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Inhibitory effects of 2-[(diethylamino)acetyl]-1,2,3,4-tetrahydro-6,7-dimethoxyl-1-[1′-(6″-methoxy-2″-naphthalenyl)ethyl]-isoquinoline on isolated guinea pig papillary muscle and heart atrium

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AIM: To investigate the cardiac actions of 2-[(diethylamino)acetyl]-1,2,3,4-tetrahydro-6,7-dimethoxyl-1-[1′-(6″-methoxy-2″-naphthalenyl) ethyl]-isoquinoline (CPU57) by comparison with nifedipine and focus on its mechanism of actions. **METHOD**: The following were measured and recorded: 1) the rate and contraction of spontaneous beating of the guinea pigs right heart atrium, 2) the isometric tension of the electrically stimulated left heart atrium and the right papillary muscles. **RESULTS**: CPU57 had negative inotropic and negative chronotropic actions in isolated heart of guinea pigs as the typical calcium antagonist, nifedipine. However, CPU57 0.01—100 $\mu mol \cdot L^{-1}$ produced less cardiac inhibitory potency than nifedipine and had much stronger negative inotropic action than negative chronotropic action. The decrease in external $CaCl_2$ concentration from 1.5 to 0.3 $mmol \cdot L^{-1}$ or increase to 7.5 $mmol \cdot L^{-1}$, potentiated or reduced respectively, the inhibitory action of CPU57 on the contraction in paced left heart atrium in normal $CaCl_2$ solution. CPU57 1—10 $\mu mol \cdot L^{-1}$ also inhibited contractile response to $CaCl_2$ in paced left heart atrium with pD_2' value of 4.77. **CONCLUSION**: CPU57 has calcium antagonism on the heart of guinea pigs.

KEY WORDS isoquinolines; CPU57; nifedipine; heart atrium; papillary muscles; myocardial contraction; heart rate

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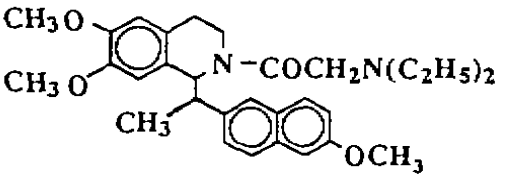
With a [^{3}H]nitrendipine binding assay, we screened a series of substituted tetrahydroisoquinolines in order to develop novel calcium antagonists based on the lead compound, tetrandrine, isolated from a Chinese medicinal herb, *Stephania tetrandra*[1-3]. 2-[(Diethylamino) acetyl]-1, 2, 3, 4-tetrahydro-6, 7-dimethoxyl-1-[1′-(6″-methoxy-2″-naphthalenyl) ethyl]-isoquinoline (CPU57) was found to inhibit both [^{3}H]nitrendipine binding to rat cerebral cortical membranes and high KCl-induced contraction of rat aorta *in vitro* with similar potency. It was therefore suggested that CPU57 may exert its vasodilation by inhibiting calcium channels on rat aorta[4]. In the present study, we investigate further its cardiac actions by comparison with nifedipine.



CPU57

MATERIALS AND METHODS

Guinea pigs ($n=27$, $285 \pm s$ 25 g,) of both sexes were stunned. Heart atrium and the right papillary muscles were mounted in organ baths containing 20 mL of normal Tyrode's solution bubbled with 95% O_2 + 5% CO_2 (pH 7.3—7.4 at 37 ℃) under a resting tension of 1 g. The rate and contraction of spontaneous beating of the right heart atrium were measured. The preparations were allowed to equilibrate for 1 h. The left heart atrium and the right papillary muscles were

electrically stimulated at 1 Hz with rectangular pulses (1 ms, 8 V) delivered through a bipolar silver electrode[4]. Isometric tension measured with a force transducer was displayed on a LMS-2B recorder. The drugs were added by stepwise. The concentration of drugs was increased only after the previous addition of the drug had produced the maximal response[5]. Less than 0.1 mL of drugs was added into the organ bath each time.

