Allergic rhinitis and its pharmacology

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Abstract

The pathophysiology of allergic rhinitis and its drug treatment is reviewed. Special emphasis is placed upon potential new treatments. Allergic rhinitis is characterized by allergen(s), symptoms (sneezing, itching, rhinorrhea, nasal congestion and nasal hypersensitivity), and signs such as invasion of nasal mucosa by inflammatory cells. Such pathological changes are due to inflammatory responses mediated by way of allergen-immunoglobulin E (IgE)-cell complex formation. The complexity of the disease and the multiple pathways involved offer many targets for drug treatment, but to date no single drug is totally effective. This review summarizes the current knowledge of allergic rhinitis, its prevalence, pathophysiology and experimental and clinical treatments. In the search for new drugs, different experimental animal models of allergic rhinitis are required. As a result the models have also been reviewed. Furthermore, particular aspects of the pathophysiology of allergic rhinitis are discussed in greater detail including the immune cells involved in the mediation of the disease, chemical mediators, their actions, and the receptors on which they act. Therapy, particularly with current drugs, targets many of the known mediators and some of the cellular processes with varying success. Other drugs, for example, vasoconstrictors given to reduce rhinorrhea, provide symptomatic relief by counteracting symptoms. Since the incidence of allergic rhinitis is prevalent and growing in many parts of the world and current treatments are not ideal, it is important to continue to study the pharmacology of this disease as part of a search for better drugs.

Keywords: Allergic rhinitis; Pathophysiology; Treatment of rhinitis; Rhinitis mediators; Rhinitis pharmacology

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1. An introduction to allergic rhinitis

1.1. Definition of allergic rhinitis

Allergic rhinitis is defined as an abnormal inflammation of the membrane lining the nose. It is characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose, and/or postnasal drainage (Bousquet et al., 2001). Additionally, airway hypersensitivity may develop. A loss of the sense of smell and an inability to taste may occur. Moreover, some patients experience sleep disturbances, decreased emotional well-being and social functioning, headache, and irritability. On physical examination, nasal obstruction can often be seen with pale to bluish nasal mucosa, enlarged or boggy turbinates, clear nasal secretions, and pharyngeal cobble-stoning (streaks of lymphoid tissue). Other characteristic signs of allergic rhinitis in children include allergic shiners (darkening of lower eyelids due edematous nasal tissue compressing the veins that drain the eye region thereby leading to pooling of blood under the orbits) and an allergic crease (a transverse skin line below the bridge of the nose caused by constant upward rubbing of the nose with the palm of the hand (the “allergic salute”). Due to chronic nasal airway obstruction, some children become chronic mouth breathers leading to craniofacial abnormalities and orthodontic disturbances, such as palatal arching, increased facial length, and a flattened mid-face. Many patients do not show all such abnormalities, although most do have sneezing, rhinorrhea, and mucosal edema (Nayak et al., 2001; Mahr & Sheth, 2005).

1.2. Prevalence and epidemiology of human allergic rhinitis

Although the onset of allergic rhinitis may occur at any age, it is most common in children and at adolescence. Allergic rhinitis is the most common atopic disorder in the United States and affects about 24 million (8% of the population), both males and females equally. The prevalence varies with age: 32% of patients are 17 years or younger, 43% are 18–44 years of age, 17% are 45–64, and only 8% are 65 years or older (Law et al., 2003).

In 1996, the overall direct costs of treating allergic rhinitis exceeded $3 billion with an additional $4 billion for treating comorbidities that are triggered or exacerbated by rhinitis. To this cost must be added indirect costs such as lowered productivity and lost work time. In the United States alone, the number of lost workdays is estimated as ∼3.5 million a year (Holgate & Broide, 2003; Mahr & Sheth, 2005).

Up to 40% of patients with allergic rhinitis also have asthma, whereas 80% with asthma have nasal symptoms. Allergic rhinitis patients are at 3 times the normal risk of developing asthma. Children who develop rhinitis in the first year of life have twice the chance of developing asthma (Settipane et al., 1994; Wright et al., 1994).

1.3. Classification and initial overview of the treatment of rhinitis

Traditionally, allergic rhinitis is classified as seasonal or perennial, and either mild, moderate, or severe. Mild allergic rhinitis involves no sleep interruption, no impairment of daily activities, and no troubling symptoms. Moderate-to-severe allergic rhinitis involves one or more of those factors. A newer classification system characterizes allergic rhinitis as intermittent, or persistent. In the intermittent form symptoms last less than 4 days per week with a total duration of less than 4 weeks. In the persistent form symptoms occur for more than 4 days per week for longer than 4 weeks (Noble et al., 1995; Bousquet et al., 2001). Seasonal rhinitis is periodic due to the occurrence of seasonal allergens. Pollens that cause seasonal allergic rhinitis in the Northern Hemisphere are from trees in springtime, grass pollens from May to July and weed pollen and mould spores in late summer and autumn. Perennial (year round) disease involves nonseasonal allergens in the air, most commonly from mites (25%; Dermatophagoides pteronyssinus/ farinae), animal dander antigens (15%; cats, dogs, rodents), fungal spores (10%; Alternaria, Cladosporium, Aspergillus,
Allergic rhinitis should be differentiated from other respiratory related nonallergic nasal diseases such as infectious rhinitis and perennial nonallergic rhinitis (vasomotor rhinitis). Infectious rhinitis is characterized by constitutional symptoms and purulent rhinorrhea. Nasal smears show neutrophils rather than the eosinophils that predominate in allergic rhinitis. Perennial nonallergic rhinitis is more frequent in women and is precipitated by such nonspecific factors such as changes in temperature, humidity, and barometric pressure; strong odours; alcohol; and cigarette smoke. Nasal congestion frequently shifts from one nasal passage to the other (see later) and is often alleviated by exercise (Zeiger et al., 1989).

The 2 major classes of drugs used to treat symptoms of allergic rhinitis are oral H1 antihistamines and intranasal corticosteroids used either as immunotherapy, or in combination, depending on the predominant symptoms and the patient’s response to therapy. Alternative drugs, such as chromolyn, may be inappropriate in some patients. The symptoms of rhinorrhea can be temporarily alleviated with adrenergic amine vasconstrictors. Their prolonged use can induce a paradoxical rhinitis known as rhinitis medicamentosa (Black & Revison, 1980).

Although each of these treatments provide short or long term relief from one or more of the symptoms of allergic rhinitis, none totally controls the disease.

2. Pathophysiological of allergic rhinitis

2.1. Relevant nasal anatomy and physiology

The external dermal aspects of the human nose surround the nostrils and cover one-third of the nasal cavities. These dual chamber cavities are 5-cm high and 10-cm long with a total surface area of about 150 cm² and volume of about 15 mL. Approximately 1.5 cm from the nares is the narrowest point of the cavities is the internal ostium (or nasal valve). This has a cross-sectional area of about 30 mm² on each side. The nasal valve provides ~ 50% of the total resistance to normal respiratory airflow (Baroody, 1997). Each of the 2 nasal cavities is bounded by septal and lateral walls and is dominated by inferior, middle, and superior turbinates. The turbinates maintain a slit-like cavity and facilitate humidification and temperature regulation of inspired air (Dahl & Mygind, 1998).

The nostrils are covered by skin, the anterior one-third of the nasal cavity by a squamous and transitional epithelium. The upper part of the cavity is covered by an olfactory epithelium and the remaining portion by a typical airway epithelium, which is ciliated, pseudostratified, and columnar. The latter consists of 4 major cell types: basal cells, ciliated columnar cells, nonciliated columnar cells, and goblet cells. Basal cells, which are progenitors of the other cell types, lie on the basement membrane and do not directly have contact with the airway lumen (Evans & Plopper, 1988). Each of the columnar cells, ciliated and nonciliated, are covered by about 300 microvilli uniformly distributed over the entire apical surface. These short and slender finger-like cytoplasmic expansions increase the surface area of epithelial cells, thus promoting exchange processes. Microvilli also prevent drying by retaining moisture that is essential for ciliary function. Cilia have a typical ultrastructure (0.3 μm wide and 5 μm long) with each cell possessing about 100 cilia (Halama et al., 1990). The anterior third of the nasal cavity is nonciliated. Ciliated cells begin just behind the front edge of the inferior turbinate and cover the posterior part of the nasal cavity. Paranasal sinuses are densely covered by cilia.

The distribution pattern of ciliated cells corresponds well with the distribution of nasal airflow; thus, the density of ciliated cells at any site in the nasal cavity is inversely proportional to the linear velocity of inspired air at that site (Cole, 1982). Another characteristic cell of airway epithelium is the goblet cell, the majority of which are located in the posterior part of the nasal cavity at an average concentration of 4000–7000 cells/mm² (Tos, 1983). Goblet cells produce small amounts of viscous mucus that contributes little to the total volume of nasal secretions. Secretions from goblet cells have been shown to be under cholinergic control (Tokuyama et al., 1990).

There are 2 types of glands in the nose: anterior serous and seromucous glands. There are 100–150 anterior serous glands on each side of the nose each of which has long excretory ducts with large openings into the upper part of the internal ostium. Small droplets of watery secretion can be seen after stimulation of the nasal mucosa. Secretions produced in the anterior portion of the nose are more watery and have a lower viscosity than those in the posterior portion (Brofeldt et al., 1979).

There are about 100,000 seromucous glands in the human nose, a number that remains constant throughout life (Tos, 1983). Thus, infants have a secretory capacity comparable to an adult. However, since the ciliated surface area is much smaller in children, limited glandular hypersecretion in children may result in more nasal discharge than occurs in adults.

Blood from the ophthalmic and internal maxillary arteries feeds an extensive network of arterioles, venules, capillaries, capacitance vessels, and shunt vessels in the nose. These supply and drain the nasal mucosa with a greater blood flow per unit volume of tissue than even the liver or brain (Grevers & Kastenbauer, 1996). Nasal arterioles conspicuously lack an internal elastic membrane. As a result, the endothelial basement membrane is continuous with the basement membrane system of smooth muscle cells (Cauna, 1970). The capillaries, lying just below the surface epithelium, and surrounding the glands, are of the fenestrated type. Thus, they are well suited for rapid movement of water through the vascular wall so that it escapes into the airway lumen and, via evaporation, conditions (i.e., humidifies) inspired air (Cauna & Hinderer, 1969).

Large venous cavernous sinusoids, mainly localized in the inferior turbinates, are characteristic of nasal mucous membranes. They are normally in a semicontracted condition as a result of sympathetic nerve-mediated smooth muscle tone. These cavernous sinusoids appear to be specialized vessels that meet the functional demands of heating and humidifying inhaled air. When distended with blood the mucosa swell and thereby tend to block the nasal airway lumen (Dahl & Mygind, 1998). In addition, inflammation-induced extravasation through the walls of...
postcapillary vessels occurs as a result of opening of intercellular junctions between endothelial cells (Cauna, 1970).

Blood can bypass the capillary bed via arteriovenous anastomoses. The role of the arteriovenous anastomoses is probably related to temperature and water control. At least 50% of the blood flow in the nasal mucosa is normally shunted through arteriovenous anastomoses and, as indicated earlier, the total blood flow per cubic centimeter of tissue is greater in the upper nasal airway mucosa than in muscle, brain or liver (Anggard, 1974; Drettner & Aust, 1974).

Nasal blood vessels are under endothelial and neuronal control. A dual (endothelial and neuronal) control exists in arterioles whereas control of the subendothelial muscular swellings of the cushion veins appears to be mainly neuronal (Riederer et al., 2002). The swelling of the nasal mucosa is achieved by a simultaneous relaxation of all smooth muscle cells which leads to dilatation of arteries as well as venous sinuses. The drainage of the vascular bed is reduced by venous muscular bolsters that protrude into the lumen of the venous sinuses. Vice versa, a contraction of all smooth muscle cells leads to a contraction of the arteries and consequently to a reduction in blood supply. Simultaneously the muscular bolsters rise out of the lumen of venous sinuses allowing blood drainage to be increased thereby reducing nasal congestion (Riederer et al., 2002; Fig. 1).

The nasal mucosa, including glands and blood vessels, are supplied by both afferent and efferent neurons. The neuronal supply can be divided into 2 parts: the first, the olfactory nerve (cranial nerve I), projects into the olfactory mucosa, and conducts the sensation of smell; the second, the trigeminal nerve (cranial nerve V), projects to the epithelium and detects perception of airflow via A fibers, and noxious stimuli via unmyelinated C fibers and Aδ fibers. Activation of these afferent nerves leads to local axonal and central reflexes (Baraniuk, 1998).

There is a rich parasympathetic innervation to nasal glands. Nervous stimulation of glandular cholinoreceptors causes marked hypersecretion and is often part of a reflex arc. Blood vessels have both sympathetic and parasympathetic innervation but are controlled mainly by sympathetic fibers. A continuous release of norepinephrine is postulated to keep the sinusoids partly contracted since the vasoconstrictor effects of stimulation of α-adrenoceptors is more marked than vasodilatation resulting from stimulation of β2-receptors (Dahl & Mygind, 1998). The release of the classic neurotransmitters, norepinephrine and acetylcholine, has in recent years been found to be accompanied by a number of peptide neurotransmitters. These neurotransmitters are secreted by afferent unmyelinated C fibers (substance P [SP], calcitonin gene-related peptide [CGRP], neurokinin A [NK-A], gastrin-releasing peptide); efferent parasympathetic nerve endings (vasoactive intestinal peptide [VIP], peptide histidine methionine), and from efferent sympathetic nerve endings (neuropeptide Y, NPY; Uddman et al., 1987; Lundblad, 1990; Baroody, 1997). Neuropeptides are capable of generating local reflexes that cause an increase in vascular permeability, plasma leakage, vasodilatation, and subsequent tissue oedema (Baraniuk, 1997; Fig. 2).

