

Patho-Pharmacological Research of Anti-allergic Natural Products Targeting Antihistamine-Sensitive and -Insensitive Allergic Mechanisms



Hiroyuki Fukui, Hiroyuki Mizuguchi, Yoshiaki Kitamura, and Noriaki Takeda

Contents

- 1 Introduction
- 2 Up- and Down-Regulations of Histamine H₁ Receptors as Rate-Limiting Mechanisms of Signal Transduction
- 3 H1R Gene as a Susceptibility Gene
 - 3.1 Activation of H1R Gene Expression in Nasal Mucosa of Allergic Rhinitis Model Rats
 - 3.2 Correlative Activation of IL-4, IL-5 and Histidine Decarboxylase (HDC) Gene Expression to H1R Gene Expression
 - 3.3 Alleviation of Symptoms in TDI Rats by *Sophorae radix (Kujin)*: An Anti-allergic *Kampo* Medicine
- 4 Antihistamine-Insensitive Mechanism of Allergy and Combination Therapy
 - 4.1 Discovery of Antihistamine-Insensitive Mechanism of Allergy Using Suplatast Tosilate
 - 4.2 Discovery and Molecular Pharmacology of Compounds Suppressing IL-9 Gene Expression from Natural Sources
- 5 Future Outlook for the Therapy of Allergic Diseases
 - 5.1 Multiple Pathological Mechanisms of Allergic Diseases
 - 5.2 A New Evaluation System to Develop New Therapeutics
 - 5.3 Therapeutic Strategy for Multifactorial Allergic Diseases
- 6 Expanding Histamine Research for the Novel Therapeutic Strategy of H1R-Related Diseases in Future
 - 6.1 H1R and Diabetes Mellitus and Other Diseases
 - 6.2 H1R Signaling-Related Diseases in the Brain
 - 6.3 Strategy of the Therapy for Diseases Susceptible to H1R Gene Expression

References

H. Fukui (✉)

Medical Corporation Kinshukai, Osaka, Japan

e-mail: hfukui@tokushima-u.ac.jp

H. Mizuguchi

Laboratory of Pharmacology, Faculty of Pharmacy, Osaka Ohtani University, Osaka, Japan

Y. Kitamura and N. Takeda

Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2021

Curr Topics Behav Neurosci

https://doi.org/10.1007/7854_2021_255

Abstract Histamine H₁ receptor (H1R) has a special up-regulation mechanism by the stimulation of H1R, mediated by protein kinase C-delta (PKC δ) signaling and H1R gene expression, resulting increase in H1R signaling. Increase in H1R mRNA in nasal mucosa was induced after the provocation of nasal hypersensitivity model rats and suppressed by the pre-treatment of antihistamines. Improvement of nasal symptoms and suppression of H1R mRNA expression in nasal mucosa were also observed by the pre-treatment of antihistamines in pollinosis patients. Elucidation of a correlation between symptoms and H1R mRNA level suggests that H1R gene is an allergic disease (AD)-susceptibility gene, targeted by antihistamines. Similar to antihistamines, pre-treatment of *Kujin* extract, an anti-allergic *Kampo* medicine improved nasal symptoms and suppressed H1R mRNA expression in nasal hypersensitivity model rats. (–)-Maackiain targeting heat shock protein 90 (Hsp90) was isolated as an inhibitor of PKC δ signaling-mediated H1R gene expression from *Kujin* extract. In addition to H1R-mediated activation of H1R gene expression as the first mechanism, nuclear factor of activated T-cells (NFAT)-mediated IL-9 gene expression is suggested to participate to allergic symptoms as the second mechanism insensitive to antihistamines. Pyrogallol and proanthocyanidin suppressing IL-9 gene expression were discovered from Awa-tea and lotus root knots, respectively. Combination therapy using medicines suppressing both H1R gene expression and IL-9 gene expression is promising for outstanding alleviation of AD. Multifactorial diseases involving H1R gene expression may be treated by the combination therapy with antihistamine and complementary drugs, and diseases involving PKC δ signaling may be treated by drugs targeting Hsp90.

Keywords Allergic disease · Heat shock protein 90 · Histamine H1 receptor gene · NFAT (nuclear factor of activated T-cells) · Protein kinase C-delta

1 Introduction

Histamine is a principal mediator of type-1 immune hypersensitivity reaction in allergy and causes serious symptoms of allergic diseases. Antihistamines are principal therapeutic drugs for allergic rhinitis, allergic conjunctivitis, and urticaria, because symptoms of these diseases are dominantly mediated through histamine H₁ receptors (H1R). Improved antihistamines have been actively developed. They are now classified into two groups, first and second generations. First generation antihistamines with side effect of strong sedation were replaced by second generation antihistamines by minimizing the side effect. However, insufficiency of alleviation by antihistamine therapy remains to be undissolved, suggesting the existence of antihistamine-sensitive and -insensitive pathological mechanisms in allergic diseases. Demonstration of antihistamine-insensitive pathological mechanisms and development of new therapeutic drugs are highly awaited.

2 Up- and Down-Regulations of Histamine H₁ Receptors as Rate-Limiting Mechanisms of Signal Transduction

The number of H1R molecules is much smaller than that of other signaling molecules, and the receptor signaling is regulated by the expression level (Ohuchi et al. 1998). Then down- and up-regulations of the receptor are the rate-limiting step mechanisms.

