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Pathophysiological Mechanisms Involved in Overactive Bladder/Detrusor Overactivity

Russ Chess-Williams[1] · Donna J Sellers[1]

Abstract

Purpose of Review To examine the latest published findings on the pathophysiological mechanisms involved in the development of overactive bladder (OAB) and detrusor overactivity (DO), and to identify common pathways linked to the risk factors associated with these conditions.

Recent Findings Evidence is accumulating, both clinical and experimental, that many of the factors linked to the development of OAB/DO, including ageing, bladder outlet obstruction, psychological stress, and obesity are associated with reduced bladder blood flow. This induces local tissue inflammation with cytokine release and enhanced oxidative stress, ultimately resulting in altered detrusor sensitivity, detrusor hypertrophy and fibrosis, together with afferent hypersensitivity. These mechanisms would explain the symptoms of urgency and frequency observed in OAB patients. Although not a characteristic of OAB, undetected low level bacterial infections of the bladder have been proposed to explain the OAB symptoms in patients resistant to standard treatments. In this condition, inflammatory responses without reductions in perfusion activate the inflammatory pathways.

Summary Evidence is mounting that poor bladder perfusion and local inflammatory responses are central mechanisms involved in the development of OAB/DO. As our understanding of these pathophysiological mechanisms advances, new avenues for drug development will be identified and ultimately treatment may become more individualized depending on the particular pathway involved and the drugs available.

Keywords Overactive bladder · Detrusor overactivity · Inflammation · Ischemia · Pathophysiology · Bladder perfusion

Introduction

Normal Bladder Physiology

The function of the bladder is to store urine and empty at appropriate times. The mechanisms involved in controlling compliance during bladder filling were thought to include the sympathetic nervous system, with noradrenaline causing

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bladder relaxation via β3-adrenoceptors. However, this latter mechanism has been challenged recently, with a study showing the sympathetic innervation to the detrusor muscle is sparse and unlikely to induce relaxation [1].

During filling, the bladder is not totally quiescent, but generates localised regions of contractions, known as non-voiding contractions or "micromotions" [2, 3]. These localised contractions can produce only small increases in intravesical pressure without initiating voiding. The origin of this contractile activity is not certain, but it may be within the muscle itself, sub-urothelial interstitial cells or the muscularis mucosa. The latter mediates spontaneous phasic contractile activity within the mucosa [4, 5], and in the pathological bladder intrinsic contractile activity of the bladder wall may be driven by the mucosa [6]. The function of the muscularis mucosa, and indeed bladder wall micromotions, is not fully understood, but they influence afferent nerve activity and may sensitise the afferent system by limiting nerve adaptation.

The urothelium also plays an important role in the perception of bladder filling. Urothelial cells possess a number of stretch-sensitive ion channels, such as piezo channels [7, 8]. In response to stretch urothelial cells release several mediators that regulate afferent nerve activity, including ATP which enhances nerve activity [9], nitric oxide to inhibit nerve activity [10] and acetylcholine (Ach), which has been reported to both increase and decrease nerve activity [11, 12]. Several mechanisms operate to influence this sensory information, including several ion channels such as transient receptor potential vanilloid-1 (TRPV1). These ion channel receptors enhance afferent nerve activity and if they are blocked, desensitized or removed genetically afferent nerve activity is greatly reduced [12, 13]. Other TRP channels may increase nerve sensitivity to stimuli such as cold, pH and stretch [14]. In recent years our understanding of the complexity and importance of the urothelium in controlling bladder function has expanded. Urothelial cells release a wide range of mediators that influence not only afferent nerve activity as discussed above, but also smooth muscle contraction, development and innervation [14, 15].

The sensory information generated within the bladder is carried via Aδ and C-afferent fibres that synapse in the sacral spinal cord. The nociceptive c-fibres are quiescent during normal bladder filling, but may become active in pathological conditions. The sensory information is carried to the periaqueductal gray (PAG) and onto the pontine micturition centre (PMC) which initiates efferent pathways to simultaneously contract the bladder and relax the urethral sphincter. This reflex micturition can be inhibited by higher brain centres and functional MRI studies have shown that the insula (frontal cortex) registers afferent sensations and becomes more active as the bladder fills; midcingular circuits determine the response to increasing bladder afferent activity and subcortical circuits (hippocampus and paralimbic regions) support continence mechanisms until micturition is triggered when convenient [16].

