

Published in final edited form as:

*Curr Opin Support Palliat Care*. 2012 March ; 6(1): 17–26. doi:10.1097/SPC.0b013e32834f6ec9.

## Visceral Pain – the Ins and Outs, the Ups and Downs

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### Abstract

**Purpose of review**—Visceral pain represents a major clinical problem, yet far less is known about its mechanisms compared to somatic pains, e.g. from cutaneous and muscular structures.

**Recent findings**—In this review we describe the neuroanatomical bases of visceral pain signalling in the peripheral and central nervous system, comparing to somatic pains and also the channels and receptors involved in these events. We include an overview of potential new targets in the context of mechanisms of visceral pain and hypersensitivity.

**Summary**—This review should inform on the recognition of what occurs in patients with visceral pain, why co-morbidities are common and how analgesic treatments work.

### Keywords

Visceral pain; visceral hyperalgesia; viscerosomatic convergence; descending modulation

### Introduction

The recent growth in interest by researchers and clinicians in pain originating from internal organs reflects an important paradigm shift in the awareness of the magnitude and impact of visceral pain disorders. Most people have experienced pain from internal organs ranging from the mild discomfort of indigestion to the agony of a renal colic, and women are subject to many forms of visceral pain associated with reproductive life. For both men and women, pain of internal origin is a common cause for seeking medical attention. In the case of visceral cancer pain, the growth of a tumour could lead to a myriad of activating stimuli leading to the pain experience, ranging from chemicals released by cancer cells, immune cells, distension or obstruction of luminal organs, and/or neuropathic events such as denervation and/or nerve sprouting and other changes in neuronal function.

Nevertheless, much of our current understanding of pain mechanisms derives from studies of somatic, but not visceral nociception, possibly due to greater complications associated with accessing visceral structures with adequate visceral stimuli in research models. Nociceptive processing in somatic and visceral pain has both common features and important differences in neurological mechanisms and psychology. Importantly, treatment of both forms of pain is progressively becoming independent of the accompanying disease and pain itself is regarded as a syndrome, rather than a symptom or by-product of illness (1).

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Functional gastrointestinal disorders (FGID) underlie the most prevalent forms of visceral pain. Irritable bowel syndrome (IBS) is one FGID characterised by abdominal pain, discomfort and altered bowel habits and creates tremendous pressure on the healthcare system affecting an estimated 10-15% of Europe and U.S. populations with consequent costs estimated to exceed US\$ 40 billion (2-5). Dysmenhorrea, severe pelvic pain during menstrual cycles, underlies one of the most common gynaecologic complaints in young women (6, 7). It also contributes to economic burdens associated with lost workdays and productivity (8, 9). Although some visceral pain disorders are not life-threatening, they still contribute significantly to a large segment of healthcare resource consumption and have a considerable negative impact on lives with psychological distress, disturbance of work and sleep and sexual dysfunction (10).

Moreover, there is increasing evidence that the progression of visceral pathology and pain is substantially affected by ageing and gender. Some visceral pain syndromes are reported to be less intense in adults of advanced age than in younger individuals, e.g. appendicitis (11, 12). IBS is also reported twice as frequently in women than in men (13, 14).

The scope of this review covers knowledge of visceral pain mechanisms gained from the clinical setting to animal and *in vitro* studies investigating visceral nociceptive signaling. Some comparisons to somatic pain are highlighted.

## Clinical features of visceral pain

Visceral pain usually has a temporal evolution and clinical features vary in different phases of pathology. 'True visceral pain' arises as a diffuse and poorly defined sensation usually perceived in the midline of the body, at the lower sternum or upper abdomen. In patients, pain from different visceral organs can have differing areas of presentation, e.g. bladder to perineal area, heart to left arm and neck, left ureter to left lower quadrant and loin. This diffuse nature and difficulty in locating visceral pain is due to a low density of visceral sensory innervation and extensive divergence of visceral input within the CNS. Visceral pain is therefore perceived more diffusely than noxious cutaneous stimulation with respect to location and timing (15).

