PHARMACODYNAMICS

Nature of Targets

- **Protein Targets:**
- Enzymes
- Ion Channels
- Transporters (Carrier molecules)
- Receptors
- Others
  - Structural Proteins

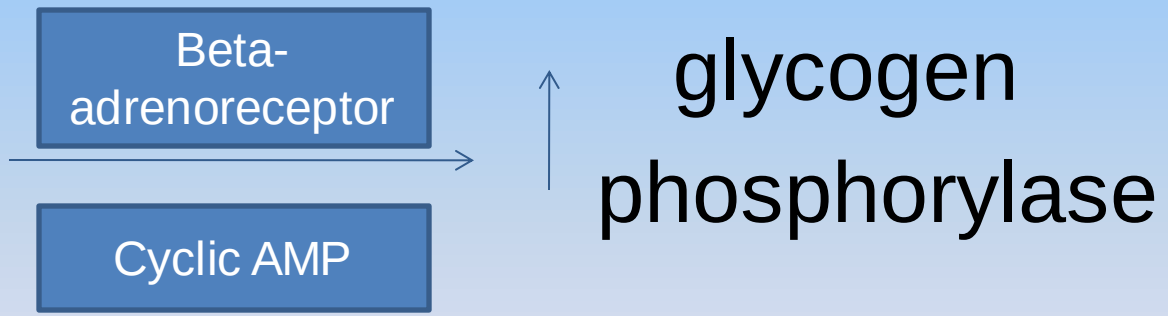
Enzymes

- Stimulated or Inhibited
- Stimulation inc. affinity to substrate
- E.g.
  - Reversible inhibition of acetyl cholinesterase by neostigmine
  - Irreversible inhibition of cyclooxygenase by aspirin

Enzymes

- Through receptors and second messengers.
- Enalapril ------- (-) ACE

- Adrenaline



Ion-Channels

- Drugs affect ion channels either directly or through specific receptor
  - Direct: Dofetilide and Amiloride block delayed rectifier K-channels.
  - May be blocked directly or modulated by drugs acting at sites other than the receptor
  - ✓ e.g. Phenytoin blocks directly & prolongs the inactivated state of neuronal Na+ channels
  - ✓ Modulators e.g. Fludrocortisone acting on Renal-tubule Na channels

Ion-channels (cont.)

- Channels may be:

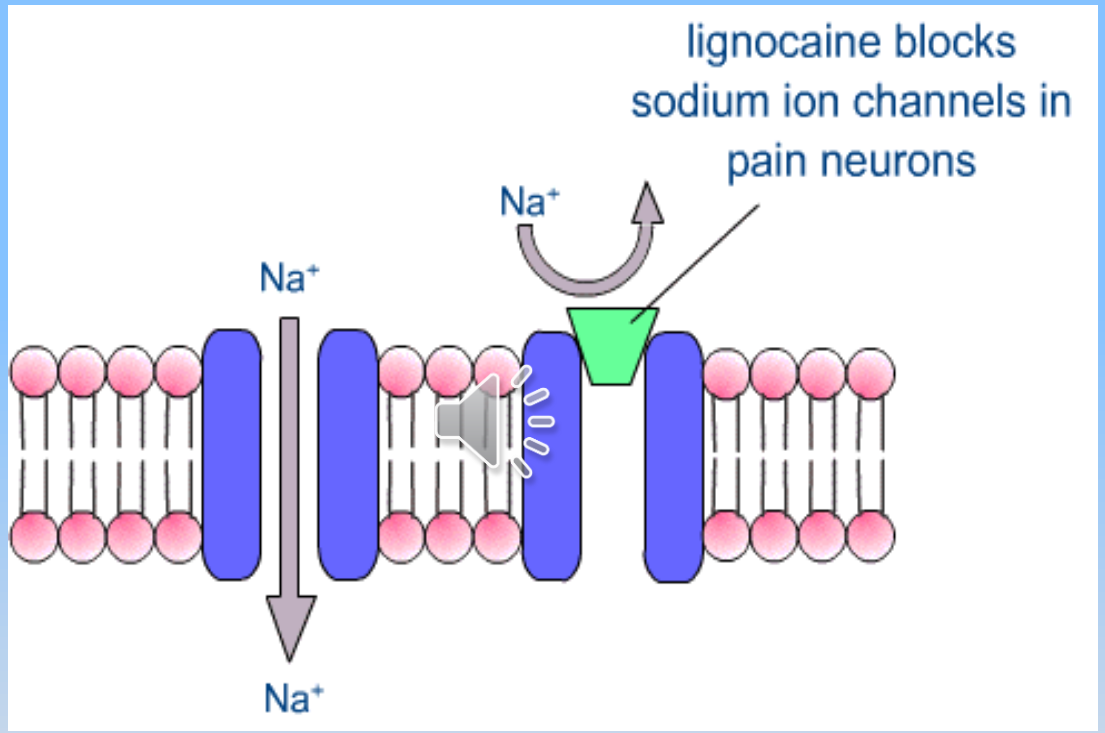
a) Ligand-gated:

– Activated or are inhibited when receptor is occupied by ligand e.g Nicorandil opens while sulfonylureas close ATP- sensitive potassium channels.

Ion Channels (cont.)

b) Voltage-gated channels:

- open when cell membrane is depolarized.
- Local anesthetics plug the voltage sensitive Na+ channels. Physically blocking ion permeation
- Minoxidil, a vasodilator, increases the membrane permeability to K+. This hyperpolarises the cell & switches off voltage dependant Ca^{2+} channels

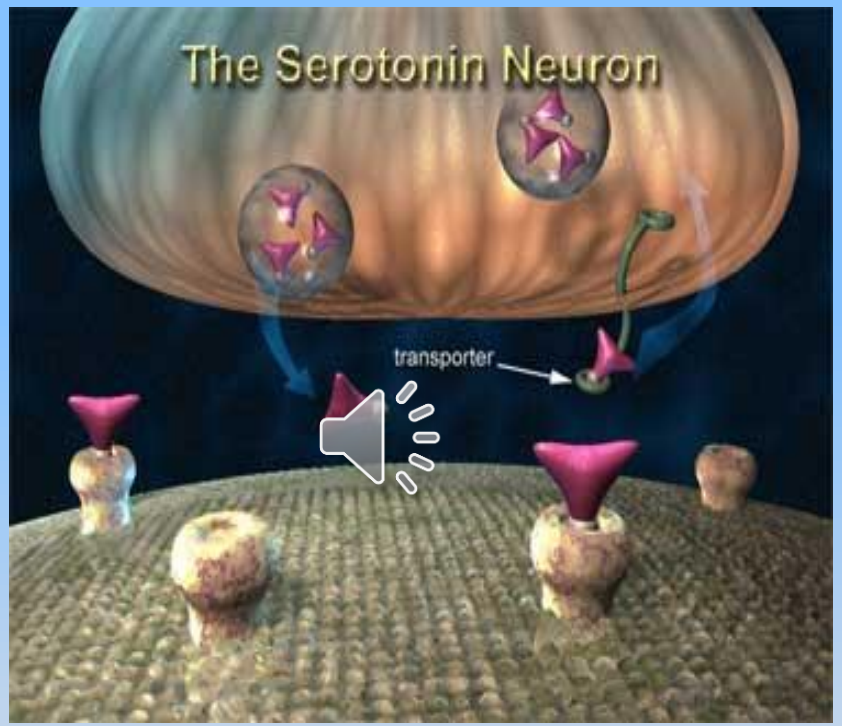


http://www.health.bcu.ac.uk/physiology/ion%20channels.gif

Transporters

- Drugs produce their action by directly acting with the carrier to inhibit the on going physiological transport of metabolite/ion.
- E.g.Desipramine : (-) Norepinephrine transporter
- SSRI's : (-) Serotonin transporter
- Hemicholinium – (-) Choline uptake