Apart from being the first part of the airways, the nose has 2 major functions: firstly, olfaction, and secondly, conditioning of the inspired air to make it suitable for the lungs by heating, humidifying and cleansing. The normal nose is characterized by slit-like passages that provide for efficient exchange of heat and moisture. The width of these nasal cavities is actively regulated via the sympathetic innervation, plus tone in the venous sinusoids.

Nasal cycling is the cyclic alteration between resistance on the 2 sides of the nose. This cycling changes from one side to the other at 2–4 h intervals with 80% of humans showing this nasal cycle (Hanif et al., 2000). It has also been demonstrated in rats, rabbits, and pigs. In addition, the nasal cycle is perceived

![Fig. 1. Schematic representation of different endothelial and neuronal control of blood flow in nasal blood vessels. NA: norepinephrine, NPY: neuropeptide Y, VIP: vasoactive intestinal peptide, NO: nitric oxide, ACh: acetylcholine, SP: substance P, ET-1: endothelin 1, CGRP: calcitonin gene-related peptide. Adapted from Riederer et al. (2002).](image-url)
by subjects with a deflected septum and by rhinitis patients (Dahl & Mygind, 1998). The nasal cycle seems to be predominately vascular, and it is mediated via the nervous control of the sinusoidal erectile tissue. Cutting the cervical sympathetic nerves or blocking the sympathetic supply by local anesthesia abolishes the nasal cycle in human and in lower animals (Widicombe, 1986).

The nose is well suited to its role as air conditioner for the following reasons:

(i) the slit-like shape of nasal cavities ensure close contact between inhaled air and mucous membranes;
(ii) the cavity width adapts rapidly to changing air flow needs by alteration in sinusoid capacity;
(iii) heat exchange is facilitated by the extensive blood flow in arteriovenous anastomoses;
(iv) nasal mucosa has a high secretory capacity. In addition the body saves about 100 mL of water per day, due to water condensation of exhaled air in the anterior nose where the temperature is 3–4 °C lower than in the lungs. This water may contribute to rhinorrhea in cold weather.

The nose acts as a filter of particulate matter. Most particles larger than 10 μm (e.g., pollen grains) are retained in the nose during normal breathing at rest, whereas particles smaller than 2 μm (mould spores) can bypass this. The nose also acts as a protective sponge for water-soluble gases (e.g., sulfur dioxide, formaldehyde). Trapped inhaled particles are cleared from the nose by mucociliary transport within 30 min (Hilding, 1963; Andersen et al., 1974).

2.2. Process of allergen sensitization

The allergic sensitization that characterizes allergic rhinitis has a strong genetic component. Thus, the chance of developing immunoglobulin E (IgE)/mast cell/T\textsubscript{H2} lymphocyte immune
responses and atopy, in general, is inherited. The hygiene hypothesis is one explanation for an increasing incidence of allergies, such as allergic rhinitis (Strachan, 1989). The hypothesis arose from epidemiological observations that suggested an inverse relationship between family size and prevalence of allergies. It was proposed that reduced contact with microbes and a diminished burden of infectious disease early in life lead to weakened immunological drive in the Th1 direction that results in over-activity of Th2 responsiveness. However, other evidence does not substantiate a causal relationship between infection and atopic diseases (Liu & Murphy, 2003).

Exposure to threshold concentrations of dust mite fecal proteins, cockroach allergen, cat, dog, and other danders, pollen grains, or other allergens for prolonged periods of time leads to the presentation of the allergen by antigen presenting cells to CD4+ T lymphocytes, which then release different cytokines along with the differentiated Th12 cytokines (see below). These cytokines drive proinflammatory processes, such as IgE production, that act against the allergens via mucosal infiltration and plasma cells, mast cells, and eosinophils. Once sensitized to allergens, subsequent exposures trigger a cascade of events that result in the symptoms of allergic rhinitis.

Allergic rhinitis is characterized by a 2-phase allergic reaction: an initial sensitization phase where allergen exposure results in IgE formation, as well as induction of the humoral response and subsequent clinical disease after repeated antigen exposure. The clinical phase can also be further subdivided into early- and late-phase responses.

The first step towards generation of a T helper lymphocyte response is the recognition and uptake of antigen by antigen-presenting cells (e.g., dendritic cells, macrophages, B cells) that have the capacity to digest antigen into short peptides that associate with major histocompatibility complex (MHC) molecules and provide co-stimulation for naive T cells (Lambrecht, 2001). Dendritic cells have been identified as the most effective antigen presenting cells for inducing and regulating the primary immune response in vivo and in vitro (Banchereau et al., 2000). The mucosa of the nose is covered with an extensive network of dendritic cells that reside in the para and intercellular channels surrounding the basal epithelial cells (Evans & Plopper, 1988).

There are 3 dominant mechanisms by which immature dendritic cells can uptake an antigen. First, antigenic material can be acquired via receptor-mediated endocytosis involving clathrin-coated pits. Immature dendritic cells express a plethora of specialized cell receptors for chemical sequences that are associated with foreign antigens, such as the C-type lectin carbohydrate receptors (Cochand et al., 1999; Ariizumi et al., 2000; Geijtenbeek et al., 2000; Mahnke et al., 2000; Valladeau et al., 2000). Secondly, an antigen can be taken up by a constitutive macropinocytosis that involves the actin skeleton-driven engulfment of large amounts of fluid and solutes (~1 cell volume/hr) by the ruffling membrane of the dendritic cell followed by concentration of soluble antigen in the endocytic compartment (de Baey & Lanzavecchia, 2000). Thirdly, dendritic cells have been shown to phagocytose particulate antigens such as latex beads, and even whole bacteria, as well as apoptotic cells. This could be the dominant mechanism of uptake of particulate allergens (Banchereau et al., 2000).

After being taken up by any of the above mechanisms, antigens accumulate in the endocytic compartment where they are loaded on newly synthesized and recycling MHC class II molecules. However, they may also be transported into the cytosol where they become accessible to the class I antigen presentation pathway (Rodriguez et al., 1999; de Baey & Lanzavecchia, 2000). Within the endocytic compartment, antigen is cleaved into short immunogenic peptides by proteolytic enzymes. Antigen is loaded on MHC class II molecules in an acidic cellular compartment rich in newly synthesized MHC class II molecules called the MIIC compartment (Nijman et al., 1995). Alternatively, immunogenic peptides can be loaded onto pre-formed MHC II molecules that have been internalized into mildly acidic endosomal vesicles after being expressed on the cell surface (Cella et al., 1997). In addition, antigen processing by proteases can occur resulting in extracellularly generating peptides that can be loaded onto empty cell surface-expressed MHC class II.

Surprisingly, proteolysis of antigen by immature dendritic cells can also occur extracellularly by the actions of secreted proteases. This results in the generation of peptides that can be loaded onto empty cell surface-expressed MHC class II (Santambrogio et al., 1999). Subsequently, dendritic cells migrate through the submucosa and present the processed antigen to naïve undifferentiated Th1 cells. Antigen-specific T cells bind the dendritic cell MHC class II-peptide complex with CD4 and this interaction, along with intercellular cell–cell signals, triggers the T cells to differentiate into Th12 cells and activation of B lymphocytes which produce antigen-specific IgE (Bousquet et al., 1996).

IgE is the principal trigger for allergic rhinitis. IgE interacts with both FcεRI and the lower-affinity receptor FcεRII (CD23). Differentiation of B cells into IgE-secreting plasma cells requires at least 2 distinct signals in IL-4 (or IL-13) and CD40L on the surface of Th1 cells with CD40, a costimulatory molecule on B cells which triggers isotype switching to IgE. IgE binds to the α-chain of the tetrameric FcεR complex on mast cells, basophils, monocytes, and dendritic cells. The molecular interactions responsible for high-affinity binding are complex and involve several sites in the C3 domain of IgE (Chang, 2000).

In its free form, IgE has a half life of only a few days. However, when bound by FcεRs it is protected against degradation and can remain on the surface of inflammatory cell for months (Brostoff, 1986). Circulating antigen-specific IgE binds, via the Fc region, to FcεRI receptors on the surface of nasal mast cells and basophils and thereby exposes the antigen-specific Fab region to the local environment and ready to be activated by further allergen exposure.

The initial exposure and the process of priming the inflammatory cells responsible for executing responses to antigen is referred to as sensitization. Re-exposure to the same allergen on a mucosal surface results in a coupling or cross-linking of the IgE molecule that leads to cellular degranulation and the release of inflammatory mediators, a process resulting in both an acute and chronic phases (Fig. 3).
2.3. Rhinitic responses to allergen challenge

Classically the sensitized human nasal response to challenge with a relevant antigen can be itemized as consisting of the following symptom and sign profile:

(i) sneezing, generally occurs as multiple events and for extended periods;
(ii) itching, in and around the nose and nasal mucosa;
(iii) rhinorrhea, a copious water secretion from the nose;
(iv) nasal congestion with airflow through one of both nasal passages being impaired, even to the point of complete blockade.

The acute signs of allergic rhinitis include the following:

i) engorged nasal mucosa, with obvious congestion and obstruction;
ii) infiltration of immune cells into the nasal mucosa as shown by taking swabs of the nasal passages or by nasal lavage.

The above signs and symptoms vary with the phase of the allergic response (see below).

2.3.1. Acute phase

During the period of sensitization, increasing numbers of IgE-coated mast cells traverse the epithelium, and once challenged, these recognize the mucosally deposited allergen and degranulate (Naclerio, 1991). Products of degranulation include preformed mediators such as histamine, tryptase (mast cell specific marker), chymase (“connective tissue”-mast cells only), kininogenase (generates bradykinin [BK]), heparin, and other enzymes. In addition, mast cells create some inflammatory mediators de novo (i.e., ones not preformed or stored) including prostaglandin D2 and the sulfidopeptidyl leukotrienes LTC4, LTD4, and LTE4 (see below).

These mediators cause blood vessels leakage, produce mucosal edema, and the watery rhinorrhea characteristic of allergic rhinitis. Glands secrete mucoglycoconjugates and antimicrobial compounds and help dilate blood vessels to cause sinusoidal filling with resulting occlusion and congestion of nasal air passages.

Mediators also stimulate sensory nerves to cause nasal itch and congestion as well as recruit systemic reflexes such as sneezing. The above responses develop within minutes of allergen exposure and are termed the early phase, or “immediate,” allergic response (Mygind & Naclerio, 1993). Sneezing, itching, and copious clear rhinorrhea are characteristic symptoms during
the early phase of allergic responses although nasal congestion may also occur.

2.3.2. Chronic phase

Mast cell-derived mediators released during early phase responses, as well as mediators released by basophils during the late phase, are thought to act on postcapillary endothelial cells to promote the expression of vascular cell adhesion molecule and E-selectin to facilitate adhesion of circulating leukocytes to endothelial cells. Chemoattractant cytokines such as IL-5 promote the infiltration of the mucosa with eosinophils, neutrophils, and basophils, T lymphocytes, and macrophages (Naclerio et al., 1985; Bascom et al., 1988b). At 4–8 hr after allergen exposure these cells become activated and release inflammatory mediators which in their turn reactivate many proinflammatory reactions involved in the immediate response.

The late cellular-driven inflammatory reaction is the “late phase response.” This reaction is clinically indistinguishable from the immediate reaction except that congestion tends to predominate (Skoner et al., 1988). Eosinophil-derived mediators such as major basic protein (MBP), eosinophil cationic protein (ECP), and leukotrienes have been shown to damage the epithelium, leading ultimately to the clinical and histological picture of chronic allergic disease. Subsets of the T-helper lymphocytes orchestrate the chronic inflammatory response to allergens. T\textsubscript{H2} lymphocytes promote allergic responses by releasing IL-3, IL-4, IL-5, and other cytokines that promote IgE production, eosinophil chemoattraction, and their own survival in tissues, as well as mast cell recruitment (Durham et al., 1992). Cytokines released from T\textsubscript{H2} lymphocytes may be the cause of the fatigue, malaise, irritability, and neurocognitive deficits commonly noted in allergic rhinitis patients (Sim et al., 1995).

2.4. Pathophysiological events in allergic rhinitis

2.4.1. Neuronal

Apart from sympathetic and parasympathetic nerves which contain norepinephrine and acetylcholine, respectively, nasal sensory nasal afferent innervation also plays a role (Baraniuk & Kaliner, 1991). Thus, sensory airway nerves have been demonstrated to play an important role in allergic rhinitis (Hepp et al., 2004).