Sustained stimulation-evoked H1R desensitization and down-regulation were documented, similar to many other receptors. Involvement of receptor phosphorylation in intracellular loops was demonstrated as a molecular mechanism (Horio et al. 2004a). Phosphorylation of serine and threonine residues, namely Thr¹⁴⁰, Thr¹⁴², Ser³⁹⁶, Ser³⁹⁸ and Thr⁴⁷⁸, in H1R was suggested to play a crucial role in receptor desensitization and down-regulation (Horio et al. 2004b).

On the other hand, sustained stimulation of H1R induced gene expression-mediated receptor up-regulation (Das et al. 2007). This mechanism is unique to H1R. Stimulation by phorbol 12-myristate 13-acetate (PMA) up-regulated H1R, suggesting the participation of protein kinase C (PKC). Both up- and down-regulation mechanisms of H1R are present in HeLa cells. Actually, H1R were up-regulated by the receptor stimulation, suggesting that up-regulation mechanism is dominant (Fig. 1).

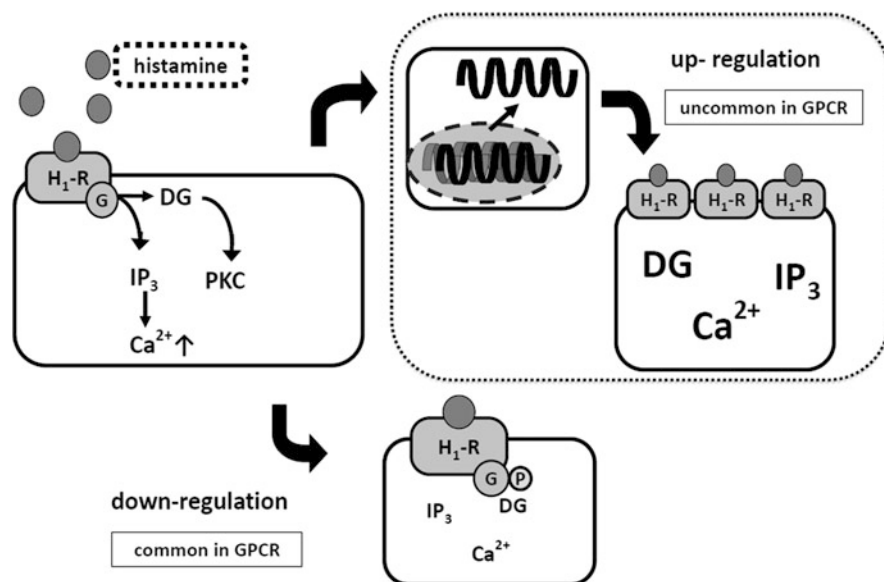


Fig. 1 Schematic representation of up-and down-regulation of histamine H₁ receptor (H1R) protein. Stimulated H1Rs were down-regulated through the common receptor desensitization mechanism. In addition, stimulation of H1R up-regulated the H1R through the H1R gene expression as an atypical mechanism. Adapted from Horio et al. (2004a)

3 H1R Gene as a Susceptibility Gene

Allergic symptoms are dominantly mediated by H1R. However, detailed mechanisms remained to be elucidated. Exacerbation of allergic symptoms was assumed by H1R up-regulation-induced increase in H1R signaling, and function of H1R gene was investigated as a susceptibility gene.

3.1 *Activation of H1R Gene Expression in Nasal Mucosa of Allergic Rhinitis Model Rats*

Nasal allergic symptoms were investigated in relation to H1R gene expression using allergic rhinitis model rats. Brown-Norway rats were sensitized by toluene 2,4-diisocyanate (TDI), and allergic rhinitis model rats (TDI rats) were created. TDI rats were employed to investigate H1R-mediated mechanism of allergic symptoms. Provocation with TDI successfully induced nasal symptoms and up-regulation of H1R protein and H1R mRNA in nasal mucosa (Mizuguchi et al. 2008). Similar to HeLa cells, target cells in nasal mucosa of Brown-Norway rats may have common H1R up-regulation mechanism. Both symptoms and gene expression were parallelly suppressed by epinastine, an antihistamine. H1R gene was suggested to be an allergic rhinitis-susceptibility gene. The H1R is a GPCR coupled with Gq/11 and PLC β (Yamashita et al. 1991). PKC activation is a downstream of PLC β . Among PKC isotypes, PKC δ activation was suggested to participate in H1R gene expression (Mizuguchi et al. 2011, Fig. 2).

Leukotrienes are major allergic mediators next to histamine, and leukotriene antagonists have been developed for the therapy of allergic diseases. When pranlukast, a cysteinyl leukotriene-receptor (LTR) antagonist, was pre-treated to TDI rats, up-regulation of H1R mRNA was suppressed and nasal symptoms were alleviated, suggesting that H1R gene expression mechanism is targeted not only by histamine but also by leukotrienes. However, detailed anti-allergic mechanism of leukotrienes remains to be elucidated. (Kuroda et al. 2013.).

