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## Expression of the Histamine H<sub>4</sub> Receptor in Human Tissue

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### 1. Introduction

The histamine H<sub>4</sub> receptor (H<sub>4</sub>R) is the most recently identified of the four histamine receptors (H<sub>1</sub>R–H<sub>4</sub>R), and belongs to the same G-protein-coupled receptor (GPCR) family. The amino acid sequence of H<sub>4</sub>R shares approximately 26%, 27%, and 58% homology with H<sub>1</sub>R, H<sub>2</sub>R, and H<sub>3</sub>R, respectively, in the transmembrane regions (Nguyen et al., 2001). Furthermore, H<sub>4</sub>R couples to Gi/o proteins and shows 10<sup>3</sup>- to 10<sup>4</sup>-fold higher ligand affinity than H<sub>1</sub>R and H<sub>2</sub>R (Thurmond et al., 2008).

Several organs express H<sub>4</sub>R, and immune tissues such as the spleen, thymus, bone marrow, and leukocytes have a wide range of expression levels (Oda et al., 2000). It has been reported that chemotaxis of mast cells and eosinophils is stimulated by histamine via H<sub>4</sub>R; the receptor is therefore attractive as a new target of research into allergic diseases (de Esch et al., 2005).

### 2. Expression of H<sub>4</sub>R in synovial tissue in rheumatoid arthritis

A role for histamine has been implicated in rheumatoid arthritis (RA). RA consists mainly of synovial tissue inflammation that may be dispersed throughout the body, but its molecular etiology remains unclear. Macrophage infiltration and excessive formation of fibroblasts cause a variety of cytokines to be secreted from synovial membranes in patients with RA, and this in turn stimulates osteolytic activity (Sweeney & Firestein, 2004). There is evidence of a significant increase in histamine concentration in synovial samples from patients with RA (Frewin et al., 1986). These observations suggest a potentially significant role of H<sub>4</sub>R in the cause, progression, and treatment of RA.

The presence of H<sub>1</sub>R and H<sub>2</sub>R in human synovial cell culture (HSCC) has been clearly shown by ligand-binding experiments (Nagata, 1991). However, there has been no definitive evidence or conclusive reports of the similar presence of H<sub>3</sub>R or H<sub>4</sub>R. Therefore, utilizing our expertise in reverse transcription polymerase chain reaction (RT-PCR) techniques, we examined the H<sub>4</sub>R-specific mRNA expression in HSCC obtained from 11 RA patients who underwent artificial knee-replacement surgery (Ikawa et al., 2005).

After excising the synovial membrane specimen under aseptic conditions, the sample was treated with collagenase and trypsin solution to separate it into single cells. The cells were cultured for 2 weeks in medium containing fetal bovine serum. When the culture reached confluence, the cells were harvested and all RNA extracted. Analysis of the expression of the 4 subtypes of histamine receptor-specific mRNA in 2 patients with RA (RA1 and RA2) by RT-PCR showed that, under the experimental conditions, H<sub>1</sub>R-, H<sub>2</sub>R-, and H<sub>4</sub>R-specific mRNAs were expressed, but H<sub>3</sub>R-specific mRNA was not (Fig. 1). Expression of H<sub>4</sub>R-specific mRNA was confirmed in all 11 samples (RA1-RA11; Fig. 2). Notably, the intensity of the separated H<sub>4</sub>R-specific mRNA bands varied considerably from one sample to another, suggesting differences in cellular concentrations of H<sub>4</sub>R between patients.

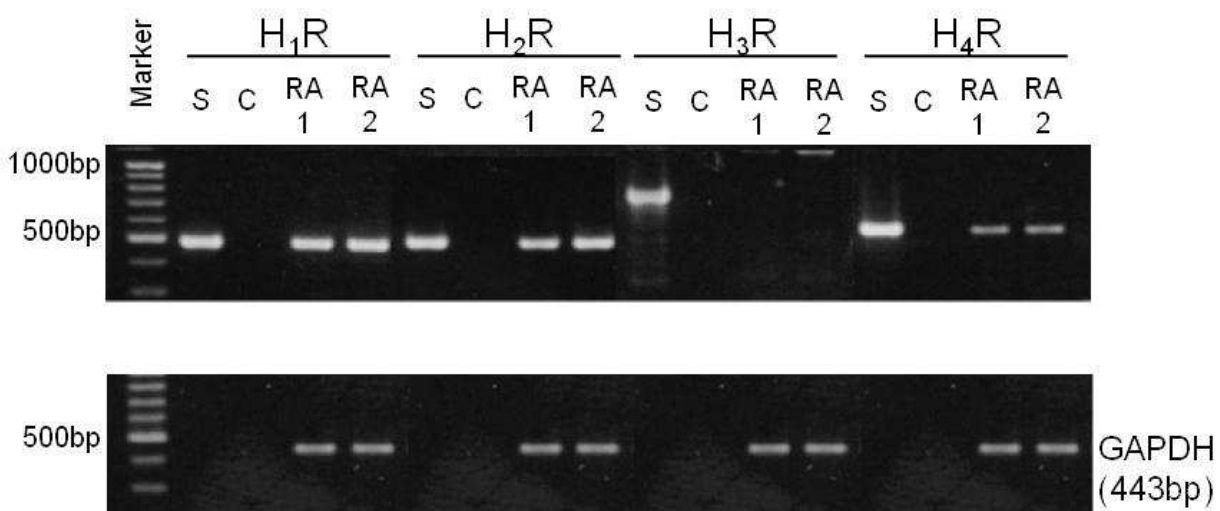


Fig. 1. Expression of mRNAs specific to 4 subtypes of histamine receptor (H<sub>1</sub>R, H<sub>2</sub>R, H<sub>3</sub>R, and H<sub>4</sub>R) in HSCC from 2 patients with RA. The gel was loaded with 5  $\mu$ L of amplified products. A 100-bp DNA ladder was used as a molecular weight marker. S: standard; C: control; samples from 2 RA patients, RA1 and RA2. Figure reprinted with permission from the Pharmaceutical Society of Japan.

