Surg Radiol Anat (2011) 33:301–312
DOI 10.1007/s00276-010-0707-4

REVIEW

Evolution in the concept of erection anatomy

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Received: 16 June 2010 / Accepted: 17 July 2010 / Published online: 5 August 2010
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Abstract
Purpose To review and to summarize the literature on anatomy and physiology of erection in the past three decades, especially the work done in our institution.
Methods A search of the PubMed database was performed using keywords *erection, anatomy and erectile dysfunction* (*ED*). Relevant articles were reviewed, analyzed and summarized.
Results Penile vascularisation and innervation vary substantially. Internal pudendal artery is the major source of penile blood supply, but a supralevator accessory pudendal artery that may originate from inferior vesical or obturator or external iliac arteries is not uncommon. Section of this artery during radical prostatectomy (RP) may adversely affect postoperative potency. Anastomoses between the supra and the infralevator arterial pathways are frequent. The cavernous nerves (CNs) contain parasympathetic and sympathetic nerve fibers and these nerves lie within leaves of the lateral endopelvic fascia. Anastomoses between the CNs and the dorsal nerve of the penis are common. Nitric oxide released from noradrenergic, noncholinergic neurotransmission of the CN and from the endothelium is the principal neurotransmitter-mediating penile erection. Interactions between pro-erectile and anti-erectile neurotransmitters are not completely defined. Finally, medial preoptic area and paraventricular nucleus are the key structures in the central control of sexual function and penile erection.
Conclusions The surgical and functional anatomy of erection is complex. Precise knowledge of penile vascularisation and innervation facilitates treatment of ED especially after RP.

Keywords Erection · Anatomy · Neurotransmitter · Erectile dysfunction

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Introduction

During the last decades, the anatomical knowledge of erection was developed due to the amelioration of research methods and techniques. Comparative studies between animal models and human dissection were the means origin of findings. In the rat, description of peripheral innervation of erection was simplified in hypogastric sympathetic nerve and pelvic splanchnic parasympathetic nerve; both nerves forming the pelvic plexus which generates the cavernous nerves responsible for erection. The erection anatomy of human has been similarly schematized with physiological and cadaveric dissection findings. This anatomy was based on the central control of somatic sensitive afferent impulse via the pudendal nerve (dorsal nerves of the penis) and efferent autonomic impulse via the autonomic plexus, which is classically divided in sympathetic anti-erectile pathways and parasympathetic pro-erectile pathways.

Penile erection is a vascular event under autonomic nervous system control; we defined erection in 1987 as an inflow of arterial blood into cavernous bodies and obstruction of venous return which is under autonomic nervous control: augmentation of parasympathetic influx associated with reduction in sympathetic tone, the role of

nitric oxide (NO) was not known yet. The spinal cord contains the autonomic preganglionic neurons that innervate the penile erectile tissue and the pudendal motoneurons that innervate the perineal striated muscles. Spinal neurons controlling erection are activated or inhibited by information from peripheral and supraspinal origin. Some pre-motor neurons of the medulla, pons and diencephalon project directly onto spinal sympathetic, parasympathetic and pudendal motoneurons [23].

The development of immunohistochemical methods allows the determination of the neurotransmitters within tissues and presents a revolutionary method to better understand the anatomy and the physiology of erection. A variety of neurotransmitters, such NO, serotonin, dopamine, acetylcholine (Ach), noradrenaline (NA), adrenaline, apomorphine, oxytocin and many other peptides, through interactions with many receptor subtypes, exert complex effects on the spinal network that controls penile erection.

We made a literature revision of the anatomical findings 20 years after our previous description of the anatomical base of the erection to demonstrate the evolution of methods, results and concepts of erection during the last three decades.

Methods

A search of the PubMed database was performed to identify original and review articles in English and French that address the anatomy of erection, without any limit to publication date. The keywords used were *erection, anatomy and erectile dysfunction* (*ED*). Relevant articles were reviewed, analyzed and summarized.

History

First description of ED dates from 2000 BC (Egyptian papyrus). Hippocrates reported male impotence after excessive horseback riding. Aristotle stated that erection is produced by the influx of air. In 1025, Avicenna described the erectile physiology as air influx from the heart. Leonardo da Vinci (1504) noted a large amount of blood in the erect penis of hanged men. In 1585, Ambroise Paré described the penis as being composed of concentric coats of nerves, veins and arteries and of two ligaments (corpora cavernosa), a urinary tract and four muscles. Hunter (1787) thought that venous spasm prevented the exit of blood.

Many theories in the nineteenth century stressed the importance of increased arterial blood flow or venous occlusion and both of the two mechanisms [43]. Other theories were also described: arterial and venous polsters [15], a sluice mechanism, an arteriovenous shunt [44], contraction of the cavernous smooth muscles [26] and a neurovascular mechanism. In 1987, we demonstrated that tumescence is due to a reduction in the alpha-sympathetic tonus permitting influx of arterial blood and to decreased venous flow from the compression of the sub-albuginal venous network against the tunica albuginea, rigidity is due to an increase in intra-cavernous arterial pressure simultaneous with contraction of bulbospongiosus and ischiocavernosus muscles under the somatic control of pudendal nerve [4]. Much of the current understanding of erectile physiology was gained in the 1980s and 1990s, after the identification of NO as the major neurotransmitter for erection and of phosphodiesterases (PDE5s) for detumescence [10].

Anatomy of the penis

The penis is composed of three cylindrical structures, the paired corpora cavernosa and the corpus spongiosum. Erectile tissues are surrounded and supported by the tunica albuginea, ligaments and muscles. The root of the penis is fixed to ischiatic branches.

Corpora cavernosa

It is composed of the tunica albuginea and the corporal erectile tissue.

