

Erectile Dysfunction Management for the Future

Minireview

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ABSTRACT: The field of erectile dysfunction (ED) management over time has witnessed assorted interventions to enable men to perform sexual intercourse. In recent times, major progress in ED research has led to increasingly effective treatments based on a refined knowledge of the scientific basis for penile erection. Current concepts suggest that therapeutic prospects on the horizon include

novel pharmacotherapies, growth factor therapy, gene therapy, and regenerative medicine. The purpose of this review is to present the foundations for future therapies in ED management.

Key words: Pharmacotherapy, growth factor therapy, gene therapy, regenerative medicine, penis, erection.

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Erectile dysfunction (ED) management has moved forward substantially in the past 25 years with the introduction of a host of remarkable therapeutic options. Not too long ago, management for ED was directed largely towards psychosocial or hormonal factors, in accordance with the presumption that these were causative conditions for the disorder. Hence, therapy was generally administered in the forms of psychoanalysis, sex therapy, and hormonal interventions. If such management did not work, alternative strategies were used, ranging from herbal supplements presumed to enhance sexual performance to mechanical devices. For the latter, early penile implants of the 1950s and vacuum-pump technology of the late 1960s were affirmed to create penile rigidity, obviating the necessity for complete knowledge or application of the physiology or biochemical properties of the erectile response.

In recent times, scientific advances in the physiology and molecular mechanisms of penile erection have spawned innovative treatments for ED. In the early 1970s, a rather ingenious approach was the description of penile revascularization, designed to restore penile blood flow function and the basis for blood engorge-

ment of the penis. It so turned out that these surgeries would represent only a limited role in the armamentarium of treatments for ED, serving the narrow group of men with ED associated with traumatic rupture of major pudendal arteries supplying blood to the penis. Subsequently, major progress was gained within the realm of pharmacologic therapies—treatments that were based on an evolving understanding of the chemistry associated with corporal tissue and vascular reactivity within the penis. In series, these were intracavernosal pharmacotherapy introduced in the early 1980s, intra-urethral pharmacotherapy introduced in the mid-1990s, and oral pharmacotherapy introduced in the late 1990s—all demonstrated through rigorous basic scientific and clinical investigation to represent valid, effective options for managing ED.

Along with this revolution in ED therapies, there came new ways of thinking about evaluating and assigning therapy to patients. First to come was the definition of the problem more accurately and euphemistically as that of “the inability to attain and maintain erections of sufficient quality to permit satisfactory sexual intercourse” (National Institutes of Health, 1992). In addition, it was accepted that ED carried a subjective attribution and correctly involved patient and partner in the identification, evaluation, and initiation of appropriate therapy. In step with this new clinical practice approach, less invasive and otherwise reversible therapies were promoted. This movement further suggested the increasing opportunity for patients to be decision-makers with regard to their ED management. Oral medication, such as oral phosphodiesterase type 5 (PDE5) inhibitors, is recognized to serve as first-line therapy; vacuum devices and penile injections represent

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second-line therapy; and penile prosthesis surgery is designated as third-line therapy.

Current interventions for ED are consequences of significant advances in the field of sexual medicine. New therapies particularly indicate an evolution in the cellular and molecular science of erection physiology. Epidemiologic associations of disease states with impaired vascular biology, neurophysiology, and endocrinology have also helped to revise thinking about the pathophysiologic mechanisms responsible for ED. It is now recognized that risk factors for ED include increasing age, cardiovascular diseases, diabetes mellitus, environmental risk factors such as cigarette smoking, and lifestyle factors such as lack of physical activity. Undoubtedly, collaborative scientific activity involving specialists from diverse biomedical disciplines has fostered new scientific understanding and engendered strategies that have led to the effective management of ED in many men worldwide.

At this critical juncture in the field, particularly with the availability of effective oral therapy for ED, the question arises as to whether we have truly achieved "ideal therapy." In fact, although current offerings are more easily administered, scientifically based, and clinically proven to be effective than those in the past, they still have their shortcomings. These include the observations that they are not always effective or convenient to use and also have limited spontaneity. Furthermore, they do not truly correct, cure, or prevent ED. These shortcomings are well recognized in the field, and many investigators continue to explore improved treatments for ED that would meet heightened objectives for ideal therapy.

