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Stress and visceral pain: from animal models to clinical therapies

Muriel Larauche, **Agata Mulak**, and **Yvette Taché**
CURE/Digestive Diseases Research Center and Center for Neurobiology of Stress, Digestive Diseases Division, Department of Medicine, David Geffen School of Medicine, UCLA, and VA Greater Los Angeles Healthcare System, Los Angeles, California, USA

Abstract

Epidemiological studies have implicated stress (psychosocial and physical) as a trigger of first onset or exacerbation of irritable bowel syndrome (IBS) symptoms of which visceral pain is an integrant landmark. A number of experimental acute or chronic exteroceptive or interoceptive stressors induce visceral hyperalgesia in rodents although recent evidence also points to stress-related visceral analgesia as established in the somatic pain field. Underlying mechanisms of stress-related visceral hypersensitivity may involve a combination of sensitization of primary afferents, central sensitization in response to input from the viscera and dysregulation of descending pathways that modulate spinal nociceptive transmission or analgesic response. Biochemical coding of stress involves the recruitment of corticotropin releasing factor (CRF) signaling pathways. Experimental studies established that activation of brain and peripheral CRF receptor subtype 1 plays a primary role in the development of stress-related delayed visceral hyperalgesia while subtype 2 activation induces analgesic response. In line with stress pathways playing a role in IBS, non-pharmacologic and pharmacologic treatment modalities aimed at reducing stress perception using a broad range of evidence-based mind-body interventions and centrally-targeted medications to reduce anxiety impact on brain patterns activated by visceral stimuli and dampen visceral pain.

Keywords

colorectal distension; CRF receptor; irritable bowel syndrome; mast cells; stress; visceral pain

Introduction

Visceral hypersensitivity reflected by enhanced perception of physiological signals from the gut and/or enhanced perception of experimental visceral stimuli along with hypervigilance to those, is commonly considered to play a major role in the pathophysiology of irritable bowel syndrome (IBS) (Choung et al., 2009; Elsenbruch et al., 2010a; Elsenbruch et al., 2010b; Lackner et al., 2010; Mayer et al., 2008; Posserud et al., 2004; Shen et al., 2009). Epidemiological studies have implicated stress (psychosocial and physical) as a trigger of

Corresponding author: Muriel Larauche, PhD CURE/Digestive Diseases Research Center, West Los Angeles VA Medical Center, 11301 Wilshire Blvd., Bldg. 115/Rm 111, Los Angeles, CA 90073 Tel. +1-310-478-3711 extension 41827, Fax: +1-310-268-4963, mlarauche@mednet.ucla.edu.

first onset or exacerbation of IBS symptoms (Blanchard et al., 2008; Dufton et al., 2008; Mayer et al., 2001). Over the past 15 years, various animal models have been developed to get insight into the underlying mechanisms of visceral hypersensitivity and the influence of stress on visceral pain pathways (Barreau et al., 2007b; Larauche et al., 2009a; Mayer et al., 2008; Qin et al., 2011; Yarushkina, 2008). In this review we will outline the recent development in stress pathways and mediators, how they contribute to stress modulation of visceral pain mechanisms, and the clinical relevance of these preclinical studies to unravel potential molecular targets to alleviate pain symptoms in IBS.

Stress: pathways and mediators

The term “stress” was first coined by the endocrinologist Hans Selye more than 70 years ago to define the physiological adaptive responses to emotional or physical threats (“stressors”) to the organism, whether real or perceived (Selye, 1936). When exposed to an acute threatening challenge, the body engages a “fight or flight” response as described originally by W. Cannon (Cannon, 1915) in 1915 which is driven by sympathetic activation leading to rapid heart rate and respiration, increased arousal, alertness, and inhibition of acutely non adaptive vegetative functions related to feeding, digestion, growth and reproduction (Selye, 1936). Concurrently, a negative feedback is activated to limit the stress response and bring the body back to a state of homeostasis or eustasis (Chrousos, 2009) through activation of neural, neuroendocrine and immune mechanisms, a process called allostasis (McEwen, 1998) or “stability through changes” (McEwen, 1998; Sterling and Eyer, 1988). However, if the stressor persists and becomes chronic, the body enters a resistance phase and tries to adapt to the strains and demands of the environment by engaging coping mechanisms. When the severity and/or chronicity of the stressors are exceeding the limits, and the adaptive system becomes defective or excessive, the organism is no longer brought back to basal homeostasis leading to a state of allostatic load (McEwen, 1998; McEwen and Stellar, 1993) recently also named “cacostasis” (Chrousos, 2009). This state is harmful to the organism and lies at the origin of a variety of stress-related diseases that develop in the context of a vulnerable background (genetic, epigenetic and/or constitutional) (Chrousos, 2009). The pathogenesis of stress-induced disorders affects the whole body, including the viscera of which the gastrointestinal (GI) tract is a sensitive target (Chrousos, 2009; Stengel and Taché, 2010).

In recent decades, the biochemical coding of the stress response was unraveled through the identification of the 41 amino acid peptide, corticotropin releasing factor (CRF), and related peptides, urocortin 1, urocortin 2 and urocortin 3 along with the characterization of CRF receptors CRF_1 and CRF_2 which display specific affinity for CRF and related agonists (Hauger et al., 2003). Activation of CRF receptors underly the various biological components of the stress response (Bale and Vale, 2004; Koob and Heinrichs, 1999; Stengel and Taché, 2010). Indeed, hypothalamic CRF was established to play a pivotal role in the activation of the hypothalamic-pituitary-adrenal (HPA) axis. When a stressor is perceived, a convergence of stimulatory inputs from different brain regions (amygdala, prefrontal cortex, pons, medulla) activates the paraventricular nucleus of the hypothalamus which releases CRF and arginine-vasopressin into the hypophyseal portal system. There, CRF binds to CRF_1 receptors located on corticotrope cells of the pituitary gland to release the adrenocorticotropic hormone while arginine-vasopressin interacts with $vasopressin_{1b}$ pituitary receptor to potentiate adrenocorticotropic hormone release leading to glucocorticoids secretion from the adrenal glands. Corticosterone (rodent)/cortisol (human) exert a negative feedback on the paraventricular nucleus of the hypothalamus and pituitary gland ultimately contributing to the termination of the response (Turnbull and Rivier, 1997). Far beyond an exclusive neuroendocrine role, CRF, which is widely distributed outside of the hypothalamus (De Souza and Grigoriadis, 2002), also acts as a neurotransmitter/

neuromodulator to coordinate the behavioral, autonomic, immune, and visceral efferent limbs of the stress response (Bale and Vale, 2004; Caso et al., 2008; Friedman and Irwin, 1995; Taché et al., 2001). For instance brain CRF activates the sympathetic nervous system inducing the systemic release of catecholamines (adrenaline and noradrenaline) involved in the ”fight or flight” response (Tsatsanis et al., 2007; Usui et al., 2009; Yorimitsu et al., 2008). The locus coeruleus is also activated and its noradrenergic projections to the forebrain provide an additional source of noradrenaline which contributes to the arousal and alertness (Valentino et al., 1993). Convergent preclinical evidence has accumulated over the years suggesting that stress-related alterations of colonic motor and visceral functions are primarily mediated by the activation of brain CRF/CRF_1 signaling pathway, while CRF_2 receptor activation may exert a counteracting influence (Fukudo, 2007; Million et al., 2005; Million et al., 2006; Taché and Brunnhuber, 2008). However, recent experimental and clinical studies point to an equally important contribution of the peripheral CRF/CRF_1 signaling locally expressed in the gut to the GI stress response (Larauche et al., 2009a; Larauche et al., 2009b).

Visceral pain pathways

The perception of pain in peripheral tissues depends on the transmission of a signal from the site of pain origin to a number of distinct regions in the cerebral cortex. This pain signal is subject to modulation at every step of its travel to and from the central nervous system (CNS) (Anand et al., 2007). In the periphery, pain is transmitted by the activation of nociceptors (receptors activated by noxious stimuli) (Basbaum et al., 2009), located in two sets of primary afferent fibers innervating the viscera that project to distinct regions in the CNS (Sengupta, 2009). The GI tract innervation from the esophagus to the transverse colon is provided by vagal afferent fibers originating in the nodose ganglia and projecting centrally to the nucleus of the solitary tract. The remaining part of the large bowel (descending and sigmoid colon, rectum) is innervated by pelvic nerve afferent fibers, originating in the lumbosacral dorsal root ganglia, and projecting centrally to the sacral spinal cord. Due to their anatomical association with parasympathetic nerves, those are often qualified of parasympathetic afferents. The entire GI tract is also innervated by afferent fibers in the splanchnic nerves projecting to the thoracic 5- lumbar 2 segments of the spinal cord, which are qualified of sympathetic afferents due to their anatomical association with sympathetic nerves (Robinson and Gebhart, 2008). Visceral afferents which constitute only 10% of all afferents are present in the mucosal epithelium, serosa, muscles and myenteric ganglia, and are able to monitor changes in the gut milieu and participate in the transmission of visceral sensory information (Blackshaw et al., 2007; Grundy, 2002). While vagal afferents do not encode painful stimuli, it is well established that changes in their activity can modulate nociceptive processing in the spinal cord and the brain (Grundy, 2002; Ness et al., 2000; Randich and Gebhart, 1992).

Upon entering the dorsal horn, visceral afferents terminate in spinal cord laminae I, II V and X (Sugiura et al., 1993). Visceral information carried out by the pelvic and splanchnic nerves converges onto spinal neurons in the lumbosacral segments and thoracolumbar segments respectively. Lumbosacral segments appear sufficient to process reflex responses to acute visceral pain. In contrast, the involvement of thoracolumbar segments in normal visceral sensation is uncertain (Wang et al., 2005). Both segments process inflammatory stimuli (Wang et al., 2005). Interestingly, activity in pelvic nerve colonic afferents inhibits thoracolumbar dorsal horn neuron processing of the same colonic stimulus through a supraspinal loop: homovisceral descending modulation (Wang et al., 2007). In addition to the well known ascending pathways involved in the transmission of nociceptive information including the spinothalamic tract, the dorsal column pathway was recently found to have a

major role in relaying visceral nociceptive information (Al-Chaer et al., 1996; Palecek, 2004; Willis, Jr. and Westlund, 2001).

