

(Selected slides)

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Allergy *(Type I Hypersensitivity)*

The many facets of allergic immune responses

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Allergy is mediated by a specific type of antibody, termed IgE. IgE-mediated allergy is also termed:

- Allergy
- Type I hypersensitivity
- Type I allergy
- Immediate type hypersensitivity
- Atopy

*When a substance (antigen) is capable of producing allergic symptoms, it is known as an **allergen**.*

People who suffer from Hay fever, asthma, and some types of eczema, usually have an immune system that reacts in an inconvenient way to one or more common substances in the environment.

Hypersensitivity reactions are exaggerations of normal defence mechanisms

There are several types of Hypersensitivity responses, only one of which is termed Allergy

Hypersensitivity, in general, can result from responses against pathogens, non-pathogens, or self-antigens, and can be mediated by antibodies, lymphocytes or innate immunity mechanisms.

The concentration of soluble IgE in the blood and other body fluids is extremely low

IgE is found mainly associated with mast cells just beneath epithelial surfaces (especially of the respiratory tract, gastrointestinal tract, and skin), and on the surface of blood basophils.

Concentration of antibody classes the serum:		
No.	Ab Class	mg/ml
1.	IgG	13.5
2.	IgA	3.5
3.	IgM	1.5
4.	IgD	0.03
5.	IgE	0.00005

IgE bind to specialized receptors on the surface of mast cells and basophils, termed FcεRI.

Soluble Ig isotypes are selectively distributed in the body

IgG monomeric antibodies are the major isotypes in extracellular fluid within the body. They can pass the placenta into the embryo's blood stream.

IgA monomeric antibodies are found in the extracellular fluid within the body. Dimeric IgA predominates in secretions across epithelia, and play a critical role in mucosal immunity. They are the main antibodies in tears, saliva, and colostrum, secretions of the genito-urinary and gastrointestinal tracts, prostate, and respiratory epithelium.

IgM are pentameric antibodies. They are found predominantly in the plasma.

IgD is a membrane-bound antibody on the surface of mature B lymphocytes. B lymphocytes do not secrete soluble IgD antibodies.

IgE is found mainly associated with mast cells, just beneath epithelial surfaces (especially of the respiratory tract, gastro-intestinal tract, and skin), and basophils, in the peripheral blood. Serum levels of IgE are extremely low. IgE has very high binding affinity to its receptor (Fc ϵ RI). It is produced by IgE-bearing B lymphocytes, after their differentiate into IgE-secreting plasma cells. Within a short time after its secretion to the body fluid, it binds to Fc ϵ RI on the surface of mast cells and basophils.

IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

Syndrome	Common Allergens	Route of entry	Type of response
Acute urticaria (wheal-and-flare)	Insect bites	Through skin	Local increase in blood flow and vascular permeability
Food allergy	Eggs, milk, nuts, fish	Oral	Vomiting, diarrhea, itching
Seasonal rhinitis	Pollens, dust-mite feces	Inhalation	Edema of nasal mucosa, sneezing
Asthma	Pollens, Animal dander, dust-mite feces	Inhalation	Bronchial constriction, mucus overproduction, airway inflammation
Systemic anaphylaxis	Drugs, serum, venoms	Intravenous	Edema, increased vascular permeability, circulatory collapse, coma, death

All IgE-mediated responses involve mast-cell degranulation, but the symptoms experienced by the patient can differ depending on whether the allergen is injected, inhaled, or eaten, and depending on the type and dose of the allergen.

A large variety of drugs can induce anaphylactic responses

Antibiotics

Penicillin

Sulfa drugs

Tetracycline

Analgesics

Codeine

Non-steroidal anti-inflammatory drugs (aspirin, ibuprofen)

Antiseizure

Dilantin

Tegretol

IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

Additional materials and conditions, which may cause allergy:

Allergy caused by contact to latex materials. Common latex materials that cause allergic reaction are:

- Rubber bands
- Carpet backing
- Hospital and dental equipment
- Rubber (latex) gloves
- Balloons
- Condoms

Exercise induced Anaphylaxis (EIA): Allergy reaction that develops after doing some strenuous exercise.

