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呼吸中枢 M 胆碱受体亚型及功能[1,2]

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Muscarinic receptor subtypes in respiratory center and their functions

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ABSTRACT Radioreceptor binding assays using [^{3}H]quinuclidinyl benzilate and [^{3}H]pirenzepine were performed on the pons and medulla oblongata (MeOb) of rat brain. The M_1 cholinergic receptor (M_1-R) was found to account for approximately 30-40% of the total muscarinic receptors (M-R) in the pons and MeOb, and the M_2 accounted for about 60-70%. The receptor binding capacities of scopolamine and atropine were compared with those of pirenzepine (Pir) and AF-DX 116 on the 2 parts of the brain. The affinity values (pK_i) suggest that the selectivity of scopolamine for M_1-R is greater than for M_2-R, and that of atropine for M_2 is greater than for M_1. In conscious rabbits, the respiratory frequency (FR), tidal volume (TV), and minute ventilation volume (MVV) were determined. Arterial blood samples were taken intermittently and analyzed for pO_2, pCO_2, and pH. When pilocarpine (a M_1-R subtype selective agonist) was given, excitatory effects on respiration were seen through FR, TV, MVV, and the pO_2, pCO_2, and pH. When 6β-acetoxy nortropane (6β-AN, a novel M_2-R subtype selective agonist) was given, the effects were inhibitory. These results were reversed after administration of Pir, scopolamine, AF-DX 116, and atropine. Thus, it shows that Pir and scopolamine inhibit respiration by blocking the M_1-R subtype of the respiratory center, while the excitatory effects of AF-DX 116 and atropine are brought about by blocking the M_2-R subtype of the respiratory center.

KEY WORDS muscarinic receptors; respiration; tidal volume; respiratory center; blood gas analysis; radioligand assay

提要 放射配位体测定表明大鼠桥脑和延脑 M_1-R 约占 30%-40%，M_2-R 约占 60-70%；东莨菪碱对 M_1-R 选择性高于 M_2-R，阿托品则相反。匹鲁卡品激动 M_1-R 引起呼吸兴奋，哌仑西平和东莨菪碱阻断 M_1-R，效应相反。两药选择性拮抗前者呼吸兴奋效应。6β-AN 激动 M_2-R 抑制呼吸，AF-DX 116 和阿托品阻断 M_2-R，效应相反，两药可选择性拮抗 6β-AN 呼吸抑制效应。

关键词 毒蕈碱受体；呼吸；潮气量；呼吸中枢；血气分析；放射配位体测定

神经递质乙酰胆碱(ACh)在中枢对呼吸的影响研究极少，我室曾报道 4-氨基吡啶(4-aminopyridine)兴奋呼吸[1]、吗啡抑制呼吸[2]分别与 ACh 释放增加或减少有关。阿托品和东莨菪碱对呼吸频率的影响相反，设想可能与阻断不同 M 受体亚型有关及呼吸中枢存在兴奋型 M_1，抑制型 M_2 胆碱受体[3]，故本文应用呼吸功能试验，血气分析与放射配位体测定来观察 M_1-R 激动剂匹鲁卡品[4]，M_2-R 激动剂 6β-乙酰氧基去甲托烷 (6β-acetoxy nortropane, 6β-AN)[5]及 M_1-R 拮抗剂 pirenzepine (Pir), M_2-R 拮抗剂 AF-DX 116[6]对呼吸的作用，以探讨中枢胆碱能系统对呼吸的影响，同时研究抗胆碱药对呼吸中枢作用及机制。

MATERIALS AND METHODS

东莨菪碱 (scopolamine, Sco)，阿托品

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(atropine, Atr)成都第一制药厂出品. 哌仑西平(pirenzepine, Pir)重庆医药研究所合成赠送. AF-DX 116 (11-2[[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6*H*[2,3-b][1,4]benzodiazepine-6-one)德国 Karl Thomae GmbH Chemisch-Pharmazeutiche Fabrik 产品. 匹鲁卡品(pilocarpine, Pil) Sigma 产品. 6β-AN 上海第二医科大学化学教研室合成. [^{3}H]pirenzepine (3.15 PBq · mol^{-1}), New England Nuclear (USA)产品; [^{3}H]quinuclidinyl benzilate ([^{3}H]QNB), 1.44 PBq · mol^{-1}, Amersham 产品, 滤膜为海光牌 69 型玻璃纤维空气过滤纸.

