Central and Peripheral Modulation of Visceral Pain and Visceral Hypersensitivity by the CRF-CRFR System

Abstract

Visceral pain refers to the pain originating from the internal organs and is the common symptom shared by many disorders. The corticotrophin releasing factor (CRF) family encompasses CRF, urocortin (Ucn) 1, Ucn2, and Ucn3 (collectively termed as CRFs in this review), while CRF receptors (CRFR) include CRF receptor type 1 and type 2 (CRF1 and CRF2)and their different splice forms. CRFs and CRF receptors are extensively expressed in both the brain and the peripheral tissues including the gastrointestinal (GI) tract, the spinal cord and so on. The CRF-CRFR system has been shown to play key roles in modulating visceral pain and visceral hypersensitivity by multiple groups in the past two decades. However, a comprehensive review to summarize and integrate the different, even contradictory results is lacking. This review summarizes the role of the CRF-CRFR system in modulation of visceral pain and visceral hypersensitivity at the layers of the brain, the spinal cord and the GI tract.

Keywords: Visceral pain; Visceral hypersensitivity; Corticotropin releasing factor (Crf), Corticotropin releasing factor receptor type 1 and Type 2 (Crf_1 and Crf_2)

Review Article

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Introduction

Visceral pain is defined as the pain sensed as arising from the internal organs of the body. It has five clinical characteristics, including not being evoked from all viscera, not always being linked to injury, poor localization, referred pain and being accompanied with motor and autonomic reflexes [1]. Etiological factors are, but not limited to, inflammation, mechanical disruption, neoplasms, and alterations in neurotransmission from the viscera, and ischemia [2]. Visceral hypersensitivity refers to the altered pain sensation to physiological stimuli, consisting of allodynia and visceral hyperalgesia [3]. Visceral pain and visceral hypersensitivity is the common feature of many disorders, including inflammatory bowel disease (IBD), interstitial cystitis/painful bladder syndrome, pancreatitis, and many gastrointestinal functional diseases, especially irritable bowel syndrome (IBS).

Irritable bowel syndrome is a functional bowel disorder that is not associated with detectable structural and biochemical abnormalities [4]. The prevalence of IBS is 7%-21% of the general population [5], casting a huge economic burden [6,7]. In addition to visceral pain, IBS is characterized by stool irregularities and bloating. According to the predominant stool pattern, the Rome III criteria divide IBS into four subtypes, IBS with constipation, IBS with diarrhea, mixed IBS and un sub typed IBS. The pathological mechanisms of IBS remain largely unknown. Disruption of epithelia barrier, dysbiosis, low-grade inflammation, and altered brain-gut axis has been proposed to contribute to the pathogenesis and symptoms of IBS [4]. An interesting observation is that IBS is highly comorbid with stress-related psychiatric disorders [8]. Depression and anxiety accounts for 20%-60% of these comorbidities [9] and psychological stress contributes to the exaggeration of visceral pain. Therefore, elaborating the roles of stress in development of visceral pain may provide insights to the underlying mechanisms of IBS.

CRF is the key mediators of stress and visceral pain. CRF is commonly believed to promote the releasing of the ACTH by binding to its receptors. However, the role of CRF and its related peptides extends far beyond mediating the endocrine component of stress [10]. Intravenous administration of CRF induces visceral hypersensitivity after repetitive rectal distention in healthy humans and mimics an IBS-specific visceral response [11], indicating that the CRF-CRFR system contributes to the pathogenesis of visceral pain and hypersensitivity and IBS. Indeed, the role of the CRF-CRFR system in visceral pain modulation has been repetitively demonstrated in both the patients and animal models.

In this review, the relationship between CRF-CRFR system and visceral pain is summarized, especially focused on the expression pattern of CRFs and CRF receptors in the brain, the spinal cord and the peripheral tissues, and on the dynamic change of the CRF-CRF system in different physiological conditions. Finally, it is analyzed how the CRF-CRFR system modulates visceral pain at both peripheral tissues and the brain.

