Regulation of gastric motility at simulated high altitude in conscious rats

Misa Yoshimoto, Mitsuko Sasaki, Nobuo Naraki, Motohiko Mohri, and Kenju Miki

1Department of Environmental Health, Nara Women’s University, Kita-Uoya Nishimachi, Nara 630-8506; and 2Coastal Research Department, Japan Marine Science and Technology Center, Kanagawa 237-0061, Japan

Submitted 1 October 2003; accepted in final form 10 March 2004

Yoshimoto, Misa, Mitsuko Sasaki, Nobuo Naraki, Motohiko Mohri, and Kenju Miki. Regulation of gastric motility at simulated high altitude in conscious rats. J Appl Physiol 97: 599–604, 2004.—The aim of the present study was to examine the effects of acute exposure to hypobaric hypoxia on gastric and colonic motilities. Wistar rats, which were instrumented chronically with strain gauge force transducer to measure gastric and colonic motilities, were exposed acutely to hypobaric hypoxia (0.5 atmosphere absolute (ATA, 380 Torr)) over 1 h. In a separate group, the gastric branches of the vagal nerves were cut and underwent the same experimental protocol. Each contraction wave of the stomach and colon was analyzed into frequency and area under the curves, which were then averaged every 10 min. Acute exposure to 0.5 ATA resulted in significant (P < 0.05) decreases in frequency and area of gastric contraction wave by 0.5 ± 0.1 cycles/min and 64.6 ± 4.0%, respectively. Gastric vagotomy abolished completely the suppression in the area observed in the intact rats during the 0.5-ATA exposures. Colonic motility increased significantly only at the start and end of exposure to 0.5 ATA and sham exposure [1 ATA (760 Torr), time control] in both intact and vagotomized rats. These data suggest that the acute suppression of the area of the gastric contraction wave that occurred during 0.5-ATA exposure is likely to be mediated by the vagal nerve.

hypoxia; mountain sickness; vagal nerve; colonic motility

ACUTE MOUNTAIN SICKNESS DEVELOPS within a few hours after arrival at high altitude and includes anorexia, nausea, vomiting, lack of energy, headache, and malaise, which are prominent at elevations >5,000 m, and affects otherwise healthy men and women (1, 9, 17, 17, 25). Today’s ability to travel rapidly to high altitude results annually in millions of people being exposed to the risk of acute mountain sickness worldwide (17, 24). Although acute mountain sickness has been recognized over the past two centuries (17, 23), little is known about the fundamental causes of these symptoms. Experimental data have been reported that high-altitude exposure delayed gastric emptying time in humans and dogs (8, 23) and was associated with reduced food consumption (5), reduced efficiency of food utilization (16), and suppression of growth in rats (5). It is therefore likely that depression of gastrointestinal function is another major factor afflicting healthy humans at high altitude. However, little information on how gastrointestinal motility is altered at high altitude is available at present.

It is well established that gastric motility is regulated through a complex interacting network of gut regulatory peptides, hormones, and sympathetic and parasympathetic nerves and enteric nervous systems (26). Kimura et al. (7) have reported that acute hypoxia, which is equivalent to oxygen tension at 5,000 m high, causes a decrease in gastric pressure and an increase in gastric vagal nerve activity in acutely prepared anesthetized rats. They suggested that gastric motility may be suppressed and that the gastric vagal nerve was likely to play an important role in its regulation during the high-altitude exposure. However, it is not known whether it is acceptable to extrapolate data obtained during hypoxia in anesthetized animals to the condition of high altitude in the conscious state. Unfortunately, the functions of these regulatory mechanisms of gastric motility at high altitude have not received much attention. To our knowledge, no attempt has been made to measure directly the gastrointestinal contraction wave during high-altitude exposure in conscious freely moving animals. Consequently, the contribution of vagal nerve activity in regulating gastric motility during high-altitude exposure remains unclear.

In the present study, we attempted to measure gastric and colonic contraction waves directly at simulated high altitude at 0.5 atmosphere absolute (ATA, 380 Torr), which is equivalent to a height of 5,065 m, in conscious rats and to quantify how gastric and colonic contraction waves were altered during 0.5-ATA exposure. In addition, the role of gastric vagal nerve activity in regulating gastric motility was studied by comparing the responses of gastric contraction to 0.5-ATA exposure between intact and gastric vagotomized rats.

