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MINIREVIEWS

Neural regulation of sexual function in men

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Abstract

Male sexual response is controlled by a series of neurally mediated phenomena regulating libido, motivation, arousal and genital responses such as penile erection and ejaculation. These neural events that occur in a hormonally defined milieu involve different neurophysiological, neurochemical, and neuropsychological parameters controlled by central mechanisms, spinal reflexes and peripheral nervous system. Epidemiologic studies have suggested the high prevalence of male sexual dysfunction worldwide with significant impact on the quality of life of patients suffering from this problem. The incidence of sexual dysfunction is particularly high among men with neurologic disorders. Sexual dysfunction in men, such as loss of sexual desire, erectile dysfunction (ED), changes in arousal, and disturbances in orgasm and ejaculation may involve organic causes, psychological problems, or both. Organic male sexual disorders include a wide variety of neurologic, vasculogenic, neurovascular or hormonal factors that interfere with libido, erection, ejaculation and orgasm. Neurogenic sexual dysfunction may result from a specific neurologic problem or it could be the presenting symptom of a developing neurologic disease. Neurologic ED could result from complications of chronic neurologic disorders, trauma, surgical injury or iatrogenic causes. These etiologic factors and the underlying pathophysiologic conditions could overlap, which should be considered when making a diagnosis and selecting a treatment. A detailed history of physical examination, neurologic disorders, as well as any past history of psychological and psychiatric disturbances, and a thorough neurological examination will provide better understanding of the underlying causes of neurogenic sexual dysfunction. In patients with spinal cord injury, the location of the lesion and the time of onset of injury should be determined. Therapeutic strategies against erectile dysfunction are initiated with the least invasive options using the phosphodiesterase inhibitors. When oral medication options are exhausted, intraurethral and intracavernosal therapies and ultimately vacuum constriction devices and penile implants are considered. Recent basic research has suggested the potential role of stem cell-based therapeutic strategies to protect penile neural integrity and reverse cavernosal neurodegeneration in experimental models. Further insight into the central, spinal and peripheral neural mechanisms of male sexual response may help precise diagnosis and better management of neurogenic sexual dysfunction in men.

Key words: Sexual function; Nerve; Erection; Penis; Neurotransmission

Core tip: Despite considerable advances in our understating of male sexual function over the past two decades, crucial central mechanisms and peripheral pathways of male sexual response are still largely unknown. Neural responses to sexual stimulation precede vascular, smooth muscle, and endothelial cell reactions and play leading role in initiating fundamental pathways of

male sexual arousal, erection, orgasm and ejaculation. These pathways involve a dedicated subset of central mechanisms, spinal reflexes, peripheral nerves, and neurotransmission systems that operate at different levels individually and in conjugation. Further research into the neurophysiology of sexual function may help better management of neurogenic sexual dysfunction in men.

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INTRODUCTION

The nervous system is intricately involved in the regulation of male sexual response. Our knowledge into the central and peripheral neural regulation of male sexual function has gained ground with remarkable scientific advances over the past two decades. However, the precise central neural events and the intercommunication between central, spinal, and peripheral nervous system during male sexual response are still largely unknown. Male sexual arousal involves a dedicated subset of neural mechanisms in central nervous system that depend on fundamental neuronal responses, generalized brain activity, initiation of spinal reflexes, and peripheral neural mechanisms that operate at different levels individually and in conjugation.

Neural aspects of male sexual function are essential to most critical phases of sexual response in men including sexual desire, penile erection, and the development of arousal, orgasm and ejaculation. Penile erection is a complex physiological process involving central and peripheral neural mechanisms, blood vessels, and penile smooth muscle and endothelial cells[1]. Male orgasm is a subjective, perceptual-cognitive event of peak sexual pleasure that coincides with ejaculation. The autonomic nerves mediate one of the most important aspects of the male sexual response as their impulses travel through the cavernous nerves to regulate penile smooth muscle and vascular tone during penile erection and detumescence.

Sexual dysfunction in men involves psychological factors and organic problems. Most cases, however, correlate with organic causes that influence the mechanistic pathways of male sexual response or alter the structure of male sexual organs. Organic sexual dysfunction in men could result from changes in central and peripheral nervous system, hormones, penile vasculature and alterations of erectile tissue endothelium and smooth muscle cells. Loss of sexual drive in men correlates with increase in age[2]. However, the degree of this decline varies, and most men seem to maintain some amount of libido well into their 60s and 70s[2]. Other underlying conditions for loss of sex drive in men include depression, stress, decrease in male sex hormones and changes resulting from medications side effects.