From this perspective, this essay is intended to present several major biomedical research directions that may foster applicable clinical therapeutics for ED in the future. Broadly speaking, such directions include pharmacotherapy, growth factor therapy, gene therapy, and regenerative medicine, all consistent with advancing knowledge of key molecular targets as well as prime biological constituents underlying erection physiology. In reviewing these, it is my hope to provide a glimpse of what may be promising, up-and-coming ways that will enable clinicians to even better manage ED beyond current options in the field.

Pharmacotherapy

Among therapeutic prospects for ED, the pharmacotherapeutic approach to managing has gained prominence over recent years. This observation is hardly a surprise, with recognition of the fact that pharmacologic agents serve to replicate effector molecules and otherwise activate signaling mechanisms involved in the production of the erectile response. In this regard,

therapeutic strategies are commonly categorized according to peripheral and central levels of effects, in reference to the neurologic system. This reference also acknowledges that regulation principally involves the neuroaxis, with contributions from endocrine and paracrine regulators. Both peripherally and centrally, pharmacologic management commonly adheres to the dichotomous strategic schemes of suppressing antierecile mechanisms or promoting proerecile mechanisms, or some combination of both.

In the periphery with reference to the pelvis and penis, current concepts of approaches to suppress antierecile mechanisms include α -adrenoceptor antagonists, endothelin receptor antagonists, and angiotensin II receptor antagonists (Andersson, 2001). Well known is the strategy of α -adrenoceptor blockade to oppose the adrenergically mediated contraction of erectile tissue (Christ et al, 1990). There is the common clinical application of the nonspecific α -adrenoceptor antagonist phentolamine via intracavernosal pharmacotherapeutic regimens. The notion of developing receptor antagonists for endothelins and angiotensin II as clinical treatments would appear to have appeal, and possibly future clinical investigations may define their applications.

Recent science of the molecular basis of penile erection has confirmed the major role of the RhoA/Rho-kinase signaling pathway as a dominant regulator of vascular smooth muscle contraction throughout the body as well as in the penis (Mills et al, 2001). The pathway actually represents a molecular site of convergence for contractile mediators (eg, norepinephrine, endothelin, and angiotensin II), such that the pathway serves as the effector basis for the molecular actions of these mediators in vascular tissue. Based on this relatively new knowledge, it is highly anticipated that pharmacotherapeutic strategies will be developed targeting the RhoA/Rho-kinase signaling pathway in the penis. A particular focus of attention for pharmacotherapeutic development is whether the actions of conceivably selective stimulatory or inhibitory binding proteins for this pathway operate in the penis and may be exploited to drive erectile responses specifically and without adverse consequences elsewhere in the body (Jin and Burnett, 2006).

Peripheral strategies that center on promoting proerecile mechanisms are quite diverse and include nitric oxide (NO) signaling pathway effectors, phosphodiesterase (PDE) inhibitors, prostanoids, cholinergic receptor agonists, vasoactive peptides, and potassium channel openers (Andersson, 2001). All of these strategies are based on scientific principles of neurophysiology and vascular smooth muscle biology having relevance for the penis. At this time, the NO/cyclic guanosine monophosphate (cGMP)/cGMP-dependent protein kinase I path-

way serves as the principal regulatory basis for penile erection (Burnett et al, 2006). This pathway offers multiple molecular sites for pharmacologic targeting, including catalytic enzymes, biochemical cofactors and products, and degradative enzymes. This pathway has already been exploited for clinical practice. Most well known are the commercially available, orally effective PDE5 inhibitors such as sildenafil, vardenafil, and tadalafil (Corbin, 2004). These medications pharmacologically act by blocking the actions of the degradative enzyme PDE5 in the penis (which degrades the second messenger molecule of NO signaling, cGMP). In this manner, PDE5 inhibitors potentiate the corporal smooth muscle relaxation effects of this signaling pathway. The nonspecific PDE inhibitor papaverine used familiarly in intracavernosal pharmacotherapeutic regimens is another example of this therapeutic strategy. The predominance of the NO signaling pathway in erection physiology indicates that it will continue to draw interest as an avenue to modulate the erectile response for clinical purposes. For the future, investigators may advance specific therapies based on targeted molecular mechanisms beyond PDE5 inhibition. Of particular interest, the development of guanylate cyclase activators that serve to drive the signaling pathway independent of NO stimulation has been studied at the preclinical level with hopeful potential clinically (Brioni et al, 2002).

