GLP-1 and the gut

Glucagon-like peptide 1 (GLP-1) is a peptide hormone found in the small intestine and colon which is released in response to luminal nutrients and which has now been found to exert a number of important functions on the gastrointestinal tract and pancreas. Its role in the modulation of insulin secretion is of great interest to diabetologists. Its functions on the upper gastrointestinal tract and potential roles in therapy of upper gut disorders are however less well known.

The mammalian glucagon precursor (pro-glucagon) is produced both in the alpha cells of the islets of Langerhans and in specialised enteroendocrine cells (L cells) of the intestinal and colonic mucosa. Processing of the pro-glucagon precursor is different in the pancreas and intestine. In the pancreas it is cleaved to produce glucagon, and glycinfet related pancreatic polypeptide. The processing pattern in the intestine however differs markedly from that in the pancreas. Very little glucagon is formed, instead glycinfet is produced and in addition two glucagon-like peptides (GLP-1 and GLP-2) are released.

Of these cleavage products, interest is currently focussed on GLP-1 because of its potent biological actions that appear to be preserved in all mammalian species, which suggests that it participates in important biological control mechanisms.

GLP-1 is secreted from the L cells by luminal nutrients, particularly carbohydrates and lipids. In addition, neuro-peptides, particularly gastrin releasing peptides and substance P, can also release GLP-1 raising the question of additional neuronal control of secretion. Following the release of GLP-1 a number of important physiological responses occur. In the pancreas, GLP-1 is the most potent peptidergic stimulus for insulin release, its effect being glucose dependent. GLP-1 enhances insulin secretion with an effect that is dependent on blood glucose level; when glucose levels are low the effect is much less than when there is hyperglycaemia. This effect has been of great interest to diabetologists as a potential treatment for type 2 diabetes and there is much interest in the development of GLP-1 analogues as therapeutic agents.

In the gastrointestinal tract GLP-1 inhibits gastric emptying and gastric acid secretion by a mechanism which appears to involve stimulation of vagal afferent nerves. This suggests that GLP-1 probably interacts with submu-colosal vagal afferent nerves expressing GLP-1 receptors in the same way as cholecystokinin modulates gastric emptying. The location of GLP-1 releasing cells in the ileum and caecum together with the gastric emptying delay effects on nutrient exposure, raises the possibility that GLP-1 may act as part of the “ideal brake” together with peptide YY. The precipitate release of GLP-1 in patients after vagotomy and after partial gastrectomy may also explain in part the development of dumping syndromes after gastric surgery.

The paper by Schirra et al in this issue (see page 622) is a useful addition to our knowledge about the physiology of GLP-1 in humans. Using a careful manometric technique, they have studied the effects of GLP-1 infusion at varying doses on the pattern of antropyloral duodenal motor activity and shown that antral and duodenal motility are reduced while pyloric tone is increased. These findings are entirely consistent with the known effects of GLP-1 on gastric emptying. Interestingly, plasma levels of pancreatic polypeptide were also dose dependently diminished by GLP-1 with and without nutrients. This suggests an effect of GLP-1 on vagovagal reflexes; either GLP-1 inhibits a basal tonic effect of the vagus on pancreatic polypeptide levels or GLP-1 provides an inhibitory input to vagal effr-.erents or pancreatic polypeptide cellular release. The development of a GLP-1 analogue which either stimulates and/or blocks GLP-1 receptors should therefore be awaited with equal interest by the gastrointestinal community as by diabetic physicians since therapeutic benefit in patients with upper gastrointestinal motility disorders seems likely.

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Why treat chronic hepatitis B in childhood with interferon α?

Advances in the understanding of hepatitis B viral infection are a major accomplishment in modern hepatology. In three decades we have progressed from rather vague clinical concepts to a remarkably complete virology of hepatitis B virus (HBV), primary prevention with recombinant vaccines, and some effective antiviral treatments. This progress is especially important for children because it provides hope for preventing severe HBV associated liver disease. It is already evident that the best way to deal with hepatitis B infection is to avoid it altogether. The effectiveness of neonatal active with passive vaccination in preventing vertical transmission of HBV infection is on the order of 90–95%. Studies from Taiwan show that universal immunisation leads to reduced prevalence of HBV.
infection and a significantly lower incidence of hepatocellular carcinoma (HCC) in childhood.1

What about children who already have chronic HBV infection? Treatment with interferon α is effective in approximately one-third, where success denotes that active viral replication has ceased, HBeAg (hepatitis B e antigen) to anti-HBe (antibody to HBeAg) seroconversion has taken place, and serum HBV DNA is undetectable by hybridisation techniques. In a large randomised controlled paediatric clinical trial,2 18 of 70 (26%) children had HBeAg seroconversion during the 24 weeks of treatment or within 24 weeks of stopping treatment. Over the same 48 weeks, eight of 74 untreated control patients had spontaneous HBeAg seroconversion. An additional five children in the original treatment group had seroconversion 49–72 weeks after starting treatment: thus the overall response rate was 35%. There were no late spontaneous responses in the control group but the numbers were very small due to trial design. Drug induced and spontaneous HBeAg seroconversion were equally durable.

