GENERAL FEATURES OF HORMONAL COORDINATION

Jorma Paranko
Institute of Biomedicine, Department of Anatomy, University of Turku, Finland

Osmo Hänninen
Department of Physiology, University of Kuopio, Finland

Keywords: amplification, feedback, homeodynamics, hypothalamus, hypophysis, protein and peptide hormones, amino acid and fatty acid derivatives, steroids, receptors, plasma membrane, nucleus, endocrine disruptors

Contents

Summary

Hormones are endocrine regulators secreted into circulation from specific glands or cells within non-endocrine tissues. In blood, hormones are stabilized and inactivated by carrier proteins. Hormones have effects only in the targets where the cells have specific cell membrane or intracellular receptors. Structurally hormones can be classified into protein and peptide hormones, amino acid and fatty acid derivatives, and cholesterol-derived steroids. Steroid hormones have intracellular receptors that act as transcription

factors that directly associate with the hormone responsive elements—specific sequences in the target gene. Transcriptional activity is modified by nuclear cofactors. Cell surface receptors are transmembrane proteins that activate catalytic second messenger systems that cause powerful amplification of the ligand-gated signalling. Depending on the ligand and receptor type, cells can utilize cyclic AMP (cAMP), cyclic GMP (cGMP), inositole phosphate three (IP_3), diacylglycerol (DAG), or SH2-associated second messenger systems. Important physiological functions are always controlled by several hormones and neuronal pathways. The complexity of hormonal regulation is further augmented by different hormone and receptor isoforms and variations in the signalling pathways. In the control of body homeostasis, feedback mechanisms, receptor desensitization, and proper hormone metabolism are key events. Because in normal cells hormonal induction is a transient event, continuous activation of the signalling pathway(s) results in inappropriate hormone action, possibly in malignant growth. Mutations in hormone receptors can explain some endocrine disorders. Several foreign compounds, like man-made chemicals can disturb the endocrine system by mimicking the action of natural hormones and compete for receptor binding. Some of these endocrine disruptors can interfere with hormone biosynthesis and metabolism and alter the levels of natural hormones with severe health effects. An intriguing question of the evolutionary origin of hormones is not yet resolved. Hormones are ubiquitous in nature and "the first hormone" could be a metabolic side product, for instance.

1. Introduction

Hormones are originally denoted as chemicals produced by cells of specific glands and distributed through the body via circulation. Some hormones, indeed, are produced in specialized glands, but often the synthesizing cells are mixed with cells having other functions like the endocrine cells in the gastrointestinal mucosa. Some hormones, like testosterone and insulin-like growth factor 1 (IGF-1), act not only as far-reaching endocrine regulators but also as paracrine and autocrine factors acting on neighbouring cells or on the secreting cell itself. Neurohormones, like epinephrine (adrenaline), are produced by neurons and may act both as a hormone and a neurotransmitter, the latter acting locally in synaptic cleft. A number of cell gowth-promoting factors act only in paracrine or autocrine fashion and, therefore, are not considered as hormones even though they fulfil one major criterion of a hormone. Namely, the Greek word "hormao" means "a substance that excites". The idea of internal secretion was introduced by Theophile De Bordeu (1855). The first substance to be called a hormone, secretin, was detected in studies of gastrointestinal control by Starling and Bayliss (1902), and adrenaline was the first isolated hormone as reported by Oliver and Schafer (1895). Insulin, the first human hormone to be produced commercially, was invented by Banting, MacLeod and Best (1926), and the second one, human growth hormone in 1956 by Li and Papkoff. The term "oestrin", for instance, was introduced to the ovarian hormone oestrogen by Parkers and Bellerby in 1926.

