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REVIEW
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Modulation of Allergic Inflammation in the Nasal Mucosa of Allergic Rhinitis Sufferers With Topical Pharmaceutical Agents

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Allergic rhinitis (AR) is a chronic upper respiratory disease estimated to affect between 10 and 40% of the worldwide population. The mechanisms underlying AR are highly complex and involve multiple immune cells, mediators, and cytokines. As such, the development of a single drug to treat allergic inflammation and/or symptoms is confounded by the complexity of the disease pathophysiology. Complete avoidance of allergens that trigger AR symptoms is not possible and without a cure, the available therapeutic options are typically focused on achieving symptomatic relief. Topical therapies offer many advantages over oral therapies, such as delivering greater concentrations of drugs to the receptor sites at the source of the allergic inflammation and the reduced risk of systemic side effects. This review describes the complex pathophysiology of AR and identifies the mechanism(s) of action of topical treatments including antihistamines, steroids, anticholinergics, decongestants and chromones in relation to AR pathophysiology. Following the literature review a discussion on the future therapeutic strategies for AR treatment is provided.

Keywords: allergic rhinitis, intranasal, antihistamines, steroids, decongestants, anticholinergic, chromones

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INTRODUCTION

Allergic rhinitis (AR) is estimated to affect between 10 and 40% of the population worldwide (Bjorksten et al., 2008; Bernstein et al., 2016) and is associated with significant medical and economic burden (Cook et al., 2007; Zuberbier et al., 2014; Marcellusi et al., 2015). AR is classified as a chronic upper respiratory disease whereby exposure to allergens induces an IgE mediated inflammation of the mucous membranes lining the nose (Bousquet et al., 2008). The disease manifests symptomatically as nasal congestion, rhinorrhoea, itchy nose and sneezing. Symptoms of post nasal drip, itchy/red eyes also occur in some sufferers. House dust mites, animals, and mold spores are major triggers responsible for perennial presentation of symptoms while exposure to pollen triggers seasonal symptoms (Cook et al., 2007). Complete avoidance of airborne allergens is not possible and without a cure, the available therapeutic options are typically focused on achieving symptomatic relief.

The nasal mucosa is the primary site for allergen exposure and the inflammatory reactions that cause AR symptoms. The mechanisms driving AR pathophysiology are multifaceted and include activation and migration of effector cells, release of mediators, chemokines and cytokines from inflammatory cells, and damage to the nasal epithelium and nerve endings. Oral (systemic)

therapies, such as antihistamines, are commonly used to treat AR symptoms. However, topical therapies offer many advantages over oral therapies and are being continuously developed to target AR symptoms. Topical therapies allow for higher concentrations of drugs to be applied directly to the receptor sites at the source of inflammation (nasal mucosa) and carry a reduced risk of systemic side effects compared to oral therapies. Current therapies target different components of the allergic response, and consequently do not always offer full coverage of symptoms. Given the numerous immune cells, signaling molecules and mediators involved in the allergic response, development of a single therapy to rapidly target all components of the allergic response represents a significant challenge as a treatment option.

This review will: (i) consider the immune cells, mediators and messenger molecules of the allergic response, (ii) outline the time course of the allergic response, (iii) identify the mechanism for each topical drug and will indicate which components of the allergic response are modulated by the drug mechanism, and (iv) highlight the gaps in current therapy and identify future therapeutic strategies for the treatment of AR.

PATHOPHYSIOLOGY OF ALLERGIC RHINITIS

Atopy occurs as a result of a genetic predisposition to produce IgE antibodies and consequently the development of allergic disease. The IgE antibody is a fundamental component of the T-helper 2 (Th2) arm of the immune system, which exists as a means for defending the human body against helminth infection or other multi-cellular parasites (Allen and Sutherland, 2014). In atopic subjects, the Th2 immune pathway is instead promoted to produce an immune response to allergenic proteins derived from animals, molds and plant pollens. The allergenic proteins are processed by specialized cells of the immune system at mucosal barriers of the nose, resulting in the production of IgE antibodies. These newly produced IgE antibodies interact with specific allergens and immune cells (mast cells and basophils) situated in the nasal mucosa. The interaction of these antibodies, allergens and specialized cells, sets off a series of reactions whereby the resident mucosal immune cells such as mast cells, eosinophils and basophils to release powerful mediators such as histamine as well as chemokines, cytokines and adhesion molecules that encourage increased production of leukocytes in the bone marrow as well as attracting circulating effector leukocytes including neutrophils, Th2 lymphocytes, basophils and eosinophils into the nasal epithelium. In a series of time-dependent phases including sensitisation, early- and late-phase responses, these effector cell types, mediators and cell signaling molecules work in a complex network of interactions resulting in specific symptoms and the inflammatory morphology of AR (Bousquet et al., 2001).

