



Review

Nutrients related to GLP1 secretory responses

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ARTICLE INFO

Article history:

Received 27 September 2012

Accepted 23 November 2012

Keywords:

GLP-1

Glucagon-like peptide1

Type 2 diabetes

Fatty acids

Protein

Carbohydrate

ABSTRACT

The hormone glucagon-like peptide (GLP-1) is secreted from gut endocrine L cells in response to ingested nutrients. The activities of GLP-1 include stimulating insulin gene expression and biosynthesis, improving β -cell proliferation, exogenesis, and survival. Additionally, it prevents β -cell apoptosis induced by a variety of cytotoxic agents. In extrapancreatic tissues, GLP-1 suppresses hunger, delays gastric emptying, acts as an ileal brake, and increases glucose uptake. The pleiotropic actions of GLP-1, especially its glucose-lowering effect, gave rise to the suggestion that it is a novel approach to insulin resistance treatment. Hormones secreted from the gut including GLP-1, which are involved in the regulation of insulin sensitivity and secretions, have been found to be affected by nutrient intake. In recent years, there has been a growing interest in the effect nutrients may have on GLP-1 secretion; some frequently studied dietary constituents include monounsaturated fatty acids, fructooligosaccharides, and glutamine. This review focuses on the influence that the carbohydrate, fat, and protein components of a meal may have on the GLP-1 postprandial responses.

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Introduction

Glucagon-like peptide 1 (GLP-1) is an intestinal endocrine L cell-derived peptide, which is cleaved from proglucagon and is expressed in the intestine, pancreas, and brain [1]. This hormone is secreted in response to a variety of nutrients [2] and neural and endocrinal factors [3]. GLP-1 exists in two biologically active forms: GLP-1 (7–37) and GLP-1 (7–36) amide. GLP-1 (7–36) amide has a higher concentration in blood circulation (almost four times) after a meal compared with GLP-1 (7–37) [4,5]. Fasting plasma levels of bioactive GLP-1 typically range between 5 and 10 pmol/L in humans and increases approximately twofold to threefold after each meals [3]. Depending on size and nutritional composition of the meal, this hormone peaks at 20 to 30 minutes after meals [3,6]. The circulating levels of intact GLP-1 decline rapidly due to enzymatic inactivation, mostly by dipeptidyl peptidase-4 (DPP-4), and also renal clearance. Additionally, proteases such as human neutral endopeptidase 24.11 may inactivate up to half of the GLP-1 entering the circulation [4,7].

GLP-1 plays a number of different roles in metabolic homeostasis including stimulation of glucose-dependent insulin release, attenuation of blood sugar, nonesterified fatty acids, and

postprandial triglyceride concentrations, and deceleration of gastric emptying, acid secretion, and food intake [8,9]. Additionally, it stimulates islet neogenesis and β -cell proliferation in experimental rodent trials [10]. GLP-1 is responsible for nearly half of the total insulin secretion that occurs after meal [11]. Furthermore, activation of GLP-1 receptor inhibits β -cell apoptosis and leads to reduction of β -cell death. GLP-1 also inhibits hepatic glucose production and stimulates glucose uptake in an insulin-dependent manner in both adipose tissue and muscle [3]. GLP-1 can affect endogenous glucose production independent of islet hormone secretion and can decrease it under fasting conditions [6].

Type 2 diabetes and GLP-1

Type 2 diabetes mellitus is the most common form of diabetes ranging from insulin resistance with relative insulin deficiency to predominantly secretory defect in insulin secretion with insulin resistance [12]. Postprandial levels of active GLP-1 is diminished in obese and insulin-resistant patients; however, it is not known if a reduced GLP-1 level is a cause or consequence of obesity and insulin resistance [13]. Because GLP-1 elimination is similar in healthy, obese, and type 2 diabetic patients, the decrease in GLP-1 levels observed in obese and type 2 diabetic individuals is likely caused by reductions in GLP-1 secretion [3]. Vollmer et al.

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suggested that GLP-1 secretion was not impaired in patients with well-controlled type 2 diabetes but it may become impaired in patients with diabetes of longer duration or those with poor glycemic control [14].

