

REVIEW ARTICLE

The role of the histamine H₄ receptor in atopic dermatitis and psoriasis

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Atopic dermatitis (AD) and psoriasis are common skin diseases with a high negative impact on patients' quality of life. Both diseases are mediated by a pro-inflammatory infiltrate consisting of several cell types, such as T-cells, antigen-presenting cells and granulocytes and display disturbed keratinocyte differentiation. Given the fact that histamine levels are also highly elevated in inflamed skin, it is likely that histamine plays a relevant role in disease pathology. However, antagonists blocking histamine H₁ receptor or H₂ receptors are largely ineffective in reducing chronic symptoms in AD and psoriasis. Over the last years, much research has been undertaken to shed light into the mode of action of the most recently discovered histamine H₄ receptor. This research has shown that H₄ receptor antagonists display antipruritic and anti-inflammatory effects not only in mouse models but also in first human clinical trials, and therefore, H₄ receptors might present a novel therapeutic target. In this review, we summarize the effects of the H₄ receptors on different cell types, mouse models and clinical studies in regard to AD and psoriasis respectively.

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Abbreviations

AD, atopic dermatitis; APCs, antigen-presenting cells; CD, cluster of differentiation; DCs, dendritic cells; DNCB, dinitrochlorobenzene; FcεRI, high-affinity IgE receptor; LCs, Langerhans cells; mDCs, myeloid dendritic cells; 4MH, 4-methylhistamine; OVA, ovalbumin; PASI, Psoriasis Area Severity Index; pDCs, plasmacytoid dendritic cells; poly I : C, polyinosinic–polycytidylic acid; SCORAD, score of atopic dermatitis; slan DCs, 6-sulfo LacNAc-expressing dendritic cells; SNP, single nucleotide polymorphism; TDI, toluene diisocyanate; TNCB, trinitrochlorobenzene; Treg, regulatory T-cells; TSLP, thymic stromal lymphopoietin

Introduction

Histamine, a pleiotropic mediator, is involved in a variety of physiological and pathological processes in both the CNS and the periphery (Panula *et al.*, 2015). Over the last century, four **GPCRs** were identified binding histamine as a ligand. The **H₁ receptor** was the first histamine receptor to be discovered, in 1937 by Bovet and Staub (1937) (Simons and Simons, 2011), followed by the **H₂ receptor** in 1972 (Black *et al.*, 1972) and the **H₃ receptor** in 1983 (Arrang *et al.*, 1983). Antagonists blocking the H₁ receptor or the H₂ receptor became successful drugs for the treatment of allergic diseases and gastric acid secretion, respectively, and they are still in use today (Thurmond, 2015). The H₃ receptor modulates histamine actions in the brain, and an inverse agonist of this receptor has been approved for the treatment of narcolepsy since 2016 (Baumann, 2017). However, no antagonists of the H₁, H₂ or H₃ receptors are able to reduce the inflammatory and pruritic symptoms in chronic inflammatory skin diseases like atopic dermatitis (AD) or psoriasis, although it is well known that histamine is elevated in inflamed skin and plays a relevant role in disease pathology (Gutzmer *et al.*, 2011). In the early 2000s, the **H₄ receptor** was described by several groups (Nakamura *et al.*, 2000; Oda *et al.*, 2000; Liu *et al.*, 2001a). Various selective H₄ receptor ligands and the use of H₄ receptor ^{-/-} mice allowed the analysis of the expression and the function of these receptors (Thurmond, 2015; Ko *et al.*, 2018). This revealed a relevant role of H₄ receptors in mediating pruritus and in the modulation of cellular responses in several immune and epithelial cells, which are important in the pathogenesis of inflammatory skin diseases (Gutzmer *et al.*, 2011; Thurmond, 2015). Moreover, in first clinical trials, H₄ receptor antagonists reduced inflammation and scratching behaviour in patients with AD (Murata *et al.*, 2015; Werfel *et al.*, 2018).

In this review, we summarize the current knowledge regarding the expression and function of H₄ receptors with respect to inflammatory skin diseases. Furthermore we focus on different human cell types, mouse models and clinical studies in the most frequently occurring skin diseases, AD and psoriasis.

The role of H₄ receptors in AD

Disease pattern

AD is a chronic inflammatory skin disease and affects up to 20% of children and up to 3% of adults, and the prevalence is still increasing (Nutten, 2015). It is associated with a characteristic distribution of eczematous skin lesions and intensive itch as dominant clinical features, which has a high negative impact on patients' quality of life (Werfel *et al.*, 2016b). The pathophysiology is complex with mainly a Th2-driven systemic immune dysfunction accompanied by an interaction with keratinocytes. Although numerous risk and trigger factors have been identified, including a genetic predisposition, skin barrier disruption or environmental conditions, such as exposure to allergens or microbes, the underlying mechanism of the development of AD still remains unclear (Werfel, 2009; Nutten, 2015). One of the

characteristics of AD is the presence of T-cells in the affected skin with an initial Th2 polarization and a more Th1-dominated milieu in chronic AD (Werfel *et al.*, 2016a). However, other cell populations are also critical for the initiation and maintenance of the disease, such as dendritic cell (DC) types expressing **high-affinity IgE receptors** (FcεR1s), which are able to take up and present antigens penetrating the epidermis. Moreover, mast cells, eosinophils, basophils and NK cells are elevated in the skin of AD patients and contribute to disease pathology, although their exact role still needs to be elucidated (Werfel *et al.*, 2016a). Accompanied by the increased number of immune cells in the skin, there are also several inflammatory mediators which are up-regulated such as **IL-4**, **IL-5**, **IL-13**, **IL-31**, the chemokine **CCL17**, thymic stromal lymphopoietin (**TSLP**) and histamine, which on one side amplify eczematous lesions and on the other side directly mediate pruritus (Werfel *et al.*, 2016a). A schematic overview is illustrated in Figure 1.

Strategies for the treatment of AD are limited. Systemic glucocorticoids and cyclosporine should not be used for long-term treatment due to various side effects. **Dupilumab**, a human monoclonal antibody against the **IL-4 receptor α chain** that is shared by the IL-4 receptor and IL-13 receptor, has been documented to significantly improve most of the clinical outcomes. Dupilumab showed long-term efficacy and an acceptable safety profile: injection-site reactions and conjunctivitis were more common in patients treated with dupilumab when compared with placebo. Therefore, dupilumab has been approved in the USA and in the European Union for the treatment of moderate-to-severe AD only (Werfel, 2018). Thus, there is still an urgent need to extend the spectrum of potential drugs for long-term therapy in AD patients.

