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Opportunities for the Treatment of Erectile Dysfunction by Modulation of the NO Axis – Alternatives to Sildenafil Citrate

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Key words: *Erectile dysfunction – NO – Nitroglycerin – Sildenafil – cGMP*

Summary

Erectile function in man depends upon a complex interaction of psychogenic, neurologic, hormonal and vascular factors, and therefore the management of erectile dysfunction (ED) reflects this complexity of control. Therapeutic options include psychological and non-pharmacological approaches as well as drug treatments. The effectiveness of the type-5 cGMP phosphodiesterase inhibitor sildenafil citrate (Viagra®) confirms the pivotal role of the NO–cGMP axis in promoting and maintaining erection. Although widely acclaimed, sildenafil leaves many questions unanswered, especially regarding its susceptibility to pharmacokinetic drug interactions, and its safety in patients with ischaemic heart disease and those taking nitrates. In view of the epidemiological link between erectile dysfunction and cardiovascular disease in the elderly, this limitation might have much broader implications. The presently available scientific documentation, although less extensive, indicates that NO donors, such as topically applied nitroglycerin (GTN; for example, 1–2 puffs of an ordinary GTN spray applied to the shaft of the penis), might be a reasonable alternative. Further larger-scale research on the efficacy and tolerability of topical GTN is needed to establish its full therapeutic potential in the treatment of erectile dysfunction.

Introduction

Penile erection is the major functional expression of sexual arousal in man and therefore plays a key role in human sexual behaviour. Historically, the term 'impotence' has been used for a wide range of male sexual dysfunctions, including low sexual desire, retarded ejaculation, and difficulties in achieving and sustaining erections[1]. Owing to pejorative connotations and lack of specificity it has now mostly been replaced by 'erectile dysfunction' or 'erectile disorder' (ED) to signify a persistent or recurrent inability to attain and/or maintain an adequate erection to permit satisfactory sexual intercourse (highlighting penile erection as a part of the multifaceted process of male sexual function)[1]. In 1992, the NIH Consensus Statement on Impotence estimated 10–20 million U.S. males to be affected, with a 5% prevalence at the age of 40 increasing to 15–25% at the age of 65 and older[2]; later surveys indicate an overall prevalence of 52% of men aged 40–70 years in the Massachusetts Male Aging Study[3].

Undoubtedly, ED is not a mere inconvenience, but the source of important distress and social isolation[4] as it may be perceived by the ego-threatened male as a vital 'insult to his manhood'[5] often

Until recently, the lack of simple definitions, appropriate wording and convenient therapeutic options may have discouraged both health-care providers and patients to consider ED as a legitimate medical issue rather than as an embarrassing psycho-social oddity: only a few patients sought medical help, which then often consisted of lengthy psychological counselling, complex medical devices, painful local intracavernous injections or surgery, etc.

The overwhelming – albeit not unequivocal – public acclaim of the introduction of sildenafil citrate (Viagra®), the first peroral treatment of ED with an adequately proven efficacy claim, redefines ED as a lifestyle rather than as a (conventional) medical issue: very many males appear to be unsatisfied with their sexual (erectile) performance – although they would probably not consider themselves 'impotent' – and are eager to seek pharmacological help for it, provided it can be achieved conveniently.

However, sildenafil citrate has important drawbacks. Safety concerns exclude an important fraction of the affected population – those with cardiovascular diseases and those taking nitrates, in particular. Against this background of well-documented experience with sildenafil citrate, which confirms the NO–cGMP hypothesis, it is appropriate to evaluate further options for the management of erectile dysfunction.

Physiology

Anatomically, the erectile system of the human male penis consists of the corpus cavernosum (two chambers adjacent to the urethra which runs on the underside of the corpora) and the corpus spongiosum (composed of large venous sinuses which contain little blood when the penis is flaccid, engorged with blood)[7].

Penile erection is a vascular event initiated by neuronal action and maintained by a critical interplay between vascular and neurological processes. Psychogenic stimulation (perception, desire, etc) and/or tactile (reflexogenic) stimulation initiate the process. Centrally mediated erection impulses reach the penis via the thoracolumbar sympathetic outflow and hypogastric plexus. The afferent fibres in the pudendal nerve carry the tactile impulses to the erection centre in the sacral cord, which returns efferent signals through parasympathetic nerve fibres. Full erection requires input from both central and reflex pathways.

