Arch. Esp. Urol. 2010; 63 (8): 581-588

PHYSIOLOGY OF ERECTION

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Summary.- *In these article we review the main mechanisms involved in human erection. We review and update in detail the biochemical (nitric oxide and Rho-kinase pathways), cellular (smooth muscle relaxation mechanisms), neural (autonomic and somatic pathways) and microscopic penile principles.*

Keywords: *Erectile dysfunction. Erection. Relaxation. Contraction. Stimulation. Cavernosal smooth muscle.*

Resumen.- *En este trabajo de revisión se repasan los principales mecanismos implicados en el fenómeno de la erección humana. Desde sus principios bioquimícos (via óxido nítrico y Rho-quinasa), celulares (mecanismos de relajación del músculo liso), nerviosos (vías autónomas y somáticas) y finalmente macroscópicos peneanos, son revisados y actualizados con detalle.*

Palabras clave: *Disfunción eréctil. Erección. Relajacción. Contracción. Estimulación. Músculo liso cavernoso.*

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HEMODYNAMICS: ERECTION AND DETUMESCENCE

Penile erection is a neurovascular event modulated by psychological factors and hormonal status. In sexual stimulation, nerve impulses cause the release of neurotransmitters from cavernous nerve terminals and of relaxing factors from the endothelial cells in the penis, resulting in the relaxation of smooth muscle in the arteries and arterioles supplying the erectile tissue and a several times increase in the blood flow to the penis. At the same time, relaxation of the trabecular smooth muscle increases the compliance of the sinusoids, facilitating rapid filling and expansion of the sinusoidal system. The venular subtunical plexes are thus compressed between the trabeculae and the tunica albuginea, resulting in almost total occlusion of venous outflow (1,2). These events trap the blood within the corpora cavernosa and raise the penis from a dependent position to an erect position, with an intracavernous pressure of approximately 100 mm Hg (the full erection phase).

During masturbation or sexual intercourse, both of which trigger the bulbocavernous reflex, the ischiocavernous muscles forcefully compress the base of the blood-filled corpora cavernosa and the penis becomes even harder, with an intracavernous pressure reaching several hundred millimeters of mercury (the phase of rigid erection). During this phase, the inflow and outflow of blood temporarily cease (3).

Detumescence can be the result of a cessation of neurotransmitter release, the breakdown of second messengers by phosphodiesterases, or sympathetic discharge during ejaculation. Contraction of the trabecular smooth muscle reopens the venous channels, the trapped blood is expelled, and flaccidity returns.

The phenomenon of detumescence may be stratified into three phases (4):

• 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 (5-7). The importance of smooth muscle relaxation has been demonstrated in animal and human studies (6,7).

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.

Smooth Muscle Physiology. Molecular mechanism of relaxation and contraction

Spontaneous contractile activity of cavernous smooth muscle has been recorded in vitro and in vivo studies. Yarnitsky et al 8 found two types of electrical activity recorded from the corpus cavernosum: spontaneous and activity-induced. Field stimulation results in a decrease in tension and intracellular calcium at low frequencies and an increase in tension with increased intracellular calcium at high frequencies. In general, the response to pharmacologic agents correlates with the change in intracellular calcium: e.g. phenylephrine produces muscle contraction and an increase in intracellular calcium, while nitroprusside causes the opposite.

Smooth muscle contraction and relaxation is regulated by cytosolic (sarcoplasmic) free Ca2+. Norepinephrine from nerve endings and endothelins and prostaglandin F2α from endothelium activate receptors on smooth muscle cells to increase inositol triphosphate and diacylglycerol resulting in release of calcium from intracellular stores such as sarcoplasmic reticulum and/or opening of calcium channels on the smooth muscle cell membrane leading to an influx of calcium from extracellular space. This triggers a transient increase in cytosolic free Ca2+ from a resting level of 120/270 to 500/700 nM (9). At the elevated level, Ca2+ binds to calmodulin and changes the latter's conformation to expose sites of interaction with myosin light-chain kinase. The resultant activation catalyzes phosphorylation of myosin light chains and triggers cycling of myosin crossbridges (heads) along actin filaments and the development of force. In addition, phosphorylation of the light chain also activates myosin ATPase, which hydrolyzes ATP to provide energy for muscle contraction (Figure 1).

