Pseudoaffective cardioautonomic responses to gastric distension in rats

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Tougas, Gervais, and Lu Wang. Pseudoaffective cardioautonomic responses to gastric distension in rats. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R272–R278, 1999.—We examined the heart rate response to gastric distension, the involvement of vagal and sympathetic sensory afferents, adrenergic and cholinergic neural pathways, and the effects of capsaicin on this response in anesthetized rats. Gastric distension volume dependently decreased heart rate by 24.5% (resting rate = 219.87 ± 14.06 beats/min, mean rate during gastric distension with 15 ml = 165.97 ± 17.36 beats/min, P < 0.05). The bradycardic response was significantly decreased after removal of the celiac plexus (9.71 ± 1.77 vs. 38.03 ± 7.06% in controls, P < 0.05) or after bilateral subdiaphragmatic vagotomy (6.38 ± 2.65%, P = 0.05). The response to gastric distension was largely prevented by systemic capsaicin (29.92 ± 4.93% in controls, 2.58 ± 4.19% after systemic capsaicin, P < 0.05) and decreased by perivagal capsaicin (18.72 ± 4.75%, P < 0.05). Atropine almost completely prevented the cardiac response to distension, while propanolol and bretylium partially blocked it, implying the response is primarily mediated by cholinergic afferents but also involves adrenergic pathways. We conclude that unmyelinated, capsaicin-sensitive vagal afferents are essential to the pseudoaffective cardioautonomic response to a noxious gastric stimulus.

visceral nociception; pseudoaffective response; vagal afferents; capsaicin-sensitive visceral afferents

THE INNERVATION of the rat stomach is organized along two distinct pathways: the sympathetic nerves and the two branches of the vagus. Traditionally, it has been held that visceral pain and sensation originating from the stomach are conducted along sympathetic afferent fibers (16). The vagus nerve is primarily a sensory nerve, with afferent fibers constituting as much as 70–90% of its total fiber content (17). The various functions of afferent vagal fibers have yet to be fully described, but their importance in activities such as ingestive behavior, satiety, nausea, and vomiting has been established. Vagal afferents are not believed to play a major role in the perception of visceral sensations or to be involved in nociception (13).

Woodsworth and Sherrington (23) defined a pseudoaffective response as the autonomic and somatic reflexes produced in response to a nociceptive stimulus. In healthy volunteers, we recently showed that mechanical distension of the distal esophagus is associated with a slight decrease in heart rate and a significant shift in sympathovagal balance toward increased vagal modulation, as measured by power spectral analysis of heart rate variability (20). Preliminary studies in the rat have suggested that gastric distension may elicit a similar response (4), but the neural pathways involved in the response are poorly characterized (8).

In the present study, we examined the cardiovascular response to gastric distension over a wide range of distension volumes and pressures in ketamine- and xylazine-anesthetized rats and determined the respective involvement of vagal and sympathetic afferent pathways as well as of capsaicin-sensitive unmyelinated C afferents. The effects of cholinergic and/or adrenergic blockade on the cardiac response to gastric distension were also examined.

MATERIAL AND METHODS

 Prior approval for this study was obtained from the Animal Care Committee of McMaster University, and all procedures were conducted in accordance with the Guidelines of the Canadian Council on Animal Care.

Animals

Adult male Sprague-Dawley rats (Charles River Breeding Laboratories, Saint Constant, QC, Canada), weighing 350–450 g, were housed in the central animal facilities in microisolator cages equipped with filter hoods under controlled temperature (20°C) and with a 12:12-h light-dark cycle with free access to food and water. Animals were fasted for 18 h before experiments, but had unrestrained access to water.

Experimental Protocol

Surgical procedures. Rats were anesthetized with a ketamine hydrochloride (90 mg/kg) and xylazine (20 mg/kg) mixture given intramuscularly and were placed on a heating pad to maintain the animal’s temperature at ~36°C throughout the duration of the study. Supplemental anesthesia was given throughout the study as required.

