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**关键词** ONO-1078; 苯并吡喃类; 辣椒素; P物质; 支气管收缩; 微血管渗漏性; 支气管; 平滑肌

**目的:** 探讨白三烯特异性拮抗剂 4-氧-8-[对-(4-苯丁氧基)苯甲酰氨基]-2-(5-四唑基)-4H-1-苯并吡喃半水合物(ONO-1078)对气道辣椒素敏感的感觉神经功能的调节作用。 **方法:** 观察豚鼠肺内压(IPP)、伊文思蓝渗出量和离体支气管平滑肌收

缩反应。 **结果:** 辣椒素 (Cap,  $0.05 \text{ mg} \cdot \text{kg}^{-1}$ , iv)、P物质 (SP,  $1 \mu\text{g} \cdot \text{kg}^{-1}$ , iv) 和白三烯  $\text{C}_4$  ( $\text{LTC}_4$ ,  $0.5 \mu\text{g} \cdot \text{kg}^{-1}$ , iv) 增高 IPP 和支气管及肺内气道伊文思蓝渗出量, ONO-1078 ( $0.03 \text{ mg} \cdot \text{kg}^{-1}$ , iv) 完全阻断  $\text{LTC}_4$  的作用, 减弱 Cap 的作用, 但不影响 SP 的作用。 ONO-1078 ( $1 \mu\text{mol} \cdot \text{L}^{-1}$ ) 还显著抑制 Cap 收缩支气管平滑肌, 对 SP 无效。 **结论:** ONO-1078 通过抑制感觉神经肽释放而部分抑制 Cap 的作用。

## Effect of nimodipine on infectious brain edema in rabbits

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**KEY WORDS** *Bordetella pertussis*; brain edema; nimodipine; water; calcium; calmodulin; sodium; Evans blue

**AIM:** To study the effect of nimodipine (Nim) on infectious brain edema (BE). **METHODS:** An infectious BE model was induced by injection of *Bordetella pertussis* suspension (BPS) into right internal carotid artery in rabbits. Eighteen rabbits were randomly divided into 3 groups ( $n = 6$ ). Group BE: BPS ( $0.6 \text{ mL} \cdot \text{kg}^{-1}$ ) was given; group NS: normal saline was given as control; group Nim: 10 min after injection of BPS, Nim,  $10 \mu\text{g} \cdot \text{kg}^{-1}$ , was injected iv as a bolus followed by continuous infusion of  $0.75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . All the rabbits were kept under observation for 4 h. Evans blue staining was assessed; water, calcium, calmodulin (Cal), and sodium contents were determined in the right brain. **RESULTS:** Nim vs BE: water  $82.2 \pm 1.0 \%$  vs  $84.4 \pm 1.2$  ( $P < 0.01$ ); calcium  $10.5 \pm 1.3 \text{ mmol} \cdot \text{kg}^{-1}$  dry tissue vs  $17.5 \pm 1.4$  ( $P < 0.01$ ); Cal  $15.9 \pm 1.8 \mu\text{mol} \cdot \text{kg}^{-1}$  wet tissue vs  $24.0 \pm 3.0$  ( $P < 0.01$ );

sodium  $173 \pm 7 \text{ mmol} \cdot \text{kg}^{-1}$  dry tissue vs  $275 \pm 38$  ( $P < 0.05$ ). No significant difference for Evans blue staining between the two groups. **CONCLUSION:** Nim had beneficial effect on the infectious BE.

Disruption of calcium homeostasis is one of the detrimental factors leading to cell death after cerebral ischemia and trauma<sup>[1]</sup>. Calcium accumulation in brain tissue plays an important role in development of infectious brain edema (BE) of rabbits<sup>[2]</sup>. Beneficial effect of calcium channel blockers after cerebral ischemia in animal and human studies have been reported<sup>[3,4]</sup>, but no reports about the effect of calcium channel blockers on infectious BE have been found yet. The purpose of this study was to investigate the effect of nimodipine (Nim) on calcium accumulation and calmodulin (Cal) content in brain tissue and brain edema, using an infectious BE model in rabbits.

## MATERIALS AND METHODS

The infectious BE models were induced by injection of *Bordetella pertussis* suspension (BPS) (produced by Beijing Research Institute of Biological Product, batch number 88-

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60) into the right internal carotid artery of rabbits<sup>(5)</sup>. 18 rabbits, weighing  $1.9 \pm 0.13$  kg, were randomly divided into 3 groups, 6 in each. Group NS: the rabbits received sterile normal saline (NS,  $0.6 \text{ mL} \cdot \text{kg}^{-1}$ ) as control; group BE: the rabbits received BPS ( $0.6 \text{ mL} \cdot \text{kg}^{-1}$ ); group Nim: 10 min after the injection of BPS, the rabbits were injected iv Nim (powder produced by Xin Hua Pharmaceutical Factory, injection produced by Department of Pharmaceutics of Xiang Ya Hospital)  $10 \mu\text{g} \cdot \text{kg}^{-1}$  as a bolus followed by continuous infusion of  $0.75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  Evans blue in NS (2.5 %,  $1 \text{ mL} \cdot \text{kg}^{-1}$ ) was injected into the right ear vein. All the rabbits were kept under observation for 4 h. Blood samples were taken from the right femoral artery catheter 5 min before the killing with pentobarbital iv. Brain hemispheres were excised. Evans blue staining in brain was assessed<sup>(6)</sup>. Water contents of the brain were measured by dry to wet ratio method, calcium and sodium contents in the dry samples and serum samples were determined by atomic absorption spectroscope (AA-680, Shimadzu of Japan), Cal contents in brain and plasma were measured according to phosphodiesterase method<sup>(7,8)</sup>.

