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H_4 receptors in mast cells and basophils: a new therapeutic target for allergy?

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1. ABSTRACT

It has long been recognised that mast cells and basophils are prominent sources of preformed histamine in humans and that this biogenic amine serves as one of the most important inflammatory mediators. In allergic diseases, histamine has previously been shown to partially modulate symptoms such as airway obstruction, mucus secretion, reddening of the skin and itch, all of which were attributed to engagement of H_1-receptors with the amine. However, more recently it has been shown that certain key biological functions of histamine, such as itch, are also crucially controlled by H_4-receptor stimulation, resulting in a growing interest in combinational anti-H_1 and -H_4 therapeutic approaches. Moreover, research is beginning to shed light on a role of H_4-receptors in mast cell precursor trafficking to various tissues commonly affected by allergic inflammation. Furthermore, H_4-receptors are also expressed on mature basophils and other effector cells of allergic reactions, such as eosinophils. This presents exciting possibilities in terms of potentially modulating the pro-allergic function of these cells as well as preventing the effects of histamine on target organs and cells.

2. ROLE OF MAST CELLS AND BASOPHILS IN ALLERGIC INFLAMMATION

Crosslinking of IgE bound to high affinity IgE receptors (Fc epsilon RI) on mast cells and basophils with allergens results in the release of a large array of inflammatory mediators that govern the signs and symptoms of allergy. As a result, these cells are key effector cells in allergic inflammation and serve as a prime target for anti-allergic therapy. Both mast cells and basophils originate from CD34+ stem cells that are produced in the bone marrow and, although they share many morphological and functional features (e.g. Fc epsilon RI expression, histamine synthesis and storage in their granules), current evidence suggests that they may arise from different precursors (reviewed in 1, 2). Basophils appear to share a common progenitor with eosinophils, and both cells types are matured within the bone marrow before entering circulation (3-5). However, each cell type requires unique cytokine growth factors to mature, with IL-3 yielding basophils (6) and IL-5 eosinophils (7). In contrast, mast cells arise from CD34+ progenitors that enter the circulation undifferentiated and, with exception of certain

forms of mastocytosis, only mature into mast cells upon contact with stem cell factor (SCF) in various tissue locations (8, 9). Mast cells are most prominently expressed in tissues that form a barrier with the external environment such as the skin, airways and gastrointestinal tract.

Because of their tissue locations, mast cells have previously been considered as more important allergic effector cells than their basophil counterparts. This view was also supported by pioneering studies by Kitamura and co-workers who generated mast cell knockout mice by virtue of their inability to either produce SCF or the corresponding receptor c-kit (10, 11). Using these models, IgE-mediated activation of mast cell deficient mice failed to elicit acute allergic reactions but late phase responses were largely unaffected (12). However, although an important role for mast cells was demonstrated a role for basophils could not be ruled out although this line of enquiry was seriously hampered by the fact that IL-3 knockout mice still generate basophils, thus also indicating a degree of redundancy for IL-3 as a basophil growth factor (13).

Indirect evidence for the relative involvements of mast cells and basophils were elegantly demonstrated based on the types of allergic mediators released in the skin or lung during allergen challenge of allergic individuals. These studies showed clear mast cell involvement during acute allergic reactions (less than 1 hour) owing to the detection of a rise in histamine levels and mast cell tryptase (a specific mast cell enzyme) or prostaglandin D_2 (also produced by mast cells but not basophils) (14, 15). However, a second rise of histamine was detected after several hours in these patients corresponding to allergic late phase responses and since there was no concomitant rise in neither tryptase or prostaglandin D_2 this suggested exclusive basophil involvement in these responses (14, 15).