A midline laparotomy was performed, and a distension device consisting of a 2 × 2-cm latex balloon (Forabco Dealers, Milwaukee, WI) affixed to polyethylene (PE-160) tubing (Becton-Dickinson, Parsippany, NJ) was inserted into the stomach through a small incision in the proximal duodenum (1.5 cm from the pylorus) and, in a retrograde manner, through the pylorus and into the stomach. A midline cervical incision was performed, through which a cannula was then inserted in the left internal jugular vein for intravenous drug administration, and a tracheostomy was performed to allow passage of a tracheal cannula for maintenance of the airway.

In some animals, after measuring the cardiac response to gastric distension (see below), a bilateral subdiaphragmatic vagotomy was performed by identifying the anterior and the posterior vagal branches immediately below the diaphragm, suturing the two branches, and then cutting the distal end. In

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other animals, the celiac plexus was identified and carefully dissected out until completely removed. In some of these animals, a bilateral vagotomy was done subsequently to the removal of the celiac plexus.

Control animals underwent cervical incision and laparotomy (for insertion of gastric balloon), but neither vagotomy nor celiac plexus removal.

Gastric balloon distension. We studied the gastric distension volume-cardiac response relationship by randomly applying a wide range of gastric distension volumes, using air, for a period of 60 s (n = 18). To let the animal recover from the previous distension, 30 min separated each gastric distension. The results of three trials of distension were used at each volume. The volumes used for gastric distension ranged from 0 to 18 ml (3, 6, 9, 12, 15, and 18 ml). In another group of animals, we subsequently examined responses over varying duration of stimulation (15, 30, 60, and 90 s, n = 6 in each group, volume 9 ml). In another group of animals, we measured the intragastric pressure associated with distension volumes ranging from 3 to 18 ml (n = 6).

Electrocardiogram Acquisition and Analysis

Continuous recordings of heart rate were performed through a surface electrocardiogram (ECG) obtained through three needle electrodes (23 gauge) applied to the left and right shoulders and the right leg of the animal. The signal was amplified and processed through a standard clinical ECG amplifier (model 7807B, Hewlett-Packard) and the Cyber-Amp 380 programmable signal conditioner (Axon Instruments, Foster City, CA) using a sampling rate of 1 kHz. The data were recorded on a personal computer using a commercial data acquisition program (Experimenter’s Workbench, DataWave Technologies, Longmont, CO). Heart rate was measured for the 60 s before, during, and after gastric distension. Changes in heart rate were expressed as percent changes in heart rate compared with average heart rate in the 1 min before onset of distension in each animal.

Pharmacological Agents and Drug Administration

To assess the involvement of capsaicin-sensitive sensory afferents, a group of adult male rats (n = 9) were treated with subcutaneous capsaicin (total dose: 125, 25, and 25 mg/kg 12 h apart on the 1st day and 25 and 50 mg/kg on the 2nd day; Refs. 6 and 7). The animals were given pentobarbital sodium (30 mg/kg im) and buprenorphine analgesia (0.05 mg/kg sc) 20 min before administration of capsaicin and buprenorphine (0.05 mg/kg sc every 8 h, as needed) in the 72 h after capsaicin administration. They were then given 2 wk to recover before subsequent studies.

To confirm the effects of capsaicin in adult rats, another group of rats (n = 14) were given capsaicin (50 mg/kg) within 48 h of birth (7), using the same anesthetic and analgesic regimen in the following 72 h. These animals were studied at the same age and in the same manner as the other animals.

In addition, we compared the effects of perivagal capsaicin treatment with those of systemic capsaicin, using the approach previously described by Raybould and Taché (15). In these animals (n = 6), after ketamine and xylazine anesthesia, atropine (0.5 mg/kg ip) was first given to reduce the acute effects of capsaicin on the heart and respiratory system. A midline laparotomy was performed, and both the anterior and posterior subdiaphragmatic branches of the vagus were isolated. Parafilm and 2 × 2 gauze were placed around the vagus to protect the surrounding tissues from the damaging effects of capsaicin. Cotton tips were soaked in capsaicin solution and applied to the nerve trunks for 30 s. The area was then thoroughly rinsed with olive oil first and then with physiological saline. It was subsequently dried using sterile cotton swabs, and the incision was closed. Any subsequent experiments were conducted 4 days later.