Nasal sensory nerve fibers contain a number of different peptides, including CGRP and the tachykinins, SP, and NK-A. These neuropeptides, metabolised by the enzyme neutral endopeptidase (NEP), are released from sensory nerves of the nonadrenergic noncholinergic (NANC) nervous system. They are capable of activating local reflexes which causes an increase in vascular permeability, plasma leakage, vasodilation, and subsequent tissue oedema (Baraniuk, 1997). This response, known as neurogenic inflammation, is mediated by tachykinin NK-1 and NK-2 receptors. In addition, eosinophils are capable of producing VIP and SP (Metwali et al., 1994). Increased levels of SP and vasoactive intestinal polypeptide (VIP) have been found in nasal secretions from allergic rhinitis patients subjected to nasal irritation (Mosimann et al., 1993). These together with other mediators, such as NPY (Groneberg et al., 2004) and GCRP (Springer et al., 2003), may participate in the pathophysiological mechanisms underlying allergic rhinitis.

The inflammatory mediators released by allergic responses can sensitize and activate sensory nerve endings by inhibiting neuronal after-hyperpolarization and increasing phosphokinase C phosphorylation of neuronal ion channels. Additionally, exposure of nerve endings to cytotoxic proteins (e.g., MBP and ECP) as well as increasing expression of the neuronal membrane receptors induced by cytokines (e.g., IL-1\textbeta and tumor necrosis factor-\alpha [TNF-\alpha]) may also increase neuronal hyperexcitability (Christiansen et al., 2002).

Neurotrophins change both sensory and other nerve phenotypes. Nerve growth factor (NGF) is one such potent trophic substance. In sensory nerves, especially C fibers, NGF appears to be the only active neurotrophin. NGF is released by several types of cells, including possibly mast cells. It can have acute effects that change neuroterminal function and even reaches the nucleus via retrograde transport, thereby producing signals that increase neuropeptide content in nerves and stimulate nerve growth. NGF is present in the nasal fluids of individuals with active chronic allergic rhinitis and it is also acutely released upon nasal allergen challenge (Sanico et al., 2000; Togias, 2000).

In allergic rhinitis, sensory neuron activation results in sneezing and bilateral parasympathetic reflexes (Baraniuk, 2000; Casale et al., 2001). Activation by mediators (histamine being the most prominent) of sensory neurons results in depolarization. In the CNS, trigeminal nociceptive neurons enter the pons through the sensory root, turn caudally in the trigeminal spinal tract and terminate in the pars caudalis of the lower medulla and upper 3 cervical segments of the spinal cord. Pars caudalis interneurons cross the midline to enter the trigeminothalamic tract and terminate in the medial part of the ventral posterior thalamic nucleus (arcuate or semilunar nucleus). Pain and itch stimuli are received at the thalamic level. Connections between the afferent interneurons of the nuclei of the trigeminal spinal tract, and the solitary tract with the nucleus ambiguous, establish the sneezing reflex. Similar connections regulate parasympathetically mediated glandular secretion in the nose (superior salivatory nucleus and facial nerve; Calliet, 1992).

2.4.2. Vascular

Acetylcholine, catecholamines, various peptides and also nitric oxide (NO) participate in nasal vascular control by inducing vasconstriction or vasodilation (Lund, 1996). These bioactive molecules arise from both sensory and autonomic nerve fibers, and from neuroendocrine cells widely dispersed in the nasal mucosa. Adult human nasal mucosa has dense nerve networks containing VIP, NPY, or its C-terminal peptide (CPON), SP, CGRP among other putative neurotransmitters. Sympathetic fibers have both norepinephrine and NPY. Immunoreactivities for NPY and CPON show them to be colocalized and mainly in perivascular nerve fibers. The nasal subepithelial region contains a dense plexus of SP- and CGRP-immunoreactive fibers, although these nerves also appear
around blood vessels (Lacroix et al., 1992; Anggard et al., 1983; Hauser-Kronberger et al., 1993).

Nasal congestion is a common symptom of acute and chronic rhinitis. It is caused by swelling of nasal blood vessels that expand and so restrict or obstruct airflow through nasal passages (Broms, 1982). During allergic reactions, a large number of inflammatory and immunological mediators derived from leukocytes, plasma, and neurons (e.g., leukotrienes, kynins, histamine, neuropeptides, NO, ACh) act via their receptors in nasal vasculature to cause either vasodilatation or vasoconstriction (Lung et al., 1984; Widdicombe, 1986, 1990). The inferior turbinate of human nasal mucosa contains arterioles and venous sinuses that are constricted (decongestion) by norepinephrine, NPY, and endothelin-1 and dilated (congestion) by acetylcholine, VIP, NO, CGRP, and SP (Riederer et al., 2002). Changes in vascular innervation could be one of the factors involved in the maintenance of rhinitis. Nasal vascular hyperinnervation has been detected in patients with allergic rhinitis when compared with nonallergic individuals (Figueroa et al., 1998).

Plasma extravasate (via vascular leakage or exudation) is unfiltered plasma containing albumin, antibodies and complement fractions (Bousquet et al., 1996). An increase in vascular permeability occurs in both seasonal allergic rhinitis and perennial allergic rhinitis (Wilson et al., 1998). Additionally, vascular permeability is increased by histamine and/or BK challenge in individuals with allergic rhinitis (Rajakulasingam et al., 1993). The concentrations of both increase dramatically after allergen challenge (Baroody et al., 1994; Paul et al., 1994). Histamine appears to be responsible for exudation of bulk plasma in seasonal rhinitis (Svensson et al., 1995).

A role for kinins inducing vascular permeability has also been proposed since nasal stimulation with histamine or LTC4 results in an increase in nasal vascular permeability that correlates with kinin concentrations found in the nasal lavage fluid formed during allergic rhinitis (Shirasaki et al., 1989).

An increase in vascular permeability is particularly marked in postcapillary venules where the opening of the intercellular gaps, together with anatomical visible fenestrations provides the plasma with an alternative route for exudation other than blood vessels (Widdicombe, 1997). Inflammatory mediators act on specific receptors in blood vessels to cause extravasation in a process involving vasodilation and increases in intravascular pressure (especially in post capillary venules) and/or increases in interendothelial gaps. The exudate forms in the interstitial space, and then is lost to the nasal cavity.

Beside nasal congestion and exudation, cellular infiltration also occurs in allergic rhinitis. The expression of adhesion molecules on endothelial cells is induced by the acute and chronic release of inflammatory mediators a process that enhances the extravasation of leukocytes to the site of inflammation. The role of the inflammatory cells in allergic rhinitis is described in the following section.

2.4.3. Glandular

Rhinorhrea (watery secretion) is one of the symptoms of allergic rhinitis. Nasal secretions come from 3 main sources: the epithelial goblet and serous cells, the submucosal seromucous glands, and the anterolateral deep glands in the nose (Widdicombe & Wells, 1982; Wells & Widdicombe, 1986). In addition transcription may contaminate secreted mucus. Nasal mucus secretion is controlled predominantly by parasympathetic cholinergic nerves (Widdicombe, 1990). In allergic rhinitis, neurotransmitters (ACh, SP) and inflammatory mediators (histamine, BK, leukotrienes) cause increases in glandular secretions (Widdicombe & Wells, 1982; Wells & Widdicombe, 1986; Knowles et al., 1987). In the nasal mucosa of human inferior turbinates, nerve fibers are found in the periglandular tissue around the acini, ducts and in the periglandular connective tissue. It has been found that VIP is in contact with acinus cells and CGRP is found in the connective tissue around glandular cells suggesting a role in controlling glandular secretions (Knipping et al., 2001).

2.4.4. Nasal airway hyperresponsiveness

Nasal airway hyperresponsiveness (AHR) is a hallmark of allergic rhinitis (Druce et al., 1985; Mullins et al., 1989). Those with allergic rhinitis show an increased response to nasal challenge to many stimuli, including histamine, BK (both released by allergen challenge), methacholine, tobacco smoke, and perfume (Baraniuk, 1997; Gerth van Wijk et al., 1999). Hyperresponsiveness is associated with nasal congestion, increased mucus production, and oedema following allergen challenge in both upper and lower airways. It is usually associated with the late phase reaction but can continue well beyond this stage. In fact, it is induced, regardless of whether the late phase of inflammation occurs (Togias et al., 1988). Most patients with allergic rhinitis, besides having chronic inflammation in their nasal mucosa that results from allergic reactions, also have chronic inflammation in the lower respiratory tract that can lead to AHR (Ma et al., 2000).

There are a number of potential mechanisms by which AHR might occur: greater receptor activation due to increased mediator release after initial exposure to allergen; increased exposure of receptors to any stimulus present (due to damage and destruction of epithelial and interstitial cells, and mucociliary clearance system by platelet activating factor (PAF) and cytotoxic proteins like MBP and eosinophil chemotactic protein); reduced the metabolism of mediators (due to loss of epithelial function); increased receptor expression (e.g., methacholine causes more secretion in allergic subjects than in nonallergic subjects); and alteration of intracellular pathways (Laitinen et al., 1985; Devillier et al., 1988; Koga et al., 1992; White, 1993; Teixeira et al., 1997).

2.5. Pathological factors in allergic rhinitis

2.5.1. Immune cell mediators

One of the hallmarks of allergic diseases is accumulation of inflammatory cells in tissue locations at specific mucosal surfaces. The presence of an increased number of mast cells, basophils, T cells, and particularly eosinophils, has been detected in nasal smears and biopsies from patients with allergic rhinitis. It has also been shown that in response to certain
mediators these inflammatory cells undergo local activation and release of their own mediators in a positive feedback that contributes to pathological features of the disease.

2.5.1.1. Mast cells. Mast cells are constitutive cells within the normal nasal mucosa. They are recognized as key cells in type I hypersensitivity reactions. Mast cells divide into connective and mucosal phenotypes. Connective tissue mast cells express chymase, tryptase, and TNF-α and constitute 85% of the IL4 positive mast cells population in the nasal lamina propria.

During allergen exposure, there is an increase in the proportion of mast cells in the epithelial cell layer (Juliusson et al., 1995). These mucosal mast cells which produce predominantly tryptase and are without chymase, constitute the remaining 15% of the IL4 positive mast cells.

In sensitized individuals, the nasal mucosa is full of IgE-binding mast cells (Enerback et al., 1986). Mast cells have long been considered to serve primarily as important effector cells in acute IgE-associated allergic reactions. Such cells, from patients with allergic rhinitis, produce Th2 type cytokines and induce IgE synthesis in B cells. They can also autoactivate via the mast cell–IgE–FcεRI cascade. In addition, mast cells up-regulate the production of a variety of cytokines/chemokines by epithelial cells and fibroblasts, and also induce the recruitment of basophils, T cells and eosinophils to sites of allergic inflammation. In a recruiting response they also induce their own intraepithelial accumulation by up regulation of adhesion molecules like VCAM-1, and through the interactions of nasal mast cells with the extracellular matrix proteins, and nasal epithelial cells. Thus, it is increasingly evident that mast cells are not only important for the genesis of allergic reactions, but also contribute to the late-phase allergic reaction as well as to on-going allergic inflammation (Pawankar et al., 2000; Pawankar, 2005).

Activation of mast cells by antigen and IgE occurs via interactions with the high-affinity receptor for IgE (FcεRI). Liberation of proteases, leukotrienes, lipid mediators, and histamine contribute to tissue inflammation and allow recruitment of inflammatory cells into tissue. In addition, the synthesis and expression of a plethora of cytokines and chemokines (such as granulocyte-macrophage colony-stimulating factor [GM-CSF], interleukin [IL]-1, IL-3, IL-5, TNF-α, and the chemokines IL-8, regulated upon activation normal T cell expressed and secreted [RANTES], monocyte chemotactic protein-1 [MCP-1], and eotaxin) by mast cells have profound influences on leukocyte biology and therefore allergic inflammation (Shakoory et al., 2004).

2.5.1.2. Eosinophils. Eosinophils, granular bilobed leukocytes readily stained by eosin, comprise ~2–5% of granulocytes in a nonallergic individual. Eosinophil progenitors released from the blood marrow into the circulation are chemically attracted to tissue sites by various chemotactic factors. The development and maturation of eosinophils also occurs in situ at peripheral sites of inflammation where there are increased numbers of tissue eosinophils (Adamko et al., 2005). Activated eosinophils play a role in allergy, asthma, parasitic diseases, granulomatous disorders, fibrotic conditions, and several malignant tumors (Munitz & Levi-Schaffer, 2004).

Immunohistochemistry of nasal mucosa shows eosinophils within the submucosa and epithelium in those with symptomatic rhinitis (Bentley et al., 1992; Bradding et al., 1993). Eosinophils are mainly involved in the late-phase reaction after they have infiltrated from the blood into tissue. Cytokines secreted by Th2 cells help recruit and activate eosinophils in the nose. IL-4 is considered to be pivotal since it up-regulates adhesion molecules that are selective for eosinophil recruitment (Krouse, 2002; Ciprandi et al., 2004).

