SECOND MESSENGER

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SIGNAL TRANSDUCTION PATHWAYS

- Signal transduction pathways are biochemical reaction networks (as are metabolic pathways).
- Metabolic pathways shuttle mass and energy through the cell;
- Signal transduction pathways propagate information across spatial domains and perform information processing tasks as well.
- Information is encoded in protein conformational shifts or covalent configurations.
- Changes are passed through in activation chains.
- Do not follow Michaelis-Menten kinetics as substrate and enzyme concentrations are comparable.

Cell membrane

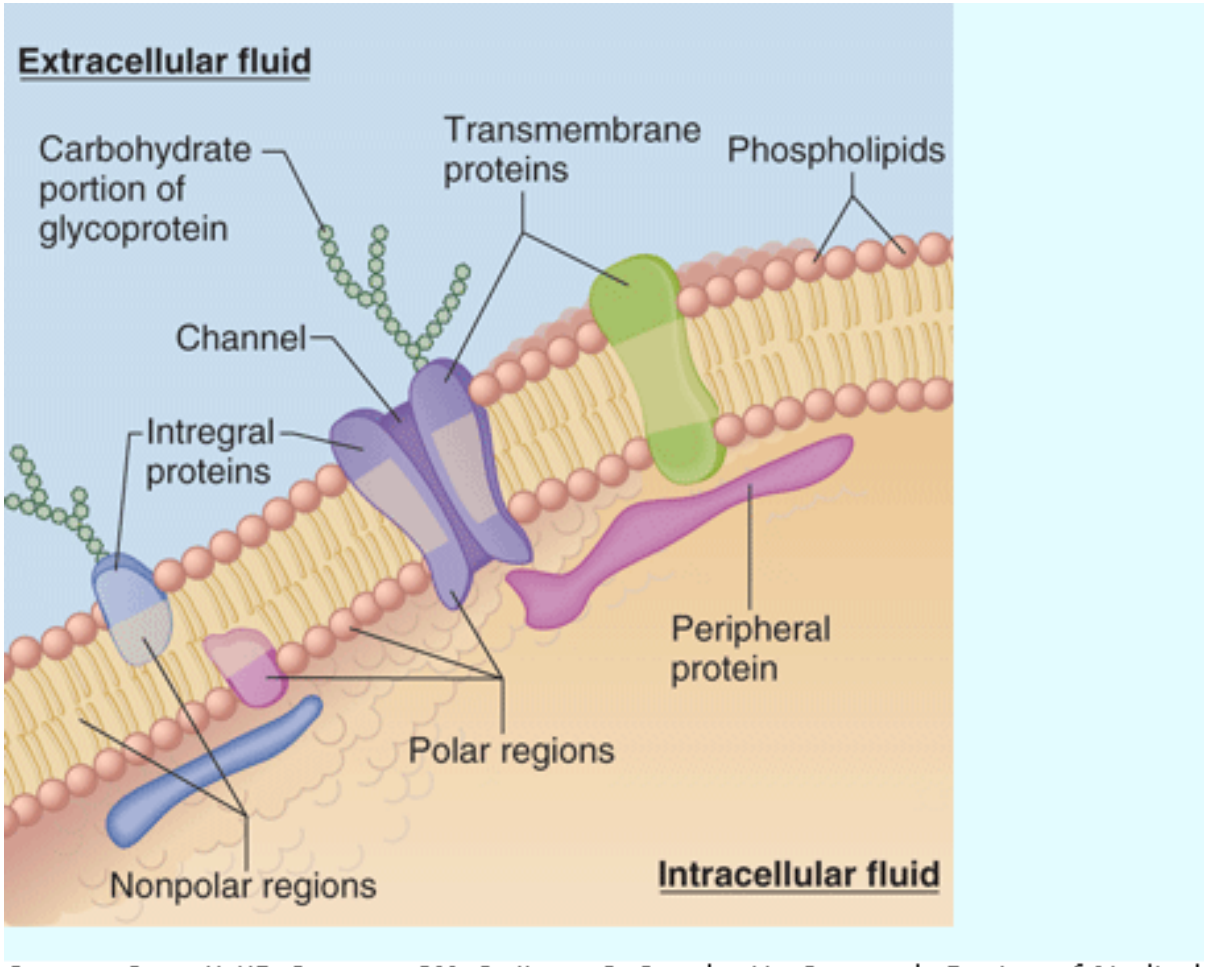

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Fig. 2-2 Accessed 07/01/2010

Signal transduction

- G-protein coupled receptors are membrane based and are linked to a trimeric G-protein that controls the activity of a secondary messenger.
- Insulin, epithelial growth factor, TSH, ACTH, LH, FSH as examples.
- Cytokine receptors are membrane based and associated with cytosolic Jak kinases.
- Activate STAT transcription factors through phosphorylation.
- Growth hormone, prolactin, cytokines as examples.

