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Does central sensitization help explain idiopathic overactive bladder?

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Abstract

The pathophysiological mechanisms underlying overactive bladder syndrome (OAB) can include dysfunction of sensory pathways of the peripheral and central nervous systems, resulting in bladder hypersensitivity. Central sensitization describes an induced state of spinal hypersensitivity that is associated with a variety of chronic pain disorders that share many attributes with OAB, albeit without the presence of pain. As such, the concept of central sensitization might be relevant to understanding the mechanisms and clinical manifestations of OAB syndrome. An understanding of the pathophysiology and clinical manifestations of central sensitization, and the evidence that supports a role of central sensitization in OAB, including the potential implications of mechanisms of central sensitization for the treatment of patients with OAB could provide a novel approach to the treatment of patients with this disease. Such an approach would be especially relevant to those patients with central sensitization-related comorbidities, and has the potential to improve the outcomes of these patients in particular.

Affecting one out of seven people in the USA[1,2], overactive bladder (OAB) places considerable strain on health-care expenditures and this burden will likely increase as the US population continues to age[2–4]. Idiopathic OAB is defined by the presence of urinary urgency (the sudden and compelling desire to pass urine that cannot be delayed), which is often, but not necessarily, accompanied by increased urinary frequency (usually defined as more than eight voids per 24-hour period), nocturia, and, in some cases, urgency-related incontinence[5,6]. Current understanding of the pathophysiology of OAB integrates mechanisms involving input from within the bladder as well as from the peripheral and central nervous systems. In the past decade, attention has become focused on the

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Author contributions

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contributions of afferent nerve function in particular, which underscores the potential importance of hypersensitivity[7,8].

Hypersensitivity of the bladder involves the activation of neurophysiological pathways that overlap considerably with those involved in the sensitivity of other pelvic and visceral organ systems. This overlap might facilitate visceral or pelvic organ crosstalk, such as between the bladder and bowel, and could explain co-dysfunction and the common co-occurrence of functional disorders, such as OAB and irritable bowel syndrome (IBS). Pelvic organ crosstalk might also explain how central sensitization, a well-recognized mechanism of centrally amplified pain perception that is believed to contribute to many chronic pain and hypersensitivity disorders[9–11], could affect bladder function and contribute to OAB. This syndrome might, in part, originate from nonpainful hypersensitivity of the bladder; the concept of central sensitization could, therefore, be relevant to understanding the mechanisms and clinical manifestations of OAB.

Fitting OAB into the broader construct of central sensitization might have important implications for understanding the underlying pathophysiological mechanisms that are relevant to OAB treatment and potentially enhance the treatment outcomes of patients with this disease. In this Perspectives, we review the pathophysiology and clinical manifestations of central sensitization, the pathophysiology of OAB and its overlap with central sensitization, the current evidence for a contribution of central sensitization to the pathophysiology of OAB, and treatment considerations for women with OAB syndrome that might have a central sensitization component.

Central sensitization

The International Association for the Study of Pain defines central sensitization as “increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold afferent input.” (REF. 12). This term describes an induced state of spinal hypersensitivity, driven by C-fibre input following activation by persistent, peripheral nociceptive signals. Once established via intraspinal mechanisms, central sensitization enhances all neuronal responses, including those derived from low-threshold inputs (signals that normally generate nonpainful sensations)[10,13]. Repetitive activation of afferent C-fibres, in particular capsaicin-sensitive nociceptive C-fibres synapsing at the dorsal horn of the spinal cord, results in heterosynaptic potentiation whereby afferent signals resulting from activation of not only nociceptive C-fibres, but also of low-threshold Aβ and Aδ mechanoreceptors, are amplified[10,13]. In the pathogenesis of central sensitization, the peripheral nerves generally function normally, but changes in function occur in central neurons. These hypersensitized spinal neurons have reduced firing thresholds, increased receptive field sizes, and ongoing stimulus-independent activity, as well as greater intensity of evoked responses compared with otherwise healthy central neurons[13]. This process, in effect, facilitates normally subthreshold signals or action potentials from Aβ and Aδ afferent fibres, elevating these to suprathreshold action potentials, thus leading to activation of central neural circuits. Owing to convergence of neural circuits and integration of larger spatial fields at the spinal level, the hypersensitivity associated with central sensitization can extend to areas remote from the conditioning C-fibre stimulus, potentially contributing to

spread of symptoms[13]. Ascending and descending projections to and from the brain integrate these spinal mechanisms with higher CNS function, which can further modulate central sensitization, resulting in direct and/or indirect (through decreased inhibition) facilitation of spinal nociceptive transmission. Because descending central processes tend to be more diffuse, bilateral, and nonsegmental than sensitized spinal circuits, descending afferent facilitation associated with central sensitization can, therefore, impart more widespread effects that occur in conjunction with ongoing changes at the spinal level[13].

At the cellular and molecular level, multiple factors seem to be involved in the development of central sensitization, although our understanding of these pathophysiological mechanisms is limited and continues to evolve. The development of central sensitization generally reflects a transition from acute to chronic pain through mechanisms that involve neural plasticity, similar to the better-established mechanisms of long-term potentiation or even memory, and has been thoroughly reviewed elsewhere[14–17]. Recruitment and activation of *N*-methyl-D-aspartate (NMDA) receptors in the dorsal horn of the spinal cord seems to be one of the principal mediators of central sensitization[14,15]. NMDA receptors respond directly to glutamate, the primary excitatory neurotransmitter involved in nociception, but are also stimulated indirectly by substance P, calcitonin gene-related peptide, and brain-derived neurotrophic factor (BDNF) released from sensory nerve terminals in the spinal cord in response to peripheral stimulation[15,17]. Neurotrophic factors, such as nerve growth factor (NGF)[18] and BDNF in particular, have an important role in triggering and maintaining central sensitization through interactions with primary and secondary spinal afferents and microglial cells in the dorsal horn of the spinal cord[19,20] and dorsal root ganglion[15]. Research published in the past 5 years also identifies a prominent role of glial cells in the pathophysiology of central sensitization[20,21].

