as opposed to more acute behavioural changes.(5,46,47)

Regarding relationship between dopamine and prolactin, it remains unclear whether hyperprolactinemia itself is causative or acts as a surrogate marker for decreased dopamine. A recent F-MRI study demonstrated an increase in blood flow to specific dopaminergic and other brain structures when 17 college men and women viewed pictures of people they love and are sexually attracted to.(48)

(e) Epinephrine

Plasma levels of epinephrine have been shown to increase prior to viewing an erotic film, slowly increase during masturbation, peak at orgasm, and return to baseline level within several minutes of orgasm.(49) The epinephrine and norepinephrine metabolite, vanillylmandelic acid, increases prior to intercourse and continue to be elevated over baseline upto 23 hours following sexual activity.(50)

(f) Norepinephrine

In men, blood plasma NE levels were positively correlated with arousal and erection during masturbation and sexual activity, increased upto 12-fold at orgasm and declined to baseline levels within 2 minutes of reaching orgasm.(51,52) Studies suggest that NE is also active during the sexual response cycle of women. Blood plasma levels of NE increased during masturbation,

peaked at orgasm, and slowly declined following orgasm in normally functioning women.(49,52)

(g) Acetylcholine

Erection occurs when the smooth muscles of the corpus cavernosum relax permitting increased blood flow into the penile tissue. The human corpus cavernosum is innervated by cholinergic nerves and contains cholinergic receptors suggesting endogenous cholinergic activity in the penile tissue.(53,54)

Acetylcholine (Ach) appears to play a less direct role in sexual functioning that is largely a function of maintaining the balance of cholinergic and sympathetic input at the genital level.(5) Ach antagonist, atropine showed no effect on either vaginal vasocongestion or orgasm in women and large doses were insufficient to block penile erection in men,(9) though in vitro administration of Ach to pre-contracted corpus cavernosum induced smooth muscle relaxation.(7) Thus Ach is sufficient to produce vasocongestion, but not essential for this effect.

There are three proposed roles for cholinergic stimulation in promoting sexual arousal specifically

- Alteration of the balance of sympathetic and parasympathetic inputs.(7)
- Facilitation of lubrication by increasing secretions. (55)

- Synthesis and secretion of NO and VIP, that are essential for arousal.(5)

(h) Histamine

Very little is known about the role of histamine in facilitating sexual functioning, but evidence suggests that activity at both H₂ and H₃ receptors in the penis can cause erection.(56) There are a few case reports of decreased desire in both men and women taking cimetidine (H₂ antagonist), the mechanism of which may be, decreased peripheral response to testosterone (7) or decreased metabolism of estradiol leading to gynaecomastia in men.(57)

(i) Gama aminobutyric acid (GABA)

GABA enhancing benzodiazepine use has been implicated in case reports of decreased libido, erectile dysfunction and anorgasmia.(58) While mechanisms are poorly understood, it is hypothesised that centrally mediated sedation and peripheral muscle relaxation may be responsible.(5)

Apart from the above mentioned ones, many other putative neurotransmitters, including arginine-vasopressin, angiotensin II, substance P, neuropeptide-Y, a-MSH, Gn RH are involved in sexual functioning, but there is little research into their precise role.(59)

Table 1: Stages of sexual response:(60)

Stages of sexual response	
Desire	The spontaneous occurrence of sexual thoughts, fantasies, dreams and wishes, along with an interest in initiating or engaging in sexual activity
Arousal: Peripheral or physical; Central or subjective	Genital (vascular engorgement and lubrication) and systemic responses (tachycardia, hyperventilation; etc.) to sexual stimulation. Psychological sense of excitement
Orgasm	Intense peak of sexual pleasure accompanied by rhythmic contractions of the genital and reproductive organs
Resolution	Return to baseline, unaroused state, characterised by loss of vasocongestion in the penis and vulva

Table 2: Summary of Role of Hormones: (60)

Stage of sexual response	Facilitate sexual function	Inhibits sexual function
Desire	Testosterone, Oxytocin	Prolactin, Cortisol
Arousal	Testosterone, Estrogen, Oxytocin	-
Orgasm	Oxytocin	-

Conclusion:

Sexual function is a complex phenomenon involving an orchestra of chemical elements ranging from small molecules like nitric oxide to peptides like oxytocin. We are aware that derangements of various hormones and neurotransmitters are involved in sexual dysfunction but their precise role is not known.

Further, putative neurotransmitters are gaining more implications in sexual dysfunction. Deeper investigation into these areas will no doubt reveal greater insight about sexual functioning which in turn assists in efficient management of sexual dysfunction

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