H1 antihistamines in allergic rhinitis: The molecular pathways of interleukin and toll-like receptor systems

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ABSTRACT

The complex interaction between inflammatory mediators in allergic rhinitis (AR) is determined by the role of genetic polymorphisms, including interleukin (IL) and toll-like receptor (TLR) genes. This study aimed to discuss the effects of H1-antihistamines on IL and TLR systems. Several ILs involved in AR pathogenesis are: IL-4 (rs2243250, rs1800925, rs1801275, rs2227284, rs2070874), IL-6 (rs1800795, rs1800797), IL-10 (rs1800871, rs1800872), IL-12R (rs438421), IL-13 (rs1800925), IL-17 (rs3819024), IL-18 (rs360721, rs360718, rs360717, rs187238), IL-23R (rs7517847), and IL-27 (rs153109, rs17855750). In the IL system, histamines stimulate the IL production in Type 2 helper T (Th2) cells through protein kinase A (PKA), janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, and the activation of H1-histamine receptor and histidine decarboxylase (HDC) genes. On contrary, antihistamines down-regulate the H1-histamine receptor gene expression through the transcription suppression of HDC and IL genes and suppress histamine basal signaling through the inverse agonistic activity. TLRs involved in AR pathogenesis are TLR2 (rs4696480, rs3804099, rs5743708), TLR4 (rs4986790), TLR6 (rs2381289), TLR7 (rs179008, rs5935438), TLR8 (rs2407992, rs5741883, rs17256081, rs4830805, rs3788935, rs178998), and TLR10 (rs11466651). In the TLR system, histamines trigger the TLR expression by stimulating interferon-γ (IFN-γ) to up-regulate mast cells and by stimulating receptor-interacting protein (RIP) to activate IκB kinase-β. Contrastingly, antihistamines suppress TIR-domain-containing adaptor protein inducing IFN-β (TRIF) and RIP protein and thus inhibit the expression of TLR. In addition, several studies indicated that H1-antihistamines inhibit the IL and TLR systems indirectly.

Keywords: H1 antihistamine; allergic rhinitis; gene expression in allergic rhinitis

INTRODUCTION

Allergic rhinitis (AR) is one of the most common allergic diseases. The incidence of AR is estimated between 10 to 25% of the world population. AR has been associated with the main reasons why people visit primary care (1). AR is not a life-threatening disease, but it can significantly impair the quality of life (2). Total funding issued to AR was estimated approximately 5.3 billion dollars per year (3). The incidence of AR in the United States (US) was estimated approximately 40 million cases (4). Nihlen et al. (5) reported that the prevalence of AR was estimated around 15% in men and 14% in women. Several studies showed different results on the age
that is most susceptible to AR. Dykewics et al. (6) reported that approximately 80% of AR cases had developed the disease at the 20 years of age, while Settipane (7) reported that the prevalence of AR was about 40% higher in children.

AR is a disease characterized by four cardinal symptoms, including: itching, sneezing, rhinorrhea, and nasal congestion. AR is classified into intermittent and persistent rhinitis. The clinical manifestations of AR are caused by allergen exposure that triggers the immune response, and this process is reversible (1). Mucous membrane inflammation in AR is caused by complex interaction between inflammatory mediators and it is triggered by the response of immunoglobulin E (IgE) against extrinsic proteins (8). This process is determined by the variation in gene expression. Study by Mizuguchi et al. (9) showed that the variation in cytokine receptor genes and H1-histamine receptors played an important role in the pathogenesis of AR. Hussein et al. (10) showed that polymorphisms of Toll-like receptors 2 (TLR-2) and TLR-4 genes were associated with susceptibility to AR. Furthermore, Testa et al. (11) showed that the variation in interleukin 4 (IL-4) gene expression determined the severity of AR. In addition, the variation in ILs gene expression have also been associated with the severity of AR (12,13).

H1-antihistamines have been used extensively for the treatment of AR (14). The role of histamines in allergic diseases is different in each individual, and it depends on the gene expression or polymorphisms involved in the pathogenesis of AR (15). Studies on the role of antihistamines in the expression of the genetic variation in AR have been limited. The main goal of this paper was to discuss the effects of H1-antihistamines on the IL and TLR systems in AR.

