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INTERACTION OF LEUKOTRIENE D_4 AND SUPEROXIDE ANION INDUCE AIRWAYS HYPERREACTIVITY. E.B. Weiss, J.R. Bellino. Saint Vincent Hospital, Inc., Worcester, MA

Recent studies from this laboratory indicated that toxic oxygen products generated from SRS-A or synthetic leukotrienes (LT) C_4/D_4 alter calcium homeostasis and induce histamine hyperreactivity in guinea pig trachealis smooth muscle in-vitro (J. All. Clin. Immunol., in press). As superoxide dismutase fully inhibited these alterations, we investigated extracellular superoxide anion (O_2^-) generation in trachealis muscle by superoxide dismutase-inhibitable reduction of ferricytochrome c at 550nm; results are expressed as nM O_2^- for 60 min/muscle creatine phosphokinse units X 10^{-2}. A concentration-response between exogenous, synthetic LTD_4 (10^{-10}M to 10^{-3}M) and O_2^- formation was observed with an EC_{50} of 2.5 X 10^{-8}M; maximum O_2^- release was 15.0 nM for 60 min/CPK unit. LTC_4 was approximately equipotent to LTD_4 in O_2^- release. Trachealis pretreatment with the semiselective LT antagonist FPL 55712 (10^{-5}M) resulted in a competitive inhibition of O_2^- formation by LTD_4, with an EC_{50} of 7.0 X 10^{-6}M. Histamine, acetylcholine and PGF 2 α (10^{-5}M) did not generate any O_2^-. 4 β-phorbol 12 myristate 13 acetate (PMA) (1 to 9 ug/ml) also exhibited a O_2^- generation-concentration response with an EC_{50} of 1.4 ug/ml. Trachealis muscle hyperreactivity to histamine in OmM Ca^{++} induced by LTD_4 10^{-8}M as assayed by isometric tension responses was not induced by exposure to PMA 6 ug/ml. It is concluded that O_2^- is released by LTD_4 in standard in-vitro trachealis ring preparations resulting in hyperreactivity to histamine. This hyperresponse is dependent upon a simultaneous interaction between O_2^- generation and the presence of leukotriene D_4.

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THE MEASUREMENT OF "FREE" SECRETORY PIECE IN SPUTUM.

R. A. Stockley, S. C. Afford and D. Burnett,

The General Hospital, Birmingham, U.K.

Free secretory piece (FSP) was measured immunologically in the sol phase of sputum from 37 patients with chronic obstructive bronchitis (16 during acute respiratory infection) and the results compared with the total secretory piece (SP; both bound to IgA as secretory IgA and that unbound) and 11S IgA content of the same samples.

Free secretory piece was found in every sample but the concentrations were higher in the infected samples (mean value = 115.3, SD $\pm$ 51.5% standard) than the non-infected samples (mean value = 79.5; SD $\pm$ 77.3% standard, $2p<0.01$). There was no correlation between the FSP and SP concentrations in the samples. However, when each sample was standardised for its 11S IgA content, there was a highly significant relationship ($2p<0.001$) between the FSP/11S IgA ratios and SP/11S IgA ratios ($r = 0.933$) suggesting that greater quantities of FSP are found when there is an immunological excess of total SP over 11S IgA. The inverse relationship between FSP and 11S IgA ($r = -0.6$; $2p<0.01$) suggests that the amount of FSP in any sample is partly dependant upon the amount of dimeric IgA present.

Comparisons of the FSP/11S IgA ratios in patients suggests that there may be defects of "local" IgA production whilst systemic production is normal and vice versa. The techniques described offer a method for studying the integrity of the "local" IgA system.

THE EFFECTS OF A VIRAL LARYNGOTRACHEITIS ON THE EPITHELIAL BARRIER OF CHICKEN AIRWAYS.

J.B. Richardson, A. De Notariis, C.C. Ferguson and R.C. Boucher. Department of Pathology, McGill University, Montreal, PQ and the Department of Medicine, Division of Pulmonary Diseases, University of North Carolina, Chapel Hill, NC.

