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Vascular permeability increased by histamine aerosol, capsaicin, and electric stimulation of vagus nerves in guinea pigs

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ABSTRACT The present study was to clarify the tissue differences in vascular permeability enhanced by 0.1% histamine aerosol, capsaicin (50 $\mu g \cdot kg^{-1}$, iv), and electric stimulation of vagus nerves (ESV, 12 V, 5 ms, 16 Hz, for 90 s) in different parts of airways, heart, esophagus, ileum, kidney, and liver of guinea pigs using Evans blue (30 $mg \cdot kg^{-1}$, iv) as a tracer. All the treatments significantly increased the dye extravasation in trachea, main bronchi, proximal and distal intrapulmonary airways (by 64-722%), as well as in the heart (by 89-126%), most remarkable for capsaicin on trachea and main bronchi. Capsaicin also markedly increased the dye content in esophagus. These results demonstrate that neurogenic inflammation induced by capsaicin and ESV primarily increases vascular permeability in the respiratory tract and heart.

KEY WORDS capillary permeability; capsaicin; electric stimulation; vagus nerve; histamine; trachea; heart

Electric stimulation of vagus nerves (ESV) and capsaicin increase airway vascular permeability, which is, at least partly, mediated via tachykinins released from capsaicin-sensitive nerve endings, or sensory afferent fibers[1-3]. The increased vascular permeability induces plasma extravasation into the submucosa, resulting in edema of the mucosa, formation of mucus plugs in the airways, and obstruction of airways[2,4]. This is termed neurogenic inflammatory reaction[2,3]. Whether or not vascular permeability increases selectively in airways remains unknown. In the investigation of changes of vascular permeability, Evans blue is widely used as a tracer of plasma extravasation because the dye leakage well correlates with extravasation of radiolabeled albumin[5-7]. Therefore, using the dye, we compared the changes of vascular permeability in various tissues of guinea pigs, different parts of the airways, heart, esophagus, ileum, kidney, and liver, induced by ESV and capsaicin with those by inhalation of histamine, an inflammatory mediator.

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MATERIALS AND METHODS

Hartley adult guinea pigs of either sex weighing 446 ± *s* 67 g (Experimental Animal Center of Zhejiang Medical University) were anesthetized with sodium pentobarbital (30 $mg \cdot kg^{-1}$, ip). Evans blue (Sigma Chemicals, USA) 30 $mg \cdot kg^{-1}$ (30 $mg \cdot ml^{-1}$ in 0.9% saline) was injected into the jugular vein 1 min before treatments with histamine aerosol, capsaicin, and ESV. After 5 min, the carotid artery was incised, and the animal was perfused with saline 50 ml via the jugular vein catheter within 1 min to remove intravascular tracer. The trachea, main bronchi, lungs, heart, esophagus, ileum (about 1.5 cm), right kidney, and liver (left lobe, about 1 g) were excised. The lungs were divided lengthwise into two equal portions, arbitrarily named proximal and distal intrapulmonary airways (IPA)[7]. All wet tissues were weighed. The Evans blue in the tissues was extracted with a mixture of acetone and 0.9% saline (7 : 3) for 48 h, and determined by light absorbance at λ 620 nm using a spectrophotometer (Model 721, Shanghai Third Analytical Instrument Factory).

Histamine aerosol The trachea was cannulated immediately distal to the larynx. The animal was exposed via the cannula to 0.1% histamine aerosolized by an ultrasonic nebulizer (WH-1, Jiangsu Fourth Electrical Apparatus Factory) for 1 min. A saline aerosol was used as control.

Capsaicin Capsaicin (Sigma Chemicals, USA) dissolved in a mixture of 0.5% Tween 80, 1% ethanol, and 0.9% saline was iv 50 $\mu g \cdot kg^{-1}$. The

Tab 1. Influence of 0.1% histamine aerosol and capsaicin (50 $\mu g \cdot kg^{-1}$, iv) on vascular permeabilities in guinea pigs. $n=5-6$, $\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* corresponding control. IPA = intrapulmonary airways.

