Allergy, Histamine and Antihistamines

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Abstract

This chapter concentrates on the role in allergic disease of histamine acting on H_1-receptors. It is clear that allergy has its roots in the primary parasite rejection response in which mast cell-derived histamine creates an immediate hostile environment and eosinophils are recruited for killing. This pattern is seen in allergic rhinitis where the early events of mucus production and nasal itching are primarily histamine mediated whereas nasal blockage is secondary to eosinophil infiltration and activation. In asthma, the role of histamine is less clear. Urticaria is characterized by mast cell driven pruritic wheal and flare-type skin reactions that usually persist for less than 24 h. Although the events leading to mast cell degranulation have been unclear for many years, it is now becoming evident that urticaria has an autoimmune basis. Finally, the properties of first- and second-generation H_1-antihistamines and their role in allergic is discussed.

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1 Introduction

While this chapter concentrates on the role in allergic disease of histamine acting on H_1-receptors, histamine may also act at three other receptor subtypes. Of these, the H_4-histamine receptor is probably most relevant to allergy (Thurmond 2015). The ability of H_4-antihistamines to reduce allergic inflammation and eosinophil accumulation in asthma (Dunford et al. 2006) and to reduce itching in skin diseases (Thurmond 2015) suggests that their development open the door to new treatments for allergic disease. The roles of the H_4-receptor in asthma and pruritic skin disease are addressed by Detlef Neumann and Rob Thurmond, respectively, in Chaps. 17 and 18.

2 The Roots of Allergy

The immune system has diverse ways of dealing with invading organisms. Invaders that have defeated the external defence line and have entered the body may be dealt with by one of the two systems, the innate immune system, which is nonspecific and does not require previous exposure and does not improve with repeated exposure to infection, and the acquired immune system which requires previous exposure and is highly specific for a particular invader. With small invaders, such as viruses and bacteria, their recognition by a variety of mechanisms is usually followed engulfment and intracellular digestion by macrophages. However, such a mechanism is not possible with larger invaders such as helminth parasites. For such invaders, the immune system uses a completely different approach. Initial infestation leads to a Th2 immune response and the production of IgE specific to parasite antigens (Murphy et al. 2008). This IgE binds to high affinity (FcεRI) receptors on mast and basophils thus arming them for any subsequent attack. On such a second attack, recognition by IgE of the parasite antigen initiates primary and secondary events. The primary event is IgE-dependent mast cell degranulation resulting the release into the extracellular environment of histamine, heparin and neutral proteases (Murphy et al. 2008). The role of histamine in particular is to make the local environment hostile for the invader by increasing mucus secretion and causing sensory nerve stimulation. The latter will induce scratching, sneezing, coughing or diarrhoea depending on the organ. The secondary event is to activate the Th2 system to stimulate eosinophil influx. Eosinophils contain a spectrum of highly toxic proteins, such as major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil cationic protein (ECP), and eosinophil derived neurotoxin (EDN), which attack and kill the invader (Kay 1985; Puxeddu et al. 2003). In addition, both mast cells and eosinophils synthesize and secrete leukotriene C_4 (LTC_4) to increase the

sequestration of eosinophils into the local environment and enhance the killing response (Kay 1985).

However, sometimes the immune system gets it wrong! It has long been recognized that the genetic make-up of some individuals renders them atopic or susceptible to allergic disease (Holloway et al. 2010b). In atopic individuals, allergens, such as house dust mite, tree and grass pollen and fungal spores, are mistakenly recognized as nematode antigens and they mount an allergic attack, which, to all intents and purposes, is identical to a parasite rejection response.

3 Allergic Rhinoconjunctivitis

Perhaps the easiest allergic response to address is allergic rhinitis. The early phase of this is shown diagrammatically in Fig. 1 (Church et al. 2016). In the upper panel of this figure, allergen, such as pollen or house dust mite, penetrates the nasal epithelium (A). This allergen then interacts with IgE (B) to stimulate mast cell degranulation and the release of its preformed mediators including histamine (C). In this early phase response, histamine has three immediate effects: first, it stimulates mucosal goblet cells to produce watery mucus (D); second, it stimulates sensory nerves to cause nasal itching and sneezing (E) and third, it induces vasodilation and tissue oedema which contribute to nasal blockage (F). Because these effects are primarily histamine mediated, H_1-antihistamines are effective in relieving these symptoms.

