# Visceral pain hypersensitivity in functional gastrointestinal disorders

**A. D. Farmer** and **Q. Aziz***

*Neurogastroenterology Group, The Wingate Institute of Neurogastroenterology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Whitechapel, London E1 2AJ, UK*

**Introduction**: Functional gastrointestinal disorders (FGIDs) are a highly prevalent group of heterogeneous disorders whose diagnostic criteria are symptom based in the absence of a demonstrable structural or biochemical abnormality. Chronic abdominal pain or discomfort is a defining characteristic of these disorders and a proportion of patients may display heightened pain sensitivity to experimental visceral stimulation, termed visceral pain hypersensitivity (VPH).

**Sources of data**: We examined the most recent literature in order to concisely review the evidence for some of the most important recent advances in the putative mechanisms concerned in the pathophysiology of VPH.

**Areas of agreement**: VPH may occur due to anomalies at any level of the visceral nociceptive neuraxis. Important peripheral and central mechanisms of sensitization that have been postulated include a wide range of ion channels, neurotransmitter receptors and trophic factors. Data from functional brain imaging studies have also provided evidence for aberrant central pain processing in cortical and subcortical regions. In addition, descending modulation of visceral nociceptive pathways by the autonomic nervous system, hypothalamo–pituitary–adrenal axis and psychological factors have all been implicated in the generation of VPH.

**Areas of controversy**: Particular areas of controversy have included the development of efficacious treatment of VPH. Therapies have been slow to emerge, mainly due to concerns regarding safety.

**Growing points**: The burgeoning field of genome wide association studies may provide further evidence for the pleiotropic genetic basis of VPH development.

**Areas timely for developing research**: Tangible progress will only be made in the treatment of VPH when we begin to individually characterize patients with FGIDs based on their clinical phenotype, genetics and visceral nociceptive physiology.

*Keywords:* visceral pain hypersensitivity/functional gastrointestinal disorders/irritable bowel syndrome/peripheral sensitization/central sensitization/functional brain imaging

# Introduction

Functional gastrointestinal disorders (FGIDs) are a heterogeneous group of disorders that represent one of the great unmet needs in modern gastroenterological practice, accounting for more than 40% of all new referrals to out patient clinics.[1] The Rome multinational consensus, now in its third incarnation, defines FGIDs as a 'variable combination of chronic or recurrent gastrointestinal symptoms which are not explained by structural or biochemical abnormalities'.[2] While considerable advances have been made in our understanding of the pathophysiology of many 'organic' gastrointestinal (GI) disorders, such as peptic ulcer disease and inflammatory bowel disease, our understanding of the processes that underpin the genesis of symptoms in FGIDs remains incomplete. Moreover, the term 'functional' is somewhat unhelpful, in that it pertains to a lack of identifiable structural or biochemical abnormality, thereby suggesting that FGIDs represent an enigma and consequentially there is a lack of acquiescence towards the 'legitimization' of symptoms and suffering in these patients by healthcare professionals.[3] Coupled with the current paucity of efficacious treatments in FGIDs, the inevitable result is symptom chronicity, patient anxiety and dissatisfaction, over investigation, recurrent consultations and significant morbidity.[4] The socioeconomic impact of these disorders is significant through a reduction in health-related quality of life and increased absenteeism. Direct and indirect healthcare costs associated with FGIDs have been estimated to be in the order of $34 billion in the seven largest western economies.[5–7]

Many hypotheses have been proposed to explain the origin of symptoms in FGIDs but no single factor has achieved primacy in the literature largely because of the heterogeneity of these disorders. However, a common feature of FGIDs is that patients often display a heightened sensitivity to experimental gut stimulation, termed visceral pain hypersensitivity (VPH). This observation has spawned a large research effort from academia and the pharmaceutical industry alike in identifying the responsible molecular mechanisms. Although these efforts have afforded great advances in our comprehension of the pathophysiology of these disorders, the development of a truly integrated understanding remains elusive.

# Aims

The aim of this review is to provide a concise review of the recent literature that is relevant to VPH in FGIDs. In particular, we aim to

examine abnormalities in peripheral and central nociceptive pathways, the central processing of visceral nociception, descending modulation of visceral nociceptive pathways as well as the mechanisms concerned with GI tract responses to stress that have been implicated in this epiphenomenon.

