

Pathology of erection

A. Fabbri*, M. Caprio*, and A. Aversa**

*Endocrinology Section, University of Rome "Tor Vergata", and **AFaR-CRCCS, Fatebenefratelli Hospital, Isola Tiberina, Rome, Italy

ABSTRACT. Erectile dysfunction (ED) is defined as the inability to achieve and maintain a penile erection which is adequate for satisfactory sexual intercourse. It is a significant male health problem affecting approximately 150 million men worldwide. This value is expected to more than double by the year 2025. The incidence of ED increases sharply with age since it is a common cross-cultural denominator, affecting 19 to 64% of men aged 40 to 80 years, both in developing and industrialized countries. Epidemiological studies may underestimate the true dimensions of the problem because of the embarrassment or stigma that is associated with ED. Men with ED may experience diminished self-image and self-esteem, anxiety and fears of rejection, and even depression as psychogenic

factors. Pathologic conditions which are commonly encountered in the ageing male (diabetes, hypertension, atherosclerosis, cardiovascular disease, etc) as well as chronic diseases (arthritis, renal and hepatic failure, pulmonary disease) represent a frequent cause of organic ED and are often treated with medications that can interfere with sexual function at central and/or peripheral level. In addition, incorrect lifestyle – i.e. obesity, cigarette smoking, alcohol or drug abuse – may all contribute to the onset of ED. Finally, trauma or surgery affecting either the nervous system or interfering with the blood supply to the penis are associated with increased incidence of ED.

(J. Endocrinol. Invest. 26 (Suppl. to no. 3): 87-90, 2003)
©2003, Editrice Kurtis

INTRODUCTION

Penile erection is a complex neurovascular event involving the interaction of three physiological systems which may be involved in the pathology of erection (1):

1. the central nervous system (CNS);
 2. the peripheral nervous system (PNS);
 3. penile vascular and cavernosal smooth muscle.
- The CNS is the major sexual organ. In the presence of an adequate androgen milieu, the brain drives the sexual response by integrating external erotic stimuli (received through the five senses or erotic fantasies), and processes them into the medial-preoptic area and the paraventricular nucleus of the hypothalamus (psychogenic erection). The main neurochemicals of erectile response include dopamine, oxytocin, α -melanocyte-stimulating-hormone (α -MSH), GnRH, and substance P

which stimulate sexual behavior, and norepinephrine, corticotropin-releasing-hormone (CRH), β -endorphin, prolactin, and neuropeptide Y which inhibit sexual behavior (2). Dopamine receptors are widely distributed in the brain, however there is a particularly high density in the basal ganglia. Both major families of dopamine receptors, D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors have been associated with central erectile functions (2). However the D2 receptor seems to be responsible for most of the pharmacological effects of dopamine. The dopamine receptor agonist apomorphine, administered systemically in male rats has been found to induce penile erection, simultaneously producing yawning, stretching and seminal emission. Interestingly, in rodents dopamine agonist-induced erections are abolished by castration and restored by testosterone replacement (2).

Physical stimulation of genital organs can elicit PNS-mediated erections which are dependent upon the S₂-S₄ parasympathetic spinal centers via the sacral spinal reflex pathway (reflexogenic erection). Thus, the erectile response is a combination of psychogenic and reflexogenic stimuli which result in an inhibition of sympathetic (T₁₁-L₂) and a stimulation of parasympathetic plus nonadrenergic-non-

Key-words: Epidemiological, depression, aging, psychogenic, organic.

Correspondence: Prof. Andrea Fabbri, Dipartimento di Medicina Interna, Università di Roma "Tor Vergata", Via Montpellier 1, Room F663, 00133 Roma, Italy

E-mail: a_fabbri@hotmail.com

cholinergic (NANC) (S_2 - S_4) fiber outflow. In particular, stimulation of parasympathetic and NANC fibers outflow determines the release of intrapenile vasoactive neurotransmitters, which are primarily acetylcholine (ACH), prostaglandin, and nitric oxide (NO), and include other neuropeptides such as vasoactive intestinal polypeptide (VIP). During male sexual arousal, NO is released at parasympathetic nerve terminals (nitrergic nerves). This causes relaxation of the smooth muscle allowing engorgement of blood into the cavernous space and leading to erection (3). The relaxation of penile smooth muscle is mediated mainly by NO, which exerts its action on smooth muscle by activating soluble guanylate-cyclase (sGC). Activation of sGC results in an elevated intracellular cGMP concentration (4) (Fig. 1). Thus, erection occurs as a result of three complementary and simultaneous processes: arteriolar dilatation, relaxation of the smooth muscle within the corpora cavernosa, and corporeal veno-occlusion (1). Noradrenaline released from sympathetic nerves causes contraction of the blood vessels and smooth muscle of the corpus cavernosum, thus leading to detumescence of the penis (Fig. 1). The enzyme phosphodiesterase-5 (PDE5) degrades cGMP. By inhibiting the degradation of cGMP, PDE5 inhibitors prolong the activity of this cyclic nucleotide second messenger within the cavernous vasculature and smooth musculature, thus potentiating the erectile response (4). The concentration of intracellular Ca^{2+} is critical for penile smooth muscle relaxation. A change in the concentration may be achieved by ma-

