What makes the difference between a human being and a fungus? A fungal network can be split in the middle - and both halves will survive and grow further. This does not happen if a human being split since our faculties and vital functions are spread over several locations within our organism. Our cells are specialized and organized into organs. The system only works if the organs work together and communicate. Hormones are the messengers in this communication system. The most important ones, the hormone receptors, and the signal cascades are explained in the following article.

Signal Transduction – Communication Between Cells and their Surroundings

Both extracellular and intracellular messengers are needed for the transmission of information. The classical definition of hormone is any member of a class of signaling molecules produced by glands in multicellular organisms that are transported by the circulatory system to target distant organs to regulate physiology and behavior. The term hormone is sometimes extended to include chemicals produced by cells that affect the same or neighboring cells.

To do that, hormones use the following mechanisms: endocrine (transportation of information to an organ via the blood stream), autocrine (produced by signaling cells that can also bind to the ligand that is released, which means the signaling cell and the target cell can be the same or occur by transferring signaling molecules across gap junctions), or paracrine (involving being directed at neighboring cells). Paracrine signaling is produced and liberated by specialized local cells where the signals elicit quick responses and last only a short amount of time. Gut hormones are frequently paracrine.

In contrast to this, the body can produce mediators in unspecialized cells and use
them for communication. Examples of this are prostaglandins. Additionally, there are transmitters, which are used in the nervous system.

The transition between these three groups is fluent. The correct transduction of the signal into the cell with the aid of receptors is crucial for successful communication.

Receptor types and their signal cascades

The most important biochemical receptor classes and the intracellular signaling pathways are outlined below. Four types of receptor classes are distinguished:

1. G protein-coupled receptors

These form the largest group of receptor classes. The receptor (G-protein coupled receptor or GPCR) consists of seven transmembrane domains and it is coupled with an inactive heterotrimeric G protein. This protein consists of three subunits (SU): α-SU a β-SU and a γ-SU. The α-SU binds GDP. β-SU and a γ-SU work together.

When a ligand binds to the GPCR it causes a conformational change in the GPCR. The GPCR can then activate the associated G protein by exchanging its bound GDP for a GTP. As a consequence, the G protein’s α subunit, together with the bound GTP, can then dissociate from the β/γ subunits to further affect intracellular signaling proteins or target functional proteins. Both complexes interact with effector proteins within the cell. With the intrinsic GTPase activity of the α-SU, GTP is hydrolyzed to GDP and the three SUs return to their original state.

Two of the most frequent signaling pathways occur via the following:

Adenylate cyclase: This effector protein is either stimulated by Gs proteins or inhibited by Gi-proteins [stimulative regulative G-protein (Gs) or inhibitory regulative G-protein (Gi)]. It catalyzes the formation of cAMP from ATP. As a second messenger, cAMP has several points of application within the cell.

IP3: The effector protein phospholipase C splits PIP2 (phosphatidylinositol-4,5-bisphosphate) into IP3 (Inositol-1,4,5-triphosphate) and DAG (diacylglycerol). IP3 increases the calcium level in the cell via other receptors, and DAG activates protein kinase C.
2. Receptors with intrinsic kinase activity

These receptors consist of an extracellular ligand binding domain, a transmembrane domain, and an intracellular kinase domain. This class is roughly divided into two versions:

**Tyrosine kinases:** The kinase phosphorylates tyrosine residues of the receptor. These are then recognized by other signal domains and the signal is transported in the cell via several pathways. Important pathways are the **MAP-kinase-pathway**, a cascade of different kinases, phospholipase Cγ, and PI3 lipase.

**Serine-threonine kinases:** The kinase phosphorylates serine/threonine residues of side chains of other signal proteins - not the receptor proteins. The information is transduced via the **Smad signaling pathway**, members of the TGF-β superfamily.

3. Receptors with associated kinases

The receptors do not possess any intrinsic kinase activity, but they bind kinases directly or via adapting proteins. These kinases are activated if a ligand binds. An example of such an associated kinase is the **Janus kinase** involving the **JAK/STAT signaling pathway**. The **JAK-STAT signaling pathway** transmits information from extracellular chemical signals to the nucleus resulting in DNA transcription and expression of genes involved in immunity, proliferation, differentiation, apoptosis and oncogenesis. Disrupted or dysregulated JAK-STAT functionality can result in immune deficiency syndromes and cancers.
4. Nuclear receptors

Nuclear receptors are located within the cell and are thus only available for lipophilic ligands, which are able to diffuse through the membrane. All of them act as ligand activated transcription factors. Steroid receptors are located in the cytoplasm. If a ligand binds, they migrate into the nucleus and act on the DNA as enhancers.