**DISCUSSION**

**Activation and inactivation models of H1-histamine receptors**

H1-histamine receptors in humans are members of the superfamily of G-protein-coupled receptors (GPCRs). This superfamily consists of approximately 500 membrane proteins that have seven transmembrane α-helix structural motifs. The H1-histamine receptor gene encodes the 487-amino-acid protein with a predicted molecular mass of 55.8 kilodaltons (kDa). The absence of introns in the H1-histamine receptor gene indicates that only the transcription of the single receptor protein encoding gene occurs (16).

Similarly to other G-protein receptors, the H1-histamine receptors have an important role in cellular activation and inactivation. Histamines cross-link areas on the III and V trans membrane domains, which leads to the receptor activation. H1-antihistamines are non-structural compounds that are not necessarily antagonists to the histamine binding, but they can bind to a different site on the histamine receptors to produce the opposite effect of histamines. For example, cetirizine cross-links the IV and VI trans membrane domains to stabilize the receptor in its inactive state. Therefore, it does not function as the H1-histamine receptor antagonist, but as the inverse agonist to produce the opposite effect of histamines (16). This process is illustrated in Figure 1.

**H1-antihistamines in interleukin system**

H1-antihistamines are not the receptor antagonists, but inverse agonists. The basic structure of H1-antihistamines consist of two aromatic rings connected with ethylamine (17). If the amount of H1-histamines and H1-antihistamines is equal, the H1-histamine receptors are in the balance state. The histamines are associated with the activation of the H1-histamine receptors and cellular stimulation, while the antihistamines are associated with their inactivation. Therefore, histamine - induced cell or tissue stimulation depends on the balance between the histamines and antihistamines (18).

The H1-histamine receptors have different effects on the immune system, including dendritic cells maturation and modulation of the balance of Type 1 and 2 helper T (Th1 and Th2) cells. The histamines also induce the release of proinflammatory cytokines. Therefore, H1-antihistamines can reduce the proinflammatory cell expression and accumulation of eosinophils and neutrophils (18). It has been showed that the expression of the H1-histamine receptor affects the severity of AR and that the expression of the H1-histamine receptor messenger ribonucleic acid (mRNA) in AR is increased (9). In addition, upregulation of the H1-histamine
receptor can be induced by ILs through the activation of the H1-histamine receptor gene (19) and histidine decarboxylase (HDC) gene transcription (Figure 2) (20). The role of ILs in regulating the mRNA expression of the H1-histamine receptor was demonstrated by Shahriar et al. (21) using a mouse model. The mice were injected with IL-4 which resulted in the upregulation of the H1-histamine receptor mRNA.

Several studies reported the association of AR with IL-4 gene polymorphisms in ethnically and geographically distinct populations. The contribution of these genes to AR pathogenesis was analyzed by Movahedi et al. (22) in Iranian patients with AR. This study analyzed IL-4 gene polymorphisms in the AR patients. The results showed that IL-4 was associated with AR and had a role in the development of AR clinical manifestation. They also
found that the C allele of the reference sequence rs2243250 of the *IL-4* gene was significantly overrepresented in the AR patients. On contrary, rs2243248, rs2243250, and rs2070874 haplotypes of the *IL-4* gene had a significant negative correlation with AR. In other study, Bottema et al. (23) analyzed *IL-13* and *IL-4* polymorphisms in AR and asthma patients in the Netherland. They showed that *IL-13* C–1111T (rs1800925) polymorphism was significantly associated with rhinitis and atopic phenotypes in AR patients, but was not associated with asthma. *IL-13* Arg130Gln (rs20541) and G870A (rs1295685) polymorphisms had a significant association with asthma and serum IgE.

