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An Overview of Hypersensitivity Reactions

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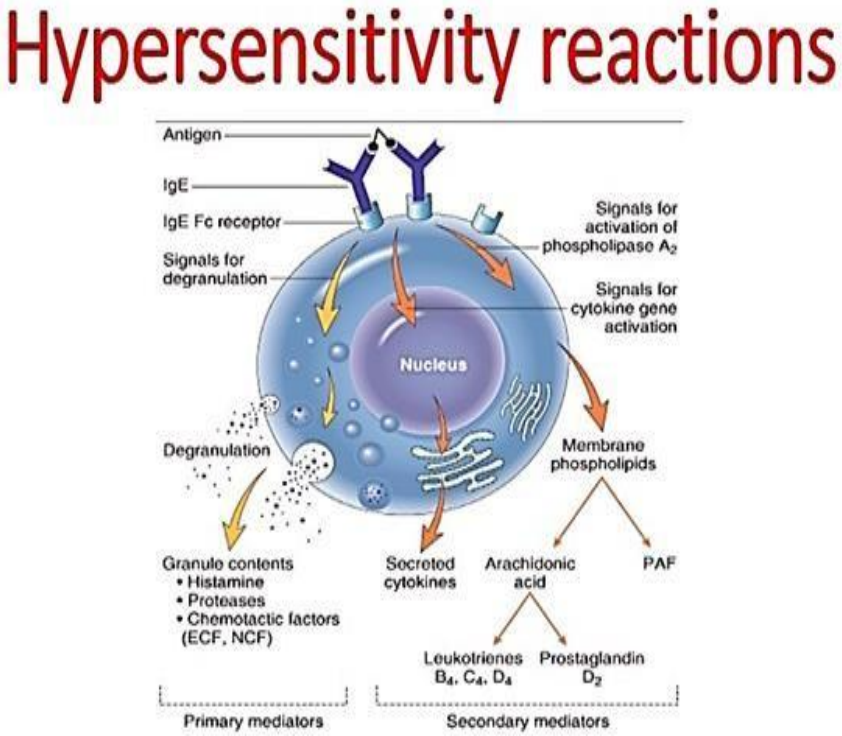
ABSTRACT: Hypersensitivity reaction (HR) is an exaggerated or inappropriate immune response against an antigen or allergen and is mediated by immunoglobulins or T lymphocytes. Hypersensitivity reaction refers to an elevated activity of normal immune system that damages the body tissues. It is characterized by abnormal immune responses (such as damaging, discomforting, & sometimes fatal). It is also termed as hypersensitivity reaction (HR). Hypersensitivity is a reaction in which the immune system responds in a negative way to a given antigen. This reaction can be caused by a combination of immune thrombocytopenia, hypersensitivity reactions, granulomatous allergies, sarcoidosis, and sarcomas. The best treatment for hypersensitivity is to initiate with a tuberculosis regimen which consist of rifampin, pyrazinamide, & isoniazid. The use of praziquantel drugs is often the preferred approach for managing anaphylaxis caused by Schistosomiasis. Asthma symptoms can be managed by using inhaled bronchodilators like salbutamol & corticosteroids in addition to oxygen therapy.

Keywords: Hypersensitivity reactions, Types, Cells, Immediate, Delayed Mode of action, Biological Effects, Etiology, Treatment & Management, Immunology



I. INTRODUCTION:

Hypersensitivity reactions (HR) refer to immune responses that are excessive or inappropriate against an antigen or allergen & carried out by either immunoglobulins or T-lymphocytes.

OR

An elevated activity of normal immune system that damages the body tissues is known as Hypersensitivity, also termed as Hypersensitivity reaction, this refers to inappropriate immune responses (like damaging, discomforting, & sometimes fatal). Hypersensitivity reactions are

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triggered by a pre-existing sensitized state of the host's immune system.