Subpopulations of neurons within the dorsal horn project to discrete nuclei within the thalamus (i.e. ventral posterior lateral thalamus) as well as other structures in the brain stem (parabrachial nucleus, periaqueductal gray). From the thalamus, the information is conveyed to cortical areas involved in sensory processing (such as the somatosensory cortex) or those involved in processing emotional or affective information (such as the anterior cingulate gyrus and insular cortex) (Basbaum et al., 2009; Price, 2002).

In addition to the ascending system, which enables pain perception described above, there is evidence of neural circuits originating from supraspinal sites that influence nociceptive activity in the spinal cord and in primary afferents, a system referred to as descending pathways (Heinricher et al., 2009). There are two types of descending control pathways: inhibitory and facilitatory. Descending inhibitory control pathways recruited to inhibit the pain response and produce analgesia include the periaqueductal gray and the locus coeruleus (Tsuruoka et al., 2010). Descending facilitatory control pathways include the rostroventral medulla and its two populations of neurons: one that stops firing immediately before the initiation of a nociceptive reflex - “OFF cells” and is involved in antinociception and another that begins firing immediately prior to the initiation of a nociceptive reflex - “ON cells” leading to facilitation of pain (Heinricher et al., 2009; Martenson et al., 2009).

Lastly, there is also critical evidence that the modulation of the nociceptive response can occur at afferent peripheral terminals and involves the sympathoadrenal and hypothalamic-pituitary-adrenal axes. Antinociception is provided by inhibitory peptides such as β-endorphin and enkephalin released by the pituitary and the adrenal medulla as well as immune cells (Busch-Dienstfertig and Stein, 2010; Stein et al., 1995). In contrast, an increase in nociception is mediated by adrenaline released from the adrenal medulla (Khasar et al., 2005; Khasar et al., 2009).

Clinical evidence of stress-related visceral pain modulation

Stress and IBS – impact on symptoms—A predominant role of stress in the pathophysiology, presentation and treatment outcome in clinical pain states, in particular functional gastrointestinal disorders such as IBS, has been well documented (Bennett et al., 1998; Gwee et al., 1999; Kearney and Brown-Chang, 2008; Monnikes et al., 2001). Epidemiological data have shown that a history of early adverse life events in the form of emotional, sexual, or physical abuse is a major predisposing factor for the development of IBS later in life (Chitkara et al., 2008; Videlock et al., 2009). Childhood trauma, especially in genetically predisposed individuals, is thought to induce persistence changes in the central response system, including the HPA axis (Videlock et al., 2009). Additionally, it may cause epigenetic programming of glucocorticoid receptor expression that affects behavioral adaptation and susceptibility to stress-related disorders (Chrousos, 2009). In adult IBS patients, the illness experience, health care-seeking behavior, and treatment outcome are adversely associated with acute stress episodes, chronic social stress, anxiety disorders, and maladaptive coping style (Leserman and Drossman, 2007; Videlock et al., 2009). Stress-related psychosocial factors like somatization, neuroticism, and hypochondriasis are also important predictors in the development of postinfectious IBS (Gwee et al., 1999; Spiller and Garsed, 2009a).

Autonomic disturbances—At the autonomic nervous system level, stress-related disturbances characterized by the decreased parasympathetic activity and increased sympathetic outflow frequently occur in IBS patients (Jarrett et al., 2003; Spaziani et al., 2008). Increased sympathetic tone has been shown to raise the level of perception to

gastrointestinal stimuli (Azpiroz, 2002). Stress can affect different aspects of visceral pain including referred pain area, as well as accompanying motor and autonomic reflexes (Cervero, 2009). In fact, in IBS patients aberrant viscerosomatic referral has been reported (Mertz et al., 1995). Alterations in the somatic nociceptive flexion (RIII) reflex indicating the presence of hyperexcitability of spinal nociceptive processes have been also shown in a large subgroup of IBS patients undergoing rectal distension (Coffin et al., 2004). Autonomic dysfunction, in particular lower parasympathetic activity, has been also suggested to represent the physiological pathways accounting for many extra-intestinal symptoms occurring in IBS patients and the frequent overlap with other chronic pain disorders such as fibromyalgia, chronic pelvic pain, chronic fatigue syndrome, migraine headache as well as psychiatric disorders (Jarrett et al., 2003; Mayer and Tillisch, 2011; Mulak and Bonaz, 2004; Palsson and Drossman, 2005; Warnock and Clayton, 2003; Whitehead et al., 2002).

Central mechanisms—The processing and evaluation of sensory information, particularly of noxious stimuli, has been confirmed to have important cognitive, motivational and emotional components, all of which are likely affected by psychological stress (Mayer et al., 2001; Van Oudenhove et al., 2007). In IBS patients hypervigilance expressed as an increased psychological tendency to report pain, which is in turn associated with psychological distress, is considered as an essential contributor to visceral hypersensitivity (Naliboff et al., 2006). Additionally, expectation of pain and perceived controllability of pain can modify reported unpleasantness of stimuli (Salomons et al., 2007; Sawamoto et al., 2000). Functional brain imaging studies in IBS patients have provided evidence of an exaggerated activation of a vigilance network (i.e., the prefrontal cortex) and a failure in activation of regions involved in pain inhibition (e.g., anterior cingulate cortex) (Chang, 2005; Derbyshire, 2003; Piche et al., 2010). The influence of cognitive aspects and emotions on the processing of sensory information is mediated by extensive neuro-anatomical network with a pivotal role of the insular cortex and anterior cingulate cortex (Seminowicz et al., 2004). Additionally, functional brain imaging studies in IBS patients revealed that negative emotions of anxiety, anger and stress correlated negatively with anticipatory downregulation within the dorsal pons, amygdala and anterior cingulate cortex during visceral pain (Berman et al., 2008). It has been also shown that anxiety and depression are associated with the subjective response to painful visceral stimuli and are correlated with brain activation during painful rectal distension (Elsenbruch et al., 2010a; Elsenbruch et al., 2010b).

Recently, a concept of “central sensitivity syndromes” has been proposed based on many common abnormalities shared by chronic pain conditions (Yunus, 2008). This concept corresponds well to the “top-down” pathophysiological model of stress-related disorders, according to which alterations in the central stress circuits in susceptible individuals play a primary role in the pathogenesis of symptoms (Chang, 2005; Mayer et al., 2000). Two main disturbances in “central sensitivity syndromes” include alterations in serotonergic system and dysregulation of the HPA-axis. Abnormalities in the level of other neurotransmitters have also been suggested such as noradrenaline, dopamine, endocannabinoid deficiency, and the increase of substance P (SP) in the spinal fluid (Binder and Nemeroff, 2010; Warnock and Clayton, 2003). Once the CNS hyper-reactivity becomes expressed, any or all the effector arms (e.g., increased visceral nociception, neurogenic inflammation, neuroendocrine disturbances and autonomic dysfunction) can be involved (Warnock and Clayton, 2003)

Experimental stress models and visceral pain

Based on stress-related modulation of visceral pain in IBS patients as well as in healthy subjects (Mayer et al., 2001; Rosenberger et al., 2009), experimental models using exposure to various clinically relevant stressors have been developed to recapture features of IBS

symptoms, of which lowered pain threshold and hyperalgesia to sigmoid distensions are hallmarks (Bouin et al., 2002; Elsenbruch, 2011). Importantly, animal models provide ways to explore hypotheses regarding the pathophysiological mechanisms underlying stress-related pain modulation. The validity of these models however should take into consideration three aspects: 1) *face validity* - how closely they mimic clinical pain features in IBS patients; 2) *construct validity* - how consistent the animal models are with the hypothetical pathogenesis; and 3) *predictive validity* - how well the models are responsive to treatments showing some efficacy in alleviating visceral pain in IBS patients and therefore can predict treatment responses to specific drugs or non pharmacological interventions in humans (Mayer and Collins, 2002).

Monitoring of visceral pain in rodents—The assessment of pseudoaffective reflex responses (and to a lesser degree of behavioral responses) to controlled isobaric distensions of the distal colon has become the primary readout and the standard assay for the measurement of visceral pain in rodents since its development in 1988 by Ness and Gebhart (Ness and Gebhart, 1988). When applied to rats, colorectal distension (CRD) produces a range of autonomic and behavioral pseudoaffective reflexes (changes in arterial pressure and heart rate, passive avoidance behaviors, and contraction of abdominal musculature). The monitoring of contraction of abdominal muscles or visceromotor response (VMR) is the most commonly used index of visceral pain response in rats and mice. In conscious animals, it can be recorded as a measure of electromyographic (EMG) signals via implantation of recording electrodes which are either externalized through the skin (abdomen, neck) (Bradesi et al., 2005; Christianson and Gebhart, 2007; Larsson et al., 2003) or connected to radiotelemetric implants in the abdominal cavity (Nijsen et al., 2003; Welting et al., 2005), but also as manometric changes in the pressure of the balloon inserted into the distal colon (Arvidsson et al., 2006; Tammpere et al., 2005) or changes in pressure inside the colonic lumen (Larauche et al., 2009a; Larauche et al., 2010a). Additional indirect approaches such as abdominal withdrawal reflex monitoring (Al-Chaer et al., 2000), operant behavioral assays (Ness and Gebhart, 1988) or functional brain imaging of integrated brain responses to nociceptive stimuli (Johnson et al., 2010; Wang et al., 2008b) have also been used in some studies.