nipulation of Ca^{2+} into and out of the smooth muscle cells or the endoplasmic reticulum. A decline in intracellular Ca^{2+} ions suppresses the activity of myosin light chain (MLC) kinase and thus increases the intracellular content of dephosphorylated MLC, which enables the smooth muscle cell to relax (5).

PATHOLOGIES OF CNS ASSOCIATED WITH ED

All conditions associated with emotional disturbances, *i.e.* performance anxiety, depression, may lead to an alteration of central regulatory mechanisms of sexual behavior thus resulting in erectile failure or the loss of erection during intercourse. There is a large body of evidence that in the brain the concentration and the activity of several neuropeptides relevant for the control of sexual behavior is regulated by testosterone and its metabolites (17β -estradiol and 5α -dihydrotestosterone). In fact, hypogonadism determines reduced interest in sex, a decline in nocturnal penile erections, and reduced semen volume, whereas erectile capacity to erotic stimuli may be retained depending on the levels of serum testosterone; below a testosterone threshold value of 1.4 ng/ml also erectile function is lost (6). Hypogonadal patients are responsive to testosterone replacement therapy which restores sexual desire and performance, in contrast to impotent men with normal circulating androgen levels in whom androgen therapy does not have any effect on erectile activity and is contraindicated. Hyperprolactinemia does not appear to modify

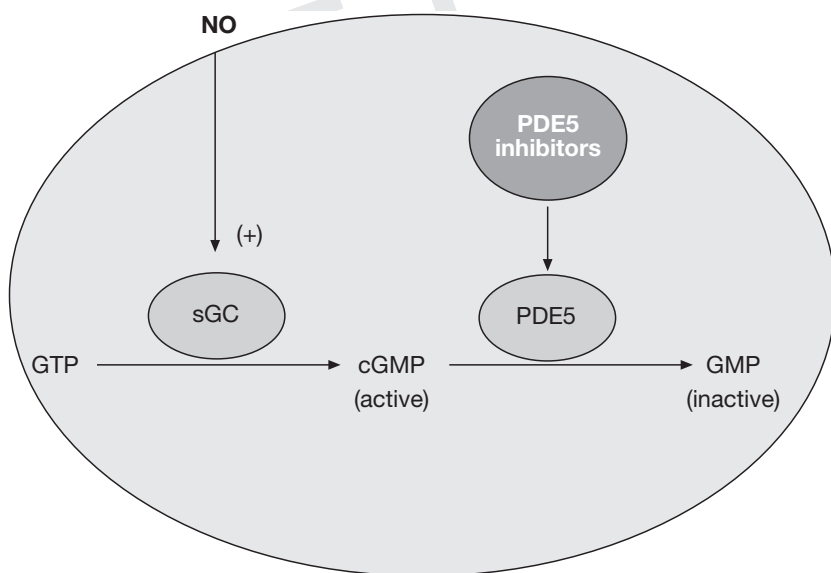


Fig. 1 - Nitric oxide (NO) released from nitrergic nerves and endothelium stimulates smooth muscle relaxation by activation of soluble guanylate-cyclase, which in turn catalyzes the conversion of GTP to the active intracellular second messenger cGMP; cGMP is then metabolized by phosphodiesterase-5 (PDE5) to GMP.

night erections or the penile response to video-erotic-stimulation, suggesting that its negative effect on libido and sexual behavior is centrally mediated. This may occur through an increase of opioid tone and consequent alteration of pulsatile GnRH release (7). However, recent *in vitro* experiments showed that acute infusion of prolactin caused a strong contraction of canine corpora cavernosa cells, suggesting a possible peripheral action of this hormone through not yet identified intrapenile receptors (8). Alteration of GnRH secretion has been suggested to be a possible cause of ED in men with non-organic impotence through a reduction of serum LH biological activity and low biological/immunological-LH ratio (7). Subsequent experimental evidence indicated that the restoration of adequate GnRH pulsatility in impotent men, such as after treatment with the opiate antagonist naltrexone, had important beneficial effects on erectile capacity. Finally, all neurological diseases like stroke, spinal cord injury, peripheral neuropathy, brain and spinal tumors, Alzheimer's disease and multiple sclerosis can all give rise to ED.

