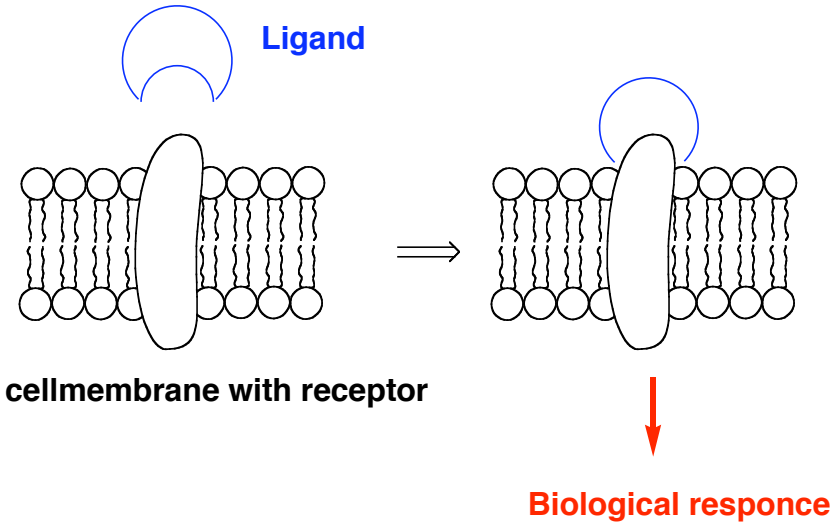
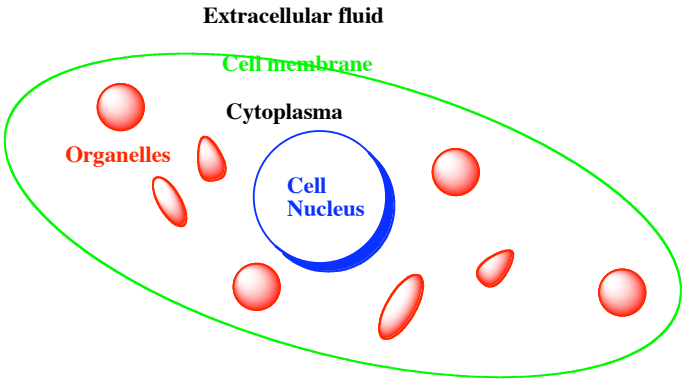
Receptors and Drug Action

Receptors:

- **Specific areas of cell membranes (proteins, glycoproteins)***
- **When bound to ligand, positive or negative biological responce**



* Few ex. of free receptors in cytoplasma

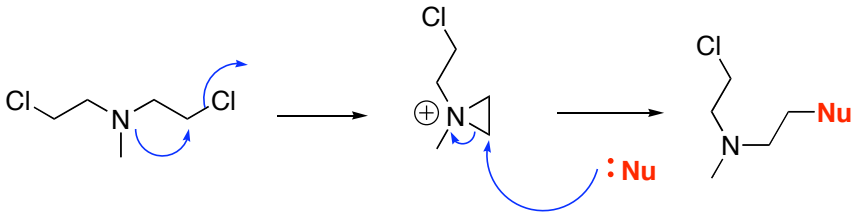


Drugs that do not act on receptors:

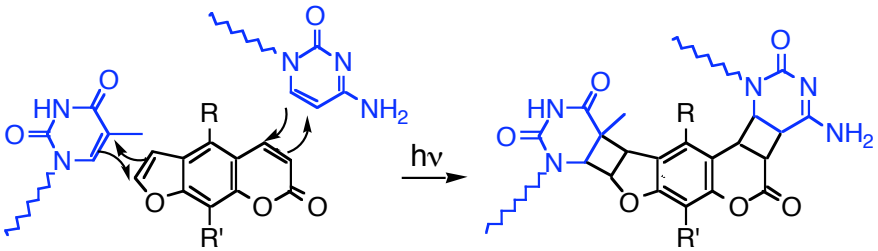
Antacida: $CaCO_3$ + HCl

Diuretica (osmotic)

Akylating agents (cancer)



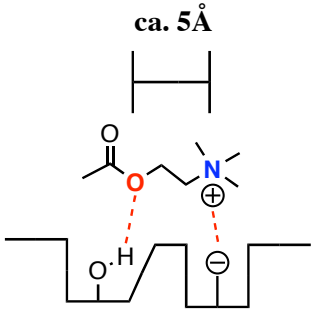
Psoralenes



Enzyme inhibitors

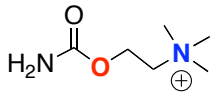
Drugs that do act on receptors:

Acetylcholin (Neurotransmittor)

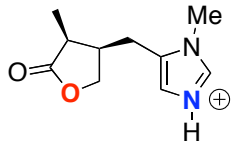


Acetylcholin Agonists

Carbacholin

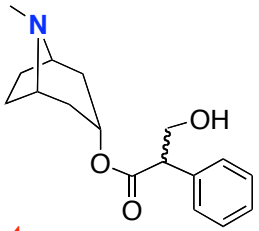


Pilocarpine

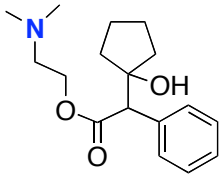


Acetylcholin Antagonists

Atropin



Cyclopentolat



Agonist:
Binds to (have affinity for) receptor
Binding leads to biolog. responce
(Agonists have intrinsic activity / efficacy)

Antagonist:
Affinity for receptor
No intrinsic activity

Partial agonist (later)

Binding of ligand to receptor

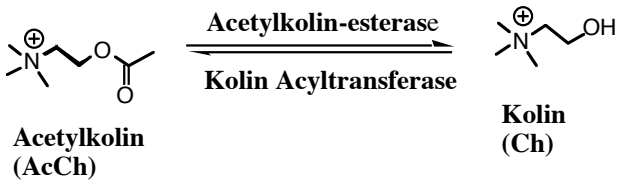
- **Covalent bond**
- **Ionic bond**
- **Hydrogen bond**
- **Hydrophobic interaction**

