Published in final edited form as:
Annu Rev Physiol. 2009 ; 71: 219–239. doi:10.1146/annurev.physiol.010908.163221.

Neuroendocrine Control of the Gut During Stress: Corticotropin-Releasing Factor Signaling Pathways in the Spotlight

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Abstract

Stress affects the gastrointestinal tract as part of the visceral response. Various stressors induce similar profiles of gut motor function alterations, including inhibition of gastric emptying, stimulation of colonic propulsive motility, and hypersensitivity to colorectal distension. In recent years, substantial progress has been made in our understanding of the underlying mechanisms of stress's impact on gut function. Activation of corticotropin-releasing factor (CRF) signaling pathways mediates both the inhibition of upper gastrointestinal (GI) and the stimulation of lower GI motor function through interaction with different CRF receptor subtypes. Here, we review how various stressors affect the gut, with special emphasis on the central and peripheral CRF signaling systems.

Keywords

motility; CRF antagonists; colon; stomach; urocortin

INTRODUCTION

More than 70 years ago, Hans Selye (1) identified the gut, along with the endocrine and immune systems, as the primary target altered by a variety of chemical and physical challenges and pioneered the concept of stress as the "stereotyped biological response to any demand." Later, the term allostasis was introduced by Sterling & Eyer (2) to refer to the "maintenance of stability through change." Subsequently, McEwens (3) applied this concept to define stress as the physiological adaptation processes that maintain stability in times of internal or external challenges. Excessive stress can result in cumulative biological changes (known as allostatic load) and can alter adaptive mechanisms, resulting in an inefficient allostatic response and a permanent change in the basal levels of stress mediators (4). A perpetual imbalance between adaptation capacity and stressors can result in allostatic overload, leading to a state of illness (4) that may affect different body systems and induce development of functional bowel diseases (5). It is now appreciated that signaling pathways involving corticotropin-releasing factor (CRF) are altered by stress and contributetofunctional bowel diseases (5).

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DISCLOSURE STATEMENT
The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

STRESS AND THE GUT

In recent years, our understanding of the circuitries and biochemical coding involved in the stress response has increased tremendously (6). Many studies have used the immediate early gene *c-fos* protein (Fos) immunohistochemistry as a marker of neuronal activity, thereby identifying brain nuclei that respond to acute or chronic stress (7) and their relation to the autonomic regulation of gut function (8–11). CRF is the primary neurohormone involved in the hallmark response to stress: the activation of the hypothalamic-pituitary-adrenal (HPA) axis. CRF also acts as a neurotransmitter/neuromodulator to coordinate the behavioral, autonomic, and visceral efferent limbs of the stress response (12–14). Convergent findings support the involvement of CRF receptors in the brain and the gut as important mediators of acute or chronic stress–related alterations of gut function (14–16). Furthermore, environmental stressors seem to play a role in the development and/or exacerbation of functional bowel diseases, such as irritable bowel syndrome (IBS), which is characterized by altered bowel habits and visceral hypersensitivity (17–20). Growing preclinical and clinical reports indicate that increased central and peripheral CRF signaling may contribute to the development and maintenance of functional bowel disorders through the alteration of autonomic, enteric nervous, and immune system activity (5,16).

THE CORTICOTROPIN-RELEASING FACTOR FAMILY AND ITS RECEPTORS

Mammalian Corticotropin-Releasing Factor and Urocortins

CRF, originally isolated by Vale and colleagues in 1981 (21), is a 41-amino-acid (aa) hypothalamic releasing peptide that stimulates the synthesis and release of adrenocorticotropic hormone and β-endorphin from the anterior pituitary. More recently, three other mammalian CRF-related peptides have been characterized: urocortin 1 (Ucn 1), a 40-aa peptide with 45% sequence identity with rat/human (r/h) CRF; urocortin 2 (Ucn 2); and urocortin 3 (Ucn 3) (22–25). Mouse Ucn 2 (mUcn 2) is a 38-aa peptide sharing 34% homology with r/h CRF and 42% with r/h Ucn 1 (24). However, the 38-aa peptide mUcn 3 shares only 26% and 21% homology to r/h CRF and r/h Ucn 1, respectively (25). Phylogenetic profiling of the CRF peptide family indicates that these four distinct genes—those encoding CRF, Ucn 1,Ucn 2, and Ucn 3—are highly conserved through evolution and can be traced back to invertebrates, indicating their important roles in survival and adaptation (26,27).

CRF_1 and CRF_2 Receptors

CRF and urocortins interact with two receptors, CRF_1 and CRF_2, which are encoded by two distinct genes exhibiting 70% sequence homology(28). The human and rat genomic structures of the CRF_1 receptor contain 14 and 13 exons, respectively. In most mammals, the active CRF_1 receptor protein results from transcription of all exons. In contrast, translation of all 14 exons in humans results in a humanspecific, 444-aa protein named CRF_{1b} that contains an extended first intracellular loop and exhibits impaired agonist binding and signaling properties (29,30). The 415-aa protein CRF_{1a} is the main functional CRF_1 variant resulting from the excision of exon 6. In addition to CRF_{1a} and CRF_{1b}, the CRF_1 gene gives rise to multiple additional splice variants (1c, 1d, 1e, 1f, 1g, 1j, 1k, 1m, and 1n) that have neither a ligand binding site nor a signaling domain, although some variants modulate CRF and Ucn 1 actions (29). The expression of these CRF_1 isoforms is tissue specific and can vary with the tissues' functional activity as well as with environmental factors (29). For instance, the onset of labor is associated with an increased transcription of myometrial CRF_{1a} gene and with differential up- and downregulation of other specific variants that may be implicated in the passage of quiescent to procontractile activity of the myometrium during labor (31). The expression and regulation of CRF_1 receptor variants under conditions of acute or chronic stress in the brain and the gut are still largely unexplored.

In humans, there are three functional splicing variants of the CRF_2 receptor (namely 2a, 2b, and 2c), whereas in other mammals only 2a and 2b are expressed (29,32). The CRF_2 variants display a distinct expression profile in mammals (29,32). The CRF_2 isoforms result from alternative splicing of exon 1 to exon 3. This splicing leads to structurally distinct N-terminal extracellular domains (34 aa for CRF_{2a}, 61 aa for CRF_{2b}, and 20 aa for CRF_{2c}), which are involved in ligand-receptor interaction (32,33). In addition to the wild-type $CRF_{2a\text{-}1}$,five additional splice variants, $CRF_{2a\text{-}2}$ to $CRF_{2a\text{-}6}$, have been identified in the rat upper gut (34). Interestingly, the mouse CRF_{2a} splice variant, originally identified in the brain as a soluble binding protein ($sCRF_{2a}$) for CRF and Ucn 1 (35), is also expressed in the rat upper gut ($CRF_{2a\text{-}6}$) (34).

