

## 樟柳碱对呼吸中枢的影响

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## Effects of anisodine on respiratory center

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**ABSTRACT** Anisodine (Ani), a new selective M receptor blocking agent, was isolated from *Scopolia tangutica* in China. The structure of Ani is similar to scopolamine. Ani (2.5, 5 mg·kg<sup>-1</sup> iv, or 0.6 mg·kg<sup>-1</sup> icv) increased the rate of phrenic nerve discharges (PND), while the time of inspiration and expiration, and the spikes in each PND were reduced in urethan-anesthetized rats. In urethan-anesthetized rabbits, Ani (2.5 mg·kg<sup>-1</sup> iv, or 0.2 mg·kg<sup>-1</sup> applied onto obex) increased the rate of PND. In tubocurarine-pretreated and artificially ventilated rabbits, Ani (2.5 mg·kg<sup>-1</sup> iv, or 0.2 mg·kg<sup>-1</sup> applied onto obex) increased the rate of inspiratory neurone firing in nucleus tractus solitariua. Oxotremorine (40 μg·kg<sup>-1</sup> iv) antagonized the Ani effects. Ani (2.5 mg·kg<sup>-1</sup> iv) partially antagonized the respiratory depression induced by morphine. These results provide the evidence that Ani stimulates the respiratory center through cholinergic M pathway and there may be some neuronal interaction between cholinergic and opiate receptors in the control of respiratory center.

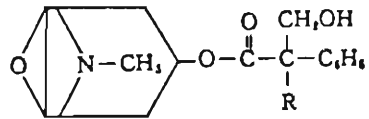
**KEY WORDS** anisodine; phrenic nerve; respi-

ratory center; scopolamine; scopolamine derivatives; oxotremorine; morphine

**摘要** 给大鼠 iv 或 icv M-受体阻滞剂樟柳碱, 可引起膈神经放电节率加快, 吸气与呼气时程缩短, 每次放电脉冲数减少. 兔 iv 或 脑内注射樟柳碱, 出现延髓孤束核区吸气相关神经元放电节率及膈神经放电节率同步加快. 氧化震颤素能拮抗樟柳碱加快膈神经放电节率的作用. 樟柳碱还能部分拮抗吗啡所致的膈神经放电节率减慢作用.

**关键词** 樟柳碱; 膈神经; 呼吸中枢; 东莨菪碱; 东莨菪碱衍生物; 氧化震颤素; 吗啡

樟柳碱 (anisodine, Ani) 是 M-受体阻滞剂, 化学结构与药理性质与东莨菪碱<sup>(1)</sup> (scopolamine, Sco) 相似. 此药用于抗晕, 血管神经性偏头痛, 眼底血管痉挛等疾病的治疗, 并曾用于静脉复合麻醉. 临床认为可能有兴奋呼吸中枢作用, 但迄今未见有关报道. 一般认为, 可能有多种中枢神经递质参与呼吸中枢调控作用<sup>(2)</sup>. 有关胆碱能系统在呼吸中枢的作用机制目前尚无定论. 本文用记录膈神经及延髓孤束核区吸气相关神经元放电技术, 对樟柳碱的呼吸中枢的作用机制进行了研究.



R=H scopolamine

R=OH anisodine

Received 1992-02-10

Accepted 1993-06-30

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**MATERIALS AND METHODS**

Wistar ↑大鼠 (210±s 11 g), NZW ↑兔 (2.3±0.2 kg)均由中国医学科学院动物中心供给. 氢溴酸樟柳碱 (anisodine HBr, Ani) 与氢溴酸东莨菪碱 (scopolamine HBr, Sco)均系成都第一制药厂出品. 盐酸吗啡 (morphine HCl, Mor, 沈阳制药厂). 氧化震颤素 (oxotremorine, Oxo, 美国 Serva). 双线示波器 (VC-10), 微电极放大器 (MZE-8201, 日本光电). 软件 (doctor-852)南京医学院生理室设计. 动物用人工呼吸机 (DH-1, 浙江医科大学实验仪器厂).

