Title: BRONCHOACTIVE MEDIATORS Released BY IRRITANT STIMULI: ANESTHETIC IMPLICATIONS

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Introduction. "Irritant-induced" airway constriction is a major problem in the anesthetic management of patients with bronchospastic disease. Atropine-like drugs block parasympathetic pathways, but may not prevent airway constriction. Furthermore, cromolyn (a mast-cell stabilizer) attenuates some types of irritant airway constriction refractory to atropine, suggesting the involvement of bronchoactive mediators. To study the role of bronchoactive mediators in irritant-induced compared to allergic or cholinergic bronchoconstriction, histamine and slow reacting substance (SRS) were measured in arterial plasma before and after aerosol challenge with citric acid (10%), Ascaris antigen and methacholine in an animal model of asthma.

Methods. Five thiopental-anesthetized Basenji-Greyhound dogs previously sensitized to Ascaris antigen, were challenged (in separate experiments) with citric acid (10%) or Ascaris antigen (3 μg/ml) administered for 5 min., or methacholine (0.15 mg/ml) administered for 5 breaths. Pulmonary resistance (R p) was calculated by the method of Von Neergaard and Wiz and dynamic compliance (Cdyn) by dividing the tidal volume by the pressure difference between points of zero flow. Arterial plasma histamine was measured by double isotope radiocenzyme assay and SRS by guinea pig ileum bioassay. Changes in mediator levels were then related to absolute values of R p and Cdyn.

Results. All 3 aerosol challenges produced comparable degrees of airway constriction: R p post-challenge ranged from 9.0 ± 0.9 (mean ± SE) to 12.8 ± 1.1 cm H 2O/l/sec. and Cdyn post-challenge ranged from 35 ± 4 to 58 ± 10 cm H 2O. Citric acid elicited plasma SRS activity without increasing histamine level (fig. 1), whereas antigen challenge provoked both an increase in plasma histamine and the release of SRS into plasma (fig. 2). After methacholine challenge, no SRS was detected and plasma histamine was not increased. Plasma extracts containing SRS were fractionated by high pressure liquid chromatography. The plasma fraction having a similar retention time to synthetic SRS (leukotriene D 4 ) was the only fraction demonstrating biological activity on guinea pig ileum. FPL 55712 (an SRS antagonist) blocked the contractile effect of synthetic leukotrienes and plasma SRS on guinea pig ileum in vitro and prevented the pulmonary response to citric acid in vivo.

Discussion. Previous studies with isolated cell preparations have shown release of SRS by both allergic and nonallergic stimuli. However, our studies are the first demonstration that SRS can be released in vivo by an irritant stimulus. Since SRS is a potent constrictor of airway smooth muscle and produces marked changes in ventilation-perfusion relationships, its possible release in vivo in response to irritant stimuli has important implications in the anesthetic management of patients with reactive airway disease.

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