3.2 *Correlative Activation of IL-4, IL-5 and Histidine Decarboxylase (HDC) Gene Expression to H1R Gene Expression*

Levels of H1R, IL-4, IL-5, and HDC mRNAs were correlatively up-regulated in the nasal mucosa of TDI rats and pollinosis patients, and suppressed by the treatment of antihistamines (Mizuguchi et al. 2008; Kitamura et al. 2012). The results suggest H1R, IL-4, IL-5, and HDC genes form a susceptibility gene group. IL-4 receptors are

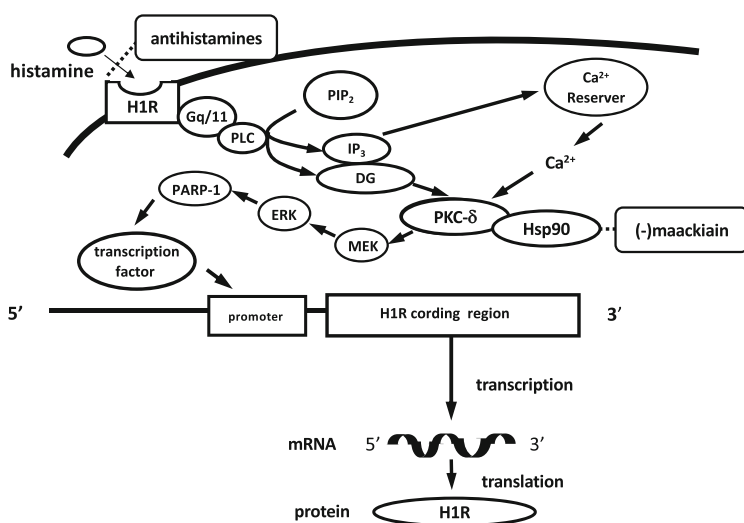


Fig. 2 Mechanism of H1R-mediated H1R gene expression through PKC δ activation. H1R gene is an allergic rhinitis-susceptibility gene whose up-regulation is suppressed not only by antihistamines but also by (–)-maackiain from *Sophorae radix* (*Kujin*). Sho-seiryu-to is also a suppressor of H1R gene expression

expressed in peripheral sensory nerves and revealed to participate in chronic itch (Oetjen et al. 2017).

3.3 Alleviation of Symptoms in TDI Rats by *Sophorae radix* (*Kujin*): An Anti-allergic *Kampo* Medicine

Kujin, an anti-allergic *Kampo* medicine, is used for the therapy of allergic diseases by *Kampo* formulae such as *Kujin-to*, *Shohu-san*, and *Sanmotsu-ohgon-to*. However, scientific basis of *Kujin* remains to be elucidated. Symptoms of TDI rats after provocation were markedly alleviated by pre-treatment of *Kujin* (Dev et al. 2009). Parallely, up-regulation of H1R mRNA was declined to the baseline, suggesting that *Kujin* targets H1R-mediated H1R gene expression signaling.

(–)-Maackiain was successfully isolated as an active substance from *Sophorae radix* (*Kujin*, an anti-allergic *Kampo* medicine) (Mizuguchi et al. 2015). Then the target of (–)-maackiain was successfully identified to be heat shock protein-90 (Hsp90) (Nariai et al. 2015, Fig. 2). Hsp90 and PKC δ form a complex. (–)-Maackiain binding to Hsp-90 resulted in the dissociation of complex, and PKC δ signaling was suppressed by the dissociation. Complex of Hsp90 and PKC δ plays an important role in H1R gene expression-mediated symptoms, and Hsp90 is a novel drug discovery target for the therapy of allergic diseases. Antihistamines and

(-)-maackiain target different molecules, H1R and Hsp90, respectively. However, H1R gene expression is the common functional target of both drugs.

Sho-seiryu-to is a popular anti-allergic *Kampo* formula in Japan, compared to *Kujin*. *Sho-seiryu-to* consists of eight medicinal plants, *Hange*; *Pinellia ternate*, *Kanzo*; *Glycyrrhiza glabra*, *Keihi*; *Cinnamomum cassia*, *Gomishi*; *Schisandra chinensis*, *Saishin*; *Asarum sieboldii*, *Shakuyaku*; *Paeonia lactiflora*, *Maou*; *Ephedra*, *Kankyo*; *Zingiber officinale*. Seven plants among eight showed suppressive activities of H1R gene expression. It is hypothesized that anti-allergic activity of seven plants is additively elevated, whereas adverse effects are not additive and remain relatively low. *Sho-seiryu-to* can be expected for its medicinal effect similar to antihistamines without sedation and sleepiness (Nakano et al. 2021).

When either antihistamine, *Kujin* or *Sho-seiryu-to* was administered to TDI rats, H1R mRNA up-regulation in nasal mucosa was completely suppressed, and degree of symptom alleviation was similar in each case. The results suggest that medicinal effect of antihistamines dominantly depends on PKC δ signaling-mediated H1R gene expression.

4 Antihistamine-Insensitive Mechanism of Allergy and Combination Therapy

4.1 Discovery of Antihistamine-Insensitive Mechanism of Allergy Using Suplatast Tosilate

Up-regulation of H1R mRNA in nasal mucosa of TDI rats was completely suppressed to the basal level by the treatment of epinastine, an antihistamine. In spite of complete suppression of up-regulation, alleviation of symptoms was only 60% (Mizuguchi et al. 2008). Remaining symptoms were assumed to be due to antihistamine-insensitive mechanism of allergy.

