In my lecture given on the occasion of the 2021 Banting Medal for Scientific Achievement, I briefly described the history of the incretin effect and summarized some of the developments leading to current therapies of obesity and diabetes based on the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). In the text below, I discuss in further detail the role of these two hormones for postprandial insulin secretion in humans on the basis of recent studies with antagonists. Their direct and indirect actions on the β-cells are discussed next as well as their contrasting actions on glucagon secretion. After a brief discussion of their effect on insulin sensitivity, I describe their immediate actions in patients with type 2 diabetes and emphasize the actions of GLP-1 on β-cell glucose sensitivity, followed by a discussion of their extrapancreatic actions, including effects on appetite and food intake in humans. Finally, possible mechanisms of action of GIP–GLP-1 coagonists are discussed, and it is concluded that therapies based on incretin actions are likely to change the current hesitant therapy of both obesity and diabetes.

The incretin effect, i.e., the amplification of insulin secretion observed when glucose is administered orally as opposed to intravenously, but reaching similar glucose excursions, has been predicted since 1930 and was substantiated when it became possible to measure insulin concentrations in plasma in the 1960s. However, it remained a curiosity in spite of accumulating evidence that the effect is essential for normal glucose tolerance and is severely compromised in patients with type 2 diabetes. Recent research has documented that new pharmaceutical agents, based on the actions of the two incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), represent the most effective therapy of the two major metabolic diseases, obesity and type 2 diabetes, improving not only metabolic parameters but also the risks of complications and mortality. Nevertheless, the uptake of these newer therapies is far less than their beneficial actions would seem to justify (according to the CAPTURE Trial [1]). It may, therefore, be timely to review critically some of the most important characteristics of the incretin actions of the two hormones in humans, with a view to explore differences and similarities in order to better understand the actions of these new therapeutics in obesity and type 2 diabetes.

