

关于 Clo 对血管内皮细胞的作用, 最初认为 +E 肌条对 Clo 的松弛作用与内皮有关<sup>(8)</sup>。但近年主张上述现象是 Clo  $\alpha_2$  受体部分激动药所致<sup>(9,10)</sup>。本文 Tab 2 结果表明由 KCl 20 mmol/L 致收缩的肌条对 Clo 的松弛作用与内皮细胞和 Yoh 的存在与否均无关系。而且, -E 肌条对 Clo 与 Pra 对抗选择性  $\alpha_1$  受体激动药 PE 1  $\mu$ mol/L 引起收缩比对抗 KCl 20 mmol/L 强得多。说明肌条对 Clo 的松弛反应主要通过 RPA 平滑肌细胞  $\alpha_1$  受体阻断引起。本实验未证实内皮细胞对 Clo 的依赖松弛作用, 这与 Angus<sup>(2,3)</sup> 的结果有矛盾。可能因 Clo 是弱的  $\alpha_2$  受体激动药, 在本实验条件下, 用 KCl 作激动药, 内皮细胞对 Clo 的松弛反应不易显示, 或因内皮对 Clo 产生弱的松弛作用被它对平滑肌  $\alpha_1$  受体较强阻断作用所掩盖。

结果还表明, 肌条对 Pra 对抗 PE 的收缩作用比对抗 Clo 3  $\mu$ mol/L 强得多 (Fig 3 A); 而 Yoh 对两者无差异 (Fig 3 B), 可以表明 RPA 平滑肌细胞以  $\alpha_1$  肾上腺素受体占优势。Clo 作为  $\alpha_2$  受体部分激动药, 阻断平滑肌细胞  $\alpha_1$  受体, 导致松弛反应。

综上所述, 兔肺动脉内皮细胞肾上腺素受体参与对平滑肌的调节, 可能对肺循环起一定的调节作用。

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### 左旋千金藤立定的降眼压作用

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#### Ocular hypotensive action of l-stepholidine

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ABSTRACT Ocular hypotension was made by

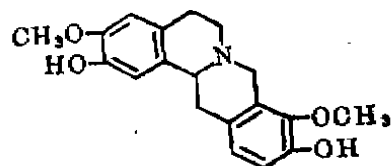
iv 20% NaCl 2.5 ml/kg in rabbits. On this model, *l*-stepholidine (*l*-SPD) lowered intraocular pressure when administered topically to the eyes. The ocular hypotensive action of 0.5% *l*-SPD was weaker than that of 0.5% timolol, but stronger than that of 0.5% pilocarpine. The maximal actions of the 3 drugs were similar. There were no significant changes of pupil diameter and carbonic anhydrase activity after *l*-SPD administered, but which suppressed aqueous humor formation. As the ciliary process of the eye behaves much like the renal glomerulus, dopamine increases the glomerular blood flow and dopaminergic antagonist decreases it, the mechanism of *l*-SPD in lowering intraocular pressure may be related to the dopaminergic receptor blocking effect of it.

**KEY WORDS** stepholidine; berbines, intraocular pressure; carbonic anhydrase; pupil; aqueous humor; timolol; acetazolamide; pilocarpine

**摘要** iv 20% NaCl 2.5 ml/kg 使兔眼压下降, 同时用左旋千金藤立定(*l*-SPD)滴眼使眼压进一步显著地下降, 0.5% *l*-SPD 的降眼压作用稍逊于 0.5% 噻吗洛尔而强于 0.5% 匹鲁卡品, 但 3 种药最大降眼压作用的%相近, *l*-SPD 不影响瞳孔, 对碳酸酐酶活性无作用, 但可抑制房水生成, 推测其降眼压机理可能与阻滞眼内多巴胺受体有关。

**关键词** 千金藤立定; 小檗因类; 眼压; 碳酸酐酶; 瞳孔; 眼房水; 噻吗洛尔; 乙酰唑胺; 匹鲁卡品

多巴胺阻滞剂能显著地降低眼压<sup>(1,2)</sup>。左旋千金藤立定(*l*-stepholidine, *l*-SPD)是从云南防己科植物河谷地不容(*Stephania intermedia* Lo)中分离获得的生物碱<sup>(3)</sup>, 已证实是一种多巴胺受体阻滞剂<sup>(4)</sup>, 并有降血压、镇痛和解热等作用<sup>(5-7)</sup>, 对眼压的作用尚未见报道。本文探讨 *l*-SPD 的降眼压作用及机理。



*l*-Stepholidine

## MATERIALS

*l*-SPD 由中国科学院上海药物研究所提

供。用  $H_3PO_4$  1.25 mol/L 加热溶解, 以 NaOH 1.0 mol/L 调整 pH 至 5.0, 再用蒸馏水稀释至所需的浓度。噻吗洛尔 (timolol, Tim) 眼药水 (天津中央制药厂); 匹鲁卡品 (pilocarpine, Pil) 眼药水系江西医学院第一附属医院药剂科配制; 乙酰唑胺 (acetazolamide) 片剂 (上海信谊制药厂); 荧光素钠注射液 (梧州市第三制药厂)。兔及小鼠由本院动物室供应。

