16.1: Immediate Hypersensitivities: Type I

Skills to Develop

1. Describe the mechanism for Type I (IgE-mediated) hypersensitivity and give 3 examples. State how they are treated symptomatically.

2. Describe how desensitization (allergy) shots work to lessen the severity of Type I hypersensitivities.

3. Briefly describe how monoclonal antibodies against the Fc portion of IgE may someday be used to prevent Type I allergies.

4. When a person has hay fever, common symptoms include runny eyes, runny nose, swollen sinuses, and difficulty in breathing. In terms of humoral immunity, discuss the mechanism behind these symptoms. Also state the reason for giving antihistamines.

Type I (IgE-mediated or anaphylactic-type) is the most common type of hypersensitivity, seen in about 20% of the population. IgE is made in response to an allergen (Figure 1 and Figure 2). In allergic individuals, the levels of IgE may be thousands of times higher than in those without allergies. Possibly this is due to a higher number of T\textsubscript{H}2 cells which produce IL-4, a cytokine that can increase production of IgE, and a lower number of T\textsubscript{H}1 cells that produce gamma-interferon, a cytokine that decreases IgE production.
**Figure 1.1.1**: Type-I Hypersensitivity: Production of IgE in Response to an Allergen. The allergen enters the body and is recognized by sIg on a B-lymphocyte. The B-lymphocyte proliferates and differentiates into plasma cells that produce and secrete IgE against epitopes of the allergen.

**Figure 2**: Type-I Hypersensitivity, Step-2. The plasma cells produce and secrete IgE which binds to receptors on mast cells and basophils.

The Fc portion of IgE binds to the surface of mast cells and basophils (Figure 3). When the allergen cross-links the Fab portions of the mast cell-bound IgE, this triggers histamine release by the mast cell, a process called degranulation, and the synthesis of other inflammatory mediators such as platelet-activating factor, leukotrienes, bradykinins, prostaglandins, and cytokines that contribute to inflammation (Figure 4). These agents cause the early phase of allergic reactions that appears within minutes after exposure to the antigen.
Figure 3: Type-I Hypersensitivity, Step-3. Allergen cross reacting with IgE on mast cell.

Figure 4: Type-I Hypersensitivity, Step-4. The next time the allergen enters the body, it cross-links the Fab portions of the IgE bound to the mast cell. This triggers the mast cell to degranulate, that is, release its histamine and other inflammatory mediators. The inflammatory mediators are now able to bind to receptors on target cells which leads to dilation of blood vessels, constriction of bronchioles, excessive mucus secretion, and other symptoms of allergy.

Flash animation showing the mechanism behind Type-1 hypersensitivity.

html5 version of animation for iPad showing the mechanism behind Type-1 hypersensitivity.
Late phase allergic reactions may begin several hours after exposure to antigen. It is thought that basophils play a major role here. Cell-bound IgE on the surface of basophils of sensitive individuals binds a substance called histamine releasing factor (possibly produced by macrophages and B-lymphocytes) causing further histamine release.

The inflammatory agents released or produced cause the following:

a. Dilation of blood vessels. This causes local redness (erythema) at the site of allergen delivery. If dilation is widespread, this can contribute to decreased vascular resistance, a drop in blood pressure, and shock.

b. Increased capillary permeability. This causes swelling of local tissues (edema). If widespread, it can contribute to decreased blood volume and shock.

c. Constriction of bronchial airways. This leads to wheezing and difficulty in breathing.

d. Stimulation of mucous secretion. This leads to congestion of airways.

e. Stimulation of nerve endings. This leads to itching and pain in the skin.

In a systemic anaphylaxis, the allergen is usually picked up by the blood and the reactions occur throughout the body. Examples include severe allergy to insect stings, drugs, and antisera. With a localized anaphylaxis, the allergen is usually found localized in the mucous membranes or the skin. Examples include allergy to hair, pollen, dust, dander, feathers, and food.

