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Review

Stress and visceral pain: From animal models to clinical therapies

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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.

Contents

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; GPCR, 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, serotonin-noradrenaline 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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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 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 of the organism to emotional or physical threats ("stressors"), 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 (1915) in 1915 which is driven by sympathetic activation leading to rapid heart rate and respiration, increased arousal, alertness, and inhibition of acutely nonadaptive 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 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 underlies 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 (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, 2006; Taché and Brunnhuber, 2008). However, recent experimental and clinical studies point to an