Recently, there has been growing interest in methods by which GLP-1 levels and action can be enhanced in diabetes. Two main adopted strategies are using GLP-1 receptor agonists and dipeptidyl peptidase-IV (DPP-IV) inhibitors. However, another alternative approach that is receiving increasing attention is direct stimulation of GLP-1 secretion from intestinal L cells. This approach offers some additional benefits, including simultaneous stimulation of peptide YY, oxyntomodulin, and GLP-2 and increases in GLP-1 9–36 concentration, a cleaved product of DPP-IV, which is a weak insulinotropic agonist that inhibits hepatic glucose production and may exert antioxidant actions in the heart and vasculature [15].

Nutrients and GLP-1 secretion

There is some evidence that the macronutrient composition of a diet may directly affect the postprandial responses of GLP-1 secretion [8]. If a nutrient can augment the secretion of endogenous GLP-1, it might provide insight for new nutritional alternatives to pharmaceutical approaches for management and/or reduction of diabetes and obesity risk [16–18]. This review summarizes the main literature findings on nutrients that affect GLP-1 secretion.

Fiber and GLP-1 secretion

Studies using fiber are summarized in Table 1.

Dietary fiber is a carbohydrate that resists digestion and absorption and is categorized into two main subtypes: soluble (prebiotic, viscose) fiber that is easily fermented into biomass, short-chain fatty acids (SCFA) chiefly acetic, propionic and *n*-butyric, lactate, and gases by the microflora of the large intestine, and insoluble fiber that is metabolically inert, is non-water soluble and non-fermented. Some examples of known soluble fibers are pectin, inulin-type fructans, and some hemicelluloses, whereas insoluble fibers contain lignin, cellulose, and some hemicelluloses [19,20].

Recent data support that nondigestible carbohydrates may change the gut microbial composition in ways claimed to be beneficial to host well-being and health. These food ingredients are called prebiotics because they allow the growth and/or activity of certain bacteria that has been shown to improve several features of metabolic syndrome [21]. Non-digestible and fermentable carbohydrates, as well as SCFAs, have been shown to increase GLP-1 levels. SCFAs produced by bacteria fermentation, stimulate L cells via the G-protein coupled free fatty-acid receptor 2 and enhance GLP-1 secretion [22].

In Sprague-Dawley rats, ingestion of a more fermentable dietary fiber, rhubarb fiber, at physiologic levels (50 g/kg diet) resulted in upregulation of ileal proglucagon mRNA and enhancement of C-peptide concentrations compared with control rats receiving cellulose [23]. Additionally, normal rats fed with a standard diet or the same diet enriched with fructans (oligofructose, synergy 1 [Syn], or long-chain inulin) were varied in degrees of polymerization. Over the period of 3 wk, the plasma GLP-1 concentration was higher in short-chain fructans (present in fructooligosaccharides [FOS], and to a lesser amount in Syn) fed rats. So administration of short-chain inulin-type fructans, which are most fermented in the proximal colon and cecum, is clearly responsible for inducing this effect [24]. In another study

performed on normal rats, it was observed that the FOS-enriched (10%) standard diet, compared with standard diet for 35 d followed by 15 d of high-fat diet or high-fat FOS diet, reduced energy intake, weight gain, and fat mass development through the mechanism of increase in GLP-1 (7–36) amide concentration. This diet, interestingly, lowered DPP-4 activity by 30% [25]. In high-fat-fed diabetic mice, FOS in the presence or absence of EX-9 (GLP-1 receptor antagonist exendin 9–39) was administered for 4 wk. Intriguingly, in GLP-1 receptor knockout mice, FOS has no beneficial effects on body weight gain, food intake, and glucose homeostasis [2]. This suggests that cecal proliferation induced by FOS reduces the effect of a high-fat diet on the incidence of diabetes and obesity within GLP-1R-dependent manner [2,26]. This might imply the role of gut hormones in the anti-lipogenic effect of FOS [26]. Finally, a recent review examined the effects of dietary intake of inulin and oligofructose on incretins production and suggested that oligofructose in the diet of rats increases GLP-1 concentration, through the mechanism requiring SCFAs, which are produced by oligofructose fermentation in intestinal tissue [27]. In contrast with this data, Parnell et al. [28] did not observe any increase in GLP-1 secretion in overweight or obese humans; also in those who received 21 g/d of oligofructose or a placebo (maltodextrin) for 12 wk. The authors suggested that the discrepancy between their results for GLP-1 in humans and those of rodent study could be due to the lower (5% of total intake) dose of oligofructose.

