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Effect of Capsaicin-Containing Red Pepper Sauce Suspension on Upper Gastrointestinal Motility in Healthy Volunteers

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Afferent nerves play a major role in the regulation of gastrointestinal motility. The questions remains if specific food ingredients can selectively activate such fibers. The aim of the study was to investigate the effect of intraesophageal application of a capsaicin-containing red pepper sauce (Tabasco) suspension on upper gastrointestinal motility in a controlled trial. After a baseline recording [esophageal motility, balloon distension, electrogastrogram (EGG)], red pepper or saline solution was infused intraesophageally in seven healthy volunteers. At 30 min gastric emptying and orocecal transit time were determined using a [^{13}C]acetate and H_2-lactulose breath test. Infusion of red pepper sauce suspension significantly increased the amplitudes (65.8 ± 3 to 78.5 ± 4.7 mm Hg, $P < 0.05$) and propagation velocity (2.9 ± 0.3 to 4.25 ± 0.3 sec, $P < 0.05$) of esophageal pressure waves and LES pressure (17.8 ± 1.4 to 23.7 ± 2.6 mm Hg, $P < 0.05$). It significantly decreased perception and discomfort threshold of intraesophageal balloon distension, reduced the percentage of normal electrical activity in the EGG, and delayed gastric emptying (saline: $T_{1/2}$ 42.9 ± 12.0 min vs red pepper: $T_{1/2}$ 66.8 ± 19.0 min, $P < 0.05$). Despite the prolongation of gastric emptying, orocecal transit time was not altered, indicating an actual increase of intestinal transit. Esophageal application of capsaicin-containing red pepper sauce suspension had profound changes on upper gastrointestinal motility, which could improve clearance and protection of the esophagus and could lead to retention of the irritant in the stomach and faster transit through the small bowel.

KEY WORDS: capsaicin; gastrointestinal motility; esophageal motility; afferent nerves; gastric emptying.

Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is the main component of red pepper, inducing hot taste, and is known to activate afferent nerve fibers (1). Capsaicin has been shown to have a protective function in the gastric mucosa as the stimulation of afferent nerve endings by capsaicin protects against aspirin or alcohol-induced gastric injury (2–5). *In vivo* and *in vitro* animal studies suggest an important role of capsaicin-sensitive afferents for upper gastrointestinal motility. The inhibition of gastric motility in the rat caused by intraperitoneal acid or laparotomy (6) as well as the inhibition of gastric emptying by CCK (7) or by intestinal lipids (8) are mediated by capsaicin-sensitive vagal afferent nerves. In the same species the luminal acid-induced and part of the glucose-induced inhibition of gastric emptying is mediated by capsaicin-sensitive small intestinal afferents (9).

In *in vitro* studies using guinea pig ileum and rabbit distal colon, capsaicin induced excitatory motor re-

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sponses in muscle strips that were mediated by releasing substance P (10). In rabbit distal colon capsaicin caused a transient stimulation of motility followed by an inhibition of the contractile activity (11). In conscious dogs the colonic motility was stimulated by intragastric administration of capsaicin (12). Histochemical evidence indicates that different populations of primary afferents with specific patterns of colocalized neuropeptides innervate different target organs (13), which could be responsible for different responses in stomach and small intestine induced by afferent nerve stimulation described in these animal studies.

In contrast to these animal studies, the effect of capsaicin on human gastrointestinal motility is mostly unknown. Ethical considerations and liability, due to possible neurotoxic effects, which, however, occur only at higher dosages (14), make it difficult to get approval for studies involving oral application of pure Capsaicin to human volunteers. In humans red pepper in different dosages and preparations failed to show a significant effect on orocecal transit time, amount of ileostomy output, or esophageal contractile amplitude (15–17). However, these studies used an oral administration and determined only motility or functional parameters at one time only, and the time interval between application and measurement is not clearly stated. We used an internationally available red pepper sauce (Tabasco, McIlhenny Company, Avery Island, Louisiana), in which we demonstrated the presence of sufficient amounts of capsaicin to activate afferent nerve fibers with HPLC, for intraesophageal application via a plastic tube to eliminate aversive sensations induced by the hot taste or smell of the red pepper solution. This application allows precise control of the application dosage and time. The aim of the present study was to determine the effect of this capsaicin-containing red pepper sauce (Tabasco) suspension on various parameters of esophageal, gastric, and intestinal motility and esophageal balloon distension in humans.

