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甲基莲心碱和粉防己碱对大鼠门静脉和乳头状肌收缩的抑制作用

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Inhibitory effects of neferine and tetrandrine on portal vein and papillary muscle in rats

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ABSTRACT To determine the vascular selectivity, the inhibitory effects of verapamil (Ver), neferine (Nef), and tetrandrine (Tet) on the spontaneous contractile force of portal vein and contractile force of the paced papillary muscle of left ventricle were studied in Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR). The vascular selectivity was expressed by the IC_{50} ratio (IC_{50} for papillary muscle / IC_{50} for portal vein). The results showed that the valscular selectivity values of Ver, Nef, and Tet were 1.15, 0.32, and 0.20, respectively in WKY and 0.80, 0.24, and 0.10, respectively in SHR. It is concluded that Nef and Tet, in contrast with Ver which is devoid of selectivity for either tissue, are more liable to inhibit the myocardium than the vascular smooth muscle. In addition, the IC_{50} value of Tet for inhibition of the portal vein in SHR was nearly 10-fold higher than that in WKY (237 and 27 $\mu mol \cdot L^{-1}$, respectively). This indicates that the response of portal vein to Tet is decreased in SHR.

KEY WORDS verapamil; neferine; tetrandrine; calcium channel blockers; papillary muscles; portal vein; inbred SHR rats; inbred WKY rats

提要 Ver，Nef 和 Tet 抑制 WKY 和 SHR 的左心室乳头状肌和门静脉的收缩. Tet 抑制 SHR 门静脉的 IC_{50} 比 WKY 高近 10 倍，分别为 237 和 27 $\mu mol \cdot L^{-1}$，提示 SHR 的门静脉对 Tet 的反应性降低. Ver、Nef 和 Tet 对 WKY 的血管选择性(抑制乳头状肌 IC_{50} 与抑制门静脉 IC_{50} 之比)分别为 1.15、0.32 和 0.20，对 SHR 分别为 0.80、0.24 和 0.10，说明 Ver 对心肌和血管缺乏选择性抑制，Nef 和 Tet 较易抑制心肌.

关键词 维拉帕米；甲基莲心碱；粉防己碱；钙通道阻滞剂；乳头状肌；门静脉；近交 SHR 大鼠；近交 WKY 大鼠

钙拮抗剂对血管和心肌的抑制作用具有一定的选择性[1]，甲基莲心碱(neferine，Nef)和粉防己碱(tetrandrine，Tet)有钙拮抗作用，能松弛血管平滑肌和抑制心肌收缩[2-5]. 本文通过观察维拉帕米(verapamil，Ver)、Nef 和 Tet 对同一大鼠的门静脉和乳头状肌的抑制作用，评价 Nef 和 Tet 对血管和心肌抑制的选择性. 另外，SHR 的血管平滑肌对药物的反应性可能发生改变[6]，故采用了 WKY 和 SHR 两种大鼠.

MATERIALS AND METHODS

Wistar-Kyoto 大鼠(WKY)和自发性高血压大鼠(SHR)，不分性别，体重分别为 278 ± *s* 69 和 230 ± *s* 23 g，由本药理教研室的动物房供应. Ver 购自北京制药厂，Tet 购自浙江金华制药厂；Nef 由中国预防医学科学院职业病研究所提取分离.

离体标本制备及给药[7,8] 大鼠颈椎脱臼处死后摘取心脏和剪取静脉，置于含 95% O_2 + 5% CO_2 的 Krebs-Henseleit 液中，再分别分离出左心室乳头状肌和长约 4 mm 的门静脉各一条，分别悬挂在含 95% O_2 + 5% CO_2 的 20 ml KH 液的浴槽中，一端连接张力换能器(LWA-20，上海光和电子电器厂)，并调静息张力分别为 400 和 500 mg，稳定 1 h 后，用方波刺激器(YSD-5，蚌埠医学院)电刺激乳头状肌，频率 3 Hz，波宽 1 ms，强度为 110%的阈刺激强度，台式平衡记录仪(XWT-264，上海大华仪表厂)记录乳头状肌的等长收缩张力和门静脉自主收缩张力. 待收缩平稳 20 min 后，记录给药前的收缩张力，其中门静脉的自主收缩张力以 2 min 内的每一次自主收缩张力的平均

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值表示，随后按累积给药法每隔 10 min 给药一次，每次给药孵育 8 min 后记录 2 min 的门静脉自主收缩张力和电刺激乳头状肌的收缩张力(每次给药的前 8 min 停止电刺激乳头状肌)，作为该浓度的收缩张力.

