中国药理学报 *Acta Pharmacologica Sinica* 1990 Jul; 11 (4) : 308-310

苯海索对兔基底动脉和大鼠脑血管循环的作用

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Effects of trihexyphenidyl on basilar artery of rabbits and cerebrovascular circulation of rats

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ABSTRACT Trihexyphenidyl (Tri) inhibited the contraction of rabbit basilar artery due to high K^+ (45.6 mmol/L). IC_{50} was 2.9± 0.7 μmol/L. The contractions of basilar and mesenteric arteries due to calcium and those of basilar artery and saphenous vein due to serotonin were noncompetitively. Tri inhibited myogenic activities of the portal vein strips of rats and increased the normal cerebral blood flow of rats to 19± 7 ml/(min · 100 g).

KEY WORDS trihexyphenidyl; basilar artery; mesenteric arteries; saphenous vein; portal vein; potassium chloride; calcium chloride; serotonin; cerebrovascular circulation; chromium radioisotopes

提要 苯海索(Tri)对高 K^+引起兔基底动脉收缩有抑制作用, IC_{50} 为 2.9± 0.7 μmol/L; 对钙(基底动脉和肠系膜动脉)、5-羟色胺(基底动脉和隐静脉)引起的血管收缩均呈非竞争性拮抗作用; Tri 抑制大鼠门静脉条自律性收缩, 增加正常大鼠脑血流量达到 19± 7ml/(min · 100g).

关键词 苯海索; 基底动脉; 肠系膜动脉; 隐静脉; 门静脉; 氯化钾; 氯化钙; 5-羟色胺; 脑血管循环; 铬放射性同位素

苯海索(trihexyphenidyl, Tri)系中枢抗胆碱药, 用于帕金森氏综合症的治疗[1]. Tri 对其症状的改善, 是否与扩张脑血管、增加脑血流量有关, 本文进行了探讨.

MATERIALS AND METHODS

Tri 系江苏省常州国营武进制药厂产品; 硫酸肌酐 5-羟色胺是瑞士 Fluka 公司生产; KCl 和 $CaCl_2$ 均为 AR, 系北京化工厂产品; ^{51}铬酸钠系中国科学院原子能研究所提供.

兔 22 只, ♀♂兼用, 体重 1.97± SD 0.14 kg, iv 戊巴比妥钠 60 mg/kg 处死. 将基底动脉、肠系膜动脉或隐静脉(saphenous vein)做成 4-5 mm 长的动脉环, 穿入银丝, 做成三角环, 置于有钙或无钙的 Krebs-Henseleit(K-H)溶液中, 通 95% O_2+5% CO_2, pH7.2-7.4, 37℃. 基底动脉环负荷 0.5g, 肠系膜动脉环、隐静脉环和门静脉条负荷 1.0g, 平衡 2h. 连于张力换能器与记录仪[2].

高 K^+引起的肌环收缩 KCl 45.6 mmol/L 可导致肌环的亚最大收缩. 待收缩张力稳定后, 用累积法求 Tri 的量-效曲线. 在上一个浓度不再继续导致松弛时, 再加下一个浓度, 用直线回归法求 IC_{50} [3].

$CaCl_2$ 量-效反应 测基底动脉和肠系膜动脉平滑肌的 $CaCl_2$ 量-效反应, 观察 Tri 对其影响, 计算 pD'_2 值.

5-羟色胺量-效反应 将基底动脉和隐静脉环[4]稳定 2h, 加 5-羟色胺, 至少观察 4 min, 用药间隔 1 h 内洗涤 3 次, 观察 Tri 对 5-羟色胺量-效反应的影响.

大鼠门静脉条的自律性收缩 大鼠 14 只, ♀♂不拘, 体重 250± SD 12 g, 门静脉剪成 1.5 × 0.5 cm 纵条, 置于 K-H 液, 负荷 1.0g, 其它条件同上. 自律性收缩稳定后, 观察 Tri 对其自律收缩的影响.

