

Hypersensitivity reactions

COURSE:

Lecture 19-20

TEACHING OBJECTIVES:

1. Understand the classification of hypersensitivity reactions
2. Know the diseases associated with hypersensitivity reactions
3. Understand the mechanisms of damage in hypersensitivity reactions
4. Know the methods for diagnosing conditions due to hypersensitivity
5. Know the modes of treating disease due to hypersensitivity and their rationale

READING:

Male, Brostoff, Roth and Roitt: Immunology, 7th Ed., Chapters 23-26.

Hypersensitivity refers to excessive undesirable (damaging, discomfort producing and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction.

Type I Hypersensitivity

It is also known as **immediate** or **anaphylactic** hypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis). The reaction may cause from minor inconvenience to death. The reaction takes 15-30 minutes from the time of exposure to the antigen. Sometimes the reaction may have a delayed onset (10-12 hours).

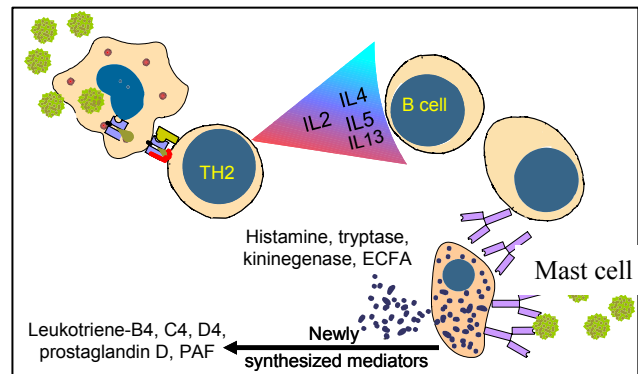


Figure 1: Induction and effector mechanisms in type I hypersensitivity

Type I hypersensitivity is mediated by **IgE**. The primary cellular component in this hypersensitivity is **mast cell** or **basophil**. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils. A biopsy of the reaction site demonstrates mainly **mast cells** and **eosinophils**. The mechanism of reaction involves preferential production of IgE, in response to certain antigens, often called **allergens** (Figure 1). The precise mechanism as to why some individuals are more prone to type-I hypersensitivity is not clear. However, it has been shown that such individuals preferentially produce more of TH2 cells that secrete IL-4, IL-5 and IL-13 which in turn favor IgE class switch. IgE has very high affinity for its receptor (Fcε; CD23) on mast cells and basophils. A subsequent exposure to the same allergen cross links the cell-bound IgE and

triggers the release of various pharmacologically active substances (Figure 1). Cross-linking of IgE Fc-receptor is important in mast cell triggering. Mast cell degranulation is preceded by increased Ca⁺⁺ influx, which is a crucial process; ionophores which increase cytoplasmic Ca⁺⁺ also promote degranulation of mast cells, whereas, agents which deplete cytoplasmic Ca⁺⁺ suppress degranulation.

The agents released from mast cells and their effects are listed in Table 1. Mast cells may be triggered by other stimuli such as exercise, emotional stress, chemicals (e.g., photographic developing medium, calcium ionophores, codeine, etc.), anaphylotoxins (e.g., C4a, C3a, C5a, etc.). These reactions mediated by agents without IgE-allergen interaction **are not typical hypersensitivity reactions**, although they produce the same symptoms.

Table 1. Pharmacologic Mediators of Immediate Hypersensitivity

mediator	Physiological effect
preformed mediators in granules	
histamine	bronchoconstriction, mucus secretion, vasodilatation, vascular permeability
tryptase	proteolysis
kininogenase	kinins and vasodilatation, vascular permeability, edema
ECF-A (tetrapeptides)	attract eosinophil and neutrophils
newly formed mediators	
leukotriene B ₄	basophil attractant
leukotriene C ₄ , D ₄	similar to histamine but 1000x more potent
prostaglandins D ₂	Eosinophil and basophil chemotactic, histamine-like but more potent edema and pain
PAF	platelet aggregation and heparin release: microthrombi

The reaction is amplified by PAF (platelet activation factor) that causes platelet aggregation and release of histamine, heparin and vasoactive amines. Eosinophil chemotactic factor of anaphylaxis (ECF-A) and neutrophil chemotactic factors attract eosinophils and neutrophils, respectively, which release various hydrolytic enzymes that cause necrosis. Eosinophil may also control the local reaction by releasing arylsulphatase, histaminase, phospholipase-D and prostaglandin-E, although this role of eosinophils is now in question.

