Review – Voiding Dysfunction

The Detrusor Muscle: An Innocent Victim of Bladder Outlet Obstruction

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Abstract

Objectives: Benign prostatic hyperplasia (BPH) is considered a frequent cause of bladder outlet obstruction (BOO) and lower urinary tract symptoms (LUTS), although the physiopathologic mechanism through which BPH causes LUTS is not clear. Several morphologic and functional modifications of the bladder detrusor have been described in patients with BPH and could play a direct role in determining symptoms. The opinion is spreading that the enlarged prostates in patients with LUTS is nothing more than a mere bystander. Evidence has accumulated, however, supporting the role of BPH-related BOO as the direct cause determining bladder dysfunction and indirectly causing urinary symptoms. The present review addresses the bladder response to BOO, particularly focusing on the physiopathologic cascade that links obstructive BPH to bladder dysfunction.

Methods: A literature review of peer-reviewed articles has been performed, including both in vivo and in vitro studies on human tissue and animal model experiments.

Results: Epithelial and smooth muscle cells in the bladder wall are mechanosensitive, and in response to mechanical stretch stress caused by BOO, undergo modifications of gene expression and protein synthesis. This process involves several transduction mechanisms and finally alter the ultrastructure and physiology of cell membranes, cytoskeleton, contractile proteins, mitochondria, extracellular matrix, and neuronal networks.

Conclusions: BOO is the initiator of a physiopathologic cascade leading to deep changing of bladder structure and function. Before being a direct cause of storing-phase urinary symptoms, the bladder is the first innocent victim of prostatic obstruction.

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1. **Introduction**

Benign prostatic hyperplasia (BPH) is a common disease in older men and is often associated with prostate gland enlargement (BPE) and lower urinary tract symptoms (LUTS) [1,2]. Bladder outlet obstruction (BOO) has long been considered the key factor in the mechanism through which BPH causes urinary symptoms [3,4], and the relief of obstruction is the traditional aim of most therapies designed to improve urinary symptoms in BPH. However, both storing- and voiding-phase symptoms do not consistently correlate with most parameters used for objectively evaluating BOO in patients with BPH, such as ultrasound-estimated prostate weight [5,6] and free urine flow and postvoid residual urine [2,7], and many patients undergoing obstruction relief procedures, such as prostatectomy, still report persistent storage symptoms [8–13]. Furthermore, how obstruction can determine storing-phase symptoms is still to be clarified.

In recent years, in the attempt to cast some light on the pathogenesis of LUTS, many investigators have progressively turned their attention to bladder abnormalities. Indeed, currently several studies support a major role for detrusor muscle alterations in determining LUTS. Consequently, the opinion has spread that the prostate, far from being responsible for the symptoms, is “often merely an innocent bystander” [14] and should be exonerated from always being the first suspect for “crimes against the micturition.”

However, if, on one hand, morphologic and functional abnormalities of the bladder detrusor are frequent in patients affected with BPH and can possibly have a more direct role in determining LUTS, on the other hand, studies conducted in men or in animal models of partial BOO show that such detrusor abnormalities can be regarded as a consequence of BOO [15–21]. According to this growing body of evidence, the role of prostatic obstruction in the mechanism causing LUTS remains crucial and the alterations of bladder detrusor muscle are nothing more than important steps in the BOO-initiated physiopathology cascade of events, ultimately leading to urinary tract symptoms.

2. **Methods**

This review focuses on the consequences of BOO on bladder detrusor muscle, particularly addressing the physical and molecular mechanisms that are suspected to couple obstruction and histologic alteration of the bladder wall. We searched for articles about histologic and molecular aspects of BOO using Medline and the Cochrane Library, with the key words “bladder outlet obstruction, detrusor hypertrophy, mechanical stretch strain, gene expression, transduction mechanism.” The PubMed function “related articles,” based on a word-related mathematical search algorithm has also been used. The research has been preliminarily limited from 1990 to 2005, and about 70 manuscripts have been selected for their relevance to the subject of the review. A few older original manuscripts have been further included in the review because they were referred to as fundamental in more recent studies.