In the flaccid penis, the blood pressure in the cavernosal sinuses is near to venous pressure and the smooth muscles of the penile arteries and the trabeculae of the corpus cavernosum are contracted in order to maximise the impedance against arterial inflow; this tone is kept by the excitatory adrenergic innervation although spontaneous myogenic activity may play an ancillary role[8]. Relaxation of the corpus cavernosum smooth muscle is the pivotal physiological event responsible for erection. Increased inflow fills the cavernous lacunar spaces increasing the pressure within the spaces so that the penis becomes erect[9].

Pharmacology

Although confounded by methodological constraints and species heterogeneity, experiments *in vitro* and *in vivo* conducted in man, animals and cultured cells, allow definition of several working hypotheses to identify suitable approaches to therapeutic intervention in ED.

Tumescence depends on the changing balance between neuronal and humoral messengers that affect myosin

tone: filling of the sinusoidal spaces with blood due to smooth muscle cell relaxation results from an increased efferent parasympathetic tone (and probably simultaneous withdrawal of the efferent adrenergic drive), with nitric oxide (NO) as the main proerectile neurotransmitter and noradrenaline as the major antierectile agent[10–12].

Central Nervous Control

Centrally, apomorphine, a D_1- and D_2-*dopaminergic* agonist, facilitates erection through stimulation of the D_1-receptors in the hypothalamic medial preoptic area, while higher doses inhibit erection by stimulation of D_2-receptors[13,14]. *Oxytocinergic* nerves appear to enhance erection both directly and by modulating limbic dopaminergic activity[15]. *Serotonin* modulates spinal reflex activity in the spinal cord, with 5-HT_2-receptor stimulation inhibiting erection and facilitating ejaculation, while 5-HT_{1C}-agonists (such as trazodone[16]) augment erectile responses by amplifying the efferent parasympathetic drive. *NO* synthase (nNOS or Type I) has been co-localised with various central nervous neurotransmitters in selective parts of the brain and spinal cord, including the paraventricular nucleus; although predominantly a peripheral modulator (see below), central nervous NO might act as a long-term synaptic modulator following its release from presynaptic neurones[17].

Peripheral Nervous Modulation

Penile erection relies on stimulation of the pelvic (nervi errigentes) and cavernous nerves. The latter originate from the pelvic plexus, which is modulated by parasympathetic (pelvic nerve), sympathetic (hypogastric nerve) and somatic (pudendal

Although cholinergic nerves have been identified in the penile effector system, muscarinergic blockade does not appear to alter nerve-evoked penile smooth muscle relaxation[18]; acetylcholine has dual, mainly indirect, effects by stimulating endothelial NO release and by releasing noradrenaline via stimulation of prejunctional muscarinic receptors.

Increased cavernosal smooth muscle tone and penile flaccidity is controlled by postjunctional α_1-adrenoceptors and increased α-adrenoceptor sensitivity has been suggested to play a role in ED[19].

Physiologically the main peripheral neurotransmission pathway to induce penile erection seems to be non-cholinergic, non-adrenergic and mediated by the EDRF-analogue NO[20]. NO is synthesised endogenously during the conversion of L-arginine to L-citrulline as catalysed by NO synthase (NOS). NO activates guanylate cyclase which then catalyses the formation of guanosine 3′,5′-cyclic monophosphate (cGMP) from guanosine 5′-triphosphate. As a secondary messenger, cGMP inhibits myosin phosphorylation and reduces intracellular calcium concentrations via activation of cGMP kinase[21]. NOS has been localised in the penile effector system in neurones (nNOS, Type I), endothelium (eNOS, Type III) and smooth muscle (inducible iNOS, Type II)[12]. Experimentally, penile NOS was found to be reduced in several conditions associated with ED (such as senescence, castration, diabetes, adrenalectomy, hypophysectomy and androgen receptor blockade), while substitution of the respective hormones prevented ED and loss of NOS[22]. NO-mediated relaxation is impaired by excess prolactin[23]. Neurogenic penile smooth muscle cell relaxation can be blocked by inhibitors of NO biosynthesis and by substances that reduce cGMP or bind directly to NO, while NO-donors, such as GTN and

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