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依立雄胺体内外致突变实验

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关键词 依立雄胺；致突变试验；染色体畸变；微核试验；精子计数

目的：评价治疗良性前列腺肥大的新药依立雄胺（Epr）的遗传影响. **方法**：1）鼠沙门氏菌体外回复突变试验测试能否诱发基因突变；2）CHL 细胞染色体的损伤和畸变实验；3）ICR 小鼠一次 ig Epr 后测试是否导致骨髓嗜多染红细胞染色体的损伤；4）昆明种小鼠连续 ig Epr 5 d，30 d 后统计精子头部异常情况. **结果**：1）Epr 不诱导细菌回复突变. 2）CHL 细胞染色体畸变低于 3 % 不造成细胞染色体损伤. 3）Epr 不诱导小鼠嗜多染红细胞微核的形成. 4）Epr 高、中、低剂量组引起的头部畸形率分别为 5.3 % ± 2.7 %，5.3 % ± 1.9 %，5.2 % ± 1.2 %，与对照组相比不引起显著的精子头部异常. **结论**：Epr 在体内外实验中没有表现出遗传毒性.

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多塞平对离体兔基底动脉环和隐动脉环的作用

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Effects of doxepin on isolated basilar and saphenous artery rings of rabbits

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KEY WORDS doxepin; norepinephrine; serotonin; arteries

AIM: To study the effects of doxepin (Dox) on cerebral artery. **METHODS**: The effects of Dox were observed using the isolated basilar and saphenous artery rings of rabbits. **RESULTS**: Dox inhibited the constriction of the basilar and saphenous artery rings evoked by KCl with IC_{50} 5.75 $\mu mol \cdot L^{-1}$ (95 % confidence limits were 2.3 – 14 $\mu mol \cdot L^{-1}$, $n = 8$) and 34.6 $\mu mol \cdot L^{-1}$ (95 % confidence limits were 3.8 – 316 $\mu mol \cdot L^{-1}$, $n = 8$), respectively. Dox also inhibited the constriction of the basilar and saphenous artery rings of the rabbits stimulated by 5-hydroxytryptamine (5-HT), IC_{50} were 6.3 $\mu mol \cdot L^{-1}$ (95 % confidence limits were 1.7 – 23.3 $\mu mol \cdot L^{-1}$, $n = 7$) and 8.0 $\mu mol \cdot L^{-1}$ (95 % confidence limits were 6.3 – 10.3 $\mu mol \cdot L^{-1}$, $n = 6$), respectively. In both samples (basilar and saphenous artery rings) $CaCl_2$ evoked, the

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pD_2 of Dox was 5.28 ± 0.40 and 4.76 ± 0.14, respectively ($n = 6$, $P < 0.01$). Dox 5.8 μmol·L^{-1} inhibited the constriction of the saphenous artery evoked by norepinephrine (NE) in Ca^{2+}-free medium. Dox 30 μmol·L^{-1} inhibited the constriction of the saphenous artery evoked both by NE and by readmission of $CaCl_2$ (1.25 mmol·L^{-1}). **CONCLUSION:** As compared with its effect on the saphenous artery, Dox selectively inhibited the basilar artery.

关键词 多塞平; 去甲肾上腺素; 血清素; 动脉

目的: 观察多塞平(doxepin, Dox)对兔脑血管的作用. **方法**: 采用离体兔基底动脉和隐动脉动脉环离体实验方法. **结果**: 多塞平抑制 KCl 45.6 mmol·L^{-1}和 5-羟色胺 10 μmol·L^{-1}诱发的兔基底动脉环和隐动脉环收缩, 其拮抗 $CaCl_2$ 量-效反应的 pD_2 值分别为 5.28 ± 0.40 和 4.76 ± 0.14 ($n = 6$, $P < 0.01$). 多塞平 5.8 μmol·L^{-1}抑制在无 Ca^{2+} 液中去甲肾上腺素引起的隐动脉环收缩, 多塞平 30 μmol·L^{-1}对无 Ca^{2+} 液中去甲肾上腺素和恢复正常 Ca^{2+} 液(1.25 mmol·L^{-1})引起的隐动脉环收缩均有抑制作用. **结论**: 与隐动脉环相比较, 多塞平对基底动脉环具有选择性抑制作用.

