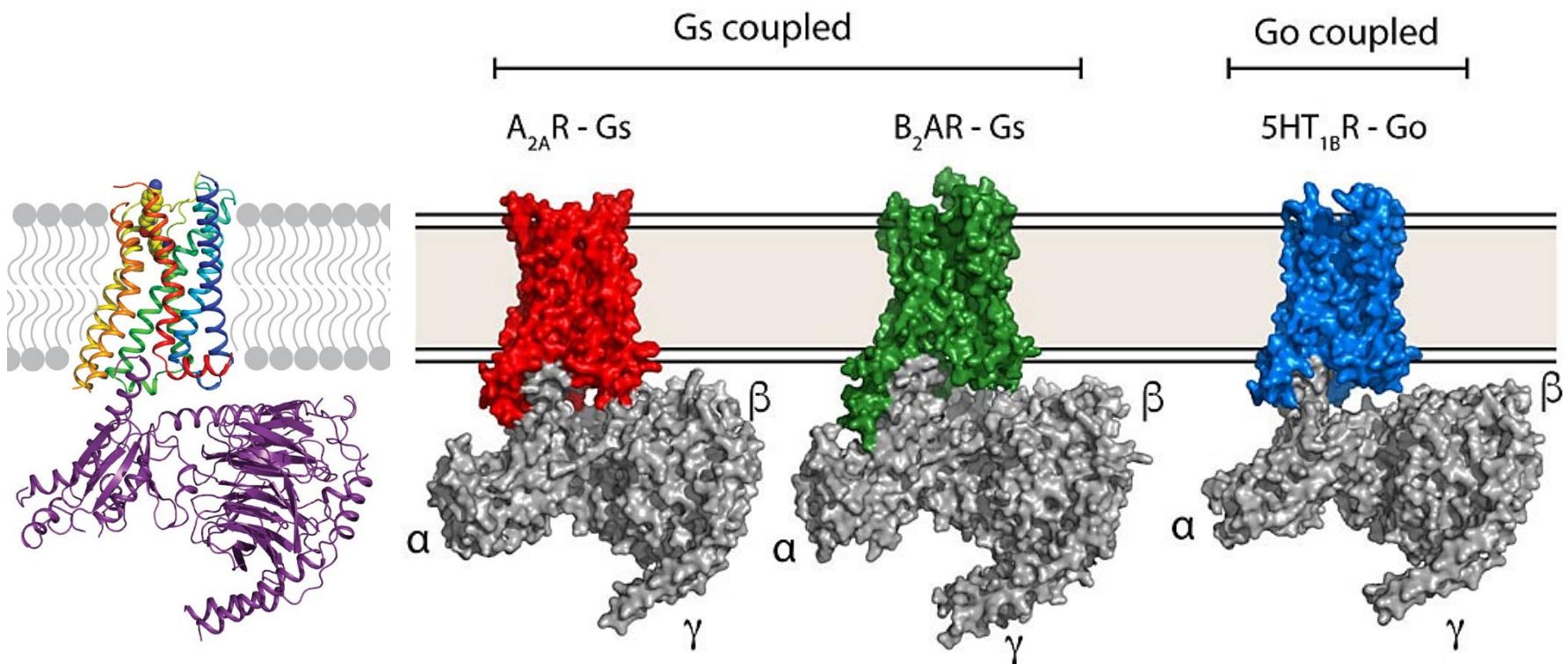
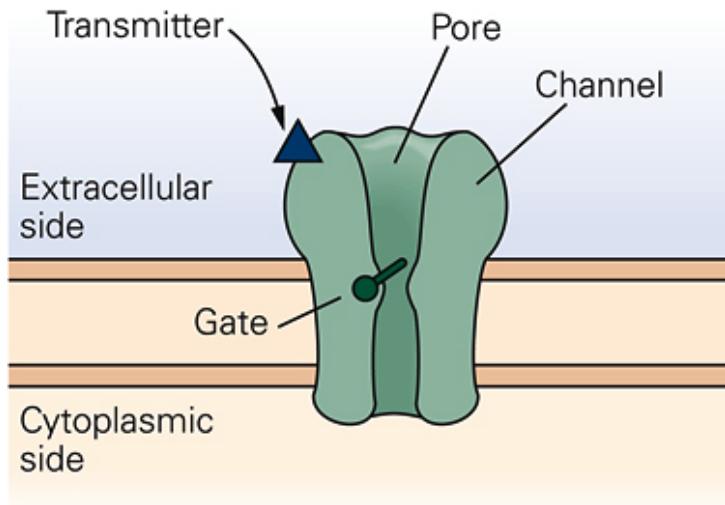


Chapter 14: Modulation of Synaptic Transmission and Neuronal Excitability – Second Messengers



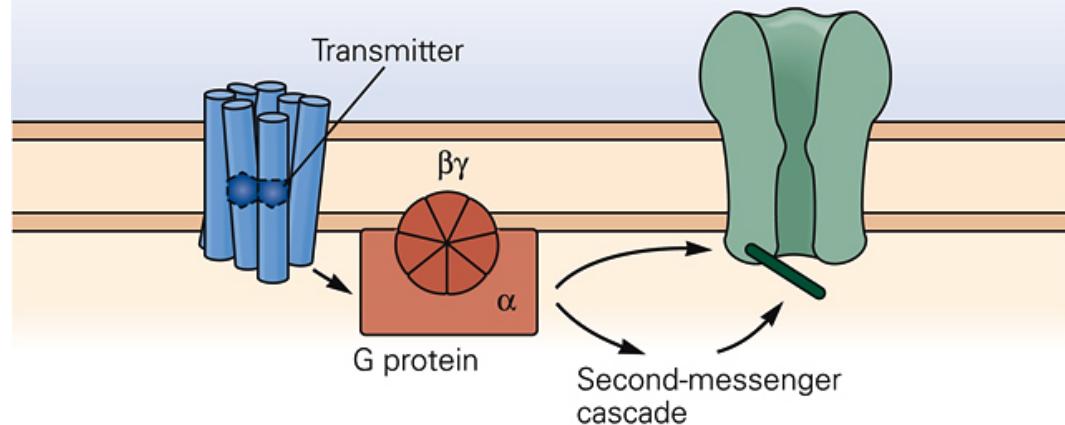
Ionotropic vs. Metabotropic Receptors

A Direct gating

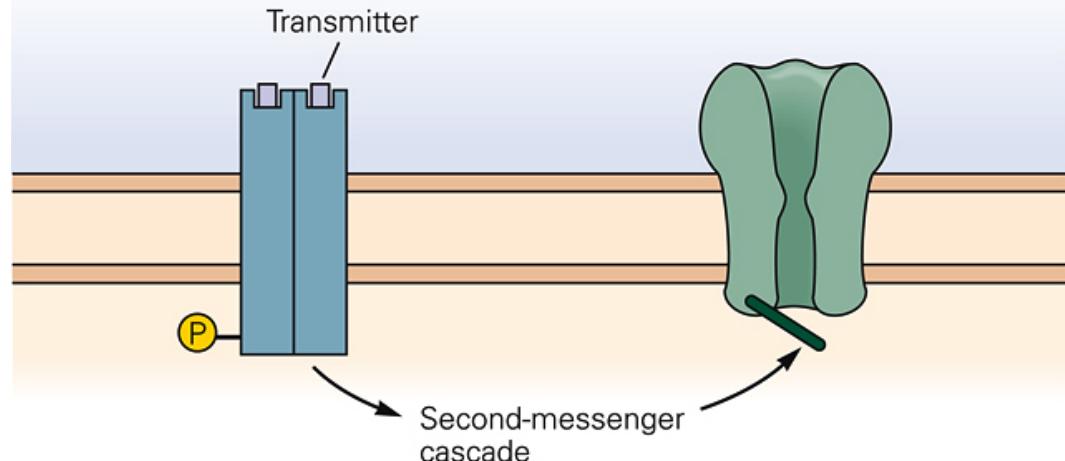


B Indirect gating

1 G protein-coupled receptor



2 Receptor tyrosine kinase



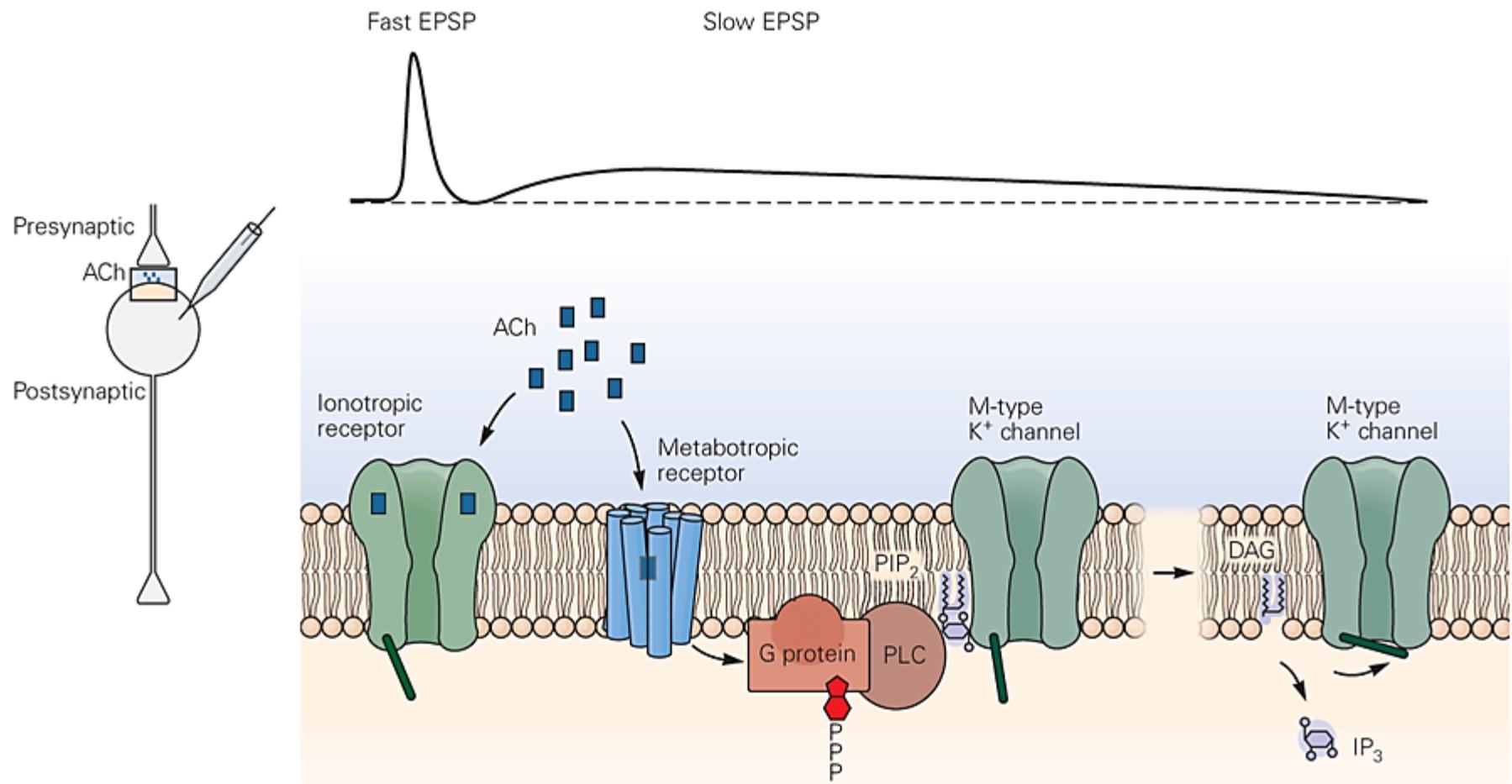
Ionotropic Receptors

- Effects are rapid, but short-lived
- Neurotransmitter causes opening of channel
- Modify the post-synaptic potential (EPSPs or IPSPs)