This early phase response is followed by the development of allergic inflammation that increases the severity and persistence of the initial symptoms, resulting in a chronic phase of allergic rhinitis. This is shown in the lower panel of Fig. 1. Cytokine production by mast cells and Th2 lymphocytes causes the attraction of more mast cells and the influx and activation of other inflammatory cells, particularly eosinophils (G) (Westergren et al. 2009). Eosinophils contain aggressive proteinaceous mediators as described above (H) that stimulate sensory neurones to dramatically increase the production and release of neuropeptides (I). These neuropeptides act on special venous capacitance vessels (J) present in the nasal turbinates, causing dilatation and reduced emptying. This is the primary cause of nasal blockage. Although these effects may be reduced by the inflammatory actions of H_1-antihistamines (Patou et al. 2006), intranasal corticosteroids or leukotriene receptor antagonists are more effective (Scadding et al. 2008).

Allergic rhinitis is often accompanied by ocular symptoms, particularly reddened, itchy and watery eyes. Originally it was believed that these conjunctival symptoms were caused by the activation of conjunctival mast cells with airborne allergen (Baroody et al. 2008). However, it is now believed that these symptoms are mainly the result of a naso-ocular reflex in which allergic inflammation in the nose stimulates the trigeminal nerve with subsequent release of neuropeptides in the tears (Callebaut et al. 2012). These neuropeptides activate conjunctival mast cells to release histamine but little cytokine. Consequently, there is little subsequent eosinophil infiltration and allergic inflammation in mild allergic