Nifedipine was purchased from Sigma Chemical Co. CPU57·HCl (mp 124—125 C) was kindly supplied by China Pharmaceutical University and dissolved in Tyrode's solution. Nifedipine was dissolved in absolute ethanol and protected from light. It was diluted in Tyrode's solution before experiments. The final concentration of ethanol was <1 %, which *per se* had no effect on the experiments.

Data were expressed as % of the control before addition of test drugs. Significant differences ($P < 0.05$) between means were evaluated by Student's paired or unpaired t tests where appropriate. IC_{50} values were accompanied by 95 % confidence limits.

RESULTS

Right heart atrium The isolated right heart atria beat spontaneously for about 3 h at a rate of 275±10 bpm and a contraction of 584 ±102 mg. Both nifedipine and CPU57 0.01—100 μmol·L^{-1} inhibited rate and contraction in a concentration-dependent manner. They inhibited the contraction stronger than the rate (Fig 1A & B). The inhibitory potency of CPU57 was less than that of nifedipine. IC_{50} values for CPU57 and nifedipine in inhibiting contraction were 2.4 (1.05—2.61) and 0.88 (0.63—1.22) μmol·L^{-1}, respectively. IC_{50} values for both drugs in inhibiting rate were >1 mmol·L^{-1}.

Papillary muscles The contraction in paced papillary muscles was 464 ± 79 mg. Both CPU57 and nifedipine 0.01—100 μmol·L^{-1} inhibited the contraction in a concentration-dependent manner (Fig 1C). CPU57 produced less inhibition than nifedipine. IC_{50} values for CPU57 and nifedipine were 11.30 (7.85—16.62) and 9.23 (4.33—20.1) μmol·L^{-1}, respectively. Contractile amplitude of papillary muscles increased with frequency

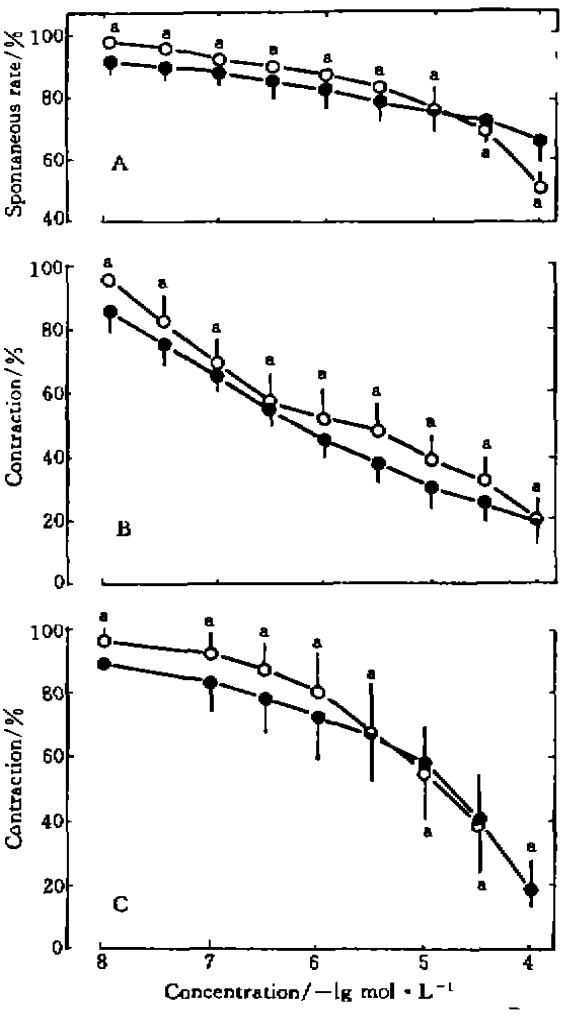


Fig 1. Effects of CPU57 (○) and nifedipine (●) on rate (A) and contraction (B) of spontaneously beating right heart atrium and on contraction in paced papillary muscles (C) in guinea pigs. $n=6-7$, $\bar{x}\pm s$. *$P>0.05$ *vs* nifedipine.

of stimulation. Both CPU57 and nifedipine 10 μmol·L^{-1} produced similar inhibitions on contraction, but the inhibitory action did not increase with frequency of stimulation (Fig 2).

