Corticotropin releasing factor receptor antagonists: potential future therapy in gastroenterology?

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New corticotropin releasing factor (CRF) antagonists in irritable bowel disease (IBS) warrant testing, and CRF1 receptors may be a promising target for the treatment of IBS

Recent years have witnessed important developments in the understanding of the biochemical coding of stress. In addition to the 41 amino acid peptide, corticotropin releasing factor (CRF), novel mammalian CRF related peptides, urocortin 1, urocortin 2, and urocortin 3 have recently been discovered. These CRF ligands display distinct affinity to the two cloned G protein coupled CRF1 and 2 (CRF2) receptors. CRF has higher affinity for CRF1 than for CRF2 receptor, urocortin 1 displays equal affinity for both subtypes, and urocortin 2 and 3 have selective affinity for CRF2 receptors. In addition to the mapping of CRF ligands and receptors in the brain and gut, the development of potent selective CRF1 and CRF2 antagonists and generation of transgenic mouse models provided tremendous insight in the investigation of the underlying mechanisms of stress. Convergent studies established the role of the brain CRF-CRF1 pathways in mediating the endocrine, autonomic, behavioural, and visceral responses to stress while CRF receptors may be important in dampening stress sensitivity.

Extensive preclinical research effort has solidified the concept that overactivity in the brain CRF-CRF1 signalling system contributes to the onset of anxiety disorders and depression. These observations have spurred the development of a number of non-peptide CRF1 receptor antagonists which can readily cross the blood-brain barrier on peripheral administration. These compounds prevent various stress related anxiogenic behaviours in rodents. Clinical studies in patients with major depression and post-traumatic disorders showed that CRF levels are elevated in the cerebrospinal fluid and lowered by effective antidepressants. In patients treated with interferon-α for chronic hepatitis C, activation of the brain CRF pathways induced by interferon-α is frequently associated with psychiatric side effects that have overlapping features with major depression. In mice, synthetic recombinant type I interferon α induced a depressive-like behaviour that is abolished by pretreatment with the CRF1 receptor antagonist CP-154,526. A first phase II open label clinical trial including patients with major depressive disorders indicated that the CRF1 antagonist R121919 was effective in reducing depression and anxiety scores. Such beneficial effects were obtained at doses that neither disrupted normal circadian hypothalamic-pituitary axis hormone production nor hampered adrenal corticotropic hormone (ACTH) or cortisol responses to CRF stimulation. Collectively, existing preclinical and clinical reports indicate that CRF1 antagonists may have therapeutic potential in the treatment of affective disorders.

Available evidence suggests that the CRF1 receptor may also be an appealing target in the context of functional bowel disorders. Irritable bowel syndrome (IBS) is a common bowel disorder with clinical features that include recurrent abdominal pain or discomfort associated with altered bowel habits in the absence of structural pathology. In studies of hospital outpatients with IBS, it has been reported that symptoms or the chronic course of the illness can be exacerbated by psychosocial stressors. A high co-prevalence of IBS with psychiatric disorders, including anxiety and depression, is also well documented. Other clinical studies showed that psychological factors predicted the occurrence of diarrhoea predominant IBS that develops in certain subgroups of patients that had acute gastroenteritis. The underlying mechanisms of such an association may be explained in the framework of overactivity of the CRF-CRF1 signalling pathways. Evidence supporting this contention came from initial experimental demonstration of an interrelationship between activation of central CRF1 receptors and stress related induction of IBS-like symptoms. Administration of CRF and urocortin 1 into the lateral brain ventricle stimulated colonic motor function in rats, mice, and gerbils and increased abdominal pain to colorectal distension in rats. Sites of action were located at a specific hypothalamic nucleus (paraventricular nucleus) or pontine area [locus coeruleus (LC), LC/Barrington nucleus] that also induced CRF related behaviours symptomatic of anxiety and depression. Studies with a number of selective CRF1 antagonists (CP-154,526, CRA-1000, NBI-35965, or NBI-27914) injected intracerebroventricularly or peripherally blunted stress related anxiogenic behaviour, visceral hyperalgesia, and activation of colonic secretory and motor function in rodents and monkeys. Moreover, female mice with deletion of the CRF1 receptor gene showed reduced anxiety-like behaviour and colonic motor response to the open field test. The colonic response to central CRF-CRF1 pathway activation is unrelated to pituitary-adrenal hormone release and is mediated by modulation of the autonomic nervous system, particularly stimulation of sacral parasympathetic activity in rodents. There is also a decrease in vagal outflow to the upper gut and activation of the sympathetic nervous system that contribute to the concomitant inhibition of gastric and small intestinal motility. Interestingly, it has been found that colorectal distension activates LC activity through CRF-CRF1 pathways in rodents. The increased discharge rate of neureones in the LC induced by stress of psychological or visceral origin leads to widespread activation of noradrenergic projections to forebrain target sites implicated in arousal and attention. These mechanisms may underlay the reported stress induced altered perceptual thresholds to colorectal balloon distension and hyper-reactivity to stress in IBS patients.