Neurologic disorders compromise penile neural integrity and may lead to neural structural damage, functional deficit, or both[2-5]. Therefore, neurogenic erectile dysfunction (ED) could be an early symptom of progressive neurologic problems. Neurogenic ED may also relate to neural risk factors including alcoholism and other forms of substance abuse, depression, anxiety, stress, surgical treatment of prostate cancer, removal of enlarged prostate, surgical injuries to the pelvic area, and side effects of certain medications[3]. In most cases, however, neurogenic ED relates to impairment of the cavernous nerve pathways by surgical procedures or traumatic injury. An accurate diagnosis and successful treatment of nerve injury associated ED would depend on functional assessment of the prospective nerves and evaluation of the extent of nerve damage using diagnostic methods to accurately confirm cavernous nerve impairment. In this review, we focus attention on the neuroanatomy and neurophysiology of male sexual response.

NEURAL INTEGRITY AND MALE SEXUAL FUNCTION

An impeccable sexual response in men depends on central and peripheral neural integrity for achieving adequate arousal, erection and orgasm. Neural regulation of male sexual function could be disrupted by changes in central control of sexual response, alterations in spinal and peripheral neural pathways, changes in neurotransmission, or loss of neural function due to traumatic injury[5,6]. Neurogenic sexual dysfunction is the inability to initiate and maintain sexual activities due to a neurologic disorder. Underlying causes of neurogenic sexual dysfunction in men includes brain and spinal cord injuries, radical pelvic surgeries, diabetes mellitus, multiple sclerosis, stroke and Parkinson disease[7,8]. The peripheral mechanisms involved in penile erection and ejaculation have been extensively elucidated in the past three decades. However, the contribution of the central mechanisms into sexual response is still less well defined.

Basic research on the central regulation of sexual response using experimental models is currently underway in several institutions. Therapeutic strategies using growth factors and gene therapy have also been used to delay neurodegeneration and stimulate new nerve fiber outgrowth in penile erectile tissue[9,10]. In clinical studies, positron emission tomography scanners and functional magnetic resonance imaging have been used to explore regional brain activities during sexual stimulation, sexual excitement, and penile erection[11-13]. Further insight into the central pathways and peripheral neural mechanisms of male sexual response may lead to more precise diagnosis and treatment of specific neural deficits in neurogenic ED, anorgasmia and ejaculation disorders.

NEUROANATOMY

The neuroanatomy of male sexual response encompasses

a wide variety of anatomical structures in the brain, spinal cord, and peripheral nervous system including autonomic, somatic, sensory and motor neuronal structures[14]. At the spinal cord at the T9 to L4 levels, the intermediolateral column of gray matter gives rise to the sympathetic preganglionic nerve bundles. At the level of S2 to S4, the intermediolateral column gives rise to the parasympathetic nerves[15,16]. Continuation of these nerves assembles the framework of the pelvic and hypogastric plexuses. The penis is innervated by both autonomic and somatic nervous system[15]. At the spinal and peripheral levels, the autonomic (parasympathetic and sympathetic) and somatic (sensory and motor) nerves extend to innervate the penis[17].

Parasympathetic nerves

The neurons in the intermediolateral cell columns of the second, third and fourth sacral spinal cord segments (pelvic nerves) provide parasympathetic nerve fibers to the penis. At the level of the pelvic plexus, the preganglionic nerves are joined by sympathetic nerves originating from the hypogastric plexus. This plexus gives rise to branches that innervate the rectum, bladder, prostate and sphincters. The pelvic plexus give rise to a neural framework called cavernosal nerves that innervate the penile corpora cavernosa including terminal arterioles and erectile tissue[18]. The cavernosal nerves pass the prostate posterolaterally and then extend lateral to the membranous urethra and anterior to the bulbous urethra where they enter the hilum of the penis. The cavernosal nerve may be easily injured during radical pelvic surgery as well as transurethral prostatectomy, external sphincterotomy or any procedure using electrocautery in that region because it is closely applied to the apex of the prostate and membranous urethra.