The tunica albuginea

It is a bi-layered structure with multiple sub-layers. The inner layer bundles support and contain the cavernous tissue and are oriented circularly. This layer gives radiating intracavernous pillars which act as struts to augment the septum and provide essential support to the erectile tissue. The outer layer bundles are oriented longitudinally, extending from the glans penis to the proximal crura; they insert into the inferior pubic rami but are absent between the 5 and 7 o'clock positions. The tunica affords great flexibility, rigidity and tissue strength to the penis [9].

The tunica albuginea of the corpora cavernosa is thought to play a major role in the erection mechanism. It functions by compressing the subalbugineae venulae, which promotes the slower venous flow during erection, and provides a fibrous frame to give an inextensible support for the vessels and nerves. The functions of the tunica albuginea result from its structure, consisting for the most part of collagen and elastic fibers.

Structural and biochemical changes occur in tunica albuginea. In men with progress of both aging and diabetes mellitus, it became thinner with diminished elastic fibers; the collagen fibers were increased while the smooth muscle was reduced which can lead to impotence by impairing the venoocclusive function.

The corporal erectile tissue

The corpora cavernosa consists of two spongy, paired cylinders contained in the tunica albuginea and surrounded by the ischiocavernosus muscles. Their proximal ends, the crura, originate at the undersurface of the puboischiatic rami as two separate structures attached to the perineal membrane, merge under the pubic arch and remain attached up to the glans. The septum between the two corpora cavernosa is incomplete in men. Within the tunica are the interconnected sinusoids separated by smooth muscle trabeculae surrounded by elastic fibers, collagen and loose areolar tissue. The terminal cavernous nerves and helicine arteries are intimately associated with the smooth muscle. Each corpus cavernosum is a conglomeration of sinusoids, larger in the center and smaller in the periphery. Both arterial and penile relaxations rely upon a change in the tone of the smooth muscle fibers constitutive of the walls of the arteries and of that of the erectile tissue. In the flaccid state, smooth muscle fibers of the penis and penile arteries are contracted, the blood slowly diffuses from the central to the peripheral sinusoids and the blood gas levels are similar to those of venous blood. During erection, the smooth muscle fibers of the penis and penile arteries are relaxed, the rapid entry of arterial blood to both the central and the peripheral sinusoids changes the intracavernous blood gas levels to those of arterial blood [37].

Many endothelium-derived factors have been detected within the sinusoidal endothelium and corpus cavernosum smooth muscle cells, some of these factors are constrictors such endothelin-1, prostaglandin, thromboxane and angiotensin, others are dilatators such NO. Endothelin-1 is a potent constrictor synthesized by the sinusoidal endothelium [28] which also potentiates the constrictor effects of catecholamines on trabecular smooth muscle. Prostaglandin I2 (PGI2), PGF2α and thromboxane A2 (TXA2) are constrictor prostanoids synthesized by the human cavernous tissue. Angiotensin II has been detected in endothelial and smooth muscle cells of human corpus cavernosum and evokes contraction of human corpus cavernosum in vitro [3]. NO released from noradrenergic, noncholinergic neurotransmission and from the endothelium is the principal neurotransmitter-mediating penile erection via cavernous smooth muscle relaxation [30].

Corpus spongiosum and glans penis

The tunica albuginea

The tunica albuginea of the corpus spongiosum is thinner and lacks an outer layer or intracorporeal struts, ensuring a low-pressure structure during erection. It is absent in the glans.

Corpus spongiusum tissue

The structure of the corpus spongiosum is similar to that of the corpora cavernosa except that the sinusoids are larger. The spongiosum is fixed to the center of the perineal membrane. It is encompassed by the bulbospongiosus muscles and traversed by the anterior urethra.

The ligaments

External penile support consists of two ligamentous structures: the fundiform and suspensory ligaments. The fundiform ligament arises from Colles' fascia and is lateral, superficial and not adherent to the tunica albuginea of the corpora cavernosa. The suspensory ligament arises from Buck's fascia and consists of two lateral bundles and one median bundle, which circumscribe the dorsal vein of the penis. Its main function is to attach the tunica albuginea of the corpora cavernosa to the pubis, and thus it provides support for the mobile portion of the penis [29]. Buck's fascia surrounds both cavernosal bodies and splits to surround the spongiosum ventrally.

The erectile bodies related muscles

Two muscles related to the erectile bodies play a role in both erection and ejaculation mechanism; the ischiocavernosus and the bulbospongiosus muscles.

Ischiocavernosus muscle

Ischiocavernosus covers the crus penis. It is attached by tendinous and muscular fibers to the medial aspect of the ischial tuberosity behind the crus and to the ischial ramus on both sides of the crus. From these points fleshy fibers succeed, and end in an aponevrosis which is inserted into the sides and under surface of the crus penis. Ischiocavernosus compresses the crus penis, and delays the return of the blood through the veins. The contraction of these muscles on a flaccid penis does not elicit erection. In contrast, when the muscles contract on an erect penis, penile rigidity and intrapenile pressure dramatically increase to maintain the organ erect [38].

Bulbospongiosus muscle

It consists of two symmetrical parts united by a median fibrous raphe. The fibers arise from the perineal body, in which they decussate and continue as the contralateral transversi and sphincter ani externus, and from the median raphe itself. The fibers diverge like the halves of a feather: a thin layer of posterior fibers disperses on the perineal membrane; the middle fibers encircle the penile bulb and

