ALIMENTARY TRACT

Nicotine Effects on Prostaglandin-Dependent Gastric Slow Wave Rhythmicity and Antral Motility in Nonsmokers and Smokers

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Background & Aims: Mechanisms of antral hypomotility with smoking are unknown. Slow wave disruption, which may be prostaglandin dependent, inhibits gastric motility. This study tested if nicotine reproduces motor effects of smoking and assessed the role of slow wave disruption in inducing hypomotility and the prostaglandin dependence of dysrhythmic responses. *Methods:* Electrogastrography and antroduodenal manometry were performed in 9 nonsmokers and 9 smokers during transdermal nicotine treatment (14 mg). Studies were repeated after administration of 150 mg indomethacin daily for 3 days to test prostaglandin requirements of nicotine responses. *Results:* Antral migrating motor complex periodicity and fasting and fed motility indices, not different in the groups under control conditions, decreased similarly in nonsmokers and smokers with nicotine. Tachygastria (>4.5 cycle/min) increased from 2% ± 2% to 16% ± 3% of recording time, and arrhythmias (frequency instability index) increased from 0.5 ± 0.1 to 1.1 ± 0.2 cycle/min with nicotine in nonsmokers ($P < 0.05$), which normalized with indomethacin. Electrogastrography results were unchanged in smokers. *Conclusions:* Nicotine evokes antral hypomotility in nonsmokers and smokers but evokes prostaglandin-dependent gastric dysrhythmias only in nonsmokers. Smokers show desensitization to nicotine-stimulated dysrhythmias. Thus, slow wave disruption is not essential to inhibit motor activity. This provides a model for the motor and myoelectric effects of smoking.

Recent studies indicate that tobacco smoking leads to inhibition of gastric motor activity. Loss of normal cycling of the antral migrating motor complex (MMC) with acute smoking has been shown in populations of both smokers and nonsmokers.[1] Similarly, acute smoking delays gastric emptying and increases duodenogastric reflux in patients with long-term smoking histories.[2] The clinical relevance of these studies is that the motor inhibitory effects of smoking may in part account for the increased incidence of peptic ulcer complications and gastric cancer with tobacco use.[3–6] Furthermore, delays in gastric emptying may provide an explanation for the appetite-suppressive effects of tobacco smoking.[7,8] The mechanisms for the gastric motor inhibitory effects of tobacco smoking in humans are uncertain. In canine models, intravenous nicotine infusion reduces gastric and duodenal contractile activity under fasting and fed conditions.[9] The role of nicotine in suppressing antral motor activity in humans is unexplored.

Phasic antral motor activity is regulated by an electrical pacemaker in the proximal gastric corpus, which produces slow waves at a frequency of 3 cycle/min. Abnormally rapid (tachygastria) or slow (bradygastria) pacemaker frequencies are observed in clinical settings in which there is impaired gastric motor activity.[10–12] Studies in canine and human models suggest that experimentally induced gastric dysrhythmias may be mediated by endogenous prostaglandin pathways.[13–15] The presence of gastric slow wave dysrhythmias resulting from tobacco smoking or from nicotine administration has not been documented. Further, the prostaglandin dependence of any such rhythm disturbances is unknown.

The present investigation had several objectives. First, we investigated if nicotine, in doses that produce plasma levels similar to those observed with smoking, has effects on fasting antral motor activity similar to those with tobacco smoking. It has been observed that individuals who begin to smoke often show gastrointestinal symptomatology such as nausea that diminish with long-term tobacco use. Thus, the effects of nicotine in nonsmoking volunteers were compared with those in persons who smoke at least 1 pack/day to determine if long-term tobacco use results in desensitization to the motor effects

Abbreviations used in this paper: EGG, electrogastrography; FI, frequency instability index; MI, motility index; MMC, migrating motor complex.

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of nicotine. We then aimed to characterize any deficits in postprandial antral motor activity in healthy nonsmokers and long-term smokers to determine if nicotine has comparable effects on fed antral motility as on fasting contractile activity. Next, we determined if nicotine administration evokes slow wave rhythm disturbances in the two subject groups to evaluate if gastric dysrhythmias are necessary for development of hypomotility. Finally, using the cyclooxygenase inhibitor indomethacin, we determined if slow wave rhythm disruption is dependent on endogenous prostaglandin production. Through these studies, we hoped to gain insight into the gastric motor and myoelectric effects of tobacco smoking.

Materials and Methods

Subject Populations

Nine nonsmoking healthy volunteers (6 men and 3 women) and 9 healthy volunteers (5 men and 4 women) who smoked at least 1 pack/day (range, 1–2.5 packs/day), ranging in age from 18 to 30 years of age, were recruited for antroduodenal manometry and cutaneous electrogastrography (EGG) studies. None of the volunteers had a history of gastrointestinal symptoms or prior gastrointestinal surgery, and none were taking medications known to alter gastrointestinal motility or electrical activity. Volunteers who smoke did not smoke for at least 24 hours before each study. The investigations were approved by the University of Michigan Human Use Committee, and each volunteer gave written informed consent before participating.

