Published in final edited form as:

Neurol Urodyn. 2012 March ; 31(3): 352–358. doi:10.1002/nau.21228.

Do the urinary bladder and large bowel interact, in sickness or in health?

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Abstract

Normal functioning of the urinary bladder and the distal gut is an essential part of daily physiological activity coordinated by the peripheral and central nervous systems. Pathological changes in one of these organs may induce the development of cross-organ sensitization in the pelvis and underlie clinical co-morbidity of genitourinary and GI dysfunctions. Experimental human and animal data suggest that the bladder and distal colon interact under both normal and pathological conditions, however, the directions of these interactions can change dramatically depending on the nature and duration of the applied stimuli. This review article aimed to summarize the clinical data on colon-bladder cross-reflexes in healthy individuals, as well as in patients with co-morbid disorders. It also discusses currently used animal models, experimental approaches, and suggested mechanisms of colon-bladder cross-talk. Additionally, it provides an overview of the potential pharmacological targets to develop treatment options for patients with co-morbid disorders. Presented work resulted from the discussion of colon/bladder interactions during “Think Tank 9” presentations at the International Consultation on Incontinence Research Society meeting held in Bristol, UK, 2011.

Keywords

colon/bladder co-morbidity; cross-organ sensitization; neurogenic inflammation; afferent convergence

INTRODUCTION

Physiological function of the pelvis correlates closely with coordinated activity of the lower urinary (LUT) and gastrointestinal (GI) tracts. The large bowel/anorectum and the urinary bladder have the same embryological origin and develop from the cloaca. Both organs are positioned close to each other in the small pelvis facilitating interactions. Their striated closing and supporting muscles are part of the same pelvic floor structure. The distal colon and urinary bladder have a similar function of the storage and evacuation of faeces and urine, respectively. A joint peripheral innervation coordinates the functioning of both viscera

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(Table 1). Additionally, the central processing and perception of afferent activity converge on the same regions of the brain.

The coordination of bladder-bowel reflexes could be compromised upon pathological alterations in one of the pelvic organs. The clinical co-morbidity of bladder and colorectal dysfunctions has been demonstrated in numerous observational reports. Many of the assessments rely purely on observations of concomitant symptoms arising in both organ systems, with exacerbation or amelioration of symptoms in one organ being related to distention or irritation/inflammation of the other system. These linkages suggest the possibilities for therapeutic modulation of one system having the beneficial effects on the other, or, in contradistinction, worsening the function of the initially non-affected system. Extensive clinical and translational studies are warranted to clarify complex cross-reflexes between healthy vs diseased bladder and colon. These findings will elucidate conjoint pathophysiologies and provide the basis for the development of future clinical treatments for co-morbid conditions.

PHYSIOLOGICAL INTERACTIONS BETWEEN THE LARGE BOWEL AND URINARY BLADDER IN HEALTHY VOLUNTEERS

Clinical studies in healthy volunteers illustrate physiological interactions between the bladder and the distal gut. In a study of young, healthy women the sensation of rectal filling was shown to be decreased when the bladder was full.¹ However, rectal distention did not affect bladder compliance during filling, but sensations of bladder filling were observed at smaller volumes and maximum bladder capacity during cystometry was significantly reduced. On the other hand, electrical perception thresholds in the bladder, as a semi-objective measurement for a different part of the afferent innervation, were higher when the rectum was full. These findings show that the state of the rectum significantly influences the handling of sensory information from the LUT and that before sensory testing of the bladder, rectal fullness should be examined and if necessary the rectum should be emptied.

Rectal distention is less likely to cause defecatory desire if the urinary bladder was empty, while increasing bladder volumes were associated with increased rectal urgency.² The reason for this is unclear but the authors hypothesized that bladder emptying needs to be timelier in order to keep the balance in the LUT and so takes precedence while the evacuation of the bowel is less critical.

Also in children with LUT symptoms rectal distension significantly but unpredictably affected bladder capacity, sensation and overactivity regardless of whether the children had constipation, and independent of clinical features and baseline urodynamic findings. Urodynamic and management protocols for LUT symptoms that fail to recognize the effects of rectal distension may lead to unpredictable outcomes.³ It has also been shown that in women with overactive bladder symptoms, rectal distention produces earlier volume at first desire than with a non-distended rectum.⁴ Additionally, in the same study detrusor overactivity was demonstrated only with rectal distention in some patients.

