

Molecular events in allergic inflammation: experimental models and possible modulation

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In recent years, a complex molecular network involving cytokines kinins and adhesion molecules has been demonstrated to operate in allergic inflammation. In particular, the adhesion machinery plays a crucial role for the recruitment and locomotion of the inflammatory cells and the Intercellular Adhesion Molecule 1 (ICAM-1) is a hallmark of the allergic inflammatory process. The role and possible modulation of ICAM-1 can be investigated using both eye and nose experimental models. Conjunctiva and nasal epithelium are easy to study either under natural allergen exposure or after specific/aspecific provocation tests; furthermore the nasal/conjunctival challenge is well tolerated by the patients. These experimental models have allowed us to investigate *in vivo* the antiallergic properties of several compounds. Many of the new antihistamines, but also deflazacort and local nasal immunotherapy, were demonstrated capable of reducing both inflammatory infiltration and ICAM-1 expression on epithelia. Because of the central role of adhesion molecules in allergic inflammation, their pharmacological modulation can be regarded as a promising therapeutic approach.

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Histamine was recognized over 70 years ago as the major mediator of allergic reactions (1). In the 40s, several drugs able to counter the main clinical effects due to histamine release were discovered and subsequently widely used in clinical practice to treat allergic disorders. Later, the H1 histamine receptor was discovered and antihistamines assumed the proper name of H1 blockers (2).

In recent years, the knowledge of physiopathological phenomena underlying the allergic reaction rapidly progressed and revealed a complex network: although tissue mast cells loaded with allergen-specific IgE still remain the primary trigger of an early allergic reaction, many other cells and mediators contribute and participate in the subsequent phases: T lymphocytes, leukotrienes, cytokines, kinins and adhesion molecules (CAMs) (3, 4). In particular, the new data about the molecular events which govern leukocyte migration and recruitment at site of allergic inflammation have completely changed previous understanding and are now leading to new strategies in the

treatment of allergic disorders (Fig. 1). In this light it has become evident that drugs, primarily considered as H1 blockers, exert presumably a number of other effects on immune-mediated inflammatory events. In fact, numerous *in vitro* and *in vivo* studies have demonstrated that many new antihistamines possess antiallergic effects: these effects are defined as inhibition of release of one or more mediators of inflammation. The older H1 antagonists are known to exert an antiallergic effect, but more in-depth studies have been devoted to the new antihistamines (azelastine, cetirizine, ketotifen, levocabastine, loratadine, oxatomide, terfenadine). *In vitro*, some of these compounds inhibit various degrees of mediator release from human and rodent mast cells and basophils (5–12).

The antiallergic effects might include modulation of the adhesion machinery, which plays a crucial role in the allergic reaction (13, 14). Interestingly, Wegner et al. (15) demonstrated, in a primate model of asthma, the expression of ICAM-1 on bronchial mucosa and demonstrated that the

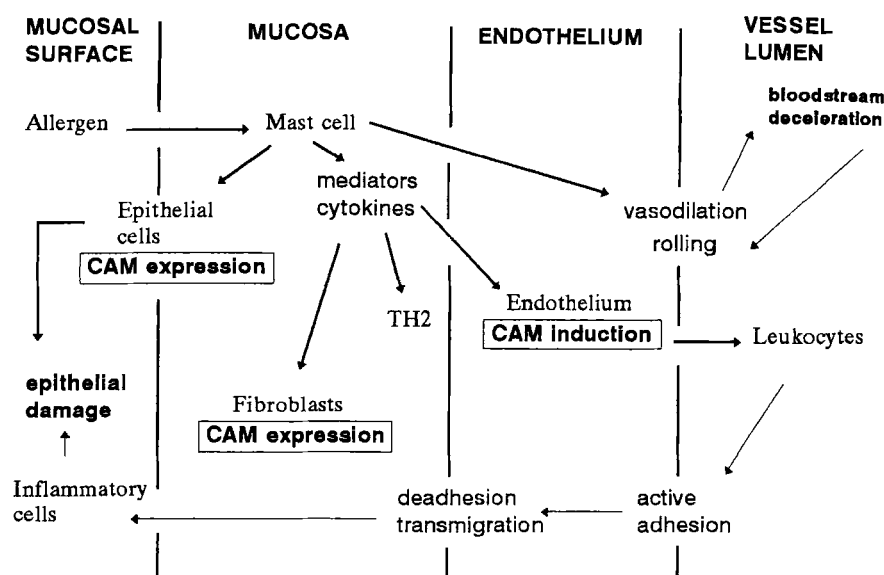


Fig. 1. New perspectives in the pathophysiology of allergic disorders.