Antigen Presentation and Sensitisation

Antigen presenting cells (APCs) are located in para- and inter-cellular channels neighboring the basal epithelial cells in the nasal mucosa (Mandhane et al., 2011). When allergens are deposited in the mucous layer of the nasopharynx their water soluble proteins are taken up by these APCs (dendritic cells and macrophages) and processed into short peptides that bind specifically to major histocompatibility complex (MHC) class II molecules (MHCII) expressed on the APCs surface (Bernstein et al., 2016). The APCs migrate to the lymph nodes and present the MHCII peptides to the naïve CD4+ T lymphocytes (Th0). CD4+ lymphocyte activation requires two distinct signals, contact with the MHCII molecules on APCs with specific surface T-cell receptors, and ligation of co-stimulatory receptors CD80 and CD86 on APCs with CD28 family receptors on T cells (Bugeon and Dallman, 2000; KleinJan et al., 2006). Under stimulation with the IL-4 cytokine, activated Th0 lymphocytes are transformed to T helper 2 (Th2) CD4+ cells. Non-atopic subjects can still mount allergen-specific T cell responses to allergen stimulus (Ebner et al., 1995; Van Overtvelt et al., 2008), whereby allergen-specific CD4+ T cells are mainly transformed into IFN-γ producing Th1 cells and IL-10 producing Treg cells (Van Overtvelt et al., 2008). In contrast, T cells in atopic patients are mostly transformed into allergen-specific Th2 cells (Van Overtvelt et al., 2008) which are involved in IgE production. Th2 cells release cytokines IL-4, IL-5 and IL-13 to initiate the inflammatory immune response (Bernstein et al., 2016). Specific B cell subsets are stimulated by IL-4 to differentiate into antibody producing plasma cells. In a process termed 'isotope switching,' plasma cells switch production from IgM to IgE antibodies that specifically recognize the allergenic protein. The class switching process is initiated by two signals. The first signal is provided by IL-4 and IL-13 released by T cells (Stone et al., 2010). These cytokines interact with receptors on the B-cell surface and signals induction of ε-germline transcription of B cells to produce IgE antibodies and successive clonal expansion of IgE expressing memory B cells (Sin and Togias, 2011). The second signal is a costimulatory interaction between CD154 (CD40 ligand) on the surface of activated T cells with the CD40 molecule expressed on the surface of B cells (Janeway et al., 2001). This second signal stimulates B cell activation and class switch recombination to induce IgE production (Sin and Togias, 2011).

IgE antibodies represent a very small fraction of the total antibody concentration in human serum (Bernstein et al., 2016). However, on binding with specific cell surface receptors and cross-linking with antigen, IgE can induce powerful inflammatory effects. Allergen specific IgE antibodies bind strongly with high affinity receptors (FcεRI) expressed on the surface of mast cells and basophils (Kraft and Kinet, 2007), which are abundant in the nasal mucosa. On re-exposure to allergen, the specific allergenic protein is recognized by the IgE antibodies bound to FcεRI receptors. On cross-linking of many dimeric or higher order oligomeric receptor molecules (Fewtrell and Metzger, 1980; Knol, 2006), a sequence of reactions is initiated, leading to the degranulation of mast cell and basophil vesicles and release of histamine, platelet activating factor and tryptase (Norman et al., 1985; Bernstein et al., 2016). Activated mast cells also release arachidonic acid from membrane stores, which is a precursor to the eicosanoid synthetic pathway, involved in the production of cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) and prostaglandins (primarily PGD_2) (Peters-Golden et al., 2006).

