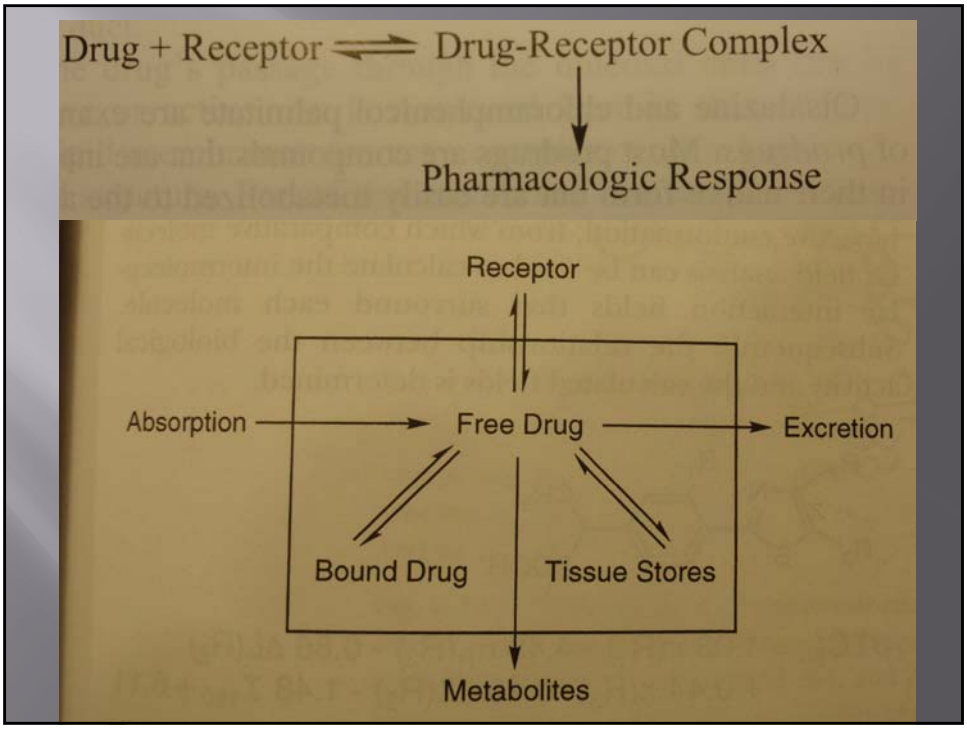
Medicinal chemistry I

RECEPTOR AND DRUG-RECEPTOR INTERACTIONS

Dr Amirhossein Sakhteman



Concept of receptor

- J. N Langley ;1900; initial interaction of the receptor with cellular components
- Paul Ehrlich; 20th century ; "recptive substance" or "receptor"; Lock and Key
- Do all drugs act on receptors?

- Osmotic diuretics ?
- Antacids?

Affinity : the role of chemical bonding

- A.V. Hill ; 1900; the nicotine and curare from muscle preparations; effect of temperature

$D + R \rightleftharpoons D\text{-}R$

Agonists?

Antagonists?

-Affinity;

Shape, Orientaion, Functional groups, Physical,..

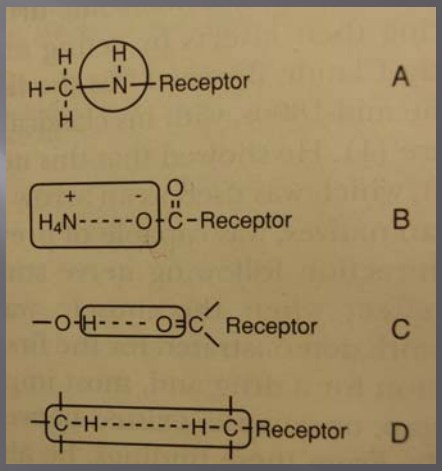
Drug receptor forces

A- Covalent

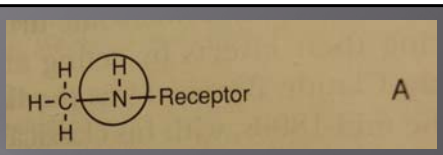
B- Ionic

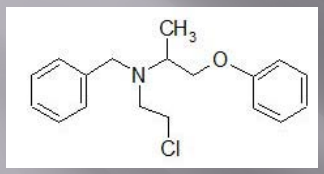
C- Hydrogen Bonding

D- Hydrophobic



A- Covalent

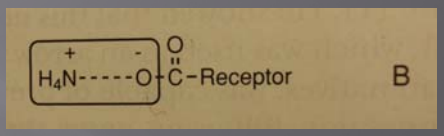




Phenoxy benzamine?

