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Visceral organ cross-sensitization – an integrated perspective

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Abstract

Viscero-somatic referral and sensitization has been well documented clinically and widely investigated, whereas viscero-visceral referral and sensitization (termed cross-organ sensitization) has only recently received attention as important to visceral disease states. Because second order neurons in the CNS have been extensively shown to receive convergent input from different visceral organs, it has been assumed that cross-organ sensitization arises by the same convergence-projection mechanism as advanced for viscero-somatic referral and sensitization. However, increasing evidence also suggests participation of peripheral mechanisms to explain referral and sensitization. We briefly summarize behavioral, morphological and physiological support of and focus on potential mechanisms underlying cross-organ sensitization.

CROSS-ORGAN SENSITIZATION

Around 600 BC, Sushruta, an Indian surgeon, described the *Hritshoola*, which literally means heart pain (Dwivedi and Dwivedi, 2007; Dwivedi and Chaturvedi, 2000). However, it was not until the late 19th century that potential mechanisms underlying this well known symptom - referred pain - were advanced as reflecting a “commotion” or “irritable focus” in spinal segments receiving input from an organ (Ross, 1888; Sturge WA., 1888). These concepts were later expanded and formulated as the “convergence-projection” theory of referred visceral sensation (Ruch, 1965), convergence denoting input from both somatic and visceral structures onto the same second order spinal neuron (see Ness and Gebhart, 1990, and Gebhart and Ness, 1991 for more extensive discussion). Whereas viscero-somatic referral and sensitization has been well documented clinically and widely investigated, viscero-visceral referral and sensitization (termed cross-organ sensitization) has only recently received attention as important to visceral disease states (e.g., see Berkley, 2005; Foreman, 2007; Malykhina, 2007).

Because second order neurons in the CNS have been widely documented to receive convergent input from different visceral organs, it has been assumed that cross-organ sensitization arises by a similar convergence-projection mechanism as advanced for viscero-somatic referral and sensitization. However, there is also a long history associated with consideration of peripheral

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mechanisms to explain referral and sensitization. We briefly summarize behavioral, morphological and physiological support of and discuss potential mechanisms underlying cross-organ sensitization.

CLINICAL AND EXPERIMENTAL EVIDENCE OF CROSS-ORGAN SENSITIZATION

Based on clinical (Table 1) and experimental (Table 2) studies of cross-organ sensitization, the organs affected can be grouped into: 1) thoraco-upper abdominal (esophagus, heart, lower airways, stomach, duodenum and gallbladder) and 2) pelvic-lower abdominal (colon, rectum, ureter, urinary bladder, pelvic urethra, uterus and prostate). The grouping is not arbitrary. Cross-sensitization typically occurs between organs within either thoraco-upper abdominal or pelvic-lower abdominal areas. However, organ cross-talk/modulation between thoraco-upper abdominal and pelvic-lower abdominal areas has also been demonstrated (see Dmitrieva et al., 2001; Morrison et al., 2006; Qin et al., 2003; 2007e).

Thoraco-upper abdominal cross-organ sensitization

Heart/esophagus/lower airways/stomach/gallbladder—Pain referred to the skin and muscle of the thorax and left arm during myocardial ischemia (angina) represents a landmark symptom recognized not only clinically, but also by the general public. However, the same symptoms and pattern of referral thought to be derived from the heart are replicated from the pathologic esophagus (Heatley et al., 2005). Growing evidence suggests that the heart is neuroanatomically and functionally related with the esophagus. Thus, it was shown both in cat (Garrison et al., 1992) and rat (Euchner-Wamser et al., 1993; Qin et al., 2004) that thoracic spinal neurons receiving somatic input also receive convergent esophageal and cardiac input. Moreover, these neurons appear to be sensitized by noxious stimulation of the two related organs (Garrison et al., 1992; Qin et al., 2004).

Convergence has also been described between the heart and stomach or gallbladder. Studies in cat (Ammons and Foreman, 1984), monkey (Ammons et al., 1984) and rat (Qin et al., 2007c) have shown that distension of the gallbladder (Ammons et al., 1984; Ammons and Foreman, 1984) or stomach (Qin et al., 2007c) activates thoracic spinothalamic tract neurons responsive to noxious chemical stimulation of the heart. Likewise, airway irritants (e.g., ammonia, cigarette smoke) have been shown to excite rat thoracic spinal neurons that also respond to esophageal distension (Hummel et al., 1997) or intrapericardial administration of bradykinin (Euchner-Wamser et al., 1994; Qin et al., 2007d).