Type I hypersensitivity is treated symptomatically with such agents as:

a. Epinephrine. Epinephrine relaxes smooth muscle, constricts blood vessels, and stimulates the heart. It is used for severe systemic reactions.

b. Histamine H1-receptor antagonists. Antihistamines block the binding of histamine to histamine H1-receptors on target cells, e.g., loratadine, fexofenadine, cetirizine.

c. Beta2- agonists. Increase cyclic AMP levels leading to relaxation of bronchial smooth muscles and inhibit mast cell degranulation, e.g., albuterol, salmeterol, formoterol.

d. Leukotriene receptor antagonists. Block smooth muscle constriction, e.g., pranlukast.

e. Sodium cromoglycate. Sodium cromoglycate prevents mast cells from releasing histamines.

f. Nasally administered steroids. Corticosteroids are potent antiinflammatory agents.

Severity may be reduced by desensitization shots (allergy shots). It is thought that when very dilute allergen is given by injection, it stimulates the production of IgG and IgA. IgG and IgA then act as blocking antibodies to bind and neutralize much of the allergen in secretions before it can bind to the deeper cell-bound IgE on the mast cells in the connective tissue. The shots also appear to suppress production of IgE by inducing tolerance and/or by activating T8-suppressor cells.
A new experimental approach to treating and preventing Type-I hypersensitivity involves giving the person with allergies injections of monoclonal antibodies that have been made against the Fc portion of human IgE. This, in turn, blocks the attachment of the IgE to the Fc receptors on mast cells and basophils and the subsequent release of histamine by those cells upon exposure to allergen. In addition, the anti-IgE binds to IgE-producing B-lymphocytes causing apoptosis. The monoclonal antibody is a humanized hybrid molecule consisting of a mouse binding (Fab) portion attached to a human constant (Fc) portion and is known as rhuMab (recombinant human monoclonal antibody).

**Summary**

1. Immediate hypersensitivities refer to humoral immunity (antigen/antibody reactions) causing harm.
2. During Type I (IgE mediated or anaphylactic-type) hypersensitivity, IgE is made in response to an allergen.
3. In allergic individuals, the levels of IgE may be thousands of times higher than in those without allergies.
4. The Fc portion of IgE binds to the surface of mast cells and basophils and when the allergen subsequently cross-links the Fab portions of the mast cell-bound IgE, this triggers the release of inflammatory mediators such as histamine release by the mast cell, as well as the synthesis of other inflammatory mediators such as platelet-activating factor, leukotrienes, bradykinins, prostaglandins, and cytokines that contribute to inflammation.
5. The inflammatory agents then lead to dilation of blood vessels (redness or erythema), increased capillary permeability (swelling or edema), constriction of bronchial airways (wheezing and difficulty in breathing), stimulation of mucous secretion (congestion of airways), and stimulation of nerve endings (itching and pain in the skin).
6. In a systemic anaphylaxis, the allergen is usually picked up by the blood and the reactions occur throughout the body and can lead to shock. Examples include severe allergy to insect stings, drugs, and antisera.
7. With a localized anaphylaxis, the allergen is usually found localized in the mucous membranes or the skin. Examples include allergy to hair, pollen, dust, dander, feathers, and food.
8. Type I hypersensitivity is treated symptomatically with anti-inflammatory agents such as antihistamines and epinephrine.
9. Desensitization shots (allergy shots) are thought to stimulate the production of IgG and IgA which then act as blocking antibodies to bind and neutralize much of the allergen in secretions before it can bind to the deeper cell-bound IgE on the mast cells in the connective tissue.
10. Monoclonal antibodies that have been made against the Fc portion of human IgE have also been used in treatment. They block the attachment of the IgE to the Fc receptors on mast cells and basophils and the subsequent release of histamine by those cells upon exposure to allergen.

**Questions**

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.
1. Describe the mechanism for Type I (IgE-mediated) hypersensitivity and give two examples. State how they are treated symptomatically. (ans)

2. When a person has hay fever, common symptoms include runny eyes, runny nose, swollen sinuses, and difficulty in breathing. In terms of humoral immunity, discuss the mechanism behind these symptoms. Also state the reason for giving antihistamines and describe how allergy shots may lessen the severity of this type of hypersensitivity. (ans)

3. Researchers are hoping that the injection of monoclonal antibodies against IgE may someday be used to prevent virtually any Type I hypersensitivity. Explain. (ans)

Contributors

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