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Physiology of Penile Erection and Pathophysiology of Erectile Dysfunction

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The molecular and clinical understanding of erectile function continues to gain ground at a particularly fast rate. Advances in gene discovery have aided greatly in working knowledge of smooth muscle relaxation/contraction pathways. Intensive research has yielded many advances. The understanding of the nitric oxide pathway has aided not only in the molecular understanding of the tumescence but also aided greatly in the therapy of erectile dysfunction. As a man ages or undergoes surgery, preventative therapies to preserve erectile dysfunction have begun. All clinical interventions derived their beginning in a full anatomical, molecular, and dynamic knowledge base of erectile function and dysfunction. In this chapter the components of erectile function will be explained.

Hemodynamics and Mechanism of Erection and Detumescence

Corpora Cavernosa

The penile erectile tissue, specifically the cavernous smooth musculature and the smooth muscles of the arteriolar and arterial walls, plays a key role in the erectile process. In the flaccid state, these smooth muscles are tonically contracted, allowing only a small amount of arterial flow for nutritional purposes. The blood partial pressure of oxygen (PO2) is about 35mmHg range. [1] The flaccid penis is in a moderate state of contraction, as evidenced by further shrinkage in cold weather and after phenylephrine injection.

Sexual stimulation triggers release of neurotransmitters from the cavernous nerve terminals. This results in relaxation of these smooth muscles and the following events:

1. Dilatation of the arterioles and arteries by increased blood flow in both the diastolic and the systolic phases
2. Trapping of the incoming blood by the expanding sinusoids
3. Compression of the subtunical venular plexuses between the tunica albuginea and the peripheral sinusoids, reducing the venous outflow
4. Stretching of the tunica to its capacity, which occludes the emissary veins between the inner circular and the outer longitudinal layers and further decreases the venous outflow to a minimum

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5. An increase in PO2 (to about 90 mmHg) and intracavernous pressure (around 100 mm Hg), which raises the penis from the dependent position to the erect state (the full-erection phase)
6. A further pressure increase (to several hundred millimeters of mercury) with contraction of the ischiocavernosus muscles (rigid-erection phase)

The angle of the erect penis is determined by its size and its attachment to the puboischial rami (the crura) and the anterior surface of the pubic bone (the suspensory and funiform ligaments). In men with a long heavy penis or a loose suspensory ligament, the angle usually will not be greater than 90 degrees, even with full rigidity.

Three phases of detumescence have been reported in an animal study.[2] The first entails a transient intracorporeal pressure increase, indicating the beginning of smooth muscle contraction against a closed venous system. The second phase shows a slow pressure decrease, suggesting a slow reopening of the venous channels with resumption of the basal level of arterial flow. The third phase shows a fast pressure decrease with fully restored venous outflow capacity.

Erection thus involves sinusoidal relaxation, arterial dilatation, and venous compression.[3] The importance of smooth muscle relaxation has been demonstrated in animal and human studies.[4, 5]

Corpus Spongiosum and Glans Penis

The hemodynamics of the corpus spongiosum and glans penis are somewhat different from those of the corpora cavernosa. During erection, the arterial flow increases in a similar manner; however, the pressure in the corpus spongiosum and glans is only one third to one half of that in the corpora cavernosa because the tunical covering (thin over the corpus spongiosum and virtually absent over the glans) ensures minimal venous occlusion. During the full-erection phase, partial compression of the deep dorsal and circumflex veins between Buck's fascia and the engorged corpora cavernosa contribute to glanular tumescence, although the spongiosum and glans essentially function as a large arteriovenous shunt during this phase. In the rigid-erection phase, the ischiocavernosus and bulbocavernosus muscles forcefully compress the spongiosum and penile veins, which results in further engorgement and increased pressure in the glans and spongiosum.