Metabotropic Receptors

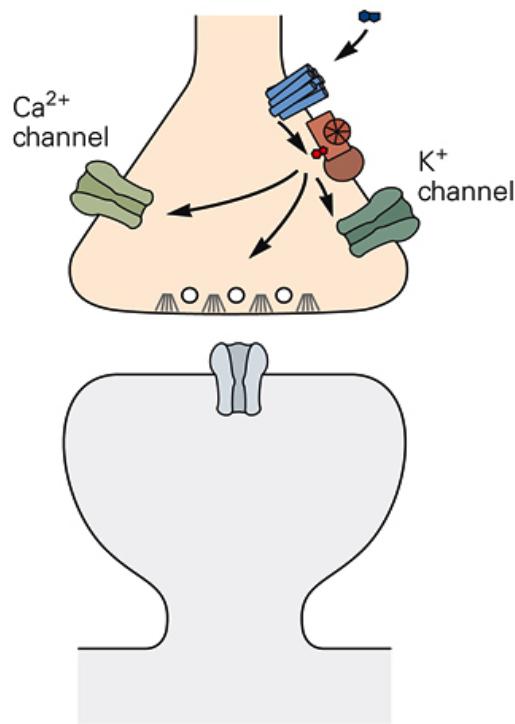
- Effects are slower, but longer-lasting
- Neurotransmitter can cause opening or closing of channels
- In addition to changing the post-synaptic potential, they modulate MANY neuronal functions
- 2nd messengers can diffuse throughout the cell, affecting distant neuronal regions

Ionotropic vs. Metabotropic Receptors

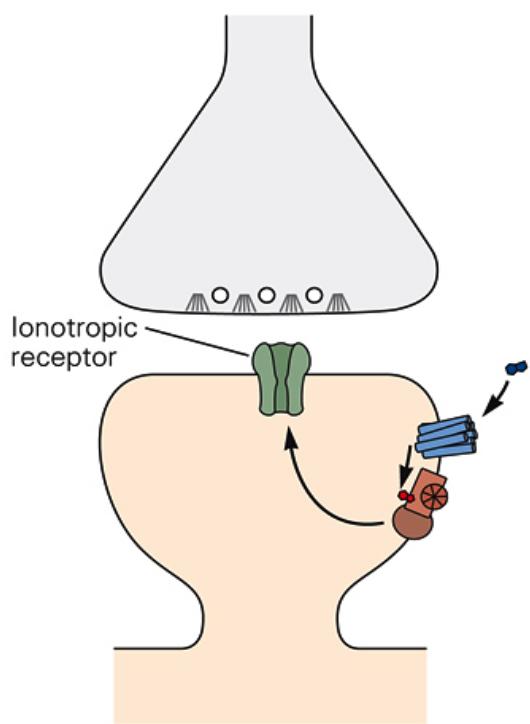


Metabotropic Receptors Modulate Neuron Function

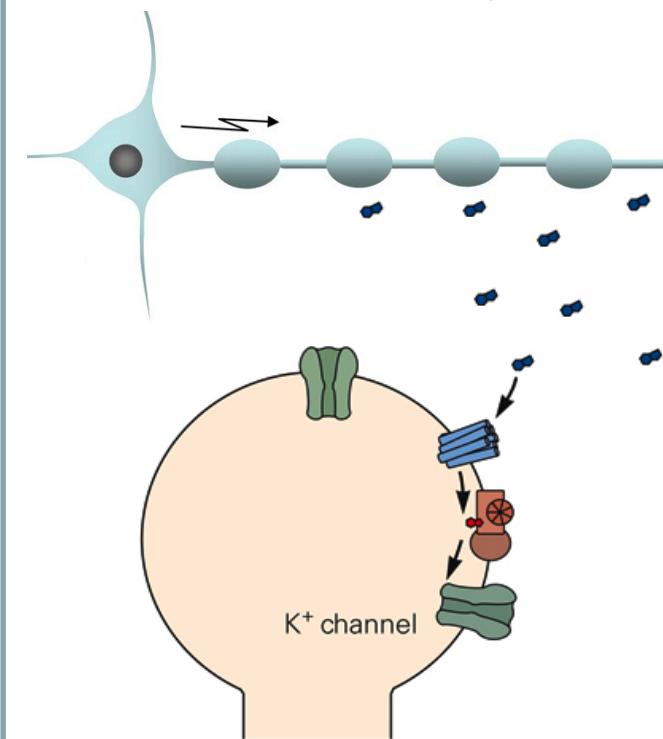
A Presynaptic modulation



B Postsynaptic modulation



C Modulation in cell body



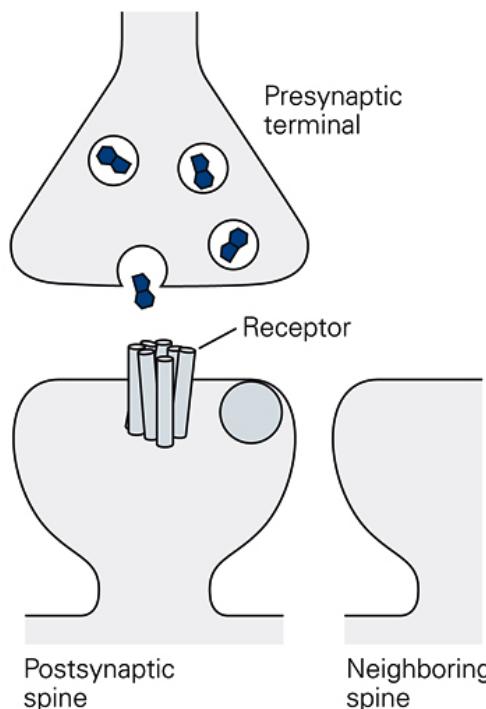
- Modify the release of neurotransmitters (presynaptic excitation and presynaptic inhibition)

- Regulate post synaptic potential (cause EPSPs or IPSPs)
- Modify the sensitivity of ligand-gated channels

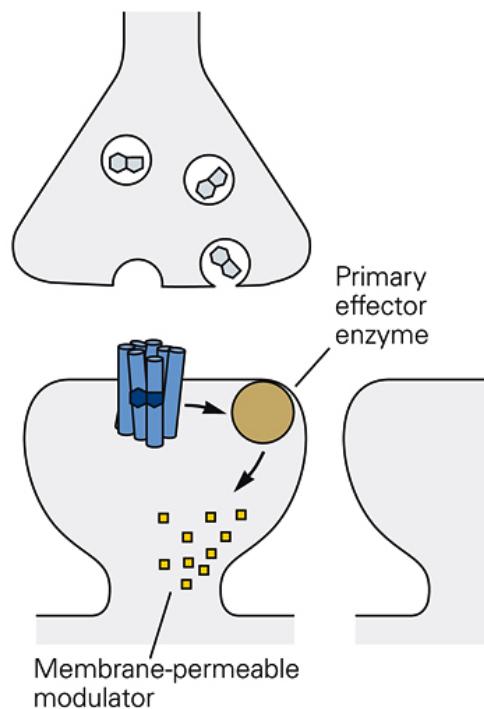
- Change resting membrane potential by affecting channels
- Modify the length constant by changing membrane resistance
- Modify the threshold or kinetics of voltage-gated channels

Metabotropic Receptors and Retrograde Signaling at Synapses

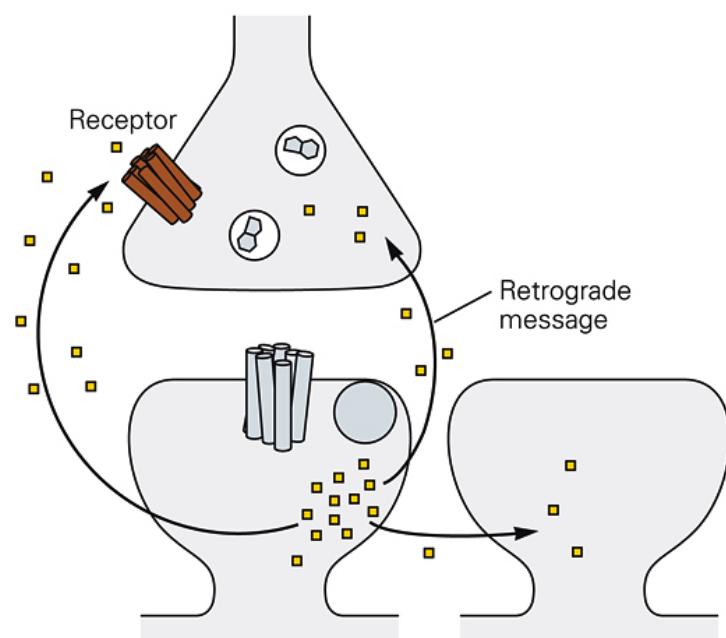
A Release of chemical transmitter



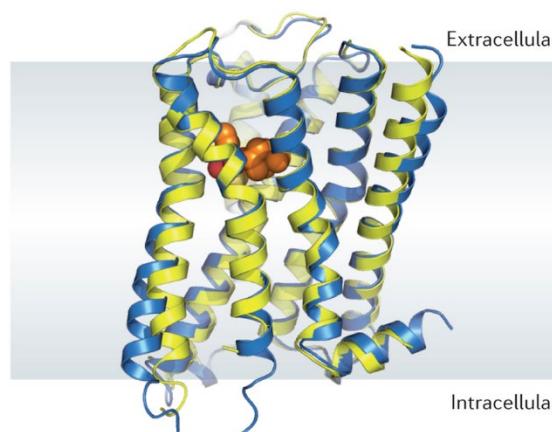
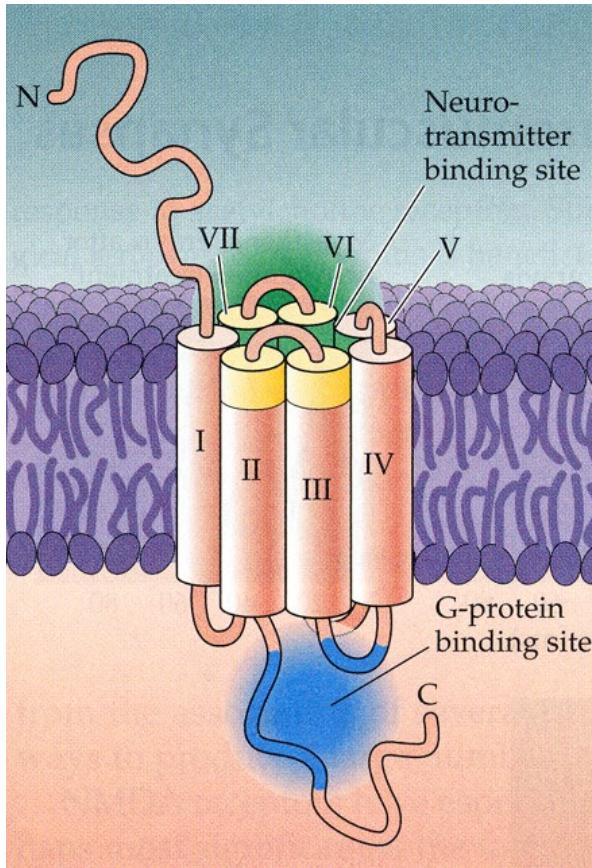
B Enzymatic reaction



