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PURIFIED MACROPHAGE MUCUS SECRETAGOGUE IS A POTENT BRONCHIAL SMOOTH MUSCLE RELAXING AGENT IN VITRO. E. N. Schachter, E. Zuskin, Z. Maron, S. Goswami, E. Gollub, N. Rienzi, and S. Maayani. Mount Sinai Medical Center, CUNY, New York, N.Y.

We have previously shown that macrophage mucus secretagogue (MMS) a peptide synthesized by alveolar macrophages acts not only as a potent secretagogue of airway mucus but also has the capacity of relaxing airway smooth muscle (ASM) in the guinea pig and in man (ARRD 133:A211,1986). We have recently described a 68Kd protein obtained from human pulmonary macrophages which possesses enhanced secretagogue activity (ARRD 141:A646,1990). We speculate that this molecule may be a precursor for the previously described 2Kd, MMS (J Exper Med 159:844-860, 1984). The smooth muscle relaxing potential of this 68Kd protein (MMS68) was assayed using guinea pig tracheal (GPT) rings suspended in a series of 12 organ baths containing Kreb's Hansielett solution at 37°C and pH7.4. Each GPT ring was divided into 4 segments so that each animal served as its own control for the drugs studied. The segments were suspended at 2 grams of baseline tension and relaxation measured as a percent of this baseline tension. Dose response characteristics were assayed using a stock solution of 1 mg/ml of MMS68 (diluted to 10^{-2} mg/ml) delivered in the following concentrations: 5,15,50, 150, 500 ng/ml in the bath. The dose response curve generated had the following response parameters: Emax=55.5 ± 2.0% (expressed as a percent of the baseline tension = 2 gm) EC50=165 ± 16 ng, slope = 1.3 ± 0.1. Contraction of GPT with carbachol (10^{-5}M) (C) and histamine (10^{-6}M) (H) did not prevent subsequent MMS 68 relaxation of the tissue. Removal of airway epithelium did not alter the response parameters. Pretreatment of the ASM with Indomethacin (I) at a concentrations of 10^{-6}M, did not alter MMS68 induced relaxation. We suggest that MMS68 exerts a potent bronchial relaxing effect on both baseline and H and C contracted GPT and that this effect is not mediated by prostaglandin synthesis inhibition.

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INTERACTION BETWEEN ATRIAL NATRIURETIC FACTOR (ANF) AND PARASYMPATHETIC NERVOUS SYSTEM IN THE LUNG. A. Robichaud°*, C. Saunier†, M. C. Michoud* and P. du Souich°*. °*Dépt. de pharmacologie, *Hôtel-Dieu de Montréal, Fac. de médecine, Université de Montréal, Québec, Canada, †INSERM U14, Vandoeuvre-les-Nancy, France.*

Recent studies have demonstrated the presence of ANF in the parasympathetic and sympathetic ganglia suggesting that this peptide could act as a neuromodulator. The aim of the present work was to establish whether an interaction between ANF and the parasympathetic nervous system is present during bronchoconstriction in anesthetized rabbits. Four groups of 5 animals were studied : SHAM (receiving the diluent only), AT (pretreated with atropine 0.5 mg/kg i.v. and receiving the diluent), ANF (infused with ANF 80 ng/min/kg i.v.) and AT-ANF (pretreated with atropine 0.5 mg/kg i.v. and receiving ANF 80 ng/min/kg i.v.). Following 75 min. of ANF infusion, bronchoconstriction was induced by the inhalation of histamine and respiratory resistance (Rrs) measured prior to and 3, 5, 10, 15 and 20 min. post-histamine challenge. The results show that plasma ANF increased from 134 ± 34 to 1312 ± 154 pg/mL (X ± SE) in the groups ANF and AT-ANF ($p<0.05$) and remained unchanged in SHAM and AT. Following histamine inhalation, Rrs increased from 17 ± 1 to 42 ± 2 cm $H_2O.L^{-1}.s$ ($p<0.001$) in the SHAM group; an increase of similar magnitude was observed in AT. In the ANF group, Rrs was 51 ± 6 cm $H_2O.L^{-1}.s$ following histamine inhalation, while in the AT-ANF group, Rrs was 30 ± 2 cm $H_2O.L^{-1}.s$. ($p< 0.05$). These data suggest that an increase in plasma ANF induces the release of acetylcholine. *This work was supported by grants from MRC and Hôtel-Dieu Foundations. A. R. is the receipient of a studentship from MRC.*

PROTEASE INHIBITORS POTENTIATE RELAXATION EVOKED BY ATRIAL NATRIURETIC PEPTIDE IN BOVINE AND HUMAN BRONCHI

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We have previously demonstrated that atrial natriuretic peptide (ANP) has a direct, if low potency, relaxant effect on methacholine (MCh)-induced tone in human isolated bronchi (Hulks *et al.*, ARRD, 1991 143:A334). In this present study, this ability of ANP to relax pre-constricted tissues was compared with the effect of pre-incubation with ANP in modulating MCh-induced contraction in both human and bovine bronchial smooth muscle *in vitro*. In addition, the possiblity that the low potency of ANP resulted from its rapid degradation by proteases was examined.