Overactive Bladder (OAB) and Detrusor Overactivity (DO)

It can be seen from the description above that normal micturition reflexes require intact bladder sensory and motor neuronal pathways, and healthy detrusor smooth muscle, urothelium and bladder outlet. Conditions affecting any of these can potentially lead to lower urinary tract symptoms (LUTS). Overactive bladder syndrome (OAB) is a set of storage symptoms that consists of urgency, frequency, nocturia, and urge urinary incontinence. The most common symptoms of OAB are urinary urgency and frequency and these may be associated with involuntary contractions of the detrusor smooth muscle (detrusor overactivity, DO). The most common cause of OAB is DO, which has been

identified on cystometry in more than 60% of OAB patients. Specifically in men, this value is even higher, and it has been estimated that almost 70% of men with urgency have DO [17, 18].

Most cases of OAB are idiopathic, with unknown pathophysiology, but several hypotheses have been proposed to explain this condition including:

(i)   A myogenic mechanism involving dysfunction of the detrusor smooth muscle resulting in spontaneous contractions. More recently changes in the initiation and propagation of microcontractions has been suggested [19].

(ii) A neurogenic mechanism involving dysfunction of the central and/or peripheral nervous control of the bladder. A degeneration of nerves fibres within the bladder wall has been a defining feature of DO, with reductions in innervation observed in patients with idiopathic and neurogenic DO [20] and in animal models of obstructive DO [21]. The original concept of a neurogenic mechanism focussed on the motor system, but more recent studies have demonstrated that sensitisation of the afferent pathways may also cause urgency and ultimately increased motor drive to the detrusor. Yamaguchi et al. [22] first defined bladder overactivity as a hypersensitive condition and this was later confirmed by Lee et al. [23] measuring perception thresholds during bladder filling and electrical stimulation.

(iii) More recently a pathological role for the urothelium has been proposed, with enhanced release of mediators such as ATP during bladder filling. Increased release of ATP from the urothelium during stretch has been observed in isolated bladder tissues from idiopathic and neurogenic OAB patients [24]. The release of ATP from the urothelium occurs during early filling in normal and DO patients and is elevated in women with DO [25].

Thus, patients with OAB/DO are a heterogeneous group with similar symptoms, but with differing epidemiology and pathogenesis. In each case, these mechanisms may not be mutually exclusive. For example, the urothelium influences both afferent nerve and smooth muscle activity, whilst smooth muscle contractile activity can greatly influence afferent nerve activity [26].

Pathophysiological Factors in OAB/DO

Several factors linked to the development of OAB/DO are known to cause changes in bladder smooth muscle, neuronal and urothelial function. These include ageing, bladder outlet obstruction (BOO), obesity, psychological stress and undetected low level bacterial infections.

(i) Ageing: It is well established that ageing is accompanied by many changes in the urinary system that may contribute to the increased prevalence of OAB in the elderly population. At the bladder level, normal ageing is associated with increasing fibrosis of the detrusor that may contribute to the reduced bladder compliance and detrusor overactivity observed in patients [27]. Changes in the efferent neuronal drive to the smooth muscle is also observed in the elderly with a change from cholinergic (Ach) to purinergic (ATP) neurotransmission [28], a change that mirrors that seen in OAB/DO [29]. The mechanisms involved have recently been shown to involve changes in the expression of the ecto-ATPase E-NTPDase-1, which is responsible for the rapid breakdown of ATP in the healthy bladder [29]. A similar change with increasing purinergic responses occurs in the urothelium with ageing [30]. Studies in mice have determined that ATP release is influenced by bladder wall stiffness and thus fibrosis may be critical, yet this factor seemed less important in regulating ATP release in the older bladder [31]. Bladder function appears to be influenced by age at all levels since afferent nerve activity is also enhanced in aged animals, although this may partly reflect changes in detrusor and urothelial function.