Corticotropin-Releasing Factor Sand CRF Receptors

Corticotropin-releasing factor and its related peptides

The mammalian corticotropin releasing factor (CRF) family consists of four members, CRF, urocortin (Ucn) 1, urocortin 2 and urocortin 3 [12]. The first member of CRF family was a 44-amino acid peptide, first isolated from ovine brain and found to

stimulate the secretion of adrenocorticotropin hormone (ACTH) and beta-endorphin [13]. Thereafter, it was named corticotropin-releasing factor (CRF). The CRF peptides are highly conserved across different species, with human, mouse and rat CRF identical (therefore termed h/m/r CRF) [14]. In addition to CRF, CRF like peptides were subsequently identified in mammals, amphibians and fish [15]. Vaughan et al. [16] first, in the rat midbrain, cloned urocortin (later normalized as Ucn1 by UPHARM guideline), which is a 40-amino acid peptide and shares 45% amino acid sequence identity with h/m/r CRF [16,17]. Reye et al. [18] isolated a new member of CRF family, Ucn2, which is a 38-amino acid peptide and shares 34% and 42% homology with rat CRF and rat Ucn1 at amino acid level, respectively [18]. Ucn3 is a 38-amino acid protein and was found to be relatively more closely related to Ucn2 than CRF and Ucn1 [19,20]. Similarly to CRF, Ucn peptides share high identity among mammals in terms of amino acid sequence of the mature peptides. Mouse Ucn1 and rat Ucn1 are identical, which share 95% identity with that of human [16]. Human Ucn3 and mouse Ucn3 are 90% identical with each other [19,20].

The biological activity of CRFs relies on the amino-terminals containing the first 21 amino acid residues, the carboxyl-terminals containing the last 5 amino acid residues, and their internal segments that have a high average probability of alpha helix formation [15,21,22].

Corticotropin-releasing factor receptors (CRFR)

The receptors for CRFs are CRF receptor type 1 and 2 (CRF_1 and CRF_2, respectively), which belong to the secret in-like, family B1 of G protein-coupled receptors (GPCR) [23]. The structure of CRF_1 and CRF_2 are typical of GPCR, consisting of 7 alpha-helical transmembrane segments, an extracellular amino-terminal and an intracellular carboxyl-terminal [15].

CRF_1 and CRF_2have different splice forms. CRF_{1a} is the main receptor variant, which is composed of 415 amino acids [24]. CRF_{1b}, CRF_{1c}-CRF_{1m} have been identified and their functional roles remains elusive [25]. For simplicity, the CRF_1 variant, designated as CRF_1 below in this paper, refers to $CRF_{1a.}$ CRF_1splice variants are differently localized, which is discussed later in this article. CRF_2 encompasses 3 main is of orms, a, b and c [26-29]. As CRF_1, CRF_2 variants are expressed differentially in tissues. However, CRF_2 splice variants exert similar pharmacological properties as compared to those of CRF_1 [26-29]. CRF_1 are highly conserved across different species with human and mouse CRF_1only differing in 10 amino acids [30]. The CRF_{2a} shares approximately 70% amino acid sequence identity with CRF_1 [26].

The primary cellular functions of CRF_1 and CRF_2 are mediated through $G_{\alpha s}$. Binding of CRFs to the receptors initiates a series of conformational change, which conveys extracellular stimuli into intracellular domains of CRF receptors, resulting in the activation of $G_{\alpha s}$-adenylatecyclase-cAMP-PKA pathway [31]. The signaling cascade manifests its diverse cellular effects by activating ERK1/2, p38 MAPK, and so on [32-35]. Additionally, CRF_1 and CRF_2 may couple to different G proteins and regulate both cAMP-dependent and cAMP-independent signalings [36].

The natural ligands of CRF_1 and CRF_2 are CRF, Ucn1, Ucn^2 and Ucn3. OCRF is relatively selective for CRF_1, while Ucn2 and Ucn3 are significantly selective for CRF_2. The other natural ligands are lack of specificity for CRF receptors (Table 1).

Non-endogenous agonists and antagonists for CRF receptors are classified into peptidic and non-peptidic groups according to the chemical nature. The non-peptidic group distinguishes from the peptidic group by its ability to freely cross the blood-brain barrier [37]. The difference in crossing the blood-brain barrier enables their differential applications for studying the CRF-CRFR system at central and peripheral levels. Specifically, for the peptidic group of antagonists, it may be subdivided into three subgroups, CRF_1selective, CRF_2 selective and non-selective (Table 1). CRF_2 selective peptidic agonists include astressin$_2$-B and anti-sauvagine 30. The representative peptides of non-selective group areα-helical CRF_{9-41}, D-Phe^{12} CRF_{12-41}, a stress in-B and a stress in. As shown in Table 1, the selective peptidic antagonists for CRF_1 and peptidic agonists are relatively underdeveloped. Non-peptidic agonists and antagonists for CRF receptors and their therapeutic utility have been extensively reviewed by John H Kehne & Christopher K Cain [37], which is not discussed elaborately in this article.