The number of molecules recognized as hormones is still increasing and at present over 300 different hormones or hormone-like compounds have been identified (see *Endocrinology*). Practically every tissue seems to synthesize hormones. For instance, adipose tissue which has previously been considered to be hormonally inactive, synthesises several kinds of hormones, including leptin. In general, one hormone has a

specific number of target cell types. Only seldom, like in the case of thyroxine, may the hormone regulate all cells of the body. Several hormones show clear oscillations, which are related to daily activity, like melatonin, but some are secreted to meet monthly cycles like estrogens and progesteron in human females. Some hormones are regulated by annual cycles, which explain the reproductive cycles seen in animals and plants (see *Endocrinology* and *Sleep*) (Hibernation-specific protein (HP) is a candidate brain hormone involved in the circannual adaptation of bears and rodents to harsh winter conditions.).

As hormones have great impact on cell metabolism, growth, differentiation, and survival, the altered serum hormone level many be a reflection of pathophysiologic change. Defective or excess hormone secretion or resistance of the target cells to respond to the hormone may be manifested in endocrine diseases, as has been described in different forms of diabetes.

Together with neuronal system, hormones control the body homeostasis (or better homeodynamics, as all body functions oscillate), responses to external stimuli, digestion, metabolism, growth, reproduction, development, differentiation, and mood. The release of a hormone from the site of synthesis and storage is regulated by other hormones or by neural messages, or by the activity of the synthesizing cell. Commonly, important physiological functions are not controlled by a single hormone but by a number of counteracting hormones and regulatory pathways. One example is the regulation of glucose metabolism by insulin, glucagon, epinephrin, and cortisol. An example of dual neural and hormonal control of hormone metabolism is the recently introduced idea of control of testicular androgen metabolism. In response to stress-related events, neuronal release of catecholamines in the brain has been shown to dampen the steroidogenic ability of Leydig cells in the testes more rapidly than the traditional, but a relatively slow, gonadotropin-dependent regulation.

Chemically, hormones can be classified into peptides and proteins, steroids, amino acid and fatty acid derivatives (Table 1). As powerful long-distance endocrine regulators, hormones have a biological effect already at extremely low nano- and picomolar concentrations and, therefore, their levels in blood are very low and lifespan is limited. The half-life of circulating hormones varies and is positively affected by stabilizing plasma proteins. For unbound peptide hormones, for instance, the half-life is only a few minutes whereas for thyroid hormones it is few days.

Molecular structure	**Number of amino acids, Aa**	**Examples**
Protein	> 100 Aa	Growth hormone, prolactin, leptin
Glycopotein	~ 100 Aa	Luteinizing hormone, thyrotpropin
Peptide	< 100 Aa	Releasing hormones, somatostatin
Amino acid derivative	1 Aa	Serotonin, epinephrin
Fatty acid derivative		Prostaglandins
Cholesterol derivative		Estrogens, androgens, vitamin D
Others		Nitric oxide

Table 1. Classification of hormones on a structural basis. Most hormones are water-soluble proteins, peptides, and amino acid derivatives. Some are fatty acid or cholesterol

derivatives. Only the latter have intracellular receptors. Some compounds, like nitric oxide, can be metabolic by-products. Some examples from different hormone classes and relative numbers of amino acids (Aa) are indicated.

Hormones and neurohormones are ligands that communicate only with a certain type of cell(s) equipped with a specific plasma membrane or intracellular receptors. Like most signal molecules, the majority of hormones are water-soluble and cannot cross the lipid bilayer of the cell membrane. Therefore, for amino-acid and peptide-derived hormones, specific cell membrane receptors have evolved for transmembrane signalling. Binding of the ligand to the receptor induces a cascade of cytoplasmic signal-transduction pathways, powerful enzymatic relay systems leading to the specific response(s) of the cell. Receptors of lipid-soluble steroid and thyroid hormones, retinoic acid and vitamin D, which can freely diffuse into cells are located in the cytoplasm or in the nucleus. Intracellular receptors of lipid-soluble hormones act as transcription factors and directly regulate gene expression and protein synthesis in the receptive cell. After binding to the receptor, most of the hormones are rapidly metabolized, receptors possibly recycled and later degraded.

