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For debate

Is glucagon-like peptide 1 an incretin hormone?

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Summary Glucagon-like peptide-1 (GLP-1) was predicted, based on the proglucagon gene sequence. It is synthesised by specific post-translational processing in L cells (lower intestine) and secreted mainly as "truncated" GLP-1 [7–36 amide] in response to nutrient ingestion. Glucagon-like peptide-1 stimulates insulin secretion during hyperglycaemia, suppresses glucagon secretion, stimulates (pro)insulin biosynthesis and decelerates gastric emptying and acid secretion. On intracerebroventricular injection, GLP-1 reduces food intake in rodents. A GLP-1 receptor antagonist or GLP-1 antisera have been shown to reduce meal-stimulated insulin secretion in animals, suggesting that GLP-1 has a physiological "incretin" function (augmentation of postprandial insulin secretion due to intestinal hormones) for GLP-1. In healthy human subjects, exogenous GLP-1 slows gastric emptying. Consequently, postprandial insulin secretion is reduced, not augmented. Thus, a participation of this peptide in the incretin effect of non-diabetic humans has not been definitely proven. Nevertheless, it has potent insulinotropic activity, especially during hyperglycaemia. This suggests new therapeutic options for patients with Type II (non-insulin-dependent) diabetes mellitus. On the other hand, most L cells are located in the lower small intestine. Potent inhibitory actions of GLP-1 on upper gastrointestinal motor and digestive functions (e.g. gastric emptying and acid secretion) in response to nutrients placed into the ileal lumen, argue for a role of this peptide as an "ileal brake". Malassimilation and diarrhea leading to the erroneous presence of nutrients in the lower gut may, via GLP-1, delay gastric emptying and reduce upper gut motility and thereby prevent further caloric losses. [Diabetologia (1999) 42: 373–379]

Keywords Glucagon-like peptide 1, incretin hormones, ileal brake, insulin, glucagon, motility, gastric emptying

Discovery of GLP-1. Glucagon-like peptide 1 (GLP-1) was predicted after its nucleotide sequence was noticed during sequence analysis of the preproglucagon gene [1]. This precursor protein contains the sequence of pancreatic glucagon and has two additional nucleotide stretches. If translated into the amino acid sequence, these are similar to glucagon (approximately 50% homology) and therefore named GLP-1 and GLP-2. Speculations about physiological functions were mainly based on sequence homology to other members of the glucagon-secretin family of gastrointestinal peptide hormones. Therefore, GLP-1 and GLP-2 were first tested for insulinotropic activity [2]. But additional effects of GLP-1 have been discovered and it is not decided what the physiological function of GLP-1 in healthy animals and humans could be.

Incretin hormones. The definition of the incretin effect and incretin hormones by Creutzfeldt [3] has been widely accepted and used: the incretin effect describes the phenomenon of oral glucose eliciting a

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Abbreviations: GLP-1, Glugagon-like peptide 1; GIP, glucose-dependent insulin-releasing peptide

greater insulin response than intravenous glucose infusions, no matter whether the same amount of glucose is infused [4] or an equivalent rise in glycaemia is caused by the parenteral route [5]. These experiments showed that up to 60 % of the insulin secretory response after an oral glucose load are not caused by a direct interaction of glucose with beta cells in the islets of Langerhans, but by the secretion and insulinotropic action of gut peptides [5]. Incretin hormones are gut factors released by oral nutrients, which stimulate insulin secretion at the typical postprandial concentrations reached in the presence of hyperglycaemia [3]. As an intravenous infusion of glucose-dependent insulin-releasing peptide (GIP) and glucose, which leads to similar concentrations of glucose and GIP as an oral glucose load, augments insulin secretion to the same extent [6–8], GIP was identified as the first incretin candidate [3, 9]. Based on the insulinotropic activity of intestinal mucosal extracts which had been depleted of GIP [10], and on a continuing incretin effect when circulating GIP was inactivated by anti-GIP antibodies [11], additional incretin hormones were, however, postulated. Then GLP-1 was discovered. This peptide was found to be insulinotropic, i.e. to stimulate insulin secretion, especially at raised glucose concentrations [2]. It had been predicted [2] and later shown that this ability was much more pronounced in the case of "truncated" GLP-1 (GLP-1 [7–36 amide]) [12, 13]. Therefore, it was suggested that GLP-1 is an incretin hormone [7, 8] contributing to meal-stimulated insulin secretory responses.

