Ginger Reduces Hyperglycemia-Evoked Gastric Dysrhythmias in Healthy Humans: Possible Role of Endogenous Prostaglandins

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ABSTRACT

Acute hyperglycemia evokes gastric slow wave dysrhythmias via endogenous prostaglandin generation. Ginger exhibits slow wave antiarrhythmic effects in other models, but its actions on hyperglycemia-evoked gastric dysrhythmias are unexplored. We hypothesized that ginger prevents disruption of slow wave rhythm by acute hyperglycemia via inhibition of prostaglandin production but not its actions. Twenty-two healthy humans underwent fasting electrogastrography during hyperglycemic clamping to 250 to 290 mg/dl after double-blind placebo or ginger root (1 g). Responses were compared with the prostaglandin E1 analog misoprostol (400 µg). Dominant frequencies (DF) and the percentage of recording times in the bradygastric [0.5–2 cycles/min (cpm)], normal (2–4 cpm), and tachygastriac (4–9 cpm) frequency ranges were analyzed. After placebo, hyperglycemia reduced normal 2 to 4 cpm activity from 94.4 ± 2.6 to 66.0 ± 10.4%, increased the DF from 2.96 ± 0.04 to 4.09 ± 0.45 cpm, and increased tachygastria from 2.0 ± 1.4 to 29.3 ± 10.7% (P < 0.05). Hyperglycemia effects on normal activity (77.3 ± 8.3%), DF (3.46 ± 0.37 cpm), and tachygastria (15.6 ± 8.6%) were significantly reduced by ginger (P < 0.05). Misoprostol evoked decreases in normal activity from 95.4 ± 2.0 to 81.7 ± 3.0% and increases in tachygastria from 31.1 ± 1.6 to 11.2 ± 2.4% (P < 0.05). However, ginger did not correct these abnormalities versus placebo (P = N.S.). In conclusion, acute hyperglycemia evokes gastric slow wave dysrhythmias that are prevented by ginger root. Conversely, the compound has no effect on dysrhythmias elicited by a prostaglandin E1 analog, indicating that ginger likely acts to blunt production of prostaglandins rather than inhibiting their action. These findings suggest novel mechanisms for the traditional Chinese herbal remedy ginger.

Ginger (Zingiber officinale), a traditional Chinese herbal remedy, has been used to treat a number of medical conditions, including headache, colds, and arthritis (Grant and Lutz, 2000). Antiemetic actions of ginger have been reported in patients with nausea during pregnancy and in subjects with motion sickness (Grontved et al., 1988; Vutyavanich et al., 2001). Its effectiveness in preventing postoperative nausea and vomiting is uncertain with some studies observing benefits and others showing no effect (Phillips et al., 1993; Arfeen et al., 1995). The active ingredient responsible for the beneficial effects of ginger is uncertain, and the mechanisms responsible for reducing nausea and vomiting are unknown, although previous investigations have demonstrated inhibitory effects on prostaglandin and leukotriene synthesis (Srivastava, 1984; Kiuchi et al., 1992). Acute hyperglycemia delays gastric emptying and induces gastric slow wave dysrhythmias in healthy volunteers (MacGregor et al., 1976; Hasler et al., 1995). Furthermore, dysrhythmias such as tachygastria are common in patients with diabetes mellitus and are increased during periods of poor glycemic control (Jebbink et al., 1994b). In healthy volunteers, the cyclooxygenase inhibitor indomethacin prevents development of tachygastria during hyperglycemic clamping, suggesting mediation of dysrhythmia formation by endogenous prostaglandin production (Hasler et al., 1995). The ability of ginger to prevent the slow wave rhythm disruptive effects of acute hyperglycemia is untested and the role of prostaglandin pathways in any antidysrhythmic effects of ginger is unknown.