Types:-Hypersensitivity reactions have been classified into 'immediate' & 'delayed' types, based on the time required for a sensitized host to develop clinical reactions on re-exposure to antigen. The differences between immediate & delayed reaction are listed in the Table 1.1.

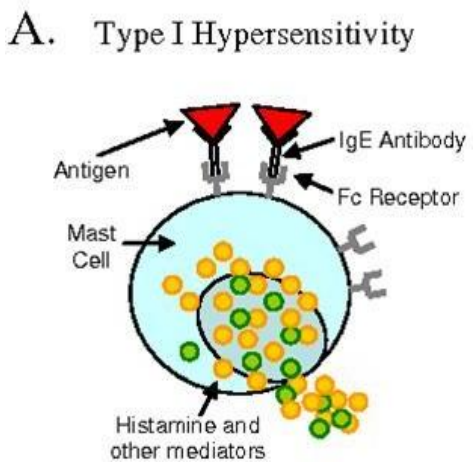
Immediate hypersensitivity	Delayed hypersensitivity
• Appears rapidly & lasts for a shorter time. • Induced by antigens or haptens. • Passive transfer possible with serum • Circulating antibodies present (antibody mediated reaction). • Desensitization easy but short lived. • Lesions are acute, exudation & fat necrosis. • Immediate hypersensitivity reactions develop in less than 12 hours.	• Appears slowly, last longer • Induced by infection, injection of antigens or haptens • Passive transfer possible with T-lymphocytes. • Circulating antibodies may be absent (cell mediated reaction). • It is difficult but long lasting. • Mononuclear cell collection around blood vessels. • Delayed hypersensitivity reactions develop in 24 to 48 hours.

Table 1.1: Differences between Immediate & Delayed Hypersensitivity

Coombs & Gell (1963) classified hypersensitivity reactions into five based on the different mechanism of pathogenesis:

- Type I: Anaphylactic, immediate, IgE or reagin dependent:
  e.g., anaphylaxis, atopy etc.
- Type II: Cytotoxic or cell stimulating:
  e.g., thrombocytopenia, hemolytic anemia etc.
- Type III: Immunocomplex or toxic complex:
  e.g., Arthus reaction, serum sickness etc.
- Type IV: Delayed or T-cell mediated:
  e.g., tuberculin type, contact dermatitis etc.
- Type V: Stimulatory or anti receptor:
  e.g., autoimmune orchitis in guinea pigs.

Type I, II, III hypersensitivity depend on the interaction of antigen with humoral antibodies & are known as immediate type reactions. Type IV hypersensitivity or delayed hypersensitivity is mediated by T-lymphocytes & macrophages shown in Table 1.2.



Type I or Anaphylactic Hypersensitivity:-

The most common hypersensitivity reaction is the type I hypersensitivity. Type I occur in two forms: the acute potentially fatal, systemic form called anaphylaxis & chronic or recurrent, nonfatal, typically localized form called atopy. To induce anaphylaxis required two doses-sensitizing & shocking. Anaphylactic Responses mediated by IgE antibodies that are produced by the immune system in response to environmental proteins (allergens) such as pollens, animal danders or dust mites.

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Mode of Action:

Upon exposure of the individual to an allergen, the B -cells are activated & IgE-secreting plasma cells are formed. These cells attach with high affinity to FC (Fragment crystalised) receptors present on the constant domains of mast cells (tissue) & basophils (blood). These mast cells & basophils are coated with IgE & are sensitised. Upon subsequent exposure to the same allergen, cross-linking of the bound IgE occurs. This results in the degranulation of the mast cells & basophils & release of pharmacologically active mediators from these cells. The released mediators cause smooth-muscle contraction, increased vascular permeability, & vasodilation.

Etiology:-

The main antibody exaggerated by immune response during this reaction is called immunoglobulin E (IgE) which attacks soluble antigens. The interaction between IgE & the antigen releases histamine & inflammatory mediators.