2. Chemical nature of hormones

2.1. Peptide and protein hormones

Most hormones are proteins, peptides or amino acid derivatives (Table 1). Biologically active protein and peptide hormones are produced from inactive prohormone precursors by proteolytic cleavage. Before maturation, the signal peptide is removed and the prohormone is cleaved in the endoplasmic reticulum at a specific site or sites by endopeptidases. Cell-specific pattern of biosynthetic processing of hormones may also involve post-transcriptional alternative pathways of mRNA splicing. In order to get biological activity, protein and peptide hormones undergo post-translational modifications, like amidication, sulphation, glycosylation, N-terminal acetylation or phosphorylation. For instance, gastric cholecystokinin peptide hormone occurs at least in five different biologically active sizes as a result of post-translational modifications of preprocholecystokinin.

Water-soluble hormones are stored in cytosolic secretory vesicles or granules and released by exocytosis in response to a proper signal. The release of thyroxine from the stored thyroglobulin in thyroid gland is a good example and another one is the release of insulin from the pancreatic β-cells. In the latter, both insulin and the enzymatically removed biologically inactive C-peptide of the proinsulin are found in blood. On the other hand, a tetrapeptide amide fragment of gastrin hormone is still a powerful stimulator of hydrochloric acid release in the gastric mucosa.

Protein hormones are large (>100 amino acids, Aa) molecules that, for instance, include growth hormone (GH, 191 amino acids), insulin and prolactin (PRL, 197 Aa), leptin (167 Aa), inhibin A (134 Aa), and inhibin B (115-116 Aa). Anti-Müllerian hormone (AMH) is a glycoprotein homodimer structurally related to inhibin and activin. Chorionic gonadotropin (CG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyrotropin (TSH) are glycoproteins composed of two proteins at a range of

96-147 amino acids. Also erythropoietin (EPO), a protein homone of 166 amino acids in length, is a glycoprotein.

Small peptide hormones that are composed of 20 or less of amino acids include thyrotropin-releasing hormone (TRH, 3 Aa), angiotensin II (8 Aa), oxytocin and vasopressin (antidiuretic hormone, ADH, 9 Aa), gonadotropin-releasing hormone (GnRH, 10 Aa), and gastrin (17 Aa). Hypothalamic lipotropin or lipotropic hormone β (LPH, 9 Aa recidues) that promotes lipolysis, is a precursor of endorphins. Melanocyte-stimulating hormones (MSH) alpha, beta and gamma are composed of 13, 18, and 12 amino acids, respectively. There are a number of peptide hormones composed of more than 20 amino acids. Somatostatin (SIF or GIF) has two active forms produced by alternative cleavage of the preproprotein: one of 14 amino acids, the other of 28 amino acids similar to atrial natriuretic peptide (ANP). Corticotropin (ACTH, 39 Aa) and corticotrophin-releasing hormone (CRH; 41 Aa), and growth hormone-releasing hormone (GRH, 44 Aa) are medium-sized hypothalamic and pituitary peptide hormones. Motilin, secretin, ghrelin and vasoactive intestinal peptide (VIP), glucagon, calcitonin, and partyhroid hormone (PTH) are 22, 27, 28, 29, 32, and 84 amino acid long peptide hormones, respectively. Insulin is a disulfide-bonded dipeptide of 21 and 30 amino acids. Insulin-like growth factor 1 (IGF-1; 70 Aa) is a large peptide hormone that mediates several effects of growth hormone.

2.2. Amino acid and fatty acid derivatives

Most serotonin (5-HT), a well known neurotransmitter in the central nervous system, is produced from the amino acid tryptophan by enterochromaffin cells of the gastrointestinal tract. Peripherally, serotonin acts both as a gastrointestinal regulating agent (secretory and peristaltic reflexes) and a modulator of blood vessel tone. In the pineal gland, serotonin is acetylated and then methylated to yield melatonin hormone. This seems to happen also in other tissues as a major part of melatonin synthesis—according to the newest information—takes place in peripheral tissues.

