

Role of plasma vasopressin as a mediator of nausea and gastric slow wave dysrhythmias in motion sickness

MICHAEL S. KIM, WILLIAM D. CHEY, CHUNG OWYANG, AND WILLIAM L. HASLER
*Division of Gastroenterology, Department of Internal Medicine,
University of Michigan Medical Center, Ann Arbor, Michigan 48109*

Kim, Michael S., William D. Chey, Chung Owyang, and William L. Hasler. Role of plasma vasopressin as a mediator of nausea and gastric slow wave dysrhythmias in motion sickness. *Am. J. Physiol.* 272 (*Gastrointest. Liver Physiol.* 35): G853–G862, 1997.—The possible role of vasopressin in nausea and gastric dysrhythmias in motion sickness was tested by electrogastrography in 14 subjects during circular vection (60°/s) and vasopressin infusion. Tachygastria was expressed as the signal percent >4.5 cycles/min. Vection evoked nausea scores of 2.6 ± 0.2 (0 = none to 3 = severe) in 10 subjects with increases in tachygastric activity (15 ± 2 to $45 \pm 3\%$) and plasma vasopressin (4.5 ± 1.5 to 8.4 ± 2.5 pg/ml) that were blocked by atropine but not indomethacin. Four asymptomatic subjects had no tachygastria or vasopressin release. Vasopressin at 0.2 U/min (plasma level = 322.1 ± 10.3 pg/ml) evoked nausea (2.6 ± 0.4) and increases in tachyarrhythmic activity ($41 \pm 5\%$) that were blunted by atropine but not indomethacin. There were no differences in nausea or dysrhythmias with vasopressin infusion in subjects who noted nausea during vection versus those who did not. To conclude, vection evokes nausea, dysrhythmias, and vasopressin release in motion sickness-susceptible humans via cholinergic prostaglandin-independent pathways. Supraphysiological vasopressin infusions evoke nausea and dysrhythmias by similar pathways to equal degrees in motion sickness-susceptible and -resistant subjects. Thus central but not peripheral actions of vasopressin may contribute to nausea and slow wave disruption with vection. Blunting of both the release and action of vasopressin by atropine may explain its beneficial action in motion sickness.

vomiting; electrophysiology; cholinergic nerves; prostaglandins

MOTION SICKNESS experimentally induced by circular vection, a stimulus that produces the illusion of self rotation, is associated with rhythm disturbances of gastric pacemaker activity known as the slow wave (20). It has been postulated that these gastric slow wave dysrhythmias are pathogenically important as they reliably develop 1–4 min before induction of nausea (7, 20, 27). The mechanisms responsible for generation of gastric dysrhythmias with motion sickness are incompletely understood. The ability of muscarinic receptor antagonists such as atropine and scopolamine to prevent both the nausea and slow wave disruption induced by circular vection suggests an important role for cholinergic neural pathways (7, 23). The efficacy of histamine receptor antagonists and certain adrenoceptor agonists to reduce symptoms of motion sickness suggests modulatory roles for these pathways as well (15, 24). Gastric slow wave rhythm disturbances in response to certain physiological stimuli are mediated by endogenous prostaglandin production

as evidenced by the ability of indomethacin to prevent their formation (8, 9, 11). However, as we have previously demonstrated, gastric dysrhythmias associated with motion sickness are mediated by prostaglandin-independent pathways (7).

Recent investigations have demonstrated elevations in plasma vasopressin levels that occur concurrently with disruption of slow wave rhythmicity during circular vection-induced motion sickness, raising the possibility that release of vasopressin into the peripheral circulation might play a pathogenic role in both the induction of symptoms and generation of gastric dysrhythmias (10, 27). It is known that some individuals who receive intravenous vasopressin clinically develop nausea (21). Furthermore, testing in primate models has shown that administration of selective vasopressin receptor antagonists can prevent motion sickness evoked by optokinetic stimuli (1, 2). However, the role of vasopressin release in human motion sickness is unknown.

The goal of these investigations was to ascertain whether vasopressin released into the systemic circulation may play a physiological role in the mediation of human motion sickness and gastric slow wave dysrhythmias evoked by circular vection. First, we compared plasma vasopressin levels in response to circular vection in those healthy volunteers who developed symptoms and slow wave disruption to levels in subjects who did not develop motion sickness. Second, we assessed the abilities of atropine, a well-characterized agent for the prophylaxis of motion sickness, and indomethacin, an inhibitor of endogenous prostaglandins, to prevent any increases in plasma vasopressin and dysrhythmic activity. Finally, the slow wave, symptomatic, and plasma vasopressin responses to intravenous vasopressin infusion were assessed to determine if the pharmacological generation of physiological vasopressin levels could reproduce the effects of experimental motion sickness. As part of this final series of studies, the responses of motion sickness-susceptible and -resistant subjects were compared to determine if motion sickness resistance is associated with no increase in plasma vasopressin (suggestive of defective vasopressin release) or with increased vasopressin levels (suggestive of a failure to respond to elevated peripheral vasopressin levels). Additionally, the abilities of atropine and indomethacin to reduce both nausea and gastric slow wave dysrhythmias in response to vasopressin infusion were tested to determine if vasopressin acts via similar pathways as vection-induced motion sickness. Through these investigations we hoped to gain insight into the pathophysiology of motion sickness.

MATERIALS AND METHODS

Study Population

Fourteen healthy volunteers (ages 20–40; 9 men, 5 women) with histories of motion sickness with automobile, boat, or air travel were recruited through campus-wide advertisement. These volunteers had no history of gastrointestinal diseases or prior gastrointestinal surgery and were on no medications at the time of study. All studies were approved by the University of Michigan Institutional Review Board. Informed written consent was obtained from all volunteers before participation in the study.

Cutaneous Electrogastrography Methodology

Cutaneous electrogastrography was performed according to a modification of the method of Stern and colleagues (20). After gentle skin abrasion to enhance electrical conduction, four Ag-AgCl electrodes (Accutac Diaphoretic ECG electrodes; New Dimensions in Medicine, 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. 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, Anaheim, CA) to a chart recorder for continuous display of the slow wave activity. Time constants were set at 10 s, and high-frequency cutoffs were set 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) on the chart recorder, and any signals exhibiting artifact clearly resulting from body movement or exaggerated respiratory activity, such as with a deep sigh or cough, 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; Metabyte, Taunton, MA).

After completion of each electrogastrographic recording, the three channels were analyzed 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 a 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 cycles/min (cpm) and below 0.5 cpm to remove high- and low-frequency noise. Power spectral analysis was performed on 2-min 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 9 cpm in 1- to 2-min intervals in an overlapping fashion. Each line in the running power spectral analysis plot represented the power 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, Cambridge, MA). The frequency range >2 and <4.5 cpm was defined to represent normal. The frequency range >4.5 and <9 cpm was defined as tachygastria. This tachygastic activity was shown to include periods of regular slow wave activity at an accelerated frequency as well as irregular tachyarrhythmic activity with a mean frequency greater than normal levels. The frequency range >0.5 and <2 cpm was defined to represent bradygastria. Frequencies <0.5

cpm were not analyzed, as no convincing gastric waveforms were observed below this frequency and human bradygastria has not been reliably characterized by other studies in this frequency range. The signal powers in the bradygastic, normal, and tachygastic frequency ranges were summed in 0.25-cpm increments and divided by the sum of the signal powers from 0.5 to 9 cpm. This computer analysis, in concert with the electrical filtering, excluded cardiac, diaphragmatic, and duodenal signals from the data interpretation. Bradygastic, normal, and tachygastic activity were thus expressed as a percentage of total signal power.

