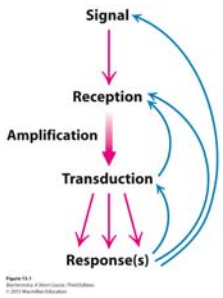
Signal Transduction Pathways

Chapter 13, Stryer Short Course

Signal Transduction

- Signal from exterior of cell must affect interior of cell
- Through the membrane
- Amplification of signal
- Ability to turn off

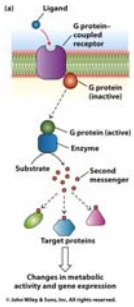


A few pathways…

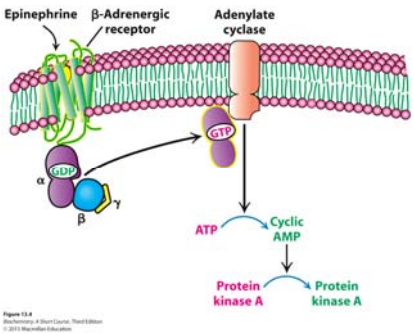
- Example pathways
  - α-adrenergic receptor (epinephrine)
  - β-adrenergic receptor (epinephrine)
  - Epidermal growth factor receptor
  - Insulin receptor
- Same hormone can elicit different responses in different tissues
- Cross-talk: different hormones elicit same response (fine tuning)

Terms for Signal Transduction Mechanisms

- Ligand (primary message)
- Receptor
- Transducer
- Effector
- Second messenger
- Target proteins/DNA

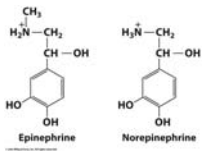


1. β-adrenergic receptor



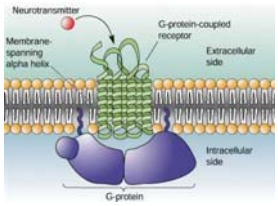
G-Protein Signaling Pathways

- Use β-adrenergic receptor as example of G-Protein Coupled Receptor (GPCR)
- 7-transmembrane helix (7-TM) receptor

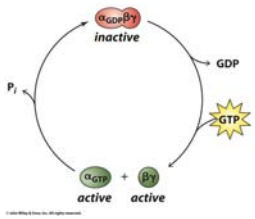


G-Protein Coupled

- Ligand binding causes G-protein to associate with receptor (figure not quite right)
- Three subunits, lipid anchored
  - α binds GDP
  - β, γ tightly associated
- Binding causes GDP release, allows GTP binding



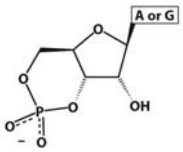
G-Protein Deactivation



- Turn off: Slow GTP hydrolysis
  - Subunits reassemble to inactive form until they can bind receptor again

Second Messenger

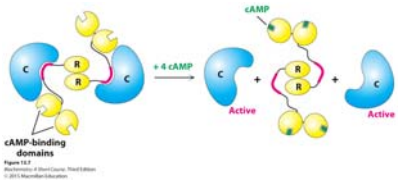
- G-protein activates Adenylate cyclase
- Catalyzes formation of cAMP
- Amplification



Cyclic AMP (cAMP), Cyclic GMP (cGMP)

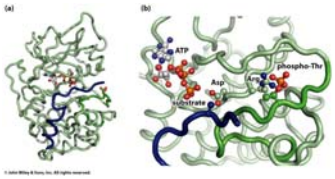
Function of cAMP

- cAMP acts as second messenger to activate Protein Kinase A (allosteric activator)
- Regulatory and catalytic subunits



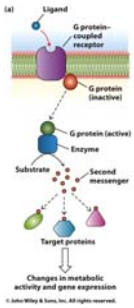
PKA: Phosphorylation

- Common activation/ deactivation strategy
- Changes protein conformation drastically
- Covalent modification
- Activates enzyme that releases sugar stored in muscle



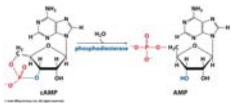
Summary

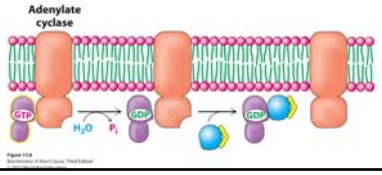
- Exercise: use basic guide to explain mechanism of epinephrine effect on sugar release in muscle



Turning Off Pathway

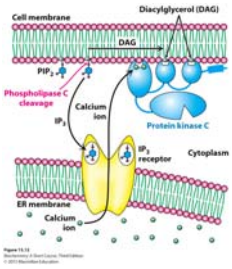
- Can turn it off at any point
  - Receptor?
  - G-protein?
  - Second messenger?
  - Phosphorylated enzyme?



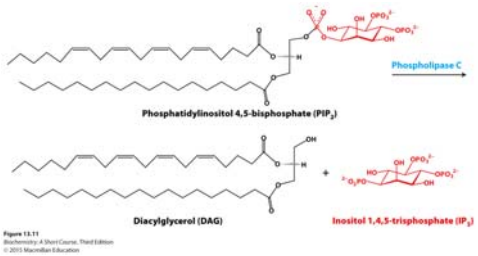


2. α-adrenergic receptor

- Epinephrine
- 7-TM helix
- G-protein
- Phospholipase C
- DAG & IP_3
- Ca^{+2}
- Protein Kinase C

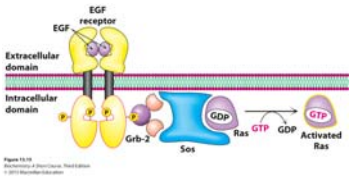


Phosphinositol Pathway



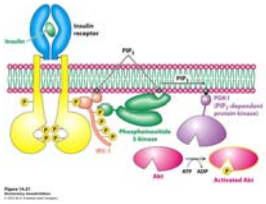
3. Epidermal Growth Factor

- Receptor Tyrosine Kinases
  - Dimerization and autophosphorylation
  - Adaptor proteins
  - G-protein: Ras
  - Kinase cascade



Insulin Receptor

- Receptor Tyrosine Kinases
  - Dimerization and autophosphorylation
  - Adaptor proteins
  - Phosphoinositide kinase
  - PIP_3
  - Kinase cascade



Summary

	β-adrenergic	α-adrenergic	EGF	Insulin
Ligand	epinephrine	epinephrine	EDF	Insulin
Receptor	7-TM helix	7-TM helix	Tyr Kinase	Tyr Kinase
Transducer	G-protein	G-protein	Ras (G-protein)	PIP2 kinase
Second messenger	cAMP	PIP_2, DAG (Ca^{+2})	(various)	PIP_3
Effector	PKA	PKC	(Various pecific protein kinases)	PKB (Akt)
Example effect	Increase blood pressure	Glucose release in liver	Cell growth	Increase glucose uptake from blood

Pathology

- Cholera
  - Covalent modification of a G-protein
  - Constitutively active
  - Opens chloride channel; leads to severe diarrhea
- Whooping cough
  - Toxin turns off an inhibitory G-protein
  - Adenylate cyclase remains active

Cancer

- Proto-oncogenes and oncogenes
- Ras targets nuclear proteins; Key signal in cell growth
- Mutant Ras proteins have been found to be associated with various types of cancer. What is the effect on a cell if the mutant Ras is able to bind GTP but is unable to hydrolyze it?