

NE 释放, 与突触前受体关系不大。高浓度 Eph (0.3 mmol/L) 能抑制电场刺激所致收缩 (Fig 2) 的原因, 尚待研究。

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中国药理学报 *Acta Pharmacologica Sinica* 1990 Mar, 11 (2) : 133-137

可乐定和去甲肾上腺素对有或去内皮兔肺动脉条的影响

郑秀凤、赵孟辉、林彬、毛连根、卞如濂 (浙江医科大学药理教研室, 杭州 310006, 中国)

Effects of clonidine and norepinephrine on rabbit pulmonary artery strips with or without endothelium¹

ZHENG Xiu-Feng, ZHAO Meng-Hui, LIN Bin, MAO Lian-Gen, BIAN Ru-Lian
(Department of Pharmacology, Zhejiang Medical University, Hangzhou 310006, China)

ABSTRACT Relaxing responses of strips of rabbit pulmonary artery (RPA) with endothelium (+E) to norepinephrine (NE) during sustained contraction with KCl 20 mmol/L in the presence of propranolol (Pro) 10 μ mol/L and prazosin (Pra) 1 μ mol/L were more sensitive than those without endothelium (-E) to NE. These responses were inhibited by yohimbine (Yoh) 1 μ mol/L

L. However, the relaxing responses of the strips to clonidine (Clo) were not different between RPA strips +E and -E in the presence of Pro + Pra or Pro + Pra + Yoh 1 μ mol/L.

Relaxing responses of RPA strips -E precontracted by phenylephrine (PE) 1 μ mol/L to Pra and Clo were greater than that of those precontracted by KCl 20 mmol/L. The relaxing responses of these strips precontracted by PE to Pra were larger than those precontracted by Clo 3 μ mol/L; but that of those precontracted by PE and Clo to Yoh were not different.

The results suggest that integrity of the endothelium is an important factor in the relaxing responses of RPA strips to NE. The relaxing effect of Clo on RPA strips precontracted by KCl 20 mmol/L may be due to α_1 -adrenoceptor blockade on smooth muscle cells of the RPA strips.

KEY WORDS vascular endothelium; vascular

Received 1988 Oct 15 Accepted 1989 Jul 3

¹ Project Supported by the National Natural Science Foundation of China, No 86031203

smooth muscle: pulmonary artery; clonidine; norepinephrine; yohimbine; prazosin

摘要 在 Pro 10 $\mu\text{mol/L}$ 及 Pra 1 $\mu\text{mol/L}$ 存在下, 由 KCl 20 mmol/L 致收缩 RPA 条对 NE 的松弛, +E 大于 -E 组, Yoh 1 $\mu\text{mol/L}$ 可抑制之。肌条对 Clo 的松弛 +E 与 -E 组间无差别。在 -E 组 Pra 和 Clo 对抗 PE 1 $\mu\text{mol/L}$ 收缩比对抗 KCl 20 mmol/L 为大。Pra 对抗 PE 收缩比对抗 Clo 3 $\mu\text{mol/L}$ 为强, 但 Yoh 1 $\mu\text{mol/L}$ 无此区别。表明内皮参与对 NE 的松弛。Clo 对 RPA 平滑肌 α_1 受体的阻断导致松弛。

关键词 血管内皮; 血管平滑肌; 肺动脉; 可乐定; 去甲肾上腺素; 育亨宾碱; 哌唑嗪

自从 Furchgott⁽¹⁾ 提出血管内皮细胞能释放内皮源松弛因子 (Endothelium-dependent relaxing factors, EDRF) 这一假说以来, 内皮在心血管疾病发病机理上所起的重要作用, 已广泛被人们认识。去甲肾上腺素 (norepinephrine, NE) 通过对内皮细胞 α_2 肾上腺素受体的兴奋释放 EDRF 所致⁽²⁻⁴⁾。本文观察 NE 和可乐定 (clonidine, Clo) 对兔肺动脉内皮和平滑肌细胞 α 受体及其亚型的影响, 以便进一步证实内皮细胞 α 受体对血管平滑肌的调节作用。