Circular Vection Studies

Circular vection was performed using a modification of the methods of Stern and colleagues (20). After an overnight fast, volunteers ingested a 1,000-kcal mixed solid-liquid meal that consisted of a roast beef sandwich on white bread with mayonnaise, a milkshake, applesauce, and water (23% protein, 32% carbohydrates, 45% fat). Thirty minutes after completion of the meal, subjects were seated vertically in the center of a drum (76-cm diameter, 92-cm height) with use of a chin rest to maintain the head position, in a quiet, dark, warm room to minimize visual or auditory distractions. The interior of the drum was painted with alternating black and white 3.8-cm vertical stripes and was illuminated by a stationary light placed above the volunteer in the center of the cylinder. After a basal electrogastrographic recording period of 15 min, clockwise drum rotation was begun at 60°/s and continued for 15 min or until the level of symptomatology precluded further stimulation, during which electrogastrographic recording continued. Before initiation of drum rotation, volunteers were instructed to report when they first perceived a sensation of nausea. Furthermore, volunteers were asked to state whether their nausea was mild, moderate, or severe. Severe nausea was defined as a sensation of impending vomiting. If severe nausea was reported, drum rotation was immediately discontinued. A nausea score was developed to quantitate symptom severity. A score of 0 represented no nausea, 1 represented mild nausea, 2 represented moderate nausea, and 3 represented severe nausea with impending vomiting. Times to maximal nausea and maximal slow wave disruption from the onset of circular vection were recorded.

The dependence of motion sickness-associated gastric dysrhythmias on cholinergic and prostaglandin-requiring pathways was assessed by repeating circular vection studies during infusion of the muscarinic receptor antagonist atropine and after pretreatment with the prostaglandin synthesis inhibitor indomethacin. It is known that healthy volunteers may develop tolerance to repeated exposure to motion stimuli with a resultant decrease in susceptibility to motion sickness (19). Thus individual circular vection studies under each of the test conditions were performed on separate days separated by at least 3 days. This protocol has been shown in our laboratory not to result in desensitization to the gastric dysrhythmic and symptomatic effects of circular vection. The role of cholinergic pathways was assessed by intravenous administration of atropine, which was given as a 1-mg bolus 30 min before induction of circular vection, followed by a continuous infusion at 0.25 mg/h until termination of the study. For circular vection studies with atropine infusion, an intravenous catheter was placed in the antecubital vein of the arm contralateral to that employed for venous blood sample withdrawal for plasma vasopressin determination (see below). During atropine administration, pulse, blood pressure, electrocardiographic activity, and oximetry were continuously recorded (model 506, Noninvasive Patient Monitor;

Criticare Systems, Milwaukee, WI). Studies were terminated if profound changes in heart rate or blood pressure, cardiac arrhythmias, or hypoxemia were detected. The role of endogenous prostaglandin pathways in the mediation of rotation-induced nausea and slow wave disruption was tested by repeating circular vection after pretreatment with 50 mg indomethacin orally three times daily for 3 days before study, with a final dose given 2 h before vection. This dosage regimen has been demonstrated to effectively inhibit prostaglandin synthesis in the stomach and other tissues (14, 17).

For all circular vection studies, an 18-gauge intravenous catheter was placed in an antecubital vein 30 min before basal recording for blood sampling for plasma vasopressin levels. Patency of the catheter was maintained by slow infusion (30 ml/h) of 0.9% normal saline supplemented with 2,000 U/l heparin. Venous blood samples were withdrawn 6 min before initiation of rotation during the baseline period and 4, 10, and 14 min after initiation of drum rotation and at report of severe nausea if termination of drum rotation was necessitated.

Vasopressin Infusion Studies

To determine if release of endogenous vasopressin into the peripheral circulation might be a physiological mediator of the nausea and slow wave disruption of motion sickness, circular vection results were compared with electrogastrographic and symptomatic results obtained during intravenous vasopressin infusions on separate days from the vection studies. An 18-gauge intravenous catheter was placed in an antecubital vein for infusion of vasopressin. A second catheter was placed as described above in the contralateral antecubital vein for withdrawal of venous blood samples for determination of plasma vasopressin levels. The subject was placed in a supine position in a warm quiet room for electrogastrographic recording. Before initiation of vasopressin infusion, volunteers were asked to report when they perceived nausea and asked to grade the nausea on a scale of 0–3 as described in *Circular Vection Studies*. If severe nausea with impending vomiting (score = 3) was reported, vasopressin infusion was immediately terminated. During vasopressin infusions, pulse, blood pressure, electrocardiographic activity, and oximetry were continuously monitored as described above. Studies were terminated in any volunteer with profound changes in heart rate or blood pressure, cardiac arrhythmias, or hypoxemia. A 30-min basal electrogastrographic recording was performed beginning 30 min after completion of the 1,000-kcal mixed solid-liquid meal as described in *Circular Vection Studies*, during which time blood samples were withdrawn at 10 and 20 min for basal plasma vasopressin determination.

Low-dose intravenous vasopressin infusion studies were performed beginning at a dose of 0.01 U/min for 30 min, during which time electrogastrographic monitoring continued. If tolerated, intravenous vasopressin infusion doses were increased in a stepwise fashion to 0.02 and then 0.04 U/min for 30 min at each dose, during which time slow wave activity was continuously recorded. On a separate day at least 3 days apart from the initial vasopressin infusion study, high-dose vasopressin was intravenously infused at 0.1 U/min and then 0.2 U/min as tolerated for 30 min at each dose after a 30-min basal electrogastrographic recording period.

The dependence of vasopressin-evoked nausea and gastric slow wave disruption on cholinergic neural and endogenous prostaglandin pathways was assessed by repeating high-dose vasopressin infusion studies during atropine infusion and after indomethacin pretreatment on separate days. For atropine infusion studies, a third intravenous catheter was placed in the same arm as for intravenous vasopressin infusion.

Thirty minutes before basal electrogastrographic recording, atropine was administered in an initial intravenous 1-mg bolus that was followed by a continuous intravenous infusion at 0.25 mg/h that was maintained throughout the vasopressin infusions. For indomethacin studies, volunteers were administered indomethacin orally at 50 mg three times daily for 3 days before study, with a final dose given 2 h before basal electrogastrographic recording. For these studies, a 30-min basal recording period was followed by consecutive 30-min vasopressin infusions at 0.1 and 0.2 U/min, as tolerated, during which electrogastrographic activity was recorded.

For all vasopressin infusion studies, venous blood samples were withdrawn at 10 and 20 min during the basal period, at 10, 20, and 30 min after initiation of each vasopressin dose, and at report of severe nausea if termination of vasopressin infusion was necessitated. Vasopressin determinations under basal and stimulated conditions were pooled for each study to provide single values for comparisons between subjects. There were no significant differences in vasopressin levels at 10, 20, and 30 min, suggesting that steady-state plasma levels were rapidly achieved.