## METHODS AND RESULTS

**降眼压作用** 兔 80 只, 体重  $2.1 \pm 0.4$  kg, 随机匀分成 8 组。从耳缘静脉缓慢 iv 3.5% 戊巴比妥钠 30 mg/kg 进行麻醉, 用 Schiøtz 眼压计测量眼压。试验组用 *l*-SPD (0.25, 0.5 及 1.0%)、药物对照组用 Tim (0.25 及 0.5%) 和 Pil (0.25, 0.5, 1.0 及 2.0%)、溶剂对照组用溶剂 (*l*-SPD 组用磷酸钠液、Tim 组和 Pil 组用生理盐水) 滴右眼, 间隔 3 min, 每次一滴, 共 3 次。滴完后立即 iv 20% NaCl 2.5 ml/kg, 1 ml/min。注完后即刻, 5, 10, 20, 40, 60 和 80 min 及以后每 30 min 测定一次眼压, 直至眼压恢复到滴药前水平为止。部分兔间隔 1 wk 后重复使用。

*l*-SPD 能显著降低眼压, 降眼压强度与其浓度成正比。0.5% 浓度时其降眼压作用小于 Tim 而强于 Pil, 但 3 种药的最大降压%相近 (Tab 1)。

**对房水动力学的影响** 兔 30 只, 体重  $2.2 \pm 0.3$  kg, 随机匀分成 3 组。用房水荧光素浓度测定法<sup>(8)</sup>测量前房水荧光素浓度 (fluorescent concentration, FC)。使用 5.0% 荧光素钠 0.5 ml/kg。用裂隙灯激发房水中荧光, 读取与裂隙灯相连的房水荧光测定仪上的读数, 查表<sup>(8)</sup>得出前房水荧光素相对浓度 ( $nA/mm^2$ ), 绘出浓度曲线 (FC curve, FCC)。3 组兔每组试验一种药物, 试验步骤相同: (1) 测定正常 FCC; 10 只兔, 每只随机选择一眼滴入拟试药物的溶剂, 每次一滴, 间隔 1 min, 共 3 次。15 min 后从耳缘静脉缓慢 iv 荧光素钠, 注完

Tab 1. Intraocular pressure (IOP) after *l*-stepholidine, timolol and pilocarpine dropped into the eyes of rabbits pretreated with iv 20% NaCl (2.5 ml/kg),  $n=10$ ,  $\bar{x}\pm SD$ , \* $P>0.05$ , \*\* $P<0.05$ , \*\*\* $P<0.01$ .

	IOP (kPa) before medication	Maximal reduction of IOP (%)	IOP recovery time (min)
<b><i>l</i>-Stepholidine</b>			
Vehicle	2.1±0.4	43±5	79±7
0.25%	1.9±0.4	52±5*	124±9***
0.5%	1.9±0.3	69±7*	207±11***
1.0%	1.9±0.4	71±4***	294±32***
<b>Timolol</b>			
Vehicle	2.0±0.5	43±6	95±9
0.25%	1.8±0.2	74±5***	240±8***
0.5%	1.8±0.4	73±4***	261±21***
<b>Pilocarpine</b>			
Vehicle	2.0±0.5	43±6	95±9
0.25%	2.1±0.4	54±8*	156±12**
0.5%	1.7±0.4	59±10*	231±5***
1.0%	2.0±0.5	62±5**	255±16***
2.0%	2.0±0.3	73±4***	249±9***

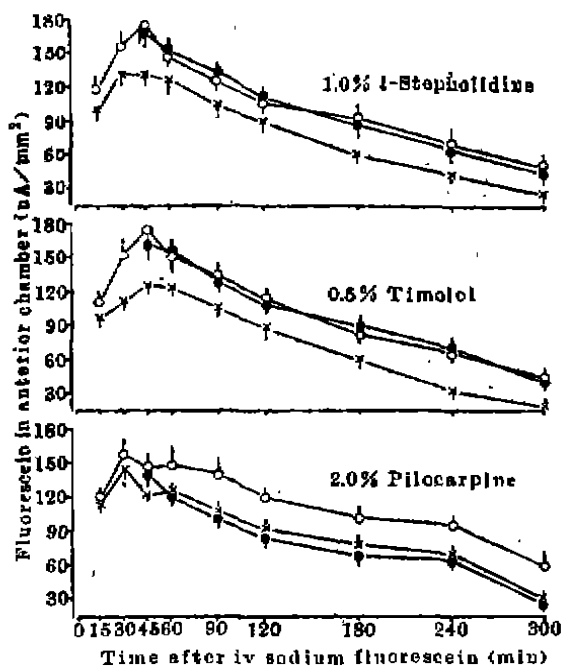


Fig 1. Relative fluorescent concentration (RFC) in anterior chamber after *l*-stepholidine, timolol and pilocarpine dropped into the eyes of rabbits treated with iv sodium fluorescein 0.5 ml/kg, (○) Normal RFC, (×) RFC with medication before iv fluorescein, (●) RFC with medication after iv fluorescein.