Eosinophils contain granules composed of 4 basic proteins. The core is MBP, whereas the surrounding matrix is ECP, eosinophil-derived neurotoxin (EDN), and eosinophil peroxidase (EPO; Gleich et al., 1994). The levels of ECP, EPO, and MBP are raised following antigen challenge in allergic rhinitis (Knani et al., 1992; Shin et al., 1994; Nishioka et al., 1995). Another mechanism by which eosinophils stimulate the late-phase allergic inflammation is by generation of arachidonic acid metabolites, such as prostglandins and leukotrienes (Krouse, 2002; Saito et al., 2004). Additionally, human eosinophils express and synthesize a number of cytokines, including GMCSF, IL-6, IL-1α, IL-2, IL-3, IL-4, IL-5, IL-8, RANTES, and TNF-α (Moqbel et al., 1991; Hamid et al., 1992; Costa et al., 1993). Thus eosinophils are equipped to play a major role in allergic inflammation since they are recruited to allergic sites where their cationic proteins, cytokines, and lipid mediators contribute to damage and dysfunction of other cell types.

2.5.1.3. Basophils. Basophils are present in very low numbers in peripheral blood, and although not found in normal noninflamed tissues, they are recruited to sites of inflammation by mediators released from other cell types. Basophils are found in nasal smears in allergic rhinitis (Okuda et al., 1985; Otsuka et al., 1985) and their number increases in allergic patients following nasal allergen challenge (Bascom et al., 1988a). Evidence of basophil infiltration into the nasal mucosa during allergen challenge can be found in the profile of mediators found in nasal secretions (Naclerio et al., 1985; Bascom et al., 1988a). Basophils, like mast cells, possess high affinity IgE receptors and are derived from CD34-positive progenitor cells (Knapp, 1990). When activated, basophils are prominent sources of the inflammatory mediators found in allergic late-phase reactions.

Basophils possess fewer larger granules and differ from mast cells in that they contain less histamine. Following IgE-dependent activation, basophils release only 20–30% of the histamine released from a comparable number of mast cells (Castells et al., 1987). Human basophils have also been shown to secrete cytokines, particularly IL-4 and IL-13, when activated by IgE-dependent stimuli. As a result they modulate the immune responses of the other cell types that participate in allergic rhinitis (MacGlashan et al., 1994; Schroeder et al., 1994, 1997).

2.5.1.4. T lymphocytes. T lymphocytes coordinate and amplify the effector functions of antigen-specific and -nonspecific inflammatory cells such as B cells and eosinophils. T lymphocytes
are divided into 2 subtypes based upon their effector functions. CD4+ T cells represent the T-helper cells, which are important in the regulation of antigen-driven inflammatory processes. Via antigen-specific T-cell receptors, CD4 T cells are capable of recognizing processed foreign antigen in association with MHC class II on specialized antigen-presenting cells (e.g., macrophages and dendritic cells; Horiguchi & Okamoto, 2005).

CD8+ T cells, T-suppressor cells, drive the cell-mediated response and respond to APC-presenting antigen in conjunction with MHC class II molecule. The T lymphocyte represents a significant nonstructural cell within the nasal mucosa and their number increases in the nose of rhinitic patients. These are generally CD4+ TH2 cells displaying the activated phenotype (CD25+; Varney et al., 1992; Calderon et al., 1994).

CD4+ TH2 lymphocytes appear to play a crucial role in the induction and maintenance of chronic allergic inflammation. The presence of T lymphocytes in allergic inflammation has been well demonstrated. However, the major reason for their importance lies on the profile of cytokines they express upon activation. Although individual T cells have the capacity to produce a wide range of cytokines, a restricted profile of cytokines is seen in chronic inflammatory diseases (Kelso, 1995).

A major feature of allergic diseases is the high expression of Th2-type cytokines. T lymphocytes of the T-helper 2 subpopulation can generate IL-3, IL-4, IL-5, GM-CSF and TNF-α (Mosmann & Coffman, 1989). The Th2 phenotype is thought to influence subsequent T cell activation and IgE production by B cells in addition to promoting the attraction, activation, growth, and differentiation of specific leukocytes such as eosinophils. In this way, activated T cells can initiate and propagate allergic inflammation and participate directly in the events responsible for allergic diseases.

Epithelial cells are part of the nasal mucosal barrier that generates the proinflammatory cytokines and chemokines that play roles in allergic rhinitis (Calderon et al., 1997). Following exposure to allergen, in-vitro nasal epithelial cells from atopic individuals release increased amounts of IL-1α, IL-8, GM-CSF, TNF-α and the chemokine RANTES, as compared with nasal epithelial cells from non-atopic individuals (Nonaka et al., 1996). Nasal epithelial cells from people with a genetic predisposition to upper airway disease appear to release increased amounts of proinflammatory cytokines upon exposure to allergen, thereby contributing to the allergic response (Calderon et al., 1997).

In medium conditioned by epithelial cells human upper airway epithelial cells secrete GM-CSF, whereas epithelial cells from inflamed nasal tissue secrete larger amounts of proinflammatory cytokines, as compared with normal nasal epithelial cells (Ohtoshi et al., 1991). During inflammation, complement activation has been shown to occur at the nasal epithelial cell membrane with the nasal epithelium being capable of regulating this process. The integrity of the nasal epithelium in inflammatory states is thought to depend on the maintenance of equilibrium between complement activation and cell membrane regulation of this activation (Varsano et al., 1996).

Other cells types have also been shown to increase in allergic rhinitis, including neutrophils, macrophages, dendritic cells, monocytes, B cells (Bachert et al., 1998) although their crucial role in the responses to allerigen challenge is controversial.

2.5.2. Chemical mediators of allergic rhinitis

2.5.2.1. Histamine. Histamine plays a pivotal role in allergic inflammation. It is released from the granules of FcεRI+ cells (e.g., mast cells and basophils), after the cross-linking of surface IgE by allergen, or through mechanisms independent of IgE (Enerback et al., 1986; Kaliner, 1994; Howarth, 1995). Nasal challenge with histamine causes sneezing, pain, pruritus, rhinorhea, and nasal blockade (Doyle et al., 1990). Sensory neurone activated by histamine causes sneezing and pruritus (Mygind, 1982) in addition to activating a neuronal increase in nasal parasympathetic activity (Hilberg et al., 1995). Increased release of parasympathetic neurotransmitters (e.g., acetylcholine) stimulates nasal submucosal glands which, together with increase in vascular permeability, cause rhinorhea (Baroody et al., 1994).

Molecular biology studies have found that 4 histamine receptors sub types (H1, H2, H3, and H4) occur in normal nasal mucosa studies (Nakaya et al., 2004) with higher expression of H1 and H2 in atopic individuals (Iriyoshi et al., 1996; Hirata et al., 1999). Most of the effects of histamine in allergic disease are mediated through H1 receptors (Schmelz et al., 1997; Schneider et al., 2002; Akdis & Blaser, 2003), but cutaneous itch and nasal congestion may involve both H1 and H3 receptors (McLeod et al., 1999; Sugimoto et al., 2004). Histamine also activates the H2 receptors on the smooth muscle cells that surround nasal capacitance vessels. Their activation causes smooth muscle relaxation thereby increase the blood volume in mucosa thereby increasing its volume. In addition, H4 receptors modulate immune cell function (Riechelmann, 2005).

In addition to its role in early allergic responses to antigen, histamine acts as a stimulatory signal for production of cytokines, expression of cell adhesion molecules and class II antigens. All contribute to the late allergic response (Fujikura et al., 2001; MacGlashan, 2003). H1 receptors exhibit agonist-independent signal transduction that is blocked by H1 antihistamines probably by stabilizing an inactive conformation of the H1-histamine receptor by acting as inverse agonists (Bakker et al., 2000). H1-receptor activation has proinflammatory activity, and is involved in the development of several aspects of antigen-specific immune response, including the maturation of dendritic cells, and modulation of the balance between type 1 helper (Th1) T cells, and type 2 helper (Th2) T cells. Histamine may increase the proliferation of Th1 cells and the production of interferon gamma and thereby block humoral immune responses by this mechanism. Histamine also induces the release of proinflammatory cytokines and lysosomal enzymes from human macrophages and has the capacity to influence the activity of basophils, eosinophils, and fibroblasts (Ma et al., 2002; Akdis & Blaser, 2003).

2.5.2.2. Eicosanoids. Eicosanoids are proinflammatory mediators resulting from metabolic degradation of arachidonic acid a constituent of cell membranes. Eicosanoids include leukotrienes, prostaglandins, and thromboxanes.
**Leukotrienes.** The name leukotriene describes their source (leukocytes) and chemical structure (3 double bonds). The first discovered was leukotriene C, initially described as the “slow reacting smooth muscle-stimulating substance” (SRS) first described almost 7 decades ago as being released by snake venom and histamine (Feldberg & Kellaway, 1938; Kellaway & Trethewie, 1940).

Leukotrienes are generated by the action of 5-lipoxygenase on arachidonic acid. They are released in both the early and late phase responses in allergic rhinitis, and in the early phase response perennial allergic rhinitis (Naclerio et al., 1985; de Graaf-in t Veld et al., 1996). The 2 classes of leukotrienes, LTC₄ and the peptidyl-cysteinyl leukotrienes (CysLT; LTC₄, LTD₄ and LTE₄) have important mediator functions in the upper airways, with implications in allergic rhinitis. There are 2 classes of receptors for cysLT1 and cysLT2 (Nicosia et al., 1999). CysLT1 receptors occur in human airway (smooth muscle cells and macrophages), on other proinflammatory cells (eosinophils and certain myeloid stem cells) and in nasal vascular beds. CysLT have been related to the pathophysiology of asthma and allergic rhinitis.

With specific regard to allergic rhinitis, leukotrienes are synthesized by mast cells, eosinophils and basophils, whereas LTC₄ and LTD₄ and are found at measurable concentrations in nasal secretions after allergen challenge (Howarth et al., 2000). Ragweed-sensitive patients, when challenged with various doses of antigens, have a dose-dependent increase in nasal lavage concentrations of LTC₄, LTD₄, and LTE₄; concentrations that correlates with nasal congestion, sneezing, and mucous secretion (Creticos et al., 1984). LTC₄, LTD₄, and LTE₄ also cause long-lasting eosinophil infiltration and have been associated with AHR in rats and man (Christie et al., 1992; Wang et al., 1993).

Nasal challenges with CysLT produce symptoms of allergic rhinitis that can be inhibited by leukotriene receptor antagonists. In normal subjects, nasal delivery of LTD₄ produces dose-dependent increases in nasal mucosal blood flow, and nasal airway resistance. A similar, but more marked, response has been seen in allergic subjects given LTD₄ (McLeod et al., 1999). The leukotriene antagonist, pranlukast, inhibits the nasal mucosal swelling induced by topical administration of LTD₄ (Numata et al., 1999).

**Prostaglandins and thromboxanes.** The most important prostaglandins are prostaglandins D₂, E₂, F₂α, tromboxane A₂, and prostacyclin (Raskovic et al., 1998). Increased concentrations of prostaglandins PGD₂ and PGE₂ are found in lavage fluid following allergen challenge in subjects with seasonal allergic rhinitis (Sugimoto et al., 1994; Wagenmann et al., 1996), as well as in those with perennial allergic rhinitis (Ramis et al., 1991). These changes are only seen in the early and not in the late response phases. More importantly cylooxygenase inhibitors (NSAIDS) do not affect response to antigen challenge in human rhinitis (Naclerio et al., 1985).

Tromboxane A₂ induces vascular permeability, eosinophil infiltration, and nasal congestion after antigen challenge in allergic patients, whereas the level of nasal tromboxane A₂ increases after challenge (Motobayashi et al., 2001).

2.5.2.3. Platelet activating factor. PAF is not stored, but produced from phospholipids mobilized from cell membranes by phospholipase A₂ in many cell types (e.g., basophils, neutrophils, monocytes, macrophages, or endothelial cells). The PAF produced by monocytes and polymorphonuclear leukocytes is secreted, whereas PAF is synthesized by vascular endothelial cells due to activation by various physiologic agonists (e.g., thrombin, BK, histamine, hydrogen peroxide, and leukotrienes C₄ and D₄) and not released (Sisson et al., 1987; Leirisalo-Repo, 1994; Cuss, 1999; Krump & Borgeat, 1999).

Of all the known inflammatory mediators possibly involved in allergic rhinitis, PAF is the most effective at inducing vascular leakage, an action that contributes to rhinorrhea and nasal congestion (Cuss, 1999; Oppenheimer & Casale, 2002). PAF has potent proinflammatory properties that have been implicated in bronchial asthma (Naclerio et al., 1985). However, its role in allergic rhinitis is less well established. Studies with the PAF receptor antagonist CV-3988 have shown in sensitized guinea pigs that they blocks vascular permeability and decreased nasal airway resistance due to topical application of PAF, whereas SM-10661 (another antagonist) attenuated antigen-induced increase in late-phase nasal airway resistance (Honda et al., 2002). The antagonist ABT-491 inhibits both antigen-induced vascular leakage and decreased airway resistance in rats and guinea pigs (Bousquet, 1998). Clinically, nasal insufflation of PAF induces many of the symptoms of rhinitis, such as an increase in nasal airway resistance, rhinorrhea, nasal neutrophil influx, and nasal hyperresponsiveness (Andersson & Pipkorn, 1988; Leggieri et al., 1991; Miadonna et al., 1996). Both PAF, and its metabolite (lyso-PAF), have been detected in the nasal fluid and plasma of patients with rhinitis (Labrakis-Lazanas et al., 1988; Miadonna et al., 1989; Shirasaki & Asakura, 1990).