Neuroanatomy and Neurophysiology of Penile Erection

Peripheral Pathways

The innervation of the penis is both autonomic (sympathetic and parasympathetic) and somatic (sensory and motor). From the neurons in the spinal cord and peripheral ganglia, the sympathetic and parasympathetic nerves merge to form the cavernous nerves, which enter the corpora cavernosa and corpus spongiosum to affect the neurovascular events during erection and detumescence. The somatic nerves are primarily responsible for sensation and the contraction of the bulbocavernosus and ischiocavernosus muscles.

Autonomic Pathways

The sympathetic pathway originates from the 11^{th} thoracic to the 2^{nd} lumbar spinal segments and passes through the white rami to the sympathetic chain ganglia. Some fibers then travel through the lumbar splanchnic nerves to the inferior mesenteric and superior hypogastric plexuses, from which fibers travel in the hypogastric nerves to the pelvic plexus. In humans, the T10 to T12 segments are most often the origin of the sympathetic fibers, and the chain ganglia cells projecting to the penis are located in the sacral and caudal ganglia.[6]

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The parasympathetic pathway arises from neurons in the intermediolateral cell columns of the second, third, and fourth sacral spinal cord segments. The preganglionic fibers pass in the pelvic nerves to the pelvic plexus, where they are joined by the sympathetic nerves from the superior hypogastric plexus. The cavernous nerves are branches of the pelvic plexus that innervate the penis. Other branches of the pelvic plexus innervate the rectum, bladder, prostate, and sphincters. The cavernous nerves are easily damaged during radical excision of the rectum, bladder, and prostate. A clear understanding of the course of these nerves is essential to the prevention of iatrogenic ED.[7] Human cadaveric dissection revealed medial and lateral branches of the cavernous nerves (the former accompany the urethra and the latter pierce the urogenital diaphragm 4 to 7 mm lateral to the sphincter) and multiple communications between the cavernous and the dorsal nerves.[8]

Stimulation of the pelvic plexus and the cavernous nerves induces erection, whereas stimulation of the sympathetic trunk causes detumescence. This clearly implies that the sacral parasympathetic input is responsible for tumescence and the thoracolumbar sympathetic pathway is responsible for detumescence. In experiments with cats and rats, removal of the spinal cord below L4 or L5 reportedly eliminated the reflex erectile response but placement with a female in heat or electrical stimulation of the medial preoptic area produced marked erection.[9, 10] Paick and Lee also reported that apomorphine-induced erection is similar to psychogenic erection in the rat and can be induced by means of the thoracolumbar sympathetic pathway in case of injury to the sacral parasympathetic centers.[11] In man, many patients with sacral spinal cord injury retain psychogenic erectile ability even though reflexogenic erection is abolished. These cerebrally elicited erections are found more frequently in patients with lower motoneuron lesions below T12.[12] No psychogenic erection occurs in patients with lesions above T9; the efferent sympathetic outflow is thus suggested to be at the levels T11 and T12.[13] Also reported, in these patients with psychogenic erections, lengthening and swelling of the penis are observed but rigidity is insufficient.

It is, therefore, possible that cerebral impulses normally travel through sympathetic (inhibiting norepinephrine release), parasympathetic (releasing NO and acetylcholine), and somatic (releasing acetylcholine) pathways to produce a normal rigid erection. In patients with a sacral cord lesion, the cerebral impulses can still travel by means of the sympathetic pathway to inhibit norepinephrine release, and NO and acetylcholine can still be released through synapse with postganglionic parasympathetic and somatic neurons. Because the number of synapses between the thoracolumbar outflow and the postganglionic parasympathetic and somatic neurons is less than the sacral outflow, the resulting erection will not be as strong.