Cyclic nucleotides appear to play a significant role in the modulation of immediate hypersensitivity reaction, although their exact function is ill understood. Substances which alter cAMP and cGMP levels significantly alter the allergic symptoms. Thus, substances that increase intracellular cAMP seem to relieve allergic symptoms, particularly broncho-pulmonary ones, and are used therapeutically (Table 2). Conversely, agents that decrease cAMP or stimulate cGMP aggravate these allergic conditions.

Table 2: Relationship between allergic symptoms and cyclic-nucleotides

Lowering of cyclic-AMP	Elevation of cyclic AMP
stimulation of α -adrenergic receptor (nor-epinephrin, phenyl-epinephrin) or blocking of β -adrenergic receptor (propranolol)	stimulation of β -adrenergic receptor (epinephrine, isoproterenol) blocking of α -adrenergic receptor (phenoxybenzamine)
Elevation of cyclic GMP	inhibition of phosphodiesterase (theophylline)
stimulation of χ -cholinergic receptor (acetyl choline, carbachol)	binding of histamine-2 or PGE to their receptors
WORSENING OF SYMPTOMS	IMPROVEMENT OF SYMPTOMS

Diagnostic tests for immediate hypersensitivity include skin (prick and intradermal) tests resulting in wheal and flare reaction, measurement of total IgE and specific IgE antibodies against the suspected allergens. Total IgE and specific IgE antibodies are measured by a modification of enzyme immunoassay (ELISA). Increased IgE levels are indicative of atopic condition, although IgE may be elevated in some non atopic diseases (e.g., myelomas, helminthic infection, etc.).

There appears to be a genetic predisposition for atopic diseases and there is evidence for HLA (A2) association.

Symptomatic treatment is achieved with **antihistamines** that block histamine receptors. **Chromolyn sodium** inhibits mast cell degranulation, probably, by inhibiting Ca^{++} influx. Late onset allergic symptoms, particularly bronchoconstriction which is mediated by leukotrienes are treated with **leukotriene receptor blockers** (Singulair, Accolate, Lukast) or inhibitors of **cyclooxygenase pathway (Zileuton)**. Symptomatic, although short-term, relief from bronchoconstriction is provided by **bronchodilators (inhalants) such as isoproterenol derivatives** (Terbutaline, Albuterol). **Thophylline elevates cAMP** by inhibiting cAMP-phosphodiesterase and inhibits intracellular Ca^{++} release is also used to relieve bronchopulmonary symptoms.

IgG antibodies against the Fc portions of IgE that binds to mast cells has been approved for treatment of certain allergies, as it can block mast cell sensitization.

Hyposensitization (immunotherapy or desensitization) is another treatment modality which is successful in a number of allergies, particularly to pollen. The mechanism is not clear, but there is

a correlation between appearance of IgG (blocking) antibodies and relief from symptoms. **Suppressor T cells that specifically inhibit IgE antibodies may play a role.**

Type II Hypersensitivity

It is also known as **cytotoxic hypersensitivity** and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals (haptens) that can attach to cell membranes can also lead to type II hypersensitivity. Drug-induced hemolytic anemia, granulocytopenia and thrombocytopenia are such examples. The reaction time is minutes to hours. It is mediated, primarily, by antibodies of IgM or IgG class and complement (Figure 2). Phagocytes and K (killer) cells may also play a role.