There are two stages of this immune response after exposure:

- **First stage**, called the sensitization stage, is where the host contacts the antigen for the first time. This contact is asymptomatic as the host recognizes the antigen for the first time.
- **Second stage** is the late phase reaction at which the sensitized host is exposed to the antigen again leading to the development of type I hypersensitivity reaction.

Types of antigens involved:-

What causes hypersensitivity? There are various types of antigens that can exaggerate the immune response such as:

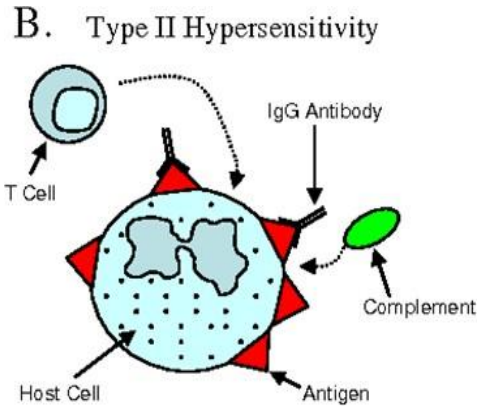
- **Food:** Some foods may cause allergies like Nuts, Soy & Wheat.
- **Animal Source:** Bee bites, cats & rat dander.
- **Environmental Source:** Dust, Pollen & Molds.
- **Drug allergy:** Antibiotics are the main drugs that induce allergic reactions. However, other such as propofol & isoflurane anaesthesia drugs may induce hypersensitivity as well.

Biological Effects

1) Anaphylactic responses give rise to mild symptoms, like hay-fever, running nose, skin eruptions (hives) or breathing difficulties.
2) The granules release certain pharmacologically active mediators that impart biological effects on the surrounding tissues.
3) ometimes anaphylactic shock may develop within 2-30 minutes which may lead to death if the individual is not attended with medical help.
4) The main effects of vasodilation & smooth muscle contraction can be systematic or localised.

Examples:-

Allergic asthma, allergic conjunctivitis, allergic rhinitis (hay fever), anaphylaxis, angioedema, atopic dermatitis (eczema), urticaria (hives), & eosinophilia.



Type II or Cytotoxic-Mediated Response:-

Cytotoxic hypersensitivity is a commonly used term for Type II hypersensitivity, which is characterized by the destruction or lysis of affected cells due to the presence of IgG or IgM antibodies directed against their surface components. Additionally, complement may contribute to these reactions by either promoting cell lysis or facilitating opsonization of the antibody-coated cell.

Mode of Action:-

The reaction during blood transfusion is an example of type II hypersensitivity reactions. In blood transfusion, reaction occurs between the host antibodies & foreign antigens present on the incompatible transfused blood cells. This reaction mediates cell destruction.

Antibody-mediated cell destruction occurs through activation of complement system. This increases membrane porosity in foreign cell by forming Membrane Attack Complex (MAC). Cell destruction can also be mediated through Antibody Dependent Cell-Mediated Cytotoxicity (ADCC). Haemolysis of the donor's erythrocytes occurs in the recipient's blood vessels as a result of faulty

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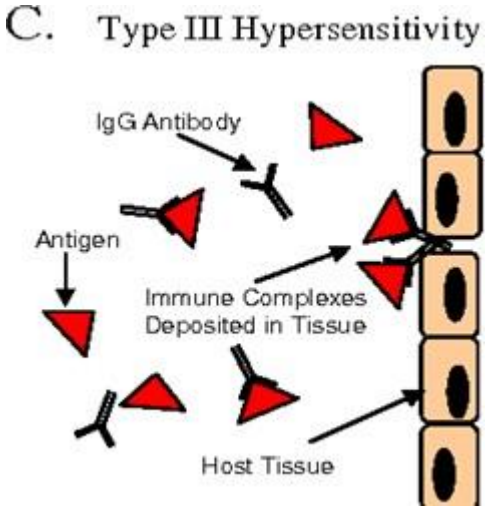
matching in which the alloantigen of the donor's erythrocytes reacts with the serum antibodies of the recipient along with the activated complement.