Analysis of the Incretin Effect Using Receptor Antagonists

The incretin effect, defined above, is quantified by comparing the insulin responses to oral administration of glucose compared with those measured after intravenous glucose infused in amounts that give rise to the same glucose responses (isoglycemia). We know today that the effect, which is responsible for keeping up to 80% of ingested glucose away from the circulation (2), is essential for normal glucose tolerance. Several compounds are able to influence glucose-stimulated insulin secretion, including several peptides that can be extracted from the intestinal mucosa, but it is generally accepted that the peptides GIP and GLP-1 are the most important responsible factors. This was recently probed...
in human experiments involving antagonists of the receptors for these hormones, the GLP-1 and GIP receptors. Both are G-protein-coupled receptors of the B1 family expressed on the β-cells in the pancreas. The GLP-1 receptor antagonist (GLP-1RA) used for this was exendin 9-39 (Ex-9), a fragment of the GLP-RA, exendin-4 (a synthetic form of which is exenatide). Ex-9 was identified as an antagonist of exendin-4 actions already in 1991 by Raufman et al. (3). Exendin-4 was later found to interact with the mammalian (and human) GLP-1 receptor, and Ex-9 also antagonized this interaction (4). Ex-9 has been given to humans in numerous experiments since 1998, and its use has been carefully validated in terms of dosing and degree of antagonism (5). During the last few years it also has been possible to antagonize the GIP receptor in humans. Based on extensive searches of truncated forms of the 42-amino-acid peptide GIP and of GIP(1-30)NH2, a truncated form of GIP(1-30)NH2, namely, GIP(3-30)NH2, was finally demonstrated to be a specific and potent competitive antagonist of the human GIP receptor with no agonist properties (6). Its originator, GIP(1-30)-amide, is itself an amidated fragment of GIP. This fragment is circulating in very low concentrations in humans (7), but since it shares the N terminus with GIP, a truncated form, (3-30)NH2, formed by the actions of the dipeptidyl peptidase 4 (DPP-4) enzyme, is also likely to circulate (although probably in concentrations too low to quantitate reliably). With those two antagonists, it was now possible to evaluate the incretin system and its effects in humans. It should be noted that while the GLP-1 system is highly conserved among mammals, the GIP system exhibits considerable differences; GIP-RAs, therefore, cannot be used interchangeably (8). In experiments with healthy individuals given oral glucose, it was shown that both antagonists impaired glucose tolerance, and when given simultaneously, they cause glucose intolerance, directly demonstrating the importance of the incretin system for glucose tolerance in humans (9). Analyzing insulin secretion on the basis of C-peptide secretion normalized for glucose, the contribution of the individual components of the stimulus could also be quantitated: glucose alone accounted for 25%, GLP-1 for 27%, and GIP for 48% of the insulin response (10). This suggests that GIP is the primary incretin hormone, consistent with the idea that GLP-1 is physiologically more responsible for the ileal brake mechanism, i.e., the endocrine inhibition of upper gastrointestinal secretion and motility as well as appetite and food intake, elicited by the presence of nutrients in the distal small intestine (11). Evidently, the validity of these estimates rests on the extent to which the effect of the individual hormone on oral glucose tolerance test-induced insulin secretion is blocked by the corresponding antagonist. For GIP, the doses of the antagonist employed have been demonstrated to block 80% of exogenous GIP when the latter was given in doses resulting in physiological elevations of GIP concentrations in plasma. A subsequent dose-response investigation gave similar results (12). Regarding GLP-1, the use of an antagonist as a tool for analyzing its actions is much more complicated. First of all, part of the action of endogenous GLP-1 on the endocrine pancreas and glucose metabolism is likely to be exerted via activation of sensory-afferent neurons of the vagus, and it is not known to what extent Ex-9 is able to interfere with this mechanism. The enteric neurons are enveloped in enteric glial cells, which may outnumber the neurons by a factor of up to 10. They are astrocyte-like cells that may provide the enteric nervous system a protective barrier (13). The accessibility issue may be more pronounced for the larger conjugated GLP-1 receptor agonists. Second, effects of activation of GLP-1 receptors in the islets may be more complex than generally believed. The most conspicuous effect of infusion of Ex-9 in humans is an invariable increase in plasma glucose and glucagon concentrations (14), whereas insulin responses are much more variable. Indeed, in several experiments, administration of Ex-9 has resulted in increasing rather than decreasing insulin concentrations. Although unproven, the most likely explanation for the hyperglycemia is the increase in peripheral glucagon concentrations. Consider that increases in the periphery are reflections of much higher increases in portal vein concentrations (because of the dilution of the splanchnic blood flow when it combines with the systemic circuitry). The increase in glucose, in turn, may explain part of the aberrant insulin response. But what is the explanation for the increase in glucagon concentrations? This immediately raises the question of the expression of GLP-1 receptors in the α-cells, but the consensus today is that the expression levels are low and probably of limited significance (15). The somatostatin-producing delta cells, however, robustly express the GLP-1 receptor, and numerous experiments have supported that the inhibitory effects of GLP-1 on the α-cell is transmitted via the somatostatin secretion of the delta cell (16). It has also been demonstrated repeatedly that the delta cells tonically inhibit glucagon secretion (17). Therefore, the stimulatory effect of circulating GLP-1 on paracrine somatostatin secretion would be expected to be blocked by Ex-9, which would result in increased glucagon secretion. However, even in the absence of circulating GLP-1, Ex-9 might still lower delta-cell somatostatin secretion, because it may act as an inverse agonist, inhibiting the spontaneous signaling of the delta cell GLP-1 receptor (18). At any rate, decreasing somatostatin would in turn result in increasing glucagon secretion. It is also now established that glucagon powerfully stimulates insulin secretion in a paracrine manner (19,20). It does so via the GLP-1 receptor (which is blocked in the Ex-9 experiments) but certainly also via the glucagon receptor (GCGR); therefore, the increased glucagon secretion would contribute to a stimulation of insulin secretion. It has also been proposed that the α-cells produce GLP-1. The problem with that hypothesis is that there is very little GLP-1 in the pancreas.
There are considerable amounts of proglucagon(72-107)-amide, the N-terminally extended form of GLP-1, which is formed in the pancreas via partial processing of the major proglucagon fragment, proglucagon(72-158) (21). This form, also designated GLP-1(1-36)-amide, cannot activate the GLP-1 receptor but cross-reacts with many antibodies against GLP-1 and has confused several investigators. Our current hypothesis is that the processing of proglucagon in the pancreas is not 100% specific and that a minor fraction of proglucagon actually is processed to GLP-1(7-36)-amide (in humans, amidation of GLP-1 seems to be rather extensive) (22). For instance, in GCGR knockout mice, which exhibit massive hypertrophy and hyperplasia of the pancreatic α-cells, about 1% or less of proglucagon is processed to GLP-1(7-36)-amide (19). In normal pancreases, this level would not be detectable, but the level increases significantly in the hyperplastic islets and results in a measurable release of GLP-1 from the pancreas, which may contribute to insulin release. In the normal pancreas, glucagon from the α-cells, acting on the GLP-1 receptor as well as the GCGR, fully explains any effects of the α-cells on insulin secretion (19). In conclusion, the results regarding insulin secretion of experiments with Ex-9 in humans may not be easy to interpret.