  depletes cholinergic neurons of acetyl-choline



http://medicineworld.org/images/blogs/10-2006/serotonin-transporter-61610.jpg

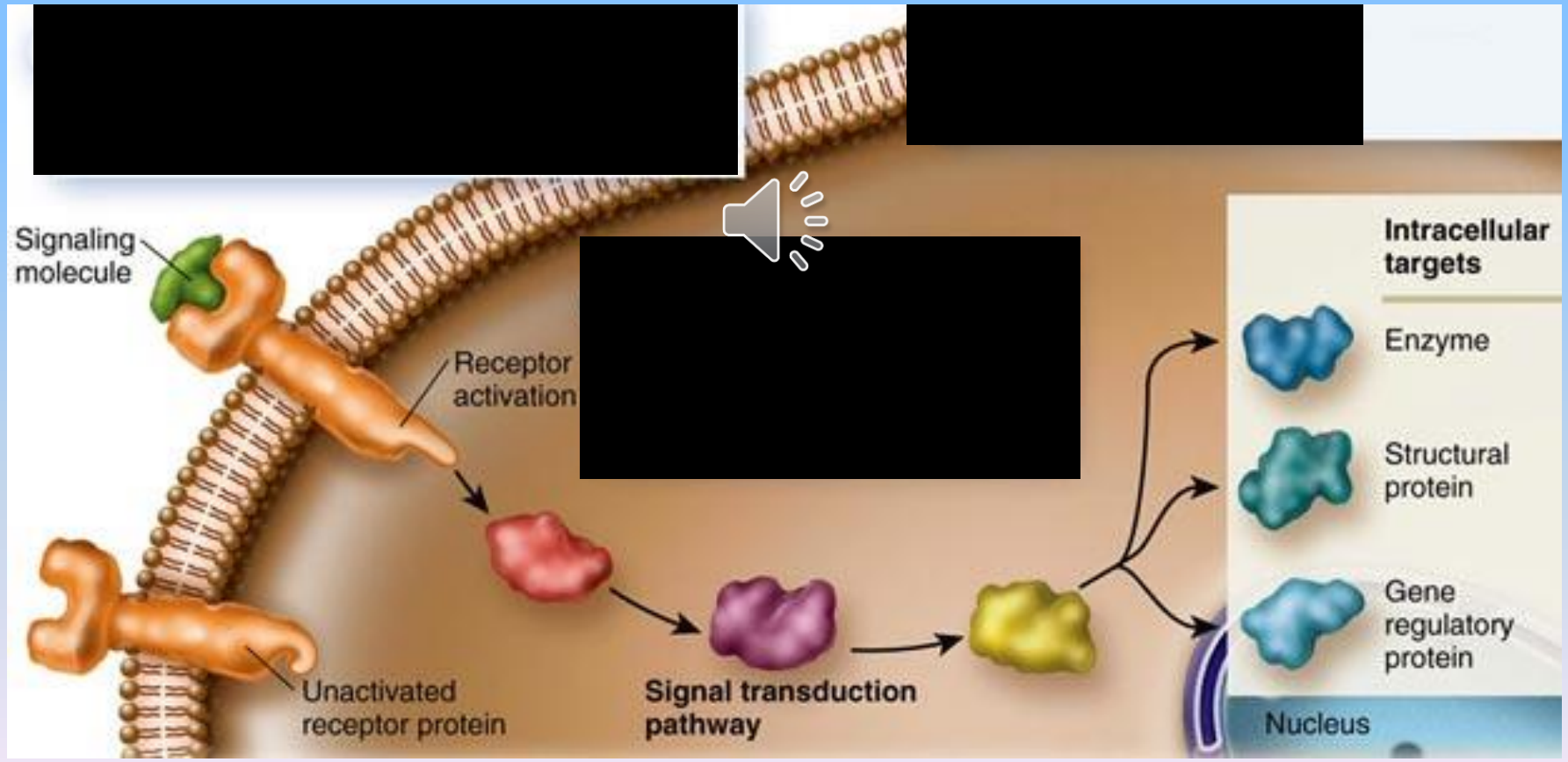
Receptors

- Macromolecules or binding site located on the surface or inside the effecter cell that serves to recognize the signal molecule/ drug and initiate the response to it, but itself has no other fn.
- Determines the quantitative relationship between dose & effect
- Selectivity of Drug action

Receptors

- G-Protein coupled
- Intrinsic ion channel
- Enzyme linked
- Transcription factor

Overview: Consequences of drug-receptor interaction



Drug-Receptor Interactions

- **Agonist:** Activates a receptor to produce an effect similar to that of the physiological molecule