Once the cytosolic Ca2+ returns the basal levels, the calcium- sensitizing pathways take over. One such mechanism is via activation of excitatory receptors coupled to G-proteins which can also cause contraction by increasing calcium sensitivity without any change in cytosolic Ca2+ This pathway involves RhoA, a small, monomeric G protein that activates Rho-kinase. Activated Rho-kinase phosphorylates and thereby inhibits the regulatory subunit of smooth muscle myosin phosphatase preventing dephosphorylation of myofilaments thus maintain contractile tone (Figure 2) (10).

RhoA and Rho-kinase have been shown to be expressed in penile smooth muscle (11,12).

Interestingly, the amount of RhoA expressed in the cavernosal smooth muscle is 17 fold higher than

in the vascular smooth muscle (12). A selective inhibitor of Rhokinase has been shown to elicit relaxation of human corpus cavernosum in vitro and to induce penile erection in animal models (13). Anesthetized rats transfected with dominant negative RhoA exhibited an elevated erectile function as compared with control animals (14). 7 The emerging consensus is that the phasic contraction of penile smooth muscle is regulated by an increase in cytosolic Ca2+ and the tonic contraction is governed by the calcium sensitizing pathways (15).

In addition to the central role of myosin phosphorylation in smooth muscle contraction, other mechanisms may modulate or fine-tune the contractile state. For example, caldesmon may be involved in the latch state in which the force of contraction is maintained at a low level of myosin phosphorylation and with a low energy expenditure.

Relaxation of the muscle follows a decrease of free Ca2+ in the sarcoplasma. Calmodulin then dissociates from myosin light-chain kinase and inactivates it. Myosin is dephosphorylated by myosin light-chain phosphatase and detaches from the actin filament, and the muscle relaxes (9).

Others suggest that the NO-cGMP inhibitory pathway in corpus cavernosum smooth muscle is not simply a reversal of excitatory signal transduction mechanisms; an unidentified mechanism may contribute to relaxation by decreasing the rate of crossbridge recruitment through phosphorylation.

cAMP and cGMP are the second messengers involved in smooth muscle relaxation. They activate cAMP- and cGMP-dependent protein kinases, which in turn phosphorylate certain proteins and ion channels, resulting in (1) opening of the potassium channels and hyperpolarization; (2) sequestration of intracellular calcium by the endoplasmic reticulum; and (3) inhibition of voltage-dependent calcium channels, blocking calcium influx. The consequence is a drop in cytosolic free calcium and smooth muscle relaxation (Figure 3).