Subsequent development of symptoms may entail referred pain to parietal somatic structures within the same metameric field as the affected organ. Spatial discrimination of visceral pain is thus typically referred to superficial structures to produce secondary hyperalgesia of superficial or deep body wall tissues due to viscerosomatic convergence (discussed later) (16). Referred pain with or without hyperalgesia is sharper, better localized and less likely to be accompanied by autonomic signs, and therefore difficult to differentiate from pain of somatic origin.

Visceral pain is often associated with marked autonomic phenomena, including pallor, profuse sweating, nausea, GI disturbances and changes in body temperature, blood pressure and heart rate (15). Table 1 lists the general characteristics of visceral pain in humans (17).

## Peripheral visceral neurotransmission

Afferent fibres innervating viscera project to the CNS through autonomic sympathetic and parasympathetic nerves - a dual sensory innervation (18, 19). Some spinal afferents travel along hypogastric, lumbar colonic and splanchnic nerves to terminate in thoracolumbar regions as part of sympathetic innervation, traversing both prevertebral and paravertebral ganglia en route to the spinal cord (20). Vagal and pelvic afferents respectively terminate in the brainstem and lumbosacral cord and contribute to parasympathetic innervation (21, 22) (see Figure 1, adapted from (23)).

Visceral fibres can serve 'sensory' and 'afferent' functions; the former can evoke conscious sensations and the latter regulate autonomic flow (24). Accordingly, activation of hepatic chemoreceptors or pulmonary stretch receptors is not perceived consciously (25), whereas sensory afferents innervating the GI and urinary tracts serve regulatory functions of the gut (e.g. absorption, secretion, propulsion) and contribute to consciously evoked sensations such as pain and fullness (26).

Visceral sensory afferents are almost exclusively thinly myelinated A $\delta$ -fibres and unmyelinated C-fibres. However, the distinction between nociceptive afferents and non-nociceptive afferents is not clear in visceral neurotransmission compared to somatic nociception, given the functional division of mechanosensitive visceral receptors into two physiological classes (20, 27, 28). 'High-threshold receptors' in organs such as the heart, oesophagus, colon, ureter and uterus respond only to noxious mechanical stimuli. 'Low-threshold receptors' are intensity-encoding and thus respond to a range of innocuous to noxious stimuli. An important contrast with somatic nociception is the role of low-threshold A $\beta$ -fibres, which *only* convey innocuous mechanical sensations in normal conditions.

Viscera are also innervated by so-called 'silent' nociceptors, more accurately designated as mechanically insensitive afferents (MIAs) (29). These can acquire mechanosensitivity following inflammation, and have been thoroughly characterised in significant proportions in rodent pelvic and splanchnic innervations (27, 30) and in human microneurographic studies of cutaneous C-afferents (31, 32).

## Viscerosomatic convergence

The neurophysiological convergence of visceral and somatic afferent inputs to the CNS is thought to underlie referred visceral pain, where noxious stimulation of viscera triggers pain referred to somatic sites (33, 34). Viscerosomatic convergence may occur as a result of the scarcity of visceral afferent fibres with spinal cord terminations; the relative contribution of visceral afferent fibres to the total spinal cord afferent input is less than 10%. Visceral afferent terminals also show extensive divergence and intraspinal distribution compared to cutaneous afferents (21).

Because of viscerosomatic convergence, somatic injury and visceral inflammation can respectively alter central processing of visceral and somatic inputs (35). Axons can send peripheral terminals to anatomically distinct segments to produce pain sensations distant to the primary site (36). Viscerosomatic convergence also accounts for altered central nociceptive processing through sensitization of primary afferent pathways, ultimately modifying neuronal input at sites of convergence in the spinal cord or higher centres (37, 38). This convergence of visceral and somatic messages may be one reason for visceral pains often accompanying somatic pain conditions or vice versa. In addition there can be viscerovisceral convergence whereby pain from one organ is referred to another.