对大鼠局部脑血流量的影响 铬生物微球的制备及局部血流量测定按文献[5]. 大鼠 10 只, 体重 316± SD 34g 分 2 组, 戊巴比妥麻醉, 气管插管, 人工呼吸, 开腹, 右髂总动脉连自动抽注机, 左股 iv Tri 3 mg/kg 后 5 min, 从心尖 1 min 内匀速注入稀释后的微球 80 ×

Received 1988 Sep 08 Accepted 1990 Feb 16

10^4/ml, 8 × 10^4cpm. 同时抽血 1 ml/min 停注后 10 s 关闭抽注机，再用手抽血 1 ml. 取心和脑，用滤纸吸干表面血液，在大脑半球冠状面切开，将脑分为左前、左后、右前、右后、小脑、脑干 6 个部分. 用单道$^{\#}$型 γ 计数器测量放射性.

局部血流量[ml/(min · 100g 组织)]=[(组织 cpm × 抽血速度(ml/min)/血 cpm × 组织重量(g)] × 100%.

心输出量(ml/min)=注入放射量(cpm) × 抽血速度(ml/min)/(血 cpm/ml)

RESULTS

Tri 对高 K^+所致肌环收缩的抑制作用 兔基底动脉和肠系膜动脉在 KCl 45.6 mmol/L 中可产生亚最大收缩，其张力在 30 min 后无明显变化. Tri 呈剂量依赖性松弛，以基底动脉为敏感，IC_{50} 为 2.9 ± 0.7μmol/L(n=6)，肠系膜则不敏感，呈相对选择性作用.

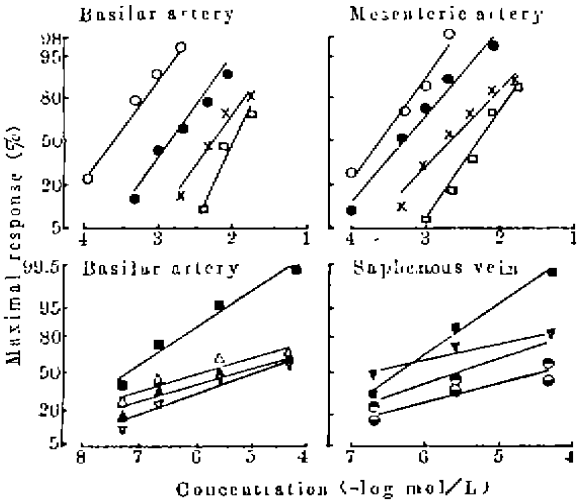

Fig 1. Effects of trihexyphenidyl (Tri) on rabbit vascular rings to $CaCl_2$ (Upper) and serotonin (Lower). (O) $CaCl_2$; (●) $CaCl_2$+Tri 1 μ mol/L; (×) $CaCl_2$+Tri 3 μ mol/L; (□) $CaCl_2$+Tri 6 μ mol/L; (■) Serotonin; (△) Serotonin + Tri 2 μmol/L; (▲) Serotonin + Tri 4 μmol/L; ( ) Serotonin + Tri 8μmol/L; ( ) Serotonin + Tri 10μmol/L; (O) Serotonin + Tri 30μmol/L; (O) Serotonin + Tri 50μmol/L.

Tri 对 $CaCl_2$ 量-效反应的影响 Tri 使兔基底动脉、肠系膜动脉的 $CaCl_2$ 最大反应降低(Fig 1). 其 pD'_2 值分别为 4.87 ± 0.07(n=5) 及 4.43 ± 0.29(n=5)，P 均<0.05.

Tri 对 5-羟色胺量-效反应的影响 Tri 使兔基底动脉和隐静脉的 5-羟色胺的最大反应降低(Fig 1)，其 pD'_2 值分别为 5.20 ± 0.17(n=11)及 4.40 ± 0.06(n=8)，P 均<0.01.

对大鼠门静脉条的自律性收缩的影响 有钙液下，Tri 30 μmol/L(n=6)使大鼠门静脉自律性逐渐减弱，至 60 μmol/L (n=4) 则明显抑制. $CaCl_2$ 可拮抗其抑制作用.

Tri 对局部脑血流量的影响 大鼠大脑左右两侧血流量分别增加 21 ± 5 和 17 ± 8ml/(min · 100g 脑). 小脑与脑干血流量无明显影响. 心肌血流增加 148 ± 17 ml/(min · 100g)，增率为 51 ± 12%. Tri 亦能增加心输出量，增值为 9.6 ± 1.6 ml/min，增率为 26 ± 7%(P<0.05)(Fig 2).

