



Collaborative Review – Voiding Dysfunction

A Refocus on the Bladder as the Originator of Storage Lower Urinary Tract Symptoms: A Systematic Review of the Latest Literature

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Abstract

Context: The focus of clinical understanding and management of male storage lower urinary tract symptoms (LUTS) has shifted from the prostate to the bladder. This is mirrored by an increasing body of experimental evidence suggesting that the bladder is *the* central organ in the pathogenesis of LUTS.

Objective: A systematic review of the literature available on pathophysiologic aspects of storage LUTS.

Evidence acquisition: Medline was searched for the period ending December 2008 for studies on human and animal tissue exploring possible functional and structural alterations underlying bladder dysfunction. Further studies were chosen on the basis of manual searches of reference lists and review papers.

Evidence synthesis: Numerous recent publications on LUTS pathophysiology were identified. They were grouped into studies exploring abnormalities on urothelial/suburothelial, muscular, or central levels.

Conclusions: Studies revealed both structural and functional alterations in bladders from patients with LUTS symptoms or animals with experimentally induced bladder dysfunction. In particular, the urothelium and the suburothelial space, containing afferent nerve fibres and interstitial cells, have been found to form a functional unit that is essential in the process of bladder function. Various imbalances within this suburothelial complex have been identified as significant contributors to the generation of storage LUTS, along with potential abnormalities of central function.

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1. Introduction

In 2009, we now recognise that lower urinary tract symptoms (LUTS) do not reliably reflect the underlying vesicourethral pathology; hence, the bladder is sometimes referred to as an “unreliable witness.” The term *LUTS* encompasses three groups of symptoms: voiding (slow stream, splitting or spraying, intermittency, hesitancy, straining, terminal dribble), postmicturition (sensation of incomplete emptying, postmicturition dribble), and storage. These symptoms are often described by the term *overactive bladder* (OAB): urinary frequency, nocturia, urgency, and urgency urinary incontinence [1].

Voiding symptoms have been reported to be the most common LUTS in men. However, women also commonly present with voiding symptoms [2,3].

Likewise, storage symptoms are not sex specific but increase in an age-related fashion and are prevalent in both male and female patients. Indeed, there is a similar distribution of both storage and voiding symptoms [4]. This paradigm shift in our clinical understanding and evaluation of LUTS [5–7] is mirrored by an increasing body of experimental evidence suggesting that the bladder has to be considered *the* central organ in the pathogenesis of LUTS.

2. Evidence acquisition

Medline was searched using the terms *overactive bladder*, *detrusor overactivity*, *lower urinary tract symptoms*, *pathophysiology*, and *ageing bladder* for dates up to December 2008. Further studies were chosen on the basis of manual searches of reference lists and review papers and from meetings of the International Continence Society, the European Association of Urology, and the American Urological Association. This approach was chosen because previous work has shown that manual search improves the database search.

3. Evidence synthesis

Whereas voiding symptoms are only poorly correlated with bladder outlet obstruction (BOO), storage symptoms have a closer association with underlying detrusor overactivity (DO) [5]. To date, three theories, each of which probably contributes in varying proportion to the complex mechanisms underlying the genesis of DO and the associated storage symptoms composing OAB, have been put forward:

- The *urothelium-based* hypothesis: Changes in urothelial receptor function and neurotransmitter release as well as in the sensitivity and coupling of the suburothelial interstitial cell network lead to enhancement of involuntary contractions [8].
- The *myogenic* hypothesis: Changes to the excitability and coupling of smooth muscle cells with other myocytes or interstitial cells lead to the generation of uninhibited contractions [9,10].

- The *neurogenic* hypothesis: Reduced peripheral or central inhibition increases activation of the micturition reflex and involuntary bladder contractions [11]. Peripherally, neurologic diseases might cause a sensitisation of C fibres that are silent under normal circumstances, thereby leading to the emergence of a C-fibre-mediated reflex.

This paper provides an overview of the contemporary evidence base on the structural and functional changes in the bladder of patients suffering from storage LUTS.

