

## Chapter 2

# Normal Erectile Physiology

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**Abstract** The human penis is composed of the paired dorsal corpora cavernosa and the ventral corpus spongiosum each of which is encased within a fibrous sheath, the tunica albuginea, and then all of which are enclosed within Buck's fascia, Colles' fascia, and the skin. The spongiosum contains the urethra and is contiguous with the glans distally. The arterial supply to the penis is from the four terminal branches of the paired penile arteries, which are themselves branches of the internal pudendal arteries. The external iliac, obturator, vesical, and femoral arteries provide accessory arterial supply to the penile artery in some cases. Venous outflow originates from post-cavernous venules that coalesce to form emissary veins. These veins empty into the cavernous vein, the deep dorsal vein, and the superficial dorsal vein depending on their origin within the penis. Efferent innervation is from parasympathetic, sympathetic, and somatic sources. Somatosensory afferents course from the penis to central sites.

The maintenance of penile flaccidity and the erectile response are controlled via intercommunicating supraspinal and spinal reflex pathways. During the flaccid state, antierectional neural input, primarily via sympathetic efferents, acts to limit blood flow to the penis to a quantity sufficient to meet physiologic needs but insufficient for erection. Following either physical or psychological sexual stimulation proerectional neural signals are

sent to the penis primarily via parasympathetic tracts. This input initiates the erectile response via neurotransmitter release onto postsynaptic smooth muscle cells within the corporal bodies. Nitric Oxide (NO) is the main proerectional neurotransmitter. The resultant molecular cascade leads to a decrease in intracellular  $\text{Ca}^{2+}$  and arteriolar smooth muscle relaxation. This relaxation allows for increased blood flow and subsequent corporal engorgement with increasing penile rigidity. As the corpora become engorged, the emissary veins are compressed by within the tunica albuginea limiting venous outflow. The increased arterial inflow and limited venous outflow increases intracorporal pressure and leads to erection. As proerectional input ceases, the secondary molecular messenger cGMP is hydrolyzed allowing for a rise intracellular  $\text{Ca}^{2+}$ , subsequent smooth muscle contraction, decreased penile blood flow and a return to flaccid state physiology.

**Keywords** Corpora • Glans • Venous drainage • Peripheral innervations • Tumescence and erection • Detumescence • Spinal and supraspinal control • Proerectional transmitters

## Anatomical Review

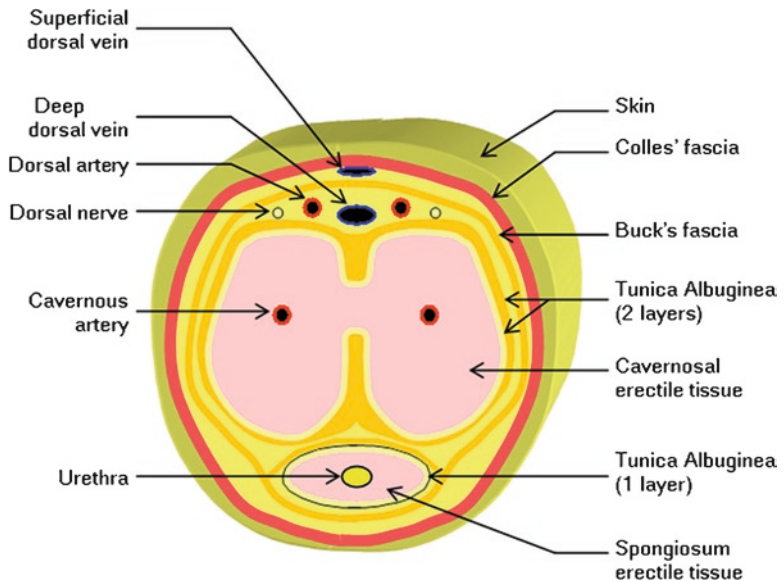
### Gross Structure

The human penis is composed of the paired dorsal corpora cavernosa and the ventrally placed corpus spongiosum. The corpus spongiosum contains the