In all experiments, capsaicin was dissolved in a solution of 10% ethanol, 10% Tween 80, and 80% normal saline in a concentration of 12.5 mg/ml. Control animals received the vehicle without capsaicin.

Atropine sulfate (7.5 mg/kg) was dissolved in normal saline and given subcutaneously in a volume of 1 ml 5–15 min before gastric distension (n = 8). Bretylium tosylate (10 mg/kg iv, n = 7) was given as a bolus in a concentration of 50 mg/ml in normal saline (Burroughs Wellcome, Kirkland, QC, Canada). This dose has previously been shown to be an effective adrenergic ganglionic blocker (3, 21). Propranolol, 1.5 mg/kg in 1 ml normal saline, was given intravenously (n = 5; Ref. 3). Control animals received equivalent volumes of normal saline.

Statistical Analysis

Unless indicated otherwise, all data are presented as means ± SE. Heart rate data are presented as averaged heart rate for a period of 10 s, at the peak of heart rate response (20 s after onset of gastric distension). Change in heart rate is expressed as percent change in heart rate compared with the immediately preceding 60-s control period before distension. Student’s t-test (paired), ANOVA (1- and 2-way and repeated measures), and Newman-Keuls multiple comparison test were used as appropriate, with P < 0.05 being interpreted as significant.

RESULTS

Heart Rate Response to Gastric Distension: Gastric Distension Volume-Heart Rate Response Relationship

Gastric distension produced a reproducible and volume-dependent decrease in heart rate in all animals tested. Resting heart rate in those anesthetized animals was between 166 and 305 beats/min, with a mean resting heart rate of 219.9 ± 14.1 beats/min. Gastric distension with balloon volumes of 3 ml had no effect on heart rate (mean heart rate during distension = 218.7 beats/min). The minimal volume required for eliciting the heart rate response was 6 ml (mean heart rate going from 227.3 to 199.4 beats/min). Greater distension volumes (9, 12, and 15 ml) further decreased heart rate (mean heart rate of 168.2, 159.6, and 131.4 beats/min, respectively, P < 0.05; Fig. 1). All volumes associated with a decreased heart rate resulted in increased intragastric pressures (Fig. 2; n = 6).

The cardiac response of bradycardia occurred almost simultaneously with the onset of gastric distension and was maximal ~20 s after onset of distension. The bradycardia was sustained at larger volumes but returned quickly to baseline values within 60 s. The greater the gastric distension volume, the longer it took for the heart rate to return to its original baseline. Varying the duration of gastric distension had no effect on the magnitude of the bradycardic response to gastric distension (see Table 1).
Effect of Bilateral Subdiaphragmatic Vagotomy or Celiac Plexus Ganglionectomy on the Cardiac Response to Gastric Distension

Bilateral subdiaphragmatic vagotomy significantly diminished the heart rate response to gastric distension (Fig. 3). Sectioning the celiac plexus also decreased the cardiac response to gastric distension, but to a lesser degree than bilateral vagotomy (Fig. 3). A subsequent bilateral vagotomy in animals that had a prior celiac plexus removal completely abolished the response to gastric distension. These data are summarized in Table 2.

Heart Rate Response to Gastric Distension in Capsaicin-Treated Animals

Systemic administration of capsaicin, either in the neonatal period (n = 14) or 2 wk before the gastric distension in adult rats (n = 6), produced a nearly complete abolition of the cardiac response to gastric distension seen in control animals treated with vehicle only.

In control animals treated with vehicle only, mean resting heart rate was 214.9 ± 37.42 beats/min. With gastric distension of 6, 9, 12, and 15 ml, mean decreases in heart rate were, respectively, 5.34, 9.53, 18.08, and 29.92% (P < 0.05 from resting heart rate). Mean resting heart rates in rats treated with neonatal capsaicin or in adult rats given systemic capsaicin 2 wk before were, respectively, 226.28 ± 37.35 and 199.46 ± 22.50 beats/min and not significantly different from resting heart rate noted in vehicle-treated animals.

