Gut pain & visceral hypersensitivity

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Abstract

Visceral pain is a highly complex entity whose experience is variable in health and disease. It can occur in patients with organic disease and also in those without any readily identifiable structural or biochemical abnormality such as in the functional gastrointestinal disorders (FGID). Despite considerable progress in our understanding of the culpable underlying mechanisms significant knowledge gaps remain, representing a significant unmet need in gastroenterology. A key, but not universal, pathological feature is that patients with FGID often display heightened sensitivity to experimental gut stimulation, termed visceral hypersensitivity. A plethora of factors have been proposed to account for this epiphenomenon including peripheral sensitization, central sensitization, aberrant central processing, genetic, psychological and abnormalities within the stress responsive systems. Further research is needed, bringing together complementary research themes from a diverse array of academic disciplines ranging from gastroenterology to nociceptive physiology to functional neuro-imaging, to address this unmet need.

Keywords

Visceral pain, functional gastrointestinal disorders, irritable bowel syndrome

Introduction

Pain is a ubiquitous but highly variable human experience in both health and disease. Chronic visceral pain is common, occurring in patients with organic disease and also in those without any readily identifiable structural or biochemical abnormality such as in the functional gastrointestinal disorders (FGID). Most individuals have experienced visceral pain in one form or another, ranging from the mild discomfort associated with heartburn to severe renal colic and childbirth. Visceral pain in FGID is a major global cause of disability and healthcare seeking¹. Visceral pain shares many features with somatic pain, yet there are important differences in underlying its sensory-discriminative, affective-emotional and cognitive-evaluative aspects.

Pain management of visceral pain is particularly problematic. Despite laudable progress in basic gastrointestinal neuroscience research and considerable investment in drug development, translation into tangible patient benefit has, to date, remained limited². Amongst the reasons for this is that a significant proportion of our

understanding of the pathophysiological mechanisms underlying visceral nociception is extrapolated from studies of somatic pain³. This is compounded by a general lack of robust animal models that precisely reflect human visceral pain syndromes⁴. For the purposes of this review paper we will “roadmap” the primary sensory pathways from the gut to the brain in health. In addition,

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we will introduce and examine the burden of chronic unexplained visceral pain and how such pain may develop through sensitization, either peripherally or centrally, and finally how it may be modulated by psychology, genetic factors and the stress responsive systems.

Primary sensory pathways from the gastrointestinal tract to the dorsal horn

The gastrointestinal tract receives dual innervation from spinal afferent neurons and the vagus nerve. This extrinsic innervation is complemented by intrinsic innervation, which comprises the enteric nervous system (ENS), which include primary afferent neurons, which are primarily responsible for gastrointestinal motility. The colon and rectum are furnished with several types of afferent fibres that can be usefully classified as responding to either innocuous or noxious stimuli or both. Amongst these, there are fibres that respond to tactile, chemical, distensile or contractile stimuli at physiological (innocuous) or noxious levels. To date, in the mouse, seven types of afferent fibres have been described in the literature ranging from mucosal, muscular mucosal, muscular, serosal, mesenteric, mechanically insensitive and silent⁴. To the best of our knowledge, these afferent fibres project to the dorsal horn of the spinal cord. Emerging data suggests that high threshold serosal and mesenteric afferents are specific nociceptors^{5,6}. From the colon their route to the thoracolumbar spinal cord is via the splanchnic nerves whereas a significant proportion of afferents arising from the rectum reach the lumbosacral spinal cord via pelvic nerves. In addition to these specific nociceptors, it has been proposed that muscular-mucosal afferents, that initially respond low threshold stimuli but increase their response, albeit in a non-linear fashion, to increasing distension into the noxious range represent the wide dynamic range afferents. It is presumed that these provide a degree of sensation "grading" from gas to urge to discomfort to pain⁷. Similarly, input into the central nervous system (CNS) from other classes of afferents including, but not confined to, physiological information intra-luminal contents with respect to its viscosity and consistency.