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**Fig. 2.1** Penile cross-section, penile cross-section showing paired dorsal corpora cavernosa and the ventral corpus spongiosum. Note the double-layered tunica albuginea surrounding the cavernosa (inner circular and outer longitudinal) and the incomplete septum allowing communication of the two cavernosa. Note urethra coursing within the corpus spongiosum and the single-layered tunica (1 circular layer)



urethra and is contiguous with the glans penis distally. Each corpus is surrounded by a fibrous sheath, the tunica albuginea. Between the two corpora cavernosa is an incomplete perforated septum allowing them to function in unison [1]. Surrounding all three corpora is an additional fibrous layer, Buck's fascia. Superficial to Buck's fascia is Colles' fascia extending from the base of the glans to the urogenital diaphragm where it is contiguous with Scarpa's fascia. Superficial to Colles' fascia is the skin (see Fig. 2.1). Proximally, the corpora cavernosa form the penile crura, which are anchored to the pubic rami and are covered by the ischiocavernosus muscles [1]. The proximal corpus spongiosum forms the penile bulb, which is enveloped in the bulbospongiosus muscle. The suspensory ligament of the penis arises from the linea alba and pubic symphysis and inserts on the tunica albuginea to support the pendulous portion of the penis [2].

## Corpora

The corpora cavernosa are two spongy cylinders comprised primarily of arterial sinusoids and smooth muscle surrounded by the tunica albuginea. The cavernosal tunica albuginea is

2–3 mm thick in the flaccid state and is composed mostly of collagen fibers with a smaller portion being elastic fibers [3]. The cavernosal tunica has an inner circular layer and an outer longitudinal layer of fibers [1].

The histologic appearance of corpus spongiosum is similar to the corpora cavernosa and it contains larger sinusoids. Additionally, the tunica albuginea surrounding this corpus is thinner, has only one circular fiber layer, and contains more elastic fibers [3].

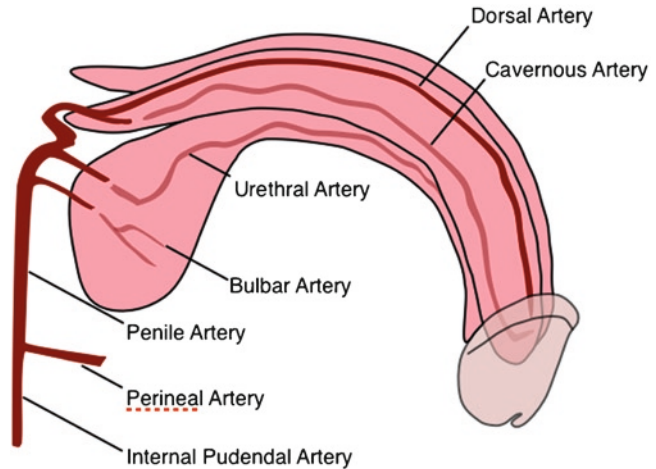
## Glans

The glans forms the distal portion of the penis. It is contiguous with the corpus spongiosum. It is covered with very thin, firmly adherent skin. Additionally, the tunica on the glans [1] albuginea is absent.

## Arterial Supply

Classically, the internal pudendal artery, a branch of the internal iliac, serves as the main blood supply to the penis [1]. After giving off the perineal artery, it becomes the penile artery. More

**Fig. 2.2** Arterial supply to the penis. The internal pudendal artery forms the penile artery after giving of the perineal artery. The penile artery has four terminal branches: the bulbar, urethral, cavernous, and dorsal artery. Penile blood supply is bilaterally symmetric; only one side of supply is portrayed in this diagram



recently, accessory pudendal arteries, arising from the external iliac, obturator, vesical, and femoral arteries, have been shown to contribute to the blood supply of the penile artery in many men [4]. The penile artery has four paired terminal branches: the cavernous (deep penile), dorsal, urethral, and bulbar arteries [1, 5] (see Fig. 2.2). Each cavernous artery pierces the ipsilateral cavernosal tunica albuginea at the hilum of the penis and enters the penile crura. It runs the length of the corpora cavernosa giving off many tortuous branches, the helicine arteries. These helicine arteries open directly into the sinusoids of the erectile tissue. Each dorsal artery lies beneath Buck's fascia and courses distally between the laterally placed paired dorsal nerves and the deep dorsal vein. They are responsible for the engorgement of the glans during erection. The urethral arteries run through the corpus spongiosum lateral to the urethra and supply blood to the corpus spongiosum, the urethra, and the glans. The bulbar arteries enter the bulb of the penis supplying the proximal urethra and Cowper's gland.

