Nitrergic contribution to gastric relaxation induced by glucagon-like peptide-1 (GLP-1) in healthy adults

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Andrews CN, Bharucha AE, Camilleri M, Low PA, Seide B, Burton D, Baxter K, Zinsmeister AR. Nitrergic contribution to gastric relaxation induced by glucagon-like peptide-1 (GLP-1) in healthy adults. Am J Physiol Gastrointest Liver Physiol 292: G1359–G1365, 2007. First published February 8, 2007; doi:10.1152/ajpgi.00403.2006.—The incret glucagon-like peptide-1 (GLP-1), which is used to treat diabetes mellitus, delays gastric emptying by inhibiting vagal activity. GLP-1 also increases fasting and postprandial gastric volume in humans. On the basis of animal studies, we hypothesized that nitric oxide mediates the effects of GLP-1 on gastric volumes. To assess the effects of nitrergic blockade on GLP-1-induced gastric accommodation in humans, in this double-blind study, 31 healthy volunteers were randomized to placebo (i.e., saline), GLP-1, or the nitric oxide synthase inhibitor Nω-monomethyl-L-arginine acetate (L-NMMA; 4 mg·kg⁻¹·h⁻¹) alone or with GLP-1. Thereafter, 16 additional subjects were randomized to GLP-1 alone or together with a higher dose of L-NMMA (10 mg/kg bolus plus 8 mg·kg⁻¹·h⁻¹ infusion). Gastric volumes (fasting pre- and postprandial gastric volume) were measured by ⁹⁹ᵐTc-single-photon-emission computed tomography imaging. GLP-1 increased (P = 0.04) fasting gastric volume by 83 ± 16 ml (vs. 17 ± 11 ml for placebo) and augmented (P < 0.01) postprandial accommodation by 688 ± 165 ml (vs. 542 ± 29 ml for placebo). L-NMMA (low dose) alone did not affect fasting or postprandial gastric volume. L-NMMA (low dose) did not attenuate the effect of GLP-1 on gastric volumes. In contrast, L-NMMA (high dose) did not affect fasting volume but blunted GLP-1-mediated postprandial accommodation (postprandial change = 494 ± 37 ml, P < 0.01 vs. GLP-1 alone). These data are consistent with the hypothesis that nitric oxide partly mediates the effects of GLP-1 on postprandial but not fasting gastric volumes in humans.

accommodation; stomach; postprandial; diabetes; vagus

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) is an incretin produced by enteroendocrine L cells throughout the small intestine (45). The GLP-1 agonist exendin-4 improves glycemic control in patients with Type 2 diabetes mellitus inadequately treated with oral hypoglycemic agents (20). GLP-1 reduces postprandial glycemia not only by its hormonal effects (i.e., reduced glucagon and increased insulin release) (20, 29), but also by its powerful effects on gastrointestinal (GI) motility and secretion (31). Thus GLP-1 is a mediator of the ileal brake, delays gastric emptying, increases gastric volume, and reduces gastric acid secretion in humans (8, 40, 41). These GI effects of GLP-1 may also contribute to its side effects at pharmacological concentrations. For example, in a multicenter study of 551 patients with inadequately controlled Type 2 diabetes mellitus, 57% of patients treated with a GLP-1 agonist reported nausea and 17% reported vomiting, and GLP-1 was discontinued because of these side effects in 6% of patients (18).

An intact vagus nerve is necessary for GLP-1 to delay gastric emptying in rats and pigs (21, 48) and to inhibit acid secretion in humans (49). GLP-1 also inhibits the plasma pancreatic polypeptide response to sham feeding in humans, indicative of vagal inhibition (39, 40). However, how GLP-1 increases gastric volumes is not understood. Since vagally mediated nitric oxide (NO) release is partly responsible for gastric accommodation (9, 23, 27, 43), vagal inhibition would be anticipated to reduce (not increase) fasting gastric volume and postprandial accommodation. There is increasing evidence to suggest that several effects of GLP-1 (e.g., inhibition of small bowel motility (33, 46) and relaxation of pulmonary arterial smooth muscle in rats (14, 37)) are mediated by NO. Therefore, we hypothesized that GLP-1 relaxes the stomach by stimulating nitrergic pathways. To examine this hypothesis, we assessed the effects of the NO synthase (NOS) inhibitor Nω-monomethyl-L-arginine acetate (L-NMMA) and GLP-1, alone and in combination, on fasting and postprandial gastric volumes in humans.

