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Research Report

Differential activation of pontomedullary nuclei by acid perfusion of different regions of the esophagus

*Ivan M. Lang**, *Bidyut K. Medda*, *Reza Shaker*

Division of Gastroenterology and Hepatology, MCW Dysphagia Research Laboratory, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA

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ABSTRACT

The objective of this study was to determine the brain stem nuclei and physiological responses activated by esophageal acidification. The effects of perfusion of the cervical (ESOc), or thoracic (ESOt) esophagus with PBS or HCl on c-*fos* immunoreactivity of the brain stem or on physiological variables, and the effects of vagotomy were examined in anesthetized cats. We found that acidification of the ESOc increased the number of c-*fos* positive neurons in the area postrema (AP), vestibular nucleus (VN), parabrachial nucleus (PBN), nucleus ambiguus (NA), dorsal motor nucleus (DMN), and all subnuclei of the nucleus tractus solitarius (NTS), but one. Acidification of the ESOt activated neurons in the central (CE), caudal (CD), dorsomedial (DM), dorsolateral (DL), ventromedial (VM) subnuclei of NTS, and the DMN. Vagotomy blocked all c-*fos* responses to acid perfusion of the whole esophagus (ESOw). Perfusion of the ESOc or ESOt with PBS activated secondary peristalsis (2P), but had no effect on blood pressure, heart rate, or respiratory rate. Perfusion of the ESOc, but not ESOt, with HCl activated pharyngeal swallowing (PS), profuse salivation, or physiological correlates of emesis. Vagotomy blocked all physiological effects of ESOw perfusion. We conclude that acidification of the ESOc and ESOt activate different sets of pontomedullary nuclei and different physiological responses. The NTSce, NTScom, NTSdm, and DMN are associated with activation of 2P, the NTSim and NTSis, are associated with activation of PS, and the AP, VN, and PBN are associated with activation of emesis and perhaps nausea. All responses to esophageal fluid perfusion or acidification are mediated by the vagus nerves.

* *Corresponding author*. Fax: +1 414 456 6215.
E-mail address: imlang@mcw.edu (I.M. Lang).

Abbreviations: ANOVA, analysis of variance; AP, area postrema; CP, cricopharyngeus; CT, cricothyroideus; DMN, dorsomedial nucleus; DMNc, caudal DMN; DMNr, rostral DMN; EMG, electromyography; ESOc, cervical esophagus; ESOt, thoracic esophagus; ESOw, whole esophagus; GH, geniohyoideus; HCl, hydrochloric acid; HR, heart rate; IP, intraperitoneal; LES, lower esophageal sphincter; MAP, mean arterial pressure; NA, nucleus ambiguus; NAc, caudal NA; NAr, rostral NA; NaCl, sodium chloride; NTS, nucleus tractus solitareus; NTScd, caudal subnucleus of NTS; NTSce, central subnucleus of NTS; NTScom, commisural subnucleus of NTS; NTSdl, dorsolateral subnucleus of NTS; NTSdm, dorsomedial subnucleus of NTS; NTSim, intermediate subnucleus of NTS; NTSis, interstitial subnucleus of NTS; NTSmed, medial subnucleus of NTS; NTSv, ventral subnucleus of NTS; NTSvm, ventromedial subnucleus of NTS; PBN, parabrachial nucleus; PVN, paraventricular nucleus; RR, respiratory rate; RVLM, rostral ventrolateral medulla; UES, upper esophageal sphincter; VN, vestibular nucleus

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1. Introduction

Prior studies (Shuai and Xie, 2004; Suwanprathes et al., 2003) have found that perfusion of the esophagus with HCl and pepsin in anesthetized animals caused activation of neurons in various brain nuclei. However, in these studies no attempt was made to prevent esophageal reflux of the perfusate to the pharynx or larynx. In one study (Suwanprathes et al., 2003) evidence of such reflux occurred as the investigators observed brief periods of aspiration, breathing difficulty, and accumulation of fluid in the pharynx. Therefore, it is difficult to be certain in these prior studies whether the observed brain responses were due to stimulation of acid sensitive receptors in the esophagus, pharynx, or larynx. A difference in the distribution of the perfusate in these studies could also account for the observed differences in brain responses.

The only prior studies of the effects of acid in the esophagus on activation of the central nervous system were conducted in rats (Shuai and Xie, 2004; Suwanprathes et al., 2003). However, the esophagus of rats is anatomically and functionally significantly different from that of humans. Unlike humans, rats have not been found to have physiological processes, i.e. emesis, eructation or regurgitation, that produce retrograde transport of contents through the esophagus. These processes are centrally mediated (Bredenrood et al., 2007; Lang and Sarna, 1987) and some are triggered by activation of acid-sensitive esophageal receptors (Baron et al., 1993; Milla, 1990). Therefore, the stimulation of the rat esophagus is not likely to activate the same physiological processes and areas of the brain as would occur with similar stimulation in humans.