Data from experimental studies demonstrate that the conditioning nociceptive stimuli that induce central sensitization can originate from sources of cutaneous pain, muscle and joint pain, and visceral pain[10]. However, owing to these aforementioned mechanisms, once central sensitization develops, normally subthreshold signals from peripheral organs can cause pain to be perceived without the presence of tissue injury or nociceptive stimulation, which is often perceived beyond the site of initial injury. In the setting of central sensitization, stimuli that generally do not provoke pain can produce pain (such as allodynia) and stimuli that normally provoke pain can produce pain of a higher intensity (such as hyperalgesia) (FIG. 1). This hypersensitivity might also increase the perceived intensity of nonpainful sensations such as warmth, cold, and touch (hyperaesthesia)[22] as well as that of visual and auditory stimuli[9]. These effects on perception of nonpainful sensations might be particularly relevant to understanding the role of central sensitization in conditions not generally considered to be painful, such as OAB.

Clinically, central sensitization is thought to contribute to the pathophysiology of a number of chronic pain and somatic conditions, referred to variably as functional somatic syndromes, somatoform disorders, medically unexplained clinical conditions or central sensitization syndromes (BOX 1). Virtually any sensory experience, including nonpainful sensation, that results in greater-than-anticipated amplitude, duration, and/or spatial extent of sensation derived from a defined peripheral stimulus potentially reflects central

amplification owing to increased excitation or reduced inhibition[10]. Features of patients' symptoms indicating central hypersensitivity in the context of pain include: pain mediated by low-threshold Aδ fibres; spread of pain sensitivity to areas with no demonstrable pathology; aftersensations; enhanced temporal summation; and the maintenance of pain by low-frequency stimuli that normally do not evoke any ongoing pain[10]. In addition to hypersensitivity to pain, patients often demonstrate 'sensory amplification' with heightened sensitivity to nonpainful stimuli, including visual and auditory stimuli (such as migraine with aura)[9].

Many conditions have been identified as central sensitization syndromes, including osteoarthritis, temporomandibular joint disorders (TMJD), fibromyalgia, chronic fatigue syndrome, headache, complex regional pain syndrome, IBS, and lower back pain, among others[9–11,23–26]. In the pelvis, central sensitization has also been implicated in chronic pelvic pain, endometriosis, vulvodynia, and dysmenorrhea as well as interstitial cystitis/bladder pain syndrome (IC/BPS)[7,27–31]. Several additional painful genitourinary conditions characteristically involve abnormal and heightened processing of sensory information, including dyspareunia, orchalgia, chronic epididymitis, and chronic prostatitis/chronic pelvic pain syndrome, and some have hypothesized a role for central sensitization in these as well[7]. OAB has also been suggested to be a hypersensitivity disorder[29].

Multiple conditions that can arise as a result of central sensitization often co-occur in the same individual; this is an important pathophysiological aspect of central sensitization syndromes. Thus, clustering of these conditions is not only common, compounding the negative effects of each individual condition on health-related quality of life, but is also considered a distinguishing characteristic of these disorders[9,11,32–37]. Indeed documenting the co-occurrence and overlap of multiple central sensitization syndromes in conditions of interest has been proposed as a valid method for defining additional conditions as central sensitization syndromes, which would also presumably share similar, or the same, underlying mechanisms of central sensitization[11,28].

Psychosocial comorbidities are common among individuals with central sensitivity syndromes and overlap with a variety of psychiatric disorders, such as depression, anxiety, obsessive compulsive disorder, bipolar disorder, panic attacks and post-traumatic stress disorder[9,11,38]. Furthermore, psychological stress can frequently exacerbate the symptoms associated with these syndromes[39], and behavioural responses — both adaptive and maladaptive — can also have profound positive and negative effects. The causation and mechanisms of such effects is not clear; however, Philips *et al.*[9] suggest that this overlap might be related to dysfunction of common neurotransmitter or neurobiological signalling pathways acting at different locations in the CNS[9]. Historically, owing to the frequent co-occurrence of central sensitivity syndromes with psychiatric disorders, and the absence of clear pathophysiological findings, central sensitivity syndromes have often been considered to be somatization disorders or to be psychosomatic in origin[9].

How is central sensitization measured?

Currently no methods of direct assessment of mechanisms of central sensitization are available in humans. However, clinical manifestation of central sensitization can be indexed using a group of psychophysical laboratory techniques known as quantitative sensory testing (QST)[40]. QST enables perceptual responses to be systematically applied and quantifiable sensory stimuli to be assessed, for the purpose of characterizing somatosensory function or dysfunction[41] (BOX 2). QST is often used in the context of chronic pain research in order to understand possible contributory mechanisms related to enhanced responses to painful stimuli, including central sensitization. Depending on the QST modality and target tissues, a variety of different peripheral afferents can be activated, and their function tested, with some degree of specificity. For example, contact thermal and mechanical methods have been shown to reliably assess the function of C-fibres and Aδ-fibres or Aβ-fibres, respectively[41]. Despite the inherently subjective nature of sensory perception of even highly standardized stimuli, data from a multicentre study investigating QST has demonstrated acceptable test–retest reliability[42].