Esophagus/stomach/duodenum—Several studies in humans have recently shown that noxious stimulation of the lower esophagus (LE) can sensitize the upper esophagus (UE). Thus, acid infusion in the LE induces hyperalgesia in the UE (Frokjaer et al., 2005; Sarkar et al., 2000; 2001; 2006). Acidification of the duodenum also induces esophageal hypersensitivity in humans (Hobson et al., 2004), a process that may involve central sensitization of spinal cord neurons receiving convergent input from both organs. Supporting this idea, it has been shown in rat that T9-T10 spinal neurons receive both duodenal and gastric afferent input, and respond to gastric distension in the noxious range (Qin et al., 2007a; 2007b).

Pelvic-lower abdominal cross-organ sensitization

Cross-organ sensitization between the lower gut and pelvic urinary or gynecologic organs has been shown to be a common and troublesome clinical circumstance, leading to significant problems in diagnosing and treating the diseased organ (see Baranowski et al., 2008; Berkley, 2005; Berkley et al., 2005; 2007; Malykhina, 2007; Saini et al., 2008; Stanford et al., 2007; Theoharides et al., 2008; van de Merwe et al., 2008; Warren et al., 2008). The organs that

appear most often involved in pelvic-lower abdominal cross-sensitization, both in humans and animals, seem to be the colon/rectum, the urinary bladder/pelvic urethra, the uterus and the prostate (see Tables 1 and 2). Interestingly, the urinary bladder may be more vulnerable to cross-modulation than other pelvic organs and, conversely, inflammatory processes in the bladder appear less effective in inducing cross-sensitization in colon or uterus (see below).

Colon/urinary bladder—In normal conditions, colon and bladder are functionally related. Studies by Denny-Brown and Robertson (1933), showing that micturition and defecation are normally alternated (Vilensky et al., 2004), and by Kock and Pompeius (Kock and Pompeius, 1963), who noted also that motility of the bladder was inhibited by distension of the anal canal or rectum and by stimulation of the perineal skin, suggested an anatomical and functional relationship between the bowel and the urinary bladder. Floyd and colleagues (1982) later showed in cats that colonic distension results in graded inhibition of spontaneous bladder contractility.

Importantly, studies in humans reveal that colon-bladder cross-sensitization could also result in painful symptoms. For example, patients with irritable bowel syndrome (IBS) often exhibit signs of urinary bladder hypersensitivity: nocturia, frequency and urgency of micturition, incomplete bladder emptying, back pain and, in women, dyspareunia (Whorwell et al., 1986). More recently, studies where acute (Pezzone et al., 2005) or chronic (Bielefeldt et al., 2006; Lamb et al., 2006) colon irritation were induced in mouse (Pezzone et al., 2005) and rat (Lamb et al., 2006; Peng et al., 2009) confirmed ‘colon-to-bladder’ sensitization, showing increased frequency of bladder contractions, reduced inter-contraction intervals (Pezzone et al., 2005), and altered micturition reflexes (Lamb et al., 2006). It is noteworthy to indicate that these signs are usually indicators of bladder/pelvic distress and pain, as their presence in humans often correlates with pain (Theoharides et al., 2008).

Urinary bladder/colon—It has been suggested that ‘bladder-to-colon’ cross-modulation may be less frequently observed than its counterpart (Winnard et al., 2006). However, an epidemiological study reported that patients diagnosed with interstitial cystitis (IC) presented concomitant chronic diseases, including IBS (Alagiri et al., 1997). Conversely, individuals with IBS showed an increased association with IC when compared with the general population. While these observations suggest the occurrence of cross-organ sensitization between bladder and colon, they do not address which organ/system is first affected. Recent studies in rat (Pezzone et al., 2005) and mouse (Bielefeldt et al., 2006) confirm ‘bladder-to-colon’ cross-sensitization; animals treated with cyclophosphamide, an antineoplastic drug that induces bladder inflammation (see Korkmaz et al., 2007; Laird et al., 2002), develop hypersensitivity to colon distension.

Uterus/prostate/ureter/urinary bladder and pelvic urethra/colon—Cross-organ modulation is a common observation in the fields of gynecology and urology (see Alagiri et al., 1997; Berkley, 2005; Berkley et al., 2005; Saini et al., 2008; Theoharides et al., 2008). Accordingly, pain originating from different organs of the lower abdomen and pelvis are often considered components of chronic pelvic pain syndrome (CPPs).

Several studies in animals have confirmed cross-organ modulation among the lower urinary tract, colon and gynecologic structures (Table 2). Thus, bladder inflammation in female rats results in the reduction of uterine contractions (Dmitrieva et al., 2001). Moreover, uterine inflammation induces plasma extravasation in the urinary bladder and to a lesser extent also in the colon, in an estrous cycle-dependent manner, suggesting cross-organ inflammation (Winnard et al., 2006). Furthermore, experimental endometriosis in female rats not only induced bladder plasma extravasation, but also urinary bladder hypersensitivity, reflected as a decrease in micturition thresholds (Morrison et al., 2006).

