The following is the abstract of the article discussed in the subsequent letters.

Ferreira, Manuel, Jr., Niaz Sahibzada, Min Shi, Mark Niedringhaus, Matthew R. Wester, Allison R. Jones, Joseph G. Verbalis, and Richard A. Gillis. Hindbrain chemical mediators of reflex-induced inhibition of gastric tone produced by esophageal distension and intravenous nicotine. Am J Physiol Regul Integr Comp Physiol 289: R1482–R1495, 2005. doi:10.1152/ajpregu.00584.2005.—The purpose of this study was to activate a vagovagal reflex by using esophageal distension and nicotine and test whether hindbrain nitric oxide and norepinephrine are involved in this reflex function. We used double-labeling immunocytochemical methods to determine whether esophageal distension (and nicotine) activates c-Fos expression in nitricergic and noradrenergic neurons in the nucleus tractus solitarii (NTS). We also studied c-Fos expression in the dorsal motor nucleus of the vagus (DMV) neurons projecting to the periphery. Esophageal distension caused 19.7 ± 2.3% of the noradrenergic NTS neurons located 0.60 mm rostral to the calamus scriptorius (CS) to be activated but had little effect on c-Fos in DMV neurons. Intravenous administration of nicotine caused 19.7 ± 4.2% of the noradrenergic NTS neurons 0.90 mm rostral to CS to be activated and, as reported previously, had no effect on c-Fos expression in DMV neurons. To determine whether norepinephrine and nitric oxide were central mediators of esophageal distension-induced decrease in intragastric pressure (balloon recording), N^2-nitro-L-arginine methyl ester microinjected into the NTS (n = 5), but not into the DMV, blocked the vagovagal reflex. Conversely, α2-adrenergic blockers microinjected into the DMV (n = 7), but not into the NTS, blocked the vagovagal reflex. These data, in combination with our earlier pharmacological microinjection data with nicotine, indicate that both esophageal distension and nicotine produce nitric oxide in the NTS, which then activates noradrenergic neurons that terminate on and inhibit DMV neurons.

Comments on “Hindbrain chemical mediators of reflex-induced inhibition of gastric tone produced by esophageal distension and intravenous nicotine”

To the Editor: A recent paper published by the research group of Richard Gillis (4) takes issue with our published work (5–7).

Gillis’ group contends that α1-modulation of noradrenergic pathways in the brain stem is not important to the gastric relaxatory reflex evoked by esophageal distension. They further claim that gastric relaxation provoked by esophageal distension is caused only by withdrawal of vagal cholinergic excitatory activity via α2-adrenoceptor activation; there is no NANC involvement. Our work (5–7) shows that noradrenergic neurons in the NTS activate both α1- and α2-adrenoceptors in DMV to produce the esophageal gastric reflex via withdrawal of vagal cholinergic excitatory activity (α2-mediated) and activation of NANC activity (α1-mediated). There are a number of reasons for a divergence of experimental data; the most significant has to do with physiological technique. The authors claim that the “specific purpose of the present study was to employ the same reflex stimulating technique as Rogers et al. . . .” This is not the case. The stimulating techniques used in these two studies are not comparable. Stimulation parameters used by our group were designed to mimic swallowing of a meal bolus: catheter 2.5 mm diameter, 160 ml distended volume (3). In contrast, Gillis’ group used a balloon distender with 10 mm diameter, 700 ml volume, i.e., a condition far from physiologic (3).

The results of these high-amplitude stimuli are reflected in their raw motility records (see Figs. 1 and 2 of Ref. 4) where a sharp gastric contraction occurs during distension and relaxation occurs after the stimulation is released. These records contrast with our data showing only a relaxation in response to limited esophageal stimulation (6, 7). Instead, Gillis’ responses are similar to those reported by Andrews et al. (1, 2) showing that proximal gastric distension provokes a vagally-mediated increase in gastric tone. Unlike our observations, Gillis group’s observations on the effects of esophageal distension are contaminated by this increase in gastric tone, probably the result of fault pump cannula placement and/or large oral stimuli. Their failure to observe involvement of an α1-mediated noradrenergic reflex mechanism is probably the result of this inadvertent elicitation of two essentially antagonistic mechanisms.