Inflamed synoviocytes consist of 3 cell types: (1) macrophage-like cells; (2) fibroblast-like cells; and (3) dendritic cells (Tanaka, 2005). High levels of lymphocyte infiltration have been observed in RA compared to other types of arthritis (Fonseca et al., 2005). A variety of cell types such as macrophage-like cells, dendritic cells, and granulocytes have also been identified in the human RA synovium. As H<sub>4</sub>R has been reported to be present in immune cells, expression of H<sub>4</sub>R mRNA seems most likely to occur in cells derived from the hematopoietic system, such as macrophage-like or dendritic cells from synovial sites. Consequently, we examined the protein expression levels of H<sub>4</sub>R in RA HSCC, and used fluorescence immunoassays (Ohki et al., 2007) to determine the types of the cells in which expression occurred by identifying co-expression of cell type-specific human proteins: PH and CD55 for fibroblast-like cells; CD68 and CD163 for macrophage-like cells; and CD1a and CD208 for dendritic cells.

First, we examined the expression patterns of prolyl-4-hydroxylase (PH) (red) and CD68 (green) using 2 morphologically distinct cell types we identified in our HSCC: fibroblast-like and macrophage-like cells. In similar experiments, no expression of human dendritic cell markers (either CD1a or CD208) was detectable. Subsequent assays for fibroblast and

macrophage markers showed that human H<sub>4</sub>R protein is expressed in both fibroblast-like and macrophage-like cells in RA synovial tissues (Fig. 3 and Fig. 4). Others have also reported identification of H<sub>4</sub>R in synovial tissue of patients with RA (Grzybowska-Kowalczyk et al., 2007).

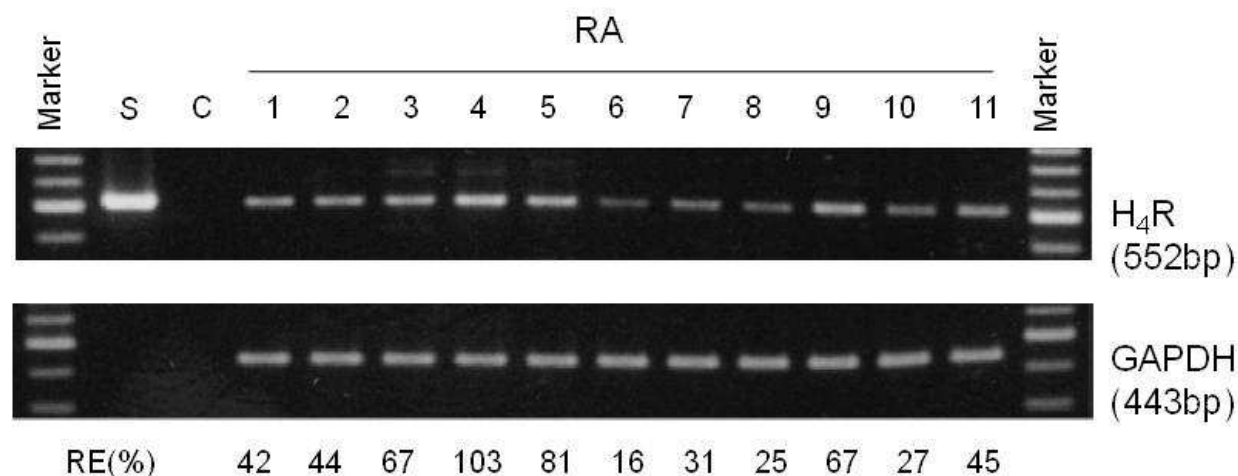


Fig. 2. Expression of H<sub>4</sub>R-specific mRNA in HSCC from 11 RA patients. The gel was loaded with 5  $\mu$ L of amplified products. A 100-bp DNA ladder was used as a molecular weight marker. S: standard; C: control; RE: relative expression; sample from 11 different RA patients, RA1 to RA11. RE of mRNA was calculated by normalizing the separated sample intensity value, taking that of the corresponding internal control (GAPDH) as 100%. Intensity values were measured using an image analyzer (IX81, OLYMPUS). Figure reprinted with permission from the Pharmaceutical Society of Japan.

Next, we focused attention on the expression of H<sub>4</sub>R mRNA in synovial tissues, and serum matrix metalloproteinase-3 (MMP-3) concentration in RA. We found a significant negative correlation between H<sub>4</sub>R expression in synovial tissues and serum MMP-3 concentration, but no correlation between MMP-3 and H<sub>1</sub>R or H<sub>2</sub>R (Yamaura et al., 2011). These observations suggest that H<sub>4</sub>R is a potential target of novel pharmacotherapeutic agents for RA, and H<sub>4</sub>R functional analysis may be useful in developing such treatments.