METHODS

This report is part of a large study assessing modulation of gastric volumes by GLP-1, nitrergic, and adrenergic pathways in 64 subjects. Observations from 17 subjects on the adrenergic modulation of gastric volumes and the interaction between GLP-1 and the adrenergic nervous system will be reported separately. Forty-seven healthy adults aged 18–54 yr (mean age 31 yr; 35 women and 12 men) participated in this study. None had previous GI surgery (other than appendectomy or cholecystectomy), significant underlying illnesses, or medication use. Functional GI disorders, anxiety, and depression were excluded by validated screening questionnaires (44), a clinical interview, and a physical examination. Glucose intolerance and diabetes mellitus were excluded by checking the fasting serum glucose. The studies were approved by the Mayo Clinic Institutional Review Board.

Experimental Design for Experiment 1

The experimental protocol is summarized in Fig. 1. Fasting and postprandial gastric volumes, plasma catecholamines, and hemodynamic parameters were studied during intravenous infusion of placebo or medication, before and after a meal. Two peripheral venous cannulae were used for drug infusion, and a separate peripheral venous cannula was used for blood sampling. Medications were given as a 10-min bolus followed by a continuous infusion lasting for the duration of the study (i.e., 55 min). Subjects were randomized, in a double-blind manner, to one of six arms [i.e., placebo, GLP-1, the...
Plasma catecholamines and glucose accommodation (42). Dose-stimulated small intestinal motility (38) and reduced postprandial venous blood sample was drawn before and after drug infusion during plasma catecholamines were measured during drug infusions. A 10-ml body mass index (BMI; i.e., $<25$ vs. $>25$ kg/m$^2$). Because of this stratification, the number of subjects randomized to each group was similar but not identical. As control or placebo, we administered 15 ml of 0.9% saline as a “bolus” followed by an infusion at 42.9 ml/h for the entire study. When only one drug was administered, saline was administered through the second intravenous cannula. As noted above, data for subjects randomized to yohimbine alone or GLP-1 and yohimbine will be reported separately.

$^{99m}$Tc-SPECT for Measuring Gastric Volume and Accommodation

Gastric volumes were assessed by single-photon-emission computed tomography (SPECT) as described previously (2, 3, 25). After intravenous injection of $^{99m}$Tc-labeled sodium pertechnetate (10 mCi), dynamic tomographic images of the gastric wall were acquired during fasting and for a total of 32 min after ingestion of a 300-ml nutrient drink (Ensure, 1 kcal/ml, Ross Laboratories, Abbott Park, IL) through a straw by a dual-head gamma camera (Helix SPECT System, Elscint, Haifa, Israel) in a multibit-mode system. Since the $^{99m}$Tc is taken up by gastric parietal and mucus-secreting epithelial cells, the entire gastric mucosa is visualized by this technique. A three-dimensional rendering of the stomach and its volume was obtained by using the AWV 3.0 (Core B; Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) image processing libraries.

Medications

GLP-1 and L-NMMA were used under investigator-initiated Investigational New Drug approvals from the US Food and Drug Administration. All infusions were prepared by standard practice in the Mayo General Clinical Research Center Research Pharmacy using current American Society of Health-System Pharmacists class III procedures for sterile preparation.

GLP-1. GLP-1 (7–36 amide) (Bachem, San Diego, CA) was infused at 2.4 pmol·kg$^{-1}$·min$^{-1}$ for 10 min followed by 1.2 pmol·kg$^{-1}$·min$^{-1}$ for the remainder of the study. This dosing regimen produced supraphysiological plasma levels, inhibited antroduodenal contractility, and increased pyloric tone in healthy subjects (39).

L-NMMA. L-NMMA (Clinalfa, Läuflingen, Switzerland), a NOS inhibitor, was infused at 4 mg·kg$^{-1}$·h$^{-1}$. In healthy subjects, this dose stimulated small intestinal motility (38) and reduced postprandial accommodation (42).

