Type I Hypersensitivity reaction

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Unit IV (1)

Introduction

- The inappropriate immune response is termed as **hypersensitivity** or **allergy.**
- Although the word *hypersensitivity* implies an increased response, the response is not always heightened but may, instead, be an inappropriate immune response to an antigen.
- Hypersensitive reactions may develop either by humoral or cell-mediated responses.

Types-

1. **Immediate Hypersensitivity-** Because the symptoms are manifest within minutes or hours after a sensitized recipient encounters antigen. It is mediated by humoral branch initiated by antibody or antigen-antibody complexes

2. **Delayed type hypersensitivity (DTH)-** It is so named in recognition of the delay of symptoms until days after exposure.

Gell and Coombs Classification

- Hypersensitive reaction can be distinguished in to several forms depending on the effectors molecules generated in the course of the reaction.
- P. G. H. Gell and R. R. A. Coombs classified hypersensitive reactions are divided into four types.

1. Immediate hypersensitive reactions- This type of types of reaction occur within the humoral branch and are mediated by antibody or antigen-antibody complexes.

a. IgE-mediated (type I), - IgE antibodies, induce mast-cell degranulation with release of histamine and other biologically active molecules.

b. Antibody-mediated (type II),

c. Immune complex–mediated (type III).

2. **Delayed-type hypersensitivity reactions**- A fourth type of hypersensitivity depends on reactions within the cell-mediated branch, and is termed delayed-type hypersensitivity, or DTH (type IV).

- The effector molecules are various cytokines secreted by activated TH or TC cells.

Each type involves distinct mechanisms, cells, and mediator molecules.

1. IgE-Mediated (Type I) Hypersensitivity

- A type I hypersensitive reaction is induced by certain types of antigens referred to as **allergens.**
- Difference between the type I hypersensitive response from a normal humoral response is that in hypersensitivity reaction the plasma cells secrete IgE, which shows with high affinity to Fc receptors on the surface of tissue mast cells and blood basophils.
- Mast cells and basophils coated by IgE are said to be sensitized.
- A later exposure to the same allergen cross-links the membrane-bound IgE on sensitized mast cells and basophils, causing **degranulation** of these cells which causes the release of pharmacologically active mediators from the granules act on the surrounding tissues.
- The principal effects—vasodilation and smooth-muscle contraction may be either systemic or localized, depending on the extent of mediator release.

Components of Type I hypersensitivity reaction

A. **ALLERGANS**- Generally, IgE response generates against parasitic infections. Some persons, however, may have abnormality called **atopy,** a hereditary predisposition to the development of immediate hypersensitivity reactions against common environmental antigens.

- In atopic individuals, the IgE regulatory defects allow non-parasitic antigens to stimulate inappropriate IgE production that causes tissue damaging type I hypersensitivity.
- The term *allergen* refers specifically to nonparasitic antigens capable of stimulating type I hypersensitive responses in allergic individuals.
- It is partially genetically- it often runs in families.
- Atopic individuals have abnormally high levels of circulating IgE and also more than normal numbers of circulating eosinophils. These individuals are more susceptible to allergies such as hay fever, eczema, and asthma.

Common allergens associated with type I hypersensitivity

1. Proteins – Foreign serum, Vaccines
2. Foods- Nuts, Seafood, Eggs, Milk, Peas, beans
3. Plant pollens - Rye grass, Ragweed, Birch trees, Timothy grass
4. Insect Products- Bee venom, Wasp venom, Ant venom, Dust mites
5. Drugs- Penicillin, Sulfonamides, Local anesthetics, Salicylates
6. Mold spores
7. Animal hair and dander

- Most allergic IgE responses occur on mucous membrane surfaces in response to allergens that enter the body by either inhalation or ingestion.
- Allergenicity is a consequence of a complex series of interactions involving not only the allergen but also the dose, the sensitizing route, sometimes an adjuvant, and most important, as noted above the genetic constitution of the recipient.

B. REAGINIC ANTIBODY (IgE)- K. and T. Ishizaka in the mid-1960s showed that the biological activity of reaginic antibody (IgE) in a P-K test (PK reaction (K. Prausnitz and H. Kustner in 1921)- The local wheal and flare response that occurs when an allergen is injected into a sensitized individual is called the P-K reaction).

- Because the serum components responsible for the P-K reaction displayed specificity for allergen, they were assumed to be antibodies, but the nature of these P-K antibodies, or **reagins** could be neutralized by rabbit antiserum against whole atopic human sera but not by rabbit antiserum specific for the four human immunoglobulin classes known at that time (IgA, IgG, IgM, and IgD)
- In addition, when rabbits were immunized with sera from ragweed-sensitive individuals, the rabbit antiserum could inhibit (neutralize) a positive ragweed P-K test even after precipitation of the rabbit antibodies specific for the human IgG, IgA, IgM, and IgD isotypes.
- The Ishizakas called this new isotype IgE in reference to the E antigen of ragweed that they used to characterize it.

