Autonomic Neuroscience: Basic and Clinical 179 (2013) 1–4

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

HIGHLIGHTS IN BASIC AUTONOMIC NEUROSCIENCES: CROSS-ORGAN SENSITIZATION BETWEEN THE BLADDER AND BOWEL

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Introduction

Chronic pelvic pain (CPP) and visceral pain (VP) are common, debilitating conditions which present a major challenge to health care providers around the world. Both are characterised by generalised, diffuse pain sensation, coupled with alterations in organ function. Often CPP and VP arise following the resolution of an acute infection and in some cases can induce functional alterations and pain from a different unaffected region. This is consistent with the concept of cross-organ sensitization. Clinical data provides compelling evidence for cross-organ sensitization between the bladder and bowel. Roughly 30% of patients presenting with irritable bowel syndrome (IBS) also present with bladder symptoms such as increased or incomplete bladder emptying, urgency, nocturia and pain (Malykhina, 2007). The same has also been reported in patients with overactive bladder syndrome (OABS) and interstitial cystitis/painful bladder syndrome (IC/PBS) who exhibit symptoms of IBS (Whorwell et al., 1986). Cross-organ sensitization has also been demonstrated between the uterus, pelvic urethra and vagina and in males cross-organ sensitization between the prostate and other pelvic organs has also been suggested. Despite the prevalence of CPP, VP and cross-organ sensitization, the underlying mechanisms are not fully understood.

"Relationship between overactive bladder and irritable bowel syndrome: a large-scale internet survey in Japan using the overactive bladder symptom score and Rome III criteria" (Matsumoto et al., 2013)

Matsumoto S, Hashizume K, Wada N, Hori J, Tamaki G, Kita M, Iwata T & Kakizaki H. (2013). Relationship between overactive bladder and irritable bowel syndrome: a large-scale internet survey in Japan using the overactive bladder symptom score and Rome III criteria. BJU Int.

Article summary

This clinical study investigates the concurrent relationship between a hypersensitivity disorder of the colon called irritable bowel syndrome (IBS), and a hypersensitivity disorder of the lower urinary tract called overactive bladder syndrome (OABS). The study employed a large scale internet based survey of 10,000 randomly selected participants. Subjects were grouped according to age and gender and the prevalence and severity of OAB were assessed using a symptom score which combined 4 diagnostic criteria into one single score. Disease status was assessed by an overall score value (5 = mild, 6–11 = moderate and >12 = severe) and IBS was assessed using the IBS module of the Rome III criteria. Similar to other studies in the literature, the study found an overall prevalence of OAB of 9.3% (with 9.7% of men and 8.9% of women affected), which was significantly increased with ageing. The prevalence of IBS was higher with 21.2% of people reporting symptoms (18.6% of men and 23.9% of women) conversely; however the incidence of IBS was reduced with age. Interestingly 33.3% of participants reporting OAB symptoms also had concurrent IBS (32.0% men and 34.8% women) but the prevalence of both conditions concurrently was not age dependent, suggesting that ageing is not a contributing factor to this co-morbidity.

Commentary

The bladder and bowel are important organs with similar functional roles in the body. Both are involved in the storage, collection and expulsion of waste products. This study, conducted in Japan, details similar clinical data to that reported in previous epidemiological studies conducted in Europe and the USA. The underlying aetiology of OABS and IBS is not clearly defined, but both conditions are characterised by changes in emptying frequency and increased motility/contraction. For the bladder this takes the form of urinary urgency and frequency and in the colon it is manifested as diarrhoea, constipation and pain. This study clearly highlights the concurrence of bladder and bowel disorders and raises the question of whether a similar underlying pathology can account for these conditions. Anatomically the bladder and colon lie in close proximity and share a similar innervation via the pelvic nerve. Moreover a host of experimental studies in rodents, such as those covered by this review, demonstrate that inflammation or injury to one organ can lead to altered function in another (Pezzone et al., 2005; Bielefeldt et al., 2006; Brumovsky et al., 2009). The main theory to explain this phenomenon is that of cross-organ sensitization whereby sensory pathways between two organs such as the bladder and bowel interact. This interaction can occur in the periphery, at the level of the spinal cord, or in

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1566-0702/$ – see front matter
http://dx.doi.org/10.1016/j.autneu.2013.05.445

the higher centres and may involve one or multiple mechanisms. There is also evidence of sensitization between somatic and visceral inputs and it is believed that this interaction provides an explanation for the phenomenon of referred pain where sensations from the viscera are experienced in a somatic sensory field. This viscero-somatic convergence has been extensively investigated (the most common example of this is angina), but only over the last decade has viscero-visceral referral such as that between the bladder and bowel received research attention. Much research is still required to understand these interactions, however this study clearly highlights the concurrence of bladder and bowel disorders. Understanding the mechanism(s) involved could have important implications for future therapeutic interventions aimed at treating both OAB and IBS.

"Cystitis increases colorectal afferent sensitivity in the mouse" (Brumovsky et al., 2009)

Brumovsky PR, Feng B, Xu L, McCarthy CJ & Gebhart GF. (2009). Cystitis increases colorectal afferent sensitivity in the mouse. Am J Physiol Gastrointest Liver Physiol 297, G1250–1258.