Early Phase Response

Histamine release from mast cells initiates the early or immediate phase response (**Figure 1**), typically occurs within 1 min of allergen exposure, and can last greater than 1 h (Wang et al., 1997). The nasal mucosa is innervated by a collection of sensory nerve fibers including Aδ and non-myelinated C fibers, sympathetic, and parasympathetic nerves. Histamine release from mast cells promotes activation of H1 receptors on sensory nerves of the afferent trigeminal system (Doyle et al., 1990; Bachert, 2002). These activated (depolarized) sensory nerves transmit signals to the central nervous system causing itching (Schmelz et al., 1997; Andrew and Craig, 2001) and motor reflexes such as sneezing. Histamine release also stimulates mucous glands to secrete watery discharge, via activation of sensory and parasympathetic nerves, which manifests symptomatically as rhinorrhoea (Al Suleimani and Walker, 2007). Nasal congestion is also caused by histamine release. Histamine stimulates H1 and H2 receptors of nasal blood vessels causing increased vascular permeability and vasodilatation leading to engorgement of blood vessels in the nasal mucosa and the sensation of nasal congestion (Secher et al., 1982; Wood-Baker et al., 1996; Togias, 2003). Histamine release regulates the function of tight junctions in the nasal epithelium via coupling of H1 receptors. This interaction increases paracellular permeability (Flynn et al., 2009; Georas and Rezaee, 2014) which allows APCs to more easily penetrate epithelial tight junctions and augment the antigen capture and processing abilities of APCs. The other mediators released by mast cells and basophils also play a role in smooth muscle contraction, mucous secretion and increased vascular permeability.

Late Phase Response

The primary effector cells of the early phase response (mast cells and basophils) release cytokines and chemokines which attract additional cell types to the nasal mucosa, including eosinophils, Th2 cells, group 2 innate lymphoid cells (ILC2s) and neutrophils (Sin and Togias, 2011). The late phase response (**Figure 2**) is characterized by an influx of these migratory immune cells and the subsequent release of additional cytokines and mediators from these cells which sustains inflammation and prolongs symptoms (Mandhane et al., 2011; Pawankar et al., 2011). The late phase reaction typically occurs between 4 and 5 h after initial allergen exposure and can last up to 24 h. Whilst symptoms of rhinorrhoea and sneezing persist, ongoing nasal congestion is typically indicative of a late phase reaction (Bousquet et al., 2001). Nasal biopsy specimens and nasal lavage samples collected during the allergy season, or under experimental stimulations using nasal allergen provocation tests, have shown that immune cells such as basophils, eosinophils, neutrophils, mast cells, CD4+ T cells and macrophages (Bascom et al., 1988a,b; Bentley et al., 1992; Fokkens et al., 1992; Lim et al., 1995; Durham et al., 1996; Godthelp et al., 1996; Pawankar et al., 2011) are increased in the nasal mucosa. It is noted that the presence of these immune cells was found to vary depending on the method of nasal mucosa sampling and the time the samples were taken (i.e., in or out of allergy season and timepoint after initial allergen provocation).

The late phase response is a highly complex pathophysiology involving various cytokines, chemokines and mediators released from different cell types, which interact together to perpetuate the allergic response. Mast cells release cytokines such as IL-4, IL-13 and TNF-α that play a role in activation of endothelial cells and upregulate expression of adhesion molecules such as (ICAM-1, VCAM-1) to allow eosinophils, T cells, basophils and neutrophils to migrate to the nasal mucosa (Okano, 2009; Pawankar et al., 2011; Amin, 2012). Release of mediators from mast cells, such as leukotrienes, prostaglandins and platelet activating factor, are responsible for inducing symptoms as well as possessing chemoattractant abilities (Bernstein et al., 2016). In particular, cysteinyl leukotrienes and prostaglandin D_2 released from mast cells are responsible for recruitment and activation ILC2 cells (Doherty et al., 2013; Chang et al., 2014). Indeed, elevated numbers of ILC2 been identified in peripheral blood (Doherty et al., 2014; Lao-Araya et al., 2014) and nasal mucosal samples (Dhariwal et al., 2017) from AR subjects during the pollen season or following nasal allergen challenge. Upon activation, ILC2 cells release large amounts of Th2 cytokines within the mucosal tissue which further aids to sustain inflammation (Zhong et al., 2017; Doherty and Broide, 2019).