3.1. Changes on the urothelial and suburothelial level

In contrast to the classical view of the urothelium as merely a passive barrier to ions and solutes, the urothelium has increasingly been recognised to have an important secretory function that allows it to undertake a neuromodulatory role. In support of this, both the urothelial metabolic rate and receptor density are higher than that of the detrusor [12]. The urothelium interacts closely with the underlying suburothelial layer, in particular the interstitial cell network contained within it, so that the whole structure can be regarded as a functional unit [8]. The urothelium is composed of three sublayers: a basal layer attached to the basement membrane, an intermediate layer, and an apical layer of large hexagonal cells referred to as umbrella cells. The suburothelium is an area composed of nerves, blood vessels, and connective tissue in intimate contact with the urothelium.

3.1.1. Urothelial sensory functions and changes in disease

Histologic studies have shown that urothelial cells themselves express sensory receptors typically found on primary afferent nerves. One example is the transient receptor potential cation channel subfamily vanilloid member 1 (TRPV1) [13,14]. TRPV1, a sensory receptor widely distributed throughout the body, is activated by heat and protons. Liu et al reported that urgency is associated with increased TRPV1 expression in the human bladder trigonal mucosa [15]. Several studies on TRPV1-null mice suggest a role for TRPV1 receptors both in inflammatory conditions [16] and during normal voiding function [17,18]. Bladder biopsies from patients with both idiopathic detrusor overactivity (IDO) [19] and neurogenic detrusor overactivity (NDO) [20] showed increased urothelial TRPV1 expression. The agents capsaicin and resiniferatoxin act on vanilloid receptors, thereby producing epithelial desensitisation by turning them less reactive to natural stimuli as well as neural degranulation and damage [21,22]. They have been shown to reduce urgency and bladder pain [23] along with urothelial TRPV1 immunoreactivity. Whether or not TRPV4, another member of the TRP receptor family that is expressed by the urothelium and has been shown to be involved in normal voiding behaviour, has a role in bladder dysfunction remains to be elucidated [24,25].

Both P2X and P2Y purinergic receptor subtypes have been identified in the bladder urothelium. It is now thought that these may respond to urothelial-derived adenosine triphosphate (ATP) release in autocrine and paracrine

signalling [26–31]. In patients with IDO and NDO as well as in patients with the bladder pain syndrome (BPS; painful bladder syndrome, interstitial cystitis), higher levels of urothelial P2X₂ and P2X₃ receptors have been detected [32,33]. After successful treatment, a reduced immunoreactivity correlated well with a reduction in urgency [34]. Auto- and paracrine mechanisms might further potentiate the enhancement of ATP release from uroepithelial cells in patients with chronic bladder disease. Interestingly, cats with a similar disease process (feline interstitial cystitis [FIC]) showed a downregulation of urothelial P2X and P2Y receptors [35]. However, Kim et al [36] reported a significant increase in P2X₃ receptor expression within the mucosa but not smooth muscle of rats with DO secondary to BOO. Cannabinoid CB 1 receptors have been found in the bladder urothelium. They were shown to be coexpressed with P2X₃ receptors in rodents, monkeys, and humans, supporting the hypothesis of an interaction between the cannabinoid and the purinergic systems in the transduction of sensory information in the urinary bladder. Further, the reduction of nerve activity induced by cannabinoid-receptor activation implicates CB 1 receptors in the peripheral modulation of bladder afferent information [37–39].

Urothelial cells express both α and β adrenoceptor subtypes, stimulation of which has been shown to trigger the release of ATP and nitric oxide (NO) [40–42]. Catecholamines could be released from nerves adjacent to the urothelium; however, neither a role for catecholamines nor an altered adrenoceptor profile has yet been shown in pathologic conditions.

The presence and localisation of muscarinic receptor protein and mRNA in the human [43–48] and mouse [49] urothelium have been studied. All five muscarinic subtypes are expressed throughout the urothelial layers with a specific localisation of the M₂ subtype to the umbrella cells and M₁ to the basal layer, with M₃ receptors more generally distributed. At therapeutic doses, antimuscarinics act mainly during the filling phase and exert little effect on detrusor contraction during emptying [50–52]. This lends support to the suggestion that urothelial M receptors might be involved in the generation of afferent impulses. Indeed, in a rat model with DO induced by BOO, immunoreactivity of M₂ and M₃ muscarinic receptors was greater in the urothelium of the BOO group than in the control group [36]. Accordingly, in a preclinical study in rats, detrusor overactivity was attenuated by intravesical instillation of antimuscarinic agents [53–55]. In contrast, a human study showed that M₃ but not M₂ muscarinic receptor mRNA expression was significantly less in urothelium from patients with IDO than from age-matched controls [56]. In cultured urothelial cells, blockade of urothelial muscarinic receptors with atropine inhibited stretch-induced ATP release [57], so it has been proposed that stretch-released acetylcholine (ACh) may act in a feedback mechanism to induce basolateral ATP release.

