GIP and GLP-1: Stepsiblings Rather Than Monozygotic Twins Within the Incretin Family

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The importance of the incretin effect for the postprandial augmentation of insulin released has long been recognized (1). However, there has been a long-standing controversy as to the relative importance of the various gastrointestinal hormones in mediating this effect. While earlier studies suggested a contribution of gastrin, secretin, and cholecystokinin (2), it later became obvious that in humans, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are the predominant incretin hormones (1). Which of the two incretins is the most relevant one is still a matter of debate.

Gasbjerg et al. (3) performed studies in healthy human subjects receiving oral glucose loads of 75 g in the fasting state on four different days. The known incretin hormones, GIP and GLP-1, which are secreted in response to glucose administration/absorption, were antagonized with the established peptide receptor antagonist exendin(9-39), blocking the stimulation of GLP-1 receptors, or with the novel GIP receptor antagonist, GIP(3-30)amide, a naturally occurring fragment of intact GIP (full sequence 1–42), which has recently been characterized as a specific GIP receptor antagonist for use in human studies (4). A similar GIP receptor antagonist, GIP(7-30)amide, had previously been used in animal studies but had not been validated for human experiments (5). These incretin receptor antagonists were compared with placebo and used alone and in combination. The result was a slight rise in postload glucose concentrations and a minor reduction in insulin secretory responses, when the GLP-1 receptor was blocked, and a substantial rise in glycemic excursions after the glucose load and a more pronounced reduction in insulin secretory responses, when the recently validated GIP antagonist GIP(3-30)amide was administered at an approximately 1,000-fold excess (~60 nmol/L) over endogenous peak GIP concentrations (~60 pmol/L). The combination of exendin(9-39) and GIP(3-30)amide further raised plasma glucose and reduced insulin secretory responses over and above the degree observed with single receptor blockers. The difference between experiments with exendin(9-39) and GIP(3-30)amide used as single receptor blockers was significant with respect to plasma glucose rises, insulin and C-peptide responses, insulin secretion rates calculated by deconvolution, and various measures of in vivo β-cell function (3). Therefore, the main conclusion from this important study is that blocking GIP receptors has more impact on postglucose insulin secretory responses and on oral glucose tolerance than interfering with GLP-1 action. GIP, thus, is the more effective and more important incretin hormone in healthy subjects receiving an oral glucose challenge of this (75 g) size, which is a standardized challenge used in diagnosing disturbances of glucose tolerance. These findings revise the commonly expressed view that GLP-1 is the most important incretin hormone, a misconception that was mainly based on its therapeutic effectiveness in patients with type 2 diabetes (6).

In previous experiments, when GIP and GLP-1(7-36)amide were administered by intravenous infusion with the aim to achieve physiological plasma concentrations, together with ascending rates of glucose infusion, their insulinotropic effects in healthy subjects were very much comparable (7). This led to the conclusion that GIP and GLP-1 contribute equally to the physiological incretin stimulation of insulin secretion. However, the concentrations of both GIP and GLP-1 reached considerably higher peaks during intravenous administration than after a mixed meal. In addition, due to this experimental design, any potential effects of GLP-1 on gastric emptying (8) were ineffective in affecting plasma glucose concentrations, as no nutrients were ingested by the volunteers. Therefore, the design was biased in favor of more prominent GLP-1 effects (7).

When exogenous GIP and GLP-1(7-36)amide were exogenously administered to achieve close to physiological concentration profiles under "isoglycemic" conditions, where plasma glucose levels were identical to those after oral glucose administration, GIP in addition to intravenous

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glucose stimulated insulin secretion to a similar extent as oral glucose (9). This provided a hint that GIP alone could explain much of the incretin effect. A caveat of all studies employing exogenous infusions of GIP and GLP-1 is that systemic infusions of incretin hormones may not sufficiently mimic their physiological secretion into the mesenteric and portal vein, leaving some uncertainty regarding their relative importance in normal physiology. The receptor antagonist approach used by Gasbjerg et al. (3) reduces such potential bias considerably.