METHODS

兔 35 只, 体重 $2.2 \pm \text{SD } 0.7 \text{ kg}$, 股动脉放血处死。取出肺动脉, 制成 $3 \times 5 \text{ mm}$ 螺旋条, 放于含 Krebs-bicarbonate 液 3 ml 浴槽中, 通 O_2 , 连接换能器, 静止张力 2 g, 平衡 2 h 后, 于浴槽中分别加入去氧肾上腺素 (phenylephrine, PE) 1 $\mu\text{mol/L}$ 或 KCl 20 mmol/L 引起收缩。然后换液 4 次, 30 min 后重复上述步骤共 2 次。待恒定后开始实验^(5,6)。

去内皮细胞实验 肌条先用 KCl 20 mmol/L 或 PE 1 $\mu\text{mol/L}$ 激动, 达高峰恒定后, 加入乙酰胆碱 (ACh) 0.1 $\mu\text{mol/L}$ 引起松弛反应, 证实内皮完整。然后去内皮⁽¹⁾, 再平衡 40 min 后, 重复上述步骤, ACh 不引起松弛反应, 证实内皮已去除^(1,7)。同时纪录有或去内皮的

肌条对 KCl 和 PE 产生收缩反应的幅度, 比较其有无区别, 再进行以下实验。

兔肺动脉 (rabbit pulmonary arteries, RPA) 内皮细胞 α 肾上腺素受体的实验 取 +E 和 -E 肌条, 于浴槽中先加入 Pro 10 $\mu\text{mol/L}$ 、Pra 1 $\mu\text{mol/L}$ 或 Pro, Pra, Yoh 1 $\mu\text{mol/L}$ 以阻断 β 和 α_1 肾上腺素受体或兼阻断内皮 α_2 受体。30 min 后加入 KCl 20 mmol/L 引起收缩, 待恒定后, 以累加法加入 NE 或 Clo 引起松弛反应。另取 -E 肌条, 不加任何阻断药, 同上步骤, 观察其对 NE 的松弛反应。实验结束前每个肌条加入 ACh 0.1 $\mu\text{mol/L}$, 观察其有无松弛, 以便证实肌条内皮细胞仍否存在^(2,8)。

Clo 对 RPA 平滑肌细胞 α 肾上腺素受体及其亚型的实验 取 -E 肌条, 先由 PE 1 $\mu\text{mol/L}$ 或 KCl 20 mmol/L 引起收缩, 待恒定后, 以累加法加入 Clo 或 Pra 引起松弛的剂量-效应曲线。比较两药对选择性与非选择性 α_1 肾上腺素受体激动药 PE 1 $\mu\text{mol/L}$ 与 KCl 20 mmol/L 引起收缩的对抗作用而产生的松弛反应有何不同。

另取 -E 肌条, 先由 PE 1 $\mu\text{mol/L}$ 和 Clo 3 $\mu\text{mol/L}$ 引起收缩, 待恒定后, 以累加法加入 Pra 或 Yoh 引起松弛的剂量-效应曲线。比较两药对选择性 α_1 与 α_2 受体激动药引起收缩的对抗作用有无差异。

上述实验结果数据处理, 以激动药收缩高度为 0%, 计算出每一剂量的松弛效应%, 再作组间 t 值测验。

RESULTS

兔肺动脉去内皮实验 +E 和 -E RPA 条对 KCl 20 mmol/L 或 PE 1 $\mu\text{mol/L}$ 均起收缩反应, 而收缩幅度无明显差别。肌条对 ACh 0.1 $\mu\text{mol/L}$ 的松弛反应, 仅在内皮完整情况下发生。一旦内皮去除, 此作用消失。在比较 KCl 与 PE 引起收缩的肌条对 ACh 的松弛反应中, 前者比后者为弱 (Fig 1)。这一结果与以

