VISCERAL PERCEPTION

Role of thyrotrophin releasing hormone and corticotrophin releasing factor in stress related alterations of gastrointestinal motor function

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Gut 2002;51(Suppl 1):i45–i49

There is a growing body of experimental and clinical evidence to indicate that stress influences gastrointestinal motility. The most common pattern of gastrointestinal motor alterations induced by a variety of different stress factors is that of delayed gastric emptying and accelerated colonic transit. Central administration of corticotrophin releasing factor mimics both of these effects. This review focuses on the effects of two centrally acting peptides known to influence gastrointestinal motility and transit in experimental animals: thyrotrophin releasing hormone and corticotrophin releasing factor. The biological actions of these peptides are discussed in relation to the motility changes and pathways involved in their actions.

SUMMARY

Thyrotrophin releasing hormone (TRH) is released from nerve terminals which influence the activity of vagal neurones projecting to the stomach and gastrointestinal tract, and is thought to act as a mediator of vagally stimulated gastrointestinal motility during cold or other stressful stimuli. Corticotrophin releasing factor (CRF) plays an important role in the regulation of behavioural and autonomic responses to stress, and it has been proposed that hypersecretion of CRF in the brain may contribute to the pathophysiology of stress related exacerbation of irritable bowel syndrome (IBS). Centrally administered CRF inhibits gastric emptying while stimulating colonic motor function. In rats, these effects are mediated by CRF₂ receptors which modulate vagal and sacral parasympathetic outflow. CRF also activates colonic transit and faecal excretion elicited by stress. This response involves CRF₁ receptors. CRF may also act peripherally, especially in patients with inflammatory or post-infectious conditions.

INTRODUCTION

During the last three decades, a large number of brain peptides have been characterised using the techniques of biochemistry, immunohistochemistry, molecular biology, and physiology. Identification of these peptides has led to an explosion in our understanding of their biological action and function in the central nervous system (CNS), spinal cord, and enteric nervous system. Two dec-

ades ago, pioneer neuropharmacological studies identified the brain as a prime site of action for peptides that alter gastrointestinal function.^{1–4} Over a dozen peptides which modify gastrointestinal motor activity and alter transit in rats, cats, rabbits, and dogs have been shown to act within the brain.^{4–7} However, the physiological role of these peptides is still unclear. The reasons for this lack of understanding are threefold.

Firstly, specific receptor antagonists are not available for most of these peptides which means that it is difficult to examine the endogenous release of these substances from the CNS in response to physical events. Secondly, it is often necessary to undertake experimental studies on surgical preparations or by insertion of needles into brain structures. Although such studies provide valuable information about the pathways that modulate gastrointestinal functions, their conclusions cannot be interpreted in terms of normal physiology. The third complication arises from the fact that many of the regulatory circuits operate under the control of more than one mechanism. Studies in unconscious animals can provide useful data about specific pathways but compensatory processes are involved in intact animals to ensure that the overall physiology remains unchanged.

This review focuses on the effects of two centrally acting peptides known to influence gastrointestinal motility and transit in experimental animals: TRH^{1–4} and CRF.^{4–9} The biological actions of these peptides will be discussed in relation to the motility changes and pathways involved in their actions. For example, a growing body of evidence suggests that TRH and CRF both play a role in mediating stress induced alterations in gastrointestinal motor function.^{6,7} Wherever possible, the review will also address how these findings relate to normal physiology.

STRUCTURE AND BIOCHEMISTRY OF TRH AND CRF

TRH (pGlu-His-Pro-NH₂) was the first hypothalamic releasing peptide to be discovered. Based on its actions (regulation of thyrotrophin or thyroid

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Abbreviations: ACTH, adrenocorticotrophic hormone; CNS, central nervous system; CRF, corticotrophin releasing factor; IBS, irritable bowel syndrome; LPS, lipopoly-saccharide; alpha-MSH, melanocyte stimulating hormone; PVN, paraventricular nucleus; TRH, thyrotrophin releasing hormone; 5-HT, serotonin.

stimulating hormone secretion) it was primarily considered to be a physiological regulator of pituitary function.^{10,11} Further studies unexpectedly identified TRH in other brain areas, and based on these findings additional experiments were performed which showed that this peptide exerts behavioural effects which are independent of its effects on the pituitary-thyroid axis.¹

