PHARMACOGENETICS

Dr. Kamlesh P. Patel
Associate Professor
Department of Pharmacology
NHLMMC

GENETIC FACTORS (Pharmacogenetics)

1) Pharmacogenetics :- Variations of drug response due to genetic abnormality.

2) Pharmacogenomics :- Variations of drug response due to defective / deficient enzyme sysytems responsible for inactivating drug.This results in accumulation of drug causing toxicity.

GENETIC POLYMORPHISM

1) PRESENCE OF ATYPICAL PSEUDOCHOLINE ESTERASE (FAULTY HYDROLYSIS OF SUCCINYLCHOLINE) :-

SCHà Hydrolysed by Atypical PsCHE à Prolonged Respiratory Apnoea and Failure.

- Atypical pseudocholine-esterase take 1-2 hrs (instead of 5 min)
- Atypical pseudocholine-esterase is inhibited 20% by dibucaine (normal – 80%)

Dibucaine number

- Measures % inhibition of pseudocholine-esterase

2. HYDROXYLASE POLYMORPHISM

hydroxylation

Phenytoin ----------à P- Hydroxylate

mixed function oxidase

- **In slow hydroxylator** à **Unable to P- hydroxylate Phenytoin à ↑ Phenytoin toxicity**

- Examples:-

I) **Tolbutamide à Hypoglycaemia**

II) **Phenformin à Lactic Acidosis**

III) **Nifidipine --à** Hypotension

3) ACETYLATOR STATUS:-

Examples :-

Rate of Acetylation status of Isoniazid (INH), Dapsone, Hydralazine, Sulfonamides à controlled by an autonomal recessive geneà Dosage of these drugs depend upon acetylation status of an individual.

Rapid acetylators ----à (Eskimos and Japanese)

or

Slow acetylators -----à (Egyptians and Swedes).

Isoniazid, procainamide, hydralazine, dapsone

metabolized by N-acetylation

Acetylator status of individual significantly affects nature of adverse effects of these drugs.

i) Isoniazid (INH) à Slow acetylators à Peripheral neuritis

INH à Fast acetylators à ↑ Acetyl Hydrazine à Hepatotoxicity

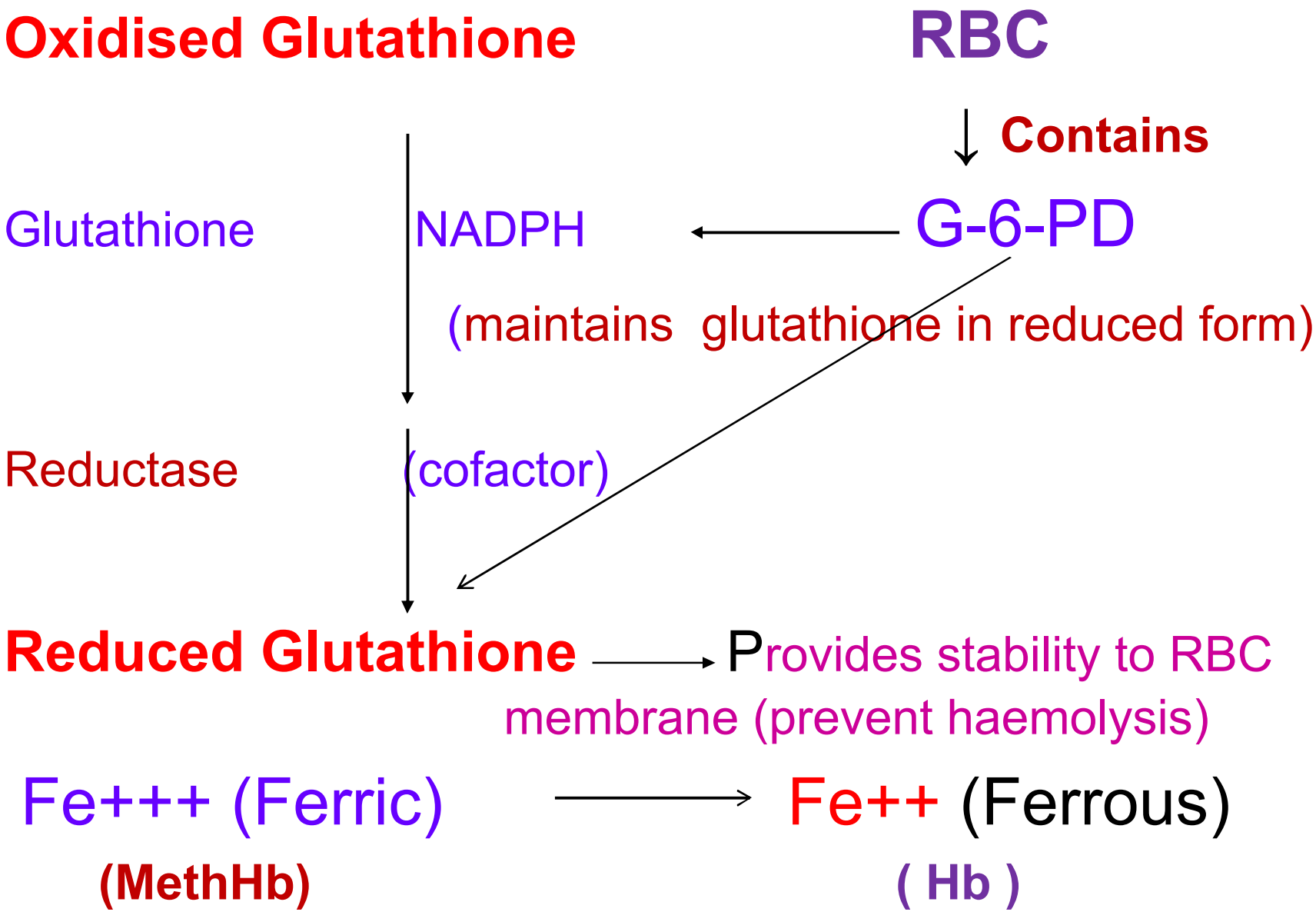
ii) Procainamide or **Hydralazine à** in Slow acetylators -à **Develop antiulcer antibodies à** causing SLE **(Systemic Lupus Erythematous)**