The significance between groups were calculated by paired *t* test.

## RESULTS

The water content of right hemisphere in group Nim was lower than that in group BE ( $P < 0.01$ ), the water content of the left side in group Nim tended to be lower than that in the group BE ( $P > 0.05$ ). The calcium and Cal contents in both hemispheres in the group Nim were lower than those in the group BE. The sodium content of right hemisphere in group Nim was lower than that in group BE, there was no significant difference of

sodium in the left hemisphere between group Nim and group BE ( $P > 0.05$ ) (Tab 1).

There were no significant difference for degree and area of Evans blue staining of both hemispheres between group Nim and group BE.

There were no significant difference of calcium and sodium contents in serum and Cal content in plasma between group BE and group Nim.

## DISCUSSION

Nim is known to inhibit voltage-sensitive calcium channel and reduce influx of calcium into neuronal cells. Our study showed that calcium content of the right hemisphere decreased significantly in the Nim treated group, so the therapeutic mechanism may be related to attenuate calcium overload in neuronal cells. The study further suggests that calcium accumulation in the brain is one of the important pathogenic factors in development of the BE. As the BE of the left hemisphere developed much more slowly as compared to the right, the effect of Nim on the BE of the left was less significant.

Though Cal is a ubiquitous cytosolic protein that mediates many calcium dependent cellular process, pathological increase of Cal activity in brain will intensify brain damage<sup>(9)</sup>. Nim was found to reduce the Cal content in the brain tissue of the rabbits with the infection BE, so its beneficial effect on the BE may be partly related to attenuate the brain damage caused by Cal.

Tab 1. Water, calcium, Cal, and sodium contents in brain hemispheres.  $n = 6$ ,  $\bar{x} \pm s$ .

<sup>a</sup> $P > 0.05$ , <sup>b</sup> $P < 0.05$ , <sup>c</sup> $P < 0.01$  vs NS. <sup>d</sup> $P > 0.05$ , <sup>e</sup> $P < 0.05$ , <sup>f</sup> $P < 0.01$  vs BE.

	Normal saline		Brain edema		Nimodipine ( $10 \mu\text{g}$ iv then infusion of $0.75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	
	right	left	right	left	right	left
Water, %	$78.6 \pm 0.7$	$78.6 \pm 0.5$	$84.4 \pm 1.2^c$	$81.1 \pm 0.8^c$	$82.2 \pm 1.0^f$	$79.6 \pm 0.4^d$
Calcium, mmol/kg dry tissue	$6.5 \pm 1.0$	$6.4 \pm 0.7$	$17.5 \pm 1.4^c$	$11.5 \pm 2.3^c$	$10.5 \pm 1.3^f$	$6.3 \pm 1.1^e$
Calmodulin, $\mu\text{mol}/\text{kg}$ wet tissue	$14.2 \pm 2.1$	$14.4 \pm 2.5$	$24.0 \pm 3.0^c$	$19.5 \pm 2.3^b$	$15.9 \pm 1.8^f$	$14.3 \pm 2.4^f$
Sodium, mmol/kg dry tissue	$146 \pm 32$	$148 \pm 28$	$275 \pm 38^c$	$170 \pm 16^a$	$173 \pm 7^e$	$148 \pm 8^d$

Nim could reduce the permeability of BBB in brain damage of rats<sup>[10]</sup>, but our result suggested that Nim had little improvement on the BBB damage of the rabbits. As the infectious BE is mixed type<sup>[3,6]</sup>, we speculated that Nim mainly attenuated the intracellular edema.

For other pathogenic factors such as acidosis may intensify the BE, excessive calcium influx via *N*-methyl-*D*-aspartate receptor channel activation also contributes the neuronal injury, but Nim has no effect on the channel, so Nim can not fully prevent the BE yet. Our study can not answer when or which case therapy of the infectious BE with Nim is better as well.

Anyhow the study suggests that calcium channel blocker is beneficial in treatment of the experimental infectious BE.

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## 尼莫地平对兔感染性脑水肿的影响

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**关键词** 百日咳杆菌; 脑水肿; 尼莫地平; 水; 钙; 钙调素; 钠; 伊文思蓝

**目的:** 研究尼莫地平对感染性水肿的影响. **方法:** 采用百日咳菌液右侧颈内动脉注射造成兔感染性脑水肿模型. 18 只家兔随机分为 3 组 ( $n=6$ ). BE 组: 注射百日咳菌液 ( $0.6 \text{ mL} \cdot \text{kg}^{-1}$ ); NS 组: 注射生理盐水作为对照. Nim 组: 注射菌液后 10 min, 静注尼莫地平  $10 \mu\text{g} \cdot \text{kg}^{-1}$ , 再以  $0.75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  持续静滴, 4 h 后观察右脑伊文思蓝蓝染, 测定右脑水、钙、钙调素及钠含量. **结果:** Nim 与 BE: 水  $82.2 \pm 1.0 \%$  和  $84.4 \pm 1.2$  ( $P < 0.01$ ); 钙  $10.5 \pm 1.3 \text{ mmol/kg}$  干脑和  $17.5 \pm 1.4$  ( $P < 0.01$ ); 钙调素  $15.9 \pm 1.8 \mu\text{mol/kg}$  湿脑和  $24.0 \pm 3.0$  ( $P < 0.01$ ); 钠  $173 \pm 7 \text{ mmol/kg}$  干脑和  $275 \pm 38$  ( $P < 0.05$ ). 两组脑蓝染无显著性差异. **结论:** 尼莫地平对感染性脑水肿有良好的治疗作用.

## Information for authors

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