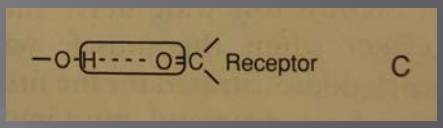
- 50-150 kcal/mol
- Endocytosis
- Chemical destruction of the receptor
- Nerve gases; organophosphates; Nitrogen mustards? Selegilene?
- Irreversible? Suicidal?

B- Ionic



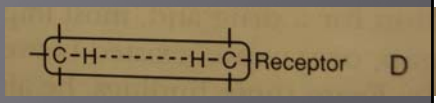
- Opposite charges
- 5- 10 kcal/mol
- Reversible; dissociation happens

C- Hydrogen bonding

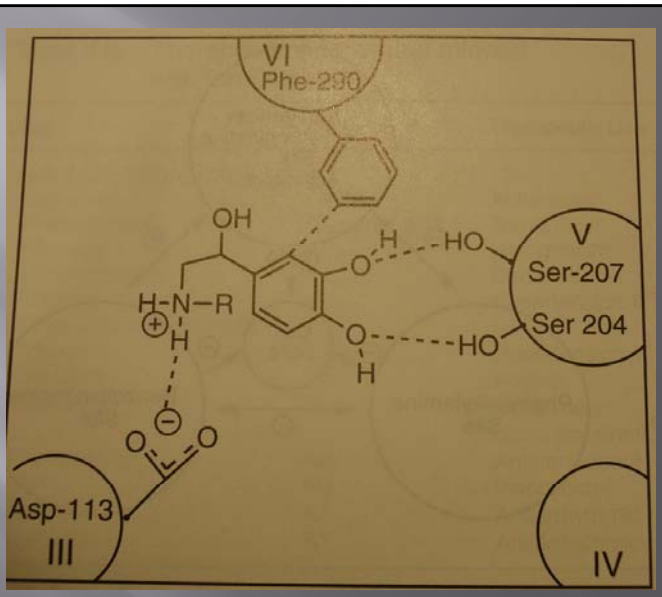


- Electronegative atoms; O, N
- 2-5 kcal/mol
- Reversible; dissociation happens
- Multiple Hydrogen Bonds

D- Hydrophobic interactions

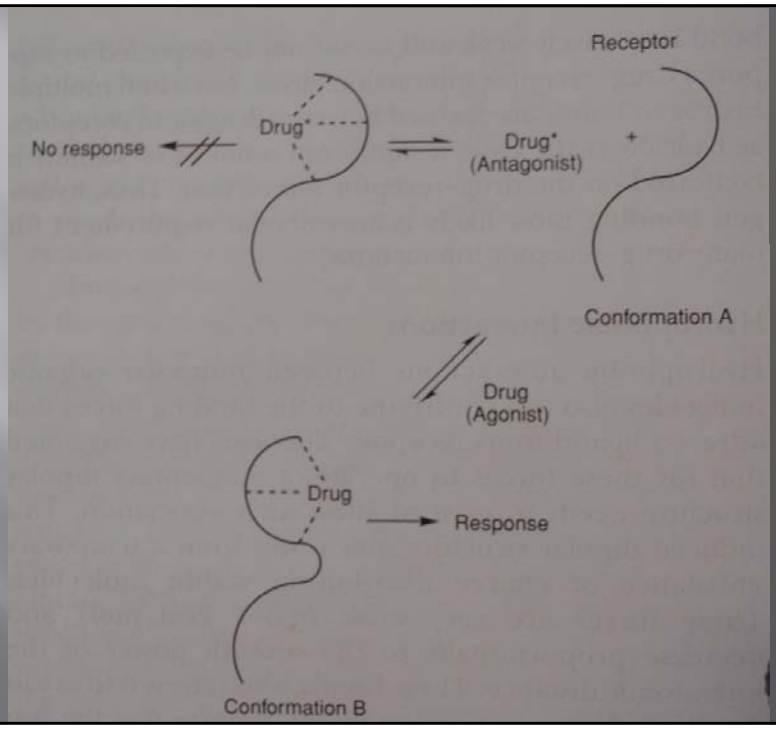


- Momentary dipolar moments
- 0.5 to 1 kcal/mol
- Van der wals, london forces



PHARMACOPHORE

- The critical portion of the drug for D-R complex
- **Occupancy theory**; response depends to the number of D-R complexes
- **Rate theory**; response depends to D-R/time
- **Induced fit theory**; D to R approaching induces conformational change in the receptor
  both agonists and antagonists can induce the change
- **Macromolecular perturbation theory;**
  induced fit theory + rate theory