QST methods can be used to accurately assess dynamic activity in pain processing pathways, including facilitation and inhibition of sensory responses that might relate to central sensitization. For example, quantifying the extent of temporal summation provides information regarding facilitatory mechanisms that are believed to be related to central sensitization and contribute to enhanced nociceptive processing in chronic pain conditions. Temporal summation refers to an increase in pain perception in response to application of a repetitive series of brief noxious stimuli delivered at constant intensity, and at a frequency that elicits C-fibre firing and activation of second-order spinal neurons (termed ‘wind-up’) (FIG. 2). Temporal summation is presumed to be the psychophysical manifestation of central sensitization[41,43] and is the most widely accepted index for measurement of central sensitization in the context of pain available in the published literature[43]. QST is frequently used for clinical assessment and phenotyping of patients with chronic conditions such as functional abdominal pain[44–46], IBS[47], TMJD[48], fibromyalgia[49,50], IC/BPS[51], and lower-back pain[44].

Other than QST, few established objective measures or markers of central sensitization are available. Several studies, using various neuroimaging techniques, have reported changes in brain morphology and function in patients with central sensitization conditions compared with the brain morphology of healthy individuals[37,38,52,53]. Unfortunately, heterogeneity in study designs and imaging protocols often makes drawing definitive conclusions across studies difficult. Thus, attributing changes in brain morphology specifically to mechanisms of central sensitization is challenging. Furthermore, the cross-sectional design of these studies limits the interpretation of the causal relationship between brain alterations and clinical symptoms related to central sensitization. As yet, no molecular biomarker has emerged that is specific to the pathophysiology of central sensitization.

Some attempts have been made to develop patient-reported questionnaires designed to tap into pathophysiological mechanisms that might relate to central sensitization. The Central Sensitization Index[54–56] is a psychometrically-validated questionnaire that differentiates

between patients with and without central sensitization syndromes that presumably reflects the underlying mechanisms of central sensitization. The Patient Health Questionnaire-15 (REFS 57,58) and short-form Somatic Symptom Scale-8 (REF. 57), although not specifically designed to assess central sensitization, have nevertheless been used successfully to quantify the degree of somatization (such as reports of excessive sensation) in many populations of individuals with, and without central sensitization syndromes[57], including fibromyalgia[59], IBS[60] and chronic prostatitis/chronic pelvic pain syndrome[61]. However, the specificity of such psychometric instruments for spinal mechanisms of central sensitization remains untested.

Central sensitization and OAB

Healthy bladder function is under the coordinated control of afferent and efferent nerves, and is integrated at multiple levels, including locally within the bladder, peripherally in the ganglia and centrally in the spinal cord and brain[62]. Onuf's nucleus in the spinal cord and the pontine micturition centre in the brain both serve as centres for the control of micturition function, mediating ascending and descending autonomic and somatic signals. Afferent nerves innervating the bladder are predominantly small-calibre, myelinated Aδ fibres that are responsible for sensing bladder volume and the contractile state of the detrusor[63]. These mechanosensitive nerves consist of a combination of low-threshold and high-threshold fibres that are responsive to changes in intravesical pressure and bladder volumes, respectively, and are important for normal physiological filling as they continually gauge the degree of bladder wall distension[64]. These Aδ-fibres convey sensations of bladder fullness to the spinal cord and have their cell bodies in the dorsal root ganglia at the S2–S4 and T11–L2 spinal segments[62,65]. Projections from Aδ-fibres synapse with spinal neurons that project to the higher brain centres. Large-calibre unmyelinated C-fibres are also present and usually only respond to high-intensity activation (such as extreme distension, cold, heat or chemical irritation) and are thus termed 'silent', as they do not participate in normal physiological bladder function[63,65]. However, in animal models of pathological bladder states such as OAB, these 'silent' C-fibres can become spontaneously active and hypersensitive to low intensity input[66,67], and these changes are mediated by second-order neurons in the spinal cord[68,69]. Similar enhancement in C-fibre activity is also observed in the context of central sensitization[10,13].

Several potential mechanisms might contribute to OAB pathophysiology; these can be broadly characterized as abnormally increased afferent signals from the bladder; or decreased capacity to modulate afferent signals in the CNS[65]. Even in a nonpathological state, continuous bladder afferent activity during the micturition cycle delivers a myriad of signals conveying pain, mechanosensation, chemical sensitivity and motor and/or sensory function to the CNS for processing[70]. Aptly named 'afferent noise', only a fraction of these signals generate sensations, although most components contribute to reflexes coordinating bladder filling, sphincter function and voiding. The CNS is responsible for modulating these signals to suppress unnecessary and/or unconscious bladder sensations and to facilitate afferent signals necessary for homeostasis. Evidence from investigations of CNS function suggests a prominent role of the CNS in the development of OAB[65].