In all of the prior studies of the effects of acid-pepsin exposure of the esophagus on the activation of brain nuclei (Shuai and Xie, 2004; Suwanprathes et al., 2003), the entire esophagus was exposed. However, prior studies have found that the proximal and distal portions of the esophagus have different functions especially related to luminal stimuli. The distal esophagus is commonly exposed to acidic gastric reflux (Grossi et al., 2001; Mittal et al., 1995) secondary to spontaneous transient lower esophageal sphincter relaxations and in normal individuals most of these episodes are not sensed (Grossi et al., 2001; Singh et al., 1993). On the other hand in adults, the proximal esophagus is less often exposed to acidic gastric reflux (Emerenziani et al., 2009; Oelschlager et al., 2006) and when it is in adults (Emerenziani et al., 2009; Oelschlager et al., 2006) or infants (Milla, 1990), it often causes nausea, vomiting, or regurgitation. In addition, esophagitis of the upper but not lower esophagus is associated with swallow-related emesis (Baron et al., 1993). One of the main functions of the distal esophagus is to promote transport of contents to the stomach whereas the primary function of the proximal esophagus is to prevent reflux to the pharynx and larynx. Therefore, it is highly likely that the proximal and distal esophagus may project different types of afferent information to different portions of the brain.

The aim of this study was to investigate the effects of hydrochloric acid in the cervical and thoracic portions of the esophagus on the activation of neurons in the brain stem of an animal model, i.e. the cat, with an esophagus similar to that of humans. Prior studies have found that the cat esophagus is both structurally (Crouch, 1969; Goyal and Paterson, 1989) and functionally (Goyal and Paterson, 1989; Lang et al., 2001) very similar to that of humans. In addition, considering the significant

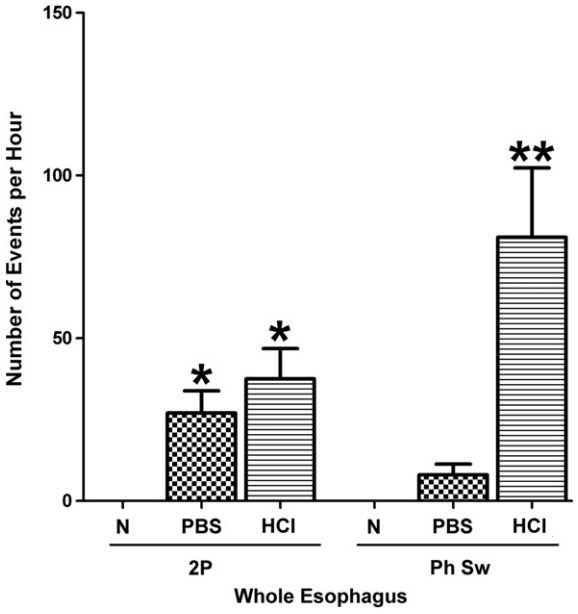

Fig. 1 – The effects of perfusion of the whole esophagus with PBS and HCl. N, no fluid; PBS, phosphate buffered saline; HCl, 0.1 N hydrochloric acid. N=4; *P<0.05 compared with N; **P<0.05 compared with PBS. Note that both PBS and HCl caused a significant increase in the rate of secondary peristalsis, but only HCl caused a significant increase in pharyngeal swallows.

Table 1 – The effects of perfusion of various regions of the esophagus with PBS or HCl on cardiovascular and respiratory variables.

	Cervical esophagus			Thoracic esophagus			Whole esophagus		
	None	PBS	HCl	None	PBS	HCl	None	PBS	HCl
MAP	110±5	110±6	109±5	105±7	104±5	109±7	108±6	106±4	108±4
HR	204±11	198±14	195±18	201±12	197±15	208±9	195±7	189±13	191±12
RR	18±4	20±6	20±4	20±3	20±4	20±3	23±4	23±3	24±5

N=4, None, no fluid administered; PBS, 0.1 M PBS; HCl, 0.1 N HCl; MAP, mean arterial pressure; HR, heart rate; RR, respiratory rate. PBS and HCl groups within each esophageal perfusion category, i.e. cervical, thoracic, and whole, were compared to the control group, i.e. None, using ANOVA with repeated measures and no comparisons were significantly different at $P<0.05$. This table excludes cardiorespiratory activity that occurred during bouts of nausea and vomiting.