Corticotropin-releasing factor and the brain-gut motor response to stress

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Y Taché, V Martinez, M Million, J Rivier. Corticotropin-releasing factor and the brain-gut motor response to stress. Can J Gastroenterol 1999;13(Suppl A):18A-25A. The characterization of corticotropin-releasing factor (CRF) and CRF receptors, and the development of specific CRF receptor antagonists selective for the receptor subtypes have paved the way to the understanding of the biochemical coding of stress-related alterations of gut motor function. Reports have consistently established that central administration of CRF acts in the brain to inhibit gastric emptying while stimulating colonic motor function through modulation of the vagal and sacral parasympathetic outflow in rodents. Endogenous CRF in the brain plays a role in mediating various forms of stressor-induced gastric stasis, including postoperative gastric ileus, and activates colonic transit and fecal excretion elicited by psychologically aversive or fearful stimuli. It is known that brain CRF is involved in the cross-talk between the immune and gastrointestinal systems because systemic or central administration of interleukin-1-beta delays gastric emptying while stimulating colonic motor activity through activation of CRF release in the brain. The paraventricular nucleus of the hypothalamus and the dorsal vagal complex are important sites of action for CRF to inhibit gastric motor function, while the paraventricular nucleus of the hypothalamus and the locus coeruleus complex are sites of action for CRF to stimulate colonic motor function. The inhibition of gastric emptying by CRF may be mediated by the interaction with the CRF_2 receptors, while the anxiogenic and colonic motor responses may involve CRF_1 receptors. Hypersecretion of CRF in the brain may contribute to the pathophysiology of stress-related exacerbation of irritable bowel syndrome.

Key Words: *Brain-gut interactions, Colonic motor function, Corticotropin-releasing factor, Irritable bowel syndrome*

La corticolibérine (CRF) et la réponse de l'axe cerveau-intestin au stress

RÉSUMÉ : La caractérisation de la corticolibérine (ou CRF, pour *corticotropin-releasing factor*) et de ses récepteurs, ainsi que le développement d'antagonistes spécifiques du CRF manifestant une sélectivité à l'endroit de certains sous-types des récepteurs, ont pavé la voie à une meilleure compréhension de l'encodage biochimique de la dysmotilité intestinale liée au stress. Les rapports ont toujours confirmé que l'administration centrale de CRF agit sur le cerveau pour inhiber la vidange gastrique tout en stimulant la motricité du côlon par l'entremise d'une modulation de l'influx vagal et parasympathique sacré chez le rat. Au niveau cérébral, le CRF endogène joue un rôle de médiateur sur diverses formes de stases gastriques dues au stress, notamment l'iléus gastrique post-opératoire; et il active le transit colique et l'émission des selles déclenchée par des stimuli aversifs ou terrifiants. On sait que le CRF cérébral participe aux échanges entre les systèmes immunitaire et gastro-intestinal parce que l'administration systémique ou centrale d'interleukine-1-bêta retarde la vidange gastrique tout en stimulant l'activité motrice colique par le biais de la sécrétion de CRF dans le cerveau. Le noyau paraventriculaire de l'hypothalamus et le complexe vagal dorsal sont d'importants sièges de l'action inhibitrice du CRF sur la motricité gastrique, alors que le noyau paraventriculaire de l'hypothalamus et le complexe du locus cœruleus sont d'importants sièges de l'action stimulante du CRF sur la motricité colique. L'inhibition de la vidange gastrique par le CRF est amenée par l'interaction avec les récepteurs du CRF_2, alors que les réponses motrices anxiogènes et coliques mettent en cause les récepteurs CRF_1. On se demande si l'hypersécrétion de CRF au cerveau ne contribuerait pas à la physiopathologie de l'exacerbation du syndrome du côlon irritable liée au stress.

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"…Should this man receive bad news, or should sad and baneful passions suddenly arise in his soul, his stomach and intestine will immediately cease to act on the foods contained in them. The very juices in which the foods are already almost entirely dissolved will remain as though struck by a moral stupor."

