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左旋千金藤立定对家兔离体基底动脉、肠系膜动脉和胸主动脉平滑肌的作用

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Effects of *l*-stepholidine on isolated rabbit basilar artery, mesenteric artery, and thoracic aorta

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ABSTRACT *l*-Stepholidine (SPD) has been shown to be effective in treating migraine, but its mechanism is not clear. So the effects of SPD on isolated rabbit basilar artery (BA), mesenteric artery (MA) and thoracic aorta (TA) were studied. The contractions of BA and MA were induced by KCl (10-160 mmol · L^{-1}) and the contraction of TA was caused by 5-HT (0.1-100 μmol · L^{-1}). Ketanserin was used as reference.

SPD (0.1-0.2 mmol · L^{-1}) relaxed the contractions of BA and MA induced by KCl in a non-competitive manner with pD_2' 3.4 ± 0.3 and 4.0 ± 0.3, respectively. SPD had no selectivity in BA and MA. SPD also inhibited the contraction of TA induced by 5-HT with pA_2 9.7 ± 2.0 and pD_2' 5.4 ± 0.6, which showed a dual of both competetive and noncompetetive antagonisms.

These results suggested that SPD had a blockade effect on the calcium channel and 5-HT_2 receptors.

KEY WORDS stepholidine; basilar artery; mesenteric arteries; thoracic aorta; drug dose-response relationship; ketanserin

提要 左旋千金藤立定(SPD)可非竞争性地松弛 KCl 引起的家兔离体基底动脉(BA)和肠系膜动脉(MA)的收缩，pD_2'分别为 3.4 ± 0.3 和 4.0 ± 0.3，提示有较弱的钙拮抗作用. SPD 亦能松弛 5-HT 引起的家兔离体胸主动脉(TA)的收缩，其特点为既有竞争性又有非竞争性的二重拮抗作用，pA_2 = 9.7 ± 2.0; pD_2' = 5.4 ± 0.6，提示 SPD 有 5-HT_2 受体拮抗作用.

关键词 左旋千金藤立定；基底动脉；肠系膜动脉；胸主动脉；药物剂量-效应关系；ketanserin

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左旋千金藤立定(*l*-stepholidine, SPD)是从防己科植物河谷地不容(*Stephania intermedica* Lo)中分离得到的生物碱，以往的试验表明，SPD 是新型的多巴胺受体阻滞剂[1-3]，已用于治疗多动症. 此外，SPD 能使高血压患者血压降低[4,5]，也是治疗偏头痛的良药[6,7]. 为了阐明 SPD 对偏头痛的疗效机制，本文研究 SPD 对离体血管 Ca^{++}通道和 5-HT_2 受体的作用.

MATERIALS

家兔体重 2.7± SD 0.2 kg，由上海医科大学实验动物部供应；5-羟色胺硫酸肌酐为瑞士 Fluka AG 产品；SPD ($[\alpha]_D$ −440°)，上海药物研究所提供；Ketanserin 是 Research Biochemicals Incorporated 产品.

METHODS AND RESULTS

兔耳 iv 50 ml 空气处死，取出胸主动脉(TA)，基底动脉(BA)和肠系膜动脉(MA)，置于改良的 Krebs 液中(组成，mmol · L^{-1}: NaCl 120; KCl 4.5; $MgSO_4 \cdot 7H_2O$ 1.0; KH_2PO_4 1.0; $CaCl_2$ 2.5; $NaHCO_3$ 20; glucose 10) pH 7.4. BA 和 MA 制成 4-5 mm 的血管环，连接于张力换能器上，浴槽容量 10 ml，通 95% O_2+5% CO_2，37±0.5℃. 标本负荷 0.5 g. TA 剪成 3 mm × 20 mm 的螺旋条，连于张力换能器上，浴槽容量 20 ml，标本负荷为 2.0 g. 血管标本每 20 min 换一次营养液，平衡 2 h.

SPD 对 KCl 致 BA 收缩的影响 BA 给予 KCl 60 mmol · L^{-1} 以试验活性，然后洗去，稳定 10 min，用累积加药法加入 KCl 10, 20, 40, 80 和 160 mmol · L^{-1}，间隔 5 min，获得 KCl 量-效曲线，然后冲洗标本至基线，加入 SPD 0.1 mmol · L^{-1}，接触标本 10 min，描记 KCl 量-效曲线. 再次冲洗标本至基线，加入 SPD 0.2 mmol · L^{-1}，重复上述 KCl 量-效曲线. 由图 1 可见，SPD 减弱 KCl 致 BA 的收缩，使量-效曲线的位置不变而最大反应压低，呈非竞争性拮抗，按徐氏方法[8]计算 $pD_2' = 3.4 \pm 0.3$ ($n=4$).

