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豚鼠气管和血管平滑肌以及心脏传导系统对异丙肾上腺素耐受性的差异

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Difference of tolerances to isoprenaline between tracheal and vascular smooth muscles and cardiac conduction system in guinea pigs

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ABSTRACT Pretreatment to guinea pigs with sc isoprenaline (Iso) 10 μg / kg tid × 7 d reduced the effect of Iso on protecting histamine-induced asthma and decreased its pD_2 values in relaxing isolated tracheal strip. This treatment did not change the asthmatic effect induced by histamine and the effect of Iso on positive chronotropic action, but elevated the blood pressure. These results suggest that it is easier to develop the tolerance of β_2-adrenoceptors of respiratory smooth muscles than that of β_1-adrenoceptors of heart. Radioligand binding assay showed that the treatment decreased the number of binding sites of β-adrenoceptors on lungs of guinea pigs but did not change the binding affinity.

KEY WORDS *beta*-adrenergic receptors; isoproterenol; drug tolerance; trachea; vascular smooth muscle; blood pressure; radioligand assay; asthma

提要 豚鼠, 反复应用异丙肾上腺素(Iso sc, 10 μg / kg, tid × 7 d)可使该药的抗组胺性哮喘作用减弱, 舒张离体气管条作用的 pD_2 值下降, 但对心脏的正性频率作用无明显变化. 耐受后, 豚鼠的基础血压升高. 放射性配位体测定结果表明, Iso 慢性耐受性

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的产生与 β 受体数目减少有关.

关键词 β 肾上腺素受体; 异丙肾上腺素; 药物耐受性; 气管; 血管平滑肌; 血压; 放射配位体测定法; 哮喘

β 受体激动剂是一类治疗支气管哮喘的药物, 但反复应用可以引起 β 受体的耐受性[1,2], 影响疗效. 曾有研究表明机体不同的组织对 β 受体激动剂的耐受性不同[3]. 本文比较了豚鼠气管平滑肌和血管平滑肌以及心脏传导系统 β 受体慢性耐受性, 观察了耐受后其生理机能的变化.

MATERIALS

盐酸异丙肾上腺素(isoprenaline, Iso, 上海天丰药厂). 磷酸组胺(histamine, His, 上海生物化学研究所). [^{3}H]双氢烯丙洛尔 ([^{3}H] dihydroalprenolol, [^{3}H] DHA, 北方同位素公司), 比放射性 1.74 TBq / mmol. ZH-3 型血压传感器(贵阳医疗器械厂). LVDT 5 型位移传感器(南京虹光仪器厂). FJ 2101G 型双道液体闪烁计数器(国营二六二厂). 20PR 5 型自动高速冷冻离心机(日立公司).

METHODS AND RESULTS

β 受体慢性耐受性模型的建立 豚鼠, 由本校实验动物中心提供, ♀♂不拘, 根据实验选择不同的体重. 随机分组, 试验组: Iso, 10 μg / kg, sc, tid ×7 d, 对照组用生理盐水(NS).

气道 β 肾上腺素受体耐受性的测定

1 *引喘试验*[4] 豚鼠, 体重 231 ± SD 15 g, 置于密闭的玻璃钟罩内, 恒压喷入 0.5% His 15 s, 记录引喘潜伏期. d 2, 先喷入 0.05% Iso, 60 s 后再喷入 0.5% His 15 s, 记录引喘潜伏期. 随机分组, 建立 β 受体慢性耐受性模型. 造型完毕后, 重复上述两次引喘试验. 由 Tab 1 比较两组造型前后的引喘潜伏期, 可知反复应用 Iso 以后, 该药的抗 His 性哮喘作用明显减弱($P<0.01$), 但不影响 His 的引喘潜伏期($P>0.05$).

Tab 1. Induction period of asthma after treatment to guinea pigs with sc isoprenaline (Iso) 10 μg / kg tid ×7 d. Histamine (His) 0.5 %, inhaled, 15 s; Iso 0.05 % inhaled, 60 s. $n=9$, $\bar{x}$ ± SD. *$P>0.05$, ***$P<0.01$, *vs* pretreatment, †$P>0.05$, †††$P<0.01$ *vs* NS.

Treatment	Drugs	Induction of asthma (s) Pre-treatment	Post-treatment
NS	His	75 ± 12	81 ± 15*
	Iso + His	296 ± 27	250 ± 22*
Iso	His	75 ± 16†	81 ± 21*†
	Iso + His	288 ± 29†	195 ± 36** †††

2. *离体气管条试验* 豚鼠, ♀♂不拘, 体重 404 ± 29 g, 建立 β 受体慢性耐受性模型后制备气管螺旋条[5], 连接位移传感器, 记录 Iso 舒张气管平滑肌的效应. 结果: 试验组和对照组的 pD_2 值分别为 7.13 ± 0.08, 7.73 ± 0.16 ($n=8$, $P<0.01$), 它们的最大效应(E_{max})分别为 81 ± 22, 90 ± 16 mm. ($n=8$, $P>0.05$).