多塞平(doxepin, Dox)属三环类抗抑郁药. 缺血性脑血管病人可伴有抑郁症状, 某些抗抑郁药具有钙拮抗作用, 可选择性扩张脑血管[1,2]. Dox 对兔脑血管作用未见报道. 本实验研究了 Dox 对兔基底动脉环、隐动脉环的作用, 旨在观察其对脑血管作用的选择性.

MATERIALS AND METHODS

药品 Dox (上海第三制药厂生产), 纯度为 99 %的类白色粉末, 批号: 881017. 硫酸肌酐 5-羟色胺(5-HT)和去甲肾上腺素(NE)系瑞士 Fluka 公司产品. KCl 和 $CaCl_2$ 均为 AR (北京化工厂生产).

兔 日本大耳白兔 59 只, 普通级, 体重 2.2 kg ± s 0.4 kg, 河南医科大学实验动物中心提供. 基底动脉环和隐动脉环的制备及离体实验方法见文献[3].

高 K$^+$引起的动脉环收缩 浴液中 KCl 45.6 mmol·L^{-1}引起基底动脉环和隐动脉环的持续收缩[4], 张力稳定后, 累积加入 Dox, 求 IC_{50}.

$CaCl_2$ 量-效曲线 在高 K$^+$ 45.6 mmol·L^{-1}等渗无钙液中测基底动脉环和隐动脉环 $CaCl_2$ 量-效曲线, 观察 Dox 对其影响, 计算 pD_2 值[5].

5-HT 引起的动脉环收缩[4] 将制成的基底动脉环和隐动脉环稳定 2 h 后, 加入 5-HT 10 μmol·L^{-1}可导致肌环的亚最大收缩, 观察 Dox 对其影响, 计算 IC_{50}.

NE 引起的隐动脉环收缩[6] 将隐动脉环稳定 2 h 后, 分别换上含有 *egtazic acid* 10 mmol·L^{-1}的 Ca^{2+}-free 液, 加入 NE 和 $CaCl_2$ 1.25 mmol·L^{-1}, 观察 Dox 对其收缩的影响.

数据处理 所有数据均用 $\bar{x} \pm s$ 表示, 两组间均数比较用 t 检验.

RESULTS

Dox 抑制高 K$^+$所致肌环收缩 Dox 对 KCl 45.6 mmol·L^{-1}引起的基底动脉环和隐动脉环的持续收缩产生浓度依赖性松弛, IC_{50}为 5.75 μmol·L^{-1} (95 %可信限为 2.3 – 14 μmol·L^{-1}, $n = 8$)和 34.6 μmol·L^{-1}(95 %可信限为 3.8 – 316 μmol·L^{-1}, $n = 6$), 对基底动脉环更敏感, 呈相对选择性作用.

Dox 对 $CaCl_2$ 量-效反应的影响 Dox 使兔基底动脉环、隐动脉环的 $CaCl_2$ 最大反应压低, 表现为非竞争性拮抗(Fig 1)其 pD_2 值分别为 5.28 ± 0.40 和 4.76 ± 0.14 ($n = 8$, $P < 0.01$).

Dox 抑制 5-HT 所致肌环收缩 兔基底动脉环和隐动脉环, 给予 5-HT 10 μmol·L^{-1}可产生亚最大收缩、Dox 可引起剂量依赖性松弛, 其 IC_{50}为 6.3 μmol·L^{-1} (95 %可信限为 1.7 – 23.3 μmol·L^{-1}, $n = 7$)和 8.0 μmol·L^{-1} (95 %可信限为 6.3 – 10.3 μmol·L^{-1}, $n = 6$).

Dox 抑制 NE 引起隐动脉环收缩 兔隐动脉环在无 Ca^{2+} 液中加入 Dox 5.8 μmol·L^{-1}对 NE 引起的隐动脉环收缩的抑制为 0.7 g ± 0.4 g (加药前为 2.2 g ± 0.6 g, $P < 0.01$), 恢复正常 Ca^{2+} 液后对其的收缩抑制为 3.1 g ± 0.4 g (加药前为 2.8 g ± 0.7 g, $P > 0.05$). 在无 Ca^{2+} 液中加入 Dox 30 μmol·L^{-1}则完全抑制了隐动脉环的收缩、在恢复正常 Ca^{2+} 液后对其收缩的抑制为 1.6 g ± 0.4 g (加药前为 2.8 g ± 0.7 g, $P < 0.01$). (Tab 1)