CLINICAL CO-MORBIDITY OF BLADDER-BOWEL DYSFUNCTIONS

The close relationship between the large bowel and the LUT has clinical relevance as pathology of both often coexist. Fecal incontinence (FI) has been associated with lower urinary symptoms including urgency, frequency, and urge incontinence. In a community-based study, the prevalence of combined faecal and urinary incontinence was reported at 6–9%.⁵ Furthermore, the age-adjusted relative odd ratio of FI among women with urinary incontinence was 1.8. A high prevalence of constipation and anorectal pain disorders in

women with urinary incontinence has also been documented. Symptoms of dysfunctional voiding and uroflow abnormalities suggestive of disordered urination occurred more frequently in women with defecatory disorders.⁵

In a group of patients with urinary incontinence complaints of FI and of constipation were found more often than in a control group.⁶ Patients with urgency and mixed urinary incontinence had significant difficulty postponing defecation than stress urinary incontinence (SUI) patients and urinary continent patients. More SUI patients reported straining during defecation.⁶ In a study of 465 women with fecal incontinence, one-third of women demonstrated a urodynamic diagnosis of detrusor instability and 21% were found to have a urodynamic evidence of stress incontinence.⁷ Similarly, in a study of 504 women, women with urinary and fecal incontinence were noted to more likely have urinary urgency than control patients.⁸ Also, in a case-control evaluation of 1,000 patients with LUT symptoms, fecal incontinence was significantly more common than in age-matched controls and more common in women with previously diagnosed sensory urgency or detrusor overactivity compared with women with the urodynamic diagnosis of stress incontinence or with controls.⁹

Therapeutic action in one system can improve or worsen symptoms in the other. Treatment of constipation in children can lead to a resolution of urinary incontinence and can prevent further recurrence of urinary tract infections. On the other hand, treatment of overactive bladder with bladder relaxing drugs can cause constipation.¹⁰ The same was found in patients with neurogenic pathology.¹¹ Urinary tract infections are quite common in patients with LUT dysfunctions and treatment with antibiotics can cause bowel problems.¹² The use of bowel segments for the treatment of urinary disorders such as bladder enlargement or replacement has the risk of side effects in both systems.¹³

Irritable bowel syndrome has been noted to be more commonly associated with urgency and frequency in patients as compared to control subjects.¹⁴ Additionally, patients may commonly present with fecal urgency and frequency as well as urinary symptoms in addition as a common manifestation of their irritable bowel syndrome.¹⁵ In a large analysis of interstitial cystitis patients (2,682 patients), a higher incidence of irritable bowel syndrome and other inflammatory bowel conditions were noted as compared to the general population.¹⁶ Additionally, in the same study, inflammatory bowel conditions were more likely to be present at the time of diagnosis of interstitial cystitis/painful bladder syndrome (IC/PBS) than in comparator groups.

Demographic data from large trials also shows a parallelism between LUT symptoms and lower GI symptoms. The EPILUTS study of 2,160 individuals indicated that subjects with OAB were much more likely to have either constipation or fecal incontinence than patients without overactive bladder symptoms.¹⁷ In another study of 820 women with LUT symptoms as compared to controls, constipation and defecatory straining were more common in women with lower urinary symptoms than among controls.¹⁸

Utero-vaginal prolapse is another condition that has been associated with both LUT symptoms and concomitant bowel symptoms. In an evaluation of 320 women with LUT symptoms, fecal incontinence was found in 16% of patients and constipation in 32%, and prolapse was the principle risk factor for incontinence.¹⁹

A significant epidemiologic correlation has also been found between constipation and overactive bladder and associate conditions such as fecal and rectal dysfunction²⁰ and urinary tract infections, skin infections, and vulvovaginitis.²¹ Patients with constipation are more likely to develop OAB symptoms as compared to those not constipated²² and constipation is frequently associated with impairment of bladder emptying or worsening of

bladder symptoms.²³ In a Chinese study of 4,684 women, the presence of constipation was associated with a nearly four-fold increase in dry OAB, however, this association was not seen between constipation and wet OAB (odds ratio 1.56).²⁴ A Danish study assessing constipation and urinary tract symptoms in 2,860 women showed that constipation was associated with both urgency and urgency incontinence (odds ratio of 1.8), SUI (odds ratio of 1.6) and urinary evacuation disorder (odds ratio of 3.9).²⁵