Plasma Catecholamines and Glucose

Because L-NMMA would have been obtained in experiment 2, the fasting postdrug period was lengthened from 15 min in experiment 1 to 30 min in experiment 2. Otherwise, the experimental design for experiments 1 and 2 were similar.

Experimental Design and Procedures in Experiment 2

After completing experiment 1, 16 additional healthy subjects were evenly randomized to GLP-1 alone or to GLP-1 combined with L-NMMA; the L-NMMA dose of experiment 2 was higher (i.e., 10 mg/kg bolus over 10 min followed by 8 mg·kg$^{-1}$·h$^{-1}$ infusion) compared with experiment 1. A comparable dose of L-NMMA reduced fasting gastric volume and postprandial gastric accommodation in humans (26). Because the effect of L-NMMA on fasting gastric volume may be delayed (26), the fasting postdrug period was lengthened from 15 min in experiment 1 to 30 min in experiment 2. Otherwise, the experimental design for experiments 1 and 2 were similar.

Statistical Analysis

Overall treatment effects on fasting post-drug and postprandial post-drug parameters were assessed by analyses of covariance (ANCOVA) using sex, BMI, and the corresponding fasting predrug values as covariates. Because of the two-phase nature of the study, the analyses evaluated treatment effects nested within phase, e.g., GLP-1 alone was considered as a distinct treatment category for experiment 1 and separately for experiment 2. In addition, a one-way ANCOVA considering the combined GLP-1 groups from experiments 1 and 2 was used to assess the overall treatment effects for all subjects who received GLP-1. After assessing overall treatment effects, we examined specific pairwise comparisons. A formal comparison between placebo and GLP-1 (experiment 1) was tested; the similar comparison of GLP-1 (experiment 2) assumed that similar placebo values would have been obtained in experiment 2. Comparisons between placebo and L-NMMA (low dose only) between GLP-1 and GLP-1 + L-NMMA (low dose), and, separately, GLP-1 (experiment 2) vs. GLP-1 + L-NMMA (high dose) were also examined. Statistical significance was set at an $\alpha$ level of 0.05, and pairwise comparisons were only considered significant when overall treatment effects were also significant. A rank transformation was used for parameters that were not normally distributed. Because this was an intent-to-treat analysis, missing data were imputed by using the corresponding mean value over all nonmissing data values. The error degrees of freedom in the respective ANCOVA models were decreased by one for each missing value imputed for a given response parameter. The data presented in the text, tables, and
figures are the “raw” means (± SE), unadjusted for covariates, and do not include any imputed values.

RESULTS

None of the subjects experienced significant adverse events during these studies. At baseline, there were no clinically important differences in age, sex, BMI, fasting serum glucose, plasma norepinephrine, plasma DHPG, or fasting gastric volume among groups in either experiment 1 or experiment 2 of these studies

Effects of GLP-1 and L-NMMA on Fasting and Postprandial Gastric Volume

Overall treatment effects on post drug fasting gastric volume were significant (P = 0.035) (Table 2, Fig. 2). GLP-1 increased (P = 0.03) fasting gastric volume, to a greater extent in experiment 2 (mean change = 101 ml, P = 0.001 vs. placebo) than in experiment 1 (mean change = 61 ml, P = 0.051 vs. placebo).

The postprandial gastric volume change (i.e., postprandial minus fasting volume) was 542 ± 29 ml for placebo and overall treatment effects were significant (P < 0.001) (Table 2, Fig. 2). The GLP-1-induced postprandial change was greater in part 2 (752 ± 62 ml, P < 0.001 vs. placebo) than in part 1 (605 ± 31 ml, P = 0.22 vs. placebo). Thus, for experiments 1 and 2 combined, GLP-1 increased the postprandial gastric volume change (i.e., accommodation) compared with placebo (P = 0.004).

The low dose of L-NMMA did not affect fasting or postprandial gastric volumes. Fasting gastric volume was not significantly different for GLP-1 and L-NMMA (high dose) combined compared with GLP-1 alone. However, the postprandial gastric volume change was lower (P = 0.004) for GLP-1 combined with L-NMMA (high dose) (494 ± 37 ml) than for GLP-1 alone (752 ± 62 ml) (Table 2, Fig. 2). In contrast, the postprandial gastric volume change was not significantly different for GLP-1 and L-NMMA (low dose) compared with GLP-1 alone (experiment 1).