Studies of penile tissue samples from human and experimental models have suggested that nitrergic nerves contributing to erection originate from the ganglia close to the corpus cavernosum[19,20]. The preganglionic cavernosal nerves are believed to synapse with nitrergic nerves within or near the tunica albuginea[19,20]. Penile erection following stimulation of the pelvic or the cavernosal nerves has been documented in both humans[21] and in animal models[22,23]. However, the precise nature of the cavernous nerve and whether or not it is a purely parasympathetic nerve remains controversial. Retrograde labeling and high resolution autoradiographic studies have suggested that some sympathetic fibers emanating from the lumbosacral sympathetic chain exist in the pelvic nerve of the male rat[24].

Sympathetic nerves

The sympathetic nerves to the male genital organs, which contribute to the regulation of penile detumescence and ejaculation, originate from the preganglionic neurons of the tenth to twelfth thoracic and first and second lumbar segments of the spinal cord. These preganglionic fibers pass *via* rami to the paravertebral sympathetic chain ganglia and descend to make synaptic connections with the postganglionic neurons then travel *via* the pelvic splanchnic nerves to the inferior mesenteric plexus, the hypogastric plexus and the perivesical plexus. Some fibers travel *via* the hypogastric nerve to the pelvic plexus. The hypogastric nerve is a discrete branch from these plexuses that enters the perivesical plexus where it may communicate with parasympathetic nerve fibers. The pelvic plexus is a crucial site in the integration of the autonomic input to the male genitalia.

Studies of experimental models have shown that stimulation of the hypogastric nerve or the sympathetic trunk has no significant effect on intracavernosal pressure in the flaccid state of penis but its stimulation during an erection causes penile detumescence[25]. These observations suggest that some sympathetic fibers may travel *via* the cavernous nerves to the penile corpora cavernosa. In the erect state of the penis, stimulation of the cut distal end of the pudendal nerve results in detumescence[25]. It is thought that some sympathetic fibers, especially the sensory branch, may travel *via* the pudendal nerve. Intracavernosal pressure rise and penile tumescence after stimulation of the sympathetic nerves has been documented in the rat model[26]. The precise mechanism of proerectile activity following sympathetic nerve stimulation remains unclear. One possibility may be the intercommunication between sympathetic fibers and nitregic nerves within the penile erectile tissue to release nitric oxide. Another possibility is sympathetic-mediated pelvic vasoconstriction and shunting of blood flow toward the penile erectile tissue.

Sensory nerves

The sensory nerves of the penis are primarily in the penile skin and glans as free and specialized nerve endings and receptors. The most numerous nerve terminals in the glans penis are free nerve endings (FNEs). Genital end bulbs are denser in the corona and near the frenulum and are present throughout the glans. The ratio of FNE to corpuscular receptors is approximately 10:1[27]. Axon terminals that resemble a tangled web of FNEs are present at the genital end bulbs unique to the glans penis[27]. Sensory nerves relaying pain and pressure sensation are also present in the urethra and corpora cavernosa[27]. Pain mediating signals and temperature sensation travel from free nerve endings *via* small diameter, thinly myelinated or unmyelinated nerve fibers. Large diameter myelinated fibers mediate the sense of vibration, touch and pressure[28]. These nerve fibers merge to assemble the dorsal nerve of the penis[27,28]. The dorsal nerve converges with other perineal nerves to become the internal pudendal nerve, which ascends to the dorsal roots of the second to fourth sacral nerves. The ascending pathways in the spinal cord travel *via* the spinothalamic tract to the thalamus and to the sensory cortex[27,28].

Somatic nerves

The ventral roots of sacral segments two through four along with coalesce form the paired pudendal nerves

provide somatic motor nerves to the penis. These nerves descend together with the internal pudendal vessels as they travel *via* Alcock's canal then provide somatic fibers to the striated muscle of the pelvis. These nerves extend as perineal nerve into the perineum and innervate the bulbocavernous and ischiocavernous muscles. These muscles are believed to provide temporary increases in intracavernosal pressure and contribute to penile rigidity during erection[29]. This is thought to aid in allowing successful vaginal penetration.