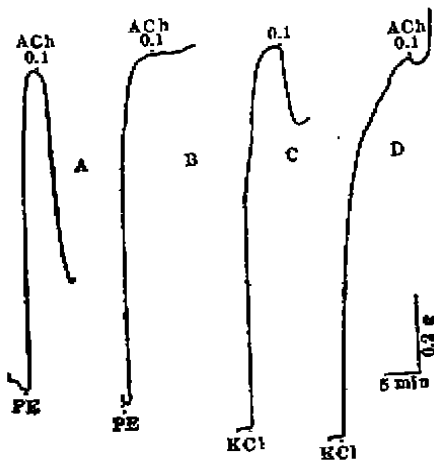


Fig 1. Loss of relaxing responses of rabbit pulmonary artery (RPA) strips precontracted by phenylephrine (PE) $1 \mu\text{mol/L}$ or KCl 20 mmol/L to ACh $0.1 \mu\text{mol/L}$ in the presence (A, C) or absence (B, D) of endothelium.

前的研究^(1,7)完全一致。

NE对RPA内皮细胞 α 受体的作用 从Fig 2和Tab 1可见: 1) Pro $10 \mu\text{mol/L}$ 和Pra $1 \mu\text{mol/L}$ 存在下, +E组(a)与-E组(b)比较, 由KCl 20 mmol/L 致收缩的肌条对NE $0.01-1 \mu\text{mol/L}$ 的松弛作用, -E组明显减弱, 表明NE的松弛作用与内皮细胞有依赖关系。2) Pro, Pra及Yoh $1 \mu\text{mol/L}$ 存在下, +E组(c)与(a)比较, Yoh明显抑制肌条对NE $0.01-1 \mu\text{mol/L}$ 的松弛反应(Tab 1)。3) 不存在阻断药的+ E组(d)与(a)比较, (d)组肌条对NE的

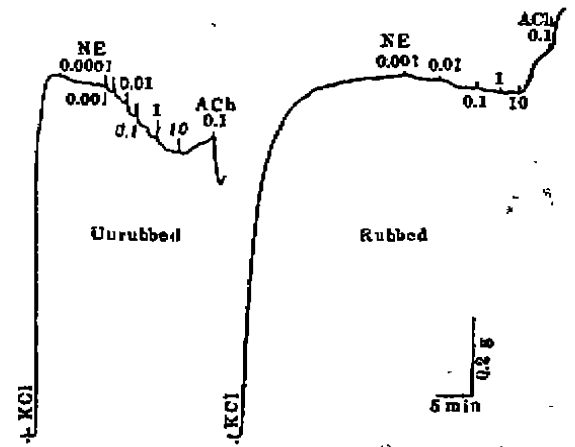


Fig 2. Relaxing responses of RPA strips to NE ($\mu\text{mol/L}$) during sustained contraction by KCl 20 mmol/L in the presence of Pro $10 \mu\text{mol/L}$ and Pra $1 \mu\text{mol/L}$. Matched pairs of intact (+E) and rubbed (-E) endothelial strips of RPA.

松弛反应, 每一对应点均较(a)明显为弱 ($P < 0.01$)。

加入不同阻断药能否影响肌条收缩从而影响NE的松弛作用? 对此, 进行了各组肌条对KCl收缩反应间的比较, 结果如下: Tab 1(a)组肌条对KCl 20 mmol/L 的收缩反应为 $1.0 \pm 0.5 \text{ g}$; (b)组为 $1.0 \pm 0.7 \text{ g}$; (c)组为 $1.2 \pm 0.3 \text{ g}$; (d)组为 $1.3 \pm 0.5 \text{ g}$ 。表明(a), (b), (c)各组与(d)组之间无显著差别 ($P > 0.05$)。说明加不同阻断药肌条对KCl的收缩反应无明显影响。

Tab 1. Effects of yohimbine (Yoh) $1 \mu\text{mol/L}$ on the relaxing action of norepinephrine (NE) strips of RPA with (+E) and without (-E) endothelium precontracted by KCl 20 mmol/L in the presence of propranolol (Pro) $10 \mu\text{mol/L}$ and prazosin (Pra) $1 \mu\text{mol/L}$. Number of strips in parentheses, $\bar{x} \pm \text{SD}$. * $P > 0.05$, ** $P < 0.05$, *** $P > 0.01$ vs (a).

