Title: CALCIUM CHELATORS INCREASE AIRWAY RESPONSIVENESS

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Introduction. Aerosol administration of citric acid produces bronchoconstriction when inhaled by human subjects with airway hyperresponsiveness, but produces minimal effect in subjects lacking this trait (1). This could reflect quantitative differences associated with airway hyperresponsiveness or qualitative differences in bronchoconstrictor mechanisms. Aerosol administration of 10% citric acid provokes marked bronchoconstriction in the Basenji-Greyhound (BG) dog model of asthma but is without measurable effect in mongrel dogs (2). Citric acid-induced bronchoconstriction in BG dogs appears to result from calcium chelation rather than from the acidity of the solution since it is reproduced by aerosols of disodium edetate (Na₂EDTA), but not by CaNa₂EDTA or acetic acid (3). To determine if calcium chelation can activate a bronchoconstrictor mechanism in dogs without airway hyperresponsiveness, we tested the effects of aerosols of Na₂EDTA in a group of dogs that in a previous study lacked airway hyperresponsiveness to methacholine or any overt bronchoconstrictor response to citric acid. To test for a possible "subthreshold" effect, we compared methacholine-induced bronchoconstriction after pretreatment with an aerosol of 6% Na₂EDTA or a placebo aerosol (6% CaNa₂EDTA or isotonic saline).

Method. The studies employed 5 purebred Basenji dogs that were unrelated to BG progenitors and that responded to methacholine in the same concentration range as nonselected mongrel dogs. In studies conducted in random order about a week apart, each dog received a 5 min pretreatment aerosol (6% Na₂EDTA, 6% CaNa₂EDTA, or saline) and 5 min later received 5 breaths of an aerosol of 0.15 mg/ml methacholine. This concentration was chosen on the basis of previous studies in these dogs to be slightly less than threshold for production of measurable changes in pulmonary mechanics. Pulmonary resistance (Rₚ) and dynamic compliance (Cdyn) at 5 min after the pretreatment aerosol were taken as baseline values, and subsequent changes elicited by methacholine were compared by analysis of variance.

Results. Pretreatment with aerosols of saline or CaNa₂EDTA produced no change in Rₚ or Cdyn (Fig 1). Aerosols of Na₂EDTA produced a slight increase in baseline Rₚ (p<0.05) but no significant change in Cdyn (Fig 1). Subsequent challenge with methacholine increased (p<0.05) Rₚ by 5.1±1.2 (SE) cmH₂O/sec in the Na₂EDTA pretreated dogs but was without effect in dogs pretreated with saline or CaNa₂EDTA. This concentration of methacholine had no significant effect on mean Cdyn (Fig 1) in any of the three pretreatment groups.

Discussion. The increase in baseline Rₚ induced by Na₂EDTA in these purebred Basenji dogs was much less than that produced in previous studies in BG dogs (3). However, the increased sensitivity to methacholine clearly shows that Na₂EDTA can increase airway reactivity in normal dogs as well as in the BG model of asthma. Since CaNa₂EDTA did not increase sensitivity to methacholine, the effect of Na₂EDTA reflects calcium chelation rather than some other action of the EDTA molecule. Since calcium chelation affects airway responsiveness in both Basenji and BG dogs, the markedly greater response in the BG dog is a quantitative rather than a qualitative difference. These studies suggest that a localized calcium deficit may contribute to reactive airway disease.

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References

Fig 1. Rₚ and Cdyn before and after challenge with 0.15 mg/ml of methacholine (M) in dogs pretreated with aerosols of saline, Na₂EDTA and CaNa₂EDTA. Mean±SE, n=5.