



Perspective

Should antihistamines be re-considered as antiasthmatic drugs as adjuvants to anti-leukotrienes?

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ABSTRACT

In spite of histamine mimicking the symptoms of allergic bronchoconstriction and severe anaphylaxis, histamine antagonists most probably represent no effective treatment for these conditions. Anti-leukotrienes proved effective for preventing attacks of allergic asthma. In vitro evidence supports a supra-additive effect of histamine H₁ receptor antagonists and anti-leukotrienes in vitro, in asthma models utilizing human bronchi. The same seems to hold true for human allergen provocation tests in vivo. We conclude that combinations of second-generation antihistamines and anti-leukotrienes deserve a large-scale clinical trial for preventing and/or treating attacks of allergic asthma. If useful, these drugs could provide a cost-effective alternative to some recent antiasthmatics. Given that redundant mechanisms may be included in asthma pathophysiology, other combinations (including thromboxane or platelet activating factor antagonists) could also be considered.

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1. Introduction

In the first half of the 20th Century there was great hope that antihistamines would suppress the symptoms of bronchial asthma and maybe other diseases involving bronchoconstriction or even anaphylaxis. Exogenous histamine induced bronchoconstriction, although with different potencies and efficacies in different animal species, humans showing an intermediate sensitivity. Histamine was detected in tissues and release of an “H-substance” – later that of histamine itself – was detected in the course of anaphylactic or other allergic reactions, from animal and human lungs (see Schild et al., 1951; Sheard et al., 1967; Sheard and Blair, 1970; Piper and Walker, 1973). Mast cells and basophils have been identified as the main source of the release of histamine, as well as other mediators of IgE-mediated reactions. These cell types (especially mast cells) are still considered as protagonists in allergic asthma, especially at its early phase. Considerable progress has been made concerning the way of mast cell activation in the course of antigen-fixed IgE reaction, the release of preformed and freshly-synthesized mediators, as well as other consequences of mast cell activation (for reviews see Holgate, 1999, 2009; Nauta et al., 2008; Rivera et al., 2008; Hamid and Tulic, 2009; Weller et al., 2011).

2. Antihistamines: no established place in allergic asthma therapy?

2.1. Histamine receptor antagonists

The hopes mentioned above were practically ruined by the very modest usefulness of antihistamines (histamine H₁ receptor antagonists) in bronchial asthma, and also in anaphylactic shock; although these antagonists could inhibit the deleterious effects of injected (exogenous) histamine and are effective in milder forms of hypersensitivity reactions, such as hay fever and urticaria.¹ They are currently among the most frequently prescribed medicines. Practically all current pharmacological textbooks label histamine H₁ receptor antagonists as essentially useless in the treatment of asthma (see Barnes, 2011), though some protection has been noted in a few studies, at least under experimental conditions of allergen provocation (Herxheimer, 1949; Popa, 1980; Rafferty et al., 1987). Patients with allergic rhinitis and comorbid asthma may benefit from antihistamine treatment in respect to the lower respiratory tract (for review see Bachert and Maspero, 2011). Combination of histamine H₁ with H₂ receptor antagonists offers no additional usefulness; connections of more

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¹ For a pharmacology teacher – hopefully also a physiology/pathophysiology teacher – this is a suitable argument to demonstrate the paramount importance of the criterion “identity of antagonism” and a considerably weaker predictive value of “identity of action” or “mimicry” in demonstrating the possible role of an endogenous substance in tissue reactions in health and disease.

recently discovered histamine receptors and asthma have not yet been clarified (Van Ganse et al., 1997).

Second-generation H₁ receptor antagonists have fewer side effects than first-generation ones, consequently, higher doses (yielding a higher receptor occupancy) can be administered (Nelson, 2003), yet these drugs alone probably cannot reliably control asthmatic symptoms (Diamant et al., 2007; Barnes, 2011; Bachert and Maspero, 2011; for some further clinical studies see below). As far as laboratory animals are concerned, histamine H₁ receptor antagonists can protect guinea-pigs against the serious consequences of antigen–antibody reaction, i.e. bronchospasm in sensitized animals, while in rats and mice the prominent feature of such antigen–antibody reactions is circulatory shock with modest bronchospasm, and antihistamines fail to provide strong protection.