Co-existence and co-release of neurotransmitters

Immunohistochemical staining have revealed the co-existence of vesicular acetylcholine transporter, neural nitric oxide synthase (nNOS), vasoactive intestinal polypeptide (VIP), tyrosine hydroxylase, and heme oxygenase in tissue samples from human corpus cavernosum and spongiosum[30]. Immunoreactivity for endothelial nitric oxide synthase (eNOS) and heme oxygenase has been detected in the endothelial lining of corpus cavernosum and penile arteries[30]. Calcitonin gene related peptide has been localized within cavernosal nerves, cavernosal smooth muscle and cavernous arterial wall[31]. Co-release of neuropeptide Y and noradrenaline in autonomic nerves and release of calcitonin gene related peptide in the sensory nerves have been documented in the rat corpus cavernosum[32]. A rich sympathetic adrenergic innervation has been demonstrated in the human penile cavernosal tissue, penile microvasculature and helicine arteries[33,34]. Co-release of norepinephrine and neuropeptide Y from the penile adrenergic nerves has been documented in rats[34]. Downregulation of cavernosal nNOS and eNOS after bilateral cavernosal nerve injury was found simultaneous with upregulation of Rho-associated protein kinase in rat erectile tissue[35]. Inhibition of Rho-kinase was associated with increased nitric oxide (NO) signaling in the rat erectile tissue[35].

NEUROPHYSIOLOGY OF MALE SEXUAL RESPONSE

Male sexual response is a complex multidisciplinary biologic process involving central pathways and peripheral neural mechanisms controlling libido, arousability, penile erection and rigidity, orgasm and ejaculation. Neurologic disorders that can compromise central pathways and peripheral neuronal mechanisms would disrupt physiological sexual response during sexual stimulation. The central, spinal, and peripheral neural mechanisms that regulate male sexual response are summarized below.

Central control of male sexual function

Central regulation of male sexual function is less explored in comparison with the peripheral neural pathways. Multi-regional central neural mechanisms and inter-regional brain communications appear to be involved in male sexual response. It is known that cerebrocortical function is crucial to the initiation of sexual response in men[36,37]. However, the precise areas of the cerebral cortex involved in regulating libido, sexual fantasy and arousal are not well characterized. Studies of patients with traumatic brain injury suggest that the temporal and frontal lobes may play a crucial role in regulating sexual interest and behavior[37]. The septal portion of the hippocampus, the anterior cingulate gyrus, the anterior thalamic nuclei, the mammillothalamic tract and the mammillary bodies control penile erectile activities[36,37]. The medial dorsal nucleus of the thalamus and the medial pre-optic area appear to play crucial roles in the control of penile erection and sexual drive[38,39].

Central neurotransmitters

Central control of male sexual response involves multiple neurotransmitters including serotonin (5-hydroxytryptamine), dopamine, norepinephrine, nitric oxide and many others. Serotonin tends to block the penile erectile pathway at both spinal[40] and supraspinal sites[41]. Gamma amino butyric acid[42], prolactin[43] and endogenous opioid peptides[44] are also known as the central inhibitors of sexual activity in men. Dopamine is thought to regulate erection by acting on oxytocin containing neurons in the paraventricular nucleus of the hypothalamus[45,46].

In experimental animal models, systemic administration of dopamine and dopamine agonists such as apomorphine induce erectile activity *via* central mechanisms[45,46]. Norepinephrine plays various roles in central regulation of male sexual function[47]. Inhibition of central alpha-2 adrenoceptors facilitates sexual function while stimulation of these receptors produces the opposite effect[47]. Increased sexual motivation has been documented after administration of yohimbine, a central alpha-2 receptor blocker[48]. Oxytocin that has been localized in descending pathways from hypothalamus to brain stem is thought to mediate the effects of dopamine on penile erection *via* the oxytocin containing neurons[49,50]. Ascending sensory stimuli from the dorsal penile nerve stimulates oxytocin-containing cells in the supraoptic nucleus[49,50]. Dense nitric oxide synthase is localized in the paraventricular nucleus of the hypothalamus[51]. Administration of nitric oxide synthase blockers to the lateral ventricles or to the hypothalamus prevents erectogenic effects of dopamine agonists and oxytocin in experimental models[52]. The role of adrenocorticotropin and related peptides (melanocortin) in penile erection and ejaculation has been documented in patients with psychogenic erectile dysfunction[53]. A synthetic analogue of alpha-melanocyte stimulating hormone was shown to reverse erectile dysfunction in these patients[53].

