Ingestion of Diet Soda Before a Glucose Load Augments Glucagon-Like Peptide-1 Secretion

REBECCA J. BROWN, MD
MARY WALTER, PHD
KRISTINA I. ROTHER, MD, MHSC

OBJECTIVE — The goal of this study was to determine the effect of artificial sweeteners on glucose, insulin, and glucagon-like peptide (GLP)-1 in humans.

RESEARCH DESIGN AND METHODS — For this study, 22 healthy volunteers (mean age 18.5 ± 4.2 years) underwent two 75-g oral glucose tolerance tests with frequent measurements of glucose, insulin, and GLP-1 for 180 min. Subjects drank 240 ml of diet soda or carbonated water, in randomized order, 10 min prior to the glucose load.

RESULTS — Glucose excursions were similar after ingestion of carbonated water and diet soda. Serum insulin levels tended to be higher after diet soda, without statistical significance. GLP-1 peak and area under the curve (AUC) were significantly higher with diet soda (AUC 24.0 ± 15.2 pmol/l per 180 min) versus carbonated water (AUC 16.2 ± 9.0 pmol/l per 180 min; $P = 0.003$).

CONCLUSIONS — Artificial sweeteners synergize with glucose to enhance GLP-1 release in humans. This increase in GLP-1 secretion may be mediated via stimulation of sweet-taste receptors on L-cells by artificial sweetener.

Diabetes Care 32:2184–2186, 2009

Consumption of sodas containing artificial sweeteners is common practice in both children and adults. It is generally assumed that glucose metabolism is not altered because these sodas contain no or extremely few calories from carbohydrate. However, recent data obtained from animal studies demonstrate that artificial sweeteners play an active metabolic role within the gastrointestinal tract. Sweet-taste receptors, including the T1R family and α-gustducin, respond not only to caloric sugars such as sucrose but also to artificial sweeteners, including sucralose (Splenda) and acesulfame-K (1,2). In both humans and animals, these receptors have been shown to be present in glucagon-like peptide (GLP)-1–secreting L-cells of the gut mucosa as well as in lingual taste buds (3–5) and serve as critical mediators of GLP-1 secretion (5). In this study, we examined the effect of artificial sweeteners in a commercially available soft drink on glucose, insulin, and GLP-1 in humans.

RESEARCH DESIGN AND METHODS

— For this study, 22 healthy subjects 12–25 years of age (18.5 ± 4.2 years, 45% male, 41% Caucasian, 32% black, 27% other, BMI 25.6 ± 4.6 kg/m^2) participated in two 75-g oral glucose tolerance tests (OGTTs) on separate days after a 10-h fast. Subjects drank 240 ml of either caffeine-free diet soda (Diet Rite cola) sweetened with sucralose and acesulfame-K or unflavored carbonated water, in randomized order, 10 min prior to the glucose load. Each subject served as his or her own control. Glucose, insulin, and GLP-1 were measured for 180 min after the glucose load.

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 intraassay CV 22%). Insulin was measured using a chemiluminescence immunoassay with a normal fasting range of 42–188 pmol/l (interassay CV 11.5% at 69 pmol/l and 8.1% at 198 pmol/l; intraassay CV 6.2% at 56 pmol/l and 4.9% at 429 pmol/l). Serum glucose was determined using the glucose oxidase method (interassay CV 3.9% at 2.4 mmol/l and 1.2% at 22.1 mmol/l; intraassay CV 2.9% at 2.4 mmol/l and 0.4% at 22.1 mmol/l).

Area under the curve (AUC) was calculated using the trapezoidal method. Data from the diet soda versus carbonated water condition were compared using paired *t* tests or Wilcoxon rank-sum test, as appropriate. Data in the text are presented as means ± SD.