Cabanis' statement in 1802 (1) is among the first prescientific recognitions that the brain affects gut function. A few years later, Beaumont (2) reported clinical observations that emotional states linked with fear or anger disturbed gastric function. Pioneer experimental reports of brain-gut interactions by Pavlov (3) and Cannon (4) demonstrated that psychological stimuli such as sham feeding and fear influence gastric secretory and motor function in dogs and cats. Hall (5) established in rodents that defecation scores are a means of measuring the fearfulness response to unfamiliar surroundings or arousing situations.

Selye (6,7), while working at McGill University, Montreal, fathered the unifying concept of stress initially reported in 1936 as a "syndrome produced by diverse nocuous agents" and later defined as the "nonspecific response of the body to any demand". The activation of the pituitary adrenal axis induced by exposure to various stressors (7) stimulated research on the biochemical coding of the hypothalamic factors triggering the endocrine response. In the 1960s, Guillemin (8) (a former doctoral student of Selye) observed independently the presence of a corticotropin-releasing factor (CRF) in hypothalamic extracts that stimulates adrenocorticotrophic hormone (ACTH) release from anterior pituitary cells. However, CRF eluded characterization until 1981, when Vale and coworkers (9) (former doctoral students of Guillemin) reported the isolation of the 41-amino acid peptide involved in the pituitary stimulation of ACTH release. Recently, a new CRF-related mammalian peptide, urocortin, was identified in rats and humans, and the 40-amino acid peptide shares 45% homology with CRF (10).

Since the discoveries of CRF-related peptides along with the development of specific CRF receptor antagonists by Rivier et al (11), Gulyas et al (12), Hernandez et al (13) and Miranda et al (14), significant advances have been made in the understanding of the neurobiological basis of the stress response. In this article, we provide a brief background on CRF distribution in the brain, CRF receptor characterization and new advances in the development of selective CRF antagonists. In addition, we review recent experimental evidence supporting a role of brain CRF in mediating the gastric and colonic motor alterations induced by stress and its possible pathophysiological relevance to irritable bowel syndrome (IBS).

BRAIN CRF AND CRF RECEPTOR DISTRIBUTION, AND BIOLOGICAL ACTIONS OF CENTRAL CRF

CRF is widely distributed in the brain, with the highest abundance in the paraventricular nucleus of the hypothalamus (PVN) (15,16). A subset of CRF-containing neurons projects to the portal capillary zone of the median eminence to stimulate the secretion of ACTH from the anterior pituitary gland. The subsequent ACTH-induced release of adrenal glucocorticoids is part of the response of the peripheral limb of the hypothalamic-pituitary axis (HPA) to stress (15,16). In addition to its neuroendocrine role, CRF, when injected centrally, elicits a wide spectrum of behavioural, autonomic and visceral responses, including anxiogenic behaviour and inhibition of food intake, increases in sympathetic outflow, decreases in vagal activity, and alterations in cardiovascular and immunological function that mimic the bodily alterations induced by various stressors (17-23).

CRF mediates its actions through interaction with specific, high affinity, membrane-bound receptors that are coupled to a guanine nucleotide stimulatory factor-signalling protein, resulting in increased intracellular cAMP levels (19,24,25). Two different CRF receptors, CRF_1 and CRF_2 subtypes, have been cloned and characterized in rats as well as in humans (24-26). These receptors show an overall 71% identity and differential pharmacological and anatomical profiles, indicative of distinct functional roles (26,27). Binding constants in transfected cells indicate that rat/human CRF (r/hCRF) exhibits a higher affinity for the CRF_1 receptor than the CRF_2 subtype (25,26,28). By contrast, CRF-related peptides, sharing a 40% to 50% structural homology with CRF, namely, sauvagine, a 40-amino acid peptide isolated from the *Phyllomedusa sauvagi* amphibian's skin, and urotensin-I, a 41-residue peptide isolated from teleost fish, as well as mammalian urocortin, display a higher affinity at the CRF_2 receptor than CRF, while having a similar affinity to CRF at the CRF_1 subtype (25,26,28). The CRF_1 receptor is the predominant form localized in the pituitary gland, olfactory bulb and cerebral cortex, while the CRF_2 subtype is found in the lateral septum, hypothalamus, amygdala and brain stem (25,26).