The role of neutrophils in allergic inflammation is being increasingly recognized (Fransson et al., 2004; Hosoki et al., 2016; Arebro et al., 2017). Neutrophils recruited to the nasal mucosa, produce compounds such as reactive oxygen species, proteases such as elastase, and enzymes including metallopeptidase 9 and myeloperoxidase (MPO) which contribute to epithelial damage and recruitment of effector cells to the nasal mucosa (Monteseirin, 2009). Recent evidence suggests that neutrophils under stimulation with cytokines Granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ and IL-3 convert to functional antigen presenting cells and activate allergen-specific effector CD4+ T cells (Polak et al., 2018). The activated T cells contribute to allergic inflammation via the release of IL-5 which activates and recruits eosinophils to the nasal mucosa (Frew and Kay, 1988).

The influx of activated eosinophils to the nasal mucosa is responsible for increased nasal hyperactivity due to exposure of nerve fibers following damage to the epithelium (Ayars et al., 1989). Epithelial damage results from the toxic effects of superoxide anions, hydrogen peroxide production and the release of granular products such as eosinophil cationic protein (ECP), eosinophil derived neurotoxin and major basic protein released from eosinophils (Mandhane et al., 2011). Eosinophils also release IL-5, which acts in an autocrine manner to promote the activation and survival of eosinophils (Akuthota and Weller, 2012). T cells and mast cells also contribute to survival of eosinophils in the nasal mucosa via release of GM-CSF and IL-5 (Yamaguchi et al., 1991; Park et al., 1998).

Direct allergen exposure as well as mediator and cytokine release from primary effector cells (mast cells, basophils and T cells) can also stimulate structural cells in the nasal mucosa, including fibroblasts and epithelial cells, to release additional inflammatory chemokines and cytokines (Sin and Togias, 2011). Epithelial cells and fibroblasts are stimulated to release cytokines and chemokines such as Regulated upon Activation, Normal T cell Expressed, and Secreted (RANTES), thymus and activation

regulated chemokine, thymic stromal lymphopoietin, eotaxin, IL-33, IL-25, granulocyte colony-stimulating factor and monocyte chemoattractant protein 4 (MCP-4). These pro-inflammatory molecules act as chemoattractants to augment the Th2 response and contribute to the recruitment of eosinophils, basophils and T cells to the nasal mucosa (Takahashi et al., 2006; Pawankar et al., 2011; Bernstein et al., 2016).

Priming Effect

Increased nasal symptoms have been reported in subjects at the end of the pollen season, despite similar levels of aeroallergens (Norman, 1969). This observation is known as the 'priming effect.' Priming to allergen refers to the occurrence of increased nasal reactivity to allergens following repeated allergen exposure and has been confirmed under experimental allergen challenge models (Connell, 1969; Wachs et al., 1989). It is believed that priming to allergen occurs in response to chronic allergen exposure, whereby increased numbers of immune cells migrate to the nasal mucosa (particularly basophils) providing additional sites for IgE – allergen interaction and mediator release (Wachs et al., 1989; Bousquet et al., 1996).

Endotypes of Rhinitis

The assessment of the pathophysiology of allergic disease has changed from a generic focus on symptoms and tissue function, to the recognition of complex immune-regulatory networks that underpin the unique clinical presentation observed between individuals with allergic disease. Rhinitis is classically divided into 3 major clinical *phenotypes*, that is, grouping based on distinct clinical observations, these include: infectious rhinitis, non-infectious, non-allergic rhinitis (NAR) and allergic rhinitis with a combination of phenotypes present in some patients (Papadopoulos et al., 2015). Disease classification based on *endotypes*, that is, based on a distinct pathophysiological mechanism, has been recently proposed and is extensively reviewed elsewhere (Papadopoulos et al., 2015; Agache and Akdis, 2016; Muraro et al., 2016; Agache and Rogozea, 2018). Briefly, the endotypes described for rhinitis include: *Type two inflammation,* associated with the presence of eosinophils/ECP release, IgE and cytokines IL-5, IL-4 and IL-13 and seen in patients with AR, chronic rhinosinusitis and nasal polyposis; *Non-type two inflammation,* associated with neutrophils/ MPO release, cytokines INF-γ, TNFα, IL-1P, IL-6 and IL-8 and seen in patients with infectious rhinitis; *Neurogenic endotype*, associated with over expression of transient receptor potential (TRP) channels, nasal hyperactivity and high concentrations of neurokinins and substance P, and is seen in patients with idiopathic rhinitis and gustatory rhinitis; and *Epithelial dysfunction*, associated with reduced expression of tight junction proteins, enhanced subepithelial migration of exogenous antigenic molecules and is seen in patients with AR, infectious rhinitis and chronic rhinosinusitis with or without nasal polyps (Agache and Akdis, 2016; Muraro et al., 2016). It has been proposed that endotype classification may explain the variation observed between patients in clinical presentation and treatment response (Papadopoulos et al., 2015).