2.5.2.4. Cytokines. Cytokines, as intercellular messenger peptides, are released by a variety of cells to influence the activity of other cells. Three cytokines are of importance in the development and regulation of eosinophil function: interleukins IL-3 and IL-5 and GM-CSF. All 3 prevent apoptosis and prolong the survival of eosinophils in vitro. In particular, IL-5 is essential for the differentiation of progenitor cells into eosinophils (Sanderson, 1993).

Both IL-4 and IL-5 have been implicated in the development of AHR (Hogan & Foster, 1997). In animals, IL-5 causes marked eosinophilia, eosinophil activation, and AHR (Van Oosterhout et al., 1996). IL-4 regulates the activity of CD4+ T-lymphocytes, cells that release a range of cytokines capable of priming and activating eosinophils (Mauser et al., 1993). IL-4 also activates neutrophils (Howarth, 1995). Furthermore, memory T cells in the nasal mucosa of patients with nasal allergy can produce IL-4 during allergen exposure. This could up-regulate inflammatory responses (Boey et al., 1989).

Patients with seasonal allergic rhinitis, or perennial allergic rhinitis, have a raised number of CD4+ T cells (Bradding et al., 1993; Gosset et al., 1993; Sim et al.,
Eosinophils are one potential source of these cytokines (Lantero et al., 1996), whereas epithelial cells from allergic rhinitic patients showed increased immunostaining for GM-CSF, IL-8, the receptors for IL-1 and TNF-α (Galli et al., 1994), and also they release more IL-1β, IL-8, GM-CSF, and TNF-α compared to epithelial cells from nonallergic subjects (Nonaka et al., 1996). Similar increases in IL-4, IL-5, and GM-CSF-positive cells are observed in the nasal mucosa of atopic patients (Calderon et al., 1997). Both interferon-gamma and TNF-α (and possibly other cytokines) cause an up-regulation of ICAM-1 on human nasal epithelial cells (Durham et al., 1992), whereas IL-4 up regulates the expression of VCAM-1. Both these adhesion molecule are unregulated in allergic rhinitis (Bradding et al., 1993).

2.5.2.5. Chemokines. Chemokines divided into groups depending upon chemical structure but all have chemotactic actions. With CC chemokines, 2 cysteine residues are adjacent to each other (e.g., RANTES, MIP-1α, eotaxin), whereas in CXC chemokines, 2 cysteine residues are separated by a third amino acid (e.g., IL-8; Barnes et al., 1998). Concentrations of RANTES, MIP-1α, eotaxin, and IL-8 in nasal lavage fluids rise following nasal allergen challenge in man (Sim et al., 1995; Gosset et al., 1997; Minshull et al., 1997, Rajakulasingam et al., 1997). In addition, mucosal cells obtained from rhinitics show increased expression of mRNA for RANTES (Rajakulasingam et al., 1997), and eotaxin (Minshall et al., 1997).

It is generally accepted that RANTES and eotaxin are important in IL-5-mediated eosinophilia. The latter mobilizes eosinophils into the circulation, whereas the local release of chemokines provides a ‘homing’ mechanism for the migration of eosinophils into tissue (Barnes et al., 1998). Nasal administration of RANTES in those with allergic rhinitis causes accumulation of eosinophils, but not other inflammatory cells (Kuna et al., 1998). However, the same study also found that after allergen challenge the administration of RANTES also caused an influx of basophils, neutrophils, lymphocytes, and monocytes, as well as causing epithelial shedding, a response similar to that observed in nasal hyperresponsiveness. It is therefore likely that chemokines have an important role in the recruitment of inflammatory cells observed during the development of nasal hyperresponsiveness.

2.5.2.6. Nitric oxide. NO is produced by NO synthase (NOS) acting on L-arginine. Different isoforms of NOS exist: neuronal, inducible, and endothelial forms. NOS activity increases in perennial allergic rhinitis (Garrells et al., 1995) and in seasonal allergic rhinitis (Martin et al., 1996; Kharitonov et al., 1997). In mice with allergic rhinitis, the distribution of the different NOS in nasal mucosa showed that neuronal and endothelial NOS were found on the surface of epithelial and vascular endothelial cells, but there were no differences in this respect between allergic and control mice. However, the amount of inducible NOS was elevated in allergic mice (Oh et al., 2003).

NO possibly has a role in the production of the cytokines necessary for eosinophil survival, such as IL-4 and IL-5 (Barnes & Liew, 1995). Interestingly, NO is thought to be the main mediator of inhibitory NANC transmission. Thus, inhibition of NOS could potentially reduce the activity of inhibitory NANC nerves, thereby potentiating neurogenic inflammation mediated by excitatory NANC nerves. In chronic allergy, excessive NO production causes AHR via the formation of the peroxynitrite free radical in guinea pigs airways (Sadeghi-Hashjin et al., 1996). Furthermore, other NO metabolites, such as nitril chloride, can be synthesized by neutrophils resulting in inactivation of angiotensin-converting enzyme in endothelial cell (Eiserich et al., 1998). This enzyme is involved in the degradation of kinins and possibly tachykinins in allergic rhinitis (Lurie et al., 1994; Chatelain et al., 1995). Inhibition of the enzyme may therefore exacerbate rhinitis.

2.5.2.7. Kinins. Kinins are proinflammatory peptides that mediate some of the vascular and pain responses to tissue injury. Two kinin receptor subtypes have been identified, B1 and B2 (Regoli et al., 1977). The B2 receptor mediates the action of BK and lysyl-BK (Lys-BK), whereas the B1 receptor mediates the action of des-Arg9-BK and Lys-des-Arg9-BK (Leeb-Lundberg et al., 2005).

Recent studies (Turner & Foreman, 1999) suggest that AHR in human nasal airway may be kinin dependent since icatibant, a BK B2 receptor antagonist, prevents PAF-induced AHR. In addition PAF causes an increase in kinin concentration in nasal lavage fluid. Kinins are produced in both perennial allergic rhinitis, and seasonal allergic rhinitis. BK causes sensitisation of C fibers in the guinea pig trachea (Fox et al., 1996), and there is evidence that, in the human nose, enhanced responsiveness to BK is mediated by neural reflexes (Riccio & Proud, 1996). BK can also release SP and other neuropeptides from sensory nerve endings (Saria et al., 1988; Geppetti et al., 1990); thus, actions on AHR are possibly neuropeptide-dependent. Alternatively, BK initiates production of cytokines IL-1, IL-6, and IL-8 in vivo (Ferreira et al., 1993), and stimulate the release of TNF-α/β and IL-1 from macrophages (Tiffany & Burch, 1989). Also BK increases the expression of the CXC chemokine receptors CXCR1 and CXCR2 in patients with allergic rhinitis (Eddleston et al., 2003). This could contribute to nasal AHR.

2.5.2.8. Neuropeptides. Neuropeptides have been previously discussed in the neuronal events subchapter. They are contained in, and released from a wide range of nerves. They vary in their amino acid compositions and have characteristic patterns of localization in the peripheral and central nervous systems. All are capable of producing a range of diverse responses. Primarily unmyelinated sensory C-fibers and myelinated Aδ-fibers contain and release neuropeptides. Such nerves provide a dense innervation to most organs and tissues, particularly blood vessels where perivascular nerves often terminate in close association with endothelial cells.

Parasympathetic nerve endings contain VIP, peptide histidine methionine, and efferent sympathetic nerve endings contain NPY. Nasal sensory nerve fibers contain a number of different peptides, including CGRP and the tachykinins SP and NK-A. These neuropeptides which are all metabolised by the enzyme NEP, are released from the sensory nerves that belong to the
NANC nervous system. Such nerves can generate local reflexes causing increases in vascular permeability, plasma leakage, vasodilatation and subsequent tissue oedema (Baraniuk, 1997).

3. An overview of animal models of allergic rhinitis

While much of the work described above was performed in humans there is a permanent need for good animal models of allergic rhinitis for both mechanism of action, and drug discovery purposes. Allergic diseases are very uncommon in the animal world and research animals suffering spontaneously from allergic rhinitis are not known (Szelenyi et al., 2000). However, allergic rhinitis can be induced in animals using different strategies.

A variety of laboratory species have been used to create animal models of allergic rhinitis, using a variety of antigens but there is no single model that mimics all of the human condition. As a result there has been a tendency, for the sake of simplicity, to concentrate on single symptoms induced in a chosen species. Among the species, guinea pigs have gained more attention as a suitable experimental model for in vivo studies of pharmacological and pathophysiological aspects of the acute and chronic phases of allergic rhinitis. This is probably because of the ease of use of this species coupled to the fact that this species produce many of the responses to allergic rhinitis seen in human allergic rhinitis. Furthermore guinea pigs have long been a commonly used species in allergic respiratory diseases.

The Dunken Hartley strain of guinea pig has been widely used to evaluate the actions of drugs as well as their potential therapeutic applicability in allergic rhinitis (Mizutani et al., 1999; Nabe et al., 2001; Yamasaki et al., 2001; Fukuda et al., 2003; Zhao et al., 2005). In addition, BALB/c mice have been utilized, mostly for immunological studies in allergic rhinitis (Saito et al., 2002; Murasugi et al., 2005). Brown Norway rats are also used for studying drugs effects on symptoms of experimental rhinitis (Shimizu et al., 2000; Sugimoto et al., 2000b; Fu et al., 2003). Dogs and pigs have been occasionally used for studies of mucus secretions and nasal congestion after allergen challenge (Revington et al., 1997; Szelenyi et al., 2000; Zhao et al., 2005). Dogs and pigs have been occasionally used for studies of mucus secretions and nasal congestion after allergen challenge (Revington et al., 1997; Szelenyi et al., 2000; Zhao et al., 2005). In addition, BALB/c mice have been occasionally used for studies of mucus secretions and nasal congestion after allergen challenge (Revington et al., 1997; Szelenyi et al., 2000; Zhao et al., 2005).

Allergic rhinitis can be induced in laboratory animals using different allergens. The process of induction of allergy requires an initial sensitization dose of allergen, followed by repeated booster doses, and finally a challenge dose. Responses that can be evoked and measured following allergen challenge include sneezing, nose rubbing, rhinorrhea, vascular permeability (exudation) and nasal congestion. In addition, biochemical and cellular changes can be quantified and evaluated after challenge.

Ovalbumin and Japanese cedar pollen are 2 commonly used allergens. The techniques used for sensitization range from injection (intraperitoneal, with or without, adjuvant), bolus instillation (intranasal) or steady-state inhalation exposures over short, or long, periods of time with different concentrations of allergen and adjuvant. In the purely nasal route for sensitization, 4% lidocaine is insufflated over a period of 5 min followed by intranasal doses of allergen absorbed onto aluminum hydroxide and given daily for 7 days (Mizutani et al., 1999; Nabe et al., 2001; Yamasaki et al., 2001; Fukuda et al., 2003; Zhao et al., 2005). Alternatively, animals can be exposed to 1% aerosol ovalbumin twice for 10 min, 1 week apart (Yamasaki et al., 1997). Ovalbumin absorbed in aluminum hydroxide can be injected peritoneally as an initial sensitization dose (Namimatsu et al., 1991; Narita et al., 1997; Fujita et al., 1999; Imai et al., 2000; McLeod et al., 2002; Sakairi et al., 2005).

Sensitization can be passive by intravenous, subcutaneous, or intraperitoneal administration of anti-OVA serum (Mizuno et al., 1991; Kaise et al., 1998, 2001a, 2001b). Following initial sensitization dose(s), animals are either exposed to repeated doses of allergen boosters, over a period of time, or directly challenged with allergen. The waiting period from first sensitization to first challenge varies between studies, but generally in the range of 2–4 weeks. Conscious animals are challenged by the intranasal route using inhalation of aerosolized allergen, or by instillation of microliters of allergen dissolved in saline. Anaesthetized animals can be challenged either via the intranasal route or from the tracheal side into the nasal cavity by infusion of high volumes of allergen (Albert et al., 1998; Mizutani et al., 1999; Sakairi et al., 2005).

Sneezing typically follows challenge in conscious animals, as probably does itching. While itching cannot be measured directly, it can be assumed to be the stimulus that results in the rubbing and/or scratching of the nose with paws, analogue to itching reported by humans. Thus individual guinea pigs can be challenged and episodes of sneezing and nose rubbing counted by direct observation, or from videoed records. Acoustic recordings made electronically are also possible. Sneezing and nose rubbing are counted immediately after allergen provocation and 10–60 min thereafter (Kaise et al., 1998; Nabe et al., 2001; Yamasaki et al., 2001; Mizutani et al., 2003; Fukuda et al., 2003; Zhao et al., 2005).