3. **Bladder response to BOO**

BOO can be caused by urethral strictures, congenital malformations such as posterior urethral valves, and, more commonly, BPH. Nonetheless, however it is produced, BOO leads to several structural and functional changes in the detrusor muscle, regarded in part as a positive compensatory response aimed to overcome the resistance to bladder emptying. Bladder hypertrophy is a consistent consequence of infravesical obstruction in animal models and men [22,23] and causes an increase of thickness and weight of the bladder wall. Although bladder wall thickness (BWT) is known to increase with age also in asymptomatic individuals, an increased BWT has been associated with LUTS and BOO, and the degree of thickness seems to depend on the severity of obstruction [24,25]. Also the ultrasound-estimated-bladder weight (UEBW) correlates significantly with obstruction in patients with symptomatic BPH [26]. The cause-and-effect relationship between BOO and BWT/UEBW is also confirmed by the finding of a significant reduction of both BWT and UEBW after surgical relief of obstruction [27,28].

Qualitative and quantitative modifications in the ultrastructural pattern of the hypertrophic detrusor muscle have been reported, showing how hypertrophy results from both smooth muscle cells (SMCs) and extracellular matrix modifications, the latter consisting mainly in an increased amount of collagen [29–32]. Changes in the neuronal control of the bladder seem also to be implied. BOO has a neurotrophic effect on bladder detrusor muscle, and a hypertrophy of bladder neurons is described both in animals and men, which facilitates the micturitional reflex [49,53]. After BOO, unmymelinated C fibres, normally “silent” during the physiologic voiding mechanism, activate in new neuronal pathways, which could cause irritative urinary symptoms and detrusor overactivity. Consequently, desensitisisation of bladder C fibres has been shown to palliate LUTS in patients with BPH, producing a durable improvement in the
Internation Prostate Symptom Score and the quality-of-life score [33].

At a molecular level, BOO seems to have a deep impact on SMCs involving membrane and cytoskeleton proteins, ion channels, mitochondrial structure and function, several growth factors, and enzyme activity [15,34–37]. Bladder urothelium, too, is highly sensitive to obstruction. Epithelial cells lining the bladder lumen have been shown to increase their permeability to sodium ions and to produce adenosine triphosphate (ATP) and other mediators, contributing to the increased bladder afferent activity secondary to outlet obstruction [38,39]. Unfortunately, the role of interstitial cells is still largely obscure, both in the normal and hypertrophic bladder. They are organised in a subepithelial network, very rich in gap junctions, that probably work as a functional syncytium [40]. After integrating stimuli from urothelium and SMCs, interstitial cells may modify the threshold for bladder activation by excitatory (ATP, prostaglandins) or inhibitory (nitric oxide [NO]) stimuli, thus regulating the micturitional reflex.

However, despite increasingly numerous studies, current knowledge on the pathophysiologic mechanisms by which BOO can lead to such a number of complex and clinically relevant modifications of detrusor is still largely incomplete. Therefore, only an interrupted line can be traced between BOO and its several final effects on the different component of detrusor muscle.

4. BOO causes detrusor alterations through modification of gene expression and protein synthesis

BOO is defined as a high-pressure/low-flow micturitional pattern. In patients with BOO, the bladder wall faces increased mechanical tension during voiding compared to that in healthy controls. This BOO-derived mechanical stretch stress has been investigated as a possible trigger for both structural hypertrophy and functional alterations reported in the detrusor muscle after obstruction. In vivo animal models and in vitro models of mechanical stretch stress, where bladder SMCs are cultured on a deformable membrane, have both been used to demonstrate that the mechanical stretch stresses modify gene expression and transcription in SMCs and epithelial cells, as well as in mitochondrial DNA, deregulating the synthesis of many proteins and enzymes, including contractile cytoskeleton proteins, growth factors, and proteins regulating extracellular matrix deposition.

4.1. Cytoskeleton and contractile proteins

In SMCs from rat hypertrophic urinary bladder after partial urethral obstruction, increased desmin-actin and filamin-actin ratios were observed [35]. In the same experiment an increase of the actin-myosin ratio was also reported due to a reduction of myosin concentration and a relative decrease of the SM2 myosin heavy-chain isoform. All of these alterations were reversible after removal of obstruction. These findings were partially confirmed in men affected with prostatic obstruction, where the actin-myosin and desmin-actin ratios were significantly higher compared to nonobstructed controls [35,41].