iii) Dapsone à in slow acetylators à causes Haemolysis

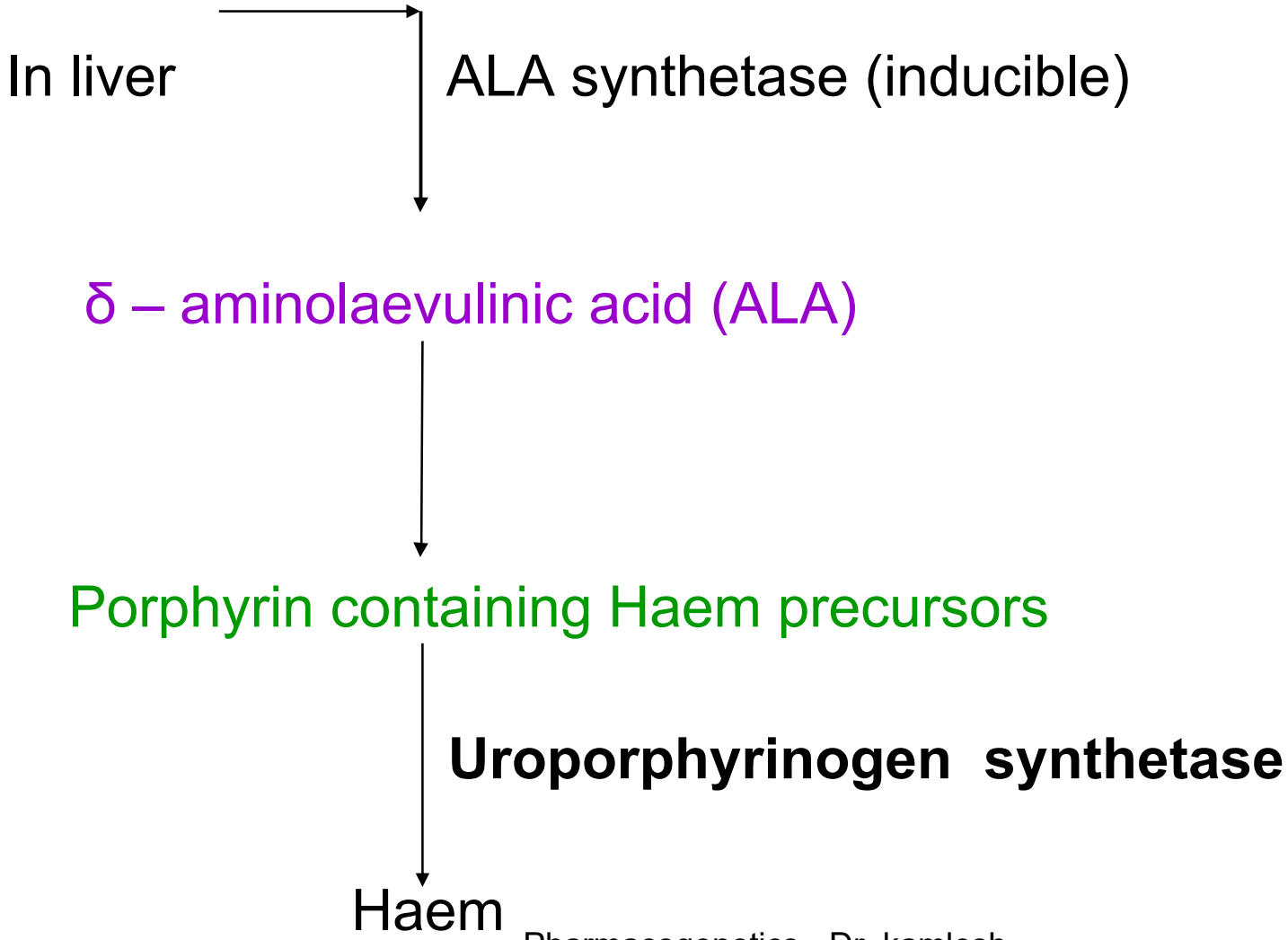
4) G -6 –PD ENZYME DEFICIENCY :-

1. **GLUCOSE – 6 – PHOSPHATE DEHYDROGENASE DEFICIENCY à Oxidant Drugs (Primaquine, Quinine, Sulphonamides, Methyldopa and Phenacetin) à Hemolytic Anaemia**