心血管系统的耐受性

1 *血压试验* 豚鼠, ♀♂不拘, 体重 405 ± 38 g, 建成 β 受体慢性耐受性的模型后用 20%的乌拉坦 1 g / kg ip 麻醉后, 颈动脉插管连接血压传感器, 颈外静脉穿刺给药. 记录基础血压后, Iso 1.25 μg / kg iv, 观察血压变化. 结果: 试验组和对照组的基础血压分别为 10.3 ± 2.4 和 7.7 ± 0.5 kPa ($n=7$, $P<0.05$), 应用 Iso 后血压降低分别为 1.9 ± 0.9 和 1.9 ± 0.7 kPa ($P>0.05$). 血压分别降低 18 ± 5%和 25 ± 5%($P<0.05$).

2 *清醒豚鼠心电测定* 豚鼠, ♀♂不拘, 体重 246 ± 24 g, 置于特制的小木盒内, 皮下固定电极, 连接心电图机 II 导联, 蔽光, 22℃保温, 安静, 稳定 20 min 后测定基础心率(HR)和 P-R 间期, 然后, Iso, sc, 2.5 μg / kg, 5 min, 再测 HR 和 P-R 间期: 随即建立 β 受体慢性耐受性模型. 模型建成后,

重复上述心电测定. Tab 2 提示反复应用 Iso 后，豚鼠基础 HR 和 P-R 均无明显改变 ($P>0.05$)，Iso 对 HR 和 P-R 的影响亦无显著性变化($P>0.05$).

Tab 2. Basal electrocardiography of guinea pigs with isoprenaline (Iso) sc 10 μg / kg tid × 7 d and effects of Iso (sc 2.5 μg / kg) on electrocardiography. $n=10$, $\bar{x}\pm$SD. $^*P>0.05$ *vs* Pre.

Treatment		Heart rate (bpm)		P-R interval (ms)	
		Basal	Iso	Basal	Iso
NS	Pre	265±20	376±16	54±6	45±6
	Post	272±18*	366±18*	55±4*	48±6*
Iso	Pre	279±40	363±19	58±4	46±5
	Post	275±10*	370±14*	64±6*	51±7*

豚鼠肺组织 β 肾上腺素受体的测定[6,7] 测心电的豚鼠同时测定其肺组织 β 受体. 制备肺组织细胞膜匀浆，用[^{3}H] DHA 进行放射性配位体测定，测定 β 受体的表观最大结合容量 R_t 和平衡解离常数 K_d.试验组和对照组的 R_t 值分别为 387±143 和 527±61 fmol / mg ($n=8$, $P<0.05$).R_d 值分别为 1.4±0.4 和 1.4±0.3 nmol / L ($P>0.05$).

DISCUSSION

本文同时观察反复应用 Iso 以后豚鼠气道和心血管系统两种 β 受体亚型对 Iso 的反应，发现在 Iso 对气管平滑肌的松弛作用明显降低的同时，其对心脏的正性频率作用不改变.提示在气管平滑肌上以 β_2 为主的受体亚型较心脏传导系统上以 β_1 为主的受体亚型更容易发生耐受性.

本文的结果表明，β 受体耐受以后，豚鼠的基础血压升高，其机理可能与 β 受体耐受以后，α 受体功能相对提高有关[7,8]. 因此，临床上应重视在伴发高血压的哮喘病人中长期应用 β 受体激动剂的问题. 由于试验组和对照组的基础血压有明显差异，所以影响了对两组 Iso 血压反应的衡量. 正如前文所述，如果以血压下降的绝对值为指标，两组无显著差异，提示血管平滑肌未出现耐受性;而如果以血压下降的%为指标，两组有显著差异，提示出现 β 受体耐受性.

一般认为,随着 β 受体数目或功能的下降，气道对致痉剂的反应性将增大[9,10]. 但是，本文结果提示，β 受体耐受后豚鼠气管对 His 的反应并不改变，与文献[1]结果一致.

对 β 受体耐受性的产生机理所进行的研究，由于涉及快速耐受性和慢性耐受性以及从整体、离体器官和培养细胞的观察角度的不同，得到的结果不完全相同[11,12]. 本文的实验结果提示，长期应用 Iso 可以使豚鼠肺组织 β 受体的 R_t 值下降而 K_d 值并不改变，表明长期应用 β 受体激动剂造成 β 受体慢性耐受性与 β 受体数目减少有关. 耐受后，β 受体的亲和力无明显变化.

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