2.2. Anti-leukotrienes

On the other hand, cysteinyl leukotriene antagonists, e.g. montelukast, as well as 5-lipoxygenase inhibitors (such as zileuton) offer partial protection against allergic asthma in humans (O'Byrne et al., 1997; Barnes, 2011; Nagai, 2012). They are usually taken orally for prevention, rather than for relieving asthmatic attacks.

2.3. Current asthma therapy

Further keystones of allergic asthma therapy are adrenergic β_2 receptor agonists and corticosteroids; inhaled muscarine receptor antagonists or injectable theophylline may provide additional relief in some cases (see Brand, 2011; Barnes, 2011; Nagai, 2012). There is progress also in this field, e.g., the widespread use of long-acting bronchodilators. Biological therapy of asthma is an emerging field (see among others Barnes, 2000; Bisset and Schmid-Grendelmeier, 2005; Holgate, 2009; Hamid and Tulic, 2009; Nagai, 2012; Chipps et al., 2012 for recent reviews). Omalizumab, a humanized monoclonal anti-IgE preparation is already in use. In general, however, it can be assumed that some of the new drugs (especially biological preparations), though effective, are rather expensive and in part still investigational; some older, well-established drugs may have disturbing side effects and important limits of single and daily dosage. Thus,

any progress in asthma therapy is still timely, especially if the drugs included are cost-effective.

3. Supra-additive relations between mediators

There are several examples of supra-additive interactions, “redundant mechanisms” of mediators (neurotransmitters, local hormones) in the mechanisms of physiological and/or pathophysiological reactions of the body. In such cases, antagonizing one of the mediators may yield no or only minor reduction in the reaction, but inhibiting additional mediators can result in profound inhibition of the process. Even simple addition offers some advantages, first of all, a reduction of dosage of the individual components.

3.1. Human respiratory mast cell-derived mediators

Mediators whose release from human respiratory mast cells or bronchial tissue in vitro has been proven include histamine, prostaglandin D₂, thromboxane A₂, peptido-leukotrienes (LTC₄, LTD₄, LTE₄), phospholipase A₂ and tryptase (Sheard et al., 1967; Paterson et al., 1976; Schulman et al., 1982; Dahlén et al., 1983; Schleimer et al., 1985; Salari et al., 1985; Flint et al., 1985; Undem et al., 1987; Broide et al., 1991; Triggiani et al., 2009; Granata et al., 2010). Mast cells are harvested from broncho-alveolar lavage fluid and bronchi from pulmonary tissue removed because of cancer. Release from dispersed lung cells is less considered in the present work. Many more tissue factors (including interleukins) have been shown to be released from mast cells of animals (for human and/or animal data see reviews by Piper, 1983; Dahlén et al., 1986; Holgate et al., 1987; Befus, 1987; Henderson, 1991; Holgate and Church, 1992; Oliver and Black, 2006; Nauta et al., 2008; Rivera et al., 2008; Hamid and Tulic, 2009; Weller et al., 2011, among others).

3.2. In vitro evidence for supra-additive interactions of mast cell-derived mediators in human allergic bronchoconstriction

Human allergic bronchospasm has been shown to occur in isolated bronchial preparations taken from allergic individuals and exposing them to the respective allergen (Schild et al., 1951). An alternative to this method is to take bronchial tissue from non-

Table 1
Effects of drug combinations on allergic bronchoconstriction in vitro, in human preparations.

