The Physiology of the Endocrine System

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By

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This tutorial is an augmentation and extension of advanced course of lections on the physiology of the endocrine system that the author delivers to students of the Department of Human and Animal Physiology of the Biological Faculty and of the Faculty of Fundamental Medicine at Lomonosov Moscow State University. The book presents the modern concepts of hormonal regulation in a brief, accessible way, with plenty of illustrative and reference material. In addition to theoretical information, the book also provides a large volume of supplementary data that illustrate the sources and types of the secretion of signalling compounds; the peculiarities of their structure; transport and reception; and the functions of hormones and other signalling compounds. A distinctive feature of this book is a visibility of presentation of the knowledge. Pathophysiological examples and cases from clinical practice make the material interesting for a wide range of readers.

TABLE OF CONTENTS

PART III. SPECIAL ENDOCRINOLOGY

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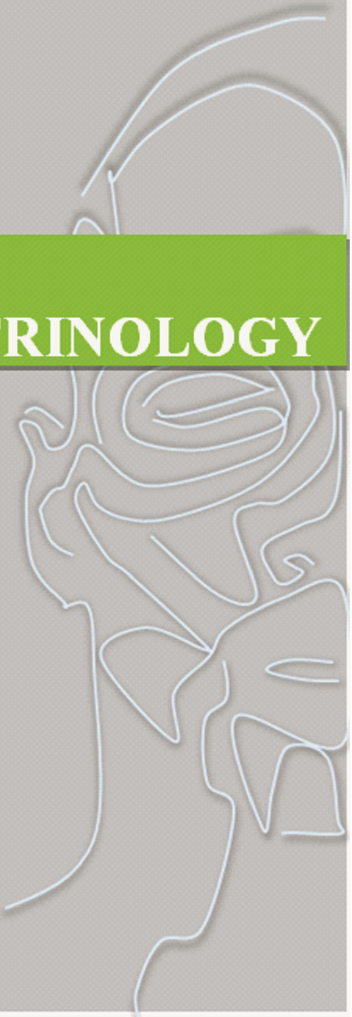
I BASIC ENDOCRINOLOGY



I

CHAPTER ONE

SYSTEMS OF INTERCELLULAR COMMUNICATION

There are two main levels of control of body functions:

- control at the cellular level
- intercellular control (coordination of the functions of various systems and organs of the whole organism)

In each case, the control system can be general (non-specialized) or specialized. In non-specialized control systems, transduction of information is a secondary function of chemical substances, whereas their primary function is to provide the body with energy and structural material. In specialized systems, the primary function of chemicals is the transduction of information. Therefore, these substances are called signalling compounds. Intracellular processing of the information is carried out by low molecular weight (secondary) messengers and high-molecular weight (protein-peptide) messengers of the signalling compounds.

There are three main systems of intercellular transduction of information: the nervous, endocrine, and immune systems, which are now often combined in the neuroendocrine-immune system. Each of them controls body functions acting distantly, but they do this in different ways involving local control mechanisms. Depending on the distance of signalling substance action, two types of control can be carried out: local (regional) and systemic control (Fig. I-1-1 and I-1-2).

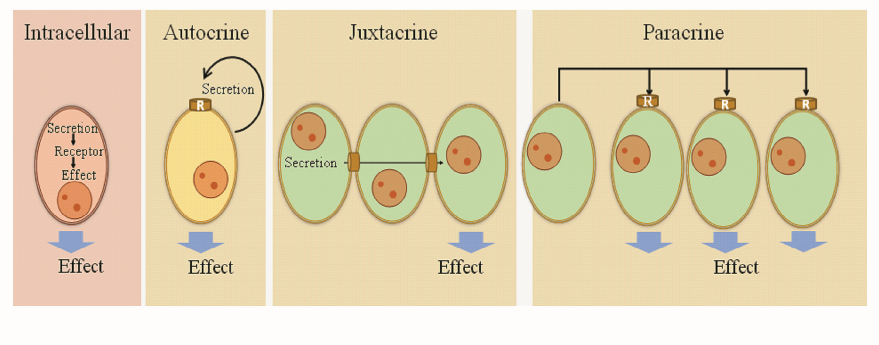


Fig. I-1-1. Types of local control

Local control includes the following mechanisms of signalling:

- Intracellular
- Autocrine
- Juxtacrine
- Paracrine

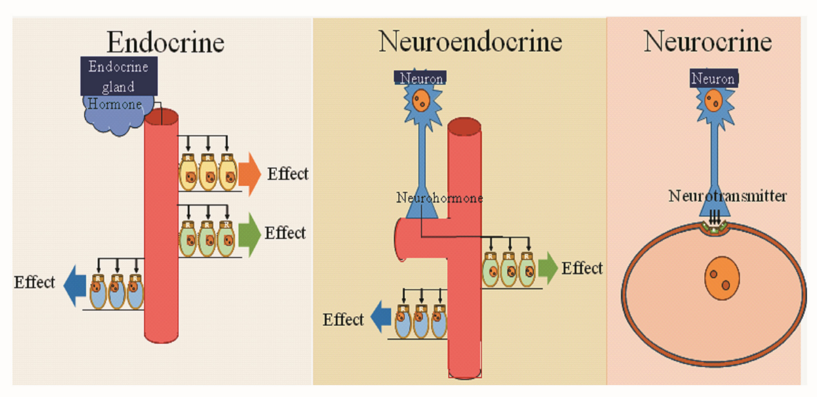


Fig. I-1-2. Types of systemic control

The systemic control includes the following mechanisms:

- Endocrine
- Neurocrine
- Neuroendocrine

Intracellular control

A signalling compound is produced in the effector cell, where it binds to its receptor and causes specific changes. Most commonly, this occurs within the endocrine cells. This is the least common type of local control.