It has been proposed that the changes in blood flow with ageing may be the link between ageing and bladder dysfunction. Pinggera et al. [32] demonstrated reduced perfusion of the bladder neck in women and the bladder/prostate in men with ageing. A strong negative correlation between bladder perfusion and the frequency of voiding was also observed. Both ageing and poor bladder perfusion are associated with LUTS, but whether changes in bladder perfusion are responsible for the initiation and/or development of LUTS remains unclear. However, ischemia is known to induce inflammatory responses which is another link with OAB/DO. With increasing age there is an increase in several markers of inflammation (NGF and MCP-1) in the urine of OAB patients [33]. Ageing is thus associated with a number of factors that may accentuate the changes (eg inflammation) involved in the development of OAB/DO.

(ii) Bladder outlet obstruction (BOO): Globally, BOO affects more men (25%) than women (19%), with BPH being the number one cause of BOO in men [34, 35]. Chronic BOO causes pathophysiological changes within all the layers of the bladder wall including detrusor hypertrophy, fibrosis, smooth muscle proliferation, urothelial dysfunction and a functional denervation [36–38].

The responses of the bladder to BOO in animal models is similar to that observed in patients. Partial obstruction of the bladder outlet in rodents results in bladder dysfunction accompanied by bladder hypertrophy and fibrosis [39]. With BOO, micturition causes cyclical ischemia, followed by repeated reperfusion that generates free radicals and ultimately tissue injury, cytokine release and inflammation

[40•]. Hypoxia of the bladder wall is evidenced by increases in hypoxia-inducible factor (HIF) and inflammatory responses are initiated by elevated levels of pro-inflammatory cytokines including interleukin-1β (IL-1β) and transforming growth factor-β (TGF-1 β) [39, 41]. Recent studies have identified toll-like receptors (TLR-4 and TLR-9) involved in the induction of inflammation, with the expression of both these receptors increased in the urothelium of animals with BOO. Antagonists of these receptors depress BOO-induced inflammatory responses in the rat and the receptors may represent a new therapeutic target for future drug development [40•].

Generally, mechanical (non-infectious) damage to cells causes the release of several chemicals known as damage associated molecular patterns (DAMPs) which trigger the formation of a multimeric structure called an inflammasome. This ultimately results in the activation of IL-1β and IL-18 that trigger local inflammatory responses [42•]. In the bladder, it is the NLRP3 inflammasome that is activated in the urothelium by BOO [43]. This promotes fibrosis and denervation of the detrusor and inhibitors of NLRP3 were recently shown to prevent these changes and to preserve bladder function following partial BOO in mice [42•].

(iii) Psychological stress: When considering factors that contribute to the development of OAB one factor that is often overlooked is the role played by psychological stress. Many studies have identified psychological stress as a factor in the development of OAB and the worsening of symptoms in patients with existing OAB [44, 45••, 46]. The strongest evidence has been obtained in studies of American military personnel returning from active duty, where high levels of stress were predictors of newly developing OAB and lack of recovery from OAB [45••].

The powerful influence of stress on bladder function can also be demonstrated in animal models of environmental and social stress [47, 48] and both local changes in bladder function, and changes within the micturition pathways of the CNS and spinal cord have been identified. Local responses to stress include detrusor hypertrophy, enhanced bladder contractile responses and afferent hypersensitivity [49••, 50, 51]. The CNS responses to stress include the release of corticotropin releasing factor (CFR) and enhanced cortisol release from the adrenal cortex. The receptors for CRF are found throughout the central micturition pathways and peripherally in the urothelium, where they increase the release of ATP and may therefore contribute to the enhanced pelvic sensory hypersensitivity. Additionally, catecholamines from the adrenal medulla can cause the release of cytokines both in the CNS and in the periphery [52]. CRF receptors are also located on inflammatory cells involved in innate immune responses. Stress-induced OAB therefore involves inflammatory responses, with elevated levels of CRF causing the release of cytokines from activated

immune cells (via CRF) and the release of cytokines (via catecholamines). This activation likely triggers inflammatory responses both locally in the bladder and centrally in the CNS, causing further cytokine release in both locations. Studies of volunteers during psychological stress tests support this idea, with stress causing elevated plasma levels of inflammatory mediators such as IL-1β, IL-6, IL-10 and TNFα [53].

