



Minireview

Expression of the histamine H₄ receptor in dermal and articular tissuesKatsunori Yamaura ^{a,*}, Azusa Shigemori ^a, Eriko Suwa ^a, Koichi Ueno ^{a,b}^a Department of Geriatric Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Chiba University, Japan^b Center for Preventive Medical Science, Chiba University, Japan

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ABSTRACT

Histamine H₄ receptor was identified in 2000 and is the most recently identified of the four histamine receptors. It is expressed primarily in immune cells and is involved in physiologic functions related to inflammation and allergy. Recently, the H₄ receptor was highlighted as a promising therapeutic target in atopic dermatitis, asthma, and chronic arthritis. In fact, some H₄ receptor antagonists have reached clinical trials for the treatment of asthma, atopic dermatitis, and allergic rhinitis. Based on an initial assessment of distribution, the H₄ receptor has been referred to as the histamine receptor of the hematopoietic system. However, the H₄ receptor has also been implicated in the regulation of other non-hematopoietic systems. Here, we review the expression and function of the H₄ receptor with a focus on dermal and articular tissues. In skin, the H₄ receptor is expressed in both the epidermis and dermis, with stronger receptor expression in the epidermis. In articular tissue, H₄ receptor expression has been detected in synovial cells. Chondrocytes, a major cell sources for cartilage tissue engineering, also express the H₄ receptor. Further understanding of the functions of H₄ receptors in non-hematopoietic cells might lead to novel treatments for diseases with unmet needs.

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Introduction

Histamine was first identified in 1910 as a physiologically active amine. It is now recognized for its multiple regulatory activities in the digestive, neuronal, and immune systems, and new roles are still being elucidated (Schneider et al., 2002; Thurmond et al., 2008). Histamine exerts its effects through four distinct receptor subtypes. These receptors are G-protein-coupled receptors that transduce extracellular

signals through the G-proteins Gq, Gs, and Gi/o. The fourth member of the family was first identified as part of the Human Genome Project and was subsequently cloned and expressed by multiple groups around the year 2000 (Oda et al., 2000). The H₄ receptor is coupled to Gi/o proteins and shows 10³- to 10⁴-fold higher ligand affinity than the H₁ and H₂ receptors (Thurmond et al., 2008). The amino acid sequence of the H₄ receptor shares approximately 26%, 27%, and 58% homology in the transmembrane regions with the H₁, H₂, and H₃ receptors, respectively (Nguyen et al., 2001).

The H₄ receptor is preferentially expressed in various cells of the immune system such as mast cells, dendritic cells, basophils, eosinophils, monocytes, and T lymphocytes (de Esch et al., 2005; Fung-Leung et al., 2004). This receptor is considered to be involved in immune responses

* Corresponding author at: Department of Geriatric Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan. Tel.: +81 43 226 2879.

E-mail address: yamaura@chiba-u.jp (K. Yamaura).

and allergic reactions (Marson, 2011). H_4 receptor antagonists may therefore provide effective treatment options for atopic dermatitis, asthma, and rheumatoid arthritis (Thurmond et al., 2004; Zampeli and Tiligada, 2009). The first clinical candidate among the H_4 receptor antagonists, UR-63325, has completed clinical phase I studies, with good safety, pharmacokinetic and pharmacodynamic results. In a phase II study of allergic rhinitis induced by allergen challenge, UR-63325 was compared with fluticasone and placebo (Walter et al., 2011). By 2009, PF-3893787 and JNJ-39758979 had entered phase I and phase II trials, respectively for the treatment of asthma. Additionally, a phase II study of JNJ-39758979 in Japanese patients with moderate atopic dermatitis was initiated in 2011 (no results are currently available), and preclinical investigations of UR-65318 for the treatment of atopic dermatitis are in advanced stages (Walter et al., 2011).

In this review, we provide an up-to-date summary of the expression of the H_4 receptor, with a focus on the skin (Fig. 1) and joints (Fig. 2), and we discuss the physiological role of this receptor. This is also summarized in Table 1.