CRF_1 and CRF_2 receptors show distinct affinities to CRF and related peptides (29,32). Although CRF has a 10-to40-fold higher affinity for the CRF_1 receptor than for the CRF_2 receptor, urocortins preferably signal through CRF_2 receptors. Ucn 1 binds with equal affinity to both CRF receptors and has a 100-fold higher affinity than CRF for the CRF_2 receptor (29,36). In contrast, Ucn 2 and Ucn 3 show high selectivity for the CRF_2 receptor (29,36) (Figure 1). Because none of the endogenous CRF ligands characterized thus far exclusively activate CRF_1 receptors, selective peptide CRF_1 agonists (namely cortagine and $stressin_1$-A) have recently been developed (36–38) (Figure 1). However, the molecular determinants that govern the binding of CRF-family peptides to their cognate receptors have been extensively characterized (29). The long N-terminal extracellular domain of CRF receptors primarily interacts with the C-terminal residues of CRF, whereas the N-terminal residues of CRF interact with the transmembrane region of the receptor, resulting in conformational changes that enable G protein activation (29).

In most tissues, signal transduction of CRF_1 and CRF_2 primarily involves coupling to the G_s–adenyl cyclase system, with subsequent cAMP generation and protein kinase A activation. In addition, CRF receptors, like most heptahelical G protein–coupled receptors, can interact with multiple G protein systems including G_q, G_i, G_o, $G_{il/2}$, and G_z to relay signals to diverse intracellular effectors in an agonist- and tissue-specific manner (29). Thus, CRF receptors (*a*) may modulate various kinases, including phosphokinases A, B, and C, (*b*) can phosphorylate and activate mitogenactivated protein kinase (MAPK), in particular the ERK1/2 and p38/MAPK pathways, and (*c*) can alter intracellular Ca^{2+} concentrations (29,34).

Brain Distribution of Corticotropin-Releasing Factor Ligands and Receptors

The distribution of CRF-immunoreactive (ir) cells and fibers in the rat brain has been extensively described (39–41). The major brain areas expressing CRF messenger RNA (mRNA) and CRF-ir cells include the paraventricular nucleus (PVN) of the hypothalamus, the cerebral cortex, the amygdalar-hippocampal complex, and Barrington's nucleus in the dorsolateral pons. The PVN is the major site of CRF-containing cell bodies projecting to the median eminence. CRF neurons in the central amygdala project to the PVN, the locus coeruleus (LC), and the parabrachial nucleus, and neurons in the bed nucleus of stria terminalis project to the dorsal vagal complex (DVC). CRF-containing neurons in Barrington's nucleus contribute to the CRF innervation of the LC and the sacral spinal cord (40,42).

CRF, Ucn 1, Ucn 2, and Ucn 3 distribution in the rat brain shows limited neuroanatomical overlap (43). In contrast to Ucn 1's widespread peripheral distribution, peptide expression in the brain is limited (22,44,45). The most prominent brain site of Ucn 1 expression and immunoreactivity is the Edinger-Westphal nucleus (44,46). Moreover, Ucn 1–ir can be detected in the lateral superior olive; the olfactory bulb; the supraoptic nucleus (SON); the ventromedial hypothalamus (VMH); and magnocellular parts of the PVN, the lateral hypothalamic area, and the ambiguous nucleus; as well as the cranial nerve motor nuclei (facial and hypoglossal) (46,47). The majority of Ucn 1–ir projections provide descending input to

the brainstem, whereas ascending projections are restricted. In particular, Ucn 1–ir fibers project to CRF_2 receptor–containing nuclei including the lateral septum, the dorsal raphé,the interpeduncular nucleus, the nucleus of the solitary tract, and the area postrema (46). Ucn 2 gene expression is localized in the parvo- and magnocellular PVN, the SON, the arcuate nucleus of the hypothalamus, and the LC, as well as several cranial nerve motor nuclei (trigeminal, facial, and hypoglossal nuclei) and the ventral horn of the spinal cord (24,48). Ucn 3 mRNA has been detected in the PVN, the amygdala (basomedial nucleus), and the basomedial nucleus of the stria terminalis (43,48). Assessment of brain distribution of Ucn 2–ir fibers has been hampered by the lack of specific Ucn 2 antibodies. Ucn 3–ir fibers innervate the lateral septum, the amygdala (except for the central nucleus), the dorsal aspect of the VMH, and the dorsal raphé, as well as the area postrema (25,48,49).

In rat brain, the CRF_1 receptorisdensely expressed in the forebrain and subcortical limbic structures in the septal region and amygdala. In the hypothalamus, expressionis low under basal conditions but can be significantly upregulated during stress or following CRF application (50–52). Dense CRF_1 receptor representation also appears in the anterior and intermediate lobes of the pituitary, which supports its role in the activation of the HPA axis by CRF (53). In contrast, CRF_2 receptor expression in rodents is confined to subfornical structures, with high expression in the lateral septum, amygdala (with the exception of central nuclei), and hypothalamus (including high levels in the VMH and SON) (54). In the hindbrain, the dorsal raphé, area postrema, nucleus of the solitary tract, and chorionic plexus express the CRF_2 receptor (54). A close association has been found between Ucn 3–ir–terminal fields and expression ofCRF_2 receptors in specific hypothalamic nuclei (49).