- **More common in Africans, American Negros, Middle east, and South East races.**


Oxidised Glutathione
RBC
Contains
Glutathione
NADPH
G-6-PD
(maintains glutathione in reduced form)
Reductase
(cofactor)
Reduced Glutathione
Provides stability to RBC membrane (prevent haemolysis)
Fe+++ (Ferric)
(MethHb)
Fe++ (Ferrous)
(Hb)

5) ACUTE INTERMITTENT PORPHYRIA with BARBITURATES



In susceptible individuals, the enzyme responsible for Haem synthesis is lacking

↓

Porphyrin containing Haem precursor accumulate

↓

Acute intermittent porphyria precipitated (gastrointestinal, neurological and behavioral disturbances)

Examples :-

Barbiturates, CPZ, Phenytoin, Cholramphenicol, Oral Contraceptives à **markedly enhances enzymatic activity of D- aminolevulic acid synthetase à leading to increased porphobilinogen synthesis à Precipitates acute attack of Porphyria in susceptible individual.**

6) Malignant Hyperthermia : -

Halothane, succinylcholine, neuroleptic drugs, like CPZ and haloperidol à **Causes Malignant Hyperthermia in an individual deficient in Ryanodine (RyR1) Receptors in Sarcoplasmic Reticulum (SR)à Increased release of Ca++ from SR à Increase Body Temp >420C, rigidity, hyper-reflexia, hypertonia, hyperventilation , hyperkalemia , cardiac arrest** and **Death.**(an Autosomal Dominant condition à **Malignant hyperthermia**

7) Erythrocyte Diaphorase (Sulfonamides, Nitrites) :-

Enzyme Erythrocyte NAD – Diaphorase à protects Erythrocytes (RBCs) à By reducing Methaemoglobin à Haemoglobin (Hb).

Sulphonamides, Nitrites à develops Methaemoglobinaemia in an individual deficient in this Enzyme.

8) Hepatic CYP2D6 Enzyme variations : -

TCA (Tri Cyclic Antidepressant like Imipramine) is metabolized by CYP2D6 enyme.

i) **Slow Metabolizers of TCA à Needs much smaller doses**

ii) **Fast Metabolizers of TCA à Needs much higher doses (Hence, treatment failure with TCA common in Ultra Fast Metabolizers)**

9) Inherited Abnormal Drug Responses :-

i) Anticoagulants :- Resistance to Coumarin develops

ii) Propranolol :- Chinese significantly metabolizes Propranolol faster, still requires much lower dose than western peoples.

iii) Alcohol :- Various ethnic groups (Whites vs Orientals) shows genetic variations in activity of alcohol dehydrogenase & aldehyde dehydrogenase enzymes in them.

Whites à Have alcohol dehydrogenase enzyme in liver à metabolizes alcohol slowly than orientals.

Asians (50%) à inactive form of alcohol dehydrogenase is observed due to mutation à have higher levels of acetaldehydeà following alcohol ingestionà causing facial flushing & other intense responses.

10) Aplastic anaemia: With single dose / low doses of chloramphenicol

11) Aspirin induced late onset asthma or chronic renal failure

12) Thaizide diuretic induced impotence

13) Warfarin (Oral anticoagulant)
à ↑Bleeding risk à with CYP2C9 low activity.

14) Warfarin à Development of Resistance to anticoagulant action à Due to abnormal CYP2C9 enzyme à that regenerates reduced form of Vit. – K à which has low affinity for Warfarin

15) 6-Mercaptopurine & Azathioprine à ↑ Risk of severe Bone Marrow Toxicity à Due to Thiopurine Methyl Transferase (TPMT) enzyme deficiency.

16) Irintecan à Induces Neutropenia & Diarrhoea à in Pts with UGTIAI*28 allele of Glucoronyl Transferase.

17) 5- Fluouracil à Increases toxicity in pts with (DPD) – Dihydropyrimidine dehydrogenase deficiency.

18) CYP2D6 Deficiency à Results in :-

i) **Failure of Codeine induced Analgesia (B'z– This enzyme generates Morphine from Codeine).**

ii) **Increases toxicity of Antidepressants & antipsychotics**

iii) **Poor Metoprolol/Debrisoquine Metabolizer status**

Pathological States of Diseases

1) **GIT Diseases :- Absorption altered (↑or↓)**

a) Coeliac Disease → Amoxicillin Abs.↓
Cotrimoxazole / Cephelexin Abs. ↑.

b) Migraine attacks → Gastric stasis → Abs.↓ of antimigraine drugs.

c) Achlorhydria → Aspirin Abs.↓→ B'Z of Increase Ionization

d) NSAIDs → Aggravates peptic ulcers.