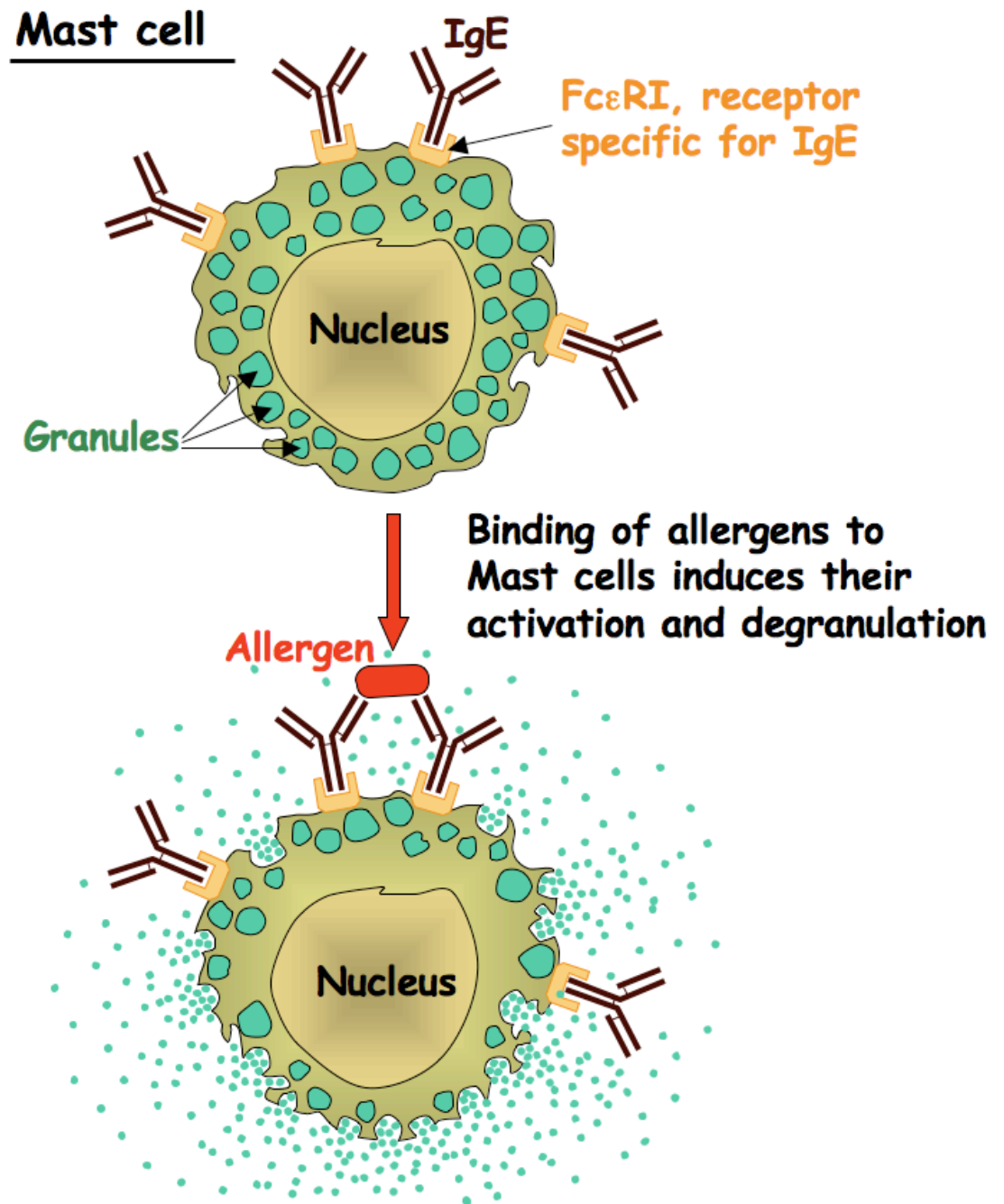
Hypersensitivity of females to seminal plasma (semen allergy).