Suplatast tosilate was developed as a Th2 cytokine suppressor (Furukido et al. 2002). Indication for suplatast is bronchial asthma, atopic dermatitis, and allergic rhinitis. Detailed efficacy mechanism of suplatast remained unknown. Partial alleviation by suplatast of nasal symptoms was observed in TDI rats (Shahriar et al. 2009). Then combination treatment of an antihistamine and suplatast resulted in marked alleviation of nasal symptoms in TDI rats, and up-regulation of IL-9 mRNA was almost completely suppressed by suplatast in the nasal mucosa of TDI rats, but not suppressed by antihistamine (Mizuguchi et al. 2016). In spite of strong suppressive activity of suplatast in TDI rats, no clear medicinal effect is observed in human. The clinical use of the drug is no popular. The reason is speculated that both affinity to the target and drug delivery system of suplatast are poor in human. Then apart from suplatast, suppressive activity of anti-allergic natural sources against IL-9 mRNA up-regulation was examined.

4.2 *Discovery and Molecular Pharmacology of Compounds Suppressing IL-9 Gene Expression from Natural Sources*

There are two traditions that Awa-tea, a product of tea leaf fermentation in Tokushima, Japan, and extract of lotus in Naruto, Japan, have anti-allergic activities. Combination treatment of an antihistamine and Awa-tea resulted in marked alleviation of nasal symptoms in TDI rats (Nakano et al. 2020). In reality, 90% of alleviation was resulted. Up-regulation of IL-9 mRNA in nasal mucosa was suppressed to the basal level by the treatment of Awa-tea, suggesting that IL-9 gene expression mechanism participates in nasal symptoms insensitive to antihistamines as a new allergic rhinitis-susceptibility gene. Nuclear factor of activated T-cells (NFAT) was revealed upstream of IL-9 gene expression (Mizuguchi et al. 2016). NFAT is downstream of calcium-calmodulin-calcineurin signaling (Wu et al. 2007). Pyrogallol was identified as a suppressor of IL-9 gene expression (Nakano et al. 2020). Poly(U)-binding-splicing factor puf60 (PUF60) was identified as a target of pyrogallol (Mizuguchi et al. 2020). Patho-physiological activity of pyrogallol seems to be the first report. NFAT forms a large cytoplasmic RNA-protein scaffold complex (Sharma et al. 2011). PUF60 has binding activity to the NFAT complex, and NFAT signaling-mediated IL-9 gene expression was suppressed by the knockout of PUF60 (Mizuguchi et al. 2020). The data suggest that PUF60 is a novel drug target for the therapy of antihistamine-insensitive allergic symptoms.

Next to Awa-tea, hot water extract of lotus root knots showed inhibitory activity of IL-9 gene expression (Wakugawa et al. 2020). Nasal symptoms of TDI rats were markedly alleviated by combination treatment of epinastine, an antihistamine, and extract of lotus root knots. Ionomycin Ca^{++} ionophore-induced up-regulation of IL-9 mRNA was completely suppressed by the extract of lotus root knots in RBL 2H3 cells. Proanthocyanidin containing gallocatechin tetramer (PAC) was isolated from lotus root knots as an active compound (Wakugawa et al. 2020). PAC showed dose-dependent suppression of IL-9 mRNA up-regulation in RBL 2H3 cells and marked alleviation of nasal symptoms by the combination treatment with epinastine in TDI rats.

Lotus root powder (LRP) was prepared from lotus root knot extract by spray dry manufacturing method. LRP standardized by determining PAC and total polyphenol levels showed symptom alleviation and suppression of IL-9 mRNA up-regulation by the combination treatment with epinastine in TDI rats. Then randomized, double-blind, parallel-group, placebo-controlled study was performed using LRP and maltodextrin as a control. LRP showed significant improvement in nasal and eye symptomatology scores of Practical Guideline for the management of allergic rhinitis in Japan, color tone of inferior turbinate mucosa, and eye symptomatology score of Japanese Rhinoconjunctivitis Quality of Life Questionnaire without any adverse effect (Nagamine et al. 2020).

IL-9 is an allergic Th2 cytokine. IL-9 is produced mainly in Th9 cells and produced in other T helper cells including Th2 cells, Th9 cells, Th17 cells and regulatory Treg cells, and mast cells (Noelle and Nowak. 2010). In addition to our

present observation that IL-9 participates pathogenesis of nasal hypersensitivity, IL-9 plays roles in other allergic diseases including bronchial asthma and food allergy, immune response to parasite infection, inflammatory bowel diseases, and malignancies including Hodgkin's lymphoma and melanoma (Neurath and Finotto 2016; Zuleta and Sanchez 2017). Pyrogallol and PAC are potential therapeutics not only for allergic rhinitis but also for other IL-9 related diseases.

5 Future Outlook for the Therapy of Allergic Diseases

5.1 *Multiple Pathological Mechanisms of Allergic Diseases*

Antihistamines gave brilliant contribution to the therapy of type-1 reaction-dominant allergic diseases. However, alleviation of the diseases by antihistamines is insufficient, suggesting the existence of antihistamine-insensitive signaling in allergy. In order to overcome the insufficiency, slow reacting substance of anaphylaxis (SRS-A) as an antihistamine-insensitive allergy signaling was investigated, and chemical mediators such as leukotrienes, prostaglandins, and platelet activation factor and many allergy cytokines have been identified. Newly developed drugs targeting SRS-A and allergic cytokines were expected high level alleviation of allergic symptoms. Unfortunately, these drugs are not effective to pollinosis and other type-1 reaction-dominant allergic diseases. It is thought essential to identify exact factors of type-1 reaction-dominant allergic diseases from multiple factors. However, the problem remains to be solved.

Alternative approach is to elucidate multiple pathological mechanisms of allergy. Although H1R is the target of antihistamines, there is no study how symptoms are alleviated. Our research results demonstrated that histamine-induced H1R gene expression participates in symptoms as an allergic rhinitis-susceptibility gene. On the other hand, as antihistamine-insensitive mechanism, IL-9 gene was identified as the second allergic rhinitis-susceptibility gene (Fig. 3).

