Key concepts

- Communication occurs via transduction of signals received from cells, organisms, or the environment.
- Cell signaling pathways share common features in all organisms.
- Cells communicate by direct contact and over short and long distances via signaling molecules.
- Second messengers are important in the functioning of many signal cascades.
- Changes in a signal transduction pathway can alter the cellular response.

Essential Knowledge

1. Use the KEY TERMS to compile a glossary for this topic.

Common Features of Cell Communication (3.D.1) pages 73-75, 174, 189

2. Explain the basis of communication, i.e. the transduction of signals from cells, organisms, or the environment. Understand and explain why there is strong selective pressure for the correct and appropriate signal transduction.

3. Using an example such as quorum sensing in bacteria, describe and explain the signal transduction pathways for response in single-celled organisms.

4. Using examples, explain how signal transduction pathways coordinate the activities of cells in multicellular organisms. Examples could include:
   - temperature-dependent sex determination in some vertebrates
   - signal transduction pathways for DNA repair
   - epinephrine-induced breakdown of glycogen to glucose
   - interactions between immune cells in the immune response

5. Describe features of cell signaling pathways. Understand and describe how the basic chemical processes for cell communication are indicative of common ancestry (e.g. the hedgehog signaling pathway in bilateral animals).


6. Using an appropriate example, e.g. contact between cells of the immune system, describe how cells communicate by cell-to-cell contact (paracrine signaling).

7. Describe and explain how cells communicate over short distances using local regulators such as neurotransmitters, autoinducers for bacterial luminescence, and morphogens such as hedgehog (in Drosophila), sonic hedgehog (in mammals), and epidermal growth factor (humans).

8. Using appropriate examples of hormones, describe and explain how signals from endocrine cells can be transported in the blood or hemolymph to influence the activity of distant target cells.

9. Using an example, explain the process of signal transduction, including with recognition of the ligand by a receptor molecule, initiation of transduction, relay of the signal, and the cellular response.

10. Explain the role of second messengers, such as cyclic AMP, in the functioning of signal cascades.

11. Describe the role of protein modification and phosphorylation cascades in signal transduction pathways.

Changes in Signal Transduction Pathways (3.D.4) pages 83-84

12. Describe and explain how changes in a signal transduction pathway can alter cellular response. Use examples to show how blocked or defective signal transduction pathways can be detrimental or preventative.
Communication between Unicellular Organisms

Unicellular organisms gather information about their environment and respond to it appropriately by using signaling pathways triggered by chemicals in the environment. These chemicals can relay information about how close a food source is, how many of the same bacteria are nearby (quorum sensing), or the location of a favorable environment. Chemical substances produced by unicellular organisms can also be used to communicate between individual cells and influence their cellular processes.

Chemical communication between bacterial cells was first investigated in 1970 by Nealon and Woodland, after the observation that the luminescent bacterium Vibrio fisheri only luminesces when the bacterial population reaches a certain density.

**Bioluminescence in Bacteria**

![Diagram of bioluminescence in bacteria]

The mechanism of luminescence is controlled by a messenger molecule called an autoinducer, which travels between bacterial cells.

**Chemotaxis** is the movement or orientation of an organism along a chemical concentration gradient either toward or away from the chemical stimulus. Chemotaxis in bacteria is controlled by signal transduction, which affects the direction of flagella rotation. Clockwise rotation of the flagellum causes tumbling and is the native condition (occurs without receptor stimulation) in bacteria. Tumbling occurs when the molecule CheA activates the molecule CheY, which attaches to the flagellum motor and causes its clockwise rotation.

When an attractant molecule (a chemical the bacterium wants to move towards) is encountered, the action of CheA is inhibited so that it can't activate CheY. Flagellum rotation is anticlockwise, causing the bacterium to swim straight (a run). After a second, the bacterium becomes insensitive to the attractant molecule and resumes tumbling. Encountering another attractant molecule causes it to start another run. In this way bacteria can move towards an attractant source, as a greater concentration of attractant molecules causes more runs and less tumbling. The protein CheZ is also able to directly inhibit CheY and stop it binding to the motor complex.