[a,b,c,d,h] The K_{is} value was determined by competitive radio ligand displacement as says by using radio labedsauvagine([a, b, c]), astressin ([d]) or h/rCRF([h]). [e]According to this article, YAM19 is a CRF_1 selective peptide. However, the supporting data is not shown. [f, g] EC_{50} was determined by measuring alteration of CRF-induced release of ACTH by rat anterior pituitary cells in culture.

[a]Rivier et al. [38].

[b]Lewis et al. [20].

[c]Dautzenberg et al. [39].

[d]Mesleh et al. [40].

[e]Tache et al. [41].

[f]Rivier et al. [42].

[g]Rivier et al. [43].

[h]Tezval et al. [44].

Central expression of CRFs and CRF receptors

To investigate the role of the CRF-CRFR system in visceral pain modulation, characterization of the expression pattern is prerequisite. The pain sensation pathway provides insights to the sites and layers that we focus in this part. The gastrointestinal (GI) tract is diffusely sensed by the afferent fibers from the vagal, pelvic and splanchnic nerves, which ascend via the vagal nerves, sympathetic and parasympathetic pathways [45]. Secondary processing occurs at the spinal cord and at the brain stem. In the spinal cord, primary visceral afferents terminates in laminaeI and V, constituting the spinothalamic tract, or in laminae VII and X, constituting the dorsal column pathway [46,47]. Then secondary neurons diffusely project into the pain matrix, including the

prefrontal cortex (dorsolateral), the insula, the thalamus, the amygdala, and the anterior cingulated cortex (ACC) [2]. Thereafter, we focus the expression of CRF and CRF receptors at the levels of the GI tract, the spinal cord and the brain.

Table 1: Pharmacological Properties of CRF Receptors.

Ligand			K_{is} or EC_{50} (nM)	
			CRF_1	CRF_2
Natural Ligands	CRF_1 selective	oCRF[a]	1.2	52
	CRF_2 selective	mUcn2[b]	>100	0.66
		hUcn2[b]	>100	0.5
		mUcn3[b]	>100	1.8
		hUcn3[b]	>100	13.5
	Non-selective	r/hCRF[a]	1.0	6.2
		rUcn1[b]	0.32	0.62
		hUcn1[c]	0.1	0.5
		Urotensin[b]	0.4	2.2
		Sauvagine[b]	0.7	4.3
Non-endogenous Antagonist (Peptide)	CRF_1 selective	YAM19[d,e]	5.9	-
	CRF_2 selective	$astressin_2$-B[f]	>500	1.3
		anti-sauvagine 30[f]	400	1.1
	Non-selective	α-helical CRF_{9-41}[f]	19	1.1
		D-Phe^{12} CRF_{12-41}[f]	19.2	4.4
		astressin[f]	0.7	0.6
		astressin-B[g]	0.3	1.2
Non-endogenous Agonist (Peptide)	CRF_1 selective	Cortagine[h]	2.6	540
		$stressin_1$[a]	1.7	222

By immunehistochemical staining, CRF was found to be densely localized, in rat, in the cell bodies of the extra-hypothalamic areas of nucleus accumbenssepti, basal nucleus of the striaterminalis (BNST), the medial preoptic region, and the central amygdaloid nucleus, and of hypothalamic areas of paraventricular nucleus (PVN) [48]. For fibers, CRF is enriched in the lateral septal region and throughout the external layer of the median eminence [48]. The distribution pattern has later been repetitively confirmed by different methods, including *in situ* hybridization in voles [49], immunohistochemical labeling by CRF specific polyclonal antibody in mice, rats [50], and tree shrews [51], and immunofluorescence by anti-GFP antibody targeting CRF-*Venus* fusion protein in the knock-in mice [52]. These studies demonstrate that the expression pattern of CRFs is conserved among species. Compared with CRF, Ucn peptides are more restrictedly expressed. Ucn1 is primarily expressed in Edinger-Westphal nucleus (EWN) [49] and the lateral superior olive [53]. In rats, Ucn2 neurons are mainly present in PVN with a few existing in the supraoptic nucleus of the hypothalamus, and Ucn3 are similarly expressed in PVN and in the extra-hypothalamus areas of the medial nucleus of the amygdala [54]. Throughout the spinal cord, CRF fibers were found to predominate the laminaeI, V-VII, and X of Rexed while Ucn1 fibers the laminae VII and X, by immunofluorescence and *in situ* hybridization [55]. As expected, the expression of CRF and its related peptides is a dynamic process in accordance with different physiological conditions, for example, diverse stressful states. Evidence includes that CRF and Ucn3 are differentially expressed in eusocial naked mole-rats and solitary cape mole-rats [56] and that Ucn1 expression in mouse brain is strain-dependent [53].