Experimental protocol	Key results	Reference
Passively sensitized human bronchus, challenged with the antigen	H ₁ receptor antagonist diphenhydramine inhibits the initial, while the SRS-A antagonist FPL 5517 the prolonged phase of the response. Combined administration strongly reduces the entire response	Adams and Lichtenstein, 1977
Preparations taken from asthmatic subjects; challenge with allergen or anti-human IgE	No inhibition with antihistamines (mepyramine <i>plus</i> metiamide); half-maximal inhibition with anti-leukotrienes (among others, ICI 198,615); full inhibition with ICI 198,615 <i>plus</i> antihistamines	Björck and Dahlén, 1993
Intralobar bronchi; spontaneous tone	Relaxation with LTD ₄ antagonists (SKF 104353 or ICI 198615) or the antihistamine pyrilamine. Additive effect with the combination of the two types of drugs	Ellis and Undem, 1994
Passively sensitized preparations; challenge with anti-human IgE antibody	Slight inhibition with the antihistamine chlorpheniramine; moderate inhibition with anti-leukotriene (MK-571) strong inhibition with combination of the two drugs	Ruck et al., 2001
Passively sensitized slices of human lung; bronchial diameter followed by videomicroscopy; challenge with grass-pollen extract or activating immunoglobulin E antibody	A combination of the leukotriene antagonist montelukast and the thromboxane receptor antagonist SQ 29548 shows a higher inhibition than either drug alone	Wohlsen et al., 2003
Bronchi passively sensitized with IgE; challenge with anti-IgE	Strong inhibition with 5-lipoxygenase inhibitors (zileuton and MK-886) in the presence of the antihistamine mepyramine*	Poaty et al., 1993
Bronchi passively sensitized with IgE; challenge with anti-IgE	Strong inhibition with the lipoxygenase inhibitor SB 202235 in the presence of mepyramine*	Chabot-Fletcher et al., 1995

* Not tested separately.

allergic individuals and passively sensitize it by incubating, for several hours or overnight, with high IgE-serum from allergic persons, then exposing it to the allergen. Pure, specific IgE can also be used. A somewhat different method is that preparations are exposed (with or without being sensitized) to anti-IgE antiserum. (There are many thousands of IgE receptors at the plasma membrane of each mast cell.) For some of the above methods references are given in Table 1. Finally, a *non-immunological* activator of mast cells, e.g., compound 48/80 can be used (Paton, 1951; Davis et al., 1983). In the study of Davis et al. (1983) an antihistamine was inferior to FPL-55712, a moderately specific SRS-A antagonist (model compound for the development of zafirlukast). Above this paper hardly any human data of the literature with compound 48/80 are available. For non-immunological release of mast cell mediators see the review by Ferry et al. (2002).

In technical terms, larger-diameter bronchi can be studied by using classical organ bath experiments, while with smaller preparations superfusion and high-sensitivity myography or video microscopy can be exploited.

In nearly all studies where this problem has been addressed, histamine H₁ receptor antagonists caused no or only modest reduction of allergic bronchospasm, while they seemed to impressively enhance the effect of cysteinyl leukotriene antagonists, the latter alone being moderately effective (Table 1). The overall effect of the combination seems to be higher in peripheral than in more proximal bronchi (Ellis et al., 1994). One study, however, indicates a favorable interaction of the antileukotriene montelukast and the thromboxane receptor antagonist SQ 29548 (Table 1), while, in a low number of preparations, combining either montelukast or SQ 29548 with the antihistamine triprolidine fails to show any notable effect (Wohlsen et al., 2003). Tested separately, the antihistamine diphenhydramine delayed the development, while the SRS-A antagonist FPL 55712 reduced the delayed phase of the antigen-evoked contractile response in passively sensitized human bronchi; combining the two drugs yielded a strong inhibition of the entire response (Adams and Lichtenstein, 1977).

A supra-additive relation between leukotrienes and histamine has been confirmed in our laboratory with non-immunologic mast cell activation. In strips prepared from human bronchi, the mast cell activator polyamine compound 48/80 (*p*-methoxyphenethyl-methylamine units, connected through methylene groups; Paton, 1951) caused contraction that was also strongly reduced by a combination of a leukotriene receptor antagonist (MK 571; Jones et al., 1989) and the histamine H₁ receptor antagonist chlorpyramine, but neither drug alone (L. Bartho, unpublished results).