NE ($\mu\text{mol/L}$)	Relaxing responses to norepinephrine (%)			
	Pro + Pra + E(a) (12)	Pro + Pra - E(b) (8)	Pro + Pra + Yoh + E(c) (6)	+ E(d) (7)
0.0001	3.2 ± 4.2	$1.0 \pm 1.8^*$	$1.2 \pm 1.2^*$	$0.8 \pm 0.9^*$
0.001	8.5 ± 5.0	$3.8 \pm 4.5^*$	$3.9 \pm 3.1^*$	$2.5 \pm 1.4^{***}$
0.01	14.9 ± 9.2	$6.6 \pm 7.1^{**}$	$6.2 \pm 6.2^{**}$	$4.1 \pm 2.2^{***}$
0.1	18.9 ± 9.5	$7.3 \pm 7.5^{***}$	$8.2 \pm 7.7^{**}$	$3.5 \pm 6.0^{***}$
1.0	22.3 ± 11.5	$1.0 \pm 13.2^{***}$	$6.2 \pm 7.1^{***}$	$2.9 \pm 12.5^{***}$

Tab 2. Effects of Yoh 1 $\mu\text{mol/L}$ on the relaxing action of clonidine (Clo) on strips of RPA with (+E) and without (-E) endothelium precontracted by KCl 20 mmol/L in the presence of Pro 10 $\mu\text{mol/L}$ and Pra 1 $\mu\text{mol/L}$. Number of strips in parentheses, $\bar{x} \pm \text{SD}$. * $P > 0.05$, ** $P < 0.05$, *** $P < 0.01$ vs (a).

Clo ($\mu\text{mol/L}$)	Relaxing responses to clonidine (%)			
	Pro + Pra + E(a)	Pro + Pra - E(b)	Pro + Pra + Yoh + E(c)	Pro + Pra + Yoh - E(d)
	(6)	(4)	(6)	(4)
0.0001	2.2 \pm 1.5	4.7 \pm 3.6*	4.6 \pm 6.3*	3.4 \pm 3.9*
0.001	4.3 \pm 2.6	6.8 \pm 5.3*	9.7 \pm 12.8*	6.1 \pm 6.7*
0.01	10.8 \pm 10.6	9.2 \pm 9.4*	15.8 \pm 18.5*	13.4 \pm 12.0*
0.1	16.4 \pm 13.3	15.3 \pm 18.5*	21.1 \pm 20.8*	18.6 \pm 15.4*
1.0	23.9 \pm 15.7	17.8 \pm 21.3*	29.3 \pm 22.1*	26.5 \pm 18.6*
10.0	29.7 \pm 17.0	25.5 \pm 22.1*	34.2 \pm 22.8*	28.5 \pm 17.8*
100.0	33.4 \pm 17.3	32.6 \pm 20.7*	36.9 \pm 22.8*	34.3 \pm 21.7*

Clo 对 RPA 内皮细胞 α 肾上腺素受体的作用 从 Tab 2 可见 Pro 10 $\mu\text{mol/L}$, Pra 1 $\mu\text{mol/L}$ + E 组与 - E 组, 与 Pro, Pra 及 Yoh 1 $\mu\text{mol/L}$ + E 组及 - E 组之间, 由 KCl 20 mmol/L 致收缩的肌条对 Clo 的松弛反应, 各组均无显著差别 ($P > 0.05$).

Clo 对 RPA 平滑肌细胞 α 肾上腺素受体的作用 由 PE 1 $\mu\text{mol/L}$ 产生收缩的 - E 肌条对 Clo 和 Pra 的松弛作用的 EC_{50} 分别为 0.9 ± 0.2 ($n = 8$), 0.2 ± 0.1 nmol/L ($n = 9$). 由 KCl 20 mmol/L 致收缩肌条对 Clo 的松弛作用的 EC_{50} 为 482.6 ± 0.7 nmol/L ($n = 6$), 对 Pra 0.1 $\mu\text{mol/L}$ 引起的松弛反应仅 $30 \pm 17\%$ ($n = 3$). 结果表明 Clo 与 Pra 都较易对抗 PE 所致的收缩作用.