CRF is a 41 amino acid peptide that was characterised two decades ago.¹² The peptide plays a regulatory role in the control of pituitary adrenocorticotrophic hormone (ACTH) secretion and, in common with TRH, it exerts behavioural, endocrine, and motility responses to stress by actions that are independent of those at the pituitary-ACTH axis.^{12,13} These findings form the basis for ongoing investigations of the role of endogenous CRF in the brain in terms of modifying gastrointestinal function and a putative role in stress induced changes in gastrointestinal motor activity.⁴⁻⁶

The actions of CRF have been shown to be mediated through activation of specific receptors.¹⁴ To date, two CRF receptors, designated CRF₁ and CRF₂, have been identified through molecular cloning from distinct genes in rats and in humans.¹⁴ Advances have also been made in the development of potent CRF receptor antagonists. These are very helpful tools for further investigating the physiological importance of CRF. One such agent, astressin (cyclo-(30-33)-[D-Phe12, Nle21,38, Glu30, Lys33] CRF₁₂₋₄₁) is a derivative of CRF which has a low intrinsic activity and a high affinity for both CRF₁ and CRF₂ receptors.¹⁵ Astressin has been shown to block the effects of exogenous CRF on gastric and colonic motor activity¹⁶⁻¹⁸ and to prevent stress related alterations of gastrointestinal motor function.^{7,17} Other non-peptide antagonists have been developed which display selectivity for CRF₁ or CRF₂ receptors.¹⁹

EFFECTS OF CENTRAL TRH ON GASTROINTESTINAL MOTILITY

Intracerebroventricular injection of TRH induces a rapid and long lasting contractile response in the stomach, small intestine, and colon of anaesthetised rats, rabbits, and unanaesthetised sheep.^{4,20} The colonic effects can be stimulated by injection of TRH either into the lateral ventricle, the third ventricle, or the cisterna magna.²¹⁻²³ Intravenous injection of the peptide is ineffective.²¹ The action of TRH is abolished by vagotomy or atropine but not by destruction of peripheral noradrenergic nerve terminals by 6-hydroxydopamine.^{4,21}

Intracisternal injection of TRH enhances gastric emptying and increases small intestinal transit in conscious rats.^{24,25} The effects of central TRH on colonic transit have largely been studied in rabbits.²⁶ Intracerebroventricular injection of TRH causes marked acceleration of colonic transit; it increases fluid output and, as a consequence, sometimes causes diarrhoea.²² The effect of the peptide can be blocked by serotonin (5-HT) antagonists and by vagotomy combined with sacral cord transection but not by doses of atropine that completely block colonic contractility.²²⁻²⁶ These results are indicative of a role for 5-HT in mediating TRH stimulated effects on fluid production and colonic transit. In the same series of investigations, cerebroventricular injection of TRH was found to enhance defecation in cats and rats.²⁷

Anatomical, electrophysiological, and neuropharmacological data support a physiological role of endogenous central TRH in the vagal stimulation of gastrointestinal motor effects. The large majority (>65%) of total medullary TRH is localised in the dorsal motor nucleus of the vagus, the nucleus of the tractus solitarius, the nucleus ambiguus, and raphé nucleus.⁴ TRH receptors have been identified in the same areas.²⁸⁻³¹ The anatomical localisation of TRH receptors therefore correlates with sites of origin of gastric vagal preganglionic neurones. These findings, combined with electrophysiological studies and retrograde tracing studies,

suggest that TRH is released from nerve terminals which influence the activity of vagal neurones projecting into the stomach and the gastrointestinal tract.^{4,29}

Environmental stress such as exposure to cold are known to stimulate brain TRH.³²⁻³⁴ Exposure to cold induces similar effects on gastric and gastrointestinal motility as those observed following central injection of TRH.⁴ Perhaps, more importantly, cold exposure has also been shown to be associated with accelerated gastric emptying and diarrhoea in rats.^{32,34} These results imply that medullary TRH may act as a mediator of vagally stimulated gastrointestinal motility during cold or other stressful stimuli.