	Extravasation of Evans blue, μg / g wet tissue			
	Saline aerosol	Histamine aerosol	Solvent iv	Capsaicin iv
Trachea	20.0 ± 7.8	45.7 ± 9.6***	10.5 ± 3.9	86.2 ± 16.7***
Main bronchi	14.3 ± 5.1	33.0 ± 10.9***	12.4 ± 4.2	77.4 ± 17.7***
Proximal IPA	9.8 ± 1.7	25.7 ± 7.3***	12.5 ± 2.8	28.0 ± 5.0***
Distal IPA	14.8 ± 2.1	24.3 ± 4.0***	15.8 ± 5.2	31.9 ± 8.0***
Heart	4.8 ± 1.6	10.3 ± 3.0***	4.4 ± 0.9	8.4 ± 1.0***
Esophagus	6.3 ± 4.9	6.9 ± 1.5*	3.6 ± 3.4	27.6 ± 18.6**
Ileum	5.5 ± 1.7	6.5 ± 1.7*	4.1 ± 0.9	3.0 ± 1.9*
Kidney	3.0 ± 0.8	2.8 ± 0.5*	3.4 ± 1.1	4.2 ± 0.7*
Liver	5.0 ± 3.5	4.9 ± 2.0*	3.3 ± 1.4	5.0 ± 1.7*

control animals were injected with solvent 1 ml · kg^{-1}

Electric stimulation of vagus nerve Bilateral cervical vagi were cut, and the distal ends were stimulated (12 V, 5 ms, 16 Hz, for 90 s) 10 min after iv atropine (1 mg · kg^{-1}) to block the muscarinic cholinergic effects of the vagal stimulation. In the control animals, the vagotomies were followed by atropine pretreatment, but were not stimulated electrically.

RESULTS

Inhalation of histamine aerosol, iv injection of capsaicin, and ESV significantly increased Evans blue extravasation in airways (trachea, main bronchi, proximal and distal IPA) and heart, but not in esophagus (except for capsaicin), ileum, kidney, and liver (Tab 1–2). Capsaicin also markedly increased Evans blue content in esophagus. The effect of capsaicin was more potent in the trachea (722%) and main bronchi (522%) than the other treatments (129–269%, $P<0.01$).

DISCUSSION

In the present study, we showed that among the tested tissues of guinea pigs, EVS and capsaicin significantly increased the vascular permeability in the different levels of airways and the heart, suggesting that the respiratory tract and the heart are primarily involved in neurogenic inflammation. Capsaicin had more potent effect on trachea, main bronchi, although its effects on the proximal and distal IPA and the heart were similar to that of ESV, indicating the abundance of capsaicin–sensitive C-fibers in larger airways. Also, the present study demonstrates that the heart is an important target organ in neurogenic inflammation.

In addition to the effect on airways, histamine aerosol also augmented vascular permeability in the heart. It seems possible

Tab 2. Influence of electric stimulation of vagi (12 V, 16 Hz, 5 ms, for 90 s) on vascular permeabilities in guinea pigs. $\bar{x} \pm s$ (n). $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control. IPA = intrapulmonary airways.

	Extravasation of Evans blue, μg / g wet tissue	
	Control	Vagal stimulation
Trachea	12.2 ± 8.3 (7)	40.1 ± 16.1 (7)***
Main bronchi	12.8 ± 7.6 (7)	42.4 ± 17.0 (7)***
Proximal IPA	8.8 ± 2.7 (7)	24.8 ± 13.7 (7)**
Distal IPA	9.7 ± 4.6 (7)	28.6 ± 14.2 (7)***
Heart	4.5 ± 3.0 (5)	10.1 ± 2.0 (5)***
Esophagus	7.9 ± 3.2 (5)	10.3 ± 3.6 (5)*
Ileum	4.1 ± 2.4 (5)	6.3 ± 2.0 (5)*
Kidney	3.3 ± 0.9 (5)	3.6 ± 0.2 (5)*
Liver	3.7 ± 0.6 (5)	4.0 ± 1.7 (5)*

that histamine aerosol increases the vascular permeability partly via tachykinins released from capsaicin-sensitive nerves as the same way as ESV and capsaicin because the vasodilator effect of histamine aerosol is markedly reduced in the bronchial circulation of capsaicin-desensitized pig[8], and histamine increases the release of tachykinins from perfused guinea pig lung[9]. However, it is difficult to explain the mechanism of vascular permeability increase in the heart induced by histamine aerosol in the present study.