**膈神经放电实验** 大鼠 ip 乌拉坦 0.6 g·kg<sup>-1</sup> 麻醉, 分离出一侧膈神经, 剪断. 将近中端置于不锈钢双极电极. 用石蜡油浸润, 稳定 15 min 开始记录. 部分大鼠剪断双侧迷走神经.

**吸气相关神经元放电实验** 兔 iv 乌拉坦 0.5 g·kg<sup>-1</sup> 麻醉, 手术区用 2% 普鲁卡因局部麻醉. 从背侧分离出膈神经. 分离剪断双侧迷走神经, 作皮兜充以石蜡油, 用不锈钢双极电极引导膈神经放电. 暴露延髓背侧网状区域, 兔耳缘静脉点滴筒箭毒 (0.1%, 1 mg·kg<sup>-1</sup>, 5 drip·min<sup>-1</sup>), 人工通气, 频率 34 bpm, 潮气量 18-25 ml, 插入玻璃微电极 (直径 3-10 μm, 灌充 NaAc 0.5 mol·L<sup>-1</sup>) 在网状部前后 2 mm 之间, 中线旁开 0.5-0.2 mm, 网状部水平以下 0.2-2.6 mm. 解剖学相当于孤束核及其腹侧区域, 包括一部分背侧网状结构<sup>(3)</sup>. 引导孤束核区吸气相关神经元放电.

**大鼠侧脑室给药<sup>(4)</sup>** 在冠状缝后 0.3-1 mm, 矢状缝旁开 1-2 mm 交界处进针, 深度 4-5 mm. 注射容量 10 μl, 时间 30 s, 浓度为 1.5%.

**兔网状部给药<sup>(5)</sup>** 网状部表面贴敷浸润药液的滤纸片 (2 mm×2 mm), 用微量注射器滴药液 10-15 μl, 以湿透纸片, 浓度为 1.5%.

**实验结果分析处理** 膈神经放电引导至苹果 II 型机, 打印出序列脉冲频率直方图, 并由直方图可得出以下指标:

- 1 膈神经放电 (phrenic nerve discharge, PND) 节率, volley·min<sup>-1</sup>.
- 2 吸气与呼气时程, 30 ms
- 3 PND 脉冲数 (spikes in each phrenic nerve discharge), number/volley

吸气相关神经元放电由玻璃微电极引导至放大

器, 然后显示于示波器拍照, 所有参数均以给药前对照进行配对 *t* 检验分析.

**RESULTS**

**Ani 对大鼠膈神经放电的影响** 大鼠 Ani 1, 2.5, 5 mg·kg<sup>-1</sup>, PND 节率明显加快 5 min 达峰值, 各剂量组 PND 节率分别由给药前 104±8, 85±7, 83±8 volley·min<sup>-1</sup> 加快至 141±10, 113±11, 96±16 volley·min<sup>-1</sup> 至 60 min 恢复到给药前水平. 随着 PND 加快, 吸气与呼气时程缩短, PND 脉冲减少. 2.5 及 5 mg·kg<sup>-1</sup> 组 PND 节率明显加快 *P*<0.01 (Tab 1, Fig 1).

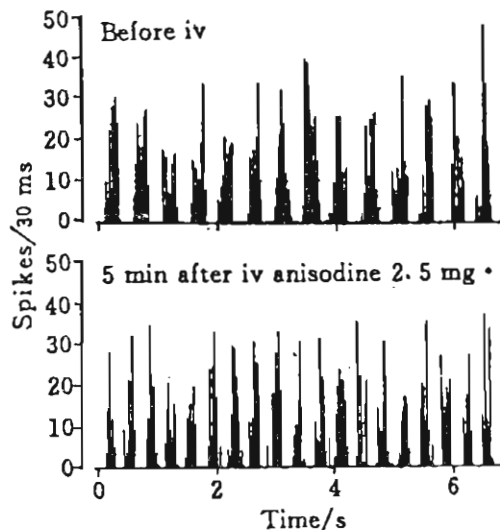


Fig 1. Frequency of rat phrenic nerve discharge in time order.

大鼠 icv Ani, 同样也能加快 PND 节率 5 min 达峰值. 由给药前 80±5 volley·min<sup>-1</sup> 加快至 99±5 volley·min<sup>-1</sup>, *P*<0.05, 随着节率加快, 吸气与呼气时程缩短, PND 脉冲减少 (Tab 1).

