Final Study Guide

Specific signaling mechanisms that use cell surface receptors to respond to water-soluble signals

- Response of liver cells to epinephrine (adrenaline)
  - Epinephrine (aka adrenaline) is a hormone and a neurotransmitter. It is released into the bloodstream from the adrenal gland as a *preparation* for physical activity —the "fear, fight or flight" reflex
  - Epinephrine mobilizes glucoses from stored glycogen in *liver cells*. The glucose enters the bloodstream in anticipation of the need for energy in muscle cells.
  - Epinephrine binds to a site on the external surface of the beta-adrenergic receptor protein found on liver cells- a trans-membrane protein.
  - Levels of the transduction cascade responding to epinephrine
    - The adrenergic receptor protein (with epinephrine bound) activates a GTP-binding protein (G-protein) on the Intracellular surface of the plasma membrane of the liver cell.
    - The G-protein activates the enzyme *Adenylate Cyclase*
    - *Adenylate Cyclase* catalyses the production of the small intracellular messenger cAMP from ATP
  - cAMP binds to and activates a protein kinase: PKA
    - Protein Kinase A (PKA) has four subunits- 2 catalytic and 2 regulatory
    - In its inactive state, the regulatory subunits inhibit the catalytic subunits
  - cAMP binds to the regulatory subunits and activates the catalytic subunits which can then phosphorylate other proteins
    - The multi-subunit nature of PKA allows it to act as a "molecular switch" which will only turn on when 2 cAMP molecules are bound *simultaneously*.
    - This greatly reduces the chance that PKA will be activated in error by small spontaneous background fluctuations in cAMP concentration.
  - Activated PKA
    - Phosphorylates and therefore inactivates the enzyme *Glycogen Synthase*- thus halting glycogen synthesis from glucose
    - Phosphorylates and therefore activates the enzyme *phosphorylase kinase*- which phosphorylates and activates the enzyme *phosphorylase*- phosphorylase stimulates breakdown of glycogen into glocuse-1-phosphate (Which then gets transformed into glucose by other enzymes)
      - **End Result**: Net glycogen breakdown and release of glucose into the bloodstream to provide energy during fight or flight adrenalin surge
- While glucose release is not the major *short term* effect of adrenaline on liver cells, there are also *long term* effects on protein synthesis.
  - Genes are activated which improve the liver cells long term ability to mobilize glucose—in preparation for late situations that result in adrenaline release.
  - This is achieved by a **second pathway activated by PKA**
    - PKA also phosphorylates a transcription factor protein called CREB- *cAMP Response Element Binding protein*-, which binds to a particular sequence in the promoter region of some genes. Binding of CREB promotes transcription of these genes- **NEW PROTEIN SYNTHESIS**

Signal transduction- how general properties apply to response of liver cells to epinephrine

- Detection of the stimulus by a receptor protein
  - *Beta-adrenergic receptor*
- Transfer of a signal from a receptor protein to a cascade of signaling proteins and enzymes
  - *G-Protein* activates *Adenylate cyclase*
- Amplification and relay of signal
  - Production of many *cAMP molecules* by adenylate cyclase
- Activation of specific effector enzymes: Short term and Long term effects
  - Activation of *PKA* and phosphorylation of target proteins- *Phosphorylase kinase, phosphorylase*
  - Activation of *gene transcription*

- Detailed mechanisms and generalization
  - So the response of liver cells to epinephrine exemplifies many of the general properties of signal transduction
  - The detailed molecular mechanisms involved in responding to epinephrine can also be generalized to the response to many other *external water-soluble stimuli*

Detailed mechanisms- receptor and G-protein activation

- The *beta-adrenergic receptor protein* is a member of a very large family of transmembrane receptor proteins: 7-alpha-helical transmembrane segments
- Members of this receptor protein family all share:
  - Similar core tertiary structure with 7-alpha-helical transmembrane segments
  - Central binding site for a small ligand molecules accessible from the **extracellular** side of the receptor protein.
  - A binding site for the alpha subunit of a *GTP-binding* protein on the **intracellular** surface of the receptor protein
  - The many members of this protein family results in a "smorgasbord" of proteins that can interact as to form thousands of possible signaling cascades in cells
- Some members of the 7-AHTS receptor family protein include:
  - Hormone receptor proteins
  - Neurotransmitter proteins- the "metabotropic" neurotransmitter receptor proteins that are not, in themselves, ion channels
  - Olfactory cell and taste cell receptor proteins
  - Distantly, rhodopsin, the receptor for light in the photoreceptor cells of eyes

General actions of cAMP in other cells

- cAMP can also bind to and directly activate ion channels that have an intracellular binding site for cAMP
  - cAMP-gated channels can *alter membrane potential*- especially important in the response of neurons to external stimuli that activate cAMP production
  - **Overall, cAMP** can
    - Initiate *enzyme activation*,
    - Initiate *protein synthesis*, and

- Initiate *changes in membrane potential* in cells

Kinase Cascades

- In liver cells, protein kinase A (PKA) starts a short **"Kinase cascade"**
  - It phosphorylates and activates *phosphorylase kinase* which then:
  - Phosphorylates and activates *phosphorylase*- the final effector enzyme catalyzing glycogen breakdown (**Phosphorylase—glycogen breakdown**)
- Kinase cascades are very common in other signaling cascades as well- leading to *enzyme* or *transcription factor activation*
  - Amplification –at each step new active kinase molecule production is catalyzed by the previous kinase in the cascade
  - Amplification also occurs at the receptor—G-protein level. One receptor molecule can interact with and activate many G-proteins

G-protein linked- signaling mechanism- the human olfactory system

- In the human olfactory system, olfactory receptor neurons attached to the olfactory nerve connect to the olfactory epithelium to pick up stimuli
  - The modified cell at the ends of these olfactory neurons help collect stimuli
  - The axon begins beyond the basal lamina
- Function of olfactory epithelial cells is measure by membrane current due to *Na+ ions flowing into the cell*.
  - When an odor is detected, the membrane potential decreases dramatically (from about 0pA to -450 pA)
  - Olfactory function (odor detection) occurs at the cilia, not so much the soma (body) of the cell
  - The **cilia** are the sensory organelles that contain the transduction machinery
- In the membrane of the olfactory receptor cell cilia:
  - Na+ and Ca2+ ions flow into the cell when odorant is present—this depolarizes the receptor cell and initiates an *action potential*
  - Action potentials travel UP the receptor cell axons into the brain

G-protein linked receptor mechanism- Phototransduction (the first step of vision)

- The retina contains the photoreceptor cells that detect light
- Two classes of photoreceptor cells exist in the retinae of vertebrates:
  - **Rods**
  - **Cones**
  - Both have stacked disks of membranes that are packed with rhodopsin protein molecules that absorb light
- Phototransduction in *rod* photoreceptors
  - Opsin +11-cis retinal
  - Opsin is a G-protein linked receptor protein located in the rod disc membranes
  - A photon of light is absorbed by 11-cis retinal
  - The light initiates a cis-trans Isomerization of the 11-cis-retinal to form **all-trans retinal**