A randomized, double-blind trial performed in 10 healthy adults reported that 16 g/d of prebiotic for 2 wk compared with 16 g/d dextrin maltose could increase the gut peptides concentration (GLP-1 and PYY), indicating that prebiotics could be a useful tool for nutrition therapy of diabetes due to their beneficial effects on food intake and glucose homeostasis [21]. Adam et al. [29] conducted a randomized crossover study and reported a 57% increase in plasma GLP-1 concentration due to addition of 50 g galactose and 2.5 g guar gum to standard breakfast in normal-weight individuals. In one study, hyperinsulinemic individuals were studied to determine the time course of effect of increased wheat fiber intake by 20 g/d on SCFA and GLP-1 concentrations. It is of interest that plasma butyrate and GLP-1 levels increased after 9 and 12 mo, respectively. The author concluded that the proliferative effect of SCFA on the intestinal lumen or a direct effect of wheat fiber on gut L cells are responsible for a gradual rise in plasma GLP-1 concentration, providing an intestinal mechanism for the epidemiologic association between high cereal fiber intake and its antidiabetic benefits [13]. Dietary resistant starch (RS) has been reported to increase plasma total GLP-1 in rodents [16,30], but its exact mechanism of action is unclear. Zhou et al. [16] aimed to understand how dietary RS modulates GLP-1 and PYY secretion. They found that only fermentable fiber increases GLP-1 and PYY levels, because higher proglucagon and PYY mRNA expressions were detected in the cecum and colon where RS ferments. Thus, inclusion of fermentable resistant starch in the diet as a bioactive functional food component is a natural way to increase the gut hormone expression [30]. Furthermore, the available data support the idea that continuous addition of fermentable fiber is another important factor for micro flora adaption to a new food source, so prospective long human studies are needed for assessment of effectiveness of RS on GLP-1 secretion [16]. In another study with healthy young adults, foods enriched with soluble fiber (psyllium) and vegetable protein (soy) modified the postprandial GLP-1 release [31]. Yet, a recent study with 14 healthy individuals demonstrated that an isocaloric breakfast including one of three

Table 1
Effect of fiber on GLP-1 secretion response

Author (year)	Time frame	Number of subjects (m:f)	Study population	Treatment diet(s) (dose)	Results
Reimer (1997) [23]	14 d	16 (16:0)	Male Sprague-Dawley rats	Rhubarb fiber diet (50 g/kg) Cellulose (50 g/kg)	No difference in proglucagon mRNA in the colon. Upregulation of proglucagon mRNA in the ileal.
Cani (2004) [24]	3 wk	24 (24:0)	Male Wistar rats	Fructan-enriched diet varying in degree of polymerization FOS, Syn, or long-chain inulin (100 g/kg)	Significantly higher concentrations of GLP-1 (7–36) amide and proglucagon mRNA.
Cani (2005) [25]	50 d	12 (12:0)	Male Wistar rats	Standard diet FOS-enriched (10%) standard diet followed by high-fat diet FOS-enriched (10%) standard diet followed by high-fat FOS (10%) diet	Doubled GLP-1 contents in the proximal colon in FOS diet. Increase in proglucagon mRNA in the cecum and the colon in FOS diet.
Cani (2006) [2]	4 wk	(N/D)	Diabetic mice or (GLP-1R)—mice	Standard diet High-fat diet FOS-enriched high-fat diet	3) Lower DPP-4 activity by 30% in high-fat FOS diet. Antidiabetic actions of FOS by the GLP-1R-dependent manner.
Parnell (2009) [28]	12 wk	39 (7:32)	Overweight or obese	Oligofructos (21 g/d) Maltodextrin	FOS supplementation did not affect plasma-active GLP-1 concentration.
Cani (2009) [21]	2 wk	10 (5:5)	Healthy adults	Prebiotic (16 g) 2) dextrin maltose (16 g)	Plasma GLP-1 concentrations were increased significantly in the prebiotic group compared with the dextrin maltose group.
Adam (2005) [29]	120 min in 2 d	30 (15:15)	Healthy subjects	Galactose (50 g) and guar gum (2.5 g) + standard breakfast Standard breakfast	Plasma GLP-1 was increased significantly due to addition of galactose/guar gum to standard diet.
Freeland (2010) [13]	12 mo	28 (6:22)	Hyperinsulinemic healthy human	High-fiber cereal (60 g) Control cereal (49 g)	Plasma GLP-1 was increased significantly in the high-fiber cereal group compared with control group.
Zhou (2008) [16]	23 d	30 (0:30)	Sprague-Dawley rats	Standard diet RS Fiber control	Total GLP-1 was increased in RS-fed rats.
Keenan (2006) [30]	24 d	10 (0:10)	Sprague-Dawley rats	RS Methylcellulose Control	Plasma GLP-1 level was increased in RS-fed rats.
Karhunen (2010) [31]	120 min	16 (3:13)	Healthy young adults	Low-protein (2.8 g), low-fiber diet (7.6 g) Low-protein (2.6 g) high-soluble fiber diet (psyllium, 23 g) High-protein (soy, 19.7 g), low-fiber diet (6.2 g) High-protein (18.4 g), high-fiber diet (23 g)	Modifying effect of soy protein in combination with psyllium on GLP-1 secretion.
Lumaga (2012) [32]	On separated days	14 (8:6)	Healthy humans	White wheat bread β -glucan beverage Fruit-based beverage Control beverage	Plasma GLP-1 concentration was not influenced by the type of beverage.