Antroduodenal Manometry

Antral and duodenal motor activity was measured after an overnight fast with a water-perfused, 8-lumen polyvinyl manometric catheter (Arndorfer Medical Specialities, Greendale, WI). Placement was achieved perorally under fluoroscopic guidance so that 6 pressure ports, spaced at 2-cm intervals, spanned the distal antrum and 2 were positioned in the duodenum. The catheter was connected by means of a pneumohydraulic water perfusion apparatus (perfusion rate, 0.25 mL/min; Arndorfer Medical Specialities) to force transducers (model P23xL; Gould, Oxnard, CA) that relayed information to a chart recorder (model R611; Beckman Instruments, Schiller Park, IL) for continuous monitoring of motor activity. At the completion of each study but before removal of nicotine patches, each volunteer underwent repeat fluoroscopy to ensure that no significant catheter migration occurred during the course of the experiment.

Fasting manometry studies. Basal fasting motor activity was recorded in the healthy volunteers for 4 hours or until two complete cycles of the MMC had propagated through the distal duodenal pressure port. One complete cycle of the MMC characteristically consists of three phases. Phase I is a period of motor quiescence that lasts 45–60 minutes. This is followed by phase II, a period of irregular phasic contractile activity that lasts 30–60 minutes. The cycle culminates in phase III, a 5–10-minute period of intense phasic motor activity that begins in the stomach and propagates through much of the length of the small intestine.[16] After basal recording, a 14-mg transdermal nicotine patch (Nicoderm; Marion Merrill Dow Inc., Kansas City, MO) was placed on a hairless area of the upper arm, and antroduodenal motor activity was recorded for 4 hours or until two MMC cycles passed through the distal duodenal recording port.

Fasting antral motility data were evaluated in two ways using visual analysis of the manometric tracings. To determine if nicotine prolonged the periodicity of the MMC, the number of antral phase III complexes per hour of recording time under basal and nicotine-stimulated conditions was measured. To further assess if nicotine reduced the number or amplitude of phasic contractions during individual antral phase III complexes that were present under basal and nicotine-stimulated conditions, antral phase III motility indexes (MIs) were calculated as the sum of the heights of all antral phasic contractions >10 mm Hg in the 10 minutes immediately preceding the onset of phase III cycling in the proximal duodenal recording port. Results for the fasting antral MI were expressed as millimeters of mercury.

Postprandial manometry studies. Studies of the effects of nicotine on postprandial antral motor activity were performed on separate days from the fasting studies. Manometry catheters were passed in fasting healthy volunteers as described above. For control studies, antral motor activity was recorded for 45 minutes after a 750-kcal mixed solid-liquid test meal that was ingested beginning 15 minutes after completion of the first antral MMC. On separate days, a 14-mg transdermal nicotine patch was placed 15 minutes after the first antral MMC. Two hours and 15 minutes after patch placement, volunteers ingested the 750-kcal test meal and postprandial antral motor activity was recorded for 45 minutes. Postprandial antral MIs were calculated as the sum of the heights of all antral phasic contractions >10 mm Hg for the duration of the 45-minute postprandial recording period. Results for the postprandial antral MIs were expressed as millimeters of mercury.

Cutaneous EGG

Cutaneous EGG was performed according to the method of Stern et al. on separate days from the antroduodenal manometry studies.[17] Subjects were placed in a semirecumbent position in a quiet, warm room without visual or auditory distractions. After gentle skin abrasion to enhance electrical conduction, four Ag-AgCl electrodes (Accutac Diaphoretic ECG 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 the umbilicus. The second electrode was placed equidistant between the first and third electrodes. A fourth reference electrode was affixed in the right upper quadrant of the abdomen. Electrodes were connected via direct nystagmus couplers (model 9859; SensorMedic Corp., Anaheim, CA) to a chart recorder for continuous display of

the slow wave activity. Time constants were set at 10 seconds and high frequency cutoffs at 0.3 Hz to minimize interference from nongastric signals. Respirations were monitored by a belt pneumograph connected to an indirect blood pressure coupler (model 9863B; SensorMedic Corp.) on the chart recorder, and any signals showing clear respiratory artifact were excluded from analysis. The chart recorder was interfaced with a personal computer (4DX2–66V; Gateway 2000, North Sioux City, ND) via an analog-to-digital converter (DAS-16; Metrabyte Corp., Taunton, MA).