MATERIALS AND METHODS

Patients. The present study was performed on seven healthy volunteers (age 22–29 years) who had given their written informed consent. The study was approved by the ethical committee of the medical faculty of the Technical University, Munich. None of the volunteers had a history suggesting esophageal disease and none had received any medication known to influence esophageal motility for at least 72 hr before the study. On two separate days the identical protocol was carried out with either infusion of saline or red pepper sauce (Tabasco) suspension (25% v/v).

Esophageal Manometry. Manometric recordings were obtained using an eight-lumen polyvinyl catheter (diameter 4.5 mm) consisting of four lateral orifices (diameter 0.8 mm) every 5 cm with 90° rotation and four radial orifices (diameter 0.8 mm) at the distal end of the catheter (Synectics Medical, Frankfurt, Germany). The catheter was continuously perfused using a low-compliance pneumohydraulic capillary infusion system (Mui Scientific, Mississauga, Ontario, Canada) at a rate of 0.5 ml/min. With this flow rate, a rate of pressure rise >400 mm Hg/sec upon occlusion of the orifice was achieved. Pressure was recorded with external pressure transducers on an eight-channel PC-Polygraph system (Synectics). Before each manometry, the system was calibrated with a mercury sphygmomanometer. Extreme caution was taken to avoid the presence of air bubbles in the manometric system.

Experimental Design and Analysis. All subjects were studied in a supine position. The catheter was inserted nasally after a 12-hr fast. The gastric position of the side holes was confirmed by demonstrating a rise in pressure during the inspiratory phase of respiration. After accommodation to the catheter (15 min) and a basal esophageal manometry (−30 and 0 min), either 10 ml 25% red pepper sauce suspension (2.5 ml Tabasco plus 7.5 ml distilled water adjusted to pH 7.0) or saline solution (pH 7.0) at 37°C was infused 10 cm above the lower esophageal sphincter (5 ml/min). Following the red pepper infusion, stationary pull-through manometry was performed at 5, 15, and 30 min. Then the resting lower esophageal sphincter pressure was measured at end exspiration using the station pull-through technique. Mean LES pressure was calculated as average of the pressure values obtained in the four circumferrential side holes from four pull-throughs across the sphincter.

For assessment of esophageal wave amplitude, duration, and propagation velocity, the four distal radial channels were positioned in the lower esophageal sphincter; thus the proximal recording points were located 5, 10, 15, and 20 cm above the LES. In this position 10 wet swallows (5 ml of water) were performed. At the beginning of each manometry, pulse rate and blood pressure were determined to monitor possible circulatory effects of the red pepper solution.

Thirty minutes after ingestion of the red pepper sauce suspension or the saline control, the test meal was ingested over a period of 3 min and gastric emptying ([^{13}C] acetate breath test), cutaneous electrogastrogram, and small intestinal transit (H_2 breath test) were analyzed. A schematic overview of the experimental protocol is given in Figure 1.