association of glucocorticoids plus anti-ICAM-1 MAbs is effective in reducing the clinical manifestations (16). Campbell et al. demonstrated ICAM-1 expression on epithelial cells of human asthmatic subjects (17) – a finding confirmed by Vignola et al. (18).

Recently, we investigated the role of adhesion molecules, mainly ICAM-1 (CD54) in allergic inflammation and its possible modulation by drugs commonly used in the treatment of allergic disorders (14, 19–21). In fact, ICAM-1 expression on epithelium is regarded as a hallmark of allergic inflammation (14) in sensitized subjects. Eye and nose, as target organs of allergic disorders have been used as study models, as described below.

Experimental models: eye and nose

Since their mucosae are largely exposed to environmental allergens, the eye and the nose are commonly involved in allergic reactions, either as the main target or as co-involved organ of respiratory allergy. Conjunctiva and nasal epithelium are easy to study because scraping, brushing and nasal lavage are well tolerated by the patient. Furthermore, these target organs allow us to perform both specific (allergen) and aspecific (histamine, hyperosmolar solution) challenges, in which the contralateral nostril/eye can be used as control. The specific challenge is performed instilling a drop of allergen extract in the conjunctival sac or spraying it into a nostril. Finally, nasal and conjunctival epithelia can be studied either after natural allergenic exposure or after specific/aspecific provo-

cation, and in symptom-free patients. Specimens are easily collected both from the eye and the conjunctiva (brushing, scraping, nasal lavage fluid collection, lacrimal fluid collection). The clinical evaluation of the result of a nasal/conjunctival provocation test is usually performed through an arbitrary symptom scale, considering the presence and grade of symptoms (i.e. 0=no symptom, 1=mild, 2=moderate, 3=severe). The symptoms considered are: conjunctival hyperemia, itching, lacrimation, eyelid edema and, for the nose, itching, sneezing, rhinorrhea, nasal obstruction. Cytological evaluation of nasal/conjunctival specimens takes account of the number of inflammatory cells (neutrophils, eosinophils, metachromatic cells), while ICAM-1 expression is revealed by immunoenzymatic staining and graded through an ordinal scale (0= no positivity, 1=mild positivity on 25% of cells, 2=mild positivity on 75%, 3=intense positivity on 75%, 4=intense positivity on all cells). A summary of the characteristics of nasal/conjunctival models is reported in Table 1.

Table 1. Characteristics and variables of conjunctival and nasal models

• Subjects: healthy, pollinosis, perennial rhinitic
• Stimulus: allergenic exposure, specific challenge, aspecific challenge (histamine, hyperosmolar solution)
• Specimen collection
– nose: nasal lavage fluid, brushing, scraping
– eye: lacrimal fluid collection, scraping
• Parameters
– on epithelium: inflammatory cells, ICAM-1 expression
– in fluids: cytokines and mediators