In addition to the role of brain CRF-CRF1 pathways, experimental studies have convincingly established peripheral stimulatory actions of CRF on colonic secretory and motor function and permeability. The peptide, injected peripherally, stimulates colonic motility, transit, secretion of mucus, prostaglandins, and ions, degranulates colonic mucosal mast cells and increases intestinal permeability to ions and macromolecules. A direct action of CRF at the enteric nervous system was established by the presence of CRF1 receptors on colonic myenteric neurones. It was also demonstrated that activation of myenteric neurones, increased colonic motility, and induction of diarrhoea induced
by intraperitoneal injection of CRF were mediated by CRF1 receptors in rodents.\textsuperscript{34-36} The relevance of peripheral CRF receptors in the stress response was established by the use of the peptide CRF antagonist α-helical CRF\textsubscript{9-41} that has poor brain penetration. This CRF antagonist injected peripherally inhibited restraint stress induced stimulation of colonic motor function, prevented mucosal mast cell degranulation, and blocked the increased colonic mucin and ionic secretion, and intestinal permeability observed in rats.\textsuperscript{31,33} Similar to animal models, intravenous administration of CRF increased colonic motility and abdominal pain in IBS patients and the response was higher compared with normal subjects.\textsuperscript{37} Other studies showed that the preferential CRF\textsubscript{1} agonist ovine CRF lowered the threshold and sensation of discomfort to colonic distension in normal subjects.\textsuperscript{38} In this issue of Gut, Sagami and colleagues\textsuperscript{39} have built on this framework and report the dampening influence of intravenous injection of the CRF receptor antagonist α-helical CRF\textsubscript{9-41} on symptoms triggered by colonic tracking distension and electrical stimulation of the rectal mucosa in IBS diarrhoea predominant patients [see page 958]. In this study, the authors show that intravenous injection of α-helical CRF\textsubscript{9-41}, given to subjects unaware of the timing of antagonist administration, blunts the exaggerated motility response in the sigmoid colon to electrical stimulation in IBS patients compared with normal subjects. They also report that the CRF antagonist reduces significantly abdominal pain and anxiety score without compromising pituitary release of ACTH. Because of the small number of subjects included in the study, this initial clinical investigation warrants replication in a larger group of IBS patients and further assessment using a placebo control group. However, these findings, put in the context of existing preclinical and clinical data, support the testing of new CRF antagonists, particularly more potent CRF\textsubscript{1} antagonists, in IBS and the view that CRF\textsubscript{1} receptors are a promising target for the treatment of IBS. CRF receptors antagonists may also have value in some forms of gut inflammation. A number of studies in rodents and humans established that CRF, acting through CRF\textsubscript{1} receptors, exerts an autocrine-paracrine proinflammatory action in peripheral tissues undergoing an inflammatory process.\textsuperscript{40} CRF, urocortin 1, and CRF\textsubscript{1} receptors have been detected at both the gene and protein levels at sites of inflammation\textsuperscript{41} in the rodent and human intestine.\textsuperscript{42-43} Peripheral administration of CRF\textsubscript{1} receptor antagonists significantly inhibit the degree of inflammation associated with an acute enterotoxigenic response, as monitored by the reduction in toxin A induced ileal secretion, epithelial cell damage, mucosal oedema, neutrophil infiltration, and mucosal content of interleukin 1β and tumour necrosis factor α.\textsuperscript{44} This points to the potential use of specific CRF\textsubscript{1} receptor antagonists in intestinal inflammatory conditions. In the upper gut, other potential clinical relevance of targeting CRF\textsubscript{1} receptors has been recently reviewed in the context of cyclic vomiting syndrome\textsuperscript{45} and postoperative gastric ileus.\textsuperscript{44}