1. (a) Explain how the autoinducer molecule in luminescent bacteria signals when to luminesce:

   (b) Explain how this enables the bacterium to detect the population density:

   (c) How might this information be of survival advantage to the bacterium?

2. Explain how the Che molecules allow a bacterium to move towards or away from a chemical source:

   Related activities: Types of Cell Signaling

   Weblinks: Bacterial Chemotaxis

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ISBN: 978-1-927173-11-4
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Types of Cell Signaling

Cells use **signals** (chemical messengers) to communicate and to gather information about, and respond to, changes in their cellular environment. The signaling and response process is called a **signal transduction pathway**, and often involves a number of enzymes and molecules in a **signal cascade**. A signal cascade results in a response in the target cell. Cell signaling pathways are categorized primarily on the distance over which the signal molecule travels to reach its target cell, and generally fall into three categories. The **endocrine** pathway involves the transport of **hormones** over large distances through the blood or hemolymph. During **paracrine** signaling, the signal travels an intermediate distance to act upon neighboring cells. **Autocrine** signaling involves a cell producing and reacting to its own signal. These three pathways are illustrated below.

**Endocrine signaling**: Hormone signals are released by ductless endocrine glands and carried long distances through the body by the circulatory system to the target cells. Examples include sex hormones, growth factors, and neurohormones such as dopamine.

**Paracrine signaling**: Signals released from a cell act upon target cells within the immediate vicinity. The chemical messenger can be transferred through the extracellular fluid (e.g. at synapses) or directly between cells, which is important during embryonic development.

**Autocrine signaling**: Cells produce and react to their own signals. In vertebrates, when a foreign antibody enters the body, some T-cells (lymphocytes) produce a growth factor to stimulate their own production. The increased number of T-cells helps to fight the infection.

**Signaling and T-Cell Activation**

Helper T-cells are activated by direct cell-to-cell signaling and by paracrine signaling using **cytokines** from macrophages. Macrophages ingest antigens, process them, and present them on the cell surface where they are recognized by helper T-cells. The helper T-cell binds to the antigen and to the macrophage receptor, which leads to activation of the helper T-cell.

The macrophage also produces and releases cytokines, which enhance T-cell activation. The activated T-cell then releases more cytokines which causes the proliferation of other helper T-cells (positive feedback) and helps to activate cytotoxic T-cells and antibody-producing B-cells.

1. Briefly describe the three types of cell signaling:
   (a) __________
   (b) __________
   (c) __________

2. Identify the components that all three cell signaling types have in common: __________

3. Activation of helper T-cells involves which signaling pathway(s)? __________
Signals and Signal Cascades

Signals that activate processes within the cell can be external signal molecules or external conditions that cause internal changes. These signals often cause a cascade of reactions that result in a cellular outcome. For example, the molecule epinephrine causes the breakdown of glycogen in mammals, and ionizing radiation activates the protein kinase ATM (Ataxia Telangiectasia Mutated) which initiates the repair of DNA. ATM belongs to a family of proteins that have been highly conserved throughout eukaryote evolution and is a key component in the repair of damaged DNA. Damage to a DNA molecule from ionizing radiation, such as UV light, induces a signal cascade that results in the repair of the DNA, arrest of cell cycle, or apoptosis.

Initiating DNA Repair

A signal cascade or transduction pathway requires an initiator. This signals the beginning of a cascade of chemical reactions within the cell that activates the required molecules and transmits the signal to the correct area of the cell. Often the signal is a molecule, such as a hormone, that is produced elsewhere in the organism and is transported to the cell. In the case of DNA damage by ionizing radiation, it is the radiation itself that activates the signal cascade.

DNA damage

Ionizing radiation (UV light)

Autophosphorylation of ATM

Phosphorylated ATM

Chk2

Phosphorylated Chk2

p53

Phosphorylated p53

p21

Apoptosis

DNA repair

Cell cycle arrest

The initial signal is passed through a series of messenger molecules. Some of these will take part in the final response while others may simply pass on the signal to other molecules.

Target molecules are activated within and at the end of the signal cascade. The mechanism for initiating DNA repair results in activating molecules that participate in DNA repair, arrest the cell cycle, and bring about apoptosis (programmed cell death).