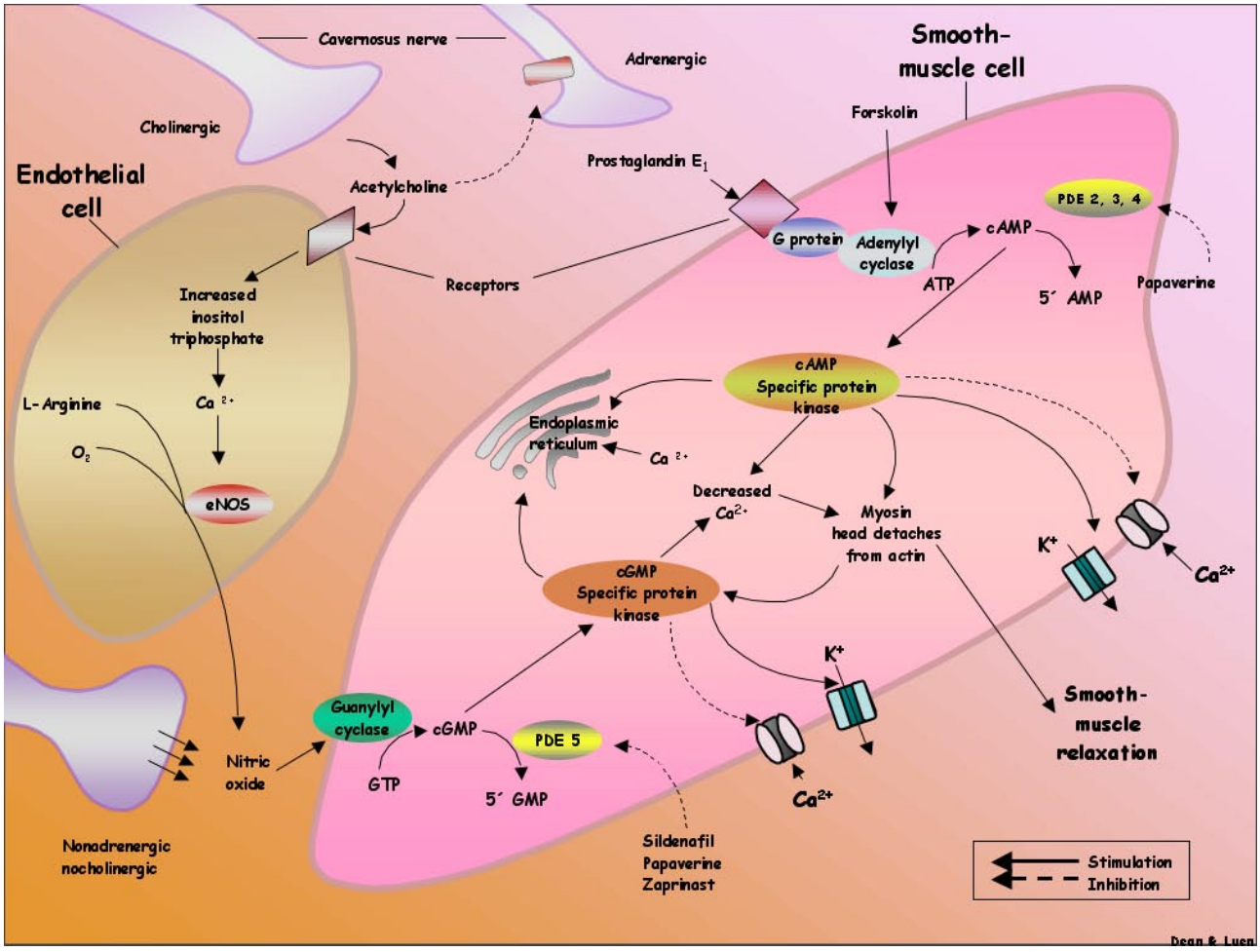

FIGURE 1.

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 11th thoracic to the 2nd 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 (16).

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 (17).

