Research Findings on Overactive Bladder

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Key Words

Ageing • Diabetes mellitus • Bladder outlet obstruction • Spinal cord injury • Stroke • Brain injury • Multiple sclerosis • Interstitial cystitis • Stress • Depression • Parkinson's disease

Abstract

Several physiopathologic conditions lead to the manifestation of overactive bladder (OAB). These conditions include ageing, diabetes mellitus, bladder outlet obstruction, spinal cord injury, stroke and brain injury, Parkinson's disease, multiple sclerosis, interstitial cystitis, stress and depression. This review has discussed research findings in human and animal studies conducted on the above conditions. Several structural and functional changes under these conditions have not only been observed in the lower urinary tract, but also in the brain and spinal cord. Significant changes were observed in the following areas: neurotransmitters, prostaglandins, nerve growth factor, Rho-kinase, interstitial cells of Cajal, and ion and transient receptor potential channels. Interestingly, alterations in these areas showed great variation in each of the conditions of the OAB, suggesting that the pathophysiology of the OAB might be different in each condition of the disease. It is anticipated that this review will be helpful for further research on new and specific drug development against OAB.

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Introduction

When talking about the overactive bladder (OAB), a question that comes into mind is what conditions are associated with the development of this physiopathologic state of the bladder. It has been observed that OAB is manifested during the following conditions: ageing, diabetes mellitus (DM), bladder outlet obstruction (BOO), spinal cord injury (SCI), stroke and brain injury, Parkinson's disease (PD), multiple sclerosis (MS), interstitial cystitis (IC), and stress and depression. The present review intends to discuss research findings from human and animal studies on OAB under these conditions. This would not only lead to an understanding of the pathophysiology of OAB, but would also contribute to proper drug development against OAB. This review does not explore the scope of treatment options for OAB. However, an update on this topic is available in recent articles [1, 2]. The terms OAB and detrusor overactivity (DO) were recommended by the International Continence Society for the pathophysiology of the lower urinary tract (LUT). According to the International Continence Society, OAB was defined as urgency, with or without urge incontinence, and usually with frequency and nocturia. DO was defined as an urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked [3]. However, OAB may be more accurately defined as a hypersensitivity disorder rather than a syndrome characterized by urgency [4, 5]. DO is the urodynamic hallmark of OAB. However, DO and OAB are not synonyms, they share therapeutic options and partially underlying physiopathological mechanisms [6, 7]. There are 2 subtypes of OAB, OAB-dry (frequency and urgency without urgency

incontinence) and OAB-wet (frequency and urgency accompanied by urge incontinence) [8]. There is a sex-specific prevalence of OAB symptoms [9] that significantly impacts quality of life and social functioning [10].

The pathophysiology of OAB and DO is not well understood. However, this might be due to neurogenic and/or myogenic factors [11, 12], alteration in the bladder afferent pathways [13], malfunctions of the urothelium and its signaling mechanism [14, 15], and moreover, due to abnormalities in the handling of afferent signals in the brain [16].

Control of the LUT Functions

LUT consists of the bladder and urethra innervated by sympathetic, parasympathetic and pudendal nerves. The major function of the LUT is to store urine in the bladder and to periodically evacuate urine at appropriate times. The neural circuitry that controls this process is complex; it involves pathways at many levels of the brain, spinal cord and the peripheral nervous system and is mediated by multiple neurotransmitters. This explains the high prevalence of urinary disturbances in neurological diseases [17–20]. Many of the neural circuits in the brain that control micturition exhibit switch-like patterns of activity that turn on and off in an all-or-none manner [21, 22].

Bladder Filling

During bladder filling, the parasympathetic function of the detrusor is inhibited, leading to the relaxation of the bladder with simultaneous contractions of the urethral sphincters (external and internal), preventing involuntary bladder emptying. This process is accomplished by norepinephrine, released from the sympathetic post-ganglionic (hypogastric) nerve. Norepinephrine acts on beta3-adrenoceptors (beta3-AR) in the detrusor, causing relaxation and enhancing bladder compliance, and also acts on alpha1-adrenoceptors (alpha1-AR) in the bladder neck and urethra, enhancing bladder outlet resistance [17, 23, 24].

Bladder Evacuation

When bladder volume reaches the micturition threshold, it activates the pontine micturition center to induce bladder contraction and relaxation of the urethra, leading to bladder emptying. Sensations of bladder fullness are conveyed to the spinal cord by the pelvic and hypogastric nerves, whereas the pudendal and hypogastric nerves

carry the sensation from the bladder neck and urethra. Afferent fibers are primarily present in the trigone, though they are also distributed in the detrusor and urothelium. Afferent fibers consist of myelinated (A δ fiber which responds to passive distension) and unmyelinated (C fiber which responds to noxious chemicals and mechanical stimuli) axons. Bladder evacuation is predominantly accomplished by the parasympathetic nerve through the release of the excitatory neurotransmitter acetylcholine along with the co-transmitter ATP. Upon release, acetylcholine mainly acts on the detrusor via M3-muscarinic receptors (M3-MR) (and M2-MR during pathological situations), while ATP acts on P2X1-purine receptors (P2X1-PR) in the detrusor to initiate contraction [13, 17, 23–26]. However, the maintenance of continence and a normal bladder micturition cycle involves a complex interaction of cholinergic, adrenergic, nitrergic and peptidergic systems that is currently not very well understood [27].

Conditions Leading to the Development of OAB

Ageing

OAB symptoms complex is one of the common causes of urinary incontinence (UI) in older people, which leads to the deterioration of bladder function [28, 29]. This might be due to weaker signals in the bladder control network of the brain [30] and sensory neuropathy as evidenced by enhanced urethral sensations [31].