Signal transduction

- Receptor tyrosine kinases are cytosolic.
- Translocate to the nucleus and activate nuclear transcription factors through phosphorylation.
- For example, the GPC receptor in the membrane activates cAMP, phosphokinase A, and translocates to the nucleus where chromosome response element binding occurs.

Signal transduction

- TGF-β receptors are cytosolic but have serine-threonine kinase activity.
- Activate SMAD transcription factors in cytosol by phosphorylation.
- Activate differentiation signals p15, p16, p18, p19 (and block cyclins).
- TNF, for example, activates NF_k- B in cytosol.
- Dimerizes.
- Translocates to nucleus.

Signal transduction

- Retinoic acid, vitamin D, steroids enter with heat shock protein chaperones and translocate to nucleus.
- Final common pathway for signaling is the chromosome binding protein (p300).

Signal transduction
G-protein coupled receptors

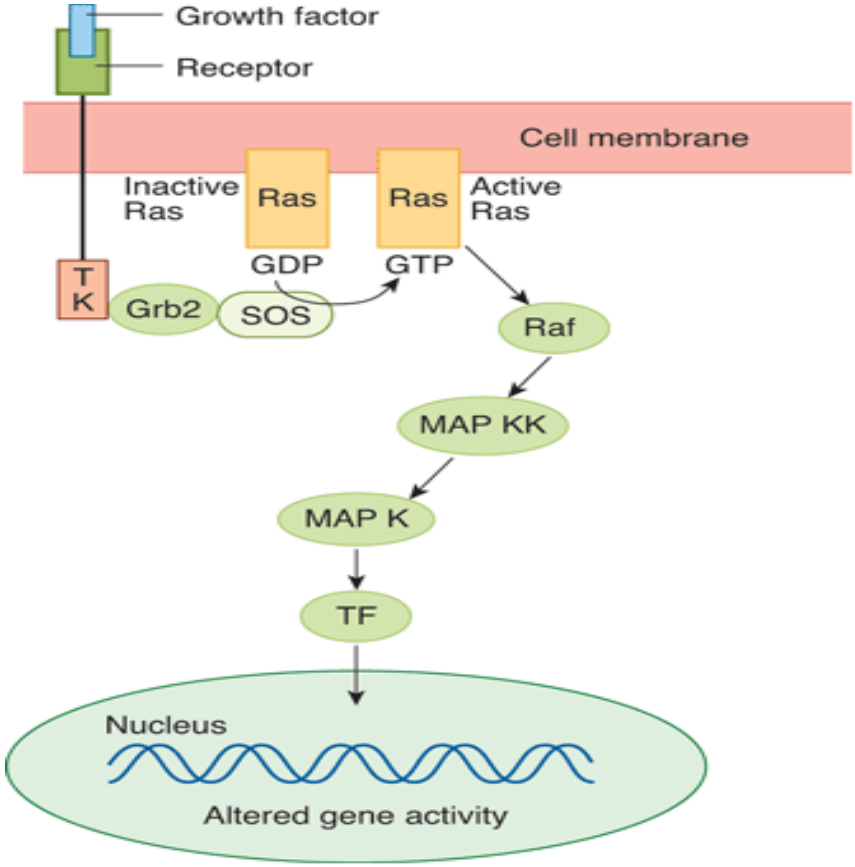
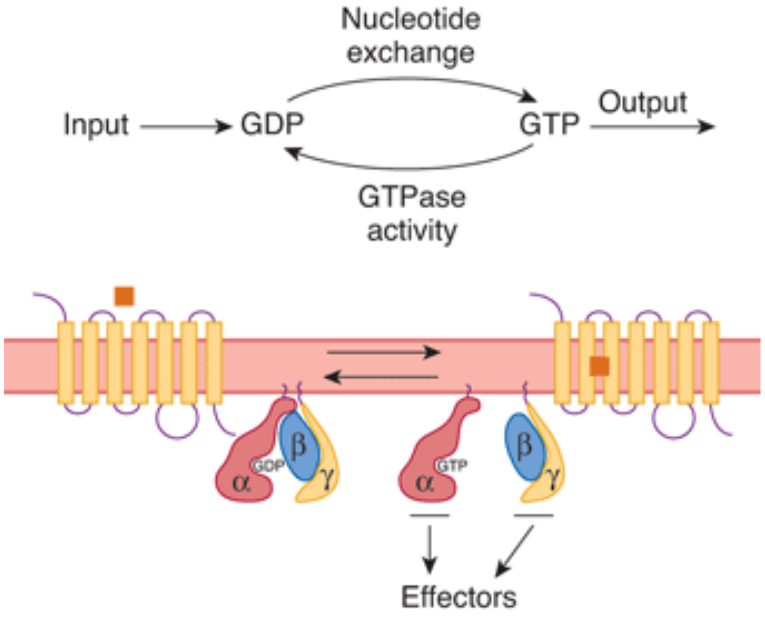


