ABSTRACT—Many kinds of drugs are used for the treatment of allergic diseases. Glucocorticoids are the most efficacious drugs and widely used for the treatment of allergic diseases. Recently, effectiveness of inhaled glucocorticoids for the treatment of bronchial asthma has been established. Beclomethasone dipropionate and fluticasone propionate, which are degraded easily after absorption, are applied by inhalation. Histamine is one of the most important mediators in allergic reactions and antihistamines have widely been applied for the treatment of allergic skin diseases. In Japan, over 20 antiallergic drugs, such as mediator release inhibitors, mediator antagonists and mediator synthesis inhibitors, have been developed. Recently developed compounds such as pranlukast and suplatast are very effective. To relieve the asthmatic attack, bronchodilators such as β₂-adrenoceptor agonists, theophylline and anti-cholinergic drugs are used. Clinical application of tacrolimus ointment has just started for the treatment of atopic dermatitis. Recently the number of allergic patients has increased. The onset and development of allergic diseases are considered to be dependent on both the genetic factors and the environmental factors. For the successful treatment of patients with allergic diseases, it is also important to consider the control of environmental factors.

Keywords: Glucocorticoid, Antihistamine, Antiallergic drug, Bronchodilator, β₂-Adrenoceptor agonist, Theophylline, Tacrolimus

The fundamental feature of the immune system is to distinguish foreign from self. The immune system is considered to have been developed against invasive microorganisms as one of the host defense mechanisms, and it evokes a variety of responses to eliminate invading microorganisms. In the immune response, lymphocytes play pivotal roles. Lymphocytes possess a capacity to specifically recognize any kind of foreign antigen and trigger a series of reactions to eliminate the antigen in concert with other cell types such as macrophages. Furthermore, a fraction of activated lymphocytes survives for a long period as memory cells, which facilitates the elimination of the same foreign antigen upon the following invasion.

The immune system originally works protective for the host, however, it also sometimes causes disadvantageous effects on the host. The overexpressed immune response against some foreign antigens, which is disadvantageous to the host, is called allergy. It is also called hypersensitivity, because healthy individuals do not respond to the allergen potently but susceptible individuals do severely. Genetic factors are considered to contribute to the susceptibility. The underlying mechanism of allergy is, therefore, identical to that of the protective immunity. Non-toxic materials such as pollens, dust mites and some foods sometimes cause allergy. The number of patients suffering from allergic diseases has increased tremendously in recent years, and many kinds of drugs have been employed for the treatment of the diseases. In this review, we briefly summarize the drugs used for the treatment of allergic diseases.

Drugs for the treatment of allergic diseases

Most allergic diseases such as bronchial asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis are caused by the exposure to allergens commonly present in our environment. Repeated exposure to allergens develops a variety of symptoms accompanied by an increased sensitivity. To prevent the onset and development of allergic diseases, therefore, complete avoidance from the allergens is the best way, although it may be impossible. Because allergen exposure triggers immunological responses resulting in allergic symptoms, drugs inhibiting any point of the process can attenuate the resultant symptoms. Many kinds of drugs such as glucocorticoids, antihistamines, antiallergic...
drugs and bronchodilators are clinically employed for the treatment of the allergic diseases to reduce the symptoms.

**Glucocorticoids**

Glucocorticoids exhibit potent anti-inflammatory, anti-allergic and immunosuppressive actions and are the most efficacious drugs for the treatment of allergic diseases, although they sometimes cause severe adverse effects.

The glucocorticoid receptor present in the cytoplasm is a ligand-operated transcription factor. Glucocorticoid binding activates the receptors to facilitate the translocation from the cytoplasm to the nucleus. The activated glucocorticoid receptor regulates the gene expression in two ways (Fig. 1). Firstly, glucocorticoid receptor binds to its responsive elements on DNA and regulates the gene expression directly. Secondly, glucocorticoid receptor interacts with other transcription factors such as AP-1, NF-κB and NF-AT to modulate their transcription activities (1, 2).

Glucocorticoids thus regulate the protein synthesis both upward and downward, which explains the physiological and pharmacological actions of glucocorticoids.

