The Role of Incretins in Insulin Secretion

4

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Abstract

The notion that gut factors produced in response to nutrient ingestion are capable of stimulating the endocrine pancreas and consequently reducing glycemic levels was introduced more than 100 years ago. These gut factors were subsequently called incretins, and the augmented insulin response to nutrient given orally compared to nutrient administered intravenously was named "incretin effect." This chapter focuses on the mechanisms of the synthesis and actions of the incretin peptides, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide. In addition, alteration in incretin axis in type 2 diabetes and therapeutic relevance of these peptides will be highlighted. Finally, the role of incretin axis in diabetes remission after gastrointestinal surgeries for treatment of obesity will be briefly discussed.

Keywords

Insulin secretion • Incretin effect • GLP-1 • GIP • type 2 diabetes • bariatric surgery

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The Glucose Tolerance and β-Cell Response

The blood glucose concentration is highly regulated, so that the increase in glycemic levels after a large carbohydrate meal consumption in a healthy individual is minimal and short-lived as glycemic levels rise only 50% of basal values and return to premeal levels in 1–2 h. The size of glucose response to meal ingestion is determined by a balance between the rate of carbohydrate entry into the gut and splanchnic glucose uptake. While gastric emptying plays a major role in variation in peak and nadir glucose levels [1],

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carbohydrate assimilation is mainly dependent on the tight regulation of pancreatic β-cell response to nutrient ingestion. A large body of evidence has indicated that the insulin response to meal ingestion is controlled by a gut-pancreas (enteroinsular) axis that integrates inputs from glycemic levels as well hormones and neural signaling initiated by eating, leading to a rapid decline of postprandial glucose levels without causing hypoglycemia. This enteroinsular axis activity is regulated as part of a feed-forward system which allows an anticipatory β-cell response to nutrient ingestion based on observation that postprandial insulin secretion that is pronounced earlier than the maximum glucose levels is reached after eating [2].

Postprandial glycemia contributes to overall glycemic control [3]; therefore, many dietary and pharmacological strategies for treatment of type 2 diabetes (T2DM) have been developed to modify the glycemic excursion by restraining gastric emptying or augmenting the enteroinsular axis.

The Enteroinsular Axis Activity (Incretin Effect)

The idea that factors from the gut stimulate pancreatic endocrine secretion was first proposed after discovery of secretin. This concept was tested by Moore and his colleagues who demonstrated that administration of gut extract improved glycosuria in patients with diabetes [4]. Shortly after development of insulin assays, a number of investigators reported that circulatory insulin concentrations are greater when glucose is given orally than that after intravenous glucose administration despite similar glycemic levels (Fig. 1) [5]. These observations confirmed the earlier hypothesis that the gut factors released in response to carbohydrate ingestion stimulate insulin release. These factors were collectively named incretins, a term that was originally used to refer to endogenous factors stimulating internal secretions in the body based on studies in which intestinal extracts free of secretin lowered glucose levels in dogs [6]. The relatively larger insulin response to oral vs. a matched IV glucose infusion was called incretin effect. Subsequently, it was recognized

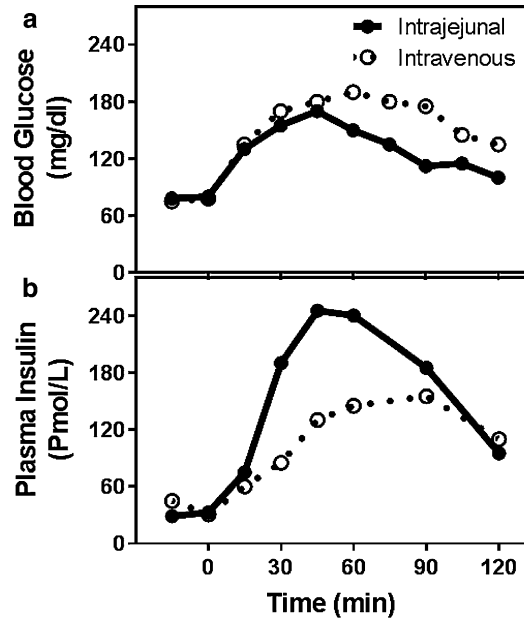

Fig. 1 Blood glucose (**a**) and plasma insulin (**b**) response to intrajejunal and intravenous glucose administration. Augmented insulin secretion elicited by intrajejunal (*solid line*, *closed circle*) as compared to intravenous (*dashed line*, *open circle*) administration of glucose despite similar glycemia is called incretin effect (Reproduced with permission [5])

that the incretin effect accounted for 30–70% of insulin secretion after meal ingestion [7].