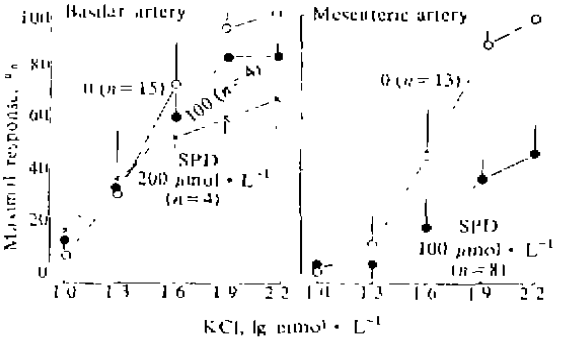

Fig 1. Effects of SPD on the contraction induced by KCl in rabbit basilar artery and mesenteric artery.

SPD 对 KCl 致 MA 收缩的影响 MA 同样给予 KCl 60 mmol · L^{-1} 以试验活性，然后洗去，稳定 10 min，描记 KCl 量-效曲线的方法同上. 结果见图 1，SPD 使 KCl 量-效曲线位置不变而最大反应压低，以非竞争性方式拮抗 KCl 的收缩 MA 作用，$pD_2' = 4.0 \pm 0.3$ ($n=8$).

SPD 和 ketanserin 对 5-HT 致 TA 收缩的影响 TA 先用 KCl 60 mmol · L^{-1} 检验活性，洗至基线后稳定 20 min，用累积加药法加入 5-HT，每次给药间隔 3 min，获得 5-HT 量-效曲线，洗至基线，分别描记 ketanserin 1, 10, 100 nmol · L^{-1} 存在时的 5-HT 量-效曲线以及 SPD 0.1, 1, 10 μmol · L^{-1} 存在时的 5-HT 量-效曲线. 结果表明 ketanserin 能竞争性拮抗 5-HT 致 TA 的收缩，按徐氏方法[8]计算 $pA_2 = 9.9 \pm 1.8$ ($n=4$). SPD 亦能拮抗 5-HT 所致的 TA 收缩，但表现为既有竞争性又有非竞争性拮抗的特点，$pA_2 = 9.7 \pm 2.0$; $pD_2' = 5.4 \pm 0.6$ ($n=4$).

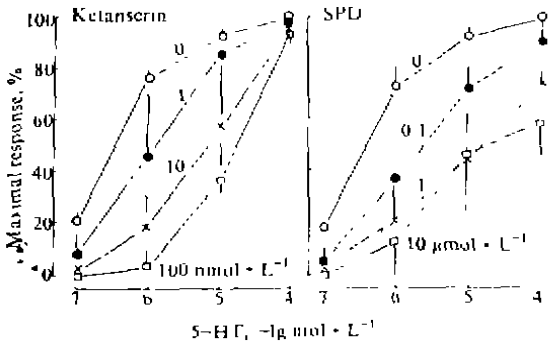

Fig 2. Effects of ketanserin and SPD on the contraction induced by 5-HT in rabbit thoracic aorta ($n=4$).

DISCUSSION

KCl 使血管收缩是因为它引起电位敏感性钙离子通道的开放及 Ca^{++}内流所致，因此，观察药物对 KCl 致血管收缩的影响是一种间接测定钙通道阻滞活性的方法[9]. 实验表明，SPD 对钙通道的阻滞作用较弱并且对颅内动脉没有选择性，这提示，SPD 的钙拮抗作用不是其主要的药理作用机制，而是其作用较广泛的一个因素.

[^{3}H]Ketanserin 结合试验表明，SPD 对 5-HT_2 受体有亲和力($K_i=35$ nmol · L^{-1}). 为了进一步了解其受体介导的生物效应，选择富含 5-HT_2 受体的 TA 进行测定并与选择作用于 5-HT_2 受体的竞争性拮抗剂 ketanserin 比较. 结果表明，SPD 对 5-HT_2 受体呈既有竞争性又有非竞争性的二重拮抗作用[10]，这可能是因为 SPD 作用于 TA 上其它受体及钙通道所致.

偏头痛的病因较复杂，可能与脑内多巴胺功能过度；细胞内 Ca^{++}超载；5-HT 受体功能失调以及脑血管肾上腺素受体功能失调都有关，表现为脑内血管先痉挛后扩张[11]. SPD 对上述各个偏头痛发病环节都有程度不同的作用[3,12]. 因而对于偏头痛的治疗具独特的优点.

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