DPP-4, dipeptidyl peptidase-4; FOS, fructooligosaccharides; GLP-1, glucagon-like peptide; GLP-1R, glucagon-like peptide receptor; RS, resistant starch; Syn, synergy 1

beverages (3 g barley β -glucan, or 2.5 g dietary fiber from fruit, or without dietary fiber [control]) did not influence GLP-1 concentration 3 h after beverage consumption [32].

Collectively, evidence supports the concept that prebiotics and high-fiber diets have potential beneficial effects on obesity and diabetes. One strong link between gut microbial and systemic activity is SCFAs, which are produced by bacterial fermentation of non-digestible carbohydrates. These substances not only act as a local nutrient supply but also account for release of anorectic and insulinotropic hormone, GLP-1 [22]; thus providing support for a link between the gut flora metabolism and key factors associated with insulin resistance [33].

Protein and GLP-1 secretion

Studies using protein and glutamine are summarized in Table 2.

There is some evidence that protein could stimulate GLP-1 release even more than carbohydrates [34,35]. In 12 healthy, normal women given either an adequate protein or a high-protein diet for two 36-h sessions, it was shown that GLP-1 concentration was increased with both diets after lunch and dinner, but only in high-protein diet was satiety related to protein intake and accompanied by an increased level of GLP-1 [36]. Yet, a study with 16 lean and overweight/obese men showed that oral supplementation with L-carnitine L-tartrate (3 g/d) for 2 wk did not affect total GLP-1 response to glucose intake [37]. Chen et al. [38] also suggested that branch chain amino acids (BCAAs), leucine and isoleucine, and the dairy proteins casein and skim milk, increase the secretion of GLP-1 in human intestinal NCI-H716 cell culture. The result demonstrated that skim milk and casein, but not whey, potently stimulated GLP-1 secretion by 1.6-fold and 2.5-fold, respectively and also that 2% leucine and isoleucine induced an increase in GLP-1 release by 4.7-fold and 2.6-fold, respectively. Due to the high proportion of BCAAs (21%) found in dairy, the results probably reflect the effect of BCAAs on GLP-1 release. Additionally, in the NCI-H716 cell line, Reimer showed that meat hydrolysate and essential amino acids are potent stimulators of GLP-1 [39]. Another research used pigs to evaluate the effect of additional dairy protein, α -casein or β -casein, to waxy maize starch on glucose homeostasis as well as on GLP-1 release. No significant differences in postprandial concentration of plasma GLP-1 were noticed [40].

In conclusion, these findings suggest that protein and amino acids are not all similarly effective in GLP-1 release. Therefore, the amino acid proportion of protein is important in stimulation of the secretion.