Thus, we designed studies with the following specific aims. First, we performed double-blind, placebo-controlled studies to test whether ginger root inhibits generation of gastric slow wave dysrhythmias during acute hyperglycemia in healthy human volunteers. Second, we compared these results to the ability of ginger root to prevent dysrhythmic activity evoked by administration of the prostaglandin E1 analog misoprostol to assess whether ginger acts to block the actions of prosta-
glandins. Through these investigations, we hoped to gain insight into the mechanisms of the traditional Chinese herbal remedy ginger.

Materials and Methods

Study Population. Twenty-two healthy volunteers (age 19–49 years, 15 males, 7 females) with no history of gastrointestinal symptoms, no prior gastrointestinal surgery, and no medications were recruited through campus-wide advertisement to study the effects of ginger root on gastric dysrhythmias occurring as a consequence of acute hyperglycemia and administration of a prostaglandin E2 analog. Subjects with underlying medical conditions or pregnancy were excluded. All subjects provided written informed consent before participation in these investigations. Studies were approved by the University of Michigan Institutional Review Board.

Study Protocol. Each volunteer underwent electrogastrographic (EGG) studies under four separate test conditions in random order on different days separated by at least 72 h: 1) hyperglycemic clamping after ginger, 2) hyperglycemic clamping after placebo, 3) misoprostol after ginger, and 4) misoprostol after placebo. Before each study day, subjects fasted for 8 h and abstained from caffeine, alcohol, and tobacco for at least 12 h. On the morning of study, volunteers swallowed either two ginger root powder capsules (500 mg each, Ginger Root; Nature’s Way Products Inc., Springville, UT) or two identical-looking placebo capsules with 20 ml of water in double-blind manner, in random order 30 min before initiation of EGG recording. Each volunteer was positioned at a 30° incline in a quiet, warm room without visual or auditory distractions, and a 30-min baseline EGG was recorded. For hyperglycemic clamping studies, 20% dextrose was then infused intravenously to achieve a plasma glucose concentration between 250 and 290 mg/dl. Once this level was reached, a 30-min EGG recording during stable hyperglycemia was obtained. For prostaglandin E2 studies, volunteers swallowed 400 μg of misoprostol (Cytotec; Searle, Skokie, IL) and 60-min EGG recordings were obtained.

Electrogastrography Methodology. EGG was performed according to a modification of methods previously described (Stern et al., 1987). After gentle skin abrasion to enhance electrical conduction, six Ag-AgCl electrodes (Acucat diaphoretic EGG electrodes; NDM, Dayton, OH) were affixed to the abdomen. The first electrode was placed in the midclavicular line below the left costal margin. The third electrode was placed midway between the xiphoid and umbilicus in the midline. The second electrode was placed equidistant between the first and the third electrodes. Three reference electrodes were affixed in the right upper quadrant below the right costal margin. Electrodes were connected via direct nystagmus couplers (model 9859; SensorMedic, Anaheim, CA) to a chart recorder for continuous display of gastric myoelectric activity. Time constants were set at 10 s and high-frequency cutoffs at 0.3 Hz to minimize interference from nongastric signals. Respiration and body movements were monitored by a belt pneumograph connected to an indirect blood pressure coupler (model 9863B; SensorMedic Corp., Anaheim, CA) on the chart recorder. The chart recorder was interfaced with a personal computer (4DX2-60V, Gateway 2000; Gateway, North Sioux City, ND) via an analog-to digital converter (DAS-16; Metabyte Corp., Taumon, MA). Signals were digitized at 1 Hz and filtered above 15 cycles/min (cpm) and below 0.5 cpm to remove high- and low-frequency noise.

The three channels of EGG recording were initially analyzed visually to determine which lead provided the signal most free of noise. The recording from this lead then was subjected to quantitative computer analysis. All tracings were analyzed in blinded manner so that the investigator did not know either the volunteers or the test conditions being studied. Any signals showing clear respiratory or movement artifact were excluded from EGG analysis. Analyses were performed across the frequency range from 0.5 to 12 cpm on 256-s segments of recording with a 76% overlap such that successive lines in the running analysis plot represented data from consecutive 60-s intervals. Recording segments were subjected to fast Fourier transformation and power spectral analysis as previously described (Hasler et al., 1995).