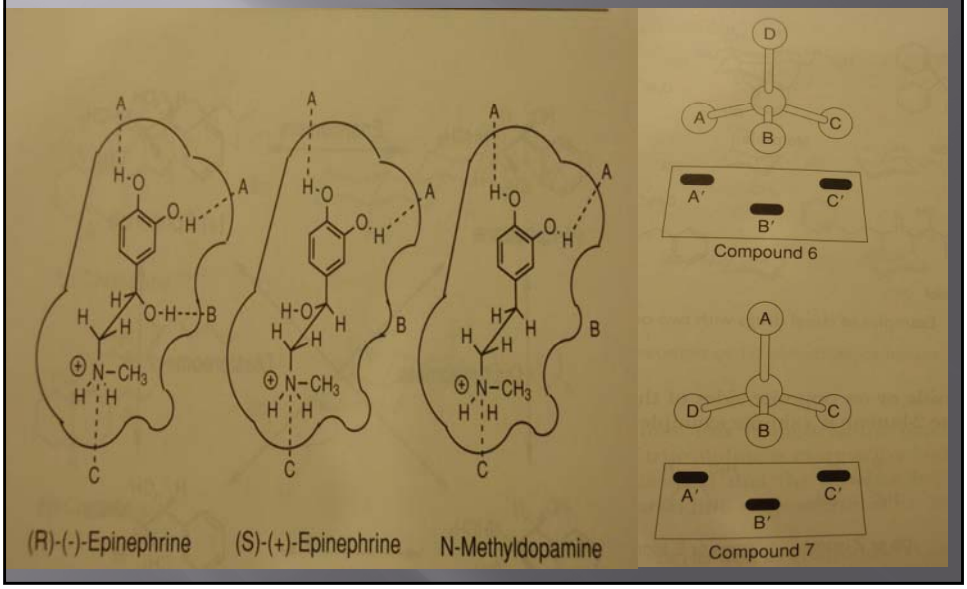
Activation aggregation theory

Antagonists

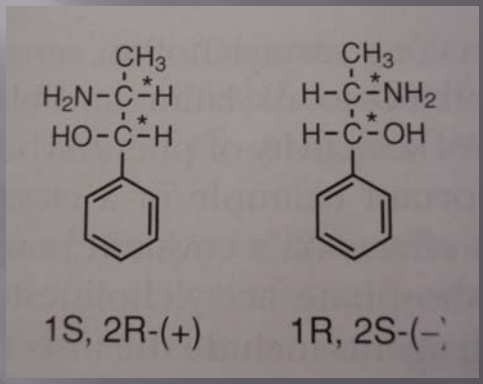
$R_{active} \rightleftharpoons R_{inactive}$