Role of spinal reflexes

Spinal reflexes are crucial determinant of both the initiation and the maintenance of male sexual response. The spinal cord, paraspinal sympathetic ganglia, and parasympathetic nerves play a direct role in regulating functional changes of the male genitals. Sympathetic nerve fibers involved in sexual response originate from the interme-

diolateral column of gray matter at the level of T9-L4 in the spinal cord. The intermediolateral column at the levels of S2-S4 gives rise to the parasympathetic nerve fibers that innervate male genitalia. These nerve fibers descend to form the most important plexuses involved in sexual physiology, the pelvic and hypogastric plexus. The cavernosal nerve originates from the pelvic plexus and travels through the pelvic fascia and posterolateral aspect of the prostate. The parasympathetic nerves exit the spinal cord through the ventral roots and constitute the pelvic nerves. Upon sexual stimulation by visual, olfactory, and imaginary stimuli, penile erection takes place as a spinal reflex that is initiated by recruitment of penile stimulation traveling *via* the dorsal penile nerve[36,37]. The reflex that involves both autonomic and somatic efferent is heavily modulated by supraspinal influences. Local segmental reflexes in the lumbosacral cord subserve penile erection[36,37]. These reflexes are generally under the net tonic inhibitory control by higher centers[37].

Peripheral mechanisms

The peripheral neural pathways of sexual response particularly penile erection have received greater research and clinical attention than the central and spinal mechanisms. Basic research on the hemodynamic of penile erection and regulation of penile smooth muscle contractility resulted in the development of oral medications for erectile dysfunction. It was shown that a dedicated subset of neuronal mechanisms involving the adrenergic, cholinergic, and non-adrenergic non-cholinergic neurotransmission regulate cavernosal smooth muscle tone which determines penile tumescence and detumescence[23,54,55].

Basic research with experimental models have shown that electrical stimulation of the pelvic plexus and the cavernous nerve leads to erection, while stimulation of the hypogastric nerve or the sympathetic trunk induces detumescence[23,54,55]. It was shown that the sacral parasympathetic regulates penile tumescence and that the thoracolumbar sympathetic input mediates detumescence[25-27]. Follow up studies demonstrated that sensory stimuli relating to initiation and maintenance of erection originate primarily from the glans and travel *via* the dorsal nerve of the penis[27,28]. The most crucial step in the peripheral motor control of penile erection depend on smooth muscle tone in the erectile tissue and penile arterioles in the corpora cavernosa[56,57]. Alterations of smooth muscle tone in the tumescence and detumescence states of the penis are regulated by sympathetic and parasympathetic nervous systems and endothelial-mediated mechanisms[54,55]. It was shown that coordinated changes in smooth muscle tone of the penile erectile tissue and arterioles control the amount of blood entering to the cavernosal sinusoids and the amount of blood exiting the corpora[54,55].

Role of the adrenergic nerves

The primary adrenergic transmitter in the penis that controls smooth muscle contraction and induces penile detumescence is norepinephrine[56-59]. The regulation of adrenergic nerve activity and neurotransmission discharge in the penis is complex and appears to involve intercommunication with the cholinergic and the non-adrenergic non-cholinergic systems. As example, norepinephrine release from adrenergic nerves is pre-junctionally regulated by the cholinergic nerves[56]. The alpha and beta adrenergic receptors are localized in both penile blood vessels[57] and cavernous smooth muscle cells[34]. Alpha-1 adrenoceptors are more abundant in the erectile tissue smooth muscle while both alpha-1 and alpha-2 receptors have been localized in the penile arterioles[58,59]. Alpha-2 receptors have been localized both on pre-junctional sites of the adrenergic nerves and on erectile tissue smooth muscle[58].

Alpha-2 adrenoceptors on prejunctional sites mediate the feedback inhibition of norepinephrine discharge from the adrenergic nerves[56]. Upon release from the adrenergic nerves, norepinephrine binds to the pre-junctional alpha-2 adrenoceptor on the adrenergic nerves and inhibits norepinephrine release. This observation suggests that inhibition of alpha-2 receptor with selective antagonists such as yohimbine would inhibit erection by increasing norepinephrine release. It is also suggested that after release from adrenergic nerves, norepinephrine binds to the pre-junctional alpha-2 adrenoceptor on the non-adrenergic, non-cholinergic nerves and inhibits nitric oxide production and bioavailability[56,59,60]. It is thought that inhibition of this reaction by selective alpha-2 receptor antagonists will increase nitric oxide synthesis and promote erection. The smooth muscle alpha-2 adrenoceptors appear to play a role in the mediation of penile smooth muscle cell contraction[60]. Erectile tissue exposure to alpha-2 adrenoceptor agonists results in smooth muscle contraction[58,59]. In contrast, inhibition of smooth muscle alpha-2 adrenoceptors induces penile smooth muscle relaxation and promotes erection[56,59,60].