C Transcellular signaling



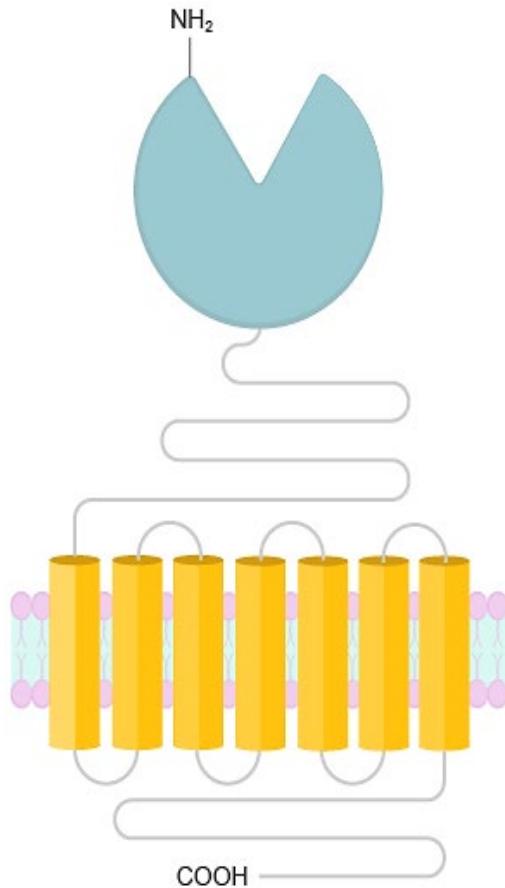
Conventional G-protein-coupled receptors (GPCRs)



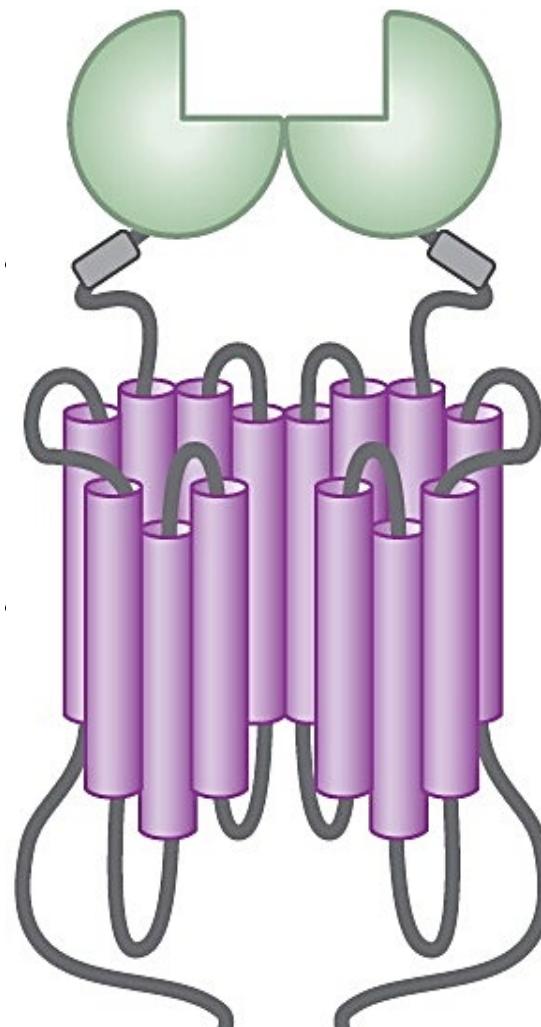
Dopamine	NE, Epi (Adrenergic)	Histamine	Serotonin	Adenosine, ATP (Purinergic)	Acetylcholine (Muscarinic)
D _{1A}	α1	H1	5-HT 1	A type	M1
D _{1B}	α2	H2	5-HT 2	A1	M2
D ₂	β1	H3		A2a	M3
D ₃	β2		5-HT 4	A2b	M4
D ₄	β3		5-HT 5	A3	M5
			5-HT 6	P type	
			5-HT 7	P2x	
				P2y	
				P2z	
				P2t	
				P2u	

Atypical GPCRs

Have large extracellular domains (called venus fly-trap domains) to bind the transmitter



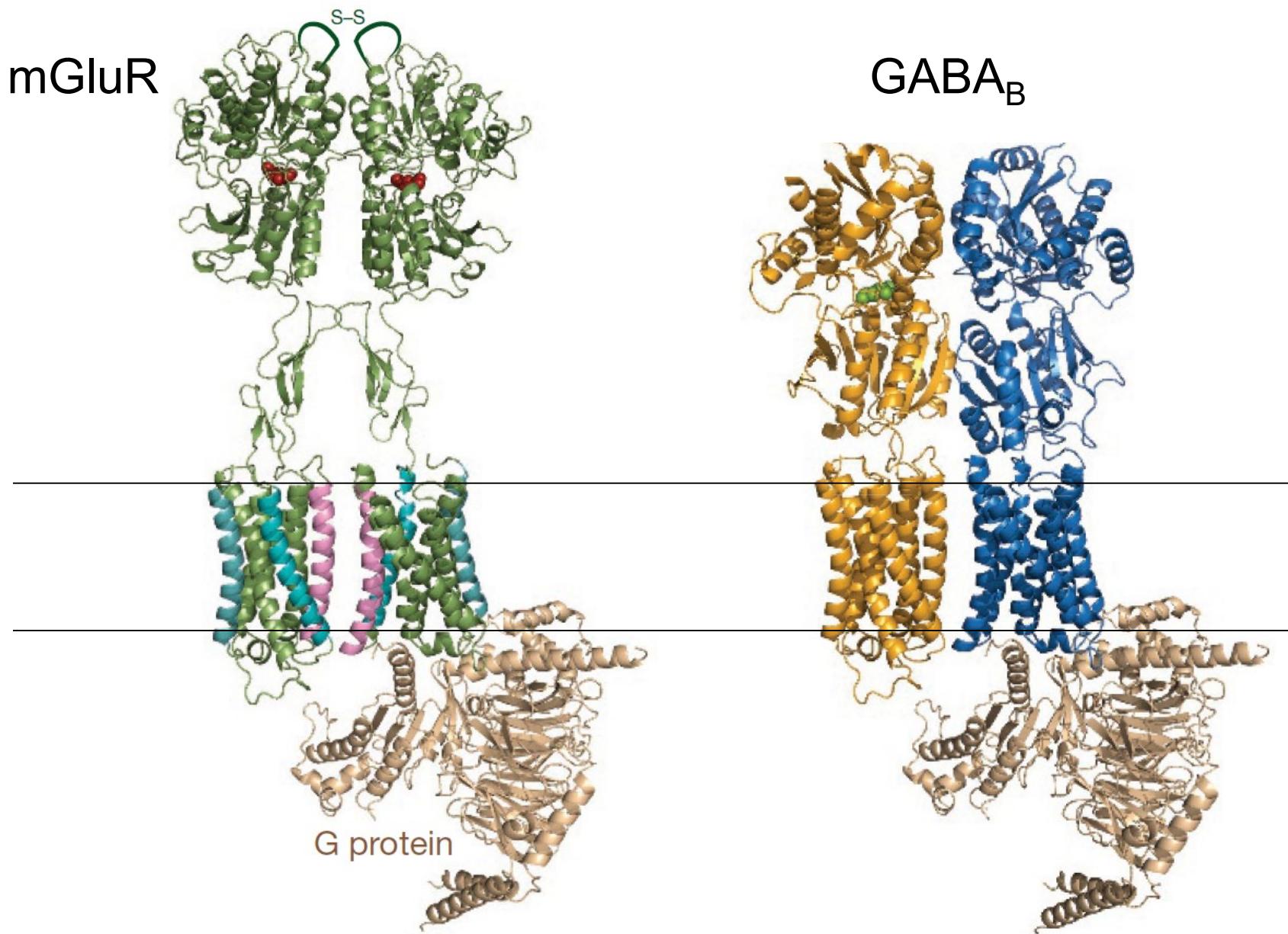
Form obligatory dimers



Include mGluRs and GABA_B receptors

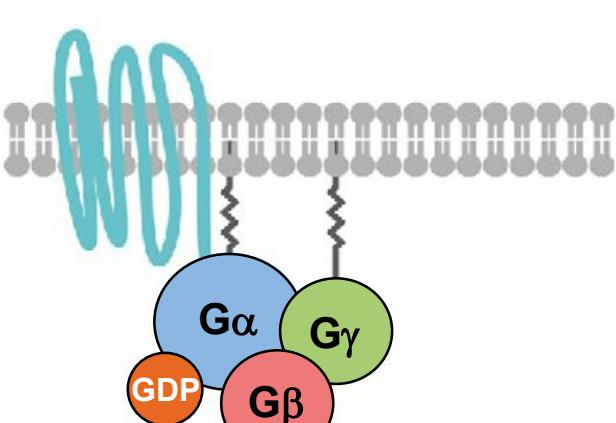
Glutamate	GABA _B
	GABA _B
Class I	GABA _B R1
mGlu R1	GABA _B R2
mGlu R5	
Class II	
mGlu R2	
mGlu R3	
Class III	
mGlu R4	
mGlu R6	
mGlu R7	
mGlu R8	

Atypical GPCRs

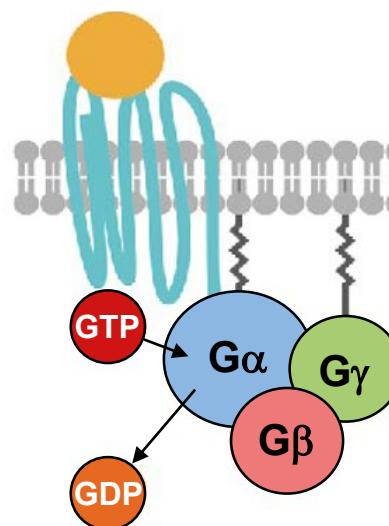


Action of G-proteins

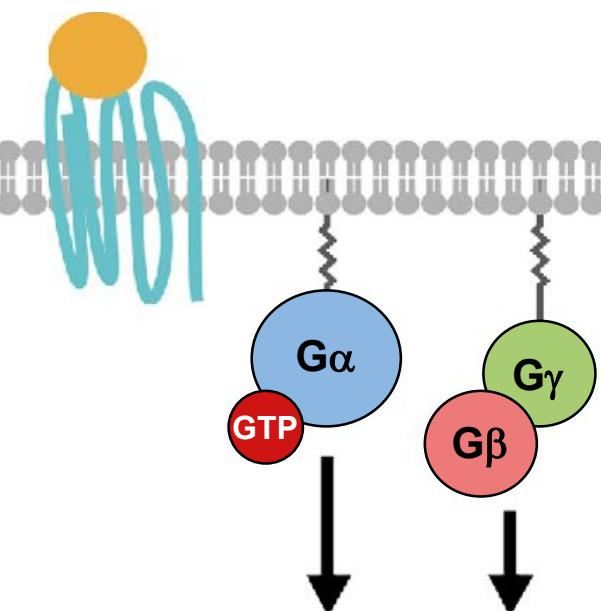
1. Inactive receptor and inactive g-protein (GDP-bound)



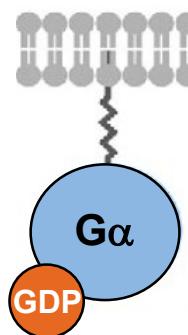
2. Neurotransmitter binds to receptor, GDP is replaced by GTP, activating the g-protein



3. The activated g-protein separates and activates downstream effectors.



4. In time, the alpha subunit hydrolyzes GTP to GDP, the g-protein subunits reassemble, and the complex returns to an inactive state