Interferon α treatment has limitations. It is most effective if commenced when serum alanine aminotransferase (ALT) levels have been consistently elevated to at least twice normal for several months, indicating that the host immune response against HBV is active but proving ineffective. Many younger children do not meet this treatment criterion. Treatment for children usually lasts for 24 weeks and may have unpleasant side effects. In children they can be similar to those in adults, including transient "flu-like" syndrome, anorexia with weight loss, neutopenia, and hair loss.3 In teens it may be difficult to differentiate typical adolescent moodiness from interferon induced affective disorders; school work may deteriorate temporarily. Febrile seizures can be problematic and require stopping treatment. Interferon induced diabetes mellitus has been found rarely in adults4 but it has not been reported in children. Pulmonary fibrosis and respiratory problems reported in adults receiving very large doses of interferon α have not been identified in children.

Given the difficulties of the treatment, its only moderate success rate, and the limited definition of success, it is reasonable to ask whether this treatment is worth the trouble, especially for children. The analysis reported by Bortolotti and colleagues (see page 715) suggests that the major effect of interferon α treatment may be only to speed up a natural history which would take place anyway. Thus the natural history of chronic hepatitis B in childhood is critical to assessing the value of this treatment. A small study from Italy predating interferon α treatment in children highlights the issue somewhat differently.5 Thirty six children with chronic hepatitis B diagnosed aged 1–9 years (mean 4.3) were followed for 10–18 years (mean 12.6). Initially most were HBeAg positive; four were anti-HBe positive and six had neither marker. At the end of follow up, all patients were spontaneously anti-HBe positive. Follow up liver biopsies showed that six had cirrhosis (progressing from severe chronic active hepatitis in four), 11 had fibrosis, three had moderately severe chronic active hepatitis, and seven had chronic persistent hepatitis. Recurrent, ineffective immune mediated assaults on HBV probably lead to chronic liver damage and cirrhosis; using a drug therapy to effect HBeAg seroconversion and viral inactivation early may therefore be beneficial.

Although natural history studies have indicated that lack of ongoing HBV replication is associated with improved outcome,6 whether treatment induced HBeAg seroconversion (indicating the end of extensive viral replication) confers an improved prognosis should be confirmed. Using HBeAg seroconversion as the primary end point for successful treatment seems to be a compromise: what the patient really wants is to get rid of the HBV infection entirely. Data from several large clinical trials of interferon α treatment for adults with chronic hepatitis B are now available. The results are mixed. In a German study of 103 patients treated compared with 53 untreated patients, both overall survival and survival without development of hepatic complications were significantly greater in patients who became negative for HBeAg after treatment; adverse outcomes in treated patients occurred only in non-responders.7 A study of male patients (17–55 years) from Taiwan suggested that successful treatment with interferon α conferred long term benefit based on approximately 10 years of follow up.8 The cumulative survival rate was significantly higher in the treated group. HCC occurred in only one treated patient who had reverted to being positive for HBeAg and in four untreated patients who remained HBeAg positive.

Other studies reserve judgment on the long term outcome in adults. In a review of several randomised controlled trials in Europe, 58 of 210 treated patients (28%) responded to interferon α with loss of HBV DNA and HBeAg and improved serum ALT and all but 14% remained the same at the end of follow up (approximately five years); 22 of 98 untreated controls (22%) responded spontaneously and all but 9% maintained this response. In these patients cirrhosis and/or HCC developed in both treated and untreated patients, with no discernible difference between the two groups. The authors could not establish a beneficial long term effect from treatment induced HBeAg seroconversion on the basis of these data.9 Another study from southern Italy showed that individuals with chronic hepatitis B had a higher mortality rate than the general population and that young patients without cirrhosis whose ALT normalised over prolonged follow up had the best prognosis. In this large but heterogeneous cohort, interferon α treatment appeared beneficial but the authors could not conclude that it prolonged survival, mainly because of the study’s design limitations.10 Thus data from adult studies are not really conclusive, even though they point toward long term benefit. Whether these data can be translated to the paediatric age group may also be questioned.

An important picture emerges from both short term and long term studies: the rate of HBsAg to anti-HBs seroconversion may be enhanced by interferon α treatment. The original report that 13 of 20 (65%) adult patients with sustained responses to interferon α eventually lost HBsAg, expressed anti-HBs, and became HBV DNA negative by PCR seemed optimistic.11 A separate report supported these findings: 23% of successfully treated adults cleared HBsAg compared with 10% of untreated patients with spontaneous response.12 In the Düsseldorf study, 19% of patients with a sustained response cleared HBsAg compared with none of the untreated controls. The five year probability of HBsAg loss was 11.6% after successful treatment.1 In the combined European trials, 34% of those with a sustained response after treatment compared with 20% of untreated patients with a spontaneous response lost HBsAg.4 HBsAg seroconversion occurred even if cirrhosis was present. In a large study of adults with chronic hepatitis B and cirrhosis the five year probability of HBsAg loss was 16% in those successfully treated and only 4% in untreated cirrhotic patients.13 On a cautionary note, there may be ethnic or racial variation: studies from the Orient reported no loss of HBsAg over prolonged follow up.14

