Effect of acute hyperglycemia on colorectal motor and sensory function in humans

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Maleki, Dordaneh, Michael Camilleri, Alan R. Zinsmeister, and Robert A. Rizza. Effect of acute hyperglycemia on colorectal motor and sensory function in humans. Am. J. Physiol. 273 (Gastrointest. Liver Physiol. 36): G859–G864, 1997.—Increased use of laxatives and constipation are more common among people with diabetes mellitus than matched nondiabetic people in the same community. The mechanism of constipation in diabetes is unclear. Acute hyperglycemia was previously reported to reduce the gastrocolonic response. Our aim was to determine the effects of acute hyperglycemia on the colon compliance and motor response to feeding and on the sensory function of the colon and rectum in healthy human subjects. Eleven healthy individuals were studied under conditions of hyperglycemia (mean blood glucose 280 ± 13 mg/dl) and euglycemia. We evaluated three parameters: 1) colonic motility and compliance by a multitumen manometry and barostatic balloon assembly in the descending colon (motility was studied during fasting and for 2 h postprandially); 2) perception of isobaric distensions of polyethylene balloons in the rectum and colon; and 3) rectal compliance.

Initial tonic response to meal ingestion (0–5 min) was slightly lower during hyperglycemia (P = 0.3). However, colonic tone, motility, compliance, and sensation, as well as rectal compliance and sensation, were not significantly different under the conditions of euglycemia and acute hyperglycemia. In healthy individuals, acute hyperglycemia does not significantly change colonic or rectal motor functions or the perception of mechanosensory stimuli in the colon or rectum compared with euglycemia. These results do not support the hypothesis that hyperglycemia abolishes the colonic response to feeding.

colon; motility; tone; compliance; sensation; perception; visceral afferents; diabetes mellitus

METHODS

Healthy volunteers. Eleven (5 female and 6 male) healthy volunteers, aged 23–45 yr (median 34 yr), were recruited by public advertisement. None had previously undergone gastrointestinal surgery. Inflammatory bowel disease, peptic ulcer disease, irritable bowel syndrome, anxiety, and depressive disorders were excluded by clinical interview and physical examination. None of the volunteers was taking medications affecting the gastrointestinal system. All underwent placement of a motility tube into the descending colon, except one volunteer in whom the tube could not be advanced beyond the junction of the descending and sigmoid colon. All women of childbearing potential had a negative β-human chorionic gonadotropin pregnancy test within 48 h of the study. The protocol was approved by the Mayo Clinic Institutional Review Board.

Experimental design. Figure 1A shows a summary of the experimental protocol. All subjects were placed on a clear liquid diet from noon of the day before the study and drank a bowel-cleansing solution of polyethylene glycol and electro-
The assembly with barostatically controlled balloons served to measure phasic pressure activity by pneumohydraulic perfusion manometry. The first three manometric ports were in the descending colon, and the last three were in the sigmoid colon and rectum. The balloon was a highly compliant polyethylene bag, 10 cm in length (Hefty Baggies; Mobil Chemical, Pittsford, NY), tied at both ends to metal rings incorporated in the device (Fig. 1B). Colonic tone was assessed by measuring the changes in the baseline balloon volume while a pressure clamp was maintained within the balloon. This operating pressure ranged from 12 to 16 mmHg and was selected at the start of the study as the pressure 2 mmHg above that associated with detection of artifact during respiration or coughing and was kept constant throughout the study. All subjects were positioned in a 30-degree head up, supine position.

Measurements of compliance and sensation were performed before colonic motility was assessed. The fluctuations in balloon volumes and intraluminal pressures were recorded for 30 min before participants ingested the study meal and for 60 min afterward.

The pressures and volumes in the barostat balloon, pressure fluctuations during the manometric phase, respiratory movement, and experimental interventions were all recorded on a computer (Microvax System and Modified Vaxlab Program; Digital Equipment, Boston, MA) for later filtering of respiratory and motion artifacts and analysis.

For the barostatic estimations of colonic tone, a computer program was used to separate baseline volume from phasic volume events. Baseline balloon volumes were calculated by excluding phasic volume events that coincided with pressure activity recorded with the manometric sensors (6, 7, 16). The average of the baseline volumes measured for 30 min before the meal represented the fasting tone. The volumes were averaged for each 5-min period postprandially; the mean change in volume for each 5-min period relative to the fasting volume was calculated. Relative volumes postprandially were assessed using fasting volumes as covariates to account for differences among subjects in fasting volumes, thereby providing an estimate of the overall postprandial change in colonic tone.