INTRANASAL PHARMACEUTICAL TREATMENT OF ALLERGIC RHINITIS

The presence of AR symptoms is associated with allergen exposure. Strategies employed to avoid allergen exposure such as staying indoors with closed windows or wearing a mask is highly impractical and is not widely practiced (Kemp, 2009). The rationale for using intranasal application of medications in the treatment of AR, is that high doses of drug can be applied directly toward receptor sites at the source of inflammation (nasal mucosa) with minimal risk of systemic side effects (Bousquet et al., 2008). Many drugs, which act via different mechanisms, have been developed for intranasal application. Antihistamines and corticosteroids are the most commonly used intranasal medications for AR symptoms. Other medications such as decongestants, anticholinergics and chromones have also been formulated for intranasal application, however they are only modestly effective and are recommended as an adjunct therapy or for mild symptoms (Bousquet et al., 2008).

INTRANASAL ANTIHISTAMINES

The interaction of histamine with H1 receptors is the primary cause for manifestation of early phase allergic responses that manifest as rhinorrhoea, itch and contraction of bronchial smooth muscles (Leurs et al., 2002). Antihistamines act on histamine receptors to ameliorate the effects of histamine by stabilizing the receptor in an inactive conformation. Azelastine hydrochloride and olopatadine hydrochloride are the only two intranasal antihistamine (INAH) spray formulations to be approved by the Food and Drug Administration for relief of AR symptoms.

The pharmacological profile and clinical efficacy of azelastine hydrochloride and olopatadine hydrochloride have been extensively reviewed elsewhere (Bernstein, 2007; Horak, 2008; Berger, 2009; Horbal and Bernstein, 2010; Kaliner et al., 2010). Both drugs are classed as second-generation antihistamines with high affinities for the H1 receptor and little affinity for the H2 receptor (Sharif et al., 1996; Bernstein, 2007). Intranasal antihistamines typically have a fast onset of action, demonstrated to significantly reduce symptoms within 15 to 30 min (Horak et al., 2006; Patel et al., 2007a,b) with effects lasting up to 12 h (Greiff et al., 1997; Patel et al., 2007c). INAH are more effective at reducing symptoms of itching, rhinorrhoea and sneezing compared to oral antihistamines, but are less effective at reducing concurrent ocular symptoms (Corren et al., 2005; Bousquet et al., 2008). Like an oral antihistamine, INAH therapy typically has variable effects on nasal congestion (Golden and Craig, 1999; Bousquet et al., 2008).

Mechanisms/Modulation

The H1 receptor is widely distributed throughout the body. Expression of the H1 receptor has been documented in smooth muscle, heart, adrenal medulla, sensory nerves, central nervous system, epithelial cells and immune endothelial cells (Mahdy and Webster, 2011). Histamine receptors are heptahelical