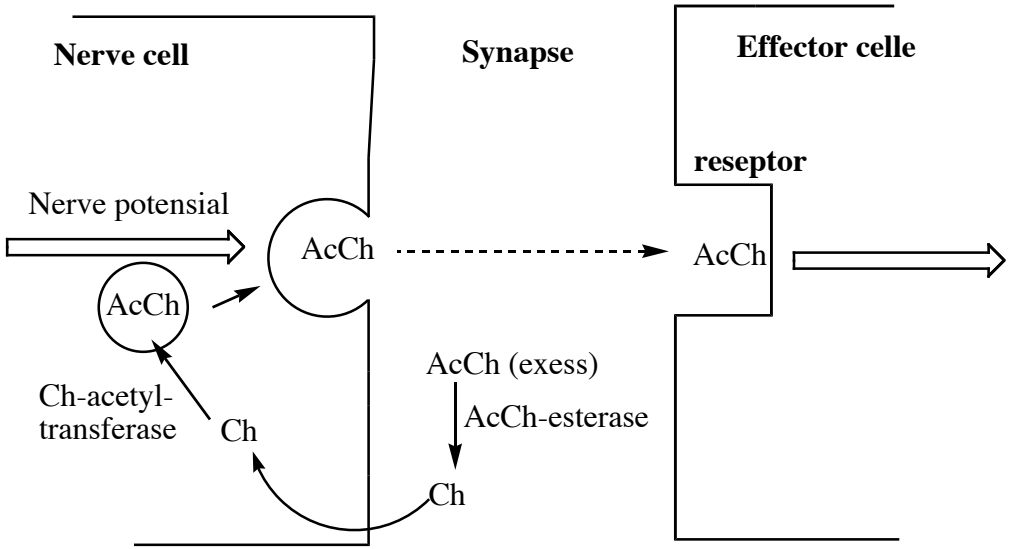
Covalent bond

strong; 50-150 kcal/mol,

Normally irreversible bonding

ex. Acetylcholine esterase (enzyme) inhibitors

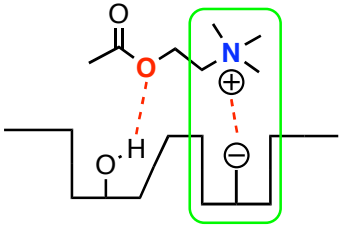




Ionic bond

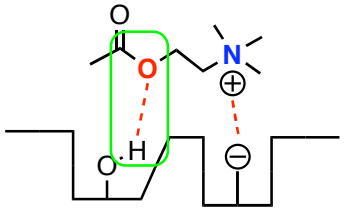
5-10 kcal/mol,
Reversible bonding

Acetylcholin



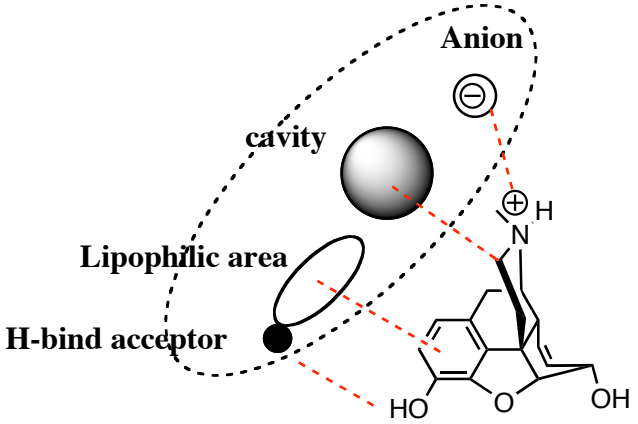
Hydrogen bond

2-5 kcal/mol,
Reversible bonding



Hydrophobic interaction

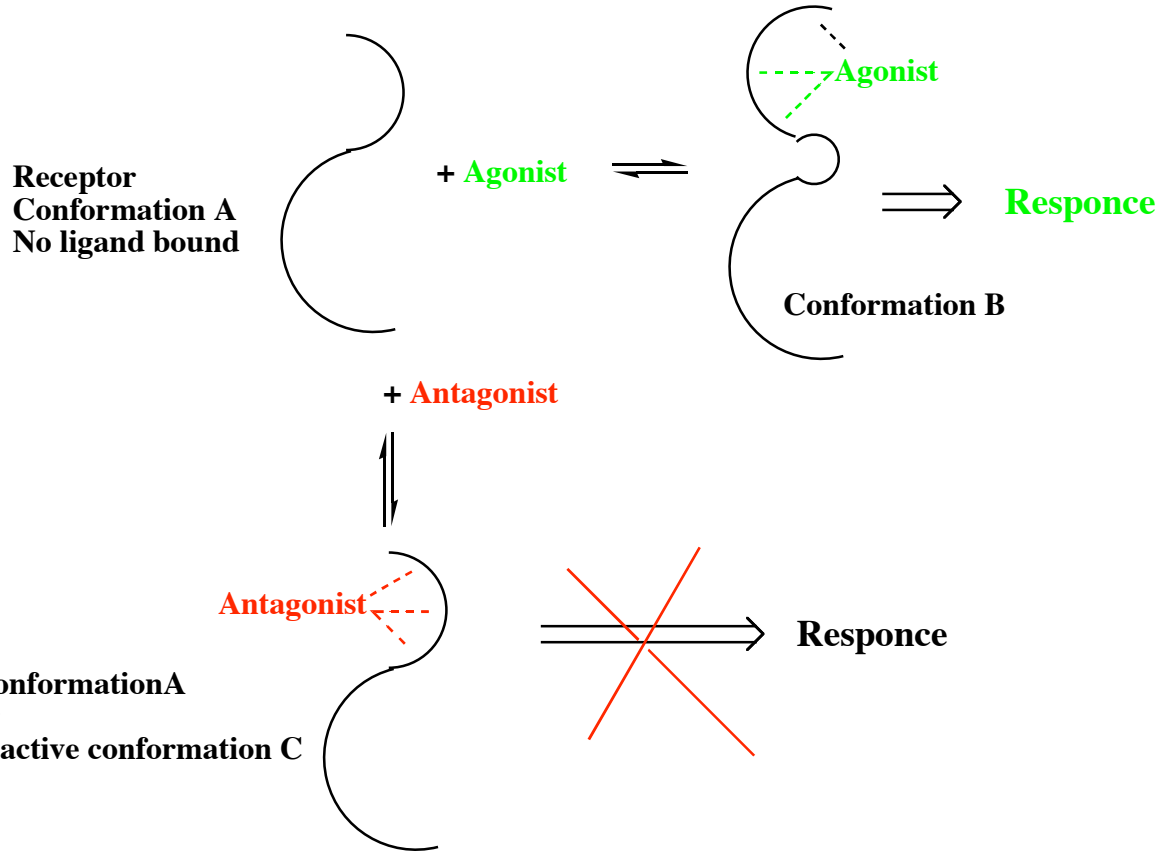
0.5-1 kcal/mol,
Reversible bonding



The occupancy theory:
The more receptors sites occupied by ligand, the stronger responce

The rate theory:
The more ligand-receptor interact / unit time, the stronger responce