Allergen exposure triggers immunological responses, including immune and inflammatory cell activation, and generation of various mediators such as cytokines, chemokines and adhesion molecules. Glucocorticoids inhibit the generation of the molecules and prevent the cell activation (3, 4). Furthermore, allergen stimulation induces some enzymes responsible for the generation of inflammatory mediators such as nitrogen oxide, leukotrienes and prostaglandins. Glucocorticoids inhibit the induction of the enzymes (5, 6). Thus glucocorticoids collectively exhibit potent anti-inflammatory, antiallergic and immunosuppressive actions that contribute to the treatment of allergic diseases.

Glucocorticoids have been the most important drugs for the treatment of allergic skin diseases, especially atopic dermatitis. Glucocorticoids are usually applied topically as ointments. On the other hand, bronchial asthma has recently been recognized as chronic airway inflammation because of the effectiveness of inhaled beclomethasone dipropionate. Based on this concept, glucocorticoids have become more important for the treatment of bronchial asthma than ever before. Now, inhaled glucocorticoids are widely applied to control the airway inflammation in mild to moderate asthmatic patients, although oral glucocorticoids are essential for severe patients (7).

Glucocorticoids are well known to cause severe adverse effects when used at high doses for a long period. To prevent systemic adverse effects, glucocorticoids are recommended to use locally. Furthermore, recently developed compounds such as beclomethasone, budesonide and fluticasone are beneficial for the local application, because they exhibit a potent anti-inflammatory action locally but easily degraded after absorption (8, 9). Although glucocorticoids are very important and efficacious drugs for the treatment of allergic diseases, they should be used carefully to prevent systemic adverse effects. Chemical structures of some glucocorticoids are indicated in Fig. 2.

**Antihistamines**

Histamine H1-receptor antagonists are usually called antihistamines. Mast cells possess high affinity IgE receptors on their surface and fix IgE molecules via the receptors. In type I allergic reactions, mast cells are activated by allergens through aggregation of cell-bound specific IgE to release chemical mediators. Mast cells are also activated by a variety of stimuli as well as the type I allergic mechanism. Mast cells store large amount of histamine and release it upon stimulation. Therefore, histamine plays an important role in type I allergy-related symptoms, and antihistamines have been very important drugs and widely applied for the treatment of allergic diseases, especially allergic skin diseases. Antihistamines are very efficacious to relieve the symptoms of urticaria, rhinitis and conjunctivitis. In contrast, although participation of histamine in bronchial asthma has been suspected for a long period, classical antihistamines sometimes worsened the symptoms of bronchial asthma.

The disadvantageous effects of classical antihistamines may be ascribed to their anti-cholinergic and local anesthetic actions. Recently, many new antihistamines with a higher selectivity have been developed. The depressive effects of the central nervous system are also reduced in these new drugs. Some of the newly generated antihistamines are applied for the treatment of bronchial asthma and they are classified as antiallergic drugs.

Antihistamines are sometimes classified into the first and the second generations (Table 1). Antihistamines of the
first generation involve classical drugs and those of the second generation involve newer drugs with low central nervous system side effects. On the other hand, antihistamines could be divided into two groups according to their efficacy for bronchial asthma. These two classifications do not seem to coincide well. Newly generated antihistamines classified as antiallergic drugs might possess additional properties beneficial for the treatment of allergic diseases, even though their selectivity to histamine H1 receptors is heightened.

**Antiallergic drugs**

Disodium cromoglycate reported in 1967 is the first antiallergic drug (10, 11). The prophylactic effect of disodium cromoglycate on asthmatic attack was firstly confirmed in humans and then the mechanism of action was examined in experimental animals. Disodium cromoglycate potently inhibits IgE-mediated mediator release from rat mast cells and human lung mast cells, whereas it never inhibits human cutaneous mast cell activation. As disodium cromoglycate is hardly absorbed from the gastrointestinal tract, its fine dry powders are inhaled for the prophylactic treatment of asthmatic patients. The discovery of disodium cromoglycate stimulated the development of analogous antiallergic drugs, which could be taken orally, in Japan. At present, over 20 compounds, such as mediator release inhibitors, mediator antagonists and mediator synthesis inhibitors, have been established as antiallergic drugs and are clinically employed for the treatment of allergic diseases (Table 2).

