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Corticotrophin-releasing factor 1 activation in the central amygdale and visceral hyperalgesia

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Abstract

Corticotropin-releasing factor (CRF)-CRF_1 receptor in the brain plays a key role in stress-related alterations of behavior including anxiety/depression, and autonomic and visceral functions. In particular, CRF_1 signaling mediates hypersensitivity to colorectal distension (CRD) in various models (early life adverse events, repeated psychological stress, chronic high anxiety, postcolonic inflammation, or repeated nociceptive CRD). So far, knowledge of brain sites involved is limited. A recent article demonstrates in rats that CRF microinjected into the central amygdala (CeA) induces a hyperalgesic response to CRD and enhances the noradrenaline and dopamine levels at this site. The visceral and noradrenaline, unlike dopamine, responses were blocked by a CRF_1 antagonist injected into the CeA. Here, we review the emerging role that CRF-CRF_1 signaling plays in the CeA to induce visceral hypersensitivity. In the somatic pain field, CRF in the CeA was shown to induce pain sensitization. This is mediated by the activation of postsynaptic CRF_1 receptors and protein kinase A signaling that increases N-methyl-D-aspartate receptor neurotransmission. In addition, the activation of tetraethylamonium-sensitive ion channels such as Kv3 accelerates repolarization and firing rate. Whether facilitation of pain transmission underlies CRF action in the CeA-induced visceral hypersensitivity will need to be delineated. CRF_1 signaling in the CeA is also an important component of the neuronal circuitry inducing anxiety-like behavior and positioned at the interphase of the reciprocal relationship between pain and affective state. The hyperactivity of this system may represent the neuroanatomical and biochemical substrate contributing to the coexpression of hypersensitivity to CRD and mood disorders in subsets of irritable bowel syndrome patients.

Keywords

central amygdala; CRF; CRF_1; antagonists; noradrenaline; stress; visceral hyperalgesia

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DISCLOSURE

No competing disclosure.

INTRODUCTION

Guillemin and Schally *et al*. reported independently in the mid 1950 the existence of the hypothalamic factor able to stimulate adrenocorticotropic hormone (ACTH) release from the pituitary gland in rats.[1] The substance contained in hypothalamic extracts was named corticotropin- releasing factor (CRF) in line with its releasing action on ACTH secretion and the fact that its chemical structure was yet to be identified.[1] In 1981, after decades of research, Vale (a former PhD student of Guillemin),[2] and his group succeeded to report the sequence of ovine CRF as a 41- amino acid peptide.[3] Soon after the isolation of CRF, the same group discovered genes encoding three paralogs, urocortin 1, urocortin 2, and urocortin 3, cloned their cognate receptors (CRF_1 and CRF_2) and developed the first peptide CRF_1/CRF_2 antagonists, α-helical $CRF_{9\text{-}41}$.[4] Corticotropin-releasing factor was established to bind with high and moderate affinity to CRF_1 and CRF_2 receptors, while urocoritn 1 displays high-affinity to both G-protein coupled receptors and urocortin 2 and 3 are selective CRF_2 receptor agonists.[4] Both CRF_1 and CRF_2 receptors are coupled to similar transduction mechanisms typically the activation of cyclic adenosine monophosphate-protein kinase A (PKA) signal transduction pathway although it encompasses coupling to diverse intracellular network in a tissue-specific manner.[5] All these successive milestone breakthroughs fostered research to unravel the biochemical coding of stress.[4]

It was unambiguously established that CRF initiates the hypothalamic-pituitary-adrenocortical (HPA) response to various stressors by binding CRF_1 receptors in the anterior pituitary after its release into the portal blood.[6] However, CRF action in the brain expands far beyond mediating the endocrine component of stress. This was in keeping with CRF-CRF_1 system being widely distributed in stress-responsive extra-hypothalamic brain areas, including the neocortex, extended amygdala, medial septum, hippocampus, thalamus, and autonomic midbrain and hindbrain nuclei.[7] Convergent reports showed that CRF injected intracerebroventricularly (icv) recapitulates and coordinates the overall bodily response to acute stress including the alterations of gastrointestinal secretory motor function. [8–10] Furthermore, blocking CRF_1 receptors by pharmacological or transgenic approaches dampened stress-related behavioral changes including anxiety/ depression, hypervigilance and autonomic and visceral alterations in several experimental species.[10–13] Subsequent extensive preclinical data indicated that dys-regulation of the CRF-CRF_1 system is implicated in the etiology and maintenance of several stress-sensitive disorders as recently reviewed.[14–17] Among those, irritable bowel syndrome (IBS) is manifested by chronic abdominal pain, altered bowel habits in the absence of detectable organic diseases.[18] Stressors of psychosocial, physical, or immune origin serve as triggers for the onset or exacerbation of IBS symptoms.[19] In particular, early adverse life events in the form of emotional, sexual, or physical abuse are also major predisposing factors for the development of IBS later in life.[19] In addition, psychiatric comorbidity, namely anxiety and depression, affects IBS patients, reaching 40–90% in tertiary care centers.[20] As recurrent abdominal pain is the hallmark symptom of IBS,[18] a number of studies focused to delineate whether the brain CRF_1 signaling system underpins stress-related enhancement of visceral pain in experimental models.[21]