Stress-induced modulation of visceral pain: animal models—Stressors are conventionally categorized into exteroceptive (psychological or neurogenic) and interoceptive (physical or systemic) classes (Herman and Cullinan, 1997; Sawchenko et al., 2000). Exteroceptive stressors are limbic-sensitive and dependent upon the forebrain cognitive circuits mediating the endocrine and autonomic responses to these types of stressors. The limbic-sensitive neural network encompasses namely the cortex (lateral, medial prefrontal, vendromedial, and infragenual cingulate), bed nucleus of the stria terminalis, lateral septum, hippocampus, amygdala, hypothalamus (mainly paraventricular nucleus) and periaqueductal gray. Interoceptive stressors in contrast are considered limbic-insensitive, the cognitive processing is bypassed and brainstem/pontine nuclei such as the lateral parabrachial nucleus, nucleus tractus solitarius, brainstem/pontine catecholaminergic neurons in the ventrolateral medulla and the locus coeruleus, respectively, receive sensory visceral input (Herman and Cullinan, 1997). The development of animal models to study the relationship between visceral pain and stress has relied on the use of those two classes of stressors based on their primary pathogenic mechanisms: those initiated by a CNS-directed (psychosocial) stressor and those initiated by a gut-directed (physical) stressor (gut inflammation, infection) (Mayer and Collins, 2002). Of note, because of the bidirectional brain-gut interactions, secondary changes in the gut are likely to occur even if the primary target may be directed at the brain and vice versa.

Two types of visceral pain responses have been described in rodents with exteroceptive stressors models: visceral hyperalgesia and visceral analgesia. Though less described and studied the latter bears very relevant implications in the understanding of visceral pain-associated pathologies. In contrast, interoceptive stressors have been most inevitably associated with the development of stress-induced hyperalgesia.

Exteroceptive stress-induced visceral hyperalgesia

• Acute stress: Exposure to water avoidance stress (WAS) that entails rodents to stand on a small platform to avoid the aversive environment of surrounding water, was originally developed to assess stress-related alterations of gut motor function (Bonaz and Taché, 1994; Enck et al., 1989). Since then, this stressor has been largely used as a form of psychological stressor to assess modulation of visceral pain (Larauche et al. 2010). Reports indicate that male Wistar exposed to WAS for 1h develop a delayed visceral hyperalgesia to CRD, appearing 24h later (Schwetz et al., 2004a). Interestingly, exposure to partial restraint stress for 2h, a stressor with stronger psychological component than WAS, was found to induce an immediate hyperalgesia to CRD in male (Gué et al., 1997) and female Wistar rats (Rosztoczy et al., 2003), even though this hyperalgesia was not reproduced in male Wistar rats in a more recent work by the same group indicative of sex difference in the response (Rosztoczy et al., 2003). Transient stressors generally trigger adaptive responses and this model has good face validity in mimicking stress-related hypersensitivity to CRD as reported in IBS patients. However it does not show good construct validity, as in clinical settings, it is most commonly the exaggerated or chronic activation of the stress system, particularly in vulnerable individuals, which is responsible for the detrimental effects on the body, including the viscera (Chrousos, 2009).

• Chronic mild stress (CMS) model: Convergent reports established that daily chronic stress predicts the intensity and severity of subsequent symptoms in IBS patients (Bennett et al., 1998; Chang, 2004; Choung et al., 2009; Elsenbruch et al., 2010b; Elsenbruch, 2011; Lackner et al., 2010). Therefore to better mimic this feature, a variety of rodent models involving chronic intermittent exposure to stress have been recently developed. One of the first chronic stress models to be adapted to the study of visceral hypersensitivity was the repeated exposure to psychological stress of WAS (Söderholm et al., 2002; Yang et al., 2006). Initial studies using this model indicate that male Wistar rats exposed to 10 consecutive days of WAS for 1 h daily developed visceral hypersensitivity to CRD (Bradesi et al., 2005; Hong et al., 2009) lasting up to 30 days after the end of the stress. In these studies, the visceral pain response was monitored using EMG recording that entails surgical implantation of electrodes and subsequent single housing of animals (Bradesi et al., 2005). However when naïve male and female Wistar rats were exposed to a similar WAS schedule, they developed visceral analgesia to CRD as monitored by intraluminal colonic solid-state manometry (Larauche et al., 2010b). Similarly, in C57Bl/6 mice, chronic WAS has been described to induce visceral hyperalgesia (Larauche et al., 2010a), visceral analgesia (Larauche et al., 2010a) or to have no influence on the VMR (Larsson et al., 2009) depending upon preconditions (surgery, housing conditions) associated with the method of recording of VMR (Larauche et al., 2010a). Therefore, the impact of repeated mild stress such as WAS in modulating visceral pain response is largely influenced by the basal state condition of the animals before applying the repeated stressor [see *Exteroceptive stress-induced visceral analgesia* and (Larauche et al., 2010a)]. Furthermore, exposure to homotypic stressors leads to habituation associated with the recruitment of endogenous mediators such as oxytocin (Zheng et al., 2010) and endocannabinoids (Patel and Hillard, 2008) which have been found to modulate visceral sensitivity (Black et al., 2009; Sanson et al., 2006). In that context, heterotypic stress models using different and alternating types of stressors have been more recently developed. Male Wistar rats exposed intermittently to a

combination of cold restraint stress, WAS or forced swimming (one stressor per day for 9 consecutive days) were found to develop visceral hypersensitivity at 8h but not at 24h or 7 days after the end of the last stressor (Winston et al., 2010). The use of more complex and long lasting heterotypic stressors including 2–3 stressors per day for up to 35–40 days (Seo et al., 2010; Tagliari et al., 2010) causes behavioral changes in rodents that parallel symptoms of depression (Gamaro et al. 2008; Ni et al. 2008; Wilner 2005; Katz and Hersh 1981). This later CMS model may display strong construct validity in the context of subset of IBS patients presenting depression symptoms (Folks, 2004) when sustained alterations in visceral sensitivity will be established in these models. Of note, the chronic mild stress model can be difficult to be characterized and be reproducible as a number of pre-existing variables may affect the response (Willner, 1997). Specifically, the strain and sex of the animal, the extent of single housing before the beginning of the procedure or even diurnal variation in sensitivity to stress seem to have major influence on the impact of CMS on animals exposed to it and the end point parameters measured (Willner, 1997). Variety within the CMS schedule appears critical to prevent or delay the habituation of rodents to the stressor, which has been shown to occur rapidly when an homotypic stressor is presented repeatedly (Babygirija et al., 2010; Griffiths et al., 1992; Muscat and Willner, 1992; Zheng et al., 2010). All of these aspects could also potentially affect the influence of CMS on the visceral pain response, as recently evaluated (Larauche et al., 2010a).

• Neonatal maternal separation stress model: Early life events and childhood trauma by biopsychosocial factors (neglect, abuse, loss of caregiver or life threatening situation) enhance the vulnerability of individuals later in life to develop affective disorders (depression, anxiety, emotional distress) and put them at a greater risk for development of IBS (Elsenbruch, 2011; Videlock et al., 2009). Early stress/childhood trauma is mimicked in rodents by isolating the pups from the dam for 2–3 hours per day during the first 2 weeks after birth from postnatal day 1–2 to postnatal day 14 (Barreau et al., 2007b; O'Mahony et al., 2011; Plotsky and Meaney, 1993; Rosztoczy et al., 2003). Maternal care in rodents affects the function of the HPA axis, and the development of both cognitive and emotional functions (Fish et al., 2004). By disrupting the normal pup-mother interaction and thereby affecting the quality of the maternal care, neonatal maternal separation stress results in permanent changes in pups' CNS, documented at the level of gene expression, neurochemistry, electrophysiology, and morphology (Szyf et al., 2007). At adulthood, rats previously subjected to neonatal maternal separation exhibit visceral hypersensitivity to CRD in basal conditions which is further exacerbated by exposure to an acute stressor (WAS; 1h) (Barreau et al., 2004; Coutinho et al., 2002). Interestingly, the protocol of separation, removal of all pups from home cage (type M) or separation of half of littermates (type P) was found to differentially affect the visceromotor responses of pups at adulthood in a sex-dependent manner (Rosztoczy et al., 2003). Under basal conditions, male exposed to type M and females exposed to both type M and P developed visceral allodynia and hyperalgesia to CRD (Rosztoczy et al., 2003). In males, an additional acute stress did not modify the VMR to CRD, while females exposed to acute WAS (1h) exhibited an exacerbated VMR (Rosztoczy et al., 2003). This model which has both face (visceral hypersensitivity) and construct (early life events induce long term changes in gut function) validity is a relevant model in the context of subset of IBS patients with history of early life traumatic events.

• Genetic models of chronic stress: Anxiety is a well established co-morbid condition in a subgroup of IBS patients (Folks, 2004; Lee et al., 2009; Thijssen et al., 2010). A study used three strains of rats known to have varying levels of baseline anxiety as determined by the acoustic startle response and open-arm exploration in the elevated plus-maze assay: high-anxiety Wistar–Kyoto rats and low-anxiety Sprague-Dawley and Fisher-344. They demonstrated that high-anxiety rats had increased VMR to CRD compared to low-anxiety

animals suggesting a direct link between anxiety and visceral hypersensitivity (Gunter et al., 2000). In addition, compared to low-anxiety rats, the sensitivity of high-anxiety rats was highly exacerbated by peripheral sensitization of the colon with a small dose of acetic acid (Gunter et al., 2000). Genetic models that blocked chronically the stress pathways by deleting CRF_1 receptors showed a decrease in anxiety and colonic sensitivity to colorectal distention (Trimble et al., 2007). Chronic stress relying on alterations of the CRF system such as CRF over-expressing mice (Million et al., 2007b) are available and could be useful to study IBS-like manifestations, but the visceral sensitivity of those transgenic animals has not been assessed yet. New promising genetic models with more selective conditional and/or region-targeted genetic manipulations including RNAi gene silencing technology to modify CRF-related genes are continuously developed (Bakshi and Kalin, 2000; Delic et al., 2008 Deussing and Wurst, 2005; Kimura et al., 2010; Kolber et al., 2010; Lu et al., 2008). These models will be suitable to explore specific stress circuitries in the context of chronic stress-related visceral pain modulation which so far is lagging behind.