Since airway wall thickness is an important factor influencing airway narrowing, the mucosa and submucosa edema in airways induced by the increased vascular permeability can more profoundly increase airway resistance[10,11]. Asthmatic subjects have also an increased vascular permeability[4], and asthma is proposed as an axon reflex[12] with many similar features to neurogenic inflammation of airways, for example, in both situations, the sensory nerve endings release tachykinins[1,2,12]. Thus, the experimental system of the present study is also useful for the investigation of asthma pathogenesis.

REFERENCES

1 Lundberg JM, Saria A, Brodin E, Rosell S, Folkers K. A substance P antagonist inhibits vagally induced increase in vascular permeability and bronchial smooth muscle contraction in the guinea pig. *Proc Natl Acad Sci USA* 1983; **80** : 1120-4.

2 McDonald DM. Neurogenic inflammation in the rat trachea 1. Changes in venules, leucocytes and epithelial cells. *J Neurocytol* 1988; **17** : 583-603.

3 Umeno E, Nadel JA, Huang H-T, McDonald DM Inhibition of neutral endopeptidase potentiates neurogenic inflammation in the rat trachea. *J Appl Physiol* 1989; **66** : 2647-52.

4 Persson CGA. Leakage of macromolecules from the tracheobronchial microcirculation. *Am Rev Respir Dis* 1987; **135** : s71-s75.

5 Udaka K, Takeuchi Y, Move HZ. Simple method for quantitation of enhanced vascular permeability. *Proc Soc Exp Biol Med* 1970, **133** : 1384-7.

6 Saria A, Lundberg JM. Evans blue fluorescence: quantitative and morphological evaluation of vascular permeability in animal tissues. *J Neurosci Methods* 1983; **8** : 41-9.

7 Evans TW, Rogers DF, Aursudkij B, Chung KF, Barnes PJ. Inflammatory mediators involved in antigen-induced airway microvascular leakage in guinea pigs. *Am Rev Respir Dis* 1988; **138** : 395-9

8 Lundberg JM, Alving K, Lacroix JS, Matran R. Local and central reflex mechanisms in the neural control of airway microcirculation. *Eur Respir J* 1990; **3 (Suppl 12)** : 624S-8S.

9 Saria A, Martling C-R, Yan Z, Theodorsson- Norheim E, Gamse R, Lundberg JM. Release of multiple tachykinins from capsaicin-sensitive sensory nerves in the lung by bradykinin, histamine, dimethylphenyl piperazinium, and vagal nerve stimulation *Am Rev Respir Dis* 1988; **137** : 1330-5.

10 Moreno RH, Hogg JC, Pare PD. Mechanics of airway narrowing. *Am Rev Respir Dis* 1986; **133** : 1171-80.

11 Hogg JC, Pare PD, Moreno RH The effect of submucosal edema on airway resistance. *Am Rev Respir Dis* 1987; **135** : s54-s56.

12 Barnes PJ. Asthma as an axon reflex. *Lancet* 1986; 1 : 242-5

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组胺气雾剂、辣椒素和电刺激迷走神经引起豚鼠血管渗透性增高

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提要 0.1%组胺气雾剂, 辣椒素(50 $\mu g \cdot kg^{-1}$, iv)和迷走神经电刺激(ESV, 12 V, 5 ms, 16 Hz, 90 s)显著增加气管、主支气管、肺内气道中心部分和外周部分(64-722%)以及心脏(89-126%)渗出标记物的含量. 辣椒素对气管和主支气管的作用更强, 还明显增加食道的标记物渗出. 结果证明辣椒素和 ESV 诱发的神经原性炎症主要增高呼吸道和心脏的血管渗透性.

关键词 毛细血管渗透性; 辣椒素; 电刺激; 迷走神经; 组胺; 气管; 心脏