More recently, it has been shown that basophils invade tissues affected by allergic inflammation (16-18) and are prominent sources of Th2-type cytokines such as IL-4 and IL-13 both *in vitro* (19-23) and *in vivo* (24, 25). Indeed, basophils, but not mast cells, have been shown to cause IgE class switching in B cells leading to polyclonal IgE synthesis in the resulting plasma cells *in vitro* (26). Since it is now thought that much of the allergen-specific IgE bound to mast cells and basophils residing in various tissues locations is locally derived (27-30), basophil-derived IL-4 and IL-13 appear to support the generation of Th2 cells as well as IgE synthesis. Additionally, basophils release not only Th2 cytokines and histamine but also LTC_4 as well as the angiogenic cytokine VEGF (31). These properties are also shared by human mast cells and play an important role in airway remodelling in asthma, although their ability to generate IL-4 following Fc epsilon RI-activation is rather limited compared to their rodent counterparts (reviewed in 32 & 33).

Despite the lack of genetically engineered basophil knockout animal models it has been possible to deplete circulating basophils in mouse models of allergy using monoclonal antibodies directed against murine basophils. Such studies have very recently clearly shown that basophils play an essential role in initiating chronic allergic inflammation as well as being able to act as antigen presenting cells and directly orchestrate Th2 immunity leading to atopy and allergic disease (34-38). Thus, although mast cells are more numerous in humans than basophils and no doubt play a major role in governing inflammation associated especially with acute allergic responses, basophils are increasingly being viewed as major immunomodulatory cells that support not only effector phases of allergy but underlying Th2 immunity.

2.1. Mast cells and basophils as a major source of histamine in humans

Ever since Riley and West discovered mast cells as the main cellular source of histamine (39) this biogenic amine has consistently generated much interest due to its major inflammatory and immunomodulatory properties. In humans, most of the tissue histamine content is indeed largely synthesised in mast cells and basophils where it is generated by removing the carboxyl group from the amino acid histidine due to the action of histidine decarboxylase. Alternative sources are enterochromaffin cells (40), where histamine is involved in gastric acid secretion, and the tuberomammillary nucleus in the brain (41), where the amine acts as a neurotransmitter controlling circadian rhythms (42). Histamine has also been detected in thrombocytes (43), which may also express Fc epsilon RI (44) and very low levels of the amine have also been reported in several leukocytes other than basophils such as macrophages and lymphocytes (45, reviewed in 46). However, there is a degree of heterogeneity regarding the cellular sources of histamine and indeed other biogenic amines throughout the animal kingdom, as well as several orders of magnitude difference in the sensitivities of various organisms to the amine. Most rodents, for example, survive histamine levels that far exceed lethal doses in humans.

Mast cells and basophils constitutively generate histamine where it is stored within cytoplasmic granules bound to negatively-charged sulphate groups on proteoglycans. These consist mainly of heparin for mast cells and also chondroitin sulphate di-B for basophils where histamine contents in these cell types in humans range from *ca.* 1-10 pg/cell (usually 2-6 pg/cell in human lung and skin mast cells and 1-2 pg/cell in basophils). Upon IgE-mediated activation (e.g. allergen-induced crosslinking of IgE bound to Fc epsilon RI), these granules fuse with the plasma membrane and histamine is liberated by displacement with extracellular sodium ions. The kinetics of IgE-mediated histamine release from mast cells and basophils is highly dependent on the degree of receptor triggering (law of mass action) but is usually complete within 30 minutes (47). This also explains the rapid onset of symptoms associated with anaphylaxis, which is largely governed by the binding of histamine released from mast cells and basophils to H_1-receptors (H_1R), and occasionally H_2-receptors (H_2R) present on the heart leading causing arrhythmias.