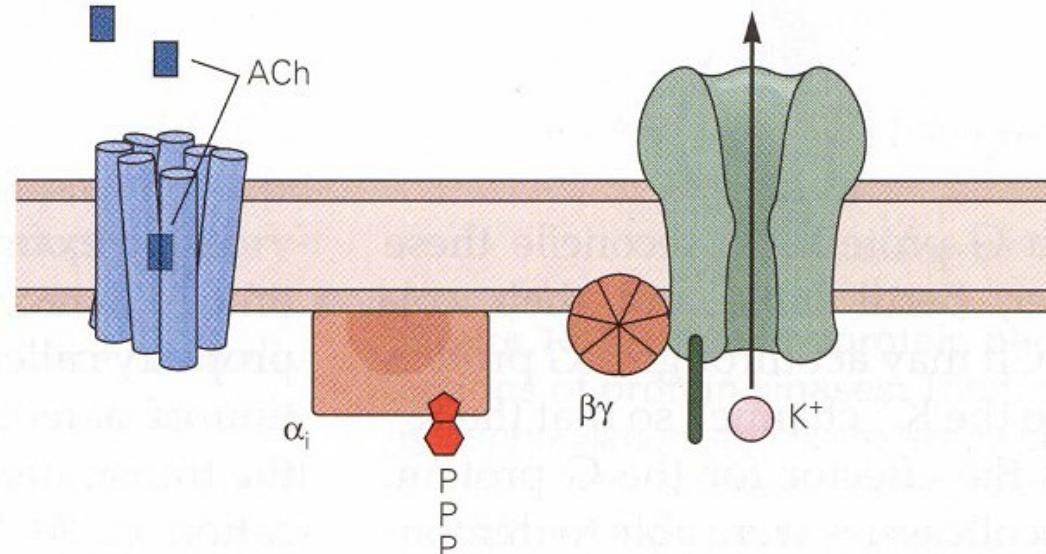
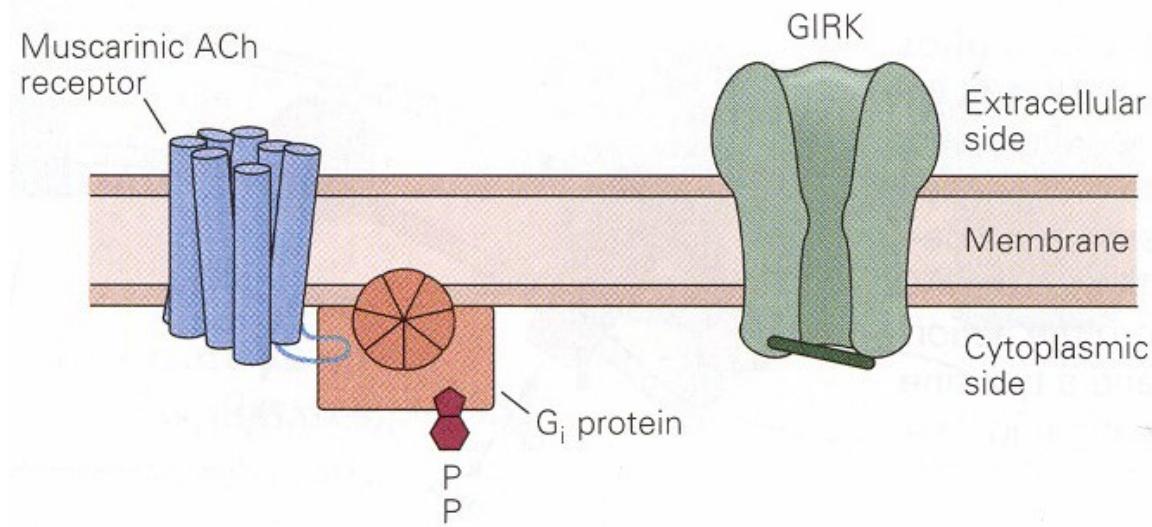


- Ion channels
- cAMP system
- cGMP system
- Phopholipase systems
- Other systems

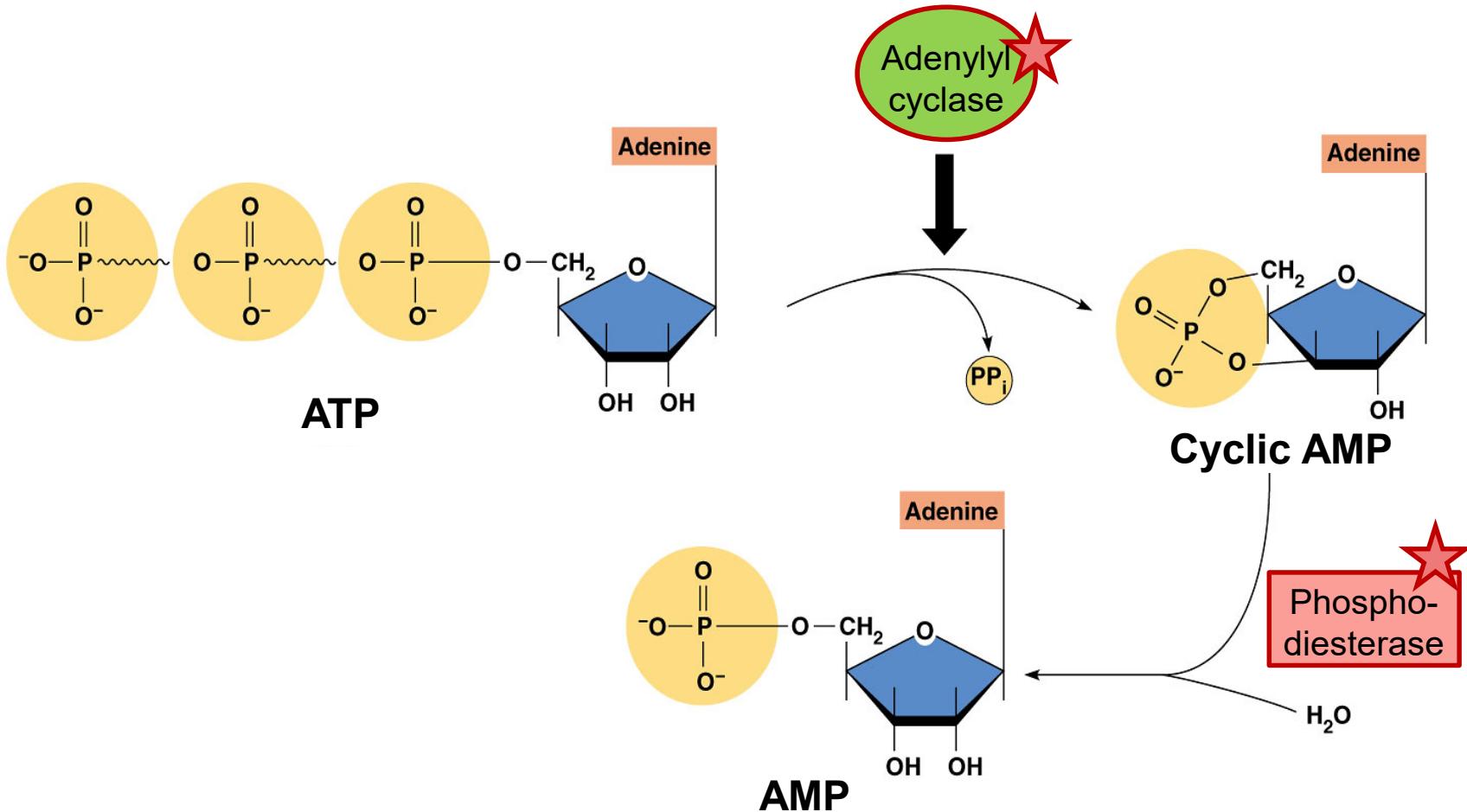
Beta/gamma subunits of G-proteins can directly affect channels

Example:

Muscarinic AChR
activation in
cardiac muscle

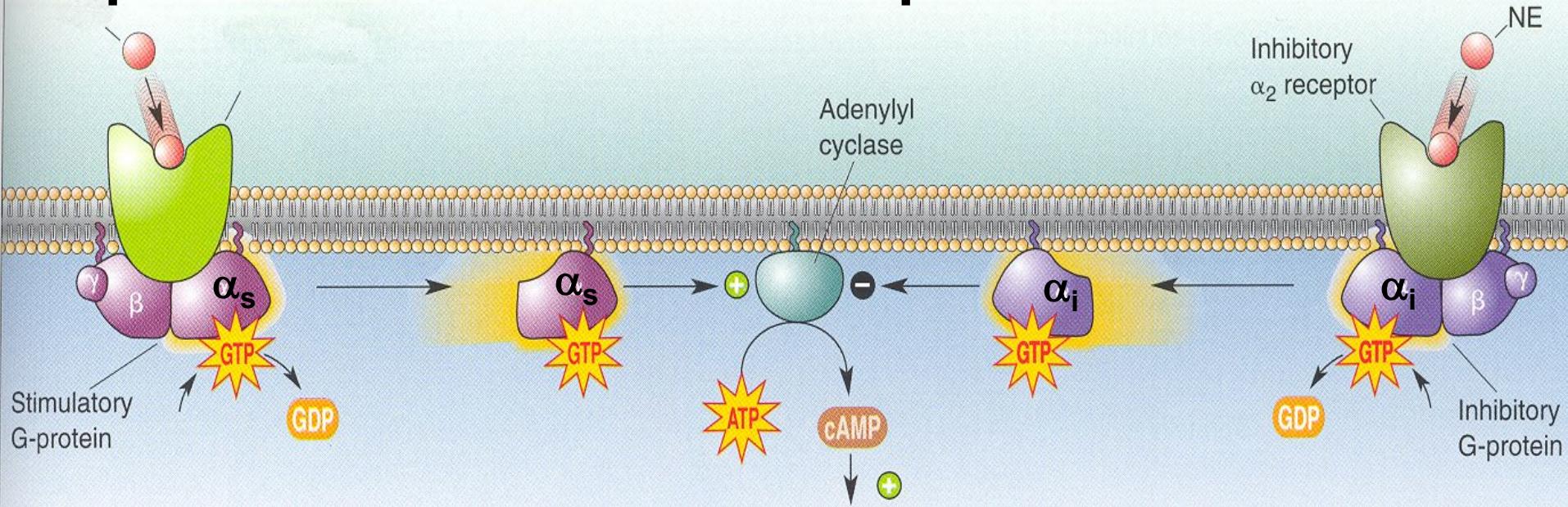


Cyclic AMP Second Messenger System



cGMP is produced in a similar manner by guanylyl cyclase
cGMP is inactivated by phosphodiesterase

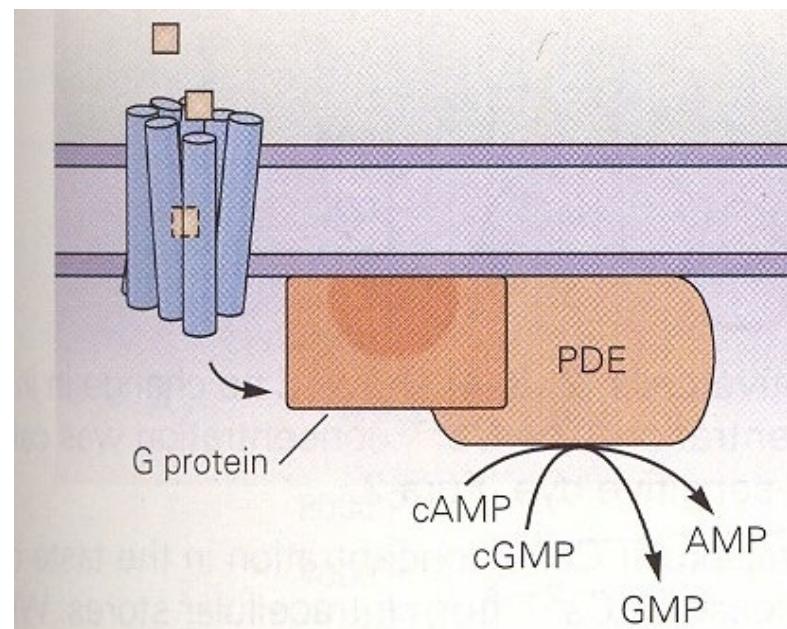
Alpha subunits influence the production of cAMP