Another challenge in estimating the relative importance of GIP and GLP-1 in stimulating postprandial insulin secretion is the strong deceleration of gastric emptying by GLP-1 (8), but not by GIP (10). Because of this, exogenous GLP-1 administration even leads to reduced rather than enhanced postprandial insulin responses, which has led to a controversy regarding its role as an incretin hormone (11).

Gasbjerg et al. (3) argue that the role of GLP-1 in stimulating insulin secretion after oral glucose might have been underestimated by the present experimental setup, since there are (in some animals [12]) or may be (in human subjects) neural circuits mediating part of the stimulated insulin secretory response after nutrient intake. It is not certain that the novel GIP receptor antagonist can access these GIP receptors, either on afferent autonomic nerve branches (probably vagal, parasympathetic) or in the central nervous system. However, there are also reasons to discuss whether the role of GLP-1 may have been overestimated by the present methodology. First, the concentrations reached of GIP(3-30)amide have previously been shown to block ~80% of the insulinotropic action of exogenous GIP (4), whereas this percentage has been higher in the case of GLP-1–induced insulin secretion blocked with exendin(9-39) (13), studied at similar exposure as achieved by Gasbjerg et al. (3). Moreover, the differences induced by exendin(9-39) regarding glycemic excursions and parameters measuring insulin secretion or β-cell function were small, sometimes even pointing into the "wrong" direction, and usually they were not significant. This was the same when using exendin(9-39) alone or on a background of GIP(3-30)amide. The notable exception was concerning glycemic excursions following oral glucose. This, however, may be related to the prominent changes in gastric emptying (acceleration) and glucagon secretion (less suppression) induced by exendin(9-39) (3,14), which presumably raised plasma glucose by enhancing hepatic glucose output. In summary, the role of GLP-1 as a physiological insulinotropic agent may be viewed as even less prominent than it appears at first sight. It will require larger studies to decide about the exact quantitative role of GLP-1.

A challenge in the interpretation of the data provided by Gasbjerg et al. (3) is in the fact that interference by incretin receptor antagonists leads to changes in both glycemic excursions (substantial rises) and in insulin secretory responses (moderate reductions), even when expressed relative to rises in plasma glucose concentrations (insulin secretion rates divided by glucose increments) induced by oral glucose. Assuming a linear relationship between plasma glucose rises and insulin secretory responses, this term can be further "normalized" to comply with glycemic excursions as they occurred after oral glucose. Thus, results are transformed mathematically to insulin secretory responses as they should look under conditions of "isoglycemia." If expressed this way, any reduction due to interference with incretin hormone action should then indicate how much the incretin effect depends on this particular hormone. Figure 1*A* shows the effects of using exendin(9-39) and/or GIP(3-30)amide on integrated incremental plasma glucose (left) and the areas under the curve for insulin secretion (middle). By correcting insulin secretion relative to glycemic excursions for the relative rise in glucose (placebo conditions = 1), the contribution of GIP and GLP-1 can be estimated. The result is shown in Fig. 1*A* (right): results with placebo are presented as 100%. Blocking incretins altogether, using exendin(9-39) and GIP(3-30)amide in combination, results in a reduction to ~33%, which is very well compatible with an incretin effect of ~67% determined for a glucose load of 75 g (1,15). It also shows that a substantial part of the incretin effect should be due to GIP, and a minor proportion can be ascribed to GLP-1. A caveat is that this calculation ascribes all changes in plasma glucose profiles to differences in insulin secretion, which may not fully apply to GLP-1 due to additional actions on gastric emptying (8) and glucagon secretion (1,6). The entero-insular axis with some quantitative estimates derived from these considerations is shown in Fig. 1*B*. The results of these studies also suggest that the contribution of autonomic nerves to the augmentation of insulin secretion after oral glucose in humans is negligible (Fig. 1*B*). One should, however, be aware that a rise in glycemia alone can elicit an insulin secretory response, while GIP and GLP-1 always depend on a permissive rise in glycemia in order to be insulinotropic (2,6). Therefore, it may be misleading to ascribe any insulin secretory response to either GIP or GLP-1 or their combination alone. Rather, their important interaction with hyperglycemia always needs to be acknowledged. In addition, these quantitative estimates of the contributions of GIP and GLP-1 signaling to overall insulin secretion and glucose tolerance after oral glucose administration are most likely also determined by receptor affinities, residence times, and pharmacokinetic properties of GIP(3-30)amide and exendin(9-39) under the conditions of the present studies.