Findings in Humans Ageing produced denervation in the bladder [32], with an increase in purinergic neurotransmission (PuNT) (increased release of ATP), decrease in cholinergic neurotransmission (ChNT) (decreased release of acetylcholine) [33], decrease in M3-MR in the detrusor, and an increase in M2-MR in the urothelium of both males and females [34]. However, a decrease in expression of P2X1-PR mRNA with age was noticed in the male detrusor [35].

Findings in Pigs There was an upregulation of mRNA levels of vascular endothelial growth inhibitor, death receptor 3 and nuclear factor kappa-B (NF- κ B) in aged porcine detrusor [36].

Findings in Rats Ageing was associated with decreased bladder capacity and spontaneous bladder contractions in rats [37], reduction in MR in the detrusor [38, 39], a reduction in the contractile response of the detrusor to carbachol (CARB) [40], a shift in the contractile phenotype from M3-MR to M2-MR in males but not in females [41], an increased expression of P2Y4-

PR and P2X3-PR [42, 43], an overexpression of the alpha-1D-AR [44], downregulation of urothelial nitric oxide synthase (NOS) [45] and endothelin receptors in the bladder [46]. Furthermore, ageing also produced a reduction in the number of spinal neurons expressing prostaglandin-21 (PG-21) androgen receptors, steroid receptor co-activator-1 (SRC-1), and phosphorylated form of C-AMP response element binding protein (pCREB) in aged males, while SRC-1 and pCREB expression was largely unchanged in aged females [47].

Findings in Guinea-Pigs Ageing produced DO, as demonstrated by short micturition interval, decreased bladder capacity, lower micturition pressure and spontaneous contractions during the filling phase [48]. Ageing also produced a functional loss of PuNT [49], reduced calcium sensitivity [50] and a significant decrease in acetylcholine esterase (AChE) positive neurons in the bladder [51].

Findings in Mice During ageing, central determinants of voiding initiation may become less sensitive to afferent input [52]. In aged mice, increased voiding frequency and enhanced low threshold afferent nerve activity was observed suggesting that ageing induces overactivity and hypersensitivity of the bladder. Moreover, ageing increased smooth muscle contractility and increased purinergic receptor sensitivity and raised P2X3 receptor expression in the urothelium suggesting ageing evokes changes in purinergic signaling from the bladder [53]. There was a disruption of postsynaptic cholinergic pathway [54], decreased cholinergic response to bethanechol and enhanced purinergic response to ATP [55], partial loss of smooth muscle myosin heavy chain isoform 2 [56] and significant decrease in total antioxidant capacity and increased levels of lipid peroxides and inducible nitric oxide synthase (iNOS) in the bladder [57].

Diabetes Mellitus (DM)

Urinary bladder dysfunction is one of the most important clinical features in poorly controlled DM, which leads to diabetic neuropathy and cystopathy [58]. Diabetic cystopathy is characterized by incomplete emptying to urgency incontinence and time dependent manifestations of storage and emptying problems [59, 60]. Patients with DM have a wide variety of voiding complaints that include DO, nocturia, incomplete emptying, urge and overflow incontinence, higher rates of OAB wet, and impairment in bladder sensation [60–63].

Findings in Humans DO due to DM involve both central and peripheral mechanisms [64] with an impairment in A delta as well as C fiber bladder afferent pathways

[65] and an upregulation of Rho-kinase (ROK) signaling in the bladder [66].

Findings in Rats Experimental diabetes in rats with streptozotocin produced higher bladder capacity, higher compliance, increased residual urine volume, lower voiding efficiency [58, 67–69], dysfunctional urethra [67, 70, 71], upregulation of M3 and M2-MR in the detrusor and urothelium [72–74], increased responsiveness to CARB and acetylcholine due to increased MR [68, 75–77], potentiation of cholinergic motor transmission due to enhanced release of acetylcholine in the detrusor [78], upregulation of P2X2 and P2X3-PR in the urothelium [74], increased release of ATP in the urothelium [79], and upregulation of P2Y2, P2Y4 and P2X4-PR in the detrusor [42, 74]. However, diabetes may induce a plasticity of the nonadrenergic noncholinergic and purinergic (P2X-type) mediated bladder contractile responses. The first one may be associated with diabetic neuropathic damage to bladder nerves, while impaired P2X purinergic contractions might be associated with detrusor hypertrophy [80]. Furthermore, experimental DM also produced decreased sensitivity of the urethral muscle to adrenoceptor agonists [71], downregulation of alpha1a-AR in the bladder [81], augmentation in beta1-AR mediated relaxation of the detrusor [82], upregulation of ROK signaling [83, 84], a decreased number of interstitial cells of Cajal (ICC) [85], the presence of c-kit-positive ICC [86], decreased production of nerve growth factor (NGF) [58, 87–90], increased synthesis of PG-E2 and PG-F2alpha [91], decreased expression of cannabinoid receptors 1 and 2 [92], altered function and/or expression of BKCa and KATP channels [93], a higher ratio of ATP/nitric oxide (NO) [79], impairment in sodium/potassium-ATPase and calcium ATPase pump [94], and over activation of Poly (ADP-ribose) polymerase and NF-kB in the bladder [95]. 5-hydroxytryptamine (5-HT)-1A receptor agonism promoted periodic external urethral sphincter (EUS) activity, thereby improving voiding efficiency [67].

Findings in Rabbits Upregulation of PuNT and a decrease in ChNT in rabbit detrusor contrary to the findings in rat may be species dependent [96]. Experimental diabetes produced a decrease in staining intensity of ICC in the bladder [97] and increased NOS binding sites in the bladder neck [98].