Analysis of Red Pepper Sauce. The composition of the red pepper sauce suspension was analyzed by routine clinical chemistry (electrolytes, osmolality, pH). The content of capsaicinoids was determined with high-pressure liquid chromatography (18) using a 3.9 × 300-mm 10-μm C_{18} μ-Bondopak Column (Waters) with a flow rate of 1 ml/min and UV detection at 235 nm. The red pepper solution was dissolved in ethyl acetate, which also served as internal standard, and filtered (pore size 0.2 μm). Then 20 μl of the filtered solution was injected and eluted with isopropanol–*n*–hexane–methanol (10:90:1). 8-Methyl-*N*-vanillyl-6-nonenamide (capsaicin) obtained from Sigma (Munich, Germany) was used as a standard. The pure Tabasco sauce had a total content of 0.35 mg capsaicinoids/ml, which

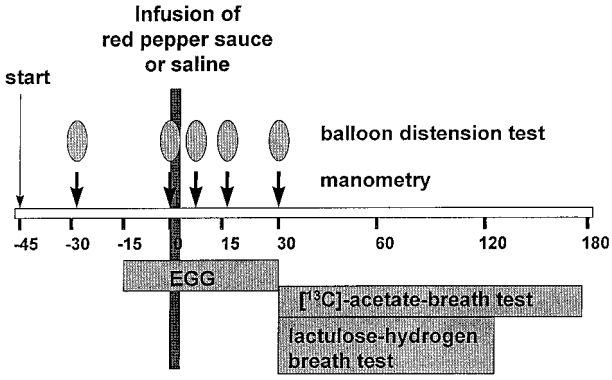

Fig 1. Schematic diagram of the experimental protocol.

complies with the capsaicinoid content in extracts from red chili or other red pepper plants (18). The content of pure capsaicin in extracts from red chili was shown to be 41–48%. Thus the total amount of pure capsaicin from the infused solution (2,5 ml Tabasco) was 0.42 mg, which is equivalent to a concentration of 1.4×10^{-4} M. The composition of the red pepper sauce suspension infused was Na^+ 70.8 mmol/liter, K^+ 8.4 mmol/liter, Ca^{2+} 0.61 mmol/liter, osmolality 560 mosm/kg, caloric content 0 kcal).

Balloon Distension Test. A custom made latex rubber balloon was tightly attached to the catheter assembly opposite the 15-cm side hole opening of the manometric catheter. The latex balloon was 3 cm in length and had maximum diameter of 3 cm at 12 ml air inflation. The balloon was placed 5 cm above the upper end of the LES. Perception threshold of the balloon distension was determined after manometry at −30, 0, 5, 15, and 30 min. Step-by-step esophageal balloon distension was performed in 1-ml increments of air with a calibrated glass syringe. The subjects were asked to avoid swallowing during the procedure. Inflation was maintained for 10 sec and was followed by deflation for 5 sec before the next step. Actual inflations were randomly interspersed with sham inflations using a three-way valve stopcock. The subjects were asked to report the first perception of any new sensation in the chest (perception threshold) and the first occurrence of chest discomfort (discomfort threshold). The balloon volumes of these two thresholds were noted.

Cutaneous Electrogastrography (EGG). For simultaneous recording of the electrogastrogram, three adhesive gel electrodes (Synectics) were fixed to the abdomen after gentle skin abrasion. The first electrode was placed between the ventral midline and left mid-axillary line, about 1 cm below the last rib. The second electrode was placed on the ventral middle line between the umbilicus and the xiphoid process. The third electrode was placed forming an equilateral triangle with the other two electrodes. EGG recordings were performed using a computerized recording unit (Digitrapper EGG, Synectics) for 15 min in the basal state and were continued until 30 min after the infusion of the test agent. Normal electrical activity was defined if the dominant frequency in the power spectrum analysis for a given 4-min recording segment was ≥2 cycle/min and ≤5 cycle/min. Tachygastria was considered at a dominant frequency of >5 cycle/min. and ≤9 cycle/min, and a dominant frequency of >0.5 cycle/min and <2 cycle/min was defined as bradygastria.

Test Meal. The liquid test meal consisted of 250 ml Fresubin (Fresenius, Oberursel, Germany), 25 g lactulose, 150 mg [^{13}C]acetate (99% Euroisotop, Saarbrücken, Germany), and 300 ml water. Total caloric content of the meal was 250 kcal. All subjects consumed their test meal within 3 min. The gastric emptying and orocecal transit tests were performed 30 min after start of the intraesophageal red pepper or saline infusion.