  e.g. Nicotine & Acetylcholine on Nicotinic Ach receptor

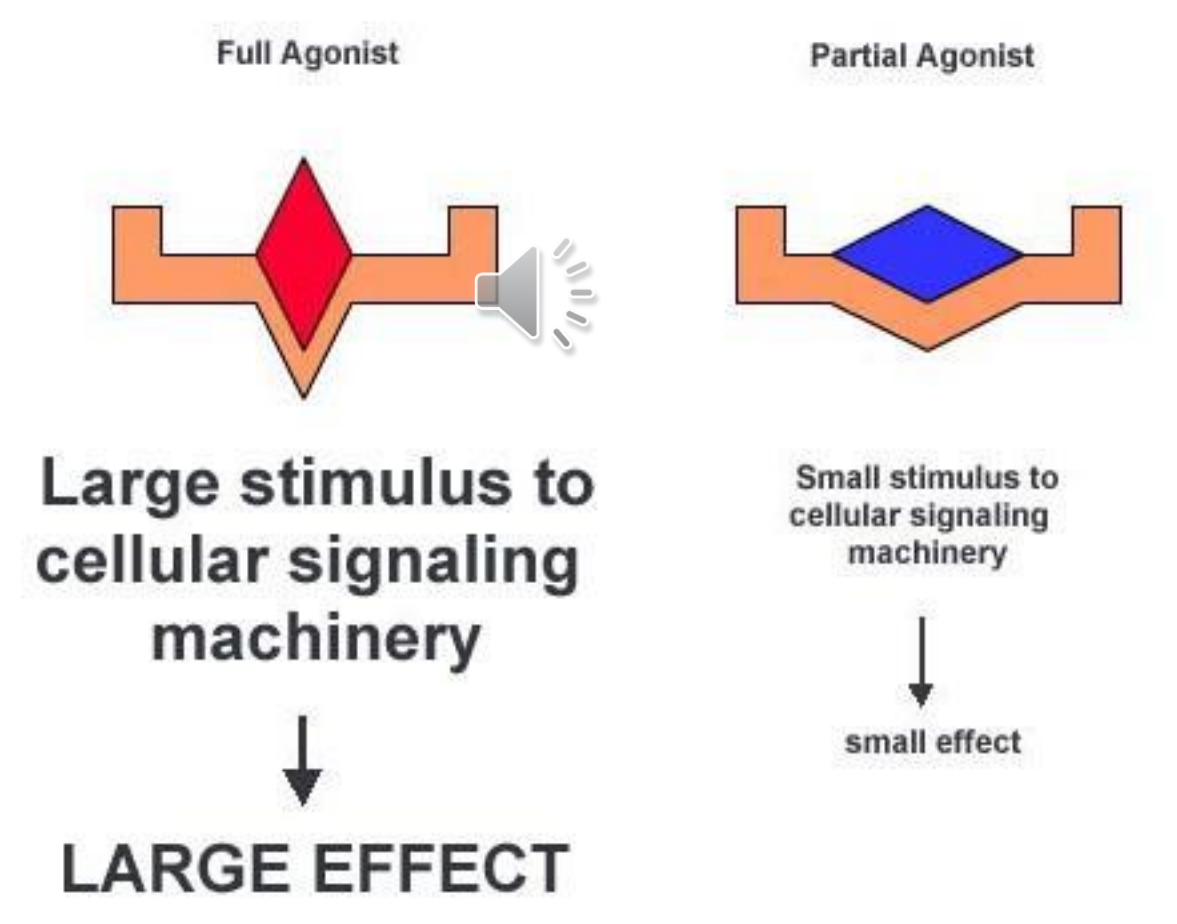
- **Inverse agonist:** Activates a receptor to produce an effect in the opposite direction to that of the agonist
- e.g. β-carboline on benzodiazepine receptor

Drug-Receptor Interactions

- **Antagonist:** Prevents the action of an agonist on a receptor or the subsequent response, but does not have any effect of its own.

  e.g. Tubocurarine on Nicotinic Ach receptor
- **Partial agonist:** Activates a receptor to produce sub maximal effect but antagonizes the action of a full agonist
- e.g. Buprenorphine on μ- opioid receptor

Agonists: Differences between a full agonist versus partial agonist



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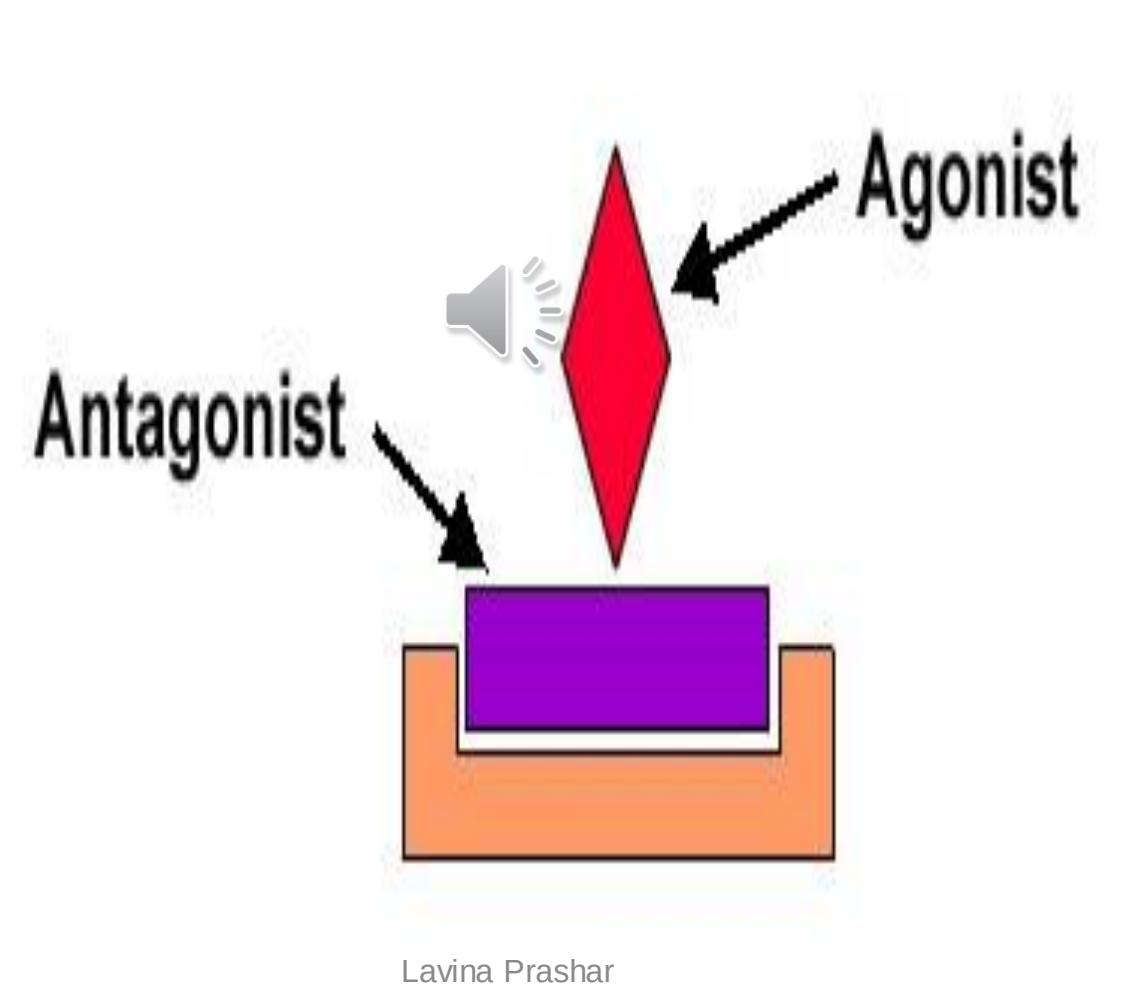