• Post-traumatic stress disorder model: There is evidence of increased prevalence of GI symptoms and IBS in post-traumatic stress disorder sufferers including women veterans (Cohen et al., 2006; Drossman et al., 1990; Irwin et al., 1996; Savas et al., 2009; White et al., 2010). Clinical and experimental studies indicate that exposure to an uncontrollable stressor can induce an alteration in the behavioral, autonomic, and neuroendocrine responses to subsequent stressors. In rats, treatment with a relatively short-lasting session of shocks or a social confrontation with a predator or aggressive conspecific animals induces long-lasting (weeks–months) conditioned fear-responses to trauma-related cues, and a generalized behavioral sensitization to novel stressful stimuli that persists or grows stronger over time (Rau et al., 2005; Stam et al., 1997; Stam, 2007; Wang et al., 2008a). Repetitive balloon distention of the distal colon causes increased cardiovascular $$`pseudoaffective' reflexes in pre-shocked rats compared to controls, 2 weeks after a single session of foot shocks (Stam, 2007). Interestingly, female rats appear to show a different pattern of sensitized behavioral responsiveness to the same challenge, possibly pointing to differential alterations in the neuronal substrates involved (Stam et al., 2002). Whether these sex differences in behavior translate into sex differences in visceral sensitivity has not been assessed yet. These rodent PTSD models mimic clinical features (stress-related visceral hypersensitivity) of IBS and have a good construct validity, relevant for a subset of IBS patients with post-traumatic stress disorder. As the visceral pain alterations observed in this paradigm of uncontrollable stress model have been mainly characterized by one group of investigator, the reliability of the model however needs further independent confirmation.

Exteroceptive stress-induced visceral analgesia—While extensively described in somatic pain (Butler and Finn, 2009), activation of descending inhibitory pathways in stress-related visceral responses has only been reported in a few studies. Opioids have been implicated in descending inhibition of visceral sensitivity following stress as evidenced by the fact that naloxone unmasked WAS-induced hyperalgesia to repeated phasic CRD in normal rats and exacerbated the pain response to CRD in maternally-separated rats (Coutinho et al., 2002). In another study, a visceral analgesic response was observed 6h after exposure to an acute session of WAS in wild-type mice and Sprague-Dawley rats, with males exhibiting stronger analgesia than females (Gui et al., 2004). This visceral analgesia was shown to be dependent on the activation of neurotensin signaling pathways, as it is no longer observed in neurotensin deficient mice. Likewise using pharmacologic approach, the intravenous administration of a neurotensin receptor antagonist unmasked the visceral hyperalgesia in male rats and to a much greater extent in female rats (Gui et al., 2004). In another experimental model, a daily short period (15 min) of separation from post natal day 2 to 14 decreased VMR to phasic CRD performed immediately after WAS as well as

prevented the development of hyperalgesia 24h after WAS in adult male Long-Evans rats (Schwetz et al., 2005). These data suggest a potential alteration of endogenous pain-modulatory systems by this mild maternal separation stress (Schwetz et al., 2005). Similar findings in adult rats have been recently reported, such that chronically handled rats develop visceral hypoalgesia in response to CRD that becomes significant 7 days after the last handling (Winston et al., 2010). However, the underlying mechanisms and potential implication of this visceral analgesia were not discussed by the authors (Winston et al., 2010).

Interestingly, we recently demonstrated that mice repeatedly exposed to WAS (1h/day) for 10 consecutive days exhibit a differential profile of VMR to CRD 24h after the last session of stress depending on the basal status of the animal before WAS, in particular the context in which they are housed and method used to monitor visceral pain. Mice that had undergone surgery for the placement of EMG electrodes on abdominal wall and were subsequently single housed to avoid deterioration of implanted electrodes by cage-mate, developed visceral hyperalgesia in response to repeated WAS while mice tested for visceral pain using the non-invasive solid-state intraluminal pressure recording and kept group housed developed a strong visceral analgesia under otherwise similar conditions of chronic WAS (Larauche et al., 2010a). Recent reports suggest that previous injury or exposure to opioids in male rats can switch stress influence on pain responses from analgesia to hyperalgesia (Rivat et al., 2007). Furthermore, paw incision in male Sprague-Dawley rats was shown to induce a long lasting visceral hyperalgesia (Cameron et al., 2008). Together these data point to the state of animals (naïve vs surgery), its social environment (group housing vs single housing, cage enrichment or not), the handling by the investigator, the methods used to record its visceromotor responses (EMG requiring surgery vs manometry not requiring surgery), as well as its sex can significantly affect the response to exteroceptive stressors and should be carefully considered and weighed in the design, conduct and interpretations of the studies addressing the influence of stress on visceral sensitivity in experimental animals. Based on recent clinical findings demonstrating that IBS patients have compromised engagement of the inhibitory descending pain modulation systems (Berman et al., 2008; Coffin et al., 2004; Piche et al., 2010; Song et al., 2006; Wilder-Smith et al., 2004), gaining a deeper understanding of the mechanisms involved in the expression of stress-induced visceral analgesia or lack thereof are promising avenues to explore that may lead to new therapeutic targets for IBS. Therefore the use of non-invasive methods of monitoring VMR that alleviates the surgical and housing impact on repeated stress modulation of visceral pain represents a step forward to gain insight into the underlying mechanisms in particular the neural substrates and neurochemistry of stress-related analgesia as established in the somatic field (Butler and Finn, 2009).

Interoceptive stressors and visceral hyperalgesia

• Neonatal inflammation/neonatal pain models: The newborn's gut may be exposed to a variety of factors resulting in mucosal inflammation and tissue irritation. Daily colon irritation during the neonatal period (days 8–21) either in the form of daily noxious colorectal distention (CRD) (two 60 mmHg-60 s distensions separated by 30 min of rest) or by performing daily intracolonic injection of mustard oil (5%), increases pain behavior to CRD from postnatal week 5 up to postnatal week 12 (Al-Chaer et al., 2000; Lin and Al-Chaer, 2003). These findings suggest that two different perturbations of the intestinal homeostasis in early life (mechanical or chemical irritation) can result in permanent central sensitization initiated and partly maintained by peripheral afferent input sensitized by neonatal events (Al-Chaer et al., 2000; Lin and Al-Chaer, 2003). The model has both face (visceral hypersensitivity) and construct validity (long lasting, permanent sensitization of dorsal horn neurons) and could apply to a subset of IBS patients, even though no

longitudinal studies exist to show that gut irritation in early life is a risk factor for IBS development at adulthood (Mayer and Collins, 2002).

• Intestinal infection: post-infectious IBS model: In approximately 10% of patients with IBS, the onset of symptoms began with an intestinal infectious illness (Collins et al., 1999). Prospective studies have shown that 3% to 36% of enteric infections lead to persistent new IBS symptoms depending on the infecting organism. In addition, the co-existence of adverse psychological factors at time of infection is also an important determinant to the susceptibility to develop post-infectious IBS (Spiller and Garsed, 2009b). While viral gastroenteritis seems to have only short-term effects, bacterial enteritis and protozoan and helminth infections are followed by prolonged post-infectious IBS (Spiller and Garsed, 2009b). Long-lasting visceral hyperalgesia has been observed in mice after transient intestinal inflammation induced by *Trichinella spiralis* infection (Bercik et al., 2004; Long et al., 2010) or in rats infected by *Nippostrongylus brasiliensis* (McLean et al., 1997). Although the vast majority of human post-inflammatory hypersensitivity symptoms are observed after bacterial infection (*Campylobacter, Shigella, Salmonella* or *Escherichia coli* infections), no animal model of hypersensitivity postbacterial infection has been developed yet. For instance mice infected with *Citrobacter rodentium*, an attaching-effacing murine enteropathogen similar in its mechanisms of infection to enteropathogenic *E. coli*, do not spontaneously develop visceral hypersensitivity symptoms (Vergnolle, 2008). These models of nematode parasites in rodents have however good construct and face validity in that they show that long-term immune modulation of smooth muscle and enteric nervous system can result in persistent altered gut motility and visceral hypersensitivity.

• Noninfectious intestinal inflammation: post-inflammatory IBS model: Despite some controversies on the origin of the symptoms (Keohane et al., 2010; Long and Drossman, 2010), “IBS-like” symptoms appear to be common in patients in remission from ulcerative colitis (Spiller and Garsed, 2009a). Several chemical irritants have been used to produce colonic inflammation resulting in visceral hyperalgesia in rodents. In rats, acetic acid (Burton and Gebhart, 1995), mustard oil (Ji et al., 2005; Palecek and Willis, 2003), and zymosan (Coutinho et al., 1996; Traub and Murphy, 2002) evoke short-term hyperalgesia associated with transmural tissue damage/colonic inflammation. Intracolonic trinitrobenzene sulfonic acid induces a severe colonic transmural inflammation and visceral hypersensitivity that develops at 4–5 days with the disappearance of symptoms by 14 days (Adam et al., 2006; Gschossmann et al., 2004). Interestingly, in 24% of rats there is reoccurrence of visceral hyperalgesia 16 weeks after the induction of inflammation, whereas no evidence of microscopic inflammation is observed in rat colonic tissues at that time point (Adam et al., 2006; Zhou et al., 2008). Mild non-specific colitis and acute dextran sodium sulfate (DSS)-induced colitis were associated with increased responsiveness to CRD on days 5 or 60 after the induction of colitis in male Balb/c mice while chronic DSS colitis was not (Verma-Gandhu et al., 2007). These results are in contrast with another study showing that DSS colitis failed to cause the development of visceral hypersensitivity in response to CRD at any of the observed time points after the induction of inflammation (days 5, 12, 16, 20, 30, 40 or 51 after the induction of colitis) in C57Bl/6 or Balb/c mice (Larsson et al., 2006). A number of factors may have contributed to these conflicting results among which the protocol of colitis induction (three 5 days DSS with a 15 days rest between cycles vs 5–7 days DSS-rest), the dose of DSS used (5% vs 4%) or even the sex of the animals, which was surprisingly not even mentioned in the latter study. While it is difficult to make any assumptions on the reasons for these differences, these results suggest that inflammation alone may not always lead to visceral hypersensitivity and that the type of inflammatory insult and severity determine whether this will result in the development of postinflammatory hypersensitivity (Adam et al., 2006). In most, but not all the studies (Larsson et al., 2009), previous exposure of rats and mice to psychological or psycho-social

stress was shown to enhance their susceptibility to colitis and to aggravate their colonic inflammatory response (Reber et al., 2006; Reber et al., 2008; Veenema et al., 2008) as well as to precipitate the reactivation of colonic inflammation in animals in which colitis had healed (Melgar et al., 2008; Saunders et al., 2006). Likewise, previous colitis was found to render the colon more susceptible to the effects of stress on enteric nerve function and to increase some parameters of inflammation in response to stress (Collins et al., 1996). Nevertheless, the relationship between stress, colitis and visceral pain remains controversial as stress was found to exacerbate post-inflammatory visceral hyperalgesia in rats (Liebregts et al., 2007) or either to have no effect in mice (Larsson et al., 2009).