Increased afferent signalling from the bladder to the spinal cord and brain results in part from inherent dysfunction of the bladder urothelium and/or detrusor smooth muscle[65]. According to hypotheses regarding the role of the urothelium in OAB[63,71] the urothelium actively responds to local mechanical, osmotic, inflammatory and chemical stimuli with alterations in expression and/or sensitivity of cell membrane receptors and channels and with release of chemical mediators that act on adjacent afferent neurons, effectively transducing stimulating signals to the afferent nervous system. This increased afferent activity then augments the afferent stimulation produced by bladder fullness to produce urinary urgency and activate the micturition reflex. According to the myogenic hypothesis, detrusor smooth muscle fibres become hyperexcitable, possibly through upregulation or activation of Ca^{2+} channels and/or downregulation of K^+ channel expression and/or activity, so that physiological detrusor micromotions become synchronized into an active, coordinated contraction that stimulates urgency and activates the micturition reflex[72]. The causes of this hyperexcitable state and increased afferent signalling are not fully understood; however, in both situations, which could hypothetically occur concurrently in the same individual, increased afferent signalling to the spinal cord and higher levels of the CNS ensues.

Bladder overactivity also can result from stimulating signals that arise separate from the bladder, but act on the bladder through common afferent pathways[64,65,73]. Emerging evidence highlights the interrelatedness of pelvic organ function through overlapping neural pathways that converge in the CNS at the level of the dorsal root ganglia, the spinal cord or the brain, in the pontine micturition centre[22,73,74]. Viscero-visceral hyperalgesia can occur between any two visceral organs with common innervation arising from sensory projections with overlapping or common origins in the spinal cord[75]; visceral organ crosstalk involving the bladder is best described relative to activation of the bowel, which shares sensory innervation in regions of the thoracic and sacral spinal cord with the bladder. Convergent neural mechanisms of activation of the bladder and the bowel, in particular, explain the reproducible interactions demonstrated in experimental models (known as pelvic organ crosstalk)[73,76,77]. For instance, in animal studies, rectal stimulation either through distension[78,79] or inflammation[80] precipitates detrusor inhibition and/or overactivity that is mediated by activation of convergent bladder and bowel C-fibre afferent nerves in the spinal cord[78]. Similarly, in animal models of pelvic pain or cystitis, colonic stimulation increases pain responses attributed to bladder inflammation[81]. Clinical studies that document overlap between bladder and bowel function[82–85] support these experimental findings from animal models. For example, rectal distension results in changes in bladder capacity, bladder sensation and detrusor overactivity[86,87], while straining to defecate and constipation can both impair bladder emptying and increase the severity of voiding and storage symptoms[84,85,88–92].

Central sensitization might contribute to several aspects of the pathophysiology of OAB (FIG. 3). The data summarized above indicates that central sensitization can lead to hypersensitivity of both Aδ and C-fibre afferent pathways, both of which are involved in the generation of OAB-related sensations in the bladder. Both central sensitization and OAB are mediated or induced by activation of C-fibre afferent nerves, which generally transmit signals derived from more intense or nociceptive stimulation. Repetitive C-fibre activitation, in conjunction with continued stimulation of low-threshold (Aδ) fibres, results in

sensitization of second order neurons in the spinal cord. In OAB, this latter type of stimulation could be provided by mechanoreceptor input from normal bladder cycling or inherent aspects of urothelial or detrusor function described above (such as afferent noise, urothelial signalling, and/or bladder micromotions). In addition, a facilitated ability of low-threshold impulses to activate central neural circuits at the level of the spinal cord, as seen with central sensitization, would explain bladder hypersensitivity, whereby greater sensations of bladder fullness, such as urinary urgency, occur at reduced bladder volumes[93].

Additional sensory mechanisms also contribute to OAB symptoms as neural pathways of pelvic-organ crosstalk could enable sensitization across separate organs. For example, central sensitization initiated by dysfunction of organs that are neurologically related to the bladder through overlapping or convergent neural pathways in the spinal cord, such as the bowel as described above, could extend to incorporate regions of the spinal cord innervating the bladder and result in concomitant bladder dysfunction or OAB, as is proposed for the overlap between OAB and IBS[94]. Variously termed ‘visceral organ crosstalk’ and ‘pelvic-organ cross-sensitization,’ this phenomenon is, in fact, attributed to central sensitization, and can also be observed in other examples of visceral pain conditions, such as heartburn, renal colic, IBS and dysmenorrhea[22]. In this scenario, the primary dysfunction arises from the bowel, but the bladder becomes affected secondarily owing to the ability of central sensitization syndromes to spread to different organs[13].

The absence of obvious bladder pathology or injury in OAB also fits with the concept of central sensitization, as the actual source of the conditioning C-fibre stimulus might be anatomically or even temporally remote. Few published data on inciting events for OAB are available, but some investigators suggest a role for UTI, urinary retention or other precipitating events, which could provide the requisite high-threshold stimulation for the ‘silent’ bladder C-fibre activation needed for induction of central sensitization[95–98]. The mechanisms of pelvic organ crosstalk described above also suggest that an inciting event might be produced by separate, but physiologically related, organ systems such as the bowel. Such precipitating events in related organs would likely be difficult to recognize.

Current evidence

Despite this potential overlap in mechanisms between central sensitization and OAB, current experimental data provide only indirect evidence for this association. QST techniques are frequently applied in the study of chronic pain conditions and central sensitization syndromes to identify underlying pathophysiological mechanisms and to phenotype patients, although their use in urological conditions is limited mostly to IC/BPS[51,99–101]. Women with IC/BPS typically demonstrate hyperalgesia in response to mechanical cutaneous pressure[51] and bladder filling[99] as well as a decreased thermal pain threshold and decreased pain tolerance levels compared with women without IC/BPS[102]. Interestingly, no reports of QST specifically assessing temporal summation in patients with IC/BPS are currently available, even though this would be the most convincing evidence of central sensitization in patients with this disorder[28]. For OAB, a few investigators[103–107] have examined urethral electrical current perception thresholds that, in theory, can be used to assess firing thresholds of specific subtypes of afferent fibres. However, results of these studies have been

inconsistent and difficult to interpret[103–107]. Peripheral QST with either mechanical or heat stimuli in patients with OAB has not been reported; therefore, it remains unknown if patients with OAB have the more generalized hyperaesthesia, allodynia or hyperalgesia to evoked pain stimuli on psychophysical testing reported in some other patients with central sensitization-related disorders[44,47,49,50]. Currently, to our knowledge, no published reports are available regarding temporal summation of evoked painful stimuli in patients with OAB, which might provide quantitative information on the existence or extent of central sensitization in this population.