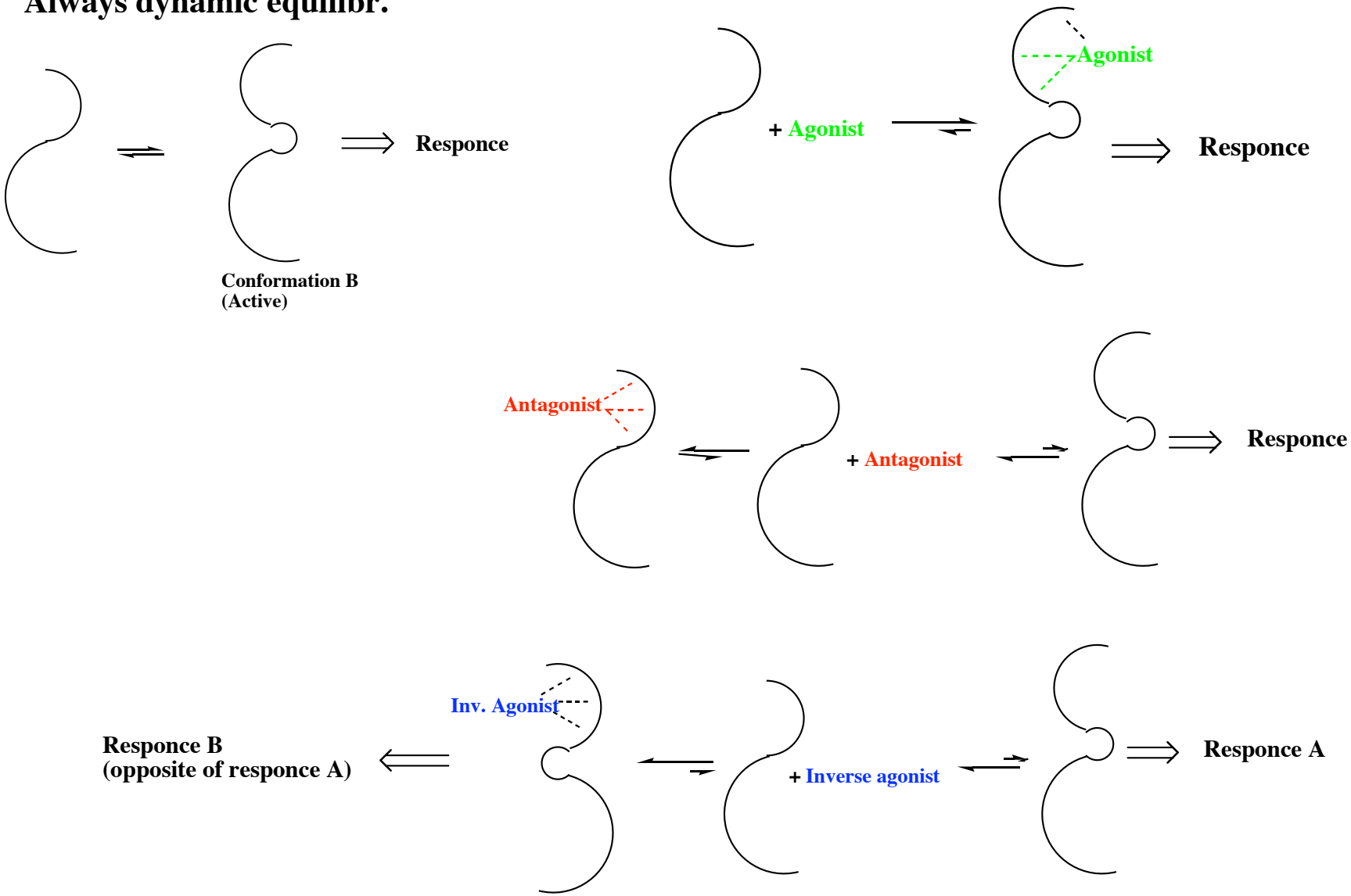
The induced-fit theory:



The macromolecular pertubation theory:
(induced fit + rate theory)

The activation -agregation theory:

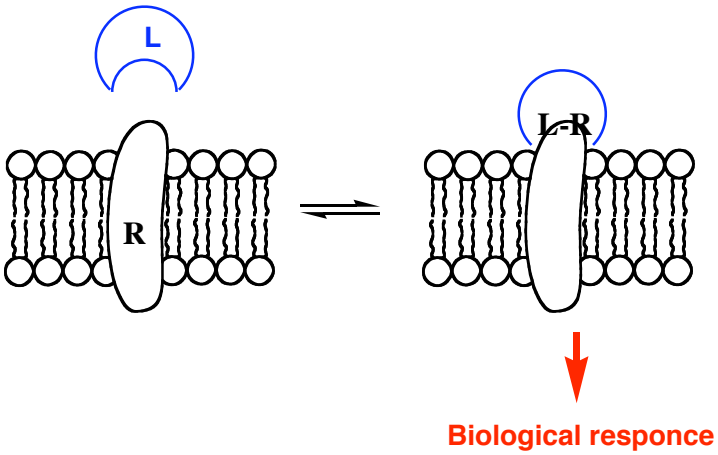
Always dynamic equilibr.



Dose-Responce Relationships

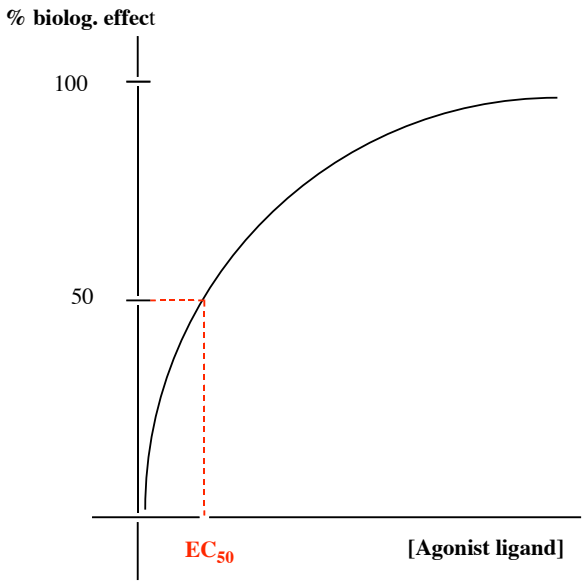
A + B ⇌ A-B ↑ [A] - equil. towards AB

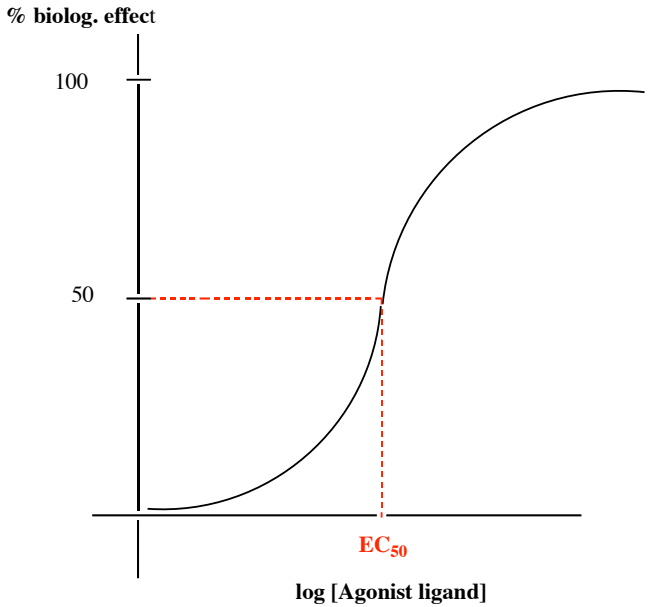
L + R ⇌ L-R ↑ [L] - equil. towards LR ??