CRF RECEPTOR ANTAGONISTS

Rivier et al (11), Gulyas et al (12), Hernandez et al (13), Miranda et al (14), Fisher et al (29) and Menzaghi et al (30) developed three generations of CRF analogues with competitive antagonistic activity at both the CRF_1 and CRF_2 receptor subtypes (Table 1). Alpha-helical CRF_{9-41}, [Met^{18},Lys^{23}, $Glu^{27,29,40}$,$Ala^{32,41}$,$Leu^{33,36,38}$]r/hCRF_{9-41} developed in 1982 and the D-Phe^{12} CRF_{12-41} analogue [D-Phe^{12}, $Nle^{21,38}$,$C^{\alpha}MeLeu^{37}$]r/hCRF_{12-41} have been extensively used in vivo to assess the physiological role of CRF in endocrine, autonomic, immune, behavioural and gastrointestinal responses to various stressors (11,13,18-21,29-33). However, these antagonists have some limitations due to their poor solubility, persistence of intrinsic activity and weak potency at pituitary receptors (12,29,30). In addition, alpha-helical CRF_{9-41} has a high affinity for the CRF binding protein (12). Further research aimed at achieving conformational stability of CRF antagonists resulted in the development of astressin, cyclo(30-33)[D-Phe^{12},$Nle^{21,38}$,Glu^{30},Lys^{33}]r/hCRF_{12-41} (12,14). Astressin's main characteristics are its low intrinsic

TABLE 1
Peptides and nonpeptide antagonists

CRF antagonist	Selectivity	Effective doses	Reference
Peptides			
alpha-helical CRF_{9-41}	CRF-R1,2	50 μg, ic, icv; 2 mg/kg, iv	11,29
[D-Phe^{12}, $Nle^{21,38}$, $C^{\alpha}Leu^{37}$]h/$rCRF_{12-41}$	CRF-R1,2	20 μg, ic, icv; 0.5 mg/kg, iv	13,30
Astressin	CRF-R1,2	3 μg, ic, icv; 0.1 mg/kg, iv	12,42
Nonpeptides			
CP-154,526	CRF-R1	5 to 30 mg/kg, iv, po	36,37
NBI 27914	CRF-R1	NT	35
Antalarmin	CRF-R1	20 mg/kg, ip	38

CRF Corticotropin-releasing factor; CRF-R Corticotropin-releasing factor receptor; ic Intracisternal; icv Intracerebroventricular; ip Intraperitonial; iv Intravenous; NT Not tested; po Oral

activity, high solubility in aqueous solutions, and high affinity to both CRF_1 and CRF_2 receptor subtypes, while lacking an affinity to the CRF binding protein (12,34). Recent reports indicate that astressin has an approximately 32-fold and 100-fold higher potency than D-Phe CRF_{12-41} and alpha-helical CRF_{9-41}, respectively, to inhibit ACTH secretion from pituitary cells in culture (12,14). Moreover, after peripheral administration in rats, astressin is 10-fold more potent than any other CRF antagonists reported to inhibit stress-induced increases in ACTH plasma levels (12).

During the past two years, nonpeptide competitive CRF receptor antagonists, namely NBI-27914, CP-154,526 and antalarmin, which exhibit a highly selective antagonist action at the CRF_1 receptor subtype, became available (35-38) (Table 1).