Left heart atrium Before the addition of CPU57, the contractile force of paced left heart atrium in normal $CaCl_2$ Tyrode's solution ($CaCl_2$ 1.5 mmol·L^{-1}) was 440±33 mg. Addition of CPU57 produced a negative

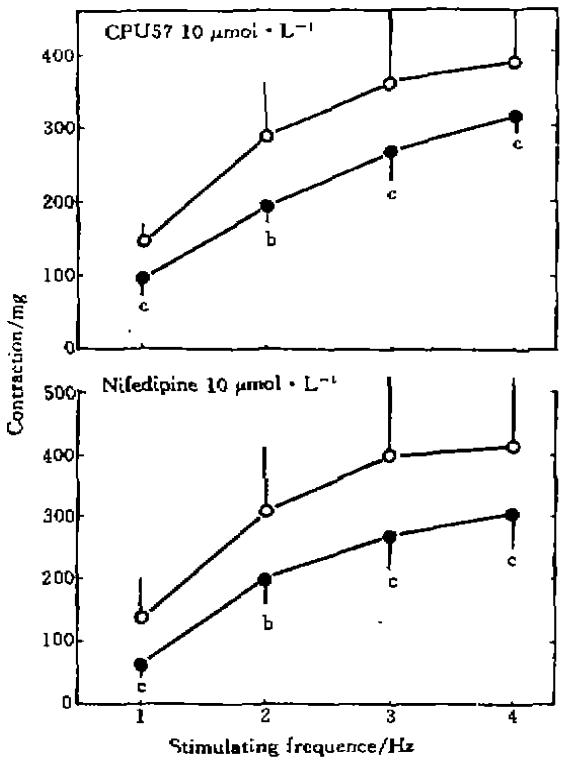


Fig 2. Effects of CPU57 and nifedipine on contraction of paced guinea pigs papillary muscles before (○) and after (●) drugs. $n=7$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* before drugs.

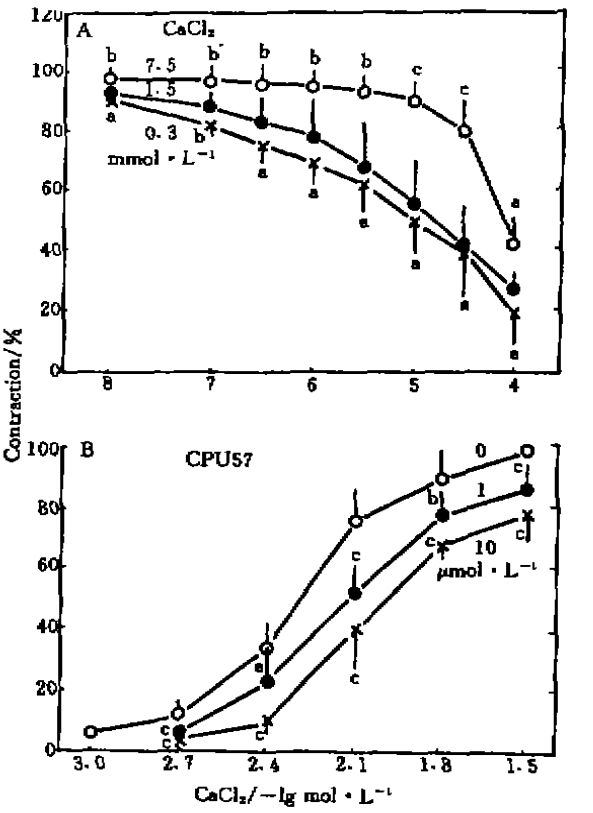


Fig 3. Effects of CPU57 on contraction in paced guinea pigs left heart atrium. (A) In different concentrations of $CaCl_2$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* $CaCl_2$ 1.5 mmol·L^{-1}, $n=7$, $\bar{x}\pm s$. (B) Different concentrations of CPU57. $n=6$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* CPU57 0 μmol·L^{-1}.

inotropic effect. IC_{50} value for CPU57 in inhibiting contraction was 15.70 (10.51 — 23.90) μmol·L^{-1}. The decrease in external $CaCl_2$ concentration from 1.5 to 0.3 mmol·L^{-1} potentiated the inhibitory action of CPU57 on the contraction with a IC_{50} value of 6.81 (4.36 — 10.47) μmol·L^{-1}. The increase in external $CaCl_2$ concentration from 1.5 to 7.5 mmol·L^{-1} reduced the inhibitory action of CPU57 on the contraction with a IC_{50} value of 0.66 (0.42 — 1.04) mmol·L^{-1} (Fig 3A). CPU57 1 — 10 μmol·L^{-1} also inhibited contractile response to $CaCl_2$. The pD_2' value for CPU57 was 4.77 (Fig 3B).