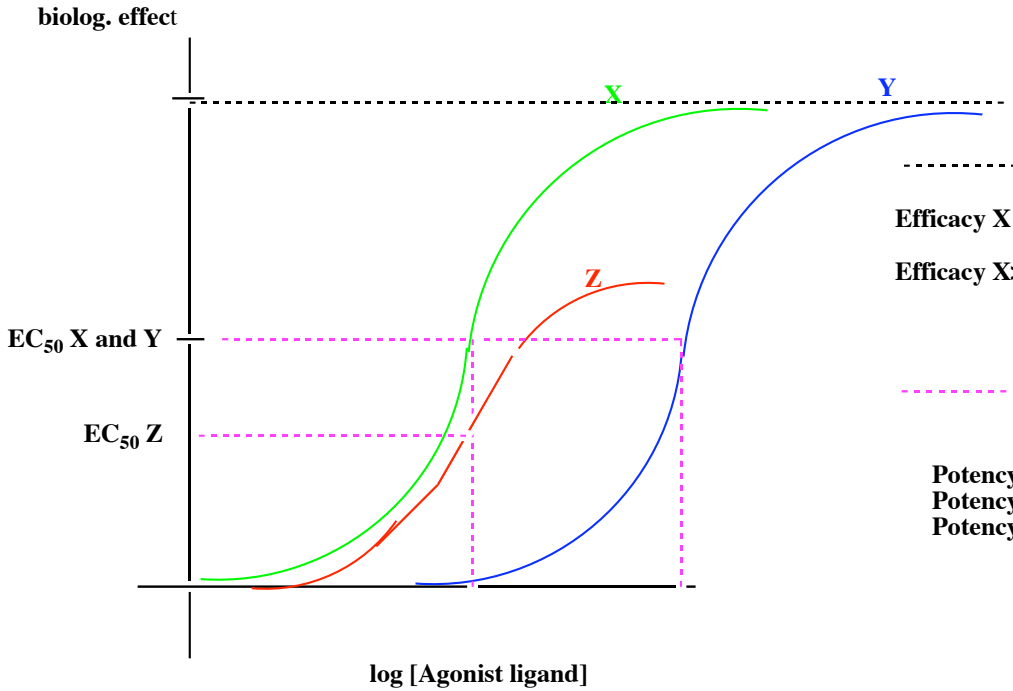
R locked in membrane (do not move freely)
L dissolved in extracellular fluid

Reaction on solid - liquid interface





IC_{XX}
EC_{XX}
MIC



Efficacy (how high activity is possible)

Efficacy X = Efficacy Y (both can give 100% responce)

Efficacy X> Efficacy Z (Z cam only give ca 30% responce)

Potency (how easily is a given responce reached (ex EC_{50})

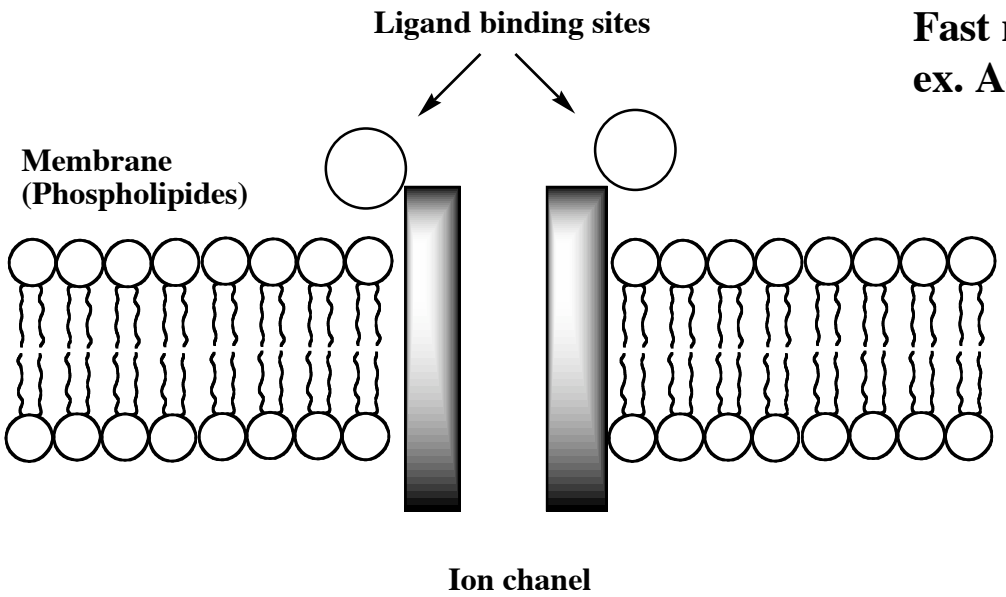
Potency X > Potency Y
Potency X = Potency Z
Potency Z > Potenzy Y

Types of receptors

Super-family	Endogenous ligands	General structures
1	Fast neurotransmittors ex. Acetylcholine	Ligand gated ion chanels
2	Slow neurotransm. ex. noradrenalin Hormones	G-Protein coupled receptors
3	Insuline Growth factors	Enzyme coupled receptors Catalytic receptors
4	Steroid hormones Thyreoid hormones Vitamin A, D	Cytoplasmic receptors

Ligand gated ion chanels

Ligands
Fast neurotransmittors
ex. Acetylcholine (nicotinic reseptors)