呼吸参数的测定 兔体重 $2.4 \pm s\ 0.2$ kg, 辛♀随机分配, 每组 6-8 只, 胸带式换能器与 RM-86 多导生理记录仪相连, 测定呼吸频率(respiratory frequency, FR), 用"面积法"[7]对呼吸波进行峰面积积分的方法测定潮气量(tidal volume, TV), 将 FR 乘以 TV 即得通气量/min (minute ventilation volume, MVV).

兔耳动脉插管, 1%肝素钠 1 ml 抗凝, 于给药前、后不同时间取血, 用 DH-100G 型血气分析仪测定 pO_2 (partial pressure of oxygen), pCO_2 (partial pressure of carbon dioxide)和 pH.

放射配位体测定 Wistar 大鼠体重 $226 \pm s\ 23$ g, 断头, 取皮层海马, 桥脑, 延脑和小脑(0-4 ℃), 按 1 : 10 (wt/vol)加入蔗糖液(0.32 mol · L^{-1}), 冰浴上匀浆, 离心 10 min ($4000 \times g$), 上清液再离心 ($28\,000 \times g$) 20 min, 沉淀蛋白按 1 : 20 (wt/vol)加入磷酸缓冲液(10 mmol · L^{-1}, Na_2HPO_4 8.1 mmol · L^{-1}, KH_2PO_4 1.9 mmol · L^{-1})再匀浆, 按 Lowry 等氏法定蛋白, 膜受体分别与[^{3}H]QNB, [^{3}H]Pir 进行饱和结合试验及竞争抑制结合试验[8-10], 后者采用 Pir, Sco, AF-DX 116, Atr 测得竞争抑制参数 K_i (受体亲和强度), 竞争抑制结合试验多位点分析用 Hofstee 法[11].

结果用配对和组间 *t* test 检验, 判断是否为协同作用以 Bürgi 氏公式($q = E_{(A/2+B/2)} / E_A$)[12].

RESULTS

对兔呼吸的影响

1 M$_1$-R 激动剂与 M$_1$-R 拮抗剂 Pir 及 Sco 单用及合用的效应 M$_1$-R 激动剂 Pil 0.5 mg · kg^{-1} icv, 5 min FR, TV 及 MVV 与给药前比, 有明显增加($P<0.05$), 10-30 min 达高峰, 作用持续 1 h 以上(Fig 1); 血气 pO_2 增加 ($P<0.05$ or $P<0.01$), pCO_2 减少 ($P<0.05$, Tab 1). M$_1$-R 拮抗剂 PZ 及 Sco 各 0.5 mg · kg^{-1} icv, FR, TV 及 MVV 比给药前均明显减少($P<0.05$ or $P<0.01$), 作用持续 1 h 以上(Fig 1); pO_2 减少($P<0.01$), pCO_2 增加($P<0.05$ or $P<0.01$, Tab 1), pH 降低