2) **Liver Diseases :-**

a) Cirrhosis of Liver → Influences drug disposition of orally administered drugs→ Increases Bioavailability (due to loss of Hepatocellular Functions & Portocaval shunting).

b) Lidocaine, Morphine , Propranolol → Metabolism & Elimination Decreases→ Reduce dose or prefer drugs which are not dependent on hepatic metabolism → Lorazepam / Oxazepam in place of Diazepam → Atenolol in place of

c) Prodrugs à Prednisone, Bacampicillin à Less Effective in Liver Disease (Needs Hepatic Metabolism)à Avoid them.

d) Morphine, Barbiturates à Sensitivity to depressant action in brain increases in cirrhotic pt. à Normal dose produces Hepatic Coma.

e) Warfarin à Increases risk of Bleeding à due to Increased Prothrombin Time à B'z of reduced clotting time in cirrhotic Pts.

f) NSAIDs à Increases Fluid Retaining Tendency

g) Metformin à Increases risk of Lactic acidosis

h) Avoid Hepatotoxic drugs in Pts with Liver Diseases.

Kidney Diseases

Affects P/Ks & P/Ds of many drugs

i) Aminoglycosides, Digoxin, Phenobarbitone à Excreted Unchanged in Urine à Their Renal Clearance decreases in renal diseases with Decreased Creatinine clearance (CLcr).

ii) Loading Dose not altered in renal diseases

iii) Maintainance dose to be reduced or Dosing interval to be prolonged

CLcr (Pt)	Dose Rate To Be Reduced To
50-70 ml / min	70%
30-50 ml / min	50 %
10-30 ml / min	30%
5-10 ml / min	20%

iv) Binding to Acidic Drugs Reduced in Renal Diseasesà Due to Low Plasma Protein (Albumin).

v) Binding to Basic Drugs not much affected in Renal Diseases.

vi) Opiates, Barbiturates, Phenothiazines, Diazepam à Blood Brain Barrier Permeabiities Increases in Renal Diseases à Increases CNS depression.

vii) Pethidine à Avoid Pethidine in renal diseases à B'z Its Metabolite Nor-Pethidine accumulates à Causing Toxicity.

viii) Antihypertensivesà Marked Postural Hypotension

ix) Renal Diseases à worsens clinical conditions with Drugs like :-

a) **Tetracyclineà Accentuate uraemiaà B'z have anabolic effect.**

b) **NSAIDsà** Increases Fluid retention tendency in renal diseases

c) **Nephrotoxic drugs à Aminoglycosides, Sulphonamides (crystalluria), Vancomycin, Cyclosporin,** Amphotericin – B **à Should be avoided in renal diseases.**

d) Thiazides à Reduces GFRà Ineffectiveà Worsens Uraemia (Use Furosemide).

e) Pethidine à Repeated doses à Muscle twitching, seizures (Due to its active metabolite Nor-pethidine) in renal diseases.

f) Urinary Antiseptics (Methenamine Mandealate, Nitrofurantoin, Nalidixic acid) à Fails to achieve High urinary concentration à Produces systemic toxicities.

Heart Diseases

- **Alter P/Ks of drugs By :-**
- **i) Decreases absorption of Procainamide, Hydrochlorthiazide à B'z of mucosal edema & splanchnic vasoconstriction.**
- **ii) Loading dose of Lidocaine, Procainamide à should be reduced à B'z of increase volume of distribution due to expansion of ECF.**
- **iii) Reduce rate of dosing of Procainamide, Lidocaine, Theophyllineà B'z of reduced perfusion, congestion in liver, Reduced GFR & Reduced rate of drug elimination.**

iv) Digitals à Decompensated Heart à More Sensitive to Digitalis à Reduce its Dose.

Thyroid Diseases

1) Hypothyroid Pts à More sensitive to Digoxin, Morphine, CNS depressants.

2) Hyperthyroid Pts à Resistant to Inotropic action , But, more prone to arrhythmic action of Digitalis (B'z Clearance of Digoxin is directly proportional to the Thyroid Functions of an individual).

Other Diseases & Pathological States

i) **Antipyretic (PCM)à Lowers raised body temperature only in fever.**

ii) **Thiazidesà Induces marked diuresis only in patients with oedema.**

iii) **MI Pts à More prone to develop arrhythmias with Adrenaline, Digitalis.**

iv) **Myaesthenicsà More prone to Curareà prolongs paralysis.**

v) **Schizophrenicsà** tolerate higher doses of Phenothiazines

vi) **Head Injuryà Prone to respiratory failure with normal doses of Morphine.**

vii) **Hypnoticsà in Pts with severe painà causes mental confusion & excitement.**

viii) **Cotrimoxazole->** Increases incidences of ADR in AIDS pts.