Fastest intracellular responce, μs

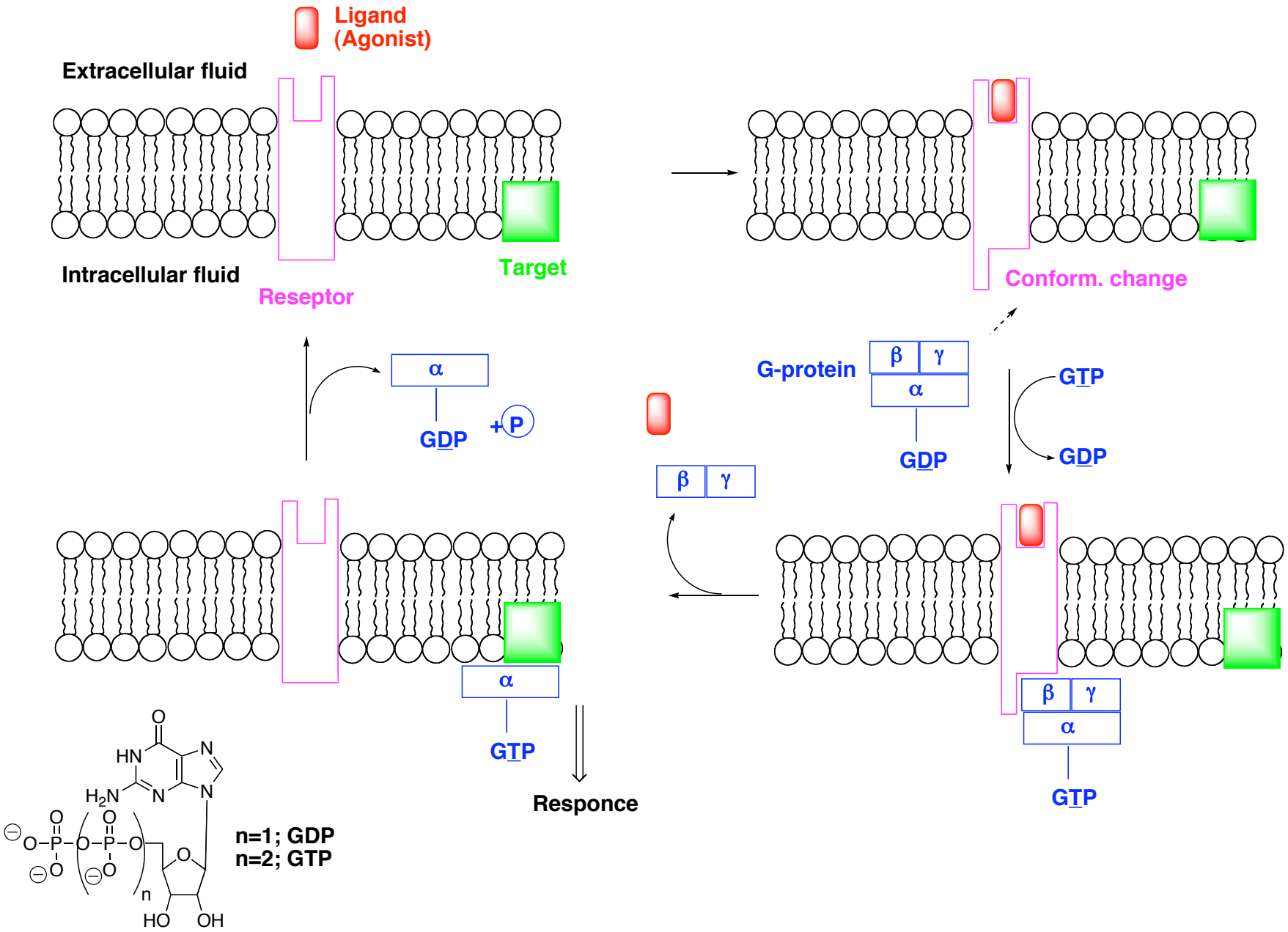
Binding of ligand - opening of chanel - ion (K^+, Na^+) in or out of cell - responce

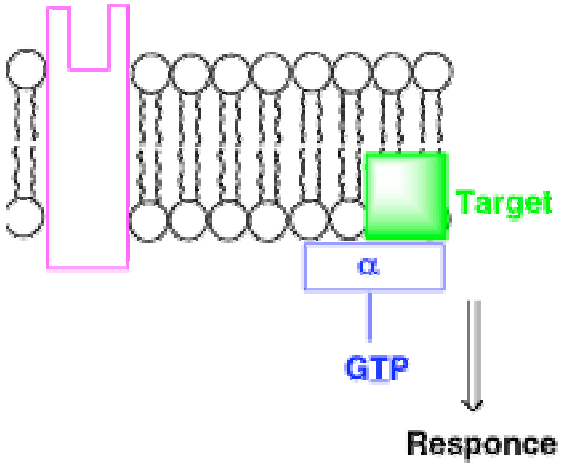
Nobel prize chemistry 2003,
Roderick MacKinnon ***"for structural and mechanistic studies of ion channels".***

http://nobelprize.org/chemistry/laureates/2003/press.html

G-Protein coupled receptors

G-protein: Guanine nucleotide binding protein





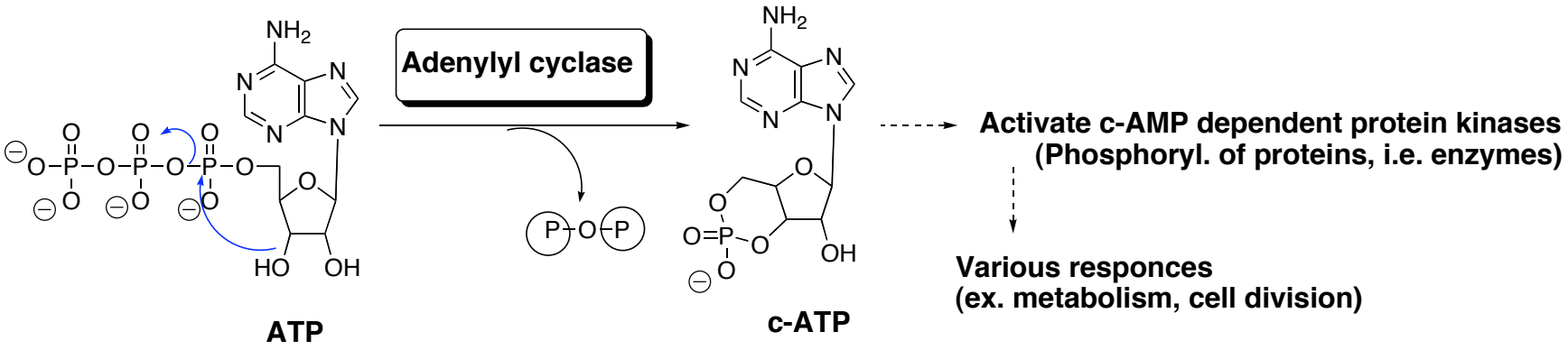
Subtypes of G-proteins - Targets (Second messenger systems)

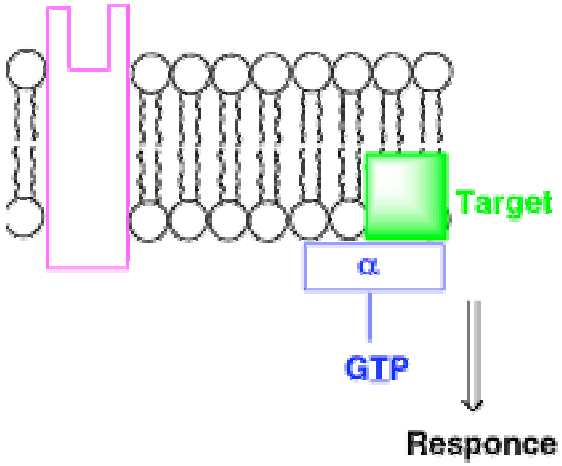
Ion chanels: G_{12} Na^+ / H^+ exchange

Enzyms:
- G_i Inhib. Adenylyl cyclase
- G_s Stimul. Adenylyl cyclase
- G_q Stimul. Phospholipase C