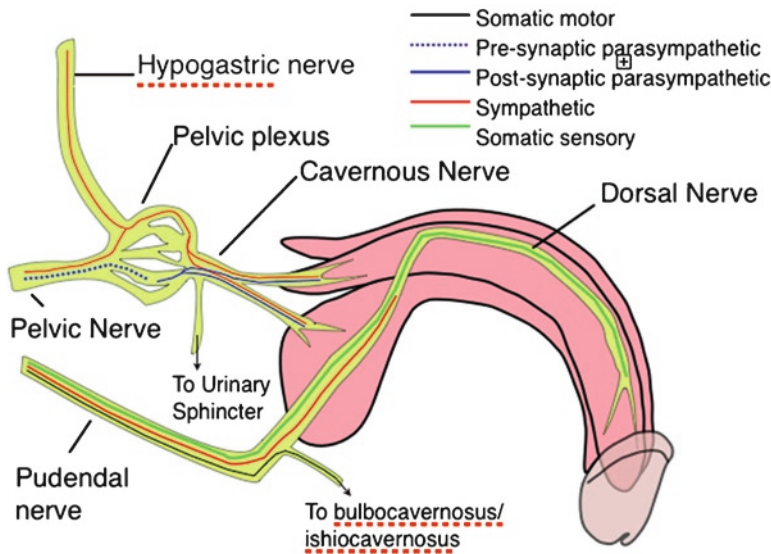
## Veins

Within the three corpora tiny post cavernous venules coalesce to form emissary veins that go

on to pierce the tunica albuginea [6]. In the proximal penis, the emissary veins drain into the cavernous vein that goes on to join the periurethral veins of the urethral bulb to form the internal pudendal vein. The emissary veins from the distal and middle penis combine to form circumflex veins that then drain into the deep dorsal vein of the penis. The deep dorsal vein runs the length of the dorsal penis and drains into the periprostatic plexus. The venous drainage of the skin and subcutaneous penile tissue is via many superficial veins that go on to form the superficial dorsal vein. This drains into the external pudendal vein.

## Peripheral Innervation

The penis receives innervation from parasympathetic, sympathetic, and somatic efferents (see Fig. 2.3). The parasympathetic penile innervation comprises the major excitatory input to the penis responsible for vasodilation of the penile vasculature and erection. Preganglionic fibers originate in the sacral parasympathetic nucleus [4, 7]. These fibers travel to the pelvic plexus via the pelvic nerve, which also carries sympathetics [7, 8]. After synapsing in the pelvic plexus, postganglionic parasympathetic fibers emerge as a part of the cavernous nerve [9]. The cavernous nerve travels along the posterolateral aspect of



**Fig. 2.3** Innervation of the penis. Presynaptic parasympathetic fibers travel via pelvic nerve to synapse in pelvic plexus, postsynaptic fibers emerge within cavernous nerve and travel to corporal bodies as well as urinary sphincter. Sympathetic fibers travel via hypogastric and pelvic nerves to join cavernous nerve as it emerges from

the pelvic plexus. Sympathetic fibers also travel to penis via pudendal nerve. Somatic motor fibers to the bulbocavernosus and ischiocavernosus travel via pudendal nerve. Somatic sensory afferent signals travel from the penis via the dorsal nerve which goes on to join the pudendal nerve

the prostate within the pelvic fascia that fuses with the prostatic capsule [10]. The cavernous nerves then exit the pelvis as two groups of fibers [10]. The first group travels to the urethral sphincter to modify urinary function. The second group travels to the penis. This group branches further as it reaches the penis with a portion of the fibers heading for the corpus spongiosum and the remaining fibers entering the penile crura along with the deep penile artery and cavernous veins [10].