Fasting EGG recordings were performed for 15 minutes, after which each volunteer ingested a 250-kcal liquid nutrient meal (Ensure; Ross Laboratories, Columbus, OH) while semirecumbent. Postprandial recording was continued for an additional 45 minutes. Three separate EGG recordings were made for each volunteer on separate days. Control studies were performed after an overnight fast. Nicotine studies involved performance of EGG recording 2 hours after placement of the transdermal nicotine patch (14 mg). The third series of studies evaluated the role of endogenous prostaglandins by repeating the nicotine study protocol after 50 mg oral indomethacin given three times daily for 3 days with an additional indomethacin dose given 2 hours before EGG recording. This dose of indomethacin has been shown to effectively inhibit prostaglandin synthesis in gastric and other tissues.[18,19]

The three channels of each EGG recording were initially analyzed visually to determine which lead provided the signal most free of noise. This lead was then subjected to quantitative computer analysis. All tracings were analyzed in blinded fashion such that the investigator did not know either the volunteer or the test conditions being studied. Signals were digitized at 4 Hz by the analog-to-digital converter and filtered above 15 and below 0.5 cycle/min to remove high- and low-frequency noise. Fast Fourier transformation was performed on 4-minute segments of recording using commercially available software (Fourier Perspective III; Alligator Technologies, Fountain Valley, CA). Running power spectral analyses were calculated across the frequency range from 0.5 to 10 cycle/min in 2-minute intervals in overlapping fashion. Each line in the running power spectral analysis plot represented the amplitude of the signal at the different frequencies. Data from the power spectral analyses were imported in spreadsheet format to commercially available software (Lotus 1-2-3, Release 2; Lotus Development Corp., Cambridge, MA) where the dominant frequency was determined in the postprandial period by assessment of the largest signal amplitude. If the maximal signal amplitude for a given 4-minute recording segment occurred at a frequency of $\geq$2 cycle/min and $\leq$4.5 cycle/min, the dominant frequency was defined as within the normal range. If the maximal signal amplitude was present at a frequency of $>$4.5 cycle/min and $\leq$9 cycle/min, the dominant frequency for that recording segment was defined as tachygastria. A dominant frequency of $>$0.5 cycle/min and $<$2 cycle/min defined bradygastria. Data were expressed as the percent of time that the dominant frequency was in either the tachygastric or bradygastric frequency range in the postprandial period. To provide a quantitative measure of slow wave arrhythmic activity, a frequency instability index (FI) (cycle/min) was calculated from the standard deviation of the dominant frequencies in all of the 4-minute recording segments during the fed period.

Plasma Nicotine Determination

For withdrawal of venous blood samples, an intravenous line was placed in the right antecubital region of all volunteers undergoing antroduodenal manometry. Patency of the line was maintained with periodic infusions of heparin flush-lock solution (100 USP U/mL). Venous samples for nicotine determination were drawn 2 hours after placement of the nicotine patch and immediately centrifuged, and the plasma was frozen and stored at -20°C. Plasma nicotine levels were measured by a high-perfomance liquid chromatographic method using the previously described methods of Hariharan et al.[20] One milliliter of plasma was extracted with methylene chloride after deproteinization with a trichloroacetic acid–eliminated emulsion formation. The extract was then evaporated and reconstituted in 30 μL of mobile phase and injected into a reverse-phase C-18 ion-pair column of an isocratic high-performance liquid chromatographic unit. Absorbance was monitored at 256 nm. The mobile phase was a citrate phosphate (30 mmol/L) buffer mixture containing acetonitrile and 1 mmol/L sodium heptansulfonate. 2-Phenylimidazole was the internal standard. The detection limit was 1 μg/L for nicotine with a linear standard curve from 0 to 700 μg/L. The mean coefficient of variation for nicotine in the concentration range of 0–100 μg/L was 6.5%.

Statistical Analysis

All results are expressed as means ± SEM. Phase III periodicities, fasting and postprandial antral MIs, EGG parameters, and plasma nicotine values were compared with use of the Student's *t* test for paired and unpaired observations. All *t* tests were two-tailed. A *P* value of 0.05 defined statistical significance.

Results

Plasma Nicotine Levels

Plasma nicotine levels reached 7.9 ± 0.4 ng/mL in the nonsmoking volunteers and 9.8 ± 1.8 ng/mL in the long-term smokers 2 hours after placement of the 14-mg nicotine patches, concentrations that approximate the 10–20 ng/mL measured in individuals who smoke 1 pack/day of standard cigarettes.[21] No differences were measured between the nonsmoking volunteers and the smokers.

Effects of Nicotine on Antral Motor Activity

Fasting manometry studies. Two parameters of fasting antral motor activity were measured under basal conditions and after placement of transdermal nicotine (14 mg). The effects of nicotine on periodicity of the

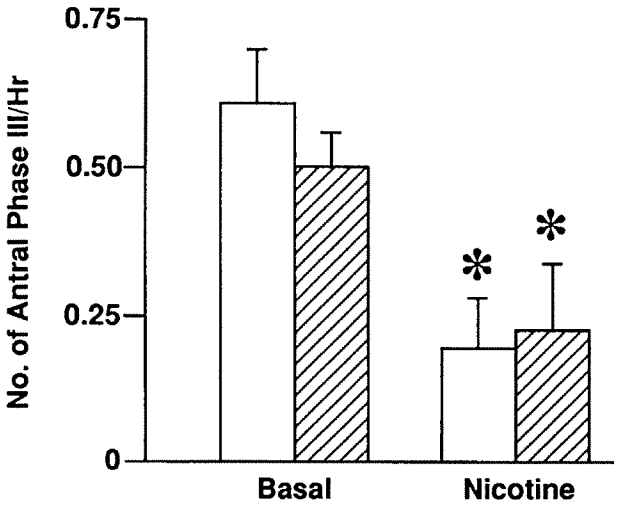

Figure 1. Nicotine effects on antral phase III periodicity are plotted for nonsmoking volunteers (□) and healthy smokers (▨). Placement of the nicotine patch reduced the number of antral phase III events per hour in both subject groups ($*P < 0.05$). There were no significant differences between nonsmokers and smokers. All results are expressed as the mean ± SEM (7 nonsmokers and 8 smokers).

