

Allergy treatment

Yotin Juprasong^{1,2,3}

MUSC Allergy Lab, K549m 5th fl., Chalermprakiet Bldg., Faculty of Science, Mahidol University, Bangkok TH

E-mail: yotin.jup@student.mahidol.edu | Tel: +662 201 5930 (Lab), +662 201 5812

Nowadays, there are three general approaches recommended for patients with allergic symptoms. They are allergen avoidance, pharmacological medication, and allergen immunotherapy (Bousquet et al., 2008; Farooque, 2012). The avoidance and immunotherapy are categorized as direct treatment options for allergy whereas the pharmacotherapy is identified as an indirect treatment because it only relieves allergic reactions but cannot treat the cause of allergy and/or prevent progression of the disease (Larsen et al., 2016).

Pharmacological medication

Pharmacological treatment is the next step to be suggested for atopic patients who severely suffer from allergic reactions. All medications like antihistamines, decongestants (vasoconstrictions), corticosteroids, antileukotrienes, single-agent antihistamine-mast cell stabilizers, anticholinergic drugs and also nonsteroidal anti-inflammatory drugs (NSAIDs) generally prescribed by physicians have been applied for allergic conjunctivitis such as rhinoconjunctivitis (Carr et al., 2016; Sur & Plesa, 2015). In details, for instance, histamine is a human chemical messenger synthesized by L-histidine decarboxylase enzyme which is expressed in many cell types (Simons & Simons, 2011). It plays a role in diverse aspects of on human health, especially in acute and chronic inflammation (Nijmeijer et al., 2010). It is divided into four subtypes, namely H1, H2, H3 and H4. The histamine H1-receptor belonging to a G-protein superfamily exhibits many influential functions involving in an activation of allergic reactions. For example, the receptor increases the efficacy of antigen presenting cells (APCs) and the release of histamine and other chemical mediators from mast cells and basophils. Basically, histamine

¹ Toxicology Graduate Programme, Medical and Graduate Education Division, Faculty of Science, Mahidol University, Ratchathewi, Bangkok TH 10400

² Center of Excellence on Environmental Health and Toxicology (EHT), Faculty of Science, Mahidol University, Ratchathewi, Bangkok TH 10400

³ Systems Biology of Diseases Research Unit (SYBiD), Faculty of Science, Mahidol University, Ratchathewi, Bangkok TH 10400

receptors are divided into 4 subtypes including H1, H2, H3 and H4. All subtypes are generally expressed in the central nervous system (CNS) or its related parts such as smooth muscle cells and involve in the immune system (Simons & Akdis, 2014). Particularly, H1-antihistamines acting as inverse agonists are widely used as an essential controller to downregulate allergic inflammation in atopic patients. However, previously, the antihistamines had been described as H1-receptor antagonists (H1-receptor blockers) for more than 50 years. Nowadays, the H1-antihistamine inverse agonists have been newly defined with perfect accuracy in their mechanism because the antihistamines are not structurally associated with histamine, so, they cannot antagonize the binding of histamine, but they can interfere with different sites on that receptor to perform the opposite effects (Bakker et al., 2000; D. S. Church & Church, 2011; Nijmeijer et al., 2010; Simons, 2004; Simons & Simons, 2011). Theoretically, when the H1-action receptors on small blood vessels and sensory neurons are bound with the given H1-histamine inverse agonists resulting in cross-linking of the transmembrane domains IV and VI, the receptor is then stabilized to be in an inactive state (D. S. Church & Church, 2011) (**Fig. 1**).

Apart from the direct effects of H1-antihistamines in the interruption of H1-receptor on such small blood vessels and sensory neurons leading to allergic reaction control, the antihistamine medication also modulates the allergic mechanism through an indirect pathway via the inhibition of downstream signals including calcium-ion channel and NF nuclear factor- κ B (NF- κ B). Thereby, the gene-related expression of APCs and the production of pro-inflammatory cytokines and other chemotactic factors are reduced (**Fig. 2**).

However, aside from all beneficial features of H1-antihistamines, many adverse results of that medication are exhibited, particularly for the first-generation H1-antihistamines. As widely known, the first generation of H1-antihistamines can cause a huge number of adverse effects by readily passing through the human blood-brain barrier (BBB) followed by occupying the H1-receptor located on the postsynaptic membranes of histaminergic neurons throughout the CNS such as in cerebrum, cerebellum, posterior pituitary and spinal cord (D. S. Church & Church, 2011; Haas & Panula, 2003). On account of the H1-receptor occupancy, the CNS functions are impaired and may lead to sedation, fatigue, drowsiness and impaired memory (Juniper et al., 2005; Simons, 2004). Other detrimental effects are listed in particular reduction of memory and learning performances. These impaired performances are affected by the interruption of circadian, also known as sleep/wake cycle, through the high occupancy of H1-receptors within the CNS.