Nasal blockade (decreased nasal patency) occurs as a result of swelling of the nasal mucosa via vasodilatation of vascular cavernous tissue plus increased glandular secretions. Such changes are biphasic in time since they occur in both the acute and late phases. In sensitized guinea pigs, both phases of nasal congestion have been detected, with the acute phase occurring during the first 30 min, and a later phase 4–6 hr after exposure to allergen. The patency in the nasal cavity can be measured in both conscious and anaesthetized guinea pigs. In conscious guinea pigs, a 2-chambered double-flow plethysmograph has been used to measure air flow through the nasal cavity. In this technique, a guinea pig is placed with its neck extending through the partition of a 2-chambered box (Albert et al., 1998; Fujita et al., 1999; Mizutani et al., 1999; Imai et al., 2000; Nabe et al., 2001; Yamasaki et al., 2002; Fukuda et al., 2003; Mizutani et al., 2003). It is reported that nasal air flow is inversely proportional to nasal blockade. This plethysmographic method has been used extensively but its use has been criticized by Swedish researchers who consider that changes in resistance measured in the plethysmograph originate at or below the larynx (Finney & Forsberg, 1994). Recently, respiratory rate has been used in conscious guinea pigs to reflect resistance changes in the upper airway (Zhao et al., 2005).
In anaesthetized guinea pigs, nasal blockade can be measured using various methods, including a ventilator flow method (Mizuno et al., 1991; Shizawa et al., 1997; Yamasaki et al., 1997; Albert et al., 1998; Fukuda et al., 2003; Sakairi et al., 2005), a forced oscillation method (Narita et al., 1997; McLeod et al., 2002), and acoustic rhinometry (Kaise et al., 1998; Kaise et al., 2001a, 2001b). In the ventilator flow method, pulsatile air (4–10 mL/stroke and 50–70 strokes/min) is forced through the nasal cavity from the tracheal side. Any change in air flow resistance is reflected as a nasal patency change.

In the forced oscillation method (also known as the flow/pressure method), one side of nasal cavity is cannulated and the flow of humidified air is restricted from cannulated side through the other side of the nasal cavity, and out the nostril. Changes in nasal patency change air flow.

Acoustic rhinometry is used to measure the volume of the nasal cavity. In guinea pigs, an ultrasonic transducer/probe can measure changes in the nasal cavity within 2 cm of the nostrils. The volume of the nasal cavity decreases when nasal blockade increases, and vice versa.

Rhinorrhea is a particularly troublesome symptom in allergic rhinitis. Watery nasal secretions appear in sensitized guinea pigs after allergen provocation although in most cases its production is not of a sufficient volume for it to be measured easily. Nasal secretions can be measured gravimetrically. For example, cotton thread, dyed with fluorescein, can be inserted into the anterior nares of guinea pigs for 1 min. The intensity of color is proportional to fluid volume, whereas any increase in weight of the thread is due to absorbed nasal secretions (Namimatsu et al., 1991). Alternatively, a preweighed swab can be used to absorb the secretions appearing at the anterior nares (Fujita et al., 1999; Fukuda et al., 2003). An alternative is to use filter paper strips inserted into the nares so as to absorb secretions over a timed period (Zhao et al., 2005).

Exudation occurs as a result of increases in vascular permeability. In sensitized guinea pigs it can be measured using dyes. Different dyes have been used including Evans’s blue (Mizuno et al., 1991; Mizutani et al., 1999, 2001), pontamine sky blue, (Yamasaki et al., 1997; Kaise et al., 1998) and brilliant blue (Shizawa et al., 1997). A dye, at concentrations that vary from one study to another (1–10%), is administered intravenously before allergen challenge in anaesthetized guinea pigs. After allergen provocation, nasal cavities are perfused with saline at a rate of 0.2–0.25 mL/min for 10–20 min. Dye concentration in the collected perfusate is quantified by spectrophotometer using the absorbance at 620 nm. Dye concentration is proportional to vascular permeability (exudation).

Instead of using dye, intravenously administered 125I-labelled human serum albumin can be recovered from nasal cavities as a measure of serum protein in the cavity and hence a reflection of serum protein exudation (Elovsson et al., 2005).

At the same time allergic rhinitis is basically an inflammatory reaction of the nasal mucosa this is reflected in the presence of inflammatory cells and their mediators in nasal lavages. In sensitized guinea pigs, both cells and mediators can be detected in nasal lavage during both the acute and chronic phases. Nasal lavage can be achieved by perfusion of the nasal cavities with saline from the tracheal side (Shizawa et al., 1997; Yamasaki et al., 1997; Imai et al., 2000; Kaise et al., 2001a; Elovsson et al., 2005). Alternatively, saline can be instilled into one nostril and simultaneously sucked out of the other nostril by applying a negative pressure (Mizutani et al., 2001; Yamasaki et al., 2001, 2002; Zhao et al., 2005). The recovered nasal lavage is centrifuged and the resulting supernatant for used for measurement of mediators (e.g., thromboxanes, leukotrienes, EPO, NO², NO³, histamine) by way of ELISA or radioimmunoassay. The nasal lavage can be assessed for its total leukocyte count using hemocytometers or semiautomated hematology analyzers, and for differential cell count using cytospin followed by staining.

All of the above techniques have been used in basic studies into allergic rhinitis in experimental animals. However, many of the techniques have been applied to humans.

4. Treatments for allergic rhinitis

The following section considers the whole spectrum of treatments that have been developed and used in the treatment of allergic rhinitis. It is reasonable to conclude that no one treatment is totally effective and that the different treatments target the different symptoms and signs of the disease. Some provide immediate relief from symptoms and others modify the underlying immunological mechanisms as exemplified by nasal application of glucocorticoid steroids.

4.1. Currently used drugs for allergic rhinitis and limitations to their use

The 2 major classes of drugs used to treat symptoms of allergic rhinitis are oral H1 antihistamines and intranasal corticosteroids. These drugs may be used as monotherapy, or in combination, depending on the predominant symptoms, and the patient’s response to therapy. Alternative drugs, such as cromoglycate, may be appropriate in some patients.

The first-generation antihistamines include brompheniramine, chlorpheniramine, and diphenhydramine. Although these drugs relieve the sneezing and rhinorrhea in allergic rhinitis, they easily cross the blood–brain barrier and efficacious doses are always associated with drowsiness and impaired mental performance.

The so-called second-generation antihistamines produce none, or considerably less, sedation than the first-generation drugs. The first of these terfenadine and astemizole could, rarely, produce a potentially dangerous (fatal) cardiac arrhythmia due to an ancillary pharmacological action, blockade of an important cardiac potassium channel. These first drugs have been taken off the market and replaced by other newer second-generation antihistamines (acrivastine, cetirizine, fexofenadine, desloratadine, loratadine) that are not associated with this arrhythmia (Kay, 2000). Fexofenadine, loratadine, and desloratadine are not considered non-sedating antihistamines although this is arguable. Acrivastine may be sedating in some patients. Cetirizine is considered low sedating.
Oral antihistamines are also first-line therapy for allergic rhinitis in children (Dykewicz et al., 1998). All members of this class of these drugs have demonstrated effectiveness in the relief of the seasonal and perennial rhinitis by reducing the symptoms of sneezing, itching, and nasal discharge. They have also been found to reduce ocular symptoms of the allergic conjunctivitis that frequently occurs in conjunction with allergic rhinitis. Their mechanism of action in producing relief derives for most of this class of drugs from their being antagonist at H1 receptors although for some, for example, cetirizine, other actions are involved.

H1 antihistamines are generally not considered effective for nasal congestion (Dykewicz et al., 1998). Therefore, in patients with this symptom, combination therapy with an oral antihistamine plus a decongestant can be helpful. Such combinations are available at fixed dose ratios that can be taken once daily. The usual decongestants used, for example, pseudoephedrine and phenylpropanolamine, can have unwanted effects, such as insomnia, loss or stimulation of appetite, and should be used with caution in patients with conditions such as arrhythmias or angina. Furthermore, prolonged and excessive use of decongestants, which are agonists on α1 adrenoceptors induce vasoconstriction, is associated with paradoxical rhinorrhea and even mucosal ulceration.

Intranasal H1 antihistamines, such as azelastine and levocabastine, are also useful in mild-to-moderate allergic rhinitis (Dykewicz et al., 1998). These topical antihistamines are administered twice daily, and have a rapid onset of action. Both azelastine and levocabastine have been shown to improve symptoms in patients with seasonal or perennial allergic rhinitis (Bousquet et al., 2001), and seem to have the potential to reduce nasal congestion.

Intranasal corticosteroids are considered first-line treatment for more severe allergic rhinitis (Dykewicz et al., 1998; Bousquet et al., 2001). The most effective of this class in controlling allergic rhinitis are nasally inhaled corticosteroids including beclomethasone, budesonide, flunisolide, mometasone, and triamcinolone (Corren, 2000; Kaszuba et al., 2001). Corticosteroids target the inflammatory mechanisms. Thus, intranasal steroids are particularly effective in ameliorating nasal congestion, which is often the main complaint in chronic allergic rhinitis, but they also relieve other symptoms of rhinitis, such as rhinorrhea, sneezing, and nasal itching. Most are administered once or twice daily for extended periods. To obtain optimal benefit therapy should begin before the onset of symptoms (for example, before the expected pollen season). The onset of action of intranasal corticosteroids is slow with maximum benefit occurring over days or even weeks. Systemic side effects are minimal in adults receiving intranasal corticosteroids. Nose bleeding or irritation may occur and these tend to diminish over time although, in rare cases, septal perforation has occurred (Cervin & Andersson, 1998).

Intranasal cromolyn relieves allergic rhinitis symptoms in some patients. Treatment is preferably begun before the onset of symptoms and does not improve symptoms once they occur. It may need to be administered up to 4 times daily (Ratner et al., 2002). Immunotherapy is appropriate in some patients with severe symptoms where their allergen is one for which potent extracts are available, and who do not respond to pharmacotherapy (Dykewicz et al., 1998). Age and concomitant illnesses are factors that help determine whether immunotherapy is appropriate. For example, immunotherapy is rarely appropriate in preschool children, the elderly and in those with severe pulmonary or cardiovascular disease. In general, effective immunotherapy requires 3–5 years of treatment.

Due to the redundancy, synergy and pleiotropism that exists for the mediators of allergic rhinitis there are limitations to the currently available drugs in terms of their effectiveness. Antihistamines (H1) provide symptomatic relief only. Steroids do not provide acute relief of symptoms and they are nonselective; unsuitable for some patients (especially young children); may cause nasal irritation, bleeding, and in rare cases even systemic side effects.

Timing of treatment is critical with anti IgE and immunotherapy needs identification of allergen and multiple injections. Moreover, anticholinergics (muscarinic antagonists) are useful only in reducing rhinorrhea.

4.2. Possible novel targets for treating allergic rhinitis

An improved understanding of the cellular and molecular mechanisms occurring in allergic rhinitis has resulted in the identification of potential novel therapies. In theory, inhibition at critical points in the upstream pathway of the allergic cascade (e.g., dendritic cells or T\textsubscript{H2} cells) should be more effective than the inhibition of a single downstream mediator (Holgate & Broide, 2003).

4.2.1. Mediator receptor antagonists

As discussed above, targeting the mediator receptors with appropriate antagonists is limited because of the large number of possible mediators. However, improvements can be expected in terms of the available antagonists in terms of pharmacokinetic profile and therapeutic utility as well as antagonists acting on more than on type of mediator receptor.

4.2.1.1. Antihistamines. The new generation H\textsubscript{1} antihistamines show improved effectiveness and safety, particularly those which also act as inverse agonists. Inverse agonists stabilize the inactive conformation of the receptor thereby reducing the proportion of the receptor in their active conformation (Oppenheimer & Casale, 2002). A number of antihistamines (e.g., fexofenadine, a metabolite of terfenadine without the potential for causing torsade) are also claimed to have anti-inflammatory actions (Baroody & Naclerio, 2000).

The recent discovery of the H\textsubscript{4} receptor expressed on mast cells, basophils and eosinophils has generated renewed interest in histamine because H\textsubscript{4} receptors mediate Ca\textsuperscript{2+} signaling and chemotaxis (Hofstra et al., 2003). It is possible that selective H\textsubscript{4} antagonists could have antiinflammatory actions in allergic disease.

4.2.1.2. Leukotrienes inhibitors. CysLT released from mast cells, basophils, eosinophils, and macrophages are particularly
important in causing nasal blockade (Higashi et al., 2003). Clinical trials of montelukast and zafirlukast (CysLT1 receptor antagonists) show that an effectiveness that is less overall than that of topical nasal corticosteroids (Pullerits et al., 2002; Philip et al., 2002; Topuz & Ogmen, 2003). The recent discovery of both CysLT1 and LT2 receptors on eosinophils, which differ in their binding to the leukotrienes LTD4 and LTC4, highlights the potential proinflammatory role of leukotrienes and the possible for antagonists with simultaneously actions on both receptors (Evans, 2002).

4.2.1.3. Prostaglandin receptor antagonists. Among the prostaglandins PGD2, a mast-cell-derived eicosanoid has potent vasodilator properties mediated by the DP1 receptor. DP1 receptor antagonists could therefore possibly provide another therapy where nasal congestion is problematic. A second PGD2 receptor, DP2 has been identified as a T12 marker but is also expressed on eosinophils and basophils where it serves a chemotactic function whose antagonism could result in anti-inflammatory responses (Arimura et al., 2001; Holgate & Brodie, 2003; Sugimoto et al., 2003).