Central pathways from dorsal horn to higher centres

The spinal dorsal horn is the critical hub in the central processing pathway of gut sensory information. From the spinal dorsal horn, neurons project to a number of regions of the brain but remain subject to considerable

modulation by local and descending interneurons, which may attenuate or diminish the information that ascends to central structures of the brain. There are a number of viscera-visceral and viscera-somatic reflexes occurring at the spinal dorsal horn, themselves modulated by both supraspinal and thalamocortical inputs. The methods for studying the central structures involved in the perception of visceral pain have traditionally relied on descriptive, and therefore subjective, methods of reporting visceral sensation. Whilst great care has been taken to eliminate subjective factors from introducing response bias, to date no objective measure has been developed to assess these descriptive factors of visceral sensation. Therefore, to a degree the advent of functional neuroimaging has facilitated the examination of the complete visceral neuraxis in an objective manner. Recent technological advances in many functional brain imaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), electroencephalography (EEG) and cortical evoked potentials (CEPs) (see reviews by Hobson *et al*⁸ and Sharma *et al*⁹), over the last decade has led to significant advances in the understanding of the central circuitry involved in mediating visceral pain. Vagal sensory afferents project to the nucleus tractus solitarius (NTS) in the brainstem whose cell bodies reside in the nodose ganglion. From the spinal dorsal horn second order neurons project to higher centres through three pathways: the dorsal column pathway, parabrachial pathway and spinothalamic tract. In combination with projections from the NTS, 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)¹⁰. Sensory discriminatory aspects of visceral pain are derived from thalamic projections to the insular and somatosensory cortices whilst the medial thalamic nuclei are posited to have a greater role in affective and motivational aspects. They thus project to the prefrontal and anterior cingulate cortex (ACC) areas that are significantly correlated with responses to visceral pain responses in functional neuro-imaging studies¹¹.

The functional gastrointestinal disorders as examples of chronic gut pain

FGID are a heterogeneous group of disorders that represent one of the great unmet clinical needs in gastroenterological practice. They account for in excess of 40% of all new referrals to general gastroenterological out patient clinics, although 83% of all sufferers are managed in primary care^{12,13}. The Rome multinational

consensus, now in its third iteration, defines FGID as “*variable combinations of chronic or recurrent gastrointestinal symptoms which are not explained by structural or biochemical abnormalities*”¹. The understanding of the processes that underpin the genesis of symptoms in FGID remains incomplete. The most prevalent example of a FGID is irritable bowel syndrome (IBS), which affects as many as 5%-20% of individuals worldwide¹⁴. The annual incidence of IBS is between 196 and 260 per 100 000¹⁵, with IBS occurring more often in women than in men and being more commonly diagnosed in patients younger than 50 years of age¹⁶. There is a current paucity of efficacious treatments in FGID and the inevitable result of this is symptom chronicity, patient anxiety and dissatisfaction, over investigation, recurrent consultations and significant morbidity. Therefore it is not surprising that the socioeconomic impact is considerable through a reduction in health related quality of life and increased absenteeism¹⁷. Direct and indirect healthcare costs associated have been estimated to be in the order of \$34 billion in the 7 largest western health-care economies^{1,18}.

Irritable bowel syndrome as an example of a functional gastrointestinal disorder where gut pain is a central defining feature

IBS is defined as symptoms of recurrent abdominal pain or discomfort associated with a marked change in bowel habit for at least six months, with symptoms experienced on at least three days of at least three months¹. Of these symptoms, untreated chronic gut pain is the symptom that is most likely to prompt a patient to seek medical advice and is often the most difficult for the clinician to successfully treat¹⁹. IBS accounts for between 40-60% of outpatient referral to the gastroenterology clinic^{20,21} and thus, with such a huge burden of disease the development of a complete understanding of the underlying pathophysiology of this complex disorder remains the prerequisite step on the road to the development of efficacious treatments. Currently, the germane hypothesis that has been proposed to account for chronic pain in IBS is visceral hypersensitivity.

Visceral hypersensitivity as a pathophysiological feature of irritable bowel syndrome

Whilst a considerable number of hypotheses have been proposed to explain the origin of pain in IBS, no single factor has achieved primacy in the literature, probably due to the significant heterogeneity of this disorder. It is