Biological Effects:-

1) When the maternal IgG antibodies specific for antigens of foetal blood-group cross the placenta & destroy the erythrocytes of foetus, haemolytic disease occurs in new-born.
2) A haemolytic medical condition affecting the new-borns is erythroblastosis fetalis in which the Rh+ foetus expresses an Rh antigen on its blood cells that the Rh– mother does not express.
3) Drug-induced haemolytic anaemia occurs when some antibiotics (**e.g.,** penicillin, cephalosporin & streptomycin) get non - specifically absorbed to proteins on erythrocyte membranes and form a complex (Like hapten - carrier complex) that induces anaemia.

Examples:-

Autoimmune haemolytic anaemia, Goodpasture syndrome, erythroblastosis fetalis pemphigus, pernicious anaemia (if autoimmune), immune thrombocytopenia, transfusion reactions, Hashimoto's thyroiditis, Graves' disease, myasthenia gravis, rheumatic fever, and haemolytic disease of the new-born.



Type III or Immunocomplex Reactions :-

Upon invasion of an antigen in an individual, the antibody reacts with it to form an immune complex which aids in the removal of antigen through phagocytosis. Type III hypersensitivity reaction occurs as a result of tissue -damage caused by large number of immune complexes. Hence, type III hypersensitivity reaction is also called **immune complex hypersensitivity**.

Mode of Action:-

When the complement system's array of immune effector molecules is activated by the immune complexes, type III hypersensitivity reactions develop. Splitting of complement components (C3a, C4a, and C5a) produce anaphylatoxins leading to degranulation of localised mast cell and rise in local vascular permeability.

The so formed bulky antigen-antibody complexes aggregate & combine with the activated complement. This chemotactically attracts the polymorphonuclear leukocytes that release large quantities of lysosomal enzymes, causing tissue damage.

Biological Effects:-

1) Antibodies are developed by the recipient of a foreign antiserum. These antibodies are specific for foreign serum proteins from circulating immune complexes. An individua l develops serum sick ness within days or weeks of exposure to foreign serum antigens. Symptoms of serum sickness include fever, weakness, vasculitis (rashes) with oedema, erythema, lymphadenopathy, arthritis & glomerulonephritis.
2) The IgG antigen complexes deposit in the blood vessels & cause local damage. When they deposit on blood vessels of kidney glomeruli, they cause Arthus Reaction.
3) Farmer's lung is a disease in which immune complexes are formed in the epithelial layers of the respiratory tract upon inhalation of bacterial & Fungal spores.
4) Systemic lupus erythematosus is an autoimmune hypersensitive reaction (autoimmune) that occurs when IgG & the nucleoproteins of the disintegrated leukocytes (auto-antigens) interact.

Examples :-

The following are some examples of conditions that can result from immune complex reactions: glomerulonephritis, rheumatoid arthritis, serum sickness, subacute bacterial endocarditis, symptoms of malaria, systemic lupus erythematosus, Arthus reaction, and Farmer's lung (which is an Arthus-type reaction).

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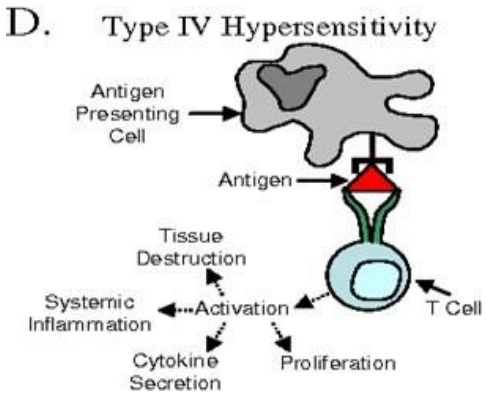

Type IV or Delayed Hypersensitivity:-

Type IV hypersensitivity reaction is a type of delayed hypersensitivity controlled by T -cells, macrophages, & dendritic cells. It does not occur as an instant response but after the second exposure to an allergen. The allergic symptoms appear after sometime.