Historically, traditional natural medicines have been used for the therapy of various diseases. Then receptors became principal drug targets after developments of antihistamines (histamine H₁ antagonists), histamine H₂ antagonists, and β -adrenaline antagonists for the therapy of allergic diseases, peptic ulcer, and cardiovascular diseases, respectively. Regarding allergic diseases, anti-allergic drugs targeting receptors such as leukotriene-receptor antagonist (LTRA), thromboxane A₂ (TXA₂) receptor antagonists, prostaglandin D₂ (PGD₂) receptor antagonists were newly developed. Alleviation of allergic rhinitis was insufficient by these anti-allergic drugs.

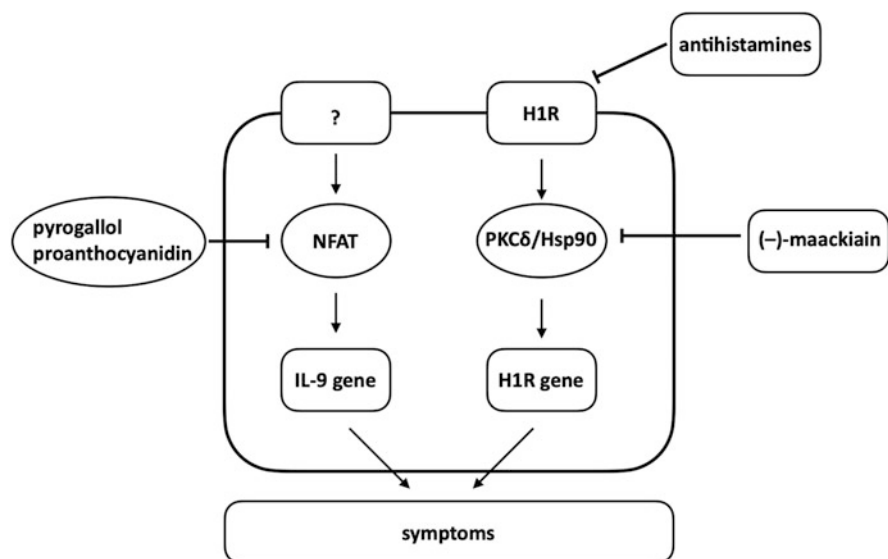


Fig. 3 Two signaling pathways of allergic symptoms. Antihistamine- and (–)-maackiain-sensitive H1R gene expression as the first mechanism and pyrogallol- and proanthocyanidin-sensitive IL-9 gene expression as the second one

5.2 A New Evaluation System to Develop New Therapeutics

In order to develop novel therapeutics with new concept, new evaluation system of symptoms is indispensable. Recently, involvement of susceptibility genes was studied in the onset of multifactorial diseases. As antihistamines are principal therapeutics of allergic diseases, their susceptibility genes are to be studied. Good correlation between symptom deterioration and H1R mRNA up-regulation and correlative symptom alleviation and suppression of H1R mRNA up-regulation by the therapy of antihistamines were demonstrated, suggesting that H1R gene is a susceptibility gene for allergic rhinitis (Mizuguchi et al. 2010; Kitamura et al. 2015).

5.3 Therapeutic Strategy for Multifactorial Allergic Diseases

Combination therapy is advanced therapeutic intervention for multifactorial diseases and highly expected for allergic diseases. IL-9 gene was identified as a susceptibility gene for antihistamine-insensitive symptoms, and pyrogallol, a suppressive compound of IL-9 gene expression, was successfully identified from Awa-tea. Combination therapy using an antihistamine and pyrogallol showed remarkably advanced alleviation of symptoms in TDI rat, compared to the single treatment of antihistamine (Nakano et al. 2020). The result is promising for the therapy of type-

1 reaction-dominant allergic diseases including allergic rhinitis, allergic conjunctivitis, and urticaria. Clinical trials are awaited.

6 Expanding Histamine Research for the Novel Therapeutic Strategy of H1R-Related Diseases in Future

6.1 H1R and Diabetes Mellitus and Other Diseases

Angiopathy and neuropathy are major pathological changes of diabetes mellitus. Recently, diabetes mellitus has been studying as an inflammatory disease (Donath and Shoelson 2011; Lontchi-Yimagou et al. 2013; Tsalamandris et al. 2019). Histamine is a principal mediator of allergic inflammation. Reports of histamine research related to diabetes mellitus have been accumulating. Increased plasma histamine level and histamine synthesis were reported (Hollis et al. 1985; Gill et al. 1989, 1990). In addition to reports on therapeutic potential of histamine H₃ receptor agonist for diabetes mellitus (Yoshimoto et al. 2006; Henry et al. 2011; Nakamura et al. 2014, 2015), H1R-mediated effects in diabetic condition were also reported. Retinopathy may be deteriorated by H1R-mediated increase in blood-retinal barrier (Enea et al. 1989; Hollis et al. 1992). H1R could contribute to diabetic nephropathy (Anbar et al. 2016). Antihistamines may be indicated to H1R-related diabetic pathologies.

Significance of glucagon in diabetes mellitus was recently reported (Hare et al. 2010). Glucagon secretion was suppressed by PKC δ activation which induces H1R gene expression (Yamamoto et al. 2017). Apart from diabetes mellitus, participation of H1R gene expression to atherosclerosis was suggested (Takagishi et al. 1995). Detailed mechanism of H1R gene expression involved in these pathologies is highly interested.