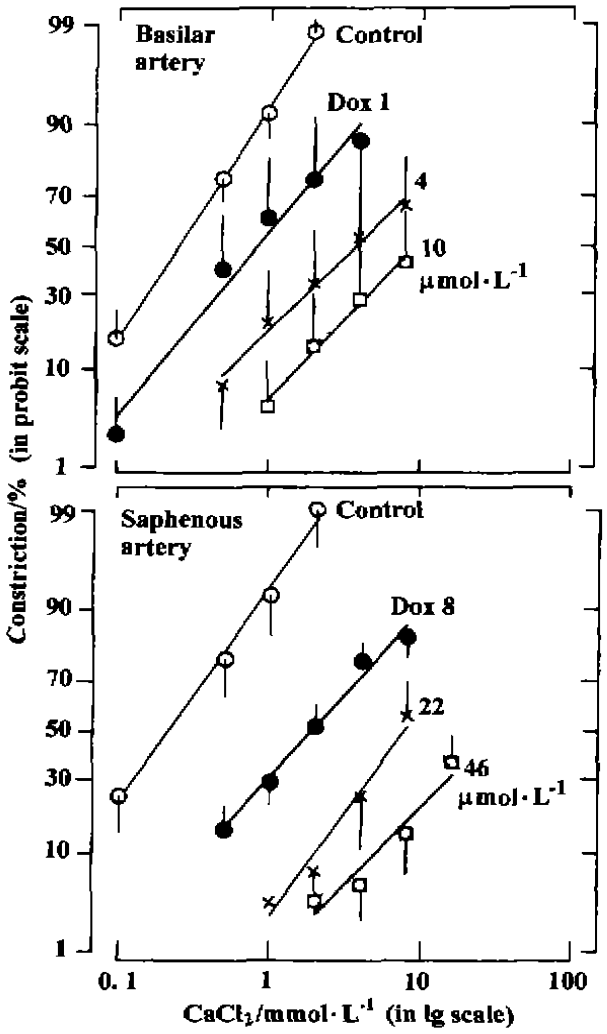

Fig 1. Effects of doxepin on constrictions of rabbit vascular rings to $CaCl_2$.

Tab 1. Effects of doxepin on the saphenous artery ring constriction induced by Nt 10 μmol·L^{-1} in Ca^{2+}-free solution and restored in $CaCl_2$ (1.25 mmol·L^{-1}) restored. n = 6 rabbits. $\bar{x} \pm s$. $^aP > 0.05$, $^cP < 0.01$ vs control.

Concentration/ μmol·L^{-1}	Tension/g	
	Ca^{2+}-free solution	Ca^{2+} 1.25 mmol·L^{-1}
0 (Control)	2.2 ± 0.6	2.8 ± 0.7
5.8	0.7 ± 0.4^c	3.1 ± 0.4^a
30	0	1.6 ± 0.4^c

DISCUSSION

以上实验发现，Dox 可抑制 KCl，$CaCl_2$ 与 5-HT 对兔基底动脉环和隐动脉环的收缩，对兔基底动脉环的作用显著强于隐动脉环，表明 Dox 可选择性扩张脑血管，其 pD_2 值与抗抑郁类药米帕明接近[2]，表明二者作用强度相近，Dox 抗抑郁和抗焦虑治疗的临床血药浓度范围大于 0.36 μmol·L^{-1}[7]，Dox 实验药物浓度在 1.73 μmol·L^{-1}以上，在治疗浓度范围．在含有 egtazic acid 的 Ca^{2+}-free 液中 NE 引起的隐动脉环的收缩与内钙释放有关，恢复正常 Ca^{2+} 液后观察到的隐动脉环的收缩与 NE 引起的外钙内流有关[6,8]，Dox 在 5.8 μmol·L^{-1}对无 Ca^{2+} 液中 NE 引起的隐动脉环的收缩具有抑制作用，对恢复正常 Ca^{2+} 液后观察到的收缩影响不明显，Dox 30 μmol·L^{-1}则对上述二种收缩均有抑制作用，可认为 Dox 小剂量可抑制内钙释放，大剂量时对内钙释放和外钙内流均有抑制作用．

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