MMC were first measured. Before nicotine administration, nonsmokers and smokers showed antral phase III complexes at rates of 0.61 ± 0.09/h and 0.51 ± 0.07/h, respectively (Figure 1). After placement of the nicotine patches, MMC periodicity decreased to 0.19 ± 0.09 antral phase III cycles/h for nonsmokers and 0.23 ± 0.11/h for smokers ($P < 0.05$) (Figure 1). In contrast, although trends to decreased activity were observed, there were no statistically significant effects of nicotine administration on duodenal phase III periodicity in healthy nonsmokers (0.52 ± 0.16/h) and long-term smokers (0.42 ± 0.12/h) compared with control conditions (nonsmokers, 0.72 ± 0.10/h; smokers, 0.65 ± 0.10/h), indicating that the effects of nicotine are relatively selective for gastric motor activity. Fasting antral MIs were calculated to determine if the intensity of individual antral phase III complexes were reduced by nicotine administration. Under basal conditions, antral phase III complexes consisted of intense, repetitive phasic contractions with fasting antral MIs of 853 ± 80 mm Hg in nonsmokers and 861 ± 103 mm Hg in smokers (Figure 2). After transdermal nicotine (14 mg) was administered, antral MIs decreased significantly to 342 ± 167 mm Hg for nonsmokers and 183 ± 84 mm Hg for smokers ($P < 0.05$) (Figure 2). Fluoroscopy performed at the end of each study but before removal of nicotine patches showed <2 cm migration of the manometry catheter in all cases over the course of each recording, indicating that reductions in fasting and fed antral motility with nicotine administration were not secondary to proximal tube movement. Thus, nicotine produced prolongations of the times between consecutive antral phase III complexes and reductions in the intensities of those antral phase III complexes that did develop. These inhibitory effects of nicotine on fasting gastric motor activity are qualitatively similar to those observed with acute tobacco smoking.[1] Furthermore, there were no quantitative differences in fasting antral motility parameters between nonsmoking and smoking volunteers under basal conditions or after nicotine administration, indicating that long-term tobacco exposure does not result in desensitization to the inhibitory fasting motor effects of nicotine.

Postprandial manometry studies. In control studies, meal ingestion resulted in induction of a characteristic fed motor pattern of irregular phasic contractions that began soon after initiation of eating and persisted beyond the end of the 45-minute recording period in all volunteers. There were no differences in the fed motor patterns in healthy nonsmoking volunteers (610 ± 185 mm Hg) and long-term smokers (390 ± 71 mm Hg), indicating that long-term use of tobacco does not prevent the postprandial increase in antral motor activity (Figure 3). As with the fasting studies, application of the nicotine patches 2 hours and 15 minutes before meal ingestion resulted in a marked reduction in fed antral motility in both healthy nonsmokers (129 ± 65 mm Hg; $P < 0.05$) and long-term smokers (140 ± 30 mm Hg; $P < 0.05$), showing that acute exposure to nicotine inhibits postprandial antral motor activity regardless of a prior history

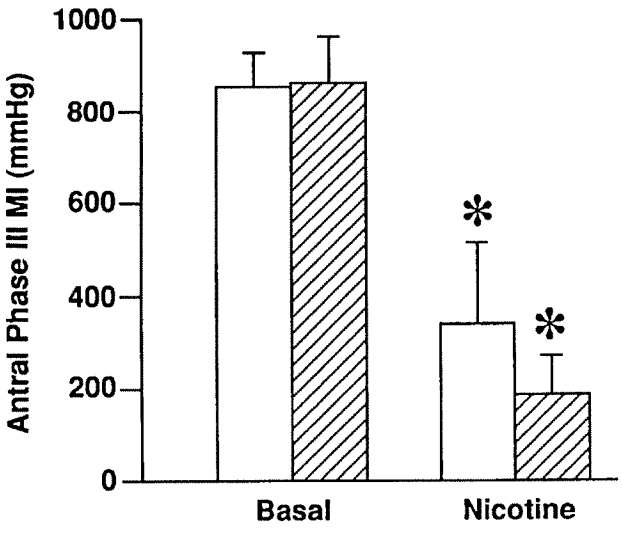

Figure 2. Nicotine effects on antral phase III MI are plotted for nonsmoking volunteers (□) and healthy smokers (▨). Placement of the nicotine patch reduced the fasting antral MI in both subject groups ($*P < 0.05$). There were no significant differences between nonsmokers and smokers. All results are expressed as the mean ± SEM (7 nonsmokers and 8 smokers).