In summary, a growing body of experimental evidence has demonstrated that CRF\textsubscript{1} receptor antagonists alleviate the development of anxiety-like behaviour and stress related alterations of gut function and enterotoxin mediated intestinal inflammation. The positive results associated with the use of CRF receptor antagonists in IBS patients reported in the present issue of Gut hold promise and warrant testing using selective CRF\textsubscript{1} antagonists.


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Leptin

Leptin in intestinal inflammation: good and bad gut feelings

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Leptin has a potent effect on T cell mediated intestinal autoimmunity and may have a role in the development of such diseases

Leptin, a molecule that is critical in the regulation of energy balance, body weight, and reproductive function, is a strong regulator of T cell function. This is one of many examples of redundant and of the overlapping roles of molecules within the neuroendocrine and immune systems. Leptin is part of the helical cytokine family along with interleukin (IL-) 6, IL-12, and IL-15, its receptor (ObR) belonging to the group of class I cytokine receptors, which includes gp-130, the common signal transducing component for the IL-6 family of cytokines—proteins that influence or mediate immune functions. Indeed, leptin enhances the activity of T cells that produce proinflammatory cytokines and that orchestrate many organ specific autoimmune diseases.

In the current issue of Gut, Siegmund and colleagues describe the potent effects of leptin on T cell mediated intestinal autoimmunity and further define the role of leptin and its receptor in the development of such disease [see page 965]. The authors elegantly demonstrate that T cells from naturally leptin receptor deficient (db/db) obese mice display a reduced capacity to induce, on passive transfer, a T cell mediated model of colitis in T cell deficient mice (scid mice). In this model, it is possible to study the function of leptin receptor deficient T cells in a normal microenvironment where insulin, glucocorticoids, and other factors are not altered as they are in db/db obese mice. Leptin and its receptor were expressed on transferred wild-type (WT) T cells and infiltrating lymphocytes. Transfer of T cells from db/db mice induced delayed disease compared with transfer of WT cells. Histological examination of the colon, early after induction of disease, revealed marked inflammation in mice injected with WT cells whereas no inflammation was observed in mice receiving db/db cells. The delayed disease could not be attributed to the effect of increased levels of glucocorticoids in db/db donor mice as treatment with glucocorticoids of WT donor lymphocytes did not change their pathogenic capacity. Lamina propria infiltrating lymphocytes (LPL) from WT and db/db mice showed no difference in terms of differentiation, expression of homing receptors, or activation markers. Interestingly, the most evident difference was an increased rate of apoptosis of LPL derived from db/db mice and reduced production of inflammatory cytokines and chemokines. Finally, the nuclear receptor peroxisome proliferator activated receptor γ (PPARγ), known to inhibit expression of inflammatory cytokines, including leptin, was highly expressed in colonic cells of mice that had received db/db cells.

Recent reports have shown that leptin secreted by the gastric mucosa is not fully degraded by proteolysis and can reach the intestine in an active form able to control the expression of sodium/glucose and peptide transporters on intestinal epithelial cells. Therefore, it may be speculated that leptin displays a dual nature: as a growth factor for the intestine, involved in the absorption of carbohydrates and proteins on the one hand, and as a mediator of the intestinal inflammation induced by T lymphocytes on the other.*+ In addition, leptin deficient ob/ob mice are resistant to a variety of experimental models of inflammation/autoimmunity. In particular, they are resistant to intestinal inflammation induced by administration of dextran sulphate sodium or trinitrobenzene sulphonic acid. In these models, resistance to colitis in the absence of leptin was associated with reduced cytokine secretion and increased apoptosis of LPL. The report by Siegmund et al further reinforces the role of leptin and particularly its receptor in intestinal autoimmunity.* It is well known that there are some confounding factors in animal models of leptin deficiency such as ob/ob and db/db mice where massive obesity, insulin

