Title: AIRWAY HYPERREACTIVITY TO ACETYLCHOLINE AND SEROTONIN IS INDEPENDENTLY DETERMINED BY NON-LINKED AUTOSOMAL RECESSIVE GENES

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Introduction. Asthma in many instances is an inherited disorder, characterized by nonspecific airway hyperreactivity to many different stimuli. A better understanding of the molecular mechanisms determining airway reactivity and the genetic regulation involved should provide improved therapeutics for use in the practice of anesthesiology. Recently we have shown that the inheritance of an autosomal recessive gene at the Ach locus determines acetylcholine (ACH) induced airway hyperreactivity. The purpose of this study was to determine if the same gene, or multiple genes regulate airway hyperreactivity to serotonin (5HT), Ach, and possibly other stimuli.

Methods. The Ach locus determines ACH-induced airway hyperreactivity in A/J and C3H/HeJ inbred mice and the progeny of crosses between them. These mice were used to evaluate the pattern of inheritance to 5HT. Four to eight week old mice were initially anesthetized with halothane at an inspired concentration of 1.5%. Each animal underwent a tracheostomy with a 20g cannula and was ventilated with air at a constant tidal volume (0.2 ml). The mice were immediately given 50 mg/kg i.p. of ketamine prior to awakening and paralyzed with 23 mg/kg i.p. of decamethonium. Airway reactivity was assessed from the time integrated change in peak airway pressure (APTI) following an IV bolus of ACH or 5HT. We evaluated the APTI to 5HT in A/J, C3H/HeJ, and F1, F2, and C3H/HeJ backcross animals. To determine whether the Ach locus or a closely linked gene determines 5HT airway hyperreactivity, F2 offspring from the cross between (C3H/HeJ X A/J) F1 X (C3H/HeJ X A/J) F1 were examined for airway reactivity to both ACH and 5HT. Each F2 animal was first challenged with 5HT and upon returning to baseline peak airway pressure was then challenged with ACH. Data were analyzed by Chi Square analysis, with pt<0.05 considered significant.

Results. Two phenotypes were distinguished on the basis of comparison to the airway response to 5HT in the parental strains of mice. These are designated HYPERREACTIVE (after the highly reactive A/J strain) and HYPOREACTIVE (after the minimally reactive C3H/HeJ strain). The A/J strain was markedly more reactive than the C3H/HeJ strain throughout the dose response range (Fig 1). The results indicate that airway hyperreactivity to 5HT in A/J and C3H/HeJ mice and the progeny of crosses between them is inherited as a single autosomal recessive trait (similar to acetylcholine) in these mice. However, we were unable to show an association between 5HT and ACH airway reactivity in 35 F2 animals given both agonists.

Discussion. This study shows that airway hyperreactivity to serotonin is inherited as an autosomal recessive trait very similar to that of acetylcholine. However, the lack of association between serotonin and acetylcholine reactivity in the F2 offspring, in linkage studies, supports the hypothesis that the loci for these two genes are separate and not closely linked. These studies suggest that single genes control airway reactivity to separate agonists and that similar linkage techniques can be used to test hypotheses about gene action and isolate these genes. Independent genes regulating airway reactivity suggest that different mechanisms probably determine airway hyperreactivity to these bronchoconstrictors. These studies imply that certain types of airway hyperreactivity may be independently inherited and why certain asthmatics respond to different therapies.

Fig 1. Dose response to 5HT in A/J and C3H/HeJ inbred mice. Airway reactivity was estimated as the integrated change in peak airway pressure over time after an IV bolus of bronchoconstrictor. This is termed the airway pressure time index (APTI). The APTI was measured in animals challenged with increasing concentrations of 5HT IV.