数据处理 全部数据用 $\bar{x} \pm s$ 表示，以药物的浓度-lg mol · L^{-1} 作为横座标，收缩张力作为纵座标作量-效曲线. 用直线回归法求 IC_{50}，药物抑制乳头状肌的 IC_{50} 与抑制门静脉的 IC_{50} 之比为血管选择性.

RESULTS

门静脉自主收缩 门静脉的自主收缩至少在 1 h 内是稳定的(Fig 1A). Ver 累积给药使门静脉的自主收缩张力剂量依赖性地降低(Fig 1B)，Nef 或 Tet 累积给药也出现类似的结果.

Ver，Nef 和 Tet 对 WKY 和 SHR 的血管选择性 WKY 和 SHR 的门静脉自主收缩和电刺激乳头状肌收缩受到 Ver (0.01–0.3 μmol · L^{-1})，Nef (1–100 μmol · L^{-1})和 Tet (1–300 μmol · L^{-1})的抑制(Fig 2)，结果 Tet 抑制 WKY 和 SHR 的门静脉收缩的 IC_{50} 分别为 27 和 237 μmol · L^{-1}，几乎相差一个数量级，其它的同一药物抑制 WKY 和 SHR 的乳头状肌或门静脉的 IC_{50} 都非常接近. 药物抑制乳头状肌的 IC_{50} 与抑制门静脉的 IC_{50} 之比为血管选择性，得出 Ver，Nef，Tet 对 WKY 和 SHR 的血管选择性分别为 1.15 和 0.80，0.32 和 0.24 及 0.20 和 0.10.

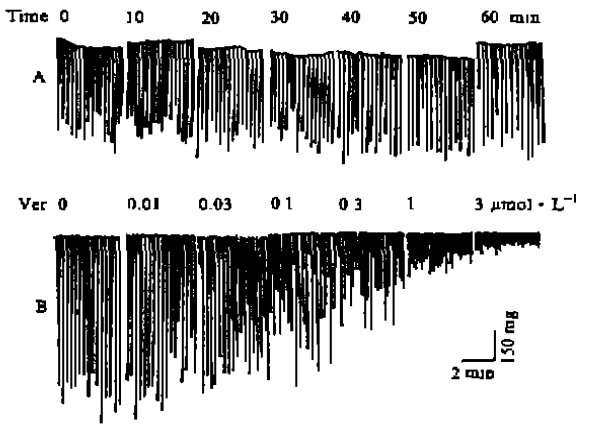

Fig 1. Spontaneous contraction of isolated WKY portal vein and effect of verapamil (Ver) on spontaneous contraction of isolated SHR portal vein.

DISCUSSION

药物抑制乳头状肌的 IC_{50} 与抑制门静脉的 IC_{50} 之比表明了药物的血管选择性. 比值接近于 1，则说明药物对血管和心肌的抑制作

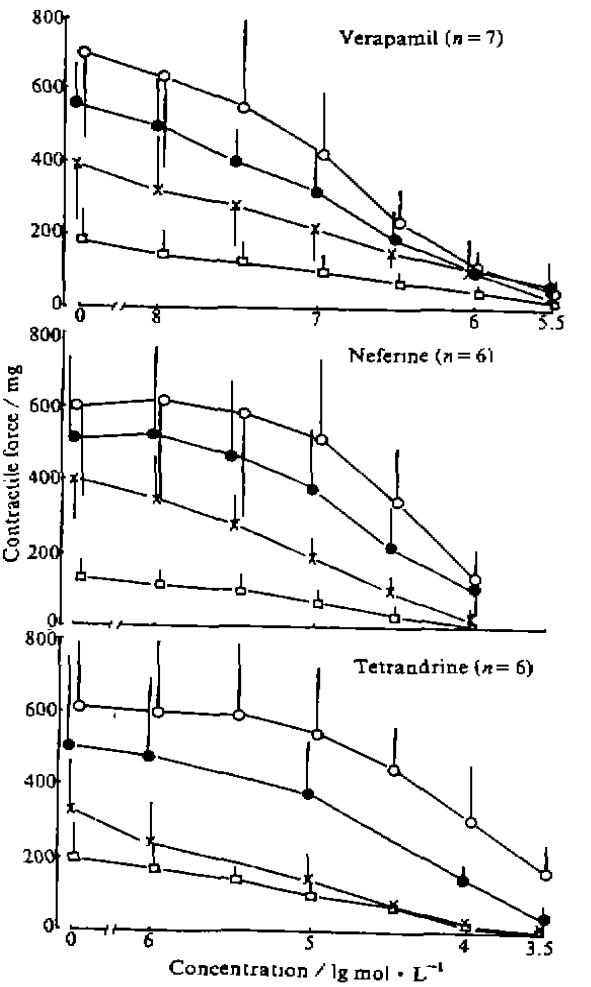

Fig 2. Inhibitory effects of cumulative administrations of verapamil, neferine, and tetrandrine on spontaneous contractile force of the rat portal vein (SHR ○, WKY ●) and contractile force of paced papillary muscle of left ventricle (WKY ×, SHR □). $\bar{x} \pm s$.