In healthy individuals with normal glucose tolerance, glycemic excursion after ingestion of 25–100 g of glucose is almost identical. The ability to maintain postprandial glycemia within a narrow range despite fourfold increase in glucose intake is due to a progressive increase in postprandial insulin secretion and the incretin effect in proportion to the amount of carbohydrate ingested [7]. Thus, while the glucose level is an important stimulus for β-cell response, the incretin effect controls the proportional increase in insulin output based on the amount of nutrient ingestion.

Findings from numerous studies over years demonstrated that two major peptides, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), act as incretins and collectively account for up to 70% of postprandial insulin secretion [7, 8]. These peptides are secreted by specialized cells in the intestinal

mucosa in response to nutrient ingestion dose dependently and act through specific G-protein-coupled receptors expressed on islet cells and other tissues [9].

While the endocrine component of the enteroinsular axis, which is the focus of this chapter, has been better characterized, incretin effect also includes direct nutrient effect as well as neural stimulation [10]. The role of autonomic nervous system activation of the β-cell has been investigated during the preabsorptive phase of insulin secretion [11] and as an anticipatory response to food intake or to oral nutrient sensory stimulation [12]. However, in addition to premeal insulin secretion, parasympathetic nervous system (PNS) activation has been shown to make an important contribution to the β-cell response to food intake [13, 14].

Glucagon-Like Peptide 1

GLP-1 (7–36), a 30-amino acid peptide and a product of proglucagon gene, is secreted from intestinal endocrine L-cells located throughout the gastrointestinal (GI) tract but primarily in the lower small intestine and colon [15], within minutes after carbohydrate and fat ingestion [16]. Plasma levels of GLP-1 parallel those of insulin with the highest levels within 30–60 min after eating [17] and proportionate to the meal size [18].

The mechanism of nutrient-L-cell coupling is not completely understood, but it has been suggested that upstream sensors activate distally located L-cells through hormonal or neural factors rather than direct nutrient sensing [19] since GLP-1 is secreted much earlier than expected arrival time of nutrient in the distal gut. While the carbohydrate is the strongest stimulator of GLP-1 secretion, ingested fat and protein as well as the nutrients combined increase L-cell products in both individuals with and without T2DM [20].

Once released from L-cells, GLP-1 is rapidly metabolized by a ubiquitous protease, dipeptidyl peptidase 4 (DPP-4), located in the circulation as well as on capillary endothelium, resulting in a half-life of 1–2 min in the circulation [21]. DPP-4 cleaves the two N-terminal amino acids from GLP-1 leaving GLP-(9–39) with no insulinotropic activity [22].

GLP-1 actions are mediated through a single G-protein-coupled receptor, GLP-1 receptor (GLP-1r), which is expressed in a variety of tissues, including pancreatic islet cells, as well as the specific brain areas (hypothalamus, hindbrain, and midbrain), vagal afferent nerves, stomach, lung, heart, and kidney [23].

The classic action of GLP-1 in β-cells is to increase glucose-stimulated insulin output [7], although GLP-1 also enhances the insulin biosynthesis [24]. Studies of mice with a targeted deletion of the GLP-1r gene (GLP-1r −/−) have supported a significant role for GLP-1 signaling in normal glucose homeostasis. Insulin secretion in these mice is reduced, and glucose tolerance is abnormal compared to control mice [25]. Islets from GLP-1r −/− mice are more susceptible to the toxic effects of streptozotocin [26], and they lack compensatory capacity to grow following partial pancreatectomy [27].