3.1.2. Urothelial secretory functions and changes in disease

ATP was the first neurotransmitter demonstrated to be released directly from the urothelium [58]. Basolateral,

nonvesicular ATP release [26,27,59–61] is evoked by chemical stimuli or by stretch proportional to the extent of bladder distension. By acting on structures such as nerves [62] and interstitial cells in the suburothelial space, it is thought to trigger the underlying afferent signalling bladder fullness and pain and possibly even to activate the micturition reflex [63]. It might also operate in an autocrine manner to enhance its own release from urothelial cells, a mechanism that has been suggested to be involved in the genesis of chronic bladder diseases [64]. A significant increase of urothelially released ATP has been reported from patients with painful bladder syndrome [64–67] or spinal cord injured rats [68] as well as from cats with FIC [57] and rats with chronic bladder inflammation [69]. Pathologically increased amounts of urothelially released ATP can be reduced on treatment with botulinum toxin [70]. Notably, ATP can potentiate the response to vanilloid stimulation by lowering the threshold for protons, capsaicin, and heat [71]. In turn, urothelial ATP release is elicited by stimulation of TRPV1 [18] and muscarinic and adrenergic receptors on urothelial cells [72].

The presence of several NO synthase isoforms (neuronal, endothelial, and inducible) within the urothelium [40,41,73] suggest that NO has a role in the control of bladder activity, presumably by inhibiting the activity of bladder afferent nerves. In support of that view, intravesical oxyhaemoglobin, a NO scavenger, results in bladder hyperactivity [74], and, consistently, intravesical application of NO donors suppresses bladder overactivity in animals treated with cyclophosphamide [75,76]. Further, there is a significant increase in baseline NO production in bladder urothelial strips in cats with FIC compared with that in healthy cats [77]. A study with 15 patients diagnosed with “classical interstitial cystitis” showed a statistically significant correlation between successful medical treatment and changes in luminal bladder NO concentration [78]. The release of NO from the urothelium is facilitated by cholinergic, adrenergic, and TRPV1 receptor stimulation [40,41].

Urothelial cells have further been shown to express ACh-synthesising enzymes such as choline acetyltransferase that release ACh following both mechanical and chemical stimulation through a nonvesicular mechanism, mediated by organic cation transporter type 3 [45,49,79,80]. It is known that the release of nonneuronal ACh increases with age, detrusor stretch, and oestrogen status [45,81,82]. Another animal study suggested the presence of a diffusible, urothelium-derived inhibitory factor, although it could not be identified [83].

3.1.3. Suburothelial afferent innervation and changes in disease

Immunohistochemistry has shown that many afferent nerve fibres are located in the lamina propria that label for receptors to urothelially released factors or contain sensory neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) [84]. Immunoreactivity is altered in conditions that result in bladder overactivity and normalised by agents designed to attenuate the condition [34,85–87]. The proximity of these afferent

nerves suggests they could interact with the urothelium to detect changes in bladder fullness. P2X₃ receptors have been identified as the purinergic receptor subtype on suburothelial afferents [61,88,89]. The inference is that P2X₃ receptors are involved in sensory activation during the filling phase, as concluded from studies of P2X₃-deficient mice who exhibited a reduced afferent firing and micturition reflex [62,89]. TRPV1 receptors on suburothelial afferents have a role in normal voiding function, as demonstrated by a decreased afferent activation during bladder filling in TRPV1-null mice [17]. These receptors also seem to be an essential component of purinergic signalling by the urothelium [18]. It is thought that both P2X₃ and TRPV1 receptors on suburothelial afferents play a key role in the pathogenesis of DO, in particular NDO and, to a lesser degree, IDO where there is increased TRPV1- and P2X₃-immunoreactive suburothelial innervation compared with controls [19,20,34]. Both intravesical instillation of resiniferatoxin [85,90] and intradetrusor injections of botulinum toxin A [34] in DO patients produced significant improvements in LUTS and urodynamic parameters [91,92] associated with a marked decrease of TRPV1 and P2X₃-immunoreactive fibres in clinical responders. TRPA1 is also expressed in C fibres and can be activated by hydrogen sulphide that is formed during infection: Activation results in bladder overactivity [93–95].