Agonists

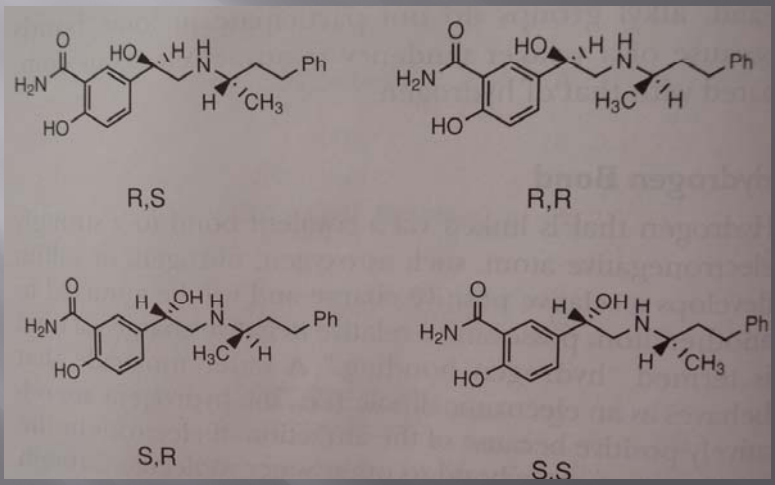
Affinity : the role of stereochemistry



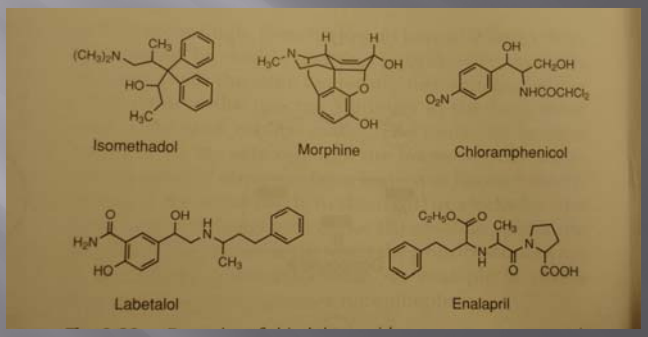
Eutomer vs Distomer



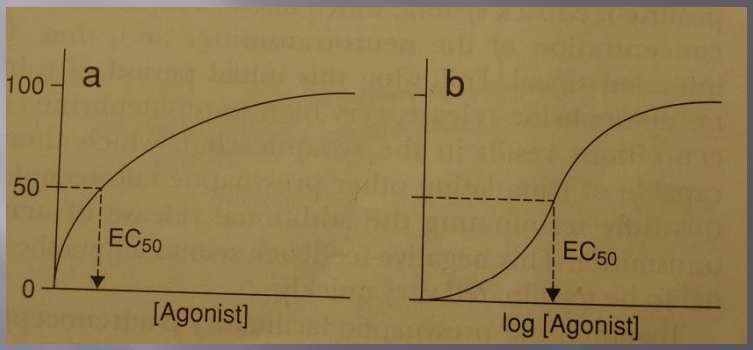
labetalol



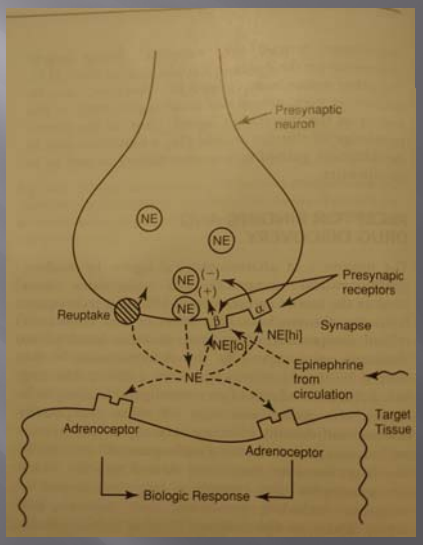
Drugs with chiral centers



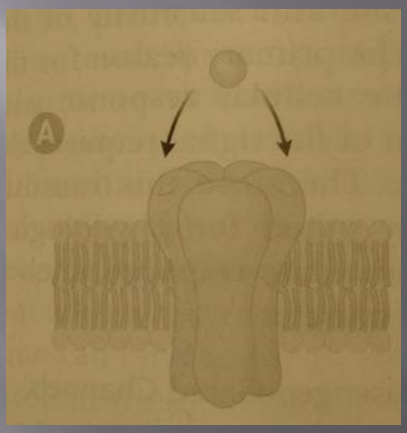
Potency vs efficacy

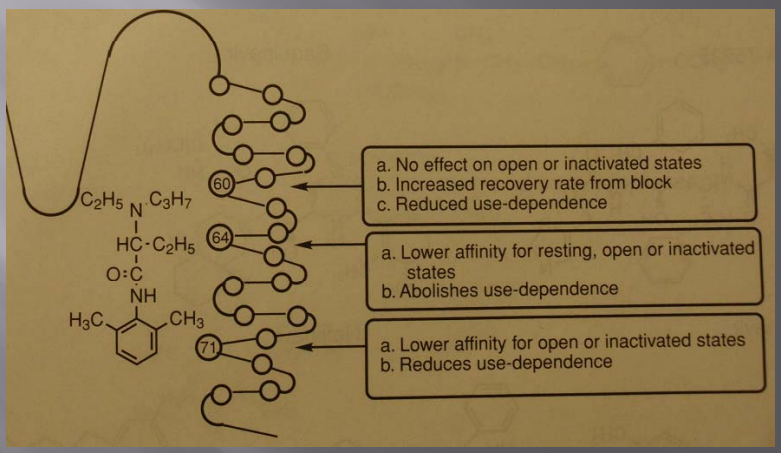


+ and – feed back



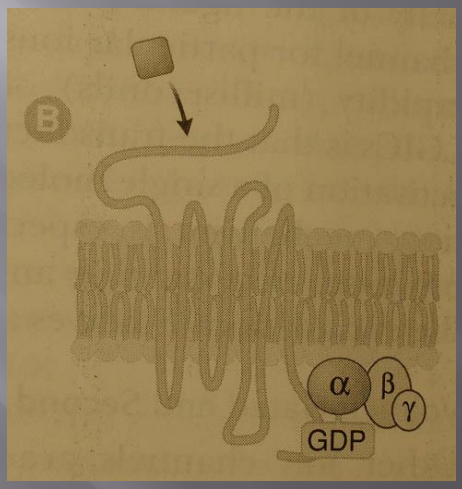
Ion channels

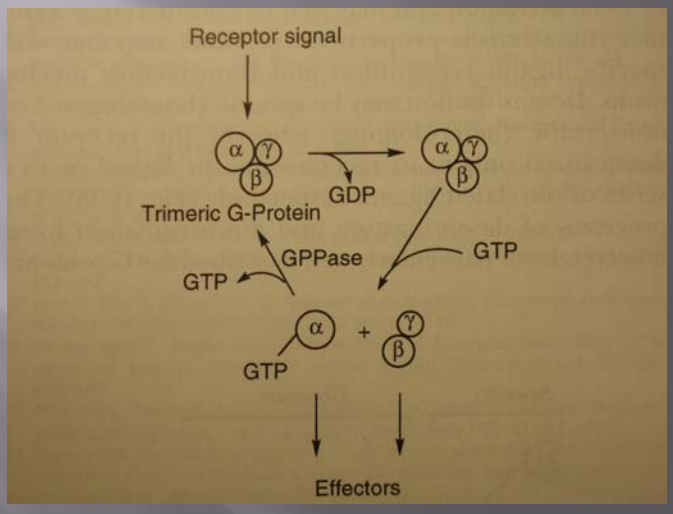




Drug	Channel	Therapeutic Us
Ligand-gated ion channels		
Diazepam	$GABA_A$	Antianxiety
Phencyclidine	Glutamic acid	Tranquilizer
Minoxidil	K^+_{ATP}	Hair growth[a]
Glibenclamide	K^+_{ATP}	Diabetes