It should be noted that degranulation and histamine release from both mast cells and basophils may also take place by non-antigen specific mechanisms leading to Fc epsilon RI engagement. These include many dietary lectins, B cell superantigens (such as HIV gp120), auto-anti-IgE/Fc epsilon RI antibodies (produced by certain urticaria patients) and several parasitic proteins present in *Schistosoma mansoni* and *Echinococcus multicularis* (reviewed in 48). Moreover, there are several IgE-independent triggers such as complement factors (e.g. C5a) and Toll-like receptor activators (e.g. *via* TLR-2 and -4) that activate both mast cells and basophils. The latter also substantially degranulate upon stimulation with the tripeptide fMLP whereas certain mast cell subtypes (connective tissue-like mast cells containing the neutral proteases tryptase and chymase) also respond to polybasic amine and bee/wasp venoms. All the above non-allergen specific (in some cases IgE-independent) activators of mast cell and basophil degranulation suggest that these cells are capable of participating in innate immune and inflammatory responses other than - or prior to - sensitization with allergen-specific IgE and subsequent crosslinking upon re-exposure to allergen. Additionally, mast cells may be directly activated during inflammatory responses due to other allergic effector cells, such as eosinophils (49) Finally, it has been shown that both mast cells and basophils may undergo a process of piecemeal degranulation during certain chronic allergic inflammatory diseases resulting in increased tissue histamine levels (50), although the consequence of this is not fully understood.

2.2. Differential expression and function of histamine receptors in mast cells and basophils

It has long been observed that histamine has autocrine effects on basophils and, to a lesser extent, on mast cells. In terms of affecting degranulation and the release of inflammatory mediators, including histamine itself, the amine displays a net inhibitory action on mast cell and basophil function (51, 52). This feedback inhibition was shown to involve mainly H_2R (52, 53), which are expressed on human skin mast cells, the human mast cell line HMC-1 and basophils, although less is known regarding human lung mast cell H_2R expression (46, 54). However, both clinical data and *in vitro* studies by other groups suggest that IgE-mediated human basophil degranulation is more susceptible to H_2R regulation than mast cells (54-56). H_2R activation leads to increases in cyclic AMP and subsequent abrogation of extracellular calcium influx into these cells (a mandatory step for degranulation and *do novo* mediator synthesis to take place) (52, 57). Thus, the H_2R agonist, impromidine mimicked the inhibitory actions of exogenously applied histamine on mast cells activated by the IgE-independent degranulating agent compound 48/80 and these effects were reduced by H_2R antagonists (58).

In contrast, H_1R expression in these cells is comparatively low, although it may be higher in immature mast cells such as the tumour cell line HMC-1 (52) and guinea pig basophils, where H_1R, but not H_2R, appear to be involved in enhancing the uptake of histidine in these cells (59). Certain H_1R antagonists such as terfenadine (but not cetirizine) have been shown to inhibit IgE-dependent mediator release from basophils (60), albeit at concentrations above 1 μM where H_1R-specificity may no longer apply. Similarly some H_1R antagonists of the new and newest generation can downregulate mast cell activation (61) It has, however, been shown that H_1R-antagonists lead to increased intracellular cAMP generation due to competitive antagonism with H_2R (52, 62).

Pharmacological modulators of histamine receptors showed that the H_3R does not affect human basophil function (63, 64). H_3R are strongly expressed in brain mast cells, which are affected by H_3R-modulating agents (65) but mast cells isolated from peripheral tissues gave rise to conflicting reports (65-67). These different findings may, in part, be due to the fact that H_3R share approximately 40% sequence homology with the more recently characterised H_4R (68, 69). H_3R and H_4R are functionally related and affected by non-specific agents such as α-methylhistamine ($H_3/_4R$ agonist) and thioperamide (antagonist) that were employed in various earlier studies.

Subsequent studies have shown a lack of H_3R expression on mast cells in contrast to high constitutive expressions of H_4R (52), which in mouse mast cells affect chemotaxis and intracellular calcium mobilization (70). Degranulatory function, however, was not affected by H_4R triggering and it appears that this receptor is primarily involved in the recruitment of effector cells into the tissues in chronic allergic inflammation (70). Although degranulation does not appear to be modified by H_4R in murine mast cells, several reports have shown that LTB_4 release is increased and supports neutrophil recruitment induced by zymosan (71, 72). Basophils also express H_4R, although the functional consequences of this receptor in either basophil migration or other cellular functions are at present unknown (70). (Figure 1)

