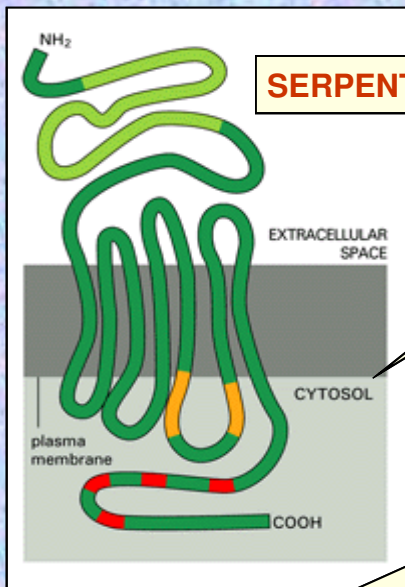
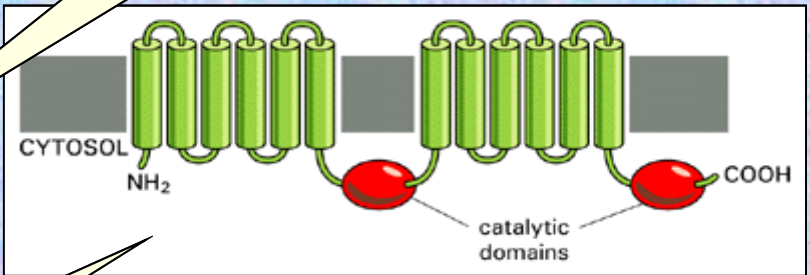


# GPCR SIGNALLING



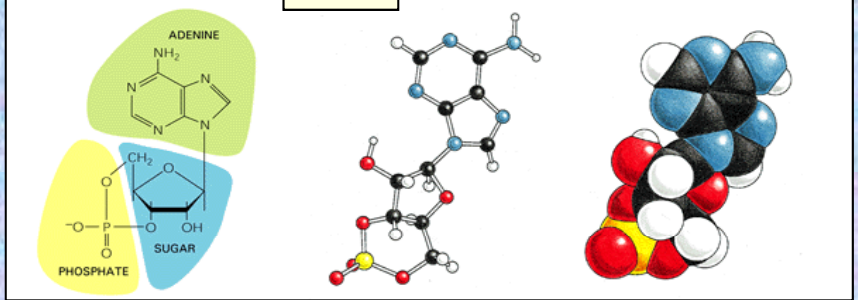
Receptor contains 7 transmembrane alpha-helical segments & intracellular and extracellular domains

## ADENYL CYCLASE

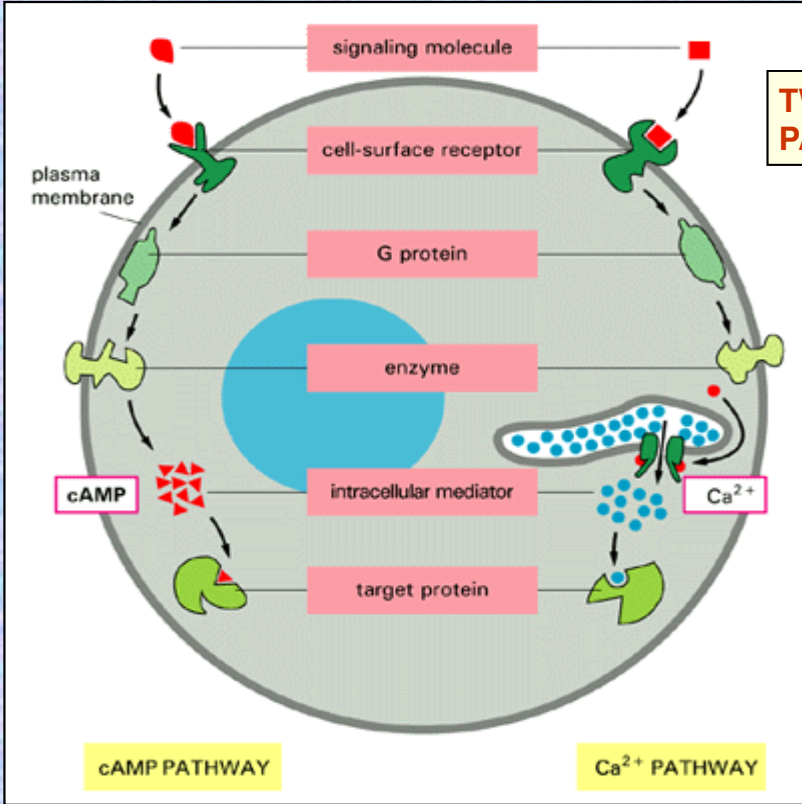


Enzyme contains about 1100 amino acids, two clusters of six transmembrane segments separating two similar cytoplasmic catalytic domains. There are at least six types of this form of adenylyl cyclase in mammals (types I-VI).

