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Effects of nimodipine, felodipine, and verapamil on isolated human arteries

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AIM: To evaluate whether there might be some difference in the action modes of nimodipine (Nim) and felodipine (Fel). **METHODS**: Compare the inhibitory effects of Nim and Fel with that of verapamil (Ver) as a representative of phenylalklamine on norepinephrine (NE)- and $CaCl_2$-evoked contractions of human arteries. **RESULTS**: In Ca^{2+}-free and high K^+ depolarized solution, inhibitory effects of Nim, Fel, and Ver were more potent on $CaCl_2$-induced contractions on isolated human arteries than those on NE-induced contractions. In $CaCl_2$-induced contraction, the pD_2 values for Nim, Fel, and Ver were 7.5, 7.42, 6.35 on uterine arteries; 7.38, 7.65, 7.20 on mesenteric arteries and 7.87, 9.10, 7.32 on renal arteries, respectively. Ver inhibited 2 components of NE-evoked contraction, while Nim and Fel only inhibited extracellular Ca^{2+}-dependent contractions. **CONCLUSION**: The result indicates that Fel has a selective action on human renal arteries.

KEY WORDS nimodipine; felodipine; verapamil; arteries; norepinephrine; calcium chloride

Nimodipine (Nim) and felodipine (Fel) are dihydropyridine calcium antagonists that preferentially dilate blood vessels and have been widely used in the treatment of hypertension, angina, and cerebral disease[1,2]. Their pharmacological actions on vascular smooth muscle were mostly studied in animals[3]. The contraction of vascular smooth muscle is initiated by an increase of intracellular calcium activity. This may be achieved either by a release from intracellular sources or by an increase of membrane permeability to extracellular calcium[4]. The present study was undertaken to compare the inhibitory effects of Nim and Fel with that of verapamil (Ver) as a representative of phenylalklamine on norepinephrine (NE)- and $CaCl_2$-evoked contractions of human arteries. We also compared the inhibitory action of Nim and Fel on 2 components of NE-evoked contraction of human mesenteric artery with that of Ver to evaluate whether there might be some difference in their action modes.

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MATERIALS AND METHODS

Human arteries were obtained from 15 patients with myometrial myoma, gastric, and renal cancer (M 9, F 6; age 50±9 a) after an operation in hospital. All tested arteries were dissected out immediately from healthy parts of the excised organs and immersed in 4 ℃ Krebs solution, then transferred to the laboratory. The arteries were cleared from connective tissue and cut into rings of about 3 mm long. The whole process was completed within 60 min. The rings were mounted in 5-ml organ baths at 37 ℃. Isometric tension was measured with a force transducer and displayed on a XMT-200 recorder. The artery rings in the baths were allowed to equilibrate for 1.5—2 h before experiment. The volume of drugs added each time was < 0.1 ml.

Nim, Fel (Hebei Medical College), Ver hydrochloride injection (Changzhou Parmaceutical Factory) and NE (Shanghai Tianfeng Parmaceutical Factory) were used. Nim and Fel were dissolved in acetone and then stored at 4 ℃. They were diluted in redistilled water before use. The final acetone concen

tration must be ~ 0.2 %, which, in preliminary test, exerted no effect on the rings. Krebs solution was composed of NaCl 118, KCl 4.75, $CaCl_2 \cdot 2H_2O$ 2.54, $MgSO_4 \cdot 7H_2O$ 1.19, KH_2PO_4 1.25, $NaHCO_3$ 24.97, glucose 11.10 (mmol·L^{-1}), bubbled with 5 % CO_2 — 95 % O_2, pH 7.2—7.4. In Ca^{2+}-free Krebs solution, $CaCl_2$ was omitted from Krebs solution and egtazic acid (Sigma Chemical Co) 0.1 mmol·L^{-1} was added. High K^+ depolarized solution was prepared from Ca^{2+}-free solution with KCl 80 mmol·L^{-1}.

In the studies of the 2 components of NE-evoked contraction, the rings were washed with Ca^{2+}-free Krebs solution for 3 times, then incubated in this solution for 30 min. NE 10 μmol·L^{-1} was added. When a fast and nonsustained contraction was achieved $CaCl_2$ 2.5 mmol·L^{-1} was restored. Then a slow and sustained one was obtained. The rings were washed again with Ca^{2+}-free Krebs solution for 3 times. One ring was used as control, whereas the others from the same human mesenteric artery were used as testing rings which were incubated for 30 min in Ca^{2+}-free Krebs solution containing Ver 10 μmol·L^{-1}, Fel 10 μmol·L^{-1}, or Nim 10 μmol·L^{-1}, then NE and $CaCl_2$ were added successively as described above.

RESULTS

Actions on contraction evoked by NE

The Nim, Fel and Ver produced a concentration-dependent inhibition (Fig 1). The pD_2' values for Nim, Fel and Ver were 4.60, 4.47, 4.72 on uterine artery; 5.22, 4.04, 5.11 on mesenteric artery; and 4.90, 4.70, 4.74 on renal artery, respectively.