RESULTS

— Glucose, insulin, and GLP-1 concentrations during the OGTTs are shown in Fig. 1. Glucose excursions were nearly superimposable in both experimental settings (AUC with carbonated water 1,123 ± 152 mmol/l per 180 min vs. diet soda 1,112 ± 138 mmol/l per 180 min; $P = 0.64$). Although insulin responses tended to be more pronounced 20 and 25 min after glucose ingestion in the diet soda condition, these differences did not reach statistical significance (20′ $P = 0.20$; 25′ $P = 0.28$). Insulin AUCs were not statistically different (carbonated water 62,540 ± 7,646 pmol/l per 180 min vs. diet soda 62,164 ± 7,688 pmol/l per 180 min; $P = 0.75$). Peak insulin levels occurred 12.3 min earlier in the diet soda condition; however, again this difference was not statistically significant ($P = 0.12$).

The GLP-1 AUC was significantly higher with diet soda (24.0 ± 15.2 pmol/l per 180 min) than carbonated water (16.2 ± 9.0 pmol/l per 180 min; $P = 0.003$). In addition, the GLP-1 peak was significantly higher with diet soda versus carbonated water ($P = 0.003$), whereas the timing of the peak was not altered.

From the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.
Corresponding author: Rebecca J. Brown, brownrebecca@mail.nih.gov.
Received 29 June 2009 and accepted 17 September 2009. Published ahead of print at http://care.diabetesjournals.org on 6 October 2009. DOI: 10.2337/dc09-1185.

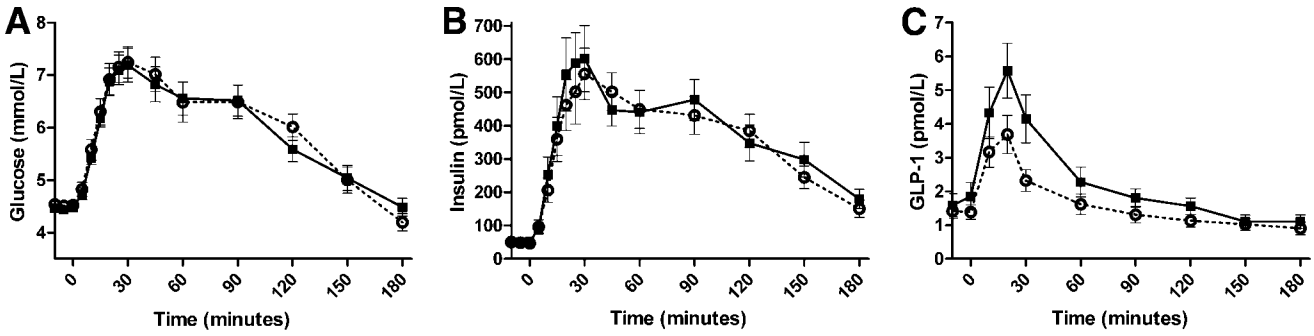

Figure 1—*Glucose* (A)*, insulin* (B)*, and GLP-1* (C) *levels during 75-g OGTTs in 22 healthy subjects. Carbonated water (○) or diet soda sweetened with sucralose and acesulfame-K (■) was given orally at time −10 min, and glucose was given at time 0 min. Data are means ± SEM.*

CONCLUSIONS — Unlike sucrose or glucose, artificial sweeteners in the absence of carbohydrate do not appear to stimulate GLP-1 secretion in humans (6) or animals (7). However, our data demonstrate that artificial sweeteners synergize with glucose to enhance GLP-1 release in healthy young volunteers. Furthermore, this effect was observed with small quantities of artificial sweetener found in 240 ml (two-thirds of a can) of a commercially available soda, suggesting that the effect may be relevant in everyday life.

Because artificial sweeteners were given by mouth in the form of diet soda, one might hypothesize that increases in insulin and GLP-1 were due to cephalic-phase insulin release. This is unlikely, because cephalic-phase insulin release typically occurs 2–10 min after taste exposure and does not occur with pure oral glucose or artificial sweeteners (8), and cephalic-phase GLP-1 response has not been observed in humans (9). Instead, we postulate that the enhancement of GLP-1 secretion observed here after diet soda ingestion was due to stimulation of gut taste receptors by artificial sweetener, synergizing with glucose-mediated stimulation of GLP-1 release.