DISCUSSION

The present study demonstrated that CPU57 had a negative inotropic effect in the paced left atrium and papillary muscle and that it also exerted both negative inotropic and negative chronotropic effects in spontaneously beating right heart atrium in a dose-dependent manner as nifedipine did. However, CPU57 produced less cardiac inhibitory potency than nifedipine and had much stronger negative inotropic action than negative chronotropic action, suggesting that CPU57 inhibited cardiac unautonomic cells stronger than autonomic cells. On the other hand, it was also found that negative inotropic effects of CPU57 in descending order were right heart atrium>papillary muscles > left heart atrium. Compared

with our previous study showing that CPU57 inhibited high KCl-induced contraction of rat aortic strips with IC_{50} value of 0.25 μmol·L^{-1} [3], it was shown that potency of CPU57 for inhibiting KCl-induced contraction of rat aorta was as approximately 45 times as that for inhibiting the contraction in paced guinea pigs papillary muscles.

Although the exact mechanism by which CPU57 produced negative inotropic and negative chronotropic actions in the isolated heart of guinea pigs can not be elucidated by means of the present results, it was supposed that CPU57 is likely to be a calcium antagonist in the light of the following evidences: 1) In our previous study[3], CPU57 was found to inhibit both [^{3}H]nitrendipine binding to rat cerebral cortical membranes and high KCl-induced contraction of rat aorta with similar potency; 2) In the present study, CPU57 exerted similar characteristic as the typical calcium antagonist, nifedipine, in many respects of cardiac inhibition[6]; 3) The decrease or increase in external $CaCl_2$ concentration potentiated or reduced respectively, the inhibitory action of CPU57 on the contraction in paced left heart atrium in normal $CaCl_2$ solution[7]. 4) CPU57 also inhibited contractile response to $CaCl_2$ in paced left heart atrium. However, further experiments, especially electrophysiological one will be needed to elucidate the precise mechanism of the cardiac inhibitory actions of CPU57.

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2-[(二乙胺)乙酰]-1,2,3,4-四氢-6,7-二甲氧基-1-[1′-(6″-甲氧-2″-萘)乙基]-异喹啉对离体豚鼠乳头状肌和心房的抑制作用

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A **目的**: 研究2-[(二乙胺)乙酰]-1,2,3,4-四氢-6,7-二甲氧基-1-[1′-(6″-甲氧-2″-萘)乙基]-异喹啉(CPU57)对心脏的作用并与硝苯地平进行比较, 着重于其作用机制的研究. **方法**: 测量并记录以下参数: 1) 豚鼠右心房自发收缩的节律及张力; 2) 电刺激左心房和右室乳头状肌的等长收缩力. **结果**: CPU57象经典的钙拮抗剂硝苯地平一样, 在0.01–100 μmol·L^{-1}浓度范围内对离体豚鼠心脏具有浓度依赖的负性频率和负性肌力作用, 而前者明显弱于后者, 且其对心脏的抑制作用比硝苯地平弱. 将正常胞外Ca^{2+}浓度从1.5 mmol·L^{-1}降低至0.3或增高至7.5 mmol·L^{-1}可分别增强或减弱CPU57对电刺激左心房收缩的抑制作用. CPU57 (1–10 μmol·L^{-1})还抑制$CaCl_2$所致电刺激左心房的量–效收缩曲线, pD_2'值为4.77. **结论**: CPU57对豚鼠心脏具有钙拮抗作用.

关键词 异喹啉类; CPU57; 硝苯地平; 心房; 乳头状肌; 心肌收缩; 心率