From this analysis, the dominant frequency was measured for each recording segment. From these values, the mean dominant frequency was calculated for each test condition. Furthermore, the percentages of recording time in which the dominant frequency was in the bradygastric (>0.5 and <2.0 cpm), normal (≥2.0 and ≤4.0 cpm), tachygastric (>4 and ≤9 cpm), and duodenal/respiratory (>9 cpm) frequency ranges were assessed.

Hyperglycemic Clamping Technique. Hyperglycemic clamping studies were performed according to the method of DeFronzo et al. (1979) to fix plasma glucose levels between 250 and 290 mg/dl. Intravenous catheters were introduced into the left and right ante-cubital veins for dextrose infusion and plasma glucose monitoring, respectively. Patency of the lines was maintained with periodic infusions of heparin flush-lock solution (100 USP units/ml). A 15-min priming dose of 20% dextrose was given, and the maintenance infusion rates were adjusted as needed by monitoring plasma glucose levels at 5-min intervals throughout the study using a portable glucose analyzer (One Touch II; Lifespan, Inc., Milpitas, CA). Using this technique, plasma glucose levels were maintained within ±10% of the desired values.

Statistical Analysis. All results are expressed as means ± S.E.M. Paired two-tailed Student’s t testing was performed to compare EGG dominant frequencies, powers of the dominant frequencies, and the percentages of recording time in the different frequency ranges. Statistical significance was defined by P values of less than 0.05.

Results

Study Population

Of the 22 volunteers recruited for participation in this investigation, one subject withdrew because of pain at the site of intravenous dextrose infusion and one withdrew after developing diarrhea and abdominal pain from oral misoprostol. Fourteen volunteers completed the hyperglycemic clamping experiments, whereas 11 finished the misoprostol studies. Gastric dysrhythmias were not inducible by hyperglycemia in two subjects or by misoprostol in one individual. Data from these studies are not included in the analysis of the effects of these interventions on EGG activity.

Effects of Ginger Root on Hyperglycemia-Evoked Gastric Dysrhythmias

Plasma Glucose Levels. Basal fasting plasma glucose levels were not significantly different after ginger root (81 ± 5 mg/dl) or placebo (78 ± 2 mg/dl) (P = N.S.). After initiation of hyperglycemic clamping, plasma glucose concentrations reached 250 mg/dl at a mean time of 26.8 ± 2.3 min for the ginger root studies and 25.4 ± 1.5 min for the placebo studies (P = N.S.). Thereafter, glucose levels were maintained at similar concentrations in the ginger root (269 ± 4 mg/dl) and placebo studies (272 ± 3 mg/dl) (P = N.S.). The volumes of 20% glucose infused were similar for ginger root (328 ± 21 ml) and placebo (332 ± 19 ml, P = N.S.).

Electrogastrography Findings. Induction of acute hyperglycemia elicited profound disruptions in EGG rhythm that persisted for the duration of the fasting recordings in the placebo studies. Representative tracings from one volunteer are shown in Fig. 1. The raw signal before infusion of 20% dextrose exhibited a uniform sinusoidal oscillation with a
period of 20 s. The grayscale plot of the frequency spectra revealed a dominant frequency of 3 cpm throughout the basal recording. During hyperglycemia, the EGG rhythm degenerated to a low-amplitude, high-frequency waveform with a period of approximately 7 to 10 s. The corresponding grayscale plot exhibited a predominant 6 to 8 cpm rhythm during this time. Conversely, after ginger root, hyperglycemia had less of a disruptive effect on the raw EGG waveform. Grayscale plots in the ginger root studies showed a persistence of 3-cpm rhythm during much of the dextrose infusion; however, some tachygastric activity with a dominant frequency of 7 cpm was observed, indicating that ginger only partially inhibited hyperglycemia-evoked dysrhythmias in this individual.

