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BRIEF ARTICLE

Brain activity following esophageal acid infusion using positron emission tomography

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Abstract

AIM: To investigate symptoms and brain activity following esophageal acid infusion.

METHODS: Fifteen healthy volunteers were recruited for the study. Hydrochloric acid (pH 1 and 2) and distilled water (pH 7) were randomly and repeatedly infused into the esophagus. The brain activity was evaluated by positron emission tomography. The severity of heartburn elicited by the infusion was rated on an auditory analog scale of 0-10.

RESULTS: The severity of heartburn following each infusion showed a step-wise increase with increasing acidity of the perfusate. The heartburn scores were significantly higher in the second pH 1 infusion compared with the first infusion. Acid and distilled water infusion induced activation of various brain areas such as the anterior insula, temporal gyrus, and anterior/posterior cingulate cortex. At pH 1 or 2, in particular, activation was observed in some emotion-related brain areas such as the more anterior part of the anterior cingulate cortex, parahippocampal gyrus, or the temporal pole. Strong activation of the orbitofrontal cortex was found by subtraction analysis of the two second pH 1 infusions, with a significant increase of heartburn symptoms.

CONCLUSION: Emotion-related brain areas were activated by esophageal acid stimulation. The orbitofrontal area might be involved in symptom processing, with esophageal sensitization induced by repeated acid stimulation.

Key words: Esophageal acid infusion; Brain imaging; Positron emission tomography

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INTRODUCTION

Gastroesophageal reflux disease (GERD) causes reflux symptoms such as heartburn and regurgitation due to reflux of the gastric contents into the esophagus, with or without mucosal damage[1]. Although there is a correlation between the severity of esophagitis and acid reflux, it is known that the severity of subjective symptoms is not necessarily correlated with that of acid reflux[2]. In particular, heartburn symptoms are weakly correlated with acid reflux in non-erosive reflux disease (NERD)[3], and NERD patients are often resistant to treatment with acid-suppressive medication[4]. Therefore, the possible involvement of esophageal hypersensitivity in NERD patients has attracted attention[5].

It has been shown that NERD patients show hypersensitivity not only to mechanical stimulation, but also to acid and/or non-acid chemical stimulation[6-8]. Some investigators have argued that the susceptibility of afferent nerve terminals to luminal acid based on the dilated intercellular space in the esophageal mucosa is important as a causative factor for acid hypersensitivity[9,10]. Recent studies have demonstrated that weak acid or gas reflux is associated with the generation of reflux symptoms[11]. However, perceived acid reflux accounts for only a minority of reflux events[12], and the mechanism of heartburn symptoms remains to be elucidated[13].

Recently, brain imaging analysis using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has been employed in visceral sensation studies as an objective evaluation tool for the processing mechanism of perception[14]. This advanced approach has demonstrated that some important brain areas, such as the anterior cingulate cortex (ACC) or insula, are involved in the processing of visceral sensation and pain, and abnormality or modulation of these brain areas in patients with irritable bowel syndrome[15-17]. Until now, these brain imaging studies of the viscera, especially of the rectum or colon, have been mainly conducted using barostat-controlled methods; a mechanically extended stimulation device[18]. Only a few studies have investigated brain activity after esophageal chemical stimulation, such as hydrochloric acid[19-21]. The aim of this study was to investigate induced symptoms and brain activity using PET in esophageal acid stimulation.

MATERIALS AND METHODS

Subjects

Fifteen right-handed healthy adult male volunteers (mean age: 26.7 years; range: 21-37 years), who had no typical reflux symptoms such as heartburn and regurgitation, were recruited for the study that was conducted from October 2005 to June 2007. All subjects were healthy volunteers with no gastrointestinal disorders and signs. It was confirmed that they had no prior history of craniocerebral trauma or intracranial diseases.

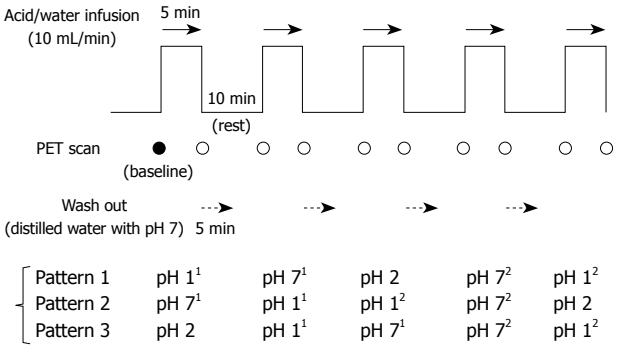

Figure 1 This schema illustrates the procedure of esophageal infusion and brain positron emission tomography scanning. The infusions were performed twice for pH 1 and 7 solutions (distilled water) and once for the pH 2 solution. In order to counterbalance the effects of the infusion order, the order was randomly selected per each subject from pH 1-7-2-7-1, pH 7-1-1-7-2 and pH 2-1-7-7-1 as shown. [1]First infusion; [2]Second infusion; PET: Positron emission tomography.

