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 (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 receptor. 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 CRF₁ 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 depression and post-traumatic disorders 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 secretion 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 neurones 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 secretary and motor function and permeability. The peptide, injected peripherally, stimulates colonic motility, transit, secretion of mucus, prostanoids, 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...
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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.1 This is one of many examples of redundancy and of the overlapping roles of molecules within the neuroendocrine and immune systems.2 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 related family of cytokines.1 Leptin is expressed particularly in adipose tissue and to a lesser extent in other tissues such as muscle, stomach, and placenta.1 More recently, leptin has also been shown to be expressed in activated inflammatory T helper 1 lymphocytes during experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis.3 In keeping with these findings, the ObR has been found not only on the hypothalamus and adipose tissue but also on immune cells such as T lymphocytes and monocytes.4 5 Addition of this hormone to T cells in culture can alter both their growth rate and pattern of production of cytokines—proteins that influence or mediate immune functions.6 7 Indeed, leptin enhances the activity of T cells that produce proinflammatory cytokines and that orchestrate many organ-specific autoimmune diseases.8 9

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.10

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.11 12 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.13 14 In addition, leptin deficient ob/ob mice are resistant to a variety of experimental models of inflammation/autoimmunity.15 16 In particular, they are resistant to intestinal inflammation induced by administration of dextran sulphate sodium or trinitrobenzene sulphonic acid.8 10 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.1 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
resistance, hyperglycaemia, and high levels of glucocorticoids could account for the altered immune response. In the present report, the model utilised elegantly rules out the possible influence on T cell pathogenicity of other factors, such as hyperglycaemia, hyper-insulinaemia, and hypercorticoosteronemia, 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. It is well known that food deprivation in the context of intestinal inflammation can improve disease symptoms and reduce the number of relapses. 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. 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. 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. 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. 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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REFERENCES


Fatty liver, hypertension, and the metabolic syndrome

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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 ultrasoundography 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 neurohumoral and immune dysfunction often ensue. 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.
Furthermore, even when untreated for insulin resistance, most individuals with fatty livers (or with hypertension, dyslipidemia, or type 2 diabetes) live with these disorders for decades without experiencing significant hepatic or cardiovascular morbidity. Because the basis for interindividual differences in clinically significant outcomes of the metabolic syndrome is poorly understood, physicians are uncertain when to "attack" insulin resistance. Therefore, research is needed to characterise factors that modulate the natural histories of hepatic steatosis and other disorders, such as hypertension, that often develop in the context of insulin resistance. This information may help us to understand when treatments to enhance insulin sensitivity are necessary, as well as why these therapies sometimes fail to prevent end organ damage in individuals with the metabolic syndrome. In turn, this knowledge will permit us to select patients who are likely to achieve the greatest benefit from insulin sensitising therapy. If fatty liver is indeed a convenient marker for dangerous insulin resistance, then it will be important to determine if implementing efforts to improve insulin sensitivity will improve hepatic steatosis, which is diagnosed prevents dreaded consequences of the metabolic syndrome, such as cardiovascular disease, cirrhosis, and hepatocellular carcinoma.

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REFERENCES
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