Glutamine

Glutamine as a nutritional supplement has been added to enteral and parenteral mixtures for gut integrity. Glutamine also is administered orally at high doses to protect the intestine from the toxic effects of chemotherapy and radiotherapy [41]. It has been demonstrated that L cells, like other gut cells, are sensitive to changes in glutamine content of meals. Glutamine can be used as nutritional therapy to enhance the endogenous GLP-1 secretion in diabetic and obese individuals. One study investigated the mechanism underlying the effect of glutamine on GLP-1 release by using the cell line GLUTag, which was treated with either 10 mmol/L glucose or a wide range of amino acids. It was observed that glutamine triggers membrane depolarization and raises the intracellular calcium by releasing the calcium stores.

Table 2
Effect of protein and glutamine on GLP-1 secretion response

Author (year)	Time frame	Number of subjects (m:f)	Study population	Treatment diet(s) (dose)	Results
Lejeune (2006) [36]	5 d	12 (0:12)	Healthy women	High-protein diet An adequate protein diet	Plasma GLP-1 was increased with both diets after lunch and dinner.
Galloway (2011) [37]	14 d	16 (16:0)	Lean and overweight/obese	L-carnitine L-tartrate (3 g) Glucose (3 g)	No effect on plasma GLP-1 concentration.
Kett (2012) [40]	1 d	8	Pigs	Starch (10%) - α -casein (10%) Starch (10%) - β -casein (10%) Starch (10%)	No significant difference in plasma GLP-1.
Greenfield (2009) [41]	3 separate days	24 (21:3)	Lean subjects and obese nondiabetic subjects and obese subjects with type 2 diabetes or impaired glucose tolerance	30 g glutamine Water	Glutamine significantly increased GLP-1 secretion.
Breitman (2011) [43]	8 wk	30 (1:29)	Patients undergoing laparoscopic gastric bypass (LGB)	Glucose (75 g) A supplement containing a leucine metabolite, glutamine, and arginine (24 g) Without receiving any supplement	No significant difference was observed in GLP-1 levels.
Samocha-Bonet (2011) [15]	180 min	15 (9:6)	Type 2 diabetes patients	30 g glutamine 15 g glutamine plus sitagliptin 15 g glutamine Water Sitagliptin	GLP-1 concentration was significantly increased when 30 g glutamine or 15 g glutamine plus sitagliptin was ingested.

GLP-1, glucagon-like peptide

Surprisingly, this amino acid enhances GLP-1 secretion about sevenfold, potentially more stimulant than glucose or other amino acids at 10 mmol/L. It is suggested that physiological changes in glutamine might have a profound effect in diabetes and obesity [42]. This finding raises the possibility that induction of GLP-1 release from L cells might contribute to its known physiological effects in vivo. A recent study recruited 24 individuals and divided them into three groups of healthy, lean, and obese with type 2 diabetes or impaired glucose tolerance. After blood sample collection, all participants ingested glucose (75 g), glutamine (30 g), and water (300 mL), to investigate whether glutamine increases circulating GLP-1, gastric inhibitory polypeptide (GIP), glucagon, and insulin levels in humans. It was observed that glutamine raises insulin secretion in parallel with GLP-1 in all three groups [41]. In a randomized crossover study conducted in 15 patients with type 2 diabetes, emphasis was placed on whether oral glutamine attenuates postprandial glycemia. The trial demonstrated that 30 g of glutamine or 15 g of glutamine plus sitagliptin reduced postprandial glycemia and increased postprandial GLP-1 responses. Because reduction in glycemia preceded the increase in insulinemia and there was no corresponding increase in C-peptide with insulin response, the authors suggested that glutamine-induced increase in GLP-1 reduces glycemia by prolonging the gastric emptying (a major determinant of glycemia after a meal) but not by increasing the insulin secretion [15]. In randomized controlled trial, 30 patients undergoing laparoscopic gastric bypass were evaluated for the effect of 24 g dietary supplement containing leucine metabolite, glutamine, and arginine twice daily on metabolic and hormonal changes at 2 and 8 wk after surgery. No significant differences were observed in GLP-1 or GIP mean levels after 8 wk and also between the control and interventional groups. This may be due to the fasting state of the patients and consequently do not reflect the secretion of incretin-related nutrient intake [43].