The effects of a virus infection on the barrier function of tracheal epithelium were compared to the effects of a chemical agent (methacholine) which selectively increases membrane permeability and both were compared to controls. The disruption of the airway epithelium induced by the virus infection caused an increased permeation of horseradish peroxidase (HRP) through this barrier. Methacholine enhanced HRP uptake from the airway lumen to the blood as compared to controls. Visualization of HRP in the tracheal epithelium by transmission electron microscopy correlated with the radioimmunoassay measurements in the blood. Serial anti-HRP antibody titers were measured by a competitive binding technique. The antigen permeation induced by methacholine was associated with an enhanced anti-HRP antibody production. The larger increase in antigen permeation seen with the viral infection was associated with depressed anti-HRP titers. It was concluded that viral disruption of the airway epithelial barrier may contribute to an increased uptake of orally inhaled antigens. The relationship, however, between the increased antigen penetration consequent to the viral infection and the development of allergy remains unclear. This work was supported by Grant MA-4536 from the Medical Research Council of Canada. p. 14

PULMONARY FUNCTION PARAMETERS OF ASTHMATIC CHILDREN ON ORAL METAPROTERENOL VERSUS THEOPHYLLINE.

Diane E. Schuller, M.D. and Philip Oppenheimer, M.D., Department of Pediatric Cardiopulmonary, Allergic and Infectious Diseases, Geisinger Medical Center, Danville, Pa.

Oral theophylline (T) is often the first drug of choice for treatment of asthma, but side effects, poor taste and blood level monitoring are disadvantages. To determine if oral metaproterenol (M) has comparable control of pulmonary function parameters, 20 asthmatic children were studied in a randomized, double-blind, crossover protocol. A minimum 2 week titration period for theophylline served as a wash-out period where no beta adrenergic drugs were allowed. Children then received either active M (dose of 10-20 mg based on weight) and placebo T or placebo M and active T on a t.i.d. basis for 4 weeks. Then they received the opposite combination. Pulmonary function testing at baseline, ½, 1, 2, 3, and 4 hours after dosing was done at the end of the 1st and 4th weeks of therapy. Results are below:

	Highest FEV_1				Highest FMF			
	Week 1		Week 4		Week 1		Week 4	
	Peak	Mean	Peak	Mean	Peak	Mean	Peak	Mean
M	10	11	10	8	12	9	9	10
T	7	9	10	12	8	11	11	10

Three cases had identical peak FEV_1 at week 1.

	Total Cases With Comparable or Better Results			
	FEV_1 (Range of 0.1L)		FMF (Range of 0.3L/s)	
	Week 1	Week 4	Week 1	Week 4
M	17	13	16	16
T	15	15	15	17

We conclude that oral metaproterenol has control of pulmonary function parameters in many children comparable to theophylline and may be used as an alternative drug.

INHIBITION OF ANAPHYLAXIS IN AIRWAYS SMOOTH MUSCLE BY THE CALCIUM CHANNEL DRUGS VERAPAMIL AND NIFEDIPINE.

E.B. Weiss and J. Markowicz, Saint Vincent Hospital, Worcester, Massachusetts.

This study examined the effects of specific calcium channel antagonists upon isometric tension during the Schultz-Dale reaction following passive in-vitro sensitization. Guinea pig trachealis smooth muscle rings were equilibrated aerobically under 2 g isometric tension for 90 minutes at 37°C. Trachealis muscle passive sensitization was accomplished with a 1:10 saline dilution of reconstituted rabbit anti-chicken egg albumin antiserum for 90 minutes. Thereafter, immunospecific anaphylaxis (ANA) was induced with 5X recrystallized ova albumin (OA)(100 ug/ml final bath concentration) and isometric tension recorded. For drug protection studies, either Verapamil (V) or Nifedipine (N) was added to sensitized trachealis before OA challenge. Drug reversal studies were performed by addition of V or N at the peak of ANA tension. Controls received Krebs-Henseleit buffer alone. Data are expressed as mean % inhibition of ANA isometric tension at cited final bath drug concentrations. Mean control ANA tension was 1658 mg $\pm$ 198 (SE), (n = 10). Drug pretreatment inhibition of ANA: V = 10 ug/ml, 29.8% $\pm$ 14 (SE); V = 100 ug/ml, 51.2% $\pm$ 10.3; V = 250 ug/ml, 91.4% $\pm$ 3.7; V = 500 ug/ml, 97.0% $\pm$ 3.0 (N = 8 per concentration). Mean EC_{50} for V was 85 ug/ml. Verapamil also produced reversal of ANA tension: V = 500 ug/ml, 100% reversal within 15 minutes; control ANA muscles at this time still exhibit 75% of initial tension. In pretreatment studies, N exhibited a 2.5 X greater potency than V (n = 6). Specific calcium channel antagonists are effective in-vitro in preventing or reversing ANA-induced isometric tension in airways smooth muscle. (Supported in part by Foundation for Research in Bronchial Asthma and Related Diseases and Biomedical Research Grant 5-S07RR05660-06 Subgrant 30.) p. 22