Synthesis, processing and secretion of GLP-1, receptor and signal transduction. For basic information on the biology of GLP-1, readers are referred to several excellent reviews [14–16]. The proglucagon gene is expressed in alpha cells of the islets of Langerhans and in L cells of the gut. These are endocrine cells present in large numbers in the ileum and colon and in much smaller numbers in the duodenum and jejunum [17]. Whereas the main product of post-translational processing of proglucagon in the endocrine pancreas is glucagon, in L cells glicentin ("enteroglucagon"), GLP-1 and GLP-2 are the main final products. Differential processing is thought to be due to different prohormone convertases. The final form of GLP-1 that is produced in L cells is "truncated" GLP-1 [12]. It occurs mainly in the C-terminally amidated form (GLP-1 [7–36 amide]). A minor product is the glycine-extended (i.e. non-amidated) GLP-1 [7–37] [18]. The term "truncation" refers to the originally proposed sequences GLP-1 [1–36 amide] (or [1–37]), which does not occur as such in larger quantities [14].

Glucagon-like peptide-1 is secreted from isolated perfused ileum preparations [19, 20] when glucose or fat are infused through the gut lumen. Nutrients infused directly into the ileal lumen release GLP-1 [21], indicating that direct stimulation of L-cell secretion is possible in humans. Oral glucose [7, 8, 22–24], sucrose [25], triglycerides [22] and mixed meals also lead to an increment in plasma GLP-1 [14–16]. These nutrient-related GLP-1 responses start early (i.e. within 5 min) after ingestion [8], and last for approximately an hour [8, 22, 26]. It is doubtful, that nutrients have reached portions of the gut with high L-cell densities by that time. Especially oral glucose is completely absorbed from the duodenum and upper jejunum [27]. Therefore, indirect signalling pathways may exist that stimulate L-cell secretion if glucose is present in the duodenum.

Glucose-dependent insulin-releasing peptide is, however, released from the duodenum and upper jejunum, where K cells are abundant [6]. First GIP increments are seen within 15 min after nutrient ingestion and can last for several hours [28]. Therefore, GIP may qualify for an incretin role especially regarding the later postprandial insulin secretory response.

Glucose-dependent insulin-releasing peptide appears to be an "upper gut signal" for the release of GLP-1 in rodents [29], but not in humans [26].

Lower gut resections (removing the most abundant stores of GLP-1) do not alter GLP-1 responses after oral glucose [23]. Quantitative considerations allow the conclusion that the amount of GLP-1 present in the upper jejunum is still several fold higher than the amount released in response to a single nutrient stimulus [23].

Glucagon-like peptide-1 has a short plasma half-life and is inactivated by dipeptidyl peptidase IV present in blood plasma [30, 31]. After intravenous infusions with GLP-1, more than 70 % of GLP-1-like material measured with non-specific assays was N-terminally degraded [31].

Binding sites for GLP-1 are present on insulinoma cells [32] and a receptor has been cloned [33, 34]. It belongs to the 7 trans-membrane-domain family of receptors and is expressed in islets of Langerhans (beta cells, delta cells, and possibly alpha cells) [35]. The major second messenger is cAMP [36]. In addition, the activation of other signal transduction pathways leading to increased intracellular Ca^{++} concentrations have also been described [37].

Effects of GLP-1 in normal animals and humans. Insulinotropic effects of GLP-1 have already been mentioned, but this is not the only biological action of GLP-1.