In addition, we detected H<sub>4</sub>R expression in human cartilage chondrocytes and in a murine chondrocytic cell line, ATDC5 (Yamaura et al., in press). Further work is needed to determine the expression mechanism and function of H<sub>4</sub>R on chondrocytes.

### 3. Expression of H<sub>4</sub>R in human skin

Following detection of H<sub>4</sub>R expression in synovial tissue, we also analyzed H<sub>4</sub>R expression in human epidermal tissue (Yamaura et al., 2009) and fibroblast cell cultures (Ikawa et al., 2008). Our immunoassays revealed that H<sub>4</sub>R is expressed in both human epidermal tissues and dermal fibroblasts.

Keratinocytes are the major constituent of the epidermis. We found that immunohistochemical staining showed strong H<sub>4</sub>R expression in keratin (K)10-positive differentiated keratinocytes in the prickle cell and granular layers of the epidermis (Fig. 5a). By contrast, H<sub>4</sub>R was weakly expressed in K14-positive proliferating keratinocytes in the basal layer (Fig. 5b).

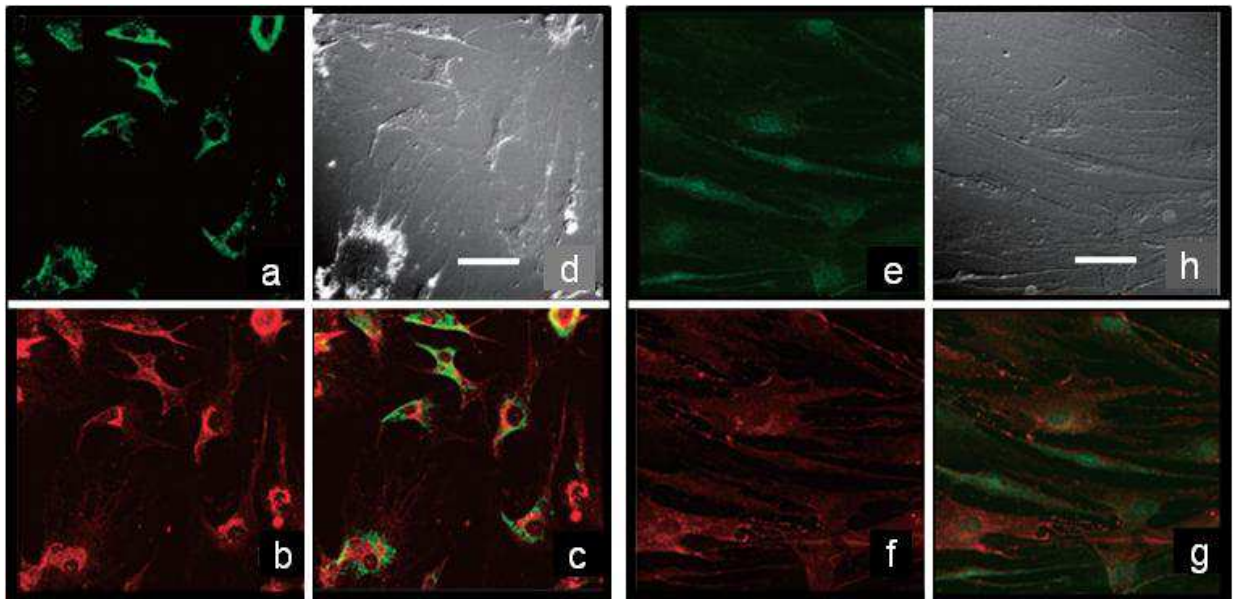


Fig. 3. Co-expression of H<sub>4</sub>R protein with fibroblast-specific marker proteins. (a) Mouse anti-PH followed by Cy2-conjugated anti-mouse (green); (b) rabbit anti-H<sub>4</sub>R followed by Cy3-conjugated anti-rabbit (red); (c) superposition of a on b; (d) Nomarski phase contrast microscopy image (NPCMI); (e) rabbit anti-H<sub>4</sub>R followed by Cy2-conjugated anti-rabbit (green); (f) mouse anti-CD55 followed by Cy3-conjugated anti-mouse (red); (g) superposition of e on f; (h) NPCMI. Scale bar: 50  $\mu$ m. Figure reproduced with permission from the Pharmaceutical Society of Japan.

