

**Pathogenetic and therapeutic implications of the histamine H4 receptor in inflammatory skin diseases and pruritus**

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**1. ABSTRACT**

Chronic inflammatory skin diseases such as atopic dermatitis (AD) are clinically characterized by erythematous and pruritic skin lesions, immunologically mediated by an inflammatory infiltrate consisting of T-cells, antigen presenting cells (APC) and eosinophilic granulocytes. Histamine levels are increased in lesions of inflammatory skin diseases. It is likely that histamine also plays a pathogenetic role since various relevant cell types such as T-cells and APC express functional histamine receptors. However, therapeutic blockade of the histamine H<sub>1</sub> and H<sub>2</sub> receptor is inefficient at least in the treatment of atopic dermatitis. We summarize here current data on the role of the recently described histamine H<sub>4</sub> receptor (H4R) in chronic inflammatory skin diseases. The H4R is functionally expressed on relevant cell types such as T-cells, APC and keratinocytes. In murine models of contact hypersensitivity and pruritus, H4R blockade had significant *in vivo* effects. Taken together, several lines of evidence suggest a role of the H4R in chronic inflammatory skin disease and the H4R might be a therapeutic target for diseases such as AD.

**2. INTRODUCTION**

Chronic inflammatory skin diseases are characterized by chronic skin inflammation and often severe pruritus. Typical and most common representatives of chronic inflammatory skin diseases are eczema, in particular atopic dermatitis (AD) and allergic contact dermatitis (ACD), and psoriasis. Various inflammatory cells, i.e., antigen presenting cells (APC), T-cells, granulocytes as well as skin resident cells, i.e., keratinocytes and nerve cells, play a role in the pathogenesis of inflammatory skin diseases. The mechanisms that are involved in inflammation and pruritus in these disorders are not entirely clear; more insight into the pathogenesis might offer new therapeutic options. One potential mediator with pathogenetic and therapeutic capabilities is histamine. Increased levels of histamine have been described in lesions of eczematous skin diseases and psoriasis (1) and can reach as high concentrations as 10<sup>-5</sup> to 10<sup>-3</sup> molar during immediate hypersensitivity reactions following mast cell degranulation (2). However, the data on histamine concentrations in chronic inflammatory skin diseases is limited thus far (Table 1). Further studies

**Table 1.** Concentration of histamine in lesions of inflammatory skin diseases (AD-Atopic dermatitis, ACD-allergic contact dermatitis)

Disease	Histamine concentration	Method	Reference
AD	Healthy, AD and psoriasis skin no difference (2.5-3 ng/ml)	Determination of histamine content in suction blister fluid with radioimmune assay	(65)
AD	AD: 262 +/- 68 ng histamine/mg protein Healthy controls: 196 +/- 30 ng histamine/mg protein (mean +/- SEM, difference Statistically not significant)	Skin biopsies, radioimmune assay	(66)
AD	Significantly increased histamine release from leukocytes in AD as compared to healthy controls	Stimulation of peripheral leukocytes with concana-valin A, double-isotope radioenzyme assay	(67)
ACD	In epidermis and dermis of ACD patients ~80% more histamine than in healthy	Fluorometric measurement	(68)
Psoriasis	Interstitial histamine concentration in lesional skin: 32 +/- 3 nmol/l, in nonlesional skin: 13 +/- 1 nmol/l	Intracutaneous microdialysis, radioimmunoassay	(69)
Masto-cytosis	Interstitial histamine concentration in affected skin: 42 +/- 14 nmol/l, in unaffected skin: 8 +/- 2 nmol/l	Intracutaneous microdialysis, radioimmunoassay	(70)
Cold urticaria	In the cold urticaria patients, an up to 80-fold increase of histamine was observed after cold challenge	Intracutaneous microdialysis, radioimmunoassay	(71)
Subjects with immediate type allergy	Histamine concentration baseline 4 ng/ml, after skin prick test in allergic subjects 81 (74-128) ng/ml	Intracutaneous microdialysis, Glass fibre fluorescence assay	(72)

applying quantitative techniques such as mass spectrometry and investigating skin and cells of the adaptive immune system and resident skin cells (which can endogenously produce histamine (3)) are needed.