ROLE OF BRAIN CRF IN STRESS-RELATED INHIBITION OF GASTRIC MOTOR FUNCTION

Stress influences gastric motor function, including motility and transit. Although the pattern of gastric motor changes can vary in function according to the stressors (pages 26A to 31A), the most consistent effect relates to the inhibition of gastric contractions and gastric emptying in experimental animals and humans (39-41).

The injection of CRF into the cerebrospinal fluid (CSF), into either the lateral or third ventricle or the cisterna magna, delays gastric emptying of a non-nutrient viscous solution and of a caloric meal, either liquid (glucose) or solid (Purina chow, Ralston Purina, Missouri), in conscious rats and mice (42-54). Active transport of CRF from the brain to the periphery exists (55,56); however, convergent evidence indicates that the delay of gastric emptying induced by injecting CRF into the CSF is a central nervous system action and not a peripheral effect due to leakage of the peptide (44,46,51,53). Brain sites responsive to CRF and resulting in the inhibition of gastric motor function include the PVN and dorsal vagal complex, whereas the locus coeruleus complex (LCC), lateral hypothalamus or central amygdala (unilateral microinjection) microinjected with CRF did not alter gastric motor function (52,57,58). CRF action is mediated by a specific interaction with CRF receptors in the brain. Central administration of either of the three peptidergic CRF receptor antagonists blocked concurrent injection of CRF-induced inhibition of gastric emptying in rats and mice (42,43,45,46,48,53). In particular, astressin proved to be six- to 16-fold more potent than the two previously developed peptidergic CRF receptor antagonists (42). Evidence based on the potency of the CRF-related peptides sauvagine and urotensin, with a higher affinity for the CRF_2 receptor subtypes, suggests that CRF_2 receptors may be preferentially involved in the intracisternal injection of CRF-induced delay in gastric emptying in rats (50,59,60). The central action of CRF can be modulated by other transmitters. Intracisternal injection of the sigma ligand JO 1784 attenuated intracisternal CRF-induced delayed gastric emptying (47).

Peripheral autonomic pathways convey CRF action from the brain to the stomach, whereas associated activation of the pituitary-adrenal axis and endorphins do not play a role. Inhibition of the gastric motor response by the central injection of CRF was not altered by hypophysectomy, acute adrenalectomy and naloxone pretreatment, but was abolished by ganglionic blockade in rats and mice (31,44,46,50,54). Most reports, except one (54), indicate that central CRF delays gastric emptying through vagal-dependent mechanisms. Intracisternal injection of CRF and sauvagine decreases the discharge of gastric vagal efferents (61), and vagotomy completely prevents the inhibition of gastric emptying induced by intracisternal or intracerebroventricular injection of CRF (44,50) and partly prevents the inhibition of gastric emptying induced by PVN microinjection of CRF (57). CRF microinjected into the dorsal vagal complex inhibits exogenous and endogenous thyrotropin-releasing hormone (TRH) in the dorsal vagal complex-induced vagal stimulation of gastric contractility (58). Further indication of an inhibition of preganglionic vagal motor neuron activity by intracerebroventricular injection of CRF also came from studies using *Fos* expression as a marker of neuronal activation (62). Cold exposure activates dorsal motor nucleus of the vagus neurons through medullary TRH release (63-65). Intracerebroventricular injection of CRF suppressed the number of *Fos*-positive cells in the dorsal motor nucleus of the vagus that were induced by cold exposure by 80% (66).

The role of endogenous brain CRF in stress-related delayed gastric emptying was further established by the use of the three peptidergic CRF receptor antagonists injected into the CSF or the PVN at doses that block the effect of exogenous CRF. Abdominal and brain surgery-, restraint-, forced swimming- and ether anesthesia-induced inhibition of gastric emptying were all prevented by the central injection of the CRF receptor antagonists (42,43,49,53,57,67) (Table 2). Recently, we reported that 3 μg astressin injected intracisternally completely inhibited abdominal surgery, and cecal manipulation induced 60% to 65% inhibition of gastric emptying 3 h after surgery. By contrast, 10 to 50 μg is re-