2.3. Therapeutic potential of modulating H4-receptor function

Despite the remaining uncertainty as to the role of H_4R on regulating mast cell and basophil mediator responses there is now clearer evidence to suggest the potential benefit of pharmacological H_4R modulation in regard to allergic effector cell trafficking. Yu *et al.* clearly showed that H_4R blockade strikingly reduces mast cell and eosinophil migration into airway epithelial tissue in guinea pigs following allergen provocation (73). H_4R also appear to play a pivotal role in the ability of human mast cell precursors to migrate in the presence of CXCL12 (74).

In addition to basophils and mast cells, H_4R (but not $H_{1-3}R$) have been shown to play a pivotal role in eosinophil degranulation, migration to eotaxin and adhesion molecule expression (75-77). H_4R similarly affect the migration of CD4+ T cells and dendritic cell function (reviewed in 78). H_4R-/- mice as well as those treated with the H_4R-antagonist JNJ7777120 have been shown to exhibit decreased Th2-type responses (79). However, this is in stark contrast to Morgan *et al* showing that the H_4R agonist 4-methylhistamine inhibits airway narrowing and

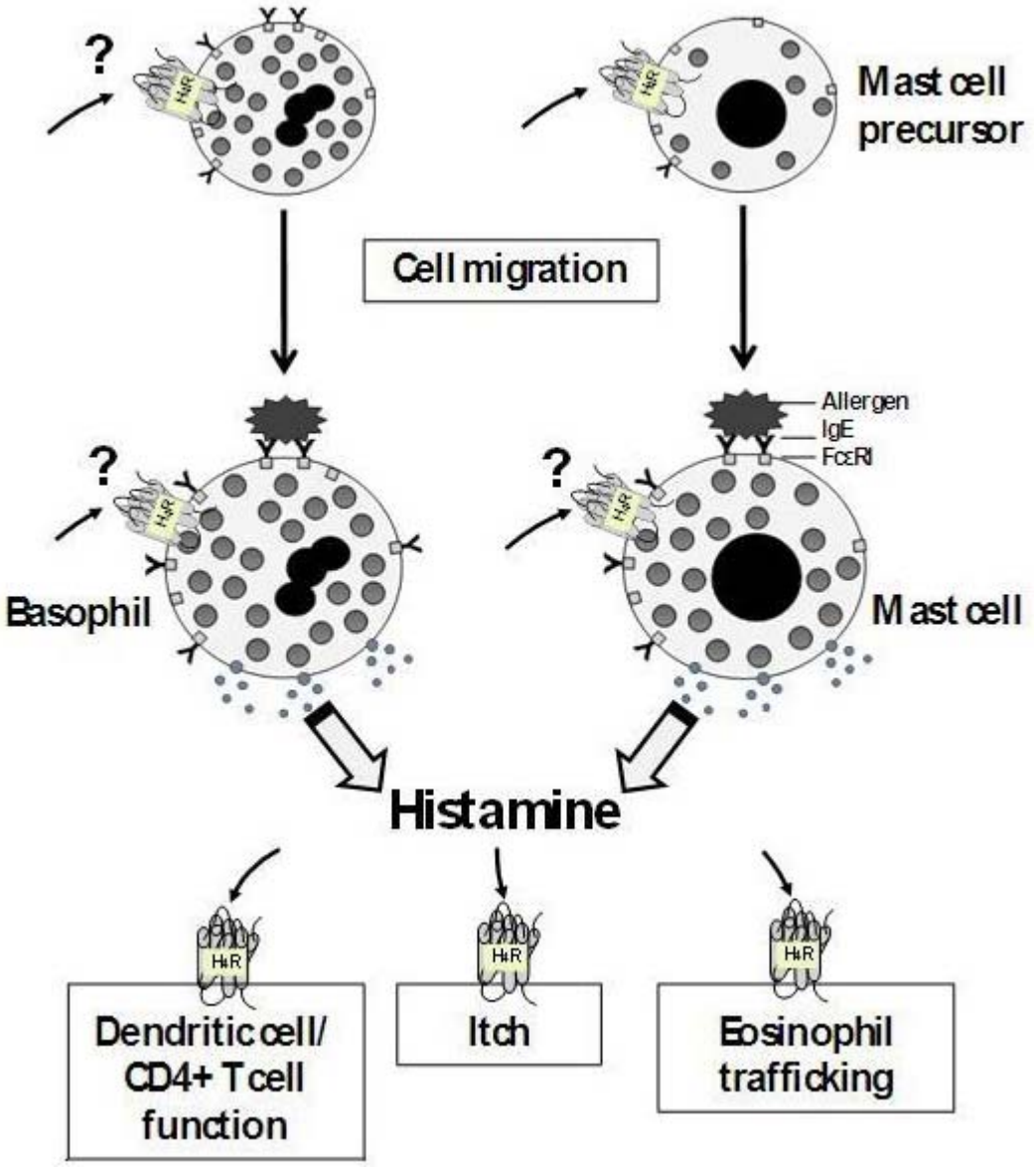

Figure 1. Schematic representation of the biological effects of histamine binding to H_4R. The receptor plays a crucial role in trafficking of mast cell precursors to various tissues locations. However, although the receptor is expressed on mature mast cells and basophils too its function is not fully understood. The H_4R is involved in altered cell function of both dendritic cells and CD4+ T cells and on C neuron afferent nerve endings where it mediates itch.

inflammation and increases the number of FoxP3+ regulatory T cells in the lungs (80). These authors speculated that these differences may be explained by the routes of administration of H_4R-modulating drugs and suggested that the directed migration of regulatory T cells may only occur after local, but not systemic, application of H_4R agonists (80).