Histamine is a pleiotropic mediator of immune and inflammatory disorders (4), and it is likely that histamine influences the course of inflammation and pruritus when it is released at sites of chronic inflammatory skin diseases. However, the therapeutic blockade of the H1R and the H2R is of limited effect in atopic dermatitis (5). A possible explanation is that histamine might exert its effects in these diseases via the H4R (6). This receptor has been shown to be expressed on a variety of immunologically relevant cell types such as antigen presenting cells, T-cells, granulocytes (7,6,8) and on nerve cells (9). Moreover, patients with AD express increased levels of the H4R on T-cells of the peripheral blood (10). A possible explanation could be particular H4R polymorphisms that result in a longer half-live and altered signal transduction of the H4R in AD (11).

We summarize here current knowledge of H4R expression and function on cell types relevant in and animal models relevant for chronic inflammatory skin diseases and pruritus.

## 3. EXPRESSION AND FUNCTION OF THE H4R ON RELEVANT CELL TYPES

Expression of the H4R and in some instances also function have been described on various cell types relevant in inflammatory skin diseases, as summarized in Table 2 and Figure 1 and in the following paragraphs.

### 3.1. APC

Human dendritic cells exposed to histamine downregulate IL-12 and prime a Th2 response (12,13,14,15,16). In first analyses of the H4R in human APC, monocytes and monocyte derived dendritic cells (MoDC) were investigated and shown to express the H4R

on the mRNA and protein level (17,18,14). The H4R was functional on such cells since H4R stimulation altered cytokine and chemokine production (suppression of IL-12 and CCL2) (18,14) and induced calcium influx and chemotaxis (17,18,14).

Recent studies focused on certain subtypes of dendritic cells that are of particular interest in inflammatory skin diseases, e.g., Langerhans cells (LC), inflammatory dendritic epidermal cells (IDEC) and inflammatory DC characterized by the 6-sulfo LacNAc group on their surface (slanDC).

Murine and human Langerhans cells express the H4R on mRNA and protein level and stimulation with histamine or a H4R agonist led to downregulation of the chemokine CCL2 in human LC. Moreover, migration of LC from the epidermis was increased after H4R stimulation in *ex vivo* migration assays using human epidermis and murine *in vivo* assays (19).

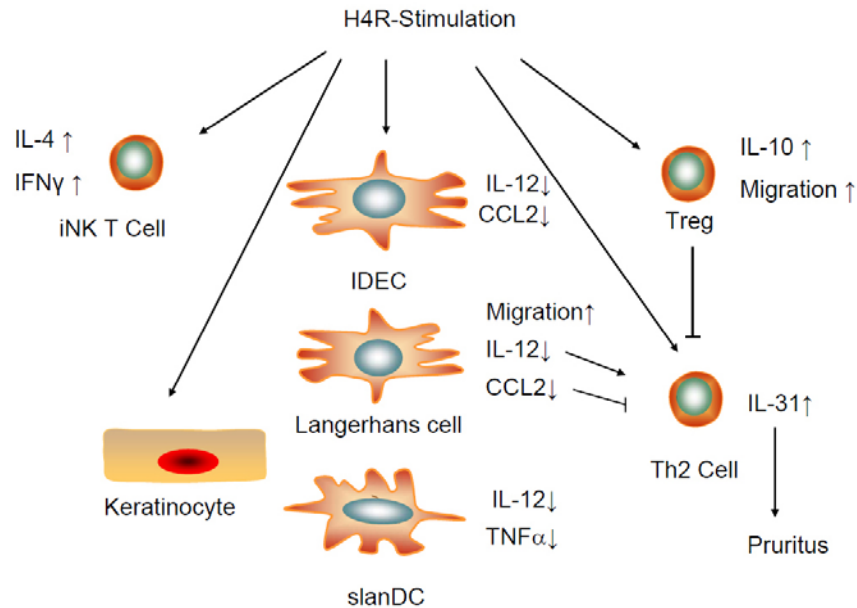
IDEC represent a particular dendritic cell type found in lesions of atopic dermatitis. The H4R is expressed on IDEC as well and its stimulation results in downregulation of IL-12 and CCL2 as described for monocytes and MoDC before (20). CCL2 (MCP-1) is involved in the migration of inflammatory cells such as granulocytes and lymphocytes and associated with a Th2 milieu. Thus, the H4R might also have anti-inflammatory effects by downregulating proinflammatory cytokines such as IL-12 and chemokines such as CCL2 under certain conditions that are not well defined yet.