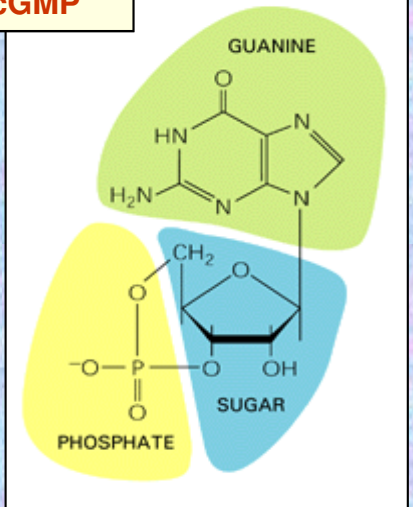
## cAMP



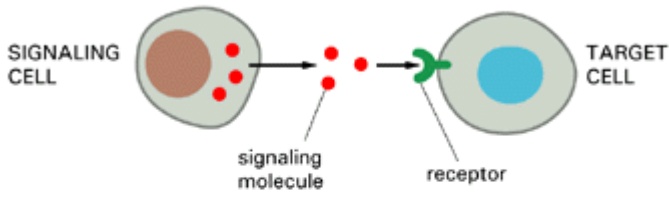
## TWO PRINCIPAL SIGNALLING PATHWAYS



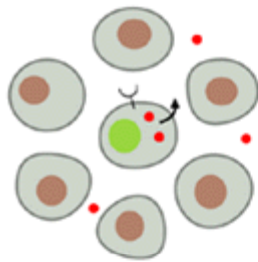
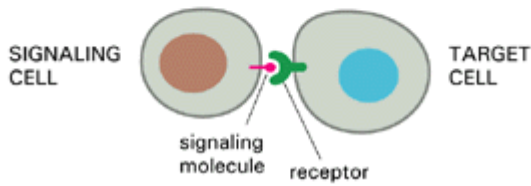
## cGMP