The computer program also identified phasic pressure peaks measured 5, 10, and 15 cm distal to the balloon for the descending colon, and 20 and 25 cm distal to the balloon for the sigmoid colon and rectum. These values were averaged and summarized as a motility index, expressed per hour, for the fasting and postprandial periods according to the following formula (6): motility index equals ln(n=number of peaks times the sum of peak amplitudes plus one).

Measurement of colonic and rectal compliance. Colonic and rectal compliance was assessed isobarically as the volume response to ramped increments in intraballoon pressures and expressed as the slope dV/dP (ml/mmHg) after subtraction of the intrinsic compliance of the closed barostat system. The compliance curve of each barostat device was measured ex vivo during calibration of the instrument immediately before every study. Previous studies (6, 14) have confirmed that the polyethylene balloon is infinitely compliant within normal operating ranges (intraballoon volumes <550 ml) and that the compliance curve of the closed system is close to linear and ranges from 5.64 to 5.68 ml/mmHg for the "Mayo"-type bellows barostat pumps used in this study. The sequence of balloon distension in the descending colon vs. the rectum was randomized, and compliance curves were obtained by increasing intraballoon pressure at 1-min intervals in 4-mmHg steps from 4 to 36 mmHg.
Measurement of colonic and rectal sensation. Colonic and rectal distensions were performed in random order as rapid, intermittent increases in intraballoon pressure in three equal steps of 8, 16, and 32 mmHg increments above the operating pressure. Each phasic pressure increment was applied only once at each site in the colon in random order and was maintained for 1 min with 1-min intervals between distensions. Ratings of sensory perception (of “gas,” pain, and desire to defecate) were assessed at 20 s after the onset of each distension step using a 10-cm long visual analog scale.

Hyperglycemic clamp. The healthy subjects had an 18-gauge intravenous catheter placed in an antecubital vein for blood sampling to estimate plasma glucose at 5-min intervals during the hyperglycemic clamp. This line was slowly infused with 0.9% normal saline with heparin (2,000 U/l) added to maintain patency of the infusion line and vein. A second intravenous catheter was placed in the antecubital vein of the contralateral arm for infusion of 20% dextrose solution hyperglycemic clamping (4). A baseline blood glucose level was obtained before the hyperglycemic clamp was started. A 15-min priming dose (100 ml) of 20% dextrose was given, and the infusion rate was adjusted as determined by measurement of the plasma glucose level at 5-min intervals throughout the study as described previously (9).

Data analysis. The data obtained for assessment of compliance (volumes at successive pressure levels) were first plotted as volume vs. reciprocal of pressure (Fig. 2). The nature of these compliance curves is reminiscent of the gastric emptying of solids, which is best fit by power exponential models. In a separate validation study, we noted this formula provided a better fit ($R^2 = 0.99$) than linear models ($R^2 = 0.94$, $P < 0.05$; A. E. Bharucha, M. Camilleri, and A. R. Zinsmeister, unpublished observations). A nonlinear (power exponential) model was used to fit volume as a function of the reciprocal of pressure

$$\text{vol}_j = V_{\text{max}} \cdot \exp[-(k \cdot rP_j)^b]$$

where $rP_j = [(P_{\text{max}} - P_j)/P_{\text{max}}]$, where $P_j$ is the pressure (mmHg) at the $j$th step, $P_{\text{max}}$ the maximum pressure (usually 36 mmHg), $V_{\text{max}}$ the maximum volume observed, and $\text{vol}_j$ the resulting volume. Estimates of the parameters $V_{\text{max}}$, $k$, and $\beta$ were obtained using this model in each subject separately for data from the descending colon and from the rectum. As in the gastric emptying test, $k$ is an expression of the slope and $\beta$ is the slope of the compliance curve. From these estimated parameters the pressure corresponding to one-half of the resulting volume $\text{vol}_{50\%}$ is

$$\text{vol}_{50\%} = V_{\text{max}} \cdot \exp[-(k \cdot rP_{50\%})^b]$$

where $rP_{50\%} = [(P_{\text{max}} - P_{50\%})/P_{\text{max}}]$ and $P_{50\%}$ is half the maximum pressure. Estimates of the parameters $V_{\text{max}}$, $1/P_{\text{max}}$, and $(P_{1/2\text{max}})^{-b} = 1/P_{50\%}$, as discussed in Data analysis.