ix) **Atropine, Imipramine, Furosemideà causes urinary**

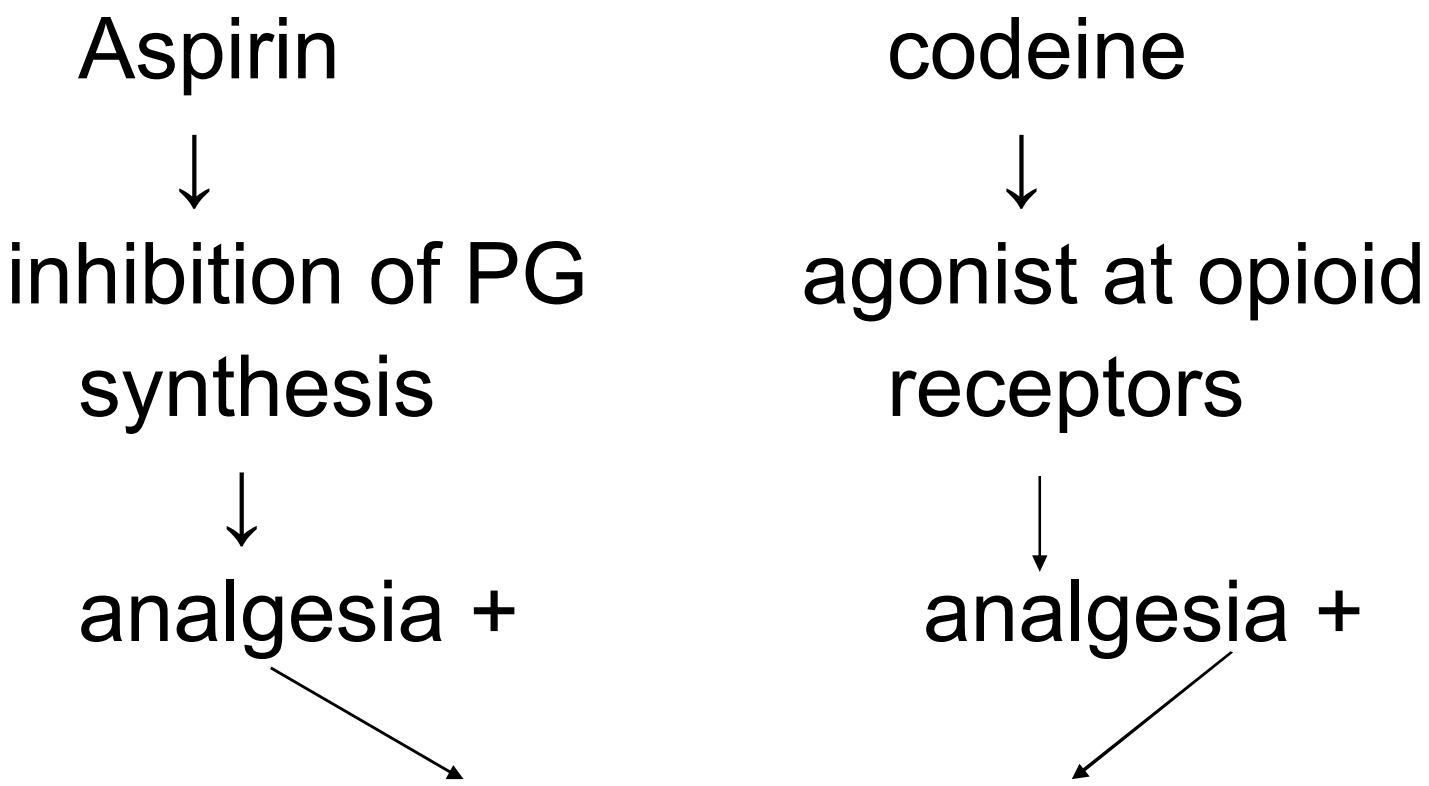
Modified drug effects after concurrent administration of two different drugs