Most drugs inhibit the mediator release from inflammatory cells and show antagonism against inflammatory mediators. In general, the effectiveness of the antiallergic drugs is recognized after the treatment for 2–4 weeks, and the drugs do not relieve the established symptoms. Antiallergic drugs are usually applied prophylactically.

Tranilast is an orally active antiallergic drug developed after disodium cromoglycate (12, 13). It inhibits mediator release from mast cells without antagonizing histamine. It is interesting to note that tranilast is also effective for inhibiting the formation of keloid, and the intimal hyperplasia after percutaneous transluminal coronary angioplasty. These actions of tranilast may be ascribed to the inhibition of cytokine production such as transforming growth factor-β1.

A group of antiallergic drugs possess a potent antihistaminic property. These antihistamines could be applied for the treatment of bronchial asthma, although the use of clas-
sical antihistamines is prohibited as mentioned above. Anti-
allergic antihistamines may possess additional properties
such as mediator release inhibition and antagonism against
other mediators, which are beneficial for the treatment of
allergic diseases. Furthermore, second generation antihista-
mines possess a reduced depressing effect on the central
nervous system. The antihistaminic action of antiallergic
antihistamines may be exhibited promptly, which may be a
benefit for these drugs.

Thromboxane A$_2$ is a labile mediator derived from the
cyclooxygenase pathway of arachidonic acid metabolism.
Thromboxane A$_2$ potently activates platelets and contracts
smooth muscles such as artery and bronchial smooth
muscle. Thromboxane A$_2$ synthesis inhibitor, ozagrel (14),
and receptor antagonist, seratrodast (15), are established as
antiallergic drugs, indicating that thromboxane A$_2$ is an
important mediator in allergic diseases. In the body, the action
of thromboxane A$_2$ is antagonized and regulated by that of
prostacyclin. Ibudilast potentiates the action of prostacyclin
(16).

In allergic reactions, cysteinyl leukotrienes are generated
in the 5-lipoxygenase pathway of arachidonic acid metabol-
ism. Cysteinyl leukotrienes cause potent contraction of
smooth muscles and increase vascular permeability. Cys-
teinyl leukotrienes, previously known as slow reacting sub-
stance of anaphylaxis, have been putative mediators for the
bronchoconstriction in bronchial asthma. Recently, an LT1
cysteinyl leukotriene-receptor antagonist, pranlukast (17),
has been developed as an antiallergic drug. Pranlukast is
one of the most efficacious antiallergic drugs for the treat-
ment of bronchial asthma at present and is expected to re-
duce the dose of glucocorticoid necessary to control airway
inflammation. Similar LT1 cysteinyl leukotriene-receptor
antagonists, zafirlukast (18) and montelukast (19), have
also been developed after pranlukast and applied clinically
in Europe and America. They will be available in Japan in
the near future. Furthermore, a 5-lipoxygenase inhibitor, zileuton (20), and a 5-lipoxygenase activating protein inhib-
itor, BAY X 1005 (21), are now under investigation. They
may also be available in the future.

Suplatast (22) is also a very efficacious antiallergic drug.
Suplatast is developed as an inhibitor for mediator release
and IgE production. It has been confirmed that suplatast re-
duces the IgE production through inhibiting the induction
of interleukin-4, which is an important factor for IgE pro-
duction (23).

**Bronchodilators**

Although glucocorticoids are used to control the airway
inflammation for the treatment of bronchial asthma, to
relieve the asthmatic attack bronchodilators such as $\beta_2$-
adrenoceptor agonists, theophylline and anti-cholinergic
drugs (Table 3) are employed.