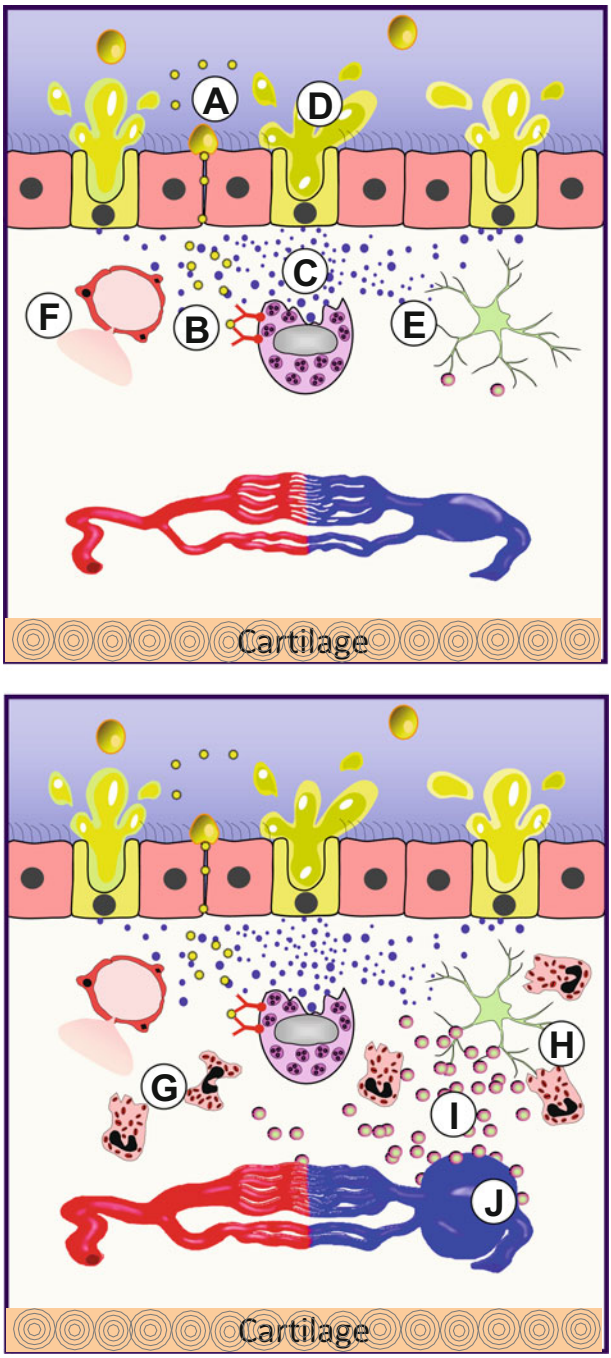

Fig. 1 The cellular basis of allergic rhinitis. The early phase is shown in the *upper panel* and allergic inflammation and nasal blockage in the *lower panel*. The *letters* are explained in the text. Adapted from Church et al. (2016)

rhinoconjunctivitis (Baroody et al. 2008). Rhinoconjunctivitis may be treated by reducing nasal inflammation, and hence the nasal reflex, with intranasal steroids, by the use of H_1-antihistamine eye drops or by topical chromones to reduce mast cell degranulation and sensory nerve activation (Baroody and Naclerio 2011).

A more severe form of allergic conjunctivitis is vernal conjunctivitis (McGill et al. 1998). This potentially sight threatening condition occurs in areas of high atmospheric pollen levels, such as the Middle East Asia, Africa and Mediterranean areas, where pollen impacts directly on the conjunctiva to initiate an allergic response. Because this is a direct allergen-induced response, complete activation of mast cells occurs (Church and McGill 2002) with the resultant cytokine production stimulating eosinophil infiltration and allergic inflammation (McGill et al. 1998).

4 Asthma

Some 30 years ago, asthma was considered to be primarily a mast cell mediated disease. Indeed, in his review of the pathophysiology of asthma in 1979, James Hogg wrote (Hogg et al. 1979) 'the initial event in an acute asthmatic attack is the release of mediators from superficial mast cells, and this amplifies the allergic response by altering the mucosal permeability so that more antigen reaches the sub-mucosal mast cells. This altered permeability may also help explain the hyper-reactivity of the airways to nonspecific airway stimulants in persons with asthma'. In line with this view, acute anaphylactic bronchoconstriction in guinea pigs (Kallos and Kallos 1984) and rats (Church et al. 1972) were used as test models in the quest to search for drugs for the treatment of asthma. No effective drugs were found. Today our view of asthma is completely different. Asthma is now viewed as a multifactorial chronic inflammatory condition whose disease progression is under the influence of a wide variety of genes which are associated with many aspects of the condition, altered lung development, response to the environment, fixed airway obstruction and response to therapy (Holloway et al. 2010a). What is most fascinating is that susceptibility to atopy/allergy is now relegated to the level of one of the contributory factors.

However, when discussing allergic asthma in particular, we cannot ignore the fact that 'the nose is the guardian of the lung' and that histamine may be involved here. In a study published in 2004, Corren and colleagues (Corren et al. 2004) investigated whether treatment with intranasal corticosteroids and/or second-generation H_1-antihistamines (SGAHs) was associated with changes in rates of asthma exacerbations resulting in emergency room visits and/or hospitalizations in patients with asthma and allergic rhinitis. Their results showed that treatment with either nasal corticosteroids or SGAHs was associated with a lower risk of asthma-related emergency room treatment and hospitalization. Combined treatment with both medications was associated with a better effect of either alone.

5 Urticaria

Urticaria is one of the most frequent skin diseases. It is characterized by mast cell driven pruritic wheal and flare-type skin reactions that usually persist for less than 24 h. Some patients have both wheals and angio-oedema, while others have only one or the other, usually the former. According to the current EAACI/GA2LEN/EDF/WAO guideline, urticaria may be divided into spontaneous urticaria, physical urticaria and other urticaria types (Zuberbier et al. 2009). Spontaneous urticaria is further divided into acute and chronic spontaneous urticaria (CSU) depending on whether the disease duration is less than or more than 6 weeks. The triggers of the physical and other urticaria types, e.g. cold, heat, scratching, pressure or exercise, are obvious. In contrast, in spontaneous urticaria the lesions usually occur without an obvious stimulus, although foods, infections and stress have been suggested as possible stimuli (Maurer et al. 2011b).