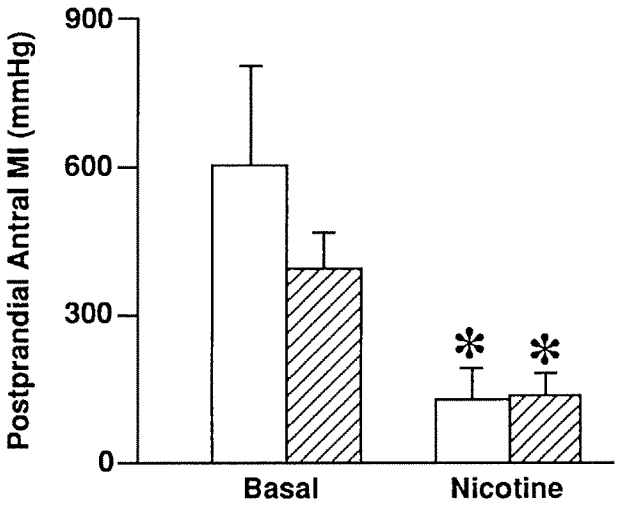

Figure 3. Nicotine effects on postprandial antral MI are plotted for nonsmoking volunteers (□) and healthy smokers (▨). Placement of the nicotine patch reduced the postprandial antral MI in both subject groups (*$P < 0.05$). There were no significant differences between nonsmokers and smokers. All results are expressed as mean ± SEM (6 nonsmokers and 6 smokers).

of tobacco use (Figure 3). In contrast, nicotine administration did not decrease the amplitudes of the fed motor responses in the duodenum in either the healthy nonsmokers or in the long-term smokers (data not shown).

Effects of Nicotine on Gastric Slow Wave Rhythmicity

Cutaneous EGG was performed for 45 minutes after a standardized 250-kcal liquid nutrient meal was administered to determine if the inhibitory effects of nicotine on antral motor activity correlate with disruption of normal gastric slow wave rhythmicity in the two subject groups. Figure 4 shows a sample raw EGG waveform and running power spectral analysis plot of the data from a control study before and after the standard meal. The raw signal shows an intense sinusoidal oscillation with a period of approximately 20 seconds. Running power spectral analysis shows that the dominant frequency throughout the control recording is in the normal frequency range from 2 to 4.5 cycle/min. EGG recordings were analyzed for the percent time that tachygastric and bradygastric activity was detected. Arrhythmic activity was quantitated by the frequency instability index, calculated from the standard deviations of dominant frequencies of all recording segments. Under control conditions, tachygastric activity was present 2% ± 2% and 5% ± 2% of the time in nonsmokers and smokers (Figure 5). Similarly, there were no significant differences in bradygastric activity between nonsmokers (11% ± 3%) and smokers (13% ± 2%). FI was 0.5 ± 0.1 cycle/min in nonsmokers and 0.6 ± 0.1 cycle/min in smokers in control studies (Figure 6). Thus, long-term tobacco use did not affect the parameters of gastric slow wave rhythmicity evaluated in the present investigation under basal conditions.

EGG studies were repeated on separate days 2 hours after placement of transdermal nicotine (14 mg) in both subject groups. Figure 7 shows the raw signal waveform and running power spectral analysis from a nonsmoking healthy volunteer after nicotine administration. The raw waveform shows a low amplitude, poorly organized oscillation with a period of approximately 10 seconds. In contrast to the control study, running power spectral analysis shows the absence of a dominant frequency for much of the postprandial period with increases in signal intensity in the frequency range from 4.5 to 9 cycle/min. Thus, in this individual, nicotine induced a gastric slow wave tachyarrhythmia. In the nonsmoking volunteer group, nicotine administration increased tachygastric activity to 16% ± 3% of recording time ($P < 0.05$) and FI to 1.1 ± 0.2 cycle/min ($P < 0.05$) (Figures 5 and 6). In contrast, placement of the nicotine patch on smoking volunteers did not increase tachygastric activity (6% ± 3%) or FI (0.7 ± 0.1 cycle/min) above basal levels (Figures 5 and 6). There were no increases in bradygastric activity