Epidermis

Skin consists of three layers, the epidermis, dermis, and hypodermis. The epidermis is the outermost layer of the skin and can be subdivided into the cornified layer, consisting of dead keratinocytes, followed by the prickle cell layer, the granular layer, and the basal cell layer comprising viable keratinocytes in various stages of differentiation (Song et al., 1997). Keratinocytes constitute about 95% of the cell mass of human epidermis and are responsible for the biochemical and physical integrity of skin via the production of numerous high molecular-weight molecules such as keratins and mucopolysaccharides (Barker et al., 1991).

The basal cell layer expresses the major keratin pair K5 and K14, while the prickle cell and granular layers express K1 and K10 as the predominant keratin pair (Porter et al., 2000).

K10-positive differentiated keratinocytes in the prickle cell layer and granular layer of the epidermis have been shown by immunohistochemical staining to strongly express the H_4 receptor. In contrast, H_4 receptor expression was weaker in K14-positive proliferating keratinocytes in the basal layer (Yamaura et al., 2009). These results suggest that the expression of H_4 receptors is increased in keratinocytes following differentiation.

Recent evidence from mice studies suggests that the H_4 receptor may be an additional histamine receptor contributing to histamine-mediated pruritic responses (Dunford et al., 2007; Rossbach et al., 2009). Specific H_4 receptor agonists were shown to induce pruritus (Bell et al., 2004). In addition, treatment of mice with a selective H_4 receptor antagonist, JNJ777120, attenuated the pruritic response to histamine; the inhibitory effect of the H_4 receptor antagonist was greater than that observed with H_1 receptor antagonists (Dunford et al., 2007).

H_4 receptor agonist-induced pruritus is observed in mast cell-deficient mice as well as in wild-type mice, which indicates that the H_4 receptors on mast cells are not required for H_4 receptor-mediated pruritus (Dunford et al., 2007). In addition, the finding that the bone marrow from wild-type mice was unable to restore H_4 receptor-mediated pruritic responses in H_4 receptor-knockout mice conflict with the notion of the involvement of mast cells or other hematopoietic cells in these events. These results suggest that the peripheral H_4 receptor mediates pruritic responses. Therefore, it is probable that histamine is acting on keratinocytes or directly on the peripheral terminals of primary sensory neurons through activation of H_4 receptors.

The expression of H_4 receptors on primary sensory neurons was detected by Rossbach and co-workers in 2011. It is assumed that histamine activates H_4 receptors on sensory neurons, resulting in the excitation of itch-mediating histamine-sensitive afferents and eliciting the sensation of itch (Rossbach et al., 2011). Furthermore, as mentioned earlier, it has been suggested that keratinocytes increase the expression of H_4 receptors following differentiation (Yamaura et al.,

2009). It was also reported that keratinocytes can produce a variety of itch-associated mediators, such as nitric oxide (Andoh and Kuraishi, 2003), thromboxane A_2 (Andoh et al., 2007), leukotriene B_4 (Andoh et al., 2009), and nociceptin (Andoh et al., 2004). Keratinocytes, as well as mast cells, release histamine in the skin (Fitzsimons et al., 2002). Substance P, which can induce histamine release from mast cells (Columbo et al., 1996), is one of the most potent pruritogenic endogenous peptides (Hägermark et al., 1978). In addition to inducing histamine release from mast cells, substance P directly stimulates the primary sensory neurons via the NK1 receptor, and the resulting itch sensation is transmitted to the brain. Substance P also directly stimulates keratinocytes which produces leukotriene B_4 , a mediator that evokes an itch (Andoh et al., 1998, 2001). Furthermore, substance P-induced pruritus was found to be resistant to H_1 receptor antagonists (Togashi et al., 2002), whereas JNJ777120, a selective H_4 receptor antagonist, reduced the pruritic response in a dose-dependent manner (Yamaura et al., 2009).

Although it remains unclear whether histamine acts on keratinocytes to produce itch-associated mediators, it is possible that keratinocytes are involved in histamine- or substance P-dependent pruritic responses via the H_4 receptor.