Sympathetic pathways begin in the intermediolateral cell column and intercalated nucleus at spinal levels T9-L2 [8, 11]. Preganglionic fibers emerge and travel to synapse on sacral and caudal lumbar ganglion cells within the sympathetic chain [12]. Postganglionic sympathetics to the penis exit the sympathetic chain via three routes. The first carries sympathetic fibers via the hypogastric nerve to the pelvic plexus where they join the cavernous nerve for the remaining distance to the penis. In the second path, postsynaptic sympathetic outflow from paravertebral ganglia

joins the pelvic nerve, which travels to the pelvic plexus to join the cavernous nerve to the penis. Finally, a portion of the sympathetic outflow is carried on a direct route to the penis from the sympathetic chain ganglia via the pudendal nerve [9]. The role of these sympathetic neurons appears to be primarily one of antierectile function. They stimulate vasoconstriction and appear to have spontaneous activity that produces an antierectile tone [9, 13]. However, total eradication of sympathetic input leads to diminished erectile function demonstrating that the sympathetic input is not entirely antierectile [9, 11, 14]. Opinions differ on the reason for this effect, however, some authors have suggested that due to the vital role of sympathetic input for arterial tone and regulation of blood distribution, a sympathetic lesion may disrupt routing of blood to the penis [14].

Somatic motor efferents arise from the ventral sacral spinal cord (Onuf's nucleus). They travel via the pudendal nerve to innervate the bulbospongiosus and ischiocavernosus muscles [9].

Neural input to these muscles in the presence of an erect penis leads to increased penile rigidity [15]. Additionally, contraction of these muscles in a rhythmic manner assists in the expulsion of ejaculate [9].

Somatosensory input from the penis arises primarily at free nerve endings and corpuscular receptors. The input is carried via C- and A-delta fibers [16]. These fibers coalesce to form the dorsal nerve of the penis, which extends into the pelvis to join the pudendal nerve. The pudendal nerve carries sensory signals to the spinal cord via spinal roots S2-S4 and terminates in the gray matter of the lumbosacral cord [17].

## Hemodynamics of Erection

### *Flaccid State*

The flaccid state of the penis is characterized by blood flow sufficient to meet nutritional and other physiologic needs, but insufficient for penile erection. During this state, sustained partial contraction of smooth muscle cells in the walls of arteries, arterioles, and in the corporal trabeculae is essential for the limitation of blood flow. The molecular mechanisms leading to this tonic smooth muscle contraction are discussed below.

### *Tumescence and Erection*

With sexual stimulation and subsequent release of proerectile mediators onto corporal smooth muscle the erectile response is initiated. Within the corpora cavernosa there is dilation of arteries and arterioles and thus increased inflowing blood. The trabecular smooth muscle additionally relaxes allowing corporal sinusoids to expand as they become engorged with blood. This cavernosal expansion begins to compress the subtunical venules decreasing venous outflow. With further engorgement, the tunica is stretched occluding the

emissary veins between the two tunical layers leading to minimal venous outflow [18]. This leads to an increase in intracavernosal pressure to approximately 100 mmHg that raises the penis to the fully erect position [18].

During heightened sexual activity, the penis enters the rigid-erection phase. The ischiocavernosus muscles contract, as a result of the bulbocavernosus reflex, compressing the base of the corpora cavernosa leading to temporary cessation of inflow and outflow of blood and increasing intracavernous pressures up to several hundred mmHg [18].

The corpus spongiosum and glans behave somewhat differently in tumescence and erection. Arterial flow increases in these locations just as in the cavernosa. Due to differences in the tunica albuginea, thin in the spongiosum and absent in the glans, venous occlusion is less in these locations. This leads to pressures in the spongiosum only one third to one half of that of the cavernosa [19]. The glans and spongiosum thus act essentially as arteriovenous shunts during erection. Similar to the corpora cavernosa, during the rigid erection phase contraction of the ischiocavernosus and bulbocavernosus muscles compresses out-flowing veins leading to further pressure increase in the spongiosum and glans. The deep dorsal vein is compressed between the engorged cavernosa and Buck's fascia contributing to rigidity of the glans [18].

### *Detumescence*

With cessation of sexual stimulus and subsequent decrease in erection inducing neural activity, the erectile response ends. Antierectile neural input leads to vasoconstriction of penile arteries and contraction of the trabecular smooth muscle resulting in reduced arterial inflow and collapse of the trabeculae [20]. With decreased arterial inflow and subsequent corporal decompression, occlusion of venous drainage subsides allowing efflux of corporal blood and return to flaccid state physiology [21].