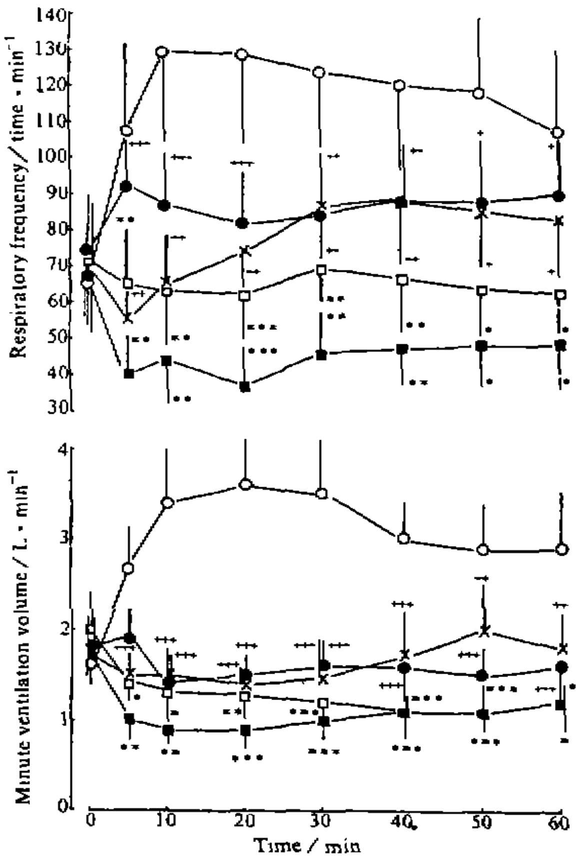

Fig 1. Effects of pilocarpine (Pil) alone and in combination with pirenzepine (Pir) or scopolamine (Sco) on respiratory frequency and minute ventilation volume in rabbits. (○) Pil 0.5 mg · kg^{-1} icv; (●) Pil 0.5 mg · kg^{-1}+Sco 0.5 mg · kg^{-1} icv; (×) Pil 0.5 mg · kg^{-1}+Pir 0.5 mg · kg^{-1} icv; (□) Sco 0.5 mg · kg^{-1} icv; (■) Pir 0.5 mg · kg^{-1} icv. $n=6$, $\bar{x} \pm s$, $^*P>0.05$; $^{**}P<0.05$; $^{***}P<0.01$ *vs* Pil+Pir or Pil+Sco. $^+P>0.05$; $^{++}P<0.05$; $^{+++}P<0.01$ *vs* Pil alone.

($P<0.05$). Pir 及 Sco 0.5 mg · kg^{-1} 分别与 Pil 0.5 mg · kg^{-1} 合用 icv，可拮抗 Pil 呼吸兴奋效应(Fig 1, Tab 1).

2 M_2-R 激动剂与 M_2-R 拮抗剂 AF-DX 116 及 Atr 单用及合用的效应 M_2-R 激动剂 6β-AN 1 μg · kg^{-1} icv, 10 μg · kg^{-1} iv, FR、TV 及 MVV 比给药前均明显减少($P<0.05$ or $P<0.01$)，作用持续 1 h 以上(Fig 2); pO_2 亦减少($P<0.05$ or $P<0.01$), pCO_2 增加($P<0.01$, Tab 1), pH 无明显变化($P>0.05$). M_2-R 拮抗剂 AF-DX 116 0.3 mg · kg^{-1} icv 及 Atr 0.5 mg · kg^{-1} icv、FR, TV 及 MVV 比给药前均显著增加($P<0.05$ or $P<0.01$)，作用持续 1 h 以上(Fig 2); pO_2 增加($P<0.05$ or $P<0.01$)，pCO_2 减少($P<0.05$ or $P<0.01$, Tab 1), pH 增加($P<0.05$). AF-DX 116 0.15 mg · kg^{-1} 及 Atr 0.5 mg · kg^{-1} 分别与 6β-AN 1 μg · kg^{-1} 合用 icv，可拮抗 6β-AN 呼吸抑制效应(Fig 2, Tab 1).

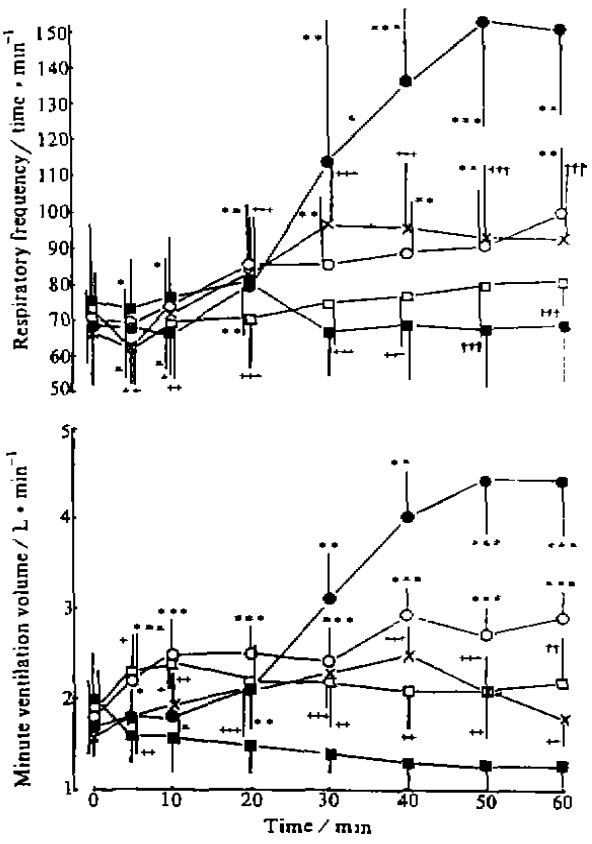

Fig 2. Effects of 6β-AN alone and in combination with AF-DX 116 or atropine (Atr) on respiratory frequency and minute ventilation volume in rabbits. (○) **AF-DX 116 0.15 mg · kg^{-1} icv;** (●) **Atr 0.5 mg · kg^{-1} icv;** (×) **6β-AN 1 μg · kg^{-1}+Atr 0.5 mg · kg^{-1} icv;** (□) **6β-AN 1 μg · kg^{-1}+AF-DX 116 0.15 mg · kg^{-1} icv;** (■) **6β-AN 1 μg · kg^{-1} icv.** $n=6$, $\bar{x}\pm s$. $^{*}P>0.05$; $^{**}P<0.05$; $^{***}P<0.01$ *vs* **6β-AN+Atr or 6β-AN+AF-DX116.** $^{+}P>0.05$; $^{++}P<0.05$; $^{+++}P<0.01$ *vs* **6β-AN alone.**