Compound 48/80 activates primary sensory nerves directly and mediates itch independent of its effects on mast cell degranulation (Eglezos et al., 1992). Treatment with JNJ777120 caused a dose-dependent inhibition of 48/80-induced pruritus (Dunford et al., 2007). These findings suggest that the H_4 receptor is also acting as a central transmitter of pruritic responses. Indeed, expression of the H_4 receptor has recently been demonstrated on itch-sensing neurons in areas such as the thalamus, the spinal cord, and the dorsal root ganglion (Strakhova et al., 2009).

It has been reported that repeated topical application of glucocorticoids might exacerbate pruritus despite the potent anti-inflammatory effect (Yamaura et al., 2011; Fujii et al., 2010). As mentioned previously, H_4 receptor antagonists could be effective compounds for the treatment of pruritus. Furthermore, the H_4 receptor antagonist JNJ777120 reduced chronic pruritus in a hapten-induced experimental model of atopic dermatitis (Suwa et al., 2011; Seike et al., 2010). Therefore, the combination of an H_4 receptor antagonist and topical glucocorticoids might provide effective therapy for intractable chronic pruritic dermatitis such as atopic dermatitis.

There are differences in sequence homology between humans and other species, ranging from 92% for monkey orthologues to 68% for mouse, with only 28–42% predicted for a variety of other species (Liu et al., 2001; Leurs et al., 2009). Moreover, the mouse H_4 receptor displayed an almost 10-fold reduction in affinity for histamine compared with the human receptor (Liu et al., 2001). Therefore, these differences between species might hamper preclinical development of future H_4 receptor antagonists.

Dermis

The dermis is the inner layer that varies in thickness from 1 to 4 mm. It is composed predominantly of type I and type III collagen, elastin, proteoglycans, and fibronectin, which represent approximately 90% of its dry weight (Fisher et al., 2000).

Dermal fibroblasts are a major cellular component of the dermis. Immunostaining demonstrated that human dermal fibroblasts express the H_4 receptor (Ikawa et al., 2008), but H_4 receptor expression in the dermis was found to be weaker than in the epidermis (Yamaura et al., 2009). Western blot analysis showed enhancement of the expression level of the H_4 receptor in dermal fibroblasts by stimulation with dexamethasone (Ikawa et al., 2008). In addition, repeated topical application of dexamethasone in mice increased the pruritic responses in a time-dependent manner (Yamaura et al., 2011). As mentioned above, H_4 receptors play an important role in evoking itch. Taken together, these findings suggest that the H_4 receptor in dermal fibroblast might play a role in itching reactions. However, further studies are needed