断双侧迷走神经大鼠 (*n*=6), iv Ani 5 mg·kg<sup>-1</sup> 及 Sco 0.25 mg·kg<sup>-1</sup>, PND 节率明显加快, 5 min 达峰值. 分别由给药前 33±4 6±3 volley·min<sup>-1</sup> 加快至 45±3, 5

Tab 1. Effect of anisidine (Ani) on phrenic nerve discharge (PND).  $n=8$  rats,  $\bar{x} \pm s$ .  $^a P > 0.05$ ,  $^b P < 0.05$ ,  $^c P < 0.01$  vs before.

	Intravenous Ani/mg·kg <sup>-1</sup>			icv Ani/mg·kg <sup>-1</sup> 0.6
	5.0	2.5	1.0	
Rate of PND, volley·min <sup>-1</sup>				
Before	104 ± 8	85 ± 7	83 ± 8	80 ± 5
After	141 ± 10 <sup>c</sup>	113 ± 11 <sup>b</sup>	96 ± 16 <sup>a</sup>	99 ± 5 <sup>c</sup>
Time of inspiration, 30 ms				
Before	11.2 ± 1.1	12.2 ± 0.9	12.6 ± 0.9	11.8 ± 0.7
After	8.8 ± 0.8 <sup>c</sup>	10.3 ± 0.9 <sup>a</sup>	11.3 ± 1.3 <sup>a</sup>	10.7 ± 0.6 <sup>b</sup>
Time of expiration, 30 ms				
Before	9.4 ± 1.0	10.9 ± 0.9	11.9 ± 1.1	13.3 ± 1.3
After	6.5 ± 0.9 <sup>c</sup>	7.9 ± 0.7 <sup>c</sup>	7.9 ± 1.0 <sup>c</sup>	9.3 ± 0.5 <sup>c</sup>
Spikes in PND, number/volley				
Before	105 ± 8	139 ± 6	137 ± 19	58 ± 6
After	73 ± 20 <sup>b</sup>	104 ± 9 <sup>c</sup>	124 ± 19 <sup>a</sup>	52 ± 6 <sup>b</sup>

volley·min<sup>-1</sup>  $P < 0.01$ . 由此可见,大鼠断双侧迷走神经消除外周对呼吸中枢自主节率的影响后, Ani 仍可加快 PND 节率,

**Ani 对兔 PND 节率的影响** 兔( $n=5$ ) iv Ani 2.5 mg·kg<sup>-1</sup>, PND 节率明显加快, 5 min 达峰值, PND 节率由给药前 58 ± 5 volley·min<sup>-1</sup> 加快至 78 ± 10 volley·min<sup>-1</sup>,  $P < 0.01$ . 15至60 min 恢复到 iv 前水平. 兔( $n=8$ )背部表面贴敷 Ani 0.2 mg·kg<sup>-1</sup>, PND 节率也明显加快, 1 min 达峰值, 由给药前 73 ± 9 volley·min<sup>-1</sup> 加快至 82 ± 10 volley·min<sup>-1</sup>,  $P < 0.05$ . 至30 min 恢复到给药前水平.

**Ani 对兔呼吸中枢吸气相关神经元放电节率的影响** 兔( $n=9$ ) iv Ani 2.5 mg·kg<sup>-1</sup>, 吸气相关神经元放电节律明显加快. 5 min 达峰值. 由给药前 48 ± 4 volley·min<sup>-1</sup> 加快至 57 ± 5 volley·min<sup>-1</sup>,  $P < 0.05$ . 兔( $n=12$ )背部表面贴敷 Ani 0.2 mg·kg<sup>-1</sup>, 吸气相关神经元放电节律也同样明显加快, 1 min 达峰值, 放电节率由给药前 50 ± 3 volley·min<sup>-1</sup> 加快至 56 ± 4 volley·min<sup>-1</sup>,  $P < 0.05$ . 随着吸气相关神经元放电节率加快, PND 节率也明显同步加快 (Fig 2).

