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Contractile effect of 6β-acetoxy nortropane on human and guinea pig airways

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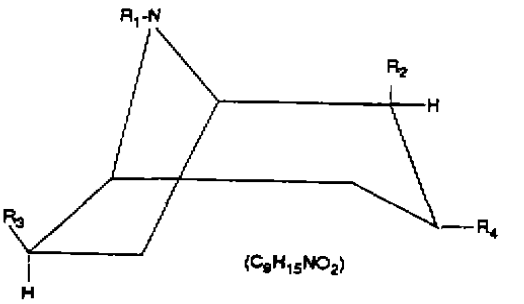
KEY WORDS bronchi; trachea; acetylcholine; nortropanes; muscarinic receptors; inositol phosphates; isoproterenol

AIM: To study the effects of 6β-acetoxy nortropane (6β-AN) on the isolated human bronchus and guinea pig trachea. **METHODS:** The contractile effect of 6β-AN was studied with 4 different muscarinic receptor antagonists on airway strips and inositol phosphates (IP) accumulation in human bronchi was determined by HPLC with radioactivity flow detector. **RESULTS:** (1) The maximal contractile effect of 6β-AN was lower than that of acetylcholine (ACh) on the human bronchus and equal to that of ACh on the guinea pig trachea. 6β-AN was more potent than ACh on both preparations (68 and 245 times, respectively). (2) The contractile effect of 6β-AN was inhibited by atropine (1 – 100 nmol·L^{-1}) or para-fluoro-hexahydro-siladifenidol (0.01 – 1 μmol·L^{-1}), but not by methoctramine (Met, 0.3 – 3 μmol·L^{-1}) or pirenzepine (0.01 – 0.1 μmol·L^{-1}), and was not enhanced by tacrine (0.1 – 10 μmol·L^{-1}) or by epithelium removal. (3) The 6β-AN induced-contraction was accompanied by an increase of IP levels in isolated human bronchial tissues. (4) 6β-AN had an inhibitory effect on isoprenaline (Iso)-induced relaxation, which was abolished or reduced by Met 0.3 μmol·L^{-1}. **CONCLUSION:** 6β-AN exerts a potent contractile effect involving muscarinic M_3 receptor stimulation on airway smooth muscle. Muscarinic M_2 receptor stimulation is furthermore partially involved in the antagonism by 6β-AN on the Iso-induced relaxation of the guinea pig trachea.

6β-Acetoxy nortropane (6β-AN) was synthesized according to the structure of the Bao Jia Sou (2β-hydroxy-6β-acetoxy nortropane) isolated in 1979 from a Chinese herb, *Erycibe Obtusifolia Benth*, traditionally used for the treatment of arthralgia or fever[1,2]. Structurally, 6β-AN belongs to the cholinergic tropane family close to atropine (Atr)[1,2]. 6β-AN, a muscarinic receptor agonist in various tissues, induces bradycardia, contraction of the ileal longitudinal smooth muscle in rats, and myosis in rabbits. These effects of 6β-AN are inhibited by Atr[2]. Besides muscarinic M_3 receptors, muscarinic M_2 receptors are present in great amounts in the bronchial smooth muscle[3,4]. The contraction of smooth muscle induced by the



6β-Acetoxy nortropane

	$-R_1$	$-R_2$	$-R_3$	$-R_4$
Tropane	$-CH_3$	$-H$	$-H$	$-H$
Nortropane	$-H$	$-H$	$-H$	$-H$
2β-Hydroxy-6β-acetoxy-nortropane	$-H$	$-OH$	$-OOC-CH_3$	$-H$
6β-Acetoxy-nortropane	$-H$	$-H$	$-OOC-CH_3$	$-H$
Atropine	$-CH$	$-H$	$-H$	$-O-C(=O)-CH(CH_2OH)-C_6C_5$

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stimulation of muscarinic M_3 receptors is linked to inositol phosphate (IP) production[5,6], whereas muscarinic M_2 receptor stimulation produces an inhibition of adenylyl cyclase activity through a G_i protein[6] and can therefore inhibit isoprenaline (Iso) action[3,7,8]. This inhibitory effect on stimulation of muscarinic M_2 receptors has however not been observed on the guinea pig trachea[9], human bronchi[4] or on bovine trachea[10].