6.2 H1R Signaling-Related Diseases in the Brain

Histamine is a neurotransmitter in the brain, and H1Rs are responsible for various histaminergic functions. Motion sickness is caused by the disorder of sense of balance. Histaminergic neurons are responsible in sense of balance, and antihistamines are used for the therapy of motion sickness (Takeda et al. 1989). In the motion sickness model rats, H1R mRNA was up-regulated in the hypothalamus and brainstem (Sato et al. 2009). Histaminergic neurons also regulate food intake (Sakata et al. 1988). Scheduled feeding induces c-Fos expression in the caudal part of the arcuate nucleus of hypothalamus (Umehara et al. 2011). The result suggests participation of H1R gene expression in the brain.

U373 cells are astrocyte in cultured cell line and express H1Rs. H1R gene expression was activated by the stimulation by histamine of the cells. However, the mechanism of H1R gene expression in U373 cells is thought different from that in HeLa cells because of different time course and no suppression by PKC δ inhibitors, although detailed mechanism remains to be elucidated (Mizuguchi et al. 2021).

6.3 Strategy of the Therapy for Diseases Susceptible to H1R Gene Expression

The H1R are expressed not only in peripheral tissues but also in the brain, suggesting that H1R gene expression participates various physiological and pathological functions. Involvement of H1R gene expression was extensively studied in allergic rhinitis as a disease susceptibility gene. H1R gene expression was suggested to play roles in diabetes mellitus, atherosclerosis, and motion sickness, and antihistamines may be effective for the therapy. However, most diseases are thought multifactorial. In addition to H1R-related mechanism, elucidation of other pathological mechanisms is indispensable. Then combination therapy using antihistamine and other complementary drugs is thought common in future.

Acknowledgements The studies in this review were financially supported in part by Grants-in-Aids for research from The Ministry of Education, Culture, Sports, Science and Technology, research grants from The Ministry of Health, Labor and Welfare of Japan, research grants from The Ministry of Agriculture, Forestry and Fisheries, and research grants from Osaka Medical Research Foundation for Incurable Diseases. The studies were conducted in part in Department of Molecular Incurable Diseases, Tokushima University Graduate School of Biomedical Sciences, endowed chair from Medical Cooperation Kinshukai.

References

- Anbar HS, Shehatou GSG, Suddek GM, Gameil NM (2016) Comparison of the effects of levocetirizine and losartan on diabetic nephropathy and vascular dysfunction in streptozotocin-induced diabetic rats. *Eur J Pharmacol* 780:82–92
- Das AK, Yoshimura S, Mishima R, Fujimoto K, Dev S, Wakayama Y et al (2007) Stimulation of histamine H₁ receptor up-regulates histamine H₁ receptor itself through activation of receptor gene transcription. *J Pharmacol Sci* 103:374–382
- Dev S, Mizuguchi H, Das AK, Maeyama K, Horinaga S, Kato S et al (2009) Kujin suppresses histamine signaling at transcriptional level in toluene 2,4-diisocyanate-sensitized rats. *J Pharm Sci* 109:606–617
- Donath MY, Shoelson SE (2011) Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 11:98–107
- Enea NA, Hollis TM, Kern JA, Gardner TW (1989) Histamine H₁ receptors mediate increased blood-retinal barrier permeability in experimental diabetes. *Arch Ophthalmol* 107:270–274

