Signal Transduction Pathways

Pratt & Cornely, Chapter 10

Terms for Signal Transduction

- Ligand
- Receptor
- Transducer
- Effector
- Second messenger
- Target proteins/DNA
Ligands

- Hormones vs Local mediators
- Polar (insulin) vs nonpolar (steroidal hormone)
- Specific—high affinity
- Agonist vs antagonist

**TABLE 10-1** Examples of Extracellular Signals

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Chemical Class</th>
<th>Source</th>
<th>Physiological Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auxin</td>
<td>Amino acid derivative</td>
<td>Most plant tissues</td>
<td>Promotes cell elongation and flowering in plants</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Steroid</td>
<td>Adrenal gland</td>
<td>Suppresses inflammation</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Amino acid derivative</td>
<td>Adrenal gland</td>
<td>Prepares the body for action</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Polypeptide (165 residues)</td>
<td>Kidneys</td>
<td>Stimulates red blood cell production</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Polypeptide (19 residues)</td>
<td>Pituitary gland</td>
<td>Stimulates growth and metabolism</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Gas</td>
<td>Vascular endothelial cells</td>
<td>Triggers vasodilation</td>
</tr>
<tr>
<td>Thromboxane</td>
<td>Eicosanoid</td>
<td>Platelets</td>
<td>Activates platelets and triggers vasoconstriction</td>
</tr>
</tbody>
</table>

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Quantitative Ligand Binding

- $K_D$ values
- Problem 7:
  Derive an expression for the $[RL]/[R]_T$ ratio.

$$K = \frac{[R][L]}{[RL]} \quad \text{and} \quad [RL] = \frac{[R][L]}{K}$$

$$\% \text{ bound} = \frac{[RL]}{[R] + [RL]}$$

Substitute:

$$\% \text{ bound} = \frac{[R][L]}{[R][L] + [R][L]} = \frac{[R][L]}{K[R][L] + [L]}$$

Hyperbolic function!
Scatchard Plot

• Problem 14: A Scatchard Plot is another method of representing ligand binding data. The slope is equal to $-1/K_D$. Use the chart to estimate $K_D$ for calmodulin binding to calcium.

G-Protein Signaling Pathways

• Use $\beta$-adrenergic receptor as example of G-Protein Coupled Receptor (GPCR)
• 7-transmembrane (7-TM) receptor
G-Protein Coupled

- Ligand binding causes G-protein to associate with receptor (figure not quite right)
- Three subunits, lipid anchored
  - $\alpha$ binds GDP
  - $\beta, \gamma$ tightly associated
- Binding causes GDP release

G-Protein Activation

- GTP binds
  - Destabilized trimer
  - Release each other and receptor as two active proteins
- Turn off: Slow GTP hydrolysis
  - Subunits reassemble to inactive form until they can bind receptor again
cAMP

- G-protein carries signal to another protein
  - transducer
- Adenylate cyclase
  - effector
- Catalyzes formation of cAMP
  - second messenger
- Amplification

Protein Kinase A

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

![Chemical diagram of Protein Kinase A activation](attachment:kinase_diagram.png)
Phosphorylation

- Common activation/deactivation strategy
- Changes protein conformation drastically
- Covalent modification
- Middle range time effect

Protein Kinase A

- PKA modulates the activity of enzymes that carry out work through phosphorylation
- For example, adrenaline binding leads to PKA activating the enzyme that releases glucose from storage to be used
- Exercise: use basic guide to explain mechanism of epinephrine affect on sugar release in muscle
Turning Off Pathway

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

Phosphinositol Pathway

• Many G-Proteins for many pathways
  – Cross-talk—different paths give same result
• \( \alpha \)-adrenergic receptor (liver but not muscle)
  – Same hormone gives different responses
  – Liver also has glucagon binding, so \( \alpha \)-receptor allows for fine-tuning of signal
  – Target of this G-protein is phospholipase C
Two second Messengers

• $\text{PIP}_2 \rightarrow \text{IP}_3$
  – Opens Calcium gates
    • Activates Protein Kinase B (Akt) to make other second messengers

• $\text{PIP}_2 \rightarrow \text{DAG}$
  – Activates Protein Kinase C
    • Also requires $\text{Ca}^{++}$
    • Especially important in cell division

Receptor Tyrosine Kinases

• Second major class of receptors
  – Insulin binding as prototype
  – Mostly monomers that bind ligand and then dimerize
    • One subunit binds ligand
    • Second subunit become active kinases
Insulin Signaling

Other Receptor Tyrosine Kinases

- Target nuclear proteins
Oncogenes

- Ras targets nuclear proteins
- Key signal in cell growth
- **Problem 46**: 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 GRP but is unable to hydrolyze it?

Lipid Hormone Signaling

- Cortisol binds intracellular Zinc finger
- Dimerization binds hormone response element
- Transcription factor—activate or inhibit
- Steroidal anti-inflammatory
Problem 53

- Steroid hormone receptors have different cellular locations. The progesterone receptor is located in the nucleus and interacts with DNA once progesterone has bound. But the glucocorticoid receptor is located in the cytoplasm and does not move into the nucleus until its ligand is bound. What structural feature must be different in these two receptor molecules?

Local Mediators

- Eicosanoids produced in response to cellular event
- Produce hormone-like responses in blood pressure, inflammation response, etc.
COX Targets

- NSAIDs (non-steroidal anti-inflammatory drugs) target cyclooxygenase
- Aspirin, ibuprofen: COX 1 and 2
- Vioxx: COX 2
- Acetominophen: COX:3
  - Less side effects
  - Worse toxicity