nearly thirty years since Ritchie first observed that patients with IBS have heightened sensitivity to experimental gut stimulation, which has been subsequently termed visceral hypersensitivity²². Rectal hypersensitivity to mechanical distension has been proposed to be a clinically useful discriminatory feature between IBS and other gastrointestinal disorders^{23,24}. However, visceral hypersensitivity is not a *sine qua non* facet of IBS with a number of studies failing to reproducing these initial observations^{25,26}. This observation of visceral hypersensitivity has spawned a considerable research effort from academia and the pharmaceutical industry alike in the attempting to identify the culpable molecular mechanisms that are responsible for this epiphenomenon. The pathophysiology of visceral hypersensitivity may be conceptualized as being due to any aberrant process arising from any level of the visceral nociceptive pathway or neuraxis. Although the molecular basis of the pathophysiology of visceral hypersensitivity has not been completely elucidated, several mechanisms have been proposed. For instance, a noxious visceral stimulus may cause the release of several inflammatory mediators such as K⁺, H⁺, adenosine triphosphate, 5-hydroxytryptamine, bradykinins and prostaglandins^{27,28}. If prolonged, these mediators may elicit a number of effects and induce changes in the chemical milieu including the activation and peripheral sensitization of nociceptive afferents through a reduction in their transduction thresholds and by inducing the expression and recruitment of previously silent nociceptors, leading to hyperalgesia.

Peripheral sensitization as an aetiological mechanism of chronic visceral pain in fgid

Whilst it is beyond the scope of this paper to review all of the mechanisms examined to date in the literature, we will highlight, in our opinion, some of the more important recent advances in our understanding of underlying molecular features of peripheral sensitization: the transient receptor potential vallinoid receptors (TRPV) 1 & 4 and the protease activated receptor 2 (PAR(2)).

Transient receptor potential vallinoid receptors

TRPV1 and 4 are members of a larger family of TRPV channels that serve many sensory functions ranging from hearing to mechanosensory transduction^{29,30}. The TRPV 1 receptor was first identified and cloned by Caterina *et al* in 1997, and is expressed on small to medium sized nerve fibres throughout the nervous system and is a non-selective cation channel³¹. The

TRPV1 receptor may be activated by capsaicin and its analogues as well as noxious heat and is thought to play an important role in mechanotransduction in the gastrointestinal tract and to the development and maintenance of visceral hypersensitivity^{29,32}. When activated, the TRPV1 receptor evokes a burning sensation and pain. When it is associated with concomitant release of substance P neurogenic inflammation may occur. Hydrogen ions strongly potentiates activation of the TRPV1 channel and thus are considered to be of particular relevance in acid related disorders such as gastro-oesophageal reflux disease³³. Several inflammatory mediators have been demonstrated to reduce the threshold for TRPV1 activation including bradykinin, adenosine and ATP. In humans there is a wealth of evidence linking TRPV1 with visceral hypersensitivity. For instance, a study by Akbar *et al.* demonstrated a 3.5-fold increase in the density of TRPV1 immunoreactive fibres in the colonic biopsies of patients with IBS compared to healthy controls³⁴. Furthermore, in rat models, TRPV1 receptor antagonists have been found to ameliorate visceral hypersensitivity³⁵. These observations have led to considerable interest in the research and development of orally bioavailable agents that may modulate the TRPV1 receptor. Both TRPV1 agonists and antagonists are currently being evaluated³⁶. Early results from human studies evaluating this novel class of analgesic have yielded promising results^{37,38}. TRPV4, a mechano-transductive osmosensitive channel, has recently been associated with visceral hypersensitivity³⁹. Further evidence for TRPV4's role in visceral hypersensitivity comes from a study in mice where a TRPV4 agonist induced visceral hypersensitivity in response to colorectal distension in mice, although this effect was lost in TRPV4^{-/-} knockouts⁴⁰.

Protease activated receptors

4 types of protease activated receptors (PAR) have been described in the literature. Of note, PAR-1 and PAR-2 are expressed on spinal afferents and contain calcitonin gene related peptide (CGRP)⁴¹. PAR-2 receptors are activated by mast cell tryptase and are G-protein coupled receptors⁴². PAR-1 is activated by a number of mediators including thrombin and trypsin and are expressed throughout the gastrointestinal tract⁴³. Interestingly, increased expression of PAR-1 has been demonstrated in patients with inflammatory bowel disease thereby providing an interesting mechanistic insight into inflammation induced sensitization with the gastrointestinal tract⁴⁴. In patients with diarrhoea predominant irritable bowel syndrome, it has been observed that the ratio of PAR-1 to PAR-2 expression is elevated in comparison to healthy controls⁴⁵.

Therefore, strategies to restore an appropriate balance of PAR-1 and PAR-2 activation in the colon may offer a promising future therapeutic strategy for IBS patients in the future. Moreover, it is interesting to observe that PAR-2 closely interacts with the TRPV4 receptor potentially providing a link between these molecular mechanisms in causing visceral hyperalgesia⁴⁶.