## Visceral pain hypersensitivity

Chronic episodic abdominal pain and discomfort cause appreciable morbidity in FGIDs and are integral components of the diagnostic criteria in these disorders. It has been 35 years since Ritchie, and subsequently others, demonstrated that a proportion of patients with FGIDs may display elevated pain sensitivity to experimental gut distension—VPH.[8–11] Whether these observed alterations in visceral sensitivity are part of a global phenomenon of generalized sensory dysfunction is controversial.[12–15] Therefore, the putative pathophysiology of VPH may be conceptualized as being due to aberrant processes that may arise at any level of the visceral nociceptive pathway (neuraxis), see Fig. 1.
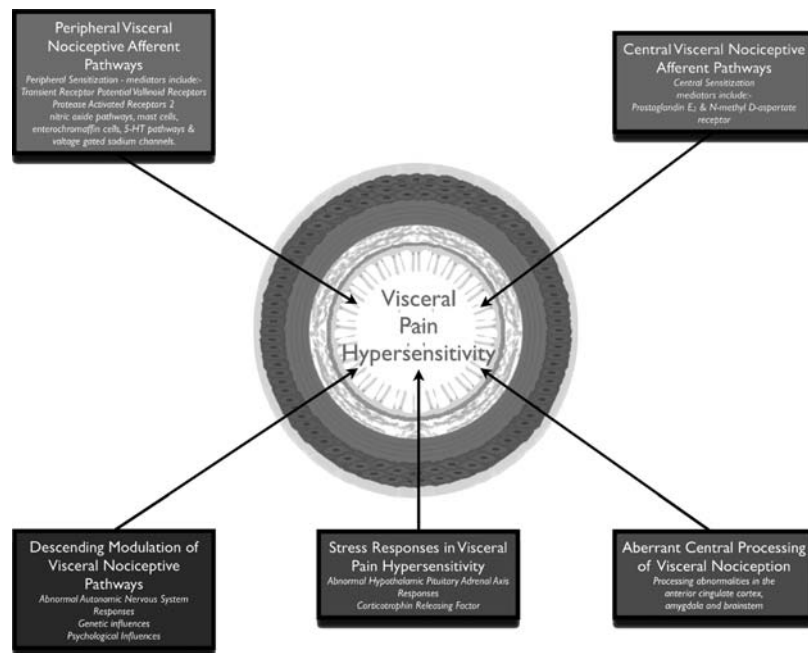


**Fig. 1** Demonstrates the processes, and some of their most important mediators, that have been implicated in the pathophysiology of VPH.

# Peripheral visceral nociceptive afferent pathways

Noxious stimuli may cause the peripheral release of several inflammatory mediators such as K+, H+, adenosine triphosphate, 5-hydroxytryptamine (5-HT), bradykinins and prostaglandins.[16,17] These mediators may elicit a number of effects, including the activation and peripheral sensitization (PS) of nociceptive afferent nerves by reducing their transduction thresholds and by inducing the expression and recruitment of previously silent nociceptors. The main consequence of these inflammatory mediators is an increase in pain sensitivity at the site of injury known as primary hyperalgesia.[18] A number of ion channels, neurotransmitter receptors and trophic factors have been implicated in the development of PS. While it is beyond the scope of this review to examine all of the possible mechanisms previously studied in the literature, we will highlight, in our opinion, some of the more important advances in our understanding of the molecular mechanisms of PS: the transient receptor potential vallinoid (TRPV) receptors 1 and 4, the protease activated receptor 2 (PAR(2)), nitric oxide (NO) pathways, mast cells, enterochromaffin (EC) cells, 5-HT pathways and voltage-gated sodium channels (VGSCs).

*Transient receptor potential vallinoid receptors and protease activated receptors*

TRPV1 and 4 are members of a larger family of TRPV channels that serve many sensory functions ranging from hearing to mechanosensory transduction.[19,20] The TRPV1 receptor may be activated by heat as well as exogenous ligands such as capsaicin and its analogues, and is thought to play an important role in mechanotransduction in the GI tract and to the development and maintenance of VPH.[19,21] A recent study by Akbar *et al.*[22] showed that there was a 3.5-fold increase in density of TRPV1 immunoreactive fibres in the colonic biopsies of patients with irritable bowel syndrome (IBS) when compared with healthy controls. Furthermore, in rat models TRPV1 receptor antagonists have been found to ameliorate VPH.[23] Early results from human studies evaluating this novel class of analgesic have yielded promising results.[24,25] TRVP4 is a mechanotransductive osmosensitive channel that has been recently associated with VPH.[26] Further evidence for TRPV4's role in VPH comes from an elegant study recently reported by Cenac *et al.*,[27] where a TRPV4 agonist induced VPH in response to colorectal distension in mice whereas this effect was lost in TRPV4−/− knockouts. The TRPV4 receptor closely interacts with PAR(2) which is expressed by nociceptive neurons in the gut and agonists of PAR(2) have been found to cause hyperexcitability of intestinal

sensory neurons.[28] PAR(2) may be preferentially activated during inflammation by serine proteases which have been found in increased quantities in colonic mucosal biopsies in patients with IBS.[29] Inhibition of serine proteases *in vitro* reduces sensory afferent nerve discharge, thereby possibly preventing TRPV4 and PAR(2) sensitization.[30] TRPV4 may present a particularly exciting potential therapeutic target for the future owing to its preferential distribution within the colon.[26]