1. (a) Describe how DNA repair is signaled in cells:

__________________________________________________________________________

__________________________________________________________________________

(b) Explain why a signal cascade can be useful in certain cell processes:

__________________________________________________________________________

__________________________________________________________________________

2. Use the example of DNA damage to explain why there is a strong selection pressure for the correct functioning of signal transduction pathways:

__________________________________________________________________________

__________________________________________________________________________

Related activities: Signal Transduction
Neurotransmitters are chemicals that allow the transmission of signals between neurons. They are found in the axon endings of neurons and are released into the space between one neuron and the next (the synaptic cleft) after a depolarization or hyperpolarization of the nerve ending. Neurotransmitters can be classified into amino acids, peptides, or monoamines. The many neurotransmitters produce various responses depending on their location in the body. They can be excitatory (likely to cause an action potential in the receiving neuron) or inhibitory (causing hyperpolarization) depending on the receptor they activate.

### Neurotransmitters Carry Signals Between Neurons

![Diagram of neurotransmitters](image)

**Related activities:** Types of Cell Signaling

1. Describe the purpose of a neurotransmitter: ____________________________

2. (a) Explain why stimulating the first frog heart with electricity caused it to change its beating rate:

   ____________________________

   ____________________________

   ____________________________

   ____________________________

(b) Explain why the second heart in the experiment reduced its beating rate after a delay:

   ____________________________

   ____________________________

   ____________________________

   ____________________________

3. Why can some neurotransmitters be both excitatory and inhibitory?

   ____________________________

   ____________________________

   ____________________________

   ____________________________
Neurohormones

A neurohormone is any hormone produced and released by specialized neurosecretory cells, which function as both nerve cells and endocrine cells. The hypothalamus is responsible for synthesizing and secreting several neurohormones. It has an important role in linking the nervous system to the endocrine system via the pituitary, with which it has a close structural and functional relationship. The posterior pituitary is neural in origin and is essentially an extension of the hypothalamus. Its neurosecretory cells release oxytocin and ADH directly into the blood in response to nerve impulses. The anterior pituitary is connected to the hypothalamus by blood vessels and receives neurohormones from the hypothalamus via a capillary network. These hypothalamic releasing hormones regulate the secretion of the anterior pituitary's hormones.

The Role of the Hypothalamus

The neurohormone is produced in the cell body of the neurosecretory cell, then packaged into droplets and transported along the axon. At the axon terminal, it is released into the blood in response to nerve impulses.

The hypothalamus monitors hormone levels and indirectly regulates many functions, including body temperature, food and fluid intake, and sleep.

The anterior pituitary is glandular. It secretes hormones in response to the releasing hormones it receives from the hypothalamus.

Releases at least seven peptide hormones in response to releasing hormones secreted by the hypothalamus.

Stores and releases oxytocin and antidiuretic hormone (ADH) produced by the hypothalamus.

1. (a) Explain how the anterior and posterior pituitary differ with respect to their relationship to the hypothalamus:

(b) Explain how these differences relate to the nature of the hormonal secretions for each region:

2. Describe the role of the neurohormones released by the hypothalamus:

3. Explain why the adrenal and thyroid glands atrophy if the pituitary gland ceases to function:

4. Although the anterior pituitary is often called the master gland, the hypothalamus could also claim that title. Explain:
Hormonal Regulation

The endocrine system regulates the body's metabolic processes by releasing chemical messengers (hormones) into the blood, which transports them to target cells. Hormones are potent chemical regulators: they are produced in minute quantities yet can have a large effect on metabolism. The endocrine system comprises endocrine cells (organized into endocrine glands), and the hormones they produce. Unlike exocrine glands (e.g. sweat and salivary glands), endocrine glands are ductless glands, secreting hormones directly into the bloodstream rather than through a duct or tube. Some organs (e.g. the pancreas) have both endocrine and exocrine regions, but these are structurally and functionally distinct. The basis of hormonal control and the role of negative feedback mechanisms in regulating hormone levels are described below.

The Mechanism of Hormone Action

Endocrine cells produce hormones and secrete them into the bloodstream where they are distributed throughout the body. Although hormones are broadcast throughout the body, they affect only specific target cells. These target cells have receptors on the plasma membrane which recognize and bind the hormone (see inset below). The binding of hormone and receptor triggers the response in the target cell. Cells are unresponsive to a hormone if they do not have the appropriate receptors.