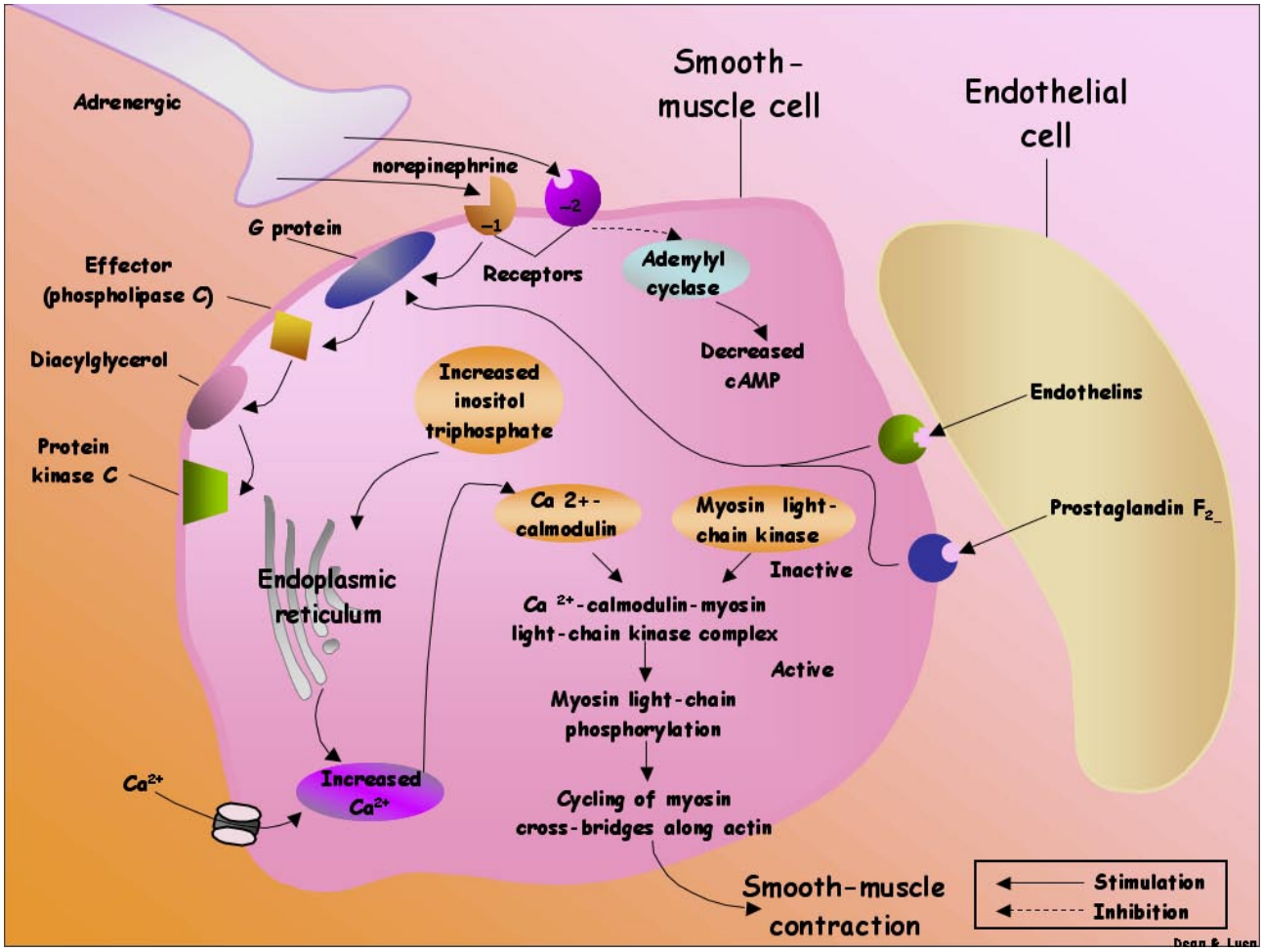

FIGURE 2.

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 (18,19).

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 (20). 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 (21). 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 (22). 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.