Actions on contraction evoked by $CaCl_2$

The 3 calcium antagoists induced the inhibitory effects on $CaCl_2$-induced contraction (Fig 1). The pD_2' values for Nim, Fel, and Ver were 7.50, 7.42, and 6.35 on uterine artery, 7.38, 7.65, and 7.20 on mesenteric artery; 7.87, 9.10, and 7.32 on renal artery, respectively.

Actions on the 2 components of NE-evoked contraction on mesenteric artery

Ver inhibited the 2 components of contraction, while Fel or Nim inhibited only the

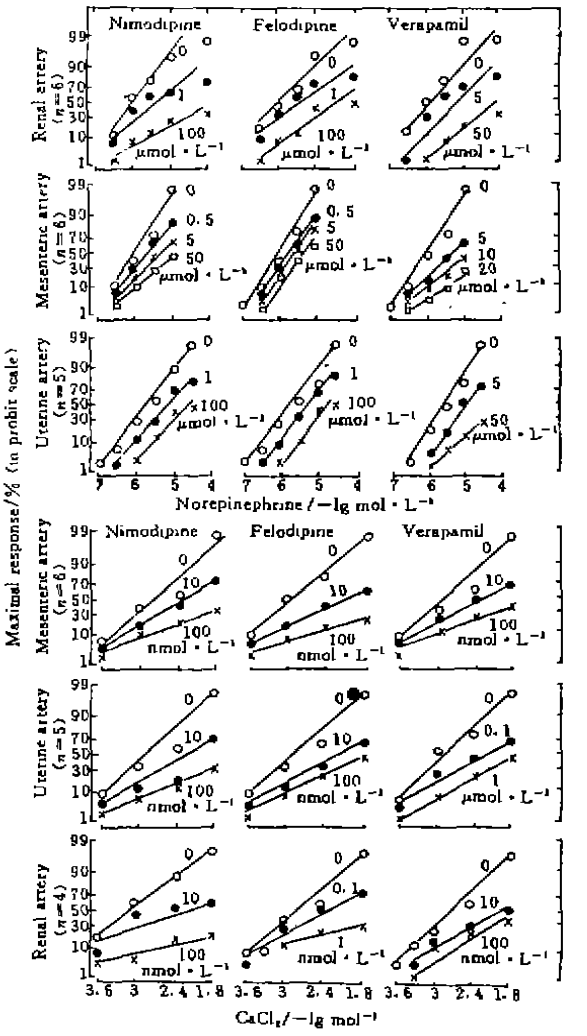

Fig 1. Effects of Nim, Fel, and Ver on NE- and $CaCl_2$-induced contractions in human arteries.

component of extracellular Ca^{2+} influx.

DISCUSSION

Our data showed that Nim, Fel, and Ver could more potently inhibit the contractile response induced by calcium than by NE in high K^+-depolarized rings. These findings were in agreement with those reported by Loutzenhiser and Epstein, which found that nitrendip-

ine-induced blocking action on PDC was more potent than on ROC in human renal artery[5]. As to our test, the present investigation is the first time to study the action of Fel on isolated human blood vessels. We found that the potency of the inhibition on calcium-induced contraction by Fel was the highest in renal artery among 3 tested arteries, but it was much less effective on NE-induced contraction. Our results indicated that Fel might have a selective action on renal artery. Some experimental evidence and clinical data suggested that Fel could produce renal vasodilation without adverse effects on the glomerular filtration or renal sodium and water excretion[6]. Our results supported the suggestion that Fel might be an idea vasodilator in treatment of renal disease[6,7]. In present study, Ver inhibited 2 components of NE-induced contraction, while Nim or Fel only inhibited the contraction by extracellular Ca^{2+} influx on human mesenteric artery. This result was similar to that of the experiments on porcine coronary artery[5]. It suggested further that the action model of Ver in our laboratory was different from that of Nim or Fel not only in animal but also in human arteries.

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尼莫地平、非洛地平和维拉帕米对离体人血管作用

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目的：观察尼莫地平（Nim），非洛地平（Fel）是否有不同的作用模式。 **方法**：比较尼莫地平（Nim），非洛地平（Fel）对去甲肾上腺素（NE）和氯化钙（$CaCl_2$）引起的人动脉收缩的不同作用，并且与维拉帕米（Ver）的作用相比较。 **结果**：Nim，Fel 和 Ver 对无 Ca^{2+} 高 K^+ 去极化时 $CaCl_2$ 所致离体人血管收缩的拮抗作用比其对 NE 引起收缩拮抗作用强。在 $CaCl_2$ 引起收缩时，Nim、Fel 和 Ver 拮抗作用 pD_2' 在子宫动脉分别为7.50，7.42，6.35；在肠系膜动脉分别为7.38，7.65 和 7.20；在肾动脉分别为7.87，9.10 和 7.32，Ver 可抑制 NE 所致的两种收缩成分，Nim 或 Fel 仅抑制外 Ca^{2+} 内流引起收缩。 **结论**：Fel 对肾血管有选择作用。

关键词 尼莫地平；非洛地平；维拉帕米；动脉；去甲肾上腺素；氯化钙