One ligand can bind to more than one type of G-prot. coupled reseptors

second messenger pathways



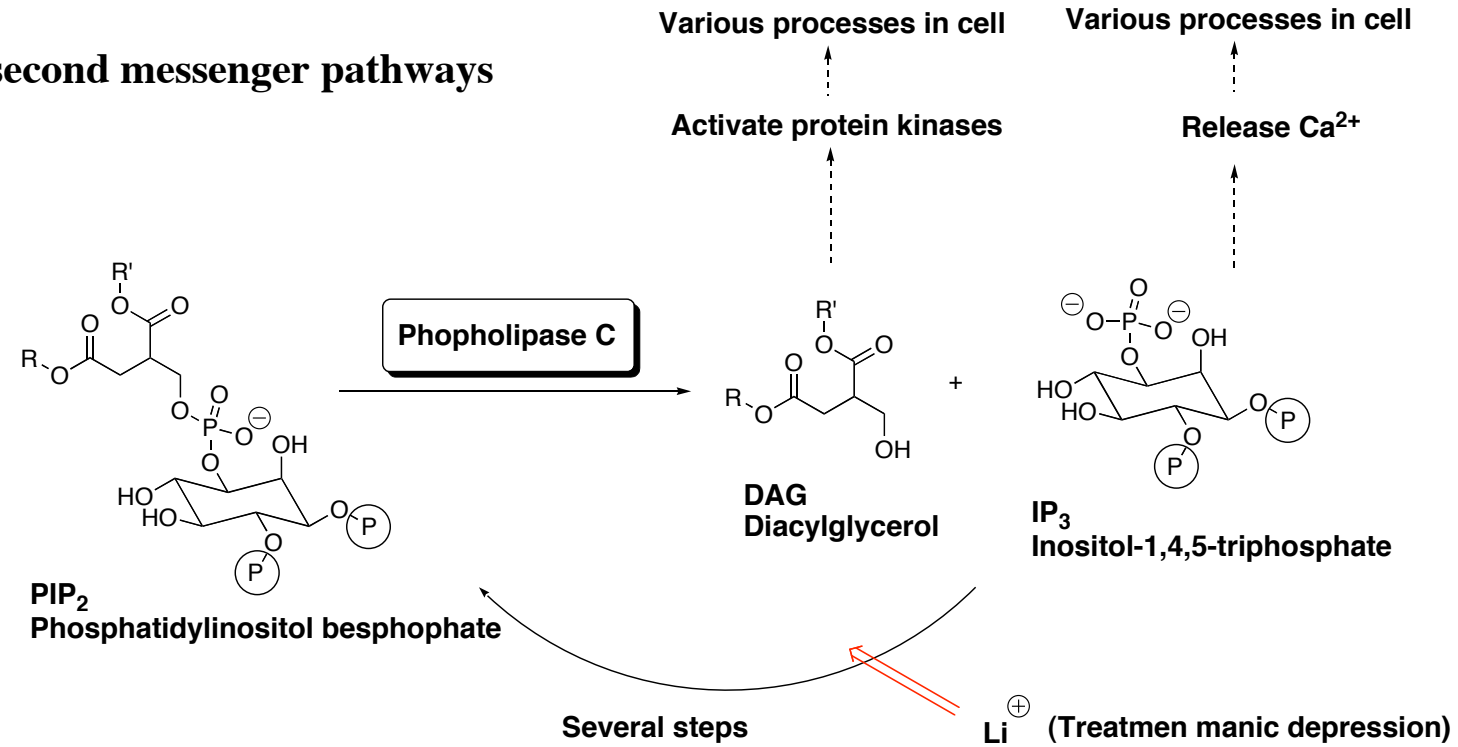


Subtypes of G-proteins - Targets (Second messenger systems)

Ion chanels: G_{12} Na^+ / H^+ **exchange**

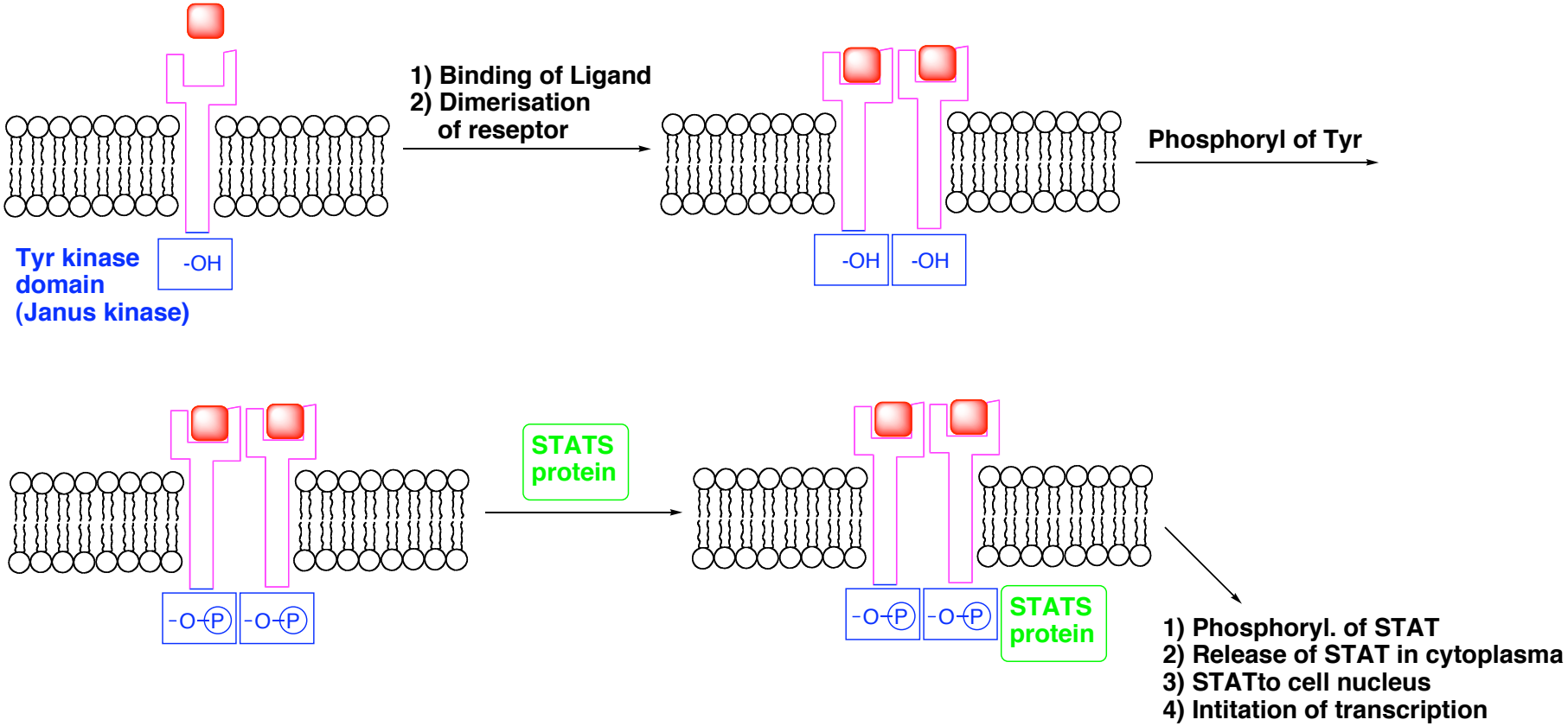
Enzyms:
- G_i Inhib. Adenylyl cyclase
- G_s Stimul. Adenylyl cyclase
- G_q Stimul. Phospholipase C