A small-diameter catheter (new enteral feeding tube 3393-5; Nippon Sherwood Medical Industries Ltd., Tokyo, Japan) was inserted transnasally into the esophagus, and fixed at 35 cm from the exterior nostril. A wired pH glass electrode (CM-181; Chemical Appliance Co. Ltd., Tokyo, Japan), pre-attached at its proximal side 3 cm from the infusion catheter, was connected to a pH meter. The placement of the catheter and pH electrode in the middle esophagus was confirmed by chest X-ray. Subjects were placed in a supine position in the PET scanner with their heads immobilized in a head immobilization device to control head movement during scanning. In order to obtain correction data for γ-ray absorption in the body, subjects initially underwent a transmission scan using a ^{68}Ge/^{68}Ga radiation source. This study was approved by the Ethics Committee for Human Research at Tohoku University Graduate School of Medicine, Sendai, Japan. Informed consent was obtained from every subject.

Esophageal acid infusion

The procedures for esophageal infusion and PET scan are schematically shown in Figure 1. Infusions of 50 mL HCl (pH 1 and 2) or distilled water (pH 7) were provided by a catheter using an automatic syringe pump (Terufusion syringe pump TE-312; Terumo Co. Ltd., Tokyo, Japan) for a total of 5 min at 10 mL/min. The infusions were performed twice for pH 1 and pH 7 solutions and once for the pH 2 solution. In order to counterbalance the effects of the infusion order, the order was randomly selected from pH 1-7-2-7-1, pH 2-1-7-7-1, and pH 7-1-1-7-2. Then ^{15}O-labeled water was administered intravenously in synchronization with the completion of each 5-min infusion. After confirming that the brain activity could be detected, a PET emission scan of the head was performed for 60 s prior to the PET scan; the subjects were instructed to remain awake during the scan that was performed in a darkened room. Using a PET scanner (Headtome-V set- 2400 W; Shimadzu, Kyoto, Japan)[22] in a 3D data acquisition mode, a total of 10 scans were taken

before and after each of the five infusions, to measure the regional cerebral blood flow in each subject. After each acid infusion, the esophagus was neutralized by an infusion of distilled water (pH 7) over 5 min at 10 mL/min and by additional swallowing. During 10-min intervals between infusions, it was confirmed that the esophageal pH was 4 or higher, as an indicator of the non-acidic status[23], and that the radioactivity in the heads of the subjects had returned to baseline (pre-scan) levels. Subjects were asked to rate the severity of heartburn symptoms on an analog scale of 0-10 after each infusion, and the resultant scores were used in the analysis of data. The incidence of heartburn symptoms and the heartburn scores elicited after the five infusions for each of the two groups were statistically analyzed by Fisher's test and the Wilcoxon signed-ranks test, respectively. Differences were considered statistically significant when the P value was < 0.05.

PET data analysis

The PET data were transferred to a super computer (NEC, SX-4/128H4, Tohoku University Cyberscience Center, Sendai, Japan) and PET images were reconstructed using a 3D filtered back projection algorithm[24]. Realignment, spatial normalization, and smoothing of images were performed using statistical parametric mapping (SPM) software (SPM 2, Wellcome Department of Cognitive Neurology, London, UK), and significantly different changes in regional cerebral blood flow were mapped. All regional cerebral blood flow images were anatomically normalized against a standard brain space such as the Montreal Neurological Institute atlas[25]. The standardized images were smoothed using a 12 mm × 12 mm × 12 mm Gaussian filter. Evaluations of regional cerebral blood flow were adjusted using analysis of covariance and mean scaling set at 50, and expressed in mL/min per 100 g. The effects of grouping and co-variability were each evaluated using a general linear model of voxels.