Article summary

In this study the authors examined the effect of chronic bladder irritation on pelvic colorectal afferents. To induce a chronic but mild bladder inflammation, a mouse model of cyclophosphamide (CYP)-induced cystitis was used and the mechanosensitive properties of afferent fibres innervating the colon and the bladder were measured using an in vitro extracellular afferent nerve preparation. In addition, the nerve terminals were exposed to a soup of inflammatory mediators (IS) for 1 min, at different pH values (neutral or acidic) to investigate sensitization after acute inflammation.

Acute inflammatory stimulation with the acidic inflammatory soup induced excitation of colonic primary afferents in response to stretch in both CYP- and saline-treated mice, with a higher proportion of responsive fibres in CYP-treated animals. However, the stretch sensitivity was not different between saline- and CYP treated mice, in absence of any acute inflammatory stimulus. In the presence of the IS the mechanosensitivity of colonic muscular afferent fibres in CYP treated animals increased and the proportion of chemosensitive colorectal afferents was higher. As CYP is metabolized by the liver to produce the bladder irritant acrolein, the authors interpreted the observed sensitization of colon afferents after bladder inflammation as supporting cross-organ sensitization between these two visceral organs. As only acidic inflammatory soup was able to induce hypersensitivity in colon sensory afferents, this study suggests also a possible involvement of acid-sensing ion channels (ASICs) in mediating mechanical-sensitization in colon afferents.

Commentary

Viscero-visceral reflexes between the lower gastrointestinal tract and urinary tracts are controlled by both autonomic and central nervous systems (CNS), suggesting the dominant role of neural pathways in pelvic organ co-morbidities. This study investigates the peripheral mechanisms which may underlie cross-organ sensitization, and in this paper, bladder irritation induced changes in colonic afferent sensitivity. This is in line with previous studies which report an important role of peripheral sensory afferents in the initiation of cross-sensitization between colon and bladder (Ustinova et al., 2006). This paper is a clear example of sensitization of colonic afferent pathways following bladder irritation; however, mechanisms involved in cross-organ sensitization pathways are unclear. The principal mechanism proposed is based on dichotomizing fibres (single sensory neuron innervating two different organs) which have been found in both bladder and colon in rat and mice (Malykhina, 2007; Brumovsky and Gebhart, 2010). However the numbers of dichotomised afferents are small, raising the question of whether other unrelated mechanisms could be involved. Neural pathways innervating distant organs may be sensitized indirectly due to systemic inflammatory processes such as increased mast cell activation or increased cytokine release (Ustinova et al., 2007). The role of the central nervous system should be also considered as a contributing factor in cross-sensitization pathways, with the participation of second and higher order central neurons. A pathological condition developed in one of the pelvic organs may cause initial sensitization of peripheral afferent fibres and sensory neurons. These primary changes then lead to amplification of nociceptive signalling in second order neurons in the CNS altering descending modulatory input from the CNS to the periphery.

"Evidence for the role of mast cells in colon–bladder cross organ sensitization" (Fitzgerald et al., 2013)

Fitzgerald JJ, Ustinova E, Koronowski KB, de Groat WC & Pezzone MA. (2013). Evidence for the role of mast cells in colon–bladder cross organ sensitization. Auton Neurosci 173, 6–13.

Article summary

This study examined the role of mast cells in mediating colon-to-bladder cross-organ sensitization. Colitis was induced by using intracolonic infusion of trinitrobenzene sulphonic acid (TNBS) and bladder function was examined using cystometry. In TNBS treated rats bladder voiding intervals were reduced consistent with increased afferent transmission and urothelial permeability was increased. These effects were blocked by pre-treatment with the mast cell stabilising agent, ketotifen for 5 days. In TNBS treated rats, mast cell numbers in the bladder were also significantly increased and again this increase in mast cell number was attenuated by pre-treatment with ketotifen for 5 days. In bladder smooth muscle strip experiments the mast cell activator compound 48–80 induced small transient bladder contractions which were profoundly increased in bladder strips taken from TNBS treated rats. These contractile responses were abolished by either pre-treatment with ketotifen or by desensitization with the protease activated receptor 2 (PAR2) ligand SLIGRL-NH2 suggesting a role for mast cells and PAR2 receptors in cross-organ sensitization. To examine the role of mast cells further, Fitzgerald and colleagues used the $Kit^a/W^a/Kit^aW\text{-}v^a$ mast cell deficient mouse and found no bladder defects as a result of TNBS treatment, providing strong evidence that mast cells contribute to bladder dysfunction arising as a result of colon–bladder cross sensitization.

Commentary

This study examines the peripheral mechanisms involved in cross-organ sensitization, where injury to one visceral organ, in this case the colon, induces functional and morphological changes of another visceral organ such as the bladder. There have been a number of theories that suggested to explain this phenomenon; this study provides evidence suggesting a local peripheral mechanism involving an interaction between mast cells and afferent nerve terminals. Afferent nerve terminals have been postulated to influence the recruitment or proliferation of mast cells via the release of sensory neuropeptides such as substance P, and in a previous study, depletion of neuropeptide stores with capsaicin prevented mastocytosis associated with TNBS induced colitis (Ustinova et al., 2007). Conversely mast cells have also been purported to modulate sensory activity