Furthermore, in response to partial BOO, not only the relative amount of myosin is changed, but also the composition of the isoforms is altered. The smooth muscle myosin heavy-chain isoform SM-B and essential light-chain isoform LC17α, in nonobstructed rabbits, account for 100% of the total, whereas after partial urethral ligation, the resulting dysfunctional bladders presented as much as 75% SM-A and 40% LC17β [42]. These isoforms proved to be associated with decreased maximum velocity of shortening, decreased void volume, and increased voiding frequency. However, the composition of the isoforms moved back to normal after removal of obstruction, thus confirming the cause-and-effect relationship. Interestingly, after experimentally induced partial outlet obstruction, the rabbit detrusor exhibits a regional variation of myosin isoforms that correlates with regional differences of contractile activity [43]. Incidentally, in the obstructed hypertrophic rat bladder, it has also been observed through immunohistochemistry techniques a transient increase of myosin heavy-chain B (NM-MHC-B, also denoted as the embryonic smooth muscle myosin heavy chain [SMemb]), a nonmuscular myosin form localised in the interstitium surrounding smooth muscle bundles, in the subserosal and submucosal layers [44]. NM-MHC-B is not synthesised in SMCs and is thought to be produced by a nonmuscle cell in response to stretch stress. This nonmuscular myosin may have a role in the production of extracellular matrix and growth factors or be involved in modulation of spontaneous contractile activity. Recently, attention has focused on the thin filament-associated proteins caldesmon, tropomyosin (Tm), and calponin (CaP). In a rabbit model of partial BOO, an enhanced expression of CaP, α-isof orm of tropomyosyn, β-actin (nonmuscular),
and γ-actin has been shown, supporting an important role of these proteins in the bladder response to obstruction [45].

Animal models of partial BOO have provided the possibility of showing, in a very controlled and reproducible setting, that bladder hypertrophy is not always successful in compensating the micturition pattern and that the same procedure of partial ligation of the urethra can unpredictably result either in compensatory hypertrophy or in bladder decompensation, characterised with higher bladder mass weight, micturitional pressure, urinary frequency, and postvoid residual urine [46]. An altered regulation of contractile proteins is hypothesised to be responsible for the decompensation of detrusor muscle secondary to obstruction. Caldesmon is an actin-associated protein expressed as two dominant isoforms: h-CaD, expressed in SMCs, and l-CaD, diffusely expressed in nonmuscle cells of various tissue types [47]. Bladder obstruction in rabbits causes an increased expression of both caldesmon isoforms h-CaD and l-CaD. Compensated bladders show increased expression of both l-CaD and h-CaD, whereas decompensated bladders show overexpression of l-CaD but very little change in h-CaD as compared to controls. Therefore, the h-CaD/l-CaD ratio has been proposed as a marker for the status of detrusor muscle remodelling and dysfunction [47].

4.2. Growth factors and cyclooxygenase 2

In vitro studies on detrusor SMCs have shown that mechanical stretch stress can increase the expression of several growth factors, including basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), heparin-binding EGF-like growth factor (HB-EGF), insulin-like growth factor 1 (IGF-1), nerve growth factor (NGF), cysteine-rich protein (Cyr61), and connective tissue growth factor (CTGF), whereas transforming growth factor β (TGF-β) expression decreases [48–51].

BOO-induced growth factors regulate bladder remodelling by different ways, in a very complex network of reciprocal intermodulation. HB-EGF is a powerful stimulator of SMC proliferation [52] and is a strong candidate mediator of SMC hyperplasia in the urinary tract after obstruction.

The increased expression of NGF is reputed to be a key factor in the neuronal hypertrophy observed in hypertrophic detrusor and described after partial urethral ligation in rats [49,53].

The mRNA levels of Cyr61 correlate well with the increased bladder weight observed after urethral obstruction, whereas CTGF overexpression has been associated with an increase of type I collagen mRNA [51]. TGF-β has been shown to inhibit proliferation and induce differentiation of SMCs, and its down-regulation in obstructed detrusor is consistent with a pro-hypertrophy effect of BOO [54].