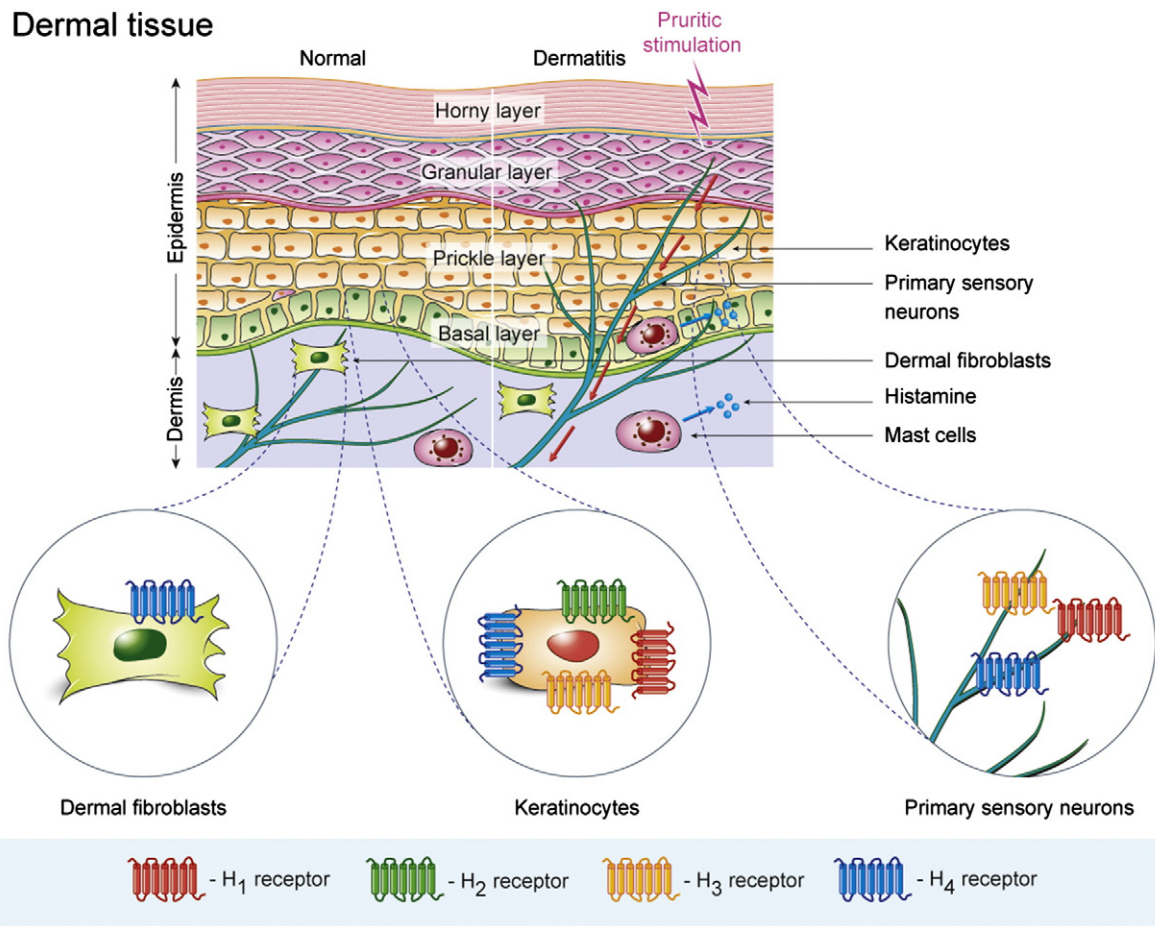


Fig. 1. Expression of histamine receptors in dermal tissues. Keratinocytes increase expression of H₄ receptors following differentiation. Histamine, typically released by mast cells in the dermis, excites the primary sensory neurons via the activation of H₁ and H₄ receptors and subsequently transmits the itch sensation. To date H₁, H₂, and H₃ receptors have not been identified on dermal fibroblasts.

to confirm the relationship between the expression of the H₄ receptor in dermal fibroblast and pruritus, which are both enhanced by dexamethasone.

Synovium

Histamine has been regarded as an inflammatory mediator of arthritic disorders and is recognized to play a role in autoimmune diseases such as RA, which is characterized by synovial tissue inflammation leading to erosion and destruction of articular cartilage with subsequent joint deformity (Woolley and Tetlow, 1997; Grzybowska-Kowalczyk et al., 2007, 2008). The majority of cell types at the cartilage–pannus junction, the putative site at which erosion formation was thought to be initiated, consist of macrophages, fibroblasts, mast cells, and polymorphonuclear leucocytes (Smeets et al., 2001). There is evidence of a significant increase in histamine concentration in synovial samples from patients with RA (Frewin et al., 1986). In addition, histamine H₂ receptor antagonists inhibit the articular inflammation in adjuvant-induced arthritis in the rat (Yamaura et al., 2003).

In 2005, we first reported the expression of H₄ receptor mRNA in human synovial cells in culture (Ikawa et al., 2005). It has been reported that the majority of rheumatoid synovial cells, regardless of morphology, consist of three different cell types: fibroblast-like synoviocytes, macrophage-like synoviocytes, and dendritic-like synoviocytes (Zheng and Wei, 2005). We demonstrated the expression of the H₄ receptor at the protein level in RA synovial cell culture and that the receptor is expressed in fibroblast-like synoviocytes and macrophage-like

synoviocytes from RA synovium (Ohki et al., 2007). However, the expression in dendritic-like synoviocytes remains to be clarified.