(1) GLP-1 stimulates insulin secretion in isolated islets of Langerhans [2], in the perfused pancreas [12, 13], and in whole organisms, both in animals and humans [7, 8, 38]. Its effects are glucose-dependent, with greater effects occurring at higher glucose con-

centrations [7, 8, 39]. At normal fasting glucose concentrations only small effects on insulin secretion can be achieved which are not strong enough to cause clinically manifest hypoglycaemia [39].
(2) GLP-1 is able to suppress glucagon secretion in islets [40], the perfused pancreas [41], and in whole organisms [7]. Recent studies indicate that even basal GLP-1 levels exert a tonic inhibitory effect on glucagon secretion [42].
(3) In insulinoma cell lines, GLP-1 is able to promote (pro)insulin biosynthesis [43], which could be important for maintaining insulin stores when secretion tends to deplete them.
(4) GLP-1 decelerates gastric emptying in normal subjects [44, 45] as well as in Type II diabetic patients [46]. Effects are found at physiological doses (plasma concentrations ~ 25 pmol/l) [45]. GLP-1 has been shown to reduce pancreatic enzyme output (exocrine secretion), probably due to retarded gastric emptying, [44]. It may also change the small intestinal motility pattern.
(5) Gastric acid secretion is reduced by 30–50 % in healthy human volunteers receiving intravenous infusions of GLP-1 [47]. Since vagotomy abolishes this effect [48], it is probably mediated by vagal fibres.
(6) GLP-1 in microgram amounts injected into the cerebrospinal fluid of rodents reduces food intake [49]. A specific antagonist at the GLP-1 receptor, exendin [9–39], enhances food intake in mice [49]. Since GLP-1 [7–36 amide] is synthesised in certain brain nuclei, a physiological, inhibitory effect on food intake involving cerebral GLP-1 receptors in the hypothalamus has been suggested. In healthy volunteers receiving an intravenous infusion of GLP-1, satiety was rated higher than with placebo and caloric intake during a second meal was considerably reduced [50]. These results point to a function for GLP-1 in the regulation of food intake.
(7) Minor effects of GLP-1 on insulin sensitivity have been described [51, 52], but questioned. Recent data indicate that metabolic actions of GLP-1 can only be expected under circumstances that allow changes in glucoregulatory hormones (insulin and glucagon). The quantitative importance of so-called "extrapancreatic or peripheral effects" is negligible [53, 54].

Physiological roles of GLP-1

Animal studies. The GLP-1 receptor antagonist exendin [9–39] [34, 55] has been used to study the importance of endogenous GLP-1 release for postprandial insulin secretion, i.e. an incretin role for GLP-1. Exendin [9–39] specifically inhibits GLP-1-induced insulin secretion but leaves the effect of other insulin secretagogues unaffected [56]. In rats, exendin [9–39] reduces insulin secretory responses to intraduodenal glucose [38] and to the oral intake of nutrients [56]. This is of interest because in the first case potential effects on gastric emptying should not be of any importance, whereas in the second, deceleration of gastric emptying due to GLP-1 might occur. An explicit measurement of gastric emptying, however, has not been taken under these study conditions.

In mice lacking a functional GLP-1 receptor (homozygous GLP-1 receptor "knockout"), a considerably reduced insulin response after oral glucose and oral as well as (less pronounced) intraperitoneal glucose intolerance has been described [57]. Fasting hyperglycaemia was only seen in male animals. Body weight was normal. Short-term responses to intracerebroventricular GLP-1 were, however, predictably missing in receptor "knock-out" mice, but could be shown in control animals.

In baboons, treatment with exendin [9–39] or specific anti-GLP-1 antibodies delayed initial insulin responses after the oral ingestion of glucose. Later, glucose increased to higher concentrations [58]. D-xylose absorption kinetics were similar with and without GLP-1 receptor antagonist/antibody treatment. Therefore, a major (confounding) effect on gastric emptying appears improbable. As far as can be ascertained from these experiments, GLP-1 is a weak physiological incretin hormone also in baboons, with most of its effect occurring in the initial postprandial phase.