Agonist
Antagonist

Receptor-Occupation Theory

- (D) + (R) $\rightleftharpoons$ (DR) $\longrightarrow$ (DR)*

  Occupation governed by Affinity

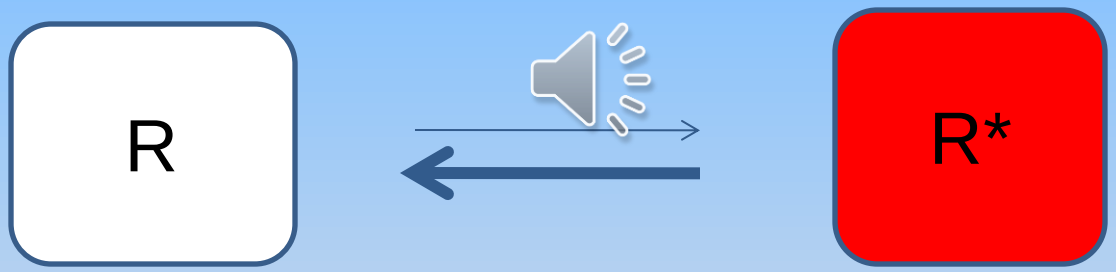
  Activation governed by Efficacy

Drug-Receptor Occupation Theory

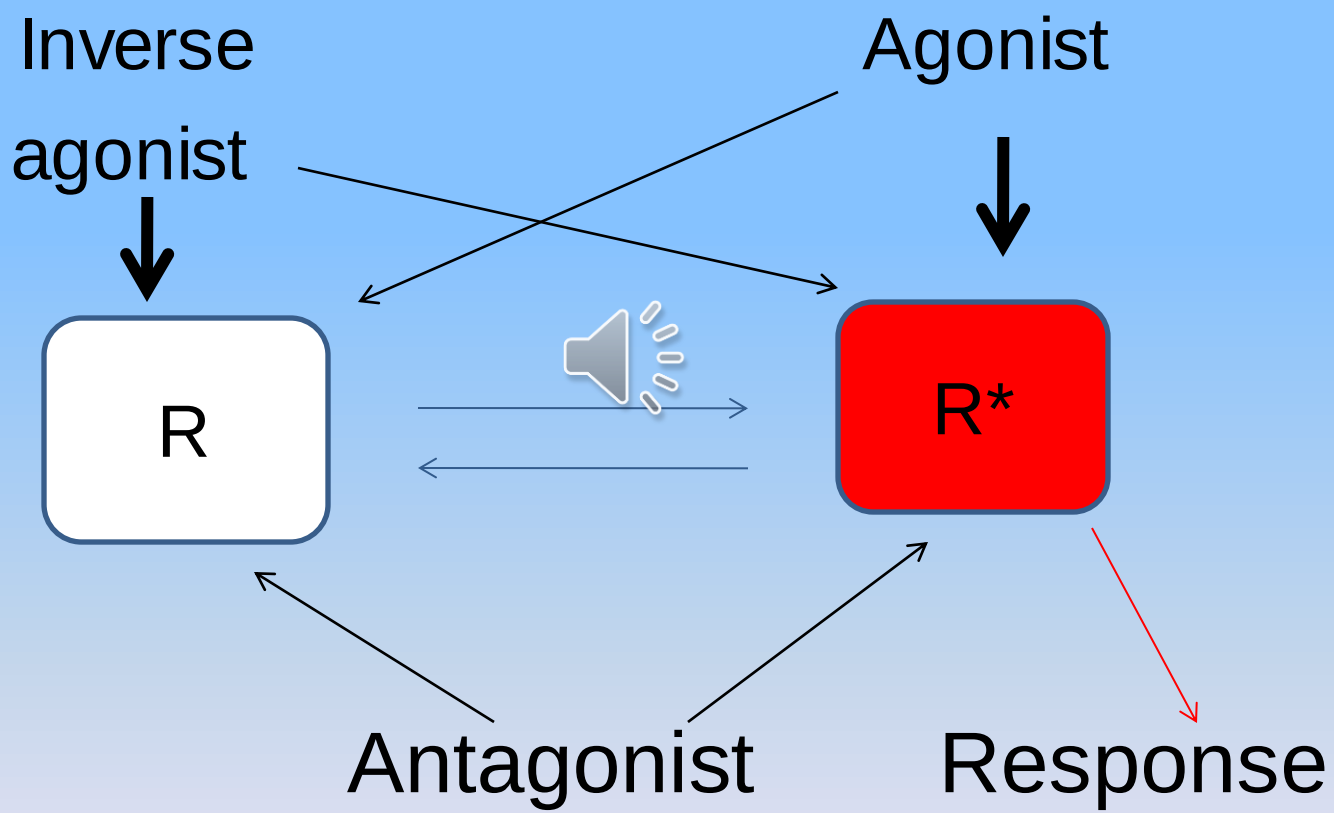
	Affinity	Intrinsic-activity
• Agonist	+1	+1
• Competitive antagonist	+1	0
• Partial agonist	>0<1	>0<1
• Inverse agonist	+1	-1

Two-State Model

In Resting state:



Two-State Model



Two-State Model

- Partial Agonist???

Antagonist

- Receptor Block
- Enzyme Inhibition
- Chemical antagonism
- Pharmacokinetic antagonism
- Physiological antagonism

Receptor Block

- **Competitive antagonism**
- **Noncompetitive antagonism**

1. Competitive antagonism
   a. Reversible (Equilibrium): Chemically similar and binds to same site as agonist.
      - Rate of dissociation is high
      - New equilibrium rapidly established on addition of agonist. e.g. Morphine - Naloxone

Receptor Block

- Irreversible (Non-equilibrium): Chemically similar to the agonist. Bind to same site
  - Dissociates slowly so agonist unable to displace the antagonist.
  - e.g. Phenoxybenzamine antagonizes adrenaline at α-receptors.

Receptor Block

2. Noncompetitive antagonism:
   - Chemically unrelated to agonist.
   - Binds to different site.
   - Alters the receptor in such a way that it is unable to combine with agonist, or unable to transduce the response, so that down stream chain of events is uncoupled.
   - e.g. Diazepam - Bicuculline