While the role of mast cell histamine in the pathogenesis of all forms of urticaria is clear from the beneficial effects of H_1-antihistamines, the mechanisms by which the mast cell is activated is far from clear. However, the recent reports that anti-IgE (omalizumab) given by subcutaneous injection at monthly intervals is highly effective in relieving the symptoms of CSU in the majority of patients (Maurer et al. 2015) is suggestive of a critical role of IgE in this condition. Because some patients respond to anti-IgE rapidly, within 1 week, while others may take up to 2 months to respond (Metz et al. 2014), we have recently postulated two possible types of Gell and Coombs hypersensitivity mechanism reactions (Coombs and Gell 1968; Kolkhir et al. 2016).

The rapid response we suggest is a Type I hypersensitivity, or allergic reaction, in which free antigens cross-link the IgE on mast cells and basophils to cause the release of vasoactive mediators (Fig. 2). This was first suggested by Rorsman in 1962 to explain urticaria associated basopenia (Rorsman 1962). That this was an autoallergic response that was postulated from the finding in 1999 of IgE autoantibodies against the thyroid microsomal antigen in the serum of a female patient who suffered from CSU (Bar-Sela et al. 1999). This work has been confirmed and extended to propose autoallergy in the pathogenesis of both CSU and chronic inducible urticaria (CindU) (Concha et al. 2004; Kaplan 2004; Altrichter et al. 2011; Maurer et al. 2011a; Shindo et al. 2012; Hatada et al. 2013).

A Type II hypersensitivity reaction in which antibodies, usually IgG or IgM, bind to antigen on a target cell was originally postulated following the identification in three of six patients with CSU of IgG antibodies against IgE which caused degranulation of leukocytes (Fig. 2) (Gruber et al. 1988). The presence of these antibodies was confirmed by Grattan and co-workers in 1991 in patients whose sera induced a wheal and flare response when injected intradermally, the autologous serum skin test (ASST) (Grattan et al. 1991). The presence of antibodies to the high affinity receptor for IgE on mast cells and basophils (IgG anti-FcεRI) was reported by the same group 2 years later (Hide et al. 1993). This has now been confirmed by many authors (Kaplan 2004; Kaplan and Greaves 2009).

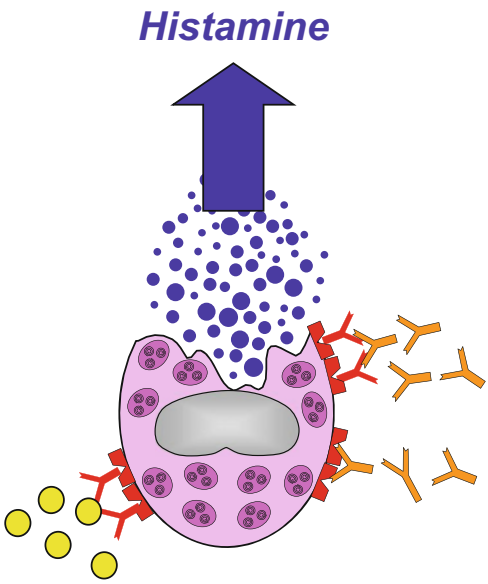

Fig. 2 Possible autoallergic mechanisms of chronic spontaneous urticaria (CSU). On the *left*, autoallergen cross-links membrane-bound IgE. On the *right*, IgG antibodies are cross-linking IgE or their receptors, FcεRI

Thus, there are still many aspects of the pathologic mechanisms of CSU that need to be resolved, but it is becoming clear that there are at least two distinct pathways, type I and type II autoimmunity, that contribute to the pathogenesis of this complex disease (Kolkhir et al. 2016).