- Serum IgE levels in normal individuals fall within the range of 0.1–0.4 micro g/ml; even the most severely allergic individuals rarely have IgE levels greater than 1 micro g/ml.
- IgE was found to be composed of two heavy ε and two light chains with a combined molecular weight of 190,000. The higher molecular weight as compared with IgG (150,000) is due to the presence of an additional constant-region domain.
- This addition aldomain (CH4) contributes to an altered conformation of the Fc portion of the molecule that enables it to bind to glycoprotein receptors on the surface of basophils and mast cells.

C. BASOPHILLS AND MAST CELLS- The cells that bind IgE were identified by incubating human leukocytes and tissue cells with either 125I-labeled IgE myeloma protein or 125I-labeled anti-IgE. In both cases, autoradiography revealed that the labeled probe bound with high affinity to blood basophils and tissue mast cells.

Basophils –Granulocytes, 0.5%–1.0% of the circulating white blood cells, granulated cytoplasm stains with basic dyes, hence the name basophil.

- They have multilobed nucleus, few mitochondria, numerous glycogen granules, and electron-dense membrane-bound granules scattered throughout the cytoplasm that contain pharmacologically active mediators.

Mast cell- They are found throughout connective tissue, particularly near blood and lymphatic vessels, skin and mucous membrane surfaces of the respiratory and gastrointestinal tracts, contain high concentrations of mast cells.

- They have numerous membrane-bounded granules distributed throughout the cytoplasm, which, like those in basophils, contain pharmacologically active mediators.

- After activation, these mediators are released from the granules, resulting in the clinical manifestations of the type I hypersensitive reaction.
- Mast cells also secrete a large variety of cytokines that affect a broad spectrum of physiologic, immunologic, and pathologic processes.

D. IgE-BINDING Fc RECEPTORS- The reaginic activity of IgE depends on its ability to bind to a receptor specific for the Fc region of the ε heavy chain.

- Two classes of Fc£R been identified, designated Fc£RI and Fc£RII, which are expressed by different cell types and differ by 1000-fold in their affinity for IgE.

Mechanism of Type 1 hypersensitivity reaction

IgE Crosslinkage Initiates Degranulation

- Although mast-cell degranulation generally is initiated by allergen crosslinkage of bound IgE, a number of other stimuli can also initiate the process, including the anaphylatoxins (C3a, C4a, and C5a) and various drugs**.**

RECEPTOR CROSSLINKAGE

- IgE-mediated degranulation begins when an allergen crosslinks IgE that is bound (fixed) to the Fc receptor on the surface of a mast cell or basophil.
- In itself, the binding of IgE to Fc£RI apparently has no effect on a target cell. It is only after allergen crosslinks the fixed IgE-receptor complex that degranulation proceeds (monovalent allergens cant fix)

Primary and secondary mediators in type 1 hypersensitivity

Primary mediators	Effects
Histamine, heparin, Serotonin	Increased vascular permeability; smooth-muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases	Bronchial mucus secretion; degradation of blood-vessel basement membrane; Generation of complement split products
Secondary medators	**Effects**
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth-muscle contraction
Cytokines- IL-1 and TNF-alpha IL-2, IL-3, IL-4, IL-5, IL-6, TGF-, and GM-CSF	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells Various effects

Type I Reactions Can Be Systemic or Localized

1. **Systemic anaphylaxis-** Systemic anaphylaxis is a shock-like and often fatal state whose onset occurs within minutes of a type I hypersensitive reaction..

- This was the response observed by Portier and Richet in dogs after antigenic challenge.
- Systemic anaphylaxis can be induced in a variety of experimental animals and is seen occasionally in humans.
- Epinephrine is the drug of choice for systemic anaphylactic reactions. Epinephrine counteracts the effects of mediators such as histamine and the leukotrienes by relaxing the smooth muscles and reducing vascular permeability.
- Epinephrine also improves cardiac output, which is necessary to prevent vascular collapse during an anaphylactic reaction. In addition, epinephrine increases cAMP levels in the mast cell, thereby blocking further degranulation.

2. **Localized anaphylaxis (Atopy)-** It is limited to a specific target tissue or organ, often involving epithelial surfaces at the site of allergen entry.

- It is inherited and is called *atopy.*
- *Atopic* allergies, which afflict at least 20% of the population in developed countries, include a wide range of IgE-mediated disorders, including allergic rhinitis (hay fever), asthma, atopic dermatitis (eczema), and food allergies.