4. Clinico-pharmacological studies with combined antihistamine–anti-leukotriene treatment

Promising human studies have been published with the combination of antihistamines and anti-leukotrienes. The studies were prospective provocation tests performed on a low number of asthmatics. Patients with allergic asthma were challenged with the allergen; bronchoconstriction was inhibited by zafirlukast or, to a lesser extent, by loratadine. Combining the two drugs yielded an approximately additive effect (Roquet et al., 1997). Similarly, a combination of azelastine and montelukast inhibited both the early and late phase of allergen-induced bronchoconstriction; used as a sole drug, either medication was less effective than the combination. Montelukast was superior to azelastine in the early, but not late, phase of the response (Reicin et al., 2000). In the study of Davis et al. (2005) montelukast was moderately, while montelukast+desloratadine strongly effective in

preventing the early phase of allergen-provoked bronchoconstriction. Desloratadine alone was practically ineffective. With the late phase, both desloratadine and montelukast offered some protection, but the strongest inhibition was again found with the combination (Davis et al., 2009).

5. Conclusions and the authors' thoughts about future perspectives

This minireview only deals with a special aspect of allergic asthma therapy, i.e., antihistamine–anti-leukotriene combination. Other types of asthma, e.g., exercise-induced bronchoconstriction, are beyond our current topic. We feel that *there is ample evidence to justify larger-scale clinical studies* with combinations of anti-leukotrienes (receptor antagonists or 5-lipoxygenase inhibitors) and second-generation H₁ histamine receptor antagonists in patients with allergic asthma, as already proposed by Holgate (1999). The latter group of drugs is very widely used in patients with allergic rhinoconjunctivitis and urticaria; hence, there is widespread clinical experience that shows a low incidence of side effects. (Drugs of higher risk have been withdrawn from the market.) Neither anti-leukotrienes nor second-generation antihistamines are particularly new drugs, hence the combination may prove cost-effective. Oral treatment with this combination could prevent asthmatic episodes and/or reduce their severity. Should this be the case, administration of an antihistamine+antileukotriene (receptor antagonists) might be tested by the parenteral route for helping relieve asthmatic attacks. A possible broadening of medical uses, especially for the injection preparations, might be other severe allergic/anaphylactic manifestations.

We also feel that specific antagonists of bronchoconstrictor prostanooids, as well as platelet activating factor antagonists (that showed disappointing clinical effects alone, see Kuitert and Barnes, 1995) would deserve clinical studies in combination with anti-leukotrienes and, possibly, antihistamines. Overall, the principle of supra-additive mediation should be kept in mind in establishing new ways of asthma therapy, possibly also as adjuvant for currently established anti-asthmatics.

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References

- Adams III, G.K., Lichtenstein, L.M., 1977. Antagonism of antigen-induced contraction of guinea-pig and human airways. *Nature* 270, 255–257.
- Bachert, C., Maspero, J., 2011. Efficacy of second-generation antihistamines in patients with allergic rhinitis and comorbid asthma. *J. Asthma* 48, 965–973.
- Barnes, P.J., 2000. Anti-IgE therapy in asthma: rationale and therapeutic potential. *Int. Arch. Allergy Immunol.* 123, 196–204.
- Barnes, P.J., 2011. Pulmonary Pharmacology. In: Brunton, L.L. (Ed.), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 12th Edition McGraw-Hill, New York, pp. 1031–1065.
- Befus, D., 1987. The role of the mast cell in allergic bronchospasm. *Can. J. Physiol. Pharmacol.* 65, 435–441.
- Bisset, L.R., Schmid-Grendelmeier, P., 2005. Chemokines and their receptors in the pathogenesis of allergic asthma: progress and perspective. *Curr. Opin. Pulm. Med.* 11, 35–42.