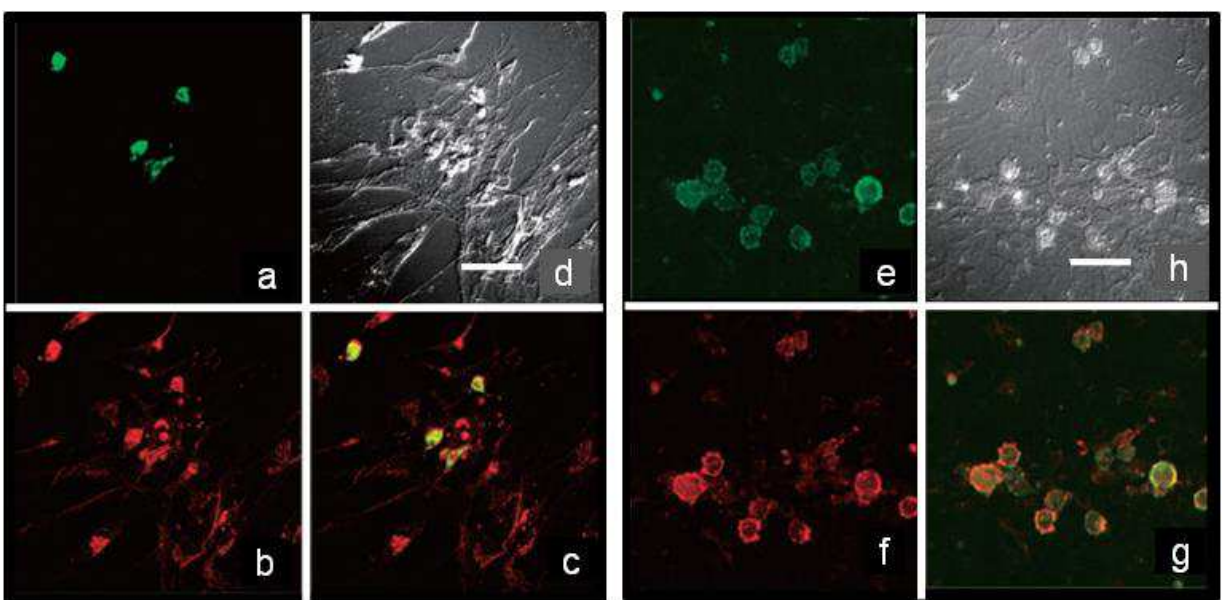


Fig. 4. Co-expression of H<sub>4</sub>R protein with macrophage-specific marker proteins. (a) Mouse anti-CD68 followed by Cy2-conjugated anti-mouse (green); (b) rabbit anti-H<sub>4</sub>R followed by Cy3-conjugated anti-rabbit (red); (c) superposition of a on b; (d) NPCMI; (e) mouse anti-CD163 followed by Cy2-conjugated anti-mouse (green); (f) rabbit anti-H<sub>4</sub>R followed by Cy3-conjugated anti-rabbit (red); (g) superposition of e on f; (h) NPCMI. Scale bar: 50  $\mu$ m. Figure reproduced with permission from the Pharmaceutical Society of Japan.