Evidence of urinary biomarkers of bladder dysfunction might support a role of central sensitization in OAB. Investigators in a number of studies have examined NGF and BDNF specifically as potential markers of OAB, both of which have important roles in nociception and central sensitization. Data from animal studies demonstrate that BDNF is involved in maintaining bladder function at the spinal cord level through modulation of glutamate receptor activation (see Song *et al.* 2014 (REF. 108) for a recent review). Clinically, elevated levels of BDNF and NGF have been found in the urine of individuals with OAB and of those with IC/BPS[109]. Data from several studies have revealed significantly increased urinary NGF levels from women with OAB compared with those without[110–113]. Furthermore, treatment with antimuscarinic agents[111] or onabotulinum toxin injections[112] results in decreased urinary NGF levels, but not in nonresponders to therapy[113]. Similarly, results suggest that patients with OAB have elevated urinary levels of BDNF compared with those without OAB[114,115] and that conservative treatments can decrease urinary BDNF levels in those with OAB[115]. Urinary BDNF levels were also increased in women with IC/BPS and decreased following successful treatment of overactive bladder symptoms with intravesical injections of onabotulinum toxin A[116]. The lack of specificity of these, or indeed any, biomarkers of OAB remains a major limitation[109].

As with research on central sensitization syndromes, CNS imaging — specifically regarding brain morphology and functionality — has increasingly been employed to elucidate the mechanisms of OAB, many of which appear to parallel those of other syndromes. For instance, Griffiths *et al.*[110] demonstrated increased activation of the anterior cingulate cortex on functional MRI associated with perception of urgency in women with urge incontinence compared with women with no symptoms of urinary urgency[117], findings that were further confirmed in 2011 by Komesu *et al.*[118] This activation is attributed to the fear of leakage associated with urinary urgency in patients with OAB[119]. Interestingly, activation of the anterior cingulate cortex also seems to be a hallmark of IBS[37,52] and fibromyalgia[53]. The presence of these common findings is certainly not conclusive or specific to the presence of central sensitization, although they do reinforce the hypothesis that similar neural mechanisms might contribute to OAB as to other central sensitization syndromes that are more typically associated with pain-related symptoms.

Comorbidity with, or clustering of, central sensitization syndromes is proposed as a hallmark of the presence of central sensitization. Indeed, the overlap observed between OAB and IBS might reflect the existence of a common pathophysiology[83,94], although the nature of the underlying mechanisms has not been examined. Various reports in the literature suggest the existence of overlap between OAB and some of the more commonly recognized

central sensitization syndromes[36,41], including IBS[77,92,94,120,121], fibromyalgia[122–126], and idiopathic back pain[127]. According to population data, over one-third of Japanese women with OAB have concomitant IBS, as defined by Rome criteria[128], whereas American women are more likely to report a diagnosis of IBS if they have more severe storage-type lower urinary tract symptoms[120]. Women with IBS are also more likely to report storage-type lower urinary tract symptoms of greater severity than those without IBS[82]. In a case–control study, women with fibromyalgia were more likely to report urge urinary incontinence and urinary frequency and more likely to have detrusor overactivity, as observed on urodynamics, than women with urinary tract symptoms without fibromyalgia[122]. In China, 40% of community dwelling women with fibromyalgia also have OAB compared with 12% without fibromyalgia (OR 3.39; 95% CI 1.82–6.31)[123]. In a self-report, questionnaire-based study, 20% of women with back pain reported the presence of urge and mixed urinary incontinence[127], and elsewhere, associations between urinary incontinence and back pain have been demonstrated to be reciprocal, in that women with back pain have a higher risk of urinary incontinence and women with urinary incontinence have a higher risk of back pain[129,130]. Data also suggest that urinary incontinence, allergies, bowel symptoms, and back pain appear in ‘clusters’, meaning that they all occur more frequently in certain women with one or more of these symptoms[129]. Clustering of central sensitization syndromes in individuals with OAB has rarely been systematically examined and all the aforementioned studies are limited regarding the specificity of diagnoses (such as an over-reliance on patient self-reported or nonvalidated measures) or in the generalizability of the findings (for example, owing to the small sample sizes).

A common role for central sensitization

The existing clinical and experimental evidence of a role of central sensitization in OAB might be limited, although an additional line of argument centres on the relationship between OAB and IC/BPS. Although generally distinguished from IC/BPS owing to the absence of pain, considerable overlap, in terms of the lower urinary tract symptoms and bladder hypersensitivity exists between OAB and IC/BPS[7,29–31]. Urinary urgency is a common symptom of both conditions[131] and many patients with OAB will describe their symptoms as being uncomfortable or even painful[7,31]. The majority of patients with IC/BPS (87%) will describe their urinary urgency as being caused by pain, pressure, or discomfort, while 40% of those with OAB will describe their urinary urgency similarly, as opposed to attributing it to fear of incontinence[31,132], which is how urgency owing to OAB is classically described[133].

