**Mechanism of penile erection**

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**Abstract:**

Sexual stimuli (tactile, visual, olfactory, and imaginative) are processed and integrated in the central nervous system which then activates certain autonomic and somatic pathways within the peripheral nervous system. This coordinated activation of the central and peripheral nervous systems leads to penile erection which is actually a result of relaxation of vascular and cavernosal smooth muscle in the penis. In flaccid (detumescent) penis, the smooth muscle tone is heightened. Penile erection (tumescence) requires a decrease in the smooth muscle tone. The tone of the penile smooth muscle therefore is the main determinant of erectile function. Relaxation of vascular smooth muscle in the blood vessels supplying the penis and simultaneous relaxation of cavernosal smooth muscle lead to an increase in arterial inflow. Once combined with the reduced outflow by compression of subtunical venules and the contraction of striated ischiocavernosus muscles, the intracavernosal blood pressure reaches above the systemic blood pressure resulting in rigid erection. In this chapter, the current information on the control of erectile function by this central-peripheral-smooth muscle axis will be reviewed.

**Keywords:** erection, penis, smooth muscle, cavernosum, autonomic, nitric oxide, nitrergic, hypogastric, plexus, PDE5

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**Anatomy of the penis:**

The penis is composed of three cylindrical masses of cavernous tissue bound together by fibrous tissue (Buck’s fascia) and covered with skin. The lateral two of the masses are known as the corpus cavernosum; the third is median and termed as the corpus spongiosum (Figure 1). The corpus cavernosum is surrounded by a thick fibrous envelope called tunica albuginea. The urethra is located within the corpus spongiosum which is surrounded by a thinner and more elastic fibrous layer than the tunica albuginea of the corpus cavernosum (Figure 1). The blood supply to the penile skin and corpus cavernosum is via external and internal pudendal arteries respectively. Internal pudendal arteries give rise to the pair of cavernosal arteries, each of which goes through the tunica albuginea at the hilum of the penis; then runs distally in the centre of each corpus while giving off numerous helicine branches. These corkscrew shaped muscular vessels open directly into the lacunar spaces in the corpus cavernosum (Figure 1). The venous drainage is via the superficial, intermediate, and deep venous systems. The superficial system, which lies above Buck’s fascia, allows blood from multiple superficial veins primarily of the skin to drain into the superficial dorsal vein, which itself drains into the external branch of the internal saphenous vein. The intermediate venous system lies beneath Buck's fascia and comprises the deep dorsal vein and the multiple circumflex veins. This system drains blood from the glans, corpus spongiosum and the distal two-thirds of the corpora. The deep dorsal vein runs in the groove dorsally between the corpus cavernosum (Figure 1) and drains into the dorsal venous complex at the urethroprostatic junction. The deep drainage system consists of the cavernosal and crural veins. Emissary veins in the proximal third of the penis join to form one or two cavernosal veins which pass between the bulb and crus of the penis to drain into the internal pudendal vein (1).

**Human sexual cycle:**

Classical human sexual cycle consists of four phases: desire, arousal, orgasm and resolution (2-4). Erection in man occurs during the arousal phase and continues through the orgasm phase until the resolution phase. During the desire and arousal phases the central nervous system receives, processes and integrates tactile, visual, olfactory and imaginative sexual stimuli. This leads to the activation of autonomic and somatic pathways which descend through the spinal cord to the peripheral tissues. Activation of the erectogenic autonomic pathways causes the relaxation of penile arterial and cavernosal smooth muscle, causing an increase in blood flow into the penis (Figure 2). The rise in the blood flow triggers further activation of endothelial cells lining the blood vessels and cavernosal sinusoidal spaces which leads to further relaxation of the underlying smooth muscle (Figure 2). Increased inflow due to arterial and cavernosal smooth muscle relaxation, decreased outflow due to physical compression of subtunical venules and contraction of striated muscles lead to further increase in intracavernosal pressure which reaches above the systemic blood pressure (Figure 2); a hallmark of rigid erection (5). In this chapter, the factors involved in this central-peripheral-smooth muscle axis will be introduced and the current knowledge around these mechanisms will be summarised.