后 15, 30, 45, 60, 90, 120, 180, 240 和 300 min 时测量前房水 FC, 绘制正常 FCC。(2) 早期滴药对 FCC 的影响: 10 d 后向同兔同眼先滴入一种药物(1.0% *l*-SPD 或 0.5% Tim 或 2.0% Pil), 滴药后 15 min iv 荧光素钠, 绘制 FCC, 与正常 FCC 比较观察药物对 FCC 上升段(房水生成)的影响。(3) 晚期滴药对 FCC 的影响: 又 10 d 后, 先 iv 荧光素钠, 30 min 后滴入试验药物, 绘制 FCC, 观察药物对 FCC 下降段(房水排出)的影响。

在 *l*-SPD 组和 Tim 组, 晚期滴药时所有 FC 与正常 FC 比较都无显著差别( $P>0.05$ ), 早期滴药时则均有降低, 差别显著( $P<0.05$ , 0.01)。Tim 早期滴药的 FC 峰值较正常 FC 峰值降低 27.8%, 而 *l*-SPD 则降低 22.8%。在 Pil 组, 早期滴药和晚期滴药的 FC 均低于正常 FC (Fig 1)。

**对碳酸酐酶活性的影响** 小鼠 90 只, 体重  $30.8\pm 2.8$  g, 匀分成 9 组。用反应时间法<sup>(9,10)</sup>测定碳酸酐酶活性。用灌胃法给小鼠一定剂量(Tab 2)的拟试药物或溶剂, 60 min 后取出双肾, 制成肾匀浆, 将肾匀浆上清液置入反应液中。当肾匀浆中碳酸酐酶活性正常时,  $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3$  的反应时间正常; 而

Tab 2. Effects of *l*-stepholidine and acetazolamide on the reaction time for full hydration of  $\text{CO}_2$  and  $\text{H}_2\text{O}$  to  $\text{H}_2\text{CO}_3$ ,  $n=10$ ,  $\bar{x}\pm SD$ , \* $P>0.05$ , \*\*\* $P<0.01$ .

Drug (mg/kg)	Reaction time (s)
<b><i>l</i>-Stepholidine</b>	
Vehicle	18±2
10	19±2*
50	17±2*
100	19±2*
<b>Acetazolamide</b>	
Vehicle	17±2
10	44±4***
50	63±5***
100	78±4***
<b>Deactivated renal homogenate</b>	
	76±4***

当活性被抑制时, 则反应时间延长。对照药为乙酰唑胺。

1-SPD对碳酸酐酶活性无显著影响, 而乙酰唑胺组的碳酸酐酶活性被显著抑制 (Tab 2)。

**对瞳孔的影响** 在所述观察1-SPD的降眼压作用时, 每次测眼压的同时用千分卡测瞳瞳孔水平直径。结果显示: 1-SPD和Tim对瞳孔直径无显著影响( $P>0.05$ ), P11则能显著缩小瞳孔。以1.0% 1-SPD, 0.5% Tim和2.0% P11为例, 点药前瞳孔直径分别为 $6.1\pm 0.4$ ,  $6.2\pm 0.5$ 和 $5.9\pm 0.6$  mm, 点药后瞳孔最小时分别为 $6.0\pm 0.6$ ,  $6.1\pm 0.4$ 和 $3.8\pm 0.4$  mm。

## DISCUSSION

1-SPD对瞳孔无明显影响, 也不抑制碳酸酐酶活性。1.0% 1-SPD和0.5% Tim早期滴眼的FC峰值分别比正常FC峰值低22.8%和27.8%, 提示1-SPD和Tim都可抑制房水生成, 该百分率基本可反映房水分泌受抑制的程度<sup>(11)</sup>; 晚期滴药的FC与正常FC比较无显著差别, 表明1-SPD和Tim都对房水排出无影响。2.0% P11滴眼后, 早期滴药的FC和晚期滴药的FC都只在注射荧光素钠45 min后(即FCC的下降段)与正常FC有显著差别, 表明P11只促进房水排出而不影响房水生成。对照药的结果可反证1-SPD抑制房水生成的作用。

邱春德等<sup>(12)</sup>认为, 睫状体血管和肾血管一样, 多巴胺可使其扩张, 使房水生成增加, 而多巴胺受体阻滞剂则对其有相反的作用。鉴于1-SPD是一种多巴胺受体阻滞剂, 我们设想它可能是通过阻滞眼内多巴胺受体而使房水生成减少并使眼压下降的。但Mekki等<sup>(13,14)</sup>用多巴胺受体兴奋剂溴麦角隐亭口服或滴眼也获得显著的降眼压作用。因此, 有关多巴胺受体药物的降眼压机理还值得研究。

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