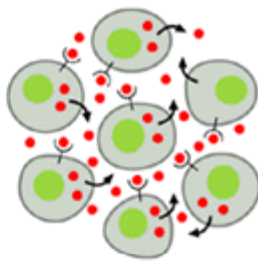
**SIGNALING BY SECRETED MOLECULES**



**SIGNALING BY PLASMA-MEMBRANE-BOUND MOLECULES**

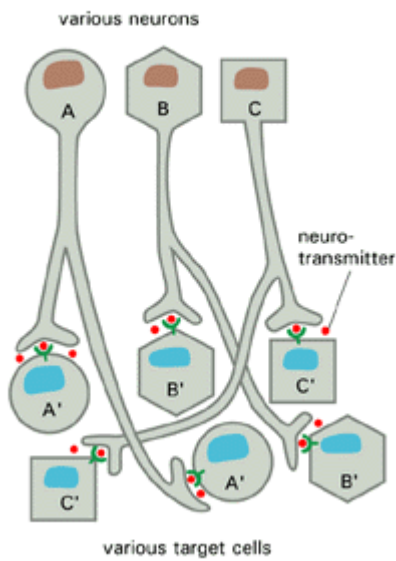


A SINGLE SIGNALING CELL RECEIVES WEAK AUTOCHRINE SIGNAL

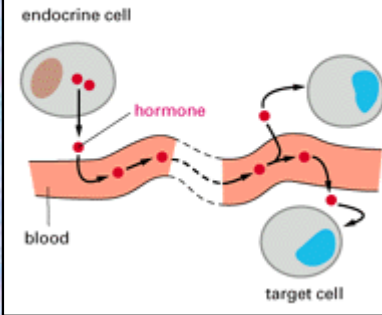


IN A GROUP OF IDENTICAL SIGNALING CELLS, EACH CELL RECEIVES A STRONG AUTOCHRINE SIGNAL

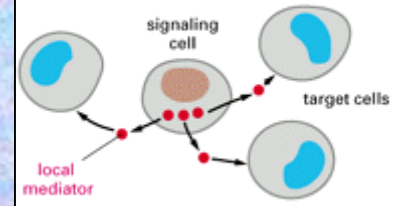
**(B) SYNAPTIC SIGNALING**



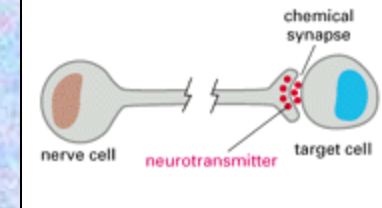
**(C) ENDOCRINE**



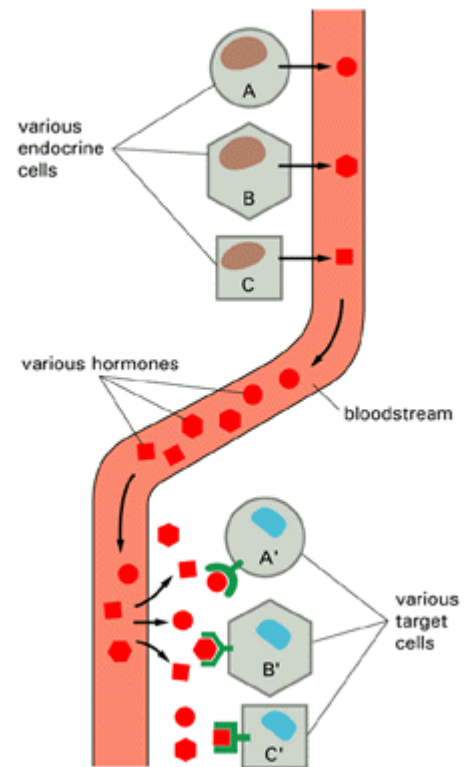
**(A) PARACRINE**



**(B) SYNAPTIC**



**(A) ENDOCRINE SIGNALING**



# RECEPTORS

## Cell surface receptors

## Intracellular receptors

without enzymatic activity

- Ion channel linked
- GPCR

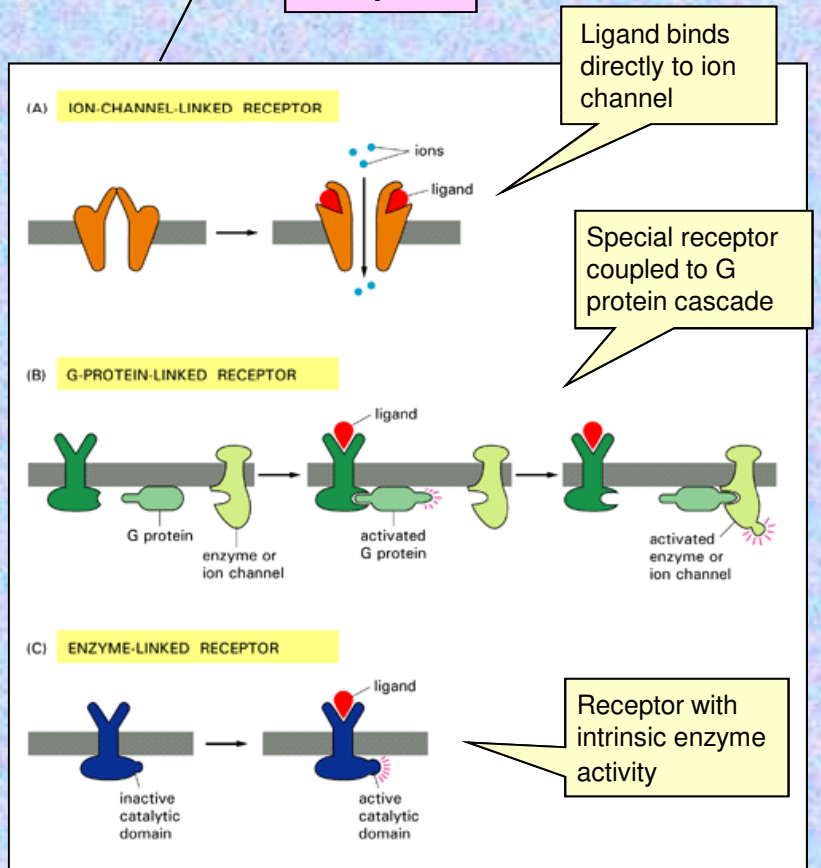
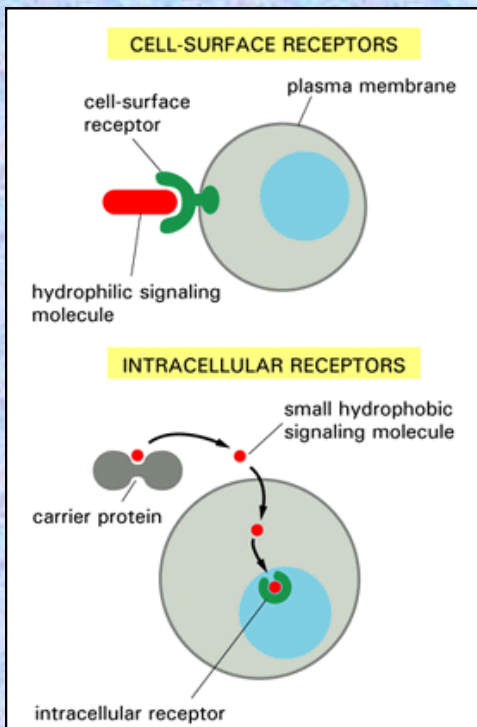
with enzymatic activity