Effect of glucose infusion on blood glucose levels in the postprandial period. Figure 3 shows the average blood glucose during each 30 min of the 2-h postprandial period under hyperglycemic clamp and euglycemic conditions. The average blood glucose levels were $280 \pm 13$ and $93 \pm 2$ mg/dl, respectively.

Effect of hyperglycemia on fasting and postprandial colonic and rectal motility. The relative postprandial balloon volume is a measurement of colonic tone. We did not find a statistically significant difference between the relative postprandial balloon volumes over the first 10 min during euglycemia and hyperglycemia (Table 1 summarizes the percentage changes). There was a modest reduction in the early (0–5 min) response to feeding during hyperglycemia compared with euglycemia ($P = 0.3$ for relative volume change).

There was no significant difference between fasting and postprandial colonic and rectosigmoid motility (phasic pressure activity) during hyperglycemia vs. euglycemia (Table 2). The colonic and rectal compliance were also unaffected by acute hyperglycemia (Table 1).
**Table 1. Effects of hyperglycemia on colonic compliance and tone in healthy subjects**

<table>
<thead>
<tr>
<th></th>
<th>Euglycemia</th>
<th>Hyperglycemia</th>
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<tbody>
<tr>
<td><strong>Compliance, mmHg for 10 min</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descending colon</td>
<td>15.5 ± 0.8</td>
<td>15.3 ± 0.4</td>
</tr>
<tr>
<td>Rectum</td>
<td>19.3 ± 0.6</td>
<td>19.7 ± 0.4</td>
</tr>
<tr>
<td><strong>Fasting colonic volume, ml (10 cm-long bag at operating pressure)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>196 ± 20</td>
<td>207 ± 24</td>
</tr>
<tr>
<td><strong>Postcibal descending colon tone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early increase</td>
<td>10.0 ± 2.4</td>
<td>4.7 ± 4.7</td>
</tr>
<tr>
<td>0–5 min</td>
<td>11.0 ± 3.1</td>
<td>9.4 ± 3.9</td>
</tr>
<tr>
<td>5–10 min</td>
<td>11.0 ± 3.0</td>
<td>8.5 ± 5.0</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5 female and 6 male volunteers. *Data from 1 participant excluded for technical reasons. †Percentage change in postprandial volume reduction relative to fasting volume; a positive number implies an increase in colonic tone.

Effect of hyperglycemia on perception of mechanosensory stimulation in colon and rectum. Table 3 shows a summary of the perception scores for pain, gas distension, and desire to defecate in response to distension of the barostatic balloons at 8, 16, and 32 mmHg above operating pressure. There were no significant differences between euglycemia and hyperglycemia in these component scores. Similarly, there were no differences in perception at each of the distension levels (data not shown).

**Table 2. Effects of hyperglycemia on colonic phasic contractility**

<table>
<thead>
<tr>
<th></th>
<th>Euglycemia</th>
<th>Hyperglycemia</th>
</tr>
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<tbody>
<tr>
<td>Descending colon</td>
<td></td>
<td></td>
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<tr>
<td>Fasting (30 min premeal)</td>
<td>8.9 ± 1.1</td>
<td>8.9 ± 0.8</td>
</tr>
<tr>
<td>Postcibal 0–30 min</td>
<td>10.4 ± 0.6</td>
<td>9.7 ± 0.8</td>
</tr>
<tr>
<td>Postcibal 31–60 min</td>
<td>10.4 ± 0.5</td>
<td>8.7 ± 1</td>
</tr>
<tr>
<td>Rectum and sigmoid colon</td>
<td></td>
<td></td>
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<tr>
<td>Fasting (30 min premeal)</td>
<td>10.2 ± 0.6</td>
<td>9.5 ± 0.8</td>
</tr>
<tr>
<td>Postcibal 0–30 min</td>
<td>10.6 ± 0.9</td>
<td>10.1 ± 0.7</td>
</tr>
<tr>
<td>Postcibal 31–60 min</td>
<td>10.5 ± 0.7</td>
<td>10.0 ± 0.7</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5 female and 6 male volunteers. Data show motility index equals ln (Σ amplitude × no. contractions + 1).

DISCUSSION

Our data show that acute hyperglycemia has no effect on colonic and rectosigmoid compliance or on fasting and postprandial tone or motility. Our data do not confirm the previous suggestion that acute changes in glycemia may be important etiologic factors in the constipation reported in people with diabetes mellitus.