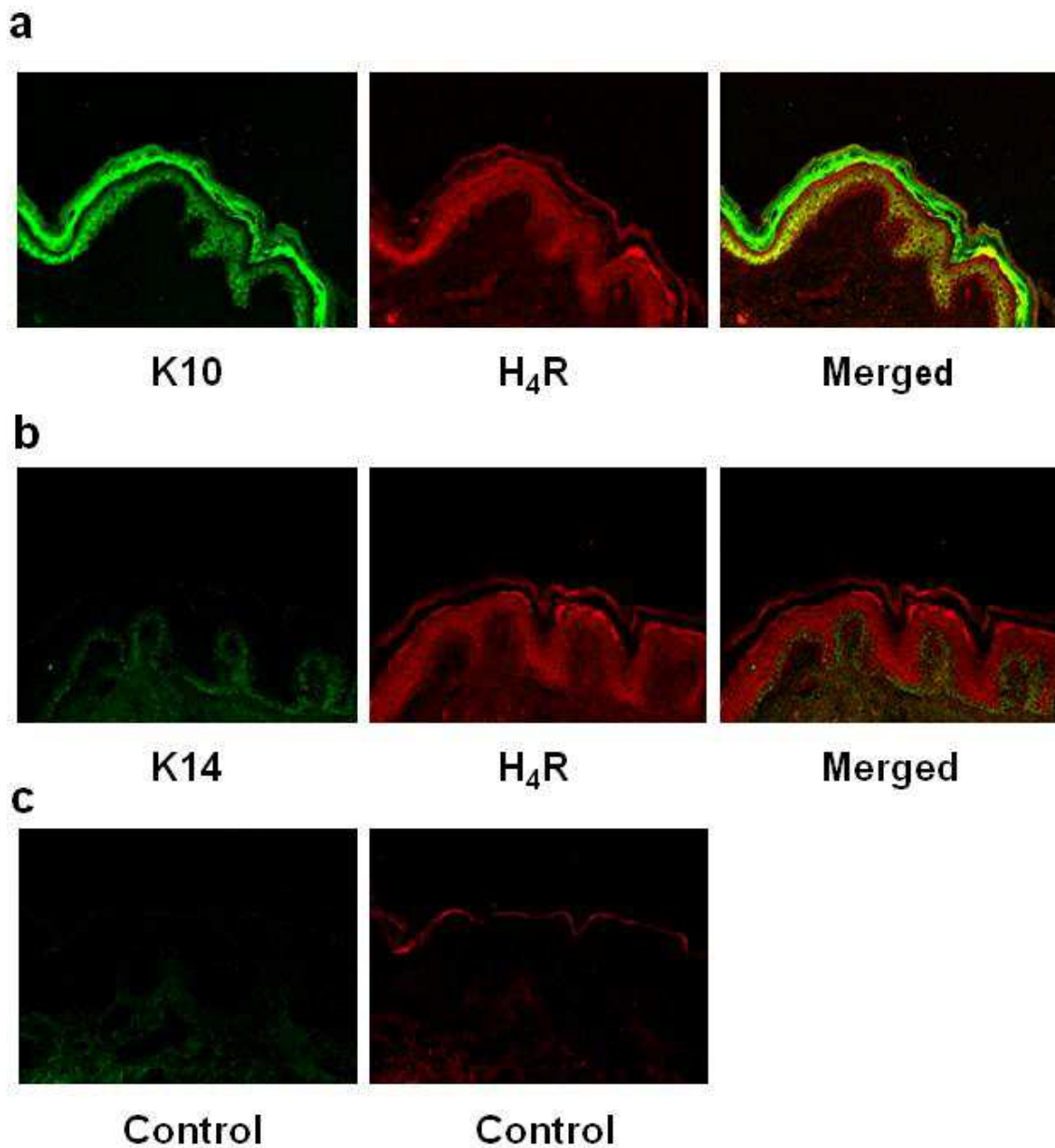


Fig. 5. H<sub>4</sub>R expression in human epidermal tissues. Double immunofluorescence staining of human epidermal tissues with anti-human H<sub>4</sub>R antibody followed by Cy2-conjugated anti-rabbit secondary antibody (red), and anti-K10 (a) or anti-K14 (b) antibody followed by Cy2-conjugated anti-mouse secondary antibody (green). (c) For the negative control, tissues were only exposed to the secondary antibody. Figure reprinted with permission from the Japanese Society of Toxicology.

Keratinization is the result of keratinocytes dividing in the basal lamina and moving to the upper layer as they mature. K10 is expressed in keratinocytes in the early stages following differentiation, whereas K14 is expressed in undifferentiated keratinocytes. Accordingly, our results suggest that keratinocytes increase expression of H<sub>4</sub>R following differentiation; however, further work is necessary to determine the expression mechanism and the physiological role of the receptors.

Increased H<sub>4</sub>R expression has been reported in CD4<sup>+</sup> T cells of patients with atopic dermatitis (Gutzmer et al., 2009), and skin mast cells have been shown to express H<sub>4</sub>R (Lippert et al., 2004). These findings suggest that dermal cells may play an important role, via H<sub>4</sub>R, in skin disorders. Dermal fibroblasts are a major component of the dermis. When the skin is damaged, they perform important roles including production of extracellular matrix molecules such as collagens. We have demonstrated the expression of H<sub>4</sub>R in human dermal fibroblast cells using immunohistochemical staining (Fig. 6). Furthermore, Western blot analysis showed enhancement of the expression level of H<sub>4</sub>R in dermal fibroblasts by stimulation with dexamethasone (Fig. 7).

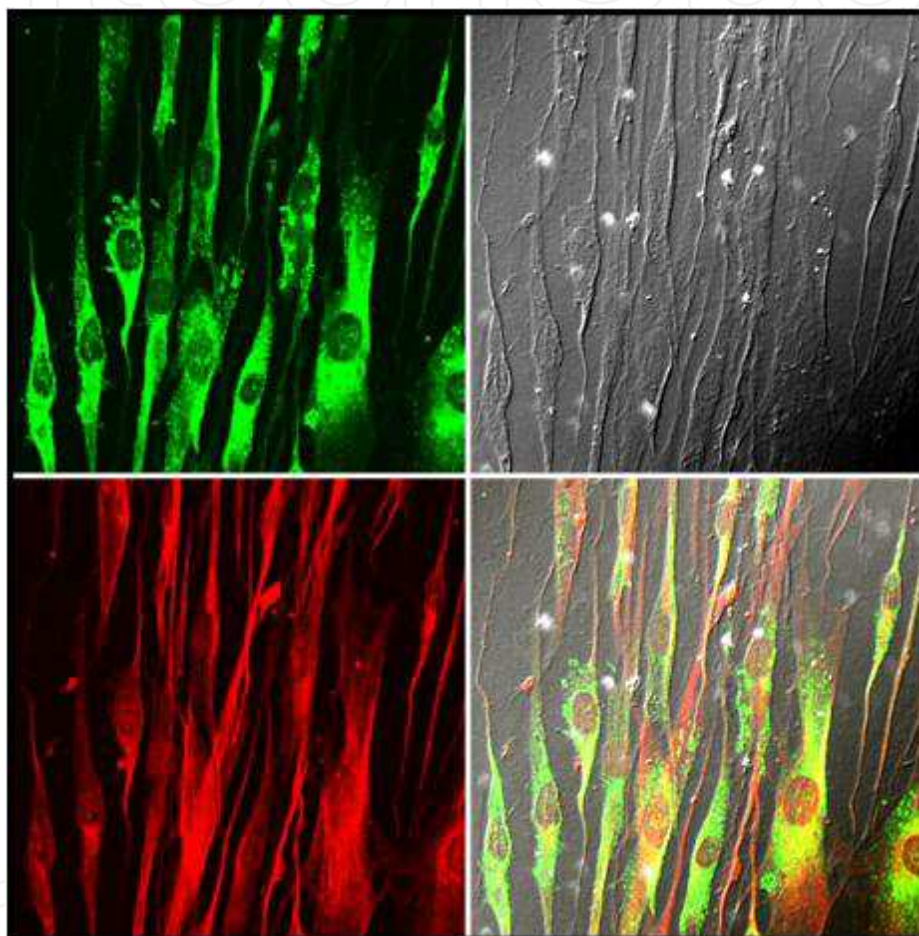


Fig. 6. Expression of H<sub>4</sub>R on human dermal fibroblasts. Double immunofluorescence staining of dermal fibroblast cells treated with anti-human PH antibody followed by Cy2-conjugated anti-mouse secondary antibody (green), and anti-human H<sub>4</sub>R antibody followed by Cy3-conjugated anti-rabbit secondary antibody (red). Magnification x 400. Figure reprinted with permission from the Japanese Society of Toxicology.