3.1.4. Suburothelial interstitial cell network and changes in disease

A network of interstitial cells in the lamina propria forms a functional syncytium through extensive connexin 43 (Cx43) gap junction coupling. It is postulated that either protons or local release of ATP from the urothelium generate depolarising Ca²⁺ waves that spread across the interstitial cell network. Furthermore, these interstitial cells are able to integrate focal signals from different regions of the bladder wall [96–100], in view of their close proximity to unmyelinated afferent nerves and the fact that their own activity is modulated by exogenous ATP (via P2Y receptors) and low pH [101–104].

Muscarinic M₂ and M₃ receptor labelling localised to suburothelial interstitial cells is increased in samples from idiopathic overactive bladders. An increase in M₂ receptor labelling is seen in samples from patients with BPS [46]. However, isolated interstitial cells do not respond to exogenous muscarinic receptor agonists by a rise of intracellular Ca²⁺, so the intracellular signalling mechanisms remain unknown [99]. Modulating the coupling strength between the cells would influence the intensity and/or travel distance of the signal within the syncytium, and consequently the number of afferent fibres stimulated. An animal study [105] in 2007 that established a link between increased gap junction expression in lamina propria interstitial cells and detrusor overactivity found three times higher suburothelial Cx43 immunoreactivity in rats with detrusor overactivity following spinal cord transection. Gap junction blockade reduced spontaneity, and it was concluded that spontaneous activity in the bladder requires gap junction upregulation in lamina propria interstitial cells. In a very recent study of >20

patients with NDO and IDO, increased gap junction formation in the suburothelial interstitial cell layer has been demonstrated compared with controls with no DO [106]. It was hypothesised that this change could have a significant role in the pathogenesis of the detrusor abnormality.

3.2. Changes at the muscular level

In the normal (stable) human bladder, ACh is the only neurotransmitter evoking contractions, whereas DO has been shown to be associated with atropine resistance, with ATP proposed as the principal additional activator [107–109]. One report has demonstrated a significant positive correlation of purinergic, and negative correlation of cholinergic, neurotransmission with age [110]. P2X₁ has been described as the purinergic receptor subtype present on human detrusor [29], although a very recent study infers a different route of purinergic activation [111]. However, the appearance of purinergic activity in the overactive bladder is not paralleled by major differences in P2X₁ immunoreactivity in smooth muscle [112]. Rather, P2X₁ receptor expression in human detrusor seems to be downregulated with age and overactivity [113], presumably to offset the increased amounts of neurally released ATP [110], although this is not a consistent observation [112]. The greater availability of ATP at the neuromuscular junction might be a result of a less effective breakdown in DO: Ectonucleotidase activity is decreased in detrusor samples from DO bladders [114], and pretreatment with the nonspecific ATPase apyrase reduces the strength of nerve-mediated contractions of muscle preparations from those bladders [115]. Moreover, the potency of the nonhydrolysable ATP analogue α , β -methylene ATP, which acts as an antagonist on purinergic receptors to elicit increases of intracellular Ca²⁺, was not different in cells from stable and overactive human bladders [116].

In the normal detrusor, M₂ receptors predominate over the M₃ subtype, and the latter mediates at least 95% of contractile activation [44]. This has raised the question as to whether M₂ receptors exert a more significant role in pathologic conditions (eg, in DO). In the rat model, hypertrophied as well as denervated—spontaneously active—bladders showed a shift in the muscarinic receptor subtype from M₃ toward M₂ [117] with different signal transduction mechanisms mediating the contractile response [118]. It was concluded that the M₂ receptor subtype can take over a contractile role when the M₃ subtype becomes inactivated by, for example, denervation or bladder hypertrophy [119], although this finding is not universal [120]. One possibility for this discrepancy is that M₂-dependent actions may derive from the urothelium [121,122], and this pathway becomes more significant in these pathologic conditions.

Prostaglandins are suggested to be involved in the pathophysiology of different bladder disorders, and enhanced prostaglandin E₂ (PGE₂) production has been reported in patients with DO. Accordingly, nonsteroidal antiinflammatory cyclooxygenase inhibitors that function

to reduce PGE2 production have been widely reported to be effective agents in models of DO. The PGE2 receptors EP3 and EP1 seem to have a role in the development of DO caused by PGE2. Taken together, these observations suggest that prostacyclin may have a facilitatory role in the micturition reflex by modulating the threshold for activation of capsaicin-sensitive and capsaicin-insensitive bladder sensory afferents [123–127].