Studies in non-diabetic humans. In healthy human subjects, an incretin activity of GLP-1 has been concluded from its influence on insulin secretory responses during combined treatment with glucose and GLP-1 [7, 8]. In such experiments, plasma GLP-1 concentrations after oral glucose have to be closely matched by intravenous infusions. It has been concluded from experiments using slightly supraphysiological GLP-1 concentrations, that GLP-1 is a physiological incretin in man [7]. Our studies, using a strictly physiological glucose increment (matched to the rise in glycaemia after oral glucose) confirmed the augmentation of insulin secretion by GLP-1. The estimated contribution to the overall incretin effect, however, was small (approximately 25 %) [8]. These experimental approaches did not take into account gastric motility which indirectly influences meal-induced insulin secretory responses [45].

Exogenous treatment with physiological and pharmacological doses of GLP-1 together with an intragastric liquid meal resulted in a dose-dependent slowing of gastric emptying [45]. While there was a dose-dependent increment in fasting insulin (GLP-1 was started 30 min prior to the meal), insulin secretion after nutrient ingestion was either not changed (low dose of GLP-1) or even depressed (higher doses of GLP-1; Fig. 1, left panels). Inhibitory effects on gastric emptying and the subsequent reduction in sub-

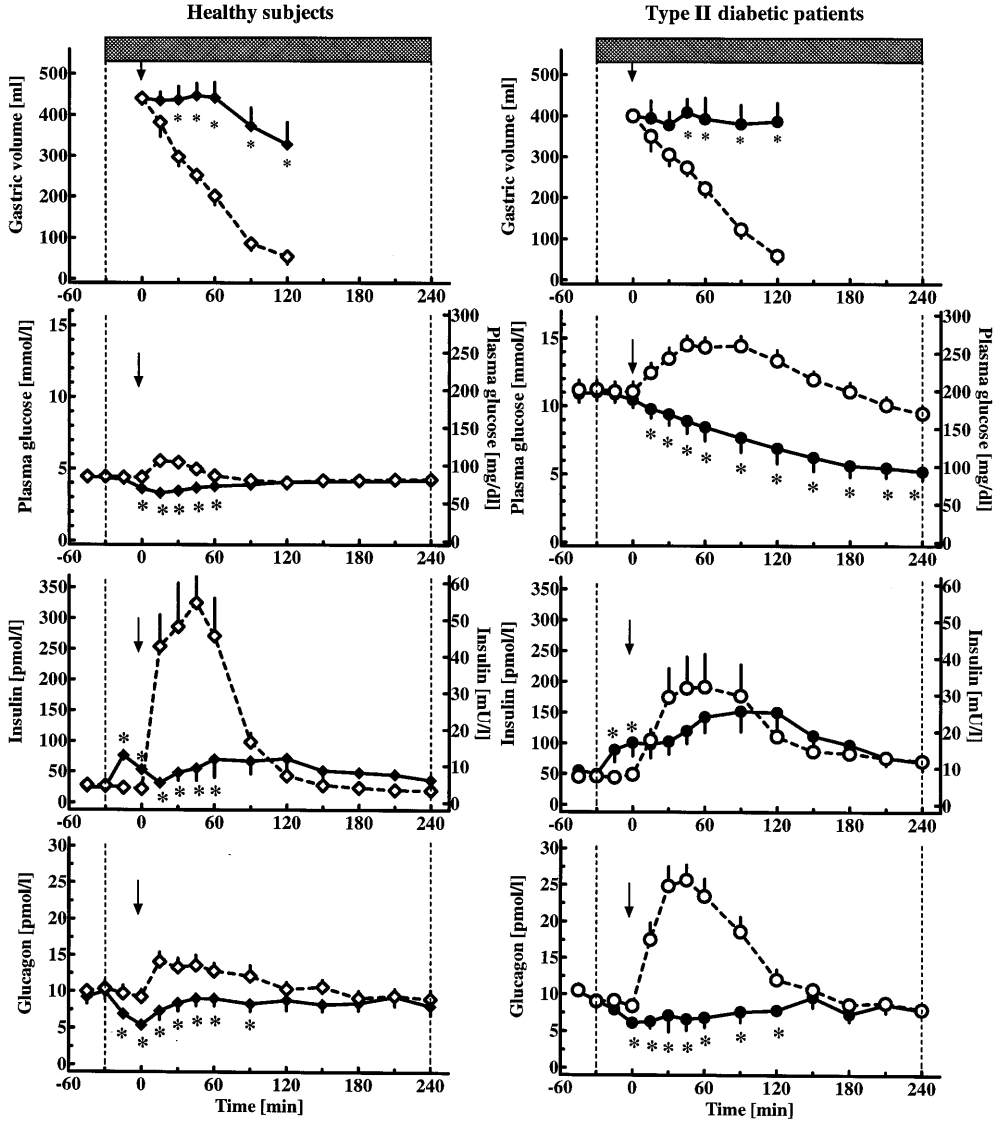

Fig. 1. Gastric volume (upper panels), plasma glucose concentrations (second row of panels), plasma insulin responses (third row of panels), and glucagon concentrations (lower panels) in response to the intravenous infusion of GLP-1 (1.2 pmol · kg^{-1} · min^{-1}) or placebo (duration indicated by the bars) starting 30 min before a liquid meal was transported intragastrically into healthy volunteers (left panels) or Type II diabetic patients (right panels). Open symbols: placebo; closed symbols: GLP-1. Mean ± SEM. Repeated-measures analysis of variance indicated p-values < 0.01 for the interaction of experiment (GLP-1 vs placebo) and time for all comparisons made. Asterisks indicate significant differences at individual time points. Redrawn with modifications from Nauck et al. [45] and Willms et al. [46]