3 Pil 与 AF-DX 116, Atr 合用及 6β-AN 与 Pir, Sco 合用的效应 AF-DX 116 0.15 mg · kg^{-1}, Atr 0.25 mg · kg^{-1} 分别与 Pil 0.25 mg · kg^{-1} 合用 icv, FR, TV 及 MVV 比给药前显著增加($P<0.05$ or $P<0.01$)，与 Pil 0.5 mg · kg^{-1} 单用相比，q 值>1，表明 AF-DX 116, Atr 与 Pil 作用协同[12]. Pir 0.25 mg · kg^{-1} 及 Sco 0.1 mg · kg^{-1} 分别与 6β-AN 0.5 μg · kg^{-1} 合用 icv, FR, TV 及 MVV 比给药前显著减少($P<0.01$)，与 6β-AN 1 μg · kg^{-1} icv 单用相比，q 值>1，表明 Pir, Sco 与 6β-AN 作用协同[12].

放射配位体测定

1 放射配位体饱和试验 [^{3}H]QNB 与桥脑，延脑结合试验表明桥脑与延脑 M-R 数相近(Tab 2). [^{3}H]Pir 与桥脑，延脑结合 nH>1 ($P<0.01$)，Scatchard 分析为高低亲和力两部分，从表示受体亲和强度 K_d 值可见，高亲和力部分 K_d 值与[^{3}H]Pir 结合皮层海马 K_d 值相近，提示其为 M_1-R 结合部分(待发表资料). 桥脑和延脑 M_1-R 分别约占 M-R ([^{3}H]QNB 结合)的 42%，46% (Tab 2).

2 竞争结合试验 从 pK_i 值可见 Sco 与 Pir 相似对桥脑和延脑 M_1-R 结合具有高亲和力，Atr 则与 AF-DX 116 相似，对其 M_1-R 结合具有低亲和力(Tab 3). 四种药物在桥

Tab 1. Arterial pO_2 and pCO_2 after pilocarpine (Pil), pirenzepine (Pir), scopolamine (Sco), 6β-AN, AF-DX 116, atropine (Atr) icv alone or in combination in rabbits. $n=6$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* 0 min.

Drugs			pO_2 / kPa			pCO_2 / kPa		
			0 min	10 min	30 min	0 min	10 min	30 min
Pil	Pir (mg · kg^{-1})	Sco						
0.5			12.3 ± 1.3	14.3 ± 1.7*	14.8 ± 1.6***	3.5 ± 0.5	2.9 ± 0.5**	2.8 ± 0.5**
0.5	0.5		12.8 ± 1.2	12.3 ± 2.0*	13.1 ± 1.2*	3.5 ± 0.7	3.3 ± 0.6*	3.5 ± 0.5*
0.5		0.5	13.1 ± 1.9	12.9 ± 1.8*	12.8 ± 1.9*	3.7 ± 0.6	3.6 ± 0.7*	3.7 ± 0.7*
	0.5		14.4 ± 1.5	12.9 ± 1.1***	13.4 ± 1.3***	3.5 ± 0.5	3.9 ± 0.4***	3.9 ± 0.5***
		0.5	12.0 ± 0.6	9.7 ± 1.3***	9.5 ± 1.4***	3.2 ± 0.4	4.0 ± 0.3***	3.6 ± 0.4**
6β-AN (μg · kg^{-1})	AF-DX 116 (mg · kg^{-1})	Atr						
1.0			15.6 ± 2.8	12.4 ± 1.1***	13.4 ± 2.1**	3.3 ± 0.5	4.4 ± 0.5***	4.7 ± 0.6***
1.0	0.15		11.5 ± 1.3	12.0 ± 1.3*	12.1 ± 2.0*	3.7 ± 0.9	3.5 ± 0.8*	3.5 ± 0.5*
1.0		0.5	12.4 ± 0.5	13.0 ± 0.9*	13.4 ± 1.0*	3.1 ± 1.0	2.7 ± 0.8*	2.4 ± 0.4**
	0.15		11.1 ± 0.7	11.6 ± 0.7**	11.7 ± 0.6**	4.5 ± 0.7	4.1 ± 0.5**	4.1 ± 0.8**
		0.5	11.8 ± 0.7	11.9 ± 0.8*	14.5 ± 0.7***	3.7 ± 0.3	3.7 ± 0.3*	3.2 ± 0.1***

Tab 2. Specific binding of [^{3}H]pirenzepine (0.5–20 nmol · L^{-1}) and [^{3}H]quinuclidinyl benzilate (0.05–2.5 nmol · L^{-1}) to pons and medulla oblongata membranes. $n=4$, $\bar{x}\pm s$.