On circulating slanDC the H4R could also be identified on the mRNA and protein level. The activation of the H4R led to the reduction of the proinflammatory capacity of slanDC, as shown by a strong decrease in the production of the proinflammatory cytokines TNF $\alpha$  and IL-12 (21).

Thus, the H4R is expressed on a variety of DC subsets relevant in inflammatory skin diseases and its engagement shows robust effects on chemokine (CCL2

**Table 2.** Expression and function of the human H4R (and the murine H4R as indicated) in cell types relevant in inflammatory skin diseases (Th-T helper cells, Treg-regulatory T cells, NKT-natural killer T cells, APC-Antigen presenting cells, LC-Langerhans cells, IDEC-inflammatory dendritic epidermal cells, MoDC-monocyte derived dendritic cells, BMDC-bone marrow derived dendritic cells, IFN $\gamma$ -interferon gamma, TNF $\alpha$ -Tumor necrosis factor alpha, m-murine, h-human)

Cell type	Expression and function H4R	Spe-cies	Reference
APC	Expression on protein level in human and murine LC, induction of migration, downregulation of CCL2	m, h	(19)
--LC		h	(20)
--IDEC	Expression on protein level, H4R upregulated by IFN $\gamma$ , downregulation of CCL2 and IL-12	h	(21)
--SLAN-DC	Expression on protein level, downregulation of TNF $\alpha$ and IL-12	h	(14)
--MoDC	Expression on mRNA and protein level, downregulation of IL-12 and induction of chemotaxis	h	(17)
--monocytes	Expression on protein level, induction of calcium influx and chemotaxis	h	(18)
Murine BMDC	Expression on protein level, H4R upregulated by IFN $\gamma$ , induction of calcium influx and downregulation of CCL2	h	(73)
	Expression on mRNA and protein level, induction of chemotaxis	m	
T-cells	Expression on mRNA level, H4R triggered IL-16 release	h	(26)
--CD8+	H4R agonists suppressed antigen-induced IFN $\gamma$ and IL-5 production, this effect could not be blocked with thioperamide	h	(23)
--CD4+ Th1/2		h	(10)
--CD4+ Treg	H4R mRNA and protein upregulated in Th2 cells, H4R stimulation on Th2 cells induced AP1 and IL-31 mRNA	m, h	(24)
--CD4+ Th17	H4R agonist 4-methylhistamine recruited Treg	h	Unpub-lished (Mommert, Werfel)
	Expression on mRNA and protein level, 4-methylhistamine induced IL-17 and AP1		
Murine NKT cells	NKT cells of H4R knockout mice and from mice lacking histamine produced significantly less IL-4 and IFN $\gamma$	m	(28)
Granulocytes	Expression on mRNA level, no effect on chemotaxis	h	(37,35,7,34)
--basophilic	Expression on mRNA level	h	(39,37,38)
--eosinophilic	Shape change, actin polymerization, calcium mobilization, upregulation of adhesion molecules, chemotaxis, migration from blood into tissue	h	
--neutrophilic	Expression on mRNA level, no functional effect on chemotaxis	m	(37,35,38,7,34)
	H4R on eosinophils and basophils, but not neutrophils		(35,74)
	Neutrophil chemotaxis		
Keratinocytes	Expression on protein level	h	(44)
	Upregulation in differentiated keratinocytes		
Fibroblasts	Expression mRNA and protein	h	(45)
	Upregulation by LPS and indomethacin on mRNA and by dexamethasone on protein level		
Mast cells	Expression on mRNA and protein level	m, h	(35,48)
	enhanced recruitment of CXCL12 expressing precursors	h	(49)
	Calcium mobilization, chemotaxis	m	(35,50)



