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Visceral sensitivity

Can modulating corticotropin releasing hormone receptors alter visceral sensitivity?

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Activation of corticotropin releasing hormone (CRH) receptor 2 (CRH-R2) reduces visceral sensitivity induced by colorectal distension in conscious rats. This finding is relevant to the increased interest in the potential use of therapeutic agents that act on CRH receptors in the treatment of irritable bowel syndrome

Clarifying the adverse effects of stress on bodily function is a crucial paradigm for medical research. Evidence that psychosocial stress aggravates digestive diseases has been accumulating and stress induced exacerbation of symptoms in patients with functional gastrointestinal disorders is well recognised.[1] Corticotropin releasing hormone (CRH), a 41 amino acids peptide produced mainly in the paraventricular nucleus of the hypothalamus, is considered to be a major mediator of the stress response.[2] Indeed, stress is known to induce release of hypothalamic CRH, resulting in pituitary secretion of adrenocorticotropic hormone (ACTH). In addition, stress related activation of CRH receptors has been reported to alter gastrointestinal functions.[3] Moreover, physical or psychological stress is known to delay gastric emptying,[4] accelerate colonic transit,[5] and evoke colonic motility[6] in rats.

Two major G protein coupled receptors for the CRH have been identified, CRH receptor 1 (CRH-R1) and receptor 2 (CRH-R2).[7–9] CRH-R1, which is highly expressed in the anterior pituitary, neocortex, hypothalamus, hippocampus, amygdala, locus coeruleus, and cerebellum, has been reported to mediate stress induced physiological changes, including stimulation of the hypothalamo-pituitary-adrenal axis, elevation of plasma levels of catecholamines, increased colonic motility,[10] and exaggerated stress related behaviour, especially anxiety.[11 12] In addition, stimulation of this receptor is believed to activate adenylate cyclase, an enzyme that catalyses the formation of cyclic AMP (cAMP).[7–9]

We have previously reported increased colonic motility and visceral perception in response to administration of CRH in patients with irritable bowel syndrome (IBS).[13] In addition, earlier studies have indicated that gastrointestinal dysmotility[14] and visceral hypersensitivity[15] are major events in the pathophysiology of IBS. Moreover, patients with IBS have been reported to suffer from a variety of chronic or acute psychiatric conditions, including depression, generalised anxiety, panic, social phobia, and somatisation.[16] Various studies have suggested a relationship between stress induced changes in colonic motility and CRH action in the paraventricular nucleus of the hypothalamus.[17] Accordingly, it has been shown that intracerebroventricular injection of CRH stimulates gastrointestinal motility in a way similar to that induced by stress[18] and that intraperitoneal injection of CRH induces defecation and clustered spike bursts longer than basal spike bursts in rats.[10]

CRH-R1 antagonists have been shown to prevent stress-like gastrointestinal motor responses following central or peripheral injection of CRH.[10] In addition, it has been reported that CRH-R1 deficient mice show impaired response to stress, as indicated by absence of increased ACTH and corticosterone levels following exposure to stress, as well as less pronounced anxiety related behaviour.[11 12] From these findings, it is reasonable to assume that CRH mediates gastrointestinal and behavioural responses to stress via CRH-R1. Actually, in a recent study,[19] we have shown that administration of an α-helical CRH or CRH-R1 antagonist attenuates hippocampal noradrenaline release and reduces the frequency of abdominal contractions induced by acute colorectal distension in rats. We have also shown that the CRH-R1 antagonist used in that study[19] reduced plasma ACTH and anxiety after acute colorectal distension but not after chronic colorectal distension, probably due to habituation. Another important finding of our previous study[19] is that pretreatment with the CRH-R1 antagonist blocked chronic colorectal distension induced increase in rats faecal pellet output. Because the CRH-R1 antagonist used in our previous study[19] is an agent that crosses the blood-brain barrier, both central CRH-R1 and

peripheral CRH-R1 are thought to be responsible for colorectal distension induced sensitisation. Nevertheless, CRH and CRH-R1 in the brain may play a major role in colorectal distension induced anxiety, ACTH release, visceral hypersensitivity, and changes in colonic motility.