The following two analyses were performed to determine the areas of regional brain activity that correlated with the esophageal acid infusion. First, brain images taken following infusion with hydrochloric acid (pH 1 and 2) or distilled water (pH 7), as well as images taken at baseline (prior to all infusions) were subjected to subtraction analysis to investigate the brain regions that were activated by each infusion. Next, the effects of repeated infusion of acid or distilled water were assessed by subtraction analysis of images obtained following the first and second infusions with pH 1 and pH 7 solutions. All statistical methods were evaluated using linear convolution and contrasts, and the voxel values for each image were constructed using a statistical parametric map of the t-statistic statistical parametric mapping. The location of statistical peaks was determined in Talairach and Tournoux atlas. P (uncorrected) < 0.001 was defined as statistically significant for increased cerebral blood flow.

RESULTS

Enhanced incidence and severity of symptoms following acid infusion

The incidence of heartburn symptoms following each infusion was 33.3% for the first pH 7 infusion, 33.3% for the second pH 7 infusion, 46.7% for pH 2, 66.7% for the first pH 1 infusion, and 80.0% for the second pH 1 infusion. The incidence of heartburn symptoms following each infusion showed a step-wise increase with increasing acidity of the perfusate. The incidence of heartburn tended to be higher after the second pH 1 infusion than after the first, and these scores were significantly increased following the second pH 1 infusion. On the other hand, the heartburn incidence and scores in both pH 7 infusions were much lower compared to the pH 1 infusions. Symptom scores were significantly increased after the pH 2 infusion compared to the second pH 7 infusion, and after the second pH 1 infusion compared to the pH 2 infusion (Table 1).

Table 1 Incidence of heartburn symptoms and heartburn scores induced by each infusion

	Heartburn incidence	Mean heartburn scores (range)
pH 7 (first infusion)	5/15	1.4 (0-7)
pH 7 (second infusion)	5/15	1.0 (0-6)
pH 2	7/15	1.9 (0-9)[b]
pH 1 (first infusion)	10/15	3.2 (0-10)[c]
pH 1 (second infusion)	12/15[a]	5.0 (0-10)[d]

[a]$P = 0.0253$ *vs* pH 7 (first infusion) and pH 7 (second infusion); [b]$P = 0.0269$ *vs* pH 7 (second infusion); [c]$P = 0.0464$ *vs* pH 7 (first infusion), $P = 0.0253$ *vs* pH 7 (second infusion); [d]$P = 0.0040$ *vs* pH 1 (first infusion), $P = 0.0075$ *vs* pH 2, $P = 0.0041$ *vs* pH 7 (first infusion), $P = 0.0071$ *vs* pH 7 (second infusion).

Activated brain areas following acid infusion

Comparison of brain images following each infusion: The brain image obtained at rest prior to all infusions was defined as the baseline image. Differences between brain images at baseline and those taken after infusion with acid or distilled water were subjected to subtraction analysis. Brain regions with increased blood flow were defined as those neurologically activated by each infusion. The details of the brain regions activated following each infusion are shown in Table 2 and are summarized in Table 3.

After the first pH 7 infusion, activation was observed in the right precentral gyrus, left superior temporal gyrus, right and left ACC, right anterior insula and, after the second pH 7 infusion, in the right middle frontal gyrus, cuneus (center), right posterior cingulate cortex (PCC), right postcentral gyrus, right ACC, left inferior frontal gyrus, left middle temporal gyrus, right and left thalamus, and right superior temporal gyrus. The regions activated at pH 2 were the left cerebellum, right inferior frontal gyrus, left superior temporal gyrus (temporal pole, BA38), right anterior insula, left putamen, left PCC, right ACC, mid pons, and left superior temporal gyrus. After the first pH 1 infusion, activation was observed in the right precentral gyrus, right superior temporal gyrus (temporal pole, BA38), left middle temporal gyrus, left parahippocampal gyrus, left ACC, and left middle temporal gyrus. After the second pH 1 infusion, activation was observed in the right parahippocampal gyrus (Figure 2A), left superior temporal gyrus (temporal

Table 2 Details of brain activated regions by acid infusion (comparison with baseline)