Effects on Hemodynamic Parameters

Treatment effects on hemodynamic parameters were as anticipated (Table 3). During the fasting period, L-NMMA (low dose) increased (P ≤ 0.04) the mean arterial pressure compared with placebo and the combination of GLP-1 and L-NMMA (low dose) increased (P = 0.03) the mean arterial pressure compared with GLP-1 alone. During fasting and both postprandial periods, L-NMMA (low dose) reduced (P ≤ 0.01) the heart rate compared with placebo and GLP-1 + L-NMMA (low and high doses) reduced the heart rate compared with GLP-1 alone.

Effects on Plasma Catecholamine and Glucose Concentrations

In experiment 1, GLP-1 alone, L-NMMA, and GLP-1 combined with L-NMMA did not affect plasma norepinephrine concentrations (Fig. 3). During experiment 2, fasting postdrug plasma norepinephrine but not DHPG concentrations were lower (P = 0.02) during infusion of GLP-1 + L-NMMA (high dose) compared with GLP-1 alone. In contrast, drug effects on plasma DHPG levels were not significant (data not shown). Plasma epinephrine concentrations were below the threshold of detection for the assay (i.e., <20 pg/ml) in most subjects (data not shown).

Neither GLP-1 nor L-NMMA alone or in combination significantly affected fasting plasma glucose concentrations (data not shown). Overall treatment effects on postprandial glucose concentrations at 10 (P = 0.07) and 20 min (P = 0.03) after a meal were observed. Pairwise comparisons revealed that plasma glucose was lower (P ≤ 0.03) during infusion of GLP-1 + L-NMMA (high dose) compared with GLP-1 alone. In contrast, drug effects on plasma DHPG levels were not significant (data not shown).

DISCUSSION

These data confirm our previous observations that GLP-1 increased gastric volume in healthy subjects, increasing

Table 1. Demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>GLP-1</th>
<th>L-NMMA (low dose)</th>
<th>GLP-1 + L-NMMA (low dose)</th>
<th>GLP-1 alone</th>
<th>GLP-1 + L-NMMA (high dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Age, yr</td>
<td>34 ± 5</td>
<td>34 ± 3</td>
<td>33 ± 4</td>
<td>28 ± 3</td>
<td>29 ± 3</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>Sex (%) female</td>
<td>75</td>
<td>86</td>
<td>86</td>
<td>67</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26 ± 6</td>
<td>27 ± 2</td>
<td>27 ± 2</td>
<td>27 ± 1</td>
<td>25 ± 1</td>
<td>26 ± 1</td>
</tr>
<tr>
<td>Plasma glucose, mg/dl</td>
<td>87 ± 2</td>
<td>88 ± 2</td>
<td>90 ± 5</td>
<td>88 ± 2</td>
<td>86 ± 2</td>
<td>86 ± 4</td>
</tr>
<tr>
<td>NE level, pg/ml</td>
<td>214 ± 31</td>
<td>177 ± 33</td>
<td>167 ± 17</td>
<td>171 ± 25</td>
<td>187 ± 20</td>
<td>203 ± 38</td>
</tr>
<tr>
<td>DHPG level, pg/ml</td>
<td>1,578 ± 266</td>
<td>1,514 ± 206</td>
<td>1,857 ± 128</td>
<td>1,830 ± 231</td>
<td>1,249 ± 177</td>
<td>886 ± 69</td>
</tr>
</tbody>
</table>

All values except sex are actual means ± SE. BMI, body mass index; NE, norepinephrine; DHPG, dihydroxyphenlyglycol; GLP-1, glucagon-like peptide-1; L-NMMA, N⁵-monomethyl-L-arginine acetate.