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resistance, hyperglycaemia, and high levels of glucocorticoids could account for the altered immune response.\textsuperscript{1,5} In the present report, the model utilised elegantly rules out the possible influence on T cell pathogenicity of other factors, such as hyperglycaemia, hyperinsulinaemia, and hypercorticoisolaemia, that characterise db/db mice.

Antagonists of the ObR may well be considered as possible agents able to alter the progression of intestinal inflammation. Recently, mesenteric adipose tissue from patients with Crohn’s disease and ulcerative colitis showed high levels of expression of leptin mRNA.\textsuperscript{14} It is well known that food deprivation in the context of intestinal inflammation can improve disease symptoms and reduce the number of relapses.\textsuperscript{15} Many controlled trials in humans have shown that fasting and dietary change can ameliorate symptoms of patients with intestinal bowel disease, rheumatoid arthritis, and multiple sclerosis.\textsuperscript{3,15–18} In view of the results of Siegmund et al, we must also consider whether fasting and changes in diet might change leptin levels, thus altering the function of T cells. The implication of this work is that the leptin/ObR axis drives the activity of proinflammatory, self-reactive T cells and that reduction in leptin secretion and/or in the ObR signalling machinery can change the pattern of cytokines generated and the disease inducing potential of intestinal T cells. The idea that leptin could also have a significant role in intestinal inflammation is strengthened by studies of the genes expressed in patients with intestinal bowel disease: leptin and related genes are overexpressed in both intestinal mucosa and mesenteric adipose tissue.\textsuperscript{16} Once again, we witness the remarkable choreography of molecules related to body weight and energy metabolism and the parallel roles of these same molecules in the finely tuned immune response.\textsuperscript{19} In the context of the whole animal, however, there is still much to understand about the potential interactions between fat, metabolism, and the immune response. Increasing experimental evidence is revealing the importance of molecules, including leptin, at the interface between the immune system and metabolic regulation. In a broader context, the work by Siegmund et al illustrates how the state of immunity is influenced by the presence of leptin whose serum levels correlate with nutritional status. Leptin enhances the transport of nutrients across the intestinal barrier and supports an immune response poised to repulse pathogens.\textsuperscript{3,15,19} But it may also represent a key substrate for the seed of autoimmunity to take root. Therefore, manipulation of the leptin/ObR axis may provide a novel means of down-regulating T cell mediated autoimmune responses.

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Fatty liver, hypertension, and the metabolic syndrome

A M Diehl

The prevalence of fatty liver in non-obese non-diabetic hypertensive patients is at least twice that of the general population and may be related to increases in insulin resistance and body weight

The clinical significance of hepatic steatosis remains controversial.

Long known to be common, fatty liver was once dismissed as an innocuous condition, particularly when discovered incidentally in individuals with normal serum aminotransferases. However, as discussed subsequently, emerging evidence challenges this old assumption by demonstrating strong associations between hepatic steatosis and other potentially life threatening diseases.

Reports that some alcohol abusers and non-alcoholic individuals with fatty livers eventually develop cirrhosis and succumb to “typical” complications of advanced liver disease are certainly concerning. Moreover, evidence suggests a detrimental interaction between hepatic steatosis and other types of chronic hepatitis because several studies have identified fatty liver as an independent predictor of progressive liver fibrosis in patients with chronic hepatitis C and at least one study demonstrated that hepatic steatosis conveys an independent risk for hepatocellular carcinoma in this population. Hepatic steatosis is also associated with a poor response to antiviral therapy although this may be because it is strongly associated with obesity, which independently decreases the efficacy of hepatitis C treatment. In any case, there is no longer any doubt that having a fatty liver increases an individual’s risk for advanced liver disease.