Findings in Mice Experimental diabetes produced an increase in M2-MR mediated contractile function and a corresponding decrease in M3-MR [99]. Later, it was shown that the upregulation of M2 receptors inhibits the development of urinary bladder neuropathy in the hyperglycemic state [100]. Experimental diabetes also pro-

duced upregulation of L-type voltage-operated calcium channels [101] and tumor necrosis factor alpha and ROK in the bladder [102].

Bladder Outlet Obstruction (BOO)

Physiological function of the bladder outlet is complex, and symptomatic consequences can result from outlet dysfunction [103]. BOO is much rarer in females than males [104]. In male patients, particularly in older age groups, BOO is comparatively common, usually as a consequence of benign prostatic hyperplasia (BPH) that leads to OAB [105, 106]. However, not all men with BPH develop lower urinary tract symptoms (LUTS). In addition, not all men with LUTS have BPH as the underlying cause [107].

Findings in Humans BOO in men produced significant changes in the bladder, including the emergence of purinergic, atropine-resistant contractions where ATP was a more potent contractile agonist [108, 109], increased P2X1-PR [110], an increased ATP/creatinine ratio [111], decreased expression of mucosal beta-3-AR [112], upregulation of alpha1-AR [113, 114], increased ROK signaling [115] and an upregulation of mucosal transient receptor potential (TRP) A1 channel [116]. BOO also produced increased urinary PGE2 [117], increased expression of iNOS in the urothelium [118], increased urinary NGF levels [119, 120] and decreased caveolin-1mRNA and protein in the detrusor of patients with BPH [121].

From the survey of research done on this topic, it is evident that different animal species (of either sex) with surgical induction of BOO have been used to study bladder function. Therefore in the following sections, research findings in animals have been categorized separately into males and females of their respective species.

Findings in Male Pigs BOO in Pigs gives a precisely defined bladder outlet resistance, closely resembling that of a human. In this animal models, BOO produced hypertrophy of the detrusor leading to the reduction in compliance. Voiding profiles showed a prolonged micturition time with high micturition pressure [122]. BOO also produced significant increase in the sensitivity of the detrusor to acetylcholine, reduction in response to intramural nerve stimulation affecting both cholinergic and non-cholinergic neurotransmission, partial denervation of the bladder and subsequent development of supersensitivity of the detrusor [123].

Findings in Male Rabbits BOO in male rabbits also seems to be an appropriate animal model with similar changes in bladder pathophysiology as those observed

in men due to BPH [124]. BOO produced an increase in PuNT and a decrease in ChNT [125], enhanced ROK [126-128], elevated PGE2 and PGF2alpha [129, 130], upregulation of ET-1 receptors [131], upregulation of vascular endothelial growth factor in the mucosa and angiotensin II in the detrusor [132], decreased expression of caveolin 1, 2 and 3 in the hypertrophied detrusor [133], down regulation of calcium-activated potassium channels [134], impairment in protein kinase C pathways [135], and bladder hypertrophy with involuntary bladder contractions [136].

Findings in Male Guinea-Pigs In this model, BOO produced DO, an increase in the population of ICC [137], a reduction in nerve density, total antioxidant capacity, glutathione and glutathione reductase [138], a reduction in sensory innervation and an increase in cholinergic innervation [139], enhanced ROK pathway [140], an increase in NO production [141], and upregulation of surface muscle ICC with M3-MR immunoreactivity in the bladder [142].

Findings in Male Rats Cystometric studies following BOO in rats revealed an increase in voiding frequency i.e. decrease in micturition interval (MI), a decrease in micturition volume, and an increase in non-voiding contraction (NVC) [143, 144]. BOO also produced an increase in the expression of M2 and M3-MR and P2X3-PR in the urothelium, an increase in M3-MR in the detrusor [145], an increase in bladder beta2 and 3-AR [146, 147], an increase in NGF and TRPV1 [144, 148, 149], an increase of 5-HT2A receptor mRNA [150], upregulation of ROK pathway [151], an increase in angiotensin II type 1 receptors [144, 152], increased level of NO [153] and decreased Maxi-potassium channel activity in the bladder [154].

Findings in Male Mice BOO mediates both functional and structural changes in the mouse bladder. Six weeks of obstruction caused an increase in bladder capacity, DO and detrusor pressure [155]. BOO produced decrease in the expression of Caveolin-1 mRNA and protein content in the bladder smooth muscle [121]. Apart from this classical obstructed model of BOO, transgenic male mice overexpressing aromatase have been used to investigate the molecular mechanism of BOO. These findings suggest the involvement of estrogen excess and/or imbalance of the androgen/estrogen ratio in the molecular pathogenic mechanism of BOO [156]. Furthermore, induction of BOO with testosterone and 17 β -estradiol produced voiding dysfunction after 2 and 4 months of hormone treatment and suggested to be a suitable model of BOO for better understanding of molecular mechanisms and for developing novel strategies to address BPH and BOO [157].

Findings in Female Pigs Obstructed bladder strips showed enhanced spontaneous phasic activity which might contribute to unstable myogenic bladder contractions observed in vivo [158] and 2-fold more sensitive to potassium depolarization [159].

Findings in Female Rabbits BOO resulted in a significant decrease in the activity of choline acetyltransferase [160].

Findings in Female Guinea Pigs In this model, BOO produced DO with NVC, a reduction in micturition interval, an increase in micturition pressure, increased populations of ICC [161] and increase in c-kit positive ICC and spontaneous calcium waves with higher frequency in cultured ICC in the bladder [162].