6 H_1-Antihistamines

Oral H_1-antihistamines are the first-line treatment used by most patients, doctors and pharmacists for allergic rhinoconjunctivitis and urticaria. Histamine acting on H_1-receptors in the brain has a completely different function to that in the periphery. In the brain, it has an arousal effect and aids concentration and learning (Church et al. 2010). Thus, when selecting an H_1-antihistamine for treatment, healthcare professionals should be aware of the significant detrimental effect of agents that cross the blood–brain barrier to cause effects on the central nervous system (CNS). First-generation H_1-antihistamines (FGAHs) such as chlorpheniramine, diphenhydramine, hydroxyzine and ketotifen readily penetrate into the brain and occupy more than 50% of the H_1-receptors therein (Yanai et al. 2011). Occupation of these receptors results in drowsiness and interference with cognitive processes in all patients (Church et al. 2010).

Studies in children have demonstrated that FGAHs exacerbate the detrimental effect of allergic rhinitis on learning ability (Vuurman et al. 1993). In another study in teenagers sitting summer mock university entrance examinations, untreated allergic rhinitis caused a 40% increased likelihood of students dropping an examination grade. FGAHs increased this to 70% (Walker et al. 2007).

In adults, FGAHs have detrimental effects on the quality of life and productivity even at the lowest doses recommended by manufacturers (Church et al. 2010). The effects of FGAHs on the CNS are similar to and additive with those produced by alcohol or other CNS sedatives, and bedtime dosing with FGAHs may have hangover effects the next day due to their long elimination half-life value (Church et al. 2010). Furthermore, FGAHs may significantly reduce the driving ability to potentially dangerous levels (Verster and Volkerts 2004; Church et al. 2010), particularly in the elderly and those who combine the drug with alcohol ingestion. One study suggests that 25% of individuals older than 65 years of age have some cognitive impairment, often with no overt sign of dysfunction (Graham et al. 1997). Administration of FGAHs to this population increases the risk of inattention, disorganized speech, altered consciousness and impaired function or alertness (Agostini et al. 2001; McEvoy et al. 2006). In addition, because of their anticholinergic activity, FGAHs significantly increase the risk for development of dementia (Gray et al. 2015).

The development of SGAHs, including loratadine, desloratadine, cetirizine, levocetirizine and ebastine, has largely overcome these problems in that they have high H_1-receptor selectivity, low brain permeability and longer durations of action. Unlike FGAHs, SGAHs are amphiphilic in that hydrophilic groups have been introduced into the molecule so that they are always positively or negatively charged and, therefore, have a greatly reduced passage across the blood–brain barrier (Yanai et al. 2011; Hiraoka et al. 2015). Because of their reduced unwanted effects, the European Guidelines for both allergic rhinitis and urticaria specify that only SGAHs should be used for symptom relief in these conditions (Scadding et al. 2008; Zuberbier et al. 2009). Although SGAHs have a much reduced brain penetration, they may only be referred to as 'minimally sedating' rather than 'non-sedating'. For example, in a study of patients' perspective of effectiveness and side effects of H_1-antihistamine updosing in CSU, more than 20% of patients reported sedation is a side effect of SGAHs (Weller et al. 2011).

More recently, two truly 'non-sedating' H_1-antihistamines, fexofenadine and bilastine, have been introduced which have no significant occupation of histamine H_1-receptors in the CNS (Hiraoka et al. 2015; Farre et al. 2014). The reason for their lack of brain penetration is that they are actively pumped out of the blood–brain barrier by p-glycoprotein (a proton pump) (Miura and Uno 2010; Church 2011). It will be interesting to see if further drugs will be developed which use membrane proton pumps to enhance their efficacy or reduce their unwanted effects.

7 Conclusions

While it is clear that histamine acting at H_1-receptors are critically involved in producing rhinorrhea, itching and sneezing, it is equally clear that it is not involved in nasal obstruction. In asthma too, histamine has only a minor role. In chronic urticaria, the application of guideline-based management following specialist review, i.e. updosing H_1-antihistamines fourfold, was associated with a good

outcome in only 78% of patients (Conlon and Edgar 2014). Whether this means that mediators other than histamine are involved or that the level of histamine is extremely high in some patients is yet to be clarified.

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