Central sensitization as an aetiology mechanism for chronic visceral pain in fgid

Sarkar *et al* have demonstrated the concept of central sensitization in a reproducible human oesophageal model in which hydrochloric acid is infused into the healthy distal oesophagus⁴⁷. Pain thresholds, to electrical stimulation, were not only reduced in the acid exposed distal region but also in the adjacent proximal unexposed region thereby suggesting the development of central sensitization in the anatomically distinct site. This effect of central sensitization was prolonged, lasting up to 5 hours after 30 minutes of acid exposure suggesting that the duration and magnitude of central sensitization in the non-exposed proximal oesophagus was directly related to the intensity of acid exposure in the distal oesophagus. Prostaglandin E₂ (PGE₂) and the n-methyl d-aspartate (NMDA) receptor have been elucidated as the most importance molecular factors in the development of central sensitization at the spinal dorsal horn⁴⁸. Human pharmacological studies have demonstrated that antagonism of the PGE₂ or the NMDA receptor prevents the development of, and can reverse, central sensitization within the oesophagus^{49,50}. Central sensitization may also occur after a noxious stimulus is applied to an anatomically distant site. For instance, oesophageal sensitization may occur after a noxious stimulus is applied to the duodenum and balloon distension in the left colon may result in rectal sensitization^{51,52}. In patients with IBS, following repetitive distension of the sigmoid colon, central sensitization may ensue as manifested by rectal hyperalgesia and increased viscerosomatic referral to experimental rectal distension²⁶.

Aberrant central processing of visceral nociception as an aetiological mechanism

Functional neuroimaging techniques have been widely utilised in evaluating central structures that may underlie chronic visceral pain in FGID. Mayer *et al.* demonstrated, using fMRI, that in response to experimental recto-sigmoid distension, IBS patients have inadequate activation in the subcortical brain

regions involved with affective-emotional aspects of pain perception such as the limbic system, the PAG and thalamic regions⁵³. Abnormal areas of activation have been observed in other areas such as the ACC, amygdala and brainstem in IBS patients suggesting that the aberrant visceral nociception observed in this group may be, in part, due to central mechanisms^{54,55}. Whilst most experts would agree that the responsiveness of the CNS is aberrant to a greater or lesser degree in those with IBS, a lack of consensus remains. We suggest that this is a direct consequence of variations in experimental paradigms and techniques of analysis. In a recent meta-analysis, Tillisch *et al.* sought to identify brain regions consistently activated by rectal stimulation in IBS patients in comparison to healthy controls. Across studies that were evaluated, there was consistent activation of regions associated with visceral afferent processing, such as the thalamus, insula, anterior mid-cingulate, among IBS patients and controls. Where IBS patients differed from controls was in activation in regions associated with emotional arousal, such as the pre-genual ACC, amygdala and activation of a midbrain cluster, a region playing a role in endogenous pain modulation. Whilst this study supports the aetiological role of central structures in mediating chronic pain, further work is needed, utilising a variable combination of functional imaging techniques associated with improvements and rationalisation of study design will further advance our understanding of the mechanisms involved.

Descending modulation of visceral nociceptive pathways

Moving from the central structures back down towards the gut, it is important to address psychological traits, genetic factors and stress response systems as these systems may modulate descending information allowing alterations in the experience of gut pain.

Psychological & genetic influences

Psychological comorbidity such as depression, somatization and hypochondriasis are common extra-gastrointestinal features of all FGID^{56,57}. In animal models, studies have shown that adverse early life events, such as maternal separation, are risk factors for the development of chronic visceral pain in adulthood⁵⁸. Similarly in humans, there is evidence that a history of sexual abuse, especially in childhood, can alter visceral pain sensitivity^{59,60,61}. Furthermore, the psychological context in which gastrointestinal symptoms are interpreted by an individual may predict the development of IBS following an episode of gastroenteritis⁶². A recent meta-analysis has suggested that

psychological treatments, as a class of interventions *per se*, are effective in symptom reduction in FGID⁶³.