Moreover, the antihistamines affect other biological processes, for example, fluid homeostasis, hormone and temperature regulations (e.g. an induction of stress-triggered release of adrenocorticotrophic hormone) and cardiovascular system (e.g. an increase rate of ventricular arrhythmias) (Brown et al., 2001; M. K. Church et al., 2010; Wyngaarden, 1951). Presently, the second generation of H1-antihistamines are widely used for allergic patients because they have lower side-effects compared to the first generation. One advantage of the second-generation medications is the limitation of the drug penetrating into the BBB (Holgate et al., 2003). Even though the second generation H1-antihistamines are safer than the first generation and their therapeutic effects are obvious, the medications are still insufficient to completely control allergic symptoms because they are needed repeatedly as long as the symptoms still occur.

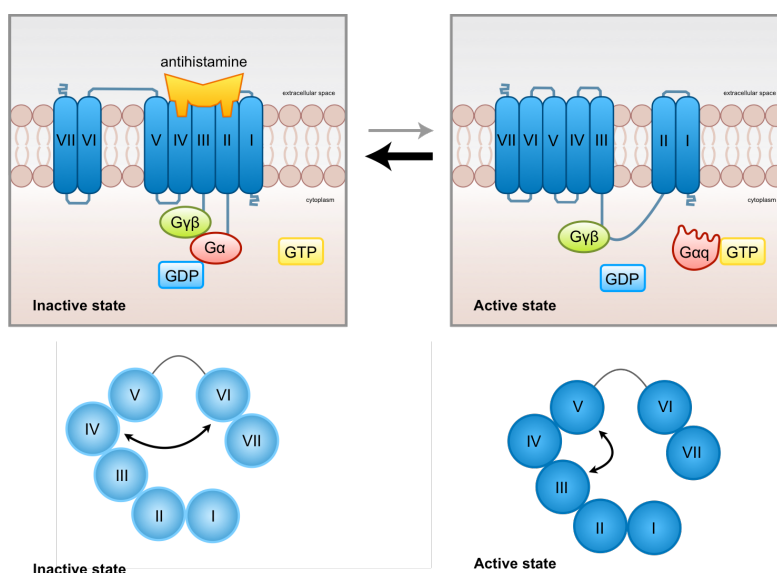


Fig. 1 Schematic mechanism of antihistamine inactivating histamine H1 G-protein coupled receptor. The above panel shows a cross-sectional view of inactive and active states of histamine receptor. The bottom panel presents a surface view of histamine-receptor transmembrane domains (modified from Church & Church, 2011; Simons & Simons, 2011).

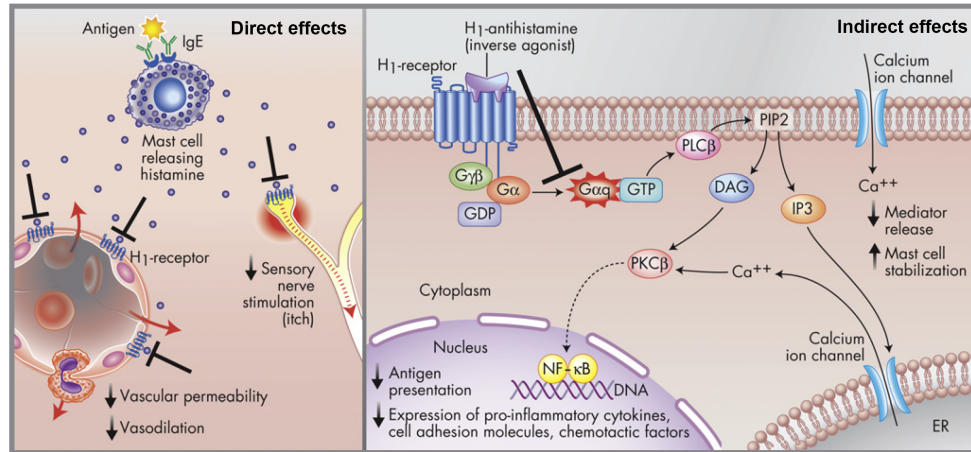


Fig. 2 Effects of H1-antihistamines on biomolecular pathway-modulated anti-allergic effects. The action of H1-antihistamines binds directly to H1-receptors on small blood vessels and sensory neurons (left panel). Indirect mechanism, the H1-antihistamines indirectly affect to downstream pathways including calcium-ion channel and NF nuclear factor- κ B (NF- κ B) via inhibition of phosphorylation at G α q subunit (right panel) (modified from Simons & Simons, 2011).

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