Plasma Vasopressin Determination

Venous samples were withdrawn at the above-specified times for each respective study and immediately centrifuged, and the plasma was frozen and stored at -20°C . The plasma vasopressin level was measured by a commercially available specific double antibody radioimmunoassay using ^{125}I -labeled vasopressin (ALPCO, Windham, NH) as standard according to previously described methods (6). Phosphate buffer (250 ml; pH 7.4) was added to 400 μl of each patient sample. Vasopressin antiserum (50 μl) was added to the samples, vortexed, and incubated for 24 h at $2-8^{\circ}\text{C}$. Vasopressin tracer (100 μl) was added to each sample, vortexed, and incubated for 24 h at $2-8^{\circ}\text{C}$. Vasopressin solid-phase second antibody (100 μl) was added to each sample, vortexed, and incubated for 20 min at room temperature. Deionized water (1 ml) was added to each sample and centrifuged for 5 min at 1,000 g , and the precipitates were retained for counting. The samples were each counted in a gamma counter for 1 min. The sensitivity of the assay was 0.8 pg/ml, and the intra- and interassay coefficients of variation were 2.3–9.5% and 6.5–20.2%, respectively.

Statistical Analysis

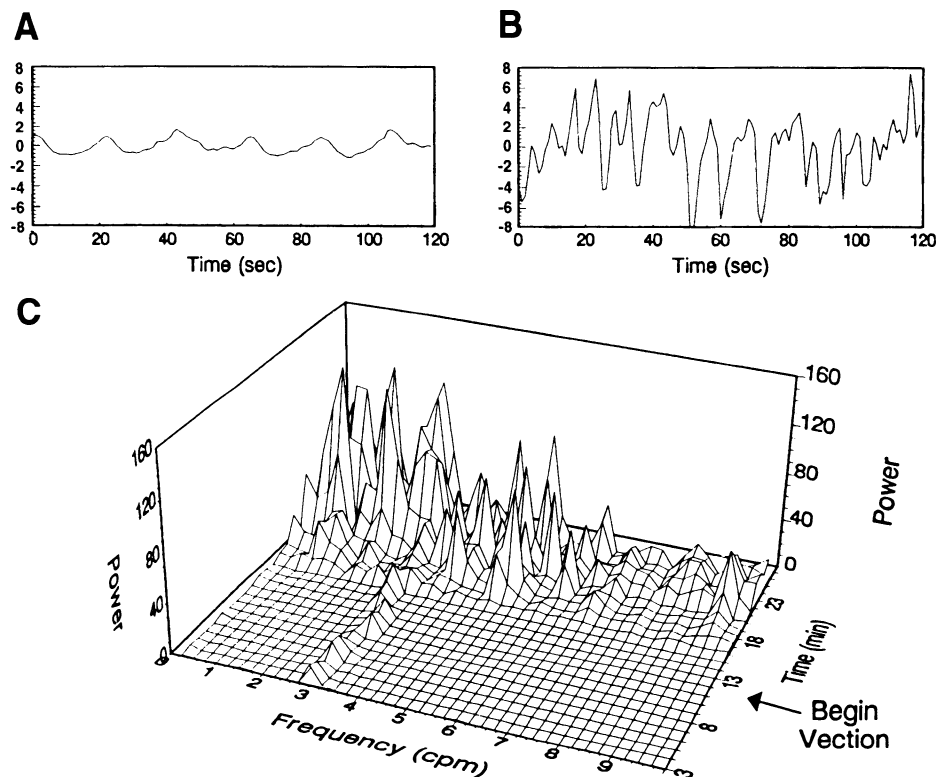
All results are expressed as means \pm SE. Electrogastrographic parameters, nausea scores, and plasma vasopressin levels were compared with use of the Student's t -test for paired and unpaired observations. All t -tests were two tailed. Effects of atropine and indomethacin on vasopressin-evoked nausea scores, activity in the tachygastric frequency range, and plasma vasopressin levels were compared with two-way analysis of variance (ANOVA) for repeated measures. A P value of <0.05 defined statistical significance.

RESULTS

Circular Vection Studies

Control studies. Of 14 healthy volunteers with a prior history of motion sickness from travel in an automobile, boat, or airplane, 10 developed nausea during up to a 15-min period of circular vection at $60^{\circ}/\text{s}$, with maximal nausea (score = 2.6 ± 0.2) occurring after 446 ± 63 s of rotation. Before drum rotation in these individuals, the gastric slow wave was regular at a rate of ~ 3 cpm. Soon after initiation of drum rotation, visible deterioration of

Fig. 1. Raw electrogastrographic signals and running spectral analysis of waveform from a representative circularvection study are shown. Under basal conditions, raw slow wave exhibits a regular oscillation with a period of ~ 20 s (A). With circularvection, there is degeneration of slow wave rhythmicity with replacement by a high-amplitude waveform with a period of 7–10 s (B). Spectral analysis of the raw signal under basal conditions shows a predominance of 3 cycles/minute (cpm) activity (C). With circularvection, total signal power increases markedly with a relative increase in power in the 4.5–9 cpm frequency range. Thus circularvection produced a gastric slow wave tachyarrhythmia in this individual.

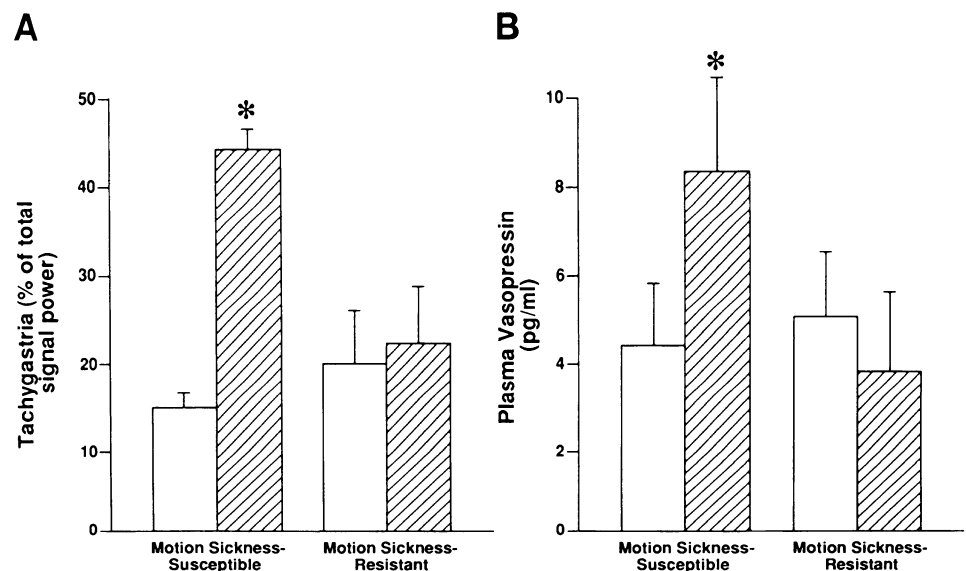


the slow wave rhythmicity was observed before reports of nausea (Fig. 1). With progressive drum rotation, a chaotic slow wave pattern was observed with markedly increased signal activity in the frequency range from 4.5 to 9 cpm, consistent with development of tachyarrhythmic activity. A maximal increase in this activity in the tachygastric frequency range from $15 \pm 2\%$ under control conditions to $45 \pm 3\%$ ($P < 0.05$) was noted at 421 ± 84 s after initiation of drum rotation, ~ 25 s before report of maximal nausea (Fig. 2). In contrast, no increases in signal percentages in the bradygastric signal range were noted in individuals who developed motion sickness in response to circularvection. Four

volunteers remained asymptomatic during 15 min of circularvection, despite a reported history of susceptibility to motion sickness. These individuals did not exhibit an increase in activity in the tachygastric frequency range ($20 \pm 5\%$ basal, $22 \pm 6\%$ vection; Fig. 2), correlating the absence of symptoms with the persistence of normal slow wave rhythmicity in these motion sickness-resistant volunteers.

