Intercellular Communication & Signal Transduction

Lecture 4- foundation

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OBJECTIVES

• By the end of this lecture you should be able to
  ➢ List the types of intracellular communication
  ➢ List the basic principles of intracellular communication
  ➢ Describe signal transduction
  ➢ Explain the role of second messenger system
  ➢ Define cell receptors and their regulation
Intercellular Communication & Signal Transduction

- Communication between cells is largely arranged by extracellular chemical messengers.

- Intercellular communication can take place either directly or indirectly.

- **Direct intercellular communication**
  - Involves physical contact between interacting cells
    - A- Gap junction
    - B- Transient direct linkup of surface makers
Intercellular Communication & Signal Transduction

- **Direct intercellular communication**
  - Involves physical contact between interacting cells
  - **A- Gap junction**
    - Bridge the cytoplasm of neighboring cells in some types of tissues, through gap junctions
    - Chemical messenger move from cell to cell without entering ECF
  - **B- Transient direct linkup of surface makers**
    - Some cells, such as those of immune system, have specialized markers on surface membrane that allow them to directly link with certain other cells that have compatible (=well matched) markers for transient (= temporary) interactions.
Direct intercellular communication

Channels are formed by pairs of adjacent connexons.
Connexons are composed of six protein subunits that span the lipid bilayer of each cell membrane.
Present more in electrically excitable tissues (heart, smooth muscle)
Direct intercellular communication

(b) Transient direct link up of cells’ surface markers
(complementary surface markers)
Intercellular communication can take place either directly or indirectly.

- **Indirect intercellular communication**
  - Through extracellular chemical messengers or signal molecules; there are four types:
    - Paracrine
    - Neurotransmitters
    - Hormones
    - Neurohormones
INDIRECT INTERCELLULAR COMMUNICATION

- extracellular chemical messengers or signal molecules
  - Paracrine
  - Neurotransmitters
  - Hormones
  - Neurohormones

Source
Distance
Means by which get to target cells
Indirect intercellular communication

- In each case, a specific chemical messenger, the signal molecule, is synthesized by specialized controlling cells to serve a designated purpose.
- By releasing of these chemicals into ECF upon stimulation, these chemical messengers bind with target cell receptors specific for it.

- These chemical messengers differ in their source, distance they travel to reach their target cells & means by which they get to their site of action.
Paracrine

- Local chemical messengers
- Products of cells diffuse in the ECF to affect neighboring cells
Paracrines

- Distributed by *simple diffusion* within interstitial fluid,
- Their action is restricted to *short distances*.
- They do not gain entry to blood in any significant quantity because they are *rapidly inactivated by locally existing enzymes*. 
—Paracrines

- Cells within an organ secrete paracrine molecules that diffuse into extracellular fluid to nearby target cells within same organ in which they are made
Neurotransmitters

- Neurotransmitter released from nerve cells, upon stimulation by action potential, act across synaptic cleft on postsynaptic cell that may be another neuron, a muscle, or a gland.

- Neurons themselves may carry electrical signals long distances (the length of the axon), but the chemical messenger released at axon terminal across synaptic cleft.
In **synaptic** signaling, 1 neuron sends messages to another cell (neuron, a muscle, or a gland), via synapses

- Nerve impulse is transmitted from axon of neuron to regulate their target cells via release of neurotransmitter
Hormones

- Long-range messengers
- Secreted into blood by endocrine glands in response to signal
- Exert effect on target cells some distance away from release site
To respond to a chemical signal, a target cell must have a receptor protein for it.

Hormones reach and bind to receptors of target cells via circulating blood.
- **Neurohormones**
  - Hormones released into blood by neurosecretory neurons to distant target cells
  - An example is ADH, a hormone produced by nerve cells in brain that promotes water conservation by kidneys during urine formation.
**Autocrine communication**

- Chemical messenger secreted by cell, bind to receptors on the same cell, i.e. the cell that secreted the messenger
### Intercellular communication by chemical mediators

<table>
<thead>
<tr>
<th></th>
<th>GAP JUNCTIONS</th>
<th>SYNAPTIC</th>
<th>PARACRINE AND AUTOCRINE</th>
<th>ENDOCRINE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Message transmission</strong></td>
<td>Directly from cell to cell</td>
<td>Across synaptic cleft</td>
<td>By diffusion in interstitial fluid</td>
<td>By circulating body fluids</td>
</tr>
<tr>
<td><strong>Local or general</strong></td>
<td>Local</td>
<td>Local</td>
<td>Locally diffuse</td>
<td>General</td>
</tr>
<tr>
<td><strong>Specificity depends on</strong></td>
<td>Anatomic location</td>
<td>Anatomic location and receptors</td>
<td>Receptors</td>
<td>Receptors</td>
</tr>
</tbody>
</table>