- Guanylyl cyclase
- Tyr- kinase
- Ser/Thr - kinase
- Ser/Thr - phosphatase

- cytoplasmatic receptors
- nuclear receptors

Cell surface receptors

### Binding of secreted signals to receptors



### Some Hormone-induced Cellular Responses Mediated by Cyclic AMP

Hormone	Target Tissue	Major Response
Thyroid-stimulating hormone (TSH)	Thyroid gland	thyroid hormone synthesis and secretion
Adrenocorticotrophic hormone (ACTH)	Adrenal cortex	cortisol secretion
Luteinizing hormone (LH)	Ovary	progesterone secretion
Adrenaline	Muscle	glycogen breakdown
Noradrenalin, Adrenaline	Heart	increase in heart rate and force of contraction
Parathormone	Bone	bone resorption
Glucagon	Liver	glycogen breakdown
Vasopressin	Kidney	water resorption
Adrenaline, ACTH, glucagon, TSH	Fat	triglyceride breakdown

### Some Cellular Responses Mediated by G-Protein-linked Receptors Coupled to the Inositol-Phospholipid Signaling Pathway

Signaling Molecule	Target Tissue	Major Response
Vasopressin	Liver	glycogen breakdown
Acetylcholine	Pancreas	amylase secretion
Acetylcholine	Smooth muscle	contraction
Antigen	Mast cells	histamine secretion
Thrombin	Blood platelets	thrombin

### Endocrine disorders associated with mutation of serpentine receptors

Mutated protein	Disorder	Type of mutation
<b>Gain of function</b>		
LH receptors	Familiar male precocious puberty	Autosomal dominant
TSH receptor	Non-autoimmune hereditary hyperthyroidism	Autosomal dominant
PTH receptor	Hyperfunctioning thyroid adenoma	Somatic
	Jansen metaphysal chondrodysplasia	Autosomal dominant
Calcium receptor	Hypoparathyroidism	Autosomal dominant
<b>Loss of function</b>		
LH receptor	Male pseudohermafroditism	Autosomal recessive
FSH receptor	Hypergonadotrophic ovarian dysgenesis	Autosomal recessive
GHRH	Laron dwarfism	Autosomal recessive
TSH receptor	Congenital hypothyroidism	Autosomal recessive
TRH receptor	Congenital hypothyroidism	Autosomal recessive
ACTH	Familial ACTH resistance	Autosomal recessive
Vasopressin	Nephrogenic diabetes insipidus	X-linked
Calcium receptor	Familial hypocalciuric hypercalcaemia	Autosomal dominant
	Neonatal severe hyperparathyroidism	Autosomal recessive