The role of H₄ receptors in human cells relevant in AD

T-cells. T-cells are considered to be the driving force of the inflammatory response in AD (Gutzmer *et al.*, 2011; Werfel *et al.*, 2016a). More specifically, Th2 cells expressing cytokines such as IL-4, IL-5 and IL-13 have been found to be elevated in skin biopsies from AD patients, compared with normal control skin from healthy subjects or to non-lesional skin from AD patients (Hamid *et al.*, 1994). It has been proposed that this Th2-dominated micromilieu observed in AD and especially the cytokine IL-4 lead to the up-regulation of H₄ receptors in CD4⁺ T-cells. In line with this, H₄ receptors are predominantly expressed in *in vitro*-differentiated Th2 cells compared with Th1-differentiated cells (Sugata *et al.*, 2007; Gutzmer *et al.*, 2009). In contrast, the stimulation of naïve CD4⁺ T-cells with IL-4 results in the down-regulation of the H₁ receptor mRNA expression levels (Jutel *et al.*, 2001).

Stimulation of the H₄ receptors in human peripheral blood mononuclear cells and Th2 cells leads to up-regulation of IL-31 mRNA expression levels (Gutzmer *et al.*, 2009), a cytokine that is strongly related to the induction of pruritus.

Antigen-presenting cells. A resident population of Langerhans cells (LCs) is located in the epidermis, and populations of monocytes, DCs and macrophages infiltrate the dermis. This heterogeneous group of antigen-presenting leukocytes

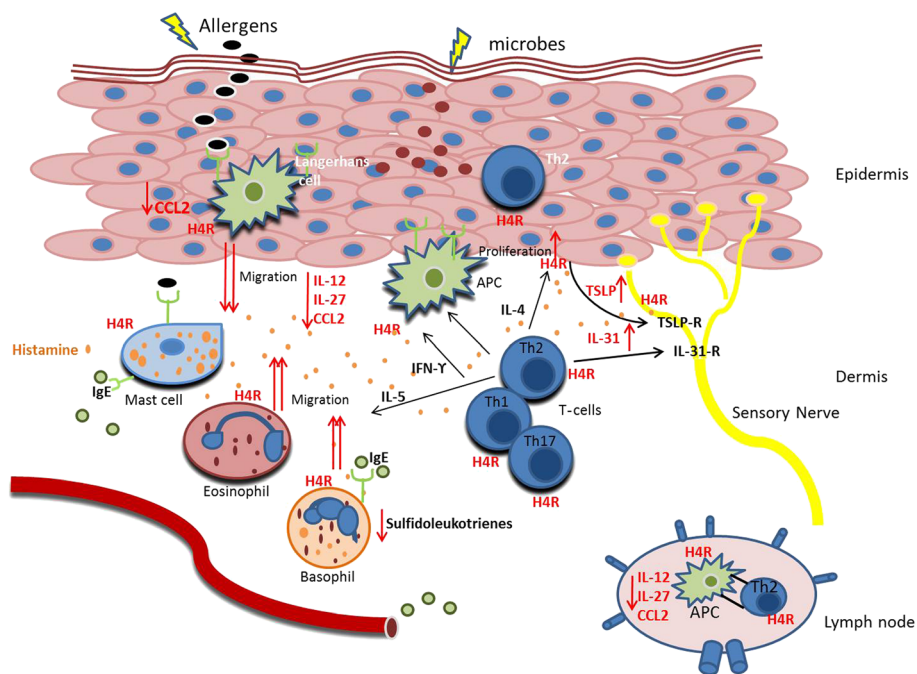


Figure 1

The role of histamine H_4 receptors on human cells relevant in AD. These receptors (H_4R) are expressed on keratinocytes and different immune cell populations, which play a role in inflamed skin of AD. In the Th2-dominated phase of acute inflammation, various cell types such as mast cells, granulocytes, Th cells, macrophages and APCs are detectable in the skin. Engagement of the $Fc\epsilon R1$ triggers release of histamine from mast cells and basophils. Histamine in turn is able to mediate several pro-inflammatory and anti-inflammatory effects *via* its binding to H_4 receptors. In basophils, stimulation of H_4 receptors reduces the $Fc\epsilon R1$ cross-linking-mediated release of sulfidoleukotrienes. In APCs, various pro-inflammatory cytokines like IL-12, IL-27 and CCL2 are down-regulated. However, the decrease of these cytokines results to an impaired Th1 polarization and to a shift towards a Th2-driven immune response, which further can lead to an exacerbation of the symptoms seen in acute AD. In line with this, histamine *via* H_4 receptors increases the chemotaxis of APCs, eosinophils and basophils that is essential for the recruitment of the cells into the skin. Moreover, stimulation of H_4 receptors up-regulates the production of IL-31 in Th2 cells and TSLP release from keratinocytes. IL-31 and TSLP are able to trigger a Th2 polarization and to directly mediate pruritus. In addition, histamine through H_4 receptors increases the proliferation rate in keratinocytes of AD patients. Conclusively, the pro-inflammatory effects of H_4 receptors seem to be more important in disease pathology. The effects mediated by H_4 receptors are highlighted in red.

is important for the activation of both the innate and adaptive arms of the immune system mainly by their capacity for potent antigen presentation and T-cell activation.

Monocytes/DCs. The mRNAs for H_1 , H_2 and H_4 receptors are expressed in human monocytes (Gutzmer *et al.*, 2005; Glatzer *et al.*, 2014; Capelo *et al.*, 2016; Mommert *et al.*, 2018c). The H_4 receptor has a functional role on these cells, as induction of calcium influx, down-regulation of the chemokine **CCL2** and down-regulation of **polyinosinic-polycytidylic acid** (poly I : C)-induced expression of **IL-12** in response to stimulation, were observed. These effects were reversed by pretreatment of the cells with H_4 receptor antagonists (Gutzmer *et al.*, 2005; Dijkstra *et al.*, 2007). In addition, **IL-27** expression is down-regulated *via* H_2 and H_4 receptors in human monocytes. Stimulating human keratinocytes with supernatants from histamine stimulated monocytes resulted in less production of the Th1-associated chemokine **CXCL10**, when compared with supernatants from unstimulated samples. This experiment demonstrates that the functional effect of histamine in monocytes

resulted in decreased activation of keratinocytes (Gschwandtner *et al.*, 2012).

