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千金藤碱、xylopine 及其它 7 种四氢异喹啉类生物碱对 α 肾上腺素受体的阻断作用[1]

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Blocking actions of *l*-stephanine, xylopine and 7 other tetrahydroisoquinoline alkaloids on α adrenoceptors

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ABSTRACT The blocking action and selectivity of 9 tetrahydroisoquinoline alkaloids on α adrenoceptors have been investigated in isolated tissues. Dehydrostephanine and berbamine suppressed the inhibition of clonidine for the electrically stimulated twitch response of rat vas deferens, with pA_2 values of 5.36 and 5.49, respectively. *l*-Crebanine, *l*-tetrahydrocoptisine, berberine, *l*-stepholidine and *l*-tetrahydropalmatine had obvious blocking effects on α_1 and α_2 adrenoceptors. *l*-Stephanine and xylopine could competitively inhibit anococcygeus muscle contraction induced by phenylephrine with pA_2 values of 6.76 and 6.68, respectively. These 2 alkaloids showed no effect on the inhibition of clonidine for contractile response of rat vas deferens to field stimulation, and their selectivity ratios to block α_1 and α_2 adrenoceptors were 57.5 and 47.9, respectively. These results indicate that *l*-stephanine and xylopine are 2 potent and highly selective α_1 adrenoceptor blockers.

KEY WORDS tetrahydroisoquinolines; alkaloids; *l*-stephanine; xylopine; adrenergic alpha receptor blockaders; anococcygeus muscles; vas deferens

提要 离体大鼠肛尾肌及输精管实验证实，克班宁、四氢黄连碱、小檗碱、四氢巴马汀及千金藤立定对 α_1 和 α_2 受体均有阻断作用。去氢千金藤碱和小檗胺有阻断 α_2 受体作用。千金藤碱和 xylopine 阻断 α_1 受体作用最强，pA_2 分别为 6.76 和 6.68，但对可乐定抑制电刺激输精管收缩无明显影响。表明千金藤碱和 xylopine 是作用较强、选择性较高的 α_1 受体阻断剂。

关键词 四氢异喹啉类；生物碱；千金藤碱；番荔枝碱；肾上腺素能 α 受体阻滞剂；肛尾肌；输精管

本实验室曾用放射受体结合法，研究了多种四氢异喹啉类(tetrahydroisoquinolines)生物碱对大鼠脑内 α 肾上腺素受体的作用。证明千金藤碱、xylopine、克班宁、四氢黄连碱及小檗胺等对 α_1 或 α_2 受体有较高亲和力和选择性[1]。为进一步阐明这些生物碱对 α 受体作用特点，我们用离体大鼠肛尾肌(α_1 受体)和输精管(α_2 受体)标本，分别以哌唑嗪和育亨宾作对照，对 9 种四氢异喹啉类生物碱(Tab 1)进行了研究。

MATERIALS AND METHODS

药品 千金藤碱(*l*-stephanine)，去氢千

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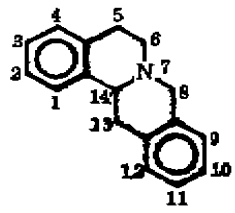
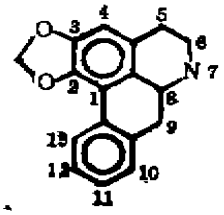
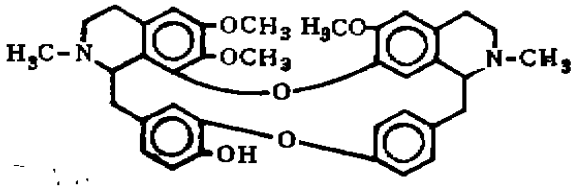
Tab 1. Chemical structures of 9 tetrahydroisoquinoline alkaloids.



Protoberberines



Aporphines



Berbamine

Alkaloids	2	3	7	8	9	10	11	13	14
Protoberberines									
l-Tetrahydrocoptisine	$O-CH_2-O$		H	H	$O-CH_2-O$		H	H	H
l-Tetrahydropalmatine	OCH_3	OCH_3	H	H	OCH_3	OCH_3	H	H	H
l-Stepholidine	OH	OCH_3	H	H	OCH_3	OH	H	H	H
Berberine	$O-CH_2-O$		$N^+=CH$		OCH_3	OCH_3	H	$CH=C$	
Aporphines									
l-Stephanine			CH_3	H	H	OCH_3	H		
Dehydrostephanine			CH_3	C =	CH	OCH_3	H		
Xylopine			H	H	H	H	OCH_3		
l-Crebanine			CH_3	H	H	OCH_3	OCH_3		

