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 tachygastric (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 3.1 ± 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; Vutyanovich 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 on 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 E1 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 E1 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 (Accutac diaphragetic 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.

Electrodes were interfaced with a personal computer (4DX2-66V, Gateway 2000; Gateway, North Sioux City, ND) via an analog-to-digital converter (DAS-16; Metabyte Corp., Taunton, 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), tachygastri (>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 US 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; Lifescan, 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 (322 ± 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).

Fig. 1. Sample raw waveforms (top), grayscale plots (middle), and frequency spectra (bottom) are shown for a volunteer undergoing hyperglycemic clamping after placebo and ginger root. Hyperglycemia produced a chaotic high-frequency waveform after placebo that was predominantly in the 6- to 8-cpm range as seen on the grayscale plot and spectral analysis. Conversely after ginger root, the disruption in EGG rhythm was less profound. Although some high-frequency elements were seen on the grayscale plot and frequency spectrum, most of the EGG activity during hyperglycemia was 3 cpm.
dominant EGG frequency rose slightly from $2.80 \pm 0.10$ to $3.46 \pm 0.37$ cpm; however, the increase was significantly less than in the placebo studies ($P < 0.01$ 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 $E_1$ 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 $2.98 \pm 0.06$ to $3.16 \pm 0.11$ 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 tachygastric 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 $2.93 \pm 0.04$ to $3.13 \pm 0.12$ 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 ($P = N.S.$).
arrhythmic activity in healthy human subjects. However, 230 mg/dl provoked significant increases in tachygastria and explored (Hasler et al., 1995). Raising the plasma glucose to hyperglycemic clamping on gastric slow wave rhythm were (Jebbink et al., 1994). In prior studies from our laboratory, the effects of nett and Owyang, 1988; Fraser et al., 1991; Hebbard et al., 1996). Acceleration of gastric emptying (Koch et al., 1989). The traditional Chinese herbal remedy ginger reduces symptoms in patients with nausea of pregnancy, motion sickness, and postoperative nausea and vomiting (Grontved et al., 1988; Phillips et al., 1993; Arfeen et al., 1995; Vutyavanich et al., 2001). In physiological testing, ginger increases fasting antral contractions and the gastric motor response to eating (Micklefield et al., 1999). Furthermore, ginger reverses cisplatin-induced delays in gastric emptying in animal models (Sharma and Gupta, 1998). In a model of experimental motion sickness, gastric slow wave rhythm disturbances evoked by circular vection were prevented by treatment with ginger root (Lien et al., 2003). The effects of ginger on prostaglandin pathways as inducers of gastric dysrhythmic activity 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 determine 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 hyperglycemia to those after oral administration of the prostaglandin E1 analog misoprostol. In canine models, prostaglandin E2 exhibits 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 hyperglycemia and after misoprostol. However, misoprostol does not disrupt slow wave activity by increasing plasma glucose because prostaglandin E analogs have no hyperglycemic actions in human volunteers (Demol and Wingender, 1989). Increases in EGG dominant frequency for the entire record were less impressive because dysrhythmic activity, when present, usually occurred 20 to 35% of the time. The magnitude of dysrhythmic activity after misoprostol tended 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 elicited by misoprostol. Given the relatively smaller increases 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 hyperglycemia studies, even small dysrhythmic responses to hyperglycemia were blunted by ginger root, whereas ginger produced no trends to decreased or increased tachygastria in the misoprostol studies. Thus, we believe our results likely indi-

![Fig. 5. Effects of placebo and ginger root on percentages of EGG recording time in tachygastria are shown under baseline (open columns) conditions and after misoprostol (filled columns). Misoprostol significantly increased the time in tachygastria after placebo (P < 0.05). In contrast to the 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.](image-url)


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References


