Effects of Diet Soda on Gut Hormones in Youths With Diabetes

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OBJECTIVE—In patients with type 2 diabetes, but not type 1 diabetes, abnormal secretion of incretins in response to oral nutrients has been described. In healthy youths, we recently reported accentuated glucagon-like peptide 1 (GLP-1) secretion in response to a diet soda sweetened with sucralose and acesulfame-K. In this study, we examined the effect of diet soda on gut hormones in youths with diabetes.

RESEARCH DESIGN AND METHODS—Subjects aged 12–25 years with type 1 diabetes (n = 9) or type 2 diabetes (n = 10), or healthy control participants (n = 25) drank 240 mL cola-flavored caffeine-free diet soda or carbonated water, followed by a 75-g glucose load, in a randomized, cross-over design. Glucose, C-peptide, GLP-1, glucose-dependent insulinotropic peptide (GIP), and peptide Tyr-Tyr (PYY) were measured for 180 min. Glucose and GLP-1 have previously been reported for the healthy control subjects.

RESULTS—GLP-1 area under the curve (AUC) was 43% higher after ingestion of diet soda versus carbonated water in individuals with type 1 diabetes (P = 0.020), similar to control subjects (34% higher, P = 0.029), but was unaffected by diet soda in patients with type 2 diabetes (P = 0.92). Glucose, C-peptide, GIP, and PYY AUC were not statistically different between the two conditions in any group.

CONCLUSIONS—Ingestion of diet soda before a glucose load augmented GLP-1 secretion in type 1 diabetic and control subjects but not type 2 diabetic subjects. GIP and PYY secretion were not affected by diet soda. The clinical significance of this increased GLP-1 secretion, and its absence in youths with type 2 diabetes, needs to be determined.

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Nonnutritive sweeteners are commonly consumed by both children and adults and have previously been thought to be metabolically inert. However, recent animal data demonstrate that nonnutritive sweeteners, including sucralose (Splenda) and acesulfame-K, play an active metabolic role within the gastrointestinal tract via sweet taste receptors identical to those found in lingual taste buds (1,2). In both humans and animals, these receptors are present in L cells of the gut mucosa secreting glucagon-like peptide 1 (GLP-1) and peptide Tyr-Tyr (PYY) (3–5). Components of the taste-signaling pathway have also been found in glucose-dependent insulinotropic peptide (GIP)-secreting K cells in the gut mucosa (5).

GLP-1 and GIP are incretin hormones that increase glucose-dependent insulin secretion in response to oral nutrients. In healthy individuals, GIP appears to be responsible for the majority of the incretin effect (6,7). GLP-1 and its analogs have numerous physiologic effects, including delayed gastric emptying (8,9), increased satiety (10), and suppression of glucagon secretion (11), in addition to increased insulin secretion (12). Patients with type 2 diabetes frequently have normal GIP but impaired GLP-1 secretion (13) and are resistant to exogenous GIP but respond normally to exogenous GLP-1 (7). This has been exploited pharmacologically using GLP-1 analogs, which cause improved glycemia and weight loss. Both GLP-1 and GIP secretion are normal in type 1 diabetes (14). PYY acts as an anorectic hormone in both lean (15) and obese humans (16), although its secretion is attenuated in obesity (17).

Sucralose has been shown to increase release of both GLP-1 and GIP in vitro in enteroendocrine cell lines (4,5). In vivo, however, the nonnutritive sweeteners sucralose (in humans and animals) and acesulfame, stevia, and D-tryptophan (in animals) do not stimulate GLP-1, GIP, or PYY secretion in the absence of caloric sugars (18,19). We recently demonstrated in a pilot study that diet soda (Diet Rite Cola, sweetened with sucralose and acesulfame-K) in the presence of glucose augmented glucose-stimulated GLP-1 secretion in healthy subjects (20). It is not known whether GIP or PYY secretion are likewise augmented by ingestion of nonnutritive sweeteners in addition to glucose or whether diet soda augments GLP-1 secretion in disease states such as type 1 or type 2 diabetes.

In this study, we investigated whether subjects with diabetes (both type 1 and type 2) would demonstrate increased GLP-1 secretion after ingestion of diet soda in addition to a glucose load, similar to the effect previously observed in healthy subjects (20). In addition, we examined whether secretion of the gut hormones GIP and PYY is increased by ingestion of diet soda.

