Summary. The incretin effect is the phenomenon whereby oral glucose elicits a greater insulin secretory response than an intravenous administration of glucose, even if the same glycemic profile is obtained ("isoglycemia") or even exceeded. The incretin effect mainly is the results of the secretion, from gut endocrine cells, of incretin hormones, which is stimulated by the ingestion and absorption of nutrients. The main incretin hormone is gastric inhibitory polypeptide (glucose-dependent insulinotropic polypeptide, GIP), produced in and secreted from upper intestinal K cells. A second incretin hormone, glucagon-like peptide-1 (GLP-1), is synthesized mainly in lower intestinal L cells. Both incretin hormones stimulate insulin secretion by interacting with specific receptors on endocrine pancreatic beta cells. This augmentation is prominent at high glucose concentrations, but stops at glucose concentrations slightly below fasting values. In patients with type 2 diabetes, the incretin effect is reduced and the reason is that GIP has lost most of its insulinotropic activity. GLP-1, on the other hand, has preserved activity, even in patients with type 2 diabetes. In addition to its insulinotropic activity, it also suppresses glucagon, retards gastric emptying, reduces appetite and food intake, and can inhibit beta-cell apoptosis and promote beta-cell regeneration and neogenesis. Therefore, these properties of GLP-1 can be exploited to treat type 2 diabetes, both in the form of incretin mimetics (GLP-1 receptor agonists) and DPP-4 inhibitors (preventing degradation and inactivation of incretin hormones by the proteolytic enzyme dipeptidyl peptidase-4).
The Incretin Effect in Healthy Subjects

Ingestion of glucose leads to an approximately 5–10 fold stimulation of insulin secretion over the fasting, basal rate [1,2]. Part of this increment in insulin secretion is due to glucose being absorbed and leading to a rise in glycemia. However, this “direct” stimulation of insulin secretion through moderate elevations in circulating glucose concentrations only partially explains the insulin secretory response after glucose ingestion: if glucose is infused intravenously at rates that lead to a duplication of the glycemic excursion after oral glucose, a greatly reduced insulin and C-peptide response is observed [3–5]. This clearly indicates that other factors beyond a rise in glucose concentrations are important determinants of insulin responses after glucose ingestion [6,7].

Based on studies dating from 1906 showing the glucose lowering effects of gut mucosal extracts in diabetic patients [8], a possible explanation for differences in insulin secretory responses to oral and parenteral (e.g., intravenous) glucose was sought in the secretion and action of gut-derived hormones, the so called incretins [3,4,6,7].

Shortly after a method to measure insulin concentrations in plasma became available [9], a higher insulin response to oral as compared to intravenous glucose became evident [3,4], even in experiments that administered the same amount of glucose via both routes (thus leading to much higher circulating glucose concentrations when glucose was infused intravenously) [10,11]. Perley and Kipnis [12] introduced the method of “isoglycemic” intravenous glucose infusions to exactly compare the effects of oral and intravenous glucose under conditions, where the glycemic stimulus was the same. They described approximately three-fold higher insulin increments with oral than with intravenous glucose in healthy subjects. With advances in the methodology to assess insulin secretion (C-peptide, calculation of insulin secretion rates by deconvolution techniques) it became possible to quantify the incretin effect more definitively. Technically, the incretin effect is the difference in insulin secretory responses to oral and “isoglycemic” intravenous glucose (Fig. 1). Usually, it is expressed as the percentage of the (“total”) response after oral glucose (=100%). It makes a difference whether insulin, C-peptide, or insulin secretion rates are used to calculate the incretin effect [5,13]. The reason is that oral glucose leads to a change in insulin elimination form the circulation, most likely through a reduction in hepatic extraction [14], which lets more insulin appear in the general circulation. Since this is not the case with intravenous glucose (at least not to the same degree), incretin effects calculated from insulin responses are greater (60%–80% for a glucose load of 50 g) than incretin effects calculated from C-peptide or insulin secretion rates.