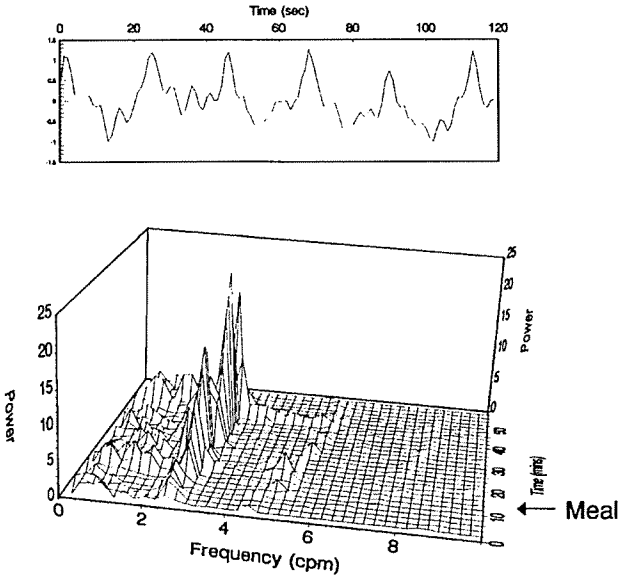

Figure 4. Sample EGG results from a healthy volunteer under control conditions are shown. In the *top panel*, the raw slow wave signal shows a rhythmic, high amplitude oscillation with a period of approximately 20 seconds. The *bottom panel* shows the running power spectral analysis of the same signal, which produces a frequency distribution of the slow wave signal as a function of time. Under control conditions, the slow wave signal shows a dominant frequency of approximately 3 cycles/min, which increases in amplitude after meal ingestion at 15 minutes.

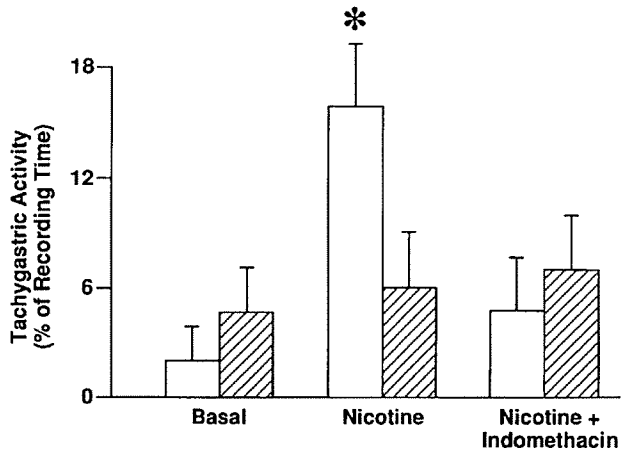

Figure 5. Tachygastric activity as a percent of recording time in the postprandial period is plotted for nonsmoking volunteers (□) and healthy smokers (▨). Under basal conditions, both subject groups show little spontaneous tachygastric activity. After placement of the nicotine patch, the nonsmokers develop significant increases in tachygastric activity (*$P < 0.05$). This increase in tachygastria is blunted by pretreatment with indomethacin. In contrast, smokers show no increase in tachygastria after nicotine administration. All results are expressed as the mean ± SEM (5 nonsmokers and 7 smokers).

with nicotine patch placement in either subject group (data not shown). These results indicate that nicotine evokes gastric tachyarrhythmias in nonsmokers only and that long-term tobacco use desensitizes gastric slow wave activity to the dysrhythmic effects of nicotine. Because there was no desensitization of antral hypomotility in the long-term smokers, these findings also indicate that disruption of slow wave rhythmicity is not a prerequisite for inhibition of gastric motor activity with nicotine administration.

Role of Endogenous Prostaglandins in Nicotine-Evoked Gastric Dysrhythmias

The role of prostaglandin pathways in nicotine-evoked slow wave rhythm disturbances was evaluated using the cyclooxygenase inhibitor indomethacin. In the nonsmoking volunteers, indomethacin pretreatment prevented the nicotine-induced increases in tachygastric activity (5% ± 3%) and FI (0.7 ± 0.2 cycle/min) (Figures 5 and 6). In the smoking volunteers, indomethacin had no effect on parameters of tachygastric (7% ± 3%) or arrhythmic (FI, 0.7 ± 0.1 cycle/min) activity (Figures 5 and 6). Indomethacin had no effect on bradygastric activity in either subject group (data not shown). These findings indicate that suppression of endogenous prostaglandin production has no effect on basal gastric slow wave activity. However, gastric slow wave tachyarrhythmias evoked by nicotine are dependent on endogenous prostaglandin pathways.

Discussion

Several studies have examined the effects of tobacco smoking on gastric motor activity. Most recent investigations show delays in gastric emptying of liquid and/or solid meals with acute smoking.[22–24] Miller et al. documented a deceleration of the linear phase of solid emptying, whereas Scott et al. showed prolongation of the lag phase.[23,24] Moreover, Scott et al. showed profound effects on liquid emptying with increases in the $t_{1/2}$ and decreases in the slope of the emptying curves. These effects on gastric emptying are similar to the effects of smoking on interdigestive antral motor activity, which show decreases in antral phase III activity.[1]

The motor inhibitory effects of smoking may have both deleterious and beneficial effects. Tobacco use is associated with increases in gastric ulcer disease.[4–6] Patients with gastric ulcer disease show increases in duodenogastric reflux of bile compared with healthy controls.[25] Muller-Lissner showed that acute smoking delays interdigestive emptying of gastric contents with associated increases in duodenogastric reflux, suggesting a possible mechanism for the increase in ulcer disease with tobacco use.[26] On the beneficial side, one of the reasons commonly given by long-term tobacco users for the decision to continue smoking is that smoking provides an appetite-suppressant effect. It is possible that the motor inhibitory effects of tobacco smoking underlie some of this satiating sensation.[7,8]

The mechanisms underlying the inhibition of gastric motor activity by smoking are incompletely understood.