Non-competitive (indirect) agonists and antagonists

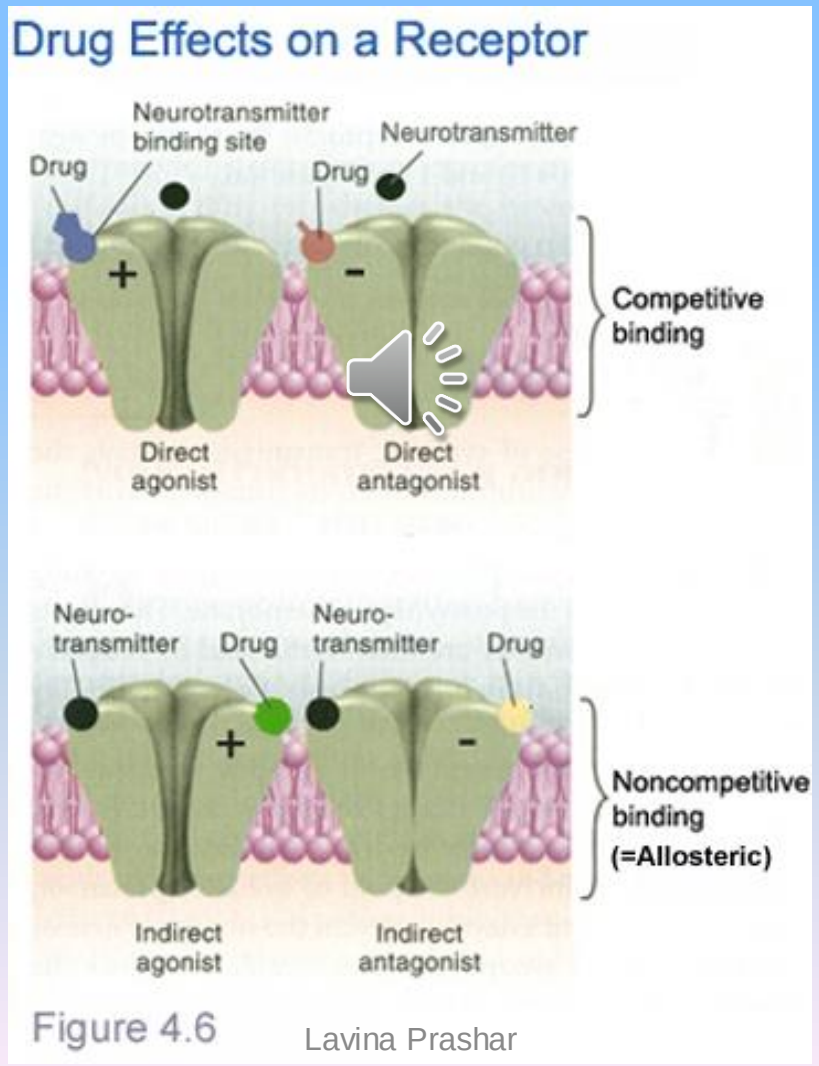


Figure 4.6

Enzyme-Inhibition

1. Competitive Inhibition
   a. <u>Reversible (equilibrium type):</u>
   - Structurally similar
   - Competes with normal substrate for catalytic binding site of enzyme.
   - Product formed or non-functional product formed
   - Inc. conc. displaces inhibitor
   - E.g. Sulphonamides compete with PABA for bacterial folate synthetase

Enzyme-Inhibition

b. Irreversible (non-equilibrium type):

- Drug reacts with same catalytic site
- Form strong covalent bond
- Normal substrate unable to displace inhibitor
- E.g. Organophosphates – esteric site of cholineesterase.

Enzyme-Inhibition

2. Noncompetitive Inhibition:
   - Drug reacts non-catalytic site
   - Alters enzyme-loses catalytic property
   - E.g. Aspirin-cyclooxygenase

Chemical Antagonism

- Two drugs react chemically to form inactive product
  - E.g Chelating agents (Bal, Cal. disod. edetate) complex toxic metals (AS,Pb)
  - May react in same syringe e.g. Heparin + penicillin

Pharmacokinetic Antagonism

- Antagonist reduces the conc. of active drug at its site of action
- Metabolism or excretion may be ↑
- or absorption ↓
- e.g. Warfarin hepatic metabolism is accelerated by Phenobarbital.

Physiological Antagonism

- Opposing actions of drug cancel each other
- e.g Histamine and omeprazole

Physical Antagonism

- e.g. Charcoal adsorbs alkaloids and prevents their absorption

Combined Effect of Drugs

- Synergism:

a) Additive:

- Action of one drug facilitated or increased by other.
- May act in same direction or may be inactive but enhance action of other
- Effect of drug A + B = effect of drug A + effect of drug B
- e.g. Amlodipine + Atenolol as antihypertensive (co-formulation Amtas-AT)

Combined Effect

b). <u>Supra additive:</u>

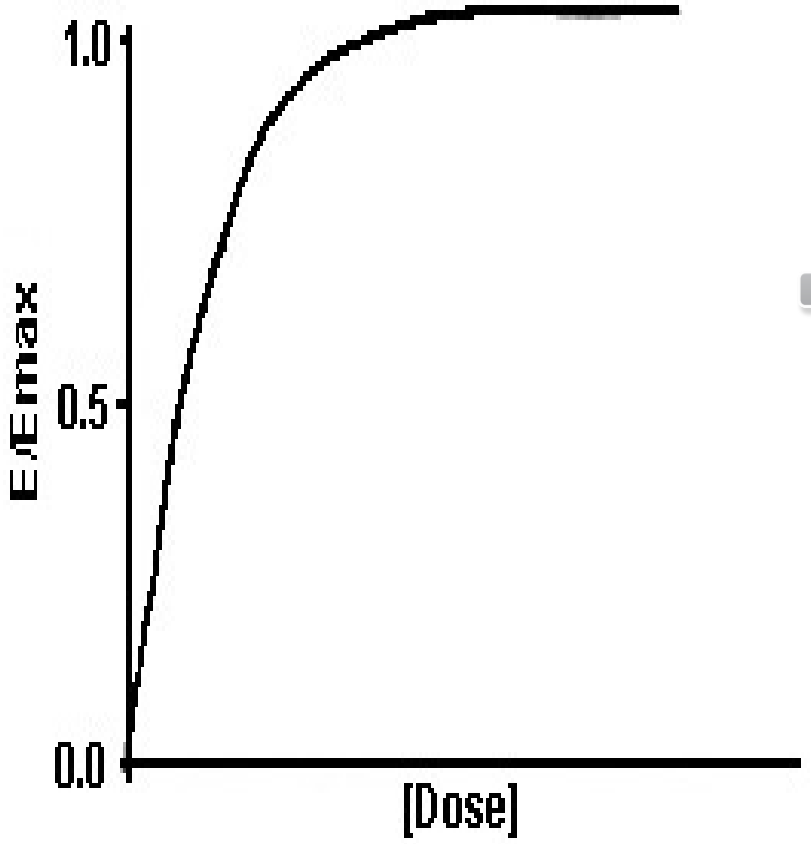
- Effect of combination is greater than individual
- Effect of drug A + B > effect of drug A + effect of drug B.
- E.g. Sulfamethoxazole + trimethoprim (Septrin)

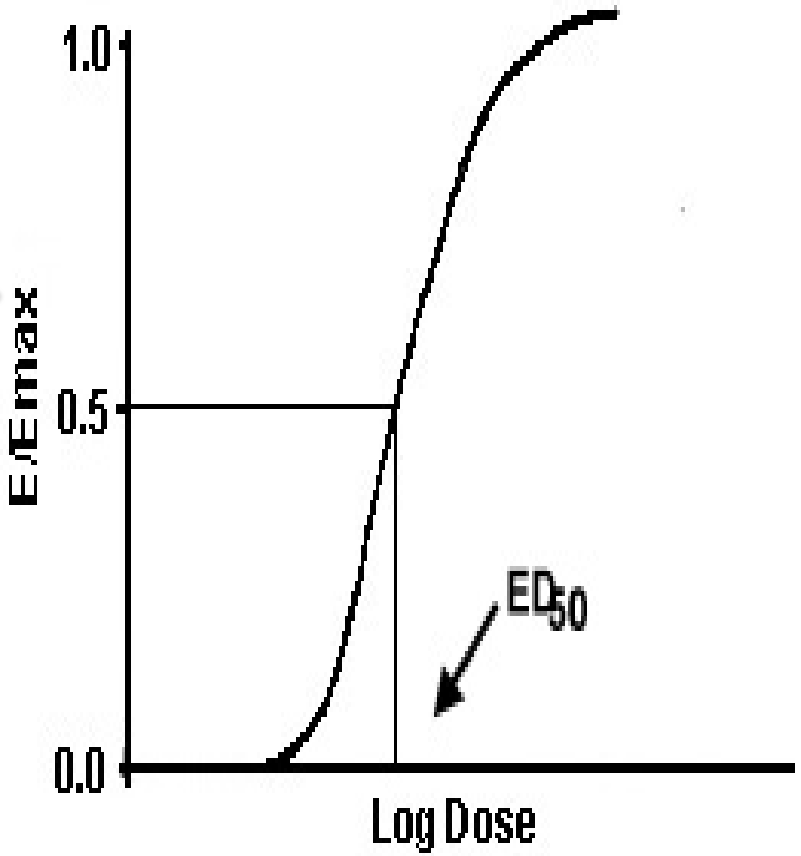
Drug Potency

- Amount of drug required to produce a certain response
- Position of Drug Response Curve on the dose axis is index of drug potency
- Relative potency: Defined by comparing the dose of the two agonists at which they elicit half maximal response (EC_{50})
  - E.g. 10mg of morphine = 100mg of pethidine as analgesic. Morphine is 10 times more potent than pethidine