Activation of GLP-1r in pancreatic β-cells initiates intracellular signaling mediated by activation of cAMP/ protein kinase A (PKA) system. It appears that acute effects of GLP-1 on β-cells, such as glucose-stimulated calcium oscillation, membrane depolarization, and insulin exocytosis, are mainly mediated by the cAMP/PKA system. However, chronic effects of GLP-1 on β-cells, such as anti-apoptotic and proliferative effects, are more likely mediated through phosphatidylinositol-3 kinase activity (PI-3K) [23].

Beyond the insulin secretagogue action of GLP-1, this peptide plays a significant role in normal islet development. GLP-1 signaling promotes the expansion of β-cell mass by direct stimulation of β-cell growth and replication [28], by differentiation of pancreatic duct cells into insulin producing cells [29], and by inhibiting β-cell apoptosis [30].

It has also been hypothesized that glycemic reducing effects of GLP-1 are partly mediated by its inhibitory effects on α-cell during both fasting and fed states. The inhibitory effect of GLP-1 on glucagon seems to be a major cause for glucose-induced glucagon suppression [31]. Along the same line of evidence, glycemic reduction of

GLP-1 in both diabetic and nondiabetic individual during fasting state is attributed to the glucagonostatic effects of this peptide [31].

Administration of GLP-1 or GLP-1r agonists at high pharmacologic doses has also been shown to reduce postprandial glucose excursion by delaying gastric emptying [32] as a result of altered autonomic nervous system activity [33].

The physiologic actions of endogenous GLP-1 on glucose metabolism have been studied using continuous infusion of a potent GLP-1r antagonist, exendin-(9–39) in human. Blockade of GLP-1r causes postprandial hyperglycemia indicating that the endogenous GLP-1 is essential for regulation of glucose [31]. However, interpretation of the effect of GLP-1r blockade on insulin response to glucose or meal ingestion is confounded because of simultaneous hyperglycemia caused by exendin-(9–39) infusion. The effect of endogenous GLP-1 on islet cell hormone secretion independent of glycemic levels has been studied using combined hyperglycemic clamp and meal ingestion. Using this setting, infusion of GLP-1r antagonist suppressed postprandial insulin secretion by 30–40% and enhanced glucagon secretion in healthy individuals [34]. Findings from these studies and others also indicated that endogenous GLP-1 (unlike pharmacological concentrations of GLP-1) has a minimal effect on gastric emptying; therefore, the insulinotropic property of this peptide at physiologic levels is not mediated by alteration in the rate of nutrient passage [34–36].

Glucose-Dependent Insulinotropic Polypeptide

GIP is a 42-amino acid peptide processed from prepro-GIP exclusively by endocrine K-cells that are located mostly in duodenum and upper jejunum, an ideal place to sense the nutrient arrival to the gut [23]. The presence of nutrient in the gut lumen does not seem to be the sole factor to trigger GIP release as conditions interfering with carbohydrate digestion or uptake have been shown to diminish GIP secretion [37]. Similar to GLP-1, all macronutrients stimulate K-cells proportionally to the size of nutrient intake [18], although adding fat and protein to glucose has a synergistic effect on GIP secretion in contrast to GLP-1 secretion [20].

Similarly to GLP-1, the full-length GIP has a short (5–7 min) circulatory half-life. Once it is released into circulation, GIP is rapidly metabolized by DPP-4, which cleaves GIP specifically between residues 2 and 3 leaving GIP-(3–42) with no insulinotropic activity [23].

All physiologic actions of GIP are mediated through a single specific G-protein-coupled receptor, GIP receptor (GIPr), which has some homology with GLP-1 and glucagon receptors. The GIPr is expressed in both α- and β-cells of the pancreatic islet, the foregut, adipocytes, adrenal cortex, pituitary, and some brain regions [23]. GIP signaling in the β-cell is relatively similar to GLP-1. Binding to its receptor on β-cell, GIP activates adenylyl cyclase and increases intracellular cAMP, but also acts through PI3 kinase and growth factor pathways [23].

