



European Association of Urology



Editorial – referring to the article published on pp. 1194–1207 of this issue

Unexpected Insights into Pelvic Function Following Phosphodiesterase Manipulation—What's Next for Urology?

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The review article concerning phosphodiesterases (PDEs) submitted by Ückert et al. is both excellent and comprehensive in its evaluation of the PDE isoenzymes and their potential role in various urologic settings [1]. The location, physiologic role, and impact of manipulation of the PDEs in disease states have revealed much basic molecular biology. These recent understandings, as detailed by Ückert and others, have allowed us a glimpse of the translational science potential of this important regulatory cascade. Because studies involving the interactions between erectile dysfunction (ED), lower urinary tract symptoms (LUTS), and the impact of PDE5 inhibitors have recently been presented, some expansion of Dr Ückert's comments seem warranted [2,3].

The role of PDE5 and interaction with cyclic guanosine monophosphate (cGMP) in the penile smooth muscle is the most prominent of many insights into this ubiquitous and highly regulated molecular cascade. Another emerging example relates to the data indicating the links in the epidemiologic, physiologic, pathophysiologic, and treatment aspects of LUTS secondary to benign prostatic hyperplasia (BPH) and sexual dysfunction. It appears that LUTS/BPH and sexual dysfunction are more than coincidental, as supported by relevant clinical management implications related to this association. For example, the treatment of one condition such as LUTS/BPH may have an impact on other conditions, such as sexual dysfunction. The relationship between these two diseases,

previously considered separate, is important because (1) additional information on risk factors for either disease could be important in patient screening, (2) many currently available LUTS treatments, medical and surgical, affect sexual function, (3) sexual problems related to LUTS are not necessarily limited to ED, (4) there is an increasing pool of affected men given the age demographics in various countries, and (5) knowing this relationship and the mechanism therein may open new avenues for the treatment of sexual dysfunction, ED, and LUTS.

An interesting and early investigation of the relationship between LUTS and ED was done using a community-based survey in France [4]. In this sentinel study, approximately 2000 men aged 50–80 yr underwent a questionnaire-based evaluation of sexual health and LUTS, in which sexual satisfaction negatively correlated with an increasing age and LUTS. Additionally, urinary symptoms adversely affected the general sense of well-being and self-esteem (such as the perception of sexual life satisfaction). The relative risk of ED stratified by International Prostate Symptom Score (IPPS) ranged from a 0 (at a relative risk of 1) to a 3.3-fold increase in a relative risk of symptom scores >19. These and subsequent important epidemiologic studies have consistently supported the relationship between ED and LUTS. This consistent relationship suggests that ED is a worthwhile symptom to query in patients who present with LUTS and vice versa.

1. How can ED and LUTS/BPH be related?

The relationship between LUTS and ED has received increased attention recently because both of these diseases are prevalent, frequently coassociated in ageing men and affecting the quality of life. If this relationship exists, what are the potential pathophysiologic mechanisms making this relationship more than a mere association? What are the potential mechanisms for this causal relationship? The theories below are listed in no particular order:

1.1. NOS/NO levels decreased in the prostate and penile smooth muscle

This hypothesis attempts to explain the link by a proposed reduced production of nitrinergic innervation and nitric oxide synthase (NOS)/nitric oxide (NO) in the pelvis, including both the penis and prostate. It is known that NOS/NO production in the prostate is reduced in BPH (transition zone) when compared to normal prostate tissue. This theory closely follows that which explains the molecular mechanism of ED and links these two diseases into a single unifying concept. It logically follows that prostate tissue levels of NOS/NO are reduced in BPH progression, reducing prostatic tone relaxation. This proposed reduction in NOS isoforms results in an altered neurogenic influence on voiding function that is recognised as progressive BPH or LUTS. This theory is supported by limited evidence in which BPH tissue nicotinamide adenine dinucleotide phosphate staining and NOS immunohistochemistry show a qualitative decrease in the otherwise dense nitrinergic innervation of glandular epithelium, fibromuscular stroma, and blood vessels. Unlike the well-developed penile model, the role of NOS and its products are not well characterised in the prostate. This hypothesis is based on a limited number of studies that depend largely on immunohistochemistry. Although these data have several methodologic flaws, the concept does have a consistent appeal [5].

The NOS/NO theory is further supported by the characterisation and functional relevance of cyclic nucleotide PDE isoenzymes of the human prostate. The most common PDEs noted in prostate tissue were PDE type 4 and PDE type 5. The functional relevance of these PDE isoenzymes is noted in the relaxing effect of nonspecific PDE inhibitors (papaverine), as well as the effect of specific PDE inhibitors (sildenafil). Of more interest to this study is the recognition that Northern and RNA dot blots for PDE11A gene expression noted its presence in testes,

skeletal muscle, and the prostate. Type 11A protein abundance was greatest in prostate compared to other organs.