Similar to the effects on monocytes, down-regulation of poly I : C-induced expression of IL-12 and spontaneous down-regulation of CCL2 *via* H_4 receptors were also described in inflammatory dendritic epidermal cells (Dijkstra *et al.*, 2008).

LCs, as immature antigen-presenting cells (APCs), resides in the supra-basal layers of the epidermis in close contact with keratinocytes. Expression of H_4 receptors was detected in *in vitro*-generated monocyte-derived LCs at mRNA level. In naturally occurring $CD207^+$ LCs, H_4 receptors were also detected by flow cytometry or by immunofluorescence. Stimulation with different histamine receptor agonists showed a down-regulation of CCL2 expression and induced migration *via* H_4 receptors. These effects were blocked by H_4 receptor antagonists (Gschwandtner *et al.*, 2010). On one hand, increased migration may foster antigen presentation by LCs, and on the other hand, down-regulation of CCL2 may restrain accumulation of immune cells in the dermis.

Beyond expression on their immature precursors, expression of mRNAs for H_1 , H_2 and H_4 receptors have been detected in different subtypes of mature APCs such as in

6-sulfo LacNAc-expressing DCs (slan DCs) and in myeloid DCs (mDCs) (Glatzer *et al.*, 2014). Agonists of H₂ and H₄ receptors down-regulated LPS-induced expression of **TNF- α** and IL-12 in slan DCs (Gschwandtner *et al.*, 2011b).

Macrophages. As a result of the pathogenic and tissue changes during AD, monocytes may differentiate into macrophages and respond to environmental cues with polarization into distinct functional phenotypes. In the presence of the Th2 cytokines IL-4 or IL-13, the M2a macrophage phenotype is induced. In human monocytes, levels of H₁, H₂ and H₄ receptors are low but are up-regulated during the differentiation process from monocytes to DCs or macrophages (Gutzmer *et al.*, 2005; Glatzer *et al.*, 2014; Capelo *et al.*, 2016; Mommert *et al.*, 2018b). Targeting the H₁, H₂ and H₄ receptors on M2 macrophages affected the M2 phenotype by differentially regulating the expression of the macrophage differentiation marker CD68 or of the scavenger receptor CD163. In addition, the expression of the anaphylatoxin **C3a receptor** was down-regulated *via* H₄ receptors (Mommert *et al.*, 2018c). The M2 phenotype is characterized by secreting specific chemokines such as CCL17 and **CCL22**, which are abundant in AD. In particular, CCL17 represents a sensitive biomarker for disease activity in AD (Morita *et al.*, 2010).

The role of histamine in CCL17 and CCL22 expression in human monocytes and M2 macrophages was investigated in a recent study by Mommert *et al.*, (2018b). Activation of monocytes or fully differentiated M2 macrophages by Th2 cytokines led to pronounced secretion of CCL17 and CCL22. Remarkably, in contrast to CCL22 expression, the IL-4-induced or IL-13-induced CCL17 mRNA and protein production was selectively potentiated by stimulating the H₂ receptors but not by agonists specific for H₁ or H₄ receptors (Mommert *et al.*, 2018b). By applying the H₄ receptor antagonist JNJ-7777120, Miyano *et al.* (2016) demonstrated that these receptors were responsible for enhanced spontaneously or peptidoglycan-induced production of CCL17 and as opposed to our study also of CCL22 production in monocyte-derived LCs in patients with AD.

Summing up, APCs and macrophages regularly express the mRNA for H₁, H₂ and H₄ receptors. Histamine may have a potent function in the physiopathology of inflammatory skin diseases through a tight control of Th1/Th2 cytokine and chemokine production. On one hand, mainly Th1-related cytokines or chemokines such as IL-12, IL-27 or CXCL10 (Gutzmer *et al.*, 2005; Gschwandtner *et al.*, 2012; Glatzer *et al.*, 2014) are down-regulated *via* H₄ receptors leading to a shift into a more Th2-dominated milieu, which may antagonize a Th1 cell-mediated inflammation. On the other hand, histamine acts as chemoattractant *via* H₄ receptors which may lead to an accumulation of immune cells building up the dermal infiltrate. In addition, up-regulation of CCL17 production in M2 macrophages or CCL17 and CCL22 in LCs *via* H₂ or H₄ receptors, respectively, provides inflammatory effects.

Granulocytes. Eosinophils and basophils infiltrate the skin under pathophysiological conditions, and an increased cell number in the blood correlates with disease severity in AD (Werfel *et al.*, 2016a). Although the specific role of both cell

types remains unclear for the pathogenesis of AD, it is possible that eosinophils and basophils trigger the inflammatory response by secreting a broad spectrum of pro-inflammatory cytokines.

It has been shown that human eosinophils express functional H₄ receptors and that histamine mediates chemotaxis, calcium influx and shape change (Buckland *et al.*, 2003; Ling, 2004; Reher *et al.*, 2012; Thurmond, 2015). Thus, it seems that H₄ receptors have a pro-inflammatory role in regard to the activation of eosinophils. However, studies of immunological functions are still lacking to elucidate the exact contribution of H₄ receptors on eosinophils in disease pathology.

Human basophils are characterized by expression of the Fc ϵ RI on their surface. We showed in a recent study that highly purified basophils express mRNAs for H₁, H₂ and H₄ receptors but not for H₃ receptors (Mommert *et al.*, 2016a). Interestingly, H₄ receptors were highly expressed and showed even higher mRNA expression levels when compared with the expression levels of the H₁ and H₂ receptors. Migration of basophils was induced by histamine and by a H₄ receptor agonist.

Peripheral blood samples from healthy donors, patients with a history of allergic diseases and hymenoptera venom-sensitized patients were stimulated with different histamine receptor specific agonists. We observed a significant reduction in Fc ϵ RI cross-linking-mediated surface expression of CD63 and CD203c on basophils and a decreased release of sulfido-leukotrienes. Both effects were mainly mediated *via* H₄ receptors. Although basophils migrate in the direction of histamine or H₄ receptor agonists and may accumulate at the site of allergic inflammation, our data indicate a substantial role of H₄ receptors in fostering an intrinsic self-termination mechanism for IgE-dependent basophil activation to prevent excessive activation of these cells (Mommert *et al.*, 2016a).