RESEARCH DESIGN AND METHODS

Experimental design

In total, 25 healthy subjects, 10 subjects with type 2 diabetes, and 9 subjects with type 1 diabetes (aged 12–25 years) were enrolled. Diabetes classification was determined by the referring physician. Subjects with type 2 diabetes were all overweight or obese (BMI >85th centile for age, or >25 kg/m^2 after age 20 years) and lacked a classic family history suggestive of monogenic diabetes. Glucose, insulin, and GLP-1 results from 22 of the 25 healthy subjects in this study have been previously reported (20). Written informed consent was obtained from subjects or their guardians, and written assent was obtained from subjects <18 years of age. The study was approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases.

Each subject underwent two 75-g oral glucose tolerance tests (OGTTs) after a 10 h fast. At 10 min before the glucose load, subjects drank 240 mL diet soda (Diet

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Rite Cola, containing the nonnutritive sweeteners sucralose and acesulfame-K) or carbonated water (Zazz Seltzer, containing only carbonated water). Each subject underwent testing with both diet soda and carbonated water on separate days in a cross-over design. The order of testing was randomized in blocks of 10 subjects stratified by diagnosis. Blood samples were collected for hormone analysis at −10, −5, 0, 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, and 180 min relative to the glucose load and analyzed for glucose and C-peptide. Additional plasma samples obtained at −10, 0, 10, 20, 30, 60, 90, 120, 150, and 180 min were frozen at −70°C and later analyzed for GLP-1, GIP, and PYY. Subjects also underwent measurement of height, weight, and A1C.

Total GLP-1 was measured using a radioimmunoassay (Millipore, Billerica, MA). The lowest detectable level of GLP-1 was 3 pmol/L using a 300-μL extracted sample (interassay coefficient of variation [CV] 23% and intra-assay CV 22%). Total GIP was measured using a sandwich ELISA (Millipore). The lowest detectable level of human GIP was 8.2 pg/mL when using a 20-μL sample volume (interassay CV 3% and intra-assay CV 6%). Total PYY was measured by a sandwich enzyme-linked immunosorbent assay based on the binding of human PYY (both 1–36 and 3–36) in plasma by rabbit anti-human PYY IgG (Millipore). The limit of detection was 10 pg/mL. Intra-assay CV was 2.3% and interassay CV was 7.4%. C-peptide was measured using a chemiluminescence immunoassay with a normal fasting range of 0.9–7.1 ng/mL. Serum glucose was determined with the glucose oxidase method (intra-assay CV 2.9% at 2.4 mmol/L and 0.4% at 22.1 mmol/L; interassay CV 3.9% at 2.4 mmol/L and 1.2% at 22.1 mmol/L). Analyses of acesulfame-K and sucralose concentrations in the diet soda were measured in duplicate using high-performance liquid chromatography with ultraviolet detection and liquid chromatography–mass spectrometry, respectively.

Statistical considerations

Baseline characteristics of subjects (age, sex, race, A1C, and BMI) in the three groups were compared using one-way ANOVA or χ^2 tests, as appropriate. Area under the curve (AUC) for serial measurements during the OGTTs was calculated using the trapezoidal method. Within each group (healthy, type 1 diabetic, and type 2 diabetic), glucose, C-peptide, GLP-1, and GIP AUC in the diet soda versus the carbonated water condition were compared using the paired *t* test or Wilcoxon signed rank test, as appropriate.

Mixed models were used to assess differences related to both diagnosis and the test condition (diet soda vs. carbonated water) while adjusting for covariates. As a result of small sample size, potential covariates were individually tested in mixed models, including main effects of the covariate, diagnosis, test condition, and diagnosis by test condition interaction. Additional interactions were not studied because of low statistical power. Potential covariates included age, BMI, fasting GLP-1, three measures of blood glucose (fasting glucose, glucose AUC, and A1C), and test order (to assess potential carryover or period effects due to the cross-over design). Significant covariates ($P \leq 0.05$) were then combined into a single model, and backward variable selection was performed to serially remove nonsignificant predictors ($P \geq 0.05$).

$P < 0.05$ was considered statistically significant. Because this was an exploratory study, adjustment for multiple comparisons was not performed. Figures show means ± SEM, while data in tables and text are means ± SD except as noted.

RESULTS—Baseline characteristics of subjects are shown in Table 1. Statistically significant differences between groups were present for BMI (higher in type 2 diabetic subjects compared with type 1 diabetic or healthy subjects) and A1C (lower in healthy compared with type 1 or type 2 diabetic subjects).