Effects of Incretins on Insulin Secretion—Direct or Indirect?

As mentioned, the role of GLP-1 on normal postprandial insulin secretion may not be prominent, and, at any rate, effects exerted by circulating GLP-1 would be expected to be minor since the circulating concentrations of GLP-1, in the intact biologically active form, are very low (23). This is because of degradation, occurring already in the gut and mediated by endothelial DPP-4. This enzyme inactivates GLP-1 to the extent that only about 10% of what was released from the gut makes it in the intact form to the pancreas (24). The insulinotropic effect of these low concentrations is likely to be very small (25). However, in situations with abnormal increases in the secretion of GLP-1, as may occur during increased exposure of the more distal small intestine with nutrients, the contributions may be very significant. Such conditions would include accelerated gastric emptying, as seen after surgery of the stomach with pyloroplasty, gastro-entero-anastomosis, or Roux-en-Y reconstruction (26), and in these situations blockade with Ex-9 markedly reduces insulin secretion, to the extent that postbariatric hypoglycemics may be prevented (27). After large meals, measurable increases in the postprandial plasma concentrations of intact GLP-1 may be observed, and these may influence pancreatic β-cell secretion. Similarly, exogenous GLP-1 is likely to reach the β-cells via the arterial circulation and may stimulate insulin secretion (and inhibit glucagon secretion) directly.

GLP is also degraded by the enzyme DPP-4 (28) but less extensively, and there is no indication that there is a local degradation of GIP and that a neural pathway is activated. In addition, circulating levels of active GIP (about 50% of total) are much higher than those of GLP-1. Therefore, GIP is probably acting directly on the pancreas via the circulation, again consistent with its role as a primary incretin hormone. This is in agreement with the proximal location of the GIP-producing K-cells with a maximum in the duodenum and proximal jejunum.

The traditional concept is that GLP-1 and GIP act via their specific receptors expressed on the β-cells, where they seem to produce very similar actions, mainly via cAMP, although other signaling mechanisms are probably also activated. In agreement with the existence of two parallel receptor systems expressed on the β-cells, the effects of GIP and GLP-1 on insulin secretion were found to be additive (29).

Effects on Glucagon Secretion

The two hormones have opposite effects on glucagon secretion. In infusion studies, mimicking meal responses, GLP-1 powerfully inhibited glucagon secretion, while GIP stimulated secretion in both controls and subjects with type 2 diabetes (30,31). In studies with RA during meal intake, GLP-1 antagonism causes hyperglucagonemia, while GIP antagonism lowers glucagon responses (32). The complicated mechanisms involved in the GLP-1-induced inhibition have already been dealt with. Regarding GIP, GIP receptors appear to be expressed by the α-cells, allowing direct effects of GIP on the α-cells (33). Otherwise, glucagon secretion is linked by glucose in the well-known feedback cycle between the liver and the α-cells; therefore, the stimulatory effect of GIP may be surprising, with GIP mainly being secreted during nutritional stimulation with increasing glucose levels. However, in healthy humans, the effect is mainly seen in the fasting state and during low glucose levels (34). It has, therefore, been proposed that GIP functions to stabilize glucose levels by promoting insulin release at higher and glucagon release at lower glucose levels (34).