The metabolic consequences of increased GLP-1 release after ingestion of both artificial sweeteners and glucose remain uncertain. In the present study, no significant differences were observed in either plasma glucose or insulin after diet soda versus carbonated water ingestion, despite the significant differences in GLP-1. In contrast, exogenous GLP-1 in healthy volunteers results in lower postprandial blood glucose and decreased insulin secretion, an effect due primarily to delayed gastric emptying rather than an incretin effect (10–12). However, the pharmacologic doses of GLP-1 used in these studies resulted in plasma levels 3- to 10-fold higher than those seen here after diet soda. In addition, artificial sweeteners likely play a role in glucose metabolism beyond changes in GLP-1. There is evidence in animals that activation of intestinal sweet-taste receptors by artificial sweeteners enhances intestinal glucose absorption via upregulation of GLUT2 (1). Thus, the kinetics of glucose and insulin observed in the present study may have been affected both by changes in GLP-1 and by altered intestinal glucose absorption.

In summary, artificial sweeteners in combination with glucose increase GLP-1 secretion, but the clinical significance of this observation remains to be determined. Additional studies are needed to isolate the effects of individual sweeteners in diet sodas and should include individuals with metabolic abnormalities such as type 2 diabetes, a condition typically associated with loss of the incretin effect. In light of the large number of individuals using artificial sweeteners on a daily basis, it appears essential to carefully investigate the associated effects on metabolism and weight.

Acknowledgments— This work was supported by the intramural research program of the National Institute of Diabetes and Digestive and Kidney Diseases.

No potential conflicts of interest relevant to this article were reported.

Parts of this study were presented at the 8th Joint Meeting of the Lawson Wilkins Pediatric Endocrine Society/European Society for Pediatric Endocrinology, New York, New York, 9–12 September 2009.

References

1. Mace OJ, Affleck J, Patel N, Kellett GL. Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. J Physiol 2007;582:379–392
2. Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS. Mammalian sweet taste receptors. Cell 2001;106:381–390
3. Dyer J, Salmon KS, Zibrik L, Shirazi-Beechey SP. Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. Biochem Soc Trans 2005;33:302–305
4. Margolskee RF, Dyer J, Kokrashvili Z, Salmon KS, Ilegems E, Daly K, Maillet EL, Ninomiya Y, Mosinger B, Shirazi-Beechey SP. T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1. Proc Natl Acad Sci U S A 2007;104:15075–15080
5. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, Kim HH, Xu X, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF, Egan JM. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. Proc Natl Acad Sci U S A 2007; 104:15069–15074
6. Ma J, Bellon M, Wishart JM, Young R, Blackshaw LA, Jones KL, Horowitz M, Rayner CK. Effect of the artificial sweetener, sucralose, on gastric emptying and incretin hormone release in healthy subjects. Am J Physiol Gastrointest Liver Physiol 2009;296:G735–G739
7. Fujita Y, Wideman RD, Speck M, Asadi A, King DS, Webber TD, Haneda M, Kieffer TJ. Incretin release from gut is acutely enhanced by sugar but not by sweeteners in vivo. Am J Physiol Endocrinol Metab 2009;296:E473–E479
8. Teff K. Nutritional implications of the cephalic-phase reflexes: endocrine responses. Appetite 2000;34:206–213
9. Ahrén B, Holst JJ. The cephalic insulin response to meal ingestion in humans is dependent on both cholinergic and noncholinergic mechanisms and is important for postprandial glycemia. Diabetes 2001; 50:1030–1038
10. Little TJ, Pilichiewicz AN, Russo A, Phillips L, Jones KL, Nauck MA, Wishart J, Horowitz M, Feinle-Bisset C. Effects of in-

travenous glucagon-like peptide-1 on gastric emptying and intragastric distribution in healthy subjects: relationships with postprandial glycemic and insulinemic responses. J Clin Endocrinol Metab 2006;91:1916–1923

11. Meier JJ, Kemmeries G, Holst JJ, Nauck MA. Erythromycin antagonizes the deceleration of gastric emptying by glucagon-like peptide 1 and unmasks its insulinotropic effect in healthy subjects. Diabetes 2005;54:2212–2218

12. Nauck MA, Niedereichholz U, Ettler R, Holst JJ, Orskov C, Ritzel R, Schmiegel WH. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol 199;273:E981–E988