Fig. 2-30 Accessed 08/01/2010

Activation of G-protein

- Hormone or neurotransmitter binds the serpentine (hepta-helical) receptor
- Crosses the membrane 7 times
- Allosteric changes in the serpentine proteins induce the associated trimeric “G-protein” to both dissociate into the monomeric α-subunit and the dimeric βγ-subunit
- Allow the α-subunit to release the GDP and to bind GTP.

G-proteins



Heterotrimeric G proteins.
Top: Summary of overall reaction that occurs in the G subunit. Bottom: When the ligand (square) binds to the G protein-coupled receptor in the cell membrane, GTP replaces GDP on the α subunit.
GTP-α separates from the βγ subunit and GTP-αα and βγ both activate various effectors, producing physiologic effects.
The intrinsic GTPase activity of GTP-α then converts GTP to GDP, and the α , β , and γ subunits reassociate.

Fig. 2-23 Accessed 07/01/2010

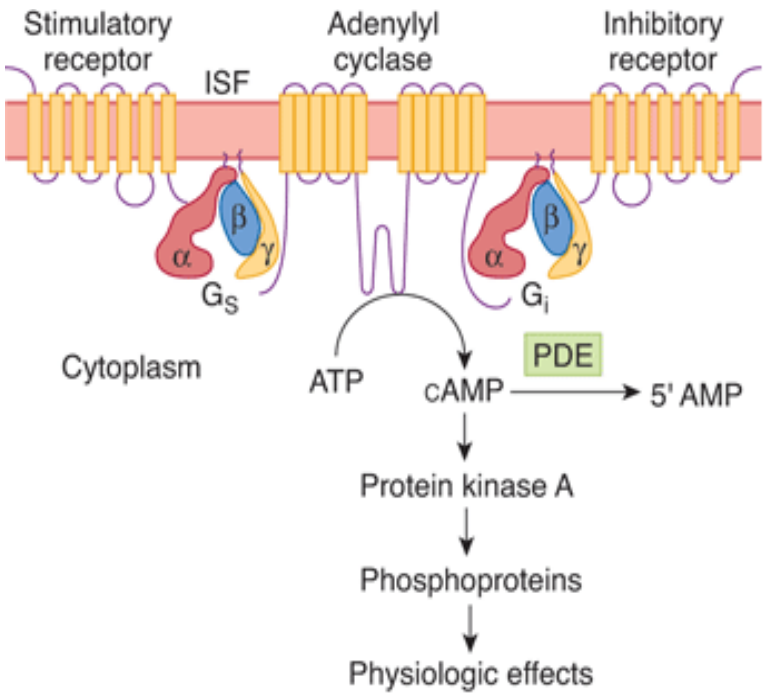
Activation of G-protein

- The activated Gα subunit is free to drift until it encounters its target enzyme
- Which is usually adenylate cyclase or phopholipase C
- The Gα subunit also has GTPase activity which will convert GTP into GDP.
- The GDP bound Gα is inactive
- This GTPase activity is slower than the time it takes the active Gα to find its target enzyme, so the Gα stays active for a limited time and then self deactivates.

Activation of G-protein

- The target enzyme, adenylate cyclase, produces cAMP until the GTP hydrolyses back to GDP and then the process stops.

Adenyl cyclase



Activation of adenylyl cyclase catalyzes the conversion of ATP to cAMP. Cyclic AMP activates protein kinase A, which phosphorylates proteins, producing physiologic effects. Stimulatory ligands bind to stimulatory receptors and activate adenylyl cyclase via G_s. Inhibitory ligands inhibit adenylyl cyclase via inhibitory receptors and G_i.