The present work was to study the contractile effect of 6β-AN and muscarinic receptors involved in the contraction on the isolated human bronchus and guinea pig trachea as well as the relationship between the contractile effect of 6β-AN and the production of IP on the human bronchi. The role of airway epithelium was also studied, since the epithelium appeared to act as a diffusion barrier or release a relaxant factor (EpDRF), or might play a metabolic role[11].

MATERIALS AND METHODS

Drugs 6β-AN was synthesized by Shanghai Second Medical University (Shanghai, China); acetylcholine HCl (ACh, Pharmacie Centrale des hôpitaux, Paris, France); atropine (Atr), isoprenaline (Iso), and tacrine (Tac) (Sigma); pirenzepine (Pir), methoctramine (Met), and para-fluoro-hexahydro-sila-difenidol (p-F-HHSiD) (RBI, Bioblock Scientific, Illkrick, France). Theophylline sodium anisate (Theo) was used as the proprietary injectable solution (theophylline Bruneau, Promidel, Courbevoie, France). All agents were dissolved in distilled water and diluted with Krebs' solution. Myo-[2-^{3}H] inositol with PT6-271 (specific radioactivity, 370 – 740 TBq·mol^{-1}) was purchased from Amersham International (Amersham, Buckinghamshire, UK).

Tissue preparation Guinea pig trachea and human bronchial tissues were obtained and prepared[8]. Each set of guinea pig or human airway rings were suspended under an initial force of 2 g in Krebs' solution, bubbled with 95 % O_2 ± 5 % CO_2 and maintained at 37 ℃. Changes in force of contraction were measured isometrically with Pioden UF-1 strain gauges (PHYMEP, Paris, France) and amplifiers (EMKA, Paris, France) and displayed on a recorder Linseis L65514 (PHEBUS, Paris, France). After 1-h equilibration with washing every 15 min, the resting load was between 2 and 2.5 g. Under these conditions, the responses obtained were reproducible

Protocol Each experiment began by contracting the airway strips with or without epithelium to maximal tension with ACh 3 mmol·L^{-1}, then, maximal relaxation was induced by Theo 3 mmol·L^{-1}. A 1-h rest period was observed with washing every 15 min before the beginning of the experimental procedure. Thereafter, cumulative concentration-response curves to ACh or 6β-AN were constructed by applying increasing concentrations of drugs at 5 – 15-min intervals in logarithmic increments. Only one concentration-response curve with 6β-AN or ACh was recorded in each ring. In a separate set of experiments, Atr (1 – 100 nmol·L^{-1}), Pir (0.01 – 1 μmol·L^{-1}), Met (0.3 – 3 μmol·L^{-1}), p-F-HHSiD (0.01 – 1 μmol·L^{-1}), Tac (0.1 – 10 μmol·L^{-1}) or 6β-AN (0.1 – 10 nmol·L^{-1}) were added to the bath 30 min before the addition of 6β-AN and/or ACh. An involvement of muscarinic M_2 receptor stimulation was investigated by studing 6β-AN-Iso interaction on the guinea pig trachea. The effect of 6β-AN on the IP accumulation was evaluted at concentrations similar to those used for functional studies in order to establish a relationship between phosphoinositide metabolism and functional responses in the human bronchus smooth muscle strips.