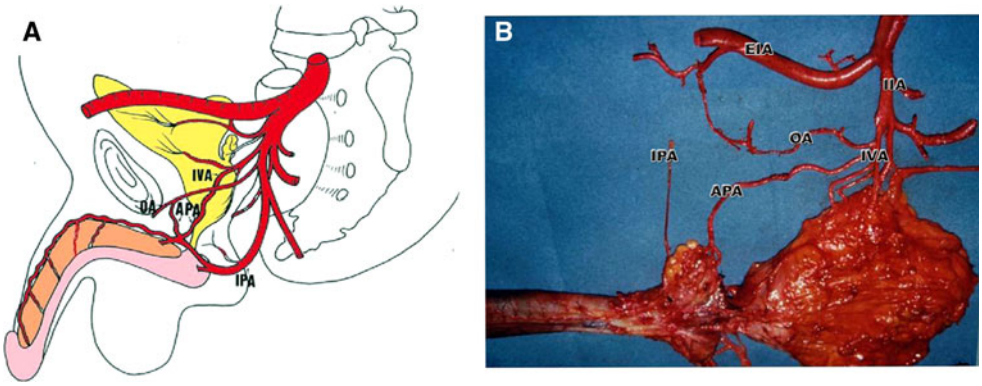


Fig. 1 Accessory pudendal artery (APA). **a** Schematic presentation, **b** cadaveric dissection. *EIA* external iliac artery, *IIA* internal iliac artery, *IPA* internal pudendal artery, *IVA* inferior vesical artery, *OA* obturator artery

adjacent corpus spongiosum and attach to an aponevrosis on the dorsal surfaces; the anterior fibers spread out over the sides of the corpora cavernosa, ending partly in them, anterior to ischiocavernosus, and partly in a tendinous expansion which covers the dorsal vessels of the penis. Bulbospongiosus muscle helps to empty the urethra, after the bladder has emptied; it is relaxed during micturition, usually contracting only at the end of the process, but able to arrest it. It assists in erection: the middle fibers probably compress the erectile tissue of the bulb, and the anterior fibers contribute by compressing the deep dorsal vein of the penis. The rhythmic activity of the perineal striated muscles participates in the saccadic expulsion of semen during ejaculation.

Vascularisation of the penis

Arteries

Blood supply to the penis comes from the infra levator internal pudendal artery, a branch of the internal iliac artery. After entering the perineum through the lesser sciatic foramen, the artery runs in a fascial sheath on the medial aspect of obturator internus, the pudendal canal (of Alcock). Early in its course, it gives off three or four inferior rectal branches to the anal canal. Its perineal branch pierces Colles' fascia to supply the muscles of the superficial pouch and continues anteriorly to supply the back of the scrotum. The internal pudendal terminates as the common penile artery, which continues in Alcock's canal, above the perineal membrane and terminates in three branches to supply the erectile bodies. The bulbourethral artery penetrates the perineal membrane to enter the spongiosum from above at its posterolateral border. It supplies the urethra and the corpus spongiosum. The cavernosal artery pierces the corporal body in the penile hilum to near the center of its erectile tissue. It gives off straight and helicine arteries that ramify to supply the cavernous sinuses; these arteries are contracted and tortuous in the flaccid state and become dilated and straight during erection. The dorsal artery of the penis passes between the crus penis and the pubis to reach the dorsal surface of the corporal bodies. It runs between the dorsal vein and the dorsal penile nerve and with them attaches to the underside of Buck's fascia. As it courses to the glans, it gives off cavernous branches and circumferential branches to the spongiosum and urethra.

The penile arteries are highly variable in their branching, courses and anastomoses. It is not uncommon for a single cavernosal artery to supply both corporal bodies or to be absent altogether. Alternatively, a supra levator accessory pudendal artery may supplement or completely replace branches of the common penile artery. This artery usually arises from the obturator or inferior vesical or external iliac arteries and runs anterolateral to the prostate to reach the penis in the company of the dorsal vein. Breza et al. [8] identified this accessory artery in 7 of 10 cadaveric specimens. In a study of 20 fresh human cadavers, we reported 3 patterns of penile arterial supply: type I arising exclusively from internal pudendal arteries (3 of 20), type II arising from both accessory and internal pudendal arteries (14 of 20) and type III arising exclusively from accessory pudendal arteries (3 of 20) [18]. Careful preservation of the accessory pudendal artery during radical prostatectomy (RP) has been shown to support and hasten the recovery of sexual function. Its resection during RP may adversely affect postoperative potency [20]. Anastomoses between the supralevator and the infralevator arterial pathways are frequent [14]. We demonstrated that accessory pudendal arteries were present in the pelvis in 70% of the cases, anastomosing in 70% with cavernous arteries that originated from pudendal artery (Fig. 1). Transalbugenieal anastomoses between cavernous artery and the spongiosal arterial network exists also, we found 6–10 trans-albugenieal caverno-spongiosus arteries anastomoses (a. profundae penis and a. urethralis) in all the specimens of 10 human cadavers [19].

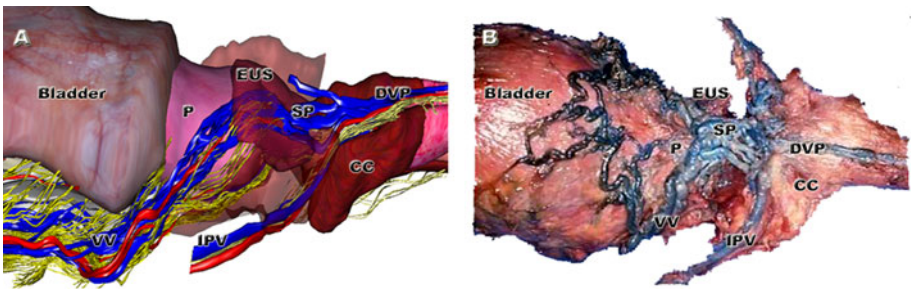


Fig. 2 Santorini plexus (SP). **a** Computer-assisted anatomical dissection of adult cadaveric specimen. **b** Cadaveric dissection. *CC* corpus cavernosum, *DVP* dorsal vein of penis, *EUS* external urethral sphincter, *IPV* internal pudendal vein, *P* prostate, *VV* vesical vein