*IL-4R* Glu375Ala (rs1805011) and Ser411Leu (rs1805013) polymorphisms were also associated with asthma. *IL-4RA* Gln551Arg (rs1801275) polymorphism was associated with AR susceptibility in Asian, but *IL-4RA* Ile50 Val as well as Ser478Pro polymorphisms were not associated with AR susceptibility both in Asian and Caucasian. In addition, genotypes combination of *IL-13* Arg130Gln with *IL-4R* Glu375Ala, and *IL-13* C–1111T with *IL-4R* Ser478Pro were associated with increased risks for asthma (24). Another study conducted by Walley & Cookson (25) investigated the association of *IL-4* gene polymorphisms with atopic diseases, including AR. They found that the rs2243250 variant among *IL-4* polymorphisms was associated with atopic diseases. Another study conducted in Canada by Zhu et al. (26) investigated the association of *IL-4*, tumor necrosis factor (TNF-α), and FcαRIβ gene polymorphisms with the risk of allergic disorders in infants. They showed that IL-4-589*T* (rs2243250) variant, but not TNF-α-308*2 or FcαRIβ *G* variants, was associated with the risk factor for the development of atopy, asthma, and rhinitis by 12 months of age. Furthermore, a study conducted in Pakistan by Michael et al. (27) analyzed the association of *IL-4* gene polymorphisms with the risk of atopic asthma and AR in Pakistani patients. They found that rs2243250 and rs2227284 single-nucleotide polymorphisms (SNPs) had a significant association with the risk of asthma and AR. Li et al. (28) conducted a meta-analysis on *IL-4* gene polymorphisms in AR. They showed that

<p>| TABLE 1. Interleukin gene polymorphisms associated with AR susceptibility in different populations |
|-----------------|-----------------|-------------------|------------------|</p>
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IL=Interleukin, rs=Reference sequence
C-590T (rs2243250) and C-33T (rs2227284) polymorphisms had a significant association with AR. Data on the interleukin genes polymorphisms associated with AR susceptibility are listed in Table 1.

Several other studies reported the correlation of polymorphisms of IL-6, IL-10, IL-12, IL-13, IL-17, IL-18, IL-23, and IL-27 genes with susceptibility to AR. Nasiri et al. (29) analyzed the association of IL-6 SNPs with the risk of AR. They found that rs1800795 and rs1800797 variants of IL-6 gene had a significant association with the increased risk of developing AR. Nasiri et al. (30) also analyzed the association of gene polymorphisms in IL-10 and transforming growth factor β (TGF-β) genes with AR. They found that rs1800896 variant of IL-10 gene and rs1982037 variant of TGF-β gene were significantly less frequent in AR, while rs1800471 variant of TGF-β gene and rs1800871 and rs1800872 variants of IL-10 gene were associated with higher susceptibility to AR. Another study conducted in Chinese Han population by Wei et al. (31) analyzed the association between IL-12Rβ1/β2 genes and AR. They showed that rs438421 polymorphism in IL-12Rβ1 gene had a significant association with AR. In addition, rs1800925 polymorphism in IL-13 gene showed a significant association with AR susceptibility in Netherland population (23). In other study conducted in Malaysian population, Yadav et al. (32) investigated the polymorphic variants of IL-13 R130Q, IL-4 T589C, IL-4 RAI50V, and IL-4 RAQ576R genes in AR patients. They found that IL-13 R130Q (rs20541) polymorphism had a significant association with increased risk for development of AR, but not IL-4 T589C, IL-4RA 150V, and IL-4RA Q576 polymorphisms. In addition, rs20541 variant in IL-13 gene was shown to be associated with AR susceptibility by Ying et al. (33) and Andiappan et al. (34). A study conducted in Chinese population by Wang et al. (35) investigated the association of IL-17A and IL-17F gene polymorphisms with the development of AR. They found that rs3819024 SNP was potentially associated with AR. Another study, conducted in Germany by Kruse et al. (36), analyzed the association of IL-18 (–920[t/c], –133[c/g], and –132[a/g]) in promoter 2 upstream of exon 2; +179[c/a; Ser35Ser] in exon 4; and +486[c/t; Phe137Phe] in exon 6 polymorphisms with AR. They found that the SNPs –133[c/g] (rs360721) had significant association with high serum IgE levels and specific sensitization to common allergens. The SNPs in exon 1 +113[t/g] (rs360718) and +127[c/t] (rs360717) and in promoter 1 –137[g/c] (rs187238) of the IL18 gene also had significant association with high IgE levels and specific sensitization. Other study, conducted by Hu et al. (37), analyzed the association of IL-23R gene polymorphisms with AR. They showed that rs7517847 variant of IL-23R gene had a strong association with AR susceptibility. A Study by Shen et al. (38) investigated the association of IL-27 gene polymorphisms with the risk of AR. They found that rs153109 and rs17855750 polymorphisms in IL-27 gene were involved in AR susceptibility. Based on these data, we can conclude that the variation in the expression of the IL genes has an important role in the pathogenesis of AR. As the result, the suppression of the transcription of the IL genes could reduce the clinical manifestations of AR.

