



Tolerance and Adverse drug reactions

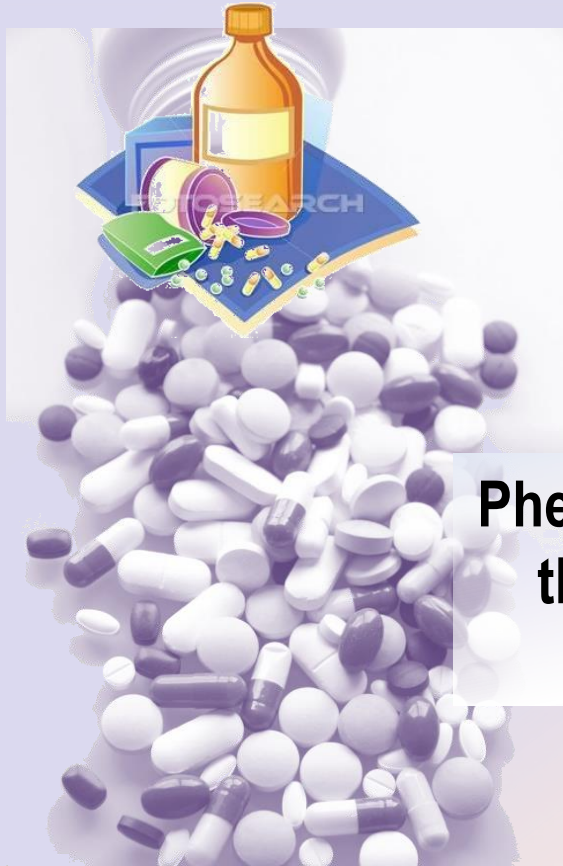
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Variation in drug responsiveness

Decrease in drug effects
Development of side effects



- Between different individuals
- Within the same individual



Phenomenon of variation in drug response, where by there is a **diminution** of the response to the drug when given continuously or repeatedly

Tolerance and Desensitization



Adverse drug reactions [ADR]

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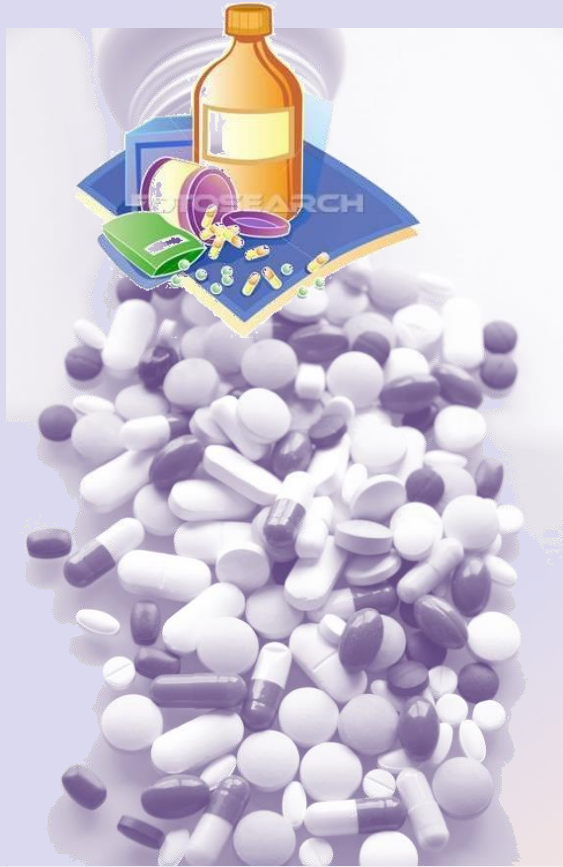
- ✚ **Harmful or seriously** unpleasant effects occurring at doses intended for **therapeutic effects**.