Keratinocytes. mRNA expression analysis as well as immunohistochemical staining revealed that human keratinocytes express H₄ receptors (Yamaura *et al.*, 2009; Glatzer *et al.*, 2013). We further showed that expression of mRNA for H₄ receptors was more abundant in keratinocytes derived from patients with AD. Moreover, stimulation of keratinocytes with histamine *via* the H₄ receptor induced proliferation, which was even more pronounced in keratinocytes derived from AD patients (Glatzer *et al.*, 2013). Thus, stimulation of H₄ receptors might contribute to the epidermal hyperplasia observed in AD patients. Regarding skin barrier function, the H₄ receptor does not seem to play a role in the histamine-induced inhibition of epidermal differentiation, which is more related to H₁ receptors (Gschwandtner *et al.*, 2013).

Although keratinocytes represent the outer barrier of the body, they also function as important regulatory and effector cells. Keratinocytes have the potential to secrete specific chemokines and cytokines, which play a relevant role in the initiation and perturbation of AD by attracting or stimulating different T-cell subtypes (Werfel, 2009). One important cytokine in the pathogenesis of AD is TSLP, which triggers a type 2 inflammatory response and additionally acts on sensory neurons and thereby triggers itch (Ziegler, 2012). In a recently published study, we found that pre-incubation with

histamine prior to challenge with poly I : C resulted in a significant increase of TSLP production compared with stimulation with poly I : C alone in normal human epidermal keratinocytes. This effect was mainly mediated *via* H₄ receptors (Schaper *et al.*, 2016). Thus, decreasing TSLP production *via* blockade of H₄ receptors could be one pathway for reducing a Th2 response and inhibiting scratching symptoms in AD patients. In another study, it has been shown that stimulation of H₄ receptors increases **IL-8** mRNA expression in HaCaT cells, which also indicates a pro-inflammatory effect of H₄ receptors on human keratinocytes (Suwa *et al.*, 2014).

Neurons. Pruritus that arises in the skin is mediated *via* exogenous and endogenous factors released by immune cells or keratinocytes. These factors induce activation of different receptors and signal cascades from periphery *via* dorsal root ganglia and spinal cord to the CNS (Steinhoff *et al.*, 2006). Some studies showed that the H₄ receptor was expressed in the CNS and in dorsal root ganglia of mice, rats and dogs, where this receptor also mediates functional effects (Strakhova *et al.*, 2009; Rossbach *et al.*, 2011; Galeotti *et al.*, 2013; Rossbach and Baumer, 2014). This aspect is further discussed below. However, in humans, the data are limited, probably due to the difficulty in obtaining suitable material for research purposes. Strakhova *et al.* (2009) showed that transcripts of the H₄ receptor are present in regions of the CNS, including spinal cord, hippocampus, cortex, thalamus and amygdala, with the highest levels of H₄ receptor mRNA detected in the spinal cord. Connelly *et al.* (2009) reported that H₄ receptors were prominently expressed in distinct deep laminae, particularly layer VI in the human cortex. However, the mechanism by which H₄ receptors possibly mediate chronic itch in humans is still elusive and remains to be identified.

The role of H₄ receptors in animal models of AD

Antagonists of H₄ receptors have been studied in several mouse models of allergic dermatitis (Hirasawa *et al.*, 2009; Rossbach *et al.*, 2009; Cowden *et al.*, 2010; Seike *et al.*, 2010; Suwa *et al.*, 2011; Kamo *et al.*, 2014) and in a canine model of AD (Baumer *et al.*, 2011). The H₄ receptor antagonists **JNJ-7777120**, **JNJ-28307474** and **JNJ-39758979** showed anti-inflammatory properties in a mouse model of allergic dermatitis induced by the hapten FITC (Cowden *et al.*, 2010), *via* reducing inflammation by down-regulating the number of skin eosinophils and mast cells as well as the expression of several cytokines. In contrast, **JNJ-7777120** did not reduce the allergic inflammation induced by the haptens dinitrochlorobenzene (DNCB) and toluene diisocyanate (TDI) (Rossbach *et al.*, 2009). It has to be taken into consideration that the models represent either an acute or a chronic inflammatory response with differences in the cell types involved. One characteristic of the FITC model is a Th2-dominated response and a distinct eosinophilia, which is less pronounced in other models of hapten-induced contact dermatitis such as the DNCB or TDI model. One possible explanation for the differing results could be that H₄ receptors are more involved in Th2-polarized inflammation. In line with this, in another hapten-induced allergic dermatitis model, the trinitrochlorobenzene (TNCB) model, **JNJ-7777120** was only effective in reducing the extent of chronic lesions

provoked by repeated application of the allergen to the skin of the back but failed to inhibit ear-swelling induced by single epicutaneous challenge of TNCB to the ear (Seike *et al.*, 2010). The attenuation of the chronic lesions was accompanied by a diminished mast cell and eosinophilic infiltration, which again suggests a relevant role for these cell populations in disease pathology (Seike *et al.*, 2010). In a picryl chloride-induced model of chronic allergic dermatitis established in NC/Nga mice, **JNJ-7777120** reduced skin lesions and inhibited the production of Th2 cytokines at lesional skin sites (Ohsawa and Hirasawa, 2012).

Antagonists at H₄ receptors have also been tested in mouse models that mimic more aspects of human AD than the hapten-induced models such as the *Dermatophagoides farinae* body allergen-induced model of chronic allergic dermatitis in NC/Nga mice and in the ovalbumin (OVA) model (Kamo *et al.*, 2014; Rossbach *et al.*, 2016; Kochling *et al.*, 2017). Dermatitis induced by *Dermatophagoides farinae* body ointment in NC/Nga mice was clearly not ameliorated either by **JNJ-7777120** or by **JNJ-28307474** (Kamo *et al.*, 2014). In line with this, in the OVA model, neither the H₄ receptor antagonist **JNJ-39758979** nor **JNJ-28307474** improved dermatitis severity (Rossbach *et al.*, 2016; Kochling *et al.*, 2017). In contrast, in H₄ receptor^{-/-} mice, OVA-induced skin lesions were clearly diminished (Rossbach *et al.*, 2016). One reason for the inconsistent results might be an insufficient concentration of the drug in the skin. Thus, it has to be examined whether additional topical treatment could improve skin symptoms. Notably, the anti-inflammatory effect could at least partially be mimicked by **JNJ-28307474**, only when this H₄ receptor antagonist was given during sensitization and provocation phase of the allergic reaction (Rossbach *et al.*, 2016). This finding indicates that it is necessary to block H₄ receptors during initiation of the allergic inflammation, which is an important point to clarify, because pharmacological interventions usually occur after the establishment of the disease.