PATHOLOGIES OF PNS AND CORPORA CAVERNOSA ASSOCIATED WITH ED

As already mentioned before, erection is locally regulated by a balance between pro- and anti-erectile

mediators. All medical conditions (vascular and neurological disease, chronic illnesses, drugs, surgery or trauma) determining an impairment of pro-erectile / anti-erectile mediators balance may cause ED (9) (Fig. 2).

Main peripheral causes of cavernous incompetence can be summarized into five types (10): 1) large veins exiting the corpus cavernosum (probably congenital when noted in young men), 2) enlarged venous channels caused by distortion of the tunica albuginea, as it occurs in Peyronie's disease or the weakening associated with aging, 3) the inability of cavernous smooth muscle to relax due to fibrosis, degeneration or dysfunction of gap junctions, 4) inadequate release of neurotransmitters, mainly NO (in neurogenic or psychogenic impotence or endothelial dysfunction), and 5) abnormal communication between the corpus cavernosum and spongiosum or glans (either congenital, traumatic or after a shunt procedure for priapism).

REFERENCES

1. Fabbri A, Aversa A, Isidori A. Erectile dysfunction: an overview. Hum Reprod Update 1997, 3: 455-66.
2. Chuang AT, Steers WD. Neurophysiology of penile erection. In: Carson CC, Kirby RS, Goldstein I eds. Textbook of erectile dysfunction. Oxford: Isis Medical Media, 1999, 59-72.

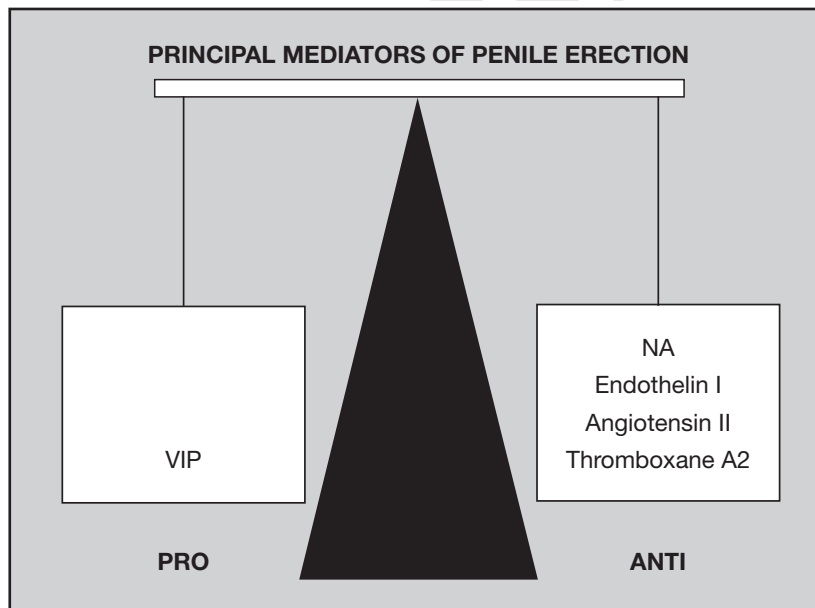


Fig. 2 - Penile erection is locally regulated by two opposing systems: pro-erectile mediators such as nitric oxide (NO), vasoactive intestinal peptide (VIP), acetylcholine (ACH) and adreno-medullin, and anti-erectile mediators such as norepinephrine (NA), endothelin 1, angiotensin II and thromboxane A2.

3. Schmidt HH, Lohman SM, Walter U. The nitric oxide and cGMP signal transduction system: regulation and mechanism of action. *Biochem Biophys Acta* 1993, 1178: 153-75.
4. Chuang AT, Strauss JD, Murphy RA, Steers WD. Sildenafil, a type-5 phosphodiesterase inhibitor, specifically amplifies endogenous cGMP-dependent relaxation in rabbit corpus cavernosum smooth muscle *in vitro*. *J Urol* 1998, 160: 257-62.
5. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue *in vitro* and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol* 1998, 159: 2164-70.
6. Carani C, Granata ARM, Faustini Fustini M, Marrama P. Prolactin and testosterone: their role in male sexual function. *Int J Androl* 1996, 19: 48-54.
7. Fabbri A, Jannini EA, Ulisse S, et al. Low serum bioactive luteinizing hormone in non organic male impotence: possible relationship with altered gonadotropin-releasing hormone pulsatility. *J Clin Endocrinol Metab* 1988, 67: 867-75.
8. Ra S, Aoki H, Fujioka T, et al. *In vitro* contraction of the canine corpus cavernosum penis by direct perfusion with prolactin and growth hormone. *J Urol* 1996, 156: 522-5.
9. Wagner G, Saenz de Tejada I. Update on male erectile dysfunction. *BMJ* 1998, 316: 678-84.
10. Lue TF. Erectile dysfunction. *N Engl J Med* 2000, 342: 1802-13.

©2003, Editrice Kurtis

NOT PRINTABLE