Plasma vasopressin levels were obtained under basal conditions and during circularvection in both motion sickness-susceptible and resistant volunteers. In those individuals who experienced nausea during circularvection, plasma vasopressin increased from 4.5 ± 1.5

Fig. 2. Effects of circularvection on tachygastric activity and plasma vasopressin levels in symptomatic and asymptomatic subjects are shown. In motion sickness-susceptible subjects ($n = 10$), vection induced significant increases in activity in the tachygastric frequency range ($*P < 0.05$; A) and plasma vasopressin levels ($*P < 0.05$; B). In contrast, motion sickness-resistant volunteers ($n = 4$) exhibited no increases in activity in the tachygastric frequency range or plasma vasopressin (data shown at 14 min of vection). All results are means \pm SE. Open bars, basal; hatched bars, during vection.



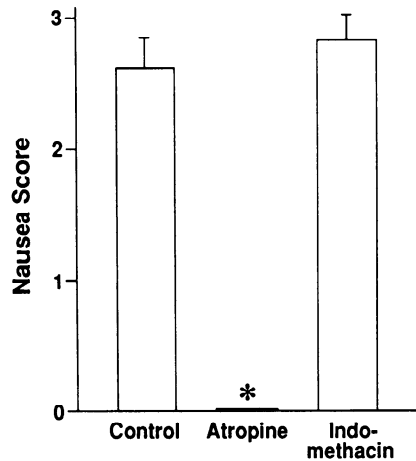


Fig. 3. Effects of atropine administration and indomethacin pretreatment on circular vection-induced nausea in motion sickness-susceptible subjects are shown. Atropine abolished vection-evoked symptoms (* $P < 0.05$), whereas indomethacin had no effect. All results are means \pm SE, $n = 10$.

pg/ml to 8.4 ± 2.5 pg/ml ($P < 0.05$), measured at the time of severe nausea or at 14 min if the volunteer completed the drum rotation protocol (Fig. 2). This time course was not delayed compared with reports of maximal nausea or determination of maximal activity in the tachygastric frequency range, indicating that vasopressin release occurs concurrently with development of symptoms and slow wave disruption. In contrast, those individuals who were asymptomatic during circular vection exhibited no increase in plasma vasopressin (4.9 ± 1.5 pg/ml basal, 2.7 ± 2.2 pg/ml at 4 min, 4.3 ± 2.3 pg/ml at 10 min, and 3.8 ± 1.9 pg/ml at 14 min of vection; Fig. 2), demonstrating the correlation of vasopressin release with induction of nausea and gastric dysrhythmias.

Mediators of Circular Vection-Induced Gastric Dysrhythmias

Atropine infusion. The effects of intravenous atropine infusion on circular vection-evoked nausea, slow wave rhythm disruption, and vasopressin release were tested in the 10 subjects who were susceptible to motion sickness to assess the role of cholinergic neural pathways in the mediation of these motion sickness-associated phenomena. In contrast to the control studies, circular vection studies performed in the presence of atropine showed no induction of nausea (nausea score = 0 ± 0 ; Fig. 3), no increased activity in the tachygastric frequency range ($18 \pm 2\%$ basal, $17 \pm 3\%$ vection; Fig. 4), and no increase in plasma vasopressin levels (5.0 ± 1.5 pg/ml basal, 3.9 ± 1.8 pg/ml vection; Fig. 5). These studies confirm the cholinergic neural dependence of symptom and gastric dysrhythmia generation in response to circular vection (7, 23). Furthermore, these investigations are consistent with the hypothesis that the blockade of cholinergic pathways by atropine inhibits induction of nausea and slow wave disruption via inhibition of vasopressin release.

Indomethacin pretreatment. As endogenous prostaglandin pathways have been demonstrated to be a

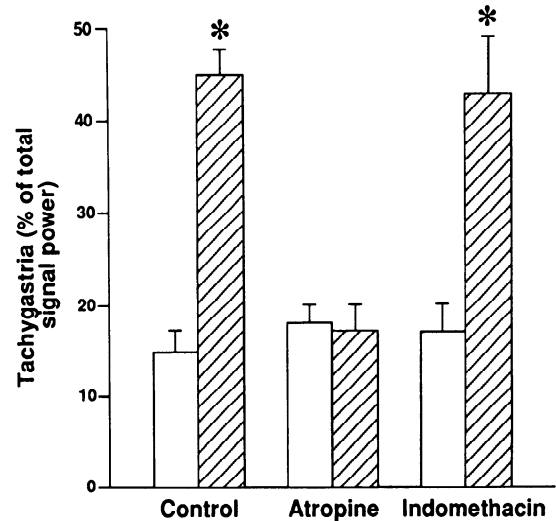


Fig. 4. Effects of atropine administration and indomethacin pretreatment on circular vection-induced increased activity in the tachygastric frequency range in motion sickness-susceptible subjects are shown. Atropine abolished the increase in activity in the tachygastric frequency range with vection (* $P < 0.05$), whereas indomethacin had no effect. All results are means \pm SE, $n = 10$. Open bars, basal; hatched bars, during vection.

common mediator of gastric dysrhythmias in response to diverse stimuli, the effects of indomethacin pretreatment on symptoms, slow wave rhythmicity, and vasopressin release in response to circular vection were tested. In contrast to the effects of atropine infusion, indomethacin pretreatment did not prevent circular vection-induced nausea (nausea score = 2.8 ± 0.2 ; Fig. 3), increased activity in the tachygastric frequency range ($17 \pm 3\%$ basal, $43 \pm 6\%$ vection, $P < 0.05$; Fig. 4), or increases in plasma vasopressin (2.4 ± 1.3 pg/ml

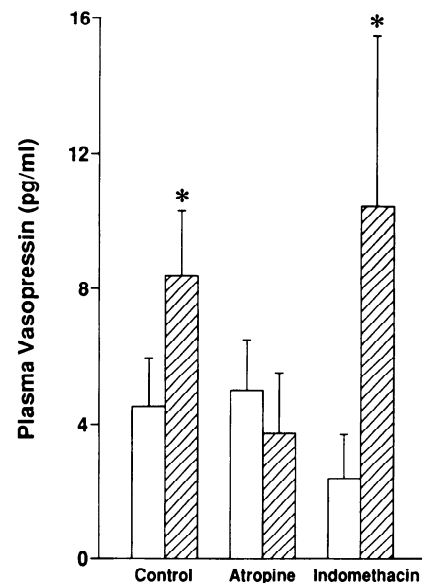
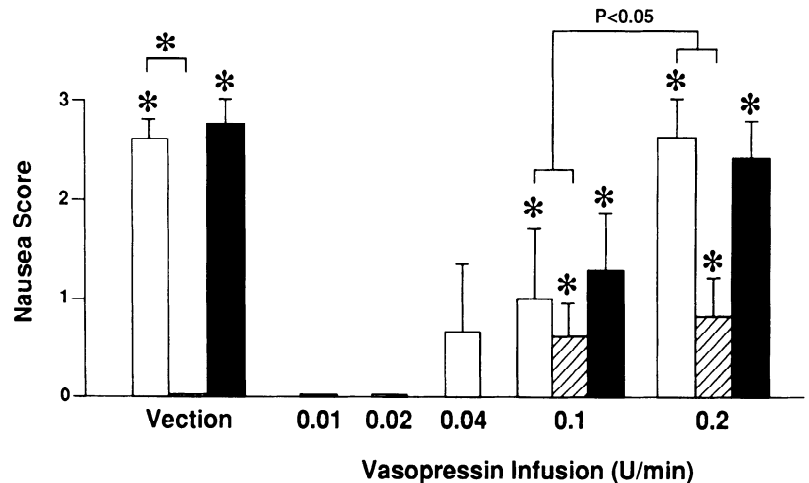


Fig. 5. Effects of atropine administration and indomethacin pretreatment on circular vection-induced plasma vasopressin release in motion sickness-susceptible subjects are shown. Atropine abolished the increase in plasma vasopressin evoked by vection (* $P < 0.05$), whereas indomethacin had no effect. All results are means \pm SE, $n = 10$. Open bars, basal; hatched bars, during vection.