Findings in Female Rats Apart from selecting male animals for BOO, considerable studies have been done in female rat BOO models. BOO produced DO with NVCs, a decrease in micturition interval, and an increase in micturition pressure and bladder capacity after 2 to 6 weeks of BOO [163–167]. At the initial phase of BOO, decompensation of bladder activity was higher; however during the later phase, there was an increasing tendency of compensated bladders [167]. Moreover, there was an initial inflammatory response to the stress of the BOO as evidenced by a significant increase in mRNA levels of transforming growth factor β , connective tissue growth factor, hypoxia inducible factor 1 α , and platelet derived growth factor that eventually leads to fibrosis in the bladder [168]. It has been suggested that the occurrence of DO and NVC following BOO might be due to the involvement of bladder mechanoreceptors, α 1-AR, ATP, and glutamate receptors [164, 169–171]. BOO produced significant changes in the bladder that include the development of bladder hypertrophy with a thick urothelium [166], increased α 1d-AR [172], an increased population of ICC with enhanced P2X3-PR [165, 173], upregulation of M2-MR [41, 174], a decrease in M3-MR mediated contractility [175], an alteration in the sensitivity of detrusor to acetylcholine and substance-P [176], upregulation of ChNT and a marginal reduction in PuNT after 3 weeks of BOO [177] and a significant decrease in acetylcholine release following 3–6 months after BOO [178]. This discrepancy in ChNT between these 2 studies [177, 178] might be due to differences in the duration of BOO. Apart from these changes in the neurotransmitter system, BOO also produced other changes in the bladder, including increased NGF [179], increased expression of cold receptor TRPM8 in the epithelium and in the afferent neurons [166, 180], upregulation of EP4 receptors [181], increased iNOS, neuronal nitric oxide synthase (nNOS)

and endothelial NOS [165, 182, 183], higher expression of nNOS in the sacral 1 spinal cord in the females than males [184], upregulation of 5-HT1A and 5-HT2A receptors in the detrusor [185, 186], upregulation of connexin 43 [187], increased L-type calcium channels [188], enhanced the function of large conductance and small conductance calcium activated potassium channels in detrusor [189], increased expression of Aquaporin 2–3 channels [183], increased fibroblast growth factor in the urothelium [190], decreased expression of angiotensin II type 1 receptor [191], and functional alterations in bladder afferent pathways [192]. Moreover, BOO also produced downregulation of TWIK-related arachidonic acid-activated potassium channels [193] and an irreversible decrease of glycinergic activity in the spinal cord [194]. It has been observed that EP1 receptor was involved in the initiation of micturition in BOO rats [195].

Findings in Female Mice BOO produced increased NVC, threshold pressure, micturition pressure, bladder capacity and residual urine volume [196, 197]. BOO also produced enhanced ChNT, reduced PuNT and an increase in ROK signalling [198], induction in cyclooxygenase (COX)-2 [199] and iNOS expression [200], upregulation of protein kinase pathway [201], upregulation of the hypoxia inducible factor-1 pathway [202] and downregulation of stretch-dependant potassium channels called TREK-1 in the bladder [203]. It has been observed that macrophage migration inhibitory factor is involved in the sequence of events leading to detrusor muscle loss and fibrosis following obstruction [204]. Furthermore, it has been observed that EP1 was not involved in controlling micturition of BOO mice [205] contrary to the finding in rat [195] suggesting a species difference in the involvement of PG receptors in bladder function following obstruction.

Spinal Cord Injury (SCI)

SCI produces bladder dysfunction, leading to the impairment of storage and voiding functions (i.e. ranging from UI to complete loss of the capacity to empty the bladder) [206]. Functionally, the bladder is initially areflexic (with complete urinary retention), but then becomes hyperreflexic due to the emergence of a spinal micturition reflex pathway. However, voiding is commonly inefficient due to simultaneous contractions of the bladder and urethral sphincter (detrusor sphincter dys-synergia) [207, 208].

Findings in Humans

Recent observations have suggested the emergence of two independent excitatory pudendal-to-bladder reflex pathways following SCI [209]. Several notable changes have been observed following SCI, including an upregulation of M2-MR [210], P2X2 and P2X3-PR in the bladder [211, 212], enhanced release of ATP in the damaged spinal tissue [213], increased TRPV1 immunoreactivity in the urothelium [214, 215], increased expression of iNOS in the urothelium [216], increased NGF in urine [120] and abnormalities in urothelial expression in epidermal growth factor (EGF) receptors [217].

Findings in Rats

This animal model closely resembles the clinical conditions of SCI. The relative low cost of this animal model and the easy maintenance makes it a valuable tool to study such a condition [218]. SCI in rats displayed NVC during bladder filling, resulting in an increased bladder afferent nerve firing [219]. At the initial phase of SCI, there might be a failure in ChNT, as revealed from a decrease in the vesicular ACh transporter-positive fibers in the bladder [220]. Furthermore, there was a higher expression of $\alpha 1d$ -AR in the detrusor [221], predominance of M2-MR in the detrusor and urothelium [222, 223], upregulation of PuNT in the bladder and an enhanced release of ATP in the spinal cord [224–227] and involvement of the P2X3/P2X2/3-PR on bladder afferent nerves in regulating sensory activity and NVCs in the bladder [228]. Other notable changes in the bladder following SCI include an impairment in urothelial function [229], upregulation of ET-1 receptors [230], increased release of PGE2 (where the urothelium partly contributes to this increase) [231], increased expression of connexin 43 and 26 in the urothelium [232], increased levels of NGF [233], upregulation of the kinin B1 and B2 receptors [234], up-regulation of TRPA1 [235], involvement of TRPV1 in producing neurogenic DO [236], decreased population of ICC [237], downregulation of voltage-gated potassium channels [238], and an upregulation of signal-regulated kinase 1 and 2 pathways [239]. Several notable changes have also been observed in the spinal cord, including the sprouting of the afferent fibers with the expression of substance P (SP) [240, 241], increased levels of NGF [233], higher expression of NOS [242], upregulation of EGF receptors [243], increased number of Fos immunoreactive cells [244], expression of pituitary adenylate cyclase activating peptide [245], increase in the excitatory amino acid glutamate, and the inhibitory amino acids glycine and taurine [246], hypofunction of

gamma amino butyric acid (GABA)-ergic mechanisms which might be responsible, at least in part, for the development of detrusor sphincter dyssynergia after SCI [247]. It has been reported that activation of 5-HT1A receptors that produce relaxation of the EUS improve voiding efficiency and LUT function following SCI [248–250].