## Local Mechanisms of Erection

As previously mentioned, partial contraction of trabecular, arterial, and arteriolar smooth muscle and subsequent limitation of blood flow is essential for maintaining penile flaccidity. Sympathetic adrenergic signaling and the activity of substances derived from vascular endothelium (endothelins and prostaglandin  $F_{2\alpha}$ ) appear to play a crucial role in this process [22, 23]. These substances activate G-protein coupled receptors that initiate a cascade leading to the increased production of inositol triphosphate and diacylglycerol. In turn, these substances lead to an increase in intracellular  $[Ca^{2+}]$  via releasing intracellular stores or opening cell membrane channels to allow influx of  $Ca^{2+}$  [19, 23, 24]. The resultant elevated intracellular free  $Ca^{2+}$  binds to calmodulin changing its conformation to expose sites that bind and activate myosin light-chain kinase [19]. The now activated myosin light-chain kinase phosphorylates myosin light chains, allowing them to initiate smooth muscle contraction [25].

This rise in intracellular  $Ca^{2+}$  is only a transient event, and further mechanisms, most notably calcium sensitization, appear to play a significant role in maintaining contraction of smooth muscle during the flaccid state. The RhoA, Rho-kinase pathway is important to calcium sensitization [26, 27]. G-proteins expressed in penile smooth muscle activate RhoA which activates Rho-kinase. Rho-kinase, in-turn, phosphorylates the regulatory subunit of smooth muscle myosin phosphatase, inhibiting its activity. This inhibition prevents dephosphorylation of smooth muscle myofilaments allowing them to maintain their contractile tone [28, 29]. The sum total of this pathway is the maintenance of smooth muscle contraction during the flaccid state without a significant change in intracellular  $[Ca^{2+}]$  [29]. RhoA is expressed at a 17-fold higher concentration in rabbit cavernosal smooth muscle when compared to other vascular smooth muscle sites supporting its important role in erectile physiology [30].

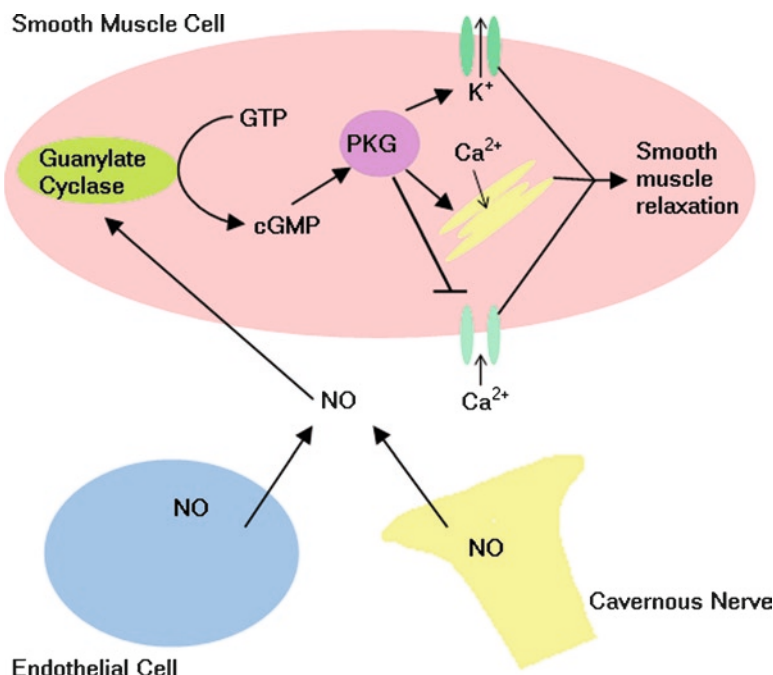
During the erectile response, a drop in intracellular  $Ca^{2+}$  is important for the relaxation of vascular and corporal smooth muscle. The release

of nitric oxide (NO) from nonadrenergic, noncholinergic nerve terminals and the endothelium is a major mediator of this response [31, 32]. NO works in the smooth muscle cell to activate a soluble guanylyl cyclase. This enzyme leads to an increase in the production of the second messenger cyclic guanosine monophosphate (cGMP). Increased cGMP concentration activates protein kinase G (PKG). The activated PKG phosphorylates multiple intracellular proteins to cause: sequestration of intracellular  $Ca^{2+}$  in the endoplasmic reticulum, inhibition of cell membrane calcium influx channels, and opening of potassium channels with resultant myocyte hyperpolarization [18]. The resultant decrease in intracellular calcium concentration and hyperpolarization leads to smooth muscle relaxation via what is essentially a reversal of the process for smooth muscle contraction described above. In brief, intracellular calcium levels fall, deactivating the calcium-calmodulin complex. This allows myosin light-chain kinase to become inactive facilitating resultant dephosphorylation of the myosin light chains deeming them unable to initiate muscle contraction (see Fig. 2.4).