4.2.1.4. Tryptase antagonists. Mast-cell granules contain high concentrations of the protease tryptase. Tryptase can initiate a range of inflammatory responses and these have been implicated in chronic tissue injury and tissue remodeling possibly involving coagulation factor II receptor-like I found on epithelial cells, fibroblasts and smooth muscle. A number of tryptase inhibitors have been described and some efficacy in nasal allergy models (Newhouse, 2002).

4.2.1.5. Nitric oxide synthase inhibitors. Allergic rhinitis is associated with increased levels of NO production in allergic rhinitis. NO causes vasodilation and glandular secretion (Baraniuk, 1997). NOS inhibitors have been shown to reduce nasal blockade in perennial allergic rhinitis, and plasma exudates in seasonal allergic rhinitis (Dear et al., 1996). However, NOS inhibitors, administered intranasally to humans, were associated to the development of upper airway hyperreactivity and significant eosinophilia (Turner et al., 2000).

4.2.2. Mast cell stabilizers

4.2.2.1. Cromones. Cromolyn, and its successor nedocromil, are thought to act as mast cell stabilizers, but their precise mechanism(s) of action is not known. They have been shown to be effective in reducing immediate phase symptoms in allergic rhinitis (Kunkel et al., 1987).

4.2.2.2. Protein kinase inhibitors. Activation of Syk kinase, a transducer of signalling through the Fcε receptor of mast cells, via binding to IgE which itself is bound to the IgE receptor leads to an array of responses including degranulation and neosynthesis of proinflammatory mediators. Clinically, an inhibitor of Syk kinase (R112) has been shown to be effective in relieving the symptoms of allergic rhinitis (Meltzer et al., 2005). Moreover, genistein, a potent inhibitor of tyrosine kinase, has anti-inflammatory actions on mast-cell-dependent early- and late-phase allergen-provoked inflammatory reaction in the airways of guinea pigs so providing some proof of the therapeutic potential for selective inhibitors of the protein kinases that are linked to mast-cell activation (Duan et al., 2003).

In addition, mast cells also express receptors that inhibit IgE-dependent degranulation through the activation of immunoreceptor tyrosine-based inhibitory motifs (ITIMS). Molecules associated with FceR1 inhibitory receptors, such as immunoglobulin-like transcripts (ILT) and leukocyte immunoglobulin-like receptors (LIR), influence IgE signaling by triggering phosphorylation of ITIM sequences on the gamma-chains of FcεR1. At present, 13 LIR are known. LIR 1, 2, 3, 5 and 8 have inhibitory effects. LIR5 (gp49A and gp49B) is highly expressed by mast cells (Katz et al., 1996). Although no natural ligands for these receptors have yet been identified, they offer targets at which to direct novel inhibitory agents.

The processes of differentiation, optimal secretion, and even survival in mast cells are dependent on stem-cell factor (SCF; Costa et al., 1996). In disorders such as mastocytosis, blockade of SCF Src kinase activity by the selective inhibitor PP1 has a marked effect in suppressing mast-cell proliferation (Tatton et al., 2003). It appears obvious that the ablation of the mast cells in nasal mucosa would produce benefit in allergic rhinitis, where the mucosal mast-cell population is inappropriately markedly increased. The implications of ablating the mast cells in non-nasal tissue are not known.

4.2.2.3. Ion channels blocking drugs. The activity of many cell types is intrinsically linked with maintenance of their transmembrane potential by Na and K and other voltage and ligand sensitive ion channels, ion pumps and ion transporters. Similarly, both secretion as well as metabolism, in its broadest sense, is regulated by intracellular calcium regulated via Ca channels, pumps and transporters. These ion-related systems are therefore obvious targets for new drugs designed to stabilize cells and preventing them secreting or manufacturing mediators. Selective blockers of inwardly rectifying and Ca2+-activated K+ channels, and Ca2+-dependent Cl− channels linked to IgE-dependent activation, expressed in mast cells, may also offer promise for a new generation of anti-allergic drugs (Duffy et al., 2001).

4.2.3. Inhibitors of neuronal pathways

Allergic rhinitis is associated with local neural activity, such as itching, sneezing and reflex-mediated secretion (Baraniuk, 1992; Barnes, 2001) making such neural activity a suitable target for drugs. Although SP induces eosinophilia in allergic rhinitis (Fajac et al., 1995), inhibition of its receptors (neurokinin 1 and 2) has so far proved disappointing when tested clinically.

BK is a potent releaser of neuropeptides. The effectiveness of a B2 BK agonist was reported in nasal allergen challenge (Austin et al., 1994) but subsequent Phase III clinical trials proved disappointing. Other neuropeptides also provide interesting targets, including CGRP in chronic vasodilation (Uddman et al., 1999) and secretoneurin, which is present in cholinergic, adrenergic and sensory nerves (Korsgren et al., 2003), and which exerts a proinflammatory effect on eosinophils (Dunzendorfer et al., 1998). If suitable antagonists for these mediators are discovered and
developed they possibly could be effective in chronic forms of allergic rhinitis in which nasal blockade dominates.

4.2.4. Immunotherapy

Certain strategies have been used in immunotherapy of allergies. These include the use of allergen-specific immunotherapy (ASIT), allergen peptide-based immunotherapy, and DNA immunotherapy.

4.2.4.1. Allergen-specific immunotherapy. The goal of ASIT is to modulate immune responses to allergen, and thereby reduce the symptoms of allergic rhinitis. ASIT is administered as a series of subcutaneous or sublingually injections of highly purified airborne allergen(s) with doses of 6–24 μg to patients with allergic rhinitis who are specifically sensitized to identified allergen(s). ASIT is effective in reducing symptoms of allergic rhinitis, as evidenced by the inhibition of both early- and late-phase nasal responses. In children sensitized to a single allergen, a reduced risk of subsequent development of sensitization to further allergens was seen (Pajno et al., 2001; Malling, 2002; Moller et al., 2002). The mechanisms by which ASIT produces its beneficial clinical effects are becoming clearer (Canonica & Passalacqua, 2003). ASIT reduces clinical symptoms by inhibiting allergen-specific T<sub>H2</sub> cells in favor of a T<sub>H1</sub> response (immune deviation; Wachholz et al., 2002), and inducing regulatory lymphocytes carrying the CD4 and CD25 antigens and CD4<sup>+</sup>CD25<sup>+</sup> T<sub>H3</sub> (immune tolerance; McHugh & Shevach, 2002). Specific immunotherapy also increases allergen-specific ‘blocking’ IgG<sub>1</sub> and IgG<sub>4</sub> antibodies, a variable decline in allergen-specific IgE, and reduces both the number and activation state of mucosal mast cells, basophils and eosinophils (Ebner, 1999).

Although SIT is effective in some cases, its administration can be associated with local and systemic allergic reactions, and so a variety of strategies have been followed in an attempt to improve effectiveness and reduce adverse effects.

4.2.4.2. Peptide-based immunotherapy. The rationale for using short peptides in ASIT is to reduce the potential for allergic side effects, while retaining the beneficial effect of those peptide epitopes recognized by T cells in modifying their response to allergens. This approach relies on peptides being unable to crosslink FccR1-bound IgE on mast cells and basophils (Holgate & Broide, 2003).

The safety and efficacy of peptides has been taken advantage of in the treatment of cat allergy using several overlapping peptides derived from chain 1 or 2 of the major cat allergen Fel d<sub>1</sub>. Weekly subcutaneous immunization with 27-amino acid peptides derived from chain 1 or 2 of the major cat allergen Fel d<sub>1</sub> reduced symptoms of rhinitis provoked by exposure to cats (Norman et al., 1996).

4.2.4.3. DNA immunotherapy. Immunostimulatory DNA sequences containing CpG motifs are strong inducers of a T<sub>H1</sub> immune response to antigen, and have therefore been investigated in the treatment of T<sub>H2</sub>-mediated diseases such as allergic rhinitis and asthma (Horner et al., 2001a). CpG DNA inhibits T<sub>H2</sub> responses to antigen indirectly by influencing the function of cells of the innate immune system, rather than exerting direct effects on T lymphocytes. Studies with TLR9-deficient mice have demonstrated that these aspects of the innate immune response are essential in mediating the immunostimulatory activity of CpG DNA, which is characterized by production of IL-12, IL-18, interferon gamma, IL-6 and IL-10 (Roman et al., 1997; Hemmi et al., 2000).

The cytokine environment induced by CpG DNA is highly effective at reducing the levels of expression of T<sub>H2</sub> cytokine receptors (for example, the IL-4 receptor; Horner et al., 2001b). In a mouse model of allergic rhinitis, CpG DNA administration prevented both the development of nasal symptoms and eosinophilic inflammation (Hussain et al., 2002).

4.2.5. IgE targeting

To avoid the problem of sensitization to foreign proteins, a humanized monoclonal antibody containing 95% human IgG<sub>1</sub> and 5% murine IgG-binding epitope has been constructed (Presta et al., 1993). This antibody recognizes IgE selectively and inhibits the binding of IgE to both FccR1 and FccR2, thereby inhibiting mast-cell and basophil activation. By this mechanism, omalizumab therapy markedly reduces inflammatory leukocytes and the expression of FccR1. The latter when not occupied by IgE becomes internalized (Plewako et al., 2002). When administered as 2-weekly, or 1-monthly subcutaneous injections, omalizumab decreases circulating free IgE by > 90% by forming small (1000 kDa), non-complement-fixing complexes that are eliminated by the reticuloendothelial system without causing side effects. In clinical trials of seasonal allergic rhinitis, omalizumab has shown efficacy (Adelroth et al., 2000; Casale et al., 2001). Furthermore, in children with allergic rhinitis, a combination of SIT with anti-IgE for 24 weeks was more efficacious than when either treatment was given alone (Kuehr et al., 2002).

4.2.6. Cytokines and chemokines inhibitors

One of the difficulties in deciding which cytokines or chemokines to target for the treatment of allergic rhinitis is the large variety of them that are expressed at sites of allergic inflammation, as well as their overlapping functions. In allergic inflammation, research has focused particularly on individual T<sub>H2</sub> cytokines (for example, IL-4, IL-5, IL-9 and IL-13) and chemokines that attract cells to sites of allergic inflammation (Kay, 2001).

To date, there are no published studies of cytokines antagonists in humans with allergic rhinitis. However, animal studies and cytokine challenges in humans help illustrate their effect in nasal allergy. The therapeutic potential of a recombinant soluble IL-4 receptor as an inhibitor of IL-4 has produced improvements in asthmatics (Borish et al., 2001). Monoclonal anti-IL-4 antibodies inhibit IgE production in mice (Zhou et al., 1997). Allergen challenge increases the level of expression of IL-13 in the nasal mucosa in vivo, whereas, in vitro, IL-13 increases the number of secretory cells in human nasal epithelial cells (Wills-Karp et al., 1998; Skowron et al., 2003). Targeting IL-13 has been investigated in allergic inflammation with mouse models of asthma. Its antagonism inhibits the allergic inflammatory response in the lower airways (Wynn, 2003).
The C-C chemokines, including eotaxin, RANTES and monocyte chemoattractant proteins 1 and 3 are particularly relevant to allergic inflammation, since increased levels of these chemokines are detected in the nasal mucosa following allergen challenge and all interact with the CCR3 receptor on eosinophils, basophils and mast cells (Terada et al., 2001). Activation of CCR3 receptors by application of eotaxin to nasal mucosa induces an influx of eosinophils (Gorski et al., 2002). Studies demonstrating that an 11-amino-acid synthetic peptide inhibits the nasal influx of neutrophils and protein exudation as induced by nasal challenge with IL-8 in normal subjects indicate the potential for inhibiting chemokine actions in the nasal mucosa (Cooper et al., 2001). Given such evidence it is not surprising that the 3 chemokine receptors CCR3, CCR4 and CCR8 that are preferentially expressed by Th2 cells, mast cells and eosinophils represent therapeutic targets in allergy.

4.2.7. Adhesion molecules inhibitors
Adhesion molecules expressed on leukocytes and endothelial cells are important for inflammatory cell recruitment during allergic inflammation. At present, there are no published studies of antiadhesion therapy in allergic rhinitis. However, the targeting of such molecules on leukocyte or endothelial cell surfaces has been studied as an approach to inhibiting allergic inflammation. One of the adhesion molecules is endothelial P-selectin which is highly expressed in nasal mucosa and has been shown to stimulate eosinophil recruitment in mouse models of allergic inflammation (Symon et al., 1994). Subsequent to endothelial tethering, eosinophils firmly adhere to either ICAM-1 or VCAM-1. Blockade of such molecules in allergic mouse with inflammation, or in those with inhibition of eosinophilic tissue recruitment in ICAM-1-deficient mice, resulted in marked inhibition of the adhesion of eosinophils to endothelium (Broide et al., 1998). Furthermore, eosinophils, basophils, monocytes and T cells, but not neutrophils, express high levels of very late antigen-4 (VLA-4), the ligand for VCAM-1 (Jackson, 2002). Binding of VLA-4 to the CS-1 region of fibronectin also induces eosinophil activation (Anwar et al., 1993), such that by targeting VLA-4, cell activation such cell recruitment might be inhibited.