* *

Mode of Action

The T-lymphocytes play a major role in maintaining delayed hypersensitivity. They are categorised into CD4 + & CD8+ cells. The former cells are required in type IV hypersensitivity reactions. The special group of CD4+ cells called T-D cells (delayed), participate in this reaction. The T-helper cell (TH cell) includes TD cells that make the bulk of CD4 + T-cells. The T H cells are categorised into TH1 & T H2 type. The latter cells activate B-cells to produce immunoglobulins & the former cells initiate inflammatory responses like delayed hypersensitivity reactions.

Biological Effects

1) Tuberculin is a purified protein derivative (PPD) of tubercle bacilli (Mycobacterium tuberculosis). It is a microbial agent that triggers delayed hypersensitivity. The microbial agents obtained from Mycobacterium leprae also stimulate delayed hypersensitivity.
2) The tuberculin skin test (or Mantoux test) determines whether a person presents T-cell mediated reactivity for tubercle bacilli (Koch's bacilli).

* *

Examples

Contact dermatitis (poison ivy rash), temporal arteritis, symptoms of leprosy & tuberculosis, transplant rejection, and coeliac disease.

Type V or Stimulatory Hypersensitivity

The type V-stimulatory hypersensitivity reactions occur when the antibody undergoes specific reactions with a key surface component, **e.g.,** hormone receptor, and switches on the cell.

Examples

A typical example of type V-stimulatory hypersensitivity is thyroid hyperreactivity in Grave's disease due to a thyroid-stimulating autoantibody.

Types & Descriptive Names	Time of development & Initiation Time	Type of cells involved	Mechanisms	Typical Manifestations
Type I IgE mediated or anaphylactic hypersensitivity.	Immediate & 2-30 min	Mast cells	Antigen (Ag) induces cross-linkage of lgE bound to mast cells & basophils, along with the release of vasoactive mediators.	Systemic & Localised anaphylaxis, hay fever, asthma, hives, food allergies, & eczema.
Type II Antibody-dependent cytotoxic hypersensitivity	Immediate & 5-8 hrs	Macrophagic cells	Antibody (Ab) directed against cell surface; antigens mediate cell destruction	Blood-transfusion reactions, erythroblastosis fetalis, & autoimmune haemolytic anaemia.

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			by complement activation or ADCC	
Type III Immune Complex mediated hypersensitivity	Immediate & 2-8 hrs	Neutrophils	Ag-Ab complexes deposited in various tissues induce complement activation & an inflammatory response.	Localised arthus reaction, generalised reactions, serum sickness, glomerulonephritis, rheumatoid arthritis, & systemic lupus erythematosus
Type IV Cell-mediated or delayed type hypersensitivity	Delayed & 24-72 hrs	Macrophages & Lymphocytes	Sensitised T DTH cells release cytokines that activate macrophages or TC cells that mediate direct cellular damage.	Contact dermatitis, tubercular lesions, & graft rejection.
Type V Stimulatory hypersensitivity	-	-	-	Thyroid hyperreactivity in Grave's disease

Table 1.2: Gell and Coomb's Classification of Hypersensitivity Reactions

IMMUNOLOGY

• Type I reactions are affected by mediators released from mast cells & basophils.

• Type II reactions result from formation of antibodies that are usually directed against cellular or matrix antigens and lead to localized disease.

• Type III reactions result, the formation of antigen-antibody complexes can lead to the activation of the complement pathway & then

recruitment & activation of neutrophils, which ultimately results in tissue damage.

• Type IV reactions are mediated by T lymphocytes; there are four subtypes. Some conditions involve more than one subtype.