H1-antihistamines inhibit the up-regulation of the H1-histamine receptor gene expression and suppress histamine basal signaling through the inverse agonistic activity (9). A study by Lippert et al. (39) examined the role of H1-antihistamines in allergic diseases. They showed that H1-antihistamines inhibit the cytokine secretion in mast cells. In addition, Shahriar et al. (21) showed that the down-regulation of the H1-histamine receptor gene expression by the antihistamines occurs through the transcription suppression of HDC and IL-4 genes (Figure 2). The role of antihistamines in the IL-4 gene suppression has also been studied by Mizuguchi et al. (40). The decrease of IL-4 in AR after H1-antihistamine treatment has been demonstrated by Testa et al. (11). A study conducted by Masamoto et al. (41) examined IL-4 cytokines in patients with AR. They showed that IL-4 and vascular cell adhesion protein 1 (VCAM-1) were increased significantly. Wang et al. (42) conducted a study on the association of histamines and IL-6 expression. They showed that histamines could stimulate the release of IL-6. Thus, the development of H1-antagonist that inhibits the release of IL-6 could be an efficient treatment for disease with elevated levels of histamines. Another study conducted by Osna et al. (43) analyzed the regulation of IL-10 secretion by histamines. They showed that histamines could stimulate IL-10 production.
in Th2 cells which is reversed by both H1- and H2- receptor antagonists and by protein kinase A (PKA) inhibitors H8 and rp-adenosine-3’,5’-cyclic monophosphothionate (Rp-cAMPS). Therefore, inhibition of histamine could suppress IL-10 production. Other study by Elenkov et al. (44) showed that histamine increased the production of IL-10 in lipopolysaccharide (LPS)-stimulated whole blood cultures. A study conducted by Elliott et al. (45) investigated the regulation of IL-13 production by histamines in cloned murine Th2 cells. They found that histamines could stimulate the IL-13 secretion and transcription through PKA and Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway. Based on these data, histamines trigger the production of IL through several mechanisms, including: (1) histamines stimulate the IL production in Th2 cells which is reversed by both H1- and H2- receptor antagonists, PKA inhibitors H8, and Rp-cAMPS (43), (2) histamines stimulate the IL secretion and transcription through PKA and JAK-STAT pathway (45), (3) histamines stimulate the IL production through the transcription activation of the H1-histamine receptor (19) and HDC genes (20). On contrary, the mechanisms of antihistamines in IL system through several pathways, i.e. (1) antihistamines inhibit the up-regulation of the H1-histamine receptor gene expression and suppress histamine basal signaling through the inverse agonistic activity (9), (2) antihistamines inhibit the cytokine secretion in mast cells (39), (3) antihistamines down-regulate the H1-histamine receptor gene expression by suppressing the transcription of HDC and IL-4 genes (21). Thus, the inhibition of histamines possibly inhibits the production of IL which plays an important role in the pathogenesis of AR. Several studies have shown the association of antihistamines with the plasma levels of ILs. Crisan et al. (46) conducted a study on the effect of H1-antihistamine therapy on cytokine profile in patients with chronic urticaria. They showed that H1-antihistamines significantly reduced the plasma levels of IL-1β, IL-2, IL-4, IL-6, IL-17, and IL-31. Elevated levels of histamines have an important role in the pathogenesis of AR and urticaria. So, it is possible that this process also occurs in AR. A study conducted by Boscan et al. (47) also analyzed the effects of H1-antihistamines in AR. They showed that H1-antihistamines could reduce the plasma levels of IL-1β, IL-6, and IL-8 after a four-week treatment.