This observation extends to children with chronic hepatitis B. In a randomised controlled trial already discussed, loss of HBsAg was observed within the time constraints of the study: seven of 70 treated children (or 39% of sustained responders to treatment) compared with
Hepatic regeneration and TGF-β: growing to a prosperous perfection†

It is widely accepted that TGF-β1 is a potent growth inhibitory and profibrotic cytokine which plays a pivotal role in the physiological process of wound healing as well as in the pathogenesis of organ fibrosis. TGF-β1 expression has been shown to be increased in a wide range of fibrotic diseases. In the liver, TGF-β1 mRNA expression has been demonstrated to correlate with ongoing fibrotic injury in both experimental animal models and in human liver diseases. TGF-β1 mediates its profibrotic actions by stimulating fibroblasts and related cell types, including in the liver the hepatic stellate cell (HSC), to secrete a wide range of extracellular matrix proteins. In pathological conditions this leads to accumulation of fibrotic matrix or in a more physiological context to the efficient healing of wounds. Furthermore, blocking TGF-β activity by a variety of strategies has been shown to inhibit fibrosis in a series of experimental models. However, TGF-β has other important actions, namely its immunomodulatory properties and its antiproliferative effects on epithelial cells, including hepatocytes. The regenerative capacity of the liver is well documented and is characterised not only by hepatocyte proliferation but also by increased TGF-β1 expression. Thus hepatocytes proliferate despite the presence of a powerful antiproliferative stimulus. Date et al have begun to examine this apparent paradox in a paper in this issue of Gut (see page 719).

Regulation of TGF-β activity is primarily achieved by the process of its activation. TGF-β1 mRNA is expressed by a wide range of cell types, including in the liver: Kupffer cells; endothelial cells; HSC; and possibly hepatocytes. Similarly, the three high affinity plasma membrane receptors through which TGF-β exerts its downstream effects have been shown to have a ubiquitous distribution. However, a cytokine with such powerful biological effects needs to be tightly regulated. TGF-β signalling can be controlled at other levels including inhibition by soluble receptor and binding of the mature peptide by other proteins, such as o2 macroglobulin. Date et al report a series of data that suggest a novel additional level of TGF-β regulation, namely that TGF-β signalling in liver injury may be regulated by differential receptor expression.

In their study, Date et al use the well defined and reproducible rat CCI1 model of hepatic injury. They have previously shown increased TGF-β mRNA expression following CCI1 administration and now demonstrate a similar increase in TGF-β1 protein, maximal at 48 hours, following a single dose of CCI1. They then go on to demonstrate that hepatocytes isolated from CCI1 treated animals have reduced sensitivity to the antiproliferative effect of TGF-β1 in comparison with hepatocytes from normal rats. Concurrently, they have shown a dose dependent induction of fibronectin expression by TGF-β1 in HSC, which is not differentially regulated by CCI1 treatment.

To attempt to account for the observed differential sensitivity of HSC and hepatocytes to TGF-β following CCI1 injury, Date and co-workers then examined binding of...
radiolabelled TGF-β1 to TGF-β receptors in HSC and hepatocytes from normal and CCl₄ treated livers. They identified proteins corresponding to the expected molecular weights of the three TGF-β receptor subtypes in hepatocytes and HSC from normal rats, and in HSC from injured rats. However, in hepatocytes extracted from rats 48 hours after CCl₄ injury, TGF-β receptors I and II (the subtypes responsible for mediating intracellular signalling) were downregulated and only returned to baseline levels of expression after 72 hours.

Date et al postulate that decreasing hepatocyte TGF-β receptor I and II expression following CCl₄ injury may provide an explanation for the observed reduction in TGF-β mediated growth inhibition of hepatocytes. This may explain the apparent paradox of hepatocellular regeneration corresponding temporally with increased TGF-β expression and increased extracellular matrix deposition. This paper provides consistent evidence to support this elegant hypothesis but raises with it further unresolved questions and many avenues worthy of investigation. For example, the present study does not quantify active TGF-β, which is perhaps the most relevant form to measure, as only the active peptide can bind to the cell surface receptors. Local activation of TGF-β may provide a further method of eliciting differential cellular responses. Moreover, it would be fascinating to ascertain the relationship between decreased TGF-β receptor expression and hepatocyte apoptosis. But the mechanism by which hepatocytes regulate TGF-β receptor expression is perhaps the key question raised by this study. By attempting to answer these questions we may obtain significant insight into the complex and sometimes apparently contradictory biological effects of TGF-β in liver injury and fibrosis, and further unravel the exquisite control of hepatic regeneration.

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†“... it will grow to a prosperous perfection”, William Shakespeare. Measure for Measure, Act 3, Scene 1.