Interestingly, the combination of H₁ receptor antagonists with H₄ receptor antagonists provided synergistic anti-inflammatory action in the OVA model as well as in NC/Nga mice (Ohsawa and Hirasawa, 2012; Kochling *et al.*, 2017). In addition, Mahapatra *et al.* (2014) revealed that local cytokine responses in skin-draining lymph nodes were only reduced by the combined application of H₁ and H₄ receptor antagonists. Such combinations of H₁ and H₄ receptor antagonists may provide a better option for the treatment of AD than H₄ or H₁ receptor antagonists alone. Corresponding with the results in allergen-induced inflammation, inhibition of allergen-induced pruritus was greater when both H₁ and H₄ receptors were blocked (Rossbach *et al.*, 2009; Ohsawa and Hirasawa, 2012).

In a dog model of AD, preventive administration of **JNJ-7777120** and **JNJ-28307474** did not affect the development of acute skin lesions (Baumer *et al.*, 2011). In this context, it has to be considered that H₄ receptor homology among different species is the lowest among the histamine receptor family, and also, binding and functional activity of numerous H₄ receptor agonists and antagonists clearly vary between different species (Liu *et al.*, 2001b). Consequently, animal studies with the focus on H₄ receptor expression and function must be interpreted with care.

In contrast to the heterogeneous results regarding the anti-inflammatory effects of H₄ receptor antagonists in the different mouse models, the antipruritic effects are very homogenous between studies. Several studies in rodents reported a reduction in scratching symptoms *via* H₄ receptors in either histamine-induced or allergen-induced itch (Dunford *et al.*, 2007; Rossbach *et al.*, 2009; Cowden *et al.*, 2010; Rossbach *et al.*, 2011; Ohsawa and Hirasawa, 2012).

H₄ receptors and SNPs mutations in AD

Genetic variations in disease-specific target genes and associations between these genetic factors and skin disorders such as AD, psoriasis or lupus erythematosus had been postulated and described in the past.

Based on the genetic background of inflammatory skin diseases and the complex picture of immunomodulatory activities of H₄ receptors, single nucleotide polymorphisms (SNPs) or copy number variations had been genotyped in a Chinese population suffering from AD or lupus erythematosus respectively (Yu *et al.*, 2010a,b; Chen *et al.*, 2013). These investigations gave first hints that genetic variations within the H₄ receptor gene may play a role in the pathophysiology of skin diseases. Polymorphisms and copy number variations within the H₄ receptor gene were found to be associated with AD (Yu *et al.*, 2010b; Chen *et al.*, 2013). Amplifications of copy number variations of this gene were also found to increase the risk of lupus erythematosus (Yu *et al.*, 2010a). Micallef *et al.* (2013) has nicely reviewed the data of genetic variations and polymorphisms within the genes of the four histamine receptors and their associations to inflammatory diseases of the CNS and cancer.

H₄ receptors and clinical studies in AD

Due to the dual function of H₄ receptor blockade (direct reduction of itch and inhibition of inflammatory response), H₄ receptors may represent a promising candidate for the treatment of AD in humans. Until now, only few reports of clinical data exist regarding H₄ receptor antagonists. The first compound used in clinical studies was JNJ-39758979, which could reduce histamine-induced scratching after 2 and 6 h. These results confirmed data from mice studies and demonstrated that H₄ receptors are involved in mediating pruritic symptoms in neurons (Thurmond, 2015). In a phase 2 clinical trial, this compound was tested in adult Japanese patients with moderate AD over a period of 6 weeks. Because of two cases of agranulocytosis, most likely related to reactive metabolites and not to H₄ receptor antagonism, the study had to be discontinued prematurely (Murata *et al.*, 2015). However, despite low patient numbers, analysis of the data revealed a significant reduction in pruritus in patients treated with JNJ-39758979 compared with placebo group, as well as an improvement of eczema (Murata *et al.*, 2015). In another randomized, placebo-controlled phase 2a study, the selective H₄ receptor antagonist **ZPL-3893787** was tested in males and females with moderate-to-severe AD and administered p.o. over a period of 8 weeks (Werfel *et al.*, 2018). Overall, the compound was well tolerated, and adverse events reported on ZPL-3893787 and placebo groups were comparable. After treatment with ZPL-3893787, patients displayed a 50% reduction in Eczema Area and Severity Index score (vs. placebo group 27%) and a reduction of 41% in the score of

AD (SCORAD) (vs. placebo group reduction of 26%). The effect on pruritus was similar between ZPL-3893787 and placebo and not statistically significant. However, the pruritus score obtained from the SCORAD revealed clear improvement for the ZPL-3893787 group compared with the placebo group (Werfel *et al.*, 2018). Based on the two latter studies, H₄ receptor antagonists showed clinically significant antipruritic and anti-inflammatory effects in AD patients. Further clinical studies with larger sample sizes are needed to clearly characterize the risk/benefit ratio and to additionally characterize groups of AD patients, who may particularly benefit from H₄ receptor antagonist and who may not. In a recently published phase 2a study with JNJ-39758979 in adults with uncontrolled asthma, the H₄ receptor antagonist did not meet the primary endpoint. However, significant improvements in pre-bronchodilator FEV₁ were observed with JNJ-39758979 versus placebo at week 12 in pre-specified subgroups, which displayed elevated sputum eosinophils or blood eosinophils at baseline (Kollmeier *et al.*, 2018). Thus, it seems that the H₄ receptor antagonist was specifically effective in asthma patients with an eosinophilic inflammation. Whether there are similar subgroups in AD patients warrants further investigations.

The role of H₄ receptors in psoriasis

Disease pattern

Psoriasis is a multifactorial chronic skin disease, affecting approximately 3% of the Western population. Genetic, environmental and behavioural factors are supposed to play a role in the pathogenesis and course of the disease. However, the exact aetiology of psoriasis remains unclear (Lowe *et al.*, 2008, 2014).