Lactulose Hydrogen Breath Test. Serial end-expiratory breath samples were obtained during fasting and every 10 min after lactulose for 2 hr. The orocecal transit time was determined as the time from ingestion of the meal until a rise of the hydrogen level to 20 ppm above fasting level. Samples of alveolar air were analyzed for hydrogen concentration with an exhaled hydrogen monitor (Stimotron, GMI Medical Ltd., Renfrew, UK). The monitor was calibrated before each experiment using a hydrogen gas sample with a known concentration of 92 ppm.

[^{13}C]Acetate Breath Test Technique. Breath samples were collected before the meal and at 5-min intervals during the first 2 hr and then at 10-min intervals for 3 hr after ingestion of the [^{13}C]acetate-labeled test meal. Breath samples were analyzed by an isotope ratio mass spectrophotometer (Delta S., Finnigan MAT, Bremen, Germany). Total CO_2 production was assumed to be 300 mmol/sqe m body surface/hr. The results were expressed as percentage of ^{13}C recovery per hour and as cumulative recovery. The results were calculated according to the formula reported by Braden et al (19).

Statistical Analysis. All data are given as mean ± SD. Statistical analysis was performed using Student's *t* test for paired data for comparison of two means. For multiple comparison, analysis of variance for multiple measures followed by Newman-Keuls *post hoc* test was used. The results were regarded as significant when the probability of an error was less than 0.05.

RESULTS

Effect on LES. In the saline group, basal LES pressure was 18.5 ± 1.2 mm Hg at −30 min without any significant change with time. Intraesophageal application of 25% red pepper sauce (Tabasco) suspension led to a significant increase of LES pressure from 17.8 ± 1.4 mm Hg at 0 min to 23.7 ± 2.6 mm Hg at 15 min ($P < 0.05$). This effect returned to basal level 30 min after application of the red pepper suspension (Figure 2). There was no influence on the swallow-induced relaxation of the LES.

Effects on Amplitude of Swallow-Induced Esophageal Pressure Waves. The amplitude of pressure waves induced by wet swallows in the saline group at −30 min was 67.1 ± 5.1 mm Hg at 5 cm, 61.8 ± 5.7 mm Hg at 10 cm, and 56.2 ± 3.9 mm Hg at 15 cm without any significant change with time. Intraesophageal application of red pepper sauce suspension

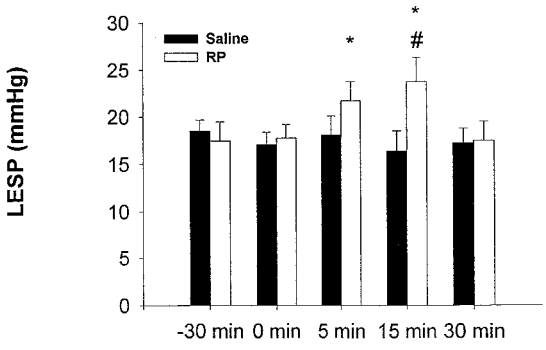

Fig 2. Effects of saline and red pepper (RP) on LES pressure (mean ± SD). Red pepper or saline (10 ml at 5 ml/min) was given after the basal recording at 0 min. $*P < 0.05$ vs basal period (0 min) before infusion was started; $\#P < 0.05$ vs saline application.

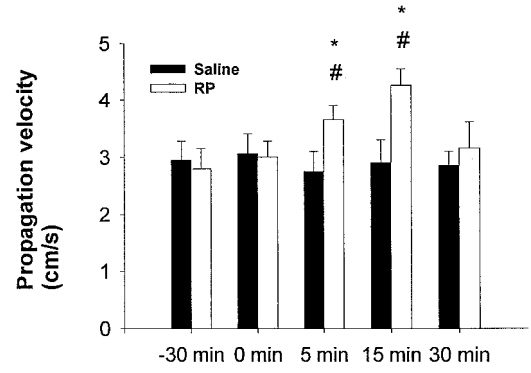

Fig 4. Effects of saline and red pepper (RP) on propagation velocity of the swallow-induced esophageal pressure wave between 5 and 10 cm above LES (mean ± SD). The results between 10 and 15 cm above LES were similar qualitatively. $*P < 0.05$ vs basal period (0 min) before infusion was started; $\#P < 0.05$ vs saline application.

