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Evidence for autocrine and paracrine regulation of allergen-induced mast cell mediator release in the guinea pig airways

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ABSTRACT

Mast cells play an essential role in immediate type hypersensitivity reactions and in chronic allergic diseases of the airways, including asthma. Mast cell mediator release can be modulated by locally released autacoids and circulating hormones, but surprisingly little is known about the autocrine effects of mediators released upon mast cell activation. We thus set out to characterize the autocrine and paracrine effects of mast cell mediators on mast cell activation in the guinea pig airways. By direct measures of histamine, cysteinyl-leukotriene and thromboxane release and with studies of allergen-evoked contractions of airway smooth muscle, we describe a complex interplay amongst these autacoids. Notably, we observed an autocrine effect of the cysteinyl-leukotrienes acting through $cysLT_1$ receptors on mast cell leukotriene release. We confirmed the results of previous studies demonstrating a marked enhancement of mast cell mediator release following cyclooxygenase inhibition, but we have extended these results by showing that COX-2 derived eicosanoids inhibit cysteinyl-leukotriene release and yet are without effect on histamine release. Given the prominent role of COX-1 inhibition in aspirin-sensitive asthma, these data implicate preformed mediators stored in granules as the initial drivers of these adverse reactions. Finally, we describe the paracrine signaling cascade leading to thromboxane synthesis in the guinea pig airways following allergen challenge, which occurs indirectly, secondary to $cysLT_1$ receptor activation on structural cells and/ or leukocytes within the airway wall, and a COX-2 dependent synthesis of the eicosanoid. The results highlight the importance of cell-cell and autocrine interactions in regulating allergic responses in the airways.

1. Introduction

Immediate hypersensitivity reactions evoked by allergen challenge or by IgE receptor crosslinking can be studied in the intact airways and in isolated airway preparations from multiple species, including humans (Adams and Lichtenstein, 1977; Lamm et al., 1984; Björk and Dahlen, 1993; Ellis et al., 1994; Nagase et al., 1995; Roquet et al., 1997; Eum et al., 1999; Ressmeyer et al., 2006; Cyphert et al., 2009). Resident mast cells are thought to be the source of the resulting mediator release and primary drivers of the end organ effects (Boyce, 2007; Weigand et al., 2009). The responses evoked, which include airway smooth muscle contraction, mucus secretion, plasma exudation and altered mucosal blood flow, are primarily attributable to the actions of preformed biogenic amines (histamine in humans and guinea pigs, serotonin in rats and mice), cysteinyl-leukotrienes, and cyclooxygenase products including prostaglandin D_2 (PGD_2) and thromboxane A_2 (TxA_2). These end organ effects acutely mimic the pathophysiological features of asthma and eventually lead to inflammation, airways hyperresponsiveness and exaggerated respiratory reflexes that ultimately drive the symptoms of upper and lower airway diseases (Roquet et al., 1997; Bradding and Arthur, 2016). An understanding of the molecular, biochemical, pharmacological and physiological processes underpinning these reactions has and will continue to contribute significantly to the development of more effective therapies for asthma and other allergic diseases of the airways.

Multiple hormones and autacoids regulate mast cell mediator release in the airways. These regulatory mechanisms include inhibitory effects of β_2 adrenoceptor agonists (Undem and Buckner, 1984; Undem et al., 1988a, 1988b; Drury et al., 1998), prostaglandin E_2 (PGE_2 acting via EP_2 receptors (Saad and Burka, 1983; Adams and Lichtenstein, 1985; Undem et al., 1987b; Undem et al., 1987c; Kay et al., 2006; Säfholm et al., 2015)) and nitric oxide (Larsson et al., 2005), but also excitatory effects mediated by agonists of adenosine A_3 receptors (Ramkumar et al., 1993; Tilley et al., 2003) and the G-protein coupled MRGPRX2 (McNeil et al., 2015). It would thus not be surprising if mast cell-derived mediators act via autoreceptors to modulate their own

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release. Circumstantial evidence both for and against autoregulation has been described in studies using purified mast cells (and basophils) in culture through lipoxygenase products, $cysLT_1$ and CRTH2 receptor activation (Peters et al., 1981, 1982; Cohan et al., 1989; Larsson et al., 1999; Glitsch et al., 2002; Jiang et al., 2006; Di Capite, et al., 2009; Moon et al., 2014), but such actions have not been convincingly documented in the target tissues of the airways and lungs.