Incretins and Insulin Sensitivity

Do the incretin hormones affect insulin sensitivity? Given that GLP-1 receptors are not expressed on the skeletal muscle cells and the adipocytes, and that these tissues are responsible for the bulk of the insulin-induced glucose uptake, it would seem unlikely that GLP-1 directly affects insulin sensitivity. GLP-1 is also unlikely to influence the glucose dynamics of the liver, although this is a controversial issue; at the least, the hepatocytes do not express the GLP-1 receptor (35). An early study by D’Alessio et al. (36) based on Bergman’s minimal model suggested an effect on glucose effectiveness, but in direct investigations of the effects of GLP-1 on glucose clearance, where the insulin-releasing effects of GLP-1 were prevented with somatostatin, this could not be confirmed (37,38), and it was concluded that the actions on plasma glucose depend
on the secretion of the islet hormones. A clear effect on insulin sensitivity was demonstrated in people with type 2 diabetes given GLP-1 as a continuous subcutaneous infusion for 6 weeks, but it was concluded that this effect was due to the concurrent weight loss (39). The GIP receptor is expressed in adipose tissue (but not in skeletal muscle), where it is thought to regulate both lipolysis and lipid uptake depending on insulin availability (40,41). Whether these actions would promote improved insulin sensitivity is unclear. However, in rodent studies overexpression of GIP and administration of long-acting GIP agonists have been reported to enhance insulin sensitivity (42,43). The direct effect of GIP on insulin sensitivity has not been studied in humans, but recent investigations have raised the possibility that the GIP/GLP-1 coagonists increase insulin sensitivity in rodents (44), and this has been proposed to explain the particular effect of the coagonist tirzepatide (45).

The Incretin Hormones and Type 2 Diabetes
When it comes to diabetes, the two hormones also differ considerably. In 1993, it was definitively demonstrated that a 4-h GLP-1 infusion in patients with type 2 diabetes could normalize fasting glucose concentrations while insulin secretion was stimulated and glucagon secretion inhibited, with those changes reverting toward basal conditions as glucose was getting normalized (46). In 2002, it was demonstrated that a 6-week continuous subcutaneous infusion of native GLP-1 in patients with longstanding type 2 diabetes greatly improved glucose control, β-cell function, and insulin sensitivity and caused weight loss (without adverse effects) (39). In contrast, it was discovered already in the mid-1980s that (porcine) GIP was incapable of stimulating insulin secretion in patients with type 2 diabetes (47). Subsequently, in comparative studies of patients and controls subjected to mild hyperglycemic clamps (to allow comparisons of effects of similar glucose concentrations in patients and controls), human GIP barely affected insulin secretion. In contrast, GLP-1 (both hormones at somewhat supraphysiological concentrations) was able to restore insulin secretion to values similar to those of the controls in response to glucose alone (48). In further studies, involving coinfusions of GIP and GLP-1, adding GIP to the GLP-1 infusion abolished the inhibition of glucagon secretion with GLP-1 (49), and when GIP infusions were given during chronic treatment with a GLP-1RA, glycemic control was impaired and glucagon concentrations elevated (50). The effect of GLP-1 on β-cell function in type 2 diabetes was studied in detail by Kjems et al. in 2003 (51), who demonstrated that the effect of GLP-1 is to dose-dependently increase β-cell sensitivity to glucose. As expected, this parameter (the slope of the relationship between elevations in plasma glucose established by step-wise increases in infusion rates and β-cell secretion rate) was severely impaired in the patients but could be improved by GLP-1, so that their β-cell responsiveness to glucose could be restored to normal values in the presence of GLP-1. Because the study also included multiple doses of GLP-1, it was possible to determine the dose-response relationship regarding this effect, which was significantly reduced. Part of this was undoubtedly due to the reduced β-cell capacity of the diabetic pancreases (functional β-cell mass), but even after correction for this, the ability of GLP-1 to improve the β-cell sensitivity to glucose was impaired. Thus, although the effect of GLP-1 may be to improve the β-cells' ability to respond to glucose, there is a limit to what can be obtained, because of 1) decreased sensitivity to GLP-1 and 2) decreased β-cell secretory capacity. It follows that the effects of GLP-1 will depend on the residual β-cell capacity in each case (52).