IP determination The human bronchi were cut into fragments with a minimum of cartilaginous tissue and were washed in Krebs' solution. They were then incubated in 15 – 25 mL Krebs' solution containing myo-[^{3}H] inositol 74 MBq·L^{-1} buffer at 37 ℃ for 4 h. After this incubation, the tissue was washed twice with 45 mL Krebs' solution. Aliquots of washed tissue (1 – 2 g) were placed in 1 mL Krebs' solution containing LiCl 10 mmol·L^{-1} and incubated at 37 ℃ for 30 min. During the stimulation with ACh or 6β-AN, LiCl was present to enhance the accumulation of IP by blocking the breakdown of inositol monophosphate to inositol. The samples were stimulated with 20 μL buffer (control), ACh (10 nmol·L^{-1} – 3 mmol·L^{-1}) or 6β-AN (10 nmol·L^{-1} – 0.1 mmol·L^{-1}) at 37 ℃ for 5 min. Stimulation was stopped by the addition of

3 mL chloroform: methanol: HCl (100:200:4) 10 mol·L^{-1} with vigorous shaking and the tissues placed in a cold water bath (4 ℃) were crushed with an Ultraturax, (Bioblock, Illkirch, France). The samples were centrifuged at 1000 × g at 4 ℃ for 10 min. The aqueous phases were brought to pH 4 with 50 μL of ammonium formate 1.2 mol·L^{-1} and stocked at −80 ℃ until analysis. Separation of IP was performed[12].

Data analysis Contractile responses and IP accumulations were expressed as % of the maximal response to ACh 3 mmol·L^{-1}. Relaxatant effects of Iso were expressed as % of the relaxation obtained with Theo 3 mmol·L^{-1}, added at the end of each experiment. The data were expressed in terms of pD_2 for potency and E_{max} for efficacy. pD_2 values were derived graphically from the lg concentration-response curves and defined as the negative lg of 6β-AN or ACh concentration that caused 50 % of its maximal effect. Iso pD_2 was defined as the negative lg of the concentration of Iso which induced a relaxation equal to 50 % of its own maximal effect. The maximal effect (E_{max}) was calculated as the maximal increase in tone induced by 6β-AN and expressed as a % of the maximal tension induced by ACh 3 mmol·L^{-1}. Antagonism with Atr was analyzed[13]. Data were expressed as $\bar{x} \pm s$, and compared with paired or unpaired t test.

RESULTS

Contractile effects of 6β-AN on the isolated human bronchus and guinea pig trachea 6β-AN induced a concentration-dependent contraction of the human isolated bronchus with a pD_2 value of 7.48 ± 0.09 and an E_{max} 85 % ± 3 % (% *vs* ACh 3 mmol·L^{-1}, n = 15). 6β-AN was 68 times more potent but less effective than ACh. On the isolated guinea pig trachea, 6β-AN was as efficent as ACh and 245 times more potent than ACh (Tab 1).

Influence of Tac on 6β-AN- or ACh-induced contraction of smooth muscle of human or guinea pig airway On both preparations, the cholinesterase inhibitor Tac (0.1 − 10 μmol·L^{-1}) did not modify 6β-AN-induced contraction, but potentiated ACh-induced contraction by increasing pD_2 values (Tab 1).

Influence of epithelium removal on contractile activity of 6β-AN and ACh The 6β-AN-induced contraction was not modified by epithelium removal in the isolated human and guinea pig airways. In contrast, epithelium removal enhanced the ACh-induced contraction on the smooth muscle in both preparations by increasing pD_2 values (Tab 1).

Effect of Atr, Pir, Met, and p-F-HHSiD on 6β-AN contraction responses Atr 1 − 100 nmol·L^{-1} concentration-dependently inhibited the 6β-AN-induced contraction on the isolated human bronchus (Fig 1A) and guinea pig trachea (Fig 1B). The pA_2 values of Atr were 9.03 ± 0.11 (n = 4) on the human bronchus and 8.80 ± 0.24 (n = 6) on the guinea

Tab 1. E_{max} **and pD_2 values of 6β-acetoxy nortropane and acetylcholine in the absence (control) and presence of tacrine, and with (intact) or without (removed) epithelium on the isolated human bronchus and the guinea pig trachea.** n **= number of human lungs or guinea pigs.** $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* control.