Cross-organ sensitization has also been documented between the uterus and the pelvic urethra, the ureter or the vagina (Table 2). The pelvic urethra reflex, understood as the reflexive closure of the urethra caused by bladder distension (see de Groat et al., 2001), and which has been related to neurogenic urethra hyperactivity (Lin, 2003; Lin, 2004), is sensitized by the instillation of capsaicin into the uterus of anesthetized rats (Peng et al., 2008b; 2008a). Moreover, studies in women (Giamberardino et al., 2001) and rat (Giamberardino et al., 2002) suggested that both existing (dysmenorrhea) and latent (pelvic congestion at ovulation/menstruation; asymptomatic endometriosis, ovarian cysts) conditions of female reproductive organs enhance referred pain due to ureteral calculosis. And, in a rat model of endometriosis, Berkley and colleagues showed that abnormal endometrial tissue growths directly influence development of vaginal hyperalgesia (Berkley et al., 2007; Cason et al., 2003) and that the resulting pain is exacerbated by estrogens (Berkley et al., 2007).

In men there is potential for cross-organ sensitization between the prostate and other pelvic organs (Pontari, 2008; Saini et al., 2008). Lower urinary tract symptoms such as urgency and nocturia often overlap with chronic pain in the perineum, testes or tip of the penis, typical symptoms of chronic prostatitis (Pontari, 2008; Saini et al., 2008).

POTENTIAL MECHANISMS OF CROSS-ORGAN SENSITIZATION

The 'central' theory

As briefly introduced above, the earliest theories on referred pain date to the late 19th century and work by MacKenzie, Sturge and Ross (see Gebhart and Ness, 1991; Ness and Gebhart, 1990). In various forms, these authors inferred from their clinical observations that increased tenderness to palpation of overlying structures, or hypersensitivity of skin in the area of referred sensation (e.g., left shoulder), arose from changes in the excitability of spinal neurons (the conceptual antecedent to 'central sensitization'). These concepts were later assimilated by Ruch (1965) into a proposal that visceral afferent input onto spinal neurons converged with afferent input from somatic structures (subsequently projected to supraspinal sites), providing a central, spinal explanation for referred viscerosomatic and viscerovisceral hypersensitivity. That is, organ disease or experimental inflammation increases the excitability of spinal neurons which is reflected as increased responses to stimuli applied in tissues providing convergent input onto the same spinal neuron. It has since been widely documented that second order spinal neurons receive visceral afferent as well as somatic afferent input, if not also convergent input from another organ(s) in the same body area (e.g., see Table 2 for references), suggesting a central basis for cross-organ sensitization (Fig. 1).

In addition to a spinal segmental contribution, convergence of viscerosomatic and viscerovisceral input has been documented in brainstem and thalamus. Regarding viscerovisceral convergence, morphological studies in Barrington's nucleus (the pontine micturition centre) demonstrated the existence of neurons responding both to bladder and colon distension (Hubscher et al., 2004; Rouzade-Dominguez et al., 2003a; 2003b). In the rat thalamus, neurons responding to electrical stimulation of the dorsal nerve of the penis and to colon distension were identified in a number of nuclei (Hubscher and Johnson, 2003). It is noteworthy that the general principle of convergence from adjacent or nearby organs may not necessarily apply in the thalamus, which receive visceral inputs from widely separated organs (e.g., Apkarian et al., 1995).

Transection of visceral nerves also provides support for central contributions to cross-organ sensitization. For example, transection of the hypogastric nerve (a major source of afferent and efferent innervation of the uterus) (Berkley et al., 1993; Sato et al., 1996) in female rats was found to reduce the plasma extravasation induced by inflammation of the colon or uterus in the urinary bladder (Winnard et al., 2006), as well as the inhibitory effects of urinary bladder

inflammation on uterine contractions (Dmitrieva et al., 2001). Convergent afferent inputs from the duodenum and colon onto vagal pre-ganglionic efferents innervating the stomach have also been demonstrated in ferrets, and shown to inhibit gastric motility (Grundy et al., 1981). Finally, it has been hypothesized that antidromically produced dorsal root reflexes (Willis, Jr., 1999), generated in microcircuits between dorsal horn interneurons receiving inputs from an inflamed organ and making synaptic contact with afferent inputs from an uninflamed organ, could promote cross-sensitization (Berkley, 2005).

