12

HORMONES

12.1 INTRODUCTION

A hormone is a chemical that acts as a messenger transmitting a signal from one cell to another. When it binds to another cell which is the target of the message, the hormone can alter several aspects of cell function, including cell growth, metabolism, or other function. Hormones can be classified according to chemical composition, solubility properties, location of receptors, and the nature of the signal used to mediate hormonal action within the cell. Hormones that bind to the surfaces of cells communicate with intracellular metabolic processes through intermediary molecules called second messengers (the hormone itself is the first messenger), which are generated as a consequence of the ligand-receptor interaction. The second messenger concept arose from an observation that epinephrine binds to the plasma membrane of certain cells and increases intracellular cAMP. This was followed by a series of experiments in which cAMP was found to mediate the effects of many hormones. To date, only one hormone, atrial natriuretic factor (ANF), uses cGMP as its second messenger.

OBJECTIVES

After reading this lesson, you will be able to

- explain the characterizing hormone
- describe functional importance of hormones

12.2 CHARACTERIZING HORMONE

The first way of characterizing a hormone is by looking at the distance over which the hormone acts. Hormones can be classified on three primary ways as following:

- Autocrine: An autocrine hormone is one that acts on the same cell that released it.

- Paracrine: A paracrine hormone is one that acts on cells which are nearby relative to the cell which released it. An example of paracrine hormones includes growth factors, which are proteins that stimulate cellular proliferation and differentiation. Specifically, consider the binding of white blood cells to T cells. When the white blood cell binds to a T cell, it releases a protein growth factor called interleukin-1. This causes the T cell to proliferate and differentiate.

- Endocrine: An endocrine hormone is one that is released into the bloodstream by endocrine glands. The receptor cells are distant from the source. An example of an endocrine hormone is insulin, which is released by the pancreas into the bloodstream where it regulates glucose uptake by liver and muscle cells.

There are three major classifications one should be aware of:

- Steroids: Steroid hormones are for the most part derivatives of cholesterol.

- Amino acid derivatives: Several hormones (and neurotransmitters) are derived from amino acids.

- Polypeptides: Many hormones are chains of amino acids.

12.3 FUNCTIONAL IMPORTANCE OF HORMONES

12.3.1 Insulin

Insulin is a polypeptide hormone synthesized in the pancreas by β-cells, which construct a single chain molecule called proinsulin. Enzymes excise a portion of the proinsulin molecule called the C peptide, producing the actual insulin molecule. When in demand, the β-cells will release insulin together with the c peptide into the blood stream via exocytosis. The role of insulin in the body is well known, with its primary role being to control the uptake of glucose by liver and muscle cells and also the storage of glucose in the form of glycogen.

Diabetes results from a lack of insulin secretion by the pancreas. Without insulin, cells take up glucose very slowly. The lack of insulin results in an inability to use blood glucose for fuel. Insulin is a signal for high blood glucose levels and increases glucose transport into cells. It stimulates synthesis of glycogen, fat, and protein. It inhibits breakdown of glycogen, fat, and protein. Insulin, secreted by the β-cells of the pancreas in response to rising blood glucose levels, is a signal that glucose is abundant. Insulin binds to a specific receptor on the cell surface and exerts its metabolic effect by a signaling pathway that involves a receptor tyrosine kinase phosphorylation cascade. Note that insulin stimulates storage processes and at the same time inhibits degradative pathways.

12.3.1.1 The pancreas secretes insulin or glucagon in response to changes in blood glucose

When glucose enters the bloodstream from the intestine after a carbohydrate-rich meal, the resulting increase in blood glucose causes increased secretion of insulin (and decreased secretion of glucagon). Insulin release by the pancreas is largely regulated by the level of glucose in the blood supplied to the pancreas. The peptide hormones insulin, glucagon, and somatostatin are produced by clusters of specialized pancreatic cells, the islets of Langerhans. Each cell type of the islets produces a single hormone: α-cells produce glucagon; β-cells, insulin; and δ-cells, somatostatin.