Spontaneous activity can be recorded from isolated detrusor muscle strips in the organ bath, and several studies report an increase in tissue from overactive bladders. Contractions are resistant to neurotoxins but can be diminished by calcium channel blockers or potassium channel openers [128]. Such activity can be recorded in isolated cells, as spontaneous changes to membrane potential and intracellular Ca^{2+} , and the incidence of such activity is enhanced in cells isolated from overactive bladders (CH Fry, personal communication). Although upregulated activity may be present in isolated cells, it does not automatically account for increased spontaneity of the intact muscle preparation. Unlike other smooth muscle tissues, human detrusor does not show extensive coupling, thus presumably allowing the spontaneously active myocytes to adjust their length to volume change without synchronous activation that would elevate intravesical pressure. However, because detrusor smooth muscle cells were discovered to be electrically coupled via gap junctions, an increase of intercellular coupling has been postulated to play a role in generating OAB [129]. Gap junctions are composed of the Cx family of proteins. In human detrusor, expression of Cx45, the main intermuscular Cx, is actually less in samples from idiopathically overactive bladders, which is correlated with a higher gap junction resistance in such samples [130]. Other studies have suggested that a different Cx isoform, Cx43, forms gap junctions between muscle cells and have found the Cx43 expression to be upregulated in overactive bladders [131–133].

However, Cx43 labels interstitial cells in the detrusor layer. These cells are characterised by their labelling for the tyrosine-kinase receptor protein c-kit [134], as are the suburothelial equivalents, close apposition to muscle bundles and nerves [101], and the generation of spontaneous and carbachol-evoked calcium and electrical activity [135–138]. It is postulated that rather than initiate spontaneous activity in the detrusor syncytium, interstitial cells modulate its activity [139], possibly by coordinating activity in different muscle bundles. Several recent studies have suggested an involvement of detrusor interstitial cells in the generation of storage LUTS associated with DO. Biers et al [140] found c-kit-positive cells on the boundaries of muscle bundles in specimens from patients with IDO and NDO to be four and seven times higher than controls, respectively. In guinea pigs with bladder overactivity induced by BOO, Kubota et al [141] demonstrated a four times higher density of c-kit-positive cells. Several studies [22,131,132] have shown an overall increase of Cx43 transcript and protein in the overactive and/or obstructed rat bladder, however, without exact structural localisation. In support of this, c-kit receptor blockers had inhibitory

effects on guinea pig and overactive human detrusor, possibly via c-kit receptors on cells resembling bladder interstitial cells of Cajal [140].

3.3. Altered innervation in neurogenic disorders

Diseases and injuries of the central nervous system that affect neural control of micturition cause various patterns of bladder disturbance depending on the neural level affected (brain, spinal cord, or peripheral nervous system). In cats with spinal cord lesions and subsequent NDO, it is reported that DO is due to the emergence of C-fibre reflexes [11]. The reflex detrusor contractions seen in response to low-volume filling might result from alterations in the peripheral afferent receptors due to an increased release of neurotrophins such as nerve growth factor (NGF) in the spinal cord or bladder that lead to sensitisation of silent C fibres [11,142,143]. Moreover, activated C fibres may release neuropeptides inducing smooth muscle contraction and immunocompetent cell migration and neurogenic inflammation. Afferent neurons undergo both morphologic [144] and physiologic changes [145] following spinal cord injury. Production of neurotrophic factors increases in the bladder after spinal cord injury: Chronic intravesical NGF administration in rats induces bladder hyperactivity [146–148].

In the bladder, NDO is characterised by an increased expression of TRPV1 and P2X₃ receptors on suburothelial afferent nerves [20,34,85,90], by an augmented suburothelial immunoreactive for SP- and CGRP-positive nerves [84], as well as by an intensified electrical coupling of suburothelial interstitial cells [106]. However, some [149,150] argue it is unlikely that abnormal DO responses to bladder filling can be accounted for simply by increased bladder afferent activity. Functional magnetic resonance imaging of the brain in subjects with poor bladder control shows responses that differ from controls. Responses are relatively small at low bladder volumes (with mild sensation) but become exaggerated (with strong sensation) above a certain volume threshold, even when there is no actual DO. Taken together, either the nature of the afferent signals or the handling of these signals in the brain is abnormal.