Epinephrine (adrenalin) and norepinephrine (noradrenalin) are tyrosine-derived hormones produced by chromaffin cells of the adrenal medulla. Also thyroxine is made of tyrosine.

Hormones derived from polyunsaturated 20-carbon fatty acids are called eicosanoids (Greek, eicosa- twenty) and include prostaglandins, prostacyclins, leukotrienes and thromboxanes involved in immunity, inflammation, and signalling in central nervous system.

Gaseous nitrix oxide (NO) is an amino acid derivative that acts as a powerful dilatator of vessels.

2.3. Cholestrol-derived hormones

Steroids are small molecules, which comprise an important group of hormone lipids of placental, adrenal and gonadal sex steroids, adrenal glucocorticoids (cortisol) and mineralocortiocids (aldosterone). They, like vitamin D3, are all derivatives of 27-carbon

cholesterol molecules. It is impressive how small changes in the cholesterol backbone specify the function of so many different steroid hormones. Cholesterol synthesis occurs in smooth endoplasmic reticulum (SER) and the first molecular modification of steroid backbone into pregnenolone occurs in mitochondria. As lipid-soluble products, steroid hormones cannot be stored in membrane vesicles and mature steroids diffuse out of membranes. For the effects of steroid hormones see *Endocrinology*.

3. Hormone transport in blood

Hormones are transported in blood to different tissues where they gain a short-lived biological activity. In general, 90% or more of hormones exist in an inactivated circulating form. Due to their water solubility, protein, peptide and amino-acid derived hormones do not necessarily need any transporters but need plasma carrier proteins to protect them against hydrolytic enzymes present in the plasma. For amino-acid derivatives, carrier proteins are also needed to protect them against filtration in the kidney glomerulus. Binding to carrier protein neutralizes the hormone and increases its half life for minutes, hours, or even days. Binding also directly regulates the amount of biologically active hormones. Thus, an important function of blood is to serve as a pool for rapid usage of the hormone.

Cholesterol-derived lipoidal hormones require carriers to gain water solubility. One of the glycoprotein carriers is sex hormone-binding globulin (SHBG), which regulates the amount of unbound androgens and estrogens, in particular. Hormones can specifically up- or down-regulate the synthesis of their binding proteins. Half lives of lipoidal hormones in blood are usually longer than those of water-soluble hormones.

4. Hormones as universal and specific regulators

Some hormones are more or less universally active in the whole organism. For instance, sex steroids control a range of reproductive functions, but they also affect body growth and development, muscle, bone and adipose tissues, and central nervous system.

Thyroxin has even wider and more universal effects, because it has receptors in every cell, where it regulates general metabolism. The effects of thyroxin are also a good example of a dose-dependent stimulation of cellular activity. The lack of thyroxin slows down metabolism while high levels increase metabolic rate. Also growth hormone has universal effects on growth in the body but many of its actions are mediated by IGF-1 that is mainly synthesized in the liver.

Some hormones, like hypothalamic liberins (releasing factors) that regulate the release of trophic peptide hormones from the adenohypophysis have quite a limited action, but they have an important role in inducing cascades of down-stream feed-forward events (Figure 5). Adrenocorticotropin (ACTH), for instance, has already wider effects, and it stimulates the synthesis of corticosteroids in the adrenal cortex. Of the final products cortisol, for instance, broadens the physiological effects into the regulation of glucose synthesis from amino acids and lipids, repression of immune reactions, and stimulation of fetal lung maturation. As an opposite example, prostaglandins are formed from fatty acids in many tissues, but most of their effects are greatest in a rather limited area. Also

nitric oxide, a short-lived (with a half-life of a few seconds), highly reactive molecule known also as the endothelium-derived relaxing factor (EDRF), behaves in a similar limited fashion best described in the control of capillary smooth muscle tonus.