(iv) Obesity/Metabolic Syndrome: There is a well-established association between metabolic syndrome and OAB/DO in men, but this link can also be shown with other urological conditions such as BPH and erectile dysfunction [54]. However, whether there is a causal relationship between metabolic syndrome and OAB/DO is difficult to conclude, since secondary factors including reduced bladder wall perfusion and ischemia-induced inflammation may play a role. However, studies in women also show the link between metabolic syndrome and OAB/DO [55]. Furthermore, a recent study by Zacche et al. [56••] examined different aspects of metabolic syndrome in women to establish which factors might be important to the development of OAB/DO. They found that obesity was the only independent predictor for OAB/DO. Other factors such as diabetes, hypertension and dyslipidaemia did not appear to be associated with either OAB or DO [56••].

Since metabolic syndrome is a chronic systemic inflammatory condition, the pathogenesis of OAB/DO in these patients again may reflect the effect of inflammatory mediators and enhanced oxidative stress on bladder function. A systematic review recently found that the link between metabolic syndrome and BOO was strong, but the link with OAB/DO was less obvious [57]. Further studies investigating individual aspects of the metabolic syndrome are clearly needed.

(v) Undetected bacterial infection: A component of the definition of overactive bladder/detrusor is the absence of infection. However, in one study where antibiotics were administered to OAB patients who had tested negative for bacterial infection based on conventional urine bacterial levels symptoms improved in about half the patients [58]. Mansfield et al. [59••] have recently reviewed the literature and concluded that when enhanced culture techniques are employed to identify low level infections up to 39% of patients who are refractory to conventional anticholinergic therapy have an underlying low level bacterial infection.

The mechanisms involved in infection-induced bladder dysfunction have recently been investigated in a mouse model by Brierley et al. [60], who concluded that during infection two factors appear to enhance sensory responses to bladder filling: (i) an increase in the sensitivity of high threshold nerve fibres and (ii) an infection-induced "recruitment" of previously silent afferent fibres. These effects occurred independently of any effects on the detrusor and

were therefore a direct effect on the primary afferent neurons. As with psychological stress, the pathological mechanism inducing these changes was considered to be elevated levels of tissue cytokines.

Common Pathophysiological Pathways

When the risk factors linked to OAB/DO are considered, inflammation and poor bladder blood flow stand out consistently. Reduced tissue perfusion can cause inflammatory responses to develop, and, during infections, where blood flow increases, there is a more direct effect to stimulate inflammatory responses. These changes in tissue perfusion and inflammation therefore appear to be primary mechanisms involved in the development of OAB/DO.

[A] Changes in Bladder Perfusion in OAB/DO

There is mounting evidence that ischemia of the bladder wall plays a role in the development of OAB/DO. Early clinical studies noted the association between cardiovascular disease and bladder dysfunction, but a direct association has been demonstrated, with blood perfusion of the bladder being negatively correlated with urinary frequency and nocturia [32]. Thus, chronic bladder ischemia is associated with LUTS [61] and ischemia plays a role in the aetiology of OAB/DO, not only in men with BOO, but also in women [62].

The main causes of bladder wall ischemia are BOO and arterial occlusive disease, which reduce delivery of blood to the bladder microcirculation. However, increased bladder wall thickness also results in tissue under-perfusion that has been linked to OAB [63], and more recently with DO [64]. A recent study in women by Hsiao et al [65] also confirmed that average bladder wall thickness, particularly the trigone region, correlates positively with symptoms of urgency in patients with OAB.

Animal models have been developed to investigate the link between blood flow and bladder dysfunction. In one atherosclerotic model vascular damage is localised to the bladder by inflating a balloon in the iliac artery to damage the endothelium before animals are fed a high cholesterol diet [66]. In this model bladder ischemia has a time-dependent effect on bladder function. Detrusor overactivity can be demonstrated on cystometrograms after 8 weeks of ischemia, but this changes to bladder underactivity after 16 weeks. These changes are matched by changes in M3 receptor expression, with an upregulation of M3 receptors at 8 weeks and a down regulation at 16 weeks of ischemia. Histologically there is a gradual progression of neural damage, and a loss of nerve fibres occurs over this time course [66].