## Brain-gut axis

The "brain-gut axis" is a theoretical model depicting bidirectional neural pathways linking cognitive, emotional and autonomic centres in the brain to neuroendocrine centres, the enteric nervous system and the immune system. Bodily visceral functions (e.g. digestion, nutrient resorption, gaseous exchange, excretion) require complex regulation in which the CNS is highly integrated with the peripheral and enteric nervous systems and hormonal controls. Accordingly, altered brain-gut interactions can contribute to autonomic dysregulation of the gut and associated pain and perceptual changes in visceral disorders like IBS (39).

Vagal afferents project to the nucleus tractus solitarius (NTS) in the brainstem with cell bodies in nodose ganglion. Spinally-converging visceral afferents terminate in the dorsal horn with second order neurones projecting to higher centres through the dorsal column pathway (DC), parabrachial pathway and spinothalamic tract (see Figure 2, adapted from (40)). Studies involving DC lesions have shown suppressed inhibition of exploratory behaviour induced by noxious visceral stimulation and inhibition of potentiated visceromotor reflexes evoked by colorectal distension during inflammation (41-43). Superficial dorsal horn projections mostly form the spinoparabrachial pathway (44), associated with autonomic and affective responses to painful stimuli (45). Along with NTS projections from vagal afferents, spinoparabrachial projections are transmitted to limbic and cognitive higher centres including parts of the brain involved in affect, such as the amygdala, hypothalamus and periaqueductal grey (PAG) (40, 46, 47).

Spinothalamic projections travel contralaterally from the deep dorsal horn in sub-primates, along with a proportion of the lamina I population in primates (40, 48). The main thalamic projections sites are located in the ventroposterior lateral thalamus and ventroposterior medial thalamus. Ensuing projections to the insular and somatosensory cortices enable sensory discrimination. The medial thalamic nuclei are thought play greater role in the affective and motivational aspects of pain processing (49), and accordingly project to the various areas of the prefrontal cortex that are significantly correlated with visceral pain responses in imaging studies, including the anterior cingulate cortex (ACC) (50-53).

Descending modulation from higher centres and limbic structures is a dynamic system producing both facilitatory and inhibitory influences on spinal cord excitability (see Figure 3, adapted from (40)). The RVM in the brain stem is a principal component of this supraspinal modulatory system and recruitment of different RVM neurones in different conditions can potentiate or suppress central sensory transmission through descending pathways to the spinal cord (54-56). Importantly, in animals, RVM neurones do not respond in the same direction to visceral and cutaneous stimulation – i.e. neurones excited by somatic stimuli can be inhibited by visceral activity and vice versa (57-59). Electrical stimulation of the RVM produces biphasic modulation of spinal neuronal responses to CRD (54, 60) and selective ablation of RVM cells prevents the maintenance of pancreatitis abdominal hypersensitivity (55). RVM neurones also show reflex-related activity to colorectal distension that is altered by systemic analgesics (57).

Functional MRI studies in humans show cortical activation following subliminal visceral stimulation (61). Cortical and subcortical circuitry can modulate brainstem pain processing, e.g. the RVM and PAG, in a top-down pain fashion, underlying possible mechanisms of distraction to decreasing both the intensity and affective components of the pain experience (62, 63). Key brainstem structures that are activated upon visceral stimulation, including the PAG and RVM, are also activated upon evoked somatic pain in humans, as has been seen in preclinical studies (64).

## Visceral hyperalgesia

In peripheral sensitisation of viscera, persistent noxious stimulation of visceral nociceptors through inflammatory mediators, ectopic activity and/or noxious stimuli can produce hyperalgesia. Inflammatory mediators released at sites of injury or tissue damage can sensitise nociceptors by reducing thresholds for activation and enhancing responsiveness to stimuli. Ensuing disruption of cells, degranulation of mast cells, secretion by inflammatory cells and induction of enzymes changes the chemical milieu at the site of injury, contributing to peripheral hyperalgesia (65, 66).

Voltage-gated sodium channels are essential for the propagation of action potentials along axons, the control of membrane excitability and may contribute to sensitisation of visceral nociceptors. TTX-resistant currents are present on a high proportion of nociceptive afferents (67) and have been identified in colon DRG neurones (68, 69) and studies using Nav1.8 knockout mice demonstrate an important role for TTX-resistant currents in visceral nociceptor sensitisation (70-73). These may provide novel drug targets in the future.