- **SUMMATION:**

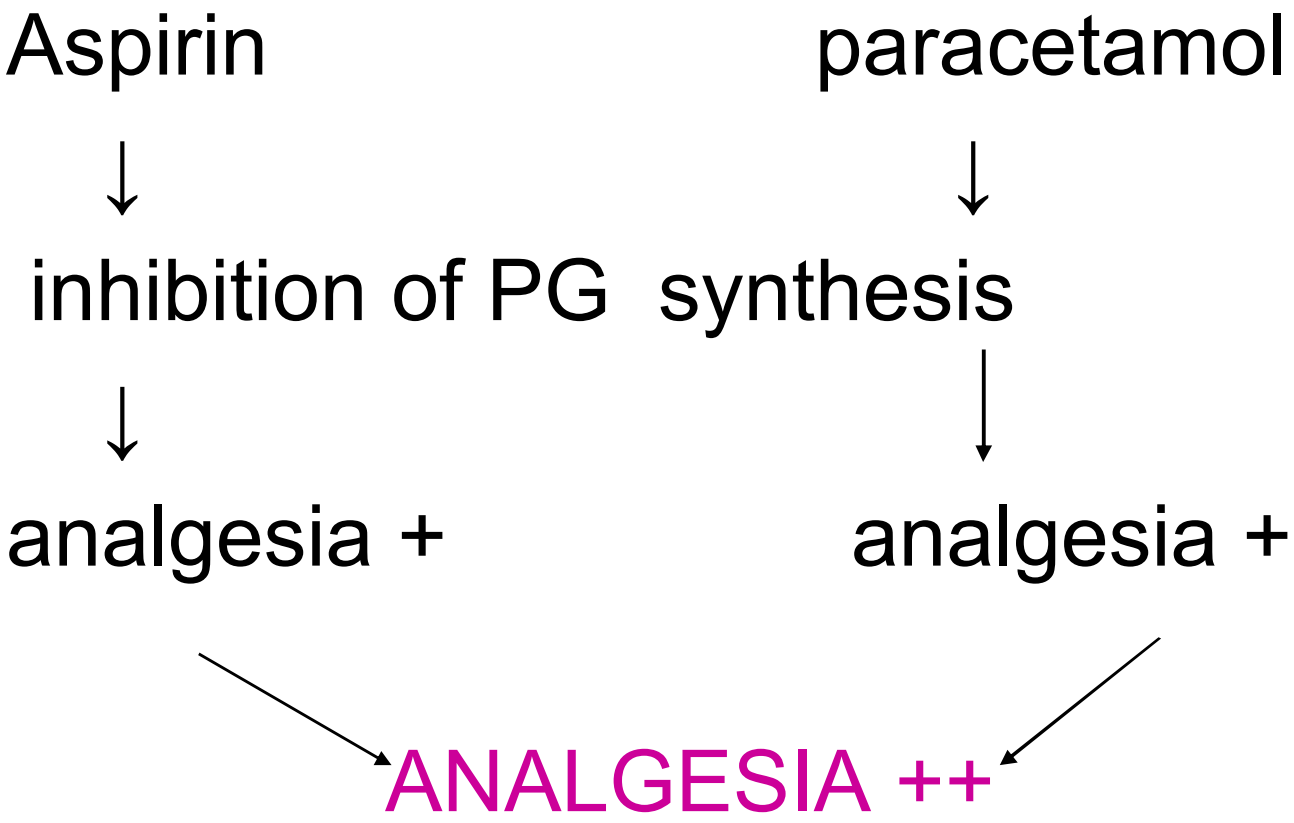
  two drugs elicit same response, BUT with ***different*** mechanism, their combined effect is equal to the algebraic sum of their individual effects. A + B = (A + B)

- **ADDITIVE EFFECTS** : combined effect of two drugs, acting by ***same*** mechanism

SUMMATION


Aspirin
inhibition of PG synthesis
analgesia +
codeine
agonist at opioid receptors
analgesia +
ANALGESIA ++

Additive effect



SYNERGISM (potentiation)

Combined effect of two drugs is greater than the algebriac sum of their individual effects.
A + B < (A+B)

pharmacodynamic

1. cotrimoxazole (sulfamethoxazole + trimethoprim)

2. Beta blockers and diuretics

Pharmacokinetics

1. Levodopa + carbidopa --

2. hypertensive crisis- resulting with a combination of tyramine + MAOI

Drug antagonism

the combined effect of two drugs is less than the sum of the effects of the individual drugs

A + B > (A+B)