Sacral neuromodulation was shown to improve the function of both the lower urinary and GI tracts. Between 30% and 100% of patients with double incontinence experienced improvement in urinary and faecal incontinence after being treated with sacral neuromodulation.²⁶ In a small pilot study early implantation of bilateral sacral nerve modulators (SNMs) in complete spinal cord injury (SCI) patients during the acute bladder-areflexia phase resulted in better urinary and bowel outcome.²⁷ Sacral anterior root stimulation in the spinal cord injured individuals improved bowel function, and patient satisfaction with this treatment was very high.²⁸

EXPERIMENTAL MODELS TO STUDY BLADDER-COLON INTERACTIONS

Clinical observations of abnormal pelvic activity in patients with co-morbid bladder and colonic dysfunctions provided a basis for initiating translational and basic science studies to reveal the underlying mechanisms. Viscerovisceral reflexes between the lower GI and urinary tracts are controlled by both autonomic and central nervous systems, suggesting the dominant role of the neural pathways. Investigation of functional changes in nerve fibers and neurons sets certain limits in conducting appropriate research in humans, making the use of animal models unavoidable. Initial animal studies conducted in cats revealed cross-inhibitory reflexes upon stimulation of either the bladder or distal gut under normal physiological conditions.^{29,30} Both mechanical (distension) and electrical (pelvic nerve afferents) stimulation of the colon induced inhibition of spontaneous bladder contractility and enhanced micturition threshold.³⁰ Additional studies on bladder afferents in the hypogastric nerve provided evidence for vesico-sympathetic reflex that was independent of the afferent input from the pelvic nerve.³¹

Very few translational animal models exist that can claim clinical relevance to co-morbidity of colon and bladder disorders in humans. The majority of animal models are acute in nature and, therefore, do not reflect the chronic/recurrent disease state. Of major interest are experimental approaches in which an initial acute stimulus (inflammation, infection, noxious distension, neonatal stress etc) is transient but powerful enough to cause long-lasting abdominal hypersensitivity and hyperexcitability of visceral afferents.^{32,33} These animal models are used to study functional pelvic disorders such as IC/BPS and IBS which fail to present with positive tests for active inflammation or infection.

Several rodent models have been established to study the mechanisms of colon-bladder cross-sensitization which is triggered by a noxious insult applied either to the distal colon or to the urinary bladder (reviewed in ³²⁻³⁴, Figure 1). Intracolonic application of 2,4,6-trinitrobenzene sulfonic acid (TNBS) is a well established model of colonic inflammation³⁵ and an advantageous one for the studies of colon/bladder interactions. In this model, inflammation in the distal colon is induced by a single intraluminal administration of TNBS, with no requirements for previous sensitization of the animal.³⁶ Additionally, local TNBS instillation significantly reduces indirect effects on the function of the adjacent pelvic organs, which is vital for the studies on pelvic organ cross-talk. After recovery from inflammation (12–15 days later) neither the colon nor the urinary bladder has any detectable histological or biochemical changes. Studies using TNBS-induced colonic inflammation determined a significant increase in bladder contractility by almost 70% in the presence of

acute colitis.³⁷ Additionally, the bladder develops signs of neurogenic dysfunction as shown by hyperactivity of bladder afferent fibers,³⁸ hyperexcitability of bladder projecting sensory^{39,40} and spinal⁴¹ neurons, increased release of pro-inflammatory neuropeptides in the urinary bladder,^{42,43} and changes in detrusor contractility *in vivo* and *in vitro*.^{44,45} Acute TNBS-induced colitis also leads to early onset of micturition and decreased intermicturition interval in mice.⁴⁶ Local segmental irradiation of the colon was shown to induce the occurrence of detrusor overactivity detected by cystometric evaluations in rats.⁴⁷ In the model of colonic irritation with intraluminal mustard oil in rats, vascular permeability in the normal bladder significantly increased after colonic treatment.⁴⁸ This effect was attenuated by transection of the hypogastric nerve⁴⁸ suggesting the importance of neural connections. Other studies also established a diminution of colon/bladder cross-sensitization upon denervation of the urinary bladder.³⁸