Corticotropin-Releasing Factor Receptor Antagonists and Binding Protein

Key to the understanding of the physiological role of the CRF signaling pathways is the early development of CRF receptor antagonists by Rivier et al. (55). The first of these antagonists to be developed are the nonselective CRF_1/CRF_2 receptor antagonists α-helical $CRF_{9–41}$, D-$Phe^{12}CRF_{12–41}$, astressin, and the long-acting astressin-B. Recently, two groups developed the peptide CRF_2 receptor antagonists antisauvagine-30, K41498, [D-Phe^{11}, His^{12}, Nle^{17}] $sauvagine_{11–40}$, and the more potent and long-acting analog $astressin_2$-B, which are competitive antagonists that bind equally to the a, b, and c variants of CRF_2 receptor (35,56, 57) (Figure 1). A common feature of these peptide antagonists is that they display poor penetrance into the brain when administered peripherally. In an early study, our group showed that an intravenous injection of astressin did not influence the inhibition of gastric transit in response to CRF injected into the cisterna magna, although the same dose blocked peripheral CRF–induced delay of gastric emptying (58). With regard to selective CRF_1 antagonists, pharmaceutical firms have developed a large number of high-affinity small hydrophobic molecules that can cross the blood-brain barrier. The impetus to create these molecules arose from their potential therapeutic application to curtail dysregulation of CRF-signaling pathways that may be relevant to the pathogenesis of human illnesses such as anxiety and depression, eating disorders, inflammatory diseases, substance abuse, preterm parturition, and functional bowel disorders (59–62). Among the CRF_1 antagonists most commonly used in experimental studies are CP-154,526, antalarmin, NBI-34041, NBI-30545, and NBI-35965 (60,63).

In addition to the synthetic antagonists that can block CRF receptors, a 332-aa endogenous CRF binding protein (CRF-BP) has been isolated across different species (64,65). The CRF-BP functions as an endogenous antagonist by sequestering CRF ligands and therefore modulating the access of CRF and related peptides to CRF receptors (64). Rat and human CRF and Ucn 1 display high (picomolarrange) affinity for the CRF-BP, whereas Ucn 2 shows a moderate (nanomolar-range) affinity and Ucn 3 displays no affinity (65) (Figure 1). The decrease in food intake and body weight, the anxiogenic-like behavior occurring in CRF-BP-

deficient mice, and, conversely, the body weight gain in CRF-BP-overexpressing mice support the contention that CRF-BP can sequester CRF/Ucn 1 and modulate endogenous CRF/Ucn 1 biological actions (66,67). Recent studies have identified distinct regions and residues of the CRF-BPthat are responsible for r/h CRF and r/h Ucn 1 binding to CRF-BP. In particular, a single alanine mutation (R56A) in CRF-BP was effective in creating an Ucn 1–specific antagonist, thereby opening new venues for the design of selective CRF versus Ucn 1 antagonists to dissect their respective role in the stress response (68). In rat brain, CRF-BP immunoreactivity is prominently expressed in hypothalamic regions involved in the neuroendocrine and autonomic responses to stress, including the subdivision of the dorsal cap of the PVN projecting to the spinal cord (64,69).

The isolation of CRF and endogenous selective CRF_2 receptor agonists, along with the development of selective CRF_1 agonists and antagonists and CRF_2 antagonists, provided essential tools to establish the pleiotropic actions of CRF and urocortins in the brain by acting at one or both CRF receptors. In particular, this pharmacological approach has allowed investigators to dissect the primary involvement of CRF_1 signaling pathways in the stress-related stimulation of the HPA axis, anxiogenic behavior, alterations in the autonomic nervous system activity, and visceral responses (5,13,70).

STRESS-RELATED ALTERATIONS OF GASTROINTESTINAL MOTILITY MEDIATED BY BRAIN CORTICOTROPIN-RELEASING FACTOR RECEPTORS

Various acute stressors most commonly delay gastric emptying in experimental animals as well as in healthy humans (12). In contrast, a range of stressors (e.g., anxiety, dichotomous listening, fear, intermittent hand immersion in cold water, and stressful interviews) increase colonic motility in healthy volunteers (12). Activation of propulsive colonic motor function has also been shown in rodents following exposure to diverse stressors such as open field tests, conditioned fear, loud sounds, restraint, cold exposure, water avoidance, inescapable foot or tail shocks, and central injection of interleukin-1 (12,71–73). Consistent experimental evidence highlights the role of central CRF recep tors in stress-related inhibition of gastric motor function and in stimulation of colonic propulsive motor activity, as shown by central injection of CRF and urocortins in nonstressed animals as well as by the injection of CRF antagonists under stress conditions.

Brain Corticotropin-Releasing Factor Receptors Mediate Stress-Related Inhibition of Gastric Motor function

A number of studies have established that central injection [intracerebroventricularly (icv), intracisternally (ic), or into the fourth ventricle] of CRF,Ucn1,Ucn2,or nonmammalian CRFrelated peptides such as sauvagine and urotensin I inhibits gastric emptying of acaloric liquid, caloric liquid, or solid meal and alters gastric motility. These changes include the suppression of propagative contractions, cyclic activity front, high-amplitude contractions, and the disruption of fasted pattern in species including rats, mice, and dogs (74). Central injection of α-helical $CRF_{9–41}$, D-$Phe^{12}CRF_{12–41}$, astressin, astressin-B, and $astressin_2$-B blocks the icv or ic CRF-, Ucn 1–, and Ucn 2–induced delay of gastric emptying and inhibition of motility in rats, mice, and dogs. However, selective CRF_1 antagonists have no effect, indicating that CRF's and urocortins' actions are primarily mediated by interaction with CRF_2 receptors (11,73,75–88). The PVN and DVC, which influence autonomic outflow to the stomach, have been identified as responsive brain nuclei for CRF-induced inhibition of gastric emptying and motility, whereas the LC seems not to be involved (89–93). The expression of CRF_{2a} receptor mRNA has been found in hypothalamic and brainstem nuclei, such as the PVN and DVC, as well as in limbic structures; this is consistent with the locations of the responsive sites (54).

The central action of CRF—inhibition of gastric transit—is independent of the activation of the HPA axis and is mediated by the autonomic nervous system, as shown by the persistence of the gastric response in hypophysectomized or adrenalectomized rats (75,94). A number of reports have shown that (*a*) delay of gastric transit induced by icv or ic injection of CRF and Ucn 1 and (*b*) alteration of motility require the integrity of the vagus nerve in rats and dogs (75,82,88,90,92,95–97). Only two studies reported different results that showed a primary involvement of the sympathetic nervous system (86,94). However, the delay of gastric emptying induced by the ic injection of Ucn 2 is not altered by vagotomy but is mediated by sympathetic pathways and peripheral α-adrenergic receptors; this indicates that CRF ligands act through both vagal and sympathetic pathways to influence gastric function (88).