**Central mechanisms:**

Sexual stimuli are received by the brain from all parts of man’s body. This information is then processed and integrated in the occipital lobe (visual), rhinencephalon (olfactory), thalamus (tactile), and limbic system (imaginative) leading to activation of two nuclei in the hypothalamus: the paraventricular nucleus (PVN) and medial preoptic area (MPOA) (6). These two nuclei send projections to autonomic and spinal centres regulating the peripheral events leading to erection. Within the PVN and MPOA, several neurotransmitters/neuropeptides such as dopamine, oxytocin, serotonin, adrenocorticotrophic hormone (ACTH), alpha-melanocyte stimulating hormone (α-MSH), gamma-aminobutyric acid (GABA), noradrenaline (NA), excitatory amino acids, opioid peptides, acetylcholine, and nitric oxide (NO) have been localised and most of them have been suggested to be involved in central regulation of penile erection (6).

Descending pathways from the brain through the spinal cord are both excitatory and inhibitory in nature. It is thought that without any sexual stimuli there is a continuous inhibitory tone on the descending pathways while the excitatory component is silent. This tonic inhibition is lifted, which is called disinhibition, when the sexual stimuli reach above a threshold level. This leads to increased pro-erectile excitatory descending output leading to activation of the peripheral autonomic and somatic pathways. The nucleus para gigantocellularis (nPGC) of the brain stem is thought to be the relay point where this tonic inhibition takes place (7).

Once through the brain stem, the descending excitatory path reaches two further critical relay points in the spinal cord: the thoracic centre at the level of T11-L2 and the sacral centre at the level of S2-S4. These two relay points are important in integrating the ascending and descending stimuli from and to periphery and higher central regions. At these points, the erectile neuronal paths leave the central nervous system and relayed to the periphery via autonomic and somatic nerves (Figure 3) (6;7).

**Peripheral mechanisms:**

Preganglionic sympathetic neurons and preganglionic parasympathetic neurons are localised in the thoracic and sacral centres of the spinal cord respectively. Preganglionic fibres reach pelvic plexus also known as inferior hypogastric plexus where they synapse with postganglionic neurons. It is important to note that neuronal cell bodies of the pro-erectile parasympathetic nerve fibres that reach the penis via the cavernous nerve are located in the pelvic plexus. Postganglionic sympathetic nerve fibres also reach penis via the cavernous nerve. Cavernous nerve therefore carries both pro-erectile parasympathetic and anti-erectile sympathetic nerve fibres to the penile vasculature and the cavernous body. Sacral motor neurons send direct projections to the striated ischiocavernosus and bulbospongiosus muscles via the pudendal nerve (Figure 3) (6).

Sympathetic nerve fibres in the penis release low concentrations of the neurotransmitter NA continuously. NA causes contraction of vascular and cavernosal smooth muscle by activating α1-adrenoceptors. The tonic release of NA therefore causes a heightened smooth muscle tone under normal conditions (i.e. without sexual stimuli) keeping the penis flaccid. It should also be noted that parasympathetic nerve fibres release small amounts of NO during the flaccid phase; it is generally accepted that the heightened tone of the penile smooth muscle is the net result of a balance between contractile NA and relaxant NO (Figure 4) (5). When the autonomic nerves are activated by higher centres as a result of sexual stimuli, two key events take place simultaneously:

1. NO released from postganglionic parasympathetic nerve fibres increases significantly which causes relaxation of vascular and cavernosal smooth muscle. These nerve fibres are also known as nitrergic (Figure 4) because of their expression of neuronal NO synthase (nNOS) which synthesises NO (8).
2. Acetylcholine released from parasympathetic nerve fibres simultaneously with NO, inhibits the release of NA from sympathetic nerve fibres (9;10).