In rodent models, using a GIPr antagonist or eliminating circulating GIP by immunoneutralization method leads to glucose intolerance as a result of reduced insulin secretion [38, 39]. Also, targeted gene deletion of the GIP receptor in mice resulted in abnormal glucose intolerance and insulin secretion in these animals despite normal fasting glucose levels and normal insulin responses to intraperitoneal glucose administration [40]. These findings are indicative of incretin properties of GIP. GIP signaling, however, also has been shown to promote obesity. Elimination of endogenous GIP effects in mice by deletion of the GIP receptor (GIP −/−) [41]or by infusion of GLP-1r antagonist [42] or by ablation of GIP secreting endocrine cells [43] protects animals against weight gain induced by high-fat diet or overeating secondary to leptin deficiency. These leaner mice have better glucose tolerance than their fat littermates.

Beyond the insulin secretagogue effect, GIP promotes proliferation of β-cell lines and protects against apoptosis [44].

Despite the insulinotropic property of GIP in healthy humans, administration of pharmacological doses of GIP in persons with T2DM fails to increase insulin secretion [45]. Additionally, GIP (in contrast to GLP-1) has stimulatory effect on α-cell secretion [46] which in turn is an undesirable effect for glucose control in patients with T2DM.

Chord and Discord Among GLP-1 and GIP

GLP-1 and GIP as well as their receptors share some sequence homology. They both are secreted in response to eating and proportionally to the amount of nutrient intake and metabolized and inactivated by DPP-4 upon secretion. They both function as incretins by activating some common intracellular signaling after binding to their specific receptors on β-cells. More importantly, the insulin secretagogue effect of these gut hormones is only present when glucose levels are higher than fasting values (5–6 mmol/l) [47–49]. These similarities between the two peptides have raised a question about a redundancy in the enteroinsular system, whose presence has been supported by studies reporting that one incretin can compensate for the lack of function of the other [50, 51].

Of note, there are several key differences in the site of synthesis and mechanism of secretion, mechanism of action, and extra-pancreatic effects between the two peptides despite apparent overlap. GLP-1 is secreted in the small intestine, but the largest concentrations of L-cells are in the ileum and colon [15], while GIP is made mainly in the duodenum and jejunum [37]. In addition, given the timing of GLP-1 peak after meal, vagal neural stimulation has been proposed to be involved in GLP-1 secretion [19, 52], while GIP secretion seems to be more stimulated by substrate-K-cell interaction [37]. Postprandial GIP concentrations rise greater than those of GLP-1 (5- vs.1.5-fold), and GIP has a slightly longer circulatory half-life (5–7 vs. 1–2 min). Therefore, endocrine properties of GLP-1 have been questioned. In fact, data indicate that GLP-1 actions are mediated through a neural mechanism initiated by sensors in the hepatic portal vein that would have access to relatively larger concentrations of GLP-1 compared to systemic levels [53, 54].

Finally, extra-incretin actions of these peptides are significantly different. GIP seems to be involved in promoting obesity as well as triglyceride storage in adipocytes [42–44] as well as in increasing glucagon secretion, which collectively worsen glucose homeostasis. On the contrary, GLP-1 suppresses glucagon secretion [31], delays gastric emptying [55, 56], causes satiety [57], and suppresses hepatic glucose production [58] – all of these effects promoting improved glucose metabolism. Apart from metabolic effects of GIP, recent data suggest that GIP signaling is a critical regulator of optimal bone mass and structure [59].

Taken together, a large body of evidence supports the notion that GLP-1 and GIP have unique physiologic actions that are complementary.

Enteroinsular Axis Activity and Type 2 Diabetes

Using the classic method for measuring the incretin effect, a 2-day study with an oral glucose tolerance test on day 1 followed on day 2 by a glycemic-matched IV glucose infusion [7] reported a significant impairment of the incretin effect in patients with type 2 diabetes [60–62]. However, in a group of patients with type 2 diabetes with better glycemic control, incretin effect, measured using 1 day study of a meal tolerance test during hyperglycemic clamp, was similar to that in healthy controls [36]. Among the diabetic patients in this cohort, fasting glucose and A1C levels were inversely correlated with the measured incretin effect [36], suggesting that poor glycemic control is associated with lower incretin effect. Diminished incretin effect has also been reported in nondiabetic individuals with abnormal glucose tolerance test [63], nondiabetic critically ill patients [64], and in heart and liver transplant

recipients taking immunosuppressive known to affect the β-cell [65]. Impaired incretin effect has been also reported in adolescents with type 2 diabetes or impaired glucose tolerance [66], suggesting that the incretin abnormalities are present in the early stage of diabetes.