12.3.1.2 Insulin secretion

When blood glucose rises, GLUT2 transporters carry glucose into the b-cells, where it is immediately converted to glucose 6-phosphate by hexokinase IV (glucokinase) and enters glycolysis. The increased rate of glucose catabolism raises [ATP], causing the closing of ATP-gated K^+ channels in the plasma membrane. Reduced efflux of K^+ depolarizes the membrane, thereby opening voltage-sensitive Ca^{2+} channels in the plasma membrane. The resulting influx of Ca^{2+} triggers the release of insulin by exocytosis. Stimuli from the parasympathetic and sympathetic nervous systems also stimulate and inhibit insulin release, respectively. Insulin lowers blood glucose by stimulating glucose uptake by the tissues; the reduced blood glucose is detected by the β-cell as a diminished flux through the hexokinase reaction; this slows or stops the release of insulin. This feedback regulation holds blood glucose concentration nearly constant despite large fluctuations in dietary intake.

12.3.1.3 Insulin counters high blood glucose

Insulin stimulates glucose uptake by muscle and adipose tissue, where the glucose is converted to glucose 6-phosphate. In the liver, insulin also activates glycogen synthase and inactivates glycogen phosphorylase, so that much of the glucose 6-phosphate is channelled into glycogen. Insulin also stimulates the storage of excess fuel as fat. In the liver, insulin activates both the oxidation of glucose 6-phosphate to pyruvate via glycolysis and the oxidation of pyruvate to acetyl-CoA. If not oxidized further for energy production, this acetyl- CoA is used for fatty acid synthesis in the liver, and the fatty acids are exported as the triglyerides to the adipose tissue. These fatty acids are ultimately derived from the excess glucose taken up from the blood by the liver. In summary, the effect of insulin is to favor the conversion of excess blood glucose to two storage forms: glycogen (in the liver and muscle) and triacylglycerols (in adipose tissue).

12.3.1.4 Diabetes Mellitus arises from defects in insulin production or action

Diabetes mellitus, caused by a deficiency in the secretion or action of insulin, is a relatively common disease. There are two major clinical classes of diabetes mellitus: type I diabetes, or insulin-dependent diabetes mellitus (IDDM), and type II diabetes, or non-insulin-dependent diabetes mellitus (NIDDM), also called insulin-resistant diabetes. In type I diabetes, the disease begins early in life and quickly becomes severe. This disease responds to insulin injection, because the metabolic defect stems from the pancreatic β-cells and a consequent inability to produce sufficient insulin. IDDM requires insulin therapy and careful, lifelong control of the balance between dietary intake and insulin dose. Characteristic symptoms of type I (and type II) diabetes are excessive thirst and frequent urination (polyuria), leading to the intake of large volumes of water (polydipsia) ("diabetes mellitus" means "excessive excretion of sweet urine"). These symptoms are due to the excretion of large amounts of glucose in the urine, a condition known as glucosuria. Type II diabetes is slow to develop (typically in older, obese individuals), and the symptoms are milder and often go unrecognized at first. This is really a group of diseases in which the regulatory activity of insulin is defective: insulin is produced, but some feature of the insulin-response system is defective. These individuals are insulin-resistant. Individuals with either type of diabetes are unable to take up glucose efficiently from the blood; recall that insulin triggers the movement of GLUT4 glucose transporters to the plasma membrane of muscle and adipose tissue. Another characteristic metabolic change in diabetes is excessive but incomplete oxidation of fatty acids in the liver. Insulin secretion reflects both the size of fat reserves (adiposity) and the current energy balance (blood glucose level). Insulin acts on insulin receptors in the hypothalamus to inhibit eating. Insulin also signals muscle, liver, and adipose tissues to increase catabolic reactions, including fat oxidation, which results in weight loss.

12.3.2 Glucagon

Glucagon, a peptide hormone synthesized and secreted from the α-cells of the islets of Langerhans of pancreas, raises blood glucose levels. Its effect is opposite that of insulin, which lowers blood glucose levels. The pancreas releases glucagon when blood sugar (glucose) levels fall too low. Glucagon causes the liver to convert stored glycogen into glucose, which is released into the bloodstream. High blood glucose levels stimulate the release of insulin. Insulin allows glucose to be taken up and used by insulin-dependent tissues. Thus, glucagon and insulin are part of a feedback system that keeps blood glucose levels at a stable level.