Plaque psoriasis (psoriasis vulgaris) is the most common form of the disease and usually presents as symmetrical erythematous papules or plaques covered with thick silvery scales. The histological characteristics of psoriasis are the marked thickening of the epidermis due to hyperproliferative keratinocytes and the elongated rete ridges. Other important histological features of psoriasis include a collection of neutrophils termed Munro microabscess, which is located in the stratum granulosum (Nograles *et al.*, 2009; Lowe *et al.*, 2014). In normal healthy human skin, relevant amounts of T-cells are present. These skin-resident T-cells composed primarily of T effector memory cells are mainly Th1 biased and are able to respond to stimulation (Clark, 2010). Besides T-cells, a population of dermal DCs such as mDCs, macrophages and in small numbers plasmacytoid DCs (pDCs) reside in the dermis and have the capacity to take up antigens. Respective cells mature during migration to draining lymph nodes and present these antigens to T-cells and B-cells (Zaba *et al.*, 2009). In psoriasis, **IL-23** is overproduced mainly by DCs and stimulates survival and proliferation of Th17 cells. A critical function of Th17 cells in psoriasis rather than of Th1 cells had been accepted and led to reclassify psoriasis as a more Th17-driven disease. Th17 cells are implicated in the pathogenesis of psoriasis by producing high amounts of **IL-17A** and **IL-22** (Boutet *et al.*, 2018).

Importantly, mast cells also reside, preferentially located in the upper dermis of psoriatic lesions, and levels of the anaphylatoxins **C3a** and **C5a** were detected in scales of psoriatic lesions (el-Lati *et al.*, 1994; Mashiko *et al.*, 2015). Histamine could be released by anaphylatoxins acting *via* their cognate receptors, which are expressed on mast cells (Giang *et al.*, 2018). The study of Krogstad *et al.* detected increased histamine levels in lesional skin when compared with uninvolved skin of psoriasis patients by microdialysis technique and demonstrated a detailed and direct proof that histamine is present in enhanced concentrations in psoriatic skin and may contribute to the inflammation (Krogstad *et al.*, 1997). Later studies gave more indirect hints that histamine is present in psoriatic skin. For instance, it has been shown in a recently published study that antihistamines (**clemastine** and **levocetirizine**) targeting H_1 receptors had a moderate effect in reducing itch in patients with psoriasis (Domagała *et al.*, 2017). In the following sections, we will discuss the expression levels of the histamine receptors, in particular of H_4 receptors, on cell populations that are present in human skin under both steady-state and inflammatory conditions. A schematic overview is presented in Figure 2. The function of histamine, with an emphasis on H_4 receptors, will be discussed regarding its potential role in contributing to the dramatic increase of the individual cell numbers in the dermal infiltrate by inducing migration and phenotypic changes

of these cells in regard to the expression of characteristic markers or release of cytokines and chemokines that occurs in the initiation phase of psoriasis.

The role of H_4 receptors on human cells relevant in psoriasis

T-cells. Besides Th1 cells and $IFN-\gamma$ that have been historically described as main drivers of psoriasis, the IL-23/IL-17 axis and IL-17 are now known to play a pivotal role in psoriasis and psoriasis arthritis. The main producers of IL-17, in response to different combinations of cytokines, are Th17 cells. Beyond Th17 cells, other immune cells such as $\gamma\delta$ T-cells or NK cells are able to synthesize IL-17. Th17 cells are detected in psoriatic skin lesions (Al-Mossawi *et al.*, 2013). IL-17 levels are elevated in the serum of psoriasis patients. The results of clinical trials targeting IL-17 and its receptor with biological agents reinforce the proposition that the IL-17 pathway is an essential target in the pathogenesis of psoriasis (Lowe *et al.*, 2008; Kirkham *et al.*, 2014; Boutet *et al.*, 2018).

We detected expression of mRNA for H_1 , H_2 and H_4 receptors in $CD4^+$ T-cells, which were polarized to Th17 cells in the presence of **IL-1 β** and **IL-23**. Importantly, H_4 receptors could be detected *in situ* on IL-17-positive cells in psoriatic skin. Stimulation of the histamine receptors on these polarized

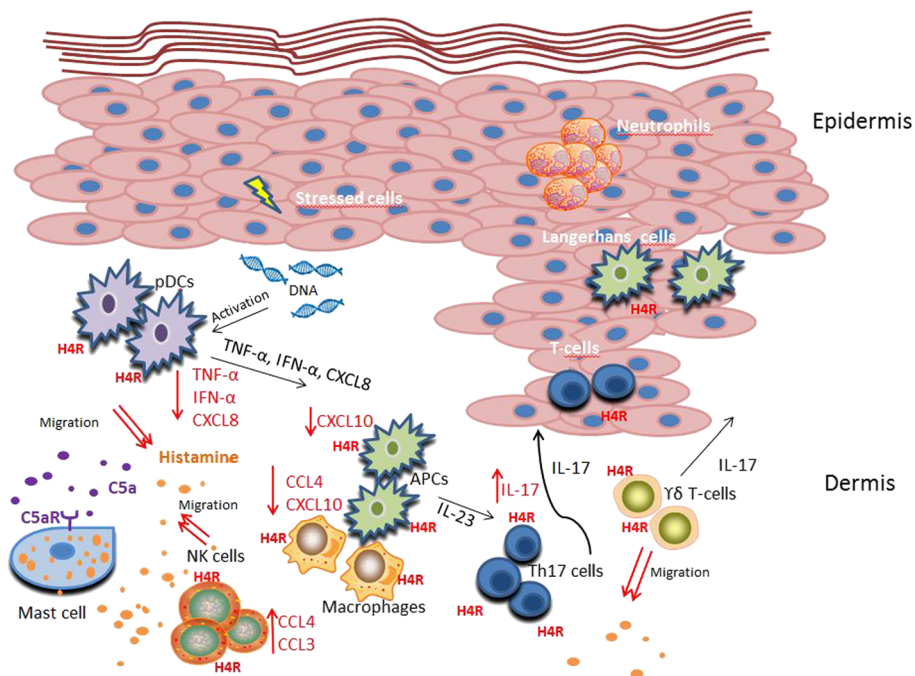


Figure 2

The role of histamine H_4 receptors on human cells relevant to psoriasis. H_4 receptors (H_4R) are expressed on keratinocytes and different immune cells, which play a role in psoriasis. Triggering the complement component 5a receptor (**C5aR**) on mast cells leads to release of histamine. Histamine acts *via* H_4 receptors on Th17 cells to release IL-17 and promotes NK cells to produce CCL3 and CCL4. Stressed keratinocytes release self-DNA, which in turn activates pDCs to produce $IFN-\alpha$. The stimulation of H_4 receptors on pDCs suppresses the secretion of the $TNF-\alpha$, $IFN-\alpha$ and CXCL8. Histamine reduces, *via* H_4 receptors, the release of the chemokines CXCL10 or CXCL10 and CCL4 in APCs and macrophages respectively. Histamine itself induces chemotaxis *via* H_4 receptors of $\gamma\delta$ T-cells, NK cells and of pDCs. The anti-inflammatory effects of the H_4 receptors seem to be more pronounced when compared with the inflammatory effects of the receptor in the pathophysiology of psoriasis. Thus, H_4 receptor agonists, rather than H_4 receptor antagonists, may prevent amplification of the symptoms. The effects mediated by H_4 receptors are highlighted in red.