Veins

The superficial drainage is located between the deep and the superficial fascia of the penis. These veins united at the penis crus to form the superficial dorsal veins which drained into the major saphenous veins. At the base of the glans, several venous channels coalesce to form the dorsal vein of the penis, which runs in a groove between the corporal bodies and drains into the supralevator pre-prostatic plexus, it passes under buck's fascia between the inferior pubic arch and the striated urinary sphincter to reach the pelvis, where it trifurcates into a central superficial branch and two lateral plexuses. We identified small arteries, which originate from the inferior vesical artery [5]. The superficial branch, which travels between the puboprostatic ligaments, is the centrally located vein overlying the bladder neck and prostate. This vein is easily visualized early in retropubic operations and has communicating branches over the bladder itself and into the endopelvic fascia. The superficial branch lies outside the anterior prostatic fascia. The common trunk and lateral venous plexuses are covered and concealed by the prostatic and endopelvic fascia. The lateral venous plexus traverse posterolaterally and communicate freely with the pudendal, obturator and vesical plexuses. Near the puboprostatic ligaments, small branches from the lateral plexus often penetrate the pelvic sidewall musculature and communicate with the internal pudendal vein. The lateral plexus interconnects with other venous systems to form the inferior vesical vein, which empties into the internal iliac vein [36]. Circumflex veins originate in the spongiosum and pass around the cavernosa to meet the deep dorsal vein perpendicularly. They are present only in the distal two-thirds of the penile shaft and number 3–10. Intermediary venules form the cavernous sinuses drain into a sub-tunical capillary plexus. These plexuses give rise to emissary veins, which commonly follow an oblique path between the layers of the tunica and drain into the circumflex veins dorsolaterally. Emissary veins in the proximal third of the penis join on the dorsomedial surface of the cavernous bodies to form 2–5 cavernous veins. At the hilum of the penis, these vessels pass between the crura and the bulb, receiving branches from each and join the infralevator internal pudendal veins. Accordingly, two venous channels draining the erectile tissue: a supralevator pathway into the lateral vesicoprostatic veins and an infralevator pathway into the internal pudendal veins (Fig. 2).

Innervation of the penis

Peripheral pathways

The innervation of the penis is both somatic (sensory and motor) and autonomic (sympathetic and parasympathetic). This innervation is transmitted via two pathways; infralevator pudendal nerve and supralevator inferior hypogastric plexus.

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 in 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. The nerve fibers from the receptors converge to form the dorsal nerve of the penis, which joins other nerves to become the pudendal nerve. The latter has the same pathway of the pudendal pedicle in the perineum and enters the spinal cord through the S2–S4 roots to terminate on spinal neurons and interneurons in the central gray region of the lumbosacral segment [34]. 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 purely somatic; however, nerve bundles testing positive for NO synthase (NOS), which is autonomic in origin, have been demonstrated in the human by Burnett et al. [11]. Guiliano et al. [24] in our group have also shown that stimulation of the sympathetic chain at the L4–L5 level elicits an evoked discharge on the dorsal nerve and that

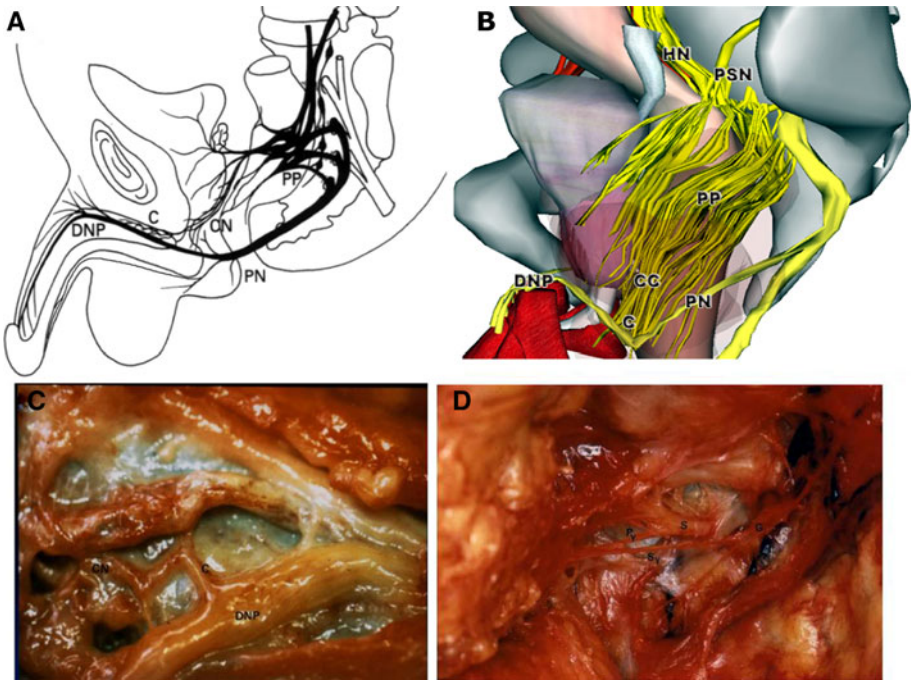


Fig. 3 Supra an infra levator nerves communication. **a** Schematic presentation, **b** computer-assisted anatomical dissection of fetal pelvis, hypogastric nerve (*HN*) and pelvic splanchnic nerve (*PSN*) joining the inferior hypogastric plexus (pelvic plexus *PP*), cavernous nerve (*CN*) emerging to join the erectile bodies. **c** Cadaveric microdissection of the communication (*C*) between the *CN* and the dorsal nerve of penis (*DNP*). **d** Cadaveric dissection showing the proximal afferent branches to the *PP*, parasympathetic branches (*Py*) from the sacral root (*S*), sympathetic branches (*Sy*) from the sacral sympathetic ganglia (*G*)

stimulation of the dorsal nerve evokes a reflex discharge in the lumbosacral sympathetic chain of rats. Moreover, we confirmed immunohistochemically the presence of both adrenergic and cholinergic nerve fibers within the dorsal nerve of the penis [1]. Caverno-pudental nervous communicating branches between the cavernous nerves and the dorsal nerve exist in the human penile hilum; we have previously described several variants concerning the number and type of these connections [5, 14, 18]. Recently, with the use of 3D reconstruction techniques of serial immunotreated histological sections, we demonstrated important communications between fibers of cavernous nerves and retrograde fibers from the dorsal nerves of the penis, just lateral to the urethral sphincter (non-published results) (Fig. 3). The presence of such communicating branches proves that the supralevator and infralevator neural pathways communicate and suggest the possibility of a kind of plasticity of the nervous supply of penile erection. These findings clearly demonstrate that the dorsal nerve has both somatic and autonomic components that enable it to regulate both erectile and ejaculatory functions.