Findings in Cats

Capsaicin-sensitive C fiber bladder afferents contribute to bladder hyperactivity and play an essential role in triggering automatic micturition in chronic SCI cats [251]. Circuitry for both the excitatory and inhibitory pudendal afferent nerves to bladder reflexes undergoes a marked reorganization after SCI [252]. Chronic SCI produces an expression of vasoactive intestinal peptide immunoreactivity in primary afferent axons in the lumbosacral spinal cord [245] and emergence of 2 populations of bladder afferent C-fibers (chemosensitive and mechanosensitive) [253]. Activation of 5-HT1A receptors produce an action on inter neuronal pathways in the spinal cord or on the C-fiber afferent limb of the spinal micturition reflex and not on bladder smooth muscle or the efferent limb of the reflex pathway to inhibit DO from SCI [254].

Findings in Rabbits

In this animal model, no micturition reflex, EUS activity, or hind-limb spasticity were observed and the flaccid state continued for 4 weeks. It is suggested that a segmental micturition reflex pathway exists initially in the rabbit sacral cord, because reappearance of the micturition reflex was extremely quick (1–2 days) compared to that of cats (2–3 weeks) [255]. ChNT increased to 75% whereas the PuNT decreased to 25% in the bladder following chronic SCI suggesting the shifting of neurotransmission to a cholinergic dominance [256].

Findings in Mice

Aquaporin-4 water channels plays a protective role after contusion following SCI by facilitating the clearance of excess water to reduce spinal cord edema, and that targeting edema after SCI may be a novel therapeutic strategy [257].

Stroke and Brain Injury

UI with various patterns of detrusor contractility is frequently observed in patients following stroke, cerebrovascular accident, and traumatic brain injury [258, 259].

Findings in Rats

Cystometric studies in the rat, following experimental cerebral infarction by occlusion of the middle cerebral artery, revealed DO with a decrease in bladder capacity, micturition volume, micturition interval and an increase in residual urine volume [260–263]. These effects are seen in the bladder, spinal cord and brain. In the bladder, there was an up-regulation of MR [262] and nNOS [264]. In the spinal cord, there was an upregulation of nNOS [264]. In the brain, there was a downregulation in the kappa opioidergic mechanism, decrease in glutamate, and glycine levels [265, 266], a downregulation of AChE [267], an alteration of the dopaminergic-glutamatergic interaction [268], a change in the GABA-ergic mechanism [269] and an increase in COX-2 and PG-E synthase (i.e. activation of the arachidonic acid cascade) [261, 270].

Parkinson's Disease (PD)

PD is an extrapyramidal neurological disorder due to the degeneration of the nigrostriatal dopaminergic pathways that produces dysfunction of the LUT with symptoms of urgency, frequency, nocturia and urge incontinence as the disease progresses [271–273]. There is a greater incidence of PD in men than in women [274].

Findings in Rats

The 6-Hydroxydopamine (6-OHDA) model is a widely used animal model of PD [275]. Male rats were observed to be more susceptible to the 6-OHDA treatment than females [276]. The 6-OHDA model produced DO, as reflected by higher micturition frequency (i.e. decreased MI, bladder capacity, micturition volume, bladder compliance and increase in maximal micturition pressure [277–279], which might be due to dysfunction of GABAergic regulation underlying the micturition reflex [279] and enhanced supra spinal adenosine A2A receptors [280].

Multiple Sclerosis (MS)

MS is an inflammatory disease that leads to disseminated lesions of the central nervous system, resulting in both somatomotor and autonomic disturbances [281]. Most MS patients suffer from DO, UI, detrusor sphincter

dyssnergia, and difficulty in emptying the bladder [282, 283].

Findings in Humans

Bladder biopsies of MS patients revealed an increase in P2X3-immunoreactive nerve fibers in the suburothelium [211], an increase in urothelial TRPV1 [215], a greater density of calcitonin gene-related peptide and SP positive nerve fibers [284] and presence of ICC in the upper lamina propria with a shift towards a fibroblast phenotype [285]. It has been observed that cannabidiol, a non-psychoactive cannabinoid, reduced ACh-induced contractions in the bladder, suggesting the efficacy of cannabis medicines in reducing UI episodes in patients with MS [286].

Findings in Rats

Induction of experimental autoimmune encephalomyelitis in rats, a model of MS produced bladder dysfunction as revealed from the increase in bladder size with detrusor hyperactivity [287, 288].

Findings in Mice

Experimental autoimmune encephalomyelitis model in mice produced enhanced expression of connective tissue growth factor and increased growth of connective tissue in the bladder [289]. Apart from the experimental autoimmune encephalomyelitis model of MS, infection with Semliki Forest Virus in mice has also been proposed as another animal model for MS. In this model, there was an increase in PuNT in the bladder without any change in ChNT [290]. Despite these few studies, it is needless to say that further research needs to be done to evaluate LUT function in animal models of MS.

Interstitial Cystitis (IC)

IC is defined as a chronic inflammatory multifactorial bladder syndrome of unknown etiology [291]. UI due to IC is more prevalent in women, affecting 1 in every 4 to 5 women and 1 in every 20 men [292], suggesting the role of female sex hormones in IC [293].