Prostanoids have been shown to control smooth muscle physiology in the penis, and their representative chemical prostaglandin E₁ (also known as alprostadil) has been used primarily for the intracavernosal pharmacotherapy of ED (Cawello et al, 1997). Ongoing studies to characterize prostanoid metabolites, receptors, and mechanisms of action in the penis may lead to meaningful pharmacotherapeutic strategies in the future. Cholinergic actions in the penis are understood to contribute to penile erection as a neuronal mechanism stimulating the endothelial release of vasoactive substances including endothelial NO (Andersson, 2001). This knowledge suggests that therapies driving cholinergic stimulation in the penis could be attractive as a therapeutic strategy for ED. The possibility of developing pharmacotherapy based on neuropeptide and vasoactive peptide actions in the penis remains of interest and is generated from strong basic scientific work showing that these chemicals do indeed contribute to the regulatory biology of erectile tissue (Becker et al, 2001; Guidone et al, 2002). Additional pharmacotherapy is likely to be generated from improved knowledge regarding electrophysiologic properties of smooth muscle, including ion channel functions involved in corporal smooth muscle biology. Therapies based on ion homeostasis mechanisms within corporal smooth muscle tissue seem attractive because of the fundamental

regulatory basis associated with ionic movements that determine tissue contractility (Christ et al, 1993). Early studies have been conducted showing that potassium channel opener mechanisms can be applied for pharmacotherapeutic purposes for ED (Holmquist et al, 1990; Venkateswarlu et al, 2002).

Pharmacotherapy at central levels of erection control offers an entirely different approach in the management of ED. The concept that central pharmacotherapeutics could be exploited for ED management seems intuitive with the understanding that a whole host of erectogenic stimuli processed at brain and spinal cord levels elicit penile erection (Giuliano et al, 1995). However, the complexity of central mechanisms governing erection physiology, in comparison to the peripheral regulation of this response, has thwarted mature therapeutic options for ED. However, several neurochemical systems at spinal and supraspinal levels have been shown to play roles in the erectile response. Prominent among these are 5-hydroxytryptamine (5-HT; serotonin), dopamine, oxytocin, and NO. 5-HT has been most strongly implicated in the spinal regulation of penile erection. Dopamine has been characterized best as a major central mediator of penile erection operating within the paraventricular nucleus of the hypothalamus (Argiolas and Melis, 2005). At this level, oxytocinergic regulation is believed to occur on the basis of dopamine signaling as well as signaling by other neurochemicals such as glutamate, NO, and oxytocin itself. The downstream neurochemistry and circuitry have remained elusive for pharmacotherapeutic targeting. However, several strategies have been investigated already at the clinical level. For instance, apomorphine acting as a dopaminergic agonist has been formulated as an oral pharmaceutical agent that has been clinically used in countries outside of the United States (Wagner, 2001).

Another mechanism that may converge on oxytocinergic neurons within hypothalamic nuclei is represented by the melanocortinergic regulatory pathway (Wessells et al, 2005). In fact, melanocortin receptor actions have been identified within hypothalamic nuclei, and Melanotan II acting as a nonselective melanocortin receptor agonist has been studied in early-phase clinical trials as a potential pharmacotherapeutic strategy for ED. The importance of central regulation of penile erection along with steady progress scientifically in this field prompts continued development of pharmacotherapeutic targeting at central levels for ED management.

Growth Factor Therapy

Growth factor therapy represents another emerging strategy for the treatment of ED, in acknowledgment of

the potential roles of chemical trophic factors in the developmental and functional biology of sexual organs. This therapy would imply the possible utility of neuroprotective and vasculoprotective interventions conceivably targeting biological elements involved in the erectile response that are damaged by neuropathic disease or injury. An extensive body of work has accumulated, primarily using experimental rodent models, showing that various neurotrophins, such as nerve growth factor, acidic fibroblast growth factor, and brain-derived neurotrophic factor, as well as atypical neurotrophic factors, such as growth hormone, the morphogenic factor Sonic hedgehog protein, and the cytokine-hormone erythropoietin, exert major roles in penile neuronal functions (Podlasek et al, 2005; Bella et al, 2008). Primarily, studies have shown that neurotrophic agents protect or facilitate recovery of autonomic penile nerves, in turn decreasing the extent of erectile tissue degeneration and promoting erectile function recovery. The molecular basis for the beneficial effects may involve various mechanisms, including activation of neuronal cell survival kinase pathways and induction of transcription factors, that lead to nerve protein synthesis and regulation of neurite outgrowth.