Bile salt malabsorption underlies some forms of postinfectious IBS (Spiller, 2003). A rodent model was developed in which a bile acid deoxycholic acid instilled intracolonically daily for 3 days induces a mild, transient colonic inflammation within 3 days of administration that resolves within 3 weeks. Adult male Sprague-Dawley rats exposed to this regimen of bile acid develop a persistent visceral hyperalgesia starting after 1 week and lasting up to 4 weeks (Traub et al., 2008).

Animal models: predictive validity—Some commonly used animal models showed the modulation of visceral pain to CRD by acute or chronic stressors presenting good face and construct validity, however, their predictive validity in humans is either unknown or has been unsatisfying in clinical trials (Bradesi and Mayer, 2009; Holschneider et al., 2011; Mayer et al., 2008). The use of novel non-invasive techniques to assess visceral pain such as intraluminal colonic pressure (Larauche et al., 2009a; Larauche et al., 2010a) by allowing for the monitoring of stress-induced visceral analgesia, may open new venues to deepen our understanding of stress-related analgesic pain pathways in the viscera. Novel strategies such as identification and characterization of endophenotypes in IBS patients, followed by reverse translation of these endophenotypes for pharmacological studies in rodents, have also been recently suggested (Bradesi and Mayer, 2009; Holschneider et al., 2011; Mayer et al., 2008).

Mechanisms involved in stress-induced modulation of visceral pain

Pathological pain refers to conditions characterized by hyperalgesia and allodynia, in which maladaptive neuroplastic changes lead to persistent increased perception and responsiveness to noxious stimuli, or response to normally non-noxious stimuli. Such neuroplastic changes can occur in primary afferent terminals (peripheral sensitization) but also in the spinal cord (central sensitization) and in the brain (supraspinal pain modulation) or in descending pathways that modulate spinal nociceptive transmission. Such alterations in the processing of sensory information are all considered as possible mechanisms of visceral hypersensitivity in IBS patients (Azpiroz et al., 2007; Sengupta, 2009).

Stress and peripheral sensitization: a role for the CRF system, mast cells, gut microbiota and ion channels—A key role for peripheral CRF signaling in the development and expression of visceral pain is well documented by several reports in both humans and rodents (La et al., 2008; Larauche et al., 2009a; Lembo et al., 1996; Nozu and Kudaira, 2006; Sagami et al., 2004; Taché and Brunnhuber, 2008; Tayama et al., 2007). Converging evidence support the involvement of peripheral CRF^1 receptors in these effects. Peripheral injection of CRF induces visceral hypersensitivity to CRD (La et al., 2008), an effect reproduced by the intraperitoneal administration of the selective CRF^1 agonist, cortagine in rats and mice (Larauche et al., 2009a) while intraperitoneal injection of selective (urocortin 2) or preferential (sauvagine) CRF^2 agonists, reduced visceromotor response to CRD in rats (Million et al., 2005; Million et al., 2006). In addition, the visceral hyperalgesia induced by peripheral injection of cortagine in rats is abolished by peripheral,

but not central, administration of the non selective CRF receptor antagonist astressin (Larauche et al., 2009a). Likewise under conditions of repeated exposure to WAS for 10 days, we found that peripheral administration of the peptide CRF^1/CRF^2 receptor antagonist astressin before each stress session prevented the development of visceral hyperalgesia supporting the participation of a peripheral component to the development of visceral hypersensitivity (Larauche et al., 2008). Of translational relevance intravenous administration of a non-selective and peripherally-restricted CRF receptors antagonists, α-helical $CRF^{9–41}$ or astressin was reported to reduce visceral hyperalgesia in diarrhea-predominant IBS patients subjected to colonic electrical stimulation (Sagami et al., 2004; Tayama et al., 2007).

Stress and peripheral administration of CRF induce mast cells degranulation in the colon in experimental animals and humans (Barreau et al., 2007a; Wallon et al., 2008)which can in turn lead to the development of visceral hypersensitivity via the release of several preformed or newly generated mediators namely histamine (Barbara et al., 2007; Cenac et al., 2007; van den Wijngaard et al., 2010), tryptase (Cenac et al., 2007), prostaglandin E^2 (Gold et al., 2002), nerve growth factor (NGF) (Barreau et al., 2004) that can activate or sensitize sensory afferents (Sengupta, 2009; van den Wijngaard et al., 2009). It is now well established that stress can disrupt the intestinal epithelial barrier which may increase the penetration of soluble factors (antigens) into the lamina propria, and lead to nociceptors sensitization (Barbara et al., 2007; Piche et al., 2009). Increased intestinal permeability appears as a prerequisite for the development of visceral hypersensitivity in both humans and rodents (Ait-Belgnaoui et al., 2005; Piche et al., 2009; Zhou et al., 2009). Alterations of epithelial permeability following stress involves the activation of the peripheral CRF system and may (Demaude et al., 2006; Santos et al., 2001; Söderholm et al., 2002; Vicario et al., 2010; Yu and Perdue, 2001) or may not be dependent from mast cell activation (Demaude et al., 2006; van den Wijngaard et al., 2009) in a time-dependent manner.

Lastly, there is mounting evidence that stress can affect the intestinal and fecal microbiota of rodents which display changes in composition, diversity and number of gut microorganisms (Bailey et al., 2011; Bailey et al., 2010; O'Mahony et al., 2009). These alterations in the microbiota can in turn have significant impact on the host and affect his behavior, visceral sensitivity and inflammatory susceptibility (Bercik, 2011; Collins and Bercik, 2009; Cryan and O'Mahony, 2011; Heijtz et al., 2011; Rhee et al., 2009).

Stress-induced intestinal epithelial permeability or intestinal injury or inflammation can lead to the sensitization of peripheral terminals. Three mechanisms can account for this sensitization: change in tissue properties, change in transduction process (increased release of mediators) or changes in the properties of protein/protein complexes underlying stimulus transduction (receptors sensitivity or number). In response to an injury such as inflammation, the intestinal mucosa leads to the release of chemical mediators (ATP, bradykinin, prostaglandins) which can directly stimulate afferent neuron terminals but also promote the release of algogenic substances (proteases, histamine, SP), serotonin, NGF and prostaglandins), leading to the amplification of the afferent chemical or mechanical stimulus (Blackshaw et al., 2007; Chung et al., 2009; Lin and Al-Chaer, 2003; Mantyh, 2002; Robinson and Gebhart, 2008; Vergnolle, 2010; Winston et al., 2010). This peripheral sensitization is mediated by a number of ion channels widely expressed in colonic afferents (Cregg et al., 2010; Holzer, 2001; Jones, III et al., 2005; McRoberts et al., 2001). Among these, the N-methyl-D-aspartate receptor (NMDA) (McRoberts et al., 2001), proteinase-activated receptor, PAR2 (Cenac et al., 2007), transient receptor potential vanilloid 1 (TRPV1) (Ravnefjord et al., 2009; Winston et al., 2007; Yu et al., 2010) and TRPV4 (Cenac et al., 2010), transient receptor potential ankyrin 1 (TRPA1) (Cattaruzza et al., 2010; Yu et al., 2010), purinergic receptor P2X (Holzer, 2001), neurokinin receptor 1 (NK1)

(Greenwood-Van Meerveld et al., 2003) and acid-sensing ion channels (ASICs) (Page et al., 2004) have all been found to be associated with visceral hypersensitivity.

Spinal cord plasticity and glia activation: role in the central processing of peripheral pain perception—Once peripheral sensitization has developed, it can in turn activates the release of spinal cord mediators. Among them, ASIC1A was recently shown to be increased in sensory neurons of rats exhibiting hypersensitivity in response to repeated colonic butyrate enemas (Matricon et al., 2010). Similarly, NK1 receptors were found to be upregulated in the spinal cord of chronically stressed rats and to mediate the development of visceral hypersensitivity (Bradesi et al., 2009b; Bradesi et al., 2006; Gaudreau and Plourde, 2003). In conscious animals subjected to psychological chronic stress, the decrease in the somatic mechanical nociceptive threshold was shown to be related to the activation of cholecystokinin (CCK)-dependent descending facilitatory nociceptive pathways (Rivat et al., 2007), a phenomenon which could also explain visceral hypersensitivity (Friedrich and Gebhart, 2000; Friedrich and Gebhart, 2003). Increase in growth factors such as NGF (Chung et al., 2007) or brain-derived neurotrophic factor (BDNF) (Chung et al., 2009) as a result of stress exposure in rodents has also been established to play a key role in mediating visceral hyperalgesia. Phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK) in the spinal cord induced by the binding of neurotrophins to their specific tyrosine kinase receptors or by neuronal activity leading to glutamate release and binding to its ionotropic and metabotropic receptors (Cruz and Cruz, 2007), are known to be nociceptive-specific signaling pathways and their upregulation is associated with visceral hyperalgesia (Million et al., 2006; Zhang et al., 2009).