TABLE 2
Reversal of stress-induced gastric and colonic motor disorder by corticotropin-releasing factor (CRF) antagonists

Stressors	Gastric/colonic motor changes	CRF antagonist	Antagonist dose (μg/rat)	Reference
Abdominal surgery	Decreased GE	Astressin	3, ic	2
Abdominal surgery	Decreased GE	D-Phe CRF_{12-41}	10, ic	67
Abdominal surgery	Decreased GE	α-helical CRF	100, ic	43
Trephination	Decreased GE	α-helical CRF_{9-41}	100, ic	43
20 min swim	Decreased GE	α-helical CRF_{9-41}	30, icv	49
Restraint	Decreased GE	α-helical CRF_{9-41}	50, PVN	57
Interleukin-1-beta	Decreased GE	D-Phe CRF_{12-41}	20, ic	48
Ether	Decreased GE	α-helical CRF_{9-41}	100, ic	43
Water avoidance	Increased defecation	Astressin	10, ic	42
Water avoidance	Increased CT, defecation	α-helical CRF_{9-41}	50, PVN, icv	53,57
Restraint	Increased CT, defecation	α-helical CRF_{9-41}	50, PVN, icv	51,53,57
Conditioned fear	Increased colonic spike burst	α-helical CRF_{9-41}	2.5, icv	87
Interleukin-1-beta	Increased colonic spike burst	α-helical CRF_{9-41}	10, icv	102

CT Colonic transit; ic Intracisternal; icv Intracerebroventricular; GE Gastric emptying; PVN Paraventricular nucleus of the hypothalamus

quired for the other CRF receptor antagonists, D-Phe CRF_{12-41} and alpha-helical CRF_{9-41}, demonstrating the enhanced potency of astressin (42,67) (Figure 1). The demonstration that the postoperative ileus is mediated by supraspinal CRF-dependent mechanisms may add to the understanding of the biochemical coding and neuronal circuitry involved in the efferent limb of the reflex (43,67,68). Indeed, earlier studies recognized the importance of sympathoadrenergic as well as vagal efferent pathways in postoperative gastroparesis (69,70). Such pathways are consistent with the release of CRF in the brain by surgery (71,72) and CRF-dependent modulation of autonomic outflow, resulting in alterations of gastric motor function (61,73-77).

In addition, CRF in the brain may play a role in functional alterations of gastric motility during immune challenge. Interleukin-1, one of the key mediators involved in the immunological and pathological response to infections and antigenic challenges (78), activates CRF neurons in the PVN (79,80). In line with a role of brain CRF in the regulation of gastric emptying in response to various challenges, interleukin-1-beta injected peripherally or into the CSF delays gastric emptying of a non-nutrient meal (48,81-83). Upon microinjection into the dorsal vagal complex, it inhibits the vagal-dependent stimulation of gastric contractility induced by coinjection of TRH (84). Central injection of the CRF receptor antagonist D-Phe CRF_{12-41} prevents the delayed gastric emptying induced by intracisternal or intravenous injection of interleukin-1-beta in rats (48,81). Taken together, these findings strengthen the important role of brain CRF in the gastric stasis resulting not only from exposure to psychological, physical or chemical stress (31) but also from immunological challenges associated with activation of interleukin-1 (48,81). By contrast, CRF in the brain is not involved in the basal regulation of gastric emptying under nonstress conditions in rats (42,45). Studies in dogs also indicate that intracerebroventricular injection of CRF abolishes the cyclic activity front of the antrum, and one mechanism may involve modulation of motilin release (85,86).