Receptors for D-vitamins or thyroid hormones, for example, bind to the DNA in an inactive form as repressors if the ligand does not bind. Ligand binding results in a change in conformation, which in turn leads to gene expression. Binding of thyroid hormone results in a conformational change in its nuclear receptor TR which displaces corepressor from the receptor/DNA complex and recruits coactivator proteins. The DNA/TR/coactivator complex then recruits RNA polymerase that transcribes downstream DNA into messenger RNA and eventually protein formation that results in a change in cell function.

Hormones – The Body’s Messengers

Insulin and glucagon - blood sugar level

Synthesis of insulin and glucagon

Insulin is synthesized in the B-cells of the endocrine pancreas. Glucagon is produced in the A-cells. Insulin consists of an A-chain (21 amino acids), and a B-chain (30 amino acids), which are connected to each other by disulphide bridges. Glucagon is a peptide consisting of 28 amino acids.

Stimuli for secretion of insulin and glucagon

Insulin secretion is triggered by an increase in blood glucose level and by amino acids, free fatty acids, gastrointestinal peptides, and parasympathetic activity. As the antagonist, glucagon is secreted during hypoglycemia or during stimulation with catecholamines or amino acids.

Insulin and glucagon receptors

The insulin molecule binds to a tetrameric membrane protein, which consists of two tyrosine kinase receptors. Glucagon causes an increase in intracellular cAMP via a G
**protein-coupled receptor** and adenylate cyclase.

**Effects of insulin and glucagon**

Insulin increases resorption of glucose into body cells, from the blood by activating the glucose receptor. Liver and pancreas glucose transporter are called GLUT 2 and muscle and fat glucose transporter is called GLUT 4. It also promotes the intake of amino and fatty acids and increases glycogen synthesis in the liver. Glucagon antagonistically promotes the degradation of liver glycogen, thereby rapidly increasing blood sugar level when it is too low.

**Adrenaline and noradrenaline**

Catecholamines are used within the body both as transmitters and as hormones. Here we discuss their function as hormones.

**Synthesis of adrenaline and noradrenaline**

Both hormones are synthesized in the **adrenal medulla** from tyrosine, resulting in 80 % adrenaline and 20 % noradrenaline. In the blood, however, the ratio is 1 : 5 since noradrenaline is liberated at many sympathetic nerve endings and escapes the synaptic cleft.

**Stimuli to the secretion of adrenaline and noradrenaline**

Synthesis is stimulated by both the **sympathetic nervous system** and glucocorticoids.

**Adrenaline and noradrenaline receptor**

Both hormones bind to **G-protein-coupled receptors**. The following are identified: α1- and α2-adrenoceptors, and β1-, β2- and β3-adrenoceptors. Noradrenaline has a preference for α-adrenoceptors; adrenaline binds better to β-adrenoceptors. The two differ in their coupled G-proteins and thus differ in their signaling pathways. Note that Gα proteins are class of G proteins which work to activate phospholipase C(PLC), participating in a variety of cellular signaling pathways. The letter “q” does not stand for any particular function.

**Overview of adrenoreceptors:**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>G-protein</th>
<th>Enzyme</th>
<th>Second messenger</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Gq</td>
<td>Phospholipase Cβ ↑</td>
<td>DAG and IP3 ⇒ Ca++ ↑</td>
<td>Contraction of musculature; stimulation of glycogenolysis</td>
</tr>
<tr>
<td>α2</td>
<td>Gi</td>
<td>Adenylate cyclase ↓</td>
<td>cAMP ↓</td>
<td>Inhibits lipolysis and insulin liberation</td>
</tr>
<tr>
<td>β1</td>
<td>Gs</td>
<td>Protein kinase A ↑</td>
<td>cAMP ↑</td>
<td>Heart rate ↑, impulse conduction velocity ↑, contractility ↑</td>
</tr>
<tr>
<td>β2</td>
<td></td>
<td>Protein kinase A ↑</td>
<td>cAMP ↑</td>
<td>Relaxation of smooth muscles, glycogenolysis ↑, lipolysis ↑</td>
</tr>
<tr>
<td>β3</td>
<td></td>
<td></td>
<td></td>
<td>Lipolysis in brown fat tissue ↑</td>
</tr>
</tbody>
</table>

**Effects of adrenaline and noradrenaline**
With respect to metabolism, catecholamines are designed to make stored energy available for use. This means that they promote **glycogenolysis** and **lipolysis** and that, among other activities, they inhibit insulin secretion and storage of glucose.