Ohnishi et al. (2008) reported that the levels of leukotriene B<sub>4</sub> receptor 1, which belongs to the GPCR family, were up-regulated by dexamethasone. This suggests that H<sub>4</sub>R, which is part of the same family, may be up-regulated by dexamethasone too. This up-regulation of H<sub>4</sub>R expression might be associated with itching that occurs as a rebound phenomenon after withdrawal of high-dose topical glucocorticoids. We confirmed that significant enhancement of pruritus occurred after chronic topical application of dexamethasone in

mice (Yamaura et al., 2011). However, further study is needed to investigate the relationship between the expression of H<sub>4</sub>R in skin and pruritus, which are both enhanced by dexamethasone.

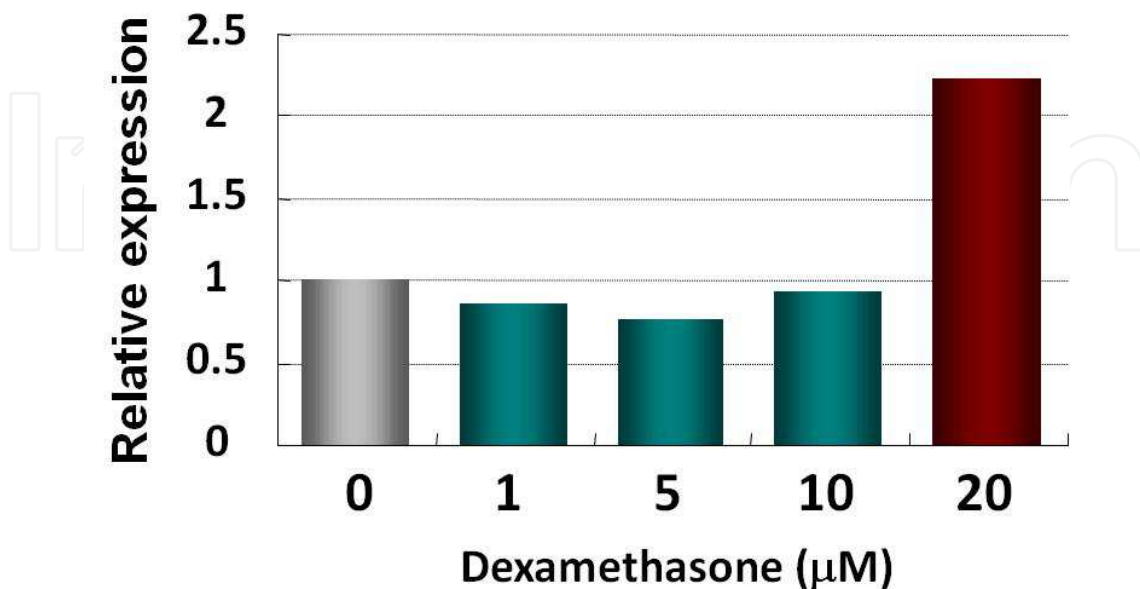


Fig. 7. Effects of dexamethasone on H<sub>4</sub>R protein expression in human dermal fibroblast cell cultures. Expression of H<sub>4</sub>R was analyzed by Western blot analysis. Protein levels of H<sub>4</sub>R were normalized to the corresponding  $\beta$ -actin protein levels. The mean value of the non-treatment group was set to 1.0. Data are expressed as means (n=2-3). Figure reprinted with permission from the Japanese Society of Toxicology.

#### 4. Effect of H<sub>4</sub>R antagonists on pruritus model

Chronic pruritus, associated with chronic conditions such as skin, liver, and kidney diseases and metabolic disorders, is a major diagnostic and therapeutic problem and can have a profound impact on the quality of life of patients. Recent studies have raised the possibility that H<sub>4</sub>R, in addition to the H<sub>1</sub>R, may contribute to histamine-mediated pruritic responses in mice (Bell et al., 2004). Both specific H<sub>4</sub>R agonists and histamine were shown to induce pruritic responses which could be blocked by pretreatment with H<sub>4</sub>R antagonists; the response was also found to be markedly attenuated in H<sub>4</sub>R-deficient mice. We thus examined the effectiveness of selective H<sub>4</sub>R antagonists as antipruritic drugs by their effect on histamine H<sub>1</sub>R antagonist-resistant acute pruritus induced by substance P in mice.

We investigated the effect of the H<sub>1</sub>R antagonist fexofenadine and the H<sub>4</sub>R antagonist JNJ7777120 on histamine-induced acute pruritus (Yamaura et al., 2009). Oral administration of fexofenadine caused a slight reduction in scratching, whereas JNJ7777120 showed a significant reduction (Fig. 8). We then examined the effect of these antagonists in substance P-mediated acute pruritus. Fexofenadine showed no reduction in substance P-induced scratching. By contrast, JNJ7777120 at 10 and 30 mg/kg doses reduced substance P-induced scratching in a dose-dependent manner (Fig. 9). Although JNJ7777120 crosses the blood-brain barrier, it does not cause sedation in rodents (Dunford et al., 2007); hence its antipruritic action is not a secondary effect of sedation. The results suggest that H<sub>1</sub>R has only limited involvement in histamine-induced pruritus. By contrast, the significant effect of JNJ7777120 suggests that H<sub>4</sub>R



has a much greater role. Substance P-induced pruritus is resistant to H<sub>1</sub>R antagonists (Togashi et al., 2002); given its occurrence in mast cell-deficient mice (Andoh et al., 2001), histamine from mast cells is unlikely to be involved. The role of H<sub>1</sub>R is also thought to be minor, with fexofenadine having no observable effect. However, the suppression of the pruritic response by JNJ7777120 suggests that histamine may act via H<sub>4</sub>R rather than H<sub>1</sub>R.