Mechanisms Involved in Ischemia-Induced Bladder Dysfunction

Generally, reduced perfusion of tissues results in hypoxia and the accumulation of cellular metabolites. This in turn may enhance production of free radicals causing oxidative stress and the activation of inflammatory responses. The degree of cellular damage depends on the severity and duration of the ischemia, with the damage caused by sustained reduction in perfusion triggering apoptosis (programmed cell death) and irreversible tissue damage. Experimental animal models suggest that moderate bladder ischemia leads to reduced bladder compliance and sensitisation of detrusor contractile responses which results in detrusor overactivity and increased urinary frequency [67, 68]. More severe reductions in perfusion lead to muscle and nerve degeneration that may be consistent with underactive bladder [66].

As previously noted, during ischemia the fall in cellular energy stores and imbalance in oxidant production and antioxidant defences resulting in excessive levels of free radicals and cellular oxidative stress [69]). The oxidative free radicals also react with nitric oxide to produce nitrosative free radicals and the resulting oxidative/nitrosative stress initiates cell stress responses causing damage to muscle, nerves and urothelium and the release of pro-inflammatory cytokines (e.g., IL-1β) and induction of inflammation [69].

The bladder responds to ischemia by upregulating antioxidant protective mechanisms, with elevated superoxide dismutase and aldose reductase. Ischaemic stress in the bladder is detected by three cellular stress sensors:

(i)   AMP activated kinase (AMPK)—which promotes antioxidant defence mechanisms. As cellular ATP levels decline and AMP levels rise, AMPK, particularly the α2 form expressed in the bladder, is activated [70]. Ischemia down-regulates levels of phosphorylated (active) AMPK, initiating cellular dysfunction. Activators of this enzyme inhibit neurogenic detrusor contractions in vitro, while in an in vivo rat ischaemic OAB model, they reduce the force of detrusor contractions, reduce nerve damage, and increase bladder capacity [70].

(ii) Apoptosis signal-regulating kinase 1 (ASK1)—this signalling molecule plays a major role in initiating inflammatory responses and it is upregulated in the hypoxic bladder causing inflammation, smooth muscle degeneration and fibrosis [71, 72••].

(iii) Caspase-3—in the ischaemic bladder caspase-3 is upregulated by ASK1. Mild cellular stress activates caspase-3 to initiate survival mechanisms [73], whilst severe ischaemic stress activates this enzyme to initiate apoptosis [72••]. This finding may have relevance to the change from bladder overactivity to

underactivity seen with increasing severity and duration of ischemia and OAB.

The rat ischaemic model of OAB/DO has also been used to identity factors released from cells during ischemia that may be responsible for changes in bladder function [74, 75]. These include: *(i) Hypoxia inducible factor* (HIF) – levels of HIF rise in hypoxic conditions and in BOO, where it alters cell metabolism, angiogenesis and apoptosis. *(ii) Transforming growth factor* (TGF-β) - another peptide that is upregulated in the ischaemic bladder where it causes remodelling of the extracellular matrix and fibrosis. *(iii) Vascular endothelial growth factor* (VEGF) – bladder ischemia induces VEGF gene expression, but also simultaneously depresses protein synthesis, the overall result being depressed VEGF levels that may result in damage to the microvasculature. *(iv) Nerve growth factor* (NGF) – NGF gene expression is increased in the ischaemic bladder, but levels of its receptor are depressed, which may explain the neurodegeneration observed during BOO in animals and patients.

[B] Inflammation and OAB/DO

Inflammatory responses, although observed in interstitial cystitis, are not typically a characteristic of OAB/DO. However, when markers of inflammation have been examined in patients with OAB, they are consistently found to be elevated. Tyagi et al. [76] investigated the presence of 12 inflammatory markers in the urine of patients with idiopathic OAB and found a more than a 10-fold increase in two markers, more than a 5-fold increase in five markers and more than a 3-fold increase in two others, with only 3 inflammatory markers being unchanged in OAB patients. This evidence of inflammation in OAB has been supported in other studies where immune cell infiltration has been identified in biopsies from OAB patients [77]. In a control group (no treatment) of patients with neurogenic DO, mild inflammation has been observed in 74% of patients and signs of more severe inflammation in 24% [77]. Similarly, signs of chronic inflammation were observed in 65% of patients with neurogenic DO and 50% of those with idiopathic DO [78].