These findings raised the question whether the incretin secretion or effectiveness are fully preserved in persons with T2DM. Postprandial plasma levels of GLP-1 have been reported to be increased [67, 68], decreased [69], or unchanged [70] in persons with T2DM compared with healthy controls. Furthermore, there is no evidence of reduced GIP secretion in diabetes; in fact, patients with diabetes seem to have higher GIP response to glucose challenge than those without [71, 72]. Therefore, it is unlikely that GLP-1 or GIP deficiency plays a major role in β-cell dysfunction in type 2 diabetes.

On the other hand, incretin-induced β-cell secretion is diminished in persons with type 2 diabetes [73]. The pathogenesis of reduced effectiveness of incretins in diabetes is not completely understood, although it is plausible that abnormal β-cell function in general contributes to reduced incretin effect and β-cell responsiveness to incretins. Supporting this hypothesis are the data demonstrating that improved glycemic control with medical intervention for 4 weeks can recover the β-cell response to GLP-1 and GIP, likely due to improved overall β-cell function [74]. It is worth to mention that the relative contribution of the GLP-1 effect to postprandial insulin secretion was shown to be similar in patients with well-controlled T2DM and matched healthy controls [36], even though the β-cell function in the diabetic individuals was reduced.

Despite reduced β-cell sensitivity to GLP-1 in individuals with T2DM [73], administration of pharmacologic amounts of GLP-1 normalizes fasting glucose levels [75–77], mainly due to increase insulin secretion and partly to glucagon suppression [78–81]. In contrast, in patients with diabetes and moderate glycemic control, administration of GIP at higher doses has trivial glycemic or insulinotropic effect [45, 76, 77, 82]. The mechanisms underlying reduced GIP effectiveness in diabetes are largely unknown, but GIP deficit can be the culprit for the overall reduced incretin effect in the affected individuals.

Enteroinsular Axis Activity and Bariatric Surgery

Most commonly performed weight-loss surgeries, gastric bypass surgery (GB) and sleeve gastrectomy, are known to induce diabetes remission independent of weight loss [83–85]. One of the early hypotheses proposed to explain weight-loss-independent glycemic effects of gastric bypass surgery was that rerouting the GI tract leads to direct rapid delivery of nutrients into the distal gut enhancing secretion of insulinotropic gut hormones and improved glycemic control. Now it is known that gastric bypass results in a larger glucose excursion after meal ingestion earlier [85], along with an earlier and higher peak of insulin and incretin (GLP-1 and GIP) secretion [86–89] (Fig. 2). In contrast, restrictive weight-loss procedures such as adjustable gastric band have no effect on postprandial glucose excursion or insulin and GI hormone responses [90] (Fig. 2).

Altered glycemic excursion after GB has been attributed in part to more rapid nutrient passage from the small gastric pouch into the gut [93–95] leading to the markedly enhanced secretions of incretins [96]. Sleeve gastrectomy appears to have similar effects on glucose, insulin, and GLP-1 responses to meal ingestion as GB, although the magnitude seems to be smaller [91] (Fig. 2).

It is also recognized that improved β-cell sensitivity to glucose in subjects with gastric bypass is exclusively postprandial since insulin secretion in response to intravenous glucose, which has no effect on the release of GI factors, is similar before and after surgery or when compared to non-operated individuals [97, 98]. While the role of enteroinsular axis function in glycemic control after sleeve gastrectomy remains to be understood, postprandial hyperinsulinemia after GB is typically attributed to the combined effects of elevated glucose [94, 99] and a greater incretin effect [88, 89, 97] (Fig. 3).