12.3.2.1 Regulation and function

Secretion of glucagon is stimulated by hypoglycemia, epinephrine, arginine, alanine, acetylcholine, and cholecystokinin. Secretion of glucagon is inhibited by somatostatin, insulin, increased free fatty acids and keto acids into the blood, and increased urea production. Glucose is stored in the liver in the form of glycogen, which is a starch-like polymer chain made up of glucose molecules. Liver cells (hepatocytes) have glucagon receptors. When glucagon binds to the glucagon receptors, the liver cells convert the glycogen polymer into individual glucose molecules, and release them into the bloodstream, in a process known as glycogenolysis. As these stores become depleted, glucagon then encourages the liver and kidney to synthesize additional glucose by gluconeogenesis. Glucagon turns off glycolysis in the liver, causing glycolytic intermediates to be shuttled to gluconeogenesis.

Glucagon is a signal for low blood glucose levels. It stimulates breakdown of glycogen, fat, and protein. It inhibits synthesis of glycogen, fat, and protein. Several hours after the intake of dietary carbohydrate, blood glucose levels fall slightly because of the ongoing oxidation of glucose by the brain and other tissues. Although its primary target is the liver, glucagon (like epinephrine) also affects adipose tissue, activating TAG breakdown by activating triacylglycerol lipase and liberates free fatty acids, which are exported to the liver and other tissues as fuel, sparing glucose for the brain. The net effect of glucagon is therefore to stimulate glucose synthesis and release by the liver and to mobilize fatty acids from adipose tissue, to be used instead of glucose as fuel for tissues other than the brain.

12.3.2.2 During fasting and starvation, metabolism shifts to provide fuel for the brain

The fuel reserves of a healthy adult human are of three types: glycogen stored in the liver and, in relatively small quantities, in muscles; large quantities of triacylglycerols in adipose tissues; and tissue proteins, which can be degraded when necessary to provide fuel. In the first few hours after a meal, the blood glucose level is diminished slightly, and tissues receive glucose released from liver glycogen. There is little or no synthesis of lipids. By 24 hours after a meal, blood glucose has fallen further, insulin secretion has slowed, and glucagon secretion has increased.

12.3.3 Thyroid Hormones

Thyroid hormones (T_4 and T_3) are tyrosine-based hormones produced by the follicular cells of the thyroid gland and are regulated by TSH made by the thyrotropes of the anterior pituitary gland, are primarily responsible for

regulation of metabolism. Iodine is necessary for the production of T_3 (triiodothyronine) and T_4 (thyroxine). A deficiency of iodine leads to decreased production of T_3 and T_4, enlarges the thyroid tissue and will cause the disease known as goitre. The thyronines act on nearly every cell in the body. They act to increase the basal metabolic rate, affect protein synthesis, help regulate long bone growth (synergy with growth hormone) and neural maturation, and increase the body's sensitivity to catecholamines (such as adrenaline). The thyroid hormones are essential to proper development and differentiation of all cells of the human body. These hormones also regulate protein, fat, and carbohydrate metabolism, affecting how human cells use energetic compounds. They also stimulate vitamin metabolism. Numerous physiological and pathological stimuli influence thyroid hormone synthesis. Thyroid hormone leads to heat generation in humans. However, the thyronamines function via some unknown mechanism to inhibit neuronal activity; this plays an important role in the hibernation cycles of mammals and the moulting behaviour of birds.

12.3.3.1 Iodine is essential for thyroid hormone synthesis

Iodide is actively absorbed from the bloodstream by a process called iodide trapping. In this process, sodium is cotransported with iodide from the basolateral side of the membrane into the cell and then concentrated in the thyroid follicles to about thirty times its concentration in the blood. Via a reaction with the enzyme thyroperoxidase, iodine is bound to tyrosine residues in the thyroglobulin molecules, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). Linking two moieties of DIT produces thyroxine. Combining one particle of MIT and one particle of DIT produces triiodothyronine. If there is a deficiency of dietary iodine, the thyroid will not be able to make thyroid hormone. The lack of thyroid hormone will lead to decreased negative feedback on the pituitary, leading to increased production of thyroid-stimulating hormone, which causes the thyroid to enlarge (the resulting medical condition is called endemic colloid goiter).