Mechanical stretch in the bladder also enhances the expression of cyclooxygenase 2 (COX-2), the inducible isoform of cyclooxygenase [55]. COX-2 participates at the bladder response to obstruction by increasing the production of prostaglandin E2 (PGE2), enabling the stimulation of the micturitional reflex through PGE-sensitive C fibres [56]. Furthermore, COX-2 also works as a growth factor, stimulating both SMCs and fibroblast proliferation [57,58].

4.3. Mitochondria

Mitochondrial enzyme function has an important role in the energy production and contractility of detrusor muscle [59]. Ultrastructural and functional impairment of mitochondria have long been described as characteristic features in BOO-derived detrusor alteration [29,59,60], and more recently the swelling and structural destruction of detrusor mitochondria have been shown to increase with severity of the partial outlet obstruction in men [18]. The negative impact of BOO on SMC mitochondrial function and energy metabolism could be mediated by ischemic suffering due to BOO and detrusor hypertrophy [18,61]. BOO-induced ischaemia, in fact, causes increased oxidative stress in detrusor muscle, which leads to a significantly higher incidence and proportion of mitochondrial DNA deletions [17]. Currently, many investigators consider the mitochondrial alteration a crucial factor in the voiding dysfunction consequent to BOO and hypothesise that severe and irreversible mitochondrial damage, marked by disruption of outer membrane [62], could explain the frequent persistence of symptoms after removal of bladder obstruction in men.

4.4. Extracellular matrix and matrix metalloproteinases

Bladder hypertrophy implies an augmented extracellular matrix deposition, characterised by an increase in total collagen and a statistically significant increase of the type III/type I collagen ratio [63].

An accurate quantitative evaluation of collagen content of bladder detrusor in patients with BPE, BOO, and LUTS, performed by computer-assisted image analysis, showed a statistically higher collagen compared to nonobstructed asymptomatic men, with no overlap between the two groups [31]. Furthermore the collagen content was higher in...
more severely symptomatic patients [31]. In the bladder as in other organs, homeostasis of collagen in the extracellular space depends on the balance between collagen biosynthesis, regulated at a transcriptional and posttranscriptional level, and collagen proteolysis. However, in vitro models of fetal BOO and SMC mechanical strain have failed to show any significant impact of stretch stress on transcription of collagen types I and III [19,64]. This observation supports a major role of unregulated proteolytic balance in determining collagen accumulation. In the latter process, a family of zinc$^{2+}$ metalloenzymes, known as matrix metalloproteinas (MMPs), play a prominent role [65].

MMP-1 has been shown to be responsible for the proteolysis of collagen types I and III, whereas MMP-2 is active on collagen types I and IV and MMP-9 on collagen type IV [66]. These enzymes are regulated at the level of gene expression and converted from a latent to an active form through cleavage of an amino terminal domain. The activated form can still be controlled by metal chelators and tissue inhibitors of metalloproteinas (TIMPs). Exposing detrusor SMCs to a sustained hydrostatic pressure of 20 to 40 cm H$_2$O, a time-dependent decrease of MMP-1, MMP-2, and MMP-9 activity and an increase of TIMP-1 levels have been observed [19].

According to such data, rather than being caused by an increased collagen synthesis, collagen accumulation in the extracellular matrix of obstructed detrusor would be consequent to a combined down-regulation of MMPs and up-regulation of TIMP-1, with results showing a net impairment of collagen proteolysis.

4.5. Epithelial cells

Epithelial cells lining the bladder lumen play an important role in the bladder response to mechanical stretch stress and are involved in the increase of bladder afferent activity observed in detrusor overactivity secondary to BOO. Epithelial cells have been described releasing a series of excitatory and inhibitory mediators, including ATP and NO, in response to mechanical stretch stress [67]. This way, urothelium acts as a mechanosensor that, in response to bladder distention, modifies the threshold for micturitional reflex, thus initiating or depressing activation of the bladder [39]. However, little is known about the molecular mechanism by which BOO increases afferent neural activity. Interestingly, mammalian bladder epithelial cells are featured with mechanosensitive epithelial sodium channels (ENaCs), which open in response to mechanical stretch stimuli [68,69]. These receptors are thought to transduce the mechanical stress signal leading to activation of bladder function after BOO. Overexpression of ENaCs has been demonstrated in the urothelial cells of patients with BOO and BPH [38]. This higher density of ENaCs after obstruction could increase the sensory excitability of detrusor, either releasing excitatory mediators (ATP) or changing the ionic environment around subepithelial sensory nerve terminals by increasing Na$^+$ passage through the epithelium.