Somatic Pathways

The somatosensory pathway originates at the sensory receptors in the penile skin, glans, and urethra and within the corpus cavernosum. In the human glans penis are numerous afferent terminations: free nerve endings and corpuscular receptors with a ratio of 10:1. The free nerve endings are derived from thin myelinated A_δ and unmyelinated C fibers and are unlike any other cutaneous area in the body.[14] The nerve fibers from the receptors converge to form bundles of the dorsal nerve of the penis, which joins other nerves to become the pudendal nerve. The latter enters the spinal cord via the S2--S4 roots to terminate on spinal neurons and interneurons in the central gray region of the lumbosacral segment.[15] Activation of these sensory neurons sends messages of pain, temperature, and touch by means of spinothalamic and spinoreticular pathways to the thalamus and sensory cortex for sensory perception. The dorsal nerve of the penis used to be regarded as a purely somatic nerve; however, nerve bundles testing positive for nitric oxide synthase (NOS), which is autonomic in origin, have been demonstrated in the human by Burnett et al. and in the rat by Carrier and coworkers.[16, 17] Giuliano and associates have also shown that stimulation of the sympathetic chain at the L4--

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L5 level elicits an evoked discharge on the dorsal nerve of the penis and stimulation of the dorsal nerve evokes a reflex discharge in the lumbosacral sympathetic chain of rats.[18] These findings clearly demonstrate that the dorsal nerve is a mixed nerve with both somatic and autonomic components that enable it to regulate both erectile and ejaculatory function.

Onuf's nucleus in the second to fourth sacral spinal segments is the center of somatomotor penile innervation. These nerves travel in the sacral nerves to the pudendal nerve to innervate the ischiocavernosus and bulbocavernosus muscles. Contraction of the ischiocavernosus muscles produces the rigid-erection phase. Rhythmic contraction of the bulbocavernosus muscle is necessary for ejaculation. In animal studies, direct innervation of the sacral spinal motoneurons by brain stem sympathetic centers (A5-catecholaminergic cell group and locus coeruleus) has been identified.[19] This adrenergic innervation of pudendal motoneurons may be involved in rhythmic contractions of perineal muscles during ejaculation. In addition, oxytocinergic and serotonergic innervation of lumbosacral nuclei controlling penile erection and perineal muscles in the male rat has also been demonstrated.[20]

Depending on the intensity and nature of genital stimulation, several spinal reflexes can be elicited by stimulation of the genitalia. The best known is the bulbocavernosus reflex, which is the basis of genital neurologic examination and electrophysiologic latency testing. Although impairment of bulbocavernosus and ischiocavernosus muscles may impair penile erection, the significance of obtaining a bulbocavernosus reflex in overall sexual dysfunction assessment is controversial.

Supraspinal Pathways and Centers

Studies in animals have identified the medial preoptic area (MPOA) and the paraventricular nucleus (PVN) of the hypothalamus and hippocampus as important integration centers for sexual function and penile erection: electrostimulation of this area induces erection, and lesions at this site limit copulation.[21, 22] Marson et al. injected pseudo-rabies virus into the rat corpus cavernosum and traced labeled neurons from major pelvic ganglia to neurons in the spinal cord, brain stem and hypothalamus.[22] Mallick and coworkers also showed that stimulation of the dorsal nerve of the penis in the rat influenced the firing rate of about 80% of the neurons in the MPOA but not in other areas of the hypothalamus.[23] Efferent pathways from the MPOA enter the medial forebrain bundle and the midbrain tegmental region (near the substantia nigra). Pathologic processes in these regions, such as Parkinson's disease or cerebrovascular accidents, are often associated with erectile dysfunction. Axonal tracing in monkeys, cats and rats has shown direct projection from hypothalamic nuclei to the lumbosacral autonomic erection centers. The neurons in these hypothalamic nuclei contain peptidergic neurotransmitters, including oxytocin and vasopressin, which may be involved in penile erection.[21] Several brain stem and medullary centers are also involved in sexual function. The A5 catecholamine cell group and locus ceruleus have been shown to provide adrenergic innervation to hypothalamus, thalamus, neocortex and spinal cord. Projections from the nucleus paragigantocellularis, which provides inhibitory serotonergic innervation, have also been demonstrated in hypothalamus, the limbic system, the neocortex and the spinal cord.