Pudendal motoneurons (Onuf's nucleus), located in the second to fourth sacral spinal segments (S2, S3 and S4) innervate the bulbospongiosus and ischiocavernosus muscles via the pudendal nerve. 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 ceruleus) has been identified. Yaici et al. in our group demonstrated adrenergic innervation of pudendal motoneurons in rats and its role in rhythmic contractions of perineal muscles during ejaculation [48]. In addition, oxytocinergic and serotonergic innervations of lumbosacral nuclei controlling penile erection and perineal muscles in the male rat has been demonstrated [39, 42].

Autonomic pathways

The presynaptic sympathetic cell bodies that project to the pelvic autonomic plexus are located in the lateral column of gray matter in the last three thoracic and first two lumbar segments of the spinal cord. They reach the pelvic plexus by two pathways: (1) the superior hypogastric plexus which is formed by sympathetic fibers from the celiac plexus and the first four lumbar splanchnic nerves. Anterior to the bifurcation of the aorta, it divides into two hypogastric nerves that enter the pelvis medial to the internal iliac vessels, anterior to the sacrum and deep to the endopelvic fascia. (2) The pelvic continuations of the sympathetic trunks which pass deep to the common iliac vessels and medial to the sacral foramina and fuse in front of the coccyx at the ganglion impar. Each chain comprises four to five ganglia that send branches anterolaterally to participate in the formation of the inferior hypogastric plexus (IHP). NA and neuropeptide Y (NPY) are released in the penis by the terminals of sympathetic fibers. NA is the major contractile agent of the smooth muscles of the penis and penile arteries and NPY increases its effects. NA plays a role in flaccidity and detumescence. Sympathetic contraction is mediated by activation of postsynaptic α1a- and α1d-

adrenergic receptors and modulated by presynaptic α2-adrenergic receptors [13, 40]. Yaici et al. [47] in our group demonstrated an intraspinal modulation of the noradrenergic and adrenergic control of the autonomic outflow to the penis by pre- and postsynaptic α2-adrenergic receptors.

Presynaptic parasympathetic innervation arises from the intermediolateral cell column of the sacral cord. Fibers emerge from the second, third and fourth sacral spinal nerves as the pelvic splanchnic nerves (nervi erigentes) to join the hypogastric nerves and branches from the sacral sympathetic ganglia, these three contingents contribute to form the IHP. We have demonstrated that the sympathetic fibers arise from sacral sympathetic ganglia. These fibers participate in the constitution of the pelvic splanchnic nerves. We confirmed that the inferior roots of the IHP are not only parasympathetic, but also sympathetic [6]. We also demonstrated that the cholinergic and adrenergic fibers coexist in both hypogastric and pelvic splanchnic nerves [1]. This finding demonstrates the mixed nature fibers in nerves which are classically considered as purely sympathetic and parasympathetic and makes the anatomy of the autonomic system much more complex than previously thought.

The IHP is a quadrangular plate which is oriented in the sagittal plane on either side of the rectum and pierced by the numerous vessels going to and from the rectum, bladder, seminal vesicles and prostate (Fig. 4). Dissection of these vessels (the so-called lateral pedicles of the bladder and prostate) risks injury to the IHP with attendant postoperative impotence [45, 46]. Branches of the IHP follow pelvic blood vessels to reach the pelvic viscera, although nerves to the ureter may join it directly as it passes nearby. Visceral afferent and efferent nerves travel on the vas deferens to reach the testis and epididymis. The most caudal portion of the IHP gives rise to the innervation of the prostate and penis via the cavernous nerves (CNs), which are responsible for erection [45]. After passing the tips of the seminal vesicles, these nerves lie within leaves of the lateral endopelvic fascia near its juncture with Denonvilliers' fascia [31]. They travel at the posterolateral border of the prostate on the surface of the rectum and are lateral to the prostatic capsular arteries and veins. Because the nerves are composed of multiple fibers not visible on gross inspection, these vessels serve as a surgical landmark for the course of these nerves (the neurovascular bundle of Walsh). During RP, the nerves are most vulnerable at the apex of the prostate, where they closely approach the prostatic capsule at the 5- and 7-o'clock positions. On reaching the membranous urethra, the nerves divide into superficial branches, which travel on the lateral surface of the striated urethral sphincter at 3- and 9-o'clock positions, and deep fibers, which penetrate the substance of this muscle and send twigs to the bulbourethral glands. As the nerves reach the hilum of the penis, they join to form one to three discrete bundles, related to the urethra at 1- and 11-o'clock positions, superficial to the cavernous veins, and dorsomedial to the cavernous arteries [8, 33] with the arteries, they penetrate the corpora cavernosa to supply the erectile tissue. Small fibers also join the dorsal nerves of the penis as they course distally. Human cadaveric dissection has revealed medial and lateral branches of the cavernous nerves (the former accompanying the urethra and the latter piercing the urogenital diaphragm 4–7 mm lateral to the sphincter) and multiple communications between the cavernous and dorsal nerves (supra and infralevator neurovascular pathways to penile corpora cavernosa). In 85 male cadavers that we examined through gross and microscopic anatomical analysis: The pelvic nerve plexus had both parasympathetic and sympathetic roots. It was distributed to the external urethral sphincter giving rise to cavernous nerves which anastomosed in 70% of the cases with the pudendal nerve in the penile root [5]. The terminals of parasympathetic fibers release ACh, vasoactive intestinal polypeptide (VIP) and NO. ACh released from parasympathetic nerves is not the predominant neurotransmitter of erection; it does contribute indirectly to penile erection by presynaptic inhibition of adrenergic neurons and stimulation of NO release from endothelial cells by acting on the presynaptic receptors on adrenergic neurons, it has been shown to modulate the release of NA, which can also be inhibited by PGE1. In the human corpus cavernosum, noradrenergic responses are under nitrergic control. Conversely, adrenergic neurons, through prejunctional α2 receptors, can also regulate the release of NO.