Wang et al. (2006) demonstrated that histamine stimulated the release of interleukin (IL)-6 from synoviocytes via the H₁ receptor. We demonstrated that histamine stimulated IL-6 and IL-8 production in fibroblast-like synoviocytes from RA patients via the H₄ receptor (unpublished data). These findings suggest that histamine is involved in synovial tissue inflammation of RA via the production of inflammatory cytokines by stimulating the H₁ or H₄ receptor on synoviocytes.

In contrast to the findings from most previous studies, Adlesic et al. (2007) reported significantly lower levels of serum histamine in RA patients compared with healthy controls. In addition, the levels of histamine in synovial fluid were even lower. Long-term anti-TNF- α treatment significantly increased circulating levels of histamine in RA patients. These findings suggest that histamine has an anti-inflammatory rather than pro-inflammatory action in the pathology of RA.

Matrix metalloproteinase-3 (MMP-3) is a marker of synovial inflammation, and serum levels are correlated with the number of joints affected, erythrocyte sedimentation rate, C-reactive protein, and IL-6 levels in patients with RA (Ribbens et al., 2002). MMP-3 is released from fibroblast-like synoviocytes and chondrocytes causing cartilage and bone destruction in RA (Akamine et al., 2012; Tetlow and Woolley, 2002). We demonstrated a significant negative correlation between serum MMP-3 concentration and the expression of H₄ receptor mRNA in synovial tissue from RA patients, but not between MMP-3 and H₁ or H₂ receptor mRNA (Yamaura et al., 2012a). The