Fig. 6. Effects of vasopressin infusion on nausea in the absence (open bars) and presence (hatched bars) of atropine administration and indomethacin pretreatment (solid bars) are compared with circular vection results. Vasopressin evoked a dose-dependent induction of nausea, which was significant at doses at and above 0.1 U/min ($P < 0.05$ compared with basal). Magnitude of symptoms at 0.2 U/min was similar to that achieved during circular vection. Atropine blunted the symptomatic effects of vasopressin [$P < 0.05$, analysis of variance (ANOVA)], although a small but significant level of nausea persisted ($P < 0.05$ compared with basal). In contrast, indomethacin did not affect vasopressin-induced nausea ($P < 0.05$ compared with basal). All results are means \pm SE, $n = 14$, * $P < 0.05$.



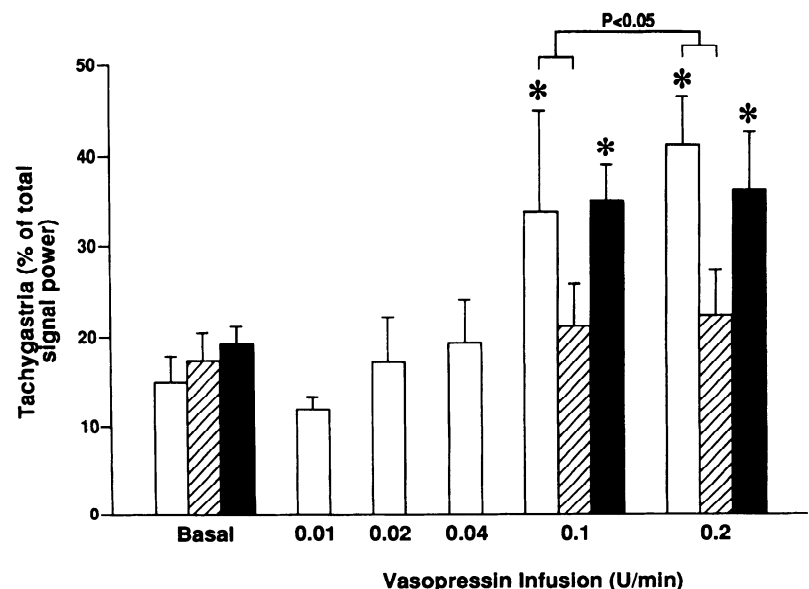
basal, 10.5 ± 5.1 pg/ml vection, $P < 0.05$; Fig. 5). These results are consistent with previous reports of the prostaglandin independence of motion sickness-associated symptoms and slow wave disruption and further show the lack of effect on peripheral vasopressin release (7).

Vasopressin Infusion Studies

Control studies. The effects of intravenous vasopressin infusions on symptoms, slow wave rhythmicity, and plasma vasopressin levels were tested to assess the role of physiological increases in peripheral vasopressin levels in the generation of nausea and tachyarrhythmic activity with motion sickness. At low doses (0.01–0.04 U/min), vasopressin did not evoke significant nausea or slow wave rhythm disruption (Figs. 6 and 7). However, these infusions did produce supraphysiological plasma vasopressin levels even at the lowest vasopressin dose (24.5 ± 5.2 pg/ml at 0.01 U/min; Fig. 8). In contrast, with infusion of higher doses of vasopressin, there was replacement of the normal 3-cpm slow wave rhythmicity with increases in signal activity in the 4.5–9 cpm

frequency range that was associated with reports of nausea (Fig. 9). At 0.1 U/min, vasopressin evoked a nausea score of 1.0 ± 0.7 and increased activity in the tachygastric frequency range to $34 \pm 11\%$ ($P < 0.05$); 0.2 U/min vasopressin induced a nausea score of 2.6 ± 0.4 and increased activity in the tachygastric frequency range to $41 \pm 5\%$ ($P < 0.05$; Figs. 6 and 7). Both of the higher doses produced markedly supraphysiological vasopressin levels (202.7 ± 5.1 pg/ml at 0.1 U/min, 322.1 ± 10.3 pg/ml at 0.2 U/min; Fig. 8). This suggests that vasopressin released into the peripheral circulation is not the sole mediator of nausea and gastric dysrhythmias in motion sickness, although it does not rule out possibilities that peripherally released vasopressin may be a cofactor in the dysrhythmic response or that centrally released vasopressin may be more important. Symptomatic and slow wave responses to vasopressin were compared in those volunteers who developed motion sickness during circular vection and those who did not. Across the entire dose range, there were no differences in reports of nausea severity and induction of gastric dysrhythmias in motion sickness-

Fig. 7. Effects of vasopressin infusion on generation of tachyarrhythmic activity in the absence (open bars) and presence (hatched bars) of atropine administration and indomethacin pretreatment (solid bars) are shown. Vasopressin evoked a dose-dependent increase in activity in the tachygastric frequency range, which was significant at and above doses of 0.1 U/min ($P < 0.05$). Magnitude of activity in the tachygastric frequency range at 0.2 U/min was similar to that observed during circular vection. Atropine blunted the dysrhythmic effects of vasopressin ($P < 0.05$, ANOVA compared with control studies). Indomethacin did not affect the vasopressin-induced increase in activity in the tachygastric range ($P < 0.05$ compared with basal). All results are means \pm SE, $n = 14$, * $P < 0.05$.



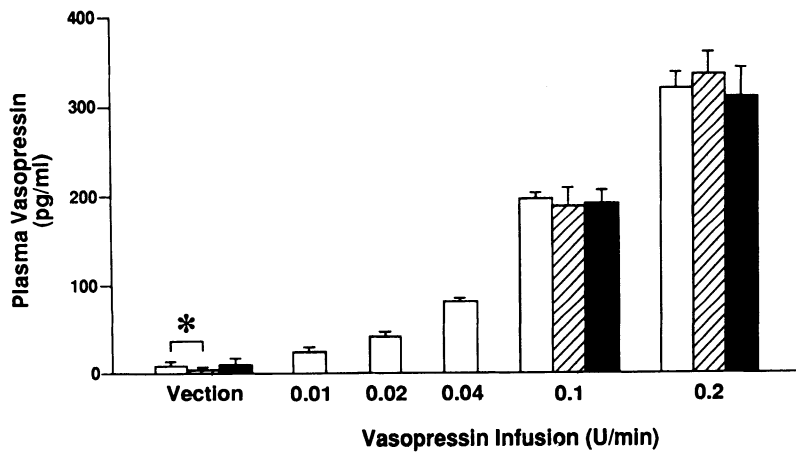


Fig. 8. Plasma vasopressin levels achieved during vasopressin infusion in the absence (open bars) and presence (hatched bars) of atropine administration and indomethacin pretreatment (solid bars) are compared with the circular vection results. Across the whole dose range, vasopressin evoked markedly greater plasma vasopressin concentrations than those measured with vection. Whereas vection-induced increases in plasma vasopressin were blocked by atropine, vasopressin-evoked vasopressin increases were atropine insensitive. Indomethacin had no effect on vection- or vasopressin-evoked elevations in plasma vasopressin. All results are means \pm SE, $n = 14$, $*P < 0.05$.

susceptible and -resistant subjects, indicating that motion sickness resistance is not secondary to impaired responsiveness to increases in plasma vasopressin.