TRPV1 is a non-selective cation channel gated by noxious heat (42-53°C), low pH and endogenous lipids (74) and is preferentially expressed in visceral afferents compared to somatic in the lower lumbar cord of rats (75). The importance of TRPV1 in visceral innervation is supported by the painful effects of capsaicin application to viscera in several experimental and therapeutic paradigms (76-80). Since viscera (or the spinal cord) are not normally exposed to noxious heat or capsaicin, the presence of TRPV1 at peripheral axons of visceral afferents renders the afferents sensitive to mediators of inflammation, thus functionally serving as nociceptors (1, 75, 81). Moreover, TRPV1 receptor expression is upregulated in tissue samples from patients with IBS, and this increase correlates significantly with visceral pain (82, 83). A possible coupling between the cooling TRPM8 channels with TRPV1 and TRPA1 on colonic high threshold sensory neurones may also underlie the desensitizing actions of TRPM8 (84).

Prolonged noxious stimulation of viscera and peripheral sensitisation of visceral nociceptors can promote excitability of the spinal cord and higher centre neurones that mediate nociceptive processing, otherwise known as central sensitisation (85). This is characterised by increased spontaneous activity of central neurones, enlarged receptive fields and an increase in stimulus-evoked responses (86). In humans with acute and chronic visceral pain states, secondary hyperalgesia in relevant dermatomes has been demonstrated (87-89). Central sensitisation has also been shown in humans following oesophageal electrical stimulation, where altered A-fibre activity produced somatic allodynia of the chest wall (90). Further evidence of central mechanisms contributing to referred visceral hyperalgesia have been shown using acid and capsaicin perfusion of the distal oesophagus to induce rectal hyperalgesia to both heat and mechanical stimulation (77).

The bottom-up hypothesis of development of visceral hyperalgesia maintains that peripheral sensitisation of visceral afferents and recruitment of MIAs increases the afferent barrage into the CNS, ultimately producing central sensitisation (29, 91). For example, colorectal distension in normal human subjects evokes increasing pain scores progressively with the application of repetitive stimuli of constant amplitude (92). Yet even when peripheral neuroplastic changes reverse to their normal state, central hyperexcitability may still persist (93).

However, the association between peripheral insult and visceral pain is not consistent; there is no detectable colonic abnormality in some IBS patients that have colonic hypersensitivity (94) and acute pain behaviours are evoked by distension of hollow organs that does not produce tissue injury in rodents (1, 95, 96). Thus, peripheral insult cannot always be implicated as a primary etiological factor in the development of chronic visceral hyperalgesia (97, 98). Alternatively, a top-down hypothesis can describe how initial central changes in higher centres may increase central excitability to produce visceral hyperalgesia. Psychological stress and trauma have been heavily linked to development of IBS, and dysfunction of the noradrenergic cluster, locus coeruleus, has been implicated in IBS aetiology (99-101). Anxiety and fear are also common aggravators of the pain experience (102, 103). Nevertheless, the two models are not mutually exclusive and differ only with respect to the primary site of abnormality. Both models share a central component with a

positive feedback loop involving visceral afferents, changes in spinal cord excitability and altered descending modulation of nociceptive processing.

## Interoception- a role of the gut in how we feel

Regardless of differences in voluntary motor control between the gut and skin, sensory inputs of our bodies relate to an evolutionarily primal need for homeostasis - signals pertaining to physiological conditions that the brain can integrate to maintain integrity of the body by optimizing energy use. In healthy humans, unique feelings and sensation of the physiological condition of the body – interoception – are perceived and contribute to background emotions that can drive behaviours that promote survival (typical visceral sensations e.g. hunger and satiation, and non-visceral sensations e.g. temperature and itch) (104).