BRAIN CRF_1 RECEPTOR: ROLE IN VISCERAL HYPERSENSITIVTY

The initial report by Gué *et al.*[22] showed that icv injection of CRF induced visceral hypersensitivity to colorectal distension (CRD) in rats, mimicking the effect of 2-h partial restraint stress. Furthermore, the icv injection of the CRF_1/CRF_2 antagonists, α-helical CRF_{9-41} prevented the effect of restraint stress providing the first evidence pointing to the involvement of central CRF signaling in acute stress-related development of visceral hypersensitivity.[22] With the emergence of number of selective CRF_1 antagonist,[11] visceral pain studies were performed in adult rats using peripheral administration of NBI-35965,[23] CP-154,526,[24–27] antalarmin,[28–31] JTC-017,[32] NBI- 30775,[33] DMP-696,[34] NGD 98-2, or NGD 9002.[35] Convergent findings supported the involvement of CRF_1 subtype in the hypersensitivity to CRD induced by icv CRF[28,35] and occurring in a variety of rodent models.[21] Those included acute or repeated exposure to water avoidance stress combined with neonatal maternal separation,[23,25,34] or consecutive sets of nociceptive CRD,[24,25,29,32,35] or repeated daily CRD performed at 6 weeks after the development of colitis,[27] intracolonic infusion of 0.5% acetic acid,[36] or a high-anxiety rat strain, the Wistar Kyoto (WKO).[28,30] Of relevance was the demonstration that chronic treatment with CP-154,526, alleviated the development and maintenance of visceral hyperalgesia induced in a model of repeated intermittent psychological stress.[26] It is important to note that the CRF system is not active under basal conditions as CRF_1 antagonists had no effect of their own in these studies. Consistent with the pharmacological approach, genetically modified mice with deletion of CRF_1 receptors displayed a reduction of visceral motor response to phasic CRD.[33] These compelling preclinical reports indicate that the CRF_1 signaling plays a critical role in the visceral hypersensitivity occurring in the context of early life adverse events, repeated psychological stress, a model of chronic high anxiety and peripherally initiated mechanisms following remission of colonic inflammation or repeated nociceptive activation of colonic mechanoreceptors. However, because all available selective CRF_1 antagonists are small hydrophobic molecules designed to cross the blood brain barrier,[11] their peripheral administration in the above studies did not provide insight to specific brain nuclei involved in preventing the hyperalgesia.

THE CENTRAL AMYGDALA AS A BRAIN SITE OF CRF_1 ANTAGONIST ACTION

So far the investigation of brain sites at which the CRF-CRF_1 system modulates visceral hypersensitivity has remained limited[32,37] compared to the knowledge of brain nuclei responsive to CRF-induced alterations of gut motor function.[38] One study showed that the CRF_1/CRF_2 antagonist, α-helical CRF_{9-41} microinjected into the hippocampus reduces abdominal contraction frequency induced by tonic CRD at maximal nociceptive range in rats.[32] Another study points to the central amygdala (CeA) as a responsive site to the CRF_1 antagonist, CP-376395 to dampen the visceral hypersensitivity to CRD at pressure >30 mmHg in the WKO rat strain.[37] In this issue of Neurogastroenterology and Motility, the article by Su *et al.*[39] demonstrated that CRF microinjected into the CeA increased sensitivity to CRD performed at 20–80 mmHg in Wistar rats and the response was blocked by intra-CeA injection of CP-15426. This provides the first evidence demonstrating the modulation

of visceral pain by CRF-CRF_1 receptor at this site.[39] In support of a role of endogenous CRF as ligand to act on CRF_1 receptor is neuroanatomical evidence that the CeA is a major extrahypothalamic source of CRF. The peptide is expressed in neuronal cell bodies with axons projecting to widespread regions of the basal forebrain and pontine/brainstem including the locus coeruleus (LC).[40,41] Additionally, CRF-like immunoreactivity and gene expression in CeA are increased in response to CRD[42] and various conditions inducing visceral pain or hyperalgesia.[43–46] While the CeA is just becoming recognized as a key element of circuitry through which CRF activating CRF_1 receptor induces visceral hypersensitivity, in the somatic pain field, accumulated evidence from biochemical,[44] behavioral, and electrophysiological studies[47] established previously that endogenous CRF-CRF_1 signaling in this limbic nucleus stimulates pain sensitization.[48] For instance, CRF_1 antagonists such as NBI-27914, MPZP or R121919 microinjected into the CeA exert antinociceptive effect to mechanical stimulation in a model of arthritis pain and attenuated mechanical hypersensitivity and thermal hyperalgesia occurring during the withdrawal of substance abuse.[43,49–52]