Glutamate and glutamate receptors, as well as capsaicin and its receptor, TRPV1, have been associated with central mechanisms of cross-organ sensitization. Instillation of capsaicin into the uterus of female rats sensitizes evoked pelvic urethra reflex activity, with a parallel increase in the content of phosphorylated NMDA subunit NR2B receptor in spinal neurons (Peng et al., 2008b). Interestingly, the urethral as well as spinal effects were attenuated by intrathecal application of NMDA (Peng et al., 2008b) or TRPV1 (Peng et al., 2008b) receptor antagonists. Similar and supporting results were obtained when assessing the effects of mustard oil-induced colon inflammation on the rat pelvic-urethra reflex (Peng et al., 2009). However, since local blockade of the TRPV1 receptor in the inflamed colon (Peng et al., 2009) or uterus (Peng et al., 2008a) attenuated effects on the urethral reflex, it could be hypothesized that peripheral mechanisms may also have a role in cross-organ sensitization (see below).

Finally, recto- (Neuhuber et al., 1993) and colo-spinal (Suckow and Caudle, 2008) afferent neurons have been reported in the rat, and partly because they express neuropeptides and receptors associated with nociception, it has been proposed that they participate in visceral pain processing (see Suckow and Caudle, 2008). While the physiological significance of these neurons remains to be confirmed, one may speculate that these neurons could transmit nociceptive information from the distal gut to spinal neurons receiving convergent input from other organs, thus contributing to central sensitization.

The 'peripheral' theory

The principal peripheral mechanism advanced to explain referral of visceral sensation and cross-tissue sensitization is based on so-called dichotomizing fibers (i.e., sensory endings of a single neuron innervating two different tissues), a concept most enthusiastically supported by Sinclair and colleagues (1948). They and subsequent investigators reported electrophysiological (Pierau et al., 1982; Sinclair et al., 1948) and morphological evidence suggesting the presence of dichotomizing fibers in the sacroiliac plexus nerves of pigeons (Taylor and Pierau, 1982) and rats (Taylor et al., 1983) (see Table 3). Subsequently, dichotomizing neurons projecting into the thoracic (intercostal) and visceral (splanchnic) nerves of rat were also described (Dawson et al., 1992). Although the number of dichotomizing sensory neurons in dorsal root ganglia (DRG) varies between animals and studies (from 0.1% to 21% of all traced neurons) (Dawson et al., 1992; Taylor et al., 1983), their identification suggested an anatomical and physiological basis for the occurrence of referred pain.

Physiological evidence of dichotomizing primary afferents between the colon, the anus and the lower urinary tract was also reported (Bahns et al., 1986) (see Table 3 and Fig. 2). Later, morphological studies in rat (Chaban et al., 2007; Chen et al., 2005; Christianson et al., 2007; Keast and de Groat, 1992; Malykhina et al., 2006), mouse (Christianson et al., 2007) and cat (de Groat et al., 1987) using two different retrogradely transported dyes injected in different organs revealed the presence of dichotomizing afferents between colon and the urogenital and sexual organs (Table 3). In contrast, it seems that autonomic neurons present in the rat major pelvic ganglion do not dichotomize, as shown by the absence of doubly labeled, colon/bladder neurons (Rouzade-Dominguez et al., 2003a). Further characterization of dichotomizing primary afferent neurons innervating the colon and uterus (Chaban et al., 2007) showed expression of TRPV1 and the purinoceptor P2X3, both involved in nociceptive

mechanisms (see Brederson and Jarvis, 2008; Broad et al., 2009). Also, up-regulation of CGRP was observed in rat bladder DRG neurons after colon inflammation (Qiao and Grider, 2007).

Dichotomizing sensory neurons would naturally cross-sensitize. In cultured lumbosacral *bladder* sensory neurons from rats with colitis, significant increases in the net inward current induced by capsaicin and in the peak amplitude of tetrodotoxin-resistant (TTX-R) Na⁺ currents were shown (Malykhina et al., 2004). In a subsequent study, acute colitis in male rats was shown to decrease the voltage and current thresholds for action potential firing in dichotomizing capsaicin-sensitive lumbosacral DRG neurons, from 3 - 30 days after the onset of colitis (Malykhina et al., 2006).

These changes in bladder or colon sensory neurons could also result in alterations in the sensitivity of their nerve terminals in the target organ. For example, *in vitro* single fiber recordings of pelvic nerve bladder afferents from rats with acute (Ustinova et al., 2006) or chronic (Ustinova et al., 2007) colon irritation revealed sensitization of bladder afferents to both mechanical (innocuous and noxious bladder distension) and chemical (capsaicin, bradykinin and SP) stimuli (Ustinova et al., 2006). These effects were abolished by afferent denervation of the bladder (Ustinova et al., 2006) and by systemic capsaicin pretreatment (Ustinova et al., 2007), suggesting a role for TRPV1-expressing bladder sensory neurons in the generation of cross-organ sensitization.