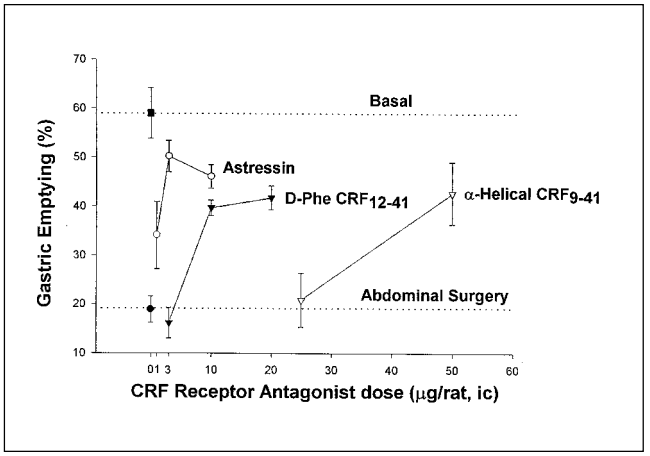

Figure 1) *Reversal of a postoperative ileus by intracisternal injection of various peptidergic corticotropin-releasing factor (CRF) antagonists in conscious rats. Fasted rats were exposed to short enflurane anesthesia for 10 mins. Saline or a CRF receptor antagonist was injected intracisternally (ic) immediately before abdominal surgery (laparotomy plus 1 min manipulation of the cecum). Gastric emptying was determined 160 to 180 mins after surgery. Each column is the mean ± SEM of four to 10 rats. Data from references 13, 42 and 67*

ROLE OF BRAIN CRF IN STRESS-INDUCED ACTIVATION OF COLONIC MOTOR FUNCTION

The stimulation of colonic motor function in response to exposure to various stressors has been recently reviewed based on experimental and clinical reports (33). Much of the recent progress in identifying the mechanisms through which

stress stimulates colonic motor function has come from the use of CRF and CRF receptor antagonists injected into the brain (31,33).

Williams et al (51) were among the first to establish that intracerebroventricular injection of CRF results in the stimulation of colonic transit and fecal output in conscious female rats. Since then, several reports have shown that CRF injected into the lateral brain ventricle activates colonic motor function assessed by the increase in colonic spike-burst frequency, contractility, transit and fecal output in conscious male rats (33,42,53,55,73,87-91). Brain sites of action for CRF to activate colonic motor function have been located in the PVN and LCC; microinjection of CRF targeted at these specific nuclei increased colonic motility, transit and fecal output as well as diarrhea at the maximally effective dose in conscious rats (52,57,92-96). By contrast, microinjection of CRF into the lateral, anterior or ventromedial hypothalamus, central amygdala (unilateral injection) or the bed nucleus of the stria terminalis did not alter the rate of colonic transit or defecation (57,93,94). CRF-induced stimulation of colonic motor function upon central injection is mediated by receptor-specific interactions in the brain as shown by the prevention of CRF action by the competitive CRF receptor antagonists alpha-helical CRF_{9-41} and astressin, injected into the CSF but not intravenously in conscious rats (42,51,53,87,96). In these functional studies, astressin proved to be more potent than the previously developed peptidergic CRF receptor antagonists (42). In anesthetized rats, microinjection of the CRF antagonist D-Phe CRF_{12-41} into the LCC abolished the stimulation of characteristic spike burst activity induced by microinjection of CRF into the LCC (97).

Pharmacological studies indicate that the central action of CRF – activation of colonic motor function – is modulated by several transmitters acting on specific receptors. The anxiolytic drug buspirone, acting through 5-hydroxytryptamine$_{1A}$ autoreceptors (88); cholecystokinin (CCK) through CCK-A receptors (89,98); neuropeptide Y (89,90); the sigma agonists (90); and arginine vasopressin receptor antagonist (91) prevented the stimulation of colonic spike burst activity in rats induced by the intracerebroventricular injection of CRF (87).

Autonomic pathways mediate the central action of CRF – simulation of colonic motor function – while the activation of the HPA axis does not play a role. This was established by the inhibition of the colonic response to CRF injected into the lateral ventricle by the ganglionic blocker chlorisondamine and the unchanged stimulatory response after hypophysectomy, adrenalectomy and naloxone pretreatment (54,87,93). The parasympathetic nervous system is involved as shown by the prevention of the central action of CRF by atropine, while noradrenergic blockade by bretylium had no effect (54,57,92,93). It is likely that the sacral component of the parasympathetic pathways also plays a role because subdiaphragmatic vagotomy does not alter the activation of colonic transit and fecal output induced by CRF microinjection into the PVN (57).