Pinacidil	K^+_{ATP}	Hypertension
Voltage-gated ion channels		
Nifedipine	Ca^{2+}	Hypertension
Diltiazem	Ca^{2+}	Angina
Lidocaine	Na^+	Antianxiety
		Local anesthet
Phenytoin	Na^+	Anticonvulsant
DDT	Na^+	Insecticide
Sotalol	K^+	Antiarrhythmic
Quinidine	K^+	Antiarrhythmic

GPCRs


B
α
β
γ
GDP


Receptor signal
α
γ
β
GDP
Trimeric G-Protein
GPPase
GTP
GTP
GTP
α
+
γ
β
Effectors

G-Protein Transducer Family	Second Messenger System
G_s	Stimulates adenylyl cyclase activity and Ca^{2+} channels
G_i	Inhibits adenylyl cyclase activity and activates K^+ channels
G_q	Stimulate phospholipase C activity
G_{12}	Modulate sodium/hydrogen ion exchanger

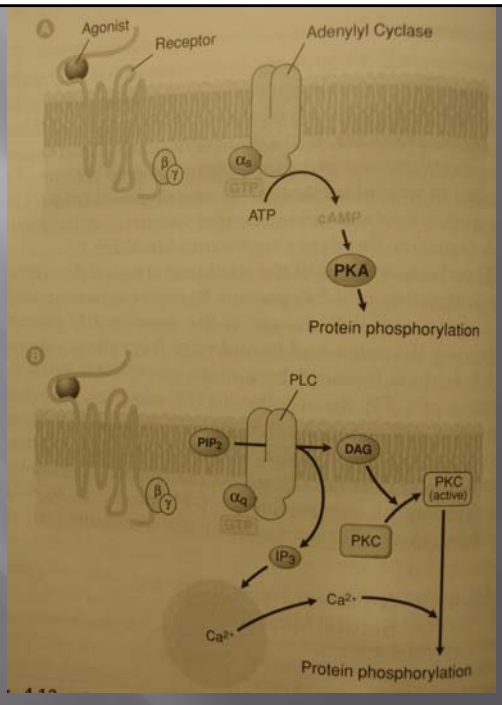
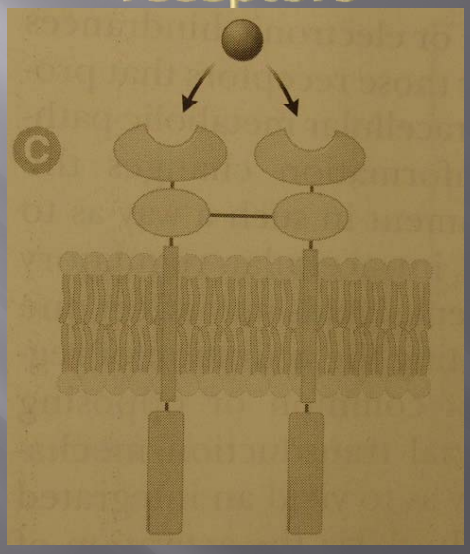