Clinical interest in exploiting scientific advances in this area is great. Experimental findings indicate that a number of possibilities may serve as effective targets for neurobiologic interventions in the penis with the intent to manage ED. At this time, only preliminary work has been done at the clinical level to establish any sort of applications for neurogenic ED disease states. Clinical trials have been conducted for corticosteroids, immunophilin ligands, and electrical stimulation, all suggesting various approaches to drive neurotrophic/neuroprotective effects, although results have only confirmed safety and have not yet proven therapeutic efficacy (Burnett and Lue, 2006). Ongoing fervent investigations may delineate the next level of compounds or strategic formulation of drugs having beneficial effects for human conditions. It is noteworthy that this therapeutic direction offers a corrective approach to the problem of neurogenic ED, with the potential to restore normal erectile function. A key issue is whether therapies related to this field can be administered without causing adverse proliferative effects on structures elsewhere in the body. This matter is of particular concern for nerve growth factor therapy that may be suited for the setting of radical prostatectomy, in which there may be concerns of growth-proliferative effects on possibly remnant prostate cancer cells after surgery. It will also be essential to develop ways to control the manner of this therapeutic effect on nerve growth.

Growth factor therapy is certainly relevant because of the predominance of vascular disease states impacting

negatively on erectile function. In fact, emphasis has been given to the role of endothelial dysfunction as a key pathogenic factor underlying a whole host of cardiovascular clinical states. It is understood that the vascular endothelium within the penile vasculature is vital for biological processes ranging from hemodynamic regulation to vascular homeostasis.

Significant experimental work in this area, also using rodent animal models primarily, has clarified the role for angiogenic factors and their likely trophic effects on vascular smooth muscle cell function in the penis (Burchardt et al, 2005; Xie et al, 2008). A host of molecular factors have been studied, such as vascular endothelial growth factor and basic fibroblast growth factor. The translation of these studies for the clinical treatment of vasculogenic ED has gained traction in recent years, and future clinical trials hold promise that this form of growth factor therapy will be useful. The idea of restoring or promoting vascular/endothelial mechanisms within the penis is attractive. Similar to the premise of nerve growth factor therapy, therapeutic strategies for the growth and function of the penile vasculature offer the potential to restore normal erectile function.

Gene Therapy

Gene therapy suggests the idea of a science fiction approach to managing ED. However, this approach may indeed represent a new frontier for the management of this problem, with possible advantages for prevention of ED or even recovery of erectile function in the face of disease states injurious to penile health (Strong et al, 2008). The concept refers to the introduction of foreign genetic material into human cells that either restores or supplements normal cellular function that is defective or otherwise antagonizes the functional effects of expression of the mutant genetic phenotype. The penis does represent an ideal location for gene therapy, given its external location and accessibility for efficient genetic manipulation. In addition, the rather homogenous content of parenchyma within the penis suggests that the delivery can be delivered and dispersed consistently. The way gene therapy works requires that only a proportion of cells become transfected, and given the properties of the erectile tissue response by which the effect of delivery can be transferred intercellularly by gap junctions of corporal smooth muscle cells, the penis is an attractive organ in which to pursue gene therapy.

Gene therapeutic approaches have been categorized according to their delivery designs, through viral (eg, adenoviruses, adeno-associated viruses, retroviruses) or nonviral (eg, naked DNA, plasmid DNA, liposomes) vectors or other cell-based (eg, myoblasts, endothelial cells) delivery systems (Christ and Melman, 1998). The categorization is further understood on the basis of such