Guinea pigs closely resemble humans in their acute response to mast cell activation in the airways, with airway smooth muscle contractions occurring primarily through the activation of histamine H_1 receptors and leukotriene $cysLT_1$ receptors (Joiner et al., 1974; Adams and Lichtenstein, 1977; Lamm et al., 1984; Björk and Dahlen, 1993; Ellis et al., 1994; Roquet et al., 1997; Ressmeyer et al., 2006; Canning and Chou, 2008). This differs substantially from rats and mice, where the contractions are due primarily to serotonin as well as a secondary activation of parasympathetic cholinergic nerves (Nagase et al., 1995; Eum et al., 1999; Cyphert et al., 2009; Weigand et al., 2009). No involvement of acetylcholine has been documented in the acute response to allergen or crosslinking of IgE receptors in airways isolated from guinea pigs or humans (Joiner et al., 1974; Canning and Chou, 2008). Human and guinea pig mast cells also store and release little if any serotonin (Joiner et al., 1974; Kushnir-Sukhov et al., 2007). Because of these similarities, we set out to further characterize the autacoid receptors regulating allergen-induced mediator release and smooth muscle contractions in the airways and lungs of actively sensitized guinea pigs. We describe extensive cross talk between the autacoids within these tissues, with both excitatory and inhibitory effects on histamine, cysteinyl-leukotriene and thromboxane release. We also provide the first evidence for a differential role for COX-2 in regulating mast cell degranulation and the delayed synthesis of eicosanoids by mast cells and resident cells modulated by mast cell derived mediators.

2. Materials and methods

Our institutional animal care and use committee approved all of the experiments described in this study. Male Hartley strain guinea pigs (100–200 g; Charles River) were purchased pathogen free and maintained in accredited animal facilities with appropriate light cycles and with food and water provided *ad libidum*. These guinea pigs were actively sensitized to ovalbumin with intraperitoneal injections of the antigen (10 mg/ml dissolved in saline and administered; 10 mg/kg in each injection) delivered on days 1, 3 and 7 of a 28-day sensitization period. No adjuvants were used. Once the sensitization period had been completed, some of these animals were used for in vivo experimentation while the majority of the guinea pigs were used for tissue harvest and in vitro studies. To harvest the trachea and lungs from these animals, the guinea pigs were killed by asphyxiation in a vessel filled with carbon dioxide followed by exsanguination. Nonsensitized guinea pigs were also used in a similar manner.