- Björck, T., Dahlén, S.E., 1993. Leukotrienes and histamine mediate IgE-dependent contractions of human bronchi: pharmacological evidence obtained with tissues from asthmatic and non-asthmatic subjects. *Pulm. Pharmacol.* 6, 87–96.
- Brand, P.L., 2011. Inhaled corticosteroids should be the first line of treatment for children with asthma. *Paediatr. Respir. Rev.* 12, 245–249.
- Broide, D.H., Gleich, G.J., Cuomo, A.J., Coburn, D.A., Federman, E.C., Schwartz, L.B., Wasserman, S.I., 1991. Evidence of ongoing mast cell and eosinophil degranulation in symptomatic asthma airway. *J. Allergy Clin. Immunol.* 88, 637–648.
- Chabot-Fletcher, M.C., Underwood, D.C., Breton, J.J., Adams, J.L., Kagey-Sobotka, A., Griswold, D.E., Marshall, L.A., Sarau, H.M., Winkler, J.D., Hay, D.W., 1995. Pharmacological characterization of SB 202235, a potent and selective 5-lipoxygenase inhibitor: effects in models of allergic asthma. *J. Pharmacol. Exp. Ther.* 273, 1147–1155.
- Chippis, B.E., Figliomeni, M., Spector, S., 2012. Omalizumab: an update on efficacy and safety in moderate-to-severe allergic asthma. *Allergy Asthma Proc.* 33, 377–385.
- Dahlén, S.E., Hansson, G., Hedqvist, P., Björck, T., Granström, E., Dahlén, B., 1983. Allergen challenge of lung tissue from asthmatics elicits bronchial contraction that correlates with the release of leukotrienes C₄, D₄, and E₄. *Proc. Natl. Acad. Sci. USA* 80, 1712–1716.
- Dahlén, S.E., Kumlin, M., Granström, E., Hedqvist, P., 1986. Leukotrienes and other eicosanoids as mediators of airway obstruction. *Respiration* 50 (Suppl. 2), S22–S29.
- Davis, C., Jones, T.R., Daniel, E.E., 1983. Studies of the mechanism of passive anaphylaxis in human airway smooth muscle. *Can. J. Physiol. Pharmacol.* 61, 705–713.
- Davis, B.E., Todd, D.C., Cockcroft, D.W., 2005. Effect of combined montelukast and desloratadine on the early asthmatic response to inhaled allergen. *J. Allergy Clin. Immunol.* 116, 768–772.
- Davis, B.E., Illamperuma, C., Gauvreau, G.M., Watson, R.M., O'Byrne, P.M., Deschesnes, F., Boulet, L.P., Cockcroft, D.W., 2009. Single-dose desloratadine and montelukast and allergen-induced late airway responses. *Eur. Respir. J.* 33, 1302–1308.
- Diamant, Z., Boot, J.D., Virchow, J.C., 1997. Summing up 100 years of asthma. *Respir. Med.* 101, 378–388.
- Ellis, J.L., Undem, B.J., 1994. Role of cysteinyl-leukotrienes and histamine in mediating intrinsic tone in isolated human bronchi. *Am. J. Respir. Crit. Care Med.* 149, 118–122.
- Ellis, J.L., Hubbard, W.C., Meeker, S., Undem, B.J., 1994. Ragweed antigen E and anti-IgE in human central versus peripheral isolated bronchi. *Am. J. Respir. Crit. Care Med.* 150, 717–723.
- Ferry, X., Brehin, S., Kamel, R., Landry, Y., 2002. G-protein-dependent activation of mast cell by peptides and basic secretagogues. *Peptides* 23, 1507–1515.
- Flint, K.C., Leung, K.B., Hudspeth, B.N., Brostoff, J., Pearce, F.L., Johnson, N.M., 1985. Bronchoalveolar mast cells in extrinsic asthma: a mechanism for the initiation of antigen specific bronchoconstriction. *Br. Med. J. (Clin. Res. Ed.)* 291, 923–926.
- Granata, F., Staiano, R.I., Loffredo, S., Petraroli, A., Genovese, A., Marone, G., Triggiani, M., 2010. The role of mast cell-derived secreted phospholipases A₂ in respiratory allergy. *Biochimie* 92, 588–593.