In addition, fatty liver is strongly associated with other disorders that are themselves major causes of morbidity and mortality. As mentioned earlier, fatty liver is often linked with obesity, a condition that significantly increases the risk of dying from any disease. Obesity, particularly visceral adiposity, is also an important component of the insulin resistance metabolic syndrome, a constellation of disorders (for example, dyslipidaemia, type 2 diabetes, and hypertension) that promote cardiovascular disease. The paper by Donati and colleagues in this issue of Gut, draws our attention to the relationship between fatty liver and hypertension [see page 1020].

Briefly, the authors of this study used abdominal ultrasonography to detect “bright” (that is, fatty) livers in hypertensive individuals who had normal liver blood tests and no obvious risk factors for hepatic steatosis. The study population was a relatively select subgroup of hypertensive individuals, given that ~80% of the hypertensive clinic population had at least one risk factor for fatty liver or hepatitis that excluded them from enrolment. Surprisingly, despite lacking all of the obvious risk factors for hepatic steatosis, ~30% of the hypertensive individuals in the present study had fatty livers. These findings demonstrate that the prevalence of hepatic steatosis in non-obese non-diabetic hypertensive adults is at least twice the historical prevalence of fatty liver in the general adult populations and almost three times the prevalence of hepatic steatosis in the age and sex matched group of concurrent controls.

Interestingly, although none of the subjects in the present study was obese or overtly diabetic, hypertensive individuals with fatty livers had higher glucose levels, body mass indices, and insulin resistance than hypertensive individuals without fatty livers. Controls with fatty livers also had higher fasting serum levels of insulin and glucose, and greater insulin resistance than controls without fatty livers, although both of the control groups had similar body mass indices.

These results are important because they complement and extend other evidence that correlates hepatic steatosis with insulin resistance. The strong association between these two conditions has tremendous clinical relevance. On one hand, it suggests that detection of fatty liver identifies an individual who is quite likely to have insulin resistance and hence should be evaluated for other disorders in the insulin resistance syndrome (for example, diabetes, hypertension, dyslipidaemia). On the other hand, it suggests that an individual with features of the metabolic syndrome should be screened for fatty liver disease.

Few would argue against more aggressive screening for diabetes, hypertension, and dyslipidaemia because effective treatment of these disorders is known to reduce subsequent morbidity and cardiovascular mortality. However, some may disagree with implementing more widespread screening for hepatic steatosis because there is, as yet, no direct evidence that reducing liver fat is beneficial. To address this concern, it is necessary to understand whether it is the hepatic lipid accumulation per se or the factor(s) that promote(s) hepatic steatosis that is/are to blame for the adverse clinical outcomes that occur in individuals with fatty livers. Studies in experimental animals, as well as in patients, suggest that both are probably involved because hepatic lipid metabolism interfaces with the interactive matrix of metabolic products, hormones, cytokines, and neurotransmitters that coordinates substrate utilisation with the energy requirements for maintaining tissue integrity. Fat accumulation within hepatocytes indicates that the master system for regulating energy homeostasis has malfunctioned. However, fatty liver is also more than a mere barometer of metabolic dysfunction because it triggers signals to normalise lipid levels in the liver. The latter may involve altering the activities of the cytokines, hormones, and neurotransmitters that regulate fat turnover in other tissues. As these regulatory factors are quite pleiotropic, collateral neurological and immune dysfunction often ensues. Thus fatty liver is both a consequence of and contributor to the “dys”-metabolic insulin resistance syndrome. As such, it represents a reasonable therapeutic target.

The validity of this concept is supported by emerging evidence that various treatments (for example, lifestyle modifications, certain types of bariatric surgery, thiazolidinediones, metformin) that improve insulin resistance generally also improve hepatic steatosis. Thus our therapeutic armoury now includes reasonably effective weapons for these disorders. Questions remain however about when to deploy our “missiles”. All therapeutic interventions incur some cost, and none is 100% effective. For example, no currently available insulin sensitising therapy uniformly prevents (or reverses) features of the metabolic syndrome.
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