Glucagon-like peptide 1 (GLP-1) is an insulinotropic peptide secreted by intestinal L-cells (mucosal cells belonging to the APUD (amine precursor uptake and decarboxylation) system in response to oral food intake. GLP-1 is co-encoded in the proglucagon gene and while post-translational processing of proglucagon in the pancreas gives rise to glucagon, GLP-1 (7–36 amide) is produced in the intestine and to a lesser extent in the hypothalamus.

The postprandial secretion of an intestinal factor that lowers plasma glucose levels (incretin) had already been hypothesized a century ago. However, only 10 years ago, when GLP-1 was discovered as a second incretin besides gastric inhibitory peptide (GIP), this concept of an entero–insular axis became established. Since then the implication of GLP-1 in glucose metabolism and the potential use of this incretin in diabetes have been studied in different models including clinical studies. Recently, GLP-1 has been reported to act centrally as a satiety factor in rodents and this hormone is now also thought of as a ‘gut–brain peptide’. Finally, a GLP-1 receptor knock-out mouse could be created, confirming the importance of GLP-1 in glucose homeostasis, but casting doubts on its role in appetite regulation. These recent findings help to clarify the physiological importance of GLP-1 and are discussed in the present highlight.

GLP-1 concentrations in the picomolar range induce insulin secretion from pancreatic β-cells in vitro and in vivo when elevated glucose concentrations (> 5 mmol/l) are present. In patients with non-insulin-dependent diabetes mellitus (NIDDM) parenteral (i.v. and s.c.) administration of GLP-1 led to reconstitution of the early phase insulin secretion and reduction of postprandial glucose excursions. Even in insulin-deficient type-1 diabetic patients GLP-1 reduced the insulin requirements, suggesting additional peripheral activities (1, 2). In contrast to sulfonylurea drugs, GLP-1 not only stimulates insulin secretion, but also proinsulin gene transcription via activation of the transcription factor CREB (cyclic AMP-responsive element binding protein), potentially counteracting the problem of insulin depletion of the β-cell (1). In patients with NIDDM, overnight infusion of GLP-1 improved basal and stimulated β-cell function to the level of non-diabetic controls (3). GLP-1 plasma levels are elevated in patients with NIDDM and even pharmacological doses of GLP-1 have attenuated glucose-lowering effects compared with healthy subjects. This partial resistance to GLP-1 in NIDDM is not due to a receptor defect (4) but is speculated to be caused by GLP-1 induced desensitization of pancreatic GLP-1 receptors.

The GLP-1 receptor, a 63 kDa protein belonging to the group of trimeric G-protein linked receptors signaling via cyclic AMP, is found on pancreatic islets (β and δ cells), adipose tissue, skeletal muscle, liver, intestine, stomach, lung and brain (hypothalamus) (1). The presence of GLP-1 receptors in hypothalamic nuclei implicated in appetite regulation raised the question whether GLP-1 might be involved in feeding behavior (5). In addition, intestinal GLP-1 secretion seems to be attenuated in obese subjects (6).

In fasted rats, intracerebroventricular (i.c.v.) injection of GLP-1 inhibited food intake in a dose-dependent manner, whereas the peptide exendin (9–39), a GLP-1 receptor antagonist, increased food intake of fed rats as did the well-known appetite stimulant NPY (neuropeptide Y) (5). Intracerebroventricular injection of the GLP-1 receptor agonist exendin-4 to rats resulted in a decrease of food intake, while the biologically inactive GLP-1 isoform, GLP-1 (1–37) amide, had no effect and exendin (9–39) reversed the inhibitory effect of GLP-1 on feeding. As peripheral administration had little or no effect on appetite a central mechanism was suggested (5, 7, 8). Even though it is tempting to speculate that the incretin GLP-1 secreted postprandially is conferring a feedback mechanism by inducing satiety, it is not clear whether this effect is specific or physiological. As both the GLP-1 receptor and GLP-1-like immunoreactivity are found in the hypothalamus (8) a paracrine effect can be hypothesized. However, there is no evidence of increased hypothalamic postprandial GLP-1 secretion. In addition, it is controversial whether i.c.v. GLP-1 induces a conditioned taste aversion and thereby reduces feeding. While Thiele and colleagues (9, 10) describe an emetic effect of GLP-1, Sheikh’s group (7) did not find any GLP-1-induced taste aversion in rats.

In order to assess the physiological relevance of GLP-1 Drucker’s group (11) constructed a mouse harboring a null mutation of the GLP-1 receptor thereby eliminating successfully all GLP-1 binding sites and effects.

Interestingly, these GLP-1 receptor knock-out mice had no obvious phenotype and showed no difference in body weight or food intake compared with wild-type mice. Intracerebroventricular GLP-1 administration to wild-type mice resulted in a similar inhibition of feeding as in rats, whereas no effect was seen in the mutant mice. Thus, the inhibitory effect of i.c.v. GLP-1 on feeding seems...
indeed to be conferred by a specific interaction with its receptor in the brain. However, the postreceptor mechanisms by which exogenous GLP-1 reduces food intake remain unclear. The disruption of the GLP-1 receptor did not lead to any changes in feeding behavior suggesting again the presence of redundant signaling systems and potentially adaptive responses in these knock-out animals.

However, GLP-1 signaling plays a crucial role in maintaining glucose homeostasis. Mice lacking the GLP-1 receptor develop glucose intolerance after oral or intraperitoneal glucose administration, and elevated plasma glucose concentrations during fasting conditions (11). These data, together with the clinical studies, confirm the physiological relevance and the therapeutic potential of this incretin. The ongoing search for agents stimulating endogenous GLP-1 secretion from the gut after oral administration as well as for preparations of GLP-1 or GLP-1 agonists with retarded release for subcutaneous use might lead to new options for the treatment of NIDDM.

References