CRF_1 is expressed with different intensity throughout the whole brain, with enrichment in neo cortices, the olfactory bulb, the hippocampus and sub cortical limbic structures in the septal region and the amygdala of the forebrain, in certain relay nucleus of the brain stem, and in the cerebellum [57-59]. The expression of CRF_2isoforms is disparate. CRF_{2a} and CRF_{2c} predominate the brain while CRF_{2b} mainly locates in the peripheral tissues [29,60]. In the brain, CRF_{2a} is enriched in the olfactory bulb, the lateral septum, BNST, the ventromedial hypothalamus, the raphe nuclei, the amygdala, the ventral hippocampus, the solitary tract, and the area postrema [58,60-63]. CRF_{2b} is primarily located in the choroid plexus [62,63] and CRF_{2c} in the septum and the hippocampus [29]. In the spinal cord, CRF_2 is relatively widespread with occurrence in laminae III-X compared to the restriction distribution of CRF_1 in laminae III-VIII [55]. Genetically or molecularly mimicking of stress does not change the general localization of CRF receptors but do influence the expression level [63]. The density of CRF receptors varies within different physiological conditions, for example, photoperiod and sociality [64] and within disease conditions like depression and gastrointestinal function disorders [65].

The amygdala is a key component of the pain matrix. It consists of several nuclei, of which, the lateral (LA), basolateral (BLA), and central nuclei (CeA) are particularly important for sensory processing. The polymodal sensory, including nociceptive, inputs from thalamic nuclei and cortical areas are transmitted into the LA, and through the LA-BLA circuitry, sensory information is added with affective contents [66]. The integrated information is finally relayed to the CeA, which is the major output nucleus for amygdala functions [67]. Additionally, the laterocapsular division of the CeA (CeLC), through the spino-parabrachio-amygdaloid pathway, directly receives the nociceptive information [68].

CRFs are apparently localized in both cell bodies and the fibers of the central nuclei of the amygdala among different species [48-52]. In the CeA, CRF is co-localized with GABA [52]. Another study using a transgenic mouse line, in which hr GFP was expressed under the control of CRF promoter demonstrates that CRF is primarily located in the interstitial nucleus of the posterior limb of the anterior commissure in addition to the central amygdala [69]. This study suggests that amygdalar CRF neurons are activated in certain stress conditions like social defeat stress and lipopolysaccharide (LPS) administration but not in restraint stress and forced-swimming stress. Neither Ucn1 nor Ucn2 is evidently expressed in the amygdala. Ucn 3 neurons are found in the dorsal division of the medial nucleus of the amygdala [54].

CRF_1 and CRF_{2a} are differentially localized in the amygdala, with CRF_1 predominant in the basolateral and medial nuclei, and CRF_{2a} in the posterior aspect of the medial nuclei [59,61]. CRF_{2c} is weakly expressed in the amygdala [29].

Peripheral expression of CRFs and CRF receptors

CRFs and CRF receptors are widely expressed in the peripheral tissues, including the heart, the muscle and the skin, in which CRF_{2a} is the dominant form [29,62]. Here, we focus the expression of CRFs and CRF receptors in the gastrointestinal tract. The CRF-CRFR system is expressed throughout the GI tract in a slightly different manner at different segments of the GI tract and at different layers in the same segment. Emphasis is put on the lower gastrointestinal tract, for example, the colon, for the usual involvement in multiple diseases manifesting visceral pain and visceral hypersensitivity.