In animals given neonatal capsaicin, gastric distension with 6, 9, 12, and 15 ml produced a markedly smaller decrease in heart rate during distension than in vehicle-treated animals (decreases of 0.02, 1.10, 0.36, and 2.58%, respectively, P < 0.007 vs. vehicle-treated animals). In adult rats treated with capsaicin 2 wk before, resting mean heart rate actually increased by 0.63% with 6 ml and 1.35% with 9 ml and decreased by only 0.01% with volumes of 12 and 15 ml (P < 0.002 vs. vehicle-treated animals).

Perivagal capsaicin treatment decreased the cardiac response to gastric distension, but the overall effect was smaller than seen with systemic capsaicin administration in the neonatal period or in adult animals (P < 0.05). In animals treated with perivagal capsaicin, gastric distension with 6, 9, 12, and 15 ml reduced mean heart rate by 1.69, 6.81, 8.93, and 18.72%, respectively, from baseline heart rate (180 ± 25.82 beats/min; Fig. 4, n = 6 for all groups).

Pharmacological Modulation of the Heart Rate Response to Gastric Distension

The cholinergic antagonist atropine (7.5 mg/kg subcutaneously) increased the resting heart rate from 250 ± 8.1 to 316 ± 18.6 beats/min and nearly completely prevented the decrease in heart rate observed with gastric distension in saline-treated controls at all gastric distension volumes (Fig. 5).

The postganglionic β-receptor antagonist propranolol (1.5 mg/kg iv) decreased resting heart rate by 30% (from 266 ± 19 to 185 ± 6 beats/min) over saline-treated controls. Propranolol decreased the bradycardia observed during gastric distension at all distension volumes, but the effect was only significant with 15-ml gastric distension volumes (Fig. 5). The residual heart rate decrease still observed after propranolol administration was nearly completely abolished by atropine (7.5 mg).

Bretylium (10 mg/kg iv), a quaternary ammonium adrenergic blocker, decreased resting heart rate by 18% (from 266 ± 18 to 218 ± 11 beats/min). At higher gastric distension volumes (12 or 15 ml), it also decreased the heart rate response to gastric distension (Fig. 5, n = 7). The magnitude of the decrease was similar to that observed with propranolol.

DISCUSSION

Involvement of Vagal Afferents in the Cardiac Response to Gastric Distension

In xylazine- and ketamine-anesthetized rats, gastric distension produces a volume-dependent bradycardia,
which is largely prevented by prior bilateral subdia-
phragmatic vagotomy, showing that vagal afferents are
the primary sensory pathway involved in the mediation
of the cardiac response to gastric distension. Complete
celiac plexus removal also partially prevents the car-
diac effects of gastric distension, but the involvement of
sympathetic afferent pathways is not essential to the
cardiac response. The effect of celiac plexus removal is
only partial, whereas a subsequent bilateral subdia-
phragmatic vagotomy effectively abolishes the cardiac
response to gastric distension. Our observations sug-
gest that the cardiac response to gastric distension is
mediated through vagal afferent pathways, possibly
with some of these vagal afferent fibers being closely
associated with the celiac plexus, although some of
these celiac fibers could also be primary splanchnic
(sympathetic) afferents.

Capsaicin Prevents the Cardiac Response
to Gastric Distension

Prior systemic administration of capsaicin, either 2
wk before gastric distension in adult rats or in the
neonatal period, prevents the cardiac response to ga-
dritic distension. We interpret this observation and the
fact that the response was largely abolished by a
bilateral subdiaphragmatic vagotomy to indicate that
the cardiac response to gastric distension depends on
vagal afferent fibers primarily comprised of small unmy-
elinated C-type sensory afferents, which are sensitive
to capsaicin.