Condition	Region	Side	BA	x	y	z	Z-score	Voxels in cluster
Frist pH 7 - base	Precentral gyrus	Right	4	56	-8	22	4.23	252
	Superior temporal gyrus	Left	42	-64	-12	6	3.80	72
	Anterior cingulate cortex	Left	24	-12	6	34	3.78	34
	Anterior cingulate cortex	Right	24	12	4	28	3.59	17
	Anterior insula	Right		30	-4	20	3.43	15
Second pH 7 - base	Middle frontal gyrus	Right	10	36	44	-4	4.51	79
	Cuneus	Center		0	-104	-2	4.02	45
	Posterior cingulate cortex	Right	23	28	-52	10	3.84	58
	Postcentral gyrus	Right	1,2	44	-20	32	3.57	19
	Anterior cingulate cortex	Right	24	12	4	26	3.49	31
	Inferior frontal gyrus	Left	47	-50	34	-2	3.49	21
	Middle temporal gyrus	Left	21	-64	-4	-22	3.45	18
	Thalamus	Left		-20	-36	4	3.44	41
	Thalamus	Right		18	16	16	3.44	26
	Superior frontal gyrus	Right	10	10	66	24	3.21	10
pH 2 - base	Cerebellum	Left		-2	-72	-20	4.01	59
	Inferior frontal gyrus	Right	45	34	10	20	3.94	40
	Superior temporal gyrus	Left	38	-52	20	-24	3.85	18
	Anterior insula	Right		30	-4	22	3.78	68
	Putamen	Left		-22	-12	10	3.60	35
	Posterior cingulate cortex	Left	31	-26	-62	12	3.36	28
	Anterior cingulate cortex	Right	24	6	32	-2	3.35	15
	Pons	Center		0	-26	-30	3.34	12
	Superior frontal gyrus	Left	10	-20	52	-8	3.34	14
First pH 1 - base	Precentral gyrus	Right	6	68	4	20	3.85	36
	Superior temporal gyrus	Right	38	32	10	-38	3.80	39
	Middle temporal gyrus	Left	21	-44	-30	-10	3.74	24
	Parahippocampal gyrus	Left		-26	-50	6	3.74	46
	Anterior cingulate cortex	Left	24	-12	26	-2	3.67	20
	Middle temporal gyrus	Left	21	-64	-2	-22	3.48	22
Second pH 1 - base	Parahippocampal gyrus	Right		28	-48	2	4.47	129
	Superior temporal gyrus	Left	38	-52	18	-26	4.12	24
	Cerebellum	Left		-20	-40	-50	4.09	58
	Posterior cingulate cortex	Left	23	-8	-20	26	3.93	15
	Caudate nucleus	Left		-14	-26	20	3.70	32
	Anterior insula	Right		36	12	-14	3.63	27
	Pons	Right		12	-42	-32	3.43	57
	Caudate nucleus	Left		-24	-38	12	3.24	16

Table 3 Summary of brain activated regions by each infusion (comparison with baseline)

Major brain region	Subregion	BA	First pH 7	Second pH 7	pH 2	First pH 1	Second pH 1
Frontal lobe	Superior frontal gyrus	10		R	L		
	Middle frontal gyrus	10		R			
	Inferior frontal gyrus	47		L			
Temporal lobe	Superior temporal gyrus	38			L	R	L
	Superior temporal gyrus	42	L				
	Middle temporal gyrus	21		L		L	
	Middle temporal gyrus	42	L		L		
	Inferior temporal gyrus	45			R		
PMA	Precentral gyrus	4	R				
	Precentral gyrus	6				R	
PSA	Postcentral gyrus	1,2,3		R			
ACC	Anterior part	24			R	L + R	
	Mid/posterior part	24′	L + R	R			
PCC				R	L		L
Insula	Anterior part		R		R		R
Cerebellum					C + L		L
Thalamus				R + L			R + L
PHG						L	R

PMA: Primary motor area; PSA: Primary somatosensory area; ACC: Anterior cingulate cortex; PCC: Posterior cingulate cortex; PHG: Parahippocampal gyrus; BA: Brodmann area; R: Right; L: Left; C: Center.