METHODS

Animal care. The experiments were performed in 20 male Wistar rats (368 ± 6 g). The room was maintained on a 12:12-h light-dark cycle (light on at 7:00 AM); ambient temperature was kept at 24°C. Food and water were available ad libitum. The animals were randomly assigned to two groups: 1) intact group (n = 10) and 2) gastric vagotomized group (n = 10). All procedures were in accordance with the Guiding Principles in the Care and Use of Animals in the Field of Physiological Sciences published by the Physiological Society of Japan (15) and with the prior approval of the Animal Care Committee of Nara Women’s University.

Surgery. All surgery was carried out aseptically in an operating room. The rats were anesthetized with pentobarbital sodium (75 mg/kg). In the gastric vagotomized group, a midline laparotomy was performed, the stomach and lower esophagus were retracted from the abdominal cavity, and the anterior and posterior branches of the gastric nerve were isolated and cut 10 mm from their junctions with the trunks. In the intact group, the gastric nerve branches were isolated but remained intact. Then, a strain gauge force transducer (E-04IS, 5 × 3 mm, Star Medical, Tokyo, Japan) was sutured to the serosa of the stomach (gastric body) and colon (descending colon) to measure the contractile activity of the circular muscle. Thereafter, rats were given antibiotics (Fradiomycin, Mochida-Seiyaku, Tokyo, Japan) intraperitoneally, and the laparotomy wound was sutured.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: K. Miki, Dept. of Environmental Health, Life Science and Human Technology, Nara Women’s Univ., Kita-Uoya Nishimachi, Nara 630-8506, Japan (E-mail: k.miki@cc.nara-wu.ac.jp).

http://www.jap.org 8750-7587/04 $5.00 Copyright © 2004 the American Physiological Society

599
Fig. 1. Schematic drawing of the experimental arrangement. Ambient pressure in the chamber was controlled by the rate of air suction. Air temperature within the chamber was controlled by circulating water attached on the wall. Air was continuously led into the chamber at rate of 3 l/min throughout the experimental period. All physiological variables were amplified within the chamber, and signals were passed through the wall and led to the outside of the chamber. Animal behavior was observed through a small acrylic window by the investigators.

Fig. 2. Schematic presentation of the wave analysis. Each point represents a 1-s data collection. Data were fitted to the Gaussian peak equation, and then amplitude, width, and area of each contraction wave were calculated. $Y = A \exp\left\{-1/2[(X - C)/W]^2\right\}$, where $Y$ is the output voltage of the strain gauge transducer, $A$ is the amplitude of the peak, $X$ is time, $C$ is the centering time, and $W$ is the width of the peak. Instantaneous frequency was calculated from reciprocal of the interval time between peaks. The mean values of frequency, amplitude, width, and area of the contraction were obtained every 10 min. To quantify the responses of width, amplitude, and area, percent changes were calculated by taking the mean of these values during preexposure period as 100%.

Statistical analysis was performed by use of ANOVA for repeated measures (20). When the $F$ values were significant ($P < 0.05$),
individual comparisons were made by use of Fisher’s least significant difference test. Values were reported as means ± SE.

RESULTS

Gastric motility. Figure 3 illustrates typical responses of gastric contraction waves before, during, and after sham exposure (1 ATA, time control) and exposure to 0.5 ATA in an intact rat (top) and in a gastric vagotomized rat (bottom). The gastric contractile wave was clearly suppressed during exposure at 0.5 ATA in the intact rat. The gastric vagotomy abolished the suppression of the gastric contraction wave induced by 0.5-ATA exposure in the intact rat.

Figure 4 represents the time course of the changes in frequency and area of the gastric contractile waves in response to 0.5-ATA exposure and sham exposure (1 ATA, time control) in the intact and gastric vagotomized rats.

The frequency of gastric contraction waves decreased significantly (*P < 0.05) in both intact and vagotomized rats after exposure to 0.5 ATA, from a control level of 5.6 ± 0.1 to an average value of 5.1 ± 0.1 cycles/min at 20–80 min and from a control level of 5.6 ± 0.1 to the average value of 5.0 ± 0.1 cycles/min at 20–100 min, respectively; then in the postexposure period they returned gradually to the control level.

The time course of the changes in area after exposure to 0.5 ATA in intact rats were significantly different from that in gastric vagotomized rats. In the intact rats, area decreased immediately after exposure at 0.5 ATA by 64.6 ± 4.0% (to 35.4%, *P < 0.05) at 10–20 min relative to the control level, and this level was maintained throughout the exposure period. After the end of exposure, area in the intact rats increased immediately and significantly (*P < 0.05, at 60–80 min) above the control level and then decreased to the control level during the recovery period. By contrast, in the gastric vagotomized
rats, the area of the vagotomized rats was maintained at the control level during the exposure except for a sudden dipping of area that occurred at 10–20 min \( (P < 0.05) \). After the end of the 0.5-ATA exposure, area gradually decreased.