EFFECT OF CRF ON GASTROINTESTINAL MOTILITY

A variety of reports have established that CRF injected into the cerebrospinal fluid acts in the brain to inhibit gastric and/or gastrointestinal motility.^{35,36} Its actions are mediated by an interaction with specific high affinity seven transmembrane bound receptors that are coupled to a guanine nucleotide stimulatory factor signalling protein.^{14,37} To date, two distinct CRF receptor subtypes, CRF₁ and CRF₂, have been cloned and characterised from rat and human brains.^{6,14} The CRF₁ receptor is the predominant form localised in the pituitary, olfactory bulb, and cerebral cortex. The CRF₂ receptor is primarily located in the lateral septum, hypothalamus, amygdala, and brain stem.⁶ CRF₂ receptors exist in multiple forms (alpha and beta) as splice variants differing in their extracellular amino acid NH₂ terminal domains and in their distribution.¹⁴

CRF₂ receptor alpha is located on brain neurones, and CRF₂ receptor beta is found in non-neural brain tissue and in the periphery (for example, gastrointestinal tract).³⁸ Several studies have established that CRF decreases gastric emptying after injection of the peptide into the cerebrospinal fluid; CRF₂ receptors are thought to mediate this action.^{19,38} In human brain, unlike rat brain, another CRF₂ receptor splice variant has been identified: the CRF₂ receptor gamma.³⁸

In addition, and in contrast with the effects of TRH, recent evidence indicates that peripheral CRF exerts specific biological actions of potential physiological relevance. In particular, intravenous administration of CRF inhibits gastric emptying in rats, mice, and dogs.^{6,19,39} It is unlikely that this response reflects a central action⁶ as studies in mice indicate that peripheral CRF is not transported from the blood into the brain. Moreover, astressin given intravenously was unable to prevent the inhibition of gastric emptying induced by intracisternal injection of CRF although it antagonised the effect of intravenous CRF.^{6,19} In the same series of experiments intravenous administration of astressin alone was unable to influence gastric emptying, providing experimental evidence that peripheral CRF is not normally involved in the regulation of gastric emptying.¹⁹

However, peripheral CRF appears to play a role in the modulation of gastric motor function under stress related conditions, such as abdominal surgery, which are known to activate CRF pathways. In a recent study in rats, laparotomy was associated with a dramatic reduction of gastric transit three hours after the procedure.^{38,40} This response was abolished by injection of a CRF antagonist.⁴⁰ These results indicate that peripheral CRF receptors, probably CRF₂ receptors, play a key role in mediating acute postoperative alterations of gastric motor functions such as postoperative ileus. Further studies from the same group have also documented that intracisternal injection of astressin prevents abdominal surgery induced gastric ileus,⁷ suggesting that both central and peripheral CRF receptors are involved in these processes.

CRF injected into the lateral ventricle or the paraventricular nucleus (PVN) of the hypothalamus has been shown to stimulate colonic transit and faecal pellet output in rats whereas CRF injected outside the PVN had no effect (fig 1).^{7,41-43} The role of CRF receptors in mediating CRF stimulated activation of colonic

Figure 1 Bilateral microinfusion of intracerebroventricular (icv) or intravenous (iv) injection of corticotrophin releasing factor (CRF) into the paraventricular nucleus or central amygdala on colonic transit time (A) and faecal pellet output (B) in rats. *** $p < 0.001$ versus vehicle. Reproduced with permission from the American Gastroenterological Association.⁴²

Figure 2 Leucocyte rolling, adhesion, and emigration in control rats (A) and effect of lipopolysaccharide (LPS), melanocyte stimulating hormone (alpha-MSH), and intracisternal (ic) injection of corticotrophin releasing factor (CRF) (B). (A) * $p < 0.05$ versus control, ic CRF+LPS and 1A29+LPS. (B) * $p < 0.05$ versus LPS. Reproduced with permission from Casadevall and colleagues.⁵¹

motor function is supported by the finding that astressin and the CRF receptor antagonist, alpha-helical CRF-(9–41), both blocked the responses to CRF stimulation.⁷ CRF receptor antagonists also prevented stress induced alterations of colonic transit.^{7,41} Further evidence is provided by studies in which stress was provoked by restraint of rats in cold water or by an aversive stimulus (cold water). Both procedures stimulated colonic transit and faecal pellet output.^{44–47}