Another indicator of inflammation is the presence of leukocytes in the urine (pyuria) and this has been reported in a significant proportion of OAB patients. Pyuria is found in about a third of OAB patients and the immune response correlated well with the severity of OAB [79]. Another study by Gill et al. [80] found strong evidence of inflammation in patients with OAB, the condition being associated with pyuria and the pro-inflammatory cytokine IL-6.

Thus, inflammation is a common feature of OAB/DO which may develop when bladder blood flow is reduced,

or the bladder is stressed mechanically by BOO, or directly during infection. It should be noted that inflammation of the whole bladder may not be required to exert significant effects on bladder function. Localised inflammation at critical locations such as the mucosa could have a large impact on overall bladder function. A number of findings are particularly relevant in this regard.

(i) The mucosa is the first bladder tissue to respond to stress with an increase in early gene responses [81].
(ii) The mucosa has a metabolic rate triple that of the smooth muscle, making it more susceptible to ischaemic damage [82].
(iii) Changes in wall perfusion tend to be greater in the mucosa than the muscle [83].
(iv) Infiltration of immune cells and signs of oedema are observed predominantly in the suburothelium [77].

Thus, the mucosa is particularly susceptible to ischemic damage and inflammation. Since the mucosa contains many suburothelial afferent nerves and it also influences muscle contraction and afferent nerve activity via the mediators it releases, changes in blood flow to this region may have a huge impact on bladder function, even if other regions remain relatively well perfused.

Inflammation will affect bladder function in several ways. Inflammation sensitizes bladder afferent nerves which may lead to urinary urgency and frequency [84]. Also, cytokines and oxidative stress cause direct sensitization of small diameter afferent c-fibres [85]. Histamine released from mast cells also sensitizes bladder afferent nerves and recruits "silent" afferent fibres that were previously unresponsive [86•]. Cytokines and oxidative stress also induce fibrosis and stimulate smooth muscle proliferation, which may explain bladder hypertrophy with OAB/DO. Interleukin-1β has been identified as a mediator that induces bladder smooth muscle proliferation in rats that is mediated via the SGK-NFAT2 signalling pathway [41]. Thus local effects of inflammation exert powerful influences over bladder function.

Central and Peripheral Inflammatory Responses

Local inflammatory responses within the bladder can trigger inflammatory responses within the CNS. Bladder inflammation can be induced experimentally by treating animals with the cytotoxic drug cyclophosphamide, its urinary metabolites acrolein and chloroacetaldehyde causing bladder irritation and an inflammatory response [87]. However, these local inflammatory responses can lead to the development of central inflammation within the brain [88]. Recent studies have identified the mechanisms involved and shown the