Experimental results

Conjunctiva

The pathological findings occurring after allergen specific challenge involve the development of a clinical early phase reaction, followed by the maintenance of the inflammatory process in the so-called "late phase reaction" (LPR). In particular the exposure of the conjunctival mucosa to specific allergen results in an immediate hypersensitivity reaction occurring few minutes after challenge, which quickly subsides (14, 19–22); this early phase reaction (EPR), similar to allergen provocation in skin, lung and nose, is characterized by clinical symptomatology, local infiltration (22, 23) of inflammatory cells (mainly neutrophils) and epithelial expression of ICAM-1. Bonini et al. described a LPR that appears after 1 hour, peaks at 6–8 hours and slowly (24 hrs) subsides (24). In the LPR, eosinophils predominate in the infiltrate. No quiescent pause between EPR and LPR seems to exist at conjunctival level. Clinical evidence and cellular infiltration may vary according to the allergen dosage: with high doses a constant EPR and a frequent LPR occur, while at low doses only cellular infiltration is observed. Allergic subjects sensitized to pollens do not show any inflammatory infiltration or ICAM-1 expression on conjunctiva when symptom-free (out of the pollen season). On the contrary, under allergenic exposure, allergic subjects show conjunctival inflammation and ICAM-1 expression on epithelial cells, while healthy subjects do not (25). Furthermore, the presence of pollen grains in the conjunctival sac of pollinosis patients has also been described (26). Thus, the inflammatory infiltration and ICAM-1 expression in allergic subjects is strictly related to the allergenic exposure.

A persistent inflammatory infiltrate has been described in asthmatic patients at bronchial level during clinical latency (27). On the basis of this experimental evidence, we attempted to demonstrate the same minimal persistent inflammation (MPI) at conjunctival level. As expected, dust mite-sensitized patients showed a conjunctival MPI (cell infiltrate and ICAM-1 expression) when symptomless (28). The MPI appears to be related to the environmental allergenic exposure. So, a moderate but continuous allergenic exposure may maintain a mucosal MPI, with epithelial expression of ICAM-1; this finding is relevant as far as the susceptibility to viral infections is concerned. In fact, ICAM-1 has been demonstrated a receptor for most of human rhinoviruses (29).

Nose

The results obtained studying the nasal mucosa are, on the whole, superimposable to those from

conjunctiva. Specific challenge provokes an immediate clinical reaction (sneezing, rhinorrhea, obstruction), the presence of inflammatory infiltration and ICAM-1 expression on epithelial cells. After nasal challenge, the LPR is less frequent than after conjunctival provocation, but the cellular infiltration is still detectable.

During the pollen season an increase of both allergic reaction mediators and inflammatory cells has been demonstrated in rhinitic patients (30). Rhinitic pollinosis patients show nasal inflammatory infiltration and ICAM-1 expression on epithelial cells only during natural allergenic exposure, while they do not out of the pollen season when they are symptom-free. This fact has been clearly demonstrated by our group for *Parietaria* sensitized patients (31). A summary of the experimental results concerning ICAM-1 expression in nasal/conjunctival models is reported in Table 2.

Pharmacological modulation of CAMs

A wealth of experimental evidence has implicated CAMs in the economy of allergic inflammation. Because CAMs, and ICAM-1 in particular, appear to be crucial for leukocyte recruitment and epithelial damage, the pharmacological modulation of their expression is an attractive hypothesis. Indeed, attempts made to block the function of these molecules by monoclonal antibodies have been encouraging (32–34). On the other hand, the new antihistamines possess antiallergic properties, including a reduction of CAM expression. Thus, a possible modulation of CAM expression has been envisaged and studied mainly using the *in vitro* and *in vivo* models.

4.1. *In vitro* models. Different epithelial cell lines (conjunctiva, gut, bronchi), all expressing ICAM-1 to various degrees (and inducible by gamma IFN or other cytokines), have been studied in culture, also by adding several pharmacological compounds.

Table 2. ICAM-1 expression on epithelial cells in different experimental conditions

	Perennial rhinitis	Pollinosis	Normal
Specific challenge	+++	+++	—
Histamine challenge	+ (MPI)	—	—
Hyperosmolar solution challenge	++	++	+
Natural exposure (symptomatic)	++	++	—
Symptom-free	+ (MPI)	—*	—

* = outside pollen season.

MPI = minimal persistent inflammation.

Antihistamines such as levocabastine, terfenadine and terfenadine active metabolite or the mast cell stabilizer lodoxamide reduce ICAM-1 expression on a continuous cultured WK cell line, both in basal condition and following IFN gamma stimulus (35–37). Similar results have been obtained with the new corticosteroid budesonide (38). Nedocromil sodium, on the contrary, does not affect ICAM-1 expression under the same conditions (35). A summary of the experimental results is shown in Table 3.

In vivo models

Nasal and conjunctival models (specific challenge) have also been used to test the effects of different compounds on ICAM-1 expression (see Table 4).