CRF is expressed in the colonic mucosal epithelia, lamina propria, crypts, and the enteric neurons (both bodies and fibers) in the rat colon [70], in healthy people and in patients with ulcerative colitis (UC) [71]. In the mice ileum, the expression pattern is slightly different with CRF primarily expressed in stromal cells and nerve fibers [72]. Specifically, enterochramffin cells (EC) that synthesize serotonin (5-HT) constitute a large proportion of CRF positive cells in the epithelia [70]. Cells expressing CRF in the lamina propria includes macrophages [71] and eosinophils [73], indicating roles of the CRF-CRFR system in the gut immunity. In the enteric neurons, CRF expressing bodies and fibers are more abundant in the sub mucosal plexus than in the myenteric plexus in the guinea pig [74] and in the rat [75], and almost all the CRF expressing neurons co-express vasoactive intestinal peptide (VIP), suggesting the VIP and CRF interaction in intestinal regulation [75]. Additionally, CRF is not co-expressed with CRF_1 in the same neurons and CRF positive neurons are usually in proximal with CRF_1neurons [74], suggesting that CRF-CRFR system modulates the neuronal activity enteric in a local circuit. Ucn1 is expressed primarily in the macrophages of the mucosa in the colon of healthy human [76] and in the plasma cells and the EC of the mucosa in the patients with UC [77], and both experiments detect weak signals of Ucn1 in the epithelial cells and in the enteric neurons. Ucn2 is expressed in the leukocytes and the external muscular layer in the wall of rat ileum [72]. Ucn3 is expressed ubiquitously in the epithelial cells and the myenteric neurons through the GI tract in rats [78].

In the rat colon, CRF_1 and CRF_2 are expressed differentially in the crypts. CRF_1 is also expressed in the lamina propria and in the enteric plexus, while CRF_2 is expressed in the blood vessels of the sub mucosa [79]. Similar results were obtained in healthy human [80,81]. Specifically, macrophages account for 79% of the cells that express CRF_1 in the lamina propria with the rest being mast cells and other cells [80].

The expression level and sites of CRFs and CRF receptors are dynamically regulated in different diseases. CRF expression is up-regulated especially in the sub mucosa plus muscular layers in response to LPS administration in a corticosteroid-independent manner in the rat colon [70] and the number of CRF expressing eosinophils is increased in the UC rat [73]. In the human UC patients, CRF is only slightly increased in the mucosal epithelia but considerably increased in the mucosal macrophages [71]. The number of Ucn1 expressing cells increases in proportion to the severity of inflammation in the UC patients [77], however, Ucn3 is down-regulated in UC [78]. CRF_1 expressing cells with macrophages in particularly increase in mucosa of UC patients [80]. In contrast, CRF_2 is down-regulated in the epithelial cells, but not the lamina propria, of mild-moderately active UC and of recovery from UC [81]. In general, CRF_1 and its natural ligands, including CRF and Ucn1, are up-regulated, while CRF_2 and its natural ligand, Ucn3 are down-regulated in the inflamed state. However, in the patients of functional bowel disease, the expression CRF_2 is similar to that in healthy people [81].

Modulation of Visceral Pain by the CRF-CRFR System

Central modulation of visceral pain by CRF-CRFR system

Intracerebroventricular (icv) injection of α-helical CRF_{9-41} was found to block the visceral pain induced by colorectal distention or by icv injection of CRF, indicating that visceral hypersensitivity is modulated by CRF-CRFR systems in the brain [82]. Consecutive experiments has shown that visceral pain is ameliorated by specifically blocking CRF_1 using small molecule antagonists including NBI-35965 [83], CP154265 [84,85], NGD 98-2, NGD 9002 [86], antalarm in [87], E2508 [88] in multiple stress models of maternal separation, acute water avoidance stress [83,86], repeated psychological stress [84,86], repeated stress in combination of colitis [85] and genetically anxious WKY rats [87]. These data demonstrate that CRF-CRF_1 is the common modulator of visceral pain and visceral hypersensitivity in multiple stress settings and that CRF_1 plays key roles in both the development and the maintenance of visceral hyper sensitivity [84]. In these experiments, the small molecule CRF_1 antagonists are administrated orally, intravenous or subcutaneously. Due to the ability of small molecules to freely cross the blood brain barrier, the peripheral roles of the CRF-CRF_1 in modulation of visceral pain cannot be excluded. The experiments of brain sites specific injection of CRF_1 antagonists further consolidated the brain as the sites of pain modulation, as shown below.

Next questions are what parts of the brain are involved in pain modulation by the CRF-CRF_1 system. As mentioned above, the amygdala is the site playing key roles in visceral pain and visceral hypersensitivity. Initial data includes that microinjection of α-helical CRF_{9-41} into the CeA significantly reduces anxiety [89]. To further characterize the role of the CeA in visceral pain modulation, either the CRF_1 specific antagonist CP-376395 was administrated into the CeA [90], or CRF was site-specifically knocked down in the CeA [91]. In both experiments, rats showed decreased visceral pain in response to colorectal distension (CRD). Similarly, site-specific injection of CRF into the CeA evokes visceral hypersensitivity [92,93]. Additionally, expression of CRF and CRF_1 is up-regulated in the CeA in the visceral hypersensitivity models of cystitis [94] and in models of comorbid depression and functional gastrointestinal disorders [65]. Taken together, these experiments demonstrate that amygdala is the site of visceral pain modulation by CRF-CRF_1.