Drug Efficacy

- Upper limit of DRC is index of drug efficacy
- Maximum response that can be elicited by a drug
- Morphine produces a degree of analgesia not obtainable with any dose of aspirin
- Efficacy is a more decisive factor in the choice of a drug


1.0
0.5
0.0
E/Emax
[Dose]


1.0
0.5
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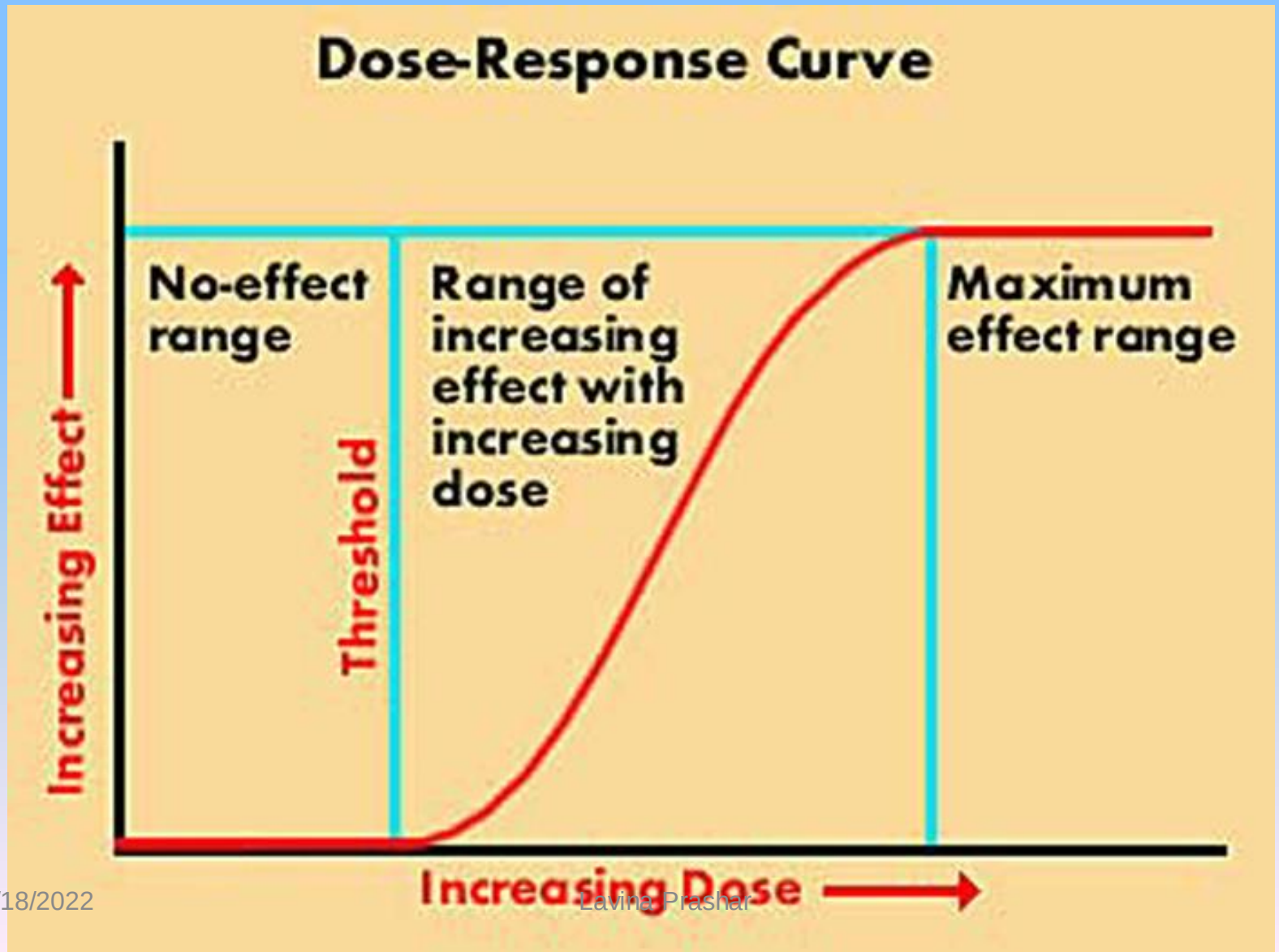
E/Emax
ED50
Log Dose

Range of dose-response curves



Selectivity

- The gap between the therapeutic effect DRC and the adverse effect DRC defines the safety margin or the therapeutic index of a drug
- Therapeutic index: $\frac{\text{median lethal dose}}{\text{median effective dose}}$