**Figure 1.** H4R effects on various cell types relevant in chronic inflammatory skin diseases. Schematic overview of known target cells relevant in inflammatory skin diseases that express the H4R. After stimulation of the H4R on antigen presenting cells (APC), IL-12 and CCL2 are downregulated and migration is enhanced. Stimulation of H4R on Th2 cells induces upregulation of IL-31, a cytokine central for the induction and maintenance of itch. Activation of H4R on invariant natural killer cells leads to an increased secretion of IFN $\gamma$  and IL-4. H4R activation may also induce migration of regulatory T-cells and production of the anti-inflammatory cytokine IL-10. The H4R is also expressed on keratinocytes, but its effects on these cells are unclear at present. Thus histamine exerts an immunomodulatory role via H4R, and both pro- and anti-inflammatory signals are mediated via H4R. Reproduced with permission from (10).

downregulation) and cytokine (IL-12 and TNF $\alpha$  downregulation) expression as well as chemotactic activities. However, from these effects it is not clear if it is beneficial to activate or to block the receptor to therapeutically influence the course of inflammatory skin diseases.

### 3.2. T-cells

H4R mRNA and protein were expressed by CD4<sup>+</sup> T-helper cells (Th-cells) and upregulated by the Th2 associated cytokine IL-4. Studies based on this observation showed that H4R expression was higher on Th2-cells as compared to Th1-cells and that stimulation of the H4R with specific agonists induced the transcription factor AP-1 in Th2- but not in Th1-cells. H4R stimulation upregulated the mRNA levels of IL-31, a cytokine that has been associated with the induction of pruritus. Interestingly this effect was more pronounced in PBMC and T-cells isolated from patients with AD. Thus, the H4R on Th2-cells could represent a new link between histamine and induction of pruritus, in particular in AD (10).

H4R activation led to downregulation of signal transducer and activator of transcription 1 (STAT1) phosphorylation in human PBMC stimulated with phytohemagglutinin (PHA). Since STAT1 is associated with Th1 signalling, this also points towards a suppressive effect of the H4R on Th1-cells, however, from this study it is not clear if STAT1 downregulation is a direct or indirect effect on Th-cells, since PBMC were investigated (22).

On PBMC and T-cell clones, stimulation of the H4R with various ligands such as 4-methylhistamine and clobenpropit resulted in downregulation of antigen induced interferon gamma and IL-5 production. However, this effect was not blockable with the H3R/H4R antagonist thioperamide, raising the question of the H4R specificity of these effects (23).

Effects of the H4R agonist 4-methylhistamine on regulatory T-cells (Treg) were also found in one study. Murine allergic airway inflammation was attenuated by intratracheal administration of 4-methylhistamine, which was ascribed to an accumulation of FoxP3<sup>+</sup> regulatory T-cells and increased IL-10 production (24). Moreover, 4-methylhistamine attracted predominantly human Treg in *in vitro* assays (24). However, since these effects were not blocked with a H4R antagonist it is possible that they might reflect signalling via the H2R that can also be activated via 4-methylhistamine. In murine models of allergic asthma, blockade of the H4R resulted in decreased T-cell recruitment into the lung (25).

Expression of the H4R on Th17 cells was detected on mRNA and protein level. Stimulation with histamine or a H4R agonist up-regulated the production of IL-17 and induced the transcription factor AP1 in *in vitro* differentiated Th17 cells (S. Mommert, T. Werfel, unpublished data).

CD8<sup>+</sup> T cells express H4R mRNA and stimulation of the H4R resulted in release of the T-cell chemoattractant IL-16 (26).

Invariant natural killer T cells (NKT cells) represent a new cell type that has been found in lesions of atopic and allergic contact dermatitis and other types of inflammation (27). After activation, they express IFN $\gamma$  and IL-4, however, it is not clear under which conditions they trigger a Th1 or Th2 response (27). A recent report showed that murine invariant NKT cells from H4R knockout mice and histidine carboxylase deficient mice (lacking histamine) produce less IFN $\gamma$  and IL-4. This was due to a functional deficit and numerical decrease of invariant NKT cells (28).