用缺乏选择性；比值愈大，血管选择性愈高；反之，则血管选择性愈低，也即较易抑制心肌。我们在 WKY 和 SHR 上所得结果，Ver 的血管选择性接近于 1，说明 Ver 对心肌和血管抑制作用缺乏选择性；Nef 和 Tet 的血管选择性远小于 1，说明 Nef 和 Tet 较易抑制心肌的收缩。这既不同于 Ver 缺乏选择性，也不同于具有血管选择性的尼非地平类(nifedipine-like)钙拮抗剂[1]，这可能由于 Nef 和 Tet 除了对乳头状肌的钙通道有阻滞作用外，对钠通道也有阻滞作用，有待证实。

SHR 的血管平滑肌对 Ver、Nef 和 Tet 的反应性有无改变未见报道，本文结果 Tet 抑制 SHR 门静脉的 IC_{50} 比 WKY 几乎高一个数量级，提示 SHR 的门静脉对 Tet 的反应性降低。

REFERENCES

1 Ljung B. Vascular selectivity of felodipine. *Drugs* 1985; **29** Suppl 2 : 46–58.

2 Fang DC, Yao WX, Qu L, Jiang MX. Effects of tetrandrine on cat papillary muscle. *Acta Pharmacol Sin* 1981; **2** : 163–6

3 Hu WS, Zhou ZH, Hu CJ, Lü FH. Effects of tetrandrine on seven vascular smooth muscles. *Acta Pharmacol Sin* 1984; **5** : 257–60.

4 Hu WS, Guo LJ, Feng XL, Jiang MX. Hypotensive effects of neferine. *Chin J Pharmacol Toxicol* 1990; **4** : 107–10.

5 Li GR, Luo FH, Qian JQ. Effects of neferine on physiologic properties and the dose-effect response of isoprenaline and Ca^{2+} in guinea pig atria. *Acta Pharm Sin* 1988; **23** : 241–5.

6 Clozel M, Kuhn H, Hefti F. Effects of angiotension converting enzyme inhibitors and of hydralazine on endothelial function in hypertensive rats. *Hypertension* 1990; **16** : 532–40.

7 Nagamine F, Murakami K, Mimura G, Sakanashi M. Effects of beta-adrenoceptor blocking agents on isolated atrial and papillary muscles from experimentally diabetic rats. *Jpn J Pharmacol* 1989; **49** : 67–76.

8 Mikkelsen EO, Nielsen TJ. Effects of the optical isomers of a novel $5\text{-}HT_2$ antagonist and (−)-Bay k 8644 on spontaneous mechanical activity in rat portal veins. *Drug Exptl Clin Res* 1990, **16** : 225–9.

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儿茶酚胺在烟碱对豚鼠乳头状肌慢反应电位影响中的作用

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Role of catecholamines in action of nicotine on slow action potentials in guinea pig papillary muscles

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ABSTRACT The action potential duration (APD) of histamine-induced slow action potentials (SAP) and force of contraction (FC) were potentiated by nicotine (0.6–1.0 mmol · L^{-1}) on guinea pig papillary muscles in a concentration-dependent manner. In the presence of atropine, nicotine concentration dependently suppressed the action potential amplitude (APA), APD, the maximal upstroke velocity (V_{max}), and FC in catecholamine-depleted (reserpine 2.5 mg · kg^{-1} ip, 15 h prior to the experiment) muscles. Nicotine (0.6 mmol · L^{-1}) itself induced SAP and enhanced FC. These 2 effects were antagonized by verapamil. A linear relationship existed between APA of nicotine-induced SAP and lg $[Ca^{2-}]_0$ with a slope of 23.2 mV for a 10-fold change in $[Ca^{2+}]_0$. These results suggested that the effects of nicotine on enhancing I_{si} were mediated by the release of catecholamines in myocardium.

KEY WORDS nicotine; catecholamine; reserpine; papillary muscles; action potentials; myocardial contraction; ion channels

提要 烟碱使组胺诱发的豚鼠乳头状肌慢反应电位(SAP)的动作电位时程(APD)及收缩力(FC)呈剂量依赖性增加。在儿茶酚胺耗竭情况下，烟碱使动作电位

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烟碱 儿茶酚胺 乳头状肌