Central Neural Activation during Sexual Arousal

Positron emission tomography (PET) and functional MRI (fMRI) have allowed a greater understanding of brain activation during human sexual arousal. PET and fMRI scanning measure increases in regional cerebral blood flow or changes in regional cerebral activity during a particular moment in time. Using this technology, sexual arousal is triggered in young heterosexual male subjects with sexually explicit pictures or videos. Scanned brain images taking during sexual arousal are compared to images taken when the male participants are shown sexually neutral images (relaxation, documentary, or humorous video clips). Brain

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activation centers as well as deactivation regions can be demonstrated. Although the simplicity of these study designs is elegant, multiple factors are involved in sexual arousal especially arousal triggered by visual clues. The authors of these studies have placed many necessary conditions in an attempt to standardize the methods and participants; however, the complexity of human emotion and sexual response is extremely difficult to regulate.

In 1999, Stoleru et al. studied eight healthy right-handed heterosexual males with PET during visually evoked sexual arousal.[24] Regions of brain activation were correlated with testosterone plasma levels and penile tumescence. Significant activation during visual evoked sexual arousal was seen in bilateral inferior temporal cortex, right insula, right inferior frontal cortex, and left anterior cingulate cortex. From this landmark study a tentative model for brain function during sexual arousal was introduced. The model suggests that there are three components of visually evoked sexual arousal associated with their neuroanatomical regions: 1) a perceptual-cognitive component – assesses the visual stimuli as sexual performed in bilateral inferior temporal cortex, 2) a emotional/motivational component – processes sensory information with motivational states performed in the right insula, right inferior frontal cortex and left cingulate cortex (paralimbic areas), 3) a physiological component – coordinates the endocrine and autonomic functions in the left anterior cingulate cortex.

Further investigations were performed using the sexually visual stimuli and PET scanning. Bocher et al. demonstrated increased activation in the inferior lateral occipital cortex, bilateral posterior temporal cortices (right greater than left), right inferior lateral pre-frontal cortex, left post-central gyrus, bilateral inferior parietal lobules, left superior parietal lobules, frontal pole (Brodmann area 10), left pre-frontal cortex, and midbrain regions.[25] Bocher also noted deactivation in the medial frontal and anterior cingulate, contrary to Stoleru's report. Again, visual association centers were noted to be activated, in particular posterior temporal cortices and the post-central gyrus. Interestingly, the midbrain activation seen in this study correlates to the location of the dopaminergic neurons. The activation of the midbrain region was not demonstrated in other studies. This activation may be associated with prolonged provocation. The visual sexual stimulus used in this study was a 30-minute continuous video clip. Other studies use brief visual sexual stimuli (2–10 minutes).

Park et al. studied 12 healthy male participants using fMRI.[26] Viewing sexual erotic film clips were alternated with non-erotic clips. Regional brain activation was generally seen in the inferior frontal lobe, cingulate gyrus, insular gyrus, corpus collosum, thalamus, caudate nucleus, globus pallidus and inferior temporal lobes. Some activation regions were similar to other studies, in particular the inferior frontal lobes, inferior temporal lobes and the insular gyrus.

In a well-designed study using fMRI and visual evoked stimuli correlated with penile turgidity, Arnow et al. demonstrated a significant region of activation in the right subinsular/insula region including the claustrum. [27] Activation of this region is similarly seen in past studies using PET.[24, 28] This region has been associated with sensory processing. Activation of the insula in this study may represent somatosensory processing and recognition of erection. Other brain regions that were activated during visual sexual stimuli were: right middle gyrus, right temporal gyrus, left caudate and putamen, bilateral cingulate gyri, right sensimotor and pre-motor regions. Also, a smaller activation was seen in the right hypothalamus. Dopamine is projected to the hypothalamus and the evidence that dopamine facilitates male sexual behavior is substantial. Again, the right middle temporal gyrus is seen activated. It is probably associated with visual processing.