### The NO pathway

Three isoforms of NO synthase (inducible, neurogenic and endothelial) catalyse the formation of endogenous NO. Inducible (NOS2) and neurogenic NO (NOS1) are ubiquitously present within the nervous system and the endothelium. Endogenous NO may modulate the efficacy and tolerability of opioid analgesics.[31] The NO pathway also aids in the regulation of GL motility and mucosal integrity.[32] Lithium, widely used in the treatment of bipolar disorder, mediates some of its actions through the NO pathway and it has been recently shown by Shamshiri *et al.*[33] that chronic lithium administration attenuated sensitivity to colonic distension, increasing nociceptive thresholds and decreasing stool frequency in a rat model of VPH.

### Mast cells, enterochromaffin cells and 5-hydroxytriptamine

Up to 20% of patients with IBS report that their symptoms were initiated following an episode of acute infection, which may be GI or non-GI; a phenomenon known as post-infectious IBS (PI-IBS).[34] In this group, increased numbers of EC cells, mast cells and T-lymphocytes may be observed in the lamina propria of colonic biopsies, suggesting the presence of a low-grade inflammatory infiltrate.[35] Piche *et al.*[36] have shown that the degree of mast cell infiltration is positively associated with the degree of fatigue and depression in IBS patients. Mast cells *per se* have been shown not to modulate visceral nociception but are essential in the development of VPH; in mast cell deficient rats the development of VPH can be ameliorated with mast cell stabilizers in a dose dependant manner.[37,38] Interestingly, treatment with a mast cell stabilizer, disodium cromoglycate, in conjunction with exclusion diets may be of some symptomatic benefit in a small percentage of patients with diarrhoea predominant IBS.[39] EC and mast cells contain 5-HT, one of the major neurotransmitters of the enteric nervous system, which is involved in signal transduction of visceral stimuli in addition to effecting changes in GI motility.[40] Increases in 5-HT bioavailability,

through increased availability and reduced uptake, have been observed in models of post-inflammatory VPH and may manifest as changes in gut sensorimotor function. Pharmacotherapeutic interventions directed towards the 5-HT pathway, most notably 5-HT$_3$ antagonists, 5-HT$_4$ agonists and most recently 5-HT$_{1A}$ antagonists have had, at best, only a modest effect in the modulation of visceral pain and the restoration abnormal bowel habit to normal mainly due to a series of adverse events and concerns over safety.[41–43]

### Voltage-gated sodium channels

Voltage-gated sodium channels (VGSCs) are pivotal in nerve impulse conduction and are targets for clinically important analgesics such as lidocaine. Data from the last decade have shown that certain VGSC isoforms (Na$_v$1.3–1.9) are predominantly expressed in peripheral sensory afferent neurones and that the expression and functional properties of these isoforms can be dynamically regulated *in vivo* in response to axonal injury or inflammation and may play an important role in generation of PS.[44]

However, sensitization is not solely confined to the periphery. When a noxious stimuli is transmitted from the periphery, it induces a constellation of changes at the spinal dorsal horn by the activation intracellular signalling cascades (comprehensively reviewed by Anand *et al.*[45]). This may lead to central sensitization (CS) and amplification of the nociceptive response to the stimuli (secondary hyperalgesia) and previously innocuous stimuli may provoke a nociceptive response (allodynia). While these observations have been long recognized in somatic pain, increasingly CS is thought to play a central role in the development and maintenance of VPH.[12,46]

## Central visceral nociceptive afferent pathways

In a landmark paper, Sarkar *et al.*[12] demonstrated the concept of CS in a reproducible oesophageal model in humans in which hydrochloric acid was infused into the healthy distal oesophagus. Pain thresholds were not only reduced in the acid exposed distal region but also in the adjacent proximal unexposed region. This effect of CS was prolonged, lasting up to 5 h after 30 min of acid exposure suggesting that the duration and magnitude of CS of the non-exposed proximal oesophagus was directly related to the intensity of acid exposure in the distal oesophagus. Prostaglandin E$_2$ (PGE$_2$) and the *n*-methyl *d*-aspartate (NMDA) receptor have been elucidated as the most importance molecular factors in the

development of CS at the spinal dorsal horn.[47] Human pharmacological studies have demonstrated that antagonism of the $PGE_2$ or the NMDA receptor prevents the development of CS within the oesophagus and antagonism of the NMDA receptor with ketamine may even reverse established VPH.[48,49] CS 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.[50,51] In patients with IBS, following repetitive distension of the sigmoid colon, CS may ensue as manifested by rectal hyperalgesia and increased viscerosomatic referral to experimental rectal distension.[52]