金藤碱（dehydrostephanine），番荔枝碱(xylopine)，克班宁(*l*-crebanine)，四氢黄连碱(*l*-tetrahydrocoptisine)，四氢巴马汀(*l*-tetrahydropalmatine)，千金藤立定(*l*-stepholidine)，小檗碱(berberine)和小檗胺(berbamine)由本校植化室提供。去氧肾上腺素(phenylephrine)上海第十制药厂针剂．可乐定(clonidine)为北京制药厂提供。哌唑嗪(prazosin)和育亨宾（yohimbine）分别为北京制药工业研究所和意大利 Mario Negri 药理研究所赠送。

大鼠肛尾肌实验[2,8] 大鼠，体重 217±SD 11 g，♀♂兼用，分离肛尾肌，标本悬吊于 10 ml Krebs 液中(37±1℃)通 95%O_2+5%CO_2，静息张力 0.5 g，平衡 1 h。收缩活动通过肌力换能器描记于台式记录仪上。实验前 15 min 加可卡因 30 nmol/L，氢可的松 40 μmol/L 及普萘洛尔 100 μmol/L。以累积浓度法，依次加入去氧肾上腺素，给药前去氧肾上腺素的量-效曲线作对照。冲洗标本至收缩张力恢复到初始水平，加待测药物，30 min 后重复去氧肾上腺素累积量-效曲线。按 Van Rossum 法计算激动剂 pD_2 和拮抗剂 pA_2 的效价强度[4]。

大鼠输精管实验[3,5] 大鼠，♂，体重 250±14 g，取靠前列腺端部分的输精管，置于恒温浴槽。静息张力 1 g，恒温条件同上。实验前 15 min 加可卡因 30 nmol/L，氢可的松 40 μmol/L 及哌唑嗪 5 nmol/L。用 3 ms，0.5 Hz，30 V 低频场刺激引起输精管收缩，α_2 受体激动剂可乐定可抑制此反应。每一标本只加一种待测药物，以给药前可乐定累积量-效曲线作对照。按上述方法计算各药对 α_2 受体作用效价。

RESULTS

对大鼠肛尾肌 α_1 受体的影响 大鼠肛尾肌对 0.1 μmol/L 去氧肾上腺素即有反应，至 0.32 mmol/L 达到最大收缩反应，其 pD_2 值为 8.60。

千金藤碱、xylopine、克班宁、四氢黄连碱及小檗碱 1，3.2，10 μmol/L 和哌唑嗪 10，

32，100 nmol/L 均使去氧肾上腺素收缩肛尾肌，其累积量-效曲线呈浓度依赖性平行右移最大反应不变(Fig 1)。求得 pA_2 值分别为 6.76，6.68，6.62，6.42 和 6.23。哌唑嗪为 8.70，与文献报道[6]一致。表明上述四氢异喹啉类生物碱均为竞争性 α_1 受体阻断剂。

四氢巴马汀和千金藤立定在 3.2，10 μmol/L 下，对去氧肾上腺素引起的肛尾肌收缩也呈竞争性拮抗，但作用较上几种生物碱弱，结果见 Tab 2。

对大鼠输精管前列腺端 α_2 受体的影响

1 可乐定对电刺激输精管收缩的抑制作用　可乐定 0.1-100 nmol/L 对电刺激输精管引起的收缩反应，有明显的浓度依赖性抑制作用，且抑制作用有一定的时效关系，一般在给可乐定 15 min 左右，其抑制作用达到最大，其 pD_2 为 8.59。

2 生物碱对输精管 α_2 受体的作用　克班宁、四氢黄连碱、小檗碱、四氢巴马汀、千金藤立定、去氢千金藤碱和小檗胺在 3.2，10 μmol/L 下，明显减弱可乐定抑制电刺激输精管收缩作用，可乐定量-效曲线平行右移(Fig 1)。实验求得各 pA_2 值见 Tab 2。育亨宾在 0.1，1 μmol/L 时，对可乐定的量效曲线也有同样影