second messenger pathways



Enzyme coupled receptors - Catalytic receptors

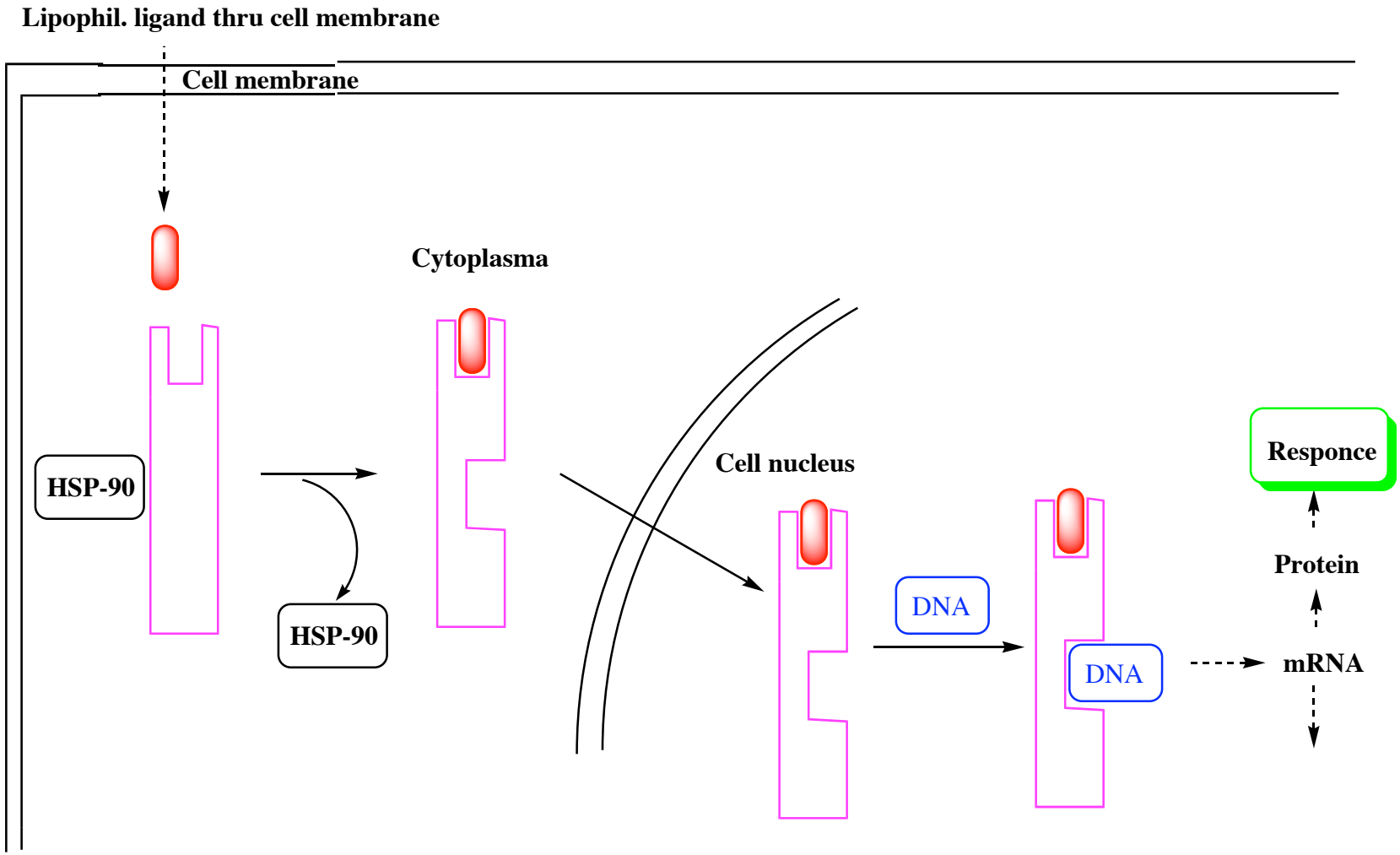
Ligands: Peptide hormones



STAT: Signal transducers and activators of transcription

Cytoplasmic receptors

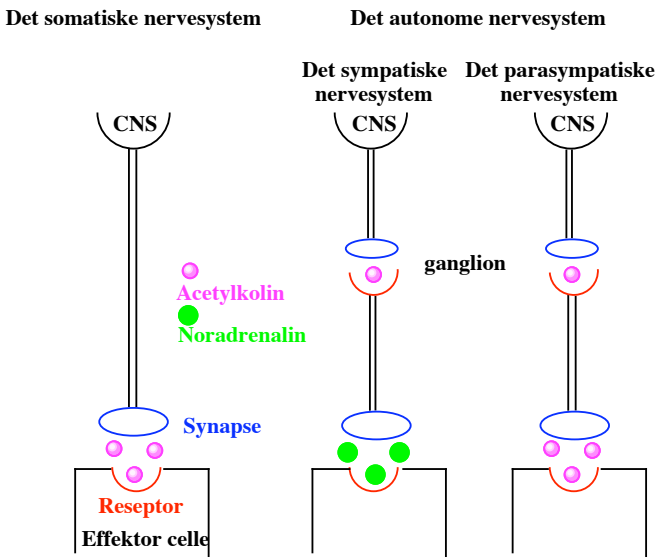
(not bound to cell membranes)



(HSP-90: Heat shock protein)

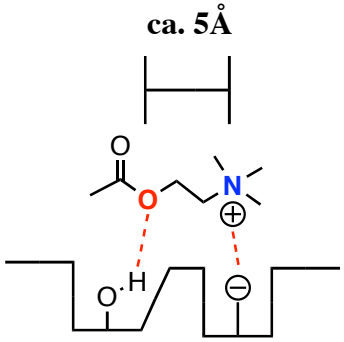
Receptor subtypes

Most receptor classes - several sub-types
Each subtypes - differend A(nta)gonists

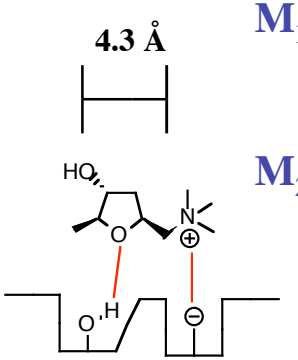


Sub types cholinerge reseptors

Acetylcholin (Neurotransmittor)