Th17 cells with histamine and specific agonists revealed an up-regulation of IL-17 mRNA expression and secretion of IL-17 protein from respective cells mediated *via* H₄ receptors. Elevated histamine levels in psoriatic skin may target H₄ receptors on T-cells leading to an increase of IL-17, which may exacerbate the inflammatory process (Mommert *et al.*, 2012). This scenario is further supported by a study from Wakahara *et al.* (2012) who showed that in the presence of **IL-3**, basophil-derived histamine augments the IL-17 production in human memory T-cells. Treatment of the basophil memory T-cell cocultures with different histamine receptor antagonists revealed that blockers of H₂ and H₄ receptors significantly suppressed IL-17 production (Wakahara *et al.*, 2012). Future research will figure out whether the promising H₄ receptor antagonists, which have been shown to improve the symptoms of AD (Werfel *et al.*, 2018), would be beneficial to support the efficacy of biological agents targeting IL-17 in psoriasis.

$\gamma\delta$ T-cells are unconventional T-cells comprising a relatively small subset of T-cells in peripheral blood. They are defined by expression of heterodimeric T-cell receptors composed of γ and δ chains. Expression of H₁, H₂ and H₄ receptors in $\gamma\delta$ T-cells isolated from human peripheral blood were detected at mRNA level by PCR and at protein level by Western blot analysis (Truta-Feles *et al.*, 2010). In these cells, histamine induced actin polymerization, intracellular Ca²⁺ mobilization and chemotaxis, through *Pertussis* toxin-sensitive G_i proteins *via* H₄ receptors (Truta-Feles *et al.*, 2010).

Antigen-presenting cells

Plasmacytoid dendritic cells. pDCs that are characterized by plasma cell-like shape and specific surface markers play an essential role in psoriasis, as increased serum levels of pDC-derived cytokines correlate with disease severity (Gschwandtner *et al.*, 2011a). pDCs obtained from blood of psoriasis patients expressed higher levels of H₄ receptors when compared with pDCs from AD patients or to pDCs from healthy controls. Agonists at H₄ receptors induced migration of pDCs (Gschwandtner *et al.*, 2011a).

Stimulation of H₂ and H₄ receptors resulted in a down-regulation of CpG dinucleotide-induced production of **TNF- α** , **IFN- α** and CXCL8 but not of the chemokine CXCL10 in human pDCs. Importantly, the histamine-induced down-regulation of these cytokine or chemokine productions was more pronounced in pDCs derived from psoriasis patients, compared with cells from healthy controls (Gschwandtner *et al.*, 2011a).

Notably, CXCL10 mRNA and protein expressions were affected by H₂ or H₄ receptors in human monocytes and mDCs. Agonists of these two receptors caused a significant decrease in poly I : C-induced expression of CXCL10 in monocytes and mDCs (Glatzer *et al.*, 2014).

Macrophages. Macrophages accumulate in the dermis in acute or chronic inflammatory skin diseases, such as AD or psoriasis, and play a central role in regulating local inflammation by secreting many subtype specific mediators and cytokines (Biswas and Mantovani, 2010).

Expression of mRNA for H₁, H₂ and H₄ receptors was up-regulated in the presence of GM-CSF during the

differentiation process of monocyte-derived human M1 macrophages. During the differentiation process of M1 macrophages, CXCL10 expression was down-regulated in response to histamine or to a H₄ receptor agonist. In fully differentiated M1 macrophages, the **IFN- γ** - and **LPS**-induced mRNA and protein expression of the Th1-related chemokine **CCL4** was decreased *via* H₄ receptors (Mommert *et al.*, 2018c).

NK cells. NK cells are a specialized subset of CD56⁺CD16⁺ cells with the ability to kill cancer and virally infected cells in a non-MHC-dependent manner. NK cells are divided into two groups depending on the relative expression levels of the NK cell marker CD56 in low (CD56 dim) or high (CD56 bright) density. In psoriatic skin, CD56 bright NK cells, which represent the more immune-regulatory cells of both subtypes, were detected in the mid-dermis as part of the cellular infiltrate (Ottaviani *et al.*, 2006). NK cells may be involved in psoriasis by releasing cytokines such as IFN- γ , TNF- α or IL-22 (Jacobs *et al.*, 2001).

The expression of H₁ and H₄ receptors was detected in permeabilized **IL-2**-activated NK cells by flow cytometry using rabbit antihistamine receptor antibodies. Histamine induced chemotaxis of NK cells that was blocked by pre-incubation with a H₃/H₄ receptor antagonist (Damaj *et al.*, 2007). In a more recently published study, we detected the expression of H₁ and H₄ receptor mRNA in purified NK cells and, in contrast to results from Damaj *et al.*, the expression of mRNA for H₂ receptors was also detectable. The expression of mRNA for H₃ receptors was not detected (Mommert *et al.*, 2015).

A comprehensive microarray-based mRNA expression profiling revealed only few genes to be differentially regulated comparing H₄ receptor-stimulated versus non-stimulated human NK cells. Among them, the mRNA of TNF- α , **CCL3**, **CCL4** and CCL3L3 showed slightly increased expression levels upon stimulation *via* H₄ receptors. Follow-up studies confirmed a significant up-regulation of CCL3 and CCL4 (Mommert *et al.*, 2015). The enhanced production of these chemokines *via* H₄ receptors may contribute to migration and accumulation of various immune cells into the dermal infiltrate.