ED due to CN injury after RP and pelvic surgery is a major problem. Its occurrence is not exclusively related to a per-operative cavernous nerve injury and also involves vascular, endocrinological, psychological and anesthetic stress factors. This complex pathophysiology may explain poor results of nerve grafts on sexual potency after cavernous nerve resection [17]. We demonstrated that a neuroregenerative approach with guides and triiodothyronine could facilitate the cavernous axonal re-growth and the recovery of erectile function [7]. We completed this finding with a pro-endothelial treatment combined with neuroregenerative guides and concluded that multimodal approach provided better results in erectile function recovery.

NO released from noradrenergic, noncholinergic neurotransmission and from the endothelium is the principal neurotransmitter-mediating penile erection. Erection is mainly due to the increased synthesis of two intracellular second messengers, the cyclic nucleotides guanosine monophosphate (cGMP) and adenosine monophosphate [41]. cGMP and cAMP are degraded by phosphodiesterases. The pro-erectile chemicals facilitate the synthesis or the accumulation, or prevent the degradation, of cGMP and/or cAMP. Increasing the amounts of intracellular

cGMP and cAMP leads to relaxation. Because smooth muscle fibers of the penis are connected with gap junctions, it is not required that chemical messengers reach all of the cells to elicit an effect. Indeed, gap junctions allow for a rapid spread of electrotonic current and intercellular diffusion of second messengers and ions. This system supports the rapid propagation of information in the erectile tissue, starting with a limited amount of chemical messengers released [25].

NO increases the production of cGMP, which in turn relaxes the cavernous smooth muscle [10]. NO derived from neuronal NO synthase (nNOS) in the nitrergic nerves is responsible for the initiation and majority of the smooth muscle relaxation whereby NO from endothelial NOS (eNOS), which is stimulated by ACh release, contributes to the maintenance of the erection [30]. The intracorporeal smooth muscle in a semicontracted (flaccid) state probably results from three factors: intrinsic myogenic activity, adrenergic neurotransmission and endothelium-derived contracting factors, such as angiotensin II, PGF2α and endothelins [2]. On the other hand, detumescence after erection may be a result of cessation of NO release, the breakdown of cGMP by phosphodiesterases (phosphodiesterases inhibitors for the treatment of erectile dysfunction), or sympathetic discharge during ejaculation. The NO-cGMP-dependent protein kinase type I (cGKI) pathway can lead to inhibition at several sites on the noradrenergic contractile pathway in the vascular smooth muscle, impairing IP3 production by phospholipase C, IP3 receptor activity and the RhoA/Rho kinase pathway. A number of factors have been reported to increase both NOS activity and NO release. These include molecular oxygen, androgen, chronic administration of L-arginine and repeated intracavernous injection of PGE. Decreased NOS activity has been associated with castration, denervation, hypercholesterolemia and diabetes mellitus. Interaction of different types of NOS may also occur.

Added to the release of transmitters by the endings of autonomic postganglionic motor fibers, there exists a release of neuropeptides by the peripheral endings of autonomic sensory fibers. Although some of these peptides [e.g. substance P (SP) and calcitonin gene-related peptide (CGRP)] display vasorelaxant effects in vitro, their physiological role in the control of erection remains to be demonstrated. Guiliano et al. believe that some proerectile mediators, such ACh, CGRP, VIP or SP, act via endothelial cells by promoting the synthesis and release of NO. In contrast sympathetic nervous system, NA, NPY and endothelin, secreted by endothelial tissues, include contraction of cavernous smooth muscle fibers, thereby opposing erection. Poor oxygenation prevents the synthesis of cGMP and predisposes to cavernous fibrosis due to increased synthesis of collagen via TGF beta [27].

Central nervous centers and pathways

Spinal centers and pathways

Three sets of motoneurons are located in the spinal cord; thoracolumbar sympathetic, sacral parasympathetic and sacral pudendal. These spinal centers are anatomically linked with the penis and functionally linked with erection. They are also located between each other via the intraspinal network. Erection can be elicited by a variety of stimuli integrated at the spinal cord level or in higher brain structures, the convergence of peripheral and supraspinal information produce a lowering of the activity of the thoracolumbar sympathetic anti-erectile pathway and an increase of the activity of both the sacral parasympathetic pro-erectile pathway and the pudendal pathway [35]. Thus, the spinal cord represents a key structure upon which excitatory and inhibitory information from the periphery and from supraspinal nuclei impinges. The stimulation of penile sensory pathways is able to recruit the different autonomic and somatic nuclei of the spinal cord that control erection. Reflexive erections are present in patients with a lesion of the spinal segments above the sacral ones.