Although capsaicin spares as much as 30–60% of
unmyelinated fibers (6), it is nevertheless clear from
the present study that the afferent fibers involved in
the cardiac response to gastric distension are capsaicin
sensitive, which is not to imply that all unmyelinated
fibers are capsaicin sensitive. There are few data on the
specific effects of capsaicin on vagal afferent fibers, but
it has been shown that there is relative sparing of
enteric neurons after neonatal administration, whereas
in adult animals, the administration of capsaicin has
relatively little effect on sympathetic and enteric neu-
rons (6). These observations further support, although
only indirectly, that the effect of capsaicin on the
cardiac response to gastric distension is primarily on
vagal afferent pathways, because enteric and sympa-
thetic neurons are unaffected by capsaicin.

Perivagal administration of capsaicin provides simi-
lar results to those observed with systemic capsaicin,
but the magnitude of the capsaicin effect on the cardiac
response to gastric distension is smaller with perivagal
administration than with systemic capsaicin. There are
few data on the effects of perivagal capsaicin on unmy-
elinated vagal afferents. One could hypothesize that
the local application of capsaicin spares a proportion of
these unmyelinated vagal afferents, as it does with
sympathetic and enteric nerves. As the response is
largely abolished by vagotomy, it could also mean that
other types of vagal afferents (e.g., myelinated affer-
ents) are also involved in addition to unmyelinated
afferents. However, the complete abolition of the re-
sponse with either systemic or neonatal capsaicin
administration suggests that the dose, the interval
between administration and gastric distension (4 days),
or the method of application is not as effective and
results in functional sparing of some vagal afferents.

Role of Cholinergic and Adrenergic Efferent Pathways

In general, reflex bradycardia will result either from
a marked increase in cardiac vagal outflow, a decrease
in sympathetic cardiac outflow, or a combination of the
two. The present study clearly indicates that the re-
sponse is primarily dependent on atropine-sensitive
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cholinergic efferent pathways, likely through the car-
diac branches of the vagus nerve, as the cardiac re-

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Table 1. Effect of varying duration of gastric distension on heart rate response

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<th>Duration, s</th>
<th>Time After Onset of Gastric Distension, s</th>
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Data are means ± SE of % decrease in heart rate after gastric distension (9 ml) of 15, 30, 60, and 90 s in duration. Maximal cardiac response occurred within 20 s of onset of gastric distension, no matter how long gastric distension was applied. * P < 0.05 vs. resting heart rate (n = 7).

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Fig. 3. Effects of bilateral subdiaphragmatic vagotomy and celiac plexus removal on cardiac response to 9 ml (filled bar), 12 ml (open bar), and 15 ml (hatched bar) gastric distension. Control was response obtained before either vagotomy or celiac plexus. Data presented as means ± SE of % change (decrease) in heart rate during gastric distension compared with resting heart rate in control rats. *P < 0.05 vs. resting heart rate before distension; # P < 0.05 vs. heart rate response to gastric distension in control animals using a similar volume of distension; + P < 0.05 vs. heart rate response to gastric distension after celiac plexus removal.
response to gastric distension is nearly completely prevented by atropine. The administration of the \( \beta \)-receptor antagonist propranolol also partially decreases the cardiac response to gastric distension, indicating that \( \beta \)-adrenergic-sensitive pathways are also involved. However, the magnitude of the effect obtained from \( \beta \)-blockade is much less than for atropine. A similar effect, but of smaller magnitude, is seen with bretylium, a quaternary ammonium adrenergic blocker. Taken together, the effects of propranolol, bretylium, and atropine indicate that the bradycardia induced by gastric distension primarily involves cholinergic (likely vagal) efferent pathways but is also partially mediated through sympathetic \( \beta \)-adrenergic efferent pathways.

### Pseudoaffective Autonomic Response to Noxious Visceral Stimuli

There are conflicting data regarding the nature of autonomic response to various visceral stimuli. This is largely due to experimental and methodological differences among the various studies. In rats, several studies have found that esophageal or gastric distension can modulate heart rate frequency. Although the role of vagal afferent pathways was evident in some of the studies (4, 11, 14), other studies concluded that the cardiac response was mediated at least in part through splanchnic or sympathetic afferents (8, 12). In the present study there is a markedly decreased cardiac response to gastric distension after abdominal vagotomy, a response that is only partially abolished by celiac plexus removal. Inasmuch as a subsequent subdiaphragmatic vagotomy abolished the remaining cardiac response to gastric distension after celiac plexus removal, we propose that the cardiac response is vagally mediated, with the vagal afferents being closely associated with the celiac plexus at some point along their course.