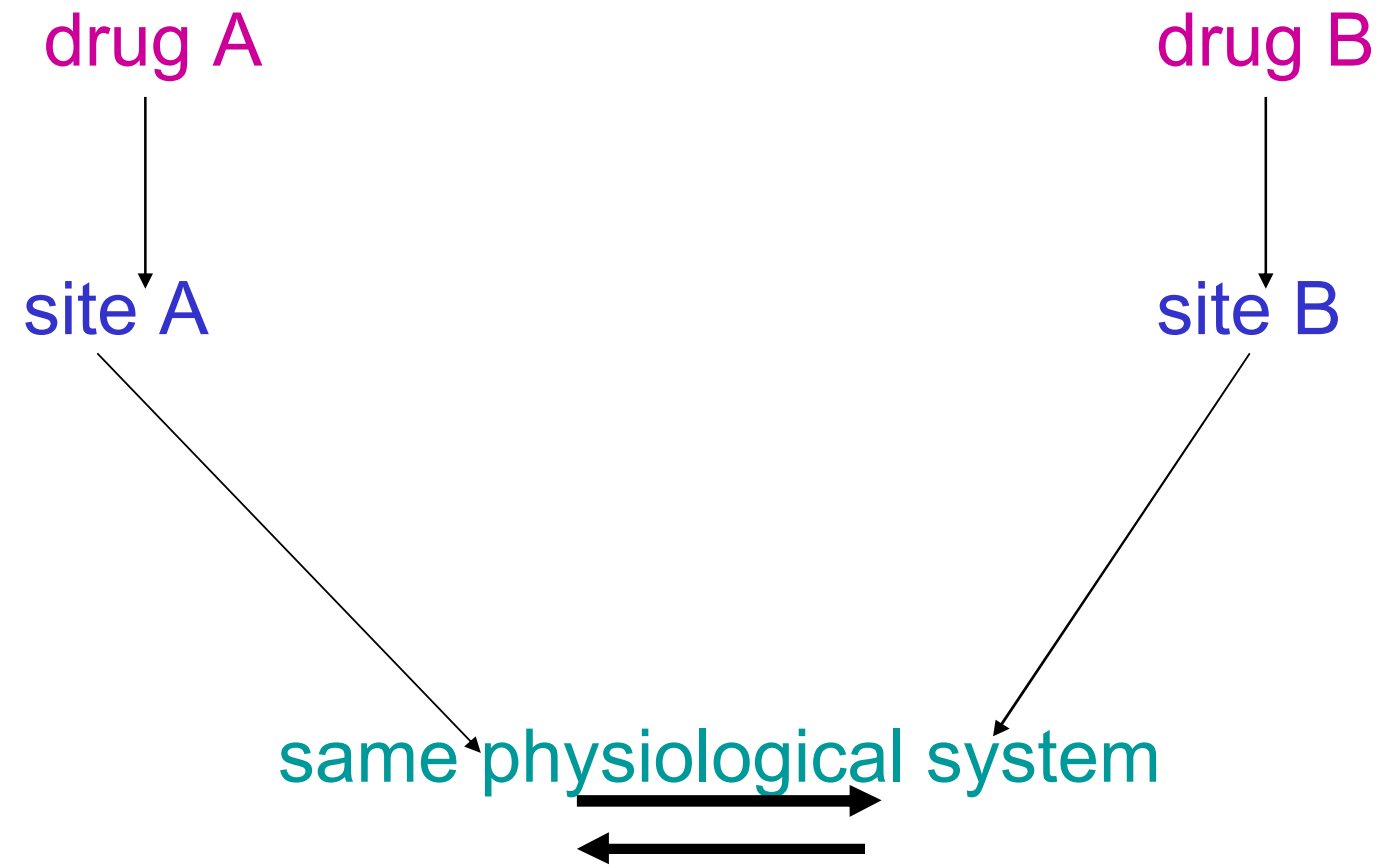
Chemical antagonism

--heparin (strong negatively charged) – protamine (highly positively charged)

-- aluminium hydroxide (antacid) – nutralize gastric acidity

- Chelating agents (e.g. BAL) à form inactive soluble complexes with heavy metals.

2. PHYSIOLOGICAL OR FUNCTIONAL ANTAGONISM



CNS stimulants antagonize effects of CNS depressants

- Histamine (vasodilatation) on blood pressure can be counteracted by norepinephrine (vasoconstriction)

3. BIOLOGICAL OR PHARMACOKINETIC ANTAGONISM

- reduction of anticoagulant effect of warfarin by enzyme inducer phenobarbitone

PHARMACOLOGICAL ANTAGONISM

REVERSIBLE (COMPETITIVE OR SURMOUNTABLE OR EQUILIBRIUM) ANTAGONISM

- overcome by ↑ing conc. Of agonist
- LDRC à parallel shift to right
- Two drugs ***acting on same receptor***

- Reversible antagonist dissociate faster

Overall antagonist occupancy falls and new equilibrium is rapidly established.

Example – atropine is competitive antagonist of Ach at muscuranic receptors

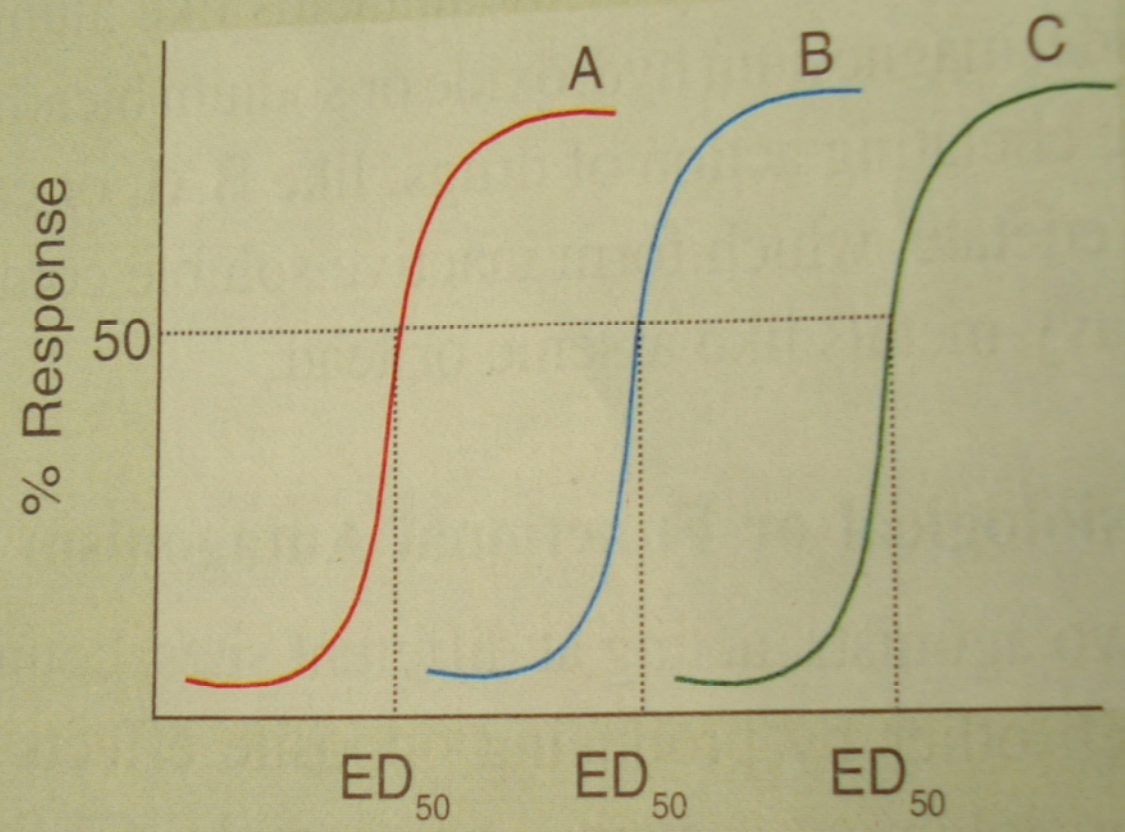


Fig. 7.39

A: LDR curve for agonist alone.