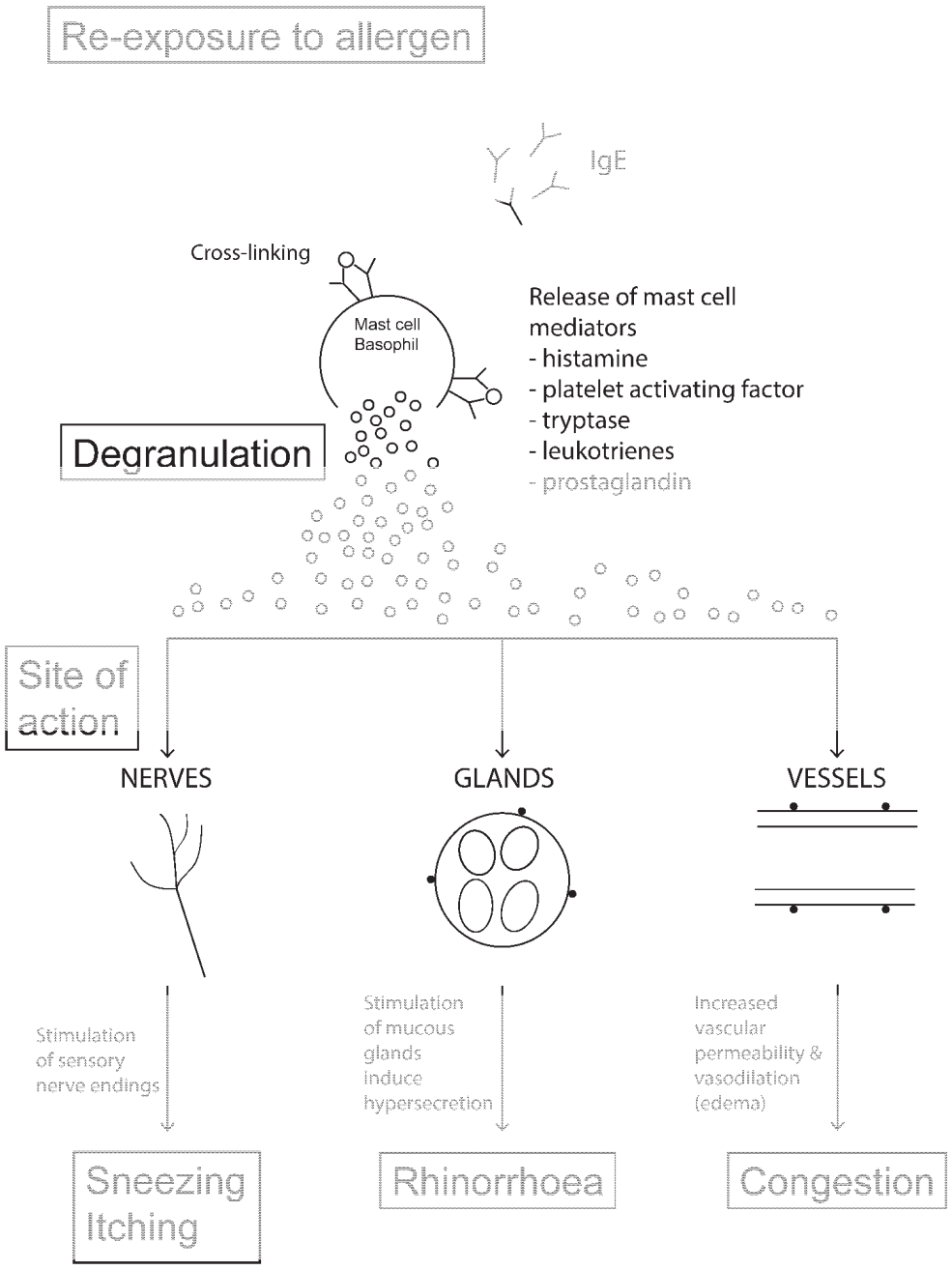

FIGURE 1 | The early phase response. Crosslinking of FCεR1-bound IgE antibodies on the mast cell surface in response to secondary allergen exposure stimulates the degranulation of mast cells. Degranulation induces the release of chemical mediators (primarily histamine) that stimulate sensory nerve endings, mucous glands and small vessels of the nasal mucosa to produce classic rhinitis symptoms: sneezing, nasal itching, rhinorrhoea and nasal congestion. The onset of action is typically within minutes of exposure and is sustained for 2–3 h forming the early-phase response.

G-protein coupled transmembrane receptors that transduce extracellular signals through G proteins to intracellular second messenger systems (Simons and Simons, 2011). Histamine receptors may be considered a 'cellular switcher,' functioning in equilibrium between two conformation states, active or inactive (**Figure 3**). Antihistamine drugs are classified as inverse agonists, as they are not structurally related to histamine and do not antagonize the binding of histamine, but instead bind to different sites on the receptor (Wieland et al., 1999; Gillard et al., 2002). Binding of antihistamines to the histamine receptor stabilizes the receptor in the inactive state thereby reducing the intrinsic activity of the receptor in response to histamine (Mahdy and Webster, 2011; Simons and Simons, 2011).

While histamine is an important mediator involved in the pathophysiology of the allergic response, other mediators

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