Investigations Of Mechanisms Of Carbon Dioxide-Induced Bronchial Smooth Muscle Relaxation

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Rationale: The challenge in acute severe asthma is to dilate mucous-constricted airways when bronchodilators are ineffective. We have developed a novel treatment for acute severe asthma which is a perfluorocarbon/carbon dioxide (CO2) mixture delivered by inhalation. The perfluorocarbon penetrates mucous-obstructed airways, where the CO2 acts synergistically as a potent and rapid bronchodilator. The mechanism underlying this bronchodilation is unknown. We therefore investigated the role of beta-adrenergic receptors and pH-dependent pathways in CO2-induced bronchial relaxation.

Methods: We used either a large-animal (sheep) or rodent model of allergen exposure to induce allergen-mediated bronchoconstriction. Pulmonary function was measured using barometric plethysmography (rats) and conventional lung mechanics (sheep). Following allergen exposure, the animals were treated with CO2 (12% or 8%) during the early phase response (sheep) or the late phase response (rats). A separate group of rats were pre-injected with propranolol (a non-selective beta-blocker) or saline (control) before the CO2 treatment was administered. The delivery of propranolol to the target site was confirmed by administration of the β2-receptor agonist, salbutamol.

Additional in vitro experiments, using bronchial rings from naïve and allergen exposed animals, examined the effect of hypercapnia (8% CO2) on carbachol pre-contracted bronchial rings. We also examined the effects of hypercapnia on Substance P-induced relaxation in both naïve and allergen exposed animals. All experiments were done with and without HEPES buffer.

Results: Carbon dioxide (12%) alone induced a significant (p=0.01) drop in airway resistance in sheep during the early phase broncho-constrictor response.

Similarly, rats administered 8% CO2 showed a significant drop (p=0.04) in peak expiratory box pressure during the late phase response. The relaxant effect of CO2 was maintained in the presence of propranolol.

In vitro studies showed a significant (p=0.03) drop in tension in carbachol pre-contracted bronchial rings under hypercapnic conditions. This relaxation was abolished in the presence of HEPES buffer. Epithelium dependent, Substance P-induced relaxation was enhanced by hypercapnia in ovalbumin exposed rat bronchial rings. This relaxation was maintained in the presence of HEPES buffer.

Conclusions: In vitro experiments suggest the presence of pH-dependent and pH-independent (epithelium-dependent) relaxant effects of hypercapnia on airway tone. The major relaxant pathway in the airways, the adrenergic pathway, does not appear to be involved in the bronchodilator response to inhaled CO2 in a rat model of allergen-induced bronchoconstriction. Our findings indicate that CO2 operates by an independent pathway from standard β2-receptor agonist bronchodilators, and represents a novel approach in the treatment of acute severe asthma.

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