Analysis of the diet soda showed acesulfame-K was present at a concentration of 108 ± 0.6 μg/mL, and sucralose was present at a concentration of 190 ± 38 μg/mL. No caloric sweeteners (e.g., sucrose, glucose, or fructose) were detected.

Glucose and C-peptide

Glucose and C-peptide during the OGTTs are shown in Table 2 and Fig. 1*A–F*. Although glucose was slightly higher in the diet soda condition for both type 1 and type 2 diabetic groups, there were no statistically significant differences between the diet soda versus carbonated water condition for glucose or C-peptide AUC in any group.

GLP-1

GLP-1 during the OGTTs is shown in Table 2 and Fig. 1*G–I*. Unadjusted GLP-1 AUC was 34% higher in the diet soda condition versus the carbonated water condition in healthy subjects ($P = 0.029$) and 43% higher in subjects with type 1 diabetes ($P = 0.020$). There was no statistically significant difference in GLP-1 AUC between the two conditions for subjects with type 2 diabetes ($P = 0.92$).

Positive predictors of GLP-1 AUC identified in the initial models were age, BMI, and fasting GLP-1. Test order was not a significant predictor ($P = 0.23$), implying

Table 1—*Baseline characteristics of subjects*

	Subject			
	Healthy control (*n* = 25)	Type 1 diabetic (*n* = 9)	Type 2 diabetic (*n* = 10)	*P* value
Age (years)	18.8 ± 4.4 (12.2–25.7)	18.2 ± 3.4 (13.5–24.3)	17.9 ± 3.3 (13.6–23.8)	0.80
BMI (kg/m^2)	25.7 ± 4.6 (19.1–35.9)	21.7 ± 2.4 (18.2–24.6)	35.0 ± 6.8 (26.4–45.4)	<0.0001[a]
A1C (%)	5.1 ± 0.4 (4.3–6.1)	8.2 ± 1.8 (5.5–11.9)	7.4 ± 1.8 (5.8–11.7)	<0.0001[b]
Sex (% male)	52	33	10	0.07
Race (%)				0.56
White	40	67	30	
Black	28	11	30	
Other	32	22	40	

Continuous variables are shown as mean ± SD (range). [a]Type 2 diabetic subjects greater than both type 1 diabetic and healthy subjects. [b]Healthy subjects less than both type 1 and type 2 diabetic subjects.

that there was no significant carryover effect due to the cross-over design. Age was eliminated as a predictor using backward variable selection. The final mixed model (Table 3) showed that diet soda altered GLP-1 secretion differently in healthy, type 1 diabetic, and type 2 diabetic subjects (Test × Diagnosis interaction, $P = 0.015$). Post hoc comparisons among the three diagnostic groups showed that the effect of diet soda on GLP-1 secretion in subjects with type 1 diabetes was significantly different from subjects with type 2 diabetes ($P = 0.004$) and borderline different from healthy control subjects ($P = 0.059$). The difference between subjects with type 2 diabetes and healthy control subjects was not significant ($P = 0.09$).

GIP

GIP during the OGTTs is shown in Table 2 and Fig. 1*J–L*. There was no statistical difference between the diet soda versus carbonated water condition for unadjusted GIP AUC in healthy subjects ($P = 0.84$), subjects with type 1 diabetes ($P = 0.21$), or subjects with type 2 diabetes ($P = 0.92$).

PYY

PYY during the OGTTs is shown in Table 2 and Fig. 1*M–O*. There was no statistical difference between the diet soda versus carbonated water condition for unadjusted PYY AUC in healthy subjects ($P = 0.95$), subjects with type 1 diabetes ($P = 0.57$), or subjects with type 2 diabetes ($P = 0.75$).

CONCLUSIONS—In this study, we examined the effects of diet soda on gut hormone secretion in three cohorts—type 1 diabetic, type 2 diabetic, and healthy control—using a cross-over design with regard to administration of diet soda. Examining each population separately, we found that diet soda increased GLP-1 secretion by 34% in healthy subjects, by 43% in subjects with type 1 diabetes, and not at all in those with type 2 diabetes, while GIP and PYY secretion were not altered in any group. Mixed model analyses, adjusting for both fasting hormone levels and A1C, confirmed that diet soda affected GLP-1 secretion differently in type 2 diabetic subjects compared with type 1 diabetic or healthy control subjects.