In previous work by Sims et al. (13), the colonic tone remained unchanged over a period of 5 min during hyperglycemic clamp despite mechanical stimulation to the stomach used as a surrogate for a meal. There are clear differences in the previous experiments and our studies. First, a gastric balloon distension is not really a suitable substitute for a meal because it does not induce intestinal neural reflexes or hormonal responses. Second, the colonic response to a meal occurs for up to 120 min after a meal, and we have quantitated this effect over 60 min rather than a 5-min period. We did observe a small reduction in the immediate response to meal ingestion, and this possibly reflects the mechanical effects of the meal in eliciting the early response to feeding (18); however, the early response to meal ingestion was not significantly different under euglycemic or hyperglycemic conditions.

We have also failed to observe any significant effect of acute hyperglycemia on colorectal sensation and compliance. We did find that the sensation of gas in both rectum and colon had a direct association with the order of the euglycemia and hyperglycemia treatments but, once this effect for order was excluded, there was no residual effect of hyperglycemia. In contrast with our studies, Sims et al. (13) reported that the sensations of threshold sensation and urge to defecate were blunted by acute hyperglycemia but that maximally tolerated pressure was not.

It must be pointed out that we did not study threshold sensations but derived a composite score for “gas,” “pain,” and “urgency” from three standardized phasic distensions. Our laboratory validated the use of this method in previous studies (7), and we chose to use it.
because it demonstrates intensity dependence and responsiveness to physiological (2, 7) and pharmacological (3) perturbations. It also avoids the multiplicity of stimuli and sensory tests required by ramp distensions and the possibility of response bias introduced by the anticipatory knowledge of sequential increases in stimulus intensity (8). Individual symptom scores were not significantly altered during hyperglycemia.

Could the differences in colonic motor responsiveness during hyperglycemia between the study by Sims et al. (13) and our study be accounted for by a humoral response to hyperglycemia or to the meal that compensated for a presumed inhibition of the neural response to gastric mechanical stimulation? This is an intriguing hypothesis, and it is conceivable that some of the upper gut hormones released by the meal, such as gastrin or motilin, may have stimulated colonic tone that “concealed” the inhibitory effect of hyperglycemia on the tonic response to mechanical gastric distension. The glucose counterregulatory hormones, such as glucagon, epinephrine, or somatostatin, are not known to increase colonic tone or motility; conversely, octreotide, the cyclized octapeptide analog of somatostatin, actually inhibited colonic tone (17). It is also conceivable that prolonged retention of the liquid meal in the stomach due to acute hyperglycemia resulted in a confounding factor compared with the euglycemic state. Thus it is possible that prolonged meal retention enhances the gastrocolonic response, masking the decreased colonic motor responsiveness secondary to the hyperglycemic state.

Our data do not confirm the proposed hypothesis that acute hyperglycemia blunts the reflex response of the colon to meal ingestion. If acute hyperglycemia has comparable effects on colonic motility in diabetic and non-diabetic subjects, our data would not support the role of acute hyperglycemia in constipation in diabetes mellitus. These hypotheses need to be further tested to explain the colonic dysfunction in people with diabetes mellitus. Several other insights are relevant from recent epidemiological and pathophysiological studies. First, in studies of diabetic communities such as those performed in Finland (9) and Olmsted County, Minnesota (11), the prevalence of constipation is far lower than was previously reported in tertiary care facilities (5). Second, the prevalence of reported constipation and intake of laxatives is higher among females with insulin-dependent diabetes mellitus than that of community controls in Olmsted County (11). This significant increase in the intake of laxatives among females with insulin-dependent diabetes mellitus was associated with medication intake (e.g., calcium channel blockers), autonomic dysfunction, and multiple somatic complaints. These factors, as well as the previously demonstrated association with autonomic dysfunction (12), should also be considered in the appraisal of the mechanism of constipation in people with diabetes. Finally, it is also necessary to exclude anatomic and mucosal disorders or outlet obstruction to defecation before attributing constipation in diabetic patients to hyperglycemia. Three of nine patients reported in previous studies with constipation and diabetes (10) had evidence of outlet obstruction to defecation rather than slow transit constipation.

In summary, we have tested the effects of a meal (i.e., physiological stimulus of the colonic response to feeding) and did not observe any effects of acute hyperglycemia on colonic compliance or motor or sensory function. Assessment of the data acquired in this study shows that we had sufficient statistical power to detect the effect of hyperglycemia, and hence we can exclude a confounding type II statistical error in this study.

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