Findings in Humans

Significant findings in the bladder of IC patients include an upregulation of purinergic signaling [294], increased expression of P2X-PR and ATP release in the urothelium [295, 296], significant upregulation of M2-MR, P2X1 and P2X2-PR in the detrusor [297], increased urinary NGF levels [298–300], loss of PGE2 from the

urothelial cells [301], enhanced expression of SP receptors in the detrusor [302], enhanced levels of bradykinin in the bladder [303], increased TRPM8 immunoreactivity [304], increased expression of TRPV1, 2 and 3, TRPM2 and NGF [305], increased expression of iNOS in the urothelium [306] and high levels of NO in the bladder [307].

Findings in Cats

Feline cystitis (FC) is used as an animal model for human IC [308]. Research findings from FC have shown increased ATP and decreased P2X1 and P2Y2-PRs in the urothelium, decreased P2X1-PRs in the detrusor [309, 310] and increased expression of iNOS in the detrusor and urothelium [311].

Findings in Rats

Apart from the FC model, cystitis was also induced in rats by cyclophosphamide treatment, which produced IC-like inflammatory changes [312]. Cystometric studies in cyclophosphamide treated rats have revealed a higher rate (83%) of DO with lower bladder capacity, lower compliance, and decreased micturition interval [313]. Cyclophosphamide treatment produced abnormalities in bladder function following downregulation of pharmacologically relevant MR and PR in the bladder [314, 315], increased expression and/or function of P2X-PR in both the pelvic and lumbar splanchnic pathways [316], upregulation of iNOS in the detrusor and urothelium [317], upregulation of BK-B1 receptors in the urothelium [318], upregulation of NOS expression in the neuronal voiding centers [319], upregulation of NGF in the detrusor and urothelium [317, 320], increased expression of COX-2 and EP4 in the bladder [321, 322], activation of TRPA1 in the bladder [323] and involvement of transforming growth factor-beta isoforms (1, 2 and 3) and their receptors in the bladder in cyclophosphamide mediated cystitis [324], increased FOS immunoreactive cells in the spinal cord [325], a higher concentration of PGE2 in the spinal cord [326], increased expression of COX-2 and EP4 in the spinal cord [322], increased urinary levels of interleukin-1 β and interleukin-17 [314]. Female rats treated with cyclophosphamide had significantly higher levels of NO₂/NO₃⁻ in urine when compared to male rats, suggesting the role of NO in the manifestation of IC predominantly found in females [327].

Findings in Mice

Experimental cystitis produced significant upregulation of P2X7-PR [328], activation of Ca_v 3.2 channels, one

of the T-type calcium channels [329], and distention-induced ATP release in the bladder [330].

Findings in Guinea-Pigs

In connection to the increased purinergic signaling and inflammatory mediators in the bladder of IC patients, it has been observed that histamine, bradykinin, and SP potentiated PuNT in the guinea-pig bladder [331, 332].

Stress and Depression

Studies have revealed an association between depression and OAB symptoms [333] and women are more likely than men to have symptoms of depression [334]. These observations are further correlated with the findings that occupational stress and a history of depression are risk factors for the development of OAB in women [335–337], where corticotropin releasing factor (CRF) [338] and central monoamines might be involved [339].

Findings in Rats

Exposure of social stress in rats induced bladder dysfunction resembling OAB due to the upregulation of CRF in the Barrington's nucleus in the brain [340]. It has also been reported that psychological stress in rats produced an increase in micturition frequency with a simultaneous increase in mast cells of the bladder [341]. Role of CRF in producing DO is strengthened by the fact that CRF itself stimulated micturition in normal [342] and cyclophosphamide treated rats [343]. Interestingly, it has been observed that CRF signaling in rats during stress is sex dependent where females are more sensitive to low levels of CRF [344]. However, other than social stress, cold stress and repeated variate stress also produced DO in rodents [345, 346]. Moreover, rats treated with clomipramine in neonatal conditions developed depression in adult condition with symptoms of OAB possibly through altered serotonin function in brain [347].

Conclusion

Studies cited in this review have shown several structural and functional changes in not only the LUT but also in the brain and spinal cord under different physiopathologic conditions of OAB (table 1). Alterations have been observed in the human and animal bladders in the following areas: neurotransmitter systems such as the cholinergic, purinergic, adrenergic, serotonergic, glycinergic, GABA-ergic, and nitrergic systems, as well as

Table 1. Summary of the major findings under different conditions of OAB in humans and animals