Table 2. Effects of drugs on fasting and postprandial gastric volumes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Difference (Post – Pre Drug) in Fasting Volume</th>
<th>Postprandial Change (Postprandial – Fasting Volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>17 ± 11</td>
<td>542 ± 29</td>
</tr>
<tr>
<td>GLP-1 (combined)†</td>
<td>83 ± 16*</td>
<td>688 ± 165*</td>
</tr>
<tr>
<td>L-NMMA (low dose)</td>
<td>14 ± 14</td>
<td>534 ± 36</td>
</tr>
<tr>
<td>GLP-1 + L-NMMA (low dose)</td>
<td>87 ± 19</td>
<td>592 ± 37</td>
</tr>
<tr>
<td>GLP-1 + L-NMMA (high dose)</td>
<td>92 ± 30</td>
<td>494 ± 37†</td>
</tr>
</tbody>
</table>

All values are actual means ± SE in ml. *P ≤ 0.01 vs. placebo, †P ≤ 0.01 vs. GLP-1 alone. ‡All subjects who received GLP-1 (i.e. in experiments 1 and 2).
An alternative explanation is that L-NMMA (high dose) inhibits nitrergic neurons without centrally stimulating vagal activity. Increases postprandial gastric accommodation by activating thereby inhibiting gastric antral motility and acid secretion in lower to those given in this study inhibited vagal activity, demonstrated that GLP-1 administered at doses comparable or healthy subjects (26, 42). Several previous studies have demonstrated that GLP-1 increased postprandial gastric volume via NO-dependent mechanisms. Several other effects of GLP-1 suggests that GLP-1 increased postprandial gastric volume via NO. Indeed, the interaction between GLP-1 and NO may be beneficial since GLP-1 also improved endothelial function in patients with Type 2 diabetes mellitus and coronary disease (36). GLP-1 may modulate vagal activity not only by central but also by peripherally mediated effects. Thus, in rats, physiological doses of GLP-1 activated vagal afferents (4) and intraportal administration of a truncated form of GLP-1 stimulated afferents in the hepatic vagus, thereby activating efferents in pancreatic branches of the vagus nerve (32). These observations suggest that GLP-1 may modulate GI functions via GLP-1 receptors on vagal afferents, which in turn activate vagovagal pathways. Similar to enteropancreatic and other vagovagal reflexes, these pathways probably entail sensory vagal afferents that travel to brain stem vagal nuclei and subsequently project to excitatory cholinergic or inhibitory nonadrenergic noncholinergic postganglionic neurons in the stomach to complete the loop (15, 34).

The postprandial change in gastric volume measured by SPECT reflects the sum total of the ingested meal, gastric secretion, swallowed air, gastric relaxation, and gastric emptying. However, SPECT does not clarify the relative contributions of these components to measured gastric volume. A recent study in which gastric volumes and emptying were simultaneously assessed demonstrated that the gastric volume measured by SPECT was, on average, 200 ml greater than the fasting gastric volume by 33% and augmenting postprandial gastric accommodation by 27% (8). Moreover, a high dose of L-NMMA blocked postprandial augmentation of gastric volume by GLP-1, suggesting that the effects of GLP-1 on postprandial gastric volume are mediated by NO.

Postprandial gastric accommodation allows time and room for solids to be triturated before they are emptied from the stomach. Postprandial accommodation is primarily attributed to nutrient-driven stimulation of vagal activity, which activates enteric nitrergic pathways to relax the stomach (9, 23, 27, 43). Thus L-NMMA blunted postprandial accommodation in healthy subjects (26, 42). Several previous studies have demonstrated that GLP-1 administered at doses comparable or lower to those given in this study inhibited vagal activity, thereby inhibiting gastric antral motility and acid secretion in humans (8, 39). Therefore our observations suggest that GLP-1 increases postprandial gastric accommodation by activating nitrergic neurons without centrally stimulating vagal activity. An alternative explanation is that L-NMMA (high dose) blocked NO-mediated postprandial accommodation (i.e., independent of GLP-1). However, the mean postprandial gastric volume change was lower for GLP-1 + L-NMMA (high dose) than not only for GLP-1 alone but also for placebo. This suggests that GLP-1 increased postprandial gastric volume via NO-dependent mechanisms. Several other effects of GLP-1 [i.e., inhibition of small bowel motility (46), protection against ethanol-induced gastric mucosal lesions (22), and relaxation of vascular endothelium (35)] are also dependent on NO. Indeed, the interaction between GLP-1 and NO may be beneficial since GLP-1 also improved endothelial function in patients with Type 2 diabetes mellitus and coronary disease (36). GLP-1 may modulate vagal activity not only by central but also by peripherally mediated effects. Thus, in rats, physiological doses of GLP-1 activated vagal afferents (4) and intraportal administration of a truncated form of GLP-1 stimulated afferents in the hepatic vagus, thereby activating efferents in pancreatic branches of the vagus nerve (32). These observations suggest that GLP-1 may modulate GI functions via GLP-1 receptors on vagal afferents, which in turn activate vagovagal pathways. Similar to enteropancreatic and other vagovagal reflexes, these pathways probably entail sensory vagal afferents that travel to brain stem vagal nuclei and subsequently project to excitatory cholinergic or inhibitory nonadrenergic noncholinergic postganglionic neurons in the stomach to complete the loop (15, 34).