increased the amplitude of the pressure waves induced by wet swallow 5, 10, and 15 cm above the LES significantly, when compared to basal level (0 min, $P < 0.05$) values and saline control at the same time ($P < 0.05$) (Figure 3). The absolute values at 10 cm above the LES at −30 min were: 66.8 ± 4.9 mm Hg; at 0 min, 65.8 ± 3.0 mm Hg; at 5 min, 75.7 ± 2.4 mm Hg; at 15 min, 87.5 ± 4.7 mm Hg; and at 30 min, 65.7 ± 4.7 mm Hg. The manometric changes at 5 and 15 cm above the LES after infusion of the red pepper sauce suspension showed similar qualitative and quantitative changes. After 30 min, the amplitudes of the pressure waves had returned to basal level.

Effects on Propagation Velocity of Swallow-Induced Esophageal Pressure Waves. In the saline group the propagation velocity of wet swallow pressure waves was 2.15 ± 0.2 cm/sec between 5 and 10 cm above the LES and 2.95 ± 0.33 cm/sec between 10 cm and 15 cm above the LES without any significant change with time. Intraesophageal application of red pepper sauce suspension significantly increased the propagation velocity of the pressure waves induced by wet swallow between 5 and 10 cm (−30 min, 2.3 ± 0.2 cm/sec; 0 min, 2.2 ± 0.2 cm/sec; 5 min, 2.7 ± 0.1 cm/sec; 15 min, 2.8 ± 0.1 cm/sec; 30 min, 2.5 ± 0.1 cm/sec) and between 10 and 15 cm (−30 min, 2.8 ± 0.3 cm/sec; 0 min, 3.0 ± 0.2 cm/sec; 5 min, 3.6 ± 0.2 cm/sec; 15 min, 4.2 ± 0.3 cm/sec; 30 min, 3.8 ± 0.4 cm/sec) above the LES, when compared to basal level (0 min, $P < 0.05$) and compared to the saline control at the same point in time ($P < 0.05$). Red pepper sauce suspension increased the propagation velocity between 5 and 10 cm and 10 and 15 cm above the LES by 44% and 28%, respectively (Figure 4).

Effects on Duration of Swallow-Induced Esophageal Pressure Waves. Intraesophageal application of red pepper sauce suspension significantly increased the duration of wet swallow pressure waves 5, 10, and 15 cm above the LES when compared to basal level (0 min, $P < 0.05$) and compared to the saline control at

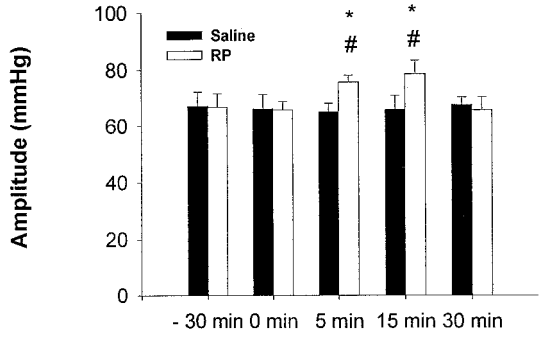

Fig 3. Effects of saline and red pepper (RP) on amplitude of the swallow-induced esophageal pressure wave at 5 cm above LES (mean ± SD). The results at 10 and 15 cm were similar qualitatively. $*P < 0.05$ vs basal period (0 min) before infusion was started; $\#P < 0.05$ vs saline application.