**Figure 1-32.** Intercellular communication by chemical mediators. A, autocrine; P, paracrine.
Two distinct groups of hormones based on their solubility properties

- **Hydrophilic hormones** (peptides e.g. insulin; catecholamines e.g. epinephrine; indoleamines e.g. melatonin)
  - Highly water soluble
  - Low lipid solubility

- **Lipophilic hormones** (e.g. thyroid & steroid hormones)
  - High lipid solubility
  - Poorly soluble in water
HORMONES

The solubility properties of a hormone determine how hormone:

1. Is processed by endocrine cell,
2. Transported in blood, &
3. Exerts its effects at target cell.
### TABLE 4-4  Chemical Classification of Hormones

<table>
<thead>
<tr>
<th>Properties</th>
<th>Peptides</th>
<th>AMINES</th>
<th>Thyroid Hormone</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solubility</strong></td>
<td>Hydrophilic</td>
<td>Hydrophilic</td>
<td>Lipophilic</td>
<td>Lipophilic</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Chains of specific amino acids</td>
<td>Tyrosine derivative (catecholamines) or tryptophan derivative (indoleamines)</td>
<td>Iodinated tyrosine derivative</td>
<td>Cholesterol derivative</td>
</tr>
<tr>
<td><strong>Synthesis</strong></td>
<td>In rough endoplasmic reticulum; packaged in Golgi complex</td>
<td>In cytosol</td>
<td>In colloid within thyroid gland (see p. 691)</td>
<td>Stepwise modification of cholesterol molecule in various intracellular compartments</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Large amounts in secretory granules</td>
<td>In secretory granules</td>
<td>In colloid</td>
<td>Not stored; cholesterol precursor stored in lipid droplets</td>
</tr>
<tr>
<td><strong>Secretion</strong></td>
<td>Exocytosis of granules</td>
<td>Exocytosis of granules</td>
<td>Endocytosis of colloid</td>
<td>Simple diffusion</td>
</tr>
<tr>
<td><strong>Transport in Blood</strong></td>
<td>As free hormone</td>
<td>Half bound to plasma proteins</td>
<td>Mostly bound to plasma proteins</td>
<td>Mostly bound to plasma proteins</td>
</tr>
<tr>
<td><strong>Receptor Site</strong></td>
<td>Surface of target cell</td>
<td>Surface of target cell</td>
<td>Inside target cell</td>
<td>Inside target cell</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Activation of second-messenger pathway to alter activity of preexisting proteins that produce the effect</td>
<td>Activation of second-messenger pathway to alter activity of preexisting proteins that produce the effect</td>
<td>Activation of specific genes to make new proteins that produce the effect</td>
<td>Activation of specific genes to make new proteins that produce the effect</td>
</tr>
<tr>
<td><strong>Hormones of This Type</strong></td>
<td>Majority of hormones</td>
<td>Catecholamines: hormones from the adrenal medulla, dopamine from hypothalamus, melatonin from pineal</td>
<td>Only hormones from the follicular cells of the thyroid</td>
<td>Hormones from the adrenal cortex and gonads and some placental hormones; vitamin D (a hormone) is steroidlike</td>
</tr>
</tbody>
</table>
Extracellular chemical messengers bring about cell responses primarily by signal transduction.

**signal transduction:** Process by which incoming signals are conveyed to target cell’s interior.
Principal mechanisms by which chemical messengers in the ECF bring about changes in cell function