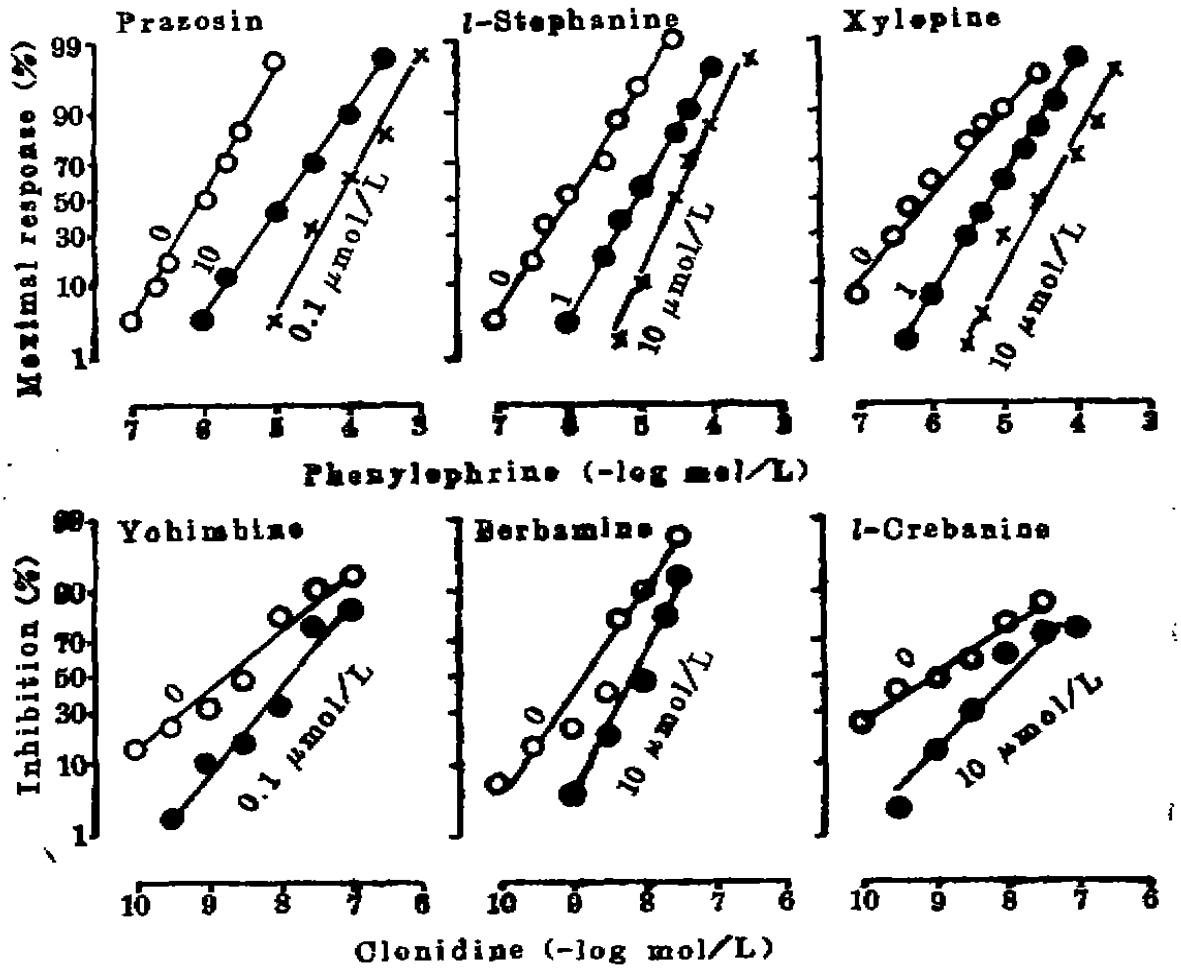


Fig 1. Effects of prazosin, *l*-stephanine and xylopine on phenylephrine-induced contraction of rat anococcygeus muscle and effects of yohimbine, berbamine and *l*-crebanine on clonidine inhibition of field stimulated rat vas deferens. The dose-response curves of absence and presence of an inhibitor were indicated by the (○) and (●), (×) curves, respectively. n = 5.

Tab 2. Effects of 9 tetrahydroisoquinoline alkaloids on α_1 adrenoceptors in rat anococcygeus muscle and α_2 adrenoceptors in rat vas deferens. n = 5, $\bar{x} \pm SD$.

Compounds	$pA_{2(\alpha_1)}$	$pA_{2(\alpha_2)}$
l-Stephanine	6.76±0.09	<5
Xylopine	6.68±0.13	<5
l-Crebanine	6.62±0.27	5.76±0.23
l-Tetrahydrocoptisine	6.42±0.13	5.54±0.41
Berberine	6.23±0.04	5.34±0.33
l-Tetrahydropalmatine	5.52±0.20	5.49±0.14
l-Stepholidine	5.16±0.12	4.91±0.04
Berbamine	<5	5.49±0.10
Dehydrostephanine	—	5.36±0.30
Prazosin	8.70±0.21	—
Yohimbine	6.49±0.25	7.63±0.15

Tab 3. Selectivity for the effect of 9 tetrahydroisoquinoline alkaloids on α adrenoceptors. The selectivity ratio to block α_1 and α_2 adrenoceptors was obtained from the antilogrithm of the differences between their pA_2 values.