Pretreatment with CRF receptor antagonists has provided pharmacological evidence that brain CRF receptors are involved in stress-induced inhibition of gastric motor function. The ic, icv, or PVN injection of α-helical $CRF_{9–41}$, D-$Phe^{12}CRF_{12–41}$, astressin, or astressin-B blocks acute stress–induced delayed gastric emptying (12,74). Stressors used in these studies fall under one of the following categories: (*a*) psychological/physical (swim stress, restraint), (*b*) visceral (abdominal surgery, trepanation, peritoneal irritation with intraperitoneal 0.6% acetic acid), immunological (intravenous or central injection of interleukin-1β), and (*c*) chemical (ether) (12,74). Of interest is the demonstration that electroacupuncture normalizes both restraint-and ic-CRF-induced delay of gastric emptying, suggesting that the beneficial action of electroacupuncture under conditions of stress may be related to interference with brain CRF pathways (98). Also supportive of a role of brain CRF pathways is the demonstration that a variety of physical, immune, and psychological stressors (e.g., abdominal surgery, immobilization, forced swimming, and interleukins) activate CRF neurons and lead to a rapid increase in CRF gene transcription and upregulation of CRF mRNA in the PVN, which is the primary site of CRF synthesis (11,99–102). The parvocellular division of the PVN contains neurons in the dorsal and ventral parvocellular caps that regulate autonomic outflow to the viscera (103), which is consistent with the role of CRF signaling in the PVN to influence gastric motor function. Ucn 1 and 2 are also expressed in the PVN and are upregulated by various stressors (104,105). However, their involvement in stress-related inhibition of gastric motor function remains to be clarified. So far, investigations in Ucn 1–deficient mice suggest that Ucn 1 does not play a primary role in heart rate increase and sympathetic activation in response to acute restraint, as monitored by epinephrine and norepinephrine levels (106).

The CRF receptor subtype(s) involved in mediating stress-related inhibition of gastric motor function has yet to be fully characterized. Because CRF and urocortins inhibit gastric emptying via a CRF_2-mediated pathway (73,85,88), it was expected that CRF_2 receptors would be primarily involved in stress-induced delay of gastric emptying. This has been demonstrated in one study, where ic injection of $astressin_2$-B blocked the restraint stress–induced delay of gastric emptying in rats (86). However, it is surprising that under conditions of surgical stress (abdominal surgery and cecal palpation), central CRF_1 receptors play a predominant role: CRF_1-knockout mice and wildtype animals injected centrally with a CRF_1 antagonist no longer develop the inhibition of gastric emptying following abdominal surgery and cecal palpation (107). Experimental data in which the central injection of CRF_1/CRF_2 antagonists or selective CRF receptor subtype antagonists blocked stress-related alterations of gastric propulsive motor function provide new insights into the role of brain CRF signaling pathways as underlying mechanisms involved in both acute postoperative gastric ileus (108) and alterations of gastric digestive function during disease states associated with cytokine release (109,110). Furthermore, pharmacological evidence indicates that several centrally administered brain-gut peptides ultimately converge on brain CRF signaling as the downstream effector to induce an autonomic-mediated suppression of gastric propulsive motor function. For instance, the delayed gastric emptying induced by icv, fourth ventricle, or ic injection of glucagon-like peptide–1 (GLP-1), cocaine and amphetamine-regulated transcript (CART) peptide, or des-

acyl ghrelin is blocked by pretreatment with CRF antagonists injected via the same route (111–113). However, central application of CRF receptor antagonists does not alter basal gastric emptying of a liquid nonnutrient or solid nutrient meal in rats, mice, and dogs, indicating that central CRF pathways do not regulate fasted and postprandial gastric propulsive motor function under basal conditions, but that they do gain importance when recruited under stress conditions (12,76,82,114).

Are Brain Corticotropin-Releasing Factor Receptors Involved in the Mediation of Stress-Related Alterations of Small Intestinal Motor Function?

Compared with our understanding of gastric motor function, much less is known about the effects of stress on small intestinal propulsive activity and the role of brain CRF receptors (74). As in the stomach, acute psychological stress, as well as central injection of CRF or Ucn 1, inhibits duodenal and small intestinal transit and motility (suppression of the occurrence of myoelectric migrating complex, disruption of the fasted pattern of duodenal motor activity to fed pattern) in rats and dogs (71,95,96,115–118). Likewise, the central action of CRF is mediated via vagal pathways and is independent of the HPA axis activation (71,94,116,119). However, the slowing of small intestinal transit induced by icv injection of CRF is not as prominent as it is in the stomach; this is probably due to the lesser vagal innervation of the small intestine compared with the stomach (120). The involvement of central CRF receptors in mediating stress-induced inhibition of small intestinal transit has been little studied, and results are conflicting. The icv injection of α-helical $CRF_{9–41}$ blocks restraint stress–induced slowing of small intestinal transit in male rats, whereas there is no such effect in female rats at a dose effective to block restraintinduced stimulation of colonic transit (71,116). Whether these divergences are sex-related or specific differences in experimental conditions needs to be clarified. Furthermore, the central CRF receptor subtype involved in the mediation of the stress-induced inhibition of small intestinal motor function has not been investigated.

Brain CRF_1 Receptors Mediate Stress-Related Stimulation of Colonic Motor Function

In contrast to its inhibitory effect on gastric and small intestinal transit, centrally injected CRF or Ucn 1 stimulates colonic transit and defecation and induces a pattern of cecocolonic myoelectrical activity characterized by clustered spike-bursts of long duration in freely moving female and male rats, mice, and gerbils (9,71–73,81,91,94,121–123) (Figure 2). Convergent evidence has established that the stimulation of colonic motor function in response to central CRF and Ucn 1, as well as various stressors, is primarily mediated via central CRF_1 receptors (5,74) (Figure 2). First, colonic propulsive motor activity in response to stress is mimicked by centrally administered CRF_1 receptor–preferential agonists such as ovine CRF, r/h CRF (56), and Ucn 1, whereas Ucn 2 and Ucn 3 are inactive in mice when centrally injected at a dose similar to that of CRF (73). Second, the central injection of peptide CRF_1/CRF_2 receptor antagonists and selective CRF_1 antagonists blocks the colonic motor stimulation induced by central injection of CRF or Ucn 1 or by various stressors (5,124) (Figure 2). For instance, central injection of astressin, α-helical $CRF_{9–41}$, and D-$Phe^{12}CRF_{12–41}$ blocks the effects of central injection of CRF, Ucn 1, or interleukin-1β; wrap or partial restraint; water avoidance; morphine withdrawal; and colorectal distention–induced stimulation of colonic transit and defecation; as well as the increased frequency of colonic spike-bursts induced by conditioned fear stress in rodents (9,71–73,81,84,116,123,125–128). Furthermore, central or peripheral application of the selective CRF_1 antagonists CP-154,526, CRA 1000, NBI-27914, NBI-35965, JTC-017, and antalarmin reduces the acceleration of colonic transit time caused by restraint, fecal pellet output induced by water avoidance, social stress, painful stimuli, and diarrhea resulting from morphine withdrawal in rodents. CRF_1-knockout mice show significantly less defecation in an open field test than do their wild-type littermates (5,12, 129) (Table 1). Lastly, central injection of the selective CRF_2 antagonist $astressin_2$-B at a dose effective to block CRF_2-mediated action on gastric emptying does not prevent the colonic