Overall, the elegant studies by Gasberg and colleagues (3,4) have demonstrated that the incretin hormones GIP and GLP-1 are rather unequal with respect to their physiological contribution to the incretin effect, thus behaving more like stepchildren than monozygotic twins within the incretin family.

The novel GIP receptor antagonist, which has been used successfully in the present set of experiments, may also

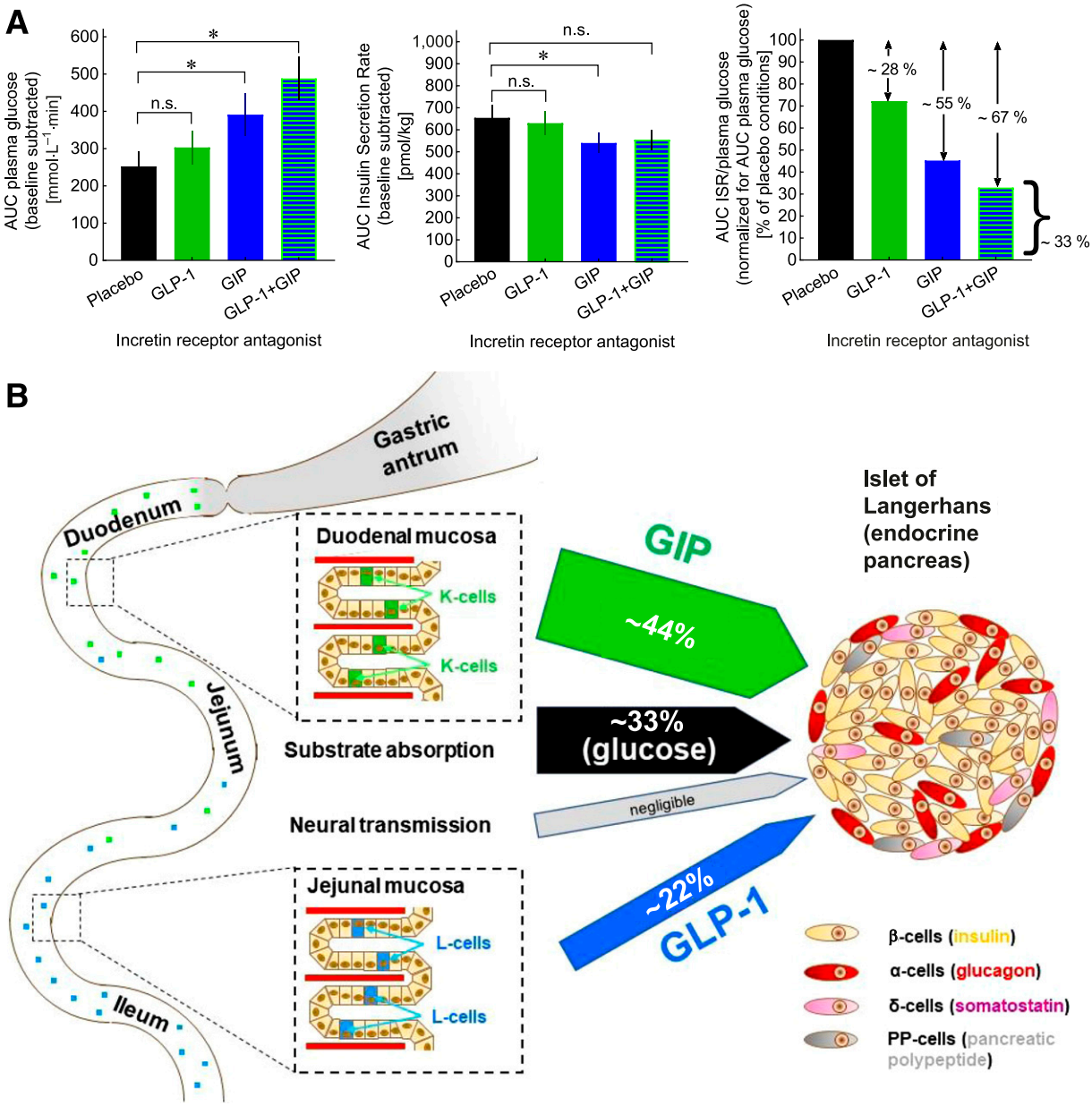

Figure 1—*A*: Role of GLP-1 and GIP (as assessed by employing specific receptor antagonists) on glycemic excursions (left), insulin secretion rates (calculated by deconvolution of C-peptide concentrations) (middle), and increments in insulin secretion rates (ISR) divided by rises in plasma glucose concentrations normalized for a glycemic rise as observed with oral glucose (in the absence of incretin receptor antagonists) (right). The difference from placebo conditions should be an estimate of the contribution to the incretin effect (overall, ~2/3, the major proportion of which is due to GIP). AUC, area under the curve; n.s., not significant. *B*: Contributions of different gut-derived factors to the augmentation of insulin release after nutrient ingestion in humans. The contribution of direct substrate stimulation (by the absorbed glucose), the incretin hormones GIP and GLP-1, and afferent neural signals has been estimated based on the results of Gasbjerg et al. (3). See *A* for how these estimates were derived from the results presented. Neural transmission is judged to have a negligible influence based on results from pancreas-transplanted subjects (20), who have a normal incretin effect. The general design of this figure is a modification of the entero-insular axis depicted by Creutzfeldt (2).