Allergic reaction to henna and tattoo.

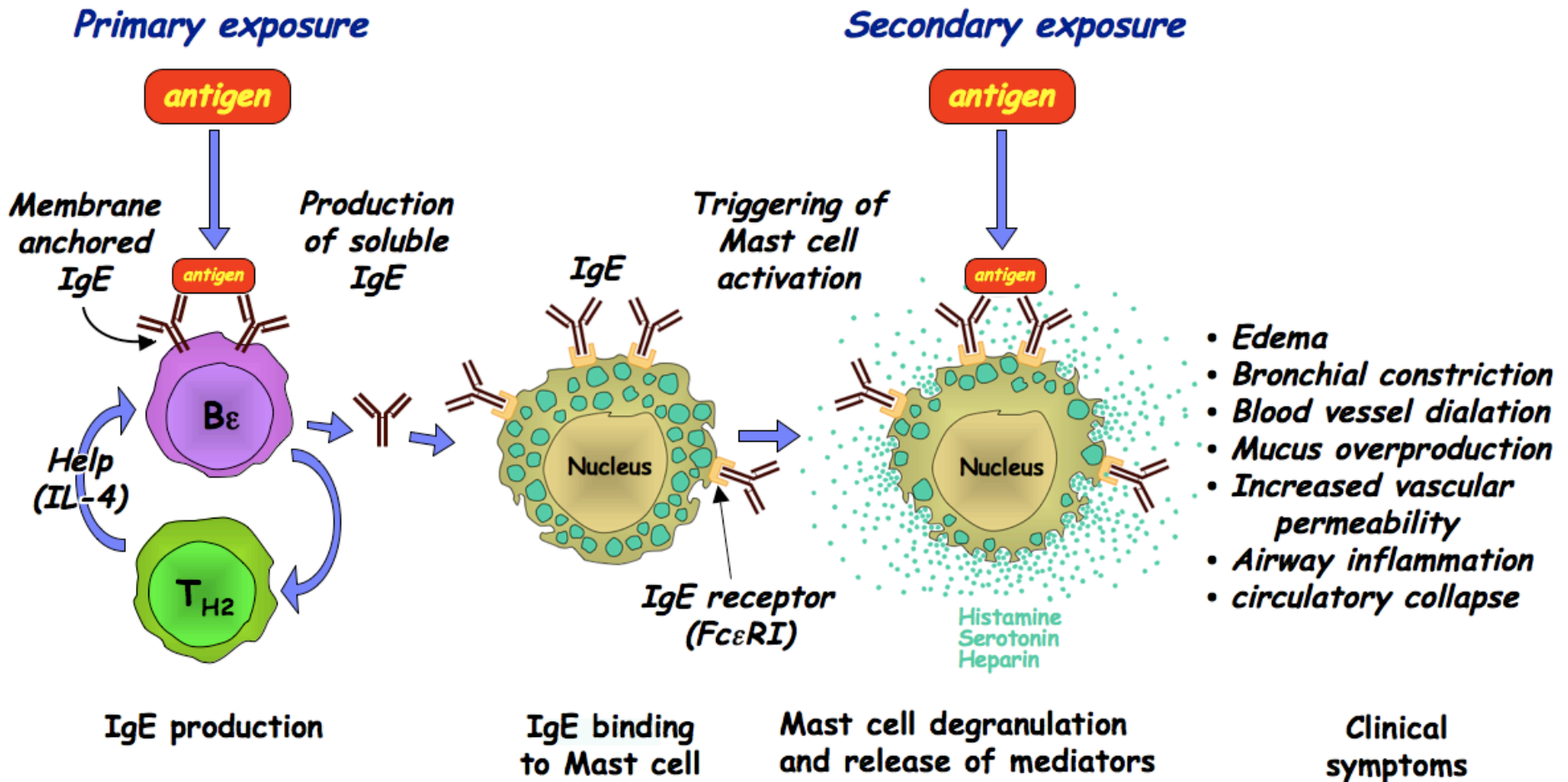
Cold weather allergy.