release of molecules known as damage-associated molecular patterns (DAMPS) which trigger the formation of an inflammasome in the urothelium (42,89*] and also in CNS microglia [90]. Once the inflammasome is established a cytokine cascade results in more wide-spread inflammation including the CNS. Evidence of this "bladder-brain axis" has recently been provided by Hirshman et al., [91] who reported inflammation in the hippocampus that was initiated by outlet obstruction of the bladder.
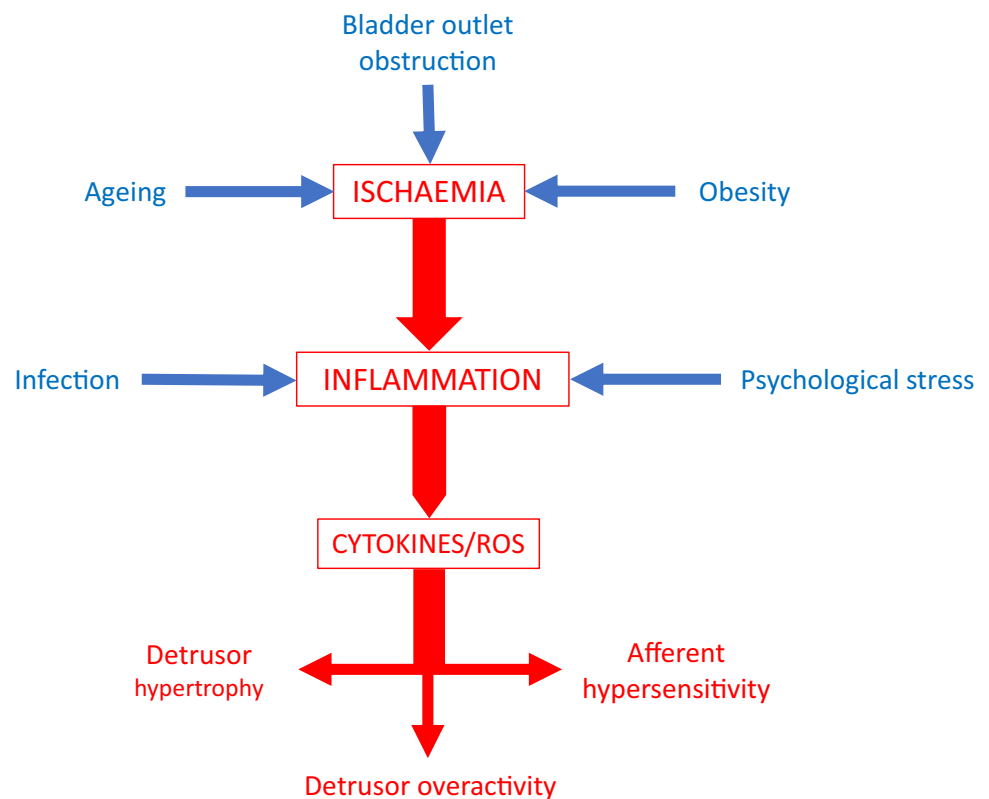
Potential Future Treatments for OAB/DO

With our increasing knowledge of the pathophysiology of OAB/DO, the potential for new agents with novel mechanisms of action also increases. Such new treatments could include drugs that reduce the effects of ischemia, the associated oxidative stress or the inflammation. These might be activators of AMPK-α2 or inhibitors of ASK-1, that could exert effects promoting antioxidant protective mechanisms in the bladder and could theoretically be given prophylactically to patients with BOO. Agents to reduce inflammation may also be beneficial and have a role to play in OAB therapy. The urothelium releases PGE2 [87] and intravesical PGE2 has recently been used to induce bladder overactivity in an animal model, demonstrating its powerful effect on micturition [92]. However, there is no strong clinical evidence for the use of non-steroidal anti-inflammatory drugs for bladder dysfunction [93] and in men these agents have been found to double the risk of acute urinary retention [94], highlighting the importance of developing a range of drug treatments to administer based on a patient's pathophysiology.

Conclusions

OAB and even DO may represent a spectrum of conditions sharing a common pathophysiological pathway (Fig. 1). The pathogenesis involves many factors that may interact to influence outcomes. For example, psychological stress itself can induce bladder dysfunction, but may also exacerbate other factors in the pathophysiological pathway. Many of the factors associated with the development of OAB/DO are also associated with bladder ischemia and inflammation (ageing, BOO, psychological stress, obesity) or directly with inflammation (undetected infection). Cytokines and reactive oxygen species released during inflammation can exert local effects such as sensitisation of detrusor smooth muscle and enhanced afferent signalling, but they also influence micturition centrally by acting on the pontine control centre. As our understanding if these mechanisms increases, the opportunity for novel drug development will also improve.

Fig. 1 Pathophysiology of bladder/detrusor overactivity. Several factors associated with the development of OAB/DO are also associated with reduced bladder blood flow which in turn may trigger inflammatory responses. Other factors associated with OAB/DO are directly linked to inflammation. Cytokines and reactive oxygen species (ROS) released locally by inflamed tissue, can induce bladder hypertrophy and also detrusor and afferent nerve hypersensitivity, whilst those reaching the systemic circulation or released in other regions of the micturition pathway may influence central micturition reflexes

Declarations

Conflict of Interest Dr Donna Sellers and Prof Russ Chess-Williams declare that they have no conflict of interest.
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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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● Of importance
●● Of major importance

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