$$\frac{LD_{50}}{ED_{50}}$$

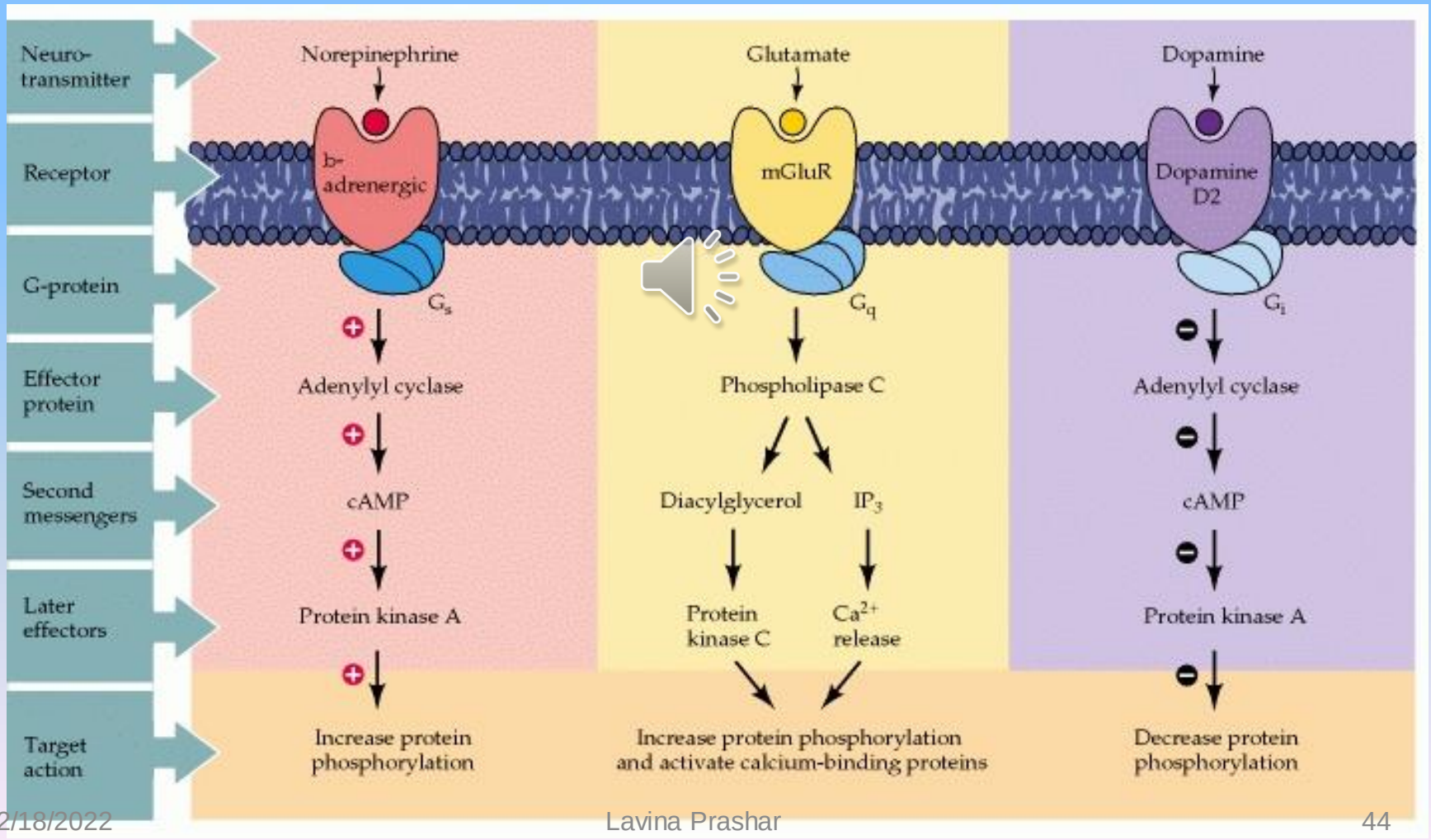
False Substrates

- Drug molecule undergoes chemical transformation. Forms an abnormal product that subverts the normal metabolic pathway.
- E.g. Fluorouracil replaces uracil as an intermediate in purine biosynthesis but cannot be converted into thymidylate.
- Thus blocks DNA synthesis and prevents cell division

G-Protein Coupled

- Gs, Gp, Gi
- Gs stimulates adenyl cyclase
- ATP $\xrightarrow{\text{Adeylyl cyclase}}$ cAMP $\xrightarrow{\text{Phosphodiesterase}}$ 5AMP
- cAMP functions through cAMP dependent protein kinases (PKA)

Common signal transduction pathways activated by G-proteins



G-Protein Coupled

- Ion channels activated or inactivated by G-proteins
- Ions involved without intervention of second messengers
- Bring about:
  - Hyperpolarization
  - Depolarization
  - Changes in intracellular Ca2+

G-Protein Coupled

- Gs opens Ca^{2+} channels in myocardium and skeletal muscles
- Gi opens K^{+} channels in heart, smooth muscles, closes neuronal Ca^{2+} channels

Receptors Linked to Enzymes

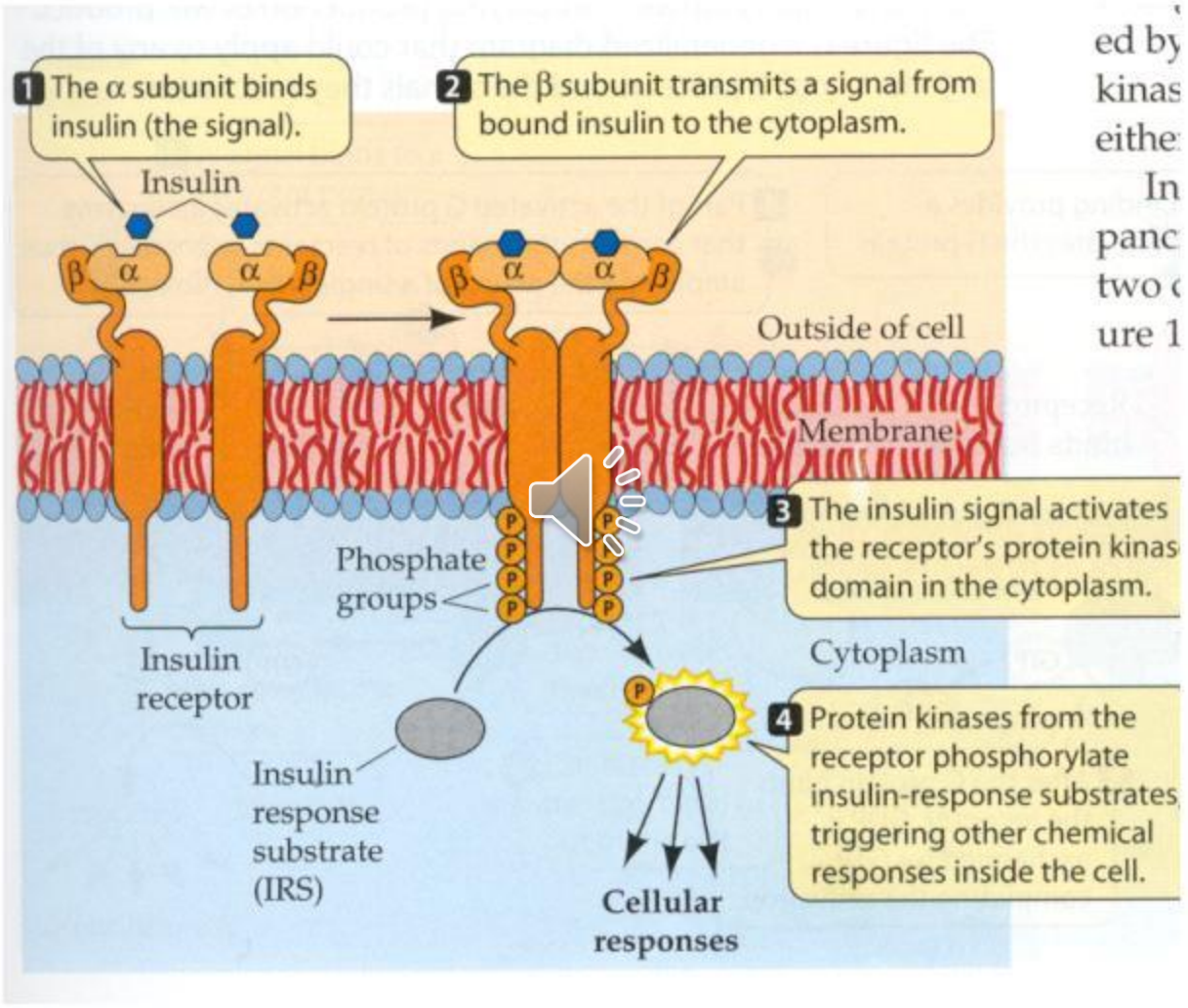
- Insulin
- Epidermal Growth Factor
- Platelet Derived Growth Factor
- Many other hormones

Receptors Linked to Enzymes

- Extracellular hormone binding domain
- Cytoplasmic enzyme domain:
- Protein tyrosine kinase, Serine kinase, guanylyl cyclase
- 2 domains connected by a hydrophobic segment of a polypeptide chain crossing lipid bilayer of plasma membrane