Collectively, this data provide evidences that even single amino acid supplementation such as glutamine could represent a novel therapeutic strategy for management of type 2 diabetes and obesity [15,41]. The longer-term effects of glutamine supplementation require further research.

MUFA, PUFA, and GLP-1 secretion

Studies using MUFA and PUFA are summarized in Table 3.

Monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and saturated fatty acids have been implicated in the production of GLP-1 in a number of animal and human studies, but delayed increases were seen compared with carbohydrates, especially with saturated fatty acids [44,45]. Free fatty acids are known to act as natural signaling molecules and also natural ligands for G-protein coupled receptors (GPCRs) such as the GPR40 family [46]. For the first time in male Wistar rats, Tanaka et al. cloned and characterized GPR120, then examined the in vivo effects of acute and long-term oral administration of α -linolenic acid (α -LA) a natural ligand for GPR120, which is plentifully expressed in gut. In this study, GLP-1 levels were enhanced by acute administration of α -LA and also an increase in insulin secretion and regeneration of islet β cells after long-term treatment by α -LA was observed. Although the exact mechanism was unknown, the authors hypothesized that enhancement of the GPR120-mediated GLP-1 secretion induced by α -LA led to this result [47]. It is demonstrated that 5-hydroxy-eicosapentaenoic acid (5-HEPE), one of the metabolites of an ω -3 unsaturated fatty acid, is a potent endogenous agonist for GPR119 that has been reported to induce insulin and GLP-1 secretion. These

Table 3
Effect of MUFA and PUFA on GLP-1 secretion response

Author (year)	Time frame	Number of subjects (m:f)	Study population	Treatment diet(s) (dose)	Results
Tanaka (2008) [47]	8 wk	24 (24:0)	Male Wistar rats	α -linolenic acid (3 μ mol/100 μ L) Octanoic acid (3 μ mol/100 μ L) Vehicle (100 μ L)	GLP-1 level was increased during oral administration of α -linolenic acid.
Brynes (2000) [18]	24 d	9 (5:4)	Overweight people with type 2 diabetes	Diet high in MUFAs (20.3 \pm 3.5% of total energy) Diet high in PUFAs (13.4 \pm 1.3% of total energy)	Neither MUFAs nor PUFAs had an effect on GLP-1 secretion.
Beysens (2002) [44]	On separated days	8 (4:4)	Healthy volunteers	MUFA test: olive oil high in oleic acid (69%, w/w) PUFA test: refined safflower oil high in linoleic acid (74%, w/w) SFA test: palm stearin high in palmitic acid (59%, w/w) Control	GLP-1 secretion was increased during fat feeding, with a higher response to the MUFA test compared with the PUFA and SFA tests.
Paniagua (2007) [8]	28 d	11 (4:7)	Offspring of obese and type 2 diabetes	Rich in saturated fat diet Rich in monounsaturated diet Rich in CHO diet	Ingestion of a virgin olive oil-based breakfast increased GLP-1 concentrations compared with CHO-rich diet.
Cohen (2011) [49]	12 wk	19 (N/D)	Healthy adults without type 2 diabetes and adults with type 2 diabetes	Diet rich in MUFA from almonds (one serving 5 g/wk) A meal without almonds	Postprandial GLP-1 response at 30 min was not affected by almond ingestion.

CHO, carbohydrate; GLP-1, glucagon-like peptide; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid

observations indicated the possibility that ω -3 unsaturated fatty acids, 5-HEPE, and its precursor eicosapentaenoic acid, may exhibit antidiabetic effects [48].

For the first time, in nine overweight subjects with type 2 diabetes, a high MUFA diet for more than 3 wk intervention was compared with a high-PUFA diet. It was found that neither MUFAs nor PUFAs had an effect on the postprandial stimulation of GLP-1, indicating that a diet rich in MUFAs is not a good alternative to PUFAs in terms of increasing insulin sensitivity in patients with type 2 diabetes [18]. However, the fatty-acid composition of a meal and the plasma pool affects the insulin secretion. Both plasma non-esterified fatty acid (NEFA) and GLP-1 could have direct effects on the β cells, or NEFA has an indirect effect via plasma GLP-1 receptor on the β cells, with the greatest effect for MUFA compared with PUFA and saturated fatty acids [44]. Paniagua et al. [8] reported that in 11 obese patients with type 2 diabetes, following the ingestion of a virgin olive oil-based breakfast, the GLP-1 response was significantly enhanced and postprandial glucose and insulin concentrations was lowered compared with those who were fed a carbohydrate-rich meal. In a well-controlled, 12 wk cross-over trial, Cohen et al. [49] were unable to show an effect of diet rich in MUFAs from almonds (one serving 5 d/wk at meal time) on GLP-1 concentrations in 19 individuals with type 2 diabetes mellitus and healthy individuals; however, almond consumption significantly reduced postprandial glycemia in diabetic individuals not in healthy individuals.