Role of the cholinergic nerves

Dense cholinergic innervation has been immunostained in penile corpus cavernosum and corpus spongiosum[30]. Immunohistochemical staining has also revealed that penile cholinergic nerves contain NO synthase and VIP. These observations led to the notion that vasodilators such as NO and VIP may be co-released along with acetylcholine from the cholinergic nerves[30,61]. These studies suggested that acetylcholine, whether released from the cholinergic nerves or applied directly to corpus cavernosum, initiates a variety of reactions in the erectile tissue.

Functional assessments of experimental models revealed erectile response to acetylcholine administered systemically or directly into the cavernosal tissue[62-64]. While having no effect on relaxed erectile tissues, acetylcholine produced concentration-dependent relaxation of erectile tissues that has been precontracted with norepinephrine[65,66]. Subsequent mechanistic studies with isolated erectile tissues from human and animals showed that the relaxing effects acetylcholine is partially blocked

by atropine but it could be abolished by removal of the endothelium[65,66]. The relaxing effect of acetylcholine that was markedly attenuated by removal of the endothelium introduced the theory of endothelial derived relaxing factor released from the endothelium under the influence of acetylcholine in the erectile tissue[67]. These findings indicated that acetylcholine may act on adrenergic nerve terminals to suppress the release of norepinephrine[65,66,68]. These observations collectively suggested that acetylcholine may induce cavernosal smooth muscle relaxation by co-release of nitric oxide and perhaps VIP from cholinergic nerve terminals, release of nitric oxide from the vascular endothelium, and suppression of norepinephrine release. The involvement of endothelium was an astonishing finding that led researchers to search for a non-adrenergic non-cholinergic mechanism of penile smooth muscle relaxation.

Role of non-adrenergic non-cholinergic neurotransmission

NO is well established as an important non-adrenergic non-cholinergic (NANC) neurotransmitter in the physiology of penile erection[67-71]. The NO/cyclic guanosine monophosphate signaling pathway has been widely recognized as the primary mediator of cavernosal smooth muscle relaxation and penile erection[67,69]. Mechanistic studies showed relaxation of human and rabbit penile smooth muscle in response to a solution saturated with NO gas[67]. Subsequent studies characterized nitric oxide synthase (NOS) as the enzyme that catalyzes the interaction of L-arginine and molecular oxygen in a process that consumes NADPH to produce NO and L-citrulline[67,69]. NOS exists in constitutive neuronal (nNOS) and endothelial (eNOS) forms, and inducible (iNOS) form. The constitutive forms of the enzyme are coupled to Ca^{2+} and calmodulin and are crucial to penile smooth muscle relaxation and erection.

Basal production of NO is regulated by constitutive NOS that is known to be involved in a variety of physiologic conditions such as cardiac and pulmonary perfusion, heart rate, myocardial contractility, vasodilation and penile erection[70]. iNOS is independent of Ca^{2+} and calmodulin and is believed to be upregulated in cellular stress and pathologic conditions[71]. In experimental models, long-term exposure of penile erectile tissue to ischemia has resulted in progressive downregulation of nNOS and eNOS and a significant increase in iNOS expression[72].

The relaxing role of NO in penile smooth muscle cells involves production and accumulation of the cyclic guanosine-3',5'-monophosphate (cGMP) in erectile tissue. Upon release from cavernous nerves and endothelium, NO diffuses locally into adjacent smooth muscle cells then activates guanylate cyclase to catalyze the formation of cGMP from guanosine-5'-triphosphate[67,69]. The increased levels of cGMP initiate a cascade of intracellular changes leading to activation of protein kinase G, also known as cGMP-dependent protein kinase Ⅰ. These events result in the reduction of cytosolic free calcium by various mechanisms leading to smooth muscle relaxation[67,69].

Relaxation of the trabecular smooth muscle and arterioles results in increased intracavernosal blood flow and activation of corporal veno-occlusive mechanism leading to penile erection. Another cellular mechanism that is thought to maintain penile erection is regulated by phosphatidylinositol 3-kinase (PI3-kinase) pathway that activates the serine/threonine protein kinase Akt, also known as protein kinase B[73]. This induces eNOS phosphorylation, reduces the enzyme's calcium requirement, and enhances NO production[73]. It is believed that after the initiation of erectile process, PI3-kinase/Akt mediated phosphorylation of eNOS result in sustained NO production and penile erection.