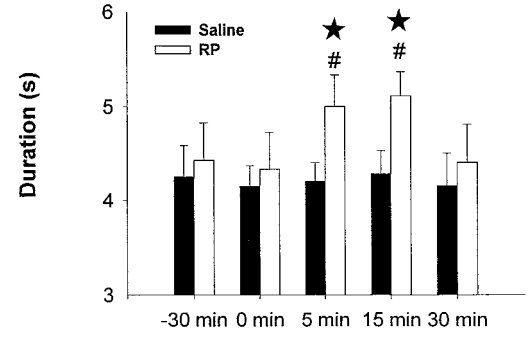

Fig 5. Effects of saline and red pepper (RP) on duration velocity of the swallow-induced esophageal pressure wave at 5 cm above LES (mean ± SD). The results were identical at 10 and 15 cm. $*P < 0.05$ vs basal period (0 min) before infusion was started; $\#P < 0.05$ vs saline application.

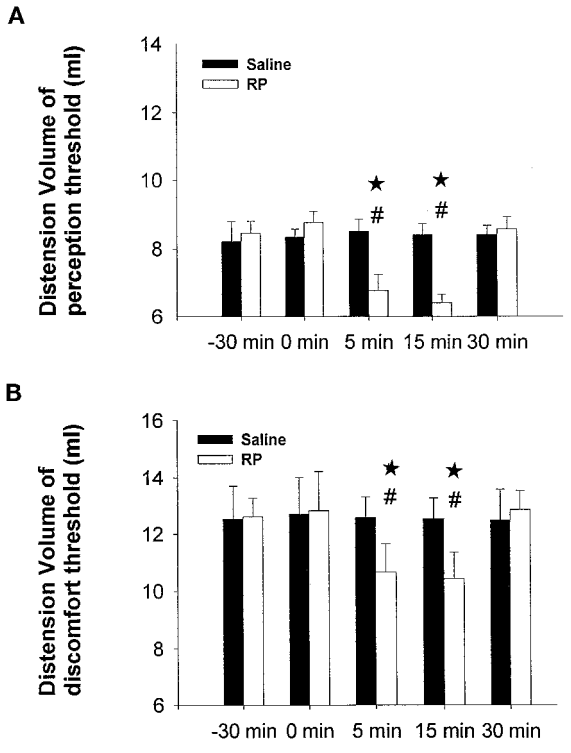

Fig 6. Effects of saline and red pepper (RP) on distension volume of perception threshold and discomfort threshold (mean ± SD). *$P < 0.05$ vs basal period (0 min) before infusion was started; #$P < 0.05$ vs saline application.

the same point in time ($P < 0.05$) (Figure 5). The absolute values at 10 cm above the LES were −30 min, 3.4 ± 0.3 sec; 0 min, 3.2 ± 0.3 sec; 5 min, 4.2 ± 0.2 sec; 15 min, 4.1 ± 0.4 sec; 30 min, 3.3 ± 0.4 sec). The changes at 5 and 15 cm above the LES showed similar qualitative and quantitative changes after infusion of the red pepper sauce suspension. After 30 min, the duration of wave pressure had returned to basal level.

Effects on Esophageal Perception and Discomfort Threshold. In the saline group, the distension volume for perception threshold was 8.2 ± 0.6 ml and that for discomfort threshold was 12.5 ± 1.2 ml without any significant change with time. Intraesophageal application of red pepper sauce suspension led to a significant decrease of the distension volume for threshold of perception from 8.8 ± 0.3 ml basal level (0 min) to 6.4 ± 0.2 ml (15 min; $P < 0.05$) and for threshold of discomfort from 12.8 ± 1.4 ml basal level (0 min) to 10.4 ± 1.0 ml (15 min; $P < 0.05$), respectively (Figure 6). Both effects had returned to basal levels 30 min after the infusion.