	Human bronchus						Guinea pig trachea					
	6β-acetoxy nortropane			acetylcholine			6β-acetoxy nortropane			acetylcholine		
	n	pD_2 − lg mol·L^{-1}	E_{max} %	n	pD_2 − lg mol·L^{-1}	E_{max} %	n	pD_2 − lg mol·L^{-1}	E_{max} %	n	pD_2 − lg mol·L^{-1}	E_{max} %
Control	15	7.5 ± 0.4	85 ± 11	15	5.65 ± 0.46	100	13	7.4 ± 0.6	99 ± 3	12	5.0 ± 1.3	100
Tacrine/μmol·L^{-1}												
0.1	4	7.2 ± 0.9	89 ± 2	4	6.2 ± 0.3^c	85 ± 14^b	8	7.2 ± 0.5	98 ± 2	8	5.8 ± 0.6^c	96 ± 4
1	7	7.6 ± 0.3	85 ± 7	9	6.9 ± 0.4^c	88 ± 7^c	8	7.2 ± 0.9	100	8	6.5 ± 1.3^c	95 ± 7
10	4	7.6 ± 0.3	85 ± 10	7	7.2 ± 0.4^c	86 ± 8^c	8	7.2 ± 0.6	97 ± 9	8	6.5 ± 1.1^c	98 ± 10
Epithelium												
intact	5	7.46 ± 0.29	82 ± 17	5	5.90 ± 0.29	100	8	7.4 ± 0.9	100	8	4.9 ± 0.7	100
removed	4	7.5 ± 0.3	77 ± 9	4	6.1 ± 0.4^c	96 ± 4	8	7.4 ± 0.8	99 ± 2	8	5.8 ± 0.8^c	97 ± 2