Stimulation of $\beta_2$-adrenoceptors is well known to cause
the elevation of intracellular cyclic AMP levels, which
leads to the smooth muscle relaxation. $\beta_2$-Adrenoceptor
agonists are very efficacious to relieve the asthmatic attack.
As non-selective $\beta_2$-adrenoceptor agonists stimulate both
$\beta_1$- and $\beta_2$-receptors, the stimulating effect on $\beta_1$-receptors

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overuse of bronchodilators. $\beta_2$-Adrenoceptor agonists also cause stimulation of membrane Na,K-ATPase resulting in hypokalemia (24). Although the bronchodilating effect of $\beta_2$-adrenoceptor agonists is very potent, the drugs sometimes cause increased bronchial hypersensitivity. Furthermore, overseuse of $\beta_2$-adrenoceptor agonists is suggested to be a cause of asthma death. Although the precise mechanism for causing asthma death is not yet defined, sufficient control of airway inflammation by glucocorticoids and proper use of $\beta_2$-adrenoceptor agonists should be strictly adhered to prevent asthma death. In most patients, $\beta_2$-adrenoceptor agonists are inhaled on demand or regularly.

$\beta_2$-Adrenoceptor agonists inhibit IgE-mediated mediator release from mast cells (25). They produce inhibition far more potent than any of the antiallergic drugs indicated in Table 2. It is interesting to note that, however, anti-inflammatory and/or antiallergic effects of $\beta_2$-adrenoceptor agonists are not detected clinically except for long-acting drugs, such as salmeterol (26) and formoterol (27). These drugs seem less tachyphylactic than other agonists. Salmeterol, a partial agonist on the $\beta_2$-adrenoceptors, will be available soon.

Theophylline has been believed to cause bronchodilating and antiallergic effects through inhibiting phosphodiesterase activity. However, research on phosphodiesterase isozyme inhibitors to develop new drugs has not succeeded yet. Adenosine antagonistic property of theophylline may be important for its action (28). The mechanism of action of theophylline is not yet elucidated. It is important to keep the plasma concentration of theophylline in an effective and safe range strictly to prevent adverse effects. Recently it has become easy to control the plasma concentration by using some new preparations that release the drug slowly.

Cholinergic stimulation causes a contraction of bronchial smooth muscle, and anti-cholinergic drugs prevent the contraction. Although some anti-cholinergic drugs are used as inhalants to relieve the asthmatic attack, the efficacy is less potent than $\beta_2$-adrenoceptor agonists.

**Tacrolimus**

Tacrolimus, a product of a fungus, is a new immunosuppressive drug used to prevent allograft rejection (29) (Fig. 3). Although the major action of tacrolimus is to inhibit T cell activation, antiallergic effects have also been recognized. Now, tacrolimus ointment is available for the treatment of atopic dermatitis. Basic research data suggest a high effectiveness of tacrolimus ointment (30), and the clinical efficacy will be established in a few years.

**Conclusion**

The number of patients suffering from allergic diseases has increased in recent years. The number of adult patients with serious atopic dermatitis has also increased. To overcome the allergic diseases, we need effective tools to treat the diseases, and the drugs mentioned above may not be sufficient. Platelet-activating factor, prostaglandin D$_2$ (31), mast cell proteases and IgE may be interesting targets for the development of unique antiallergic drugs, and the effectiveness of humanized anti-IgE antibodies has already been confirmed clinically (32). Furthermore, in the future, immunological methods to induce unresponsiveness to particular allergens will be developed. The genetic factors, which determine the susceptibility for allergy, may become targets for the treatment of allergic diseases.

Allergic diseases are considered to be caused in individuals with some genetic factors under the influence of environmental factors. The recent increase in the number of allergic patients has demonstrated that many individuals possess the genetic factors and that our environment is filled with allergens and adjuvants facilitate the onset and development of allergic diseases. On the other hand, it has also been demonstrated that all individuals possessing the genetic factors do not always suffer from allergic diseases if the other factors are properly regulated. It suggests, therefore, that it is possible to induce and maintain a symptom-free condition in patients. Not only for preventing the increase in the number of allergic patients but also for the successful treatment for the allergic diseases, we should also consider the control of our environmental factors.

**REFERENCES**