Effects on Liquid Gastric Emptying. Red pepper sauce suspension significantly decreased liquid gastric

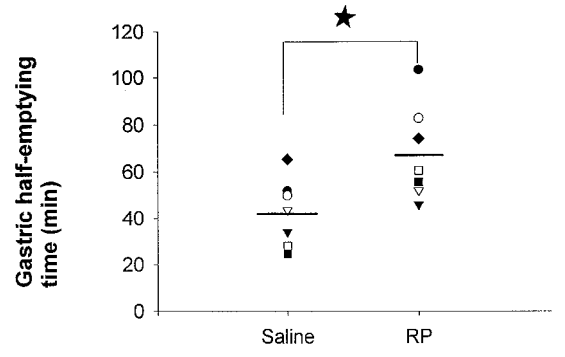

Fig 7. Effects of saline and red pepper (RP) on the individual and mean liquid gastric half-emptying time. The mean of all seven subjects is given by the horizontal lines. The gastric emptying was significantly delayed after red pepper application ($P < 0.05$).

emptying. The average time for half-emptying [^{13}C]acetate after red pepper suspension (66.8 ± 19.5 min) was significantly delayed compared with the saline treatment (42.9 ± 12.9 min) ($P < 0.05$) (Figure 7).

Effects on Gastric Electrical Activity. Cutaneous EGG was performed for 15 min before and 30 min after either saline or red pepper sauce suspension. Under saline treatment, the percentage of time with normal electrical activity (2–5 cpm) was 82.2 ± 9.4% without any significant change with time. However, it decreased from 85.0 ± 6.4% to 54.1 ± 18.2% ($P < 0.05$) after red pepper sauce suspension application (Figure 8).

On the other hand the percentage of time with tachygastric activity was 8.1 ± 4.0% in the control without any significant change during the study. After red pepper sauce suspension, the tachygastric activity increased from 6.3 ± 4.9% to 35.2 ± 13.3% ($P < 0.05$).

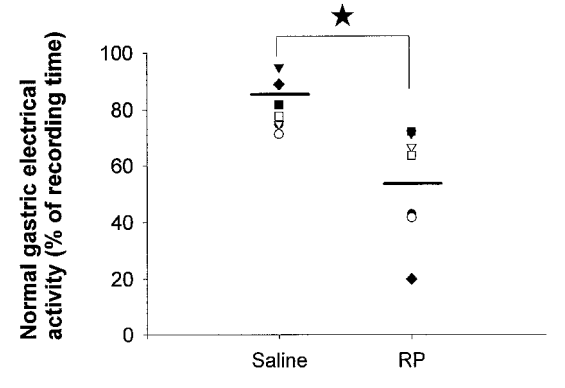

Fig 8. Effects of saline and red pepper (RP) on the individual and mean normal gastric electrical activity as measured by the EGG. The mean of all seven subjects is given by the horizontal lines. The normal electrical activity was significantly delayed after red pepper application ($P < 0.05$).

Effects on Orocecal Transit Time (OCTT). The basal mean OCTT in the seven subjects was 68.5 ± 16.4 min. The mean OCTT after red pepper sauce suspension application was 75.7 ± 16.7 min. Five of seven subjects showed prolongation in OCTT results, one subject showed no change from basal OCTT levels, and another subject showed a decrease in OCTT.

Other Effects. During the observation period, no complications occurred as a consequence of the performed esophageal infusion studies. No increase or decrease in systemic blood pressure or heart rate was observed after intraesophageal application of red pepper sauce. After 5 min of red pepper administration all except one subject noted slight heartburn, six subjects reported an increased production of saliva, and one itching of the outer ear. At 30 min all volunteers had no symptoms.

DISCUSSION

In this study we demonstrated that intraesophageal application of a capsaicin-containing red pepper sauce suspension in healthy volunteers increased the swallow-induced esophageal contractile amplitude, duration, and propagation velocity and delayed gastric emptying significantly. As saline infusion with a similar infusion velocity had no effect on these esophageal and gastric parameters, we concluded that the mechanism by which the red pepper sauce suspension increased the esophageal motility and delayed the gastric emptying is caused by the ingredients of the red pepper sauce. The predominant pungent ingredient in red peppers is 8-methyl-*N*-vanillyl-6-nonenamide (capsaicin) (1). The amount of capsaicin infused in the present study was 0.42 mg, which results in an actual concentration of 10^{-4} M, sufficient to activate nerve fibers even after dilution with saliva and gastric juice. Short-term administration of capsaicin to peripheral nerve endings is known to have an excitatory action on thin, unmyelinated primary afferent neurons and simultaneously stimulates the release of substance P, CGRP, and possible other neurotransmitters from the peripheral endings of these sensory neurons (14–16).