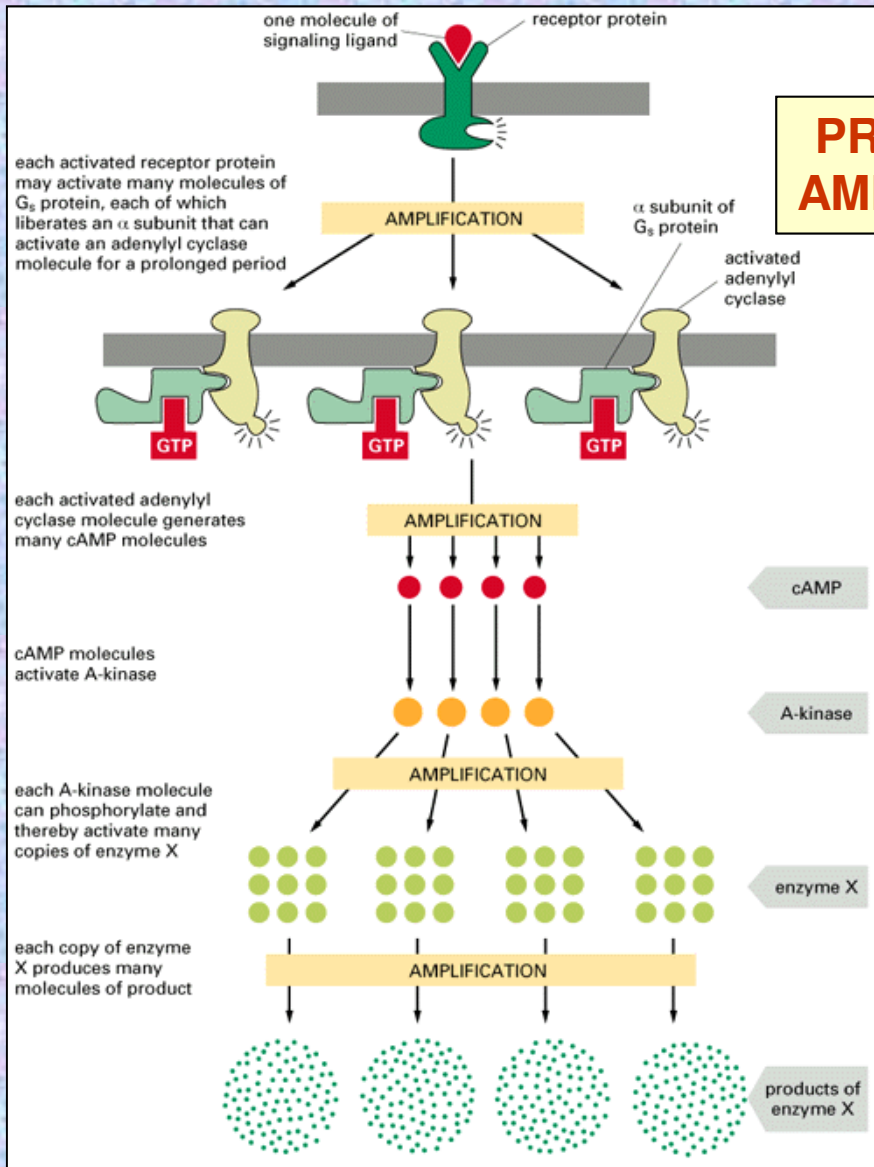
# INOSITOL-PHOSPHATE DEPENDENT SIGNALLING

Substance	Receptor	Transduction
Acetylcholin	→ M <sub>1</sub> , M <sub>3</sub> , M <sub>5</sub>	<p><b>G<sub>q/11</sub> → ↑ IP<sub>3</sub>/DAG</b></p>
Catechoamines	→ α <sub>1A</sub> , α <sub>1B</sub> , α <sub>1C</sub> , α <sub>1D</sub>	
Serotonin	→ 5-HT <sub>2A</sub> , 5-HT <sub>2B</sub> , 5-HT <sub>2C</sub>	
Histamin	→ H <sub>1</sub>	
Adenosin	→ A <sub>1</sub> , A <sub>3</sub>	
Purines	→ P <sub>2U</sub> , P <sub>2Y</sub>	
EAMA	→ mGlu <sub>1</sub> , mGlu <sub>5</sub>	
Vasopressin	→ V <sub>1A</sub> , V <sub>1B</sub>	
Oxytocin	→ Oxy	
Cholecystokinin	→ CCK <sub>A</sub> , CCK <sub>B</sub>	
Melanin	→ ML <sub>2</sub>	
Angiotensin	→ AT <sub>1</sub>	
Bradykinin	→ B <sub>1</sub> , B <sub>2</sub>	
Tachykinins	→ NK <sub>1</sub> , NK <sub>2</sub> , NK <sub>3</sub>	
Bombesin	→ BB <sub>1</sub> , BB <sub>2</sub>	
Endothelin	→ ET <sub>A</sub> , ET <sub>B</sub> , ET <sub>C</sub>	
Prostanoids	→ EP <sub>1</sub>	
Leukotriens	→ LTB <sub>4</sub> , LTD <sub>4</sub>	
PAF	→ PAFR	