Fig. 2-28 Accessed 07/01/2010

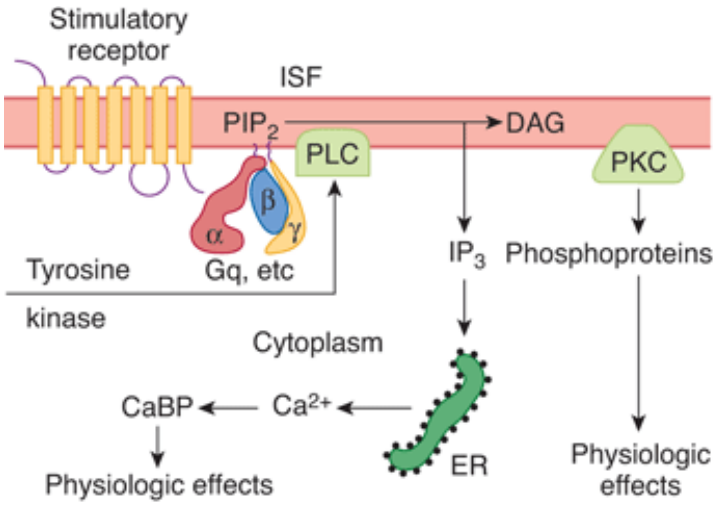
Adenylate cyclase pathway

Excitatory Hormones or Neurotransmitters	**Receptor**
Glucagon	Glucagon
Epinephrine	β
Glycoproteins (FSH, LH, TSH, HCG)	FSH, LH, TSH, HCG
Histamine	H_2
Serotonin	$5HT_4$, $5HT_6$, $5HT_7$
Dopamine	D_1, D_5
Inhibitory Neurotransmitters	
Dopamine	D_2, D_3, D_4
Acetylcholine	M_2, M_4
Norepinephrine	α
Serotonin	$5HT_1$, $5HT_5$
Glutamate	mGluR2, mGluR3

Modifiers

- Cholera toxin prevents $G\alpha_s$ from hydrolyzing GTP. Results in increased cAMP.
- Pertussis toxin prevent $G\alpha_i$ from binding GTP. Results in increased cAMP.
- β-blockers prevent activation of $G\alpha_s$. Results in decreased cAMP.
- Theophylline is a phosphodiesterase inhibitor. Results in increased cAMP.

Phospholipase C



Binding of ligand to G protein-coupled receptor activates phospholipase C (PLC). Alternatively, activation of receptors with intracellular tyrosine kinase domains can activate PLC . The resulting hydrolysis of phosphatidylinositol 4,5-diphosphate (PIP2) produces IP_3, which releases Ca^{2+} from the endoplasmic reticulum (ER), and DAG, which activates protein kinase C (PKC). CaBP, Ca^{2+}-binding proteins.

Fig. 2-26 Accessed 07/01/2010

Activation of G-protein

- PLC is activated by Ga_q
- PIP_2 cleavage by phospholipase C (PLC) yields diacylglycerol and IP_3.
- PIP_2 phosphorylation yields PIP_3 which activates protein kinase C (PKC).

Phospholipase C pathway

Hormones or neurotransmitters	Receptor
Angiogenin	Angiogenin
Gonadotropin releasing hormone	GHR
Platelet derived growth factor	PDGF
ATP	P_{2x}, P_{2y}
Acetylcholine	M_1, M_3, M_5
Glutamate	mGluR1, mGluR5
Serotonin	$5HT_2$

Systems:	cAMP	cGMP	Phospho Inositol	Arachidonic	Tyrosine Kinase
First Messenger neuro-transmitters	Epinephrine (α_2, β_1, β_2) Acetylcholine M2		Epinephrine (α_1) Acetylcholine M1, M3	Histamine receptor	
First Messenger hormones	ACTH, CRH, ANP, CT, LH, FSH, HCG, MSH, PTH, TSH, glucagon	ANP NO	GnRH, GHRH, AGT, TRH, Oxytocin		IGF, PDGF, INS
Signal Transducer	Gs: β_1, β_2 Gi: α_2, M2		Gq	Unknown G	RTK
Primary Effector	Adenylyl cyclase	Guanylate cyclase	PL C	PL A	RasGEF
Secondary Messenger	cAMP	cGMP	IP_3, DAG, Ca^{2+}	Arachidonic acid	RASGTP
Secondary Effector	PK A	PK G	PK C, CaM	5-Lipoxygenase Cyclo-oxygenase	MAP3K