The role of central CRF in mediating stress-related activation of colonic motor function is supported by several neuropharmacological studies in conscious rats. Alpha-helical CRF_{9-41} injected into the lateral brain ventricle or PVN abolishes partial wrap restraint- or water avoidance stress-induced stimulation of colonic transit and defecation (51,53,57,92). In other studies, intracerebroventricular injection of alpha-helical CRF_{9-41} and astressin reduced the water avoidance stress-induced fecal output in fed rats by 60% (42,95). Interestingly, water avoidance stress stimulates *Fos* expression in specific populations of neurons, mainly in the PVN, LCC, septum and bed nucleus of the stria terminalis, and the alpha-helical CRF_{9-41} selectively decreases the activation of neurons located in the PVN and LCC in tandem with the suppression of colonic output in conscious Sprague-Dawley rats (96). In addition, simultaneous recording of locus coeruleus neuronal and cecocolonic myoelectric activity showed that microinjection of CRF at the locus coeruleus induces a similar onset of activity in both locus coeruleus neurons and colonic myoelectric activity. Both responses are abolished by microinjection of the CRF antagonist into the LCC (95). Female Lewis rats, which display a defective CRF response to immune challenge stress (99,100), have a 50% lower fecal output response to water avoidance stress in association with a significant decrease in *Fos* expression in the PVN, LCC and sacral parasympathetic neurons compared with female Fischer rats (101). These observations suggest that the activation of PVN and LCC neurons by CRF may have a bearing on the neuronal network involved in the stimulation of colonic motor function in this model of water avoidance stress. Conditioned fear-induced increases in the frequency of cecal and colonic spike bursts were also prevented by intracerebroventricular injection of alpha-helical CRF_{9-41}. Interleukin-1 injected into the lateral brain ventricle stimulates colonic spike burst frequency through brain CRF mechanisms as shown by the reversal of the response by intracerebroventricular injection of alpha-helical CRF_{9-41} (102). These data further support the concept that immunological stress may influence colonic motor function through interleukin-1-mediated activation of CRF in the brain. By contrast, central CRF does not play a role in the basal regulation of colonic motor function in nonstressed rats (42,51,53,57, 87,93).

RELEVANCE OF BRAIN CRF PATHWAYS TO IBS

The possible relevance of brain CRF pathways in the pathophysiology of IBS has been recently suggested (33). Of significance is the association of IBS in patients who scored higher on psychological vulnerability than normal subjects, and in those with a diagnosis of psychiatric illness involving depression, panic disorders or anxiety (103-109). A correlation between stressful life events and bowel symptoms has also been reported (110). In addition, for patients with IBS, the improvement of psychological status by psychological or pharmacological treatments led to parallel improvements in bowel symptomatology, particularly in patients suffering from anxiety or depression associated with diarrhea, and in-

termittent abdominal pain exacerbated by stress (105,111). Consistent with a possible role of brain CRF is the link between psychological and IBS symptoms and recent findings that the sites in the brain inducing stimulation of colonic motor function such as the PVN and LCC are also sites of CRF action to increase emotional, antigenic and fear-related behaviours in several mammals including monkeys (17-20). In addition, CRF antagonists injected into these nuclei or into the CSF abolished both stress-induced anxiogenic behaviour (112-115) and stimulation of colonic motor function (92,95). Recent reports suggest that both the anxiogenic and colonic motor responses to stress are mediated by endogenous CRF interaction at the CRF_1 subtype (36,37,116-118). These findings indicate that enhanced CRF activity may be associated with neuropsychiatric disorders and IBS manifestations.

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