Articular tissue

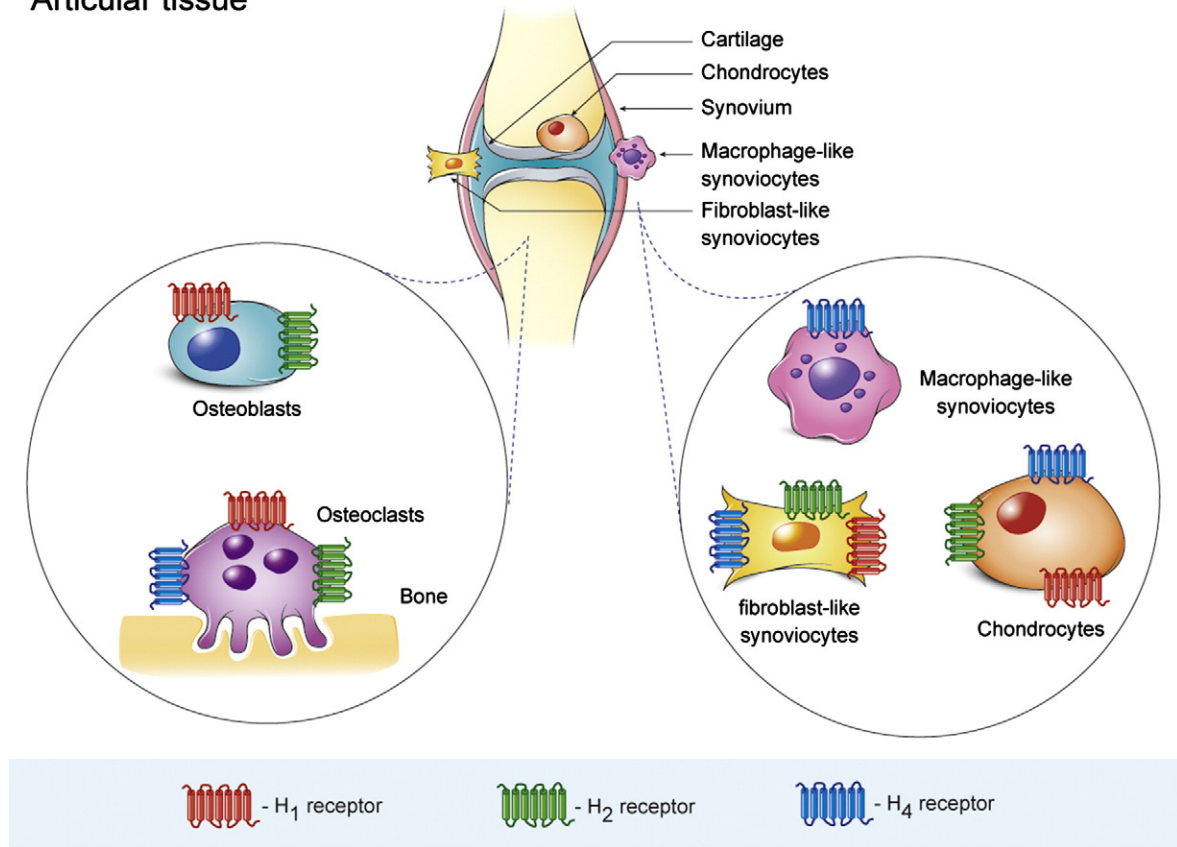


Fig. 2. Expression of histamine receptors in human articular tissues. To date H_1 , H_2 , and H_3 receptors have not been identified on macrophage-like synoviocytes.

H_4 receptor in synovial tissue may play a role in cartilage and bone destruction by influencing the secretion of MMP-3 in patients with RA. However, further research is needed to clarify the role of histamine and the H_4 receptor in the pathology of RA.

Cartilage

Destruction of cartilage is a common pathological feature in RA and osteoarthritis (OA). OA is also characterized by marked osteophyte formation consisting of new cartilage and bone at the joint edge (Felson, 2009). Osteophyte formation closely resembles the process of chondrogenesis and endochondral bone formation as can be seen during embryogenesis (van der Kraan and van den Berg, 2007). Therefore, endochondral ossification is an essential process in pathologic disorders such as osteophyte formation during OA progression (Kronenberg, 2003; Kawaguchi, 2008).

Hypertrophic chondrocytes predominantly express type X collagen and cause mineralization of the surrounding matrix by deposition of apatitic crystals and are subsequently replaced by marrow, vascular, and bone cells via the process of endochondral ossification (Tamamura et al., 2005). The hypertrophic chondrocytes produce MMP-13 and adamalysin with thrombospondin motifs 5 (ADAMTS5), which play a pivotal role in collagen and aggrecan degradation in cartilage, respectively (Kawaguchi, 2008; Troeberg and Nagase, 2012).

Therefore, laboratory investigations have focused on the hypertrophic chondrocyte as an attractive target for therapeutic intervention. Recently, histamine and histidine decarboxylase (HDC), a key enzyme for histamine production, were detected in OA chondrocytes (Tetlow and Woolley, 2005). Moreover, Grzybowska-Kowalczyk et al. (2008) reported the presence of H_4 receptor-like protein in human OA cartilage. However,

the expression and function of the H_4 receptor in chondrocytes have remained unclear.

The mouse chondrogenic cell line ATDC5 has been shown to be a useful in vitro model for examining chondrogenic differentiation (Shukunami et al., 1997; Yamashita et al., 2009). Using this model of chondrogenic differentiation, we demonstrated that chondrocytes express both HDC and the H_4 receptor, especially during the hypertrophic stage of late chondrocyte differentiation (Yamaura et al., 2012b). In addition, the majority of hypertrophic chondrocytes express the H_4 receptor (Yamaura et al., 2012b). The levels of histamine receptors may change during different stages of cell development. For example, H_1 receptor expression increases following the in vitro differentiation of monocytes into macrophages (Triggiani et al., 2007). Therefore, it is possible that the H_4 receptor may be involved in hypertrophic differentiation of chondrocytes in an autocrine manner and that the regulation of H_4 receptor expression in the chondrocytes is relevant to the pathogenesis of OA. However, further investigation is needed to elucidate the role of the H_4 receptor in hypertrophic differentiation of chondrocytes.