DISCUSSION

放射性微球法测脑血流量具有快速、准确、可同时测定多个部位、器官血流量的特点.本文系用蛙红细胞制作的生物微球，证实

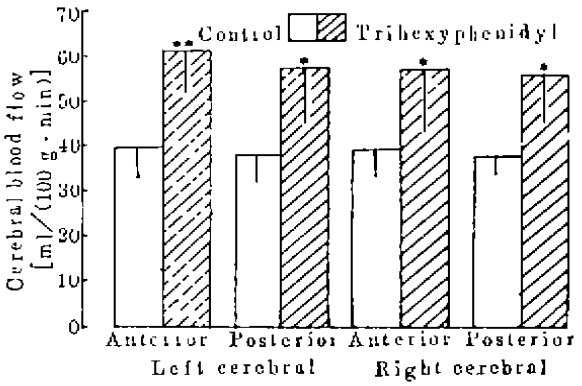

Fig 2. Effects of Tri on the blood flow in different parts of rat cerebrum, determined by ^{51}Cr radioactive biomicrosphere assay.

Tri 具有增加脑血流量的作用.

Tri 的作用机理可能是多方面的，但其钙拮抗作用及抗 5-羟色胺作用，不容忽视，因其与一般钙拮抗剂不同，在选择扩张脑血管增加流量的同时，对心输出量及心肌血流量亦均有明显增加，提示 Tri 更适合于伴有心功能不良的缺血性脑血管疾病.

REFERENCES

1 Koll WC. Pharmacological treatment of parkinsonism tremor. *Arch Neurol* 1986; 43 : 126

2 Liu YB, Ke J, Weng SA. Effects of atropine on basilar, mesenteric artery rings and portal vein strips. *Acta Pharmacol Sin* 1987; 8 : 224

3 郭祖超. 医用数理统计方法. 第3版. 北京: 人民卫生出版社, 1988 : 667-9

4 Toward R. The selective inhibition of serotonin-induced contraction of rabbit cerebral vascular smooth muscle by calcium-antagonistic dihydropyridines: an investigation of the mechanism of action of nimodipine. *Circ Res* 1981; 48 : 650

5 Wang JX, Yu ZJ, Jin HZ, *et al*. Estimation of regional blood flow in animals using ^{51}Cr- and ^{99m}Tc-biomicrospheres. *Acta Pharmacol Sin* 1985; 6 : 248

中国药理学报 *Acta Pharmacologica Sinica* 1990 Jul; 11 (4) : 310-314

Electrophysiological effects of *m*-nisoldipine and nisoldipine on papillary muscles of guinea pig

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ABSTRACT The effects of *m*-nisoldipine (*m*-Nis) and nisoldipine (Nis) on action potentials of papillary muscles in guinea pigs were studied using intracellular microelectrodes. The results : (1) APD and V_{max} in normal papillary muscles were reduced by *m*-Nis and Nis. However, the APA, V_{max} and overshoot were not affected. (2) In the partially depolarized papillary muscles, the APA, overshoot, V_{max} and APD were depressed in a dose-dependent manner. The inhibitory effects of Nis on APA, APD_{50} and PPD were greater than those of the *m*-Nis. (3) There was a good correlation between APD_{50} and PPD derived from a linear regression. By the linear equation, PPD was easily calculated from APD_{50}.

KEY WORDS *m*-nisoldipine; nisoldipine; microelectrodes; papillary muscles; action potentials; electrophysiology

New calcium antagonist *m*-nisoldipine (*m*-Nis) reduced the ischemic arrhythmias by improving the electrical stability in conscious and ancasthetized rats[1,2]. In this article, the effects of *m*-Nis and Nis on action potentials (AP) in normal and partially depolarized papillary muscles of guinea papillary were studied with intracellular microelectrodes.

MATERIALS AND METHODS

Guinea pigs weighing 0.45± SD 0.10 kg (both sexes) were used. The animals were stunned by heavy blow on the head. The papillary muscle was excised from the right ventricle. One end of the papillary muscle was fixed to the silicon rubber placed on the bottom of perfusing chamber by stainless steel needle. The other end was connected to the force transducer (TB-612T). The preparation was perfused with modified Krebs-Henseleit solution (K-H solution) at a flow rate of 4 ml / min for at least 30 min before experiment. The perfusate maintained

Received 1989 Oct 9 Accepted 1990 Mar 10