The nerves, and therefore preganglionic neurons, responsible for corpus cavernosum erection are different from those eliciting corpus spongiosum erections. Privileged connections must exist within the spinal cord between sacral parasympathetic preganglionic neurons to the corpus cavernosum and dorsolateral motoneurons to the

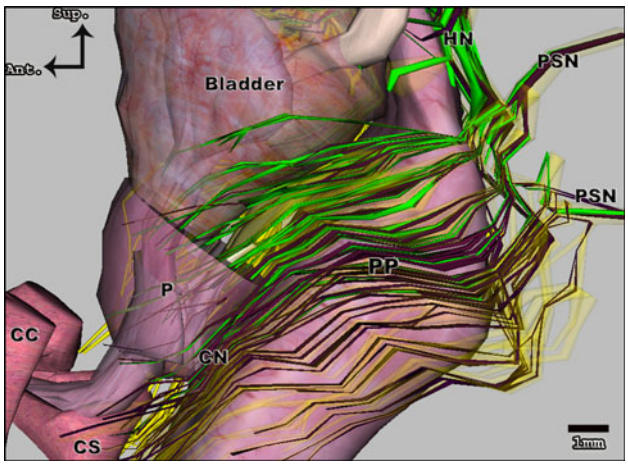


Fig. 4 Computer-assisted anatomical dissection of fetal pelvis. Lateral view with transparency of the inferior hypogastric plexus (pelvic plexus *PP*) nervous, adrenergic fibers (*green*) and cholinergic fibers (*purple*), hypogastric nerves (*HN*) and pelvic splanchnic nerves (*PSN*) contain both fibers' types. The majority of adrenergic fibers distributing in the bladder neck, the seminal vesicles, the vas deferens and the prostate (*P*); the cholinergic fibers innerve the same structures and continue via the cavernous nerve (*CN*) with few adrenergic fibers to reach the erectile bodies (*CC* corpus cavernosum, *CS* corpus spongiosum)

ischiocavernosus muscle, as well as between preganglionic neurons to the corpus spongiosum and dorsomedial motoneurons to the bulbospongiosus muscle [38].

Supraspinal centers and pathways

Several different areas of the brain contribute to the occurrence of erections in the different contexts. The contribution of each area to erection depends upon the amount of excitatory and inhibitory information that it receives from the periphery and from other central nuclei. Studies in animals have revealed that sensory information from the penis reaches the spinal cord, as well as pons, the brainstem, the hypothalamic medial preoptic area (MPOA) and paraventricular nucleus (PVN), the thalamus and the cortex. This balance would be under endocrinological control of the thyroid function [12].

MPOA and PVN of the hypothalamus and hippocampus were defined as a key structure in the central control of sexual function and penile erection [30]. The MPOA is not the source of projections to the spinal cord and its lesions do not affect either noncontact or reflexive erections [32]. Efferent pathways from the MPOA enter the medial forebrain bundle and the midbrain tegmental region (near the substantia nigra). Guiliano et al. [22] demonstrated that MPOA stimulation elicits erectile response via (1) the activation of the parasympathetic outflow convoyed by the pelvic and CNs and (2) the activation of neural fibers conveyed by the sympathetic fibers running in the paravertebral sympathetic chain responsible for vasoconstriction of non-penile areas to divert blood to the penis, allowing the dramatic increase of penile arterial inflow required for erection. Guiliano et al. [21] reported that apomorphine exerts pro-erectile effects by acting on neurons in the PVN of the hypothalamus and also by acting at the spinal cord level, in cord injured rats. Veronneau-Longueville et al. [42] in our group demonstrated that apomorphine exerts pro-erectile effects by acting on neurons in the PVN of the hypothalamus, and that in spinal cord injured rats, systemic apomorphine elicits erection by acting at the spinal cord level. Dopaminergic neurons activate oxytocinergic neurons in the paraventricular area and the release of oxytocin produces erection. In men, apomorphine which stimulates both D1 and D2 receptors, induces erection that is unaccompanied by sexual arousal [16].

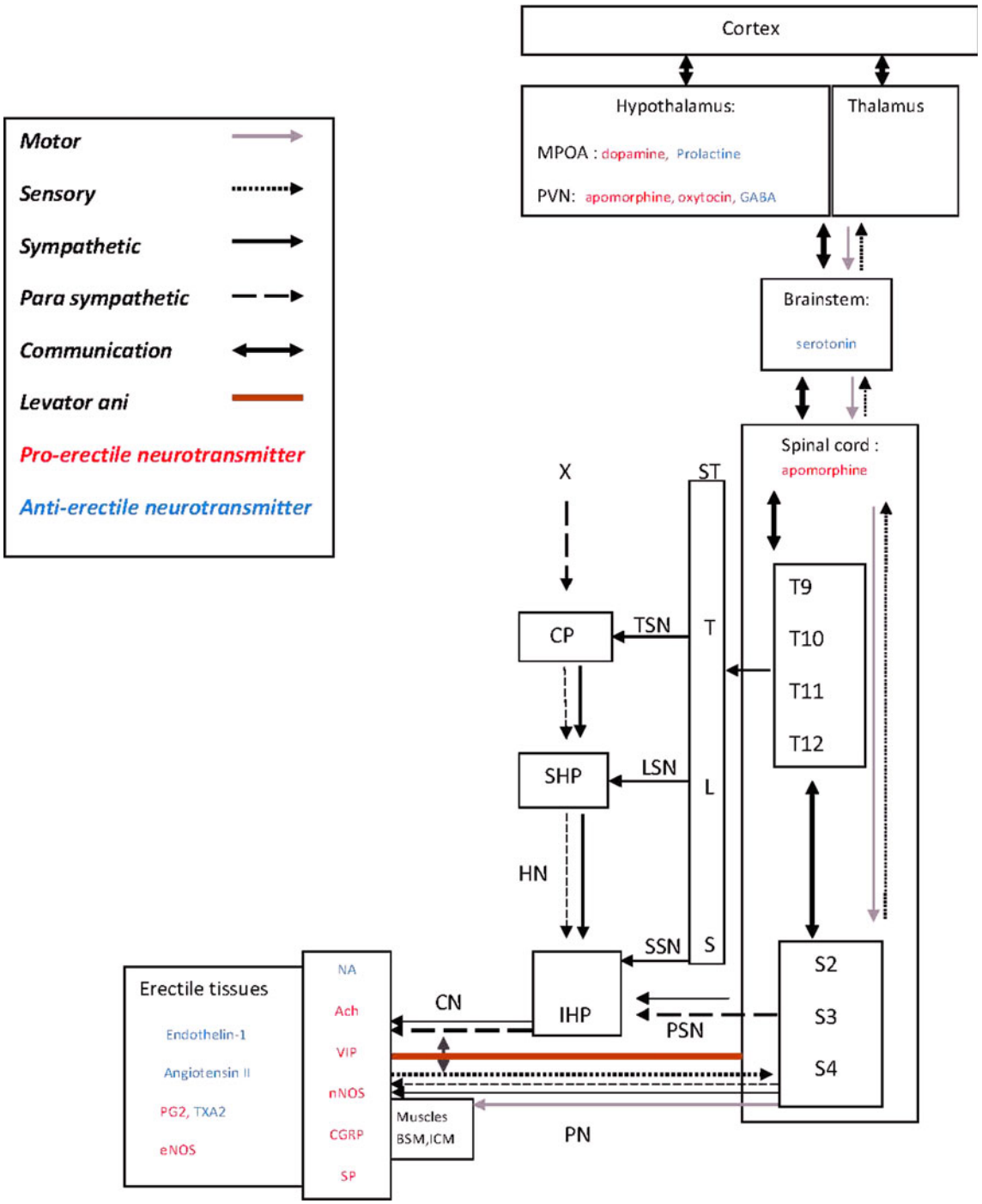
Veronneau-Longueville et al. [42] demonstrated also that the PVN of the hypothalamus contributes oxytocinergic fibers to the dorsal horn and preganglionic sympathetic and parasympathetic cell columns. Oxytocin is a neural hormone secreted by the neurons into the circulation. These are found in the posterior pituitary gland, but, they are also found in the neurons projecting from the PVN to the brain stem and spinal cord, oxytocin can also function as a neurotransmitter. This findings support the hypothesis that oxytocin, released by descending paraventriculo-spinal pathways, activates proerectile spinal neurons. Because neurons in the paraventricular area have been shown to contain NOS and NOS inhibitors prevent apomorphine- and oxytocin-induced erection, it is suggested that oxytocin acts on neurons whose activity is dependent on certain levels of NO. Endogenous opioids may exert an inhibitory control on central oxytocinergic transmission. The agonists of the γ-aminobutyric acid (GABA) B receptor subtype in the PVN inhibit proerectile signaling.