### 3.3. Natural Killer Cells

Natural killer (NK) cells (CD56<sup>+</sup>/CD3<sup>-</sup>) comprise about 15% of the lymphocytes in human peripheral blood representing an important early effector cell of the innate immune system. In lesional skin of atopic eczema NK cells were observed in close proximity to dendritic cells which points to a role of NK cells in modulating the function of DCs in atopic dermatitis. (29). The expression of the H1R and H4R on human activated NK cells was identified on protein level. (17). In this study the induction of chemotaxis of NK cells upon histamine stimulation and the inhibition of this effect by the H3R and H4R antagonist thioperamide was shown. Since NK cells lacked the expression of H3R this points towards the H4R mediated induction of NK cell chemotaxis.

### 3.4. Granulocytes

Granulocytes play an important role in the pathology of inflammatory skin diseases: Increased numbers of circulating eosinophils are frequently observed in patients with AD and activated eosinophils are present in the lesional skin (30,31). Clark *et al.* showed already 35 years ago that histamine influences the function of eosinophils by acting as chemoattractant (32) and it was known that the effect was mediated by a novel histamine receptor, since agonists at the H1R and H2R (histamine receptors known at that time) were ineffective (33). Decades later the H3R and H4R were identified and H4R expression was shown on human eosinophils and neutrophils (7,34). In the murine system the H4R was detected on eosinophils and basophils, but not on neutrophils (35). The first study identifying the novel H4R as inducer of chemotaxis in human eosinophils was performed in 2002 (36). Two subsequent studies (37,38) showed in more detail that histamine acting via the H4R functions as classical leukocyte chemoattractant by the induction of actin polymerization, calcium mobilization, alteration in cell shape and the upregulation of adhesion molecules CD11b/CD18 and CD54. Moreover migration of eosinophils from blood into inflamed tissue was shown in response to H4R activation (39). In contrast, for human neutrophils and basophils no effect of H4R on chemotaxis was observed (37,38).

### 3.5. Skin cells

Resident skin cells play important roles in the pathology of AD and other inflammatory skin diseases: in the epidermis residing keratinocytes (KC) and Langerhans

cells (see chapter on APC), and in the dermis fibroblasts and mast cells.

As the main cellular constituent in the skin KC play many important roles in the course of inflammation. They establish the local cytokine and chemokine milieu, which is necessary for the attraction of other cell types to the site of the immune response and they represent the front-line defence against hazardous agents. KC were already shown to express the H<sub>1</sub>R and several immunomodulatory effects of histamine have been observed (40,41,42,43). Concerning the role of H4R it was shown by immunostaining that human epidermal tissues express the H4R and higher expression was observed in differentiated KC as compared to basal KC (44). Our own studies confirm the expression of the H4R on KC (unpublished data). Until now the regulation and function of the H4R on KC was not addressed in any study.

Ikawa *et al* showed that human dermal fibroblasts express the H4R on mRNA and protein level. In addition they described upregulation of the H4R on mRNA level by LPS and indomethacin and on protein level by dexamethasone (45). The role of fibroblasts in AD is not very well understood, however changes in morphology and cell mediated cytotoxicity against skin fibroblasts were shown in AD skin (46). Based on proteomics a recent study suggests that fibroblasts show gene expression profiles associated with AD and therefore might play a role in the pathogenesis of AD (47).

Mast cells are located in the dermis close to adjacent blood vessels and upon degranulation, an array of Seike *et al.* used trinitrochlorobenzene as hapten to elicit ACD in mice, a hapten similar to dinitrochlorobenzene. Even doses of the H4R antagonist JNJ7777120 up to 100 mg/kg did not reduce the acute allergic response. By chronification of the lesions, however, a reduction of inflammatory response accompanied by a diminished mast cell and eosinophilic infiltration was observed in this study published by Seike *et al.* on 2009 (53).

More recently reduction of the inflammatory response induced by topical administration of the hapten fluorescein isothiocyanate (FITC) was seen also in the acute phase of allergic dermatitis by treatment with JNJ7777120 (2 x 20 - 50 mg/kg) (54). One characteristic of the FITC model is a distinct eosinophilia, which is less pronounced in other models of hapten induced contact dermatitis (e.g. by DNCB or TDI). In this respect, it is interesting that the dual H3/H4 receptor antagonist thioperamide was effective in reducing inflammation in a modified model of picryl chloride induced allergic dermatitis, in which blood eosinophilia was induced by cyclophosphamide. A combination of thioperamide with the H1R antagonist pyrilamine even enhanced the anti-inflammatory effect (55).