Conditions	Species	Research findings
Ageing	humans	<ul style="list-style-type: none"> ↑ PuNT and M2-MR in the urothelium of both male and female bladder ↓ ChNT and M3-MR in the detrusor, ↓ P2X1-PR in the male detrusor
	pigs rats	<ul style="list-style-type: none"> ↑ expression of vascular endothelial growth inhibitor, death receptor 3 and NF-κB in the detrusor ↓ contractile response to carbachol due to ↓ in MR in the bladder ↓ NOS and ET receptors in the bladder shift of contractile phenotype from M3-MR to M2-MR in male bladder ↑ expression of P2Y4-PR, P2X3-PR and alpha-1D-AR in the bladder ↓ expression of PG-21 androgen receptors, SRC-1 and pCREB in male while SRC-1 and pCREB was unchanged in female spinal cord
Diabetes mellitus	guinea-pigs mice	<ul style="list-style-type: none"> ↓ PuNT, AChE positive neurons and calcium sensitivity in the bladder ↓ response to bethanecol and cholinergic pathway in the bladder ↑ expression of P2X3-PR in the urothelium ↑ response to ATP, lipid peroxides and iNOS in the bladder ↓ total antioxidant capacity and partial loss of SMM2 in the bladder
	humans rats	<ul style="list-style-type: none"> ↑ ROK signaling and impairment in A delta and C fibers in the bladder ↑ expression of M3-MR and M2-MR in the detrusor and urothelium ↑ responsiveness to carbachol due to ↑ in MR in the bladder potentiation of ChNT due to ↑ release of ACh in the detrusor ↑ expression of P2Y2, P2Y4 and P2X4-PR in the detrusor ↑ expression of P2X2 and P2X3-PR and ↑ level of ATP in the urothelium, ↑ ROK, ratio of ATP/NO, PGE2 and PGF2α in the bladder ↑ poly(ADP-ribose)polymerase and NF-κB in the bladder ↑ beta1-AR mediated relaxation of detrusor ↓ alpha1a-AR, number of ICC, c-kit positive ICC and NGF in the bladder ↓ expression of cannabinoid receptors 1 and 2, altered function and/or expression of BKCA and KATP channels, impairment in sodium/potassium ATPase and calcium ATPase pump in the bladder
Bladder outlet obstruction	rabbits mice	<ul style="list-style-type: none"> ↓ ChNT and staining intensity of ICC in the bladder ↑ PuNT in the bladder and ↑ NOS binding in the bladder neck ↑ M2-MR mediated contraction with a ↓ in M3-MR in the bladder ↑ L-type VOC channels, TNF-alpha and ROK in the bladder
	men	<ul style="list-style-type: none"> ↑ PuNT where ATP is the potent contractile agonist in the bladder ↑ expression of P2X1-PR and ↑ ATP/creatinine ratio in the bladder ↑ expression of alpha1-AR, iNOS, ROK and TRPA1 in the bladder ↓ expression of urothelial beta3-AR and caveolin-1 mRNA in the bladder ↑ PGE2 and NGF levels in urine
Bladder outlet obstruction	pigs (m)	<ul style="list-style-type: none"> ↑ sensitivity of detrusor to acetylcholine ↓ response to intramural nerve stimulation affecting both cholinergic and noncholinergic neurotransmission and a ↓ in compliance in the bladder
	rabbits (m)	<ul style="list-style-type: none"> ↑ PuNT and a ↓ ChNT in the bladder ↑ ROK, ET-1 receptors, PGE2, PGF2α, vascular endothelial growth factor and angiopoietin 1 in the bladder ↓ expression of caveolin 1, 2 and 3 in the detrusor ↓ calcium activated potassium channels in the bladder impairment in protein kinase C pathways in the bladder
Bladder outlet obstruction	guinea-pigs (m)	<ul style="list-style-type: none"> ↓ sensory innervations and ↑ Cholinergic innervations in the bladder ↑ number of ICC, ICC with M3-MR, ROK and NO in the bladder ↓ antioxidant capacity, glutathione and glutathione receptors in the bladder
	rats (m)	<ul style="list-style-type: none"> ↑ expression of M2-MR, M3-MR, P2X3-PR in the urothelium ↑ expression of M3-MR in the detrusor, ↑ beta2 and beta3-AR, NGF, TRPV1, ROK and NO in the bladder ↑ expression of 5HT2A and angiotensin II type 1 receptors in the bladder ↓ maxi-potassium channel activity in the bladder
Bladder outlet obstruction	mice (m)	<ul style="list-style-type: none"> ↓ expression of Caveolin-1mRNA in the detrusor ↑ EST-alpha pathway and/or imbalance in AND/EST ratio in the bladder
	pigs (f)	<ul style="list-style-type: none"> ↑ spontaneous phasic activity in the bladder ↑ sensitivity to potassium depolarization in the bladder
Bladder outlet obstruction	rabbits (f)	<ul style="list-style-type: none"> ↓ activity of choline acetyltransferase in the bladder
	guinea-pigs (f)	<ul style="list-style-type: none"> ↑ number of ICC and c-kit positive ICC in the bladder ↑ frequency of spontaneous calcium waves in ICC in the bladder
Bladder outlet obstruction	rats (f)	<ul style="list-style-type: none"> ↑ ChNT with ↑ Expression of M2-MR in the bladder ↑ population of ICC with enhanced P2X3-PR in ICC in the bladder ↑ alpha1d-AR, 5-HT1A, 5-HT2A and EP4 receptors in the bladder ↑ expression of mRNA of TGF-beta, connective tissue growth factor, hypoxia inducible factor 1alpha,

Table 1. (continued)