The existence of overlap between these two conditions has encouraged some to consider OAB and IC/BPS as spectrum diseases that are united by an underlying, common pathophysiology[7,29–31], which, according to the proposed argument, might reflect the presence of central sensitization. As proposed by Yukio Homma[8], when classified together under the rubric of Hypersensitive Bladder, OAB and IC/BPS are both manifestations of an underlying disorder of hyperactivity of sensory nerves with differing features of pain and incontinence. Interstitial cystitis is a further subdesignation in patients with specific bladder pathology. Similarly, J. Quentin Clemens[7] classifies OAB and IC/BPS primarily as genitourinary sensory disorders with an underlying dysfunction of the afferent nervous

system, referring to them as afferent urological and/or pelvic disorders[7]. Others disagree and maintain that IC/BPS and OAB are separate conditions, distinguished primarily by the presence of pain with bladder filling in patients with IC/BPS and the generally episodic nature of urinary urgency (relatively fast onset and/or disappearance) in patients with OAB compared with the progressive build-up of bladder pain and discomfort with bladder filling in paatients with IC/BPS[133,134], while acknowledging that the two conditions can also occur in the same patient. Diagnostic criteria and clinical definitions of IC/BPS have undergone considerable revisions in the past decade, but the ongoing lack of agreement or uniformity in how these conditions are defined certainly adds to the confusion in understanding the underlying contributory mechanisms.

IC/BPS has been considered a central sensitization syndrome for many years and exhibits many of the clinical characteristics that define these syndromes[11,28,135]. On psychophysical testing, individuals with IC/BPS have impaired inhibition of descending pain pathways that might be a result of central sensitization[102], including hyperalgesia[51,99–101] and hypersensitivity (including increased startle reflexes) in responses to acoustic stimuli[136,137]. However, most of these studies only include small numbers of patients and employ a variety of psychophysical techniques, thus limiting the generalizability of the reported findings. Brain imaging data published in 2015 from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain project indicate that women with IC/BPS have white matter abnormalities that are consistent with those observed in the brains of patients with other chronic pain conditions, thus reinforcing the suggested mechanistic commonality of these disorders[138]. Women with IC/BPS also demonstrate susceptibility to comorbid central sensitization syndromes, and frequently report the co-occurrence of IC/BPS with fibromyalgia, chronic fatigue syndrome, IBS, TMJD, chronic pelvic pain, migraine, lower-back pain, and vulvodynia[33,36,139,140]. In addition, evidence suggests that the increased number of comorbid syndromes is associated with a greater risk of IC/BPS[140–145]. In fact, many of these comorbid conditions seem to predate the onset of IC/BPS, suggesting the existence of an underlying predisposition[33,139,142,144,146–149].

Evidence published in 2014 on temporal relationships in women with IC/BPS also suggests that urinary symptoms such as those associated with OAB might predate the onset of IC/BPS. In a case–control study comparing women with IC/BPS to those without, women with a history of nonbladder pelvic pain with urinary features, urinary frequency and/or prior episodes of bladder pain before diagnosis (prodrome symptoms) were more likely to develop IC/BPS[142]. Furthermore, women with prodrome symptoms were more likely to have antecedent nonbladder syndromes that might reflect underlying central sensitization, such as chronic fatigue syndrome, IBS, and fibromyalgia, before the onset of IC/BPS. Although these findings might be limited owing to major flaws in the study design, these results suggest the possibility that central sensitization might explain progression from nonpainful lower urinary tract symptoms (such as an increased urinary frequency) in some women to painful IC/BPS and hint that some of the urinary symptoms of OAB might reflect the presence of central sensitization as an underlying mechanism. If this is indeed the case, early identification and treatment of OAB might help prevent worsening of the condition and progression to IC/BPS.

Implications for OAB treatment

The presence of central sensitization in patients with OAB, if this hypothesis is confirmed, and how this relates to patient management might be an important consideration for future treatment approaches. Few therapies exist that have demonstrated direct effects on any aspects of central sensitization. Clinical and preclinical evidence regarding ketamine[150,151], gabapentanoids (such as gabapentin, pregabalin, and agents with effects on γ-aminobutyric acid signalling, such as carbamazepine)[152–155] and certain antidepressants (such as duloxetine)[156] indicate reversed or diminished central sensitization and decreased allodynia and hyperalgaesia upon treatment[10]. Research published in 2005 has shown that gabapentin and carbamazepine reduce the intensity of temporal summation-induced pain, consistent with an ameliorating effect of these agents on central sensitization[157]. Interestingly, gapapentin[158] and pregabalin[159] have both been investigated as treatments of OAB in studies with small cohort sizes, but with encouraging results. Treatment with duloxetine, compared with placebo, also improves the outcomes of patients with OAB[160], but these results have not been confirmed in other clinical trials. Data published in 2012 also suggest that duloxetine might have a beneficial role as a treatment of OAB in women with multiple sclerosis[161].