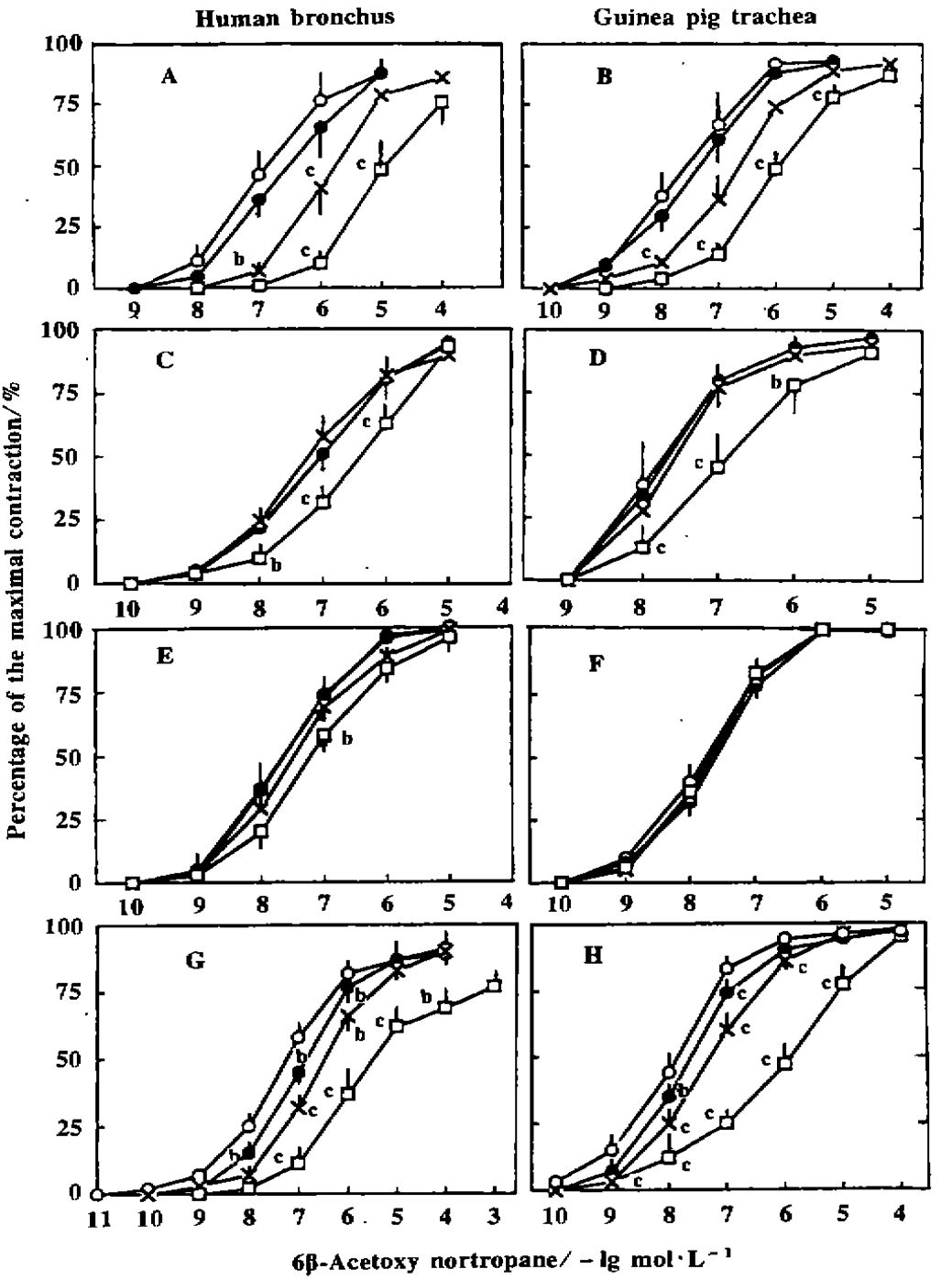

Fig 1. Inhibitory effects of atropine (A, B, ○ control, ● 1, × 10, □ 100 nmol·L^{-1}), pirenzepine (C, D, ○ control, ● 0.01, × 0.1, □ 1 μmol·L^{-1}), methoctramine (E, F, ○ control, ● 0.3, × 1, □ 3 μmol·L^{-1}) and para-fluoro-hexahydro-difenidol (G, H, ○ control, ● 0.01, × 0.1, □ 1 μmol·L^{-1}), on the contraction evoked by 6β-AN on the human bronchus and the guinea pig trachea. $n = 4-8$ human lungs or guinea pigs. $\bar{x} \pm s$. $^{b}P < 0.05$, $^{c}P < 0.01$ *vs* control.

pig trachea. Under similar conditions, pA_2 values of Atr on ACh were 9.41 ± 0.22 ($n = 4$) and 8.60 ± 0.22 ($n = 6$), on the human bronchus and the guinea pig trachea, respectively.

Pir, a selective muscarinic M_1 receptor

antagonist, decreased the contraction induced by 6β-AN only at 1 μmol·L^{-1}(Fig 1C, D). Met, a selective muscarinic M_2 receptor antagonist, at 0.3 or 1 μmol·L^{-1}, did not influence the contraction by 6β-AN on the human bronchus (Fig 1E) and the guinea pig trachea (Fig 1F). A small but significant inhibition was observed for Met 3 μmol·L^{-1} on the human bronchus.

p-F-HHSiD (0.01 – 1 μmol·L^{-1}), a selective muscarinic M_3 receptor antagonist, significantly inhibited the contration of isolated airways (Fig 1G, H). The pA_2 values of p-F-HHSiD on 6β-AN were 7.74 ± 0.08 (n = 8) with a slope of 0.99 ± 0.09 on the human bronchus and 7.80 ± 0.12 (n = 6) with a slope of 1.03 ± 0.07 on the guinea pig trachea, respectively. The antagonism appeared to be the competitive type.

Influence of 6β-AN on ACh-induced contraction 6β-AN did not modify the concentration-response curves for ACh in the guinea pig trachea (Fig 2).