**Oxo 对抗樟柳碱加快 PND 节率的作用**

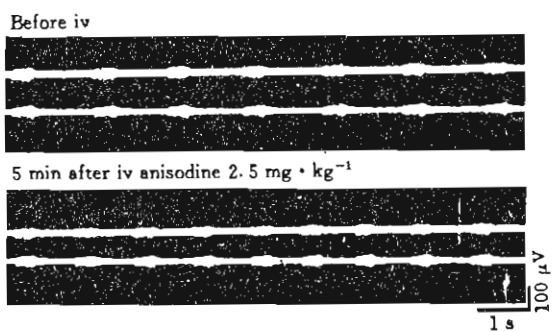


Fig 2. Effect of anisidine on rate of inspiratory neurone firing (upper tracing) and phrenic nerve discharges (lower tracing) in the region of nucleus tractus solitarius in tubocurine-pretreated rabbits.

大鼠( $n=10$ ) iv Ani 后, PND 节率明显加快, 至 5 min 达峰值, 由给药前 105 ± 15 volley·min<sup>-1</sup> 加快至 140 ± 31 volley·min<sup>-1</sup>,  $P < 0.01$ . 此时 iv Oxo, PND 节率即明显减慢, 并可恢复到给 Ani 前水平. 给 Oxo 后 1, 3, 5, 10 min PND 节率分别为 108 ± 14, 108 ± 12, 108 ± 14, 109 ± 28 volley·min<sup>-1</sup>, 与给 Ani 后 5 min 相比  $P < 0.01$ . 其中一例给 Oxo 后, PND 节率明显减慢, 9 min 后 PND 节率又突然增快, 并出现震颤及竖毛症状.

**Ani 和 Sco 对抗 Mor 呼吸抑制作用** 大鼠( $n=8$ ) iv Mor 1.25 mg·kg<sup>-1</sup>, PND 节率明

显减慢, 至 5 min 达最慢, 由给药前  $9.9 \pm 9$  volley  $\cdot$  min<sup>-1</sup> 降至  $76 \pm 8$  volley  $\cdot$  min<sup>-1</sup>,  $P < 0.01$ , 至 45 min 恢复到给药前水平。

大鼠 iv Mor 1.25 mg  $\cdot$  kg<sup>-1</sup> 后, PND 节率明显减慢, 由给 Mor 前  $107 \pm 5$  volley  $\cdot$  min<sup>-1</sup> 减慢至  $84 \pm 3$  volley  $\cdot$  min<sup>-1</sup>,  $P < 0.01$ 。随着 PND 节率减慢, 吸气与呼气时程延长, PND 脉冲数增加。给 Mor 后 10 min, iv Ani 2.5 mg  $\cdot$  kg<sup>-1</sup>, PND 节率即明显转快, 由给 Mor 后 10 min 的  $84 \pm 3$  volley  $\cdot$  min<sup>-1</sup> 加快至  $96 \pm 4$  volley  $\cdot$  min<sup>-1</sup>,  $P < 0.01$ 。随着 PND 节率转快, 吸气与呼气时程又明显缩短, PND 脉冲数也明显减少, 但 PND 节率, 吸气与呼气时程, PND 脉冲数均未恢复到给 Mor 前水平 (Tab 2)。

大鼠 iv Mor 1.25 mg  $\cdot$  kg<sup>-1</sup> 后, PND 节率明显减慢, 由给 Mor 前  $110 \pm 11$  volley  $\cdot$  min<sup>-1</sup> 减慢至  $73 \pm 3$  volley  $\cdot$  min<sup>-1</sup>,  $P < 0.01$ 。随着 PND 节率减慢, 吸气与呼气时程延长, PND 脉冲数增加。给 Mor 后 10 min, iv Sco 0.25 mg  $\cdot$  kg<sup>-1</sup>, 此后, PND 节率明显转快, 由给 Mor 后 10 min 的  $73 \pm 3$  volley  $\cdot$  min<sup>-1</sup> 加快至  $83 \pm 4$  volley  $\cdot$  min<sup>-1</sup>,  $P < 0.01$ 。随着 PND 节律转快, 吸气与呼气时程又明显缩短, PND 脉冲数也减少, 但 PND 节率, 吸气与呼气时程, PND 脉冲数均未恢复到给 Mor 前水平 (Tab 2)。