Patients affected by FGIDs suffer from an alteration in the attentional, perceptual and affective responses to stimuli from internal sources (105). Symptoms are not only limited to visceral pain and discomfort, but often embrace a range of other feelings of physical and emotional distress. Ongoing pain that outlasts its homeostatic role is pathological and reflects a chronic dysfunction of nociceptive processing in the nervous system (106).

Projections from lamina I are involved in homeostatic signalling, terminating in autonomic (spinal cord sympathetic cell column) and homeostatic centres (PB nucleus, RVM, PAG and locus coeruleus). Together with parasympathetic afferent activity from the NTS, which has neural connections with the hypothalamus and amygdala, the spinal and bulbar projections from lamina I generate a thalamocortical representation of the physiological state of the body (48).

## Treating visceral pain

Opioids form the core of pain management for a range of acute to chronic visceral pain conditions and cancer pain, yet are not always optimal due to their analgesic actions being accompanied by side-effects of constipation and sedation (107). Moreover, the paradoxical development of analgesic tolerance and nociceptive sensitisation with prolonged opioid use, opioid-induced hyperalgesia, has also proved an unfortunate obstacle in the clinic for patients with prolonged exposure to opioid analgesia (108).

NSAIDs, paracetamol and serotonergic compounds form other treatment options for a range of visceral pain conditions with minimal controlled studies, but generally none of these compounds are selective for visceral conditions and are also used to treat other forms of chronic pain (109).

This review has covered some other potential targets such as sodium channels and heat and cold sensors of the TRP channel family that could be used to treat visceral pain syndromes. Recently there has also been a convergence of preclinical and human data showing analgesic efficacy of pregabalin in acute and chronic visceral pain conditions, acting through subcortical mechanisms that likely include the spinal cord and RVM (57, 102, 110-113).

Major challenges still exist in developing analgesics in visceral pain disorders, largely due to a lack in understanding of the aetiopathogenesis and mechanisms of chronic pain development in FGIDs and other visceral pain disorders (114, 115). It is often difficult to identify whether the primary abnormality leading to the observed enhanced perception of visceral signals is due to increased peripheral encoding and transduction of stimuli, due to central pain amplification or due to both.



## Conclusion

Research into the mechanisms mediating visceral nociception and the role of higher centres in modulating excitability through changes in biphasic descending modulation can provide a better understanding of the differences between visceral neurotransmission and the more thoroughly explored signalling mechanisms of somatic stimuli. Ultimately, appreciating these contrasts and similarities between the development and maintenance of somatic and visceral pain states and the means by which central excitability occurs in visceral disorders, in its own right, is also crucial for providing a better understanding of therapeutic treatments for visceral pain syndromes.

## Acknowledgments

This work was supported by IMI European and the Wellcome Trust London Pain Consortium. There are no conflicts of interest.

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- of special interest
- of outstanding interest

