*Acta Pharmacologica Sinica* 1984 Jun; **5** (2) : 104-105

# EFFECT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITOR HOE-498 ON NORADRENALINE-INDUCED VASOCONSTRICTION IN ISOLATED PERFUSED MESENTERY OF RATS

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ABSTRACT Oral administration of Hoe-498 (1 mg/kg) to rats attenuated the vasoconstriction of perfused mesenteric vessels induced by NE. It is suggested that Hoe-498 interferes in the angiotensin-mediated facilitation of adrenergic neurotransmission.

KEY WORDS Hoe-498; isolated perfused rat mesentery; kininase II inhibitor; norepinephrine

Hoe-498, *N*-(1 (*S*)-carbethoxy-3-phenylpropyl)-(*S*)-alanyl-cis, endo-2-azabicyclo (3, 3, 0)-octan-3-(*S*)-carboxylic acid, is a novel orally active nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor which inhibits the conversion of angiotensin I (ANG I) to angiotensin II (ANG II) and potentiates the action of bradykinin (BK) in the isolated guinea pig and rat hearts[1,2]. Hoe-498 has also potent antihypertensive effects in spontaneously hypertensive rats and conscious hypertensive dogs[3]. Since ACE is also present in rat mesentery[4] and the role of ANG II in the modulation of adrenergic transmission in rat mesentery is evident[5,6], we examined the effect of oral administration of Hoe-498 on vasoconstrictor responses to noradrenaline (NA) in isolated perfused rat mesentery.

## METHODS AND RESULTS

Twenty Wistar ♀ rats (285±SD 33 g) were fasted overnight except water *ad lib*. Hoe-498 (1 mg/kg) in 2 ml saline was given po 30 min before the isolation of mesentery under ether anesthesia or exsanguination. The superior mesenteric artery was cannulated with a PE-50 catheter and perfused as described previously[7]. Krebs solution gassed with 95% $O_2$ +5% $CO_2$ was used to perfuse 3 ml/min at 37℃. The perfusion pressure was measured by a Statham P-23 transducer and a servotrace recorder. After an equilibration period of 30 min the basal perfusion pressure reached a constant level of 20-30 mm Hg. NA was infused in 0.05 ml Krebs-bicarbonate buffer. The pressure response (mm Hg) of 3 test infusions for each dose was averaged.

NA 0.1, 0.3, 1 and 3 μg added to the perfusate induced dose-dependent increases in perfusion pressure in saline-pretreated rats. These increases were significantly reduced by 45%, 48%. 56% and 65%, respectively in rats pretreated with Hoe-498 (Fig 1). Thus,

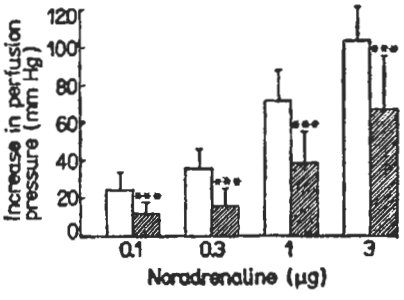


**Fig 1. Effects of po Hoe-498 (1 mg/kg) ▨ on noradrenaline-induced vasoconstriction in isolated perfused mesentery. 10 rats/group $\bar{x}$±SD. ***p<0.01**

Received 1983 Oct 28

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Hoe-498 attenuated the vasoconstrictor responses to NA in rat mesenteric vascular bed.

## DISCUSSION

In the present study, Hoe-498 po 1 mg/kg caused an attenuation of the NA-induced vasoconstriction in the isolated perfused rat mesentery. This correlates with the finding that ANG II enhances adrenergic transmission in this vascular bed, and indicates that ACE-inhibitor Hoe-498 may interfere with these mechanisms by inhibiting ANG II formation. A further possible explanation is bradykinin potentiation.

Perfusion with captopril, another ACE-inhibitor, in the isolated rat mesenteric vascular bed also produced an attenuation of the vasoconstrictor responses induced by NA. This attenuation was considered to be due to a direct action on the vascular bed and not to be dependent on the inhibition of ACE[8,9], since the tissue was perfused with ACE-inhibitor, In the present study the ACE-inhibitor was administered orally to rats, hence it is likely that ACE-inhibition plays a more important role.

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中国药理学报 1984年6月; **5** (2): 104-105

# 血管紧张素转化酶抑制剂 HOE-498 对去甲肾上腺素引起离体灌流大鼠肠系膜血管收缩的作用

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**提要** 大鼠口服 Hoe-498 (1 mg/kg) 可减弱去甲肾上腺素引起的灌流肠系膜血管的收缩作用.提示Hoe-498可能干扰肾上腺素能神经传递时血管紧张素介导的 接通.

**关键词** Hoe-498; 离体灌流大鼠肠系膜; 激酶 II 抑制剂; 去甲肾上腺素

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