Sex steroid hormones represent examples from the regulatory and growth-promoting factors exhibiting sex-dependent mode of actions. Their levels are quite different in human females and males, although both sexes have low levels of the hormones high in the other sex. Synthesis of sex steroids is under the control of central nervous system, which becomes sexually differentiated during the late fetal and infantile period. In sexually mature women, the levels of sex steroid hormones oscillate remarkably during reproductive oestrus cycle. As for sex steroids, relative amounts of the hormones in circulation are more crucial for the control of gender-specific homeostasis than the expression pattern of the receptors. Interestingly, male and female tissues express receptors both for estrogens and androgens and their cellular functions are sensitive to altered hormone levels.

5. Hormone receptors

Hormones have effects only if they find the target tissue where they can bind to specific receptor proteins (Figure 1), which elicit the cellular response(s). Only the target cells have proper receptors; others have none or significantly fewer. The number of receptors correlates with the hormone-responsiveness of the cell. Because the level of hormone is perhaps millions or even billion times lower than that of other molecules in blood circulation, receptors have to have very high specificity to and affinity for the ligand. After binding to the receptor, the cell becomes activated, hormone metabolized, and the receptor is recycled or metabolized.

Receptor proteins are synthesized in the endoplasmic reticulum and are either transferred via the Golgi complex to the plasma membrane or nucleus, or stored in the cytoplasm. Water soluble hormones have their receptors in the plasma membrane. Steroid hormone receptors mainly exist in the cytoplasm where they are bound to heat shock proteins until ligand binding.

A minority of the known nuclear receptors are directly transported to and retained in the nucleus. They are called Type II nuclear receptors. Among those, retinoid X receptor (RXR) is one of the best characterized but it may also exist in the cytoplasmic Type I pool. The endogenous ligand for RXR is 9-cis retinoic acid (RA), which plays an important role in many fundamental biological processes such as reproduction, cellular differentiation, bone development, hematopoesis and pattern formation during embryogenesis.

5.1. Cell surface receptors

There are three types of plasma membrane hormone receptor proteins and all of them have three domains (Figure 1). The extracellular domain recognizes and binds the ligand. The next one is the hydrophobic transmembrane domain that anchors the receptor in the plasma membrane. The intracellular or cytoplasmic catalytic domain is the effector that interacts with the second messenger system. Signalling into the nucleus

or cytoplasmic components is mediated by a cascade of enzymatic pathways that result in the powerful actions of the hormone. In the process, the hormone is called the first messenger and the intracellular amplification system is generated by the second messengers, which mediate the real effects (Figure1).

-
-
-

Bibliography

Gardner D.G. and Shoback D. (eds.) (2007). *Greenspan's Basic & Clinical Endocrinology*, 8th edition, 960 pp. Boston, Massachusetts, USA: The McGraw-Hill Companies, Inc. [This includes the description of hormone actions, regulation of hormone responsiveness, and cell signalling].

Huether S.E. and McCance K.L., (eds.) (2000). *Understanding Pathophysiology*, 2nd ed., 1195 pp. Mosby St. Louis, MO, USA. [Valuable book which covers both key points of physiology and which more important the pathophysiology of the human diseases, endocrine effects included].

Kavlock R.J., Daston G.P., DrRosa C., Fenner-Chrisp P., Gray L.E., Kaattari S., Lucier G., Luster M., Mac M.J., Maczka C., Miller R., Moore J., Rolland R., Scott G., Sheehan D.M., Sinks T. and Tilson H.A. (1996). Research needs for the risk assessment of health and environmental effects of endocrine disruptors: A report of the US EPA-sponsored workshop. *Environmental Health Perspectives* 104 (Supplement 4) 715-740. [A good overview of most studies that have been published and recommendations for future research activities].

Metzler M. (ed.) (2001). *Endocrine Disruptors: Pt. 1 (The Handbook of Environmental Chemistry)*, 223 pp. Springer-Verlag Berlin and Heidelberg GmbH & Co. K. [This includes basic chapters on the mode of action of endocrine active chemicals and on the etiology of the associated diseases].