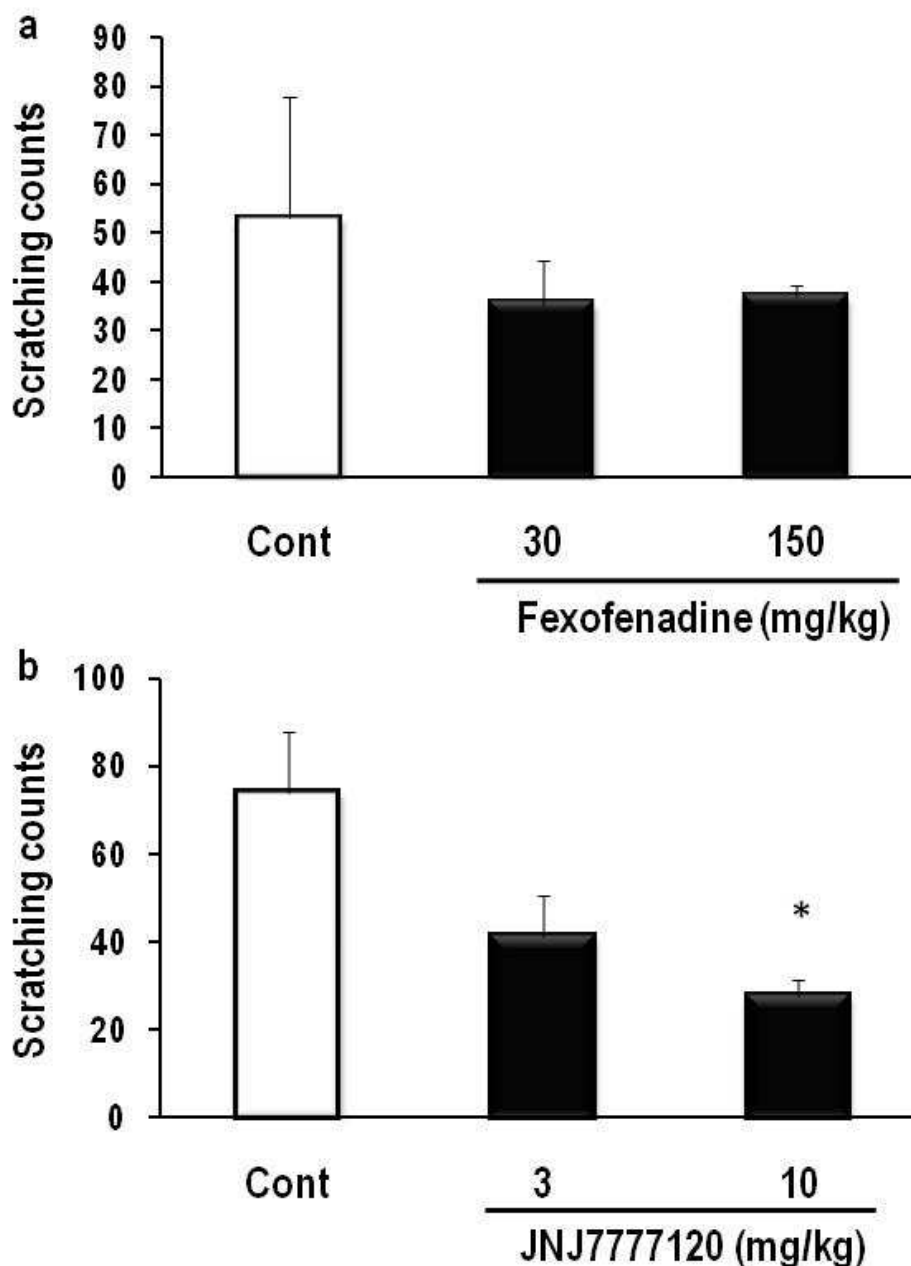


Fig. 8. Effect of H<sub>4</sub>R on scratching behavior induced by histamine. Histamine (300 nmol) was injected intradermally into shaved skin on the back of each mouse. Immediately after the injection of pruritogen, scratching events were counted for 30 min using the MicroAct apparatus (Neuroscience Inc., Tokyo, Japan). Fexofenadine (a) or JNJ7777120 (b) was administered orally 20 min before the injection of pruritogen. Values represent the mean ± SEM of four mice. \* $p < 0.05$  vs. control (Dunnett's multiple comparisons). Figure reprinted with permission from the Japanese Society of Toxicology.