3.4. Ageing bladder

The increasing prevalence of OAB and urgency urinary continence in the elderly [2,151,152] is mirrored by clinical data showing decreased bladder capacity and increased nonvoiding contractions of the detrusor. However, the underlying pathophysiology of age-related bladder dysfunction is much less clear. Elbadawi et al could demonstrate that although the gross morphology remains unchanged with age, the detrusor is partially denervated [153], an observation that has also been made in overactive bladders [9]. However, the contractile machinery appears intact in the aged bladder. Animal studies have shown that atherosclerosis-induced chronic ischaemia leads to fibrosis, smooth muscle atrophy, and noncompliance, possibly by

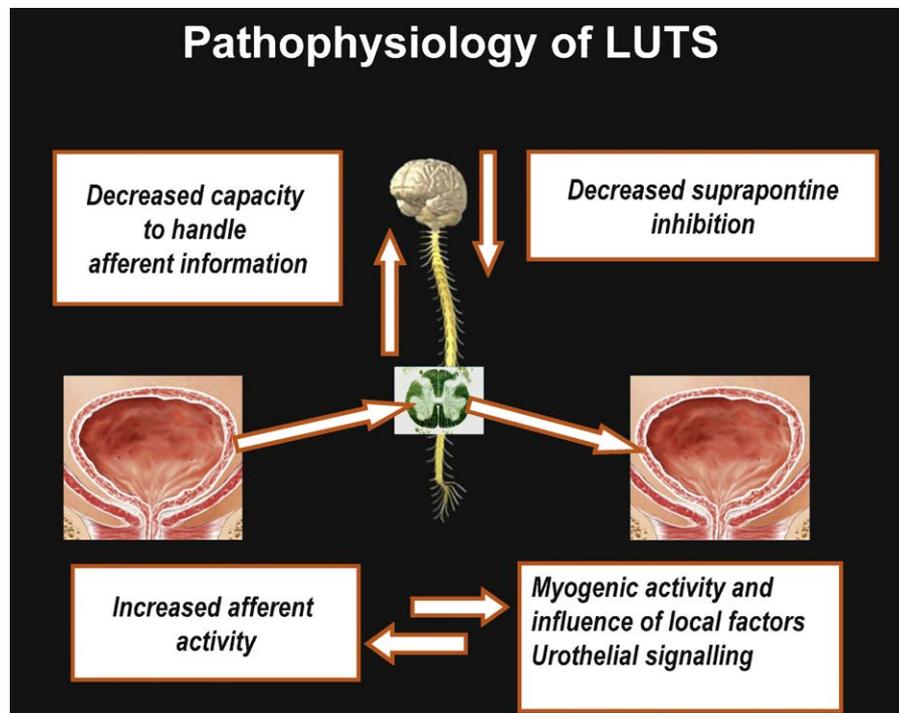


Fig. 1 – Various central and peripheral pathophysiologies in the development of detrusor overactivity. LUTS = lower urinary tract symptoms.

increasing transforming growth factor- β 1 expression in the bladder. Further, arterial insufficiency was associated with DO and increased smooth muscle contractility, and it has been postulated that ischaemia-induced structural damage in the urothelium and possible chronic exposure of the underlying tissue and nerves to the urine may play a role in this process. These studies suggest that arterial insufficiency and hypercholesterolemia, common ageing-associated disorders, may play important roles in the pathophysiology of voiding dysfunction in the elderly [154,155]. However, animal studies have not been particularly helpful due to differences between species and strains [156]. The limited human data available [110,157] suggest there are no alterations in muscarinic excitability. Accordingly, an alteration in the M2/M3 receptor protein ratio has not been demonstrated [47]. Animal data suggest that ageing has no major effect on α -1- or β -adrenoceptor function [156]. Atropine resistance and additional purinergic activation in the unstable aged bladder were discussed earlier [110]. The overall picture does not suggest major ageing-related alterations of muscarinic or α -1-adrenergic receptor-mediated contractility or of β -adrenergic relaxation of the urinary bladder [156]. (Fig. 1).