IgE antibody is produced in response to allergens. It binds special receptors (Fc ϵ RI) on the outer surface of mast cells and basophils. Upon challenge with the same allergen, the soluble allergen binds to and cross-links the surface IgE bound to Fc ϵ RI, thereby triggering mast cell activation and degranulation.

The granules include many types of soluble molecules, such as histamine, which mediate the allergic reactions.



Mechanisms of activation of Mast cells and Basophils



IgE are "cytophilic" antibodies. They bind to Fc_εRI receptor on the surface of mast cells (in tissues) and basophilic cells (in peripheral blood) and sensitize them.

Molecules released from activated mast cells and basophils

Histamine

It is toxic to many parasites.

Histamine exerts its actions by combining with specific cellular histamine (H) receptors. The four histamine receptors that have been discovered are designated H1 through H4.

Type	Location	Function
H1	smooth muscle, endothelium, central nervous system tissue.	Causes vasodilation, increases vascular permeability, promotes bronchoconstriction, bronchial smooth muscle contraction, separation of endothelial cells (responsible for hives), pain and itching due to insect stings; H1 are the primary receptors involved in allergic rhinitis symptoms and motion sickness.
H2	Located on parietal cells.	Primarily stimulate gastric acid secretion.
H3	Found on central nervous system and to a lesser extent peripheral nervous system tissue.	Decreased neurotransmitter release: histamine, acetylcholine, norepinephrine, serotonin.
H4	Found primarily in the basophils and in the bone marrow. It is also found on thymus, small intestine, spleen, and colon.	Plays a role in chemotaxis.

Molecules released from activated mast cells and basophils

Prostaglandins

Prostaglandins are potent but have a short half-life before being inactivated and excreted. Therefore, they send only paracrine (locally active) or autocrine (acting on the same cell from which it is synthesized) signals.

There are currently ten known prostaglandin receptors expressed on different cell types. The diversity of receptors means that prostaglandins act on an array of cells and have a wide variety of effects. Among others, prostaglandins can:

- cause constriction or dilation in vascular smooth muscle cells
- cause aggregation or disaggregation of platelets
- sensitize spinal neurons to pain
- decrease intraocular pressure
- regulate inflammatory mediation
- regulate calcium movement
- control hormone regulation
- control cell growth

Molecules synthesized and released by mast cells on stimulation by antigen binding to IgE

Class of product	Examples	Biological effects
Enzyme	Tryptase, cathepsin G, chymase, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin, serotonin	Toxic to parasites, increase vascular permeability, induce smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T _{H2} cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNF α (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by a variety of cell types
Chemokine	MIP-1 α	Attracts monocytes, macrophages and neutrophils
Lipid mediator	Leukotriens C4, D4, E4	Cause smooth muscle contraction, increase vascular permeability, stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes, amplifies production of lipid mediators, activates neutrophils, eosinophils, and platelets
	Prostaglandin D2	Affect vascular smooth muscle cells

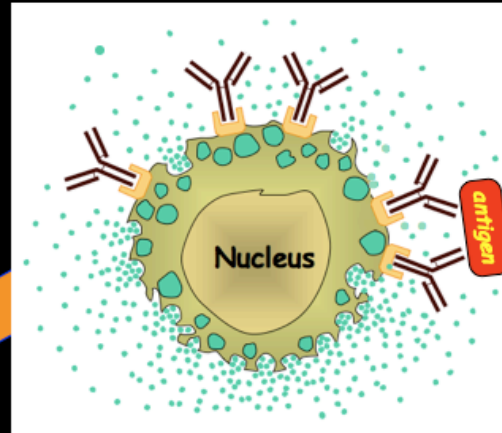
*Mast-cell products have different effects
on different tissues*