In conclusion, not all studies have reported the potential capability of MUFA and PUFA in control of postprandial glycemia. Further research on the role of MUFA and PUFA in GLP-1 secretion is warranted, considering the described mechanisms.

Non-nutritive sweeteners and GLP-1 secretion

Studies using non-nutritive sweeteners are summarized in Table 4.

Non-nutritive sweeteners (acesulfame K, sucralose, neotame, saccharin, and aspartame) are new chemosensory signaling compounds that affect the ingestion process and could maintain diet palatability by delivering a sweet taste without adding calories or any glycemic effect [50,51]. Jang et al. [52] observed that stimulation of NCI-H716 enteroendocrine L cells with high-potency sweetener sucralose induced GLP-1 secretion in a concentration-dependent manner. Similar results were also reported when the effect of sucralose on enteroendocrine L cells in mice (STC-1 and GLUTag) were analyzed [53]. Likewise, in STC-1 cells, exposure to sucralose increased GLP-1 levels, whereas the same result was not observed in human duodenal biopsies [54]. One study showed that soda sweetened with sucralose and acesulfame K (called diet soda) significantly increased GLP-1 release in healthy humans compared with carbonated water. Furthermore, this effect was observed with a small amount of artificial sweetener [55]. In disagreement with these findings, ingestion of aspartame or its constituent amino acids decreased GLP-1 secretion in human subjects [56]. Surprisingly, very recent findings from rat models showed diminished results in GLP-1 release during the oral glucose test in a saccharin-exposed group. This reduction was seen in two experimental groups; the first group was supplied with a bottle containing 30 g of either a 10% glucose-sweetened or a 0.3% saccharin-sweetened liquid in a high-fat, high-sugar diet. The other group received 30 g of plain or sweetened yogurt in the same diet [57].

Collectively, there is contradictory evidence about whether non-nutritive sweeteners are able to stimulate GLP-1 secretion.

Table 4
Effect of nonnutritive sweeteners on GLP-1 secretion response

Author (year)	Time frame	Number of subjects (m:f)	Study population	Treatment diet(s) (dose)	Results
Brown (2009) [55]	180 min	22 (N/D)	Healthy participants	Diet soda (240 mL) Carbonated water (240 mL)	Plasma GLP-1 was increased with artificial sweeteners in combination with glucose.
Hall (2003) [56]	120 min	6 (2:4)	Healthy young adults	Aspartame (400 mg) Aspartic acid (176 mg) + phenylalanine (224 mg) Control (400 mg)	Plasma GLP-1 concentrations were decreased when aspartame or aspartic acid ingested.
Swithers (2012) [57]	Group (1): 24 d Group (2): 4 wk	Group (1): 30 (30:0) Group (2): 72 (72:0)	Sprague-Dawley rats	Group (1): High-fat diet + glucose-sweetened bottle (30 g) High-fat diet + saccharin-sweetened bottle (30 g) Group (2): High-fat diet + plain yogurt (30 g) High-fat diet + saccharin-sweetened yogurt (30 g)	Plasma GLP-1 was diminished with both saccharin-sweetened diets in two groups.

GLP-1, glucagon-like peptide

Future artificial sweeteners dose–response studies evaluating GLP-1 secretion are warranted.

Conclusion

The concept of stimulation of GLP-1 secretion by nutrients seems an attractive alternative to minimize postprandial glucose excursions. Regarding this strategy, a better understanding of the factors regulating GLP-1 release including food components is needed in order to modify the diet in a way that obesity as well as diabetes could be better managed. The combined effects of specific dietary compounds on GLP-1 secretion are still poorly understood. Thus, further research is needed to assess the nutrient effects on GLP-1 response.

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