We hypothesize that the nonnutritive sweeteners contained in diet soda caused increased GLP-1 secretion by binding to sweet taste receptors located on enteroendocrine L cells in the gastrointestinal tract, initiating a signal transduction cascade that ultimately results in GLP-1 release. Human

Table 2—*OGTT results*

	Subject											
	Healthy control ($n = 25$)				Type 1 diabetic ($n = 9$)				Type 2 diabetic ($n = 10$)			
	Diet soda	Water	Δ	*P* value	Diet soda	Water	Δ	*P* value	Diet soda	Water	Δ	*P* value
Glucose AUC (mg/dL · 180 min)	19,875 ± 2,733	20,109 ± 2,756	−234 ± 1,911	0.55	66,636 ± 17,778	56,956 ± 8,017	9,679 ± 16,844	0.12	45,766 ± 14,967	42,537 ± 12,503	4,153 ± 8,978	0.28
C-peptide AUC (ng/mL · 180 min)	1,203 ± 420	1,238 ± 479	35 ± 239	0.47	14.25 ± 37.7	15.56 ± 50.6	1.3 ± 3.0	0.50	1,466 ± 619.6	1,524 ± 435.2	60 ± 280	0.55
GLP-1 AUC (pmol/L · 180 min)	1,390 ± 885	1,039 ± 564	351 ± 740	0.03	3,157 ± 1,752	2,205 ± 1,036	952 ± 989	0.02	2,240 ± 1,881	2,201 ± 1,270	38 ± 1,210	0.92
GIP AUC (pg/mL · 180 min)	21,626 ± 8,067	21,917 ± 9,522	−291 ± 7,129	0.84	37,953 ± 13,492	34,324 ± 11,766	3,628 ± 7,950	0.21	34,554 ± 13,837	34,347 ± 14,091	207 ± 6,643	0.92
PYY AUC (pg/mL · 180 min)	16,818 ± 7,257	16,750 ± 8,698	68 ± 5,445	0.95	20,284 ± 11,249	21,521 ± 9,445	−1,238 ± 6,188	0.57	16,428 ± 7,558	15,834 ± 6,772	593 ± 6,075	0.75

Glucose, C-peptide, GLP-1, and GIP AUC during OGTTs preceded by either 240 mL noncaffeinated diet soda sweetened with sucralose and acesulfame-K or 240 mL carbonated water. Data are unadjusted means ± SD. *P* values are from paired *t* tests or Wilcoxon signed rank tests, comparing the diet soda with the carbonated water condition within each group.