During the return to flaccid state physiology phosphodiesterase type 5 (PDE-5) hydrolyzes cGMP to the inactive guanosine monophosphate. As cGMP concentration falls intracellular  $[Ca^{2+}]$  rises and the vascular and corporal smooth muscle cells again contract [31].

## Spinal Control of Erection

Erection can originate from both tactile stimulation of the penis (reflexive erection) and supraspinal stimuli (psychogenic erection). The sacral spinal cord appears to integrate and coordinate the excitatory and inhibitory neural inputs from both peripheral and supraspinal sources. Complete destruction of the sacral spinal cord or its outflow eliminates erectile function [33, 34]. However, patients with suprasacral spinal cord transection have shown erectile function to be at least partially maintained in response to tactile stimulation of the penis [8, 33–35]. This has led to



**Fig. 2.4** Smooth muscle relaxation – Nitric oxide (NO) released from endothelium and cavernous nerve terminals stimulate guanylate cyclase within smooth muscle cell leading to the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). cGMP activates protein kinases (PKG)

which phosphorylate proteins leading to potassium efflux, calcium sequestration in the endoplasmic reticulum, and blockage of calcium membrane channels. Calcium sequestration and hyperpolarization lead to smooth muscle cell relaxation via inactivation of myosin contractile units

postulation that sacral centers are essential for erection regardless of origin (i.e., reflexive or psychogenic) [12]. The sacral spinal reflex, which can function in the absence of suprasacral signals, coordinates sensory input from the dorsal nerve of the penis and proerectile output via sacral parasympathetics facilitating erection in response to direct penile stimulation. Additionally, sacral centers are vital to the integration of psychogenic erectile stimuli from supraspinal origins and the resultant erectile response, as evidenced by the absence of psychogenic erection in patients with sacral destruction.

## Supraspinal Control of Erection

Supraspinal control of erection is poorly understood with almost all evidence being from

experimental animal models. Erections in response to imaginative, visual, tactile, and olfactory stimuli are thought to originate from supraspinal centers. Hypothalamic and limbic pathways have been shown to play a key role [9].

## Paraventricular Nucleus

The hypothalamic paraventricular nucleus (PVN) contains premotor neurons that project from the parvocellular layer directly into the spinal cord [36–38]. These neurons have been shown to contain a variety of neurotransmitters: oxytocin, vasopressin, enkephalins, and dopamine [39, 40]. In rat models injection of a variety of neuromediators (oxytocin, glutamate, nitric oxide, dopamine agonists) into the PVN has been shown to elicit penile erection [39, 40]. Additionally, in both rats and monkeys, stimulation of the PVN

elicits erection [41]. Lesion of the parvocellular layer of the PVN causes longer latencies and fewer noncontact erections in rats [42]. Parvocellular PVN neurons have been shown to respond to stimulation of the dorsal nerve of the penis in rats, suggesting that the PVN may be a supraspinal reflex center for erections [43]. The PVN also receives input from the medial preoptic area (MPOA) suggesting that the PVN serves to integrate MPOA input before sending it downstream via autonomic pathways selectively activated within the PVN [9, 44].

### ***Medial Preoptic Area***

The MPOA of the hypothalamus is key to sexual behavior [45, 46]. In rats and monkeys, MPOA stimulation elicits erection [41, 47]. In monkeys, increases in MPOA neuronal activity have been recorded during erection [48]. Interestingly, MPOA lesions do not affect reflexive or noncontact erections [49, 50]. All of this has led to debate as to the role of the MPOA in erectile function. The emerging theory is that the MPOA likely serves as an integration center of hormonal and sensory inputs for sexual behavior and redistributes these signals to the hypothalamic and brainstem structures thought to be more directly linked to erectile control, such as the PVN [17, 44, 51].