- Furukido K, Takeno S, Ueda T, Hirakawa K, Yajin K (2002) Suppression of the Th2 pathway by supalast tosilate in patients with perennial nasal allergies. *Am J Rhinol* 16:329–336
- Gill DS, Barradas MA, Fonseca VA, Dandona P (1989) Plasma histamine concentrations are elevated in patients with diabetes mellitus and peripheral vascular disease. *Metabolism* 38:243–247
- Gill DS, Thompson CS, Dandona P (1990) Histamine synthesis and catabolism in various tissues in diabetic rats. *Metabolism* 39:815–818
- Hare KJ, Vilsbøll T, Asmar M, Deacon CF, Knop FK, Holst JJ (2010) The glucagonostatic and insulinotropic effects of glucagon-like peptide 1 contribute equally to its glucose-lowering action. *Diabetes* 59:1765–1770
- Henry MB, Zheng S, Duan C, Patel B, Vassileva G, Sondey C et al (2011) Antidiabetic properties of the histamine H₃ receptor protean agonist proxyfan. *Endocrinology* 152:828–835
- Hollis TM, Kern JA, Enea NA, Cosgarea AJ (1985) Changes in plasma histamine concentration in the streptozotocin-diabetic rat. *Exp Mol Pathol* 43:90–96
- Hollis TM, Sill HW, Butler C, Campos MJ, Gardner TW (1992) Astemizole reduces blood-retinal barrier leakage in experimental diabetes. *J Diabetes Complications* 6:230–235
- Horio S, Ogawa M, Kawakami N, Fujimoto K, Fukui H (2004a) Identification of amino acid residues responsible for agonist-induced down-regulation of histamine H₁ receptors. *J Pharmacol Sci* 94:410–419
- Horio S, Kato T, Ogawa FK, Fukui H (2004b) Two threonine residues and two serine residues in the second and third loops are both involved in histamine H₁ receptor downregulation. *FEBS Lett* 5:226–230
- Kitamura Y, Mizuguchi H, Ogishi H, Kuroda W, Hattori M, Fukui H, Takeda N (2012) Pre-seasonal prophylactic treatment with antihistamines suppresses IL-5, but not IL-33 mRNA expression in the nasal mucosa of patients with seasonal allergic rhinitis caused by Japanese cedar pollen. *Acta Otolaryngol* 132:434–438
- Kitamura Y, Nakagawa H, Fujii T, Sakoda T, Enomoto T, Mizuguchi H (2015) Effects of antihistamine on up-regulation of histamine H₁ receptor mRNA in the nasal mucosa of patients with pollinosis induced by controlled cedar pollen challenge in an environmental exposure unit. *J Pharmacol Sci* 129:183–187
- Kuroda W, Kitamura Y, Mizuguchi H, Miyamoto Y, Kalubi B, Fukui H, Takeda N (2013) Combination of leukotoriene receptor antagonist with antihistamine has an additive suppressive effect on the up-regulation of H₁ receptor mRNA in the nasal mucosa of toluene 2,4-diisocyanate-sensitized rat. *J Pharmacol Sci* 122:55–58
- Lontchi-Yimagou E, Sobngwi E, Matsha TE, Kengne AP (2013) Diabetes mellitus and inflammation. *Curr Diab Rep* 13:435–444
- Mizuguchi H, Hatano M, Matsushita C, Umehara H, Kuroda W, Kitamura Y et al (2008) Repeated pre-treatment with antihistamines suppresses transcriptional up-regulations of histamine H₁ receptor and interleukin-4 genes in toluene-2,4-diisocyanate-sensitized rats. *J Pharmacol Sci* 108:480–486
- Mizuguchi H, Kitamura Y, Kondo Y, Kuroda W, Yoshida H, Miyamoto Y (2010) Preseasonal prophylactic treatment with antihistamines suppresses nasal symptoms and expression of histamine H₁ receptor mRNA in the nasal mucosa of patients with pollinosis. *Methods Find Exp Clin Pharmacol* 32:745–748
- Mizuguchi H, Terao T, Kitai M, Ikeda M, Yoshimura Y, Das AK et al (2011) Involvement of PKC {delta}/ERK/poly(ADP-ribose) polymerase-1 (PARP-1) signaling pathway in histamine-induced up-regulation of histamine H₁ receptor gene expression in HeLa cells. *J Biol Chem* 286:30542–30551
- Mizuguchi H, Nariai Y, Kato S, Nakano T, Kanayama T, Kashiwada Y et al (2015) Maackiain is a novel antiallergic compound that suppresses transcriptional upregulation of the histamine H₁ receptor and interleukin-4 genes. *Pharmacol Res Perspect* 3:e00166. <https://doi.org/10.1002/prp2.166>