## Aberrant central processing of visceral nociception

PS and CS are not exclusive entities in explaining VPH in humans. Central processing of nociception involves input to a number of cortical and subcortical brain structures. Methods for studying VPH have traditionally relied on descriptive, and therefore subjective, methods of reporting visceral sensation. While great care has been taken to eliminate subjective factors from introducing response bias, no objective measure has been developed to assess these descriptive factors of visceral sensation. Functional neuroimaging has facilitated the examination of the complete neuraxis implicated in VPH 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) (the relative strengths and weaknesses of these techniques have been reviewed by Hobson et al.[53] and Sharma et al.[54]), over the last decade have led to significant advances in the understanding of the central changes that may be in response to, or as a consequence of, VPH. For example, Mayer[55] demonstrated in an fMRI study, that in response to experimental rectosigmoid 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 periaqueductal grey (PAG) matter and thalamic regions. Abnormal areas of activation have been observed in other areas such as the anterior cingulate cortex (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.[56,57] Future studies using a combination of these functional imaging techniques, in conjunction with improvements in study design, will no doubt further advance our understanding of the mechanisms involved.

# Descending modulation of visceral nociceptive pathways

## Autonomic nervous system

Central communication to the GI tract is via the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) pathways of the efferent autonomic nervous system (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.[58,59] 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.[60–65] 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.[66] and more recently Thoua et al.[67] using rectal mucosal blood flow techniques have allayed some of these concerns. Notably, Mazur et al.[68] has demonstrated that in IBS patients increased sympathetic drive may be responsible for dysmotility in the upper GI tract, yet vagal dysfunction in IBS patients has been shown in response to rectal distension by Spaziani et al.[69] 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 VPH.[70,71]

## Psychological influences

Psychological comorbidity such as depression, anxiety and hypochondriasis is common in FGIDs and it has been estimated that over half of patients with IBS suffer from these disorders to one degree or another.[5,6] In animal models, studies have shown that adverse early life events, such as maternal separation, are risk factors for the development of VPH in adulthood.[72] In humans, there is evidence that a history of sexual abuse, especially in childhood, can alter visceral pain sensitivity.[73–75] Furthermore, the psychological context in which GI symptoms are interpreted by an individual may predict the development of IBS following an episode of gastroenteritis.[76] A recent meta-analysis has suggested that psychological treatments, as a class of interventions *per se*, are effective in symptom reduction in FGIDs.[77]

### Genetic influences

FGIDs 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 disorder, albeit small.[78] While 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 under powered to detect what is probably a small influence (recently reviewed by Saito and Talley[79]). Interestingly, Camillieri et al.[80] have recently proposed that the endophenotype of VPH in IBS may have a genetic salience. 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 FGIDs in the future.

## Stress responses in visceral pain hypersensitivity

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 GI tract is coordinated by the brain gut axis; a bidirectional communication system from the enteric nervous system to the brain via the ANS and reciprocally via autonomic efferents, the hypothalamo–pituitary–adrenal (HPA) axis and neuroimmune interactions.[81]

### Hypothalamic–pituitary–adrenal axis

The HPA axis exerts important influences on GI motility, sensation and immune function.[82,83] Dysfunction of the HPA axis has been recognized in a number of chronic pain syndromes.[84] 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-8.[84] Moreover, the former has been recently been proposed as a potential measurable index of pain severity.[85,86]

Corticotrophin-releasing factor (CRF) is considered to be central in the coordination of 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 VPH. 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 VPH.[87] In humans, Nozu and Kudaira[88] have shown that CRF may induce rectal hypersensitivity in response to repeated rectal distension in a cohort of healthy volunteers. Furthermore, recent data from Larauche et al.[89] demonstrates that CRF receptor subtype 1 (CRF(1)) plays an important role in the development and maintenance of VPH induced by repeated stress. CRF(1) antagonists inhibit the development of VPH in rat models[90] and represent a novel target for drug development (reviewed by Martinez and Tache[91]).

## Conclusions

Great strides have been made in advancing our understanding of the role of VPH in the pathophysiology of FGIDs through convergent and complementary research strategies from a number of academic disciplines: neurogastroenterology, molecular pharmacology, neurophysiology to psychology to name but a few. However, if the scientific community is to unravel the mysteries of VPH in FGIDs, we need to adopt a tailored individualistic approach by characterizing our patients in terms of their clinical phenotype, genetics and visceral nociceptive physiology.

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