Very recently, another potential mechanism through which spinal sensitization may occur in response to stress has been suggested in the form of spinal cord glia activation. While this phenomenon is now considered an important component in the development and maintenance of allodynia and hyperalgesia in various models of chronic pain, including neuropathic pain and pain associated with peripheral inflammation, it is only recently that the possibility of spinal cord glia changes in relation with visceral hypersensitivity and stress-induced visceral hypersensitivity have been addressed (Bradesi, 2010). One study using a model of visceral hypersensitivity induced by neonatal colonic irritation showed an increase spinal immuno-reactivity for OX42 (indicating microglia proliferation) in sensitized rats compared to controls (Saab et al., 2004). Visceral hypersensitivity to CRD in these animals was blocked by an acute treatment with minocycline, a microglia inhibitor. Likewise, chronic WAS in male Wistar rats increases p38 phosphorylation in OX42 positive cells, and this effect was blocked by treatment with minocycline (Bradesi et al., 2009a). The concomitant visceral hyperalgesia exhibited by those rats was blocked by intrathecal treatment with minocycline or the p38 inhibitor SB203580, supporting a functional role of spinal microglia activation in the development of visceral hypersensitivity (Bradesi et al., 2009a). The modulatory influence exerted by spinal microglia on visceral nociception was further supported by the findings that spinal injection of the microglia activator fractalkine in naïve rats, induces visceral hyperalgesia (Bradesi et al., 2009a; Saab et al., 2004). Candidate molecules involved in glia activation signaling include neurotransmitters such as SP or glutamate, but also purinergic agents, opioids, chemokines and glucocorticoids [for review see (Bradesi, 2010)].

Glutamate uptake through spinal glutamate transporters is critical for maintaining normal sensory transmission under physiologic conditions (Liaw et al., 2005; Lin et al., 2009). A potential deficiency in glutamate reuptake by astrocytes associated with the activation of spinal cord glia (Svensson et al., 2003) has been recently suggested to play a role in the spinal sensitization and the development of visceral hypersensitivity in rats (Gosselin et al., 2010).Together, these data strongly support the concept that transmission of visceral

nociceptive signals may be enhanced in various conditions of spinal microglia activation (Tjong et al., 2010).

Supraspinal pain modulation: a fine-tuning between pain facilitation and inhibition—Various supraspinal sites are involved in the modulation of visceral pain signals. Rectosigmoid distension in humans activates sensory (insula, somatosensory cortex), and limbic and paralimbic regions (including anterior cingulate cortex and amygdala) (Tillisch et al., 2011). Many of these regions were also found to be significantly affected by colorectal distension in rats (Wang et al., 2008b; Zhang et al., 2011).

The anterior cingulate cortex mediates key emotional-aversive aspects of pain and may also have a mnemonic role in which it allows transient storage of information during pain processing (Chang, 2005; Mayer and Tillisch, 2011). The cingulate cortex contains specific subareas for integrating visceral sensation (Ladabaum et al., 2000) and has direct connections to the amygdala, periaqueductal grey, and orbitofrontal cortex (Devinsky et al., 1995). Wistar-Kyoto rats, high-anxiety rats exhibiting visceral hypersensitivity (Gunter et al., 2000) have greater prefrontal cortex activation in response to CRD compared to Sprague-Dawley (Gibney et al., 2010).

Another key limbic system structure that has been implicated in the affective component of pain is the central amygdala. It is involved in the processing of visceral information, attention, emotion and integrating the physical and psychological components of the stress response (Dayas et al., 2001). Additionally, the central amygdala plays a crucial role in the generation and development of fear and anxiety (LeDoux et al., 1988; Rosen and Schulkin, 1998). Specifically, the central nucleus of the amygdala (CeA) has been shown to facilitate the activation of the HPA axis in response to stress and increase the release of CRF, adrenocorticotropic hormone, and corticosterone (Feldman and Weidenfeld, 1998; Shepard et al., 2003). Increased glucocorticoid levels in turn upregulates CRF gene expression in neurons within the CeA and implants of corticosterone in the CeA have been found to induce visceral hypersensitivity in rodents (Greenwood-Van Meerveld et al., 2001; Myers et al., 2007; Myers and Greenwood-Van Meerveld, 2007). The interaction between the CRF signaling system in the CeA and visceral nociception has been recently reported by showing that noxious CRD increases CRF expression and p-ERK in the CeA and fos in the spinal cord (Kim et al., 2010).

The locus coeruleus is a well established target of stress, expressing CRF_1 receptors, which receives CRF innervation from nearby Barrington nucleus and increases firing in response to CRD in the same neurons responsive to central injection of CRF (Curtis et al., 1995; Kosoyan et al., 2005; Lechner et al., 1997; Reyes et al., 2007; Reyes et al., 2008; Rouzade-Dominguez et al., 2001; Valentino et al., 1993). Electrophysiological studies in anesthetized rats showed that the $CRF_{1/2}$ antagonists, $[DPhe^{12}]CRF_{12–41}$, administered into the lateral brain ventricle or microinfused into the LC, or astressin injected into the cisterna magna, and selective CRF_1 antagonist crossing the blood brain barrier, NBI 35965 given intravenously prevented LC neuronal activation and bursting activity in response to central injection of CRF and CRD at submaximal distention (40 mmHg) (Kosoyan et al., 2005; Lechner et al., 1997). In addition, peripheral injection of CRF_1 antagonist which enters into the brain, JTC-017, reduced the rise in noradrenaline levels in the hippocampus induced by CRD in rats. Bursting activity in the LC is associated with the release of noradrenaline in the cortical and limbic rostral efferent projections of the LC leading to arousal, hypervigilance and anxiogenic response (Koob, 1999; Koob and Heinrichs, 1999). Therefore these pontine sites are well positioned to coordinate gut-brain interaction with visceral information from the gut impacting on cortical and limbic activities under stress conditions and may modulate visceral pain responses (Tsuruoka et al., 2010; Valentino et al., 1999).

Thalamic relay nuclei have a key role in gating, filtering and processing sensory information en route to the cerebral cortex and are subject to similar activity-induced plasticity processes as the spinal cord (Kuner, 2010). Two modes of firing of thalamocortical neurons, tonic and burst firing, are believed to reflect the divergent states of sensory signal transmission from the thalamus to the cortex and have been shown to modulate visceral pain (Cheong et al., 2008; Ren et al., 2009). Upregulation of CRF_1 receptor in the thalamus is associated with visceral hyperalgesia in the rat model of NMS (Tjong et al., 2010).

Lastly, spinal visceral nociceptive reflexes are subject to facilitatory modulation from the RVM, providing the basis for a mechanism by which visceral sensations can be enhanced from supraspinal sites (Sanoja et al., 2010; Zhuo and Gebhart, 2002) under stress conditions associated with development of visceral hyperalgesia (Martenson et al., 2009). Compromised engagement of descending pain inhibitory pathways as observed in maternally-stressed rats may also contribute to increasing the visceral pain responses in those animals (Coutinho et al., 2002).

Sex differences in stress-induced alterations of visceral sensitivity

Female predominance in IBS patients (women to men ratio about 2:1) is consistent with an observation that women are more susceptible to stress-related disorders (Adeyemo et al., 2010; Heitkemper and Chang, 2009). A number of clinical studies have documented sex differences in the stress response and stress-induced pain modulation (Fillingim et al., 2009). However, although there is a dearth of preclinical studies assessing the effect of sex on stress-induced modulation of visceral sensitivity, most preclinical studies addressing stress-related modulation of visceral pain have been conducted in male rodents (Gui et al., 2004; Taché et al., 2005).

There is convergent evidence that sex hormones, in particular estrogens, strongly modulate the HPA axis regulation, for example estrogen receptors α and β have been shown to increase CRF gene expression (Chen et al., 2008; Mulak and Taché, 2010). Fluctuations in estrogen levels during ovarian cycle cause also changes in the serotonergic system (e.g. estrogens enhance serotonergic postsynaptic responsiveness in the brain) and interactions between the serotonergic and reproductive endocrine systems have implication in the etiology as well as treatment of stress-related disorders (Heitkemper and Chang, 2009; Linthorst, 2005; Lu et al., 2009; Mulak and Bonaz, 2004; Warnock and Clayton, 2003). Sex hormones have been shown to significantly affect visceral sensitivity in rodents (Aloisi et al., 2010; Holdcroft et al., 2000; Ji et al., 2008; Sapsed-Byrne et al., 1996; Taché et al., 2005). Addressing the influence of sex in the modulation of visceral pain by stress appears critical to find novel therapies (Adeyemo et al., 2010; Ouyang and Wrzos, 2006).

Therapeutic interventions targeting stress reduction: outcome in IBS

The modulatory role of stress-related psychological factors, emotional state, and established brain-gut interactions in the pathophysiology of IBS (Mulak and Bonaz, 2004; Mayer and Tillisch, 2011), has been confirmed by the encouraging outcome of nonpharmacological approaches by treatment modalities using a broad range of evidence-based mind-body interventions such as psychotherapy, cognitive behavioral therapy, hypnotherapy, relaxation exercises or mindfulness mediation (Kearney and Brown-Chang, 2008; Palsson and Drossman, 2005; Whorwell, 2009). Different forms of therapies are focused on teaching better stress coping strategies, both at a cognitive level (catastrophic or self-defeating thoughts) and at a behavioral level (problem solving, especially interpersonal problems) (Blanchard et al., 2007; Whorwell, 2009). The symptomatic improvement seems to result from the modulation of stress response, restoration of the autonomic system balance, and changes in the brain activation pattern in response to visceral stimuli. Several well-designed

IBS studies of hypnotherapy, including randomized, controlled trials, have shown substantial long-term improvement not only of gastrointestinal symptoms but also of anxiety, depression, quality of life, disability and excess healthcare (Kearney and Brown-Chang, 2008). However, a few recent large-scale randomized controlled trials of cognitive behavioral therapy have failed to show significant advantages in reduction of gastrointestinal symptoms in comparison of psychological control conditions (Blanchard et al., 2007; Boyce et al., 2003; Drossman et al., 2003). The results of study by Blanchard et al. (Blanchard et al., 2008) suggest that there is rather a reciprocal than a causal relation between stress and symptoms. Thus, as described by Miller and Whorwell (Miller and Whorwell, 2009), more direct targetting to gastrointestinal symptoms including abdominal pain, such as with gut-directed hypnotherapy might be more effective.