ILOs

By the end of this lecture you will be able to :

- Distinguish difference between **tolerance** and **desensitization** (tachyphylaxis) and reasons for their development
- Recognize patterns of **adverse drug reactions (ADRs)**





Tolerance and Desensitization

Diminution of a response

Rapid, in the course
of few minutes

**Tachyphylaxis /
Desensitization**

Gradual in the course of few
days to weeks

Tolerance

These should be distinguished from



Loss of effectiveness of
antimicrobial agent

Resistance



Tolerance

- Tolerance may be defined by either of the following:
 - a. a need for markedly **increased amounts** of the substance to achieve intoxication or desired effect
 - b. markedly **diminished effect** with continued use of the same amount of the substance

Reasons for development of tolerance



Pre-receptor events

↓ drug availability at the relevant receptors due to pharmacokinetic variables

Drug becomes:

- > metabolized or excreted
- < absorbed
- altered distribution to tissues

e.g. Barbiturates (enzyme inducers) ↑ metabolism of Contraceptive pills = ↓ it availability

Events at receptors

Post receptor events

Nullification of drug response by a physiological adaptive homeostatic response

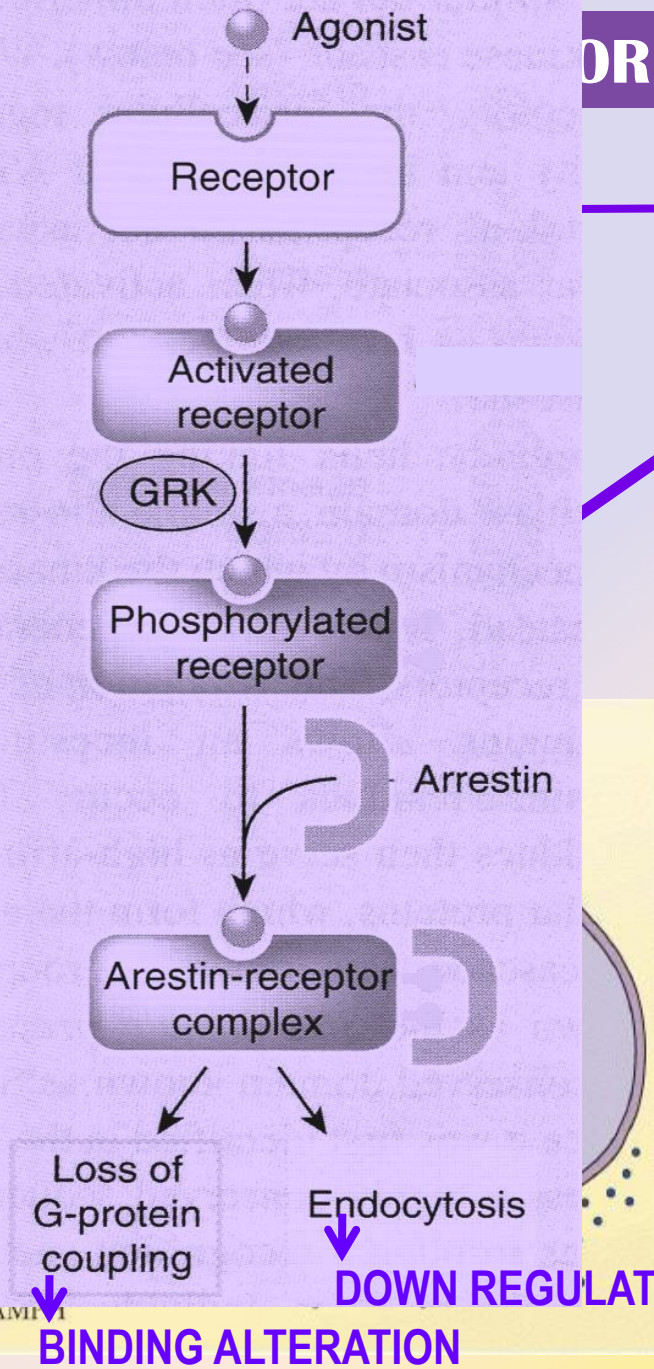
Antihypertensive effects of ACEIs become nullified by activation of renin angiotensin system (RAS) by

NSAIDs

Loss of therapeutic efficacy

Refractoriness

FOR DEVELOPMENT OF TOLERANCE



G protein-coupled receptor kinases (GRKs) : regulate the activity of GPCRs by phosphorylating their intracellular domains after their associated G proteins have been released and activated.

Arrestin is a protein that prevent the re-association of the G proteins with their receptors, thereby preventing reactivation of the signaling pathway.