Evidence supporting the concept that peripheral CRH and CRH-R1 play important roles in brain-gut sensitisation is increasing. Several studies have identified immunoreactive CRH[20] and urocortin [21] as well as CRH-R1 and CRH-R2 mRNAs in human colonic mucosa.[21] In addition, reverse transcription-polymerase chain reaction (RT-PCR) has revealed expression of CRH-R1 mRNA in both the myenteric and submucosal plexus in the guinea pig.[22] Application of CRH has been shown to evoke depolarising responses associated with elevated excitability in both myenteric and submucosal neurones.[22] On the other hand, peripheral injection of CRH has been reported to induce discrete effects on colonic secretory and motor function, and permeability.[23] We have previously reported that intravenous administration of a non-selective CRH antagonist (α-helical CRH) blunts the exaggerated motility response in the sigmoid colon to electrical stimulation in IBS patients compared with normal subjects.[24] In the same study, we have shown that administration of α-helical CRH induces a significant increase in barostat bag volume in normal subjects but not in IBS patients, and a significant reduction in the ordinate scale of abdominal pain and anxiety evoked by rectal electrical stimulation in IBS patients. However, plasma ACTH and serum cortisol levels were generally not suppressed following administration of α-helical CRH at 10 μg/kg. Although the precise sites of action of α-helical CRH are unknown, we suggested in our previous study that blunting the colonic motor response is mainly due to blockage of peripheral CRH-R1 and that drug anxiolytic or antinociceptive effects are probably based on inhibition of central CRH-R1 via circumventricular organs, which are relatively unprotected by the blood-brain barrier.[24] These findings and concepts, which put in the context of existing preclinical and clinical data, support the testing of new CRH antagonists, particularly potent CRH-R1 antagonists, in IBS and the view that the CRH-R1 receptor is a promising target for the treatment of IBS.[25]

In this issue of *Gut*, however, Million and colleagues[26] provide a new theory for modifying gut sensitivity via CRH-R2 ***(see page 172)***. Using RT-PCR, they proved the existence of CRH-R2 in the dorsal root ganglia and spinal cord and hypothesised that CRH-R2 activation may influence visceral pain induced by colorectal distension in conscious rats. By assessing the possible sites and mechanisms of action for CRH-R2 activation, they showed that two repeated colorectal distensions produced visceral sensitisation and phosphorylation of extracellular signal related kinase 1/2 (ERK 1/2) and that intravenous administration of human urocortin 2, a selective CRH-R2 agonist, prevented visceral sensitisation and reduced the second response compared with the first one. Million *et al* also demonstrated that administration of human urocortin 2 dampened distension induced phosphorylation of ERK 1/2 and robust inferior splanchnic afferent spike activity and that treatment with astressin$_2$-B, a CRH-R2 receptor antagonist, reversed the inhibitory effects of human urocortin 2 both in vivo and in vitro.[26]

CRH-R2 is highly expressed in the anterior pituitary, hypothalamus, hippocampus, amygdala, lateral septum, and other peripheral tissues, including the spleen, stomach, and gut.[7–9] Compared with CRH-R1, the functional role of CRH-R2 is relatively obscure. However, recent reports put forward the concept that activation of CRH-R2 signalling pathways may be important to reduce anxiety and stress response.[27 28] There are other functional differences between CRH-R1 and CRH-R2. For example, activation of CRH-R1 causes a proinflammatory response whereas stimulation of CRH-R2 provokes anti-inflammatory changes.[29] In addition, the study by Million and colleagues[26] offers evidence of the contrasting roles of CRH-R1 and CRH-R2 in visceral nociception. While CRH-R1 is involved in the pronociceptive effects of visceral pain, CRH-R2 mediates antinociceptive responses. These findings are supported by a recent report from another group.[30]