Early reports on the existence of dichotomizing visceral sensory neurons were generally discounted on technical grounds, but recent studies using improved tracers and experimental strategies have reinforced the presence of dichotomizing sensory neurons innervating different organs and stimulated additional studies. One caution when considering dichotomizing sensory neurons as principal players in the generation and maintenance of cross-organ sensitization is their low percentage relative to the proportion of all visceral sensory neurons. Of all labeled colon and bladder sensory neurons, only 5-27% dichotomizing neurons were found in rat (Christianson et al., 2007; Malykhina, 2007; Qiao and Grider, 2007) and ~21% in mouse (Christianson et al., 2007). Likewise, a relatively small proportion (~3-15%) of uterus and colon dichotomizing neurons were detected in rat (Chaban et al., 2007; Li et al., 2008). The percentage of visceral sensory neurons in a given DRG is not well established. However, considering that ~16,000 neurons are present in the L6/S1 DRGs from young rats (Mohammed and Santer, 2001), and that ~600 project to the bladder and/or colon (Christianson et al., 2007), only ~4% of the total number of neurons project to these organs. Accordingly, the proportion of dichotomizing visceral neurons is small and their role in cross-organ sensitization remains to be confirmed as functionally significant.

There exist other peripheral mechanisms, discussed below, that may potentially contribute to cross-tissue/organ sensitization.

Alterations in afferent processing of DRG neurons and their projections—

Sensory neurons innervating different organs could be cross-sensitized in a number of additional ways that do not require dichotomizing fibers (Fig. 3). Cross excitation could occur at the level of the sensory neuron in the DRG. Studies in cultured DRG neurons innervating the hindpaw showed that A- and C-neurons (i.e., neurons with myelinated and unmyelinated axons, respectively; see Lawson, 2002) are electrically coupled (Amir et al., 2002; Amir et al., 2005; Amir and Devor, 2000). Interestingly, electrical excitability of neuron somata seems not to be required for through conduction of afferent input from the periphery to the spinal cord (Amir and Devor, 2003). If not electrical, then chemical coupling could play a role (Amir and Devor, 1996; Mantyh et al., 1994). Intraganglionic release of substance P (SP) (Harding et al., 1999; Huang and Neher, 1996; Neubert et al., 2000) and of calcitonin gene-related peptide (CGRP) (Eberhardt et al., 2008; Ulrich-Lai et al., 2001) has been shown in trigeminal

(Eberhardt et al., 2008; Neubert et al., 2000; Ulrich-Lai et al., 2001) and dorsal root ganglia (Eberhardt et al., 2008; Harding et al., 1999; Huang and Neher, 1996) of rats. SP (e.g., (Mantyh, 2002)) as well as CGRP (e.g. Hill and Oliver, 2007) are nociceptive modulators/transmitters and provided that 1] their receptors are present and functional in DRG neurons and/or their axons and 2] they are in close anatomical proximity (including with satellite glial cells), electrical and/or chemical coupling (for review, see Brumovsky et al., 2007) could contribute to cross-talk between neighboring DRG neurons innervating different visceral organs.

Extensive studies on rats with spinal nerve ligation suggest that the Wallerian degeneration and subsequent inflammation of injured axons leads to the sensitization of uninjured neighboring axons (Campbell and Meyer, 2006; Meyer and Ringkamp, 2008). Alternatively, bladder and colon afferents in the pelvic nerve, for example, could be cross-sensitized through local, axonal release of excitatory neurotransmitters (Amir and Devor, 1992; Hoffmann et al., 2008) (Fig. 3). Thus, noxious heat and chemical stimulation were shown to induce axonal release of CGRP from sciatic nerve fibers in rat (Sauer et al., 2001) and mouse (Bernardini et al., 2004), probably through vesicular exocytosis (Bernardini et al., 2004). Moreover, this effect was dependent on the activation of TRPV1 receptors (see Fischer and Reeh, 2007; Leffler et al., 2008). These observations are neurophysiologically significant. Heat stimulation of unmyelinated peripheral nerve axons in mouse produces responses similar to those when the stimulus is applied to the receptive field (Hoffmann et al., 2008). Accordingly, a human psychophysical study revealed transduction of thermal energy by the superficial radial nerve, producing pain perceived in the corresponding distant receptive field (Hoffmann et al., 2009).