Mediators of Vasopressin-Evoked Gastric Dysrhythmias

Atropine infusion. The effects of atropine infusion on vasopressin-induced nausea and tachyarrhythmias were tested to determine if vasopressin acts via similar pathways as circular vection to produce symptoms and slow wave disruption. As no impressive symptoms or dysrhythmias were noted with low-dose vasopressin infusion, atropine effects were assessed only during high-dose vasopressin administration. During atropine infusion, developments of nausea (nausea score = 0.8 ± 0.4 at 0.2 U/min; $P < 0.05$, ANOVA) and increased activity in the tachygastric frequency range ($22 \pm 5\%$ at

0.2 U/min; $P < 0.05$, ANOVA) were blunted but not abolished in response to high-dose vasopressin (Figs. 6 and 7). In contrast, no effects of atropine were observed on plasma vasopressin levels in response to intravenous vasopressin administration (Fig. 8). These studies, in concert with those reported above, indicate that the release as well as a significant portion of the symptomatic and dysrhythmic effects of vasopressin are dependent on cholinergic neural pathways.

Indomethacin pretreatment. To confirm the prostaglandin independence of vasopressin-evoked nausea and slow wave dysrhythmias, high-dose vasopressin infusions were repeated after pretreatment with the prostaglandin synthesis inhibitor indomethacin. As with its effects on responses to circular vection, indomethacin did not prevent vasopressin-induced nausea (nausea score = 2.4 ± 0.4 at 0.2 U/min) or increased

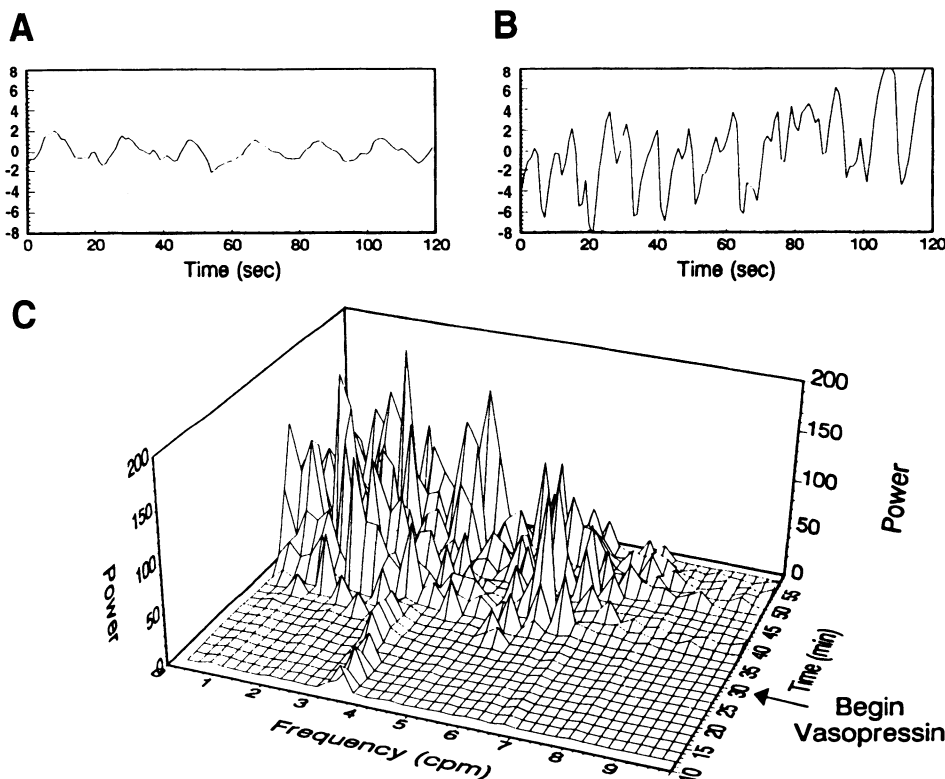


Fig. 9. Raw electrogastrographic signals and running spectral analysis of the waveform from a representative vasopressin infusion study are shown. Under basal conditions, the raw slow wave exhibits a regular oscillation with a period of ~ 20 s (A). With vasopressin infusion (0.2 U/min), there is degeneration of slow wave rhythmicity with replacement by a high-amplitude waveform with a period of ~ 10 s (B). Spectral analysis of the raw signal shows a predominance of 3 cpm activity (C). With vasopressin infusion, the total signal power increases markedly with a relative increase in power in the 4.5–9 cpm frequency range. Thus vasopressin produced a gastric slow wave tachyarrhythmia in this individual.

activity in the tachygastric frequency range ($36 \pm 7\%$ at 0.2 U/min) and did not affect plasma vasopressin levels (Figs. 6–8). Thus, as with circular vection, vasopressin acts to induce nausea and slow wave disruption via pathways not dependent on endogenous prostaglandin production.

DISCUSSION

Motion sickness, experimentally induced by rotary stimuli, is associated with stereotypic alterations in gastrointestinal function. A variety of motor abnormalities have been characterized, including delays in gastric emptying, loss of antral contractility, reduction in gastric tone, and disruption of small intestinal contractile activity (22, 26). Additionally, disruptions in the normal rhythmicity of the gastric slow wave have been described in response to optokinetic stimulation-evoked experimental motion sickness (20). The pathogenic role of these gastric slow wave dysrhythmias in the generation of symptoms is uncertain, but the reproducible finding that the slow wave rhythm disruptions precede reports of nausea suggests a possible causative relationship (20, 27).

A variety of neural mediators appear to be important for induction of nausea and gastric dysrhythmias with motion sickness. The therapeutic efficacy of antimuscarinic medications in control of nausea suggests a pivotal role for cholinergic pathways in the mediation of motion sickness (3, 15). Recent studies have further shown that antimuscarinic agents prevent induction of gastric dysrhythmias during vection-evoked motion sickness (7, 23). The inability of the peripherally acting muscarinic receptor antagonist methscopolamine, which crosses the blood-brain barrier to a very limited degree, to prevent vection-evoked symptoms or slow wave rhythm disruption provides evidence that these cholinergic neural pathways reside within the central nervous system (4, 7). Other neural mediators may play modulatory roles in motion sickness. Agents such as ephedrine and amphetamines exhibit therapeutic efficacy, suggesting involvement of adrenergic pathways as well (24). However, the role of adrenergic pathways in mediating motion sickness is controversial, as the α_2 -adrenoceptor antagonist yohimbine reduces susceptibility to motion sickness in cats, suggesting in some models that α -adrenergic influences may cause rather than prevent motion sickness (13). Furthermore, we have demonstrated reduction in both symptoms and gastric tachyarrhythmias during circular vection-induced motion sickness by pretreatment with the α -adrenoceptor antagonist phentolamine (7). Histaminergic pathways have been postulated to play a role in motion sickness, and antihistamine agents have shown effectiveness in preventing the tachygastric response to circular vection (15, 16, 24). However, the effectiveness of a given histamine antagonist in treating motion sickness correlates closely with its intrinsic anticholinergic activity, suggesting that the histamine pathways per se may be relatively unimportant in the response to motion stimuli (24).