**H1-antihistamines in toll like receptor system**

The inflammatory process involving intracellular adhesion molecule 1 (ICAM-1) in nasal epithelial cells has an important role in AR pathogenesis. This process is stimulated by TLR3. The TLR3 expression is modulated by histamines (48). TLR3-mediated signaling pathways are induced by myeloid differentiation factor 88 (MyD88) adapters and TIR-domain-containing adapter protein inducing IFN-β (TRIF) or Toll-like receptor adapter molecule 1 (TICAM-1). This process induces the response of interferon-β (IFN-β) and the activation of nuclear factor-kappa B (NF-kB) and c-Jun N-terminal kinase (JNK). The C and N terminal regions of TRIF activate NF-kB through a different mechanism. The N terminal region of TRIF activates NF-kB through TNF receptor associated factor 6 (TRAF6). Another mechanism for the NF-kB activation is the interaction between homotypic receptor – interacting protein (RIP) with the RIP homotypic interaction motif (RHIM) domain in the C terminal of TRIF which attracts RIP1 serine threonine kinase to induce the activation of NF-kB (49).
Besides TLR3, histamines also induce other TLRs to stimulate the inflammation in endothelial cells (50) (Figure 3). The role of histamines in inducing the expression of TLR2 and TLR4 in endothelial cells was described by Stechschulte et al. (51). They showed that histamines had an important role in the mRNA and protein expression of TLR2 and TLR4. Histamines are inflammatory molecules released by mast cells and have been shown to activate endothelial cells. The role of TLR2 and TLR4 in the activation of mast cells was investigated by Varadaradjalou et al. (52). They described that the mast cell activation by TLR2 and TLR4 caused mast cells to produce TNF-α, IL-5, IL-10, and IL-13. Other study conducted by Greiff et al. (53) analyzed the TLR7 stimulation in AR. They found that TLR stimulation by AZD8848, a TLR7 agonist, was responsible for allergen sensitization in AR. A study conducted by Fransson et al. (54) investigated the upregulation of TLR2, TLR3, and TLR4 in AR. They found that the increase of the mRNA and protein expression of TLR2, TLR3, and TLR4 had a significant association with AR, and the highest increase of mRNA was in the TLR3. Another study by Fransson et al. (55) analyzed the expression of TLR9 in AR patients. They found that the widespread expression of TLR9 was associated with AR. A study in a mouse model by Zhang et al. (56) analyzed the association of TLRs and NF-kB with AR. They found that AR could upregulate the levels of TLR4 and NF-kB and stimulate the infiltration of eosinophils and the expression of IgE. Cui et al. (57) also investigated the expression of TLRs in AR. They found that the mRNA expression of TLR2 and TLR4 was significantly higher in patients with AR. In addition, the mRNA expression of IL-6 and IL-8, but not IL-1,

**FIGURE 3.** TLR signaling pathways. TLR signals trigger the activation of transcription factors, including interferon regulatory factors (IRFs) and NF-kB, which are required for the transcription of inflammatory genes. Except for TLR3, all types of TLRs attract MyD88 to trigger downstream signaling, resulting in the activation of NF-kB. Whereas NF-kB activation by TLR3 occurs through the TRIF dependent pathways, IRAK: IL-1 receptor-associated kinases; MAL: MyD88-adaptor like; MyD88: Myeloid differentiation protein 88; TLR: Toll-like receptor; TRAF: Tumour necrosis factor receptor-associated factor; TRAM: TRIF-related adaptor molecule; TRIF: TIR domain-containing adaptor inducing interferon-β [adapted with permission from reference 50].
IL-12, IFN-α, and TNF-α, was upregulated in patients with AR. They concluded that TLR2 and TLR4 were increased in patients with AR and could be one of the major contributors to the persistence and aggravation of allergic inflammation in AR. Furthermore, Okumura et al. (58) explained that TLR4 plays an important role in the specific gene expression in mast cells. They also showed that the expression of TLR4 occurred when mast cells were up-regulated by IFN-γ. Thus, the inhibition of histamines causes the disruption of TLR2 and TLR4 expression. Therefore, antihistamines are possible to cause disturbance of mast cell gene expression profile to cause inflammation.