Table 1–8. Principal mechanisms by which chemical messengers in the ECF bring about changes in cell function.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open or close ion channels in cell membrane</td>
<td>Acetylcholine on nicotinic cholinergic receptor; norepinephrine on K⁺ channel in the heart.</td>
</tr>
<tr>
<td>Act via cytoplasmic or nuclear receptors to increase transcription of selected mRNAs</td>
<td>Thyroid hormones, retinoic acid, steroid hormones.</td>
</tr>
<tr>
<td>Activate phospholipase C with intracellular production of DAG, IP₃, and other inositol phosphates</td>
<td>Angiotensin II, norepinephrine via α₁-adrenergic receptor, vasopressin via V₁ receptor.</td>
</tr>
<tr>
<td>Activate or inhibit adenyly cyclase, causing increased or decreased intracellular production of cyclic AMP</td>
<td>Norepinephrine via β₁-adrenergic receptor (increased cyclic de-AMP); norepinephrine via α₂-adrenergic receptor (decreased cyclic AMP).</td>
</tr>
<tr>
<td>Increase cyclic GMP in cell</td>
<td>ANP; NO (EDRF). ANP=Atrial natriuretic peptide</td>
</tr>
<tr>
<td>Increase tyrosine kinase activity of cytoplasmic portions of transmembrane receptors</td>
<td>Insulin, EGF, PDGF, M-CSF.</td>
</tr>
</tbody>
</table>
Principal mechanisms by which chemical messengers in the ECF bring about changes in cell function are either

- Opening or closing chemically gated receptor-channels
- By activating receptor-enzymes
- Activating second-messenger systems
  - Activated by first messenger
  - Relays message to intracellular proteins that carry out dictated response
Opening of *receptor-channel* when an extracellular messenger binds

In this case, R- itself serves as an ion channel.

When extracellular messenger binds to R-channel, channel opens or closes, depending on signal.

An example, is opening of chemically gated R-channels in subsynaptic membrane in response to neurotransmitter binding. E.g EPSPs & IPSPs.

On completion of response, extracellular messenger is removed from receptor site & chemically gated channels close once again.
- Receptor itself functions as an enzyme, so-called receptor-enzyme.
- Has a **protein kinase** site on its portion that **faces cytoplasm**.
E.g. Insulin, which plays a major role in maintaining glucose homeostasis, exerts its effects via tyrosine kinases & also, many growth factors that help regulate cell growth & division.
Activation of second messenger pathway via G-Protein coupled receptors.
• Mechanism of action of hydrophilic hormones via activation of cyclic AMP second-messenger pathway.

1. Binding of extracellular messenger to receptor activates a G protein, the α subunit of which shuttles to and activates adenyl cyclase.
2. Adenyl cyclase converts ATP to cAMP.
3. cAMP activates protein kinase A.
4. Protein kinase A phosphorylates inactive designated protein, activating it.
5. Active designated protein brings about desired response.

KEY

P = Phosphate
Mechanism of action of hydrophilic hormones via countercurrent activation of IP$_3$/Ca$^{2+}$ 2$^{nd}$ messenger pathway & DAG pathway
Mechanism of action of lipophilic hormones via activation of genes
RECEPTORS AND THEIR REGULATION

The receptors on target tissues are not static. They are dynamic & mobile & their number also changes during process of regulation.

**Up Regulation of Receptors**

The number of receptors is increased on target tissue. This happens when there is less concentration of ligand in ECF.

**Down Regulation of Receptors**

The number of receptors is decreased on target tissue. This happens when ligand concentration is more in ECF.
<table>
<thead>
<tr>
<th>Property</th>
<th>Nervous System</th>
<th>Endocrine System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic Arrangement</td>
<td>A “wired” system: specific structural arrangement between neurons and their target cells, with structural continuity in the system</td>
<td>A “wireless” system: endocrine glands widely dispersed and not structurally related to one another or to their target cells</td>
</tr>
<tr>
<td>Type of Chemical Messenger</td>
<td>Neurotransmitters released into synaptic cleft</td>
<td>Hormones released into blood</td>
</tr>
<tr>
<td>Distance of Action of Chemical Messenger</td>
<td>Very short distance (diffuses across synaptic cleft)</td>
<td>Long distance (carried by blood)</td>
</tr>
<tr>
<td>Specificity of Action on Target Cell</td>
<td>Dependent on close anatomic relationship between neurons and their target cells</td>
<td>Dependent on specificity of target cell binding and responsiveness to a particular hormone</td>
</tr>
<tr>
<td>Speed of Response</td>
<td>Generally rapid (milliseconds)</td>
<td>Generally slow (minutes to hours)</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>Brief (milliseconds)</td>
<td>Long (minutes to days or longer)</td>
</tr>
<tr>
<td>Major Functions</td>
<td>Coordinates rapid, precise responses</td>
<td>Controls activities that require long duration rather than speed</td>
</tr>
</tbody>
</table>