Vasopressin is a peptide released into the peripheral circulation from the pituitary during experimental motion sickness in a time course similar to induction of nausea and gastric slow wave rhythm disruption in human and animal models (5, 10, 12, 27). Furthermore, when administered intravenously, vasopressin induces a range of gastrointestinal symptoms, including cramping, nausea, and retching in most human subjects tested (21). Finally, selective antagonists for the vasopressin V_1 receptor prevent induction of motion sickness in squirrel monkeys during rotatory stimulation (1, 2). These studies raise the possibility that endogenous vasopressin release may be a pathogenic mediator of the nausea of motion sickness. However, against this hypothesis is the report that hypophysectomy, with presumed removal of all vasopressin-synthesizing tissue, does not prevent motion sickness in experimental models (15).

Thus the aim of the current investigations was to determine if peripherally released vasopressin might be an important physiological mediator of the nausea and gastric dysrhythmias associated with motion sickness in healthy humans. In our first experiments, we showed that circular vection evokes increases in plasma vasopressin that occur temporally in association with development of nausea and induction of activity in the tachygastric frequency range in subjects who are susceptible to experimental motion sickness, a finding that confirms previous reports (10, 27). In contrast, individuals resistant to circular vection showed no increases in plasma vasopressin. Thus if vasopressin is a mediator of motion sickness, resistance to motion sickness in asymptomatic humans stems from impaired release of vasopressin and not necessarily from an end organ insensitivity to its effects. Next, the effects on plasma vasopressin levels of a muscarinic antagonist known to block symptoms and dysrhythmias in response to circular vection were tested. In this experiment, atropine blockade of vection-evoked nausea and increased activity in the tachygastric frequency range was associated with abolition of the increase in plasma vasopressin, supportive of the hypothesis that a potential mechanism for the beneficial effects of muscarinic antagonists in treating motion sickness is the prevention of vasopressin release.

The circular vection results were correlated with vasopressin infusion studies in healthy humans to determine if the physiological increases in plasma vasopressin during motion sickness might be responsible for induction of symptoms and slow wave disruption with rotatory stimulation. Vasopressin evoked dose-dependent induction of nausea and increased activity in the tachygastric frequency range. At 0.2 U/min, vasopressin-induced symptoms and gastric dysrhythmias were quantitatively similar to those observed with circular vection. Of note, individuals who were susceptible to the rotatory effects of circular vection and those who were resistant exhibited similar symptomatic and slow wave responses to intravenous vasopressin, indicating that resistance to motion sickness does not stem from insensitivity to the effects of vaso-

pressin. Across the doses tested, vasopressin infusions produced plasma vasopressin levels in excess of those observed with circular vection, indicating that peripheral levels of vasopressin by themselves are not responsible for induction of motion sickness, a phenomenon for which several possible explanations exist. However, the ability of vasopressin to reproduce the symptomatic and electrogastrographic effects of circular vection suggests that the increase in plasma vasopressin with experimental motion sickness is not caused by nausea itself. It is conceivable that cofactors in addition to vasopressin release may be needed for full induction of the symptomatic and slow wave disruptions with motion sickness. Additionally, as central neural rather than peripheral neural muscarinic antagonists are prophylactic against induction of motion sickness and as vasopressin is presumably released by the posterior pituitary into a local portal circulation, it is possible that central rather than peripheral actions of vasopressin are responsible for nausea and increased activity in the tachygastric frequency range with motion sickness.

The present studies show a clear association of vasopressin release and actions with motion sickness-induced symptoms and slow wave disruption; however, a cause and effect relationship cannot be proven at this time. Confirmation of the physiological importance of centrally released vasopressin in mediating motion sickness-associated symptoms and tachygastria will require approval in humans of vasopressin antagonists which cross the blood-brain barrier. This issue has therapeutic importance because the development of a short-acting well-tolerated vasopressin receptor antagonist for treatment of motion sickness would obviate the need for many present medications such as scopolamine, ephedrine, and dimenhydrinate, all of which measurably impair cognitive function in humans (25).

The effects of atropine on vasopressin-evoked nausea and slow wave disruption were tested to assess the dependence of these responses on muscarinic neural pathways. In these studies, atropine blunted the symptomatic and dysrhythmic effects of high-dose vasopressin infusion without affecting peripheral circulating vasopressin levels. This finding suggests that, in addition to the muscarinic dependence of vasopressin release, at least some of the actions of vasopressin are dependent on neural cholinergic pathways as well. As vasopressin levels did not increase during vection studies with atropine, it is not possible to assess if this mechanism is operative with experimental motion sickness. The presence of residual nausea during coinfusion of atropine and vasopressin raises the possibility that noncholinergic pathways may mediate a small fraction of the effects of vasopressin. It is known that epinephrine and cortisol increase during motion sickness; it is conceivable that these or other mediators may be responsible for this noncholinergic component. This issue is worthy of further investigation. The role of noncholinergic pathways in the dysrhythmic response to vasopressin is less clear. Although there was in-

creased dysrhythmic activity compared with basal recordings after atropine, this did not reach statistical significance.

The final studies tested the role of endogenous prostaglandins in mediating vasopressin-evoked nausea and increased activity in the tachygastric frequency range. Animal and human studies have shown the importance of prostaglandin pathways in inducing slow wave rhythm disturbances in response to diverse stimuli. In dogs, the cyclooxygenase inhibitor indomethacin prevents slow wave disruption in response to epinephrine and Met⁵-enkephalin, whereas prostaglandin E evokes gastric dysrhythmias (9). Indomethacin also prevents tachygastric responses to acute hyperglycemia and nicotine administration in humans (8, 11). Studies of *ex vivo* human gastric smooth muscle show increases in the tissue pacemaker frequency during prostaglandin E₂ perfusion and decreases with indomethacin (18). These studies suggest that prostaglandin production may be a common mediator for a broad range of emetic and dysrhythmic stimuli. However, we have previously shown that indomethacin does not affect vection-induced nausea and tachyarrhythmic activity, indicating that this stimulus acts via prostaglandin-independent pathways (7). In the present study, we further showed that indomethacin had no effect on vasopressin release, providing supportive evidence for the prostaglandin-independent nature of motion sickness. Thus we tested the ability of indomethacin to blunt vasopressin-evoked nausea and increased activity in the tachygastric frequency range. Had the responses to vasopressin been mediated by prostaglandin-dependent pathways, this would have been inconsistent with the hypothesis that vasopressin is a potential mediator in motion sickness. In fact, indomethacin pretreatment had no effects on the symptomatic or dysrhythmic responses to vasopressin infusion and did not affect plasma vasopressin levels. Thus this indicates that, as with vection, vasopressin-induced nausea and increased activity in the tachygastric frequency range are mediated by prostaglandin-independent pathways.