REFERENCES


To the Editor: Rogers et al. (3) raise the issue that the esophageal stimulation techniques used in their studies and ours are not comparable. The purpose of our study (2) was to employ a similar esophageal reflex-stimulating technique as Rogers et al. (3). Although the general method was the same, the stimulation parameters were different (indicated on page R1491 of Ref. 2). This was because the stimulation parameters were dictated by the end point of the response that was measured. As a marker of gastric relaxation evoked by esophageal distension, we used a decrease in intragastric pressure (via balloon recording). Using this end point, esophageal distension of 0.2 ml failed to elicit a significant effect on intragastric pressure (see Fig. 1 of Ref. 2) in our experimental preparation. A decrease in intragastric pressure was noted in some animals when the volume of distension was 0.6 ml and this decreased further when the volume was increased in 0.1-ml increments up to 1.0 ml. To elicit stable responses, we
Letters To The Editor

R1152

used a volume that ranged from 0.6 to 0.8 ml for most of our pharmacological microinjection studies. Our data are comparable to those of Wei et al. (5) who reported that esophageal distension with 0.5 ml reduced intragastric pressure in the rat. In an earlier study of Rogers et al. (4), they used 0.4 ml to distend the esophagus of the rat and observed a reduction in gastric motility as registered with a strain gauge sewn to the exterior of the fundus was used to measure tension. Rogers and colleagues did find an effect with esophageal distension performed using 160 μl (3) but it is not clear how their effect (a decrease in voltage of approximately 0.7 V) relates to a decrease in intragastric pressure. Because we saw no effect on intragastric pressure with esophageal distension using a slightly higher volume than 160 μl (200 μl), we conclude that different end points require different stimuli.

Rogers et al. in their letter refer to the study of Dong et al. (1), as employing a physiologic condition. However, Dong et al. (1) also did not use the end point of gastric relaxation; instead, their end point was a change in distal esophageal rhythmic contractions.

Rogers and colleagues further comment in their letter on the unphysiologic nature of our esophageal distension stimulus. They state that “The results of these high-amplitude stimuli are reflected in their raw motility records (see Figs. 1 and 2 of Ref. 4) where a sharp gastric contraction occurs during distension and relaxation occurs after the stimulation is released. These records contrast with our data showing only a relaxation in response to limited esophageal stimulation (6, 7).”

Although, in Figure 2A of our paper (2), there is a sharp gastric contraction at the start of esophageal distension, the predominant response was a decrease in intragastric pressure that was comparably long lasting. This decrease in intragastric pressure was always evident before the cessation of the esophageal balloon distension (see Figs. 1 and 2 of Ref. 2). This contrasts with the statement of Rogers et al. in their letter that the relaxation is present after the withdrawal of stimulation.

Furthermore, the sharp gastric contraction did not always occur; and when it did, it was not due to faulty cannula placement. As indicated in the METHODS of our paper (p. R1484, Ref. 2), visual inspection was made of the dissected esophagus at the end of the experiment, and correct cannula placement was confirmed. It is possible, however, that the initial sharp gastric contraction may have been an artifact due to a transient pressure gradient arising from injection of the fluid used to distend the balloon.

Rogers and colleagues final comment in their letter is “Their failure to observe involvement of an α1-mediated noradrenergic reflex mechanism is probably the result of this inadvertent elicitation of two essentially antagonistic mechanisms.”

As indicated above, two antagonistic mechanisms, i.e. gastric contraction and gastric relaxation were, not consistently observed with esophageal distension. Indeed, we interpret the gastric contraction when it did occur as an artifact. In our study, we found that α2-adrenoreceptor blockade elicited a response in our study equivalent to that of the combined α2 and α1-receptor blockade in the study of Rogers et al. (3). An example of blockade with the α2-receptor antagonist yohimbine can be seen in Fig. 10 of our article (2). In that figure, only esophageal distension-induced relaxation was observed in the control response.

REFERENCES


Manuel Ferreira, Jr.
Niaz Sahibzada
Min Shi
Mark Niedringhaus
Matthew R. Wester
Allison R. Jones
Joseph G. Verbalis
Richard A. Gillis
Departments of Pharmacology and Medicine (Endocrinology)
Georgetown University Medical Center
Washington, District of Columbia