strate-stimulated insulin secretion, therefore, outweighed the small direct (stimulatory) effects on beta cells. Insulinotropic effects of GLP-1 are probably limited by the lack of appropriate hyperglycaemia under these conditions [39]. These findings question a physiological incretin role for GLP-1 in healthy (non-diabetic) human subjects. Additional information is expected from the use of exendin [9–39], which has been tested as a GLP-1 receptor antagonist also in humans [42, 67].

Possible differences in the relative importance of incretin hormones between animals and humans. The contribution of incretin hormones to postprandial insulin secretion appears to be similar in rats [38] and healthy human subjects [5]: more than 50 % are contributed by insulinotropic gut hormones. Peptide antagonists of GLP-1 (exendin [9–39]) [38] and of GIP [59] considerably reduce postprandial insulin responses after oral, intragastric or intraduodenal glucose loads. Since GIP releases GLP-1 in rats (and other rodents) [20, 29], antagonising GIP actions should also partly take away the GLP-1 response. Based on a similar glucose-concentration dependence of their insulinotropic activities, but higher plasma concentrations of GIP both in the basal and postprandial state, it has been concluded that GIP is probably the quantitatively more important incretin

hormone in rodents [60]. In human subjects, GIP does not change GLP-1 secretion even at pharmacological levels [26].

Insulinotropic actions of GLP-1 in Type II diabetic patients. In contrast to GIP [26, 61], GLP-1 has a well preserved insulinotropic [26] and glucagonostatic [26, 62] activity in Type II diabetic patients. Furthermore, deceleration of gastric emptying is observed in Type II diabetic patients and in healthy subjects (Fig. 1; [46]).

