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Effect of phencyclidine on contraction of porcine coronary vessel strips

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ABSTRACT Classic muscular contraction experiment was used to study the effect of phencyclidine (Phe) on spiral strips of porcine coronary vessels. It showed that Phe and its analogs: 1-[1-(2-thienyl)cyclohexyl] piperidine (TCP), (+)-5-methyl-10, 11-dihydro-5 *H*-dibenzo [a, d] cyclohepten-5, 10-imine maleatel (dizocilpine maleate) and sigma receptor ligand *N*-allyl-*N*-normetazocine (SKF10047) all exhibited a concentration-dependent contraction of porcine coronary vessel strips. Phe had no effect on the electrically stimulated contraction of the spiral strips. Dextromethorphan (Dex), a Phe receptor antagonist, and haloperidol (Hal), a sigma receptor antagonist, partially antagonized and suppressed the actions of Phe in a non-competitive manner. these results suggested that Phe, TCP, dizocilpine maleate, and (+), (−)-SKF10047 cause contraction through Phe and sigma opioid receptors.

KEY WORDS phencyclidine; coronary vessels; haloperidol; dextromethorphan; muscular contraction

1-(1-Phenylcyclohexyl) piperidine (Phe) and sigma opioid receptor regulated vasoconstrictions. Phe markedly enhanced the electrically stimulated constriction (ESC) of central rabbit ear vessels[1], rat mesenteric vessels[1], and porcine cerebral vessels[5]. These actions were closely related to the release of norepinephrine (NE) by presynaptic stimulation. Radioligand binding assay demonstrated the existence of Phe receptors on porcine coronary vessels. The present study is to investigate the function of Phe receptors on coronary vessel constriciton.

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MATERIALS AND METHODS

Phe was synthesized by Pharmacy College of Shanghai Medical University. TCP and dizocilpine maleate were purchased from Sigma Co. SKF10047 was purchased form Du Pont Co. Dex and Hal were purchased from Shanghai Meiyou Pharmaceutical Factory and Shanghai Tianfeng Pharmaceutical Factory, respectively.

Porcine hearts were purchased from Shanghai Ronghua Slaughter House.

The right proximal coronary vessels, isolated from fresh adult porcine hearts were kept at 4℃ in Krebs-Ringer solution. Connective tissue was removed and vessels segments were cut into 15×2 mm helical strips. Strips were suspended in 5 ml glass organ chambers filled with Krebs-Ringer solution at 37±0.5℃ and gassed with 95% O_2+5% CO_2.

1 Contractile effects of drugs without electric field stimulation After being equilibrated at a resting tension of 2 g for 2 h, the preparation was exposed to Phe, TCP, dizocilpine maleate, and SKF10047. Before injection of Phe into the bath medium, Dex and Hal were injected into the bath medium separately. After the injection of Phe 100 $\mu mol \cdot L^{-1}$ into the bath medium, Dex was injected into the bath medium.

2 Effect of Phe on strip contraction induced by electric field stimulation After 2 h equilibration, the strips were stimulated by ESC (45 V, 10－15 Hz, trains of 100 pulses, 0.5 ms per pulse, 3 min interval). Phe was injected 1 min before the stimulation.

RESULTS

Effects of Phe and sigma opioid receptors on contraction of porcine coronary vessels Phe, TCP, SKF10047, and dizocilpine

maleate all induced contraction of the vessels, when the concentration was 100 μmol · L^{-1}, the rank order was: *l*-SKF10047 (2.18 g±0.07)>Phe (1.64 g±0.32), TCP (1.72 g±0.16)>*d*-SKF10047 (0.92 g±0.3), dizocilpine maleate (0.83 g±0.43). At the range of 0.1—100 μmol · L^{-1}, they enhanced the contraction in a concentration-dependent manner (Fig 1).