Alkaloids	Selectivity Ratio	
	$K_{I(\alpha_2)}/K_{I(\alpha_1)}$	$K_{B(\alpha_2)}/K_{B(\alpha_1)}$
l-Stephanine	357.1	>57.5
Xylopine	153.9	>47.9
l-Crebanine	25.7	7.2
l-Tetrahydrocoptisine	28.1	7.6
Berberine	4.7	7.1
l-Tetrahydropalmatine	1.1	1.1
l-Stepholidine	1.0	2.0
Berbamine	0.6	0.3

响，其 pA_2 值为 7.63，与文献(6)相符。说明上述几种生物碱同育亨宾一样，都能竞争性拮抗 α_2 受体。

DISCUSSION

本实验研究的 9 种四氢异喹啉生物碱均为有效的 α_1,α_2 受体阻断剂.千金藤碱和 xylopine 阻断 α_1 受体作用最强，对 α_2 受体作用不明显，其对 α_1,α_2 受体阻断作用选择比 $K_{B(\alpha_2)}/K_{B(\alpha_1)}$分别大于 57.5 和47.9 (Tab 3)。这与受体结合实验结果，它们对 α_1 受体有较高亲和力及选择性完全一致[1]。可以认为千金藤碱和 xylopine 是作用较强、选择性较高的 α_1 受体阻断剂。

克班宁、四氢黄连碱、小檗碱、四氢巴马汀和千金藤立定对 α_1 和 α_2 受体均有阻断作用.克班宁、四氢黄连碱和小檗碱的阻断作用有一定选择性，选择比分别为 7.2，7.6 和 7.1。小檗碱的类似作用在兔主动脉条上也有报道[7]。四氢巴马汀和千金藤立定对 α_1，α_2 受体阻断作用缺乏选择性，选择比接近 1 .已知阻断突触前 α_2 受体与阻断突触后 α_1 受体效应截然不同[8].因此上述两种生物碱作用 α_1,α_2 受体的双相效果对其最终降压效应的影响有待探讨。

Timmermans 等研究药物对 α 受体亲和力与其效应间关系时，发现11 种经典 α 受体阻断剂在体外对 α_1，α_2 受体亲和力选择比$K_{I(\alpha_2)}/K_{I(\alpha_1)}$与整体动物实验中对 α_1，α_2 受体阻断作用选择比 $K_{B(\alpha_2)}/K_{B(\alpha_1)}$间存在明确定量关系[9]：$\log K_{B(\alpha_2)}/K_{B(\alpha_1)} = 0.735 \log K_{I(\alpha_2)}/K_{I(\alpha_1)} + 0.064$ ($r = 0.912$)，同样，我们比较了上述 9 种生物碱对 α 受体亲和力与其阻断效应。结果表明，它们对 α_1，α_2 受体亲和力选择比 $K_{I(\alpha_2)}/K_{I(\alpha_1)}$与其阻断作用选择比 $K_{B(\alpha_2)}/K_{B(\alpha_1)}$也存在类似关系：$\log K_{B(\alpha_2)}/K_{B(\alpha_1)} = 0.709 \log K_{I(\alpha_2)}/K_{I(\alpha_1)} + 0.071$ ($r = 0.958$)。这说明药物对 α_1，α_2 受体亲和力选择比与其阻断作用选择比间，不论在体外，还是体内都存在良好的相关性及类似的定量关系。这种定量关系为我们由受体结合实验结果预测其生物效应提供了更明确的依据。

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肾上腺皮质激素对豚鼠腹腔神经节细胞的快速膜效应[1]

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Rapid membrane effects of adrenocorticoids on celiac ganglion cells of guinea pig[1]

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ABSTRACT Intracellular recording technique was used to determine the effects of corticosterone, dexamethasone, aldosterone and cholesterol on the resting membrane potentials and membrane resistance of cells in isolated celiac ganglion of guinea pigs. Hyperpolarization was elicited by corticosterone in 15 out of 83 cells, but was not caused by dexamethasone, which depolarized the membrane in 2 out of 18 cells. In addition, depolarization was also elicited by corticosterone in 2 out of 83 cells. Aldosterone and cholesterol caused no detectable changes of membrane potential and membrane resistance. It is suggested that the membrane effects of adrenocorticoids, which obviously could not be explained by traditional genomic mechanism for their short latency, may indicate the existence of membrane receptors for adrenocorticoids in celiac ganglion neurons of guinea pigs.

KEY WORDS adrenal cortex hormones; membrane receptors; membrane potentials; sympathetic ganglia

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