The effects of acute hyperglycemia on EGG activity were compared before and after ginger root versus placebo. There were no significant differences in baseline EGG parameters after ginger root or placebo. With placebo, hyperglycemia produced significant increases in the dominant EGG frequency from 2.96 ± 0.04 to 4.09 ± 0.45 cpm (Table 1) (P < 0.05 compared with baseline). The percentage of recording time in normal 3-cpm rhythm decreased significantly and the percentage of time in tachygastria increased (both P < 0.05 compared with baseline) (Figs. 2 and 3). After ginger root, the
dominant EGG frequency rose slightly from 2.80 ± 0.10 to 3.46 ± 0.37 cpm; however, the increase was significantly less than in the placebo studies (Table 1) (P < 0.01 compared with placebo). Similarly, the degree of tachygastria was much lower after ginger root than after placebo (P < 0.05 compared with placebo) (Fig. 3). This correlated with a trend to a reduction in the percentage of recording time in normal 3-cpm rhythm (Fig. 2). When comparing the decreases in recording time in 3-cpm rhythm (value during hyperglycemia subtracted from value during euglycemia), the effects of ginger root were significant compared with placebo (P < 0.05). Indeed, the percentage of recording time in 3-cpm rhythm with hyperglycemia in the ginger root studies was not significantly different than during euglycemia (Fig. 2). Hyperglycemia did not affect percentages of recording time in bradygastric or duodenal/respiratory frequency ranges in both placebo and ginger root studies (P = N.S.).

Effects of Ginger Root on Misoprostol-Evoked Gastric Dysrhythmias. Administration of the prostaglandin E1 analog misoprostol elicited significant gastric dysrhythmias qualitatively similar to those observed during hyperglycemic clamping. The effects of misoprostol on EGG activity were compared before and after ginger root versus placebo. There were no significant differences in baseline EGG parameters after ginger root or placebo. In placebo studies, increases in dominant frequency did not reach statistical significance after misoprostol (from 2.98 ± 0.06 to 3.16 ± 0.11 cpm; P = N.S.) (Table 1); however, significant decreases in percentage of recording time in 3-cpm rhythm (P < 0.01 compared with baseline) and increases in tachygastria activity (P < 0.05 compared with baseline) were observed (Figs. 4 and 5). In ginger root studies, dominant frequencies did not significantly increase after misoprostol (from 2.93 ± 0.04 to 3.13 ± 0.12 cpm; P = N.S.) (Table 1). In contrast to the hyperglycemia studies, ginger root did not affect the decrease in 3-cpm activity or the increase in tachygastria elicited by misoprostol compared with placebo (P = N.S.) (Figs. 4 and 5). Misoprostol did not affect percentages of recording time in bradygastric or duodenal/respiratory frequency ranges in both placebo and ginger root studies (P = N.S.).

### Table 1

<table>
<thead>
<tr>
<th>Test Condition</th>
<th>Hyperglycemia Study</th>
<th>Misoprostol Study</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.96 ± 0.04</td>
<td>4.09 ± 0.45*</td>
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<tr>
<td>Ginger root</td>
<td>2.80 ± 0.10</td>
<td>3.46 ± 0.37**</td>
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* P < 0.05 versus baseline; ** P < 0.01 versus placebo.
volunteers pretreated for 3 days with indomethacin did not
arrhythmic activity in healthy human subjects. However,
hyperglycemic clamping on gastric slow wave rhythm were
1996). In prior studies from our laboratory, the effects of
fundus tone, and stimulation of pyloric motor activity (Bar-
cluding inhibition of antral contractions, reduction of gastric
abnormalities that mimic those of diabetic gastropathy, in-
E2 preparations are readily available for use in humans.
Unfortunately, no oral prostaglandin analog misoprostol. In
canine models, prostaglandin E2 exhibits potent disruptive
effects on slow wave rhythm very similar to those observed with prostaglandin E1 anal-
log misoprostol. In contrast, induction of acute hyperglycemia studies, ginger root had no effect on the increase in time in
tachygastria in response to misoprostol (P = N.S.). Results are expressed
as means ± S.E.M., n = 10.