In addition to amygdala, CRF-CRF_1 may modulate visceral pain in PVN, BNST, EWN, the hippocampus, and locus coeruleus (LC). Under acute pain stress, expression of CRF and Ucn1 peaks at different time point in PVN, BNST and EWN, suggesting that CRF in the PVN acts in the initiation phase, while Ucn1 in the EWN acts in termination of the adaptation response to APS [95]. Intra hippocampal administration of α-helical CRF or intra peritoneal administration of JTC-017, a CRF_1 specific antagonist, significantly attenuates hippocampal noradrenalin release and visceral hypersensitivity induced by acute distention [96]. In the anterio lateral BNST, micro infusion of CP-376395, a CRF_1 specific antagonist, reduces visceral pain in response to CRD under non-stressful baseline conditions or following water avoidance stress [97]. In the rats that experienced CRD in the neonatal phase, CRD during adulthood induces visceral pain by activating the microglial cells and CRF expressing neurons in the PVN, which are prevented by intra-PVN infusion of small interference mRNA that targets CRF [98]. Injection of D-$Phe^{12}CRF_{12-41}$ into LC attenuates the activation of noradrenergic LC neurons in response to CRD [99,100] and similar results were obtained by LC-specific administration of CRF_1 antagonist, NBI-35965 in response to CRD and intracisternal injection of CRF [100]. Noradrenergic LC neurons also project into the CRF neurons of the CeA [101]. And injection of CRF into the CeA increases noradrenalin release in the CeA and evokes visceral hypersensitivity, which is blocked by CRF_1 antagonists [92]. The CRF expressing neurons in the CeA and the noradrenergic neurons in the LC form a circuit that may underlie the mechanisms of visceral pain modulation.

The studies of the roles of CRF-CRF_2 in modulation of visceral pain are relatively scant and remain controversial. Ideas are borrowed from the somatic pain hypersensitivity, which may share similar mechanisms with visceral hypersensitivity. CeA-specific blockade of CRF_1 inhibits evoked responses and background activity in arthritis but not in healthy controls, while blocking CRF_2 in the CeA only increases neurons' response in healthy controls but has no effect in arthritis [66,102]. This indicates that in the CeA, CRF_1 is activated under arthritis but not normal conditions and contributes to pain sensation while CRF_2 is inhibitory to pain sensation under normal conditions but the inhibitory effect is lost in arthritis. This concept is in consistent with the observation that in stress models of WKY rats or maternal separation, CRF_1 mRNA was higher in the amygdala, PVN and dorsal raphe nucleus (DRN) while CRF_2 mRNA is lower in the dorsal raphe nucleus in comparison with control rats [65]. In BNST, the opposing roles of CRF_1 and CRF_2 holds true under different conditions. Specifically, under baseline conditions, blocking of CRF_2 reduces anxiety, somatic pain and visceral pain in response to high CRD pressure, but the ameliorating effect is lost under water avoidance stress [97]. Confusingly, in the normal rats in the absence of tissue damage, CRF increases somatic pain behavior, which is blocked by CRF_1 antagonists but not by CRF_2 antagonists [103]. The complexity of the CRF-CRF_2 in modulating visceral and somatic pain may be attributed to the differential regulation of CRF_2 under different stress conditions and in different strains, to the differential localization of CRF_2 in the brains and to the different behaviors under investigation.