从 Fig 3 可见, - E 肌条对 Pra 对抗 PE 1 $\mu\text{mol/L}$ 的收缩作用比对抗 Clo 3 $\mu\text{mol/L}$ 明显得多, 每一对应点都呈显著差异 ($P < 0.01$); 然而对 Yoh 对抗 PE 与对抗 Clo 的收缩作用之间无区别, 两条曲线近于重叠 (Fig 3).

DISCUSSION

Fig 1 结果表明兔肺动脉由 KCl 20 mmol/L 或 PE 1 $\mu\text{mol/L}$ 引起收缩与内皮细胞无关, 因为 + E 与 - E 组收缩幅度无差别. 肌条对 ACh 0.1 $\mu\text{mol/L}$ 引起的松弛反应仅在内皮完

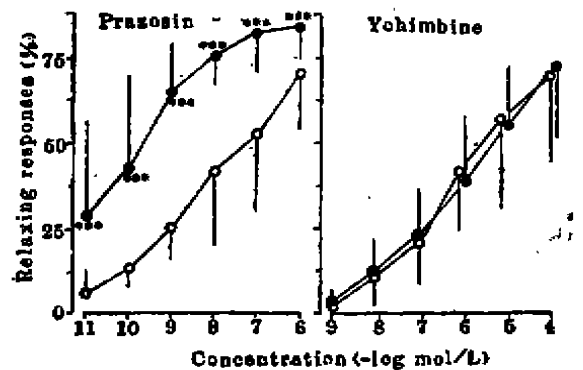


Fig 3. Effects of Pra and Yoh on relaxing responses of RPA strips without endothelium precontracted by PE (●) 1 $\mu\text{mol/L}$ and Clo 3 $\mu\text{mol/L}$ (○). $n = 5-10$ strips, $\bar{x} \pm \text{SD}$. * $P > 0.05$, ** $P < 0.05$, *** $P < 0.01$.

整情况下发生, 说明 ACh 的松弛作用与内皮有关, 由内皮细胞 EDRF 的释放引起^(1,7).

当用 Pro 10 $\mu\text{mol/L}$ 和 Pra 1 $\mu\text{mol/L}$ 分别阻断 RPA 平滑肌 β 和 α_1 肾上腺素受体后, + E 肌条对 NE 0.01-1 $\mu\text{mol/L}$ 的松弛反应比 - E 强得多, α_2 受体阻断药 Yoh 可对抗之 (Tab 1). 可以说明肌条对 NE 的松弛作用由内皮细胞 α_2 受体释放 EDRF 所致^(2,3).

Tab 1 还可见, 不加 Pro, Pra 组肌条对 NE 的松弛反应明显减弱 (d 与 a 比). 这可能由于平滑肌的 α_1 受体未阻断, 却被 NE 激动, 致使其松弛反应减弱所致.

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⁽⁸⁾。但近年主张上述现象是 Clo α_2 受体部分激动药所致^(9,10)。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 α_1 受体激动药 PE 1 μ 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 α_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^(2,3) 的结果有矛盾。可能因 Clo 是弱的 α_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 α_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 μ 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 α_1 肾上腺素受体占优势。Clo 作为 α_2 受体部分激动药, 阻断平滑肌细胞 α_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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中国药理学报 *Acta Pharmacologica Sinica* 1990 Mar; 11 (2) : 137-140

左旋千金藤立定的降眼压作用

夏小平、陈彼得、孙周¹、金国章²

(江西医学院第二附属医院眼科, ¹药理教研室, 南昌 330006; ²中国科学院上海药物研究所, 上海 200031, 中国)

Ocular hypotensive action of l-stepholidine

XIA Xiao-Ping, CHEN Bi-De, SUN Zhou¹
(Ophthalmology Department of the 2nd Affili-

ated Hospital, ¹Pharmacology Department, Jiangxi Medical College, Nanchang 330006, China)

JIN Guo-Zhang

(Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China)

Received 1989 Apr 11 Accepted 1989 Aug 3

ABSTRACT Ocular hypotension was made by