DISCUSSION

本文结果表明, Ani 及 Sco 加快大鼠和兔 PND 节率, 缩短吸气与呼气时程, Ani 加快约束核区吸气相关神经元放电节率, Oxo 拮抗 Ani 加快 PND 节率的作用, 据此提示, 至少在本文所用剂量范围内, Ani 对呼吸中枢的作用主要为其选择性作用于胆碱能神经系统 M-通路的结果。这与前人报道 M 受体阻滞剂对呼吸中枢作用的实验结果基本相符<sup>[6,7,8]</sup>。吸气与呼气时程缩短, PND 节率加快, 说明呼气向吸气转换速度加快。Ani 和 Sco 具有上述作用, 而且还能对抗 Mor 减慢 PND 节率作用, 因此, 就呼吸中枢兴奋性指标 PND 节率, 吸气和呼气时程来说, Ani 和 Sco 对呼吸中枢有兴奋作用。当然, 对于其它呼吸中枢兴奋性指标潮气量, PND 幅度也应进行综合研究。至于本实验中, 自然通气兔比人工通气兔对 Ani 敏感, 此乃二者生理状态有别所致<sup>[9]</sup>。

综合本文及前人有关资料, 可以认为, 中枢 M 胆碱能系统的正常功能是呼吸调节的必需条件, 然而其确切的调节机制仍要大量实验来阐明。Ani 及 Sco 均能对抗 Mor 减慢膈神经放电节率作用, 提示在呼吸调节机制中, 胆碱能系统与阿片受体间可能存在着一定神经功能联系与相互作用, 值得探索。

Tab2. Effect of Ani and Sco on respiratory inhibition induced by morphine in rats,  $n = 8$ ,  $\bar{x} \pm s$ . <sup>a</sup> $P < 0.05$ , <sup>c</sup> $P < 0.01$  vs control. <sup>d</sup> $P > 0.05$ , <sup>e</sup> $P < 0.05$ , <sup>f</sup> $P < 0.01$  vs 10 min.

	0 min	10 min	12 min	0 min	10 min	12 min
	Control	iv Mor	iv Ani	Control	iv Mor	iv Sco
Rate of PND, volley $\cdot$ min <sup>-1</sup>	$107 \pm 5$	$84 \pm 3^c$	$96 \pm 4^f$	$110 \pm 11$	$73 \pm 3^c$	$83 \pm 1^f$
Time of inspiration, 30 ms	$8.6 \pm 0.4$	$11.1 \pm 0.6^c$	$9.9 \pm 0.7^e$	$11.4 \pm 0.8$	$13.5 \pm 1.5^b$	$12.1 \pm 1.3^d$
Time of expiration, 30 ms	$13.0 \pm 0.4$	$16.0 \pm 0.7^c$	$14.5 \pm 0.5^e$	$14.0 \pm 0.5$	$17.5 \pm 0.8^c$	$15.9 \pm 0.7^e$
Spikes in PND, number/volley	$34 \pm 3$	$49 \pm 3^c$	$40 \pm 3^e$	$58 \pm 3$	$65 \pm 3^b$	$59 \pm 3^e$

Phrenic nerve discharge (PND).

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BIBL.ID: ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1994 Mar; 15 (2); 169-172

槲寄生黄酮甙对心脏快反应动作电位的效应

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Effects of *Viscum coloratum* flavonoids on fast response action potentials of hearts

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**ABSTRACT** The effects of the total flavonoids of *Viscum coloratum* (VCF) on the fast response action potentials (FAP) of canine Purkinje fibers and guinea pig ventricular papillary muscles were studied by glass-microelectrode technique. The effects of VCF on the

ionic currents through cellular membrane were analysed with selective ion blockers (CsCl, verapamil, and TEA<sup>+</sup>), respectively. VCF (100 μg · ml<sup>-1</sup>) accelerated the repolarization of FAP and increased ΔERP/ΔAPI ratio, which were related to decreasing I<sub>Na</sub> and increasing I<sub>x</sub>. It was suggested that the anti-tachyarrhythmic mechanism of VCF was attributed to prolonging ERP relatively and to abolishing reentrant excitation.

**KEY WORDS** *Viscum coloratum*; flavones; anti-arrhythmia agents; action potentials

**摘要** 用玻璃微电极术观察 VCF 对狗心脏浦氏细胞和豚鼠心室乳头状肌细胞快反应动作电位 (FAP) 的影响; 并利用选择性膜通道阻滞剂初步分析 VCF 对 FAP 各相跨膜离子流的影响。100 μg · ml<sup>-1</sup> VCF 加速 FAP 复极进程, 使

Received 1992-01-30 Accepted 1993-04-24  
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