1. (a) Explain what is meant by antagonistic hormones and describe an example of how two such hormones operate:

   Example:

(b) Explain the role of feedback mechanisms in adjusting hormone levels (explain using an example if this is helpful):

2. How do hormones bring about a response in target cells even though all cells may come into contact with the hormone:

3. Explain how hormonal control differs from nervous system control with respect to the following:
   (a) The speed of hormonal responses is slower:

   (b) Hormonal responses are generally longer lasting:
The **hypothalamus** is located at the base of the brain, just above the pituitary gland. Information comes to the hypothalamus through sensory pathways from the sense organs. On the basis of this information, the hypothalamus controls and integrates many of the body’s activities, including the reflex activity of the **autonomic nervous system**. The pituitary gland comprises two regions: the **posterior pituitary** and the **anterior pituitary**. Interactions between the hypothalamus, the pituitary gland, and the adrenal glands constitute what is called the hypothalamic-pituitary-adrenal (HPA) axis. This axis is a multi-step biochemical pathway in which each step in the pathway passes on information to the next but also receives feedback for its own regulation. It constitutes a major part of the neuroendocrine system, controlling reactions to both short and long term stress and regulating many physiological processes, including digestion, immune response, emotion, sexuality, and energy storage and expenditure.

**Hormones and Their Effects**

The hypothalamus develops as an extension of the anterior pituitary. The release of its two hormones, oxytocin and antidiuretic hormone, occurs directly as a result of nervous input to the hypothalamus.

### Posterior Pituitary

The posterior pituitary secretes two hormones:

- **Oxytocin**: Acts on the mammary glands to stimulate milk ejection (let down). Oxytocin also acts on the uterus to stimulate contraction during labor.

- **Antidiuretic Hormone**: Acts on the kidney to increase water reabsorption from the filtrate (urine).

### Anterior Pituitary

The anterior pituitary releases at least seven peptide hormones (below) into the blood from simple secretory cells. The release of these hormones is regulated by releasing and inhibiting hormones from the hypothalamus.

- **Thyroid Stimulating Hormone**: Increases synthesis and secretion of thyroid hormones (T3 and thyroxine) from the thyroid gland.

- **Growth Hormone**: Stimulates protein synthesis and growth in most tissues; one of the main regulators of metabolism.

- **Prolactin**: Stimulates growth of the mammary glands and synthesis of milk protein.

- **Adrenocorticotropic Hormone (ACTH)**: Usually abbreviated to ACTH, this hormone increases synthesis and secretion of hormones (aldosterone and cortisol) from the adrenal cortex.

- **Follicle Stimulating Hormone**: In females: Stimulates maturation of the ovarian follicles. In males: Increases the production of sperm in the seminiferous tubules.

- **Luteinizing Hormone**: In females: Stimulates secretion of ovarian hormones, ovulation, and formation of the corpus luteum. In males: Stimulates synthesis and secretion of testosterone.

- **Melanophore Stimulating Hormone**: Increases melanin synthesis and dispersal in the skin's melanocytes.

- **Melanophore Stimulating Hormone**: Increases melanin synthesis and dispersal in the skin's melanocytes.

**Related activities**: Neurohormones

**Weblinks**: Hypothalamic, Pituitary, Endocrine Axis, Drag and Drop Hormone Match
1. (a) Describe the metabolic effects of growth hormone: 

(b) Predict the effect of chronic GH deficiency in infancy: 

(c) Predict the effect of chronic GH hypersecretion in infancy: 

(d) Describe the two main mechanisms through which the secretion of growth hormone is regulated: 

2. “The pituitary releases a number of hormones that regulate the secretion of hormones from other glands”. Discuss this statement with reference to growth hormone (GH) and thyroid stimulating hormone (TSH):

3. Using the example of TSH and its target tissue (the thyroid), explain how the release of anterior pituitary hormones is regulated. Include reference to the role of negative feedback mechanisms in this process:

4. Iodine is needed to produce thyroid hormones. Explain why the thyroid enlarges in response to an iodine deficiency:
Signal Transduction describes the process by which an extracellular signal brings about an intracellular response. A signal cascade is initiated by a signaling molecule, such as a hormone, binding to a receptor of a target cell. The signal cascade amplifies the original signal and results in a specific cellular response (e.g. enzyme activation). Water soluble hormones operate by interacting with transmembrane receptors and activating a second messenger system (e.g. cyclic AMP, Ca^{2+}, or inositol triphosphate), which links the hormone to the cellular response. Signal transduction pathways involving phosphorylation cascades, such as the one illustrated below for epinephrine, involve the activation of protein kinases. Steroid hormones, being lipid-soluble, are able to enter the cell freely to interact directly with intracellular receptors and a membrane receptor is not involved. In both cases, the response of the target cell is recognized by the hormone-producing cell through a feedback signal and the hormone is degraded.

**Structure of a Transmembrane Receptor**

The binding sites of cell receptors are very specific: they only bind certain ligands (signal molecules). This stops them from reacting to every signal bombarding the cell. Receptors fall into two main categories:
- **Cytoplasmic receptors**: Cytoplasmic receptors, located within the cell cytoplasm, bind ligands which are able to cross the plasma membrane unaided.
- **Transmembrane receptors**: These span the cell membrane and bind ligands which cannot cross the plasma membrane on their own. They have an extracellular domain outside the cell, and an intracellular domain within the cell cytosol.

**Examples of cell signaling molecules**
- Epinephrine (peptide)
- Progesterone (steroid)
- Insulin like growth factor 1 (protein)

**Second Messenger Activation of a Signal Cascade**

When activated by G protein, the enzyme adenylate cyclase catalyzes the synthesis of cyclic AMP (cAMP).

The hormone (epinephrine) is the first messenger. It operates through cAMP as a second messenger.

- G-protein linked receptor (β-adrenergic receptor)
- Hormone binds to receptor
- 1 molecule

- cAMP activates protein kinase A, beginning a phosphorylation cascade which amplifies the original signal and brings about a cellular response.

- When a ligand binds to the G-protein linked receptor, GDP is exchanged for GTP on the G-protein α subunit, activating it.

- A kinase transfers phosphate groups from ATP to specific substrates (phosphorylation).

- Activated glycogen phosphorylase<br>Glucose-1-phosphate<br>Cellular response 10^6 molecules

- Inactivated G protein is trimeric (has three parts)

- Activated G protein<br>Activated phosphorylase kinase

- Inactive phosphorylase kinase

- ATP ADP P

- Glucose-1-phosphate

- Activated glycogen phosphorylase<br>ATP ADP P

- Inactive glycogen phosphorylase

**Related activities**: Signals and Signal Cascades  **Weblinks**: Second Messengers, G Protein Signal Transduction (IP3), G Protein Coupled Receptors
Gene Activation by Steroid Hormones

Steroid hormones are steroids (fatty molecules) that act as hormones. They have wide-ranging metabolic effects and are involved in regulating metabolic activity, inflammation, immune function, salt and water balance, development of sexual characteristics, and response to stress and injury.

Steroid hormones are lipid soluble and diffuse freely from the blood through the plasma membrane and into the cytoplasm of target cells. In the cytoplasm, the steroid binds to a specific steroid receptor (transcription factor) to form a functional hormone-receptor complex. The complex is able to enter the nucleus and bind to specific DNA sequences to induce transcription of its target genes.

The best-studied steroid-binding receptors are called nuclear receptors (examples below). Their ability to interact directly with DNA and control gene expression makes them important in embryonic development and adult homeostasis.

1. Explain why a second messenger is needed to convey a signal inside a cell from a water soluble first messenger:

2. Explain why each molecule in the cAMP signal cascade is phosphorylated:

3. Describe and explain the role of G proteins in coupling the receptor to the cellular response:

4. Describe the basis of signal amplification and explain its significance:

5. (a) How does the action of steroid hormones differ from that of water soluble signaling molecules?

(b) Suggest why steroid hormones are important in developmental processes:

Related activities: Cell Signaling, First Messenger Systems

Weblinks: Signal Transduction, First and Second Messenger System