Other NANC factors in penile erection

Vasoactive neuropeptides including VIP, substance P, neuropeptide Y, somatostatin, peptide histidine-isoleucine, enkephalins and calcitonin gene-related peptide have been localized along the nerves supplying the penis[74-76]. The precise role of these neuropeptides is not well understood. VIP is believed to be co-released with NO from the cholinergic nerves[74,75]. Vasoconstrictive paracrine factors such as endothelin[77], angiotensin[78], prostaglandin F2-alpha[79], thromboxane[80] and histamine[81] have also been localized in penile erectile tissue but whether they synergize with other neurotransmitters or are modulators of smooth muscle tone is unclear.

Endothelins localized in the penile erectile tissue are potent constrictors of smooth muscle cells[77]. Three isoforms of endothelin called ET-1, ET-2 and ET-3 and two different receptors named ET_A and ET_B have been reported in penile erectile tissue[77]. The ET_A and ET_B receptors are located on vascular smooth muscle and endothelial cells, respectively. ET_A receptor mediates contraction and proliferation while the ET_B receptor contributes to vasodilation[77]. Angiotensin Ⅰ and Ⅱ and two subtypes of angiotensin Ⅱ receptor (AT1 and AT2) have been characterized[82-84]. It was shown that AT1 receptor is expressed in the erectile tissue[83] and that angiotensin Ⅱ causes a dose-dependent contraction of cavernosal smooth muscle[84].

Some of the prostaglandins (PGs) in the penis appear to act as modulators of cavernosal smooth muscle reactivity[85,86]. $PGF_{2\alpha}$, PGI_2 and thromboxane A_2 cause cavernosal smooth muscle contraction while PGE_1 and PGE_2 induce relaxation[87]. In addition to direct vascular smooth muscle relaxation, PGE_1 may also act to inhibit the release of neuronal norepinephrine[88]. A variety of pathologic conditions interfere with the production and action of prostaglandins in erectile tissue. For example, hypoxia was shown to inhibit production of prostanoids in the cavernosal tissue[89,90]. Castration in experimental models was shown to diminish cavernosal smooth muscle relaxation in response to PGE_1, suggesting that androgens may be a prerequisite for their action[91].

Bradykinin relaxes corpus cavernosum tissue and its effects appear to be mediated through cyclic adenosine monophosphate and cGMP[78]. It is thought that bradykinin acts on cavernosal BK2 receptors and stimulates the release of endothelial nitric oxide[92]. Histamine appears to induce endothelium-independent relaxation of erectile tissue and penile microvasculature[81,93]. The relaxatory effects of histamine seem to be mediated by histamine H2 receptors located on vascular smooth muscle. Histamine appears to act on smooth muscle cells without the intervention of nitric oxide or relaxant prostanoids[93].

SUMMARY

Neurophysiology of male sexual response involves multi-regional central neural mechanisms, inter-regional brain communications, and intricate spinal and peripheral neural mechanisms. Our knowledge into the central and peripheral neural regulation of male sexual function continues to gain ground with remarkable scientific advances over the past two decades. Peripheral neural events in male sexual response and the mechanism of penile smooth muscle relaxation have been extensively studied and newer components in these pathways are emerging. A variety of neurologic disorders contribute to the development of male sexual dysfunction and, in some cases, neurologic sexual dysfunction may be a presenting symptom of the impending neurologic disease. Mechanistic knowledge into downstream pathways of NO/cGMP signaling introduced newer concepts in the molecular mechanism of erection and led to the investigation of innovative therapeutic strategies against erectile dysfunction, including the possibility of gene therapy and use of stem cells. However, despite such advances, the precise diagnosis of central problems and peripheral neural factors in neurogenic sexual dysfunction still remain as a major clinical challenge. Nonspecific therapies have been somewhat effective in early-state neurogenic erectile dysfunction but have failed to restore erection in most patients with advanced neurologic problems. Further research into the central, spinal and peripheral neural regulation of sexual function may help the development of more precise diagnostic tools, newer therapeutic strategies, and better management of neurogenic sexual dysfunction in men.

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