5. Mechanotransduction pathways

How mechanosensitive cells sense and transduce the extracellular mechanical signals into the cell nucleus resulting in quantitative and qualitative changes in gene expression is an interesting and important research field. The process through which mechanical stress is converted to biochemical intracellular and intranuclear signals is termed “mechanotransduction.” In the bladder, both epithelial cells and SMCs seem to be sensitive to mechanical stress, thus contributing to the morphologic and functional changing of bladder wall after outlet obstruction. It has been demonstrated that mechanical stress rapidly induces phosphorylation of the platelet-derived growth factor (PDGF) receptor, activation of integrin receptor, stretch-activated cation channels, and G proteins, which might serve as mechanosensors [70]. Once perceived by the cell, mechanical stimuli usually activate a signal transduction pathway that eventually induces gene expression and protein synthesis. At least 10 transcription factors have been shown to correlate with the stretch-induced gene expression profile (Table 1). Of these, c-Jun, cyclic adenosine monophosphate (cAMP) response element binding protein 1 (CRE-BP1, also known as ATF-2), activator protein 1 (AP-1), and neurofibromin 1 (NF-1) are the most significant [71].

5.1. c-jun NH2-terminal kinase (JNK) and transcription factor AP-1

Deriving information from studies on cardiac myocytes [72], where signal transduction has been extensively investigated, the hypothesis has been raised that mechanical stretch stimulus in bladder could be transduced by mitogen-activated protein kinases (MAPKs). The MAPK family consists of three different subsets, namely (1) c-jun NH2-terminal kinase (JNK), (2) p38, and (3) extracellular signal-regulated kinase. In the in vitro models of
detrusor SMCs, MAPKs have shown activation in response to sustained or cyclic stretch stress [73]. Of the three subsets of MAPK proteins, JNK showed maximum activation, whereas activation of p38 was very weak and extracellular signal-regulated kinase did not show any activation. Evidence is also available suggesting that activation of MAPKs is initiated by stretch-activated ion channels (SACs) that open in response to mechanical stimulation and increase the intracellular content of Ca^{2+}, thus activating JNK [73].

It is known that JNK activation causes phosphorylation of c-jun, which is a component of the transcription factor AP-1. As a matter of fact, it has been shown that AP-1 mediates the transcription of HB-EGF in SMCs in response to mechanical stress [74]. More recently, in primary culture human bladder SMCs subjected to repetitive mechanical stimulation, oligonucleotide arrays and real-time reverse transcription-polymerase chain reaction identified 14 stretch-sensitive genes [71]. Apart from fibroblast growth factor 9 (FGF-9), which was downregulated by mechanical stress, the other 13 genes increased their expression. In 10 cases the increase was statistically significant: HB-EGF; bone morphogenetic protein 2 (BMP-2); soluble urokinase plasminogen activator receptor (SUPAR); thrombomodulin (THBD); COX-2; guanosine triphosphate (GTP)-binding protein overexpressed in skeletal muscle (GEM); leukemia inhibitory factor (LIF); dual specificity phosphatase 1 (DUSP-1); elongation factor, RNA polymerase II, 2 (ELL-2); and protease-activated receptor 2 (PAR-2). Nine of these genes present an AP-1–binding site.

AP-1 has also been involved in MMP-1 function because the MMP-1 gene contains a binding domain for AP-1 and the AP-1 inhibitor curcumin abolishes the MMP-1 overexpression consequent to mechanical stretch stress [74]. Data currently available, then, strongly support a role for the JNK/AP-1 pathway as a transduction mechanism in the BOO-derived stretch stress signal.

### 5.2. Protein kinase C

Protein kinase C (PKC) is an important second messenger system, which is translocated from the cytosol to the cell membrane on cell stimulation [75]. The PKC family of serine/threonine kinases consists of at least 11 mammalian isoforms, which show slight differences in their molecular structure and enzymatic properties. PKC isoforms are involved in a wide variety of intracellular signalling events and play an important role in tumour promotion and cell growth control in general.