Taken together, these results indicate that H4R blockade can reduce inflammation in chronic ACD and acute ACD with predominant Th2 milieu, but there appears to be only a minor role for H4R-antagonism in lesions of acute ACD with predominant Th1 milieu.

pre-stored and newly synthesized mediators is released, which regulate the recruitment and function of other immune cells involved in the inflammatory response in the skin. The expression of the H4R on human mast cells on mRNA and protein level was shown by diverse methods (35,48) and another study showed that H4R activation might promote allergic inflammation by enhanced CXCL12 mediated recruitment of precursor mast cells into the dermis (49). Accordingly also in murine mast cells H4R induced calcium mobilization and chemotaxis were observed (35,50). These studies indicate that the H4R on mast cells is of great relevance for mast cell accumulation in allergic tissues. In contrast no effect of H4R activation on mast cell degranulation and subsequent mediator release was observed (35).

## 4. ANIMAL MODELS

Effects of H4R antagonists have been tested in murine models of allergic dermatitis, in skin of laboratory beagles and in a canine model of atopic dermatitis.

In two studies acute models of allergic contact dermatitis were used and in one additional study acute lesions were compared to chronic lesions induced by repetitive topical administration of the relevant hapten.

The selective H4R antagonist JNJ7777120 (3 x 15 mg/kg) did not reduce the ear swelling induced by the haptens dinitrochlorobenzene (DNCB) and toluenediisocyanate (TDI) which differ in their induction of a Th1 and Th2 dominated inflammatory response (51,52).

To explore the role of H4R in canine skin, in a first setting histamine and H4R agonists were injected intradermally to laboratory beagles with the intention to study a classical wheal and flare reaction and pruritus. A wheal and flare reaction was also seen after intradermal injection of histamine and the H4R agonists clobenpropit and VUF4830, however, pruritus could not be induced by either substance (56). Interestingly, topical pre-treatment with JNJ7777120 before histamine application reduced the wheal and flare reaction by approximately 30% indicating also a role of the H4R in this reaction (56).

The prevention of skin lesions by H4R antagonists was also tested in an alternative canine model of atopic dermatitis (57). Six atopic Maltese-beagle crossbred dogs experimentally sensitized to *Dermatophagoides farinae* (Df) were enrolled into this blinded placebo and active controlled experiments. H4R antagonists (JNJ7777120 or JNJ28307474) were applied topically before allergen challenge. JNJ28307474 was also given orally after allergen challenge. A triamcinolone acetonide solution applied topically was used as a positive control. Skin lesions that developed after the application of Df allergen were graded at the site of allergen application. Twenty four hours after challenge, placebo treated animals and animals treated with topical and oral JNJ28307474 or topical JNJ7777120 showed a comparable lesion score, whereas the triamcinolone solution prevented all dogs from having any lesions. These data provide evidence that the

preventive administration of H4R antagonists has no impact on the development of acute inflammatory skin lesions induced by the topical administration of a relevant allergen. It is thus intended to study effects of H4R antagonists in chronic skin lesions (Bäumer *et al.*, manuscript submitted).