Local/inflammatory changes—Histological examination of bladders from rats with chronic colitis revealed an increase in bladder mast cell density and sensory fiber sensitization compared with control (Ustinova et al., 2007). Acute signs of inflammation such as plasma extravasation have also been described in the bladder after colon or uterine inflammation, with smaller changes in colon and uterine horn when the bladder was inflamed (Winnard et al., 2006). Moreover, rats with experimental endometriosis show increased urinary bladder plasma extravasation and decreased micturition thresholds (Morrison et al., 2006). Interestingly, some of these changes were dependent on the oestrus cycle of the rat, suggesting participation of gonadal hormones in cross-organ sensitization (Winnard et al., 2006).

Studies by Foreman and colleagues, supporting the role of central sensitization as the main player in cross-organ sensitization between the colon and bladder, showed no detectable histological changes in the bladder wall of rats with chronic colitis (Malykhina et al., 2004; Qin et al., 2005). However, acute (but not chronic) colitis in rats was shown to alter the contractility of the detrusor muscle in response to electrical field stimulation, cholinergic agonism with carbachol or exposure to potassium chloride, in the absence of morphological changes or inflammatory infiltration of the bladder (Noronha et al., 2007). Thus, while differences in the outcome of several studies may relate to different methodological approaches, the absence of histological changes in a cross-sensitized organ does not imply lack of functional alterations.

An alternative approach to assess possible local changes during cross-organ sensitization is altered response to drugs. For example, cannabinoids dose-dependently increase uterine contractions, an effect that is reduced in the presence of bladder inflammation (Dmitrieva and Berkley, 2002), suggesting alterations in the expression of uterine cannabinoid receptors. Therefore, cross-organ sensitization could not only arise from organ inflammation or alterations in the sensitivity of afferent terminals or sensory neurons, but also in the number/affinity of tissue receptors and the ability to respond to drugs and endogenous mediators in different pathological conditions.

A role for the autonomic nervous system (ANS)?—“The ANS is that system of neurons that controls visceral organs, effectors in the skin, and the cardiovascular system” (Furness, 2006). Earlier, Langley (1916) posited that the autonomic nerves, including the paravertebral and prevertebral ganglionic chains, coordinate the activities of the organs and the sensations generated from them. Prevertebral ganglia (e.g., inferior mesenteric and major pelvic ganglia) typically consist of a mixture of cell bodies of sympathetic and parasympathetic postganglionic neurons, receiving both sympathetic and parasympathetic input (Furness, 2006). Interestingly, peptidergic varicosities are very abundant in autonomic ganglia from different species (see de Groat, 1987), possibly derived from passing afferent fibers projecting towards their corresponding target organ (see Houdeau et al., 2002; Kaleczyc et al., 2003).

Autonomic ganglia could thus also contribute to cross-organ sensitization (Fig. 4). As illustrated, axon collaterals in an autonomic ganglion from afferents innervating a pathologic organ could excite ganglionic secretory and motor neurons innervating a different, non-diseased organ. In fact, several neuropeptides have been shown to exert facilitatory or inhibitory effects on cells in autonomic ganglia (e.g., Cohen et al., 1996; de Groat, 1987). Moreover, activation of postganglionic parasympathetic efferents by electrical stimulation of the sphenopalatine ganglion elicits extravasation in the ipsilateral dura (Asztely et al., 1998; Delepine and Aubineau, 1997). Thus, a primary afferent driven ‘cross-organ neurogenic inflammation’ could arise, resulting in events such as plasma extravasation and inflammation in a non-diseased organ.

One more potential peripheral mechanism of cross-organ sensitization should be considered: the intestinofugal afferent neuron (see Szurszewski et al., 2002). This unique myenteric ganglion neuron relays mechanosensory information to sympathetic prevertebral neurons, and their activation by colon distension induces acetylcholine release in the ganglion and subsequent excitatory postsynaptic potentials of ganglionic neurons (see Szurszewski et al., 2002).

Taken together, the important anatomical and functional relationship between sensory and autonomic neurons/fibers present in prevertebral ganglia, innervating both healthy and pathologic organs, offers an additional arena for the contributing to cross-organ sensitization.

An integration of concepts

We have presented different views on how cross-organ sensitization could arise and be maintained. Most studies have emphasized either central or peripheral mechanisms, but it has long been appreciated (e.g., Sinclair et al. 1948) that neither central nor peripheral mechanisms alone are capable of fully explaining cross-organ sensitization. Clinical observation reveals that both peripheral and central mechanisms are involved in the generation and maintenance of cross-organ sensitization, and that they possibly intervene in an orchestrated manner. Recently, it was indicated that “the greater abundance of convergent neurons in the spinal cord likely indicates a central amplification process in cross-organ sensitization” (Qin et al., 2005). This amplification process could also be understood in a much broader sense, involving a number of amplification steps contributing to cross-organ sensitization. Thus, taking an inflammatory process in any given organ as an example for initiation of cross-organ sensitization, one could hypothesize that the following series of events would take place (Fig. 2):

- organ insult/inflammation
- peripheral excitation/sensitization
- central sensitization.