The area of the gastric contractile wave in the intact rats exposed to 0.5 ATA were significantly \( (P < 0.05) \) lower at 10–60 min and then higher at 60–80 min when compared with those in gastric vagotomized rats exposed at 0.5 ATA.

In the time control experiment, there were no significant changes in any variable in either group throughout the experimental period.

**Colonic motility.** Figure 5 illustrates the time course of the changes in frequency and area of the colonic contraction wave in the intact and gastric vagotomized rats exposed to 0.5 ATA or after a sham exposure (1 ATA, time control).

Frequency and area of the colonic contraction wave in both intact and gastric vagotomized rats increased significantly \( (P < 0.05) \) but only transiently after the start (0–10 min) and end (60–70 min) of exposure to 0.5 ATA and the sham exposure (1.0 ATA). There was no statistical difference in any of these responses between sham vs. 0.5-ATA exposure in the intact rats and between sham vs. 0.5-ATA exposure in gastric vagotomized rats.

**Cardiovascular and EMG responses.** Figure 6 illustrates the time course of the changes in Pa, Pcv, HR, and EMG in the intact and gastric vagotomized rats exposed at 0.5 ATA and sham exposure (1 ATA).

Pa decreased gradually during the exposure to 0.5 ATA from a control level of 98.0 ± 4.2 mmHg to the lowest point of 78.8 ± 3.7 mmHg at 50–60 min \( (P < 0.05) \) in the intact rats and from a control level of 105.5 ± 3.6 mmHg to the lowest point of 73.6 ± 3.2 mmHg at 50–60 min \( (P < 0.05) \) in the gastric vagotomized rats; thereafter, Pa recovered to the control level.

Pcv decreased significantly only after the end of exposure to 0.5 ATA, from a control level of 0.35 ± 0.56 mmHg to 0.80 ± 0.64 mmHg at 60–70 min \( (P < 0.05) \) in the gastric vagotomized rats, whereas it tended to decrease at 60–70 min in the intact rats.

HR increased significantly after exposure to 0.5 ATA from a control level of 353.1 ± 14.0 beats/min to the highest point of 398.2 ± 9.9 beats/min at 0–10 min \( (P < 0.05) \) in the intact rats and from a control level of 379.7 ± 15.3 beats/min to 452.8 ± 16.1 beats/min at 0–10 min \( (P < 0.05) \) in gastric vagotomized rats; thereafter, HR decreased gradually and reached the lowest point of 253.5 ± 10.5 beats/min at 50–60 min \( (P < 0.05) \) in the intact rats and 252.4 ± 19.1 beats/min at 50–60 min \( (P < 0.05) \) in the gastric vagotomized rats and then gradually recovered to the control level.
In the time control experiment, Pa, Pcv, and HR did not change significantly throughout the experimental period in either intact or gastric vagotomized rats.

EMG was presented in percent changes from the control level and did not change after exposure to 0.5 ATA and sham exposure (1 ATA) in either the intact or gastric vagotomized rats throughout the experimental period.

**DISCUSSION**

The present study demonstrated that acute 0.5-ATA exposure resulted in significant reductions in the magnitude of frequency and area of the gastric contraction wave in the intact conscious rats. Gastric vagotony abolished the reductions of the area of the gastric contraction wave. These results suggest that the gastric vagal nerve seems to play a critical role in reducing gastric motility during acute exposure at 0.5 ATA.

Because the changes in gastric motility were prominent at elevations >5,000 m (25) as well as during hypoxia below ~10% oxygen concentration (27), 0.5-ATA (10.5% oxygen) exposure was chosen to compare the results obtained in the present study with those of previous reports (3–5, 16, 22, 27).