In addition to psychological mind-body interventions, clinical trials confirm the effectiveness of centrally acting pharmacological interventions such as with antidepressants, and anxiolytics, or combination of drugs from both groups in the treatment of chronic pain disorders (Palsson and Drossman, 2005; Verdu et al., 2008; Warnock and Clayton, 2003). Tricyclic antidepressant amitriptyline has been shown to reduce brain activation during rectal distension in IBS patients, but only during mental stress (Morgan et al., 2005; Thoua et al., 2009). Based on the reduced activation in cognitive and affective cortical regions, it was postulated that amitriptyline improves symptoms in IBS due to a CNS effect rather than a peripheral one, most likely reducing the affective and hypervigilance component to pain or stress-related exacerbation of symptoms (Morgan et al., 2005). Another antidepressant – fluoxetine (selective serotonin reuptake inhibitor) reduces abdominal pain in IBS, but only in patients displaying hypersensitivity to rectal distension, thus adequate patients selection would determine treatment effectiveness (Kuiken et al., 2003) (Table 1).

As serotonin plays a critical role not only in stress-related alterations of gut motility, visceral sensitivity, and intestinal secretion (ligands of 5-HT_3 and 5-HT_4 receptors belong to the most effective treatments in IBS), but also in the pathophysiology of many extra-intestinal stress-related disorders frequently associated with IBS such as anxiety, depression or chronic pain syndromes (e.g., migraine headaches) and therefore points to the development of efficacious and safe serotonergic agents to alleviate IBS symptoms (De Ponti and Tonini, 2001; Maneerattanaporn et al., 2011). For example, buspirone, a partial 5-HT_1 receptor agonist, with anxiolytic activity displays analgesic effect in the CRD-induced visceral pain model in rats (Sivarao et al., 2004). Similarly, robalzotan tartrate monohydrate (AZD7371), a selective competitive 5-HT_{1A} receptor antagonist, initially developed as a potential treatment for depression and anxiety disorders significantly reduces the visceromotor response to CRD in rats (Lindström et al., 2009). However, the clinical development of AZD7371 has been discontinued due to severe adverse events including hallucinations, and the inability to demonstrate significant efficacy in IBS patients compared with placebo (Drossman et al., 2008). Recently, a new piperazinylpyridine derivative, TZB-20810 with mixed 5-HT_{1A} agonistic and 5-HT_3 antagonistic activities has been proposed as a promising drug in the treatment of IBS (Asagarasu et al., 2009).

Data from preclinical and clinical studies on triptans, 5-$HT_{1B/D}$ agonists used for migraine treatment revealed that, although they do not exert anxiolytic effect, can influence the perception of colorectal and gastric distension (Mulak and Paradowski, 2006; Tack et al., 2000; Vera-Portocarrero et al., 2008). Furthermore, based on experimental data, the role of 5-HT_{2B} receptor antagonist (RS-127445), probably involved in the descending pain modulatory pathway, has been suggested as a potential therapeutic target in IBS (O'Mahony et al., 2010).

Apart from serotonergic agents, some other compounds including $GABA_B$ receptor agonist, baclofen and the positive allosteric modulator CGP7930 (Brusberg et al., 2009b) as well as the α_2-receptor agonist, clonidine (Bharucha et al., 1997a; Brusberg et al., 2008), reveal sedative or anxiolytic-like action on stress-related behavior along with analgesic effect on visceral pain. Preliminary data suggest that anxiolytic activity of γ-aminobutyric acid-ergic agent (gabapentin) and α2δ ligand (pregabalin) may be also efficient in reducing central sensitization in hyperalgesia (Camilleri and Andresen, 2009) as shown in experimental model (Million et al., 2007a). New centrally acting agents providing analgesic effects include dextofisopam (2,3-benzodoazepine receptor modulator) and quetiapine (atypical antipsychotic agent ameliorating anxiety, sleep disturbances and augmenting the effect of antidepressants) (Camilleri, 2010).

The central as well as peripheral role of CRF_1 receptors in stress-related visceral pain response has been intensively studied over the past decade based on convergent preclinical data and phase I clinical studies showing blockade of acute and chronic stress-related visceral hyperalgesia using selective small molecule CRF_1 antagonists that cross the blood brain barrier such as antalarmin, NBI 35965, JTC-017, CP-154,526 or GW876008 (Martinez and Taché, 2006; Taché and Brunnhuber, 2008)(Table 1). However, despite encouraging data from preclinical animal models of IBS, recently published results from a randomized, double blind, placebo controlled, crossover study did not confirm the effectiveness of GW876008 in IBS patients regarding the global improvement scale, daily selfassessment of pain/discomfort or individual lower gastrointestinal symptoms (Dukes et al., 2009). Currently, there are several CRF_1 receptor antagonists undergoing clinical trials (Phase II/III) for depression (GSK561679, GW876008 and pexacerfont), IBS and anxiety (GSK561679 and GW876008) (Zorrilla and Koob, 2010). The results of these trials should provide definitive conclusion as to whether this is still a viable target.

Growing evidence has accumulated suggesting that the endogenous cannabinoid system is also an important signaling system playing a key role in mediating and/or modulating behavioral, neurochemical, neuroendocrine, neuroimmune and molecular responses to stress (Finn, 2010). Activation of cannabinoid receptors (CB_1, CB_2, and G protein-coupled receptor GPR_{55}) induces analgesic effect in several experimental models, including visceral pain originating from the gastrointestinal tract (Izzo and Sharkey, 2010; Sanson et al., 2006). The allodynic and hyperalgesic responses induced by a selective CB_1 receptor antagonist suggest the existence of endogenous cannabinoid tone and the activation of CB_1 receptors during noxious CRD in rodents (Brusberg et al., 2009a). However, in a recent clinical trial the mixed CB_1/CB_2 receptor agonist delta-9-tetrahydrocannabinol (dronabinol) has failed to reduce visceral perception to rectal distension in healthy volunteers and IBS patients (Klooker et al., 2011). These initial data dampen the potential use of centrally acting cannabinoid agonists as therapeutic agents to treat IBS.

While opioids may also exert antidepressant- and anxiolytic-like effects, their clinical use for gastrointestinal conditions has been limited by CNS side effects. A new generation of peripheral opioid receptor ligands free of these side effects has been developed (Healy, 2009; Moultry et al., 2011). Interestingly, in a recent study an on-demand dosing schedule of asimadoline, a peripheral kappaopioid agonist, was not effective in reducing the severity of abdominal pain in IBS, but modestly reduced the anxiety score (p = .053) (Szarka et al., 2007).

Tachykinin neuropeptides including SP, neurokinin A, neurokinin B and their receptors (NK1, NK2, NK3) localized in brain areas known to be implicated in stress-mechanisms, mood/anxiety regulation, emotion-processing and pain modulation and also modulating the CRF system may present another potential therapeutic targets in stress-related disorders such

as IBS (Ebner et al., 2009; Frisch et al., 2010). However, although in a pilot study in IBS patients, the NK1 receptor antagonist, ezlopitant, reduced the emotional response to rectosigmoid distension, it did not significantly decreased rectal sensitivity (Oh-Young et al., 2000).

Recent studies have pointed to CCK as being involved in stress-induced sensory hypersensitivity, through neuroinflammation in the dorsal horn of the spinal cord (Rivat et al., 2007). Whether these preclinical observations will translate as potential good therapeutic candidate in the context of anxietyinduced hyperalgesia remains to be established. The potential role of other peptide signaling pathways such as somatostatin or melatonin in the modulation of visceral pain in the context of their anxiolytic and antidepressant properties requires further studies (see Table 1).

The better understanding of a recently developed concept of the brain-gut-enteric microbiota axis and the critical interdependence between the composition and stability of the microbiota and sensorymotor function of the gut as well as stress-related behavioral changes indicate a novel approach for IBS with a use of probiotics, prebiotics, and antibiotics (Collins et al., 2009b; Rhee et al., 2009). Whether the uprising new line of investigations related to specific modulation of the enteric microbiota will open new promising strategy for stress-related disorders, in particular co-morbid aspects of functional gastrointestinal disorders such as IBS (Cryan and O'Mahony, 2011) is still to be defined.

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Abbreviations

ASICs	acid-sensing ion channels
BDNF	brain-derived neutrophic factor
ATP	adenosine triphosphate
CB	cannabinoid
CeA	central amygdala
CNS	central nervous system
CRD	colorectal distension
CRF	corticotropin releasing factor
CRF_1	CRF receptor subtype 1
CRF_2	CRF receptor subtype 2
DRG	dorsal root ganglia
DSS	dextran sodium sulfate
EMG	electromyography
ENS	enteric nervous system
ERK	extracellular signal-regulated kinases
GABA	gamma-amino butyric acid
GI	gastrointestinal

GPR	G-protein coupled receptor
5-HT	5-hydroxytryptamine
HPA	hypothalamic-pituitary-adrenal
IBS	irritable bowel syndrome
IFN	interferon
NK	neurokinin
NMDA	N-methyl-D-aspartate receptor
P2X	purinergic receptor 2X
PAR2	proteinase-activated receptor 2
PGE_2	prostaglandin E_2
PTSD	post-traumatic stress disorder
SNRI	serotoninnoradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SP	substance P
TRPA	transient receptor potential ankyrin
TRPV	transient receptor potential vanilloid
VMR	visceromotor response
WAS	water avoidance stress