help to clarify other questions. What is the contribution of incretin hormones to insulin secretion after mixed meals (considering the contribution of other substrates, such as amino acids [16], free fatty acids [17], etc.)? Does endogenous GIP play a role for hypoglycemia counterregulation (18)? What is the relative importance of GIP receptor stimulation for the impressive clinical effects of dual (GLP-1 and GIP receptor) agonists (19), also called "twincretins"? The prominent role of GIP in the physiology of the entero-insular axis confirmed by Gasbjerg et al. (3) helps explain the severe metabolic consequences of a major loss in GIP receptor signaling in subjects with type 2 diabetes. Details will have to be explored in future studies. Gasbjerg and colleagues (3,4) are to be congratulated to

have introduced highly promising tools for the study of incretin physiology and pharmacology.

Duality of Interest. M.A.N. has been member on advisory boards or has consulted with AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Fractyl, GlaxoSmithKline, Menarini/Berlin-Chemie, Merck Sharp & Dohme, Novo Nordisk, and Intarcia/Servier. He has received grant support from Eli Lilly & Co., Menarini/Berlin-Chemie, Merck Sharp & Dohme, and Novartis Pharma. He has also served on the speakers' bureau of AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Menarini/Berlin-Chemie, Merck Sharp & Dohme, Novo Nordisk, and Sun Pharma. J.J.M. has received consulting and speaker honoraria from AstraZeneca, Eli Lilly & Co., Merck Sharp & Dohme, Novo Nordisk, and Sanofi. He has received research support from Eli Lilly & Co., Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk, Novartis, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

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