The role of H₄ receptors in murine models of psoriasis

Apart from several human *in vitro* studies, which focused on the effect of H₄ receptors in various cell types relevant for the pathogenesis of psoriasis, only one *in vivo* mouse study exists until now. In this study, the **imiquimod**-induced skin inflammation model, first described by van der Fits *et al.* (2009), was applied. In this widely used murine model of preclinical studies of psoriasis, daily application of **Aldara**-creme[®] onto the skin leads to an inflammation, which mimics several aspects of human psoriasis. Kim *et al.* (2016) demonstrated that the H₄ receptor agonist **4-methylhistamine** (4MH) (20 to 40 mg·kg⁻¹) significantly attenuated the psoriatic characteristics, including epidermal, hyperplasia, hyperkeratosis and lymphocyte infiltration. Furthermore, the number of CD4⁺CD25⁺Foxp3⁺ regulatory T-cells (Treg) was significantly increased by

treatment with 4MH (40 mg·kg⁻¹). However, when interpreting the data, it should be taken into account that 4MH shows considerable *in vivo* agonist activity at H₂ receptors, at doses >3 mg·kg⁻¹ i.v. in rodents (Lim *et al.*, 2009). Thus, the high doses of at least 20 mg·kg⁻¹·day⁻¹ 4MH for 10 consecutive days applied by Kim *et al.* may have had agonist action at H₂, rather than at H₄ receptors.

More studies with specific histamine receptor ligands are needed to really distinguish between effects mediated *via* H₂ or H₄ receptors.

H₄ receptors and SNPs mutations in psoriasis

Here, we summarize our recently published data about genetic variations within the promoter region of the human H₄ receptor gene in psoriasis patients. Three SNPs in the promoter region and one SNP located in an intron of the H₄ receptor gene were analysed by PCR and pyrophosphate DNA sequencing in patients diagnosed with chronic psoriasis and healthy controls (Mommert *et al.*, 2016b).

The genotype distributions and allele frequencies of the four SNPs in the H₄ receptor gene did not show obvious differences between the whole group of psoriasis patients and healthy controls. However, we found differences by trend in subgroup analysis: we detected that mutant genotypes of two SNPs located within the promoter region, rs17203314 and rs615283, were more frequent in patients with severe psoriasis according to the Psoriasis Area Severity Index when compared with the control groups. A significant association of rs615283 with psoriasis palmoplantaris, a severe form of psoriasis, was detected. To sum up, our study revealed possible associations of variations in the H₄ receptor gene between severe psoriasis, subtypes of psoriasis and special clinical features of psoriasis in relationship to the control groups. Further studies are needed to confirm these results with larger sample sizes (Mommert *et al.*, 2016b).

H₄ receptors and clinical studies in psoriasis

In contrast to the H₄ receptor antagonists JNJ-39758979 and ZPL-3893787, which have been used in clinical trials in the field of AD, another H₄ receptor antagonist, toreforant (**JNJ-38518168**), has completed efficacy studies in psoriasis and rheumatoid arthritis. The phase 2 testing in the rheumatoid arthritis patients was terminated prematurely because of patient fatality and secondary haemophagocytic lymphohistiocytosis (NCT00941707). However, *post hoc* analysis showed no significant improvement with toreforant. In the phase 2 study for the treatment of subjects with moderate-to-severe psoriasis (NCT02295865), toreforant was generally safe and well tolerated, but the study did not meet predefined success criteria (Frankel *et al.*, 2018).

Summary

A range of *in vitro* studies in human cells as well as in mouse models, have pointed to a relevant role of H₄ receptors in the pathogenesis of inflammatory skin diseases. However, it is worth noting that there are contradictory results regarding the anti-inflammatory and pro-inflammatory function of H₄ receptors in different cell types.

In regard to the disease pathology of AD, studies in T-cells (up-regulation of IL-31), keratinocytes (up-regulation of TSLP and increased proliferation) and AD mouse models (ameliorated symptoms in H₄ receptor^{-/-} mice and *via* blocking H₄ receptors in Th2-related models) clearly show a more pro-inflammatory role of H₄ receptors. In contrast, the results in APCs (down-regulation of IL-12, IL-27 and CCL2) and basophils (down-regulation of mediator release) point to a more anti-inflammatory profile. However, the decrease of the latter cytokines results in an impaired Th1-polarization and consequently leads to a shift towards a Th2-driven immune response. This shift towards a Th2-dominated response in conjunction with the up-regulation of Th2 cytokines in turn can lead to an exacerbation of the symptoms seen in AD. Thus, even if H₄ receptors are able to mediate the down-regulation of some pro-inflammatory cytokines, the Th2-driven effects mediated *via* these receptors seem to dominate the immune response in AD. Consequently, blocking H₄ receptors represents a promising treatment option in AD, and first positive results in clinical trials with H₄ receptor antagonists in patients with AD strengthen this hypothesis.

As opposed to AD, *in vitro* studies on human immune cells, which play a role in psoriasis, provide more conflicting results to predict a successful treatment of the disease with H₄ receptor antagonists. On one side, the enhanced production of IL-17 and histamine-induced migration of immune cells may foster the inflammation, and on the other side, down-regulation of pro-inflammatory cytokines or chemokines most pronounced in pDCs from psoriasis patients may control the inflammation. Psoriasis is mainly a Th1-/Th17-mediated disease. Because cytokines or chemokines such as IL-12, IL-27, TNF- α , IFN- α and CXCL10 or CXCL8 provide the local environment for polarizing Th1 or Th17 cells, down-regulation of these mediators *via* H₄ receptors is more in focus in psoriasis when compared with AD. Thus, in psoriasis, H₄ receptor agonists may prevent the amplification of the symptoms, rather than H₄ receptor antagonists. In line with this, an initial clinical study of an H₄ receptor antagonist in psoriasis did not meet its endpoints.

Apart from AD and psoriasis, also other skin diseases accompanied by inflammation and pruritus may potentially be regulated by blockers of H₄ receptors. For example, urticaria and prurigo are skin diseases characterized by intense itch. As H₄ receptor antagonists display constant results in inhibiting pruritus in murine models, these histamine receptors may also be interesting therapeutic targets in patients suffering from urticaria or prurigo.

However, while further clinical trials are planned, more research is still needed to better understand H₄ receptor regulation and immunomodulatory functions.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b,c).

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Conflict of interest

The authors declare no conflicts of interest.

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