characteristics as transfection efficiency, durability, and safety profile. Viral vectors, in general, offer high cellular transduction efficiency. However, these vectors may trigger immune and inflammatory responses, which result in attenuated effects. There is also the concern of possible DNA integration into the host genome and subsequent activation of oncogenes. Nonviral vectors, in contrast, carry low risks of immune or inflammatory responses. Cell-based gene therapy offers the stable delivery of genetic information via an altered cellular vehicle and relies on the adherence and persistence of the cell within incorporated tissue. Several gene therapeutic approaches for the penis have been amply investigated at the preclinical level. These encompass various vectors and methods along with various erectogenic molecules that have been delivered. Among molecules, vascular endothelial growth factor, NO synthase, preprocalcitonin gene-related peptide, vasoactive intestinal peptide, brain-derived neurotrophic factor, and the calcium-sensitive potassium (maxi-K) channel have been studied. Simply stated, assorted approaches have demonstrated successes in facilitating erection responses in animal models of ED. Consequently, they provide proof of concept that gene therapy could work at the clinical level in men with ED and suggest that various molecular pathways governing the erectile tissue response can be exploited favorably to produce penile erection.

Remarkably, gene therapeutic approaches have recently been studied preliminarily at the clinical level. A phase I clinical trial in which the maxi-K gene was delivered by DNA plasmid has shown safety effects and possibly efficacy benefits (Melman et al, 2006). This trial consisted of only a small number of patients and did not include a control arm. Thus, definitive judgments about the success of gene therapy in humans to treat ED remain limited. However, this study has provided enough interest to stimulate further investigation in this area.

The future management of ED based on gene therapeutic prospects is highly considered. It is attractive to propose a therapeutic approach that may have long-term effects in managing or even preventing ED. This option may well be considered in combination with other therapies, thereby reducing dose requirements and lessening adverse effects associated with other therapies. With this promise ahead, it is important to acknowledge challenges that persist and will need to be overcome to bring this therapy to fruition. Attention will need to be given to the selection of preferred gene products or combinations thereof that will be broadly useful or otherwise specifically advantageous for select presentations of ED. In addition, it will be necessary to overcome safety hurdles, which have been associated with gene therapeutic management in general at the clinical level.

Regenerative Medicine

Concepts of tissue reconstruction have been applied to biological constituents structurally responsible for penile erection. Accordingly, regenerative medicine for the penis implies techniques ranging from tissue engineering to stem cell therapy, which are designed to reconstitute tissues relevant for the erectile response from penile nerves to the corpus cavernosum itself.

Scientific work in the area of structural repair or reconnection of penile nerves has been done preclinically and clinically with primary interest for the application of post-radical prostatectomy ED (Burnett and Lue, 2006). The rationale is to provide a substitute for injured or excised cavernous nerves that may occur during radical prostatectomy. Nerve-grafting conduits have been described, ranging from autotransplanted nerve structures to synthetic nerve guides, which can be interposed in the course of the autonomic penile innervation. On a grander scale, progress has been made to recompose corporal tissue, which would have applications in clinical conditions of significant penile tissue loss (Falke et al, 2003). This therapeutic discipline combines engineering of corporal tissue components and advanced delivery methods for genes and growth factors that promote organogenesis. Despite the impressive body of preclinical work that has been done, significantly more progress is needed to bring concepts of regenerative medicine to the clinical arena for the management of ED. The feasibility of grafting procedures for penile nerve restoration is certainly understood, although convincing support for the success of this therapeutic endeavor remains unclear. For corporal tissue reconstruction, a greater objective will be needed to fulfill architectural, biomechanical, and functional requirements of native corpora cavernosa. The development of cell delivery vehicles and vectors for genes and growth factors required for functional penile tissue will be paramount for advancing this therapeutic approach.

Summary

From antiquity to the present, the management of ED has progressed substantially. Historical therapies derived largely from rudimentary if not theoretical beliefs regarding the psychological, hormonal, or chemical factors impacting penile erection. Alternatively, mechanical devices were developed, obviating scientific understanding of erection mechanisms, although they produced an effective means for rigidity of the penis when needed for sexual intercourse. More recently, biological research surrounding this topic has yielded an increasingly advanced understanding of the science of the erectile response. This research has contributed to scientifically purposeful treatments for ED, and as such work has

rapidly continued, a new stage has been set for developing therapeutic options that may correct or even prevent this sexual dysfunction. Several categories of therapeutic advances are apparent, including novel pharmacotherapies, growth factor therapy, gene therapy, and regenerative medicine. Amid these exciting scientific developments, the future of ED management is full of promise.

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