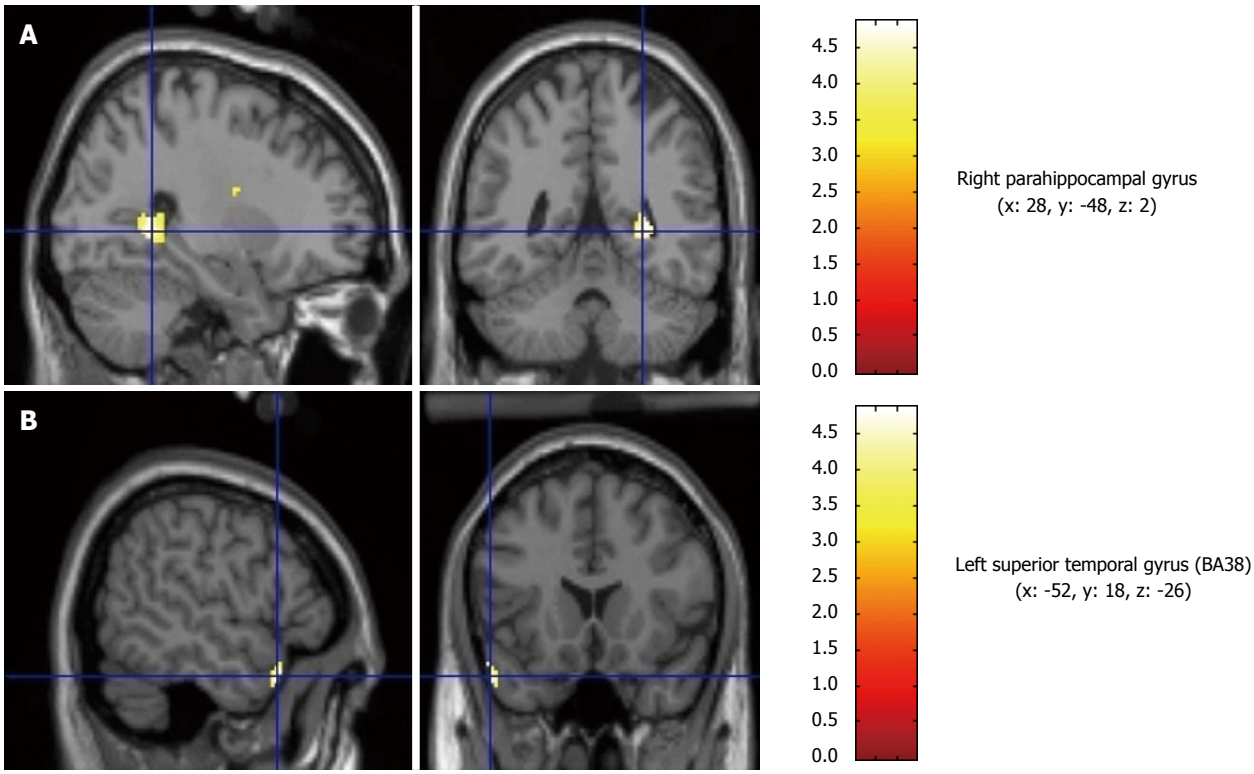

Figure 2 Representative images from the subtraction analysis of the second pH 1 infusion minus the baseline. Left: Sagittal view; Right: Cranial view. A: Right parahippocampal gyrus (x: 28, y: -48, z: 2); B: Left superior temporal gyrus (temporal pole, BA38) (x: -52, y: 18, z: -26).

pole, BA38) (Figure 2B), left cerebellum, left PCC, left caudate nucleus, right anterior insula and right pons.

In view of the acidity level of the perfusate, brain activation was observed in the prefrontal area at pH 2 and 7 but not at pH 1. In the insula, activation was observed at the second pH 1 and 2 and first pH 7 infusions. Activation in the cingulate cortex was observed in nearly all infusions, with no particular trend observed for the topography of the activated sub-regions. At pH 1 and 2, activation was observed in the more anterior (rostral) part of the ACC (BA 24a) and, at pH 7, in the more posterior (dorsal) part of the ACC (BA 24a'). Many activated areas were observed in regions of the temporal gyrus, with no particular trend observed for the topography. After infusions at pH 1 and 2 but not pH 7, activation was observed in the temporal pole (BA 38). Activation was also observed in the cerebellum following infusions at pH 1 and 2, and in the parahippocampal gyrus after both pH 1 infusions. On the other hand, the frontal area, precentral gyrus, and thalamus were less activated after each infusion.

Comparison of brain imaging with first and second infusion at pH 1 and 7: As described above, the scores for heartburn symptoms after the pH 1 infusions were significantly increased after the second infusion compared to the first. When we analyzed the difference of these two conditions using subtraction analysis, the second pH 1 infusion minus the first showed that cerebral blood flow was increased in the right orbitofrontal cortex (Figure 3A), right cuneus, left cerebellum, right superior temporal gyrus, right middle frontal gyrus (Figure 3B), right pons, right lingual gyrus, left putamen, and right caudate nucleus. On the other hand, the result of the second pH 7 infusion minus the first showed an increase in cerebral blood flow in the right middle frontal gyrus, left cerebellum, right midbrain, left PCC, and right superior frontal gyrus. Those brain areas are summarized in Table 4.