response to central injection of CRF in rodents (12). As described above for gastric motor function, central CRF_1 receptors are not involved in the basal and postprandial regulation of colonic motor function under nonstress conditions (5,12,73). Of interest, however, is the growing pharmacological evidence that a number of brain peptides influencing food intake, such as neuropeptide Y, GLP-1, CART, and ghrelin, act in the brain to stimulate colonic motor function by recruiting brain CRF signaling pathways (130–133).

The central CRF- and stress-induced CRF_1-dependent stimulation of colonic motor function (transit and increased frequency of spike-burst activity) is not altered by blocking the activation of the HPA axis (72,94). Rather, it is mediated by an increased parasympathetic outflow to the colon via vagal celiac branches innervating the proximal colon and via sacral parasympathetic fibers innervating the distal colon and rectum (72,90,94,125,126). Effector mechanisms within the colon involve parasympathetic-mediated activation of myenteric cholinergic and nitrergic neurons regulating the peristaltic reflex as well as serotonin (5-HT) acting on 5-HT_3 and 5-HT_4 receptors. This is supported by the demonstration that icv CRF-induced defecation is blocked by the peripheral administration of atropine and the 5-HT_3 antagonists ramosetron, ondansetron, azasetron, alosetron, and cilansetron, as well as the 5-HT_4 antagonist SB-204070, whereas the icv injection of these antagonists has no effects (123,134–136). In addition, restraint stress or icv injection of CRF increases the 5-HT content in the feces of rat proximal colon (134). Taken together, these data suggest the cholinergic recruitment of peripheral serotonin pools from either enterochromaffin cells or enteric neurons by restraint stress and central CRF.

Consistent with the pharmacological evidence engaging the CRF_1 signaling pathways in the colonic response to stress, functional mapping and gene regulation studies support the PVN and LC/Barrington's complex in stressrelated, CRF-mediated activation of colonic propulsive motor function (Figure 2). Tracing studies have shown that CRF neurons in the dorsal cap of the parvocellular part of the PVN have trans-synaptic connections to the colon (42). Also, CRF-synthesizing neurons in Barrington's nucleus project to the noradrenergic LC, as well as to the intermediolateral column of the sacral spinal cord, which contains the sacral parasympathetic nucleus innervating the descending colon (42,120). There are CRF-efferent fibers projecting directly from the PVN and Barrington's nucleus to the LC, as shown by anterograde tracing (137,138). Neuroanatomical and functional studies have demonstrated that water avoidance stress activates the PVN and LC/Barrington's nuclei and CRF gene transcription in the PVN (9,139), whereas icv injection of α-helical $CRF_{9–41}$ reduces Fos expression selectively in these hypothalamic and pontine nuclei in correlation with defecation score (9). Likewise, Lewis rats known to have a blunted hypothalamic CRF response to stress exposure (140) displayed a reduced activation of neurons in the PVN and sacral parasympathetic nucleus and showed a lower defecation response than did Fisher rats (126). Consistent with a role of CRF/CRF_1 signaling in the PVN, α-helical $CRF_{9–41}$ injected directly into the PVN blocks partial restraint– and water avoidance–induced stimulation of colonic transit and defecation, and various neurogenic and systemic stressors activate the transcription of the CRF_1 receptor gene in the PVN (50,90,125). CRF increases the firing rate of noradrenergic neurons in the LC and releases noradrenalin into the brain cortex, which results in arousal and anxiogenic behavior (137, 141). Therefore, CRF/CRF_1 signaling pathways in the PVN and LC may physiologically regulate the behavioral and autonomic responses to stress that influence colonic function as part of the brain-gut axis (91,137). These pathways may play a role in diarrhea-predominant IBS patients with psychic comor-bidities such as anxiety and depression (5).

STRESS-RELATED ALTERATIONS OF GASTROINTESTINAL MOTILITY MEDIATED BY PERIPHERAL CORTICOTROPIN-RELEASING FACTOR SIGNALING

Like many peptides once thought to be restricted to the brain and pituitary that were later detected in peripheral tissues, CRF ligands and receptors are widely expressed outside the brain in spinal cord and peripheral organs, including the gastrointestinal tract in animals and humans (12,25,142–146). This overlapping expression pattern of CRF ligands and receptors in the gastrointestinal tract gives rise to a local CRF signaling pathway that can act directly on the gut in either a paracrine or an autocrine manner (143,144,146–48).The potent actions of CRF ligands upon peripheral injection and CRF receptor blockade are consistent with the notion that peripheral activation of CRF_1 and CRF_2 signaling pathways may be part of the local effectors involved in gastric and colonic motor alterations induced by stress.

Peripheral Corticotropin-Releasing Factor Signaling Alters Gut Motor Function

When injected peripherally, CRF strongly alters gut motility and transit in several mammalian species including rodents, dogs, and humans (71,75,149–152). The iv or intraperitoneal (ip) injection of CRF or Ucn 1 in rats inhibits gastric emptying, delays small intestinal transit, and stimulates colonic transit and defecation with a potency similar to that of centrally injected (icv or ic) CRF (71,152,153). However, although the patterns of gut motor response are similar, distinct sites and mechanismsofaction are involved in mediating the effects of centrally and peripherally injected CRF (58,94,96,154). Ganglion blockade, which inhibits the icv CRF-induced delay of gastric emptying and acceleration of colonic transit, does not influence the ip CRF-induced alteration of gut transit (94). Likewise, sympathetic blockade, which prevents ic Ucn 2–induced delayed gastric emptying, does not influence iv Ucn 2–inhibitory action on gastric emptying in rats tested under otherwise-similar conditions (88). More importantly, peptide action can be reproduced in vitro in antral and colonic preparations. Studies performed on muscle strips of rat gastric antrum showed that perfusion of CRF, Ucn 1, or Ucn 2 decreases the amplitude of circular and longitudinal muscle contractions (148,155). Moreover, in an isolated colonic rat preparation, CRF increased basal myoelectrical peristaltic activity (153, 156).