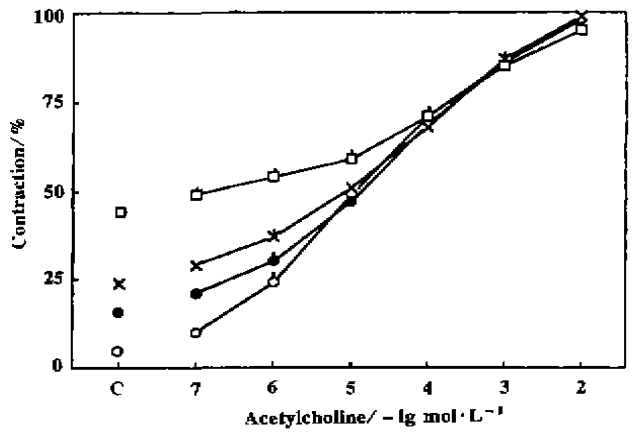

Fig 2. Influence of 6β-AN (● 0.1, × 2, □ 10 nmol·L^{-1}) on the ACh concentration-response curves (○ control) on the guinea pig trachea. c = control before addition of ACh. n = 6 guinea pigs, $\bar{x} \pm s$.

Influence of 6β-AN and ACh on IP accumulation in human bronchus Incubation of bronchial fragment with 6β-AN 10 nmol·L^{-1} – 0.1 mmol·L^{-1} for 5 min induced a concentration-dependent increase of total IP with EC_{50} value (95 % confidence limits) 8 (6 – 14) μmol·L^{-1} and an E_{max} 76 % ± 3 % (% *vs* ACh 1 mmol·L^{-1}). Under similar conditions, EC_{50} of ACh was 63 (45 – 91) μmol·L^{-1} and E_{max} 100 % (Fig 3).

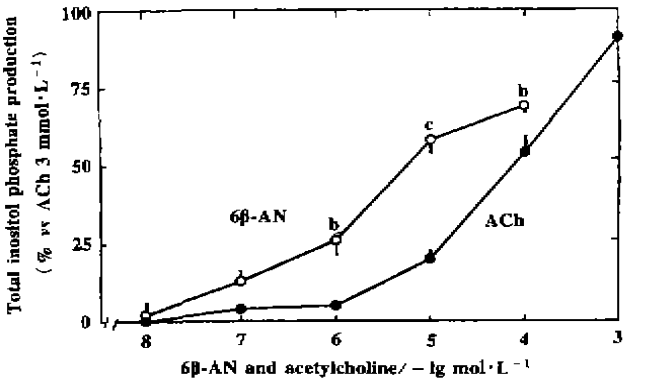

Fig 3. Total [^{3}H]inositol phosphates accumulation of human bronchial tissues induced by 6β-AN 10 nmol·L^{-1} – 0.1 mmol·L^{-1} and ACh 10 nmol·L^{-1} – 1 mmol·L^{-1}. n = 4 – 6 human lungs, $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* ACh.

Effect of 6β-AN on the Iso-induced relaxation in the guinea pig trachea Iso-induced relaxation of the guinea pig trachea was concentration-dependently inhibited by 6β-AN (2, 10, or 100 nmol·L^{-1}) with a maximum shift of 17-fold with 6β-AN 10 μmol·L^{-1} (Fig 4A, C). The inhibition of Iso-induced relaxation by 6β-AN was markedly reduced in the presence of Met 0.3 μmol·L^{-1}(Fig 4B, D).

There was no significant effect of Met 0.3 μmol·L^{-1} on the basal tone or on the magnitude of tension induced by 6β-AN prior to performing concentration-response curves for Iso (Fig 4A, B).

DISCUSSION

6β-AN induced a concentration-dependent contraction of smooth muscle of human or guinea pig airways, *in vitro*. 6β-AN is a very potent agonist, 68 and 245 times more potent than ACh on the isolated human bronchus and guinea pig trachea, respectively. In addition, the efficacy of 6β-AN was very similar to that of ACh in both preparations, showing that 6β-AN is a full agonist, at least on guinea pig trachea.