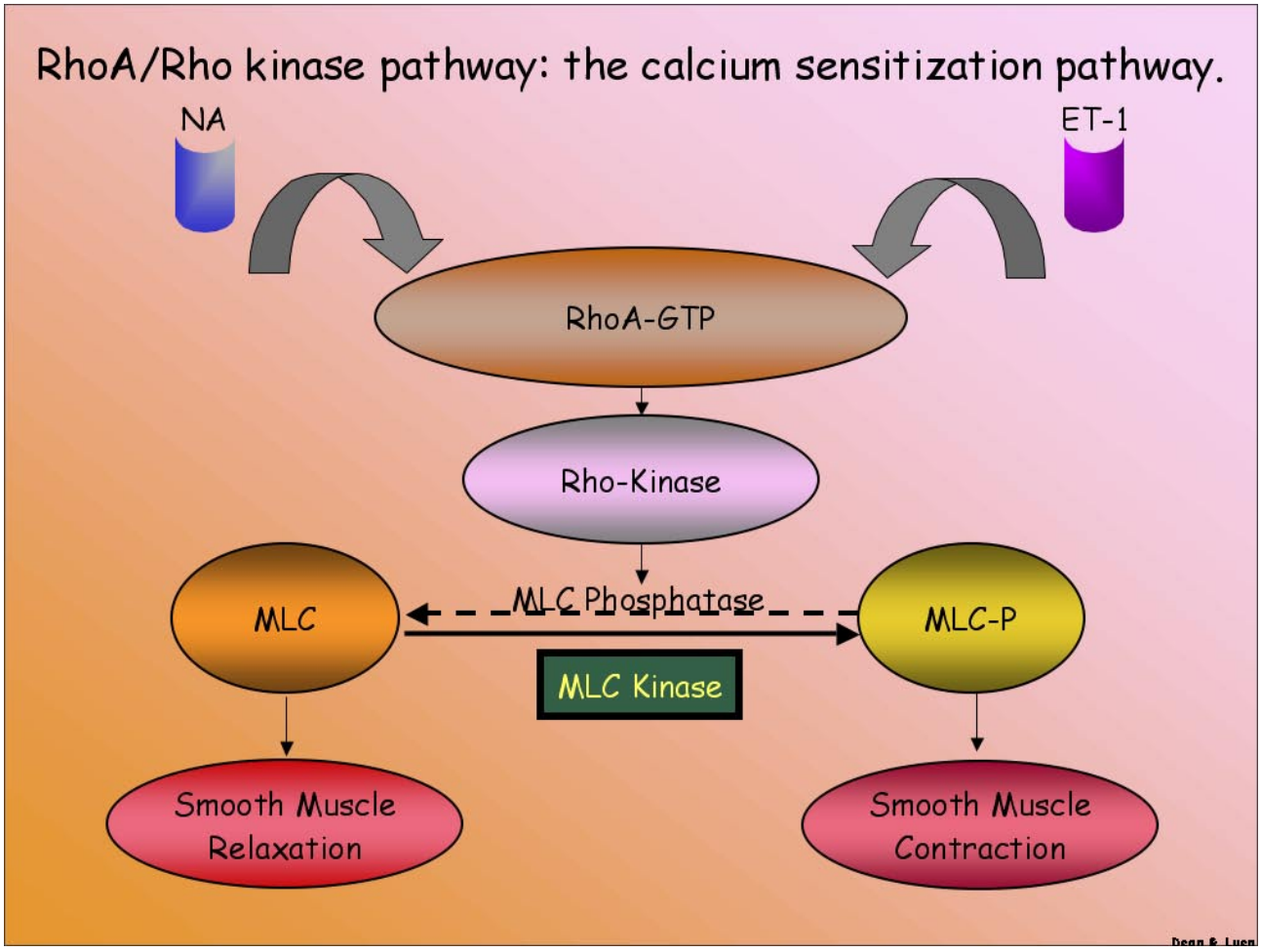

FIGURE 3.

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 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 (23). 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 (24,25).

Giuliano and associates have also shown that stimulation of the sympathetic chain at the L4– 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 (26). 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 (27). 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 (28).

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 (29,30).

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 (23). 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.

CONCLUSIONS

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 (T11-L2 and S2-S4) 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 amygdales 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.

REFERENCES AND RECOMMENDED READINGS (*of special interest, **of outstanding interest)

**1. Lue TF. Erectile dysfunction. N Engl J Med, 2000; 342: 1802.

**2. Dean RC and Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am, 2005; 32: 379.

3. Lue TF, Tanagho EA, McClure RD. Hemodynamics of erection, In. Contemporary management of impotence and infertility, Contemporary management of impotence and fertility Williams & Wilkins, Williams & Wilkins, 1988; 28-38.

4. Bosch RJ, Benard F, Aboseif SR et al. Penile detumescence: characterization of three phases. J Urol, 1991; 146: 867.

5. Lue TF, Takamura T, Schmidt RA et al. Hemodynamics of erection in the monkey. J Urol, 1983; 130: 1237.

6. Saenz de Tejada I, Goldstein I, Azadzoi K et al. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N Engl J Med, 1989; 320: 1025.

7. Ignarro LJ, Bush PA, Buga GM et al. Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem Biophys Res Commun, 1990; 170: 843.

8. Yarnitsky D, Sprecher E, Barilan Y et al. Corpus cavernosum electromyogram: spontaneous and evoked electrical activities. J Urol, 1995; 153: 653.