The postprandial change in gastric volume measured by SPECT reflects the sum total of the ingested meal, gastric secretion, swallowed air, gastric relaxation, and gastric emptying. However, SPECT does not clarify the relative contributions of these components to measured gastric volume. A recent study in which gastric volumes and emptying were simultaneously assessed demonstrated that the gastric volume measured by SPECT was, on average, 200 ml greater than the

![Graph showing effects of drugs on gastric volumes](image)

**Table 3. Effects of drugs on hemodynamic parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline MAP, mmHg</th>
<th>Baseline Heart rate, min⁻¹</th>
<th>Postdrug MAP, mmHg</th>
<th>Postdrug Heart rate, min⁻¹</th>
<th>Postdrug Postprandial MAP, mmHg</th>
<th>Postdrug Postprandial Heart rate, min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>84±4</td>
<td>64±7</td>
<td>83±4</td>
<td>67±4</td>
<td>83±6</td>
<td>71±3</td>
</tr>
<tr>
<td>GLP-1</td>
<td>82±4</td>
<td>65±3</td>
<td>84±3</td>
<td>68±3</td>
<td>87±7</td>
<td>69±2</td>
</tr>
<tr>
<td>L-NMMA (low dose)</td>
<td>87±5</td>
<td>66±6</td>
<td>94±6*</td>
<td>57±2†</td>
<td>86±6</td>
<td>61±3†</td>
</tr>
<tr>
<td>GLP-1 + L-NMMA (low dose)</td>
<td>80±4</td>
<td>59±3</td>
<td>91±5‡</td>
<td>56±3§</td>
<td>93±4‡</td>
<td>57±3§</td>
</tr>
<tr>
<td>GLP-1</td>
<td>80±4</td>
<td>63±3</td>
<td>84±3</td>
<td>64±3</td>
<td>85±3</td>
<td>65±3</td>
</tr>
<tr>
<td>GLP-1 + L-NMMA (high dose)</td>
<td>88±3</td>
<td>61±4</td>
<td>96±5</td>
<td>51±2§</td>
<td>109±8‡</td>
<td>53±3§</td>
</tr>
</tbody>
</table>

All values are actual means ± SE. MAP, mean arterial pressure. *P ≤ 0.05 vs. placebo; †P ≤ 0.01 vs. placebo; ‡P ≤ 0.05, §P ≤ 0.01 vs. GLP-1 alone.
with previous studies demonstrating that a high dose of L-NMMA reduced plasma catecholamines, consistent with the observed effect of GLP-1 on gastric emptying and volumes. Indeed, atropine, which also increases gastric volume, delays gastric emptying, and reduces plasma pancreatic polypeptide response to sham feeding, induced GI symptoms (e.g., nausea and bloating) in response to an oral nutrient load at maximal satiation and at 30 min thereafter (7). It is difficult to dissect the relative contributions of delayed gastric emptying and increased gastric volumes to GI symptoms (e.g., satiety) related to GLP-1. Because experiments 1 and 2 employed similar protocols and the analyses corrected for individual variations in fasting volume, it is unclear why GLP-1 increased fasting and postprandial gastric volume to a greater extent in experiment 2 than in experiment 1. Further studies are necessary to understand whether the observed interindividual differences in these effects explain the GI side effects of GLP-1 and whether these differences can be explained by inherited polymorphisms resulting in loss of function at the GLP-1 receptor (1).

In summary, these observations suggest that, in humans, GLP-1 increases fasting gastric volume and augments postprandial accommodation via different mechanisms. The effects of GLP-1 on postprandial but not fasting gastric volumes in humans are mediated in part by NO. Further studies are required to understand how GLP-1 increases fasting gastric volume in humans.

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