Details contributing to the above events could include: **1)** an inflammatory process in an organ increases the excitability of dichotomizing and non-dichotomizing sensory neurons that innervate the organ and leads to cross-inflammation of a nearby organ; **2)** the production of inflammatory mediators **AND/OR** electrical and/or neurochemical coupling between axons and cell bodies of sensory neurons increase the excitability of afferent fibers innervating the non-diseased organ; **3)** the affected sensory neuron cell bodies increase their expression of receptors/ion channels and axonal transport of excitatory neurotransmitters, including neuropeptides, which in turn are released in the affected organs to further promote inflammation and sensitization of receptive endings in the organs; and **4)** augmented release of excitatory neurotransmitters in the dorsal horn onto second order neurons that receive convergent input from more than one organ and also from somatic structures. These central neurons would complete the process of ‘amplification’ by transmitting information to higher levels of the nervous system. The amplification process could also be aided by alterations in spinal or supraspinal glial-neuronal relations. Peripheral inflammation activates microglia in the spinal cord that release proinflammatory cytokines (e.g., Milligan and Watkins, 2009) and can influence the excitability of central neurons. In such a scenario, a broad activation of glial cells in the dorsal horn could lead to the excitation of neurons receiving diverse afferent input. It is appreciated that these ‘details’ exclude consideration of changes in descending modulatory influences in what is ultimately experienced, and instead focus principally on peripheral events and the first central synapse.

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Figure 1.

Hypothetical mechanisms of centrally mediated cross-organ sensitization. (A) The general model illustrates convergence of inputs from colon and bladder onto the same second order spinal neuron. An insult to colon (represented by a lightning bolt) increases the excitability of the spinal neuron (central sensitization) such that 'normal' input from the bladder is also amplified by the second order spinal neuron. (B) Alternatively, activation by input from the colon of an inhibitory spinal interneuron (filled circle) could lead to an increase in primary afferent depolarization, generation of dorsal root reflexes (DRR; Willis 1999) and neurogenic inflammation in the bladder.

Figure 2.

Hypothetical mechanisms of peripherally mediated cross-organ sensitization – The dichotomizing primary afferent neuron. The general model illustrates innervation of the colon and bladder by a single sensory neuron. The inset shows DRG neurons that innervate the colon (green; arrowheads), the bladder (red; double arrowheads) and both the colon and bladder, as evidenced by the colocalization of both green and red signals (yellow; arrows) in the merged channel. See Christianson et al 2007 for details. Images (unpublished) were provided courtesy of Drs. Julie C. Christianson and Brian M. Davis, University of Pittsburgh. Scale bar: 20 μ m.

Figure 3.

Hypothetical mechanisms of peripherally mediated cross-organ sensitization – intraganglionic (A) and interaxonal coupling (B). (A) Intraganglionic release of neuropeptides and excitatory neurotransmitters such as glutamate may participate in the interaction between spatially close colon (green) and bladder (red) DRG neurons (a). This mechanism obviously requires expression of functionally active neurotransmitter receptors. Alternatively, electrical coupling (b) could have a role in cross-organ sensitization between DRG neurons. (B) Chemical (a) as well as electrical (b) coupling between injured and healthy primary afferent fibers have been described in nerves supplying skin and muscle. A similar mechanism could also be present in visceral nerves, thus allowing for cross-sensitization within nerve bundles. Images (unpublished) depicting colon (green) and bladder (red) DRG neurons (A) or biotinamide-traced pelvic nerve axons (B), were provided courtesy of Drs. Julie C. Christianson and Brian M. Davis, University of Pittsburgh and Pablo R. Brumovsky, respectively. Scale bars: 20 μm (A); 10 μm (B).

Fig. 4. Hypothetical mechanisms of autonomic/afferent interactions leading to cross-organ neurogenic inflammation. In this scenario, the sensitization of afferent fibers due to organ insult would not only result in the transmission of information to the central nervous system, but also in the activation of autonomic neurons in prevertebral ganglia. For example, axon collaterals of sensitized bladder primary afferent fibers would synapse onto postganglionic neurons in the major pelvic ganglion (MPG) that innervate the colon. These autonomic neurons, by release of various neurotransmitters, may in turn contribute to changes in secretory and motor function as well as generation of neurogenic inflammation in the colon. Abbreviations: IMG: inferior mesenteric ganglion; MPG: major pelvic ganglion; PN: pelvic nerve.

