GLP-1 based therapy of diabetes

GLP-1, a brain and gut product of the proglucagon, was searched for because of data indicating that glucose-dependent insulinotropic polypeptide (GIP) could not be the only incretin hormone. Neither of the 2 glucagon-like sequences (GLPs) identified in the predicted proglucagon precursor were insulinotropic, but the natural peptide (Holst et al FEBSletters 1987), a truncated, amidated peptide (GLP-1 7-36amide) strongly stimulated insulin secretion and inhibited glucagon secretion, and has powerful glucose lowering effects in patients with T2DM. It is an incretin hormone and the incretin effect is lost in T2DM. This is because GLP-1 has lost insulinotropic potency, while GIP looses insulinotropic efficacy. In addition, meal-stimulated GLP-1 secretion is frequently impaired. Both defects appear to be secondary to T2DM: similar losses are seen early in secondary diabetes (chronic pancreatitis) and induction of glucose intolerance (gestational diabetes, glucocorticoid treatment) leads to a similar loss of incretin effect. Intensive metabolic control in T2DM improves incretin function and activity of GLP-1 and GIP. Therefore, the loss of incretin effect contributes importantly to diabetic hyperglycemia, and restoration of the effect (with GLP-1 agonists) greatly improves metabolic control. Conversely, accelerated gastric emptying causes exaggerated GLP-1 secretion and explains postprandial reactive hypoglycemia in insulin sensitive individuals.

GLP-1 has also turned out to be a physiological negative regulator of appetite and food intake, and chronic administration leads to weight losses. BMI is inversely correlated to meal-induced GLP-1 secretion, and loss of gut-derived appetite regulation may represent a pathophysiological trait of obesity. Gastric-bypass operations in morbidly obese diabetic subjects are associated with rapid transfer of nutrients to the distal small intestine and hugely elevated (10-fold) GLP-1 responses. Because of its effects on appetite and metabolic control, GLP-1 is likely to contribute importantly to the beneficial results of these operations. Currently, GLP-1 based therapy of diabetes includes several GLP-1 receptor agonists and a growing number of dipeptidyl-peptidase-4 (DPP-4) inhibitors, which improve the survival of endogenous GLP-1 and thereby enhances its actions as shown in our laboratory in 1995. Current research tries to identify means to
stimulate the endogenous secretion of GLP-1 trying to mimic the success of bariatric surgery with respect to both weight loss and diabetes therapy.