12.3.3.2 Thyroid hormones are transported by Thyroid-Binding Globulin

Thyroxinebinding globulin (TBG), a glycoprotein binds T4 and T3 and has the capacity to bind 20 µg/dL of plasma. Under normal circumstances, TBG binds – noncovalently – nearly all of the T4 and T3 in plasma, and it binds T4 with greater affinity than T3. The small, unbound (free) fraction is responsible for the biologic activity. Thus, in spite of the great difference in total amount, the free fraction of T3 approximates that of T4, and given that T3 is intrinsically more active than T4, most biologic activity is attributed to T3. TBG does not bind any other hormones.

12.3.3.3 Circulation and transport

Most of the thyroid hormone circulating in the blood is bound to transport proteins. Only a very small fraction of the circulating hormone is free (unbound) and biologically active, hence measuring concentrations of free thyroid hormones is of great diagnostic value.

When thyroid hormone is bound, it is not active, so the amount of free T_3/T_4 is what is important. For this reason, measuring total thyroxine in the blood can be misleading.

12.3.3.4 Related diseases

Both excess and deficiency of thyroxine can cause disorders.

- Hyperthyroidism (an example is Graves Disease) is the clinical syndrome caused by an excess of circulating free thyroxine, free triiodothyronine, or both. It is a common disorder that affects approximately 2% of women and 0.2% of men.

- Hypothyroidism (an example is Hashimoto's thyroiditis) is the case where there is a deficiency of thyroxine, triiodiothyronine, or both.

12.3.4 Parathyroid Hormone

Parathyroid hormone (PTH), parathormone or parathyrin, is secreted by the chief cells of the parathyroid glands. It acts to increase the concentration of calcium (Ca^{2+}) in the blood, whereas calcitonin (a hormone produced by the parafollicular cells of the thyroid gland) acts to decrease calcium concentration. PTH acts to increase the concentration of calcium in the blood by acting upon the parathyroid hormone 1 receptor (high levels in bone and kidney) and the parathyroid hormone 2 receptor (high levels in the central nervous system, pancreas, testis, and placenta). PTH was one of the first hormones to be shown to use the G-protein, adenylyl cyclase second messenger system. Parathyroid hormone regulates serum calcium through its effects (Table 12.1).

Table 12.1: Effect of parathyroid hormone in regulation of serum calcium.

Region	Effect
Bone	PTH enhances the release of calcium from the large reservoir contained in the bones. Bone resorption is the normal destruction of bone by osteoclasts, which are indirectly stimulated by PTH forming new osteoclasts, which ultimately enhances bone resorption.

MODULE

Biochemistry

Notes

Kidney	PTH enhances active reabsorption of calcium and magnesium from distal tubules of kidney. As bone is degraded, both calcium and phosphate are released. It also decreases the reabsorption of phosphate, with a net loss in plasma phosphate concentration. When the calcium:phosphate ratio increases, more calcium is free in the circulation.
Intestine	PTH enhances the absorption of calcium in the intestine by increasing the production of activated vitamin D. Vitamin D activation occurs in the kidney. PTH converts vitamin D to its active form (1,25-dihydroxy vitamin D). This activated form of vitamin D increases the absorption of calcium (as Ca^{2+} ions) by the intestine via calbindin.

12.3.4.1 Regulation of PTH secretion

Secretion of parathyroid hormone is controlled chiefly by serum $[Ca^{2+}]$ through negative feedback. Calcium-sensing receptors located on parathyroid cells are activated when $[Ca^{2+}]$ is low. Hypomagnesemia inhibits PTH secretion and also causes resistance to PTH, leading to a form of hypoparathyroidism that is reversible. Hypermagnesemia also results in inhibition of PTH secretion. Stimulators of PTH includes decreased serum $[Ca^{2+}]$, mild decreases in serum $[Mg^{2+}]$, and an increase in serum phosphate. Inhibitors include increased serum $[Ca^{2+}]$, severe decreases in serum $[Mg^{2+}]$, which also produces symptoms of hypoparathyroidism (such as hypocalcemia), and calcitriol.

12.3.4.2 Clinical significance

- Hyperparathyroidism, the presence in the blood of excessive amounts of parathyroid hormone, occurs in two very distinct sets of circumstances. Primary hyperparathyroidism is due to autonomous, abnormal hypersecretion of PTH in the parathyroid gland while secondary hyperparathyroidism is an appropriately high PTH level seen as a physiological response to hypocalcemia

- A low level of PTH in the blood is known as hypoparathyroidism and is most commonly due to damage to or removal of parathyroid glands during thyroid surgery.