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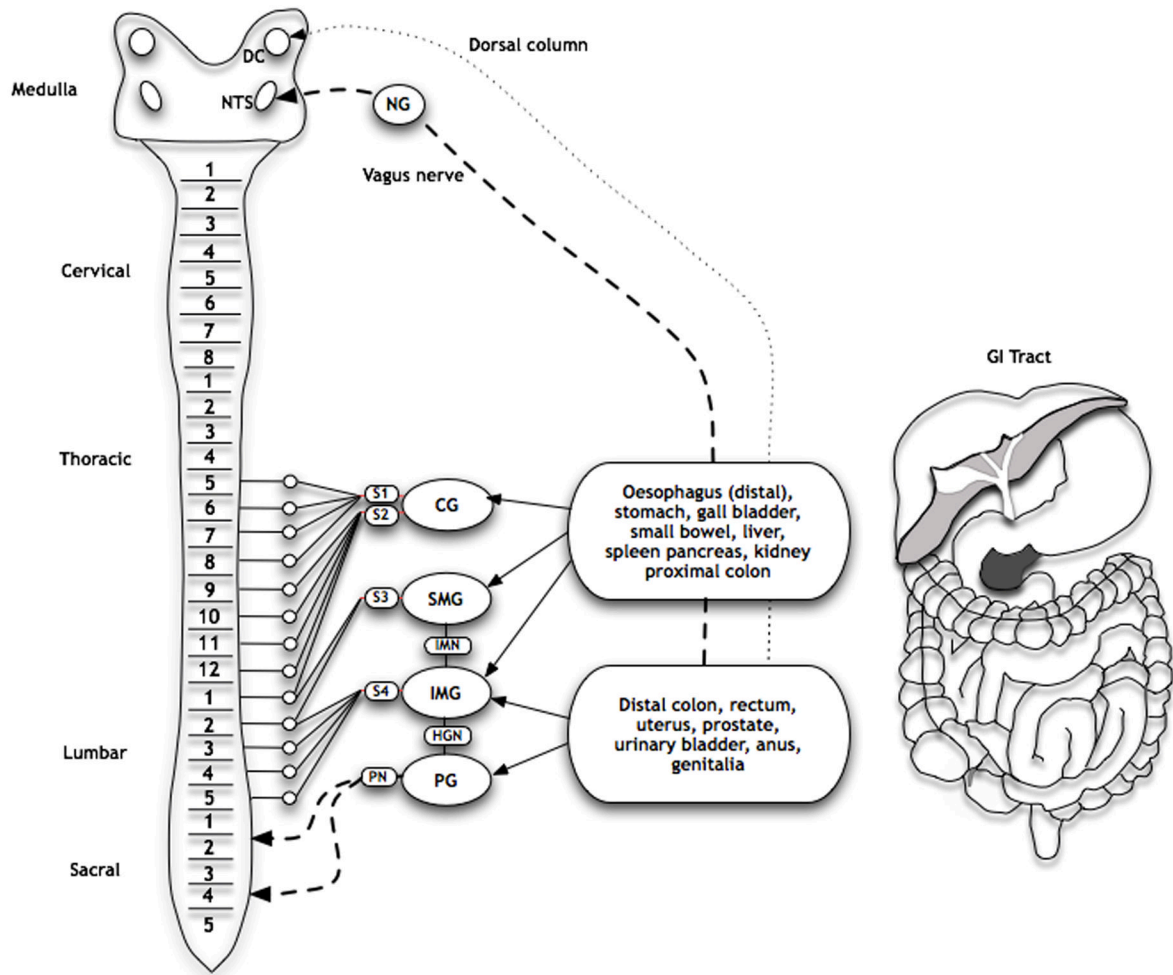
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### Key Points

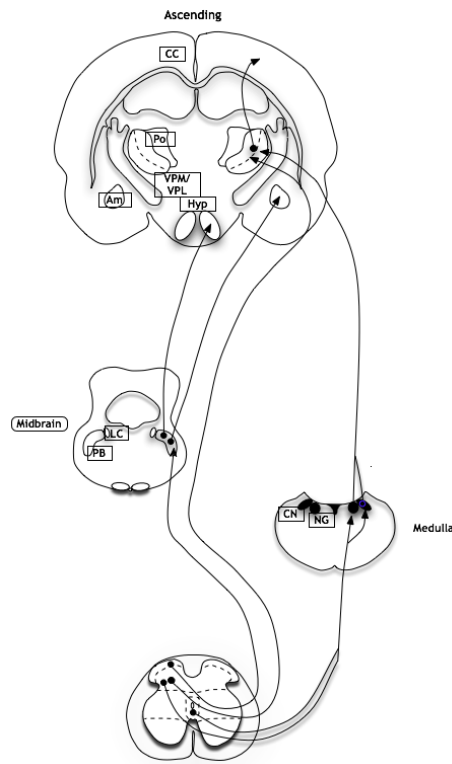
- Visceral pain can manifest using some mechanisms also seen in somatic pain syndromes, although there are also crucial differences in central nociceptive processing of pain from these different origins.
- Changes in the balance of facilitation and inhibition of central excitability along the brain-gut axis can contribute to prolonged chronic pain seen in some visceral pain disorders.
- Visceral pain can negatively affect the general physiological state of how we feel along with changes in autonomic controls.
- Visceral pain typically has a strong affective component, and therefore can be reinforced by anxiety and depression.