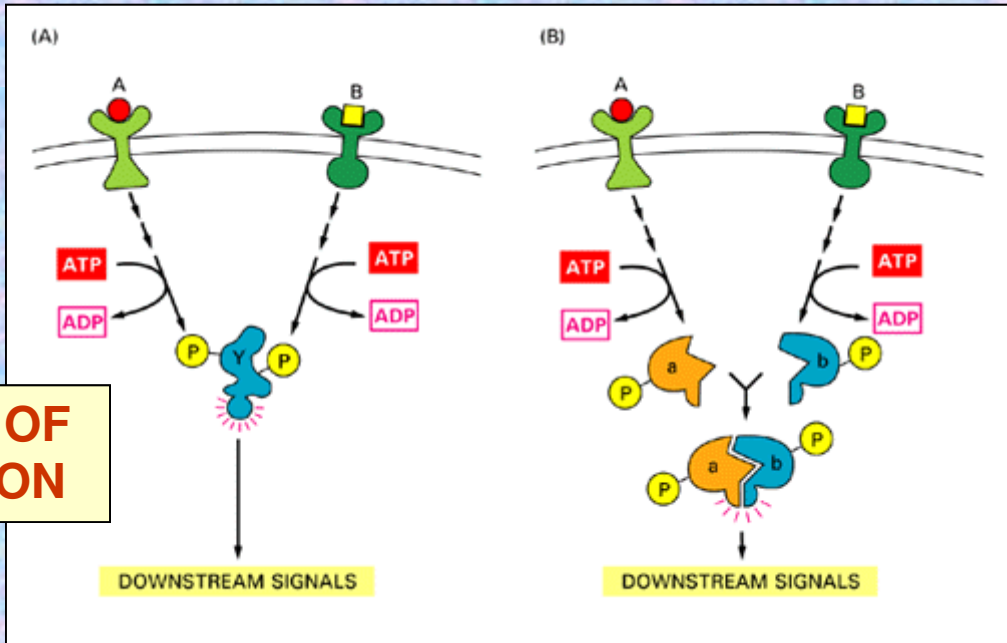
## c-AMP DEPENDENT SIGNALLING

Substance	Receptor	Transduction
Catecholamines	→ $\beta_{1,2,3}$	<p style="border: 1px solid black; padding: 5px; display: inline-block;"><b>Gs → ↑ cAMP</b></p>
Serotonin	→ 5-HT <sub>4,5,6,7</sub>	
Dopamin	→ D <sub>1</sub> (D <sub>1A</sub> ),D <sub>5</sub> (D <sub>1B</sub> )	
Histamin	→ H <sub>2</sub>	
Adenosinn	→ A <sub>2A</sub> ,A <sub>2B</sub>	
Vasopressin	→ V <sub>2</sub>	
VIP	→ VIP <sub>1,2</sub> ,GRF	
Prostanoidy	→ EP <sub>2</sub> ,EP <sub>4</sub>	
Octopamin	→ OA <sub>2A</sub> ,OA <sub>3</sub>	
CGRP	→ CGRPR	

Substance	Receptor	Transduction
Acetylcholin	→ M <sub>2</sub> ,M <sub>4</sub>	<p style="border: 1px solid black; padding: 5px; display: inline-block;"><b>Gi/o → ↓ cAMP</b></p>
Catecholamines	→ $\alpha_{2A,2B,2C,2D}$	
Serotonin	→ 5-HT <sub>1A,1B,1D,1E,1F</sub>	
Dopamin	→ D <sub>2</sub> ,D <sub>3</sub> ,D <sub>4</sub>	
GABA	→ GABA <sub>B</sub> ,	
Adenosinn	→ A <sub>1</sub> ,A <sub>3</sub>	
Purines	→ P <sub>1</sub> , P <sub>2T</sub>	
EAMK	→ mGlu <sub>2,3,4,6,7,8</sub>	
Opioides	→ $\mu,\delta,\kappa$	
Somatostatin	→ SST <sub>2,3,4</sub>	
Melanin	→ ML <sub>1A,1B</sub>	
Intereleukines	→ IL <sub>8A,IL8B</sub>	
Chemokines	→ CCCK <sub>1,2,3</sub>	
Protease	→ PAR <sub>1</sub>	
NPY	→ Y <sub>1</sub> ,Y <sub>2</sub> ,Y <sub>3</sub>	
Galanin	→ Gal	
Prostanoids	→ EP <sub>3</sub>	