Convergent studies to characterize the CRF receptors involved in these processes have established that the delayed gastric emptying following peripheral injection of CRF, Ucn 1, Ucn 2, and Ucn 3 is mediated by CRF_2 receptors, whereas the stimulation of colonic motility after peripheral administration of CRF and Ucn 1 involves CRF_1 receptors located on the myenteric neurons of rats and mice (145). Ucn2 (and, less potently, Ucn 3) injected peripherally delays gastric emptying of a solid or liquid meal without modifying distal colonic transit (152,157). In contrast, ip injection of $stressin_1$-A induces defecation alone, without altering gastric emptying (38). In contrast, (*a*) ip or iv CRF and (*b*) Ucn 1 interacting with both CRF receptors inhibit gastric motor function while stimulating colonic propulsion and fecal pellet output in rats and mice (96,152,157). The use of selective CRF antagonists has shown that the peripheral injection of $astressin_2$-B and antisauvagine-30 blocks peripheral CRF- and Ucn 1–induced inhibition of gastric emptying without affecting the increase of distal colonic transit (152,157). Conversely, the selective CRF_1 receptor antagonists CP-154,526 and NBI-27914 block peripheral CRF- or Ucn 1–induced stimulation of colonic motor function (clustered spike-burst activity, distal transit, defecation, and diarrhea) without influencing the delay of gastric emptying (152,153,157,158). Consistent with a peripheral action within the gut, CRF receptors have been localized throughout the gastrointestinal tract in guinea pigs (147). In rat colon, CRF_1 receptor has been detected both at the gene level and by immunohistochemistry in goblet and stem cells of the crypts, as well as on surface epithelial cells, lamina propria, and,

prominently, in the myenteric nervous plexus (144,159). CRF_2 receptors are highly expressed at the gene and protein levels in the rat upper gut, including the esophagus and stomach (34, 148). Evidence for a pivotal role of the CRF_2 receptors, which are expressed on gastric myenteric neurons (148), comes from in vitro studies on gastric antral strips, in which CRF- and Ucn 2–induced reduction of spontaneous circular and longitudinal muscle contraction was tetrodotoxin dependent (148,155).

Underlying alterations of motility linked with changes in gut transit have been characterized. In the upper gut, the iv injection of CRF decreases gastric intraluminal pressure in rats and inhibits motilin-induced jejunal migrating motor complex in dogs (155,160). Likewise, in healthy humans, iv CRF reduces the basal fundic tone and stimulates the nonpropulsive postprandial duodenal motor activity as well as the pyloric and duodenal pressure wave (150, 161,162). Ucn 1 injected intravenously disrupts the fasted motor pattern of gastroduodenal motility, which in conscious rats is replaced by the fed-like motor pattern (96). In contrast, when Ucn 1 is injected intravenously in ad libitum–fed animals, the fed motor pattern remains, but there is a decrease in antral and an increase in duodenal motor index (96). However, the increase in duodenal motility index is nonpropagative, as shown by the reduction of duodenal transit (96). In the colon, peripheral injection of CRF and Ucn 1 increases clustered spike-burst propagative activity in rats (153,163). Clinical studies show that systemic application of CRF induces a colonic motility response that includes the occurrence of clustered contractions in the descending and sigmoid colon, which is more prominent in IBS patients than in healthy controls (151). The mediation of the CRF and Ucn 1 effect on colonic motor activity may involve a direct interaction with colonic myenteric neurons (159). Peripheral injection of CRF or of $stressin_1$-A induces robust Fos expression selectively in the myenteric ganglia of the colon; this expression can be blocked by peripheral application of astressin and CP-154,526 (159,164). In addition, the activation takes place in cholinergic and nitrergic colonic myenteric neurons that are known to be involved in the peristaltic reflex and that bear CRF_1 receptors (144,159).

Stress-Related Alteration of Gut Motor Function: Involvement of Peripheral Corticotropin-Releasing Factor Receptors

The functionality of the CRF signaling system in the gut during stress is supported by reports that peripherally injected peptide antagonists, namely α-helical $CRF_{9–41}$, D-$Phe^{12}CRF_{12–41}$, and astressin, block abdominal surgery–induced delay of gastric emptying (58,165,166). The inhibition of gastric emptying induced by acute wrap restraint stress is also blocked by peripheral application of a CRF_2 antagonist, whereas application of CP-154,526 has no effect (157). Likewise, the stimulation of distal colonic transit and fecal pellet output induced by acute wrap restraint or water avoidance stress is blocked or blunted by peripheral injection of α-helical $CRF_{9–41}$ or astressin (71,123,153,167). However, peripheral CRF receptors seem not to be involved in the regulation of fasted and postprandial gut motor functions under basal conditions (71,145,153,157). Researchers speculate that stress may recruit CRF ligands, which are expressed in the gut through autonomic alterations. For instance, CRF and Ucn 1 mRNA are detected in the submucosa and muscle layers, and immunoreactivity shows a cellular distribution in myenteric neurons, serotonin-containing enterochromaffin cells, and lamina propria cells of the mucosa in stomach and colon (148,168,169).