Several studies have also reported the association of AR with TLR gene polymorphisms in ethnically and geographically distinct populations. The contribution of these genes to AR pathogenesis was analyzed by Hussein at al. (10) in Egyptian patients with AR. This study analyzed the association of TLR2 and TLR4 gene polymorphisms with asthma and AR. They found that the allele frequencies of TLR2 Arg753Gln (rs5743708) and TLR4 Asp299Gly (rs4986790) polymorphisms were not significantly different between asthmatic or AR children compared to the controls. However, a significant association between these genetic variants and the severity of the diseases was suggested. In other study, Qian et al. (59) investigated the association of polymorphisms in TLR2 subfamily with the risk of asthma and AR in Chinese population. They found that rs11466651 variant of TLR10 gene was negatively associated with AR, and rs7656411 polymorphism of TLR2 gene had a significantly reduced risk of asthma. On contrary, rs2381289 polymorphism of TLR6 gene was significantly associated with AR and asthma. Another study, conducted by Nilsson et al. (60), investigated 73 SNPs in TLR7 and TLR8 genes in AR. They found that SNPs rs2407992, rs17256081, and rs5741883 in TLR8 and rs5935438 in TLR7 had significant association with AR in Swedish population. They also found that SNPs rs2407992, rs4830805, rs17256081, rs3788935, and rs178998 in TLR8 gene had a significant association with AR in Chinese population. Furthermore, a study conducted by Gao et al. (61) analyzed TLR gene polymorphisms in AR. They found that rs4696480 variant (German and Austrian population) and rs3804099 variant (Korean population) of TLR2 gene, rs4986790 variant of TLR4 gene (Canadian population), rs2381289 variant of TLR6 gene and rs11466651 variant of TLR10 gene (Chinese population), rs179008 variant of TLR7 gene (Danish population), as well as rs2407992 and rs5741883 variants of TLR8 gene (Danish population) had a significant association with AR susceptibility. Data on the TLR gene polymorphisms associated with AR susceptibility is listed in Table 2.

**TABLE 2.** TLR genes polymorphisms associated with AR susceptibility in different populations

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</table>

IL=Interleukin, rs=Reference sequence
the expression of TLR and the inflammatory process in nasal epithelial cells (48). Study by Kaiser et al. (62) reported that TRIF and RIP proteins were essential for the TLR activation. Other study by Cusson-Hermance et al. (63) suggested that RIP use ubiquitin-dependent mechanism to activate IkB kinase-β in response to TNF-α and TLR ligands. Study by Meylan et al. (49) revealed that RIP was essential mediator in the TLR-induced NF-κB activation. The correlation between the TLR expression and histamine treatment has been reported. Jang et al. (64) analyzed the expression of TLRs stimulated by histamine in cultured human skin fibroblast. They found that the expression of TLRs 2, 3, 6, 7, 8, and 9 was decreased after six hours of the histamine treatment. Among the TLRs with the decreasing expression pattern, TLRs 7 and 8 showed a persistent tendency to decrease. Interestingly, therapy that has a target site in the TLR system recently has been shown to have better benefits. Study by Creticos et al (65) showed that the AIC vaccine, AR vaccine, has a target site in the TLR system, has a good efficacy to cope AR. Based on these data, histamines trigger the TLR expression through several mechanisms, including: (1) stimulating IFN-γ to up-regulate mast cells (58), (2) stimulating RIP through the ubiquitin-dependent mechanism to activate IkB kinase-β. On contrary, antihistamines suppress TRIF and RIP proteins and thus inhibit the expression of TLR (48).

CONCLUSION

In the IL system, histamines trigger the IL production in Th2 cells, which is reversed by both H1- and H2-receptor antagonists, PKA inhibitors H8, and Rp-cAMPS through PKA, JAK-STAT pathway, and the activation of H1-histamine receptor gene and HDC gene transcription. On contrary, antihistamines inhibit or down-regulate the H1-histamine receptor gene expression through the suppression of HDC and IL gene transcription and suppress histamine basal signaling through the inverse agonistic activity. In the TLR system, histamines trigger the TLR expression by stimulating IFN-γ to up-regulate mast cells and by stimulating RIP through the ubiquitin-dependent mechanism to activate IkB kinase-β. In addition, antihistamines suppress TRIF and RIP proteins and inhibit the expression of TLR.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES