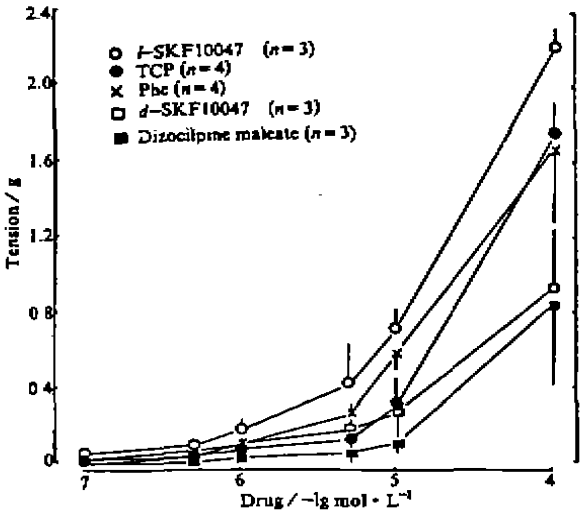

Fig 1. Effects of *l*-SKF10047, TCP, phencyclidine, *d*-SKF10047, and dizocilpine maleate on contraction of porcine coronary artery. $n=3-4$ pigs, $\bar{x}\pm s$.

Antagonization and suppression of Dex on Phe Dex (10 and 50 μmol · L^{-1}) inhibited the contraction of Phe in a dose-dependent manner (Fig 2, $n=4$, $pD'_2=4.78\pm0.13$). Dex (50, 100, and 1000 μmol · L^{-1}) suppressed the contractile effect of Phe (100 μmol · L^{-1}). Though there was little change of contraction after Hal, Hal inhibited the contractile effect of Phe. (Fig 3, $n=4$, $pD'_2=5.05\pm0.25$).

No effect of Phe on contraction induced by electric stimulation. One minute before stimulation, Phe was added into the bath medium (final concentration: 0.1—100 μmol · L^{-1}), there was not any influence of Phe on ESC, but the tension of blood vessel was intensified as the concentration increased.

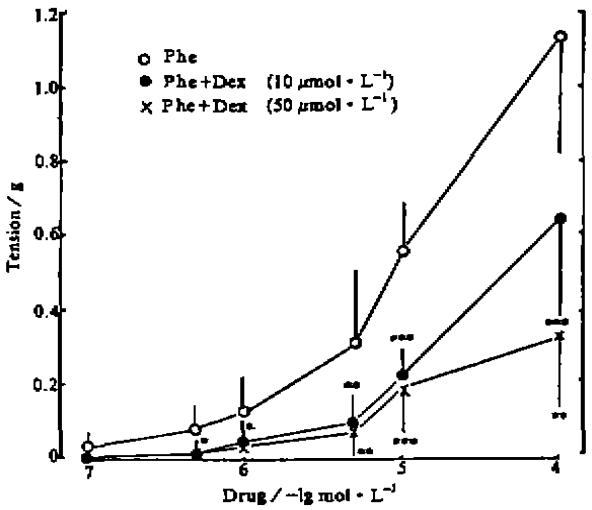

Fig 2. Effect of dextromethorphan on phencyclidine contraction. $n=4$ strips from 4 pigs, $\bar{x}\pm s$. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* phencyclidine.

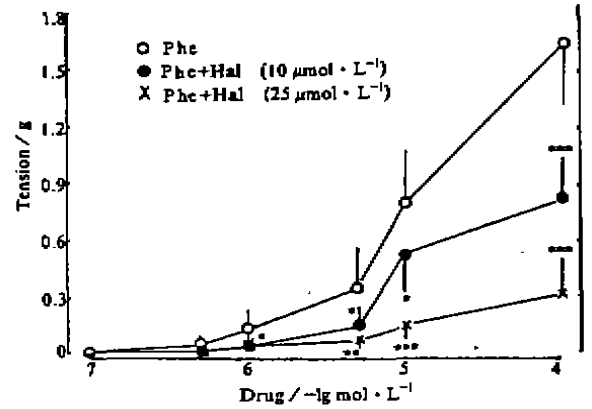

Fig 3. Effect of haloperidol on phencyclidine contraction. $n=4$ strips from 4 pigs, $\bar{x}\pm s$. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* phencyclidine.

DISCUSSION

Radio-ligand binding assay demonstrated that Phe receptors existed in porcine coronary vessels[4]. Phe, TCP, and dizocilpine maleate were proven to be selective Phe receptor agonists and Dex, its antagonist[7,8]. SKF10047 and Hal were selective sigma receptor agonist

and antagonist, respectively[9]. Contractions of porcine coronary vessels were induced by Phe, TCP, dizocilpine maleate, and SKF10047, while Dex inhibited and suppressed such actions of Phe, Hal inhibited the actions in non-competitive manner. These results suggested that the effects of all the drugs were induced through Phe and sigma opioid receptors. The Phe receptor and sigma opioid receptor on the coronary vessels were partialy overlapping.

There were some difference between the results in this test and other reports[1]. Phe increased ESC in mouse mesenteric vessels and those central rabbit auricular vessels, and in our investigation Phe caused contraction of coronary vessels directly, while it had no effect on ESC. These results may be caused by the charicteristics of Phe and sigma opioid receptors on coronary vessels, or by difference of animal species.

We had found the effect of *l*-SKF10047 was greater than that of *d*-SKF10047, and in this experiment, both Dex and Hal inhibited the effect of Phe, while the contractile effect of *l*-SKF10047 was more potent than that of Phe. It showed that SKF10047 had stereoselectivity for contraction. Thus further investigation is needed to reveal what kind of receptor (Phe or sigma) has priority on the coronary vessels.

It was found that Phe receptor did not exist in porcine coronary vessels. This experiment showed that dizocilpine maleate, the selective agonist of Phe receptor, had the weakest effect. This revealed that most of Phe receptors in coronary vessels were not Phe receptors.

REFERENCES

1 Zhu H, Zhang AZ, Zhang LM, Xu XR, Le WL. Phencyclidine receptor in blood vessels. *Chin J Physiol* 1986; **2**: 47－54.

2 Lu YF, Sun FY, Zhang AZ. Effects of phenyclidine analogs and phenclidine/sigma ligands on vasoconstrictor response of rat mesenteric arteries induced by electrical field stimulation. *Acta Pharmacol Sin* 1990; **11**: 293－5.

3 Lu YF, Sun FY, Zhang LM, zhang AZ. Phencyclidine receptors in porcine cerebral arteries. *Acta Pharmacol Sin* 1989; **10**: 508－11.

4 Shu GG, Xu SF. Phencyclidine receptor in porcine coronary artery. *Acta Pharmacol Sin* 1993; **14**: 39－41.

5 Vignon J, Chicheportiche R, Chicheportiche M, Marckamenka J, Geneste P, Lazdunski M. [^{3}H]TCP: a new tool with high affinity for the PCP receptor in rat brain. *Brain Res* 1983; **280**: 194－7.

6 Steinfels GF, Tam SW, Cook L. Electrophysiological effects of selective-receptor agonists, antagonists, and the selective phencyclidine receptor agonist MK-801 on midbrain dopamine neurons. *Neuropsychapharmacology* 1989; **2**: 201－7.

7 Church J, Shacklock JA, Bainbridge KG. Dextromethorphan and phencyclidine receptor ligands: Differential effects on K- and NMDA-evoked increases in cytosolic free Ca concentration. *Neurosci Lett* 1991; **124**: 232－4.

8 Bao WL, Sun FY, Zheng FC, Zhang AZ. Antagonistic effects of dextromethorphan on vasoconstriction of phencyclidine. *Acta Pharmacol Sin* 1991; **12**: 242－4.

9 Largent BL, Gundlach AL, Snyder SH. Pharmacological and autoradiographic discrimination of sigma and phencyclidine receptor binding sites in brain with (+)－[^{3}H]SKF10047, (+)－[^{3}H]－[3－hydroxyphenyl]－N－(1－propyl)piperidine and [^{3}H]－1－[1－(2－thienyl)cyclohexyl]piperidine. *J Pharmacol Exp Ther* 1986; **238**: 739－48.

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苯环利定对猪冠状动脉肌条的作用

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摘要 本文利用生物检定法研究苯环利定(Phe)对猪冠状动脉肌条的作用，发现 Phe 可以引起冠脉肌条的收缩，其同类物 TCP，dizocilpine maleate 和 sigma 受体配基SKF10047也有同样作用. Phe 受体拮抗剂 dextromethorphan 和 sigma 受体拮抗剂 haloperidol 均可非竞争性的拮抗或翻转 Phe 的作用. 以上提示 Phe 及其同类药物引起猪冠状动脉肌条收缩是通过 Phe 和 sigma 受体.

关键词 苯环利定；冠状血管；氟哌啶醇；右美沙芬；肌收缩