- Mizuguchi H, Orimoto N, Kadota T, Kominami T, Das AK, Sawada A (2016) Suplatast tosilate alleviates nasal symptoms through the suppression of nuclear factor of activated T-cells-mediated IL-9 gene expression in toluene-2,4-diisocyanate-sensitized rats. *J Pharmacol Sci* 130:151–158
- Mizuguchi H, Nakano S, Kitamura Y, Takeda N, Fukui H. Up-regulation of histamine H1 receptor gene expression in U373 astrocytoma In: Abstract of the 92rd annual meeting of the Japanese Biochemical Society. Yokohama, 18-20 September 2019.
- Mizuguchi H, Nakano T, Nishida K, Ito T, Wakugawa T, Kaminuma O, Kitamura N, Ishida T, Michinaga S, Yabumoto M, Kitamura Y, Takeda N, Fukui H. Mechanism of NFAT-signaling suppression by pyrogallol. In: Abstract of the 22rd annual meeting of the Japanese histamine research Society. Hiroshima, 1-2 February 2020.
- Mizuguchi H, Miyamoto Y, Terao T, Yoshida H, Kuroda W, Kitamura Y, Takeda N, Fukui H (2021) Signaling pathway of histamine H1 receptor-mediated histamine H1 receptor gene upregulation induced by histamine in U-373 MG cells. *Curr Issues Mol Biol* 43:1243–1254
- Nagamine K, Takeuchi S, Nakagawa H, Ebihara S, Wakugawa T, Kitamura Y, Fukui H, Mizuguchi H, Takeda N (2020) Verification of improvement effects with lotus-root extracts in eye- and nose-related allergic conditions –randomized, placebo-controlled, double-blind, parallel-group study – in Japanese. *Jpn Pharmacol Ther* 48:1559–1569
- Nakamura T, Yoshikawa T, Noguchi N, Sugawara A, Kasajima A, Sasano H, Yanai K (2014) The expression and function of histamine H(3) receptors in pancreatic beta cells. *Br J Pharmacol* 171:171–185
- Nakamura T, Yoshikawa T, Naganuma F, Mohsen A, Iida T, Miura Y, Sugawara A, Yanai K (2015) Role of histamine H3 receptor in glucagon-secreting alphaTC1.6 cells. *FEBS Open Bio* 5:36–41
- Nakano T, Ikeda M, Wakugawa T, Kashiwada Y, Kaminuma O, Kitamura N et al (2020) Identification of pyrogallol from Awa-tea as an anti-allergic compound that suppresses nasal symptoms and IL-9 gene expression. *J Med Invest* 67:289–297
- Nakano S, Yamamoto S, Etsu T, Naniwa S, Konishi Y, Wakugawa T, et al. (2021) Effects of Syo-seiryu-to and its constituent crude drugs on phorbol ester-induced up-regulation 2 of IL-33 and histamine H1 receptor mRNAs in Swiss 3T3 and HeLa cells. *Allergies* 1: 163–175. <https://doi.org/10.3390/allergies1030015>
- Nariai Y, Mizuguchi H, Ogasawara T, Nagai H, Sasaki Y, Okamoto Y et al (2015) Disruption of heat shock protein 90 (Hsp90)-protein kinase Cδ (PKCδ) interaction by (–)-Maackiain suppresses histamine H₁ receptor gene transcription in HeLa cells. *J Biol Chem* 290:27393–27402
- Neurath MF, Finotto S (2016) IL-9 signaling as key driver of chronic inflammation in mucosal immunity. *Cytokine Growth Factor Rev* 29:93–99
- Noelle RJ, Nowak EC (2010) Cellular sources and immune functions of interleukin-9. *Nat Rev Immunol* 10:683–687
- Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, Chen S, Trier AM, Xu AZ, Tripathi SV, Luo J, Gao X, Yang L, Hamilton SL, Wang PL, Brestoff JR, Council ML, Brasington R, Schaffer A, Brombacher F, Hsieh CS, Gereau RW, Miller MJ, Chen Z-F, Hu H, Davidson S, Liu Q, Kim BK (2017) Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell* 17:217–228
- Ohuchi Y, Yanai K, Sakurai E, Fukui H, Yanagisawa T, Watanabe T (1998) Histamine-induced calcium mobilization in single cultured cells expressing histamine H₁ receptors: a relationship between its sensitivity and the density of H₁ receptors. *Int J Mol Med* 1:355–360
- Sakata T, Fukagawa K, Ookuma K, Fujimoto K, Yoshimatsu H, Yamatodani A, Wada H (1988) Modulation of neuronal histamine in control of food intake. *Physiol Behav* 44:539–543
- Sato G, Uno A, Horii A, Umehara H, Kitamura Y, Sekine K, Tamura K, Fukui H, Takeda N (2009) Effects of hypergravity on histamine H₁ receptor mRNA expression in hypothalamus and brainstem of rats: implication for development of motion sickness. *Acta Otolaryngol* 129:45–51
- Shahriar M, Mizuguchi H, Maeyama K, Kitamura Y, Orimoto N, Horio S, Umehara H, Hattori M, Takeda N, Fukui H (2009) Suplatast tosilate inhibits histamine signaling by direct and indirect down-regulation of histamine H₁ receptor gene expression through suppression of histidine decarboxylase and interleukin-4 gene transcriptions. *J Immunol* 183:2133–2141

- Sharma S, Findlay GM, Bandukwala HS, Oberdoerffer S, Baust B, Zhigang Li Z, Schmidt V, Hogan PG, Sacks DB, Rao A (2011) Dephosphorylation of the nuclear factor of activated T cells (NFAT) transcription factor is regulated by an RNA-protein scaffold complex. *Proc Natl Acad Sci U S A* 108:11381–11386
- Takagishi T, Sasaguri Y, Nakano R, Arima N, Tanimoto A, Fukui H, Morimatsu M (1995) Expression of the histamine H₁ receptor gene in relation to atherosclerosis. *Am J Pathol* 146:981–988
- Takeda N, Morita M, Hasegawa S, Kubo T, Matsunaga T (1989) Neurochemical mechanisms of motion sickness. *Am J Otolaryngol* 10:351–359
- Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis G-A, Vogiatzi G, Papaioannou S et al (2019) The role of inflammation in diabetes: current concepts and future perspectives. *Eur Cardiol* 14:50–59
- Umehara H, Mizuguchi H, Mizukawa N, Matsumoto M, Takeda N, Senba E, Fukui H (2011) Deprivation of anticipated food under scheduled feeding induces c-Fos expression in the caudal part of the arcuate nucleus of hypothalamus through histamine H₁ receptors in rats: potential involvement of E3 subgroup of histaminergic neurons in tuberomammillary nucleus. *Brain Res* 1387:61–70
- Wakugawa T, Nagamine K, Hiramatsu M, Takeda M, Kawata C, Kashiwada Y (2020) Identification and characterization of the anti-allergic compound from lotus root. *Trad Kampo Med* 7:85–95
- Wu H, Alys Peisley A, Graef IA, Crabtree GR (2007) NFAT signaling and the invention of vertebrates. *Trends Cell Biol* 17:251–260
- Yamamoto K, Mizuguchi H, Tokashiki N, Kobayashi M, Tamaki M, Sato Y et al (2017) Protein kinase C- δ signaling regulates glucagon secretion from pancreatic islets. *J Med Invest* 64:122–128
- Yamashita M, Fukui H, Sugama K, Horio Y, Ito S, Mizuguchi H et al (1991) Expression cloning of a cDNA encoding the bovine histamine H₁ receptor. *Proc Natl Acad Sci U S A* 88:11515–11519
- Yoshimoto R, Miyamoto Y, Shimamura K, Ishihara A, Takahashi K, Kotani H et al (2006) Therapeutic potential of histamine H₃ receptor agonist for the treatment of obesity and diabetes mellitus. *Proc Natl Acad Sci U S A* 103:13866–13871
- Zuleta WGR, Sanchez E (2017) IL-9: function, sources, and detection. *Methods Mol Biol* 1585:21–35