Commentaries

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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.[1] 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.[2] Processing of the proglucagon precursor is different in the pancreas and intestine. In the pancreas it is cleaved to produce glucagon, and glycentin related pancreatic polypeptide. The processing pattern in the intestine however differs markedly from that in the pancreas. Very little glucagon is formed, instead glycentin 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, neuropeptides, particularly gastrin releasing peptides and substance P, can also release GLP-1 raising the question of additional neuronal control of secretion.[3] 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.[4] 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.[5] This suggests that GLP-1 probably interacts with submucosal 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 "ileal brake" together with peptide YY. The precipitate release of GLP-1 in patients after vagotomy and after partial gastrectomy[6] may also explain in part the development of dumping symptoms 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 efferents 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