Neurons containing 5-HT have their cell bodies in the midline raphe nuclei of the brain stem and project to a portion of the hypothalamus, the limbic system, the neocortex, and the spinal cord. General pharmacologic data indicate that 5-HT pathways inhibit copulation but that 5-HT may have both facilitory and inhibitory effects on sexual function, depending on the receptor subtype, the receptor location and the species investigated.

In man, many patients with sacral spinal cord injury preserve a 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; no psychogenic erection occurs in patients with lesions above T9. The efferent sympathetic outflow is thus suggested to be at levels T11 and T12. The cell bodies of the NA-containing neurons are located in the locus ceruleus and the A5-catecholaminergic cell group in the pons and medulla. The axons of these noradrenergic neurons ascend to innervate the paraventricular, supraoptic and periventricular nuclei of the hypothalamus, the thalamus and neocortex. They also descend into the spinal cord and the cerebellum. Central NA transmission seems to have a positive effect on sexual function. In both humans and rats, inhibition of NA release by clonidine, an α_2-adrenergic agonist, is associated with a decrease in sexual behavior and yohimbine, an α_2-receptor antagonist, has been shown to increase sexual activity. We found that there is a catecholaminergic control of autonomic and somatic motoneurons regulating erection at the spinal level via α_1 and α_{2a} and α_{2c} [47]. Pathologic processes in these regions, such as Parkinson's disease or cerebrovascular accidents, are often associated with ED.

Hormonal environment plays a role in neural control of erection. In the male brain, both androgens and estrogens play an important regulatory role. Increased levels of prolactin suppress sexual function in men and experimental animals. It is suggested that the mechanism of prolactin's action is through inhibition of dopaminergic activity in the MPOA and decrease testosterone. In addition, prolactin may have a direct effect on the penis through its contractile effect on the cavernous smooth muscle.

Algorithm



Algorithm: neuro-anatomy of erection.

MPOA medial preoptic area, *PVN* paraventricular nucleus, *X* vagus nerve, *ST* sympathetic trunk, *CP* celiac plexus, *SHP* superior hypogastric plexus, *TSN* thoracic splanchnic nerve, *LSN* lumbar splanchnic nerve, *HN* hypogastric nerve, *SSN* sacral splanchnic nerve, *IHP* inferior hypogastric plexus, *PSN* pelvic splanchnic nerve, *CN* cavernous nerve, *PN* pudendal nerve, *BSM* bulbospongiosus muscle, *ICM* Ischiocavernosus muscle, *NA* noradrenaline, *Ach* acetylcholine, *VIP* vasoactive intestinal polypeptide, *nNOS* neuronal nitric oxide synthase, *eNOS* endothelial nitric oxide synthase, *CGRP* calcitonin gene-

related peptide, *SP* substance P, *PG2* prostaglandin E2, *TXA2* thromboxane A2.

Conclusions

Erection involves complex anatomical structures and mechanisms. This revision of literature summarizes the main anatomical and physiological basic findings of the past three decades and the future fields of studies that are necessary to finalize the understanding of the erection. After the description by Walsh and Donker in 1982 of the CNs along the prostate which enabled the nerve-sparing surgeries, another important key step was the identification of NO as the major neurotransmitter for erection. Unfortunately, distal part of CNs near the erectile bodies is not well described and especially communication and interaction with the dorsal nerve of penis. A study is ongoing in our institution to describe the distal route of cavernous nerves. Many other central and peripheral neurotransmitters have pro or anti-erectile functions and complex interactions with endocrinological and psychological balances which are not completely understood. The anatomical and physiological future studies in our institution are designed to investigate these two main fields of the erection.

Conflict of interest None of the authors has any financial or personal relationship with other people or organisations that might have influenced the present work.

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