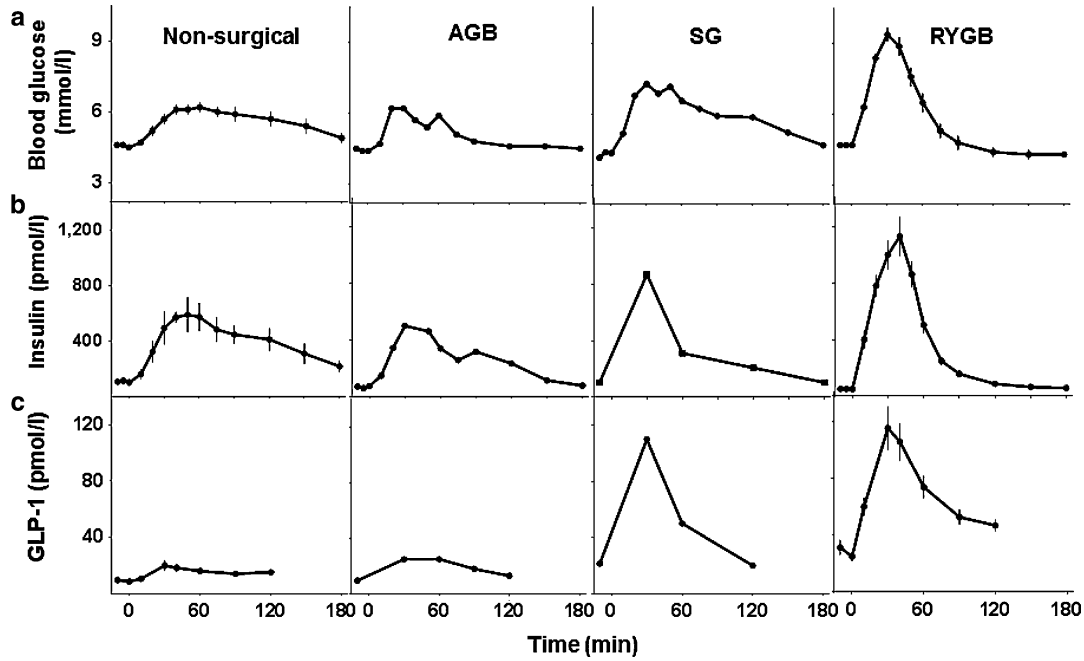

Fig. 2 Blood glucose (**a**), insulin (**b**), and GLP-1 (**c**) response to liquid meal or oral glucose ingestion in nonsurgical healthy controls and those after adjustable gastric band (AGB), sleeve gastrectomy (SG), and gastric bypass (RYGB) surgeries. Data adjusted for baseline values (Reproduced with permission [92])

The role of GIP or nonhormonal components of enteroinsular axis after GB is also not known, but a large body of data shows that blockade of the GLP-1r has a disproportionately greater effect on meal-induced insulin release and β-cell glucose sensitivity in GB subjects compared to controls [97, 100, 101] (Fig. 3).

Taken together, the two most commonly performed procedures for weight loss, gastric bypass surgery [83], and, to a lesser extent, sleeve gastrectomy [102], lead to diabetes remission immediately after surgery, encouraging the consideration of these procedures for treatment of diabetes in affected mildly obese individuals [103, 104]. The weight-independent effects of GB to improve diabetes have been mostly attributed to altered postprandial glucose metabolism and islet function as a result of changes in enteroinsular axis function [88, 89].

Incretin-Based Therapies for Treatment of Type 2 Diabetes

Over the last two decades, the enteroinsular axis components, especially those targeting GLP-1 signaling, have been the focus of development of therapeutic options for diabetes. The early studies demonstrated that the insulinotropic effects of GLP-1, unlike GIP, are preserved in patients with T2DM [77–79], invigorating drug development efforts around GLP-1r signaling rather than GIP [105]. Furthermore, GLP-1 was recognized to have a broad range of actions promoting improved glucose metabolism, including stimulating insulin secretion [7] and biosynthesis [24], inhibiting glucagon release [31, 106], delaying gastric emptying [107], and suppressing hepatic glucose output [58, 108]. However, there were limitations to the use of this peptide as a