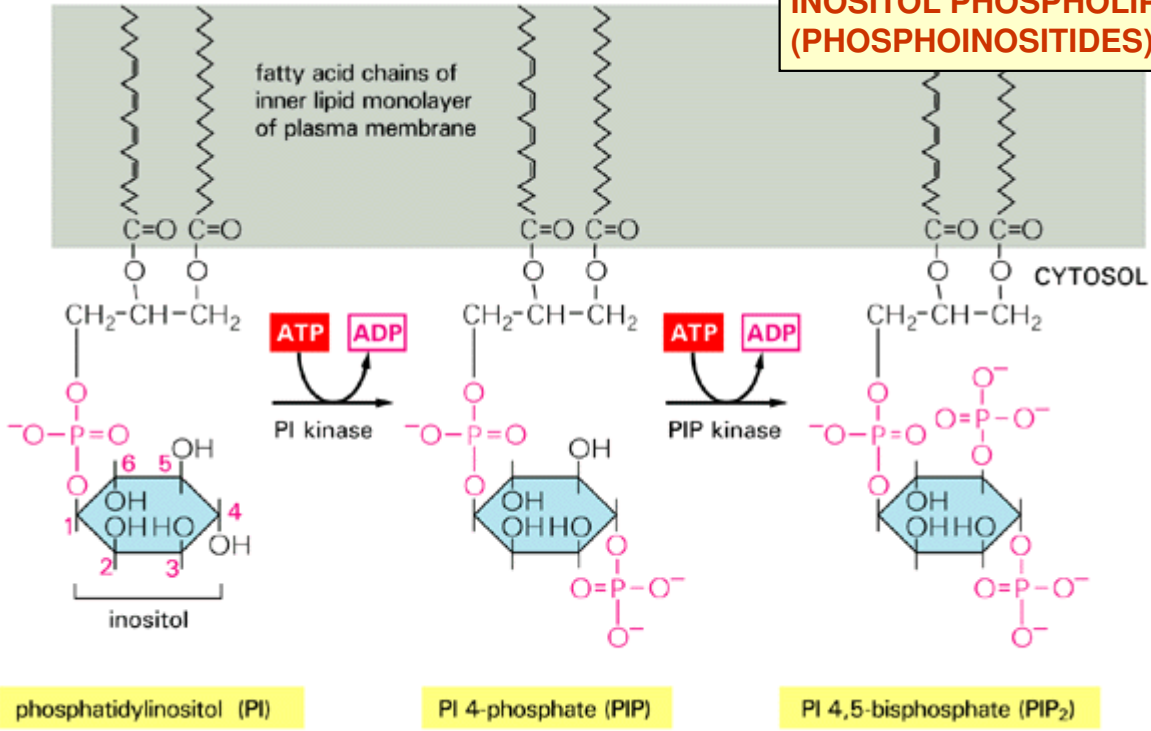


**PRINCIPLE OF AMPLIFICATION**

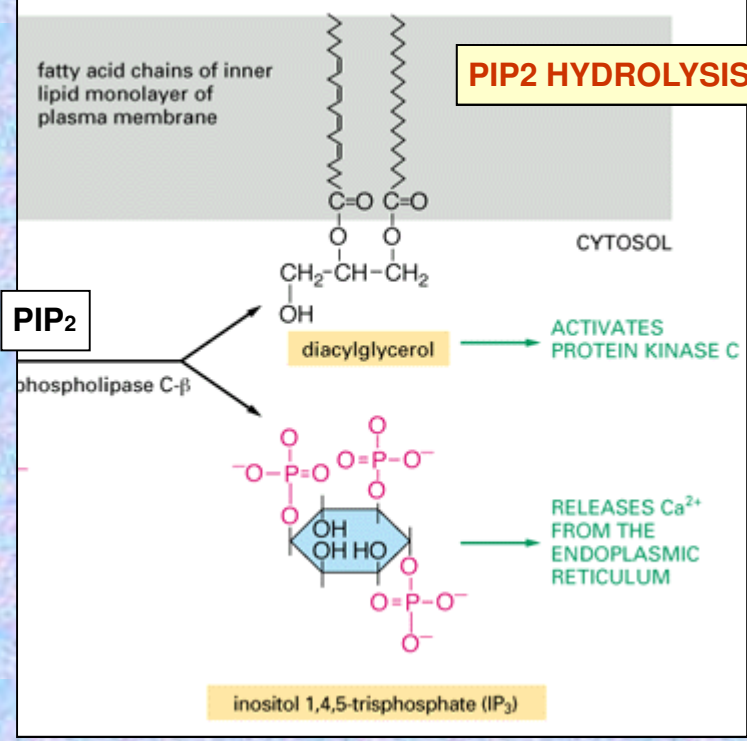


**PRINCIPLE OF INTEGRATION**

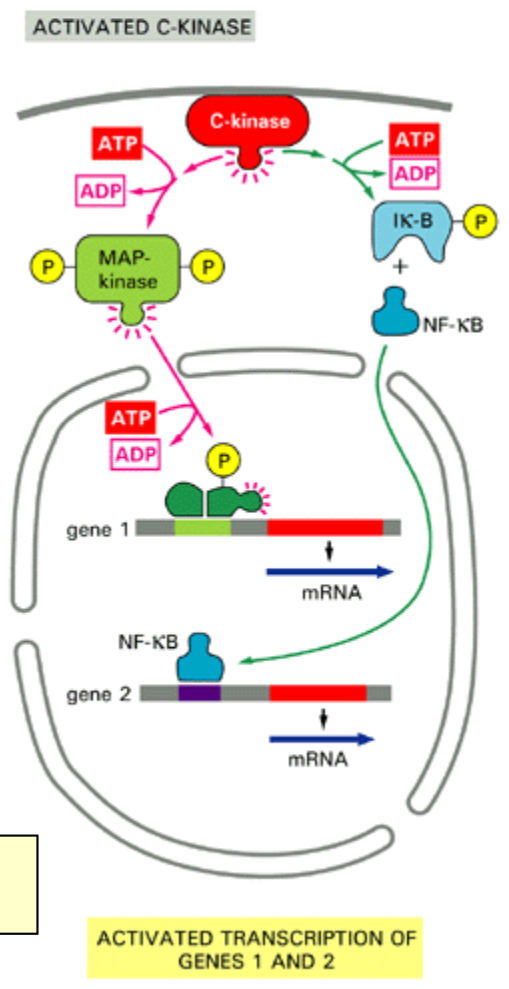
**INOSITOL PHOSPHOLIPIDS (PHOSPHOINOSITIDES)**



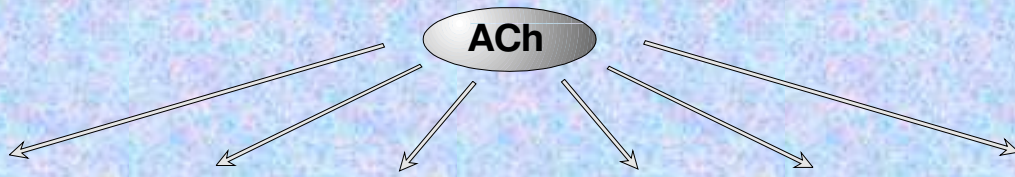
**PIP<sub>2</sub> HYDROLYSIS**



**C-KINASE ACTIVATED GENE TRANSCRIPTION**



**Same ligand can bind to different receptors**



ACh(N)	ACh(M <sub>1</sub> )	ACh(M <sub>2</sub> )	ACh(M <sub>3</sub> )	ACh(M <sub>4</sub> )	ACh(M <sub>5</sub> )
+ Nikotín α - Anatoxin Epibatín Epiboxidín	+ McN-A-343 Oxotremorín-M	+ Oxotremorín-M	+ Oxotremorín-M	+ Oxotremorín-M	+ Oxotremorín-M
- Neosurugatoxín α - Bungarotoxín α - Kobraoxín α - Konotoxín Tubokurarín Dekametónium Hexametónium Metyllykátónium Gallamín	- Pirenzepín Telenzepín QNX hemioxalát Atropín Skopolamín	- Metoktramín Gallamín Himbacín 3α - Cl-Imperialín Atropín Skopolamín	- Hexahydrozyl Odifenidol 4-DAMP Atropín Skopolamín	- Himbacín Tropicamid Atropín Skopolamín	

**Different Cells Can Respond Differently to the Same Chemical Signal**