DISCUSSION

In the present study, we found that brain activity was substantially increased in the cingulate cortex and frontal lobe following esophageal acid infusion, with little activity observed in the thalamus and somatosensory areas. The insula was not consistently activated by acidic or non-acidic stimulations in this study, but in previous studies, the activation of the insula and ACC has been highly reproducible, and is considered to play a central role in the integration of visceral sensation[14,17]. ACC is functionally and anatomically divided into several subregions[26]. The more anterior part of the ACC (BA 32, 25, 24) is involved in affective and emotional responses and the dorsal part (BA 32', 24') is involved in cognitive processes[27]. Activation of the ACC predominantly occurred in the anterior part (BA 24) at pH 1 and 2, and in the posterior part (BA 24') at pH 7 in this study, which supports the fact that heartburn is uncomfortable and troublesome[1].

The heartburn symptom scores following infusions at pH 1 and 2 were higher compared with those at pH 7. We found that the parahippocampal gyrus was activated only by pH 1 infusion. This area is an important part of the limbic system, which plays a major role in the processing

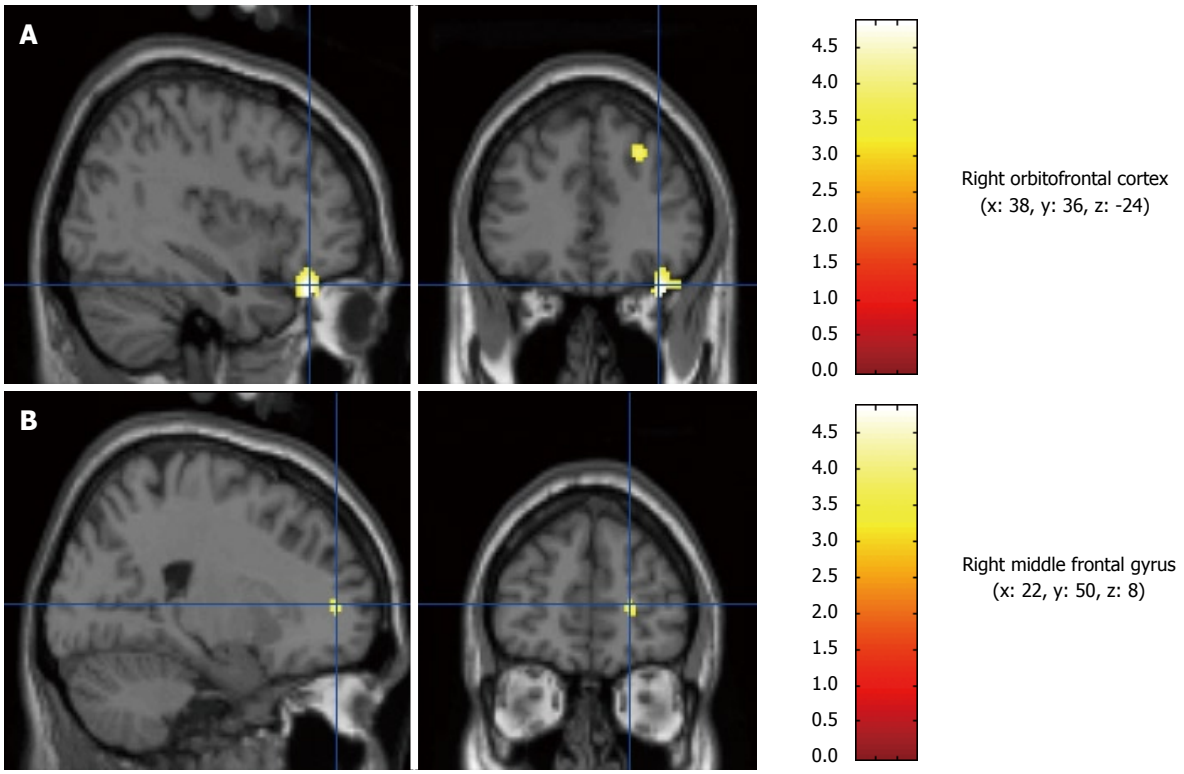

Figure 3 Representative images from the subtraction analysis of the second pH 1 infusion minus the first. Left: Sagittal view; Right: Cranial view. A: Right orbitofrontal cortex (x: 38, y: 36, z: -24); B: Right middle frontal gyrus (x: 22, y: 50, z: 8).