Corticotropin-releasing factor-CRF_1 signaling in the CeA is also a well-established key component of the neuronal circuitry contributing to anxiety-like behavior [47] and is positioned to drive the reciprocal relationship between pain and affective state.[53] Based on these preclinical data, it can be speculated that overactivity of the CRF-CRF_1 in the CeA may underlie the comorbidity of subset of IBS patients who display hypersensitivity to CRD[54] and mood disorders.[55] A recent clinical study using functional magnetic resonance imaging showed that an acute oral administration of the CRF_1 antagonist, GW 876008 dampened the amygdala activation produced by the anticipation of visceral pain compared to placebo drug in IBS female patients.[56] Whether the existing or newly developed CRF_1 antagonists[11] will progress to show therapeutic benefits for stress-sensitive visceral hyperalgesia in subsets of IBS is still a work in progress. An early clinical trial involving IBS patients with diarrhea did not show beneficial effect of oral administration of the CRF_1 antagonist paxacerfont (BMS-562086) on IBS symptoms although a dose-related trend to reduce pain was observed.[57]

MECHANISMS INVOVLED IN CRF-CRF_1 MEDIATED MODULATION OF VISCERAL HYPERSENSITIVITY IN THE CENTRAL AMYGDALA

The underlying neuronal mechanisms through which the blockade of CRF_1 receptor in the CeA alleviates the development of visceral hyperalgesia still remain unknown. The latero-capsular division of the CeA is defined as the ‘nociceptive amygdala’ as it receives nociceptive-specific input directly from the parabrachial area through the spinal-parabrachial-amyloidal pathway.[53] Studies in the somatic pain field established that CRF in the latero-capsular subdivision of CeA facilitates synaptic transmission of pain. Whole-cell patch-clamp recording of CeA neurons located in the latero-capsular division in brain slices established that CRF acts on postsynaptic CRF_1 receptors leading to protein kinase A dependent increases of *N*-methyl-D-aspartate (NMDA) receptor transmission. There is also a CRF_1-mediated activation of tetraethylamonium-sensitive ion channels such as Kv3 that accelerates action potential repolarization and increases firing rate.[47,51,52] Under condition

of chronic somatic pain hypersensitivity, there is also evidence that CRF_1 receptors 'switch on' silent NMDA receptors through PKA-dependent mechanisms in the CeA.[52] Additional studies in genetically modified mice with selective deletion of CRF_1 receptors on glutaminergic neurons in the CeA clearly demonstrated that CRF facilitates excitatory transmission by a CRF_1-mediated direct action on glutaminergic neurons.[13] Whether similar cellular mechanisms are involved in CRF-CRF_1 mediated visceral hyperalgesia in the CeA will be relevant avenues to investigate.

In addition to the critical role that CRF_1 receptors expressed on glutaminergic neurons of the CeA play,[13,58] there is evidence that catecholamine signaling may also regulate CeA glutaminergic transmission. [58] Several studies indicate that various stressors increase extracellular noradrenaline in the CeA.[59] In this issue of *Neurogastroenterology and Motility*, Su *et al.*[39] showed that CRD increases levels of noradrenaline in the CeA and the response is enhanced by CRF injected intra-CeA. These changes are CRF_1 mediated as shown by the blockade of CP-15426.[39] Of interest was the specificity of CRF-CRF_1 action to noradrenaline. The heightened levels of dopamine in the CeA induced by CRF were unchanged by CP-15426 while 5- HT levels were not modified by either treatment.[39] The pronounced interaction of CRF and catecholaminergic systems during stress has been established early on as a feed-forward mechanism taking place at multiple levels of the pons and basal forebrain, whereby CRF activates noradrenaline that in turn activates CRF.[60] The CeA received input from LC catecholaminergic nuclei.[61] We previously reported that colonic distension at nociceptive range markedly activates catecholaminergic neurons in the ventrolateral medulla (A1/C1), nucleus tractus solitarius (A2/C2), and LC cell group as shown by double labeling of Fos and thyrosine hydroxylase.[62] In addition the activation of LC noradrenergic neurons by CRD are prevented by systemic injection of the CRF_1 antagonist, NBI 35965 as shown by electrophysiological recording.[63] Whether the activated noradrenergic neurons in the LC contributes to the increased levels of noradrenaline after CRD through their projections to the CeA[61] remains to be established. Still to be addressed is whether changes in noradrenaline levels by intra-CeA after injection of CRF contribute to the visceral hyperalgesia. Recent studies showed that β-adrenergic receptor activation in the CeA could increase presynpatic glutamate release[58,59] while α_2 – adrenergic receptor agonist inhibits CeA excitability and induces somatic antinociception.[64]

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Key Messages

This review describes the role of CRF-CRF_1 receptor signaling in experimental models of visceral hyperalgesia with a focus on brain sites and mechanisms of action in the central amygdala.