This initial relaxation as a result of increased vasorelaxant NO and decreased vasoconstrictor NA leads to an increase in blood inflow into the cavernosal space. Increased blood flow generates increased shear stress on the endothelial cells lining the blood vessels and cavernosal sinusoids. Shear stress causes activation of endothelial NO synthase (eNOS) in the endothelial cells (11) which synthesises further NO. At this point the NO concentrations reaching the penile smooth muscle rise to a peak level due to the contribution of its synthesis by both nNOS in the parasympathetic nerves and eNOS in the endothelium (Figure 4). Other neurotransmitters and factors such as acetylcholine, vasoactive intestinal peptide (VIP), endothelium-derived hyperpolarising factor (EDHF), prostaglandins, angiotensin, and endothelin have also been suggested to be involved in regulation of penile smooth muscle tone (5).

**Smooth muscle:**

As mentioned above, in flaccid state vascular and cavernosal smooth muscle tone in the penis is elevated by continuous release of NA from sympathetic nerve fibres. NA causes smooth muscle contraction primarily by eliciting a release of calcium from intracellular stores into the cytoplasm secondary to activation of α-adrenoceptors (Figure 4). Elevated intracellular free calcium concentrations trigger activation of calcium-calmodulin dependent myosin light chain kinase (MLCK) which in turn phosphorylates the myosin light chain which is essential for smooth muscle contraction. During this continuous contractile period, it is generally accepted that calcium-sensitising pathways such Rho-kinase may also play a role in maintaining the high tone. Calcium sensitising pathways do not require elevated intracellular free calcium levels to activate MLCK. Once activated via α-adrenoceptors, calcium sensitising pathways can keep the smooth muscle tone high for prolonged periods (8).

During erection, as the NA concentration reaching the smooth muscle decreases, the concentration of NO increases. This causes a shift in the smooth muscle from contractile phase to relaxant phase. This shift is a result of combination of decreased activation of contractile pathways (i.e. direct activation of MLCK by increased calcium and calcium sensitising pathways) and increased activation of relaxant pathways which in turn has inhibitory effects on contractile pathways via different mechanisms. The main relaxant mechanism among many others is the activation of soluble guanylate cyclase (sGC) enzyme by NO. Activation of sGC leads to an increased level of cyclic guanosine monophosphate (cGMP) concentrations in the smooth muscle cells (Figure 4). cGMP acts then on several pathways leading to relaxation. cGMP is quickly metabolised to inactive 5’-GMP by an enzyme called phosphodiesterase type 5 (PDE5) in the penile smooth muscle (Figure 4) (5). Inhibition of PDE5 therefore causes an increase in cGMP concentrations in the penile smooth muscle leading to potentiation of NO-driven erectile process.

Relaxation of vascular and cavernosal smooth muscle causes an increase in blood flow into the cavernosal space. This leads to engorgement of sinusoidal spaces with blood which results in reduced outflow due to compression of subtunical venules. Such an increased inflow and decreased outflow causes the intracavernosal pressure to reach the level of systemic arterial pressure. The pressure is further increased which provides further rigidity when striated muscles such as ischiocavernosus muscle contracts as a results of activation of pudendal nerve fibres.

**Conclusions and the gaps in our knowledge:**

A brief summary of current understanding of mechanisms involved in the regulation of penile erection is given. Although the main players in this important physiological function such as NO and noradrenaline have been identified and characterised, there remain several unanswered questions: What are the contribution of other factors (e.g. EDHF, VIP) to penile erection in men? Which central neurotransmitters are involved in regulation of erectile response in men and how are they linked to psychological aspects of sexual function? What are the relative contribution of eNOS and nNOS? What are the characteristics of a human nitrergic neuron (i.e. how does a nitrergic neuron transport nNOS enzyme through its axon)? It is hoped that with the help of technological breakthroughs these questions will be answered in near future which will eventually lead to better and newer treatment modalities for erectile dysfunction.

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