### ***Other Supraspinal Centers***

Many other supraspinal areas have been shown in animal studies to be related to erectile function. In monkeys, isolated stimulation of the medial dorsal nucleus of the thalamus, ventral tegmental area, precallosal cingulate gyrus, and subcallosal and caudal gyrus led to erections [41]. Hippocampal stimulation in anesthetized rats increased intracavernous pressures as did desynchronization of the somatosensory cortex following cocaine administration [52, 53]. A center for descending the inhibition of spinal sexual reflexes has been localized

to a group of neurons in the paragigantocellular reticular nucleus of the ventral medulla [54]. The exact role each supraspinal area plays in mediating erection is currently unclear. However, it is apparent that there are extensive interconnections between many supraspinal centers that contribute to descending pathways and exert powerful control, both inhibitory and excitatory, on the spinal responses driving erection [51].

## **Central Neurotransmission**

### ***Oxytocin***

Proerectile projections from the supraoptic area of the hypothalamus and the PVN travel to the spinal centers for erection and oxytocin has been shown to be a key neurotransmitter in these neurons [1, 55, 56]. In lab animals, intracerebroventricular or intrathecal injection of oxytocin antagonists blocks the induction of erection that is seen with intrathecal oxytocin injection. Additionally, antagonist injection into the lateral ventricles leads to a dose dependant reduction in noncontact erections [57]. This has led to the belief that oxytocin plays a role in facilitating nonreflexive erections.

### ***Dopamine***

Dopaminergic neurons project to the MPOA and PVN [58] and also have been discovered to travel from the caudal hypothalamus to the lumbosacral spinal cord [59]. Dopamine is thought to participate in central regulation of the autonomic and somatic penile reflexes. The dopamine receptor agonist, apomorphine, induces penile erection in rats when administered systemically [60]. Additionally, apomorphine injection into the MPOA facilitated erections while dopaminergic antagonist injection into the MPOA decreased penile reflexes [60–62]. In the PVN, dopaminergic neurons appear to stimulate oxytocinergic



neurons, which then more directly account for the erectile response. This is supported by the prevention of apomorphine-induced erections in the presence of oxytocin receptor antagonists [63].

## Serotonin

In experimental animal models, bulbospinal neurons containing serotonin (5-HT) project to the lumbar spinal cord [22]. Serotonergic fibers have been demonstrated in close proximity to retrogradely labeled sacral preganglionic neurons [64]. One study showed 5-HT in general had an inhibitory effect on male sexual behavior [65]. However, there have been conflicting reports with another study showing that the stimulation of 5-HT<sub>2c</sub> receptors mediated the erectile response [66]. Thus, the full function of 5-HT in erectile function has not been fully elucidated. It appears to serve various functions likely acting as a major modulator of the central control of erection [22].

## Nitric Oxide

NO is emerging as an essential neurotransmitter within the CNS for erectile response. NO appears to act in several regions of the brain, including the MPOA and PVN [67–70]. Injection of NO-synthase (NOS) inhibitors into the PVN prevents penile erection induced by dopamine agonists and oxytocin [71]. NO production increased in the PVN of rats during noncontact erections, confirming the role of NO production during erection [72].

## ACTH and $\alpha$ -MSH

Adrenocorticotrophic hormone (ACTH) and its related peptide  $\alpha$ (alpha)-melanocyte stimulating hormone ( $\alpha$ -MSH) have been shown to elicit erectile responses in addition to increased

grooming, stretching, and yawning behaviors when given intracerebroventricularly to lab animals [73]. This proerectile effect appears to be due to the stimulation of melanocortin-3 (MC<sub>3</sub>) receptors which are prevalent in the hypothalamus and limbic system [74]. The role of these peptides in erectile response is not entirely known, but they appear to induce erection by acting at sites distinct from those in the PVN stimulated by dopamine and oxytocin [75]. Additionally, Melanotan II, an  $\alpha$ -MSH synthetic analog, has had proerectile effects in humans with psychogenic impotence [76].

## Other Neurotransmitters

Excitatory amino acids, such as l-glutamate, N-methyl-d-aspartate (NMDA), amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), and trans-1-amino-1,3-cyclo-pentadecarboxylic acid (ACPD) have been shown to have proerectile effects when injected into the MPOA or PVN of lab animals [77–79]. Gamma-amino butyric acid (GABA) appears to function as an inhibitor in the reflex pathways for penile erection [80]. Stimulation of opiod  $\mu$  receptors appears to centrally prevent penile erection and impair copulation likely through the prevention of the increased NO production in the PVN during sexual activity [81].

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