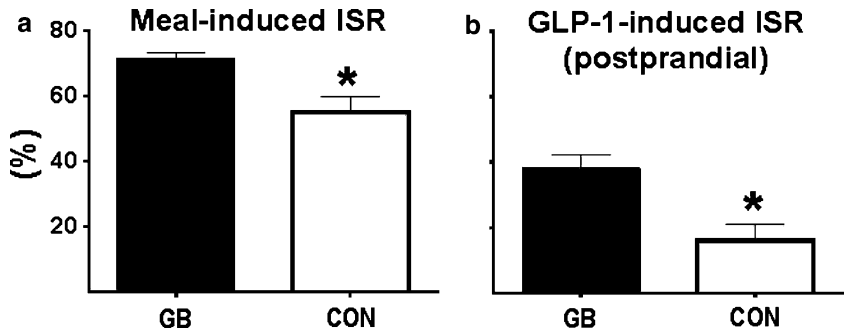

Fig. 3 Incretin effect (**a**) and GLP-1 contribution to post-meal insulin secretion rates (ISR) (**b**) during hyperglycemic clamp in subjects after gastric bypass ($n = 24$, *black bar*) and non-operated healthy controls ($n = 11$, *white bar*), $^*p < 0.05$ compared to gastric bypass surgery [97]

therapeutic option given its extremely short half-life in the circulation. Two strategies designed to circumvent the rapid degradation of GLP-1 by DPP-4 were developed. One involved modified GLP-1 or GLP-1r agonists that are less susceptible to DPP-4 metabolism. The other focused on the development of molecules that inhibit the action of DDP-4. The first approach led to the class of drugs that promote GLP-1r signaling using pharmacological concentrations of these compounds and administered subcutaneously and the second to a group of small molecules that increase the circulatory levels of endogenous GLP-1 and are administered orally. Due to glucose dependency of GLP-1 action on insulin and glucagon secretion [48], hypoglycemia is not associated with neither of these drugs unless other insulin secretagogue or insulin is co-administered with these drugs [109–114]. While DPP-4 inhibitors share the insulin and glucagon effect of GLP-1r agonists, they have minimal effect on gastric emptying [115]. Similarly increasing endogenous GLP-1 as a result of DPP-4 inhibitors seems to have no effect on body weight, whereas GLP-1r agonists in pharmacologic doses have been shown to induce weight loss along with glycemic improvement [116].

Exenatide (Byetta) was the first GLP-1r agonist to be approved in the USA in 2005 and sitagliptin (Januvia) the first DPP-IV inhibitor in 2006. Thus far, liraglutide (Victoza), exenatide long-acting release (LAR, Bydureon), dulaglutide (Trulicity), and albiglutide (Tanzeum) from the class of GLP-1r agonists and saxagliptin (Onglyza), linagliptin (Tradjenta), and alogliptin (Nesina) from the class of DPP-4 inhibitors have been approved for treatment of T2DM in the USA as an add-on to metformin, thiazolidinediones, sulfonylureas, and basal insulin or a combination of these drugs. Lixisenatide, a short-acting GLP-1r agonist, is approved in Europe and is under review for FDA approval in the USA. A long list of compounds or combination products based on incretin physiology is currently in development. The recommendation by the ADA/ESD guidelines [117] is to use GLP-1-based drugs as second-line agents after metformin mainly due to weight loss with GLP-1r agonist or weight neutrality with DPP-4 inhibitors as well as lack of hypoglycemia despite glycemic improvement.

Altogether, GLP-1-based drugs have gained popularity in a short period of time mainly due to their safety, efficacy, and extra-pancreatic beneficial effects, suggesting that they can be used in the early treatment of diabetes according to the international guidelines. Both incretin and non-incretin effect of GLP-1r agonists contribute to glycemia-reducing effect of this peptide as administration of GLP-1 in persons with T1DM, and no residual β-cell function has been shown to normalize hyperglycemia [106, 118]. To date, the use of these drugs is restricted to the treatment of T2DM.

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