Table 4 Results of subtraction analysis of brain images after the first and second infusions at pH 1 and 7

Condition	Region	Side	Brodmann area	x	y	z	Z-score	Voxels in cluster
Second pH 1 - first	Orbitofrontal cortex	Right		38	36	-24	4.44	167
	Cuneus	Right	19	2	-82	36	3.79	51
	Cerebellum	Left		-22	-40	-50	3.74	23
	Superior temporal gyrus	Right	8	26	36	40	3.69	37
	Middle frontal gyrus	Right	32	22	50	8	3.69	23
	Pons	Right		10	-36	-12	3.47	31
	Lingual gyrus	Right	19	4	-60	-2	3.37	12
	Putamen	Left		-24	-8	2	3.32	16
	Caudate nucleus	Right		18	-34	16	3.30	16
Second pH 7 - first	Middle frontal gyrus	Right	10	36	46	0	4.03	47
	Cerebellum	Left		-18	-98	-18	3.98	40
	Midbrain	Right		2	-40	2	3.65	27
	Posterior cingulate cortex	Left	23	-14	-16	30	3.61	11
	Superior frontal gyrus	Right	8	14	22	42	3.57	33

of emotional reaction or memory[28]. Therefore, activation of the parahippocampal gyrus is compatible with induction of uncomfortable heartburn by acid infusion. Also, activation was observed in the temporal pole following infusions at pH 1 and 2, but not at pH 7. The temporal pole (BA 38) is located at the anterior extremity of the temporal lobe, which includes the superior and middle temporal gyri. There have been few reports regarding activation of the temporal pole in previous studies of esophageal sensation. However, a recent study has shown that this area is activated by distention in the proximal stomach[29], and another report has described activation of the temporal pole by distention of the descending colon, with a feeling of anxiety[30]. In a study using photographs as visual stimulation, the temporal pole was activated by emotions of comfort and discomfort, wakefulness, and attended stimulation[31]. Therefore, the activation of the temporal pole observed in our study could have been due to alterations in the level of arousal, attention and emotion following acid infusion. These observations also suggest that, as shown by the activation pattern of the ACC in this study, high-acidity stimulation in the esophagus can induce emotional responses.

It has been shown that heartburn is apt to be perceived when preceding acid reflux or prior acid stimulation exists[11,32,33]. Also in this study, the heartburn scores were significantly higher after the second pH 1 infusion compared to the first, which suggests that esophageal sensation was

sensitized by repeated acid infusion. These changes were not observed after repeated infusion at pH 7. Visceral sensitization, which can occur at the primary afferent nerve level (peripheral sensitization) and/or the spinal cord level (central sensitization), is considered as a very important phenomenon in the development of visceral sensation[34]. Finally, visceral sensation is perceived through intracerebral processing and modulation[34]. Recent studies using cortical evoked potentials or fMRI have reported that esophageal sensitization induced by acid stimulation results in alterations in the neural activity of the ACC and insula[35-37]. In our present study, subtraction analysis of the second pH 1 minus the first showed that increased brain activity occurred in several areas, including the right orbitofrontal cortex, right supratemporal gyrus and right middle frontal gyrus. Of those brain areas, the orbitofrontal cortex had the highest Z-score and cluster level in our study. The orbitofrontal cortex, which is frequently observed to be activated following stimulation of the lower gastrointestinal tract, was less activated following esophageal stimulation in previous studies[14,38,39]. As a higher center of sensory integration, this area is thought to participate in the assessment of reward, punishment, comfort, discomfort, and memory or its verification[40]. Thus, our findings showed that the orbitofrontal cortex, besides the ACC or insula, shown in other studies[35-37], might also play a role in symptom processing with esophageal acid sensitization.

Chemoreceptor stimulation of the esophagus is also thought to activate fine sympathetic and parasympathetic afferents. Fine sympathetic afferents ascend the lamina I of the spinal cord, and parasympathetic afferents provide input to the solitary tract nucleus[28]. These activities are integrated in the parabrachial nucleus, which projects to the posterior dorsal insula by way of (or by passing) the ventromedial thalamic nuclei[28]. In humans, this cortical image is represented in the anterior insula[28]. This is compatible with our findings documenting the activation of the anterior part whenever the insula is activated, although its activation was not detected under condition with the second pH 1 infusion minus the first. However, these representations provide the foundation for a subjective evaluation of the interoceptive state, which is forwarded to the orbitofrontal cortex, where hedonic valence is represented[40], and was depicted as discrimination between the first and the second acidic stimuli in the present study.