• All types of reactions can be caused by Penicillin including:

Type I, which involves anaphylaxis & urticaria

Type II, which results in haemolytic anaemia

Type III, which leads to a serum sickness-like reaction

Type IV, which causes delayed type drug rash or contact dermatitis.

• Pre-treatment with corticosteroids & antihistamines can prevent non- IgE mediated hypersensitivity reactions, such as anaphylactic reactions to radiocontrast media, whereas IgE-mediated anaphylaxis cannot be prevented by corticosteroid pre-treatment.

Treatment/Management

It is important to seek medical advice before taking any of these treatments, which are intended for informational purposes only. Consulting a healthcare professional is crucial in determining the most appropriate therapeutic approach for the treatment or management of hypersensitivity.

Immediate hypersensitivity reactions

Immediate control is necessary when dealing with anaphylaxis, which is linked to type 1 hypersensitivity. The following are common treatments used for this purpose:

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- The initial treatment for anaphylaxis is administering an intramuscular injection of adrenaline.
- To manage asthma symptoms, administering inhaled bronchodilators like salbutamol in combination with corticosteroids via inhalation can be used alongside oxygen therapy.
- In Addition to oxygen therapy, Inhaled bronchodilators such as salbutamol with inhalation of corticosteroids can be used to manage asthma symptoms.
- Using antihistaminic drugs by intravenous injection.
- Regulate blood pressure through intravenous administration of fluids.
- Methotrexate & Omalizumab can be used in small quantity.

Delayed hypersensitivity reactions

Delayed hypersensitivity treatment depends on the causative agent:

- **Contact dermatitis**: This type of hypersensitivity is classified as a subtype of type 4 & occurs when the sensitive skin comes into direct contact with the antigen. Typically, the treatment regimen for this condition involves the application of topical steroids, along with the administration of oral antihistamines. One such rapidly-acting antihistamine used for this purpose is chlorpheniramine.
- Granulomatous allergy: Sarcoidosis, which is classified as a granulomatous disease, can present in both ocular & systemic forms. The initial treatment approach for sarcoidosis typically involves the use of steroids, while methotrexate may be used as a supplementary therapy.
- If a tuberculin test is positive, the best treatment is to begin a tuberculosis regimen which includes rifampin, pyrazinamide, and isoniazid.
- Anaphylaxis can result from schistosomiasis, & praziquantel drugs are typically the most effective means of managing the condition

II. CONCLUSION:

Type I or Anaphylactic Hypersensitivity The most common hypersensitivity reaction is the type I hypersensitivity. After an individual is exposed to an allergen, their B-cells are stimulated, leading to the formation of plasma cells that secrete IgE antibodies. This is the mechanism of action.

This results in the degranulation of the mast cells & basophils & release of pharmacologically active mediators from these cells. During the second stage, known as the late-phase reaction, the previously sensitized host encounters the antigen once more, resulting in the manifestation of a type I hypersensitivity reaction.

Mode of Action The reaction during blood transfusion is an example of type II hypersensitivity reactions. The recipient's blood vessels experience haemolysis of the donor's red blood cells due to an erroneous cross-matching process. This happens when the alloantigen from the donor's red blood cells interacts with the recipient's serum antibodies & the activated complement system.

Mode of Action When the complement system's array of immune effector molecules is activated by the immune complexes, type III hypersensitivity reactions develop. Type IV or Delayed Hypersensitivity Type IV hypersensitivity reaction is a type of delayed hypersensitivity controlled by T -cells, macrophages, & dendritic cells. The former cells are required in type IV hypersensitivity reactions. The approach to managing delayed hypersensitivity reactions relies on identifying the underlying trigger. In the case of contact dermatitis, which is a type 4 hypersensitivity reaction, the antigen directly touches the sensitivity & causes a specific subtype of delayed hypersensitivity reaction.

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