Conditions	Species	Research findings
Spinal cord injury	mice (f)	platelet derived growth factor and fibroblast growth factor in the bladder ↑ iNOS, nNOS, eNOS, NGF, Connexin 43 and TRPM8 in the bladder ↑ L type calcium channels, calcium activated potassium channels and AQP 2-3 channels in the bladder ↓ expression of angiotensin II type 1 receptors in the bladder ↓ TWIK-related arachidonic acid-activated potassium channels, nNOS and glycinergic activity in the spinal cord. EP1 receptors contribute in DO ↑ ChNT and ↓ PuNT in the bladder ↑ ROK, COX-2, iNOS, protein kinase and HIF-1 pathway in the bladder ↓ stretch dependent potassium channels in the bladder MMIF is involved to induce detrusor fibrosis following BOO EP1 receptors do not contribute in DO
	humans	↑ expression of M2-MR, P2X2-PR and P2X3-PR in the bladder ↑ expression of TRPV1 and iNOS in the urothelium ↑ ATP in the spinal cord and ↑ level of NGF in urine abnormal expression of EGF receptors in the urothelium
	rats	↑ expression of M2-MR, alpha1d-AR and ET-1 receptors in the bladder ↑ PuNT in the bladder ↑ PGE2 and connexin 43 and 26 in the urothelium ↑ NGF, BK-1, 2 receptors, TRPA1, kinase 1 and 2 pathway in the bladder ↑ ATP, NOS, SP, EGF and PCAP-IR in the spinal cord ↑ glutamate, glycine, taurine in the spinal cord ↓ number of ICC and voltage operated potassium channels in the bladder ↓ GABA activity in the spinal cord P2X3/P2X2/3-PR regulates sensory function. TRPV1 involved in producing DO in the bladder
	cats	↑ vasoactive intestinal polypeptide-IR in the spinal cord emergence of chemosensitive and mechanosensitive C fibers in the bladder. activation of 5-HT1A receptors in the spinal cord
	rabbits mice	↑ ChNT and ↓ PuNT in the bladder protective role of AQP-4 water channels in spinal cord edema
Stroke and brain injury	humans	UI with various patterns of detrusor contractility
	rats	↑ expression of MR and nNOS in the bladder ↑ expression of nNOS in the spinal cord ↑ expression of COX2 and PGE synthase in the brain ↓ kappa opioids, glutamate, glycine and AChE, altered dopaminergic, glutaminergic and GABAergic function in the brain
Parkinson's disease	humans	dysfunction of LUT as PD progresses. PD is higher in men than women degeneration of nigrostriatal dopaminergic pathway in the brain
	rats	↑ expression of supraspinal adenosine A2A receptors impairment of GABAergic system in the brain
Multiple sclerosis	humans	↑ expression of P2X3-IR nerve fibers and TRPV1 in the urothelium ↑ expression of CGRP and SP positive nerve fibers in the bladder ↑ number of ICC with fibroblast phenotype in the bladder cannabidiol ↓ ACh induced contractions of detrusor
	rats	induction of experimental autoimmune encephalomyelitis (EAE) – a model of MS, produced an increase in bladder size and hyperactivity
	mice	↑ expression of CTGF and connective tissue in the bladder in EAE model ↑ PuNT in the bladder in Semliki Forest Virus model of MS
Interstitial cystitis	humans	↑ PuNT, P2X-PR, ATP, TRPM8, iNOS in the urothelium ↑ expression of M2-MR, P2X1-PR, P2X2-PR in the detrusor ↑ expression of SP receptors. ↑ Level of bradykinin and NO in the bladder ↑ expression of TRPV1, 2 and 3, TRPM2 in the bladder ↑ level of NGF in urine and bladder ↓ PGE2 in the urothelium
	cats	↓ expression of P2X1-PR (detrusor). ↑ Expression of iNOS in the bladder ↓ expression of P2X1-PR, P2Y2-PR and ↑ ATP in the urothelium
	rats	↓ expression of MR and PR in the bladder ↑ expression of P2X-PR in the Pelvic and Splanchnic nerve ↑ COX-2, NGF, iNOS, TRPA1, EP4 and BK-B1 receptors in the bladder ↑ PGE2, COX-2, EP4 and Fos IR cells in the spinal cord ↑ levels of NO2/NO3, interleukin-1beta and 17 in urine ↑ expression of NOS in the voiding center
	mice	↑ P2X7-PR and ATP release, activates Cav 3.2 channels in the bladder

Table 1. (continued)

Conditions	Species	Research findings
	guinea-pigs	potentiation of PuNT by histamine, bradykinin and SP in the bladder
Stress and depression	humans	stress and depression are risk factors for OAB in women
	rats	social stress produces bladder dysfunction resembling OAB ↑ CRF in Barrington's nucleus in the brain. ↑ Mast cells in the bladder sex difference in CRF sensitivity which is higher in female than male

↑ = Increase; ↓ = decrease; M = male; F = female; MR = muscaric receptor; PR = purine receptor; NF-κB = nuclear factor kappa-B; ET = endothelin; SRC-1 = steroid receptor co-activator-1; pCREB = phosphorylated form of C-AMP response element binding protein; AChE = acetylcholine esterase; SMM2 = smooth muscle myosin heavy chain isoform 2; VOC = voltage operated calcium; TNF = tumor necrosis factor; EST = estrogen; AND = androgen; TGF = transforming growth factor; HIF = hypoxia inducible factor; MMIF = macrophage migration inhibitory factor; EGF = epidermal growth factor; BK-1, 2 = bradykinin 1 and 2; PCAP = pituitary adenylate cyclase-activating peptide; CGRP = calcitonin gene related peptide; SP = substance P; CTGF = connective tissue growth factor.

in other areas such as PG, NGF, ROK, ICC, TRP and ion channels. M2-MR was increased in ageing, DM, BOO, SCI and IC. PuNT was increased in ageing, BOO, SCI, MS, DM and IC. ROK was increased in BOO and DM. TRP channel activity was enhanced in BOO, SCI, MS and IC. Furthermore, ICC was increased in BOO and MS. As these areas [25, 348–355] play crucial roles in the central and peripheral regulation of LUT functions, further research should be conducted in order to find better therapeutic targets against OAB. However, apart from these areas, cannabinoids seems to be a promising area for future drug development research on OAB due to their involvement in controlling LUT function in animals and humans [356, 357] especially, in patients with MS [286, 358–360], BOO [361], rat models of DM [92] and mouse models of cystitis [362, 363]. Interestingly, there was a lack of similar alterations between human and animal studies with respect to the structural and functional changes in the LUT due to the conditions of OAB. From the perspective of human studies, this might be due to the presence of different disease conditions, and in the case of animal studies, this might be due to either the use of different animal models [364, 365] or a sex difference that affects the physiology and pharmacology of the LUT [9, 366–368]. However, the existence of different mechanisms in the pathophysiology of the LUT cannot be ruled out for each of the conditions of OAB. In fact, this would be justified by the fact that patients with different conditions of OAB may appear to have similar symptoms, but in reality, the underlying mechanisms may be diverse [369, 370]. Therefore, the same treatment is unlikely to be effective for OAB since different conditions require different approaches for optimal manage-

ment [371, 372]. It is anticipated that this review would be helpful for future research on OAB with a prospect of improved and more specific drug development in order to find satisfactory relief for OAB patients.

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