Parameters	[^{3}H]pirenzepine		[^{3}H]quinuclidinyl benzilate	
	Pons	Medulla	Pons	Medulla
K_d, nmol · L^{-1}	9.1 ± 1.1	8.4 ± 1.9	0.079 ± 0.005	0.097 ± 0.005
K_{d_1}	7.8 ± 0.7	7.2 ± 0.5		
K_{d_2}	58.7 ± 7.5	56.4 ± 6.5		
B_{max}, fmol / mg protein	640.0 ± 41.4	626.3 ± 66.0	944.5 ± 129.7	785.2 ± 28.5
B_{max_1}	394.0 ± 19.5	358.7 ± 88.0		
B_{max_2}	247.3 ± 30.0	266.6 ± 24.0		
nH	1.43 ± 0.14*	1.49 ± 0.20*	1.06 ± 0.06	1.04 ± 0.04

* Hill slope was different from unity ($P<0.01$).

脑，延脑结合[^{3}H]QNB 均可分出高低亲和力部分. 与[^{3}H]Pir 受体结合，等效克分子 Pir : AF-DX 116 的亲和力比为 200 : 1, Sco : Atr 的亲和力比为 10 : 1 (Tab 3). 且 Sco 对皮层海马(M_1-R)的亲和力是对小脑(M_2-R)亲和力的 22.8 倍，Atr 对小脑的亲和力则是对皮层海马亲和力的 4.9 倍.

DISCUSSION

本文放射配位体测定表明桥脑和延脑存在较丰富的 M-R. [^{3}H]Pir 受体结合试验表明大鼠桥脑和延脑存在两个 M-R 结合部分，pir 及 AF-DX 116 取代[^{3}H]QNB 受体结合桥脑和延脑存在两个亲和力点且数值互补(Tab 3)，说明桥脑和延脑 M-R 存在两种亚型. 从 Tab 2 和 Tab 3 中可见其 M_1-R 数约占 M-R 数的 30%–40%, M_2-R 约为 60–70%. 有人报道[9]脑干(桥脑和延脑)M_1-R 数少. 作者认为本实验所用 10 mmol · L^{-1} Na^+-K^+磷酸缓冲液是较适宜的[^{3}H]Pir 与 M_1-R 结合环境[10]，增加了结果可靠性.

Pil 选择性激动 M_1-R，6β-AN 选择激动

Tab 3. pK_i of scopolamine, atropine, pirenzepine, and AF-DX 116 in displacement [^{3}H]quinuclidinyl benzilate ([^{3}H]QNB) and [^{3}H]pirenzepine binding assays on rat pons and medulla oblongata (MO) membranes. The data in the displacement [^{3}H]QNB binding assay were analyzed by a two-model of Hofstee analysis method. $n=5$, $\bar{x}\pm s$.

		[^{3}H]quinuclidinyl benzilate						[^{3}H]pirenzepine		
	pK_i	nH	pK_i (high)	%	pK_i (low)	%	+A	pK_i	nH	§ B
Pons	Scopolamine									
	8.2±0.5	0.76±0.08*	8.8±0.3	39.4	7.9±0.2	60.6	7.8	9.3±0.5	0.93±0.06	12.59
	Atropine									
	8.8±0.3	0.94±0.09	9.0±0.3	89.8	8.4±0.3	10.2	4.0	8.4±0.4	0.90±0.06	0.46
	Pirenzepine									
	5.6±0.2	0.77±0.07*	6.7±0.3	28.9	5.3±0.3	71.1	22.9	7.8±0.2	0.95±0.08	138.0
	AF-DX 116									
	6.7±0.5	0.57±0.07*	7.5±0.3	64.5	6.2±0.2	35.5	17.4	5.4±0.3	0.89±0.07	0.05
MO	Scopolamine									
	8.6±0.4	0.79±0.11*	9.2±0.3	41.3	8.1±0.2	58.7	10.7	10.0±0.6	0.96±0.06	25.7
	Atropine									
	9.1±0.2	0.96±0.05	9.5±0.2	84.5	8.9±0.2	15.5	3.7	9.3±0.4	0.89±0.09	0.6
	Pirenzepine									
	6.0±0.3	0.72±0.08*	6.4±0.3	28.4	5.2±0.2	71.6	15.5	8.3±0.3	0.94±0.09	229.1
	AF-DX 116									
	6.6±0.2	0.56±0.06*	7.6±0.2	69.6	6.3±0.2	30.4	22.4	5.5±0.4	0.90±0.07	0.09