While the immunomodulatory effects of H_4R-stimulation have not been clearly elucidated there is now a wealth of evidence showing the importance of this receptor in controlling histamine-induced itch. This is of course a major symptom of cutaneous reactions involving mast cells and basophils and, while it has long been recognised that H_1R is involved in pruritic responses, itch is often not substantially alleviated by the use of H_1R-antagonists. It is now apparent that both H_1R and H_4R are involved in governing histamine-dependent itch responses. In mouse models, the H_4R antagonist JNJ7777120 has been shown to be more effective at controlling pruritic responses caused by IgE-dependent and –independent stimulation of histamine release *in vivo* than H_1R antagonists (81). H_4R antagonism has recently been demonstrated by Rossbach *et al* to strongly attenuate pruritic responses, but not inflammation *per* se, to the contact allergen 2,4-dinitrochlorobenzene (82). Cowden *et al* likewise reported

reduced pruritic responses in a mouse model of skin inflammation mimicking the features of atopic dermatitis (83). However, in contrast to Rossbach *et al* (82), Cowden *et al* also observed anti-inflammatory properties using the H_4R antagonist JNJ7777120 (83), properties that these authors additionally observed in a mouse models of allergic airway inflammation (84). Anti-inflammatory properties have also been recently ascribed to another H_4R-antagonist A-940894 in a mast cell dependent model of zymosan-induced peritonitis (85). Overall, these studies suggest that combinational therapy with H_1R and H_4R antagonists may therefore prove highly beneficial for eliminating symptoms of itch, and possibly inflammation as well in certain settings.

To date, there is sufficient evidence to suggest a major role of histamine acting through the H_4R in the trafficking of allergic effector cells such as mast cells to tissue locations affected by allergic inflammation as well as in controlling itch. However, other functional effects of this receptor on allergic effector cells as well as antigen presenting cells and T cells have yet to be fully resolved but do suggest an important contribution of this receptor to immune responses that govern allergy. On balance, a combined approach to blocking both H_1R and H_4R effects may well prove to contribute substantially to more effective anti-allergic therapy.

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Abbreviations: TLR: Toll-like receptor

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