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RESPIRATION I

A975

TITLE: MECHANISM OF GLUCOCORTICOIDS IN THE PERIPHERAL AIRWAYS.

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Introduction Preoperative preparation of the asthmatic patient often includes the administration of glucocorticoids. Glucocorticoids reduce reactivity to pulmonary aerosol challenge when administered either acutely or chronically to basenji-greyhound (BG) dogs, which have nonspecific airway hyperresponsiveness. Glucocorticoids may act through several different mechanisms, including a reduction in mediator release, a decrease in airway permeability, or an alteration in sensitivity of the smooth muscle. We questioned whether chronic administration of methylprednisolone (MP) to BG dogs alters peripheral airway responses to acetylcholine (ACH), which directly constricts smooth muscle, or to calcium chelator aerosols, which act indirectly, probably through mediator release.
Methods Ten BG dogs were anesthetized, intubated, and mechanically ventilated. A wedged bronchoscope technique was used to measure peripheral airway resistance (Rp) in two sublobar segments, one in each lung. Maps were constructed to locate the individual segments. Aerosol challenge with either ACH (10 μg/ml) or 4% Na_2 EDTA was administered through the bronchoscope, and Rp was measured postchallenge. The following week, 5 dogs began chronic treatment with MP (2mg/kg/day, s.c.), and the other 5 dogs served as controls. The experiment was repeated each week for 4 weeks. Maps were followed to identify the original sublobar segments. Data were analyzed using ANOVA for repeated measures.
Results Before MP treatment, aerosol challenge with 4% Na_2EDTA produced a 142$\pm$25% (mean $\pm$ SE, N=5) increase in Rp (Fig.1). MP attenuated the response to 4% Na_2EDTA, so that by 4 weeks the response was 40$\pm$8% ($p<0.05$) over baseline. In the control group, initial response to 4% Na_2 EDTA was 135$\pm$13% (N=5), and did not change significantly (P=0.54) over 4 weeks. Responses to ACH did not change over time in control (initial %Rp=191$\pm$14%,N=5) or treated (initial %Rp=148$\pm$28%,N=5) animals.
Discussion In BG dogs, chronic treatment with MP reduced peripheral airway responses to a calcium chelator aerosol, but not to ACH. Because ACH acts directly, these data suggest that glucocorticoids reduce peripheral airway responses at a level other than the smooth muscle. The ability of MP to attenuate the response to a calcium chelator aerosol suggests that one important action of glucocorticoids may be in a reduction of mediator release. Since many intraoperative stimuli for bronchospasm act indirectly, these data support the use of glucocorticoids to reduce the risk of peripheral airway constriction in asthmatic subjects. Supported by HL 38435, HL02417, and the W.M. Keck Foundation.

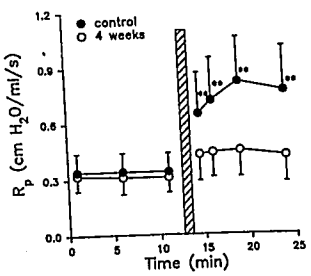

Fig 1. 4% Na_2EDTA challenge (vertical bar) before and after 4 weeks MP treatment. N=5. ** P<0.01.

A976

TITLE: ALTERED β-ADRENERGIC CHOLINERGIC INTERACTION IN AIRWAYS OF BASENJI-GREYHOUND DOGS

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The mechanisms involved in asthma are poorly understood. In our search for the mechanism we have recently found that airways of basenji-greyhound (BG) dogs show decreased sensitivity to β-adrenergic agonists *in vivo*[1] and *in vitro*[2]. To identify the site of this defect, we examined the efficacy of relaxant agonists with putative effects at different steps in the β-adrenergic cascade that could lead to inhibition of contractile responses to methacholine, histamine and KCl.
Methods: 8 BG and 11 mongrel dogs were sacrificed, tracheas removed and trachealis muscle dissected free. Muscle strips were suspended in 10 ml baths containing Krebs Henseleit solution, maintained at 37°C and aerated with 95% O_2 and 5% CO_2. Preparations were pretreated for 15 minutes with isoproterenol (ISO 10^{-6}, 10^{-5}M), forskolin (FSK 10^{-5}, 10^{-4}M), PGE_2 10^{-5}, 10^{-6}M, dibutyryl cAMP 10^{-3}, 10^{-4}M, IBMX 10^{-3}, 10^{-4}M or nitroprusside (NTP 10^{-3}, 10^{-4}M). Methacholine, histamine or KCl were then added in cumulative doses until a maximal response was obtained. Results were expressed as percent of maximal contraction and as the dose ratios (DR) of EC_{50} pretreatment/EC_{50} control. Comparisons between DR (mean $\pm$ SEM) of BG and mongrel were analyzed by Mann-Whitney U test with a $p < 0.05$ considered significant.
Results: Trachealis muscle from BG was significantly less sensitive to methacholine in the presence of ISO (10^{-6} and 10^{-5}M) (fig.1), FSK 10^{-5}M (DR 7.7 $\pm$ 1.8 BG and 19.5 $\pm$ 3.9 mongrel; $p < 0.05$), and PGE_2 10^{-6}M (DR 3.3 $\pm$ 0.8 BG and 9.7 $\pm$ 2.5 mongrel; $p < 0.05$) than trachealis from mongrels. No differences in methacholine sensitivity were found in BG and mongrel muscle pretreated with dibutyryl cAMP, IBMX and NTP. Moreover, histamine and KCl sensitivity in muscle from BG and mongrels pretreated with ISO were not different.
Discussion: The reduced methacholine sensitivity in trachealis muscle of BG pretreated with ISO and PGE_2 (which stimulate adenylyl cycase [AC] through their respective receptors and G_s) and FSK (which directly stimulates AC) localizes the defect at a site distal to the beta receptor. Supported by NIH 45974.

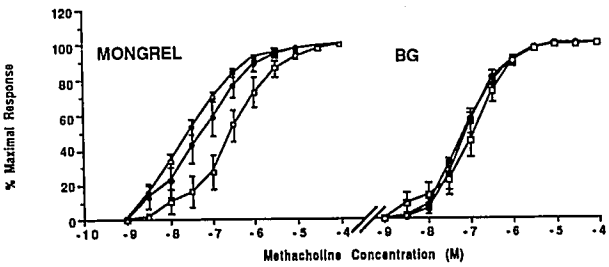

Fig 1. Isoproterenol effects on methacholine sensitivity in mogrel and BG airway smooth muscle.(control ●, Iso 10^{-6} ●, Iso 10^{-5} □)

1. (J. Appl. Physiol. 69:1212, 1990)
2. (J. Pharm. Exp. Ther. 287: 214, 1986)