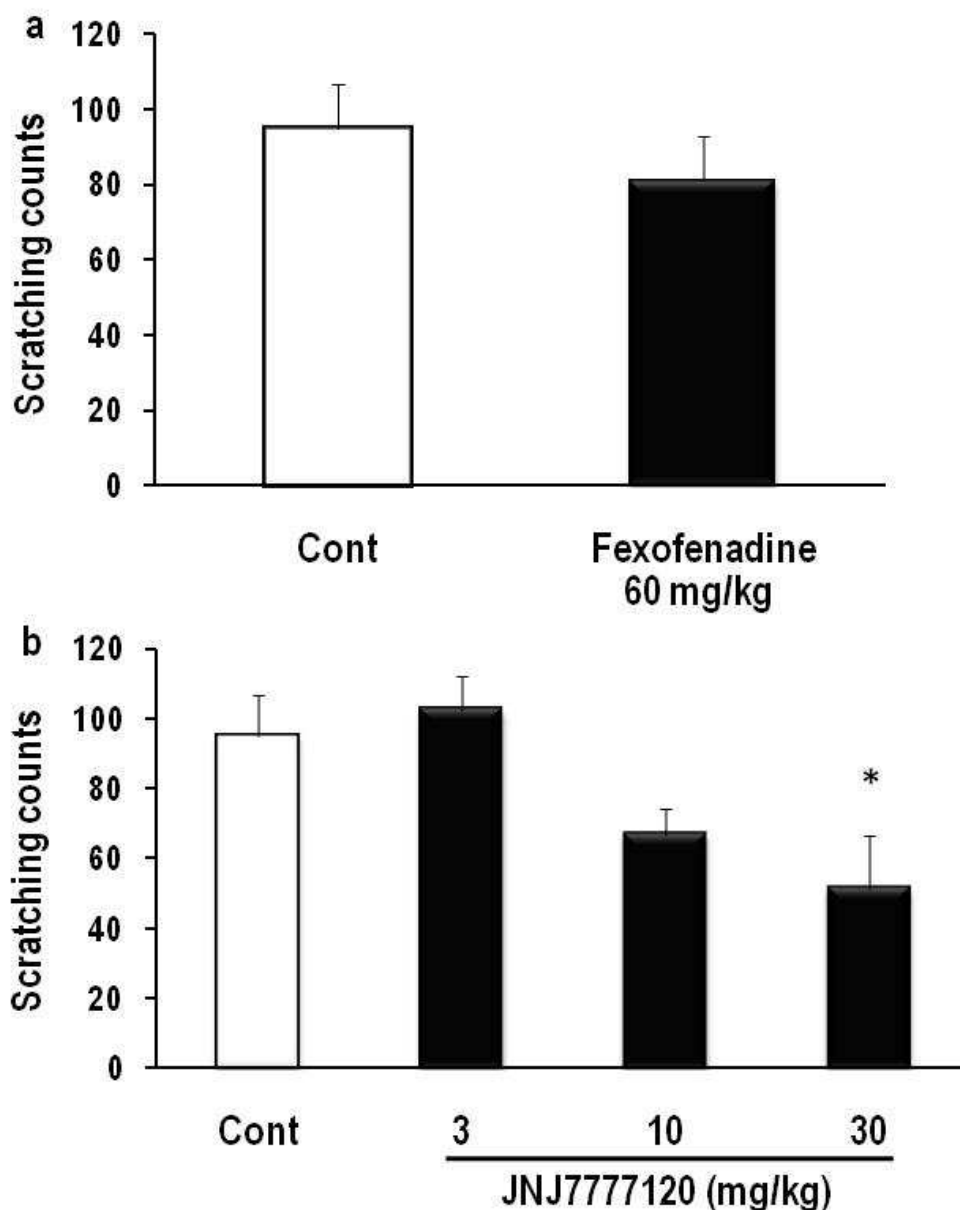


Fig. 9. Effect of H<sub>4</sub>R on scratching behavior induced by substance P. Substance P (100 nmol) was injected intradermally into shaved skin on the back of each mouse. Immediately after the injection of pruritogen, scratching events were counted for 30 min using MicroAct. Fexofenadine (a) or JNJ7777120 (b) was administered orally 20 min before the injection of pruritogen. Values represent the mean ± SEM of four mice. \* $p < 0.05$  vs. control (Dunnett's multiple comparisons). Figure reprinted with permission from the Japanese Society of Toxicology.

Further, we created a chronic itch model in which repeated application of 2,4,6-trinitrochlorobenzene to the back skin of HR-1 mice was seen to elicit frequent scratching behavior at 24 h after challenge. JNJ7777120 at 10 and 30 mg/kg doses reduced this scratching behavior, whereas fexofenadine had no such effect (Suwa et al., 2011). These results suggest that H<sub>4</sub>R antagonists may be useful for treatment of H<sub>1</sub>R antagonist-resistant chronic pruritus such as atopic dermatitis.

## 5. Conclusion

We have demonstrated the expression of H<sub>4</sub>R in human synovial cells from patients with RA and found a significant negative correlation between H<sub>4</sub>R expression in RA synovial tissues and serum MMP-3 concentration. Furthermore, we have shown expression of H<sub>4</sub>R in human skin and demonstrated that an H<sub>4</sub>R antagonist ameliorates both H<sub>1</sub>R antagonist-resistant acute and chronic pruritus. Taken together, these results suggest that histamine H<sub>4</sub>R could be a new drug target for therapeutic use in RA or pruritic skin disorders such as atopic dermatitis.

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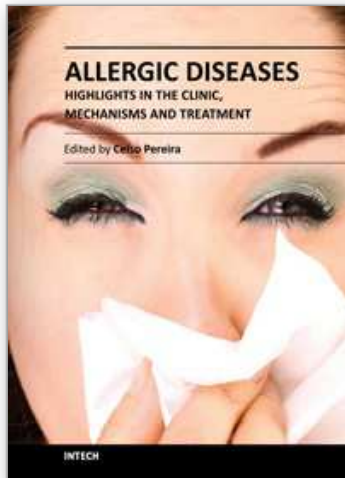
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