Concerning the upstream mediators that may modulate the CRF-CRFR system in the modulating visceral pain and visceral hypersensitivity, corticosterone (CORT) is of great interest, which is commonly considered as the stress hormone in the hypothalamus-pituitary-adrenal gland (HPA) axis. Stereotaxic delivery of CORT into the amygdala induced anxiety-like behaviors and colonic hypersensitivity in rats [104,105], which are mediated via glucocorticoid receptors (GR) or mineralcorticoid receptors (MR) [106]. Decreased expression of GR and increased expression of CRF and HCN1 channel with no change of CRF_1 and CRF_2 expression was observed in the CeA in exposure to elevated CORT [107]. Visceral hypersensitivity was triggered by knocking down of steroid receptors (either GR or MR) in the CeA [108,109] and was blocked by knocking down of CRF in the CeA [91]. One of the interesting observations is that transient exposure of CeA to

CORT resulted in long lasting increases of visceral sensitivity and anxieties [110]. The maintenance of chronic anxiety and visceral hypersensitivity is mediated by epigenetically deacetylation of his tone 3 at lysine 9 (H3K9), which sequesters the GR expression, leading to disinibition of CRF [111,112]. However, contradictory results were found in WKY rats, a high anxiety strain, compared to the results from the low anxiety F344 rat strain. In WKY, visceral hypersensitivity is mediated by CRF_1 instead of steroid receptors [90]. The difference indicates the heterogeneous nature of visceral hypersensitivity in terms of strains [113] and stresses.

Above all, the central mechanisms of visceral pain modulation by CRF-CRFRs systems include, but are not limited to, dysregulation of CRF and CRFR expression, loss of balance between CRF_1 and CRF_2, altered circuits plasticity in the brain pain matrix and dysregulation of noradrenergic release in different brain sites, in response to different stress and in different strains.

Peripheral modulation of visceral pain by CRF-CRFR system

Administration of small molecule CRF_1antagonists ameliorates visceral pain and visceral hypersensitivity [83-88], as mentioned above. The pharmacological effects are likely to happen at both central and peripheral layers. The major peripheral organ we focus on is the GI tract. The peripheral role of the CRF-CRFR system has been corroborated by subcutaneous administration of astressin, a peptidic nonselective CRF_1 and CRF_2 antagonist, which blocks the visceral hypersensitivity induced by repeated water avoidance stress [84]. Both CRF_1 and CRF_2 participate in the peripheral modulation of visceral pain and visceral hypersensitivity. Intraperitoneal injection of cortagine, a CRF_1 specific peptidic agonist exacerbates the visceral pain in response to CRD [114]. On the other hand, subcutaneously injection of astressin2-B, a CRF_2 specific peptidicantaogonist, blocks visceral hyposensitivity [115].

Sensitization of peripheral afferent nerves is the major mechanisms accounting for the visceral pain and hypersensitivity of peripheral origin. The nerves may be sensitized by lipids, hormone, cytokines, immune mediators and substances from the GI lumen [8]. These sensitizers activate different neuronal receptors and ion channels that associates with pain signaling, such as transient receptor potential cation channel subfamily V type 1 (TRPV1), protease-activated receptors (PAR), cholecystokinin receptors, serotonin receptors, cannabinoid receptors, ATP gated ion channels, sodium channels, calcium channels, and acid-sensing ion channel [116]. The interaction between epithelia cells, EC, mast cells and other inflammatory cells, and neurons determines the synthesis and release of these sensitizers. The CRF-CRFR system regulates this interaction, therefore modulates visceral pain peripherally.

Increased permeability has been shown to induce visceral pain in response to acute CRD stress [117]. Increased permeability results in the translocation of gut microbiota, antigens and other luminal contents, which activate gut immunity and facilitates nerve sensitization. Cortagine administered intraperitoneally induces visceral hypersensitivity, which is blocked by the CRF_1 specific antagonist, astressin [114]. *In vitro* experiments using healthy human colon tissues demonstrate that CRF increases mucosal permeability, which is inhibited by α-helical CRF_{9-41} and mast cell stabilizer, suggesting mast cells mediates the effect of increased permeability [118]. Interestingly, administration of astressin or antalarmin, which are CRF_1 and CRF_2 antagonists respectively, only induces partial inhibition, indicating both receptors on the mast cells regulates the permeability. Mast cells activated by CRF release proteases and TNF-α, and these molecules facilitate intestinal epithelia barrier injury, increased permeability and nerve sensitization [119]. The increased permeability is facilitated via either the paracellular [117] or the transcellular [118] pathway according to two different contradictory experiements. However, roles of different pathways in increased permeability under different conditions await clarification, as different pathways determine differential gut immune reactions in response to different substances leaked in.