Alpha subunits influence the destruction of cAMP

cGMP is produced by guanylyl cyclase

cGMP is inactivated by phosphodiesterase

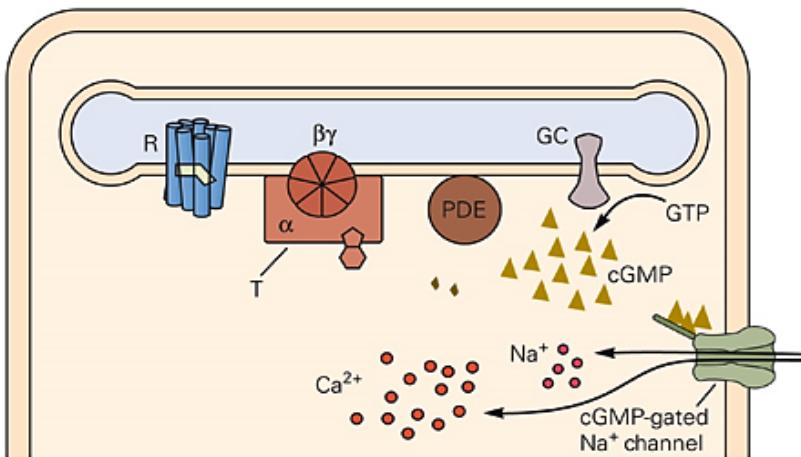


cAMP & cGMP regulate channel function directly

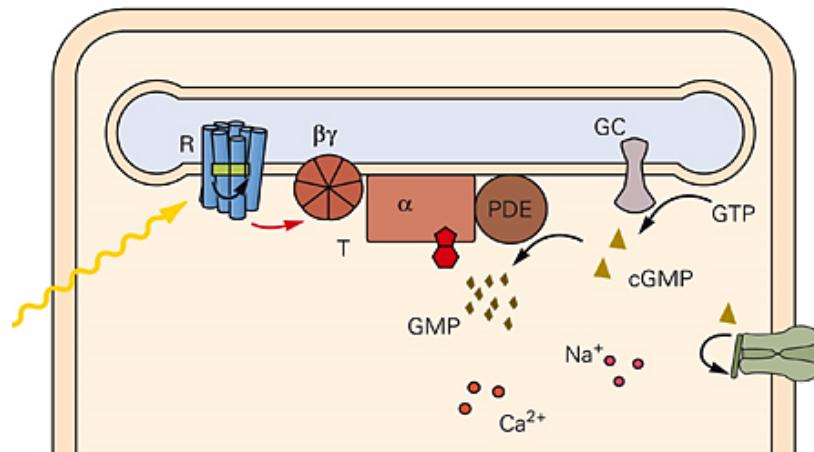
Rods of Eye

(cGMP increases Na^+ conductance)

Dark

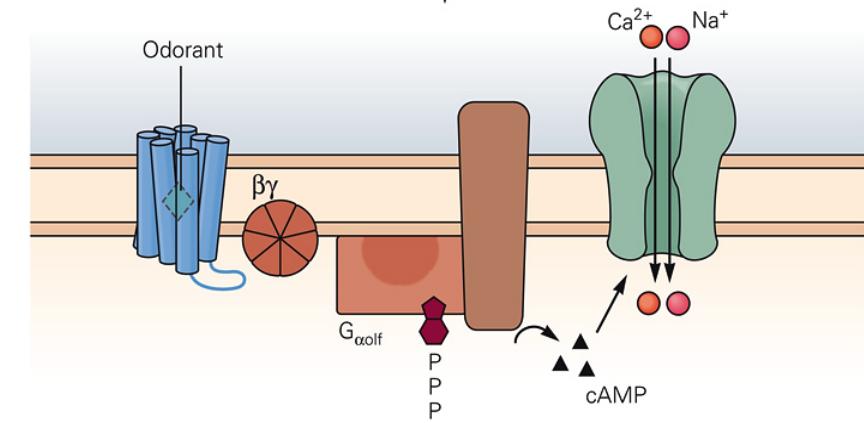
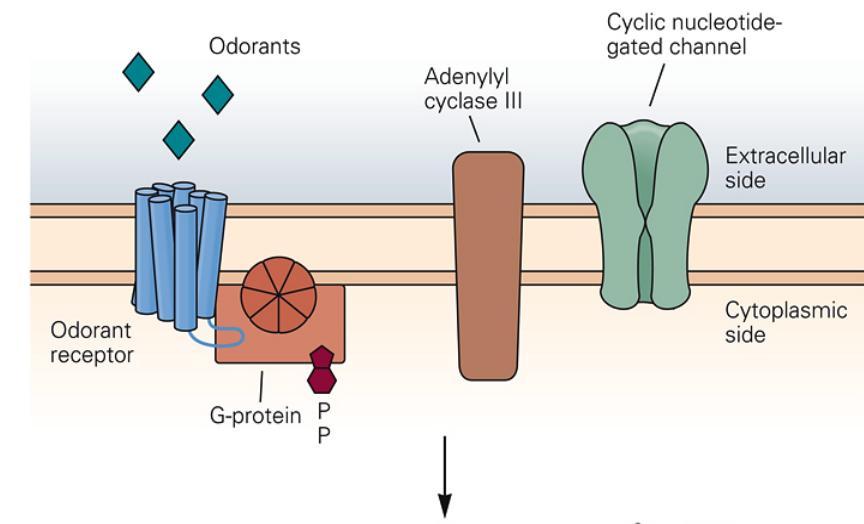


Light



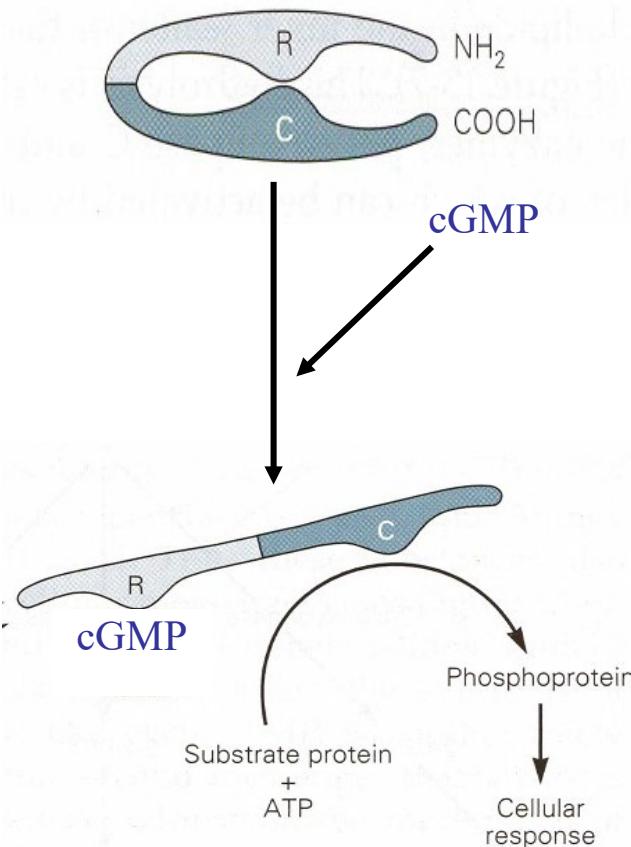
Odorant Receptor

(cAMP increases Na^+ and Ca^{2+} conductance)

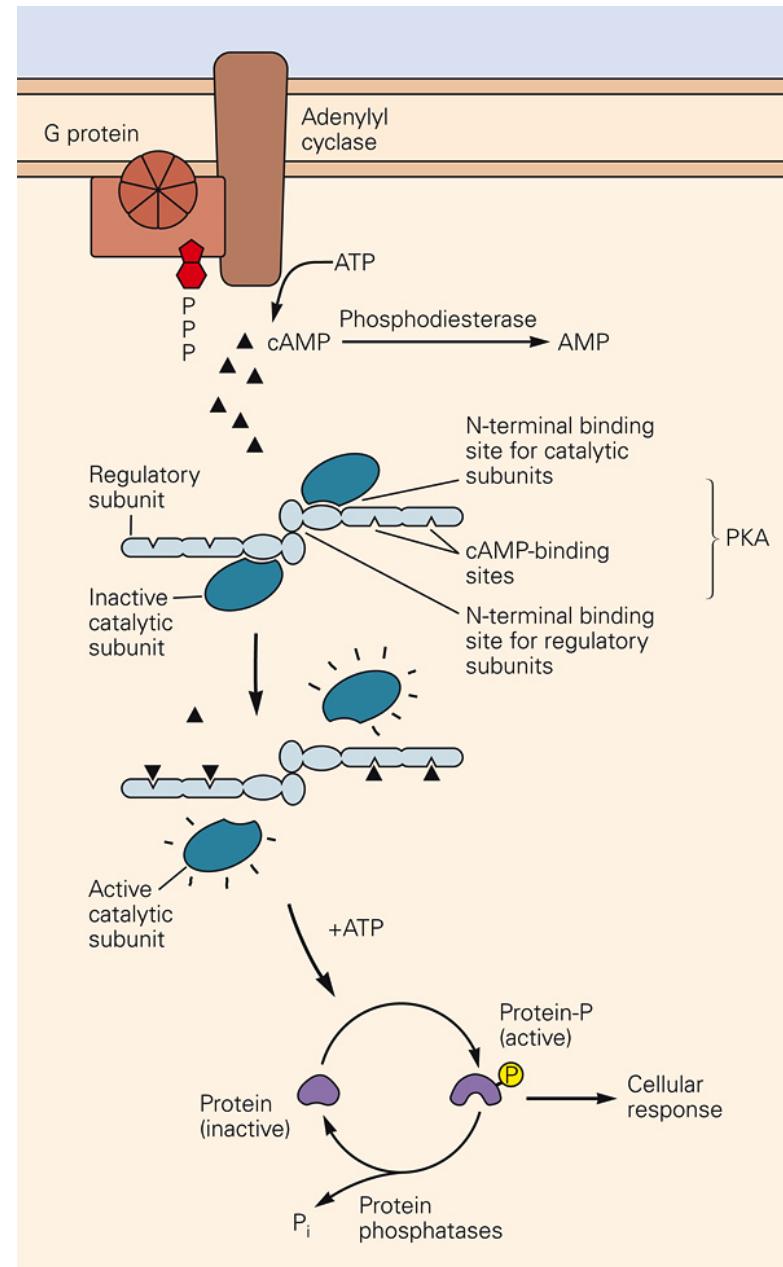


cAMP and cGMP activate kinases

cGMP-dependent protein kinase (PKG)