1.2. Effects of autonomic hyperactivity on LUTS, prostate growth, and ED

Our laboratory identified the relation of autonomic neural input to the prostate as providing an environment that induced rat prostatic growth; absence of this input results in regression of the gland [6]. These findings were supported by additional animal studies using a strain of spontaneously hypertensive rats that develop increased autonomic activity, prostate hyperplasia, and erectile dysfunction [7]. The improvement in erectile function after brief aggressive treatment may be related to improvement in structurally based vascular resistance within the penis and the decrease in responsiveness of α_1 -adrenoceptor-mediated electrolytic signalling. This putative explanation is attractive because it links established clinical physiologic findings of LUTS, BPH, and ED with an established basic science support. It remains unclear whether the increase in LUTS or ED is the result of a central increase in sensitivity to peripheral signals or a consequence of an alteration in the function of the bladder/penis itself that generates increased central activation. The various animal models suggesting a role between autonomic nervous system (ANS) overactivity and increased prostate growth is further supported by epidemiologic investigations linking the clinical diagnosis of BPH with increased autonomic tone [8]. Autonomic hyperactivity or increased ANS activity is significantly associated with the signs and symptoms of BPH. This has implications for understanding the pathophysiology of BPH, prostate growth, ED, and BPH progression. The ANS is known to be intimately involved in the mechanisms of voiding. We also described the quantitative relation between ANS tone and the subjective experience of dysfunctional voiding [9], suggesting the ANS acts as mediator that can modulate voiding symptoms or ED or both about their anatomically designated baseline, perhaps in part under the influence of central, mood-related factors. Similarly, autonomic hyperactivity or increased sympathetic tone is a known regulator of smooth muscle relaxation and penile reactivity.

1.3. Pelvic ischaemia as a mechanism for LUTS and ED

An additional theory relating both ED and LUTS is diffuse atherosclerosis of prostate, penis, and bladder [10]. Major risks for this include hypertension,

smoking, hypercholesterolaemia and diabetes, all which similarly affect ED. Animal models mimicking pelvic ischaemia and hypercholesterolaemia show a striking similarity in the smooth muscle alterations of the detrusor and corporal smooth muscle. There are several potential mechanisms for this, including hypoxia induced overexpression of transforming growth factor- β 1 and altered prostanoid production. Understanding how this could adversely affect penile smooth muscle function is consistent with our current understanding of the penile pro-erectile response. The relevant mechanism explaining the bladder effects may be very similar with an associated bladder ischaemia (bladder outlet obstruction or pelvic vascular disease), inducing the same smooth muscle loss with replacement of collagen deposition and fibrosis as well as loss of compliance, hyperactivity, and impaired contractility.

2. PDE5 inhibitors affect LUTS

Several studies have attempted to assess the relationship between ED and LUTS by treating one symptom (ED) and measuring the impact of the other disease (LUTS). The concept that PDE5 inhibitors could be used to improve LUTS is provocative. Investigators treating patients with both ED and LUTS using sildenafil noted a lower IPSS following treatment. Those with a lower IPSS at baseline have had a better response to ED therapy. Recently, McVary et al. reported on the impact of nightly sildenafil to improve LUTS in men with both this and ED (compared to placebo) using a once-a-day dosing of sildenafil 100 mg, improving ED and LUTS secondary to BPH as measured by improvement in the International Index of Erectile Function (IIEFF) score and IPSS ($p < 0.001$) [2]. The magnitude of the IPSS improvement observed in this study appears comparable to that achieved with α -blockers and 5 α -reductase inhibitors. A recent abstract presentation at the Annual Meeting of the European Urologic Association (Paris, April 2006) reported on the efficacy of daily tadalafil on IPSS in men with LUTS, revealing IPSS decreased by 3.8 points after patients were titrated from 5 to 20 mg of daily tadalafil (-1.7 placebo); from the start of the 4-wk run in-phase IPSS decreased 7.1 for tadalafil and 4.5 for placebo [3].

In the tadalafil study, 5 mg and 20 mg significantly improved erectile function (IIEF-EF domain) scores and improved LUTS (IPSS) for sexually active men with both LUTS and ED. Significant correlations between change from baseline values for IPSS and IIEF-EF domain in this subset of patients were not

observed after tadalafil. This suggests that LUTS improvement is unlikely to be explained solely by erectile function improvement. A similar finding was noted in the placebo-controlled sildenafil study quoted above.

A consistent finding of both the sildenafil and tadalafil for LUTS trials was a clear improvement in urinary symptoms with a lack of improvement in flow rate between treated and placebo groups. This surprising finding may shed light on a potential new basic pathophysiology paradigm in which the impact of PDE5 activity on LUTS symptoms may reveal an alternate explanation for the etiology of LUTS not involving relaxation of prostatic smooth muscle. Likely avenues for exploration include bladder compliance changes, improvement in bladder wall perfusion, or central nervous system impact. Again, PDE pathway exploration is likely to offer an increased number of avenues for basic and translational science investigation. This new basic pathophysiology paradigm needed to explain the etiology of LUTS and the potential of PDE5 inhibitors in the treatment of it suggest that LUTS may be a bladder-neck issue or the result of some other anatomic abnormality, bladder relaxation, central effect, or the result of some other biologic mechanism.

In summary, our urologic world will continue to be challenged as the physiologic and regulatory role of PDEs are explored and manipulated.

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