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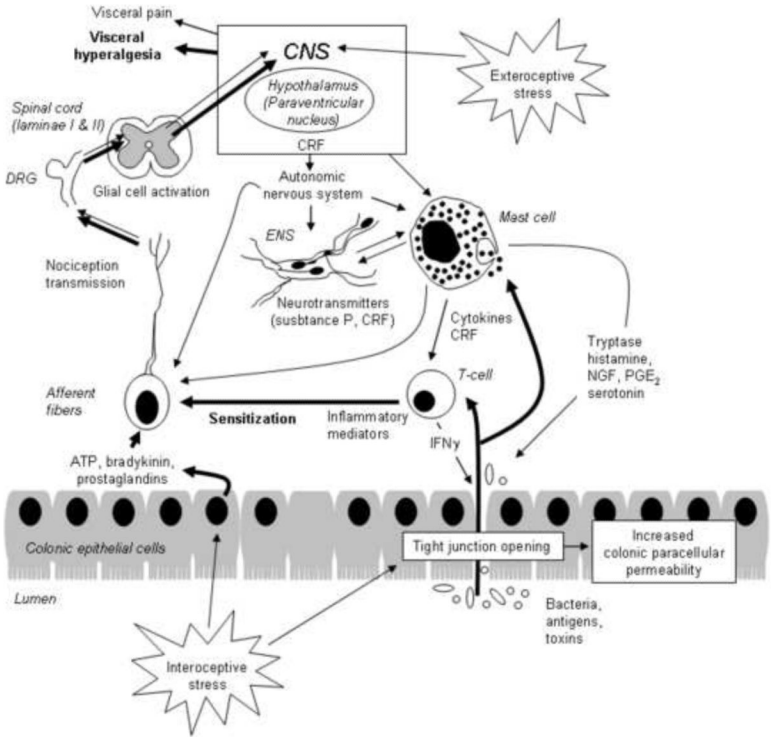

Figure 1. Putative mechanisms involved in exteroceptive and interoceptive stress-induced visceral hyperalgesia

Exteroceptive stress when perceived by the CNS, induces the activation of the paraventricular nucleus of the hypothalamus and the release of CRF centrally leading to the activation of the pituitary-adrenal axis and the release of corticosterone and catecholamines, and peripherally stimulating the ENS to release peptides (SP, CRF). These peptides stimulate mast cells degranulation and release of preformed and newly synthesized mediators (tryptase, histamine, NGF, prostaglandins, cytokines, serotonin) leading to T-cell activation and increased colonic paracellular permeability. This in turn, increases the transfer of bacteria and antigens into the mucosa, further activating mast cells and T-cells, with an increased release of inflammatory mediators that sensitize the afferent fibers to mechanical stimuli leading to the development of visceral hypersensitivity. Interoceptive stressors can induce the release of inflammatory mediators by epithelial cells (ATP, bradykinin, prostaglandins) which can directly sensitize afferent fibers or induce the additional release of algogenic substances (histamine, SP, NGF, serotonin). Sensitization of afferent nerves can lead to long term alterations in the spinal cord and hyperactivation of spinal glial cells, which once the peripheral insult or stressor is resolved can perpetuate the visceral hypersensitivity. ATP: adenosine triphosphate, CNS: central nervous system, CRF: corticotropin-releasing factor, DRG: dorsal root ganglia, ENS: enteric nervous system, IFN: interferon, NGF: nerve growth factor, PGE_2: prostaglandin E_2, SP: substance P.

Table 1

Drug class	Compounds	Effect on visceral sensation	References
Tricyclic antidepressant	Amitriptyline	Reduces brain activation in cognitive and affective cortical regions during rectal distension in IBS	(Morgan et al., 2005; Thoua et al., 2009)
Antidepressant SSRI	Fluoxetine	Reduces abdominal pain but only in patients with hypersensitivity to rectal distension	(Kuiken et al., 2003)
	Citalopram	Reduces abdominal pain in IBS patients with coexisting depression	(Ford et al., 2009)
Antidepressant SNRI	Venlafaxine	Increases compliance, decreases tone and sensation in healthy humans	(Chial et al., 2003)
5-HT$_1$ agonist	Buspirone	Induces analgesic effect in the CRD model in rats	(Sivarao et al., 2004)
		Not significantly alters colonic compliance, tone, or sensation in healthy humans compared to placebo	(Chial et al., 2003)
	Robalzotan tartrate monohydrate (AZD7371)	Induces analgesic effect in the CRD model in rats	(Lindström et al., 2009)
		Ineffective in clinical trial in IBS	(Drossman et al., 2008)
5-HT$_3$ antagonist	Alosetron	Inhibits stress-induced visceral hyperalgesia in a rat model	(Bradesi et al., 2007)
		Increases colonic compliance in IBS patients	(Delvaux et al., 1998)
		No significant effect on gastrointestinal transit or rectal sensory and motor function in IBS	(Thumshirn et al., 2000)
		Reduces symptom ratings, emotional stimulus ratings as well as regional blood flow in various limbic structure including the amygdala	(Mayer et al., 2002)
GABA$_B$ receptor agonist	Baclofen and CGP7930 (positive allosteric modulator)	Exert anxiolytic-like action on stress-related behavior and inhibit visceromotor response to CRD in rats	(Brusberg et al., 2009b)
GABA analogue	Gabapentin	Reduces rectal mechanosensitivity and increases rectal compliance in diarrhea-predominant IBS patients Reduces central sensitization?	(Lee et al., 2005)
$\alpha_2\delta$ ligand	Pregabalin	Reduces the viscerosomatic and autonomic responses associated with CRD-induced visceral pain and increased colonic compliance in rats	(Million et al., 2007a; Ravnefjord et al., 2008)
		Reduces visceral sensation in hypersensitive IBS patients Reduces central sensitization?	(Houghton et al., 2007b)
2,3-benzodiazepine receptor modulator	Dextofisopam	Reduces visceral pain in the CRD animal model but not in preliminary study in IBS patients	(Leventer et al., 2008)

Drug class	Compounds	Effect on visceral sensation	References
α_2-adrenergic receptor agonist	Clonidine	Inhibits visceromotor response to CRD in rats	(Brusberg et al., 2008)
		Induces sedative and analgesic response during CRD in humans	(Bharucha et al., 1997b)
Nonselective CRF receptor antagonist	α-helical CRF	Reduces colonic distension-induced sensitivity in IBS patients	(Sagami et al., 2004)
	Astressin	Attenuates post-inflammatory visceral hypersensitivity	(La et al 2008)
CRF_1 receptor antagonist	Antalarmin NBI 35965 JTC-017 CP-154,526	Blocks stress-induced visceral sensitivity in rats	(Greenwood-Van Meerveld et al., 2005; Million et al., 2003; Million et al., 2005)
	GW876008	Not effective in IBS patients regarding global improvement and pain/discomfort	(Dukes et al., 2009)
μ-opioid agonist	Fentanyl	Prevents the sensitizing response to repetitive CRD in mice	(Arvidsson et al., 2006)
κ_1-opioid agonist	Fedotozine	Reduces visceral hypersensitivity in a model of colonic irritation Increases thresholds of perception during CRD in IBS patients	(Delvaux et al., 1999; Langlois et al., 1997)
	Asimadoline	Not effective in reducing severity of abdominal pain in IBS, but has a tendency to reduce the anxiety score	(Szarka et al., 2007)
Nociceptin receptor (ORL-1) agonist	Nociceptin/Orphanin FQ	Injected peripherally, reduces visceral hypersensitivity triggered by inflammation or stress in rats	(Agostini et al., 2009)
CB_1 receptor agonist	SAB-378	Inhibits pain-related responses to repetitive noxious CRD in rats	(Brusberg et al., 2009a)
CB_1/CB_2 receptor agonist	WIN55,212-2	Inhibits pain-related responses to repetitive noxious CRD in rats	(Brusberg et al., 2009a; Hong et al., 2009)
	Dronabinol	Failed to reduce visceral perception to CRD in healthy subjects and IBS patients	(Klooker et al., 2011)
NK1 receptor antagonist	SR140333	Diminishes the enhanced visceromotor reflex to CRD in rats	(Bradesi et al., 2006)
	Ezlopitant (CJ-11974)	Reduces the emotional response to rectosigmoid distension but does not decrease rectal sensitivity in IBS patients	(Oh-Young et al., 2000)
NK3 receptor antagonist	Talnetant	Reduces nociception associated with CRD and hypersensitivity induced by stress but not inflammation	(Fioramonti et al., 2003)
		No benefit in clinical trial in IBS	(Houghton et al., 2007a)
CCK_2 receptor antagonist	Cl-988	Blocks anxiety-induced hyperalgesia in rats	(Rivat et al., 2010)

Drug class	Compounds	Effect on visceral sensation	References
Somatostatin receptor agonist	Octreotide ($sst_{2,3,5}$ agonist)	Exerts antinociceptive effect on responses to CRD at the central level in rats	(Su et al., 2001)
		Normalizes visceral perception thresholds in IBS patients	(Schwetz et al., 2004b)
		Failed to improve IBS symptoms in a long-term treatment	(Klooker et al., 2007)
	sst_2 agonist	Inhibits mesenteric afferents involved in nociceptive transmission and induce anxiolytic-like and antidepressant-like behavior effect in rats	(Booth et al., 2001; Engin and Treit, 2009)
Melatonin	Melatonin	Decreases abdominal pain and improve overall IBS symptom scores in patients	(Mozaffari et al., 2010)
		Exerts antinociceptive effect in a rat model of post-inflammatory visceral hyperalgesia via a centrally mediated process	(Mickle et al., 2010)
	Neu-P11 (melatonin agonist)	Exerts antidepressant and anxiolytic activities in rodent models - effect on visceral sensitivity not studied yet	(Tian et al., 2010)
Antibiotics	Rifaximin, neomycin	Inhibit stress-induced visceral hyperalgesia in animal models and alleviate symptoms in IBS patients modulating also stress-related behavioral changes via the brain-gut-enteric microbiota axis	(Pimentel et al., 2006; Pimentel et al., 2011b; Pimentel et al., 2011a)
Probiotics	VSL#3 *Lactobacilus spp. Bifidobacterium spp.*		(Collins et al., 2009a; McKernan et al., 2010; Messaoudi et al., 2011; Moayyedi et al., 2010; Verdu et al., 2006)
Prebiotics	Enzyme-treated rice fiber Transgalactooligosaccharide		(Kanauchi et al., 2010; Silk et al., 2009)