In the intact rats, acute 0.5-ATA exposure resulted in an immediate and sustained reduction ($P < 0.05$) of the area of the gastric contraction wave, whereas the frequency of the gastric contraction decreased gradually and significantly ($P < 0.05$) during the exposure, indicating that the gastric motility was inhibited by acute exposure to 0.5 ATA in conscious rats. Although, to our knowledge, no attempts have been made to measure directly the gastric contraction wave during either hypoxia or hypobaric condition in conscious intact animals, the present results are consistent with previous reports in which changes in gastric motility under high altitude and hypoxia were obtained indirectly. Fang and Chen (4) measured gastric emptying time by roentgenograms and showed averaged gastric emptying time increased by ~50% during hypoxia at a simulated altitude of 5,400 m in conscious rats. Yamaji et al. (27) demonstrated in conscious rats that 7.6% O$_2$ hypoxia resulted in a significant increase in gastric residue compared with the normoxic condition, indicating an increase in gastric emptying time. Furthermore, Szabo et al. (22) reported that acute 10% hypoxia caused an increase in gastric residual volume within 10 min in the newborn piglet. The observed reductions of the frequency and area of the gastric contraction wave (Fig. 4) in the present study could explain the increase in gastric residue and gastric emptying time observed during hypoxia. The outcome of the reduction in area of the gastric contraction wave would be a reduction in the pressure gradient to drive gastric contents into the duodenum. Furthermore, the gradual decrease in the frequency of the gastric contraction wave also may reduce the total driving force for the flow rate of gastric contents toward the duodenum over unit time, which would cause an increase in gastric residue and gastric emptying time.

The present study further demonstrated that gastric vagotomy abolished the reductions in the area of gastric contraction wave observed during 0.5-ATA exposure in intact rats, suggesting that the vagal nerve seemed to play a critical role in modulating the area of the gastric contraction wave. It has been generally recognized that the multiple factors and networks are involved in the regulation of gastric motility (26). Kimura et al. (7) have reported that 10% and 6% hypoxia causes an immediate increase in gastric vagal nerve activity within a few seconds, associated with the decrease in gastric tone and amplitude of contraction measured by the balloon inflation method. This suggests that 0.5-ATA exposure might cause an increase in gastric vagal nerve activity, which in turn exerts a tonic inhibitory influence on the amplitude of the gastric contraction wave. However, direct electrical stimulation of gastric vagal branch causes an increase in gastric antral contractions (2), which is consistent with the view that gastric vagal nerves have both inhibitory and excitatory influences on the gastric motility (2). Although it is not evident from the present study how the gastric vagal nerves attenuate the area of gastric contraction during 0.5-ATA exposure, it is safe to conclude that the gastric vagal nerves are critically involved in the reduction in the area of the gastric contraction wave, which in turn determines the gastric emptying time during 0.5-ATA exposure and hypoxia (~10% O$_2$).

Gastric vagotomy had no effect on the reduction of frequency of the gastric contraction wave that was observed in intact rats exposed to 0.5 ATA. This suggests that the vagal nerve may play a minor role in modulating frequency of gastric contraction wave during 0.5-ATA exposure. It is of interest that, in both intact and gastric vagotomized rats, the time course of change in the frequency of gastric contraction wave during and after 0.5-ATA exposure was similar to that of systemic arterial pressure, which is consistent with a previous report utilizing systemic hypoxia in anesthetized rats (12). This may suggest the possibility that a decrease in gastric perfusion pressure might be related to the decrease in frequency of gastric contraction wave, but it remains to be studied.

The frequency and area of colonic contraction wave were increased transiently during the transition between 1- and 0.5-ATA exposure in both the intact and the gastric vagotomized group. Because those variables were also increased temporally during the transition during sham exposure (1 ATA), these temporal increases may not be attributed to the changes in atmospheric pressure per se but may be possibly related to the noise occurring transiently during the decompression and compression phases in the chamber.

Information originating from the stomach, including vagal afferent nerve activity and peptides such as ghrelin, has been shown to be involved in food intake and energy metabolism (21). The sustained decrease in gastric motility consistently observed in the present and previous studies may induce a decrease in delivery rate of gastric content, an increase in gastric residual volume, and then a distension of the gastric wall, which in turn may modulate the neurohumoral signals stemming from the stomach, causing an increased sensation of satiety and suppression of feeding behavior (10, 26, 28). The reduced delivery rate of gastric contents may also result in a decrease in absorption rate of nutrients and fluid, causing fatigue due to lack of energy source at high altitude. It is also probable that forced intake of food may cause an overdistension of the gastric wall when there is considerable gastric residual volume caused by the reduction in gastric motility, which may trigger nausea (6) or vomiting at high altitude. Therefore, the suppression of gastric motility, which is attributed to the changes in vagal nerve activity (10), may be a key factor causing anorexia, nausea, and lack of energy at high altitude (5, 17, 25).
ACKNOWLEDGMENTS

The authors thank Dr. Edward J. Johns (Department of Physiology, University College Cork, Cork, Ireland) for critical reading of the manuscript and Dr. Miyako Takaki (Department of Physiology, Nara Medical University, Nara, Japan) for valuable discussion.

REFERENCES