Post-receptors events

Down regulation

↓ number of receptors.
Isoprenaline activation to β receptors \rightarrow \uparrow R recycling by endocytosis
[structural defect]

What is Addiction?

- It is well known that the initial decision to use drugs is voluntary
- Addiction is a **chronic, relapsing brain disease** characterized by:
 - **Compulsive** behavior of a person (loss of control)
 - **Continue taking drugs** despite their many adverse health and negative consequences
 - **Craving: dysphoric and feels very bad**
- **Two components involved:**
 - 1- Physical dependence (withdrawal symptoms), neurons adapt to the repeated drug exposure and **only function normally in the presence of the drug.**
 - 2- Psychological dependence (craving)

Drugs of addiction

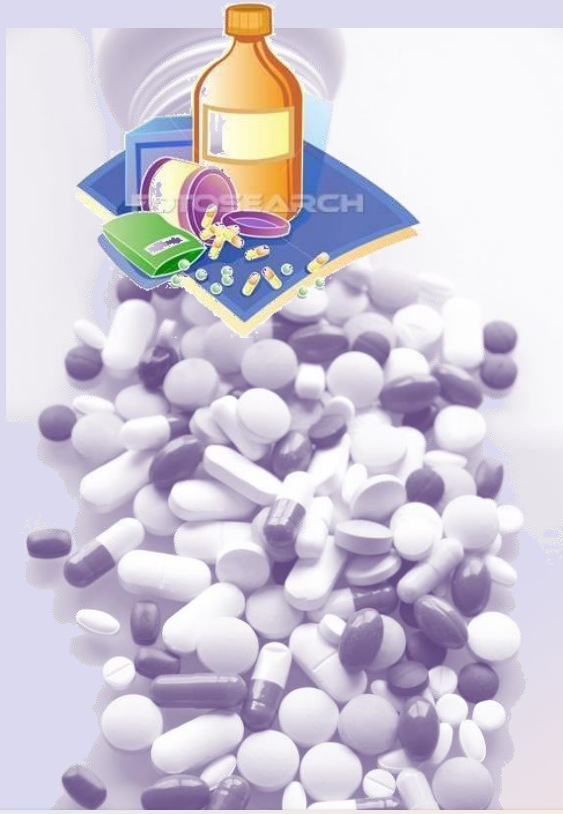
Stimulants - stimulate the central nervous system
- **amphetamines, cocaine, nicotine**

Depressants - depress the CNS
- **alcohol, barbiturates, benzodiazepines**

Analgesics - powerful painkillers
- from opium poppy , morphine, heroin

Hallucinogens - dramatically alter perception
- **LSD, cannabis, Marijuana**





Adverse drug reactions [ADR]

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- ✚ **Harmful or seriously** unpleasant effects occurring at doses intended for **therapeutic effects**.

Types of ADR

Type A

Augmented

Predictable

Occurs consequent but in excess of drug primary pharmacological effect. Of quantitative nature

Type B

Bizzare

Unpredictable

Occurs different [heterogenous / idiosyncratic] to known drug pharmacological effect usually due to patient's genetic defect or immunological response. Of qualitative nature

Type C

Continuous

Occurs during chronic drug administration

Type E

End-of-Use

Occurs upon sudden stoppage of chronic drug use due to existing adaptive changes present

Type D

Delayed

Occurs after long period of time even after drug stoppage

TYPES OF ADR

Type C

Continuous

e.g. Patients can develop

1. **Osteoporosis**
secondary to chronic **corticosteroid** intake
2. **Dependence**
 - a. **Psychological [Craving]** as by **cannabis**
 - b. **Psychological [Craving] + Physical withdrawal manifestations (syndrome)**
= **Addiction** as by **morphine**

End-of-Use

Type E

- e.g. Patients on stoppage of
- **Clonidine** develop rebound hypertension
 - **Morphine** develop withdrawal syndrome

Type D

Delayed

Long after patients can show:

- **Teratogenicity** after **retinoids**
- **Carcinogenicity** after **tobacco smoking**