9. Walsh MP. The Ayerst Award Lecture 1990. Calcium-dependent mechanisms of regulation of smooth muscle contraction. Biochem Cell Biol, 1991; 69: 771.

10. Somlyo AP and Somlyo AV. Signal transduction by G-proteins, rho-kinase and protein phosphatase to smooth muscle and non-muscle myosin II. J Physiol, 2000; 522 Pt 2: 177.

11. Rees RW, Ziessen T, Ralph DJ et al. Human and rabbit cavernosal smooth muscle cells express Rho-kinase. Int J Impot Res, 2002; 14: 1.

*12. Wang H, Eto M, Steers WD et al. RhoA-mediated Ca2+ sensitization in erectile function. J Biol Chem, 2002; 277: 30614.

*13. Rees RW, Ralph DJ, Royle M et al. Y-27632, an inhibitor of Rho-kinase, antagonizes noradrenergic contractions in the rabbit and human penile corpus cavernosum. Br J Pharmacol, 2001; 133: 455.

14. Chitaley K, Bivalacqua TJ, Champion HC et al. Adeno-associated viral gene transfer of dominant negative RhoA enhances erectile function in rats. Biochem Biophys Res Commun, 2002; 298: 427.

15. Cellek S, Rees RW and Kalsi J. A Rho-kinase inhibitor, soluble guanylate cyclase activator and nitric oxide-releasing PDE5 inhibitor: novel approaches to erectile dysfunction. Expert Opin Investig Drugs, 2002; 11: 1563.

16. De Groat W and Booth A. Neural control of penile erection, The Autonomic Nervous System. Nervous Control Of The Urogenital System Harwood, London, Harwood, 1993; 465-513.

17. Walsh PC, Brendler CB, Chang T et al. Preservation of sexual function in men during radical pelvic surgery. Md Med J, 1990; 39: 389.

18. Root W and Bard P. The mediation of feline erection through sympathetic pathays with some reference on sexual behavior after deafferentation of the gentalia. Am J Physiol, 1947; 151: 80.

19. Courtois FJ, Macdougall JC and Sachs BD. Erectile mechanism in paraplegia. Physiol Behav, 1993; 53: 721.

20. Paick JS and Lee SW. The neural mechanism of apomorphine-induced erection: an experimental study by comparison with electrostimulation-induced erection in the rat model. J Urol, 1994; 152: 2125.

21. Bors E and Camarr A. Neurological disturbances in sexual function with special reference to 529 patients with spinal cord injury. Urol Sur, 1960; 10: 191.

22. Chapelle PA, Durand J and Lacert P. Penile erection following complete spinal cord injury in man. Br J Urol, 1980; 52: 216.

*23. McKenna KE. Central control of penile erection. Int J Impot Res, 10 (Suppl 1): S25 (1998).

*24. Burnett AL, Tillman SL, Chang TS et al. Immunohistochemical localization of nitric oxide synthase in the autonomic innervation of the human penis. J Urol, 1993; 150: 73.

25. Carrier S, Zvara P, Nunes L et al. Regeneration of nitric oxide synthase-containing nerves after cavernous nerve neurotomy in the rat. J Urol, 1995; 153: 1722.

26. Giuliano F, Rampin O, Jardin A et al. Electrophysiological study of relations between the dorsal

nerve of the penis and the lumbar sympathetic chain in the rat. J Urol, 1993; 150: 1960.
27. Marson L and McKenna KE. CNS cell groups involved in the control of the ischiocavernosus and bulbospongiosus muscles: a transneuronal tracing study using pseudorabies virus. J Comp Neurol, 1996; 374: 161.
28. Tang Y, Rampin O, Calas A et al. Oxytocinergic and serotonergic innervation of identified lumbosacral nuclei controlling penile erection in the male rat. Neuroscience, 1998; 82: 241.
29. Sachs BD and Meissel RL. The physiology of male sexual behavior, Anonymous New York, Raven Press, 1988 ; 1393-1423.
30. Marson L, Platt KB and McKenna KE. Central nervous system innervation of the penis as revealed by the transneuronal transport of pseudorabies virus. Neuroscience, 1993; 55: 263.