Discussion

Diabetic gastropathy produces upper gastrointestinal
symptoms that may be disabling in severity. The pathogen-
esis of diabetic gastropathy is likely multifactorial. Motor
disturbances such as delayed gastric emptying, reduced an-
tral contractions, decreased fundic tone, abnormal intragas-
tric distribution, and pylorospasm have been described in
diabetic patients (Mearin et al., 1986; Jones et al., 1995;
Samsom et al., 1995, 1997). Hypersensitivity to gastric dis-
tension has been reported in symptomatic diabetics similar to
that observed in patients with functional dyspepsia (Samsom et al., 1995). Finally, rhythm disturbances of the gastric slow
wave have been demonstrated in patients with long-standing
diabetes that are associated with impairments of antral con-
tractility (Jebbink et al., 1994a,b; Mantides et al., 1997).

The importance of gastric dysrhythmias in the genesis of diabetic
gastropathy is suggested by the observation that symptom
improvements on medication therapy of the condition corre-
late with normalization of slow wave rhythm rather than
acceleration of gastric emptying (Koch et al., 1989).

In diabetic patients, the degree of glycemic control can
influence the magnitude of gastric motor and myoelectric
dysfunction. Gastric emptying is delayed in diabetes during
periods of hyperglycemia (Fraser et al., 1990). Similarly,
gastric slow wave dysrhythmias such as tachygastria are
more prominent during hyperglycemia compared with
euglycemia (Jebbink et al., 1994b). Induction of acute hyper-
glycemia in healthy volunteers evokes gastric physiological
abnormalities that mimic those of diabetic gastropathy, in-
cluding inhibition of antral contractions, reduction of gastric
fundus tone, and stimulation of pyloric motor activity (Bar-
nett and Owyang, 1988; Fraser et al., 1991; Hebbard et al.,
1996). In prior studies from our laboratory, the effects of
hyperglycemic clamping on gastric slow wave rhythm were
explored (Hasler et al., 1995). Raising the plasma glucose to
230 mg/dl provoked significant increases in tachygastria and
arrhythmic activity in healthy human subjects. However,
volunteers pretreated for 3 days with indomethacin did not
develop slow wave dysrhythmias during hyperglycemia, in-
dicating mediation of the slow wave rhythm disruption by
endogenous production of prostaglandins. This finding pro-
vides an in vivo correlate of demonstrations of prostaglandin
dependence of tachygastrias in isolated gastric muscle tis-
ues excised from patients with refractory gastroparesis
(Sanders et al., 1979).

The traditional Chinese herbal remedy ginger reduces
symptoms in patients with nausea of pregnancy, motion sick-
ness, and postoperative nausea and vomiting (Grontved et al.,
1988; Phillips et al., 1993; Arfene et al., 1995; Vutyavan-
ich et al., 2001). In physiological testing, ginger increases
fasting antral contractions and the gastric motor response to
eating (Micklefield et al., 1999). Furthermore, ginger re-
verses cisplatin-induced delays in gastric emptying in animal
models (Sharma and Gupta, 1998). In a model of experi-
mental motion sickness, gastric slow wave rhythm disturbances
elicited by circular vection were prevented by treatment with
 ginger root (Lien et al., 2003). The effects of ginger on prost-
taglandin pathways as inducers of gastric dysrhythmic activ-
ity are unknown; however, it exhibits inhibitory effects on
prostaglandin and leukotriene synthesis in other models,
including platelets and RBL-1 cell lines (Srivastava, 1984;
Kiuchi et al., 1992).