Membrane-bound PKC undergoes conformational changes in response to mechanical stretch stress. The stress-activated conformation of PKC initiates a downstream signalling cascade, leading to the regulation of nuclear events, either promoting or inhibiting cell growth. Recent work has shown that PKC isoforms can act either in the cytoplasm, and cause nuclear effects indirectly by triggering signalling pathways directed towards the cell nucleus, or, after translocation and activation, can themselves act in the cell nucleus [76]. PKC has been shown to activate after mechanical stretch stress in bladder SMCs, and has been particularly related to NGF overexpression [77].

### Table 1 – Transcriptional factors identified in primary culture human bladder smooth muscle cells subjected to repetitive mechanical stimulation for 4 h

<table>
<thead>
<tr>
<th>Accession no.</th>
<th>Name</th>
<th>No. of genes regulated</th>
<th>Significance (p)</th>
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</thead>
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<td>c-jun</td>
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<td>0.011</td>
</tr>
<tr>
<td>P15336</td>
<td>CRE-BP1</td>
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<tr>
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<td>AP-1</td>
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<tr>
<td>P10275</td>
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<td>0.053</td>
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</table>

Frequency of transcription factor binding sites in the promoters of genes identified as differentially expressed by microarray analysis. Transcription factors listed are those that achieved statistical significance. AP-1 = activator protein-1; CRE-BP1 = cyclic adenosine monophosphate response element binding protein-1; NF-1 = neurofibromin-1; AhR:ARNT = dimer of aryl hydrocarbon receptor precursor and AhR nuclear translocator; ER-α, estrogen receptor-α; USF = upstream stimulatory factor; ATBF1-A, AT-binding transcription factor 1, isoform A; DBP = D-site binding protein; AR = androgen receptor. Reproduced with permission from Adam et al. [71].
5.3. Angiotensin II

Angiotensin is considered an important mediator of gene expression in SMCs after mechanical stretch [78,79]. Angiotensin II is released by bladder SMCs in response to stretch stress, and induces overexpression of HB-EGF [50].

Fig. 1 – Mechanical stretch stress activates bladder wall mechanosensors, which activate intracellular transduction pathways leading to modify gene expression. BOO = bladder outlet obstruction; PDGF-R = platelet-derived growth factor receptor; JNK = c-jun NH2-terminal kinase; AP-1 = transcription factor activator protein-1; AT2 = angiotensin 2; AT1 = angiotensin receptor 1; PKC = protein kinase C; HB-EGF = heparin-binding epidermal growth factor; BMP-2 = bone morphogenetic protein 2; SUPAR = soluble urokinase plasminogen activator receptor; THBD = thrombomodulin; COX-2 = cyclooxygenase 2; GEM = guanosine triphosphate-binding protein overexpressed in skeletal muscle; LIF = leukemia inhibitory factor; DUSP-1 = dual specificity phosphatase 1; ELL-2 = elongation factor; PAR2 = protease-activated receptor 2; NGF = nerve growth factor.
HB-EGF gene expression was significantly suppressed in the presence of losartan, an angiotensin receptor 1 (AT1) antagonist, but was not affected by PD-123319, an AT2 receptor inhibitor. These data would support an autocrine angiotensin II-AT1-mediated modulation of gene expression in SMCs subjected to mechanical stretch stress, which would cooperate with the MAPK transduction mechanism in the modulation of possibly common target as HB-EGF genes.

6. Conclusions

BOO is perceived by the bladder wall as a mechanical stress, which activates stretch-inducible signals leading to important morphologic and functional modifications in the epithelium, in the SMCs, in the extracellular matrix, and in the neuronal network. Molecular mechanisms supporting this complex process are currently being investigated, and only an incomplete and questionable model can be traced. However, strong evidence is available that both epithelial cells and SMCs are featured with mechanosensitive systems and are able to change gene expression and protein synthesis in response to obstruction, through several transduction signals (Fig. 1). The latter include mainly JNK/AP-1 pathway, PKC, and autocrine angiotensin II stimulation loop.

Therefore, although urinary storage-phase symptoms can be more easily and directly linked to bladder detrusor modifications than to prostatic obstruction, in patients with BPH, the BOO is the first initator of a cascade of events ultimately leading to LUTS, in which the bladder participates essentially as the earliest innocent victim.

References