Since the insulinotropic actions of GLP-1 depend on increased glucose concentrations [39], the fasting hyperglycaemia of Type II diabetic patients permits augmentation of postprandial insulin responses despite retardation of gastric emptying and delayed nutrient absorption (Fig. 1, right panels [46]). The result is a reduction in glucose concentrations even with nutrients present in the stomach. This is based on (a) a reduced nutrient inflow and (b) a rise in insulin concentrations. The increment in insulinaemia is similar to placebo conditions, when gastric emptying proceeds at its normal rate and insulinotropic substrates like glucose are absorbed. Even in the absence of nutrient stimulation, insulin secretion is augmented to a similar degree by the combined action of hyperglycaemia and GLP-1. This is in contrast to healthy subjects (Fig. 1, left panels [45]), in whom only minor effects of exogenous GLP-1 on postprandial glycaemic excursions were seen, probably because slowed gastric emptying leads to reduced substrate-stimulated insulin secretion. A lack of hyperglycaemia precludes prominent insulinotropic effects of GLP-1. The result is a net inhibition of insulin secretory responses by GLP-1 except for a short initial insulin response after starting GLP-1 infusions at euglycaemia (Fig. 1).

Glucagon-like peptide-1 as a pharmacological agent appears to have a definite therapeutic potential in Type II diabetic patients [51, 62, 63]. The responsible mechanisms need not necessarily be a copy of its physiological functions. The glucose-lowering activity of GLP-1 in Type II diabetic patients appears to be the consequence of insulinotropic actions during hyperglycaemia [26, 62], a suppression of glucagon secretion [26, 62], and decelerated gastric emptying [46, 51] (e. g. Fig. 1, right panels).

Pathophysiology of abnormal GLP-1 secretion. Intestinal resections at the level of the jejunum, ileum or colon do not reduce the GLP-1 secretory response after oral glucose [23]. Nutrient-induced GLP-1 secretion can be augmented by α-glucosidase inhibition [25, 64, 65]. Acarbose or voglibose, under these conditions, induce maldigestion of disaccharides, and move intestinal contents downward. Delayed absorption takes place in GLP-1-rich intestinal segments (e. g. the ileum). Nutrients infused directly into the ileum also release GLP-1 [21].

Malassimilation (diarrhea) due to other causes has been shown to augment the secretion of enteroglucagon [66]. Since GLP-1 and enteroglucagon (glicentin) are co-secreted, GLP-1 responses can be predicted to be more prominent under conditions of incomplete absorption of nutrients, for instance in the case of rapid small intestinal transit.

GLP-1 participation in "ileal brake" mechanisms. Under such abnormal circumstances, a signal from the lower gut (e. g. GLP-1) that (a) stops or retards gastric emptying and (b) slows digestive functions (gastric acid and pancreatic juice secretion) would limit nutritional losses. The secretion of GLP-1 in response to nutrients transported into the ileum is accompanied by inhibitory actions on the upper digestive tract [21]. Participation in such "ileal brake" mechanisms are probably a predominant function of GLP-1. In this context, the location of L cells in the lower gastrointestinal tract is much more plausible than in connection with a potential incretin role.

Conclusion. Glucagon-like peptide-1 is a multifunctional peptide hormone from the lower gut. Among the many possible functions reported, a physiological incretin role in healthy human subjects is unproven and is possibly of minor physiological importance. This peptide may function as a safeguard against intestinal nutrient overload in case of carbohydrate or fat malassimilation, i. e. as a mediator of "ileal brake" mechanisms. Only in the presence of hyperglycaemia, such as in Type II diabetes, are insulinotropic actions of GLP-1 prominent enough to provide a rationale for new therapeutic strategies.

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Note added in proof: The physiological role of GLP-1 after an oral glucose load has recently been examined using exendin [9-39] *in vivo* in human volunteers [67]. The insulinotropic effect of exogenous GLP-1 was totally blunted by the GLP-1 antagonist, and plasma and insulin increments during the first 90 min after oral glucose were enhanced by 35 % ($p < 0.05$) and 24 % (not significant), respectively. This suggests a main action of GLP-1 on gastric emptying (which appears to be accelerated in the presence of exendin [9-39]) and does not easily support an incretin role for GLP-1. The latter would require a reduction in insulin responses in the presence of the GLP-1 antagonist.