Cell-to-Cell Signaling

Signaling software – GPCR

Signaling process

- Recognition – receptor
- Transduction - G proteins, phosphorylation, adapter proteins
- Execution – multiple cellular enzymes, cytoskeleton, ion channels, pumps etc.

Finally, it is time to put it all together

- Single proteins work as binary switches
- A series of binary switches makes a signaling cascade

Few examples

- Regulation of metabolism by epinephrine
- Insulin signaling
- Sensory transduction in retina
- Activation of T lymphocytes
- Cytokine signaling
- Odorant detection and processing

Few examples

- Regulation of metabolism by epinephrine
- Odorant detection and processing
- Both processes are mediated by G protein coupled receptors

Epinephrine

- A hormone produced by adrenal glands
- A.k.a. adrenaline
- Catecholamine
- Secreted in stressful situations from adrenal medulla
- Works through seven helix/G protein coupled receptors
  - There are two different GPCR that use two different second messengers to convey the effect of epinephrine

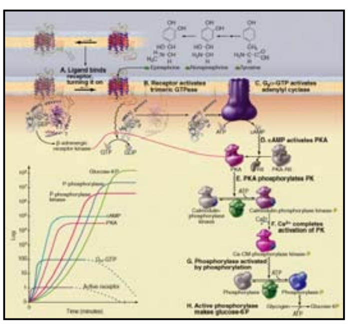
Adrenergic receptors

- α adrenergic receptor
  - Smooth muscle of blood vessels, smooth muscle of GI tract, liver
  - Couples to Gq and phospholipid metabolites (IP3 and DAG)
- β adrenergic receptor
  - Heart, liver, skeletal muscle
  - Works through activation of adenylyl cyclase and cAMP

Adrenergic receptors - effects

- α adrenergic receptor
  - Contraction of smooth muscle of blood vessels – increase in BP
  - Relaxation of smooth muscle of GI tract
  - Glycogenolysis in liver
- β adrenergic receptor
  - Heart – increased contraction
  - Glycogenolysis in liver
  - Glycogenolysis in skeletal muscle

Signaling by β adrenergic receptor



Signaling by β adrenergic receptor

- Epinephrine binds to β adrenergic receptor on cell surface
- Receptor speeds up the GDP replacement with GTP (activation of G protein)
  - Gs
- αs subunit activates adenylyl cyclase to produce cAMP

Signaling by β adrenergic receptor continued

- cAMP activates of cAMP dependent protein kinase (PKA)
- PKA phosphorylates phosphorylase kinase
  - Supported by calmodulin (Ca2+)
  - Plus many other enzymes

Signaling by β adrenergic receptor continued

- Phosphorylase kinase phosphorylates phosphorylase
  - And inhibits protein phosphatase 1
- Phosphorylated phosphorylase catalyzes conversion of glycogen to glucose-6 phosphate (glycogenolysis)
  - Glucose is necessary for the efficient fight or flight response to stress

Receptor adaptation

- Receptor has to adapt to constant exposure to transmitter
- A.k.a. tachyphylaxis, desensitization, tolerance
- Diminished cellular effects in response to continuous activation of the receptor
- “negative feedback” mechanism for the receptor

Molecular mechanisms of receptor adaptation

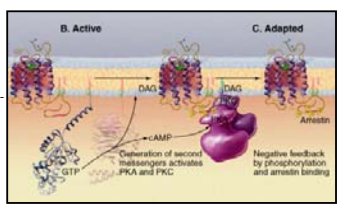
- Remember phosphorylation sites on C-terminus of G protein coupled receptors?
- Second messengers or activated receptor itself activate protein kinases
- Protein kinases phosphorylate receptor

Molecular mechanisms of receptor adaptation

- Phosphorylated receptor is less active

and/or

- Phosphorylated receptor binds arrestin



Molecular mechanisms of receptor adaptation

- Arrestin prevents interaction with G proteins and/or
- Arrestin promotes endocytosis of the receptors and receptor removal
- Dephosphorylation causes dissociation of arrestin and return of activity

Adaptation of the β adrenergic receptor response

- βγ subunit activates β adrenergic receptor kinase (βARK)
- βARK phosphorylates β adrenergic receptor

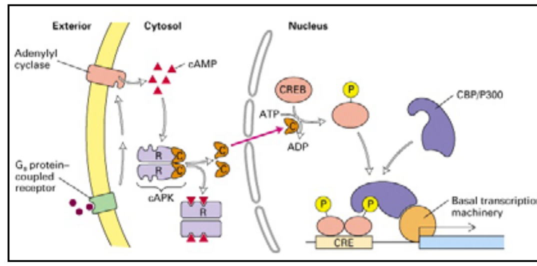
Adaptation of the β adrenergic receptor response

- Phosphorylated receptor binds β-arrestin
  - Prevents the interaction with G protein (adaptation)
  - Causes clathrin polymerization and receptor endocytosis

In addition

- cAMP activates cAMP gated ion channels in some cells
- βγ subunits open calcium channels in some cells
- Entering Ca^{2+} activates calmodulin
- PKA activates also CREB transcription factor and production of more enzymes

CREB activated response



In other cells such as cardiac myocytes…

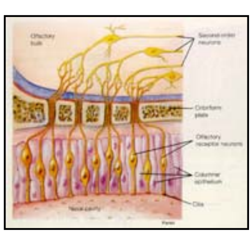
- Epinephrine working through β- adrenegic receptor increases cAMP levels
- Activates PKA
- PKA phosphorylates MLCK (myosin light chain kinase)
- Increased cardiac muscle contractility

Odorant receptors

- Smell receptors are chemoreceptors
- All smell receptors are GPCR
- All are coupled to a single type of G protein Golf
- Each senses only one odorant
- There are thousands of them

Olfactory receptors

- Olfactory receptors are localized on olfactory neurons
- Olfactory neurons converge on olfactory bulb neurons that process information from many primary neurons



Smell

- G_{olf} activates adenylyl cyclase
- cAMP opens cAMP gated cation channel unique to olfactory epithelia
- Cations (Na^+ and Ca^{2+}) enter the cell
- **Depolarization** of olfactory cell membrane initiates action potential
- Brain determines the smell based on the activity of neurons in olfactory bulb