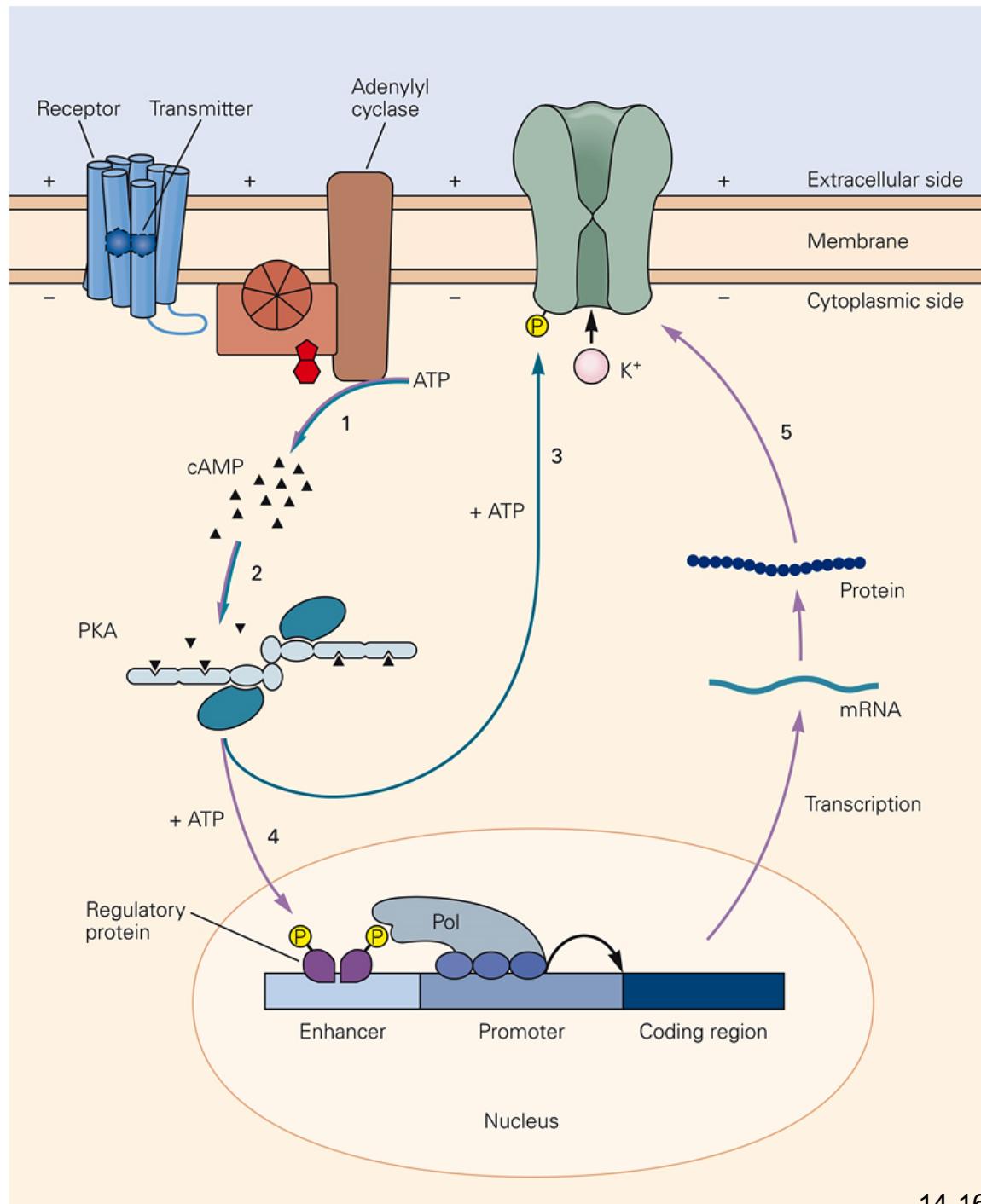


cAMP-dependent protein kinase (PKA)



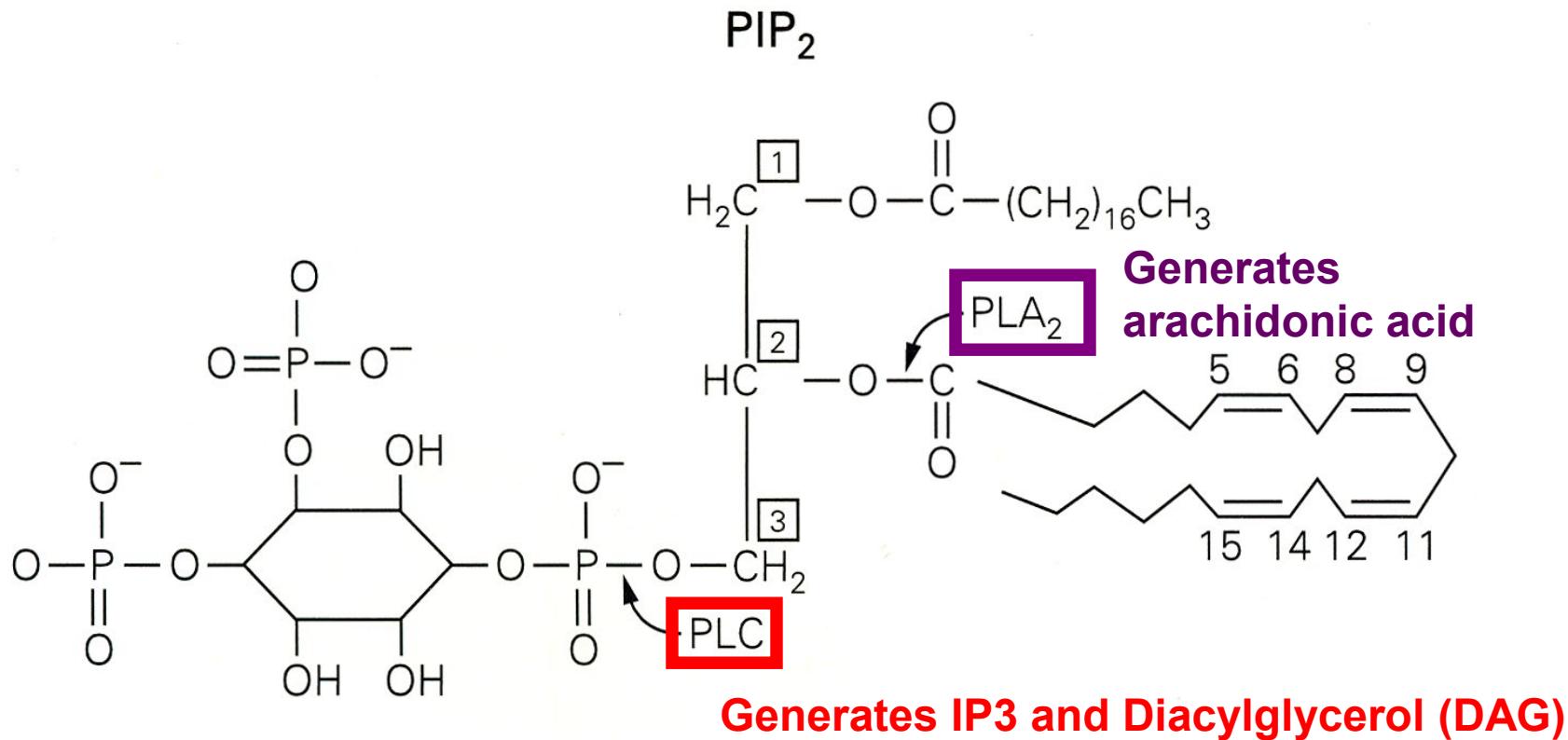
Example of the cAMP system in action

Activation of the cAMP system can have short-term and long-term effects!!

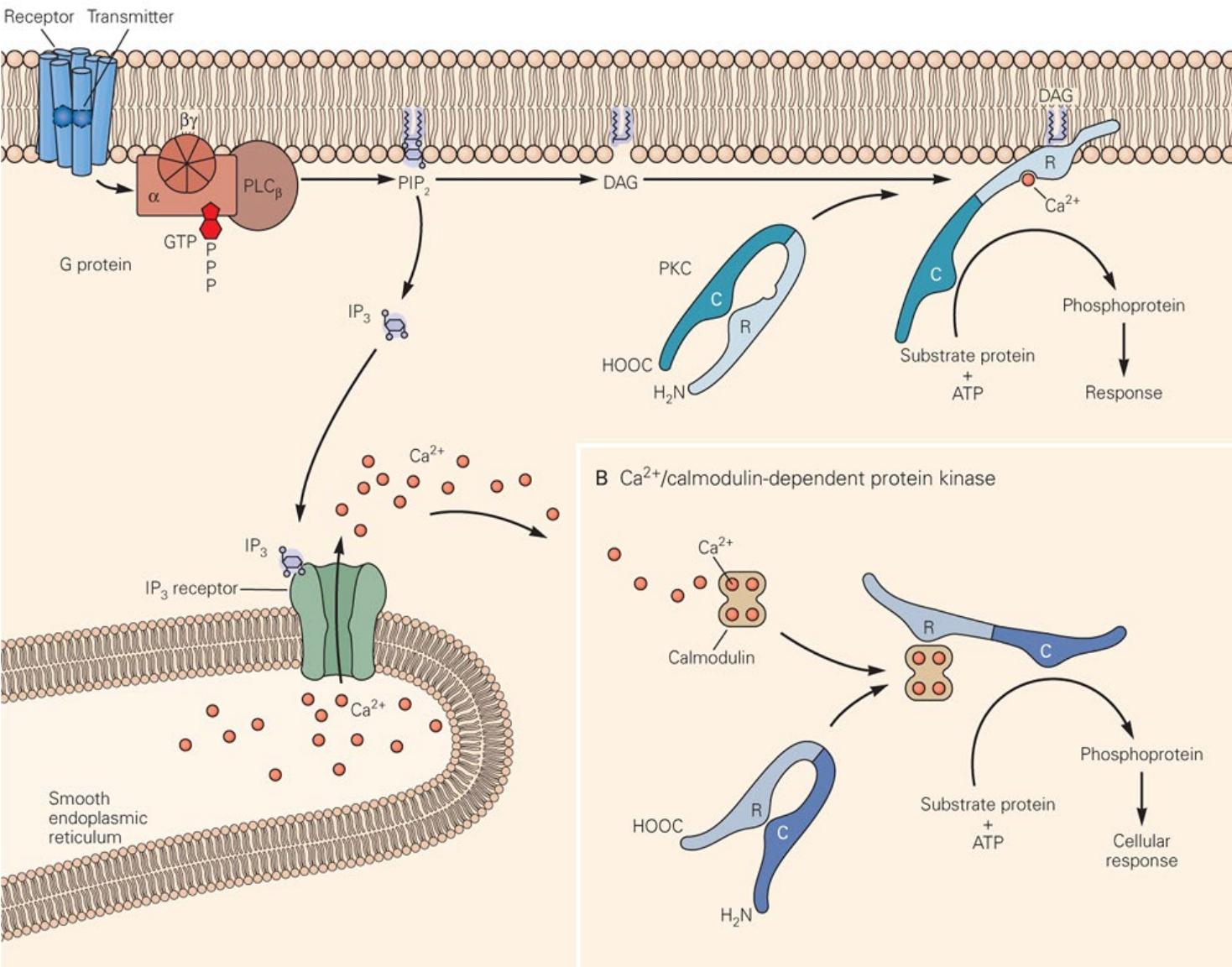


G-proteins activate phospholipases

Phosphatidylinositol 4,5-bisphosphate (PIP_2)