Inflammation or irritation of the urinary bladder leads to colonic dysfunction in animal models of experimental cystitis. Thus, bladder irritation by intravesical protamine sulfate/potassium chloride in rats³⁷ and overexpression of NGF in the urinary bladder of mice⁴⁹ lowered threshold of colonic afferents to colorectal distension. Neurogenic cystitis induced by the injection of Bartha's strain of pseudorabies virus in female C57BL/6J mice enhanced abdominal hypersensitivity which was significantly abolished by either intravesical (direct effect) or intracolonic (cross-effects) application of lidocaine.⁵⁰ Similarly, cyclophosphamide-induced cystitis in mice increased mechanical sensitivity of colorectal afferents from colonic smooth muscle layer and increased the proportion of chemosensitive colonic afferents.⁵¹ Neonatal cystitis induced at day 14 postpartum in mice resulted in colonic hypersensitivity in adult rats without significant histological changes in the colon or mechanosensitive properties of colonic afferents.⁵²

Although the development of colon-bladder cross-sensitization is bidirectional, the effects of colonic damage on the function of the urinary bladder seem to be more substantial than *vice versa*. There are several reasons which may explain this observation. First, the intraluminal surface of the distal colon is larger in size, therefore, the number of receptors and pathways affected by an initial insult could be proportionally increased. Second, the colon, as the entire gut, has an enteric nervous system with the number of sensory and motor neurons in the GI tract totaling around 100 million, approximately the number found in the spinal cord.⁵³ The large number of intrinsic neurons can convey the information more precisely and amplify the initial insult by several times. Third, the structure and function of the colonic and bladder epithelium is different. The colon is lined by a simple columnar epithelium, the function of which is to absorb water and electrolytes. On the contrary, the bladder has a transitional epithelium which, though having many dynamic functions, also plays a protective role (barrier) in preventing the absorption of urine content. Therefore, intravesical instillations may result in lesser effects of the instilled drugs on sensory fibers in the bladder wall in comparison to faster absorption and activation of sensory fibers in the colon.

MECHANISMS OF COLON-BLADDER CROSS-SENSITIZATION

Pathological changes in the distal gut or the bladder may shift colon/bladder reflexes from cross-inhibitory to cross-excitatory.³² The phenomenon of sensitization of afferent nerves due to an initial acute insult in one of the pelvic organs was called cross-organ or viscerovisceral sensitization.^{32,41} The development of cross-sensitization in the pelvis is conveyed predominantly by *neural* mechanisms, however, *endocrine*, *paracrine* and *immune* responses may significantly influence the neural pathways. Interconnections and interrelationships between the proposed mechanisms are not well established. Hormonal status (*endocrine* mechanisms) can set up a background for the severity of changes caused

by an initial insult. The triggering stimulus of the same nature and magnitude can cause differential effects during low and high level of estrogens as it was observed in female rats.^{54,55} Psychological state (anxiety, persistent stress) could be as influential as hormonal status and may keep modulating sensory processing long after the recovery from the initial peripheral damage.

Activation of sensory fibers innervating either the colon or bladder plays the main role in initiating primary response as part of peripheral cross-sensitization. *Neural* pathways are activated by an initial peripheral insult (inflammation, ischemia, trauma, infection etc.) followed by the development of peripheral excitation/sensitization in afferent fibers and sensory neurons. Activation of peripheral neural pathways leads further to central sensitization (amplification of the signaling in the spinal cord and brain), followed by the efferent input from the CNS in response to activation of the afferent limb. The efferent response from the brain may either facilitate or inhibit nociceptive transmission in the periphery (modified from^{33,34}).