With respect to the heart, they have a positive effect on **cardiac output**, and in the vascular system they cause both **vasoconstriction** and **vasodilation** – depending on whether α1-adrenoreceptors or β2-adrenoreceptors are expressed.

### Renin-angiotensin-aldosterone system

The RAAS connects kidney function with blood pressure and is an important part of blood pressure regulation.

#### Synthesis of the renin-angiotensin-aldosterone system

The different components of the system are formed at different locations within the body:

- **Renin**: Synthesized in the epitheloid cells of the juxtaglomerular apparatus in the kidney, near the macula densa. The active enzyme is liberated via exocytosis.

- **Angiotensinogen**: Produced in the liver and in fat tissue.

- **Angiotensin-I-converting-enzyme (ACE)**: Synthesized in the endothelium, mainly in the lung.

- **Aldosterone**: Produced in the zona glomerulosa of the adrenal cortex.

#### Effects of the renin-angiotensin-aldosterone system

When blood pressure decreases in the efferent arteriole of the glomerulus or sodium is low in the macula densa, renin is liberated. It splits angiotensinogen into angiotensin I. This is converted into angiotensin II by ACE. **Angiotensin II has several effects**:

- Stimulation of sodium reabsorption in the proximal tubule
- Stimulation of aldosterone secretion: Aldosterone increases sodium resorption in the collecting ducts and the connecting tubules
- Central stimulation of the sensation of thirst and a desire for salt resulting in increased intake of water and salt
- Stimulation of ADH secretion resulting in increased water retention
- Contraction of vascular smooth muscles cells.

Blood volume and consequently blood pressure are increased via the first four mechanisms.

#### Renin-angiotensin-aldosterone system receptors

Angiotensin acts via several **angiotensin receptors**, which signal by means of both phospholipase C and inhibition of adenylate cyclase. There are different isoforms. One of them inhibits renin liberation in an autoregulative manner.

### Hypothalamic-pituitary-adrenal axis

This axis plays a central role in the hormone system of the body. As the name suggests, it consists of the **hypothalamus**, the **hypophysis** (the pituitary gland), the **adrenal gland**, and other target organs.

The **hypothalamus** produces releasing hormones which lead to a release of the respective hormones in the pituitary gland and also inhibiting hormones, which inhibit the
release of certain hormones.

The **pituitary gland** consists of the **posterior lobe/neurohypophysis** and the **anterior lobe/adenohypophysis**.

The **neurohypophysis** is the location for storage and release of ADH and oxytocin.

**Attention:** The hormones of the posterior hypophysis are synthesized in the hypothalamus. They are then taken to the neurohypophysis via axonal transport. The **adenohypophysis** synthesizes and secretes six hormones under regulation by hypothalamic releasing hormones. Their release is solely triggered by the hormones of the hypothalamus. Four of the six hormones are glandotropic, that is, they have an effect on other glands. Individual hormones are given their own specific sections below.

The system is kept within its limits via negative feedback to the hypothalamus by the hormones released in target organs. Thus, pathologically absent feedback can lead to defective regulation.

<table>
<thead>
<tr>
<th>Hypothalamus</th>
<th>Pituitary Gland</th>
<th>Target Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRH (thyrotropin-releasing hormone)</td>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Thyroid gland</td>
</tr>
<tr>
<td>CRH (corticotropin-releasing hormone)</td>
<td>Corticotropin (ACTH), melanotropin (MSH, forms from Pro-opiomelanocortin (POMC) during ACTH-synthesis)</td>
<td>Adrenal gland: mineralocorticoids, glucocorticoids, sex hormones Skin: melanin production</td>
</tr>
<tr>
<td>GnRH (gonadotropin-releasing hormone)</td>
<td>Follicle-stimulating hormone (FSH), luteinizing hormone (LH)</td>
<td>Ovary and testicle: sex hormones, ovulation, spermatogenesis</td>
</tr>
<tr>
<td>PRH (prolactin-releasing hormone)</td>
<td>Prolactin (PRL)</td>
<td>Mammary glands lactation</td>
</tr>
<tr>
<td>GHRH (growth-hormone-releasing hormone)</td>
<td>Somatotropin (STH, growth-hormone = GH)</td>
<td>Liver: IGF-1</td>
</tr>
</tbody>
</table>

**ADH and oxytocin – hormones of the neurohypophysis**

**Antidiuretic hormone** acts on the collecting ducts of the kidney. It binds to **V2-receptors** and causes the integration of **aquaporin 2** into the apical membrane of the cells. The consequence is increased water retention, thus compensating the stimulus for ADH-release, which is hyperosmolarity of the blood.