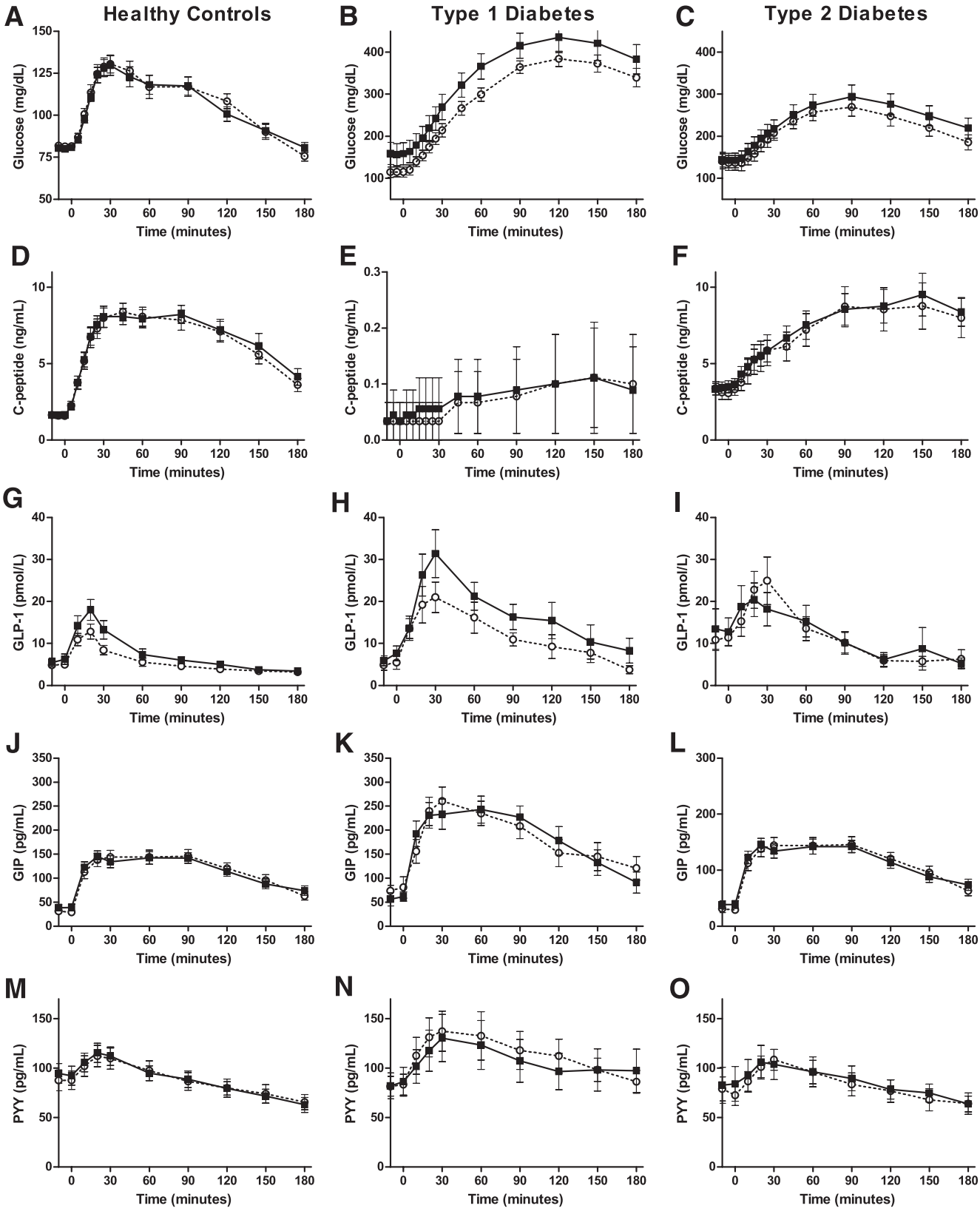

Figure 1—*Serial data from OGTTs. Serial glucose and hormone levels after ingestion of either 8 oz diet soda (■ with solid line) or carbonated water (○ with dotted line) at time −10 min, followed by 75-g glucose at time −0 min. Glucose AUC was not statistically different in the diet soda vs. carbonated water condition in healthy control* (A)*, type 1 diabetic* (B)*, or type 2 diabetic* (C) *subjects. There was no difference in C-peptide AUC for diet soda vs. carbonated water in any group* (D–F)*. GLP-1 AUC was higher after diet soda in healthy control* (G) *and type 1 diabetic* (H) *subjects but not in type 2 diabetic subjects* (I)*. Neither GIP* (J–L) *nor PYY* (M–O) *AUC were statistically different between the diet soda and carbonated water condition in any group.*

Table 3—*Mixed model of GLP-1 AUC*

Model parameter	*P*	β
Intercept	0.94	719
BMI	0.028	43.2
Fasting GLP-1	<0.0001	110.6
Test (reference = water)	0.024	969
Diagnosis (reference = type 1 diabetes)	<0.0001	
Healthy		−1,323
Type 2 diabetes		−1,231
Test × Diagnosis (reference = water, type 1 diabetes)	0.015	
Diet soda, healthy		−666
Diet soda, type 2 diabetes		−1,216

sweet taste receptors, located on the lingual epithelium and the intestinal L cells, consist of a heterodimer of the G-protein–coupled receptors T1R2 and T1R3 (21), which is coupled to the G-protein gustducin. These receptors bind to a wide variety of sweet stimuli, including sugars, sweet amino acids and proteins, and nonnutritive sweeteners (21). Stimulation of these sweet taste receptors is important for glucose-stimulated secretion of GLP-1 in humans and can be inhibited using the sweet taste receptor antagonist lactisole (22). The observed increase in GLP-1 secretion from diet soda likely requires the presence of a caloric, metabolizable sugar as well because nonnutritive sweeteners alone do not appear to alter gut hormone secretion in vivo (18,19). Several groups have demonstrated the presence of additional glucose-sensing molecules in both lingual and enteroendocrine cells that express taste receptors, including components of ATP-sensitive K^+ channels (SUR1 and Kir 6.1), GLUTs, sodium-glucose linked transporter 1, and glucokinase (23,24). These glucose sensors may serve as a primary signal for GLP-1 secretion, with stimulation of sweet taste receptors (by caloric or nonnutritive sweeteners) serving as a secondary signal.