Smooth muscle → Contraction

Capillary → Dilatation

Mucous gland → Increase secretion

Mast-cell products have different effects on different tissues



Mast-cell activation and granule release

Gastrointestinal tract	Airways	Blood vessels
<p>Increased fluid secretion Increased peristalsis</p>	<p>Decreased diameter Increased mucus secretion</p>	<p>Increased blood flow Increased permeability</p>
<p>Expulsion of gastrointestinal tract contents (diarrhea, vomiting)</p>	<p>Congestion and blockage of airways, leading to wheezing, coughing and phlegm. Swelling and mucus secretion in nasal passages</p>	<p>Increase fluid in tissues causing increased flow of lymph to lymph nodes. Increased cells infiltration and proteins concentration in tissues. Increased effector response in tissues</p>

Anaphylaxis

- Anaphylaxis is the most severe form of IgE-mediated allergy.
- It is an immediate life-threatening reaction that requires urgent treatment.
- The urgency of anaphylaxis is such that a patient could die before qualified help is available.
- It is very important therefore, that patients and also their relatives know how to observe, and if necessary, give treatment before symptoms become life-threatening.

Fortunately...

- The severest form of anaphylaxis is very uncommon.
- Anaphylaxis responds very well to treatment with **adrenalin**.
- Death from anaphylaxis is very rare.

Symptoms that are often associated with anaphylaxis (1)

- Usually only some of these symptoms will be experienced
- The symptoms at the "mild" end of the scale may require no treatment at all
- The symptoms at the severe end of the scale may become very serious

Symptoms that are often associated with anaphylaxis (2)

Mild to moderate

- Tingling or unusual taste in mouth
- Running nose and eyes, sneezing
- Itchy skin
- Hives - red, itchy nettle-rash, urticaria
- Swelling- puffiness of eyes, lips and limbs. Whole face may appear swollen

Symptoms that are often associated with anaphylaxis (3)

Moderate to severe

- Vomiting
- Abdominal cramps
- Uterine cramps
- Elevation of heart rate
- Mild wheezing

Symptoms that are often associated with anaphylaxis (4)

Severe to life-threatening

- Hoarseness or difficulty swallowing due to throat swelling
- Extreme distress, anxiety, panic, feeling of impending doom
- Difficulty breathing due to severe asthma or throat swelling
- Lips turn blue along with "loss of colour"
- Weakness, dizziness, feeling faint, drop in BP
- Collapse and/or unconsciousness
- Convulsions

Adrenaline is the most effective treatment available in the prevention of anaphylaxis

- “Rescue medication” is prescribed by a doctor for patients who have some risk of an anaphylactic reaction.
- Patients carry it at all times and must be well trained how to use it.
- Rescue medication contains **adrenaline** and sometime also antihistamines and an asthma inhaler.

Adrenaline can be administered using the EpiPen, a device for the autoinjection used by people who suffer from severe allergies and risk anaphylactic shock.

Can we immunize against allergens?

Immunologic desensitization Allergen-specific immunotherapy

Immunotherapy via repeated exposure to a specific allergen can lead to allergen-specific 'desensitization' and reduction in the allergic symptoms.

In this form of 'immunotherapy', the patient is vaccinated with increasingly larger doses of an allergen with the aim of inducing immunological 'tolerance'. Allergen-specific immunotherapy is the only known treatment strategy that affect the allergy response. This strategy may result in an improved quality of life and a reduction in allergic- and allergen-related asthma.

The exact mechanism of desensitization is not fully understood but it is assumed that 'immunotherapy' induces modification of the immune system. Allergen immunotherapy is likely to induce the production of allergen-specific IgG that neutralize the allergen, instead of inducing allergen-specific IgE.

Future therapy for allergies

In addition to the available drugs, that counteract symptoms of the allergic reaction, several large pharmaceutical companies are trying to develop new and better drugs that will prevent the allergy response.

One such 'drug' is the **Omalizumab**, an anti-IgE 'humanized' antibody, which was approved for patients with moderate-to-severe or severe allergic asthma. The effectiveness of this 'drug' is very limited.