CONCLUSIONS

In summary, we have made major advances both in unraveling the components of CRF signaling pathways that encompass CRF, urocortins, CRF receptors, and CRF-BP and in mapping their expression in the brain and the gut. There are conclusive experimental data showing that activation of brain and colonic CRF_1 pathways by exogenous CRF or Ucn 1 or

stress recapitulates cardinal features encountered during stress, including the stimulation of colonic motility, defecation/watery diarrhea, and visceral hypersensitivity (5). SelectiveCRF_1 antagonists abolish or reduce exogenous CRF-and stress-induced anxiogenic/depressive behavior, defective intestinal barrier, stimulation of colonic motility, myenteric neurons, mucus secretion, mast cell activation, defecation, diarrhea, and hyperalgesia (5, 170). Therefore, sustained activation of the CRF_1 system at central and/or peripheral sites may represent a key underlying mechanism whereby stress alters colonic function and can lead to stress-related functional bowel disorders such as IBS (15–20). In the upper gut, the brain and gastric CRF_2 signaling systems are more prominently involved in CRF ligands– and stress-related suppression of gastric motor function. Both central ligands (e.g., CRF and Ucn 1, Ucn 2, and Ucn 3) and stress inhibit propulsive gastric motor function through autonomic and enteric nervous system alterations.

Additional investigations on the stress-related regulation of CRF ligands and their receptors, including their variants in the gut and their mechanisms of action at the cellular level, may provide insight into new venues for effective therapies for patients suffering from stressrelated functional bowel disorders.

SUMMARY POINTS

1. In recent years, our understanding of how stress alters the function of the gastrointestinal tract via the brain-gut axis has increased dramatically.
2. The discovery of the CRF peptide family; Ucn 1, Ucn 2, and Ucn 3; and the cloning of CRFreceptor subtypesCRF_1, CRF_2, and CRF-BP;as well as the development of selective CRF_1 and CRF_2 antagonists, has provided relevant tools to characterize the primary implications of the brain CRF/CRF_1 signaling pathways in the endocrine, anxiogenic, autonomic, and visceral responses to stress.
3. Among the viscera, the gut functions are highly susceptible to the effects of stress, as has been shown by alterations of gut motility such as slowing of gastric transit and stimulation of colonic propulsive motor activity, along with altered intestinal barrier function.
4. Components of the CRF signaling system are expressed in brain nuclei influencing autonomic outflow to the viscera such as the PVN, the Barrington's nucleus/LC complex, and the DVC, along with myenteric, endocrine, and immune cells within the gut.
5. The stimulation of colonic motor function induced by various stressors is mediated by the brain (PVN, Barrington's nucleus/LC) and gut (enteric) CRF_1 signaling system, which contributes to the activation of the sacral parasympathetic and the colonic myenteric nervous systems, respectively. Such CRF_1 activation also contributes to the recruitment of colonic serotonin-containing enterochromaffin and mast cells.
6. The inhibition of gastric motor function by CRF ligands is mediated by activation of CRF_2 receptors both in the brain and in the stomach. CRF receptors are involved in the modulation of autonomic and gastric myenteric activity, which influences gastric function during stress.
7. Further studies on the regulation of the CRF signaling system in the gut in response to stress and specific mechanisms of action may provide the basis for effective therapeutic venues for stress-related functional bowel disorders.

Glossary

Irritable bowel syndrome (IBS), a functional disease characterized by altered bowel habits and visceral pain; Urocortins (Ucns), mammalian CRF-related peptides; Paraventricular nucleus (PVN), hypothalamic brain nucleus implicated in autonomic regulation of gastrointestinal functions; Locus coeruleus (LC), pontine catecholaminergic nucleus involved in physiological responses to stress; Astressin-B, long-acting CRF_1/CRF_2 receptor antagonist; $Astressin_2$-B, long-acting selective peptide CRF_2 receptor antagonist.

ACKNOWLEDGMENTS

The authors were supported by National Institutes of Health grants R01 DK-33061 and DK 57238 (Y.T.), Center grant DK-41301 (Animal core, Y.T.), P50 AR 049550 (Y.T.), VA Career Scientist and Merit Award (Y.T.), and German Research Foundation grant STE 1765/1–1 (A.S.).

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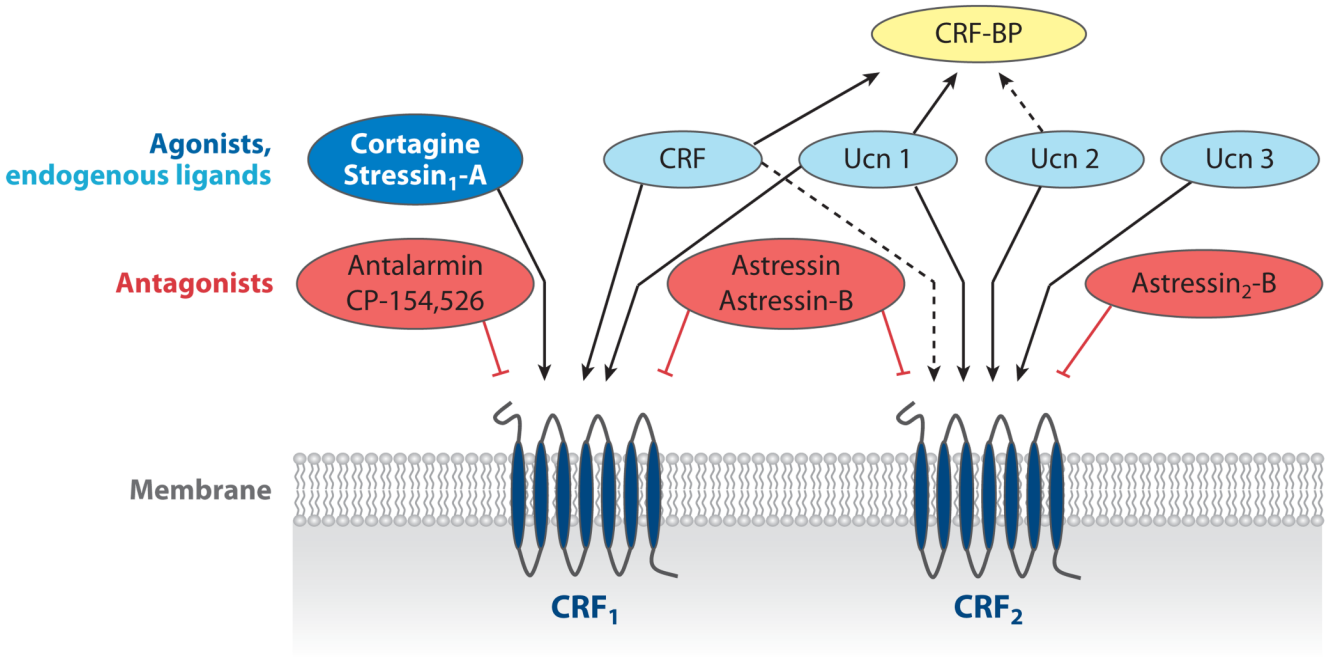

Figure 1.
Schematic overview of preferential binding affinities and specificities of endogenous or synthetic corticotropin-releasing factor (CRF) receptor ligands. The CRF_1 and CRF_2 receptors share 70% homology and belong to the family of seven-transmembrane G protein–coupled receptors. BP, binding protein.