On this background, it came as a surprise when it was demonstrated that the GIP/GLP-1 coagonist, tirzepatide, had antidiabetic activities that exceeded those of GLP-1RA comparators (dulaglutide and semaglutide) (53,54). As is already well known and was widely presented at the ADA scientific sessions of 2021, the antidiabetic effects of tirzepatide are truly remarkable, with about 50% of patients with type 2 diabetes reaching A1C values at or below 5.7% (39 mmol/mol), which are, of course, normal values. The interest clearly focuses on the specific agent tirzepatide, since other GIP/GLP-1 coagonists investigated in previous clinical trials did not show results that were distinguishable from those obtained with comparator GLP-1RAs (e.g., see Frias et al. [55]). The unusual features of tirzepatide are currently under intense investigation (see below). Recent rodent studies suggested that one important mechanism was a massive increase in insulin sensitivity (44), in large part due to increased glucose uptake in brown adipose tissue (BAT). Humans do not have large amounts of BAT, and in infusion studies, GIP did not seem to influence insulin sensitivity (56), questioning the relevance of this mechanism for humans. Remarkably, the side effect profile of tirzepatide is highly reminiscent of that of the GLP-1RAs, and, judging from the frequency of these mainly gastrointestinal side effects and also the discontinuation rates in the phase 3 SURPASS studies, they correspond to what would be expected from high doses of GLP-1RAs (53,54). Indeed, it has not been excluded that tirzepatide is mainly a very powerful GLP-1.

Appetite and Food Intake
Regarding extrapancreatic actions of the two hormones, they also differ markedly, at least when judging from the results obtained in humans. GLP-1 profoundly influences upper gastrointestinal functions and appetite (57), and for endogenous GLP-1 this apparently occurs again via activation of sensory afferents of the vagus (58,59). In contrast, exogenous GLP-1 and GLP-1RAs may predominantly access the leaks in the blood-brain barrier (the area postrema, the median eminence, and the subfornical organ), where the underlying neuronal tissue shows a
dense expression of GLP-1 receptors (60). At any rate, GLP-1 powerfully inhibits efferent vagal activity with marked consequences for gastrointestinal motility and gastropancreatic secretion in general and gastric emptying in particular (57). For instance, GLP-1 infusion in humans powerfully inhibits gastric acid secretion (particularly together with PYY); it also abolishes vagally induced secretion (in sham feeding experiments), whereas there is no effect on stimulated secretion after truncal vagotomy (reviewed in Gregersen et al. [61]). In contrast, exogenous GIP does not have any effect on these parameters in humans (62). Infusions of GLP-1 were demonstrated to inhibit appetite and food intake in humans in 1998 (63), and the first GLP-1RA (liraglutide) was approved for treatment of obesity in 2013. The most recent data have shown that a related GLP-1RA, semaglutide given weekly at 2.5 mg, may provide an 18% weight loss after 68 weeks (64). Thus, GLP-1RAs are the most powerful weight-losing agents available. GLP-1RA administration is often accompanied by initial mild-moderate nausea, and it has been speculated how much of the appetite effect is due to the nausea. However, it is clear that the majority of patients experience the effect without feeling nausea. In animal experiments, the effect of GLP-1RAs on food intake is entirely dependent on central nervous system mechanisms (65), and in humans this is supported by numerous imaging experiments (66). Importantly, GLP-1 has effects on the reward system (67). If overeating in obesity is viewed as a disturbance of appetite regulation, related to other forms of abuse, the GLP-1RAs might also be useful in other forms of abuse (68), and this is currently being investigated.