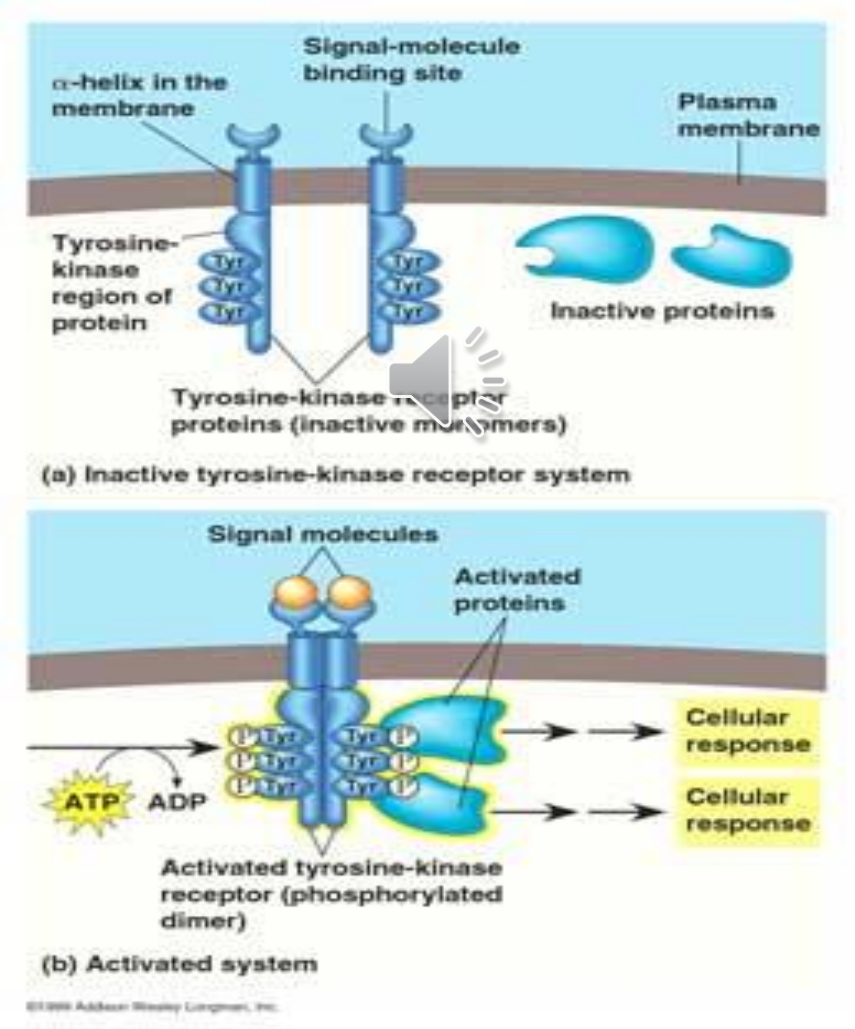
Receptors Linked to Enzymes

- Ligand binds to receptor's extracellular membrane →
- Changes in receptor confirmation →
- Receptor molecules bind each other →
- Brings together tyrosine kinase domains →
- Becomes enzymatically active →
- Phosphorylate downstream signalling proteins



http://www.bio.davidson.edu/Courses/Molbio/MolStudents/spring2003/Williford/picturefrombook/Slide2.JPG

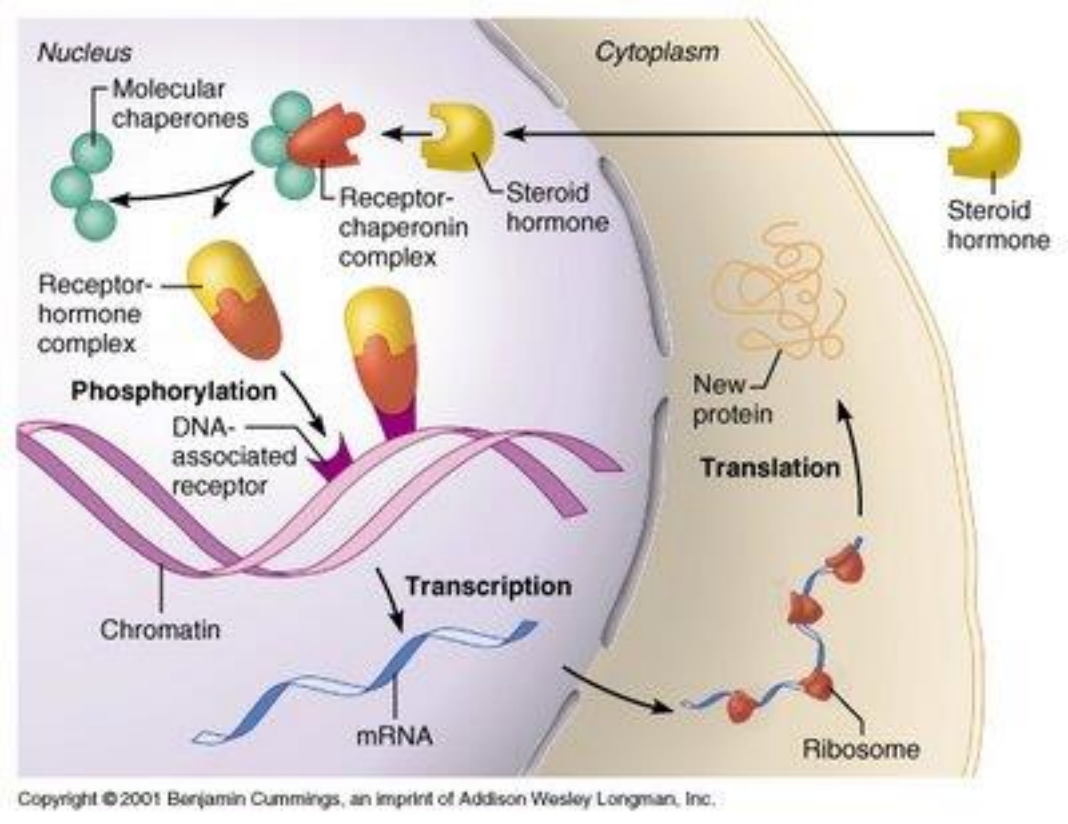
Tyrosine – Kinase linked Receptor



Endogenous ligands for nuclear receptors

- Ligands have to be lipophilic
  - Steroid hormones
  - Thyroid hormones
  - Stress hormones
  - Vitamins A, D

Nuclear receptors



These ligands need to cross into the cell to have an effect

Desensitization

- When a drug is given continuously or repeatedly the effect of the drug gradually diminishes
  - Desensitization and tachyphylaxis are synonymous as they occur of a few minutes or hours
  - Tolerance: More gradual decrease in response to a drug
  - Refractoriness: Is a general term used in relation to loss of therapeutic efficacy

Desensitization

- Drug Resistance: Used to describe loss of effectiveness of antimicrobials or anti-tumour drugs

Mechanisms

- Change in Receptor
- Loss of receptors
- Homologous desenstization
- Exhaustion of mediators

THANKS