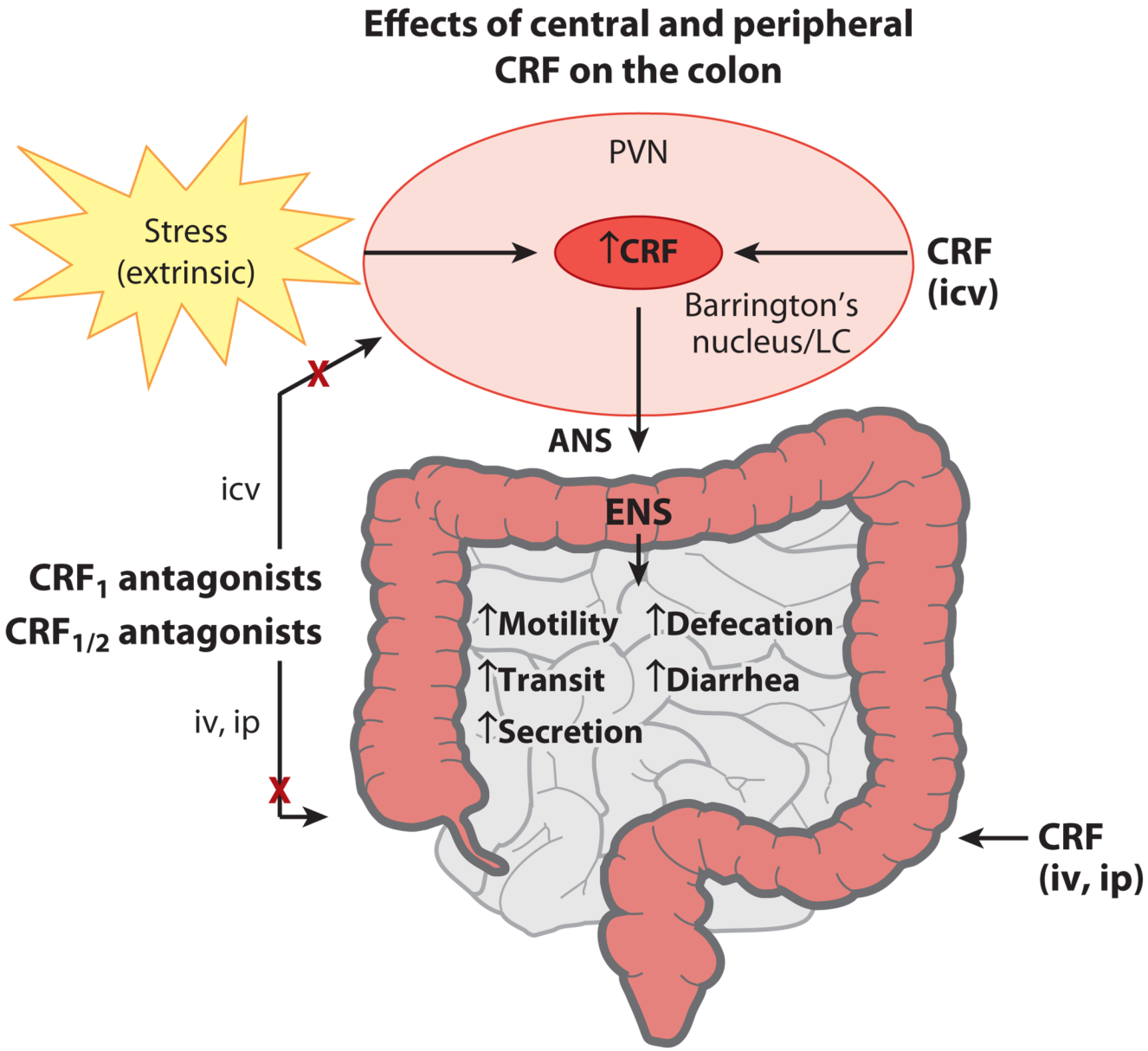

Figure 2.
Summary of corticotropin-releasing factor (CRF) actions on colonic function. Central and peripheral CRF stimulates various colonic functions, which recapitulate the effects of stress and are blocked by nonselective and CRF_1-selective CRF receptor antagonists. Abbreviations: ANS, autonomic nervous system; ENS, enteric nervous system; icv, intracerebroventricularly injected; ip, intraperitoneally injected; iv, intravenously injected; LC, locus coeruleus; PVN, paraventricular nucleus of the hypothalamus.

Table 1

Blockade of acute stress–induced stimulation of colonic motor functions by selective **CRF$_1$** antagonists[a]

Antagonist	Dose	Route	Species	Stress	Inhibition	Reference
Central administration						
NBI-27914	100 μg	Icv	Rats	Water avoidance	Defecation (67%)	84
NBI-35965	50 μg	Icv	Mice	Restraint	Defecation (100%)	73
Peripheral administration						
CP-154,526	20 mg kg^{-1}	Sc	Rats	Water avoidance	Defecation (55%)	153
CP-154,526	30 mg kg^{-1}	Sc	Rats	Morphine withdrawal	Diarrhea (50%)	127
CRA 1000	20 mg kg^{-1}	Sc	Mice	Morphine withdrawal	Diarrhea (50%)	171
CP-154,526	20 mg kg^{-1}	Sc	Rats	Partial restraint	Transit (55%)	157
NBI-35965	20 mg kg^{-1}	Sc	Rats	Water avoidance	Defecation (53%)	172
Antalarmin	20 mg kg^{-1}	Ip	Rats	Restraint	Defecation (49%)	173
JTC-017	10 mg kg^{-1}	Ip	Rats	Colon distention	Defecation (100%)	128
Antalarmin	20 mg kg^{-1}	Po	Monkeys	Social intruder	Defecation (40%)	174

[a]Abbreviations: CRF, corticotropin-releasing factor; Icv, intracerebroventricular; Ip, intraperitoneal; Po, per pos; Sc, subcutaneous.