- Hamid, Q., Tulic, M., 2009. Immunobiology of asthma. *Annu. Rev. Physiol.* 71, 489–507.
- Henderson Jr., W.R., 1991. Eicosanoids and platelet-activating factor in allergic respiratory diseases. *Am. Rev. Respir. Dis.* 143, S86–S90.
- Herxheimer, H., 1949. Antihistamines in bronchial asthma. *Brit. Med. J.* 2, 901–905.
- Holgate, S.T., 1999. Experimental models in asthma. *Clin. Exp. Allergy* 29 (Suppl. 3), S82–S86.
- Holgate, S.T., 2009. Novel targets of therapy in asthma. *Curr. Opin. Pulm. Med.* 15, 63–71.
- Holgate, S.T., Twentyman, O.P., Rafferty, P., Beasley, R., Hutson, P.A., Robinson, C., Church, M.K., 1987. Primary and secondary effector cells in the pathogenesis of bronchial asthma. *Int. Arch. Allergy Appl. Immunol.* 82, 498–506.
- Holgate, S.T., Church, M.K., 1992. Asthma. The mast cell. *Br. Med. Bull.* 48, 40–50.
- Jones, T.R., Zamboni, R., Belley, M., Champion, E., Charette, L., Ford-Hutchinson, A.W., Frenette, R., Gauthier, J.Y., Leger, S., Masson, P., 1989. Pharmacology of L-660,711 (MK-571): a novel potent and selective leukotriene D₄ receptor antagonist. *Can. J. Physiol. Pharmacol.* 67, 17–28.
- Kuiter, L., Barnes, N.C., 1995. PAF and asthma—time for an appraisal? *Clin. Exp. Allergy* 25, 1159–1162.
- Nagai, H., 2012. Recent research and developmental strategy of anti-asthma drugs. *Pharmacol. Ther.* 133, 70–78. (Epub 2011 Sep 6).
- Nauta, A.J., Engels, F., Knippels, L.M., Garssen, J., Nijkamp, F.P., Redegeld, F.A., 2008. Mechanisms of allergy and asthma. *Eur. J. Pharmacol.* 585, 354–360.
- Nelson, H.S., 2003. Prospects for antihistamines in the treatment of asthma. *J. Allergy Clin. Immunol.* 112, S96–S100.
- O'Byrne, P.M., Israel, E., Drazen, J.M., 1997. Antileukotrienes in the treatment of asthma. *Ann. Intern. Med.* 127, 472–480.
- Oliver, B.G., Black, J.L., 2006. Airway smooth muscle and asthma. *Allergol. Int.* 55, 215–223.
- Paterson, N.A., Wasserman, S.I., Said, J.W., Austen, K.F., 1976. Release of chemical mediators from partially purified human lung mast cells. *J. Immunol.* 117, 1356–1362.
- Paton, W.D., 1951. Compound 48/80: a potent histamine liberator. *Br. J. Pharmacol. Chemother.* 6, 499–508.
- Piper, P.J., 1983. Leukotrienes: possible mediators in bronchial asthma. *Eur. J. Respir. Dis. Suppl.* 129, S45–S64.
- Piper, P.J., Walker, J.L., 1973. The release of spasmogenic substances from human chopped lung tissue and its inhibition. *Br. J. Pharmacol.* 47, 291–304.
- Poaty, V., Riquet, M., LeGall, G., Frossard, N., 1993. Effect of 5-lipoxygenase inhibitors on the anti-IgE-induced contraction of passively sensitized human bronchus in vitro. *J. Lipid Mediat.* 8, 105–110.
- Popa, V.T., 1980. Effects of an H₁ blocker, chlorpheniramine, on inhalation tests with histamine and allergen in allergic asthma. *Chest* 78, 442–451.
- Rafferty, P., Beasley, R., Holgate, S., 1987. The contribution of histamine to immediate bronchoconstriction provoked by inhaled allergen and adenosine 5'-monophosphate in atopic asthma. *Am. Rev. Respir. Dis.* 136, 369–373.