- There are a number of rare but well-described genetic conditions affecting parathyroid hormone metabolism, including pseudohypoparathyroidism, familial hypocalciuric hypercalcaemia, and autosomal dominant hypercalciuric hypocalcaemia.

MODULE

Biochemistry

12.3.5 Growth hormone

Growth hormone (GH or HGH), also known as somatotropin or somatropin, is a peptide hormone that stimulates growth, cell reproduction and regeneration in humans. It is a type of mitogen which is specific only to certain kinds of cells. Growth hormone is a single-chain polypeptide that is synthesized, stored, and secreted by somatotropic cells within the lateral wings of the anterior pituitary gland. The anterior pituitary gland secretes hormones that tend to elevate the blood glucose and therefore antagonize the action of insulin. Growth hormone secretion is stimulated by hypoglycemia; it decreases glucose uptake in muscle. Some of this effect may not be direct, since it stimulates mobilization of free fatty acids from adipose tissue, which themselves inhibit glucose utilization. Growth hormone increases amino acid transport in all cells, and estrogens do this in the uterus. A deficiency of this hormone produces dwarfism, and an excess leads to gigantism.

Notes

12.3.5.1 Regulation of growth hormone secretion

Secretion of growth hormone (GH) in the pituitary is regulated by the neurosecretory nuclei of the hypothalamus. These cells release the peptides Growth hormone-releasing hormone (GHRH or somatocrinin) and Growth hormone-inhibiting hormone (GHIH or somatostatin) into the hypophyseal portal venous blood surrounding the pituitary. GH release in the pituitary is primarily determined by the balance of these two peptides, which in turn is affected by many physiological stimulators (e.g., exercise, nutrition, sleep) and inhibitors (e.g., free fatty acids) of GH secretion. A number of factors are known to affect GH secretion, such as age, sex, diet, exercise, stress, and other hormones.

12.3.5.2 Regulation

Stimulators of growth hormone (GH) secretion include peptide hormones, ghrelin, sex hormones, hypoglycemia, deep sleep, niacin, fasting, and vigorous exercise. Inhibitors of GH secretion include somatostatin, circulating concentrations of GH and IGF-1 (negative feedback on the pituitary and hypothalamus), hyperglycemia, glucocorticoids, and dihydrotestosterone.

12.3.5.3 Effects of growth hormone

Increased height during childhood is the most widely known effect of GH. In addition to increasing height in children and adolescents, growth hormone has many other effects on the body such as:

- Increases calcium retention, and strengthens and increases the mineralization of bone
- Increases muscle mass through sarcomere hypertrophy
- Promotes lipolysis
- Increases protein synthesis
- Stimulates the growth of all internal organs excluding the brain
- Plays a role in homeostasis
- Reduces liver uptake of glucose
- Promotes gluconeogenesis in the liver
- Contributes to the maintenance and function of pancreatic islets
- Stimulates the immune system

12.3.5.4 Clinical significance

12.3.5.4.1 Excess

The most common disease of GH excess is a pituitary tumor composed of somatotroph cells of the anterior pituitary. These somatotroph adenomas are benign and grow slowly, gradually producing more and more GH. For years, the principal clinical problems are those of GH excess. Eventually, the adenoma may become large enough to cause headaches, impair vision by pressure on the optic nerves, or cause deficiency of other pituitary hormones by displacement.

Prolonged GH excess thickens the bones of the jaw, fingers and toes. Resulting heaviness of the jaw and increased size of digits is referred to as acromegaly. Accompanying problems can include sweating, pressure on nerves (e.g., carpal tunnel syndrome), muscle weakness, excess sex hormone-binding globulin (SHBG), insulin resistance or even a rare form of type 2 diabetes, and reduced sexual function.

GH-secreting tumors are typically recognized in the fifth decade of life. It is extremely rare for such a tumor to occur in childhood, but, when it does, the excessive GH can cause excessive growth, traditionally referred to as pituitary gigantism.