4. Conclusions

Several recent population-based surveys in Europe and the United States have clearly demonstrated that storage LUTS increase with age at a similar rate in both men and women, with little correlation with underlying disease processes such as benign prostate enlargement. In support of that view, numerous recent studies have revealed both structural and

functional alterations in bladders from patients with LUTS symptoms or animals with experimentally induced bladder dysfunction. In particular, the urothelium and the suburothelial space—containing afferent nerve fibres and interstitial cells—have been found to form a functional unit that is essential in the process of bladder sensation and characterised by a variety of interrelated neurotransmitter interactions. Various imbalances within this suburothelial complex have been identified as significant contributors to the generation of storage LUTS, along with potential abnormalities of central function. Thus an increasing body of experimental data supports the importance of focusing on both bladder function and dysfunction in the management of LUTS. Current research on the pathophysiology of these symptoms has revealed a number of peripheral mechanisms potentially involved [63,158], some of which may be realistic targets for drugs. However, signals obtained should be critically analysed, keeping in mind that direct translation from preclinical models to clinical reality is rarely possible.

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Study concept and design: Roosen, Chapple, Dmochowski, Fowler, Gratzke, Montorsi, Roehrborn, Stief, Andersson.

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Critical revision of the manuscript for important intellectual content: Chapple, Dmochowski, Fowler, Gratzke, Montorsi, Roehrborn, Stief, Andersson.

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Editorial Comment on: A Refocus on the Bladder as the Originator of Storage Lower Urinary Tract Symptoms: A Systematic Review of the Latest Literature

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Twenty years ago, the Italian group, chaired by Maggi, pioneered the role of a specific capsaicin-sensitive subset of primary sensory nerves in the lower urinary tract [1]. With brilliant intuition, Maggi and colleagues showed that intravesical instillation of capsaicin—the source of red pepper's pungent taste—in six patients with lower urinary tract symptoms (LUTS) produced a concentration-related reduction of the first desire to void and of cystometric bladder capacity. Clinically, the patients reported disappearance or marked attenuation of their symptoms after repeated instillations, providing the first indication that afferent nerves were present in the human urinary bladder. More recent studies have confirmed Maggi's theory, and that success is summarized by Roosen and colleagues in this issue of *European Urology* [2].

When approaching this article, I think the reader should know what has been changing in recent years, what has been the basic science and the clinical rationale for investigating alternative pathways to cholinergic and adrenergic regulation of the lower urinary tract, and what lies ahead. The idea of local afferent modulation by targeting afferent nerves that control the lower urinary tract has gained the trust of urologists as a potential alternative to current drug therapies for LUTS [3]. For treating overactive bladder, the emerging concept is that it would be more desirable to prevent the micturition reflex by blocking the afferent branch instead of blocking the contraction of detrusor smooth muscle, as it results from the activation of efferent branch. In the past, many factors, such as the complex neurology of the voiding reflex; the simple, uncontroversial idea of antagonistic, parasympathetic cholinergic, and sympathetic adrenergic control of the lower urinary tract; and the interrelationship between voluntary somatic and involuntary control of micturition reflex, discouraged extensive research of a new approach for the treatment of LUTS. In recent years, neuropharmacology has gained advantages from basic science research, and the experimental results have been translated into clinical practice. Today we know that the neuromuscular junction is not a "fixed synapse junction," with pre- and postjunctional specialization, and it releases multiple neurotransmitters such as monoamines, purines, amino acid, peptides, and nitric oxide. Further achievements included accepting the principles of cotransmission (axons

release more than one transmitter for each action potential) and neuromodulation (locally released agents may modulate the amount of neurotransmitters released prejunctionally) and recognition that a subset of sensory nerves that are selectively sensitive to capsaicin and its transient receptor potential (TRP) family are of primary importance in functional regulation of the lower urinary tract [4].

New varieties of bladder receptors have been identified as being involved in regulating bladder sensory afferent nerve conduction [5], but as yet, the story seems far from over. Members of the TRP family Ca^{2+} and Na^{+} permeable channels involved in promoting cellular death and inhibiting the growth of normal and neoplastic cells are showing altered expression in bladder and prostate cancer. TRP (TRPV1/TRPV2/TRPV6 and TRPM8) proteins have been shown to be valuable markers in predicting the progress of bladder and prostate cancers and are now under consideration as potential targets for chemoprevention and chemotherapy [6–8], in anticipation of a connection between functional and neoplastic diseases.

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