Conflicting data about GLP-1 secretion in type 2 diabetic patients exist, with reports of increased, decreased, or equivalent GLP-1 secretion relative to healthy control subjects (13). The mechanisms accounting for altered GLP-1 regulation in type 2 diabetic patients have not been elucidated, but both poor glycemic control and long-standing disease are associated with impaired GLP-1 secretion (7). The elevated fasting GLP-1 with normal glucose-stimulated GLP-1 AUC (in the absence of diet soda) observed in our subjects with type 2 diabetes is thus consistent with their short duration of disease and good metabolic control. The reason for the absence of a GLP-1 response to diet soda in these subjects requires replication and further investigation. One potential explanation for the absent GLP-1 response to diet soda in subjects with type 2 diabetes comes from a study comparing the expression of taste-signaling molecules in the upper gastrointestinal tract of healthy subjects versus those with type 2 diabetes (25). Although overall expression did not differ between the two groups, among the subjects with diabetes, sweet taste receptor expression was inversely correlated with fasting blood glucose at the time of testing (i.e., higher blood glucose levels were associated with lower expression of sweet taste receptors). This suggests that blood glucose concentration may acutely regulate nutrient-sensing pathways in the gastrointestinal tract, with attendant results on downstream effects, such as GLP-1 secretion. Thus, in our subjects with type 2 diabetes, in whom glucose concentrations were much higher during OGTTs compared with healthy control subjects, intestinal taste-signaling pathways that respond to nonnutritive sweeteners may have been downregulated, accounting for the absence of a diet soda effect on GLP-1 secretion. The presence of a GLP-1 response to diet soda in subjects with type 1 diabetes, in whom blood glucose was even higher, makes this hypothesis much less compelling, but the regulation of taste-signaling pathways in type 1 diabetic subjects has not been studied and may differ from type 2 diabetic subjects. For example, if the effect of high blood glucose on taste receptor expression in type 2 diabetic patients was mediated via hyperinsulinemia, this effect would not be observed in type 1 diabetic patients, who have minimal endogenous insulin secretion.

Few studies examine the effects of nonnutritive sweeteners on gut hormones in humans, and to our knowledge, none have previously been performed in subjects with diabetes. Studies by Ma et al. (18,26) show that the sweetener sucralose, when given by intragastric or intraduodenal infusion, did not alter GLP-1 or GIP secretion in healthy subjects, in either the absence or the presence of glucose (18,26). In the Ma et al. (26) study in which sucralose was given in combination with glucose, 600 mg sucralose (infused during 150 min) and 30 g glucose (infused during 120 min) were administered, whereas in our study, subjects ingested 46 mg sucralose in combination with 26 mg acesulfame-K as an oral bolus, followed by a 75-g glucose load. Several explanations in addition to the differences in sucralose and glucose concentrations and infusion rates may account for the different findings. First, acesulfame-K, rather than sucralose, may have been responsible for the increased GLP-1 secretion observed in our study. Second, the rise in GLP-1 secretion observed after diet soda ingestion in our study may have been mediated through oral sweet taste receptors via the central nervous system, rather than intestinal sweet taste receptors. Finally, an ingredient in the diet soda other than nonnutritive sweeteners may have mediated the GLP-1 effect. In addition to sucralose and acesulfame-K, Diet Rite Cola contains caramel color, gum acacia, natural flavors, citric acid, potassium benzoate, phosphoric acid, and potassium citrate (http://www.dietrite.com/textonly/cola.aspx) and, thus, unflavored carbonated water may have been an imperfect control. While we are unaware of data supporting a direct effect of any of these compounds on GLP-1 secretion, it is possible that one or more of these ingredients might act alone or in synergy with nonnutritive sweeteners to enhance glucose-stimulated GLP-1 secretion.

GLP-1 is generally considered to be beneficial in the context of diabetes and obesity, via its effects on appetite, gastric emptying, insulin secretion, and glucagon suppression. In patients with type 2 diabetes, commercially available GLP-1 analogs are an effective treatment option because they lower both A1C and body weight (27). GLP-1 and its analogs have been less well studied in type 1 diabetic patients, but one study using high-dose exenatide in subjects with type 1 diabetes shows reduced body weight, lower insulin requirements, and reduced blood glucose variability without significant changes in C-peptide secretion or A1C (28). It is unknown whether changes in endogenous GLP-1 secretion as observed in the current study have any clinically relevant consequences, such as increased satiety and slowed gastric emptying. Future studies should include measures of these clinically relevant parameters, as well as assessment of oral versus gastric administration.

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R.J.B. designed the study, collected and analyzed data, and wrote the manuscript. M.W. analyzed data and critically reviewed the manuscript. K.I.R. designed the study and critically reviewed the manuscript. R.J.B. and K.I.R. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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