Novac N. and Heinzel T. (2004). Nuclear receptors: overview and classification. *Current Drug Targets. Inflammation and Allergy* 3(4):335-346. [Gives a general outline of nuclear receptor functions].

Porterfield S. and White B. (eds.) (2007). *Endocrine Physiology*, 3rd Edition, 344 pp. Mosby Physiology Monograph Series, St. Louis, Missouri, USA [Explains the fundamentals of endocrine physiology in a clear and concise manner. It provides a basic understanding of how the endocrine system functions in health and disease].

Russell D. (ed.) (2003). *Nuclear Receptors*, Volume 364 (Methods in Enzymology), 545 pp. Academic Press [Analysis of the function and structure of nuclear receptor ligands and receptors].

Vander A.J., Sherman D. and Luciano D. (2000). *Human Physiology: The Mechanisms of the Body Function*, 8th ed., 864 pp. McGraw-Hill Education, Boston, Massachusetts, USA. [Describes fundamental principles and facts of human physiology and offers accurate explanations of mechanisms].

Biographical Sketches

Dr. Jorma Paranko was born in Hauho, Finland, in 1951. He has a PhD (1986) in animal physiology from the University of Turku and has served as a researcher and teacher at the University of Turku. He worked for two years in Prof. Werner Franke`s Laboratory at German Cancer Research Center, Heidelberg, Germany. His research interests are in reproductive physiology, endocrine disruption and developmental biology. He is currently acting as a senior lecturer in Medical Biology at the Department of Anatomy in the University of Turku, Finland.

Dr. Osmo Otto Päiviö Hänninen, D.M.S., Ph.D., Professor of Physiology and Chairman of the Department of Physiology, University of Kuopio, Finland, was born in 1939 in Lahti, Finland. He studied at the University of Helsinki and the University of Turku, Finland, where he received his Master of Sciences (Biochemistry) in 1962, Licentiate of Medicine (M.D.) in 1964, Doctor of Medical Sciences (D.M.S.) in 1966, and passed his dissertation in biochemistry for his Ph.D. in 1968. He has also studied genetics. He has been a specialist in sports medicine since 1986. He served as the Research Assistant of Professor K. Hartiala, 1962–1964; Assistant of Physiology, 1964–1965; Laborator of Physiology, 1966–1967; Docent of Physiology, from 1967, and Associate Professor of Biochemistry, 1969–1971, at the University of Turku. He was Acting Professor in the Planning Office, 1971–1972, and from 1972, Professor of Physiology and Chairman of the Department of Physiology, University of Kuopio. He served as Vice-President of the University of Kuopio, 1972–1979; and as President of the University from 1981 to 1984.

Furthermore, he served as Visiting Professor of Physiology at Shanghai Medical University, China, 1991–1992, and at Sun Yat Sen Medical University, Guangzhou, China, 1998–1999; as Foreign Member of the Russian Academy of Natural Sciences, from 1994; and as Secretary General, International Council for Laboratory Animal Science, 1988–1995. He was the President of Societas Physiologica Finlandiae, 1990–1999, and has been President of the International Society for Pathophysiology and a Member of the Executive Committee since 1994, and the Treasurer of the International Union of Biological Sciences 1997-2003.

His special interests in research are: biotransformation and adaptation to chemical loading, biomonitoring of toxicants, comparative biochemical toxicology, muscle metabolism and function, and ergonomics.
He has contributed more than 300 papers in refereed journals and 88 in proceedings, and written 61 reviews, and 36 books or book chapters. He serves on the editorial board of four international journals and is at present the European Journal Editor of Pathophysiology. Of his post-graduate students (32 in biotransformation, 28 in muscle metabolism and physiology, and five others), some twenty serve or have served as professors in Australia, China, Finland, Greece, Russia, Sweden, and USA.