### 5. PRURITUS AND H4R EXPRESSION ON NERVE CELLS

Although histamine is one of the major mediators in allergic diseases and H1R antagonists are effective in animal models of pruritus (58,52) the classical H1-antihistamines show insufficient efficacy in treatment of pruritus and allergic inflammatory processes (5). The H2R seems not to be involved in pruritus as H2R agonists do not induce scratching and the H2 antagonist cimetidine does not reduce histamine-induced scratching (58). The role of the H3R in pruritus is still debated in literature. Intradermal injection of the H3R/H4R antagonist thioperamide induced scratching behaviour in mice (59). On the other hand, systemically administered thioperamide dose dependently reduced histamine- or clobenpropit-induced scratching behaviour in mice (58), which is in agreement to our own observations. First indications that the H4R is involved in pruritus have been made by Bell *et al.* (58). It was demonstrated that intracutaneously administered clobenpropit (H3R antagonist/H4R agonist) induced scratching behaviour in mice which was antagonised by systemic administration of the H3/H4R-antagonist thioperamide. Moreover, the selective H4R agonist 4-methylhistamine was found to cause itch in mice after intradermal injection similar to that seen with histamine (60). Furthermore, H4R antagonists showed similar or even superior effects compared to traditional H1R blocking antihistamines in the attenuation of experimental pruritus, supporting this point of view (60). In a model of allergen mediated pruritus induced by repetitive administration of strong sensitizers a combination of the H1R antagonist cetirizine and the H4R antagonists JNJ7777120 led to a reduction of scratching bouts to up to 90% (52). Interestingly, itch inducing properties of histamine and inhibitory effects of H4R antagonist were unaltered in mast cell-deficient mice, indicating that mast cells are not involved in this model of histamine induced itch (60). Based on findings of antipruritic and antinoceptive properties of H4R antagonists in a mast cell independent fashion, a possible presence of the H4R on sensory neurons was postulated (61,60). In 2009, Strakhova *et al.* reported the expression of the H4R in peripheral nervous tissue, mRNA of the H4R was found in human and rat dorsal root ganglia (DRG) (62). High levels of mRNA were detected in primary cultures of rat DRG neurons, but not in glial cells. As DRG neurons contain cell bodies of sensory afferents, these findings further corroborate the hypothesis that the H4R is involved in neural transmission of itch and pain. Furthermore, an earlier study located the H4R on the nerves by immunohistochemical staining of human nasal mucosa (63). Recent studies revealed the expression of H4R in several regions of human and rat CNS, including the spinal cord (9,62). Moreover, Connelly *et al.* reported that activation of H4R directly hyperpolarized cortical neurons

(9). However, even so JNJ7777120 crosses the blood-brain barrier it does not affect the measures of sedation in rodents, indicating that the inhibitory effects of H4R antagonism on pruritus are not secondary to sedation (60). The neurophysiological basis for the itch sensation was unclear for decades until microneurographic studies revealed the existence of mechano-heat-insensitive C-fibres that are dedicated for the transmission of itch. These “itch” fibers are preferentially activated by pruritogens like histamine and respond to histamine application with a time course of excitation that reflects the sensation of itch (64). Although it can not be completely excluded that other cells than mast cells in the skin, such as keratinocytes, are required for initiation of H4R-mediated itch, it can be assumed that the induction of histamine (H4)-induced itch is possibly due to direct activation of H4R located on nerve endings of nociceptive C fibres in the skin.

### 6. SUMMARY

There is accumulating evidence that the histamine H4R plays a pathogenetic role in chronic inflammatory skin disease. On the cellular level, the H4R modulates the function of relevant cell types. In animal models, blockade of the H4R results in reduction of pruritus and, at least under certain not yet defined conditions in the reduction of inflammation. Thus, the H4R represents a promising therapeutic target in chronic inflammatory skin diseases.

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## Histamine H4 receptor in inflammatory skin diseases

**Abbreviations:** AD: Atopic dermatitis; ACD: Allergic contact dermatitis; APC: antigen presenting cell; BMDC: murine bone marrow derived dendritic cells; DC: dendritic cell; H1R, H2R, H3R, H4R: histamine H1, H2, H3, H4 receptor; IDEC: inflammatory dendritic epidermal cells; IFN $\gamma$ : Interferon gamma; KC: keratinocyte; LC: Langerhans cell; MoDC: monocyte-derived dendritic cells; NK cells: natural killer cells; NKT cells: natural killer T-cells; PBMC: peripheral blood mononuclear cells; S1aDC: DC bearing a 6-sulfo LacNAc group on their surface; Th-cells: T-helper cells; TNF $\alpha$ : Tumor necrosis factor alpha; Treg: regulatory T cells

**Key Words:** Histamine, H4 receptor, Atopic Dermatitis, Eczema, Psoriasis, Pruritus, Review

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