Azelastine. The topical administration of azelastine to nose and eye is able to reduce ICAM-1 expression after allergen-specific challenge in pollinosis subjects (39, 40). Furthermore, azelastine reduces ICAM-1 expression and inflammatory infiltration also in pollinosis patients during natural allergenic exposure (Ciprandi G. et al., submitted).

Cetirizine. The administration of cetirizine for a short period (3.5 days) reduces ICAM-1 expression and inflammatory cells on conjunctiva after allergenic challenge in asymptomatic pollinosis patients (20). It has also been demonstrated to reduce the minimal persistent inflammation on nasal cells in perennial rhinitis (41), and the allergic inflammation under pollen exposure (Ciprandi G. et al., submitted).

Deflazacort. This glucocorticoid inhibits the molecular and cellular phenomena of the LPR after specific ocular challenge, but it does not affect the EPR (21).

Levocabastine. Levocabastine eye drops (single administration) affords protection against conjunctival specific challenge and reduces ICAM-1 expression in symptom-free allergic patients (36).

Table 3. Effect of antiallergic drugs on ICAM-1 expression on continuously cultured epithelial cell lines

	ICAM-1 baseline	ICAM-1 (550 U/ml IFN)	Soluble ICAM-1
Budesonide (10^{-7} M)	↓	↓	↓
Levocabastine (1 mcg/ml)	↓	↓	↓
Lodoxamide (1%)	↓	↓	=
Nedocromil (1%)	=	=	=
TAM	↓	↓	↓
Terfenadine	↓	↓	↓

Table 4. Effects of different treatments on ICAM-1 expression

Treatment	Allergen specific challenge				Natural exposure
	Nose EPR	Nose LPR	Eye EPR	Eye LPR	
Azelastine	↓	↓	↓	↓	↓ (1)
Cetirizine	na	na	↓	↓	↓ (1, 2)
Levocabastine	na	na	↓	↓	na
Mizolastine	na	na	=	=	na
Oxatomide	na	na	↓	↓	na
Terfenadine	na	na	na	na	↓ (1)
Lodoxamide	na	na	=	na	na
Deflazacort	na	na	↓	↓	na
Nasal IT	↓	↓	na	na	na

1 = nose, pollen.

2 = nose, dust mite.

EPR = early phase reaction.

LPR = late phase reaction.

na = not assessed.

Local Nasal Immunotherapy. It has been demonstrated that local desensitization can reduce the inflammatory infiltrate and ICAM-1 expression on nasal epithelial cells after allergenic challenge in symptom-free pollinosis patients. This finding correlates well with the clinical effectiveness (42).

Lodoxamide. Administered as eye drops, lodoxamide significantly reduces the allergic inflammation following specific challenge in symptom-free pollinosis patients (43).

Mizolastine. Under the same experimental conditions, mizolastine appears not to affect ICAM-1 expression (35).

Oxatomide. This antihistamine protects against allergen specific challenge, reducing the inflammatory infiltrate and ICAM-1 expression on conjunctiva, both in the early and in the late phase (44).

Terfenadine. In symptomatic rhinitic patients, terfenadine can reduce inflammatory infiltration, ICAM-1 expression and soluble ECP level in nasal lavage, after a 7-day course of therapy (45).

Conclusions

It has been clearly demonstrated that adhesion molecules play a crucial role in allergic inflammation, their effect being exerted mainly on leukocyte migration. In particular, ICAM-1 has been recognized as a major hallmark of allergic inflammation (25, 46). Nasal and conjunctival *in vivo* models provide a reliable and safe experimental

tool, for the study of inflammatory phenomena occurring during allergic reaction: with these models one may study the antiallergic properties of several compounds widely used for the treatment of allergic diseases. Most of the new antihistamines, but also corticosteroids and local immunotherapy, have been demonstrated to reduce both inflammatory infiltrate and ICAM-1 expression on nasal and conjunctival epithelial cells. The experimental data obtained from clinical studies, in addition to earlier basic results, confirm the role and the importance of the modulation of CAMs as a new therapeutic approach for the treatment of allergic disorders.

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