Our results are not in agreement with the findings of Yeoh et al (17), who previously demonstrated that some of the upper gastrointestinal symptoms produced by red pepper (chili) are mediated by direct stimulation of afferent nerve endings in the esophageal mucosa, but the symptoms were not accompanied by changes in esophageal motility. We used a fixed amount of capsaicin-containing red pepper sauce suspension and an intraesophageal application route via a plastic tube to eliminate possible aversive sensations induced by the hot taste or smell of the red pepper solution and to allow precise administration of this rather high dose of red peppers. In addition, Yeoh et al (17) performed only a single manometry after chili administration and the time interval of this manometry was not given, which could explain their negative findings. We think the negative results of Yeoh et al (17) on the effect of chili on esophageal motility are due mainly to a different experimental design. However, we cannot rule out that another ingredient of the red pepper sauce suspension could influence the upper gastrointestinal motility.

The red pepper sauce suspension significantly decreases the distension volume for perception and discomfort threshold. The phenomenon of sensing to noxious locally applied stimuli has been suggested in esophageal nociceptors (23), and capsaicin can induce secondary hyperalgesia by activation of C-fibers (24–27). Nevertheless, it is surprising that red pepper could sensitize both thresholds. Interestingly, the sensitizing effect of the red pepper infusion had disappeared 30 min after the infusion and the distension levels of both perception and discomfort thresholds had returned to control levels. Whether this return to basal level is due to limited local activity or due to desensitization can not be answered from the present series of experiments as no second red pepper infusion was tested.

Our results strongly suggest that red pepper sauce suspension decreased normal gastric electrical activity and delayed gastric liquid emptying. This could suffice to retain the irritant agent in the stomach. In the rat capsaicin induced an increase of gastric volume that by itself was enough to elicit protection through luminal dilution and was completely abolished by sensory denervation (28). It was suggested that in the rat mild irritants may provide a fluid pooling effect partly by inhibiting gastric emptying (28). Thus, it is conceivable that the delay of gastric emptying by red pepper solution could provide mucosal protection through luminal dilution.

Slow-wave rhythm disturbances, including tachygastria have been reported in diseases with reduced antral motility (29), and abnormalities of the postprandial EGG were suggested to be a possible indicator of delayed gastric emptying (30). In the present study the percentage of time with normal electrical slow-wave frequency (2–5 cpm) decreased after red pepper sauce suspension and the tachygastria in-

creased. It is speculated that the induction of gastric dysrhythmias in our volunteers after red pepper application have contributed to the delay of gastric emptying.

Physicians are often concerned about spices and whether they may affect peristaltic activity and should be excluded from the recommended diet. In humans, orocecal transit time was unchanged by orally administered red peppers in a gelatin capsule (19). In our study the OCTT was also not significantly different after red pepper sauce suspension despite the delayed gastric emptying, indicating a possible increase of intestinal transit.

In conclusion, these results suggest that esophageal application of capsaicin-containing red pepper sauce (Tabasco) suspension causes an increase in esophageal contractile amplitudes and LES pressure, a decrease of normal gastric electrical activity and gastric liquid emptying, and probably an increase in intestinal transit. These motility changes could contribute to a protection of the esophagus and could promote retention of the irritant in the stomach and faster transit through the small bowel. As capsaicin is present in sufficient concentrations to activate afferent nerve fibers, these data could add supportive evidence for the involvement of capsaicin-sensitive afferent fibers in the modulation of upper gastrointestinal motility in man.

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