2.1. Muscle contraction studies performed in vitro

Tracheae from the sensitized guinea pigs were prepared as tracheal strips for tissue bath experiments. Segments of 2–3 adjacent cartilage rings were taken from the trachea, sutured to a tissue holder and an isometric force transducer positioned over a 10 ml organ bath filled with Krebs bicarbonate buffer (composition (mM) NaCl (118), KCl (5.4), $NaHPO_4$ (1), $MgSO_4$ (1.2), $CaCl_2$ (1.9), $NaHCO_3$ (25) and dextrose (11.1), pH = 7.4). The tissues were suspended in the organ baths with an initial baseline tension of ~1.5 g (overall mean ± S.E.M. after the development of spontaneous tone (no differences amongst treatment groups): 1.79 ± 0.02 g (range: 1.23–2.85 g); 52 tracheal strips from 9 animals). After a 60 min equilibration period with fresh buffer added at 15 min intervals, the tissues were pretreated with various drugs (or relevant vehicles for control experiments) prior to ovalbumin challenge. Ovalbumin was administered in cumulatively increasing concentrations (1 ng/ml – 1 μg/ml), or as a single concentration (0.3 μg/ml) to study the kinetics of the evoked contractions. The single dose of ovalbumin used in the kinetic studies was selected to achieve a near maximal contraction (≥80% of maximum), but not a supramaximal dose that would have hindered assessments of the response kinetics. Ovalbumin was not administered until the effects (if any) of the pretreating drugs on baseline tone had reached equilibrium (~45 mins). At the end of each experiment, 300 mM barium chloride ($BaCl_2$) was administered to establish the maximum/ reference contraction for each tissue. In some experiments, we evoked comparable responses in the trachealis of nonsensitized guinea pigs using the MRGPRX2 selective and mast cell selective agonist compound 48/80. The data were recorded digitally using a Biopac MP data acquisition system.

2.2. Bronchospasm studied in vivo

The effects of ovalbumin inhalation on pulmonary inflation pressure (PIP) in anesthetized, paralyzed, mechanically ventilated guinea pigs were also studied. Animals were anesthetized with urethane (1.5 g/kg i.p.), with supplemental anesthetic administered as needed. The trachea was cannulated and attached to a ventilator (60 breaths/ min, 6 ml kg), generating a peak pulmonary inflation pressure of ~10 cmH_2O at baseline. A positive end-expiratory pressure of 3–5 cmH_2O was maintained to limit airway closure. Pulmonary inflation pressure was measured using a transducer attached to a side port adjacent to the tracheal cannula. Once mechanical ventilation had started, the guinea pigs were paralyzed with succinylcholine (2.5 mg/kg sc). The lower abdomen was then exposed for cannulations of the vena cava and abdominal aorta for drug administration and for monitoring of heart rate and blood pressure, respectively. Ovalbumin (10 mg/ml) was delivered as an aerosol using an ultrasonic nebulizer for 5 mins or until PIP had increased 25% over baseline.

2.3. Mediator release assays

Mediator release evoked by ovalbumin challenge was studied in parallel with the functional studies performed on the tracheae. We used lung instead of the extrapulmonary airways to increase our tissue yield thus increasing the number of interventions that could be studied in each animal. Lungs were quickly removed from the animals after euthanasia, placed in chilled, oxygenated Krebs buffer and trimmed of all large airways and visceral pleura. The remaining tissue was then cut into progressively smaller pieces until each tissue fragment was 1–2 mm in thickness, length and width. These pieces were then impaled in groups of 2–3 onto fine tungsten wires and placed in test tubes containing warmed, oxygenated Krebs buffer. The tissues were moved sequentially from test tubes with solutions of differing composition for an equilibration period (30 mins), baseline and pretreatment (30 mins in the absence or presence of various drugs or vehicle), ovalbumin challenge (1 mg/ml with the same drugs present during the baseline and pretreatment), and finally into 0.4 M perchloric acid to extract histamine for measurement of total histamine content. Mediator release is shifted ~100-fold to the right of smooth muscle contractile responses evoked by ovalbumin (Undem et al., 1987a, 1987b, 1987c). Consequently, the dose of allergen used to study mediator release was selected to evoke maximal release, a response that functionally (if not pharmacologically) approximated the maximal/ near-maximal contractions evoked in the kinetic studies of smooth muscle contraction.

Histamine was measured fluorometrically and the results were expressed as a percentage of total histamine. The cysteinyl-leukotrienes (LTC_4 and LTD_4) and thromboxane (measured as the stable metabolite thromboxane B_2 (TxB_2)) were measured by immunoassays (Cayman) and expressed as pg/ mg tissue. Tissue supernatants were analyzed immediately for histamine, or frozen for subsequent measurements of the eicosanoids. Tissue pieces averaged 32.4 ± 0.7 mg and contained

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