Oxytocin, the hormone for lactation, is liberated during mechanical stimulation of the nipple when an infant sucks. It causes constriction of the **myoepithelium** of the **mammary glands**. This aids the infant when drinking.
Growth hormone (GH)

The growth hormone (GH), or somatotropin, influences body growth and metabolism.

**Growth hormone - Location of synthesis and stimuli**

Growth hormone is produced and secreted in the **adenohypophysis**. Release is mainly triggered by the **GH-releasing hormone** of the hypothalamus. Other stimuli are: Ghrelin, thyroid hormones, steroid hormones, amino acids, low glucose level, physical activity, and deep sleep.

**Growth hormone receptors**
GH binds to receptors associated with tyrosine kinase. Especially in the liver, insulin-like growth factors (IF) are induced and released into the blood plasma, thus initiating growth-enhancing effects. Furthermore, IFs are produced in the growth plate, which promotes bone growth by a paracrine fashion. IFs acts on the target cells via tyrosine kinase receptors.

**Effect of the growth hormone**

Postnatal growth is promoted by GH/IF. These also mediate several metabolic effects, such as the promotion of bone growth, the growth of organs, and growth in muscle mass. In the adult organism the system contributes to tissue homeostasis and regeneration processes.

With respect to metabolism, GH reinforces protein biosynthesis, promotes the release of glucose, and inhibits its utilization. It also promotes lipolysis and the degradation of fatty acids.

**Glucocorticoids**

**Synthesis of glucocorticoids**

Glucocorticoids originate from the zona fasciculata (the middle zone) of the adrenal medulla and are steroid hormones, that is: They diffuse through membranes and directly act within the cell.
**Stimuli for secretion of glucocorticoids**

The release of glucocorticoids is a part of the hypothalamic-pituitary-adrenal axis. In the hypothalamus, the **corticotropin-releasing hormone (CRH)** is liberated; in turn, it causes the release of **adrenocorticotropic hormone (ACTH)**, which causes secretion of cortisol, the main representative of the glucocorticoids.

**Glucocorticoid receptors**

Cortisol binds to two receptors in the cytosol. The **type I receptor** has a high affinity to cortisol, but also binds aldosterone. However, the intracellular concentration of cortisol is usually greater so that the receptor binds almost exclusively to cortisol. The **type II receptor** specifically binds to cortisol, but with a lower affinity. At high concentrations the receptor plays a particular role in stress situations.

**Effects of glucocorticoids**

Cortisol is a stress hormone, and most of its functions can be deduced from this designation: It promotes **gluconeogenesis**, it increases the fatty acid level in the blood and it decreases anabolic **metabolism** by impeding the synthesis of muscle proteins. It also sensitizes smooth vascular musculature to **catecholamines**, making for better blood supply to the working muscles.
Thyroid hormones

The thyroid hormones are important for the body metabolism and for the growth and development of children.

Synthesis of thyroid hormones

The thyroid cells synthesize thyroglobulin, which contains a lot of tyrosine molecules. Via the addition of iodine atoms they become triiodothyronine T3 or tetraiodothyronine T4. This is the form in which it is stored in the thyroid follicles.

For liberation of T3 and T4, thyroglobulin is split off. Some T4 is transformed into T3 in the blood. Most T3 is therefore formed outside the thyroid gland.

Stimuli for secretion of thyroid hormones

The thyroid gland is a part of the hypothalamic-pituitary axis. The thyrotropin-releasing hormone of the hypothalamus releases thyroid-stimulating hormone (TSH) within the anterior lobe of the pituitary gland. In turn, this hormone stimulates the production of T3 and T4. Both have a negative feedback effect on the hypothalamus and the pituitary gland.

Thyroid hormones receptors and effects

Like the steroid receptors, the receptors for the thyroid hormones are located in the nucleus. When activated, they enhance the expression of certain genes. This affects numerous proteins and enzymes. Overall, the thyroid hormones cause an increase in energy turnover.

Sex hormones

The sex hormones estrogen, progesterone and testosterone are also regulated by the hypothalamic-pituitary-adrenal axis. The hypothalamus liberates a releasing-hormone, the Gonadotropin-releasing hormone (GnRH). The pituitary gland then releases FSH and LH, which stimulate hormone production in the gonads. Testosterone production is regulated by LH.