Enter chromaffin cells are an important source of CRFs and express CRF receptors. Two independent studies using different BON cell lines, which share functional similarities with intestinal EC cells, demonstrate that CRF stimulates serotonin release and synthesis from BON cells in a cAMP-dependent manner [120,121]. In the experiment using BON-1N cell line, only activation of CRF_1, but not CRF_2 leads to increased release of 5-HT [121]. In the experiment using another BON cell line, increased CRF release is not inhibited by CRF_2 specific antagonists [120]. The discrepancy indicates differential involvement of CRF_1 and CRF_2in BON cells, which is partially explained by differential expression of CRF receptors on different BON cell lines. Serotonin, as an enteric neurotransmitter, induces excitatory postsynaptic potentials (EPSPs) participating in mucosal sensory transduction and stimulates vagal and intrinsic afferent nerve fibers, contributing to the visceral pain and visceral hypersensitivity [122].

The CRF-CRFR system also modulates visceral pain peripherally by regulating the local immune response. In a post-infectious IBS model, infection induces increased number of EC cells, mastocytosis and visceral hypersensitivity, which is blocked by T cell receptor knockout cells [123], indicating the involvement of immune cells and immune mediators in modulating visceral hypersensitivity. This is supported by the expression of CRF and CRF receptors in the immune cells including eosinophils, mast cells, macrophages, and plasma cells. Mast cells activated by CRF releases tryptase and histamine, directly sensitizing the nerve ends and contributing to visceral pain in IBS patients, as mast cells are in proximity with mucosal innervations [124]. In addition to directly regulate the activity of immune cells, CRF increases the permeability and exposes the luminal contents to these cells. CRF also promotes the release of immune mediators, such as TNFα, IL-1β and IL-6, from two lines of macrophages in vitro [125]. Antalarmin, a CRF_1 specific antagonist, administered before injection of LPS reduces TNFα, IL-1β and IL-6 production in the endo toxic shock mice model [125]. Blocking of IL-1, IL-6 or CRF ameliorates the LPS induced visceral hypersensitivity in rats [126]. In the model of visceral hypersensitivity induced by repeated CRD, CRD induces acute and chronic pain sensitization through CRF and IL-1, respectively [127]. These two experiments indicate in the presence and absence of inflammation, the roles of the CRF-CRFR system are different as different immune cells

are involved and the expression of CRF receptors is differentially regulated.

The specific roles of CRF_1 and CRF_2 remain controversial. Activation of CRF_2 by intravenously injection of Ucn2 induces visceral hyperalgesia in response to colorectal distention, which is reversed by the CRF_2 specific antagonist, astressin$_2$-B [128]. This is believed to involve the peripheral neurons and the spinal cord as increased activity of inferior splanchnic nerve and phosphorylation of Erk in laminae II and I were recorded. Another mechanism that may contribute to the inhibitory role of CRF_2 is by inducing colonic hyperemia through nitric oxide pathway upon activation5 [129]. However, other studies indicate that both CRF receptors contribute to the visceral pain by increasing the epithelial permeability, as mentioned above.

Summary

Visceral pain and visceral hypersensitivity is a common feature of many disorders including IBS. However, the underlying mechanisms are not fully understood. The CRF-CRFR system plays critical roles in modulating visceral pain and visceral hypersensitivity. CRFs including CRF, Ucn1, Ucn2 and Ucn3 initiate differential regulations of visceral pain and visceral hypersensitivity by binding selectively to CRF_1 or CRF_2.

In the brain, the amygdala integrates the stress and pain information and is a key component of the pain matrix. Under stressful conditions, increased level of CORT leads to down-regulation of GR and MR but increased expression of CRF in the amygdala. In the pain matrix of the amygdala, the hippocampus, EWN, BNST, PVN and LC, activation of CRF-CRF_1 system leads to visceral pain and visceral hypersensitivity. Additionally, dysregulation of CRFs and CRFR expression, loss of balance between CRF_1 and CRF_2, altered circuit plasticity in the brain pain matrix and dysregulation of noradrenergic release in different brain sites all contribute to the visceral pain and visceral hypersensitivity.

In the GI tract, activation of CRF-CRF_1 results in epithelia injury and increased permeability, which is facilitated by the immune cells. Increased permeability exposes luminal contents to the local immune cells, including eosinophils, macrophages, mast cells, T cells and plasma cells. Activation of these cells results in increased synthesis and release of cytokines and other immune mediators. CRFs, luminal contents and the immune mediators sensitize the nerve ends, contributing to the visceral pain and hypersensitivity. Although the role of CRF-CRF_2 remains controversial in different experimental settings, it is generally accepted that in the normal conditions, CRF_2 activation inhibits visceral pain and hypersensitivity, and that the inhibitory roles are lost under pathological conditions.

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