Several questions arise from these animal experiments. Do endogenous CRH-R2 ligands such as CRH, urocortin 1, urocortin 2, urocortin 3 (stresscopin), and stresscopin related peptides play an inhibitory role in visceral hypersensitivity in IBS patients? If so, are selective CRH-R1 antagonists more effective for visceral hypersensitivity than non-selective CRH antagonists? Moreover, do agents that block CRH-R2 have any adverse effects on the pathophysiology of IBS? Do CRH-R2 agonists have therapeutic value for IBS and/or allied functional gastrointestinal disorders, even though stress induced inhibition of gastric emptying is mainly mediated via CRH-R2? What are the major steps from the synthesis of cAMP by activated CRH-R2 in the dorsal root ganglia and spinal cord to reduced phosphorylation of ERK 1/2 in the laminae I and II? Thus the disclosed nature of CRH-R2 reported in the present issue of *Gut* brings us an exciting paradigm on research and drug development of the CRH neuropeptide family.

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Incretin

To be or not to be—an incretin or enterogastrone?

M Horowitz, M A Nauck

Glucagon-like peptide 1 does not comfortably fulfil the criterion of a gut derived factor responsible for an enhanced meal related insulin response; it appears logical to add the definition of a ''physiological incretin hormone''

Incretin hormones are gut derived peptides that augment the insulin releasing action of hyperglycaemia. In his seminal review, based on the 1978 Claude Bernard lecture, delivered at the European Association for the Study of Diabetes Meeting, Werner Creutzfeldt defined the term incretin as ''an endocrine transmitter produced by the gastrointestinal tract which is: (a) released by nutrients, especially carbohydrates and (b) stimulates insulin secretion in the presence of glucose if exogenously infused in amounts not exceeding blood levels achieved after food ingestion''.[1] At that time, the best characterised incretin candidate was glucose dependent insulinotropic polypeptide (GIP), although there was evidence that GIP was not the only incretin.[1 3] An incretin role for GIP was established, along the lines of Creutzfeldt's definition,[1] by intravenous infusion in healthy subjects, both alone and in combination with glucose, and demonstrating that the insulinotropic property of GIP was dependent on a permissive rise in blood glucose.[2] Subsequent experiments, performed under more physiological conditions, with plasma GIP and glucose concentrations mimicking the postprandial state, confirmed these observations.[4] That relatively uncomplicated infusion experiments had the capacity to predict the physiological role of GIP with regard to its effects on insulin secretion is testimony to the fact that, metabolically speaking, GIP is apparently devoid of additional actions which have the potential to confound such experiments.[5]

The situation with glucagon-like peptide 1 (GLP-1) is far less straightforward. The GLP-1/glucose infusion experiment results in effects similar to those observed with GIP,[6] and GLP-1, accordingly, fulfils the definition of an incretin hormone, as put forward by Creutzfeldt.[1] However, studies which have evaluated the effects of GLP-1 on the metabolic response to a meal, by infusing physiological or pharmacological amounts of GLP-1,[7] or interfering with endogenous GLP-1 action with the well characterised GLP-1 antagonist exendin(9–39),[8–10] have revealed a complex pattern of GLP-1 actions. In particular, as a result of its effect on slowing gastric emptying substantially, exogenous GLP-1 attenuates the postprandial rise in glycaemia, leading to lesser substrate (glucose) mediated insulin secretion and an overall reduction, rather than an increase, in the insulin secretory response to a meal.[7 11 12] In other words, inhibition of gastric emptying by exogenous GLP-1 outweighs its direct insulinotropic effects. This was highlighted in a recent study demonstrating that intravenous erythromycin, as a result of its prokinetic properties, abolishes the deceleration of gastric emptying induced by exogenous GLP-1 in healthy subjects and that this is associated with a marked reduction in its glucose lowering effect.[12] Furthermore, the GLP-1 antagonist exendin(9–39) increases, rather than lowers, the insulin response to a meal.[13] Based on these observations it is clear that GLP-1 does not comfortably fulfil the criterion of a gut derived factor responsible for an enhanced meal related insulin response; furthermore, it appears logical to add the definition of a ''physiological incretin hormone'' to that provided by Creutzfeldt,[1] and assigning such a role to GLP-1 appears inappropriate based on current data.[11]

In their important study in the current issue of *Gut*, Schirra and colleagues[14] have introduced a new approach to evaluation of the incretin role of GLP-1 in healthy subjects ***(see page 243)***. They used intraduodenal administration