The mechanisms of peripheral colon/bladder cross-sensitization have been previously discussed in several papers.^{32–34,42,44,56,57} Peripheral cross-sensitization includes convergence of sensory inputs at the level of dorsal root ganglia and occurs due to: 1 – the existence of convergent DRG neurons with dichotomized peripheral axons which may release neurotransmitters and neuropeptides via “axon-reflex” mechanism from their peripheral terminals; 2 – cross-depolarization between sensory neurons within the same dorsal root ganglion receiving single input from either the colon or urinary bladder; 3 – activation of bladder sensory neurons by the input from colon/bladder convergent spinal cord neurons via dorsal root reflexes (reviewed in^{33,34}). Sensory neurons within a single dorsal root ganglion are electrically^{58–60} and chemically⁶¹ coupled. Electrical “cross-depolarization” includes cross-excitation of a silent small diameter neuron (with unmyelinated C-type axon) by a stimulation of a neighboring neuron.⁵⁸ Chemical coupling is usually a result of intraganglionic release (*paracrine* mechanism) of neurotransmitters and neuropeptides from sensory neurons activated by a peripheral insult.⁶¹ For instance, colonic inflammation was shown to up-regulate the expression of calcitonine gene-related peptide in bladder DRG neurons in rats.⁶² Inflammation and infection are the most common triggering factors in colon-bladder cross-talk, therefore, activation of *immune* cells (lymphocytes, macrophages, mast cells) could be an additional modulatory mechanism in colon-bladder cross-sensitization. Experimental TNBS colitis also induced long lasting outgrowth of catecholaminergic fibers in the thoracolumbar DRG neurons suggesting an increase in sympathetic input after pelvic inflammation.⁶²

Afferent inputs from the bladder and colon converge not only onto the same primary sensory neurons^{40,56} but also on the second order neurons within the spinal cord^{41,63} and in the brain.⁶⁴ A genetically modified strain of pseudorabies virus with different fluorescent tags injected in the colon and the bladder of anesthetized rats was used for transsynaptic labeling to trace colon and bladder projecting neurons in the brain.⁶⁴ These studies revealed three populations of neurons in the Barrington’s nucleus, which is a well known micturition center located in the pons of the brainstem. Majority of Barrington’s neurons (75%) received convergent input from both the colon and urinary bladder, whereas the small population of dorsal neurons was labeled exclusively from the bladder and a group of ventral neurons was colon-labeled.⁶⁴ Convergence of sensory information in the spinal cord and brain underlies the central mechanisms of colon-bladder cross-sensitization and may contribute to the development of colon-bladder co-morbidities in humans.

PHARMACOLOGICAL APPROACHES TO TARGET NEUROGENIC INFLAMMATION UPON COLON-BLADDER CROSS-SENSITIZATION

Neurogenic inflammation is one of the mechanisms underlying colon-bladder cross-sensitization and is mainly triggered by the release of proinflammatory neuropeptides such as substance P (SP), neurokinin A, and calcitonin gene-related peptide (CGRP) from the peripheral terminals of afferent nerves.⁶⁸ There are several possibilities to pharmacologically interfere with and reduce the contributions of various components of neurogenic inflammation in order to prevent or inhibit the effects of colon-bladder cross-sensitization.

Preventing the release from C-fibers through TRPV1 pathways

It is well established that agonists of TRPV1 receptors, capsaicin and resiniferatoxin, can desensitize the nerves and abolish the transmitter release following initial stimulation of TRPV1 receptors. Pan et al.⁴² demonstrated that colonic inflammation induced the release of SP and CGRP via activation of TRPV1 signaling pathways. Desensitization of TRPV1 receptors prior to the induction of colonic inflammation prevented the release of these peptides from the peripheral nerve terminals and reduced the development of neurogenic cross-talk between the colon and urinary bladder. Blocking TRPV1 receptors also was found to be effective for reducing inflammatory effects.⁶⁵ Charrua et al.⁶⁶ showed that GRC-6211, selective TRPV1 antagonist, counteracted the bladder hyperactivity and noxious input induced by acute cystitis.