Prolactin

Prolactin is also produced within the anterior lobe of the pituitary gland. Its liberation is both inhibited by the prolactin-inhibiting hormone, and promoted by TRH and by stress. It is a peptide hormone and it promotes growth and differentiation of the mammary glands. It also inhibits the release of LH and FSH, and influences the immune system.

Gastrointestinal hormones

These hormones influence the gastrointestinal tract in several ways. They regulate intestinal motor function, digestive secretions, feedback to the CNS. The gastrointestinal system has not yet been thoroughly investigated. Only the most important hormones are presented below.

Synthesis of gastrointestinal hormones

Almost all gastrointestinal hormones are peptides, which are synthesized and secreted by
different cells throughout the enteral system. They act by both endocrine and paracrine pathways.

Effects of gastrointestinal hormones

Gastrin is produced and liberated by the G-cells in the antrum and the duodenum. It acts via the G protein-coupled CCKB-receptor and the ensuing phospholipase C.

On the one hand, gastrin directly stimulates the production of gastric acid in the parietal cells. On the other hand, it releases histamine from the ECL-cells, which in turn activates adenylate cyclase in the parietal cells via the H2-receptor, and increases acid production. Gastrin also stimulates the release of pepsinogen and other digestive secretions.

The release of gastrin is stimulated by the vagal nerve, distension of the gastric wall, peptides, alcohol, caffeine, and by an increase in pH.

Secretin is secreted into the duodenal blood by S-cells and it has an antagonistic effect with respect to gastrin. On the one hand, it inhibits gastrin and gastric acid production. On the other hand, it promotes secretion of bicarbonate and water by the pancreas, the bile ducts and the small bowel. It is stimulated by a pH of less than 4.

Cholecystokinin (CCK) is produced in the duodenum and jejunal I-cells. Like secretin and gastrin, it’s a peptide hormone. It binds to CCKA- and CCKB-receptors in the pancreas. Both are Gq-protein-coupled receptors, which cause an increase in intracellular calcium concentration when activated.

This results in more digestive enzymes being liberated from the vesicles, aiding overall digestion and additionally aiding contraction of the gallbladder and the sense of satiety. The release of CCK is stimulated by the products of protein degradation and by lipids in food.

Calcium phosphate balance

The various regulators affecting calcium balance and the functions of these regulators must always be considered in relation to the whole body. There are three hormones with synergistic effects that are only employed when there is lack of calcium. This section is therefore organized so as to reflect these three hormones.
1. Parathyroid hormone (PTH):

PTH is released from the parathyroid glands when levels of calcium are low. It stimulates osteoclasts, i.e. osteolysis, and also liberation of calcium into the blood. It additionally increases phosphate excretion and inhibits calcium excretion within the kidney. The release of calcitriol is stimulated as well.

2. Calcitriol:

Calcitriol (1,25-dihydroxycholecalciferol or 1,25-dihydroxyvitamin D3, the hormonally active metabolite of vitamin D) is formed in the kidneys from vitamin D, which needs to be ingested. Calcitriol increases the absorption of calcium in the intestine.

3. Calcitonin:

Calcitonin is released by the thyroid gland’s C-cells when there is an acute oversupply of calcium, e.g. as a consequence of undersupply. It inhibits osteoclasts and promotes the incorporation of phosphate into the bones. It also has an antagonistic effect with respect to calcitriol and inhibits the absorption of calcium in the intestine.

Review Questions

The answers are found below the references.

1. Which statement is correct in relation to antidiuretic hormone?
A. It is synthesized and released in the pituitary gland.
B. It is a hormone of the anterior lobe of the pituitary gland.
C. It is synthesized in the hypothalamus.
D. It is liberated as a result of hypoosmolarity.
E. It causes the excretion of wastewater, hence, affecting blood volume.

2. Which of the following statements is correct?

A. The growth hormone GH is especially important during development.
B. The growth hormone GH acts via tyrosine kinase receptors.
C. Insulin-like growth factors are only produced in the liver.
D. The growth hormone GH acts via tyrosine kinase-associated receptors.
E. Once its development is complete, growth hormone GH no longer serves any purpose.

3. Which of these statements is false?

A. In the adrenal medulla, noradrenaline and adrenaline are synthesized at a ratio of 1 : 4.
B. The ratio of the concentrations of adrenaline and noradrenaline in the blood is 1 : 5.
C. Adrenaline has a higher affinity to $\alpha$-adrenoreceptors than noradrenaline.
D. Noradrenaline accesses the blood circulation by leaving the synaptic cleft of postganglionic neurons.
E. $\alpha_2$-adrenoreceptors are coupled with inhibitory G proteins.

References


Correct Answers: 1C, 2D, 3C

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