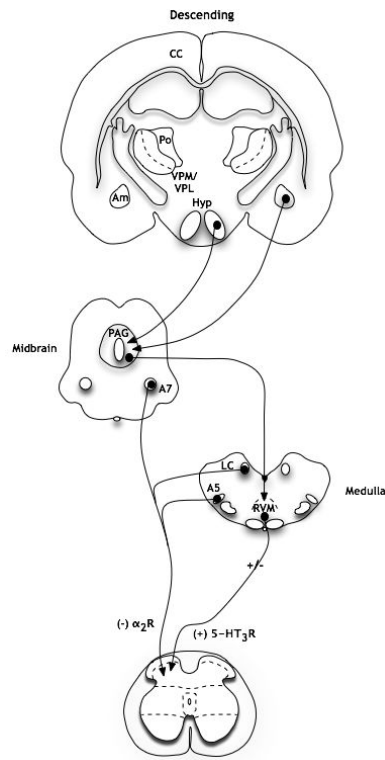


### Figure 1. Innervation of the rat GI tract

Some visceral afferents innervating organs in thoracic and abdominal cavities travel either along the vagus nerve with cell bodies in the nodose ganglion (NG) and central terminals in the nucleus tractus solitarii (NTS), or along the dorsal column pathway (dotted line) with cell bodies in dorsal column nuclei (DC) in the brainstem. Other afferents innervating the same organs have terminals in the spinal cord, before passing through pre- and/or paravertebral ganglia en route with cell bodies in dorsal root ganglia (not illustrated; (23)). Straight lined pathways indicate sympathetic innervation and hyphenated pathways indicate parasympathetic innervation. (Prevertebral ganglia- CG: coeliac ganglion; SMG: superior mesenteric ganglion; IMG: inferior mesenteric ganglion; PG: pelvic ganglion. Nerves- S1, S2, S3, S4: greater, less, least and lumbar splanchnic nerves, respectively; IMN: intermesenteric nerve; HGN: hypogastric nerve; PN: pelvic nerve (adapted from (23)).



**Figure 2. Ascending pathways from spinal cord neurones in visceral nociception (in rodents)**  
 Ascending projections from lamina I neurones in the spinal cord travel along the spinoparabrachial pathway to the parabrachial nuclei (PB) with ensuing projections to the amygdala (Am) and hypothalamus (Hyp), whereas projections from deep dorsal horn neurones travel along the spinothalamic tract to thalamic nuclei (VPM and VPL), with further projections to the insula, somatosensory cortex and prefrontal cortex. Neurones from lamina III-IV and X can also travel along the post-synaptic dorsal column with medullary cell bodies, with further projections to thalamic nuclei (LC, locus coeruleus; Po, posterior thalamic nuclei; CC, cingulate cortex; CN: cuneate nucleus; GN: gracile nucleus; adapted from (40).



**Figure 3. Descending pathways in nociception (in rodents)**

Descending projections from higher centres are integrated in the midbrain and brainstem. Inhibitory controls from the locus coeruleus complex (A5, locus coeruleus, A7) are mediated by pre- and postsynaptic  $\alpha_2$ -adrenergic receptors in the dorsal horn. Descending controls from the RVM can be both inhibitory and facilitatory, although one facilitatory pathway is mediated by presynaptic 5-HT<sub>3</sub> receptors (Am: amygdala; Hyp: hypothalamus; VPM and VPL: thalamic nuclei; Po: posterior thalamic nuclei; CC: cingulate cortex; LC: locus coeruleus; PAG: periaqueductal grey; RVM: rostral ventromedial medulla; adapted from (40).

**Table 1**

## General characteristics of pain due to visceral pathology

|  |
|--|
| 1. Is poorly localized with referral to somatic structures     |
| 2. Produces nonspecific regional or whole-body motor responses |
| 3. Produces strong autonomic responses                         |
| 4. Leads to sensitization of somatic tissues                   |
| 5. Produces strong affective responses                         |