12.3.5.4.2 Deficiency

The effects of growth hormone deficiency vary depending on the age at which they occur. In children, growth failure and short stature are the major manifestations of GH deficiency, with common causes including genetic conditions and congenital malformations. It can also cause delayed sexual

Notes

maturity. In adults, deficiency is rare, with the most common cause a pituitary adenoma, and others including a continuation of a childhood problem, other structural lesions or trauma, and very rarely idiopathic GHD. Adults with GHD "tend to have a relative increase in fat mass and a relative decrease in muscle mass and, in many instances, decreased energy and quality of life".

INTEXT QUESTIONS 12.1

I. Choose the best answer

1. The hormone that is released into the bloodstream having the receptor cells at distant from the source is

    (a) Exocrine   (b) Paracrine

    (c) Endocrine   (d) None

2. This hormone is a chain of amino acids

    (a) Thyroxine   (b) Insulin

    (c) Vitamin D_3 (d) Epinephrin

3. Glucose transporter to the plasma membrane of muscle and adipose tissue is

    (a) GLUT1   (b) GLUT2

    (c) GLUT3   (d) GLUT4

4. The storage form of lipid in adipose tissue is

    (a) Triacylglycerol   (b) Free fatty acid

    (c) Low density lipoprotein (d) Phospholipid

5. Excess of somatotropin leads to

    (a) Dwarfism   (b) Gigantism

    (c) Goitre   (d) Diabetes Mellitus

II. Fill in the blanks

6. Hormones communicate with intracellular metabolic processes through intermediary molecules called ....

7. .... transporters carry glucose into the b-cells of pancreas

8. .... stimulates breakdown of glycogen, fat, and protein.

9. Thyroid hormones are transported by ....

10. Vitamin D3 increases the absorption of calcium (as Ca^{2+} ions) by the intestine via ....

III. Match the following

11.	Frequent urination	(a)	Insulin
12.	Endocrine hormone	(b)	Glucokinase
13.	Second messenger	(c)	Hypothyroidism
14.	Hashimoto's thyroiditis	(d)	cAMP
15.	Hexokinase IV	(e)	Polyuria

WHAT YOU HAVE LEARNT

- A hormone acts as a messenger by transmitting signal from one cell to another.

- Hormones are derived from steroids, amino acids and polypeptides.

- Insulin secreted from β-cells of pancreas controls the uptake of glucose by liver and muscle cells and also the storage of glucose in the form of glycogen.

- Diabetes Mellitus results from the lack of insulin secretion by the pancreas.

- Glucagon, a peptide hormone synthesized and secreted from the α-cells of pancreas, raises blood glucose levels.

- Secretion of glucagon is stimulated by hypoglycemia, epinephrine, arginine, alanine, acetylcholine, and cholecystokinin. Inhibited by somatostatin, insulin, increased free fatty acids and keto acids into the blood, and increased urea production.

- Thyroid hormones (T_4 and T_3) are tyrosine-based hormones produced by the follicular cells of the thyroid gland.

- The thyroid hormones are essential to proper development and differentiation of all cells of the human body. These hormones also regulate protein, fat, and carbohydrate metabolism.

- The free thyroid hormones in the circulation are the active form, and is of great diagnostic value.

- The diseases associated with the excess and deficiency of thyroid hormones are Graves disease and Hashimoto's thyroiditis, respectively.

- Parathyroid hormone (PTH), parathormone or parathyrin, is secreted by the chief cells of the parathyroid glands.

- PTH acts to increase the concentration of calcium (Ca^{2+}) in the blood.

● Growth hormone (GH or HGH), also known as somatotropin or somatropin, is secreted from anterior pituitary gland, is a peptide hormone that stimulates growth, cell reproduction and regeneration in humans.

● A deficiency of this hormone produces dwarfism, and an excess leads to gigantism.

Notes

TERMINAL QUESTIONS

1. Classify Hormones

2. Write short notes on

   Insulin

   Thyroid Hormone

   Growth Hormone

ANSWERS TO INTEXT QUESTIONS

I.   1. (c)   2. (b)   3. (d)   4. (a)   5. (b)

II. 6. second messengers

     7. GLUT2

     8. Glucagon

     9. Thyroxine binding globulin

     10. calbindin,

III. 11. (e)   12. (a)   13. (d)   14. (c)   15. (b)