In the present investigation, we demonstrated that ginger
blunts the induction of tachygastria in response to acute hyperglycemia in healthy humans. We further aimed to de-
termine whether inhibition of prostaglandin synthesis or its
actions may play a role in the slow wave-stabilizing effects of
 ginger. To accomplish this goal, we contrasted the effects of
 ginger on gastric myoelectric responses during hyperglyce-
mia to those after oral administration of the prostaglandin E1
analog misoprostol. In canine models, prostaglandin E2 ex-
hibits potent disruptive effects on slow wave rhythm very
similar to those observed with prostaglandin E1 in humans
(Kim et al., 1987, 1988). Unfortunately, no oral prostaglandin
E2 preparations are readily available for use in humans.
Increases in tachygastria activity and reductions in normal
3-cpm cycling were qualitatively similar during hyperglyce-
mia and after misoprostol. However, misoprostol does not
disrupt slow wave activity by increasing plasma glucose be-
cause prostaglandin E analogs have no hyperglycemic ac-
ations in human volunteers (Demol and Wingender, 1989).
Increases in EGG dominant frequency for the entire record-
ing periods were less impressive because dysrhythmic activ-
ity, when present, usually occurred 20 to 35% of the time. The
magnitude of dysrhythmic activity after misoprostol tended
it to be less than with acute hyperglycemia; however, we
believe this is secondary to the dose of misoprostol that could be
administered. Unfortunately, doses higher than 400 μg tend
to be poorly tolerated by healthy volunteers because of side
effects, including diarrhea and abdominal cramps. However,
unlike its effects on hyperglycemia-evoked dysrhythmias,
 ginger root had no effect on slow wave rhythm disruptions
elicted by misoprostol. Given the relatively smaller in-
creases in tachygastria activity with misoprostol compared
with hyperglycemia, it is conceivable the lack of effect of
 ginger is secondary to a type II error. However, in hypergly-
cemia studies, even small dysrhythmic responses to hyper-
glycemia were blunted by ginger root, whereas ginger pro-
duced no trends to decreased or increased tachygastria in the
misoprostol studies. Thus, we believe our results likely indi-
cate that the mechanism for the antidiysrhythmic effects of ginger does not stem from inhibition of the actions of prostaglandins. Because endogenous prostaglandins mediate the slow wave response to hyperglycemic clamping in healthy humans, it is possible that ginger prevents prostaglandin production during periods of elevated plasma glucose.

It is conceivable that pathways other than those relating to endogenous prostaglandins may explain the antidiysrhythmic actions of ginger in this investigation. In addition to inhibiting cyclooxygenase and lipoxygenase activity, ginger exhibits effects on 5-HT3-mediated functions (Huang et al., 1991; Shibata et al., 1999). In experimental motion sickness in healthy humans, ginger blunts the increase in plasma vasoressin levels in response to circular vection, indicating possible actions on the release of this transmitter (Lien et al., 2003). Finally, loss of nitric oxide function has been proposed as a cause of impaired gastric motor function in rodent models of diabetic gastroparesis (Watkins et al., 2000). The effects of ginger on nitrergic pathways are unexplored. Another possibility that this agent may have some therapeutic benefit in patients with diabetic gastropathy. Future investigations provide novel insight into the mechanisms of action of the actions of ginger warrant further investigation.

In conclusion, the present study demonstrated that ginger root effectively prevents induction of gastric slow wave dysrhythmias by acute hyperglycemia in healthy human volunteers, myoelectric abnormalities that have been previously shown to be mediated by endogenous prostaglandin pathways. Conversely, ginger root has no effect on tachygastrias elicited by the prostaglandin E1, analog misoprostol. These findings are consistent with the conclusion that ginger acts to blunt production of endogenous prostaglandins rather than inhibit their actions. The results of the current investigation provide novel insight into the mechanisms of action of the traditional Chinese herbal remedy ginger and raise the possibility that this agent may have some therapeutic benefit in patients with diabetic gastropathy. Future investigations should test the efficacy of ginger in affected diabetic patients.

References


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