Bone

Bone loss represents a major unsolved problem in RA. Osteoclasts play a pivotal role in joint destruction in RA (Redlich et al., 2002). Histamine has been implicated in the modulation of bone metabolism, particularly in bone resorption processes (Nakamura et al., 1996). Biosse-Duplan et al. (2009) demonstrated that osteoclast precursors were a potential cellular source of histamine in the bone environment. Previously, we reported that a histamine H_2 receptor antagonist inhibits articular osteopenia in rats with adjuvant-induced arthritis (Yamaura et al., 2003).

Table 1
Expression and function of human H₄ receptors on cells in dermal and articular tissues.

Cell type	H4 receptor expression	Function via the H ₄ receptor	Reference
<i>Epidermis</i>			
Keratinocytes	mRNA and protein level; upregulated in differentiated keratinocytes (human)	Not described	Yamaura et al. (2009)
<i>Dermis</i>			
Dermal fibroblasts	mRNA and protein level (human)	Not described	Ikawa et al. (2008)
Primary sensory neurons	mRNA level using single-cell RT-PCR (mouse)	Calcium increase via H ₄ receptors	Rosbach et al. (2011)
<i>Synovium</i>			
Macrophage-like synoviocytes	mRNA and protein level (human)	Not described	Ikawa et al. (2005), Ohki et al. (2007)
Fibroblast-like synoviocytes	mRNA and protein level (human)	Upregulation of IL-6 and IL-8 mRNA and protein	Ikawa et al. (2005), Ohki et al. (2007), Yamaura et al. (2012a), unpublished data
Dendritic-like synoviocytes	Undetermined	Not described	Ohki et al. (2007)
<i>Cartilage</i>			
Chondrocytes	mRNA and protein level	Not described	Yamaura et al. (2012b)
<i>Bone</i>			
Osteoclasts	mRNA level; low and inconsistently detected (mouse)	Not described	Biosse-Duplan et al. (2009)
Osteoblasts	Not detected (mouse)	Not described	Biosse-Duplan et al. (2009)

ATDC5, mouse chondrogenic cell line; IL, interleukin.

H₁ and H₂ receptor mRNA were expressed in osteoclasts, whereas H₄ receptor mRNA expression was low and inconsistently detected (Biosse-Duplan et al., 2009). In addition, H₁ and H₂ receptor mRNA was expressed in primary osteoblasts, whereas H₄ receptor mRNA was not detected. Moreover, histamine-induced osteoclast formation was significantly decreased by H₁ or H₂ receptor antagonists, while H₄ receptor antagonists failed to show a significant effect (Biosse-Duplan et al., 2009; Yamaura et al., 2003).

These findings are limited and require further research to elucidate the expression and function of the H₄ receptor in osteoblasts and osteoclasts.

Conclusions

Histamine has a key role in many physiological processes including inflammation, and drugs that target H₁ receptors have provided successful treatment of allergy, but not without limitations. H₄ receptor antagonists ameliorate H₁ receptor antagonist-resistant pruritus (e.g. substance P-induced pruritus). H₄ receptors may account for other functions of histamine that are not blocked by H₁ receptors. Therefore, H₄ receptor antagonists are expected to demonstrate effectiveness against the numerous forms of H₁ receptor antagonist-resistant pruritus observed in patients such as atopic dermatitis, chronic cholestasis, and chronic urticaria (Duncan et al., 1984; Ponticelli and Bencini, 1995; Wahlgren et al., 1990). Moreover hypertrophic chondrocytes, which are abnormally observed in joint lesions in OA, express H₄ receptors. Therefore, it is possible

that H₄ receptor antagonists are efficacious in OA, for which no proven disease-modifying therapy is currently available.

Here we focused on the expression of the H₄ receptor in dermal and articular tissues, however the H₄ receptor may also be expressed and function in other tissues. Novel studies suggest further potential indications for H₄ modulators in cancer, neuropathic pain, vestibular disorders, and type 2 diabetes (Kiss and Keserü, 2012).

Recent data regarding the expression and functions of H₄ receptors should lead to new understanding and breakthrough therapies for the treatment of many diseases with unmet medical needs.

Conflict of interest statement

None.

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