Comparison between type A & B -ADRs

	Type A Augmentation	Type B Idiosyncratic
Pharmacological predictability	Yes	No
Nature	Quantitative [extension of pharmacology effect]	Qualitative [immune or genetic base]
Dose- dependent	Yes (dose response relationship present)	No (dose response relationship absent)
Onset of symptoms	Usually Rapid	Usually delayed
Incidence and morbidity	High	Low
Mortality	Low	High
Treatment	Dose adjustment or Substitute by > selective + Antagonize unwanted effect of 1 st drug	Stop drug + Symptomatic treatment
Example	Bradycardia → β - ADR Blockers Hemorrhage → Warfarin	Apnea → succinylcholine Thrombocytopenia → Quinine

Examples of TYPE A & B -ADR

EXAMPLES OF TYPE A & B -ADR

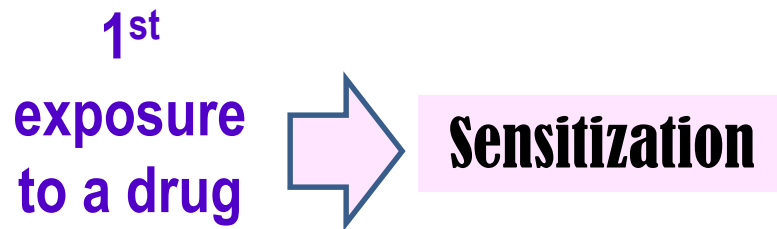
Drug	Type A	Type B
Chlorpromazine	Sedation	Cholestatic jaundice
Naproxen	GIT haemorrhage	Agranulocytosis
Phenytoin	Ataxia	Hepatitis, lymphadenopathy
Thiazides	Hypokalaemia	Thrombocytopenia
Quinine	Tinnitus	Thrombocytopenia
Warfarin	Bleeding	Breast necrosis

**Genetics Variation / defect
Immunological Predisposition**

TYPE B

Immunological Predisposition

The drug or its bi-product [*protein macromolecules or haptens*] react as antigens and provoke immune response that results in damage to the tissue → **Hypersensitivity Reaction**



Classification of hypersensitivity reactions

Type I – Immediate (atopic, or anaphylactic)

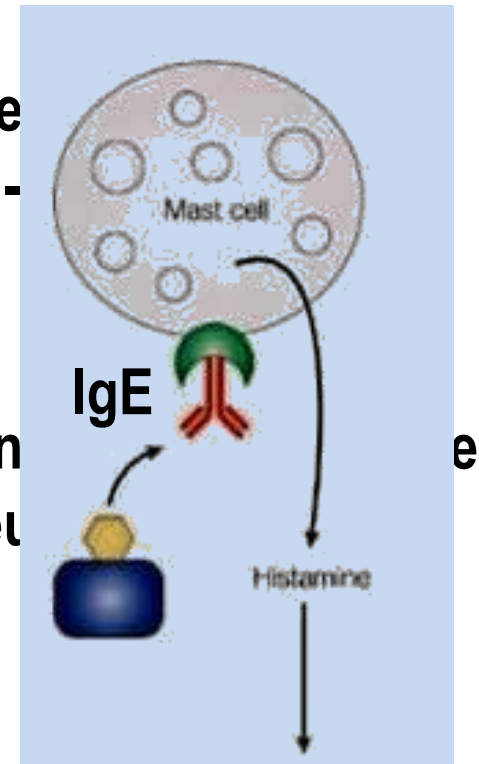
Type II – Cytotoxic

Type III – Immune complex

Type IV – Cell-mediated or delayed

Type I hypersensitivity: Anaphylactic

- Type I hypersensitivity is an allergic reaction provoked by re-exposure to a specific **antigen**
- Fast response which occurs in **minutes**, rather than hours or days. The reaction usually takes 15 - 30 minutes after the time of exposure to the antigen.
- The reaction is mediated by **IgE antibodies** and the immediate release of histamine, serotonin, leukotrienes, and prostaglandins from **tissue mast cells or blood basophils**