Our studies show that 6β-AN is a cholinergic agonist since its action was inhibited by Atr. Morever, 6β-AN contracted airway smooth muscle through stimulating muscarinic M_3 receptors since its effect was inhibited by p-F-HHSiD, a muscarinic M_3 receptor antagonist, but not by Met, a muscarinic M_2 receptor antagonist or by

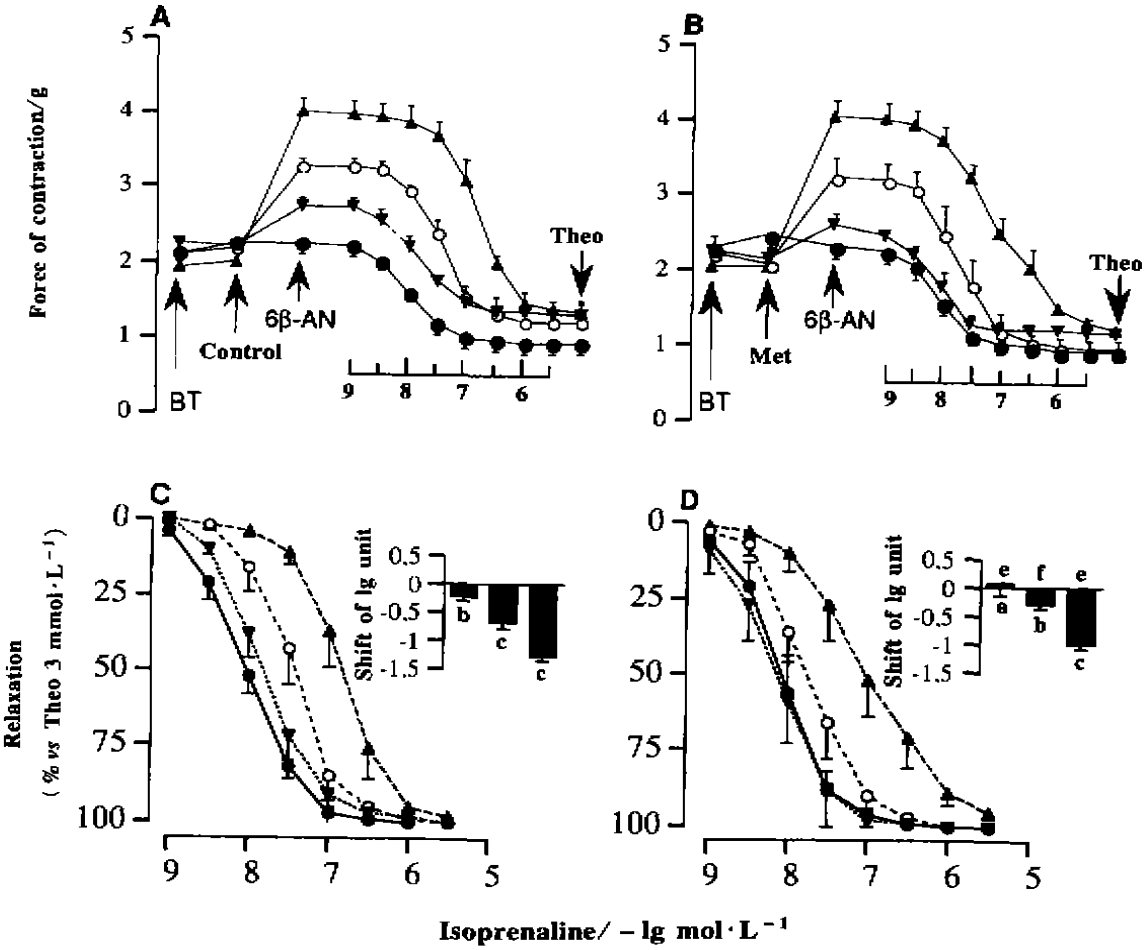

Fig 4. Relaxation of the guinea pig trachea induced by isoprenaline at basal tone (●) or following contraction induced by increasing concentration of 6β-AN (▲ 2, ○ 10, ▲ 100 nmol·L^{-1}) in the absence (A, C) or in the presence (B, D) of methoctramine 0.3 μmol·L^{-1}. Results are expressed as relaxation *vs* theophylline 3 mmol·L^{-1} (C, D) or as force of contraction (g) (A, B). In the inset, are represented the shifts to the right of the concentration-response curves for isoprenaline induced by the 3 different concentrations of 6β-AN (2, 10, 100 nmol·L^{-1}) and determined at 50 % of relaxation. BT = basal tone, Met = methoctramine, Theo = theophylline. $n = 6$ guinea pigs, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control. $^eP < 0.05$, $^fP < 0.01$ *vs* in the absence of Met.

Pir except in concentrations where Pir is no longer specific for muscarinic M_1[14]. This result was confirmed by increasing IP production induced by 6β-AN.

Our results demonstrated that the effects of ACh were significantly potentiated by epithelium removal[15], and that, contrast to ACh, 6β-AN appeared in human bronchi as well as in the guinea pig trachea independent of cholinesterases, since the effects of 6β-AN were not potentiated by tacrine, an inhibitor of cholinesterases. Taking the 2 first hypothesis into account (see introduction), our results suggest that the diffusion of 6β-AN in the lung tissues seem to be better than that of ACh, and that 6β-AN do not participate in the release of the epithelial relaxant factor.