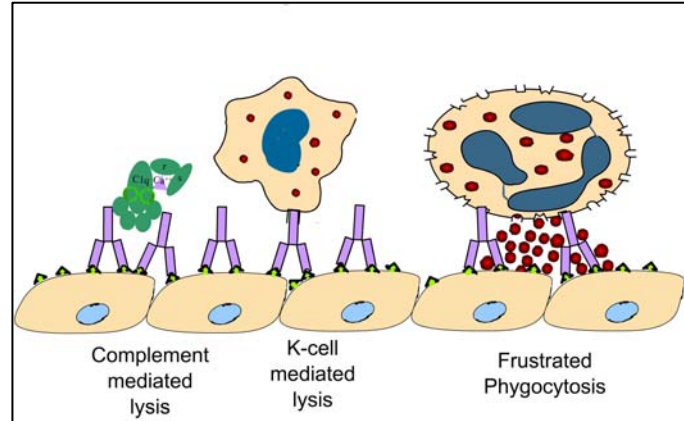


Figure 2: Type II hypersensitivity mechanisms

The lesion contains antibody, complement and neutrophils. Diagnostic tests include detection of circulating antibody against tissues involved and the presence of antibody and complement in the lesion (biopsy) by immunofluorescence. The staining pattern is normally smooth and linear, such as that seen in Goodpasture's nephritis (renal and lung basement membrane) and pemphigus (skin intercellular protein, desmosome).

Treatment involves anti-inflammatory and immunosuppressive agents.

Type III Hypersensitivity

It is also known as **immune complex hypersensitivity**. The reaction may be **general** (*e.g.*, serum sickness) or may involve **individual organs** including skin (*e.g.*, systemic lupus erythematosus, Arthus reaction), kidneys (*e.g.*, lupus nephritis), lungs (*e.g.*, aspergillosis), blood vessels (*e.g.*, polyarteritis), joints (*e.g.*, rheumatoid arthritis) or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms.

The reaction may take 3-10 hours after exposure to the antigen (as in Arthus reaction). It is mediated by soluble immune complexes. They are mostly of IgG class, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity: *e.g.*, systemic lupus erythematosus-SLE). The antigen is soluble and not attached to the organ involved. Primary components are soluble immune complexes and complement (C3a, 4a and 5a). The damage is caused by platelets and neutrophils (Figure3).

The lesion contains primarily neutrophils and deposits of immune complexes and complement. Macrophages infiltrating in later stages may be involved in the healing process.