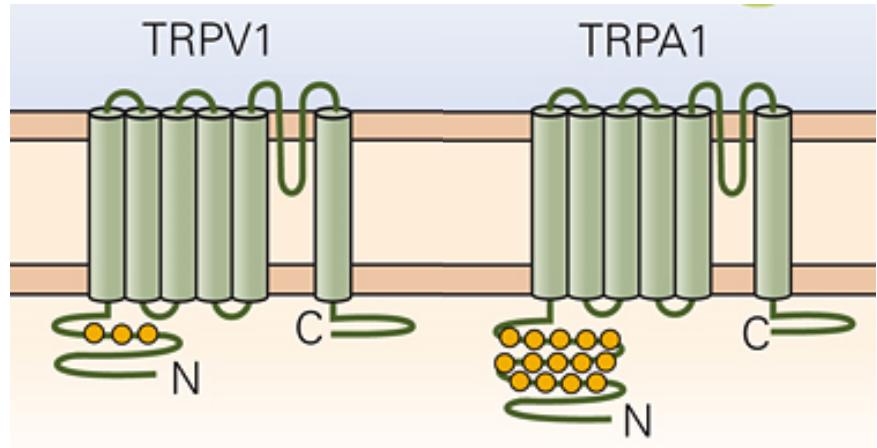
Phospholipase C System



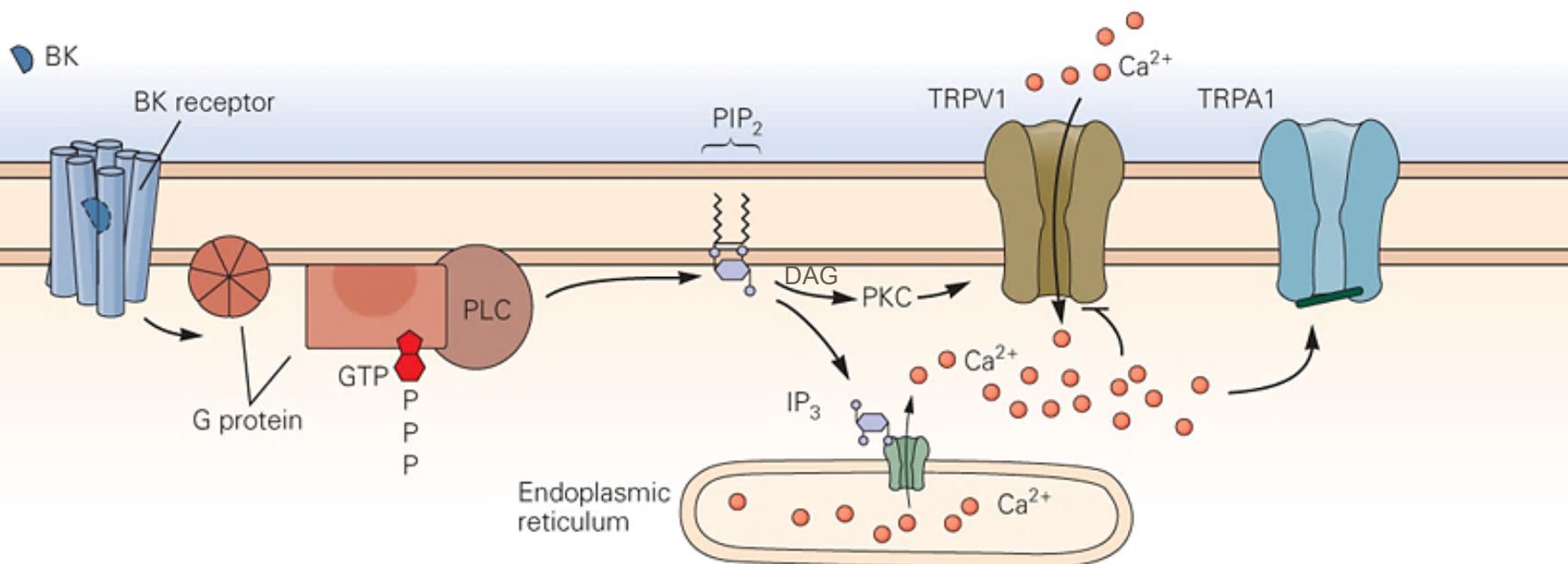
Results

- Calcium can directly modulate ion channels
- DAG activates protein kinase C. Calcium is also required to activate some isoforms of PKC.
- Ca^{2+} /calmodulin can also activate or inactivate other enzymes (such as CAM Kinases)

Example of the Phospholipase C system in action

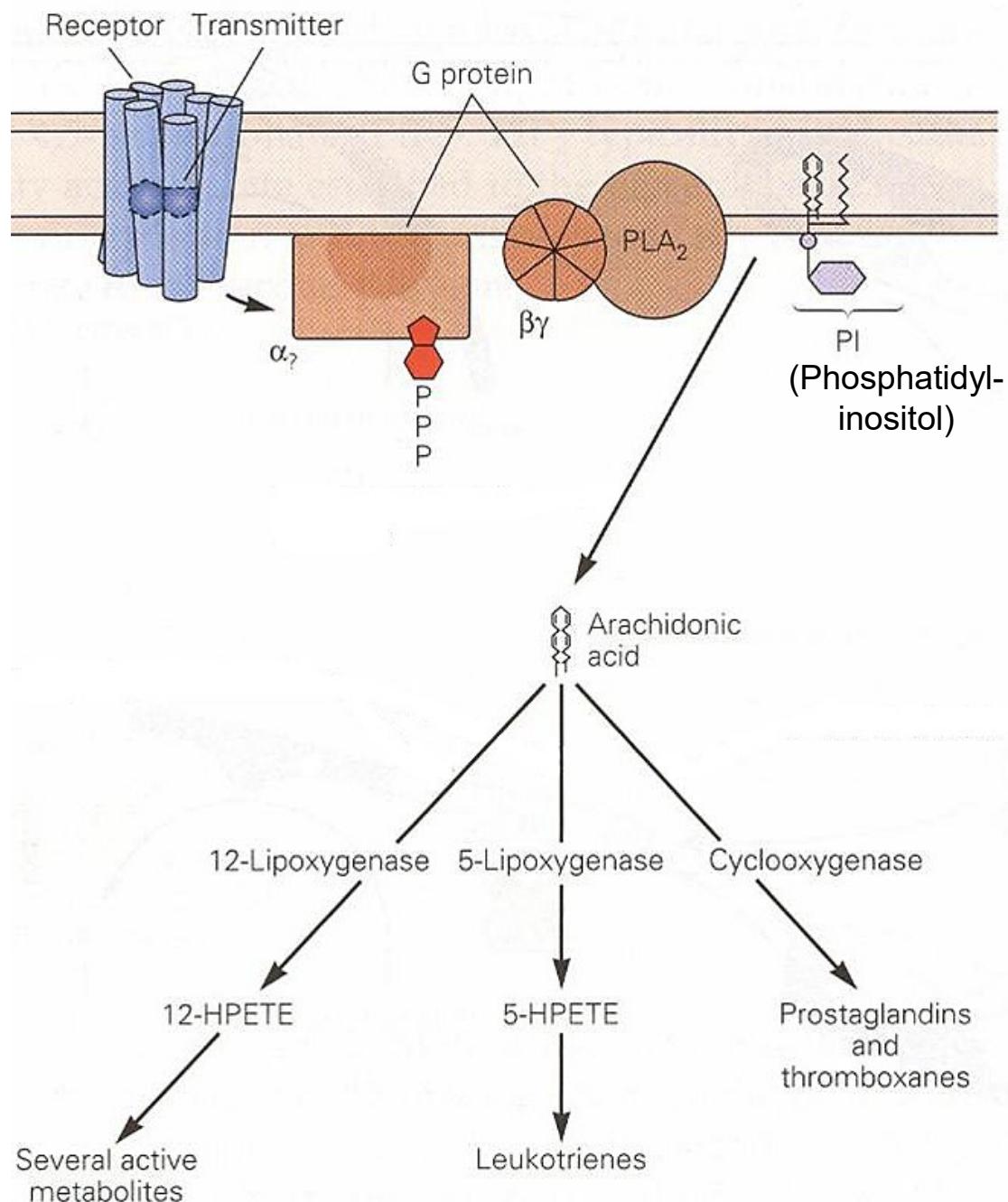


Bradykinin promotes inflammation and activates the pain pathway



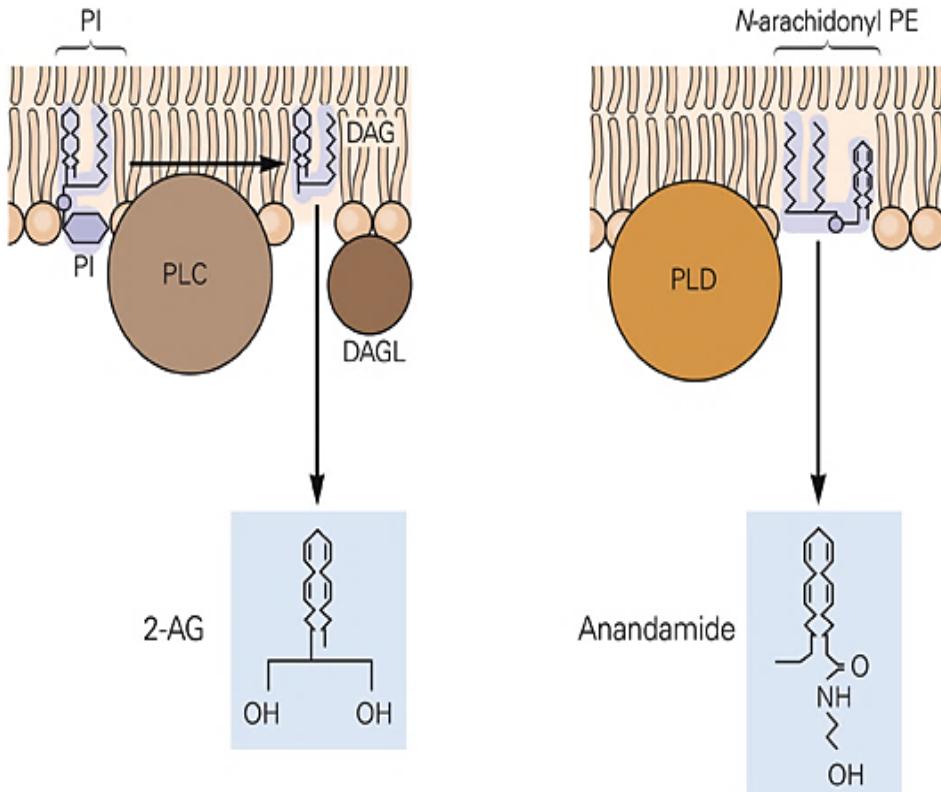
Phospholipase A₂ System

- Arachidonic acid is converted into 100's of different metabolites
- Arachidonic acid metabolites are lipid soluble and cross membranes easily to activate neighboring cells
- Metabolites directly or indirectly influence ion channels and the target cells' biochemistry