Serious attempts to identify effects of GIP on appetite in humans have only been carried out in a few acute studies and with negative results, and in a recent investigation of the effects of GIP infusion in patients with type 2 diabetes alone or in combination with GLP-1, the inhibitory effect of GLP-1 was even abolished by coinfusion of GIP (69). In further studies, GIP was infused to patients during chronic treatment with a GLP-1RA, but again this did not result in changes in food intake (50). These data contrast strikingly with those obtained with the GIP/GLP-1 coagonist tirzepatide (53). Unfortunately, human studies with long-acting GIP agonist are not available; such studies are presumably underway, but no results have been revealed so far. In rodents, long-acting GIP agonists were reported to inhibit food intake and cause weight reductions, although the effect is small (70,71), and recently GIP receptors have been identified in neurons of the hypothalamus of mice, the activation of which resulted in reduced food intake and weight loss (71,72). Again, the effects of GIP agonists are small compared with those that can be elicited by GLP-1, but in several studies the addition of a GIP agonist to a GLP-1RA potentiated the weight-losing effect. Indeed, in a recent study, the effect of tirzepatide was lost in mice with central deletion of the GLP-1 receptor (44). The simplest interpretation of this result would be that tirzepatide mainly acts on the GLP-1 receptor. It is also possible that there is an interplay between the GLP-1 and GIP receptors, which may set in if and when the two receptors are expressed on the same cell. Very few cells in the rodent hypothalamus seem to coexpress these receptors (44), and it is not known if the few cells that apparently do so are responsible for the effect of the coagonist. In the islets, the β-cells express both the GIP and the GLP-1 receptor, and here some of the consequences of activation with tirzepatide have been studied. It is well documented that tirzepatide is an agonist of both receptors, not only by design but also as demonstrated in direct experiments, and in fact is more potent on the GIP receptor than on the GLP-1 receptor (73). Activation of GPCRs of this family has several consequences, one of them being receptor internalization, often associated with arrestin recruitment. Both natural GLP-1 and GIP cause internalization of their receptors, in the case of the GIP receptor in an arrestin-dependent manner (8), whereas the GLP-1 receptor may internalize arrestin independently (74). Moreover, it has been demonstrated that the responsiveness of cells expressing GIP receptors decreases as a consequence of the internalization (41,75). GIP exposure therefore desensitizes the target cell, and it has been proposed that this downregulation in fact would be indistinguishable from the actions of a GIP-RA (76). Therefore, downregulation by internalization might explain that GIP-RA and antagonists sometimes appear to behave identically; this is also true in terms of regulation of food intake. However, in cells expressing GLP-1 and GIP receptors, arrestin recruitment and internalization of the GIP receptor were completely identical after tirzepatide and native GIP administration (77). This contrasted with the interaction with the GLP-1 receptor, where arrestin recruitment and internalization were almost completely abolished with tirzepatide. This might result in permanently high expression of the GLP-1 receptor on the cell surface, allowing stronger and durable activation of receptor signaling. This would support tirzepatide as a particularly powerful GLP-1 receptor agonist, consistent with the side effects observed during clinical treatment with high doses of tirzepatide in the clinical studies (whereas such side effects have never been observed with GIP) and with the results of the knockout studies referred to above. Note that the particularly powerful actions of tirzepatide are not observed with other GIP/GLP-1 coagonists and, therefore, must depend on the specific features of tirzepatide.

Summary
Physiologically there is little doubt that GIP is an important first-in-line incretin hormone, whereas GLP-1 may serve mainly as a hormone of the ileal brake mechanism, limiting food intake and upper gastrointestinal motility and secretion in situations of nutritional abundance. For
reasons that are still not understood, GLP-1 but not GIP is capable of restoring some of the β-cell responsiveness to glucose in patients with type 2 diabetes, which, together with the inhibition of glucagon secretion by GLP-1 (while GIP stimulates glucagon secretion), explains its effectiveness to improve glucose control in type 2 diabetes. In agreement with its ideal brake function, GLP-1 is a powerful suppressor of appetite and, hence, of food intake, and modern GLP-1RAs are the strongest appetite and food intake suppressors developed so far. GIP is traditionally viewed as an obesity hormone, but expression of GIP receptors in the rodent hypothalamus associated with regulation of food intake has revived interest in the possible role of this peptide in regulation of food intake, although differences between species may exist. Moreover, different molecular mechanisms in the regulation of receptor expression and internalization patterns may contribute to the differences between the two systems. A recently developed coagonist, tirzepatide, has provided unprecedented results concerning not only glucose regulation in type 2 diabetes but also weight reduction, raising questions regarding the possible mechanism of action that remain unresolved. The remarkable effects of tirzepatide and the newer GLP-1RAs, however, suggest that we are entering a new era with hitherto unprecedented treatment effects of both type 2 diabetes and obesity.

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