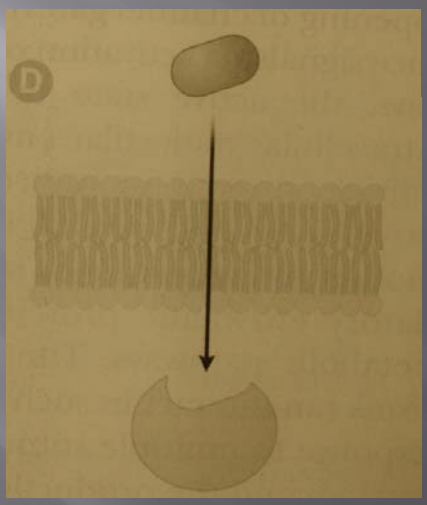
Table II.4. G protein–coupled Receptors As Therapeutic Targets

Receptor	Drug	Indication
Acetylcholine (muscarinic)	Bethanchol	Gastrointestinal
	Ipratropium	Pulmonary
Norepinephrine		
β_1	Atenolol	Cardiovascular
β_1/β_2	Propranolol	Cardiovascular
β_2	Albuterol	Pulmonary
α_1	Terazosin	Cardiovascular
α_2	Clonidine	Cardiovascular
Angiotensin (AT_1)	Losartan	Cardiovascular
Dopamine (D_2)	Haloperidol	Central nervous system
Serotonin (5-HT_{ID})	Sumatriptan	Central nervous system
Histamine (H_2)	Cimetidine	Gastrointestinal
Opiod (μ)	Morphine	Central nervous system

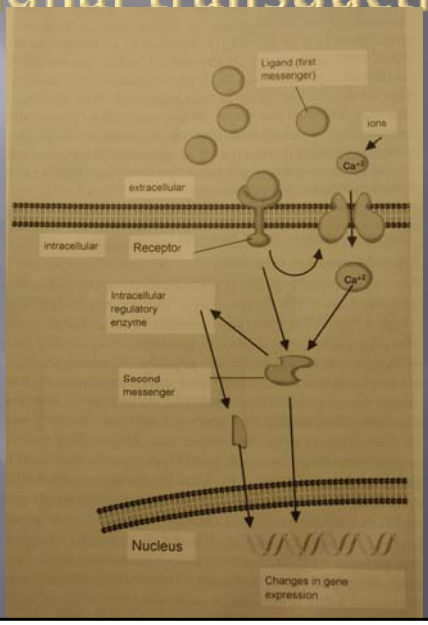
Transmembrane coupled receptors



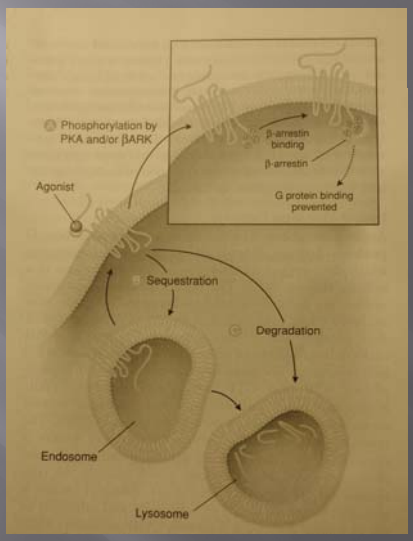
Cytoplasimic/nuclear receptor



Signal transduction



Receptor regulation



Thanks for your attention