4.2.8. Selective phosphodiesterase 4 inhibitors
One promising development is the use of selective phosphodiesterase 4 (PDE4) inhibitors which exert anti-inflammatory actions by blocking the breakdown (hydrolysis) of cyclic 3′5′-AMP (cAMP) in lymphocytes, eosinophils, neutrophils and monocytes. Reduced cAMP attenuates release of mediators and cytokines (Giembycz, 2000). Although known to be effective in the treatment of asthma, and chronic obstructive pulmonary disease, oral once-daily therapy with the PDE4 inhibitor roflumilast in patients with allergic rhinitis subjected to repeated allergen exposure proved to be efficacious, especially on nasal blockade (Sorbera et al., 2000; Schmidt et al., 2001).

4.2.9. Heparin
The anticoagulant, heparin, a straight-chain, highly sulfated glycosaminoglycan, is present in mast cells at high concentra-

tions. Anti-inflammatory and antiallergic properties of heparin have been demonstrated both in vitro and in vivo (Matzner et al., 1984; Lider et al., 1990). Despite these positive effects very little research has been undertaken over the past years to systematically investigate heparin in the treatment of allergic rhinitis. In one clinical study, intranasal heparin significantly reduced symptom scores 10 min after antigen challenge. In addition, eosinophil influx in airway mucosa, and ECP concentrations in nasal lavage fluids were reduced (Vancheri et al., 2001). Moreover, heparin prevents the nasal mucosa mast cell degranulation induced by adenosine monophosphate (Zeng et al., 2004).

4.2.10. Phototherapy
Ultraviolet (UV) light has been shown to exert both local and systemic immunosuppression (Salo et al., 2000; Duthie et al., 2000) and has been widely used for decades in the therapy of various skin diseases. The major mechanisms for UV irradiation-induced immunosuppression involves induction of apoptosis in infiltrating T cells, reductions in the number of dendritic cells and their function, and induction of immunosuppressive cytokines such as IL-10 in the skin (Garssen & van Loveren, 2001; Nghiem et al., 2002). In addition, UV irradiation inhibits histamine release from mast cells in vitro and in vivo (Gollhausen et al., 1985; Danno et al., 1988). Recently, the immunosuppressive action of UV radiation has been investigated in allergic rhinitis. In a clinical study, intranasal irradiation with the 308 nm xenon chloride (XeCl) ultraviolet-B laser and irradiation with a combination of ultraviolet-B (UVB), ultraviolet-A (UVA) and visible light (VIS) had a beneficial therapeutic effect in allergic rhinitis (Csoma et al., 2004; Koreck et al., 2005). Furthermore, intranasal therapy with 8-methoxypsoralen (8-MOP), plus UVA radiation therapy for 3 weeks inhibited the symptoms of allergic rhinitis (sneezing, rhinorrhea, itching and congestion; Csoma et al., 2006). These results suggest that intranasal phototherapy is effective in the treatment of allergic rhinitis.

5. Drugs effects in animal models of allergic rhinitis

The actions of various putative mediators of the various responses seen in allergic rhinitis have been tested on different animals with allergic rhinitis including guinea pigs, rats, mice, dogs and pigs. Among the mediators that have been tested, histamine, leukotrienes (LTB4, LTC4 and LTD4), cytokines, NO, thromboxane (TXA2 and TXB2) and kinins have mostly been studied. These mediators and their antagonists have been applied to mimic or block either acute, late or both phases of allergic rhinitis. In one clinical study, intranasal heparin significantly reduced symptom scores 10 min after antigen challenge. In addition, eosinophil influx in airway mucosa, and ECP concentrations in nasal lavage fluids were reduced (Vancheri et al., 2001). Moreover, heparin prevents the nasal mucosa mast cell degranulation induced by adenosine monophosphate (Zeng et al., 2004).

4.2.10. Phototherapy
Ultraviolet (UV) light has been shown to exert both local and systemic immunosuppression (Salo et al., 2000; Duthie et al., 2000) and has been widely used for decades in the therapy of various skin diseases. The major mechanisms for UV irradiation-induced immunosuppression involves induction of apoptosis in infiltrating T cells, reductions in the number of dendritic cells and their function, and induction of immunosuppressive cytokines such as IL-10 in the skin (Garssen & van Loveren, 2001; Nghiem et al., 2002). In addition, UV irradiation inhibits histamine release from mast cells in vitro and in vivo (Gollhausen et al., 1985; Danno et al., 1988). Recently, the immunosuppressive action of UV radiation has been investigated in allergic rhinitis. In a clinical study, intranasal irradiation with the 308 nm xenon chloride (XeCl) ultraviolet-B laser and irradiation with a combination of ultraviolet-B (UVB), ultraviolet-A (UVA) and visible light (VIS) had a beneficial therapeutic effect in allergic rhinitis (Csoma et al., 2004; Koreck et al., 2005). Furthermore, intranasal therapy with 8-methoxypsoralen (8-MOP), plus UVA radiation therapy for 3 weeks inhibited the symptoms of allergic rhinitis (sneezing, rhinorrhea, itching and congestion; Csoma et al., 2006). These results suggest that intranasal phototherapy is effective in the treatment of allergic rhinitis.

5. Drugs effects in animal models of allergic rhinitis

The actions of various putative mediators of the various responses seen in allergic rhinitis have been tested on different animals with allergic rhinitis including guinea pigs, rats, mice, dogs and pigs. Among the mediators that have been tested, histamine, leukotrienes (LTB4, LTC4 and LTD4), cytokines, NO, thromboxane (TXA2 and TXB2) and kinins have mostly been studied. These mediators and their antagonists have been applied to mimic or block either acute, late or both phases of allergic rhinitis. Analogous studies have been performed in humans and generally there is reasonable concordance between the effects seen in laboratory animals and those seen in humans. Thus the various mediators found to be involved in producing allergic rhinitis symptoms in the animals mimic the situation found in humans. Table 1 summaries the effects of various drugs and the roles of inflammatory mediators involved in allergic signs and symptoms in different experimental animals. The actions of these mediators have been deduced either from
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mediator (targeted by the drug)</th>
<th>Effect (alleviated by the drug)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea pig</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepyramine, pranlukast</td>
<td>histamine (H1), CysLT</td>
<td>sneezing, nasal obstruction</td>
<td>Mizutani et al., 2003</td>
</tr>
<tr>
<td>LY303870 (NK1 receptor antagonist), SR48968 (NK2 receptor antagonist), CGRP (8-37) (CGRP-1 receptor antagonist)</td>
<td>histamine (H1), pLTs</td>
<td>sneezing, nasal obstruction</td>
<td>Kaise et al., 1998</td>
</tr>
<tr>
<td>Olopatadine</td>
<td>histamine (H1), TXA2, histamine (H1)</td>
<td>sneezing, nasal obstruction</td>
<td>Mizutani et al., 2001</td>
</tr>
<tr>
<td>AIBT-491 (PAF antagonist)</td>
<td>TXA2, histamine (H1)</td>
<td>sneezing, nasal obstruction</td>
<td>Albert et al., 1998</td>
</tr>
<tr>
<td>Mepyramine, naphazoline (α-adrenergic)</td>
<td>histamine (H1)</td>
<td>nasal obstruction</td>
<td>Mizutani et al., 1999</td>
</tr>
<tr>
<td>Flutropium</td>
<td>histamine (H1) + other allergy mediators</td>
<td>sneezing, nasal obstruction</td>
<td>Mizutani et al., 1999</td>
</tr>
<tr>
<td>Oxatomide</td>
<td>tachykinins</td>
<td>sneezing, nasal obstruction</td>
<td>Kaise et al., 1997</td>
</tr>
<tr>
<td>TMRG688 (5-lipooxygenase inhibitor)</td>
<td></td>
<td>sneezing, nasal obstruction</td>
<td>Shizawa et al., 1997</td>
</tr>
<tr>
<td>Mepyramine</td>
<td>histamine (H1)</td>
<td>sneezing, nasal obstruction</td>
<td>Nabe et al., 2001</td>
</tr>
<tr>
<td>Pranlukast</td>
<td>CySLT</td>
<td>nasal obstruction</td>
<td>McLeod et al., 2002</td>
</tr>
<tr>
<td>Fexofenadine, terfenadine</td>
<td>LTD4, NO</td>
<td>sneezing, nasal obstruction</td>
<td>Sakairi et al., 2003</td>
</tr>
<tr>
<td>Mepyramine, chlorpheniramine</td>
<td>histamine (H1)</td>
<td>nasal obstruction</td>
<td>Mizutani et al., 2001</td>
</tr>
<tr>
<td>Oxatomide</td>
<td></td>
<td>sneezing, nasal obstruction</td>
<td>Imai et al., 2001</td>
</tr>
<tr>
<td>Rat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone fluticasone</td>
<td>Cytokines</td>
<td>sneezing, nasal obstruction</td>
<td>Sugimoto et al., 2000a</td>
</tr>
<tr>
<td>Hlorpheniramine, ketotifen, astemizole, epinastine</td>
<td>histamine (H1)</td>
<td>nasal obstruction</td>
<td>Sugimoto et al., 2000b</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>CySLT</td>
<td>sneezing, nasal obstruction</td>
<td>Shimizu et al., 2000</td>
</tr>
<tr>
<td>AIBT-491 (PAF antagonist), mepyramine, methysergide, N-79175 (5-lipooxygenase inhibitor)</td>
<td>histamine (H1), TXA2, pLTs</td>
<td>nasal obstruction</td>
<td>Albert et al., 1998</td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cell epitope (P2-246-259)</td>
<td>histamine (H1), cytokines (IFN-gamma, IL-2, IL-4)</td>
<td>sneezing, nasal obstruction</td>
<td>Murasugi et al., 2005</td>
</tr>
<tr>
<td>Cetirizine, epinastine, ramatroban, zafirlukast</td>
<td>histamine (H1), IL-5, Mediators from basophils, eosinophils, CD4+ cells, IL4 and IL5 cells</td>
<td>sneezing, nasal obstruction</td>
<td>Iwasaki et al., 2003</td>
</tr>
<tr>
<td>Dog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zileuton</td>
<td>LTD4, NO</td>
<td>sneezing, nasal obstruction</td>
<td>Cardell et al., 2000</td>
</tr>
<tr>
<td>Phenylephrine, α-pseudoephedrine</td>
<td>histamine (H1)</td>
<td>nasal obstruction</td>
<td>Tiunakov et al., 2003</td>
</tr>
<tr>
<td>NPY 24-36 (selective NPY Y2 receptor agonist)</td>
<td>histamine (H1)</td>
<td>nasal obstruction</td>
<td>Revington et al., 1997</td>
</tr>
<tr>
<td>α-pseudoephedrine, chlorpheniramine</td>
<td></td>
<td>nasal obstruction</td>
<td>Rudolph et al., 2003</td>
</tr>
<tr>
<td>Pig</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelastine, levocabastine, beclomethasone, ipratropium</td>
<td>CGRP, histamine (H1), cytokines, pLTs, ACh</td>
<td>mediates ILK and histamine induced nasal obstruction</td>
<td>Malis et al., 2001</td>
</tr>
</tbody>
</table>

Cys Ts: cysteinyl leukotrienes; pLTs, peptideyl leukotrienes; PAF: platelet activating factor; TXA2, thromboxane A2; LT, leukotriene; EPO: eosinophil peroxidase; TXB2, thromboxane B2; eNOS, endothelial nitric oxide synthase; NO: nitric oxide; IFN-gamma, interferon gamma; IL: interleukin; TNF-a: tumor necrosis factor alpha; AHR: airway hyperresponsiveness; NPY: neuropeptide Y; CGRP: calcitonin gene related peptide.
their direct application, or via the action of the appropriate mediator antagonists.

It is clear from such findings that the guinea pig has been the most used species. In this species the symptoms of allergic rhinitis appear to be alleviated by those drugs that also alleviate the same symptoms seen in humans suffering from allergic rhinitis. Thus H1 antihistamines, leukotriene antagonists and steroids all alleviate allergic rhinitis in humans and guinea pigs. Alpha adrenoceptor agonists are used routinely to alleviate the nasal congestion of rhinitis in humans but such drugs have rarely been investigated for such actions in laboratory animals, even in guinea pigs.

While there is a respectable body of evidence from many studies in guinea pigs, the number of analogous studies in other laboratory species is limited. Thus there are insufficient studies in rats, mice and dogs to warrant comparing the profile of actions of the drugs used in man to treat allergic rhinitis with their actions in these species. As a result of all of the work conducted in guinea pigs, compared with the body of work in other species, it is probably best to assume that, until further evidence refutes such an assumption, the actions of drugs in allergic rhinitis in guinea pigs best represents the situation in humans.

In conclusion, despite our understanding of allergic rhinitis we are still some way from understanding all of the mechanisms involved in all of the various stages of the disease, from the mechanisms that result in hypersensitivity, to the mechanisms involved in all the associated pathological changes. It is not surprising therefore that the ideal drug treatment for this disease has yet to be discovered. There are many possible molecular sites at which to theoretically attack the underlying pathology but the very existence of such a large number of sites argues for the necessity for simultaneous actions at a number of sites.

In the absence of a single molecular mechanism being responsible for the condition, we have to be content to try and identify the most critical sites.

References


on a guinea pig model of asthma. Am J Respir Crit Care Med 167(2), 185–192.