α_1 -Adrenoceptor antagonists

There is evidence that α_1 -adrenoceptor agonists and antagonists, respectively, increase and decrease neurogenic inflammatory responses in the bladder.⁶⁷ It has been reported that neurons expressing both α_1 -adrenoceptors and TRPV1 are expressed in lumbosacral DRG and that exposure of these neurons to phenylephrine stimulated the release of SP. Beneficial effects of α_1 -adrenoceptor antagonists in the amelioration of storage symptoms in the lower urinary tract derives, in part, from their inhibitory effects on neurogenic inflammation.⁶⁷ Other studies reported that adrenergic nerves have the capacity to synthesize, and, on stimulation, release SP, neurokinin A, and CGRP, confirming that the sympathetic nervous system contributes to the development of neurogenic inflammation in the pelvis.⁶⁸

Blocking SP and CGRP receptors

Since SP and CGRP are the major players in neurogenic inflammation causing plasma extravasation (SP) and vasodilatation/hyperemia (CGRP), blocking their receptors would decrease the inflammatory response. Antagonists of SP receptors have been used clinically with some success in the treatment of OAB.^{69,70} Several blockers of CGRP receptors were successfully used to reduce neurogenic inflammation in migraine.⁷¹ Likewise, in a murine model of neurogenic cystitis induced by the injection of Bartha's strain of pseudorabies virus, Rudick et al.⁵⁰ showed that antagonists of NK1 receptors attenuated abdominal hyperalgesia and pelvic pain.

Increasing degradation of SP and CGRP

Mechanisms that terminate neurogenic inflammation include neutral endopeptidase (neprylisin) degradation of SP at the cell surface to prevent NK1 receptor activation.⁷² By degrading endocytosed SP, endothelin-converting enzyme-1 (ECE-1) was shown to promote the recycling and re-sensitization of NK1 receptors in the endothelial cells. EC1-inhibitor abolished these effects, and ECE-1 inhibition was suggested to be able to ameliorate the pro-inflammatory actions of SP.⁷³ Systematic studies of the therapeutic approaches that can

interfere with and reduce neurogenic inflammation in the pelvis can serve as the tools to further elucidate the mechanisms of how colonic pathophysiology may lead to the dysfunctions of LUT.

CONCLUSIONS

There are ample clinical and experimental data that show interactions between LUT and lower GI activity. Clinically, LUT dysfunctions often coincide with gastrointestinal dysfunctions and vice-versa, and therapeutic modulation of one system may improve the other system's function. Under normal conditions, most animal studies describe cross-inhibitory reflexes between the bladder and rectum/colon, but these may change to cross-excitatory reflexes under pathological conditions, such as in inflammatory states or when noxious stimuli are used. The exact mechanisms and the timespan of these interaction changes are still largely unknown, and both states may represent different entities. Extrapolation of these animal data appears to be very challenging as very few translational animal models exist that can claim clinical relevance to co-morbidity of colon and bladder disorders in humans.

Most of our knowledge on the underlying mechanisms for the bi-directional bladder/colon interactions is derived from models in which cross-sensitization occurs due to bladder and/or colon inflammation. From a clinical point of view, once sensitization has occurred, pathology appears to be very difficult to treat (*e.g.* bladder pain syndrome/interstitial cystitis). It would, therefore, be desirable to have experimental models that study bladder/colon cross interactions before sensitization develops, or models that study interventions that reduce or eliminate sensitization. This may support clinical efforts to modulate inflammation as early as possible, thereby, improving treatment efficacy.

Acknowledgments

The work in Dr. Malykhina's laboratory is supported by NIH/NIDDK grants DK077699 and DK 077699-S2 (ARRA). The work in Prof. Wyndaele's laboratory was supported by the Antwerp University Hospital Urology Research Fund.

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Figure 1. Experimental models of colon-bladder dysfunctions

Top part of the figure lists the stimuli (left panel) applied to the distal colon and the respective effects on the function of the urinary bladder (right panel). Bottom part of the figure shows the stimuli applied to the bladder (right panel) and effects on the distal colon (listed on the left side).

Table 1

Innervation of the lower urinary and gastrointestinal tracts

ORTHO SYMPATHETIC BRANCH		
	Lower Urinary tract	Colorectum
Spinal	T10-L2	L1-L3
Peripheral	Hypogastric Nerve	Hypogastric Nerve
Function	Continence	Continence
PARASYMPATHETIC BRANCH		
Spinal	S2–S4	S2–S4
Peripheral	Pelvic Nerve	Pelvic Nerve
Function	Micturition	Defecation
SOMATIC BRANCH		
Spinal	S2–S4	S2–S4
Peripheral	Pudendal Nerve	Pudendal Nerve
Function	External Urethral Sphincter	External Anal Sphincter