In general, only a few attempts to tailor OAB treatment approaches based on pathophysiological profiling or on a mechanistic approach have been made, despite the availability of a large body of scientific and experimental evidence on pathophysiology. In a systematic review published in 2014, only 48 of 239 (20%) of published randomized controlled trials on OAB profiled participants regarding the underlying pathophysiology of their disease and only 20 (8%) reported the efficacy of OAB treatment based on pathophysiological disease subtype[162]. This might, in large part, reflect a lack of translational opportunities or techniques for assessing the relevant pathophysiological features of OAB *in vivo* in the context of clinical trials. However, established methods for assessing manifestations of central sensitization in other conditions are available (using temporal summation assessment in particular), and considering OAB within the broader construct of central sensitization provides an opportunity to directly measure the role of central sensitization in the context of OAB using these techniques. In addition, owing to the clustering of central sensitization syndromes having presumed central sensitization-related mechanisms, phenotyping patients with OAB based upon comorbidity with these other syndromes might help identify subgroups with underlying central sensitization in a clinically pragmatic way. Presently, comorbidities that increase the risk of OAB are acknowledged to be a knowledge gap that is relevant to OAB therapy[163]. In other conditions, such as IBS[34,164], the presence and number of comorbid functional somatic syndromes seems to differentiate individuals into subgroups that vary by symptom severity, quality of life, and treatment outcomes. Examinations of the clustering of central sensitization syndromes in individuals with OAB might help to identify certain phenotypes of OAB subgroups that reflect specific pathophysiological mechanisms (such as central sensitization), and these phenotypes might have implications for the prognosis and treatment of patients with this disease. Such a mechanistic approach to OAB management would represent a positive initial step towards personalized treatment of OAB.

A number of widely-used treatments of OAB also have effects on other organ systems and, as such, many treatments commonly employed for OAB might also be effective as treatments of comorbid central sensitization syndromes. First-line therapies for OAB include lifestyle modifications, such as fluid intake and dietary management[165], and use of psychological therapies (such as cognitive behavioural therapy; CBT)[166,167]. Both are also effective as treatments of IBS, and CBT in particular is an important treatment modality[168]. Antimuscarinic agents, which are widely used treatments of OAB, are known to act on the bowel, and, in fact, constipation is considered an adverse effect, occurring in up to 15% of patients receiving these drugs[121]. However, this 'adverse effect' could also be considered advantageous in the setting of overactive bowel or functional diarrhoeal states, and possibly even in IBS. Antidepressants (including duloxetine, imipramine and amitriptyline) have a long history of clinical use in the management of OAB and urinary incontinence[169] and afford an opportunity to concurrently treat OAB and certain central sensitization syndromes in carefully selected patients, such as those with fibromyalgia[170] or IBS[168]. Finally, sacral neuromodulation has direct effects on bladder and bowel function and is indicated for the treatment of faecal incontinence, in addition to OAB[171]. Neuromodulation certainly has a role as a treatment of dual incontinence (such as urinary and faecal incontinence)[172]. However, given emerging reports of efficacy in patients with additional bowel conditions, such as constipation[173], functional anal pain[174], IBS[175], and pelvic conditions[175] such as IC/BPS[176–178], sacral neuromodulation might have a role in individuals with multiple pelvic comorbidities. Additional research into how patients with comorbidities such as those described above respond to OAB therapies is needed[163].

Conclusions

OAB remains a clinical enigma in many patients owing to the existence of a disconnect between our understanding of the clinical features and of the pathophysiology. While a number of mechanisms have previously been proposed that might contribute to the symptoms of OAB, central sensitization provides an explanation that also appears likely to contribute to the underlying pathophysiology of OAB, at least in a subgroup of patients. In addition, a role of central sensitization in OAB might explain the comorbid occurrence of this syndrome with many central-sensitization-related syndromes. How central-sensitization-related factors affect the experience of individuals with OAB or their therapy outcomes remains unknown. Nonetheless, evaluating patients with OAB for evidence of central sensitization and the comorbid occurrence of other central sensitization syndromes affords the potential opportunity for directed management based upon pathophysiological profiling, and represents an important initial step towards personalized medicine in the management of OAB. Additional research specifically evaluating the hypothesized role of central sensitization in OAB seems to be warranted.

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Box 1

Central sensitization syndromes[26]

- Restless legs syndrome
- Periodic limb movement disorder
- Endometriosis
- Fibromyalgia syndrome
- Irritable bowel syndrome
- Primary (dysfunctional) dyspepsia
- Tension-type headache
- Migraine
- Myofascial pain syndrome
- Myofascial temporomandibular disorder
- Primary chronic neck pain
- Primary lower back pain
- Primary dysmenorrhea
- Painful bladder syndrome/ interstitial cystitis
- Vulvodynia/vulvar vestibulitis
- Chronic prostatitis/chronic male pelvic pain
- Post-traumatic stress disorder
- Multiple chemical sensitivity (chemical intolerance)
- Primary burning mouth syndrome
- Primary chronic cough
- Primary chronic tinnitus/primary chronic hearing loss

Box 2

Available methods of QST[41]

Modalities of stimulation

- Thermal (heat, cold)
- Mechanical (tactile, pressure, vibration)
- Electrical
- Ischaemic
- Chemical

Location of stimulation

- Cutaneous
- Muscle
- Visceral organs

Common QST measurements

- Perceptual responses
  - Pain threshold
  - Pain tolerance
- Dynamic responses
  - Spatial summation
  - Temporal summation

QST, quantitative sensory testing.