Table 1

Clinical observations of cross-organ sensitization

	Organs involved	References
THORACO-UPPER ABDOMINAL CROSS-ORGAN SENSITIZATION	Lower esophagus and upper esophagus	(Sarkar et al., 2000; Sarkar et al., 2001; Frokjaer et al., 2005; Sarkar et al., 2006)
	Lower esophagus and duodenum	(Frokjaer et al., 2005)
	Lower esophagus and rectum	(Frokjaer et al., 2005)
	Duodenum and esophagus	(Hobson et al., 2004)
	Hypoalgesia of esophageal and duodenal distension in painful chronic pancreatitis patients	(Dimcevski et al., 2006)
PELVIC-LOWER ABDOMINAL CROSS-ORGAN SENSITIZATION	Colon and other viscera	(Whorwell et al., 1986)
	Bladder and colon	(Alagiri et al., 1997)
	Sigmoid colon and rectum	(Naliboff et al., 1997; Lembo et al., 1997; Munakata et al., 1997)
	Reproductive organs and upper urinary system	(Giamberardino et al., 2001)

Table 2

Experimental behavioural and physiological evidence of cross-organ sensitization.

	Organs involved	Species	References
THORACO-UPPER ABDOMINAL CROSS-ORGAN SENSITIZATION	Esophagus and heart	Male rat	(Garrison et al., 1992; Euchner-Wamser et al., 1993; Qin et al., 2004)
	Stomach and heart		(Qin et al., 2007c)
	Gallbladder and heart	Cat	(Ammons and Foreman, 1984)
		Male rat	(Ammons et al., 1984)
	Stomach and duodenum	Male rat	(Qin et al., 2007a; Qin et al., 2007b)
	Heart and lower respiratory airways		(Qin et al., 2007d)
PELVIC-LOWER ABDOMINAL CROSS-ORGAN SENSITIZATION	Colon and bladder	Cat	(Floyd et al., 1978; Floyd et al., 1979; Floyd et al., 1982)
		Male rat	(Malykhina et al., 2004; Qin et al., 2005; Malykhina et al., 2006; Noronha et al., 2007)
		Female rat	(Pezzone et al., 2005; Ustinova et al., 2006; Ustinova et al., 2007)
		Male mouse	(Lamb et al., 2006)
	Colon and pelvic-urethra	Male rat	(Peng et al., 2009)
	Colon and uterus	Female rat	(Winnard et al., 2006)
	Bladder and colon	Cat	(Bouvier et al., 1990)
		Female rat	(Pezzone et al., 2005) 2005.
		Male mouse	(Bielefeldt et al., 2006)
		Female mouse	(Rudick et al., 2007)
	Lower respiratory airways and colon	Male rat	(Qin et al., 2007e)
	Bladder and uterus	Female rat	(Dmitrieva et al., 2001; Dmitrieva and Berkley, 2002; Winnard et al., 2006)
	Bladder and heart	Male rat	(Qin et al., 2003)

	Organs involved	Species	References
	Uterus and colon	Female rat	(Winnard et al., 2006)
	Uterus and bladder		(Winnard et al., 2006); (Morrison et al., 2006)
	Uterus and pelvic-urethra		(Peng et al., 2008a; Peng et al., 2008b)
	Uterus and vagina		(Cason et al., 2003; Berkley et al., 2007)

Table 3

Anatomical demonstration of dichotomizing primary afferent neurons

	Organs involved	Species	References
NON-VISCERAL DICHOTOMIZING NERVES	Dichotomizing neurons in the leg	Pigeon Male rat	(Taylor and Pierau, 1982) (Taylor et al., 1983)
THORACO-UPPER ABDOMINAL NERVES	Dichotomizing neurons projecting to the intercostal (somatic) and splanchnic (visceral) nerves	Male rat	(Dawson et al., 1992)
PELVIC-LOWER ABDOMINAL DICHOTOMIZING NERVES			
<u>COLON/BLADDER</u>	Convergent colon and bladder DRG neurons	Male rat	(Keast and de Groat, 1992) (Malykhina et al., 2006)
	Up-regulation of CGRP and TrkB in rat bladder afferent neurons after TNBS	Male rat and mouse Male rat	(Christianson et al., 2007) (Qiao and Grider, 2007)
<u>UTERUS/COLON</u>	Convergent colon and uterus DRG neurons		(Chaban et al., 2007)
	TRPV1 and P2X3 expression of dually projecting colon and uterus DRG neurons	Female rat	(Chaban, 2008)
	Upregulation of molecules in convergent colon and uterus DRG neurons		(Li et al., 2008)