FGID display a certain degree of heritability; for instance twin and family studies in IBS suggest that there may be a genetic influence in the development of this disorder⁶⁴. Whilst several candidate genes have been proposed, no study to date has identified an "IBS" gene, although it must be noted that several of the published studies are small and statistically underpowered to detect what is probably a small influence (see the review by Saito and Talley⁶⁵). Large population based, genome wide association studies represent one of the most exciting potential avenues for delineating the genetic factors that contribute to the development of FGID in the future but the prerequisite step is the further definition of the clinical phenotype based on pathophysiological features rather than purely symptom based criteria.

The stress responsive systems – the autonomic nervous system & the hypothalamic pituitary adrenal axis

Stress may be defined as an acute threat to homeostasis that engenders an adaptive, or if chronic, potentially maladaptive response. The response to stress in the gastrointestinal tract is coordinated by the brain gut axis; a theoretical bidirectional communication system from the ENS to the brain via the autonomic nervous system (ANS) and reciprocally via autonomic efferents, the hypothalamo-pituitary-adrenal (HPA) axis and neuro-immune interactions⁶⁶.

Central communication to the gastrointestinal tract is via the parasympathetic (PNS) and sympathetic (SNS) pathways of the efferent ANS. In a number of syndromes where chronic pain is a feature, such as IBS, fibromyalgia and chronic pelvic pain, it has been observed that autonomic dysfunction may co-exist^{67,68}. Within the FGID literature, specific types of central autonomic dysregulation have not been consistently demonstrated. This is probably due to the heterogeneity of these disorders, lack of control for psychological factors and the multiple differences in methodologies employed for recording and analysing autonomic data, although work is currently being undertaken by our group to address this^{69,70,71,72,73,74}. An important methodological consideration in the interpretation of results from ANS studies is whether measuring cardiac chronotropy, i.e. heart rate variability, as a surrogate marker of ANS parameters truly reflects specific gut autonomic innervation, although studies by Emmanuel *et al* and more recently Thoua *et al* using rectal mucosal blood flow techniques have allayed some of these concerns^{75,76}. Notably, Mazur *et al* has demonstrated that in IBS patients increased

sympathetic drive may be responsible for dysmotility in the upper gastrointestinal tract⁷⁷, yet vagal dysfunction in IBS patients has been shown in response to rectal distension by Spaziani *et al*⁷⁸. It is being increasingly suggested that the SNS may be pro-nociceptive and the PNS may be anti-nociceptive and this observation may provide a unifying link in explaining the divergent findings of these studies with respect to chronic visceral pain^{79,80}.

The HPA axis exerts important influences on gastrointestinal motility, sensation and immune function^{81,82}. Dysfunction of the HPA axis has been recognised in a number of chronic pain syndromes⁸³. In a study by Dinan *et al*, the HPA axis was examined in a group of 76 IBS patients and 75 healthy controls. It was found that in the IBS group, irrespective of IBS sub-type as defined by predominant stool consistency, there was over activity of the HPA axis and an excess of the pro-inflammatory cytokines interleukin (IL)-6 and IL-8⁸⁴. Moreover, the former has been recently been proposed as a potential measurable index of pain severity^{84,85}.

Corticotrophin releasing factor (CRF) is considered to be pivotal in coordinating the stress response through its influences on autonomic, emotional and immunological pathways. Its release is particularly dependant on input from the limbic system, an area that we have already highlighted as displaying abnormalities in central nociceptive processing in chronic visceral pain. CRF is up-regulated in response to intestinal inflammation, stress and psychopathologies such as anxiety and depression and has recently been shown to mediate enhanced visceral nociception in a rat model of visceral hypersensitivity⁸⁶. In humans, Nozu and Kudaira have shown that CRF may induce rectal hypersensitivity in response to repeated rectal distension in a cohort of healthy volunteers⁸⁷. Furthermore, recent data from Larauche *et al* demonstrates that CRF receptor subtype 1 (CRF(1)) plays an important role in the development and maintenance of chronic visceral pain induced by repeated stress⁸⁸. CRF(1) antagonists that inhibit the development of chronic visceral pain in rat models thereby representing an exciting novel target for drug development⁸⁹.

Conclusions

Great strides have been made in advancing our understanding of mechanisms that underlie both the development and maintenance of gut through convergent and complementary research strategies from a number of academic disciplines; neurogastroenterology, molecular pharmacology, neurophysiology to psychology to name but a few. Further significant challenges lie ahead in the improvement of our understanding of the molecular

basis of visceral pain with the hope of translation into pharmacological agents for patient benefit.

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Conflict of interest

The authors declare that there are no conflict of interest.

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