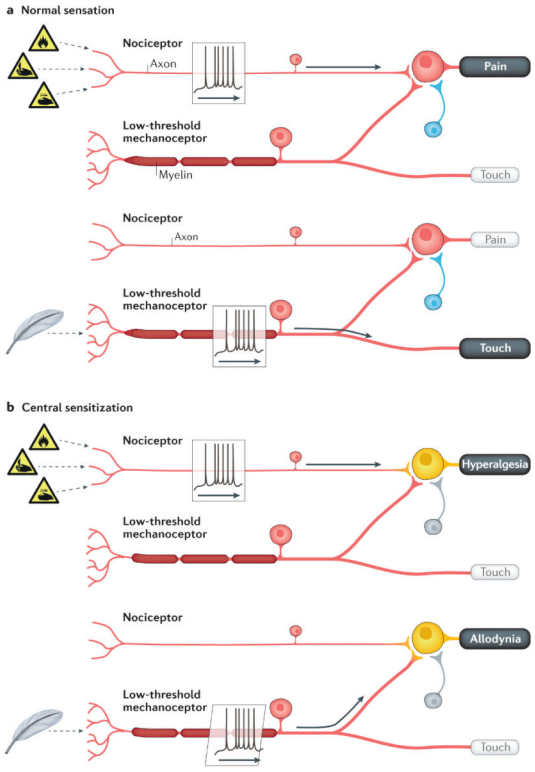

Figure 1. Mechanisms of central sensitization

a | Normal sensation. The somatosensory system is organized in separate, parallel pathways, such that low-intensity stimuli only activate the central pathways that lead to innocuous sensations such as touch, whereas high-intensity stimuli that activate nociceptors only activate the central pathways that lead to pain. This effect is mediated by the strong synaptic inputs between the particular sensory pathways and by inhibitory neurons that focus activity to these dedicated circuits. **b** | Central sensitization. With the induction of central sensitization, the pain response to noxious stimuli is enhanced (hyperalgesia), whereas the sensitivity of the normally ineffective convergent synapses is strengthened, allowing low-threshold sensory inputs to activate the pain circuit (allodynia). Reproduced with permission obtained from Lippincott Williams & Wilkins © Woolf, C. J. *Pain* **152**, S2–S15 (2011).

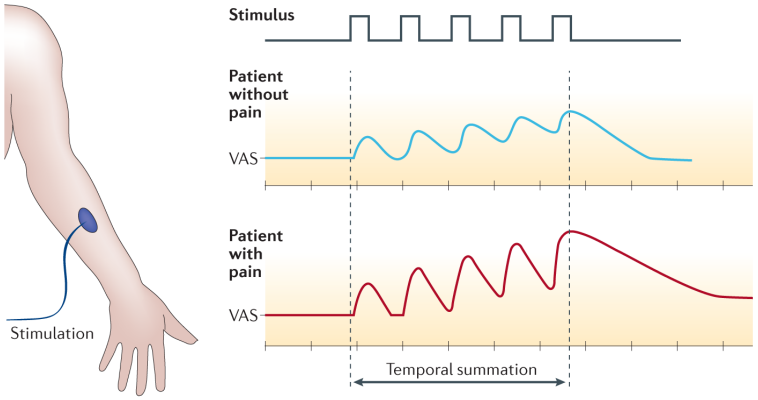

Figure 2. Temporal summation

During quantitative sensory testing, the perception of pain intensity assessed with a visual analogue scale (VAS) in response to a repetitive thermal stimulation of uniform intensity applied to the forearm will gradually increase owing to central sensitization. In a patient with chronic pain, central sensitization facilitates temporal summation, whereas, in a healthy person, this intensity does not increase owing to habituation to the stimulus. Modified with permission obtained from Springer © Arendt–Nielsen, L. *Handb. Exp. Pharmacol.* **227**, 79–102 (2015).

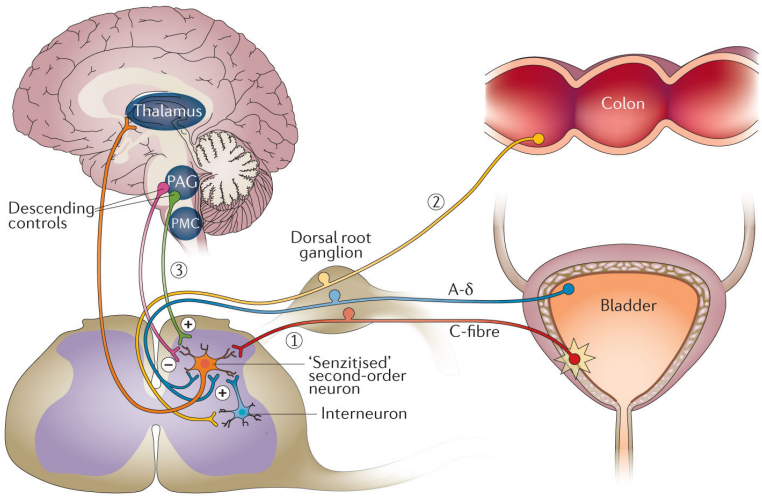

Figure 3. Hypothetical roles of central sensitization in overactive bladder (OAB)

Persistent activation of peripheral nociceptive C-fibres, such as those that project from the bladder or related pelvic organs (such as the colon), could induce central sensitization in second-order spinal neurons. Once established, central sensitization might contribute to overactive bladder by (1) facilitating ascending transmission of normally low-threshold mechanoreceptor signals from bladder afferents (afferent noise) or (2) from other pelvic organs via crosstalk with afferent signalling pathways that project from other organs. In addition (3), descending neural projections might also facilitate afferent spinal transmission of bladder signals in the setting of central sensitization. Modified with permission obtained from Nature Publishing Group © Thakur, M. *et al.* Osteoarthritis pain: nociceptive or neuropathic? *Nature Reviews Rheumatology* **10**, 374–380 (2014).