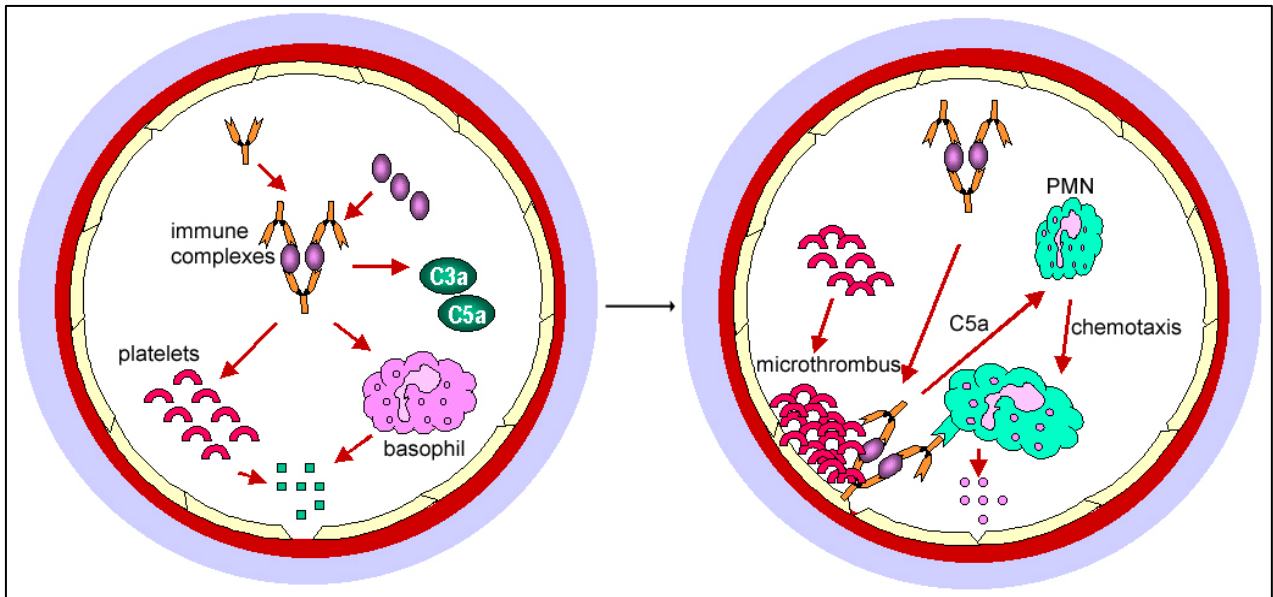


Figure 3: Mechanism of damage in type-III hypersensitivity

The affinity of antibody and size of immune complexes are important in production of disease and determining the tissue involved. Diagnosis involves examination of tissue biopsies for deposits of Ig and complement by immunofluorescence. The immunofluorescent staining in type III hypersensitivity is granular (as opposed to linear in type II: Goodpasture). Presence of immune complexes in serum and depletion in complement level are also diagnostic. Treatment includes anti-inflammatory agents.

Type IV Hypersensitivity

It is also known as cell mediated or delayed type hypersensitivity. The classical example of this hypersensitivity is **tuberculin (Montoux) reaction** that peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.

Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, etc.) and granulomas due to

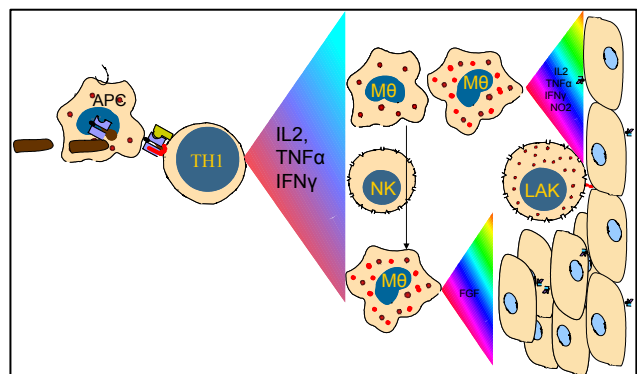


Figure 4. Mechanisms of damage in delayed hypersensitivity

infections and foreign antigens. Another form of delayed hypersensitivity is **contact dermatitis** (poison ivy, chemicals, heavy metals, *etc.*) in which the lesions are more papular. Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation (Table 3).

Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. The pathogenesis is triggered primarily by helper T (TH1) cells that secrete cytokines that activate and recruit macrophages, which cause the bulk of the damage (Figure 3). The delayed hypersensitivity lesions mainly contain monocytes and T cells.

Major lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, interleukin-2, interferon- γ , TNF α , *etc.*

Table 3. Delayed hypersensitivity reactions

type	reaction time	clinical appearance	histology	antigen and site
contact	48-72 hr	eczema	lymphocytes, followed by macrophages; edema of epidermis	epidermal (organic chemicals, poison ivy, heavy metals, <i>etc.</i>)
tuberculin	48-72 hr	local induration	lymphocytes, monocytes, macrophages	intra-dermal (tuberculin, lepromin, <i>etc.</i>)
granuloma	21-28 days	hardening	macrophages, epitheloid and giant cells, fibrosis	persistent antigen or foreign body presence (tuberculosis, leprosy, <i>etc.</i>)

Diagnostic tests *in vivo* include delayed cutaneous reaction (*e.g.* Montoux test) and patch test (for contact dermatitis). *In vitro* tests for delayed hypersensitivity include mitogenic response, lympho-cytotoxicity and IL-2 production.

Corticosteroids and other immunosuppressive agents are used in treatment.

A comparative summary of all four types of hypersensitivity reactions have been presented in Table 4 below.

Table 4. Comparison of Different Types of hypersensitivity

characteristics	type-I (anaphylactic)	type-II (cytotoxic)	type-III (immune complex)	type-IV (delayed type)
antibody	IgE	IgG, IgM	IgG, IgM	None
antigen	exogenous	cell surface	soluble	tissues & organs
response time	15-30 minutes	minutes-hours	3-8 hours	48-72 hours
appearance	wheal & flare	lysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	macrophages and T cells
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, poison ivy, granuloma