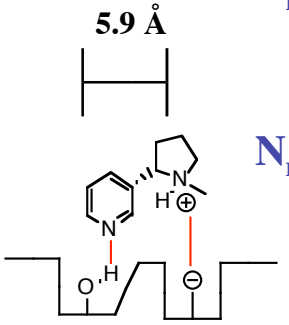
Muscarinerge receptors



M_1: G-Protein coupled receptors
Stimulate phopholipase A

M_2: G-Protein coupled receptors
Inhib. adenylyl cyclase

Nicotinerge receptors



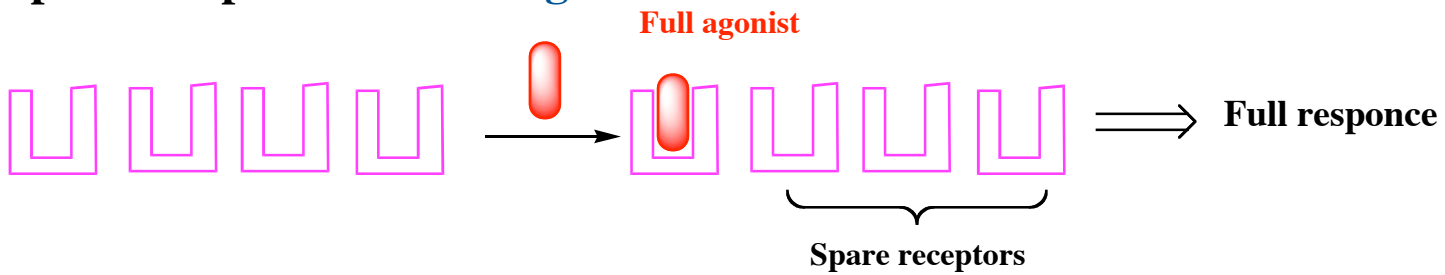
N_{muscle}: Ligand gated ion chanels
Incr. Na^+/Ca^{2+}

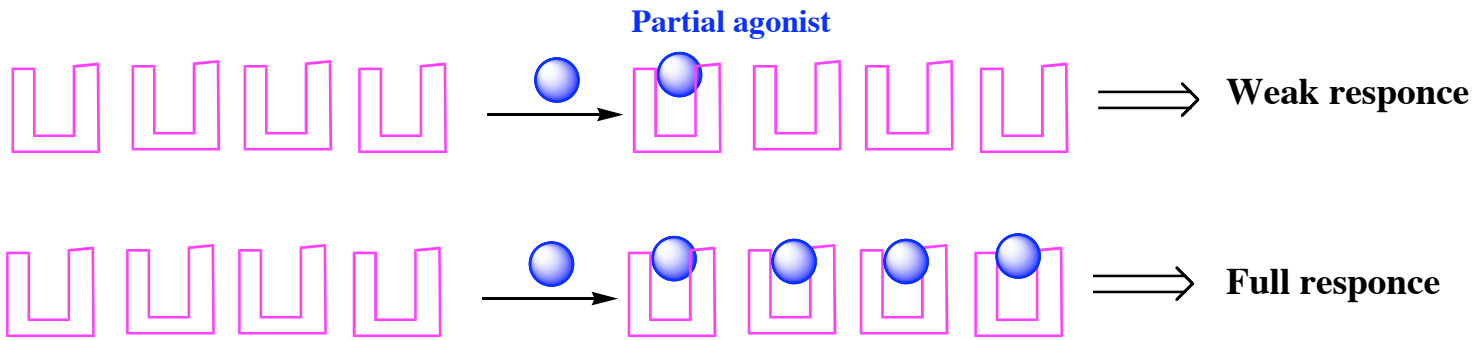
N_{neuro}: Ligand gated ion chanels
Incr. Na^+/Ca^{2+}

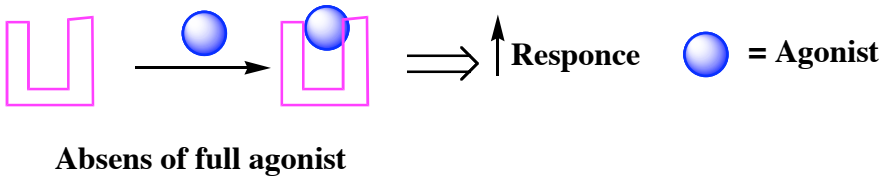
Agonists

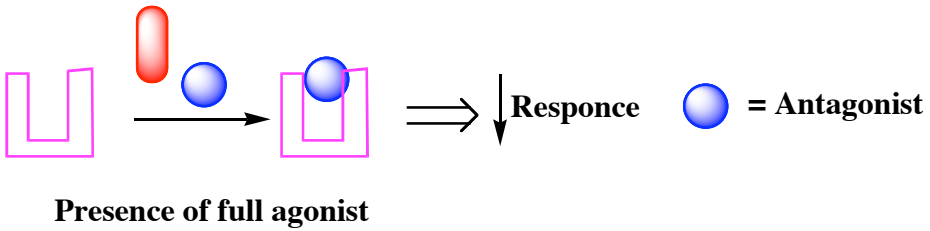
Antagonists

Spare receptors - Partial agonist



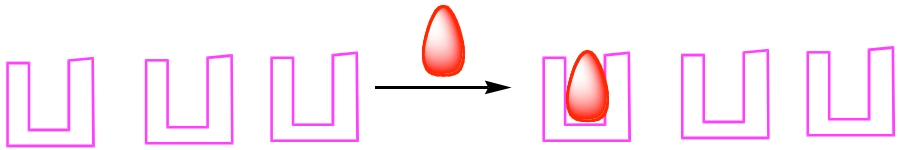




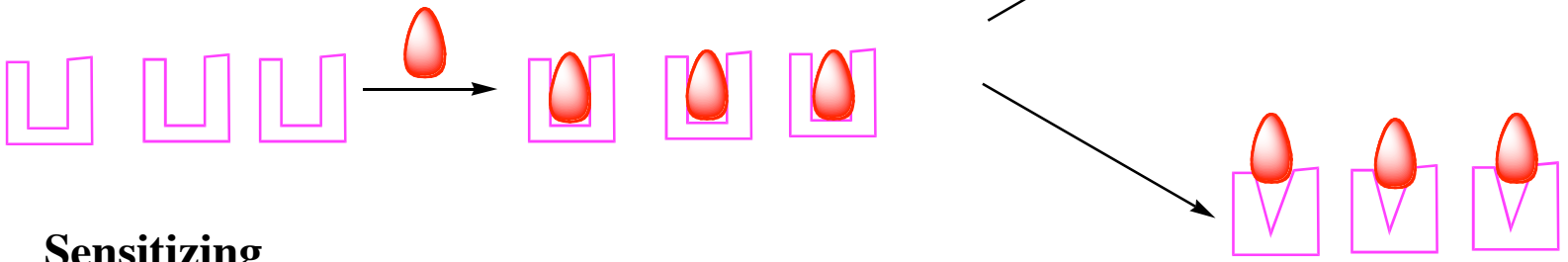


Desensitizing

Receptor and normal amount of ligand = agonist



Overstimulated receptor



Sensitizing

Receptor and normal amount of ligand = Antagonist

Overstimulated receptor