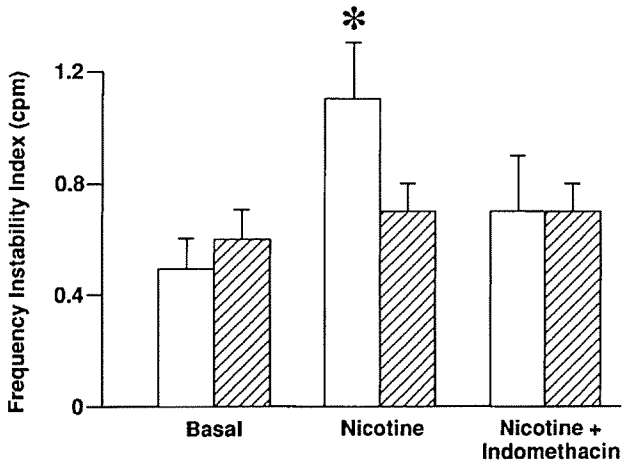

Figure 6. Slow wave arrhythmic activity was quantitated by the FI, which is plotted for nonsmoking volunteers (□) and healthy smokers (▨). Administration of nicotine resulted in significant increases in FI in the nonsmokers (*$P < 0.05$), which was prevented by prior treatment with indomethacin. In contrast, smokers showed no increase in FI with nicotine. All results are expressed as the mean ± SEM (5 nonsmokers and 7 smokers).

Evidence in dogs suggests that nicotine may have similar effects as smoking, although a careful correlation of nicotine levels with smoking and nicotine administration has not been performed.[9,27] In dogs, intravenous nicotine abolishes gastric and duodenal phase III activity and replaces it with motor quiescence, effects that are blocked by reserpine, suggesting that the actions of nicotine are mediated via increased sympathetic activity.[9,27] Studies of nicotine effects in humans have been minimal with only one study showing no effects on gastric emptying with nicotine chewing gum.[23] The present investigation shows that transdermal nicotine produces inhibition of fasting and fed antral motor activity that is qualitatively and quantitatively similar to the effects of tobacco smoking.[1] Furthermore, these effects are observed at plasma nicotine levels that closely reproduce those observed in tobacco users who smoke 1 pack of cigarettes/day.[21] The 14-mg transdermal nicotine patch delivers an average steady-state concentration of 12 ± 3 ng/mL in 4 ± 3 hours, while smoking 1 pack/day of standard 1.2-mg cigarettes produces sustained levels of 10–20 ng/mL with peak levels as high as 50 ng/mL.[21] Plasma nicotine levels obtained in the present study averaged 7.9 and 9.8 ng/mL in nonsmokers and smokers, respectively, 2 hours after patch placement, which approximates levels observed in long-term tobacco users. The inhibitory effects of nicotine on fasting and postprandial gastric motility

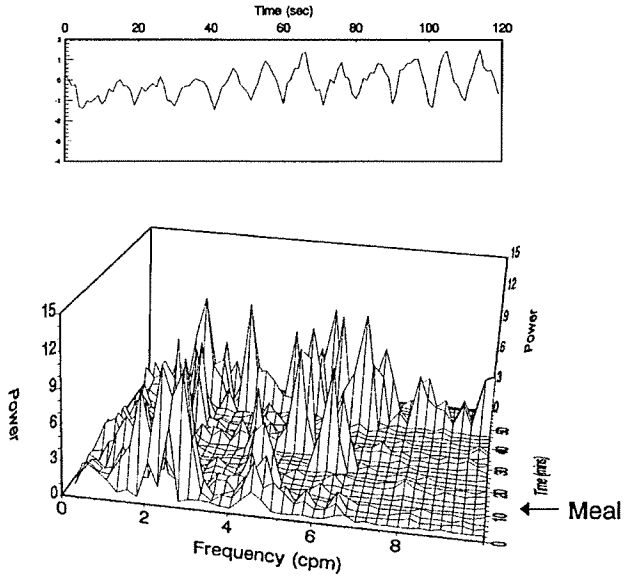

Figure 7. Sample EGG results from a healthy nonsmoking volunteer after placement of the nicotine patch are shown. In the *top panel*, the raw slow wave shows a low amplitude, rapid oscillation with a period of approximately 10 seconds. In the *bottom panel*, running power spectral analysis shows a marked increase in signal activity in the tachygastric frequency range (4.5–9 cycles/min) without a clear single dominant frequency.

were nearly identical in nonsmoking volunteers and in healthy volunteers with a history of smoking more than 1 pack of cigarettes/day, indicating that the motor effects of nicotine are not readily desensitized by long-term tobacco use. These findings are similar to those of McDonnell and Owyang, who showed similar suppression of antral phase III activity in nonsmokers and smokers.[1] It is conceivable that these persistent inhibitory effects on gastric motility contribute to the gastric pathological and physiological changes resulting from long-term smoking described above.