- Reicin, A., White, R., Weinstein, S.F., Finn Jr, A.F., Nguyen, H., Peszek, I., Geissler, L., Seidenberg, B.C., 2000. Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a histamine receptor antagonist, in the treatment of chronic asthma. *Arch. Intern. Med.* 160, 2481–2488.
- Rivera, J., Fierro, N.A., Olivera, A., Suzuki, R., 2008. New insights on mast cell activation via the high affinity receptor for IgE. *Adv. Immunol.* 98, 85–120.
- Roquet, A., Dahlén, B., Kumlin, M., Ihre, E., Anström, G., Binks, S., Dahlén, S.E., 1997. Combined antagonism of leukotrienes and histamine produces predominant inhibition of allergen-induced early and late phase airway obstruction in asthmatics. *Am. J. Respir. Crit. Care Med.* 155, 856–863.
- Ruck, L.M., Rizzo, C.A., Anthes, J.C., Eckel, S., Egan, R.W., Cuss, F.M., Hey, J.A., 2001. Synergistic antiallergic activity of combined histamine H₁- and cysteinyl leukotriene₁-receptor blockade in human bronchus. *Life Sci.* 68, 2825–2834.
- Salari, H., Borgeat, P., Fournier, M., Hebert, J., Pelletier, G., 1985. Studies on the release of leukotrienes and histamine by human lung parenchymal and bronchial fragments upon immunologic and nonimmunologic stimulation. Effects of nordihydroguaiaretic acid, aspirin, and sodium cromoglycate. *J. Exp. Med.* 162, 1904–1915.
- Schild, H.O., Hawkins, D.F., Mongar, J.L., Herxheimer, H., 1951. Reactions of isolated human asthmatic lung and bronchial tissue to a specific antigen. Histamine release and muscular contraction. *Lancet* 258, 376–382.
- Schleimer, R.P., Fox, C.C., Naclerio, R.M., Plaut, M., Creticos, P.S., Togias, A.G., Warner, J.A., Kagey-Sobotka, A., Lichtenstein, L.M., 1985. Role of human basophils and mast cells in the pathogenesis of allergic diseases. *J. Allergy Clin. Immunol.* 76, 369–374.
- Schulman, E.S., Adkinson Jr, N.F., Newball, H.H., 1982. Cyclooxygenase metabolites in human lung anaphylaxis: airway vs. parenchyma. *J. Appl. Physiol.* 53, 589–595.
- Sheard, P., Blair, A.M., 1970. Disodium cromoglycate. Activity in three in vitro models of the immediate hypersensitivity reaction in lung. *Int. Arch. Allergy Appl. Immunol.* 38, 217–224.
- Sheard, P., Killingback, P.G., Blair, A.M.J.N., 1967. Antigen induced release of histamine and SRS-A from human lung passively sensitized with reaginic serum. *Nature* 216, 283–284.
- Triggiani, M., Giannattasio, G., Calabrese, C., Loffredo, S., Granata, F., Fiorello, A., Santini, M., Gelb, M.H., Marone, G., 2009. Lung mast cells are a source of secreted phospholipases A₂. *J. Allergy Clin. Immunol.* 124, 558–565.
- Undem, B.J., Pickett, W.C., Lichtenstein, L.M., Adams 3rd, G.K., 1987. The effect of indomethacin on immunologic release of histamine and sulfidopeptide leukotrienes from human bronchus and lung parenchyma. *Am. Rev. Respir. Dis.* 136, 1183–1187.
- Van Ganse, E., Kaufman, L., Derde, M.P., Yernault, J.C., Delaunois, L., Vincken, W., 1997. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur. Respir. J.* 10, 2216–2224.
- Weller, C.L., Collington, S.J., Williams, T., Lamb, J.R., 2011. Mast cells in health and disease. *Clin. Sci. (Lond.)* 120, 473–484.
- Wohlsen, A., Martin, C., Vollmer, E., Branscheid, D., Magnussen, H., Becker, W.M., Lepp, U., Uhlig, S., 2003. The early allergic response in small airways of human precision-cut lung slices. *Eur. Respir. J.* 21, 1024–1032.