Bilateral microinjection of a CRF antagonist into the PVN has been shown to abolish the colonic response to stress whereas the CRF antagonist given alone was found to have no effect on basal colonic function in non-stressed rats.^{45,46} Recent pharmacological evidence supports the notion that CRF₁ receptors are primarily involved in the stimulation of colonic propulsion induced by central administration of CRF.⁴⁷ Of importance, the anxiogenic behavioural response to central administration of CRF or stress is also mediated by brain CRF₁

receptors. This has been established by the use of selective CRF₁ receptor antagonists, by CRF₁ receptor antisense technology, and by the use of CRF₁ receptor knockout mice.⁷

The observation that specific CRF₁ receptor antagonists can alleviate manifestations of anxiety and depression is of potential clinical importance.^{48,49} Preliminary reports of beneficial effects with CRF₁ receptor antagonists in depressive symptoms in patients with major depression opens new therapeutic avenues for other disorders. Based on the biological effects of CRF, the therapeutic potential for CRF₁ receptor antagonists can be envisaged in patients with IBS who have psychiatric illness and gastrointestinal symptoms of enhanced bowel motor function.

INTERACTION OF CRF WITH THE ANTI-INFLAMMATORY SYSTEM

Hypothalamic CRF is known to be involved in activation of the neuroendocrine system in response to inflammatory insult.⁵⁰

Table 1 Stressors which can induce inhibition of gastric emptying and stimulation of colonic motor function

Stressor	Details
Psychological	Restraint in cold water Forced swimming
Immunological	Interleukin 1 β
Visceral	Abdominal surgery Intraperitoneal acid
Chemical	Corticotrophin releasing factor

Recent information strongly supports the idea that immune activation of the neuroendocrine system provides a counter-regulatory mechanism that modulates inflammatory events.^{50, 51} The major pathway probably involves CRF mediated activation of the pituitary-adrenal axis with subsequent hypersecretion of glucocorticoids.⁵² However, CRF also has actions at multiple levels including stimulation of other stress hormones such as the melanocyte stimulating hormone (alpha-MSH) and catecholamines which have complex interactions with the cytokine network.^{50, 53}

A possible physiological role for hypothalamic CRF in modulating inflammatory responses is supported by studies showing that immune challenge or cytokine administration activates CRF neurones and increases expression of CRF mRNA in the PVN of the hypothalamus.⁵¹ Central administration of CRF mimics many of the effects induced by inflammatory injury by interacting with CRF receptors on cerebral areas reached by the peptide.⁵¹ The availability of potent and specific CRF receptor antagonists has been extremely helpful in further elucidating the physiological role of CRF and the pituitary-adrenal axis with respect to inflammation. Astressin given peripherally at a dose capable of inhibiting CRF mediated stress induced ACTH release was unable to modify the cellular response (ICAM1 expression, leucocyte migration) to high doses of lipopolysaccharide (LPS) challenge (fig 2) but it potentiated the response caused by a lower dose of LPS.⁵¹ Blockade of endogenous glucocorticoids (fig 2A) but not of alpha-MSH receptors (fig 2B) reversed the inhibitory action of CRF on leucocyte-endothelial cell interactions during endotoxaemia. These results indicate that the anti-inflammatory action of intracisternal CRF involves downregulation of leucocyte-endothelial cell interactions and attenuation of recruitment of leucocytes during endotoxaemia. The anti-inflammatory effects of CRF therefore appear to be mediated by adrenocortical activation and by additional mechanisms but are independent of alpha-MSH activation.

CONCLUSION

There is a growing body of experimental and clinical evidence to indicate that stress influences gastrointestinal motility. The most common pattern of gastrointestinal motor alterations induced by a variety of different stress factors is that of delayed gastric emptying and accelerated colonic transit. Central administration of CRF mimics both effects (table 1).

New experimental data related to the CRF receptor subtypes involved in the central effects of CRF on gastrointestinal motor function point to a role of medullary CRF₂ receptor subtypes in the inhibition of gastric emptying whereas colonic motor responses to central CRF appear to involve activation of CRF₁ receptor subtypes.⁷ Identification of the exact neuronal circuits whereby CRF interacts with CRF₁ and CRF₂ receptors and the way in which this interaction translates into autonomic dependent alterations of motor function in response to various stressful stimuli requires further investigation.

The first clinical report that a CRF₁ receptor antagonist reduced depression and anxiety scores in depressed patients supports experimental findings from animal studies and implies a potential therapeutic application of CRF₁ receptor antagonists in patients with IBS and depression/anxiety or chronic stress.⁴⁹

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