B: LDR curve for agonist in presence of competitive antagonist.

C: LDR curve for the agonist plus increasing concentration of competitive antagonist.

- IRREVERSIBLE (NONEQUILIBRIUM) COMPETITIVE ANTAGONISM

when antagonist dissociates , very slowly or not at all (formation of covalent bond)

-- antagonism is insurmountable à the maximal agonist response cannot be obtained

-- exa. OP compounds

- Efficacy decreases
- Duration of action of antagonist is longer as rate of dissociation is very slow
- Example : phenoxybenzamine

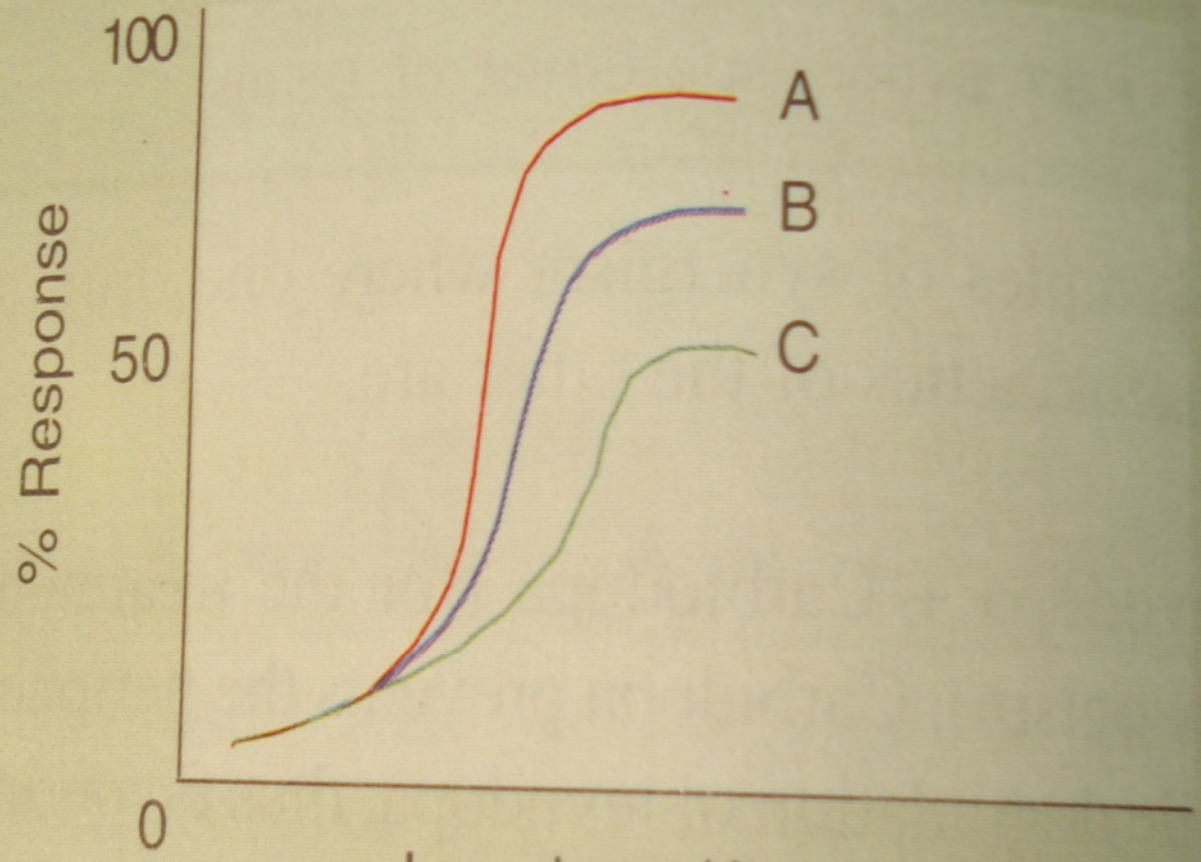


Fig. 7.40

A: LDR curve for agonist alone.

B: LDR curve for agonist in presence of irre
tagonist.

C: LDR curve for the agonist plus increasing conc
of irreversible antagonist.

NON COMPETITIVE ANTAGONISM:

- Binds to another site of receptor
- Antagonist does not resemble
- Flattening of agonist DRC
- Insurmountable antagonism

- Antagonist apparently reduces efficacy of agonist or appears to have inactivated a certain number of receptors

- Intensity of response depends only on conc. of antagonist

- Exa.: CCB - Noradrenaline