* Hill slope was different from unity ($P<0.01$).
+A = K_i (low) / K_i (high).
§ B = selectivity ratio representing the ratio K_i ([^{3}H]QNB) / K_i ([^{3}H]Pir).

M_2-R[4,5]. 本文结果、Pil 引起呼吸兴奋，Pir 引起呼吸抑制且可选择性拮抗 Pil 引起的呼吸兴奋、6β-AN 则引起呼吸抑制，AF-DX 116 引起呼吸兴奋并选择性拮抗 6β-AN 的呼吸抑制，我室曾报道[13]膈神经放电结果表明 Pir、AF-DX 116 分别抑制和兴奋呼吸中枢. 上述提示激动呼吸中枢 M_1-R 致呼吸兴奋、激动 M_2-R 引起呼吸抑制，阻断之则作用相反.

本文发现，在四种脑组织膜受体结合试验中，Sco 均表现出对 M_1-R 亲和力高于 M_2-R、Atr 则相反. 在 Fig 3 中证明 Pir、Sco 对 M_1-R 选择性高，而 AF-DX 116、Atr 对 M_2-R 选择性高. Sco 抑制呼吸且选择性拮抗 Pil 的呼吸兴奋，Atr 兴奋呼吸且选择性拮抗 6β-AN 的呼吸抑制，加上 Sco 和 Atr 分别抑制和兴奋兔膈神经放电[13]. 这些结果表明 Sco 与 Pir 一致、引起呼吸抑制可能与阻断呼吸中枢 M_1-R 有关，Atr 与 AF-DX 116 一致、引起呼吸兴奋可能与阻断呼吸中枢 M_2-R 有关.

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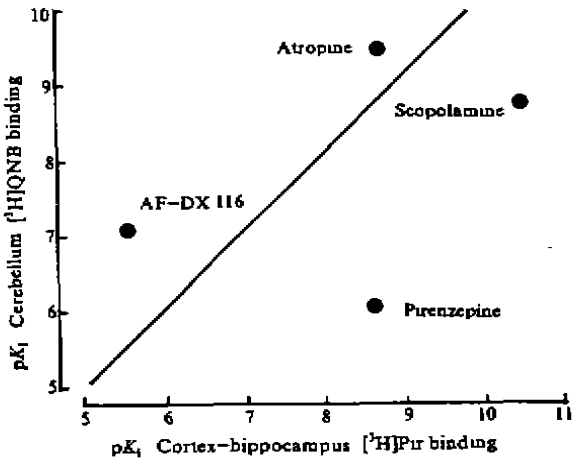

Fig 3. Affinities of antimuscarinic drugs for muscarinic binding sites in cortex-hippocampus (M_1) and cerebellum (M_2).

加部分技术工作.

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美西律对小鼠脑缺血后能量代谢的影响

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Effect of mexiletine on energy metabolism of ischemic brain in mice

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ABSTRACT After 30 s ischemia induced by decapitation, the contents of ATP and phosphocreatine (PC) in mouse brain reduced, while that of lactic acid (LA) increased. When mexiletine (3.1-50 mg · kg^{-1}) was injected ip 30 min before decapitation, the brain ATP and PC reduction, and LA accumulation were both alleviated in a dose-dependent manner. These findings suggested that mexiletine was effective in ameliorating the energy exhaustion in the ischemic brain.

KEY WORDS mexiletine; cerebral ischemia; adenosine triphosphate; phosphocreatine; lactates

提要 小鼠断头缺血 30 s 后, 脑 ATP, 磷酸肌酸(PC)含量明显下降, 乳酸(LA)含量显著增高. 缺血前 30 min ip 美西律 3.1-50 mg · kg^{-1} 能减轻小鼠脑缺血时 ATP, PC 的减少和 LA 的增高, 且均具有剂量与效应关系. 这说明美西律可减少缺血脑组织耗能.

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