- **The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock.**

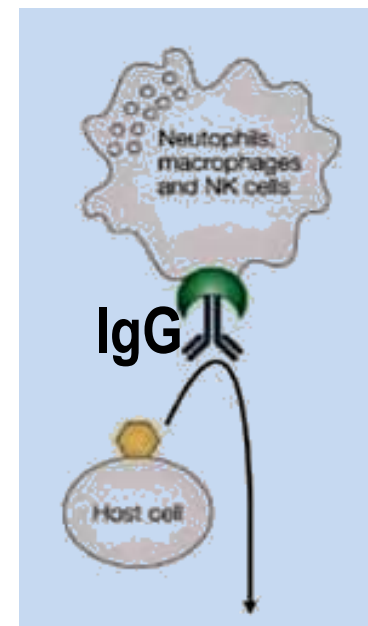
Some examples:

- **Allergic asthma**
- **Allergic conjunctivitis**
- **Allergic rhinitis "hay fever"**
- **Urticaria (hives)**
- **Anaphylaxis**

- may be caused by Penicillin, Streptomycin

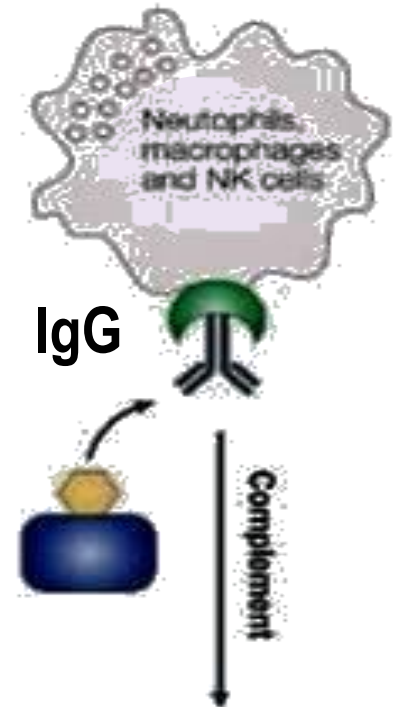
Type II hypersensitivity : Cytotoxic

- Antibody-dependent
- The antigens may be **endogenous** or **exogenous** chemicals (haptens) which can attach to cell membranes
- The antibodies (**IgM or IgG**) produced by the immune response bind to **antigens** on the patient's own cell surfaces that is perceived by the immune system as foreign, leading to cellular destruction.
- The reaction takes hours to a day
- **Examples:** Drug-induced haemolytic anemia , thrombocytopenia by **Penicillin, Quinidine**



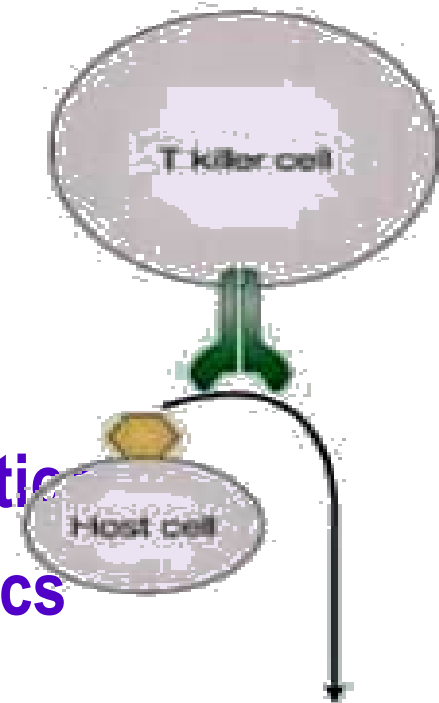
Type III hypersensitivity : Immune complex

- Soluble immune complexes (aggregations of antigens and **IgG and IgM** antibodies) form in the blood, are not completely removed by macrophages and are deposited in various tissues (typically the skin, kidney and joints)
- The reaction takes hours to days to develop
- **Example:** Serum sickness (*fever, arthritis, enlarged lymph nodes, urticaria*)
- by **Sulphonamides, Penicillin, Streptomycin**



Type IV Hypersensitivity: Cell-mediated

- also known as **delayed type** hypersensitivity as the reaction takes two to three days to develop.
- Unlike the other types, it is **not antibody-mediated** but rather is a type of cell-mediated response.
- **Cytotoxic T cells** cause direct damage whereas **helper T cells** secrete cytokines that attracts inflammatory cell infiltrate
- **Example** : Contact dermatitis by **local anesthetic creams, anti-histamine creams, topical antibiotics**





GOOD LUCK