Human or bovine bronchial rings were suspended in Krebs-Henseleit solution at 37°C. Tissues were attached to isometric transducers for measurement of tension. MCh was added in concentrations evoking 25-30% of the maximum response, and the effect of ANP (10^{-6}M) alone, or in the presence of protease inhibitors (phosphoramidon, leupeptin and aprotinin; each 20µg/ml) was examined. Mean percentage inhibition (SEM) of the MCh response was calculated. In addition, cumulative concentration-response curves (CRCs) to MCh were compared in the presence and absence of ANP (10^{-6}M) and of the protease inhibitors. Mean -log EC_{30} values (SEM) were calculated.

	% Inhibition		- log EC_{30}	
	bovine	human	bovine	human
(*p<0.01)	(n=6)	(n=6)	(n=6)	(n=6)
Control	---	---	5.53 (0.09)	6.66 (0.1)
+ANP	7.14 (6.8)	38.09 (1.9)*	5.35 (0.08)	6.28 (0.09)*
+ANP+ Inhibitors	60.2 (7.1)*	70.23 (4.0)*	5.17 (0.08)*	5.06 (0.37)*

In bovine tissue, ANP was low in potency and small, though significant effects were seen only when protease inhibitors were present, regardless of the time of application of ANP. By contrast, in human tissue ANP relaxed pre-constricted bronchi as well as evoking a rightward shift of the CRC to MCh. Both these effects of ANP were significantly enhanced by the presence of protease inhibitors. We conclude that in human tissue, ANP confers protection against MCh-induced contraction and that airway proteases modulate the bronchodilator effects of ANP.

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EFFECT OF INHALED FUROSEMIDE AND TORASEMIDE ON BRONCHIAL RESPONSE TO ULTRASONICALLY NEBULIZED DISTILLED WATER (UNDW) IN ASTHMATIC SUBJECTS. A.Foresi, A.Pelucchi, B.Mastropasqua, G.Cavigioli, R.M.Carlesi, M.Sale, L.Marazzini. Serv. di Fisiopatologia Respiratoria "G.Campari", Sesto San Giovanni, Milano, I.

Inhaled furosemide (F) has been shown to reduce the bronchoconstriction induced by UNDW. Since this effect could be due to the inhibition of the $Na^+/2Cl^-/K^+$ cotransport system of bronchial epithelium, we have compared the protective effect of inhaled F with inhaled torasemide (T), a new and more potent loop diuretic, on UNDW-induced bronchoconstriction in a group of 12 asthmatics(age range 19-52 yr,6F). PC20FEV1 methacholine ranged between .36-1.77 umol. UNDW challenge was performed with 5 increasing volume outputs of UNDW (from 0.5 to 5.2 ml/min) and the bronchial response expressed as the provocative output causing a 20% fall in FEV1(PO20 UNDW). On different days,each subject inhaled an equal dose(28 mg) of F and T following a randomized, double-blind,placebo controlled design,5 minutes prior to UNDW challenge.Neither F or T had a significant effect on resting lung function. PO20UNDW measured before and after the study days was highly reproducible (intra class correlation c.:0.92).The GMean PO20UNDW measured after placebo was 1.73 ml/min(range 0.64-5.13). This was significantly lower than that recorded after F(4.25 ml/min:range 2.45->5.2;p<.025),but not after T(3.05 ml/min:range 1.19->5.2;p=0.07).Inhaled F totally blocked bronchial response to UNDW in 5 subjects. In 2 of these 5 subjects the response was also blocked by T.A remarkable increase in diuresis was noted only after T in most subjects.We conclude that inhaled F has a greater protective effect than T against UNDW.However,the effect of F is variable, with some asthmatics showing no change in the bronchial response to UNDW. The minor effect of T suggests that,in spite of their mechanisms of action, the protective effect could be dependent on the pharmacokinetic of inhaled diuretics.

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ABSTRACTS

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