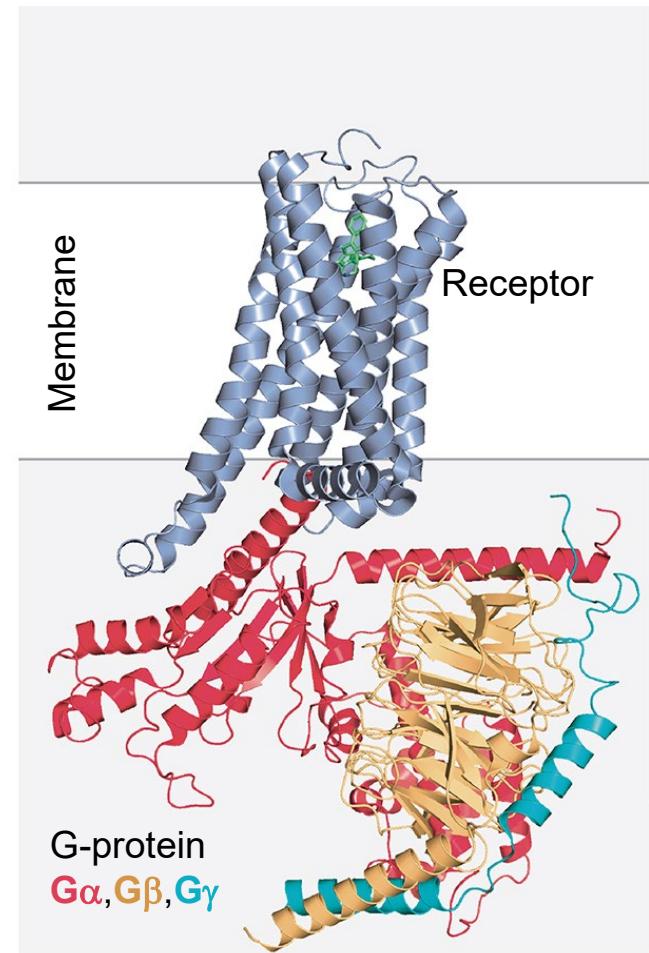


Production and Action of Endocannabinoids

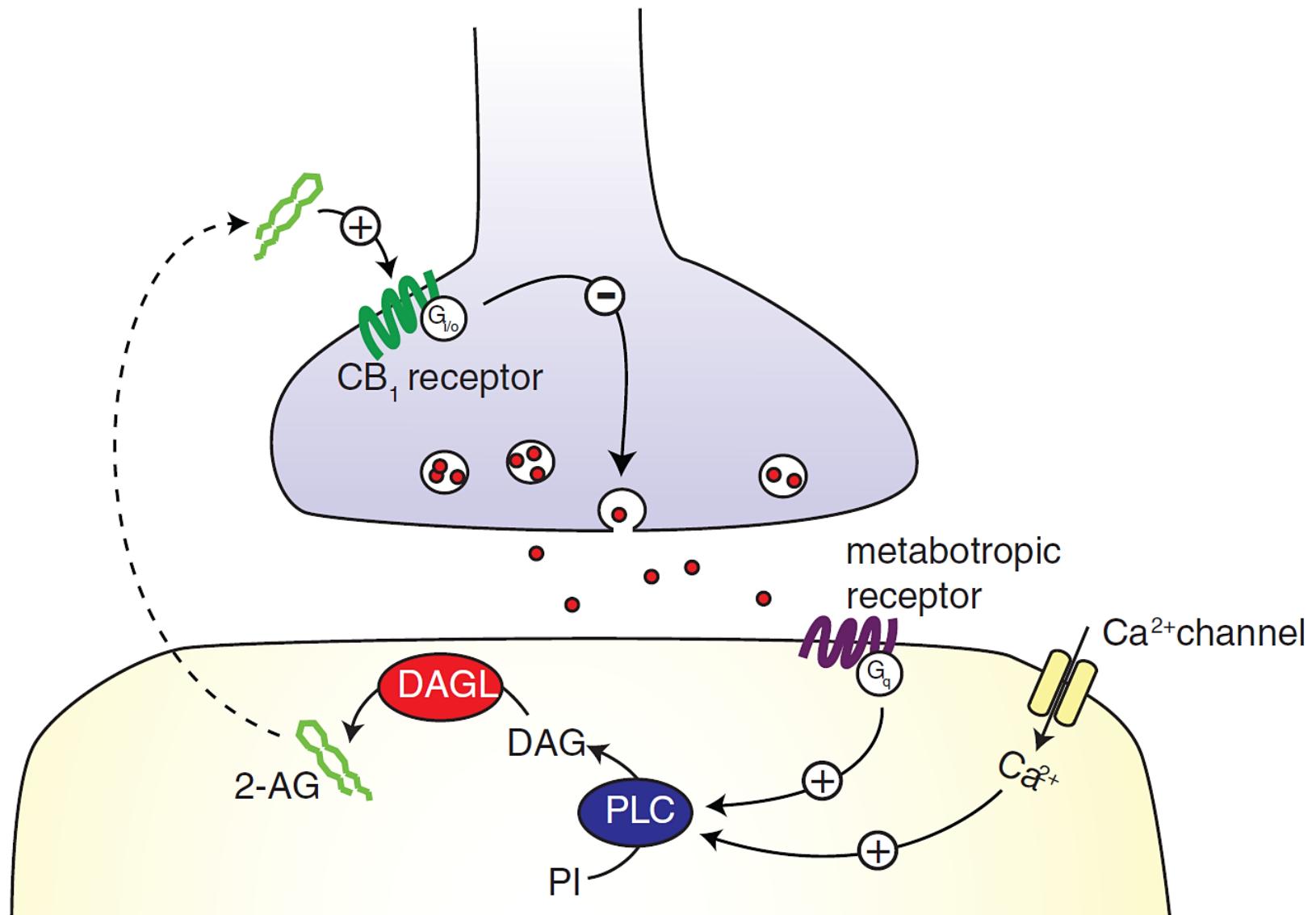
Endocannabinoids (2-AG and Anandamide) are produced by phospholipase systems



Endocannabinoid receptors (CB1 and CB2) are conventional GPCR's

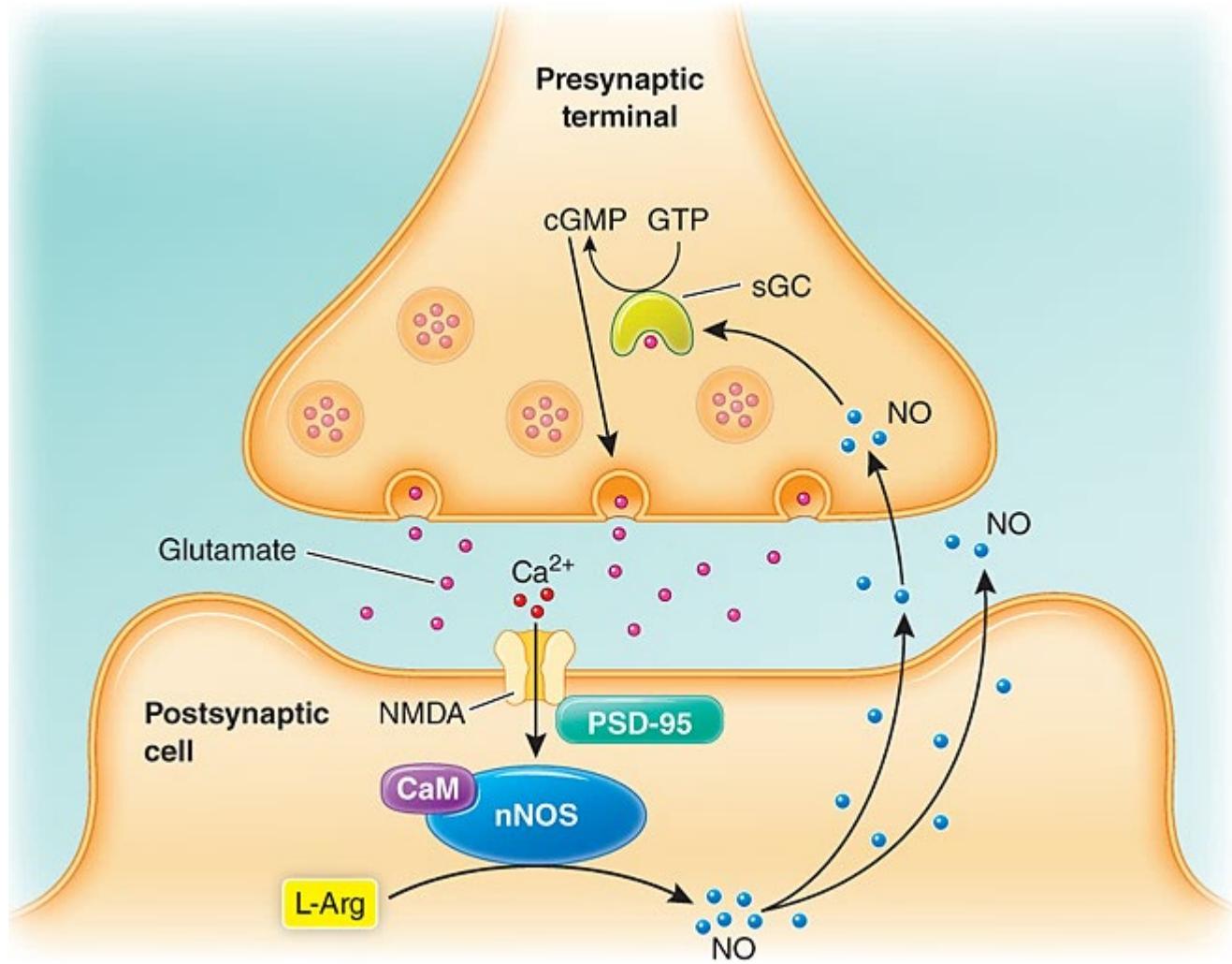


Endocannabinoids are Retrograde and Transcellular Messengers

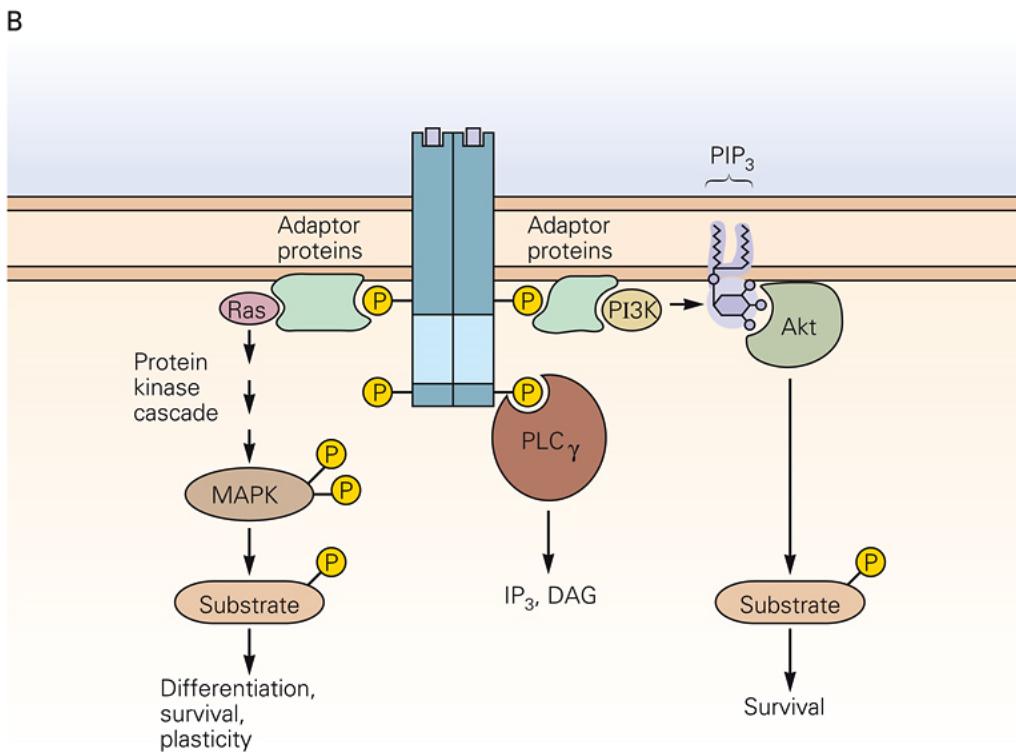
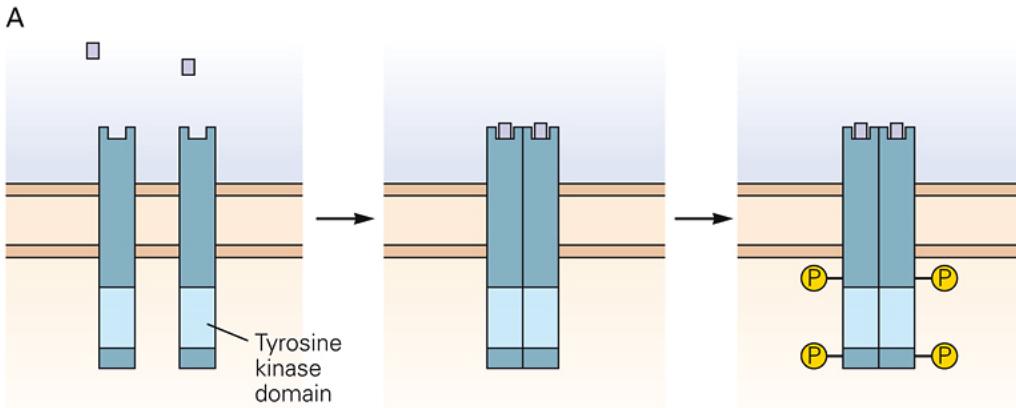


Nitric oxide is a gaseous second messenger and transcellular signal

- Some neurons produce nitric oxide (using nitric oxide synthase, nNOS)
- Nitric oxide is a gas and can easily cross membranes
- Nitric oxide activates guanylyl cyclase (GC), resulting in cGMP production
- cGMP has many downstream effects



Receptor Tyrosine Kinases (RTKs)



Activated by growth factors

- Nerve growth factor (NGF)
- Epidermal growth factor (EGF)
- Fibroblast growth factor (FGF)
- Brain-derived neurotrophic factor (BDNF)

General effects

- Promote neurite growth and differentiation
- Promote cell survival
- Promote plasticity and stabilize memory formation