In 2003, Mouras et al. studied 8 men using fMRI; however, video clips were not used.[29] Instead still photographs (neutral and sexually arousing) were shown quickly to participants. Using

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shorter visual sexual stimuli, they believed early neural responses would be generated instead of neural responses to the perception of penile tumescence. Again, activation of the middle and inferior occipital gyri was demonstrated, most likely linked to the visual stimuli not necessarily the sexual component. In addition to multiple brain centers that showed activation with visual sexual stimuli (bilateral parietal lobules, left inferior parietal lobule, right postcentral gyrus, right parietoccipital sulcus, left superior occipital gyrus, bilateral precentral gyrus), the cerebellum demonstrated activation in 3 subjects and deactivation in 4 subjects. Multiple other reports have demonstrated activation of the cerebellum in response to erotic films and viewing pictures of love partners. Therefore, it appears that visual sexual stimuli create activation in regions within the cerebellum.

With the advances with fMRI, detailed comparisons of brain activation in response to visual sexual stimuli has been performed on varied groups. Stoleru et al. studies healthy male subjects as compared to men with hypoactive sexual desire disorder (HSDD).[30] The left gyrus rectus, a portion of the medial orbitofrontal cortex remained activated in men with HSDD, which contrasts with its deactivation in healthy men in response to visual sexual stimuli. This region is believed to mediate inhibitory control of motivated behavior. Continued activation of this region may help explain the pathophysiology of HSDD. Montorsi et al. compared men with psychogenic erectile dysfunction (ED) and potent controls following the administration of apomorphine.[31] In men with psychogenic ED extended activation of the cingulated gyrus, frontal mesial and frontal basal cortex was seen during visual sexual stimuli. This extended activation may suggest an underlying organic etiology for psychogenic ED. With the administration of apomorphine, the fMRI image in psychogenic ED patients was similar to the potent controls. Apomorphine caused additional activation of foci in the psychogenic ED patient (seen in the nucleus accumbens, hypothalamus, mesencephalon). Also the right hemisphere was significantly more activated then the left following apomorphine administration. Right greater left hemisphere activation is a common finding within sexually evoked brain activation studies.

Brain scanning with PET and fMRI has become a powerful tool in the study of central activation of sexual arousal. Many brain regions of activation have been demonstrated in these reports. Some common brain centers of activation can now be described through these reports (Table 1). Psychogenic ED, premature ejaculation, sexual deviations, orgasmic dysfunction are just a few conditions that may have an alterations in higher brain function and perhaps now can be studied. As we begin to understand the brain function within normal sexual response and arousal, the cause of the sexual dysfunction conditions may become elucidated.

In summary, the structures above are responsible for the three types of erection: psychogenic, reflexogenic and nocturnal. Psychogenic erection is a result of audiovisual stimuli or fantasy. Impulses from the brain modulate the spinal erection centers (T_{11}-L_2 and S_2-S_4) to activate the erectile process. Reflexogenic erection is produced by tactile stimuli to the genital organs. The impulses reach the spinal erection centers; some then follow the ascending tract, resulting in sensory perception, while others activate the autonomic nuclei to send messages via the cavernous nerves to the penis to induce erection. This type of erection is preserved in patients with upper spinal cord injury. Nocturnal erection occurs mostly during rapid-eye-movement (REM) sleep. PET scanning of humans in REM sleep show increased activity in the pontine area, the amygdalas and the anterior cingulate gyrus but decreased activity in the prefrontal and parietal cortex. The mechanism that triggers REM sleep is located in the pontine reticular formation. During REM sleep, the cholinergic neurons in the lateral pontine tegmentum are activated while the adrenergic neurons in the locus ceruleus and the serontonergic neurons in the midbrain raphe are silent. This differential activation may be responsible for the nocturnal erections during REM sleep.