A recent study that examined the cardiac response to esophageal distension also found that vagal afferent pathways were the primary pathways involved (11), although Kidd et al. (8) described the involvement of afferent fibers closely associated with sympathetic nerves in the increased blood pressure associated with gastric distension. This was unaffected by bilateral vagotomy. This study of Kidd et al. failed to obtain any effect of gastric distension on heart rate, possibly because urethan, which was the anesthetic used, depresses parasympathetic activity. In the cat, under \( \alpha \)-chloralose anesthesia, gastric distension failed to produce any effects on heart rate (10), whereas in pigs, gastric distension actually increased heart rate, a response prevented by a prior subdiaphragmatic vagotomy, indicating again involvement of vagal afferent pathways in the response (21, 22).
In a recent study, Loomis et al. (11) carefully examined the cardiac response to esophageal distension in urethan-anesthetized rats and found a pressure-dependent increase in heart rate in response to esophageal distension, a response that was also primarily mediated via vagal afferent pathways. The intraesophageal pressures used by Loomis et al. (25–150 mmHg) are very similar to the intragastric pressures we obtained in our study (which ranged from 30 mmHg with 3-ml distension to 150 mmHg with 15–18 ml), and which, at least in the highest ranges, would likely be perceived as increasingly painful without the presence of a general anesthetic. Therefore the heart rate response we describe in response to gastric distension likely represents a pseudoaffective autonomic response to a noxious stimulus, as proposed by Sherrington (18), which, in our model, is mediated though vagal afferent pathways.

In humans, electrical or mechanical esophageal stimulation reproducibly increases vagal cardiac outflow while decreasing sympathetic efferent cardiac outflow (2, 20). Because the cardiac response to gastric distension observed in the present study is almost completely abolished after atropine administration, the response must be largely mediated through atropine-sensitive cholinergic vagal efferent pathways. However, given the attenuation of the cardiac response to gastric distension after administration of bretylium and propranolol, it is likely that adrenergic sympathetic pathways are partly involved. The magnitude of the effect observed with atropine is much greater than with adrenergic blockers, suggesting that cholinergic pathways are primarily involved.

These observations are in agreement with those of Grundy and Davison (4), who also found the cardiac response to gastric distension to be atropine sensitive in rats. However, Pittam et al. (14) did not find that atropine had any effect on the cardiac response in rats, which was instead found to be particularly sensitive to β-blockade, suggesting a sympathetic modulation. The different responses noted in the present study are likely due in part to the different anesthetics used in our respective studies.

In pigs, gastric distension also has cardiac effects, which are also abolished by subdiaphragmatic vagotomy. However, in pigs the cardiac response was also clearly dependent on sympathetic efferent pathways as it was completely blocked by bretylium tosylate but unaffected by atropine administration, albeit with a much smaller dose of atropine than in the present study (22).

Clinical Perspectives

In clinical practice, distension of the stomach, gut, or other hollow viscus, which can be exquisitely painful, is often associated with a bradycardic episode. Furthermore, altered autonomic responsiveness has also been proposed in the pathophysiology of conditions such as dyspepsia (5), noncardiac chest pain (19), inflammatory bowel disease (9), and the irritable bowel syndrome (1). It is clear that noxious mechanical stimuli can result in significant autonomic effects and that these noxious stimuli are associated with activation of vagal afferent pathways. It remains to be seen whether these vagal afferents are playing a clinically important role in the perception of visceral sensations.

Studies, such as those of Loomis et al. (11) and the present one, provide models suitable for the examination of the possible mechanisms underlying the altered autonomic responsiveness seen in conditions such as dyspepsia and noncardiac chest pain. In addition, by providing a quantifiable and dose-dependent physiological response to a noxious visceral stimulus, it also represents a pseudoaffective model for the study of these noxious visceral stimuli in animals that are much better suited to the examination of the mechanisms and pharmacological modulators of nociceptive visceral perception.

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