In conclusion, circular vection induces nausea, gastric dysrhythmias, and peripheral vasopressin release in motion sickness-susceptible but not -resistant humans via cholinergic neural, prostaglandin-independent pathways. Vasopressin infusions that produce supraphysiological plasma levels evoke symptoms and gastric dysrhythmias via similar neural pathways to equal degrees in motion sickness-susceptible and -resistant subjects, indicating that motion sickness resistance is not mediated by end-organ unresponsiveness to vasopressin. Therefore, the central neural but not the peripheral actions of vasopressin may contribute to induction of nausea and disruption of slow wave rhythmicity with motion sickness. Furthermore, the ability of atropine to blunt both the release of vasopressin and the symptomatic and dysrhythmic effects of vasopressin provides insight into the beneficial clinical effects of antimuscarinic agents in the treatment of motion sickness.

This work was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases Grants RO1-DK-35783 and P30-DK-34933 and by Grants MO1-RR00042 and 3 MO1-RR00042-32S1 from the General Clinical Research Centers Program.

Address for reprint requests: W. L. Hasler, 3912 Taubman Center, Box 0362, Univ. of Michigan Medical Center, Ann Arbor, MI 48109.

Received 2 October 1995; accepted in final form 2 October 1996.

REFERENCES

- Cheung, B. S. K., R. L. Kohl, K. E. Money, and L. B. Kinter. Etiologic significance of arginine vasopressin in motion sickness. *J. Clin. Pharmacol.* 34: 664–670, 1994.
- Cheung, B. S. K., K. E. Money, R. L. Kohl, and L. B. Kinter. Investigation of anti-motion sickness drugs in the squirrel monkey. *J. Clin. Pharmacol.* 32: 163–175, 1992.
- Dahl, E., D. Offer-Ohlson, P. E. Lillevold, and L. Sandvik. Transdermal scopolamine, oral meclizine, and placebo in motion sickness. *Clin. Pharmacol. Ther.* 36: 116–120, 1984.
- Domino, E. F., and G. Corasen. Central and peripheral effects of muscarinic cholinergic blocking agents in man. *Anesthesiology* 28: 568–574, 1967.
- Fox, R. A., L. C. Neil, N. G. Daunton, and J. Lucot. Vasopressin and motion sickness in cats. *Aviat. Space Environ. Med.* 58, Suppl. 9: A143–A147, 1987.
- Glick, S. M., and A. Kagan. Radioimmunoassay of arginine vasopressin. In: *Methods of Hormone Radioimmunoassays*, edited by B. M. Jaffe and H. R. Behrmann. New York: Academic, 1979, p. 341–351.
- Hasler, W. L., M. S. Kim, W. D. Chey, V. Stevenson, B. Stein, and C. Owyang. Central cholinergic and α -adrenergic mediation of gastric slow wave dysrhythmias evoked during motion sickness. *Am. J. Physiol.* 268 (Gastrointest. Liver Physiol. 31): G539–G547, 1995.
- Hasler, W. L., H. C. Soudah, G. Dulai, and C. Owyang. Mediation of hyperglycemia-evoked gastric slow wave dysrhythmias by endogenous prostaglandins. *Gastroenterology* 108: 727–736, 1995.
- Kim, C. H., A. R. Zinsmeister, and J.-R. Malagelada. Mechanisms of canine gastric dysrhythmia. *Gastroenterology* 92: 993–999, 1987.
- Koch, K. L., J. Summy-Long, S. Bingaman, N. Sperry, and R. M. Stern. Vasopressin and oxytocin responses to illusory self-motion and nausea in man. *J. Clin. Endocrinol. Metab.* 71: 1269–1275, 1990.
- Kohagen, K., W. Hasler, M. Kim, W. M. McDonnell, W. D. Chey, and C. Owyang. Transdermal nicotine evokes gastric dysrhythmias via a prostaglandin-dependent pathway with associated antral hypomotility: a model for decreased gastric motility with smoking (Abstract). *Gastroenterology* 106: A525, 1994.
- Kohl, R. L. β -Endorphin and arginine vasopressin following stressful sensory stimuli in man. *Aviat. Space Environ. Med.* 63: 986–993, 1992.
- Lucot, J. B., and G. H. Crampton. Xylazine emesis, yohimbine and motion sickness susceptibility in the cat. *J. Pharmacol. Exp. Ther.* 237: 450–455, 1986.
- Mogard, M. H., V. Maxwell, T. Kovacs, G. VanDeventer, J. D. Elashoff, T. Yamada, G. L. Kauffman, and J. H. Walsh. Somatostatin inhibits gastric acid secretion after gastric mucosal prostaglandin synthesis inhibition by indomethacin in man. *Gut* 26: 1189–1191, 1985.
- Money, K. E. Motion sickness. *Physiol. Rev.* 50: 1–39, 1970.
- Muth, E. R., R. M. Stern, M. Jokerst, and K. L. Koch. Effects of dimenhydrinate (Dramamine) on gastric myoelectric activity and vection-induced motion sickness (Abstract). *Gastroenterology* 104: A1054, 1993.
- Rane, A., O. Oelz, J. C. Frolich, H. W. Seyberth, B. J. Sweetman, J. T. Watson, G. R. Wilkinson, and J. A. Oates. Relation between plasma concentration of indomethacin and its effect on prostaglandin synthesis and platelet aggregation in man. *Clin. Pharmacol. Ther.* 23: 658–668, 1978.
- Sanders, K. M., and J. H. Szurszewski. Does endogenous prostaglandin affect gastric motility? *Am. J. Physiol.* 241 (Gastrointest. Liver Physiol. 4): G191–G195, 1981.
- Stern, R. M., S. Q. Hu, M. W. Vasey, and K. L. Koch. Adaptation to vection-induced symptoms of motion sickness. *Aviat. Space Environ. Med.* 60: 566–572, 1989.
- Stern, R. M., K. L. Koch, W. R. Stewart, and I. M. Lindblad. Spectral analysis of tachygastria recorded during motion sickness. *Gastroenterology* 92: 92–97, 1987.
- Thomford, N. R., and K. R. Sirinek. Intravenous vasopressin in patients with portal hypertension: advantages of continuous infusion. *J. Surg. Res.* 18: 113–117, 1975.
- Thornton, W. E., B. J. Linder, T. P. Moore, and S. L. Pool. Gastrointestinal motility in space motion sickness. *Aviat. Space Environ. Med.* 58A: 16–21, 1987.
- Uijtdehaage, S. H., R. M. Stern, and K. L. Koch. Effects of scopolamine on autonomic profiles underlying motion sickness susceptibility. *Aviat. Space Environ. Med.* 64: 1–8, 1993.
- Wood, C. D. Antimotion sickness and antiemetic drugs. *Drugs* 17: 471–479, 1979.
- Wood, C. D., J. J. Stewart, M. J. Wood, J. E. Manno, B. R. Manno, and M. E. Mims. Therapeutic effects of antimotion sickness medications on the secondary symptoms of motion sickness. *Aviat. Space Environ. Med.* 61: 157–161, 1990.
- Wood, M. J., C. D. Wood, J. E. Manno, and H. M. Redetzki. Nuclear medicine evaluation of motion sickness and medications on gastric emptying time. *Aviat. Space Environ. Med.* 58: 1112–1114, 1987.
- Xu, L. H., K. L. Koch, J. Summy-Long, R. M. Stern, J. F. Seaton, T. S. Harrison, L. M. Demers, and S. Bingaman. Hypothalamic and gastric myoelectrical responses during circular vection-induced nausea in healthy Chinese subjects. *Am. J. Physiol.* 265 (Endocrinol. Metab. 28): E578–E584, 1993.