6β-AN induced a concentration-dependent inhibitory effect on Iso by progressively shifting to the right the concentration-response curves of this compound. Met 0.3 μmol·L^{-1}, which did not affect the contractile effect of 6β-AN (that is to say supposed M_2 selective), abolished or significantly reduced the 6β-AN inhibitory effect. This suggests that besides its muscarinic M_3 agonistic effect, 6β-AN has muscarinic M_2 receptor agonistic effect on airways. Met did not completely reduce the 6β-AN-induced functional antagonism, which was compatible with the

participation of muscarinic M_3 receptors in the functional antagonism. Indeed, it has been shown that the increase of IP synthesis, in particular inositol triphosphates, on the one hand, and diacylglycerol, on the other hand, induces phosphorylation of the β-adrenoceptor and participates in the inhibition, by cholinergic agonists, of adrenoceptor agonistic effects[5].

To conclude, 6β-AN exerts a very potent cholinergic activity on airway smooth muscle. 6β-AN-induced contractile response was mediated mainly by stimulating muscarinic M_3 receptors and increasing the IP synthesis. 6β-AN exerts an agonistic effect on muscarinic M_2 receptors, revealed by the functional antagonism to Iso.

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6β-乙酰氧基去甲托烷对人和豚鼠呼吸道的收缩作用

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关键词 支气管; 气管; 乙酰胆碱; 去甲托烷; 毒蕈碱受体; 肌醇磷酸类; 异丙肾上腺素

目的: 研究 6β-乙酰氧基去甲托烷(6β-AN)对支气管平滑肌的收缩作用. **方法**: 不同 M-R 拮抗剂对 6β-AN 作用的影响; HPLC 法测定 6β-AN 对支气管平滑肌细胞内磷酸肌醇(IP)的影响; 通过 6β-AN 对异丙肾上腺素(Iso)功能拮抗模型, 观察 6β-AN 对 M_2-R 的作用. **结果**: (1) 6β-AN 对人及豚鼠气管的收缩强度大于 ACh, 分别为 68 和 245 倍; (2) 阿托品 (M_1 – M_3) 和 para-fluoro-hexahydro-siladifenidol (M_3)抑制 6β-AN 的作用; (3) 6β-AN 引起平滑肌细胞内 IP 浓度升高; (4) 6β-AN 对 Iso 的功能性拮抗作用, 在 methoctramine (M_2) 0.3 μmol·L^{-1}时减弱或消失. **结论**: 6β-AN 通过激活 M_3-R 引起支气管平滑肌收缩; 其对 Iso 的功能拮抗, 部分是激活 M_2-R 所致.