In the present study, little activation was observed in the thalamus and primary somatosensory cortex. Based on previous reports of visceral and somatic sensation, the activation in the primary somatosensory cortex has poorer reproducibility compared with activation in the insula; possibly due to variations in the intensity, property, and spatial and temporal amount of stimulation in the respective studies[14,17,41]. Especially in visceral sensation, the total amount of spatial and temporal stimulation is very difficult to evaluate, which could account for the variation in brain activation. Alternatively, the lower activation in the primary somatosensory cortex suggests vague localization of pain originating from the viscera[17]. Moreover, in esophageal acid infusion tests, including our present and previous studies, it is necessary to take into account the differences in the acidity, infusion rate, total volume of the perfusate, and the position during infusion, which probably influence the induction of symptoms and concomitant brain activation[20,21,42,43]. Kern *et al*[21] have reported in an fMRI study that activation in the sensory motor cortex among GERD patients with luminal/perceived esophageal acid exposure was substantially higher than that in healthy controls with subliminal acid stimulation. This study suggests that the sensory motor area is associated with the perception of heartburn symptom in GERD patients, although it does not apply to healthy controls. A further study of our patients with GERD is needed.

In the present study, pH 1 and 2 hydrochloric acid was chosen as an acidic stimulant of the esophagus. pH 1 hydrochloric acid has been traditionally and widely used as an esophageal chemical stimulant[6,20,21,32,33,44], and there is a report that pH 2 represents a critical level of acidity in inducing heartburn symptoms[45]. Due to the time constraints of our PET facility, infusions at pH 2 were performed only once, whereas infusion at pH 1 and 7 was performed twice. This could be a limitation of our study. We also randomly selected one of the three aforementioned infusion orders for each subject to counterbalance the influence of the infusion order. The infusion order was not revealed to the subjects, but anticipation of the infusion might have influenced the brain activation[46]. On the other hand, the physical and mental stress associated with keeping still for a long period, the gag reflex and swallowing with an indwelling intranasal tube might have an adverse effect on brain activation[43].

In summary, this present study using PET showed that the insula, cingulated gyrus, temporal gyrus, and cerebellum were activated in esophageal acid perception in healthy volunteers, and that involvement of the somatosensory and prefrontal areas was minimal. In particular, emotion-related brain regions such as the anterior part of ACC, the parahippocampal gyrus and the temporal pole were activated under acidic conditions in the esophagus. It is also suggested that activation of the orbitofrontal area is involved in esophageal sensitization to repeated acid stimulation at the cerebral level. Dysfunction of these brain areas may be associated with the pathogenesis of functional heartburn or non-erosive reflux disease. Further studies of brain imaging to elucidate the mechanism of esophageal acid perception and sensitization in healthy subjects and patients with GERD, including NERD and functional heartburn, are warranted.

COMMENTS

Background

Esophageal hypersensitivity is a potentially causative factor in the pathogenesis of non-erosive reflux disease (NERD) or functional heartburn. In those patients, there may also be a neural alteration at the brain level against esophageal acid reflux, but little is documented on this issue.

Research frontiers

Using brain positron emission tomography (PET), we sought to analyze the symptoms and brain activity following esophageal acid infusion with different pH levels in healthy volunteers.

Innovations and breakthroughs

Several emotion-related brain areas such as the anterior part of the anterior cingulate cortex, parahippocampal gyrus or the temporal pole were activated by esophageal acid stimulation. In addition, a strong activation of the orbitofrontal cortex was observed with repeated pH 1 HCl perfusions, with a significant increase of heartburn symptoms.

Applications

This preliminary study might contribute to the authors' understanding of the pathogenesis of NERD or functional heartburn, and could provide a newly therapeutic agent that targets an alteration in brain activity induced by acid reflux.

Peer review

The authors investigated the symptoms and brain activity following esophageal acid infusion, by PET and auditory analog scale in healthy volunteers. They found that emotion-related areas were activated under conditions of high acidity, with heartburn symptoms, and that the orbitofrontal area might be involved in symptom processing, with esophageal sensitization induced by repeated acid stimulation. Their observations could contribute to an elucidation of the pathogenesis of NERD or functional heartburn, and could be helpful for development of new therapeutic options.

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