Phasic antral contractions are regulated by rhythmic electrical depolarizations (slow waves) at 3 cycle/min generated by a pacemaker in the proximal gastric body, which controls the contractile direction and maximal frequency.[17] In diseases with reduced antral motility, slow wave rhythm disturbances, including abnormally fast (tachygastric), slow (bradygastric), or irregular (arrhythmic) rhythms, have been documented, suggesting a possible pathogenic role in the reduction in contractile activity.[17] Support for the role of slow wave abnormalities in gastric hypomotility was provided by You and Chey, who induced gastric dysrhythmias in dogs with intravenous epinephrine.[11] Antral contractions were eliminated for the time that dysrhythmias were present and returned on recovery of a normal slow wave rhythm. More recently, glucagon-evoked dysrhythmias and delays in gastric emptying in dogs were reversible with electrical pacing of the stomach, emphasizing the importance of normal pacemaker activity.[28] In the present study, slow wave disruption was shown in nonsmoking healthy volunteers after nicotine administration with development of tachygastria and gastric arrhythmias. Of note, 2 of the 5 nonsmokers developed significant nausea on the nicotine patch during EGG. It is conceivable that induction of gastric dysrhythmias may precede the onset of and may be causative of symptoms in a population that has not chronically been exposed to nicotine-containing products. In fact, the 2 individuals with nausea also showed tachygastric activity greater than the mean for the nonsmoking group as a whole (24% and 21% of recording time), indicating that a threshold level of slow wave rhythm disruption may be necessary for symptom induction in some models. It is common for first-time tobacco users to experience a broad range of side effects, including nausea, which may be mediated by slow wave disruption. In contrast, no changes in rhythmicity were observed in volunteers with smoking histories, who remained asymptomatic, showing a desensitization to the dysrhythmic effects of nicotine with long-term tobacco use. These results have significant implications. First, mechanisms that regulate slow wave activity and antral motor activity

are clearly distinct because of their differential selectivity to desensitization by long-term smoking. Second, induction of gastric dysrhythmias is not a prerequisite for development of antral hypomotility because antral hypomotility was as prominent in smokers as in nonsmokers after nicotine administration.

The final aim of the present investigation was to evaluate mechanisms by which nonsmoking volunteers develop gastric dysrhythmias in response to nicotine. Animal and human models indicate that endogenous prostaglandin production is necessary for disruption of slow wave rhythmicity. In vivo studies in dogs showed that prostaglandin E_2 infusion induces prominent gastric dysrhythmias.[14] Furthermore, dysrhythmias evoked by exogenous infusion of epinephrine or met-enkephalin were prevented by pretreatment with indomethacin.[14] In humans, tachygastria induced by acute hyperglycemia is prevented by oral indomethacin in doses sufficient to abolish gastric prostaglandin production.[15] The potential importance of endogenous prostaglandins in clinical slow wave rhythm disturbances was emphasized in a report of a 26-year-old woman with chronic nausea, vomiting, gastric retention, and severe weight loss with associated spontaneous tachygastria.[13] In vitro studies of her postgastrectomy gastric smooth muscle tissue showed an intrinsic acceleration of electrical pacemaker activity that rendered the tissue insensitive to contractile stimuli. Perfusion of the tissue with indomethacin normalized the accelerated rhythm with recovery of contractile function; reintroduction of prostaglandin E_2 reproduced the electrical and contractile abnormalities that were spontaneously present. These investigations suggest that prostaglandin production mediates slow wave disruption induced by a broad variety of stimuli. In the present investigation, indomethacin was administered in a regimen known to nearly abolish gastric prostaglandin production to determine if nicotine-evoked gastric dysrhythmias are also mediated by endogenous prostaglandin pathways. Indomethacin pretreatment blocked increases in tachygastric and arrhythmic activity in the nonsmoking volunteers, confirming the importance of prostaglandin pathways. The indomethacin findings also provide a potential explanation for the lack of dysrhythmia induction by nicotine in the healthy smokers. It is known that tobacco smoking reduces gastric prostaglandin production, with two studies showing decreased prostaglandin E_2 levels in long-term smokers.[29,30] These findings suggest that the milieu for induction of gastric dysrhythmias is not present in long-term smokers and that by virtue of a preexisting reduction in gastric prostaglandin levels, smoking may be protective against the prostaglandin-dependent dysrhythmic effects of nicotine.

In conclusion, nicotine induces fasting and postprandial antral hypomotility in nonsmoking volunteers and healthy smokers. In contrast, gastric slow wave tachyarrhythmias are evoked by nicotine only in nonsmoking volunteers, which are mediated by prostaglandin-dependent pathways and may be important for symptom development in a population that has not chronically been exposed to tobacco products. Furthermore, these findings indicate that nicotine-evoked reductions in contractile activity are mediated by distinct pathways from nicotine-induced slow wave disruption and that loss of normal slow wave rhythmicity is not essential to inhibit antral motor activity. It is conceivable that the lack of dysrhythmic response to nicotine in healthy smokers stems from previously documented decreases in gastric prostaglandin production. These findings provide a model for the gastric motor and myoelectric effects of acute and long-term tobacco smoking.

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