Regional control

Autocrine control

Autocrine control also takes part in the self-regulation of the cell, but it is accompanied by the secretion of signalling molecules. After the release, the signalling molecule binds to a receptor on the same secretory cell and induces the alterations in its activity.

Juxtacrine control

A signalling compound is not secreted, but is transported through the pores of gap junctions—thus reaching the neighboring cells and affecting those cells.

Paracrine control

A signalling compound is released by the cells of a certain organ or tissue and affects the adjacent cells of the same organ. This is the most common type of local control. Signalling compounds with a predominance of paracrine effects are often called *paracrine factors* or *histohormones*. The transduction of signals by the neurotransmitters is one of the examples of specialized paracrine signalling.

Endocrine (hormonal) control

Hormones are secreted by the endocrine gland, endocrine or effector cell and enter the bloodstream, acting on all the body structures possessing the appropriate receptor. The effects of a hormone depend on the types of the receptor and on the responsive tissue.

Neuroendocrine control

A neurohormone is secreted by axon terminals and enters the bloodstream through the capillary plexus. Further events are similar to endocrine type of regulation.

Neurocrine control

The nervous system can be considered as being a system with a paracrine way of regulation, because the neurotransmitters act within a restricted spatial range on the nearby elements through specialized receptors. Distant action is achieved by the length of the axon and the amount of synaptic switches.

Chapter Two

Hormones and Hormone-Producing Cells

Hormones

The diversity of signalling functions of hormones is achieved by a combination of distant and local effects (Fig. I-2-1). However, the range of effects at the systemic and local levels may vary considerably (Fig. I-2-2). It is worth noting that the signalling substance is considered as being a hormone if it demonstrates not only paracrine effects, but also pronounced systemic effects.

Systemic effects are used to control the vital processes in the organism. Hormones regulate the processes of growth and development, sexual differentiation, reproduction, metabolism; they are involved in the non-specific adaptation and mutual regulation of the hormonal network. Systemic effects of hormones are divided as follows:

- irreversible programming (determining) effects
- reversible regulatory effects

A chemical substance usually demonstrates programming effects if it exerts a primary influence on gene expression within limited critical periods of ontogenesis (often during the embryonic and neonatal periods). Furthermore, irreversibly altered expression of these genes changes the phenotype of the cell, which then is maintained in its progenies, even in the absence of hormone. If the expression of only a few genes is affected, the activity of metabolic systems is irreversibly changed in the cell, but its phenotype remains the same.

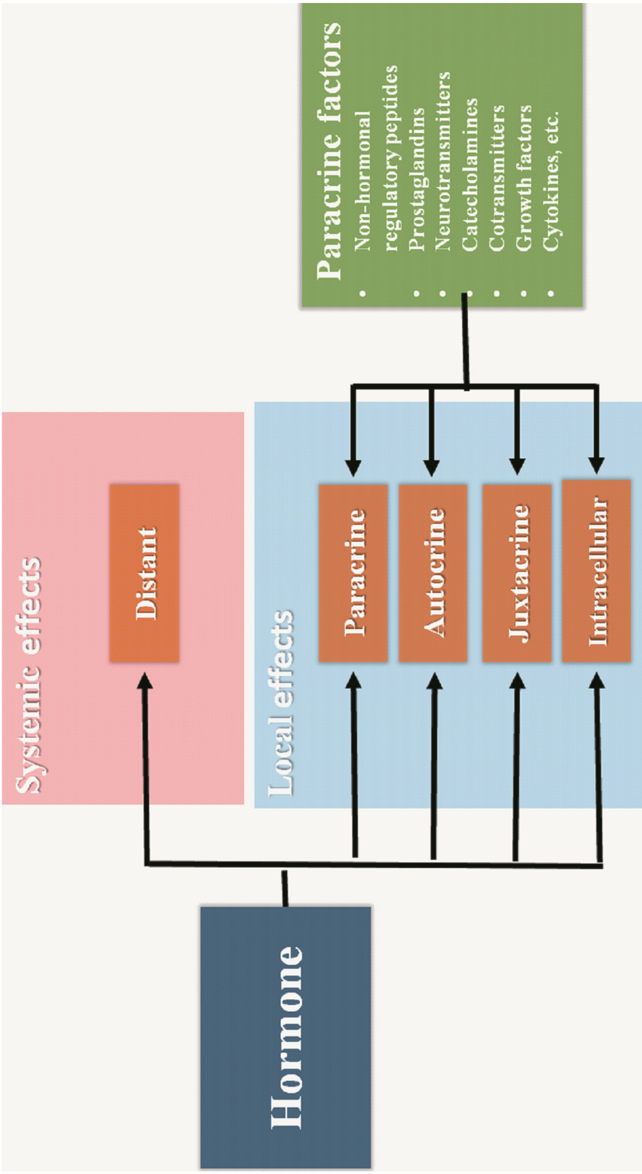


Fig. I-2-1. Distant action of hormones

The paracrine action of hormones is intended to integrate the input signals in the tissue, to coordinate its integrative response to the external signal, and to reinforce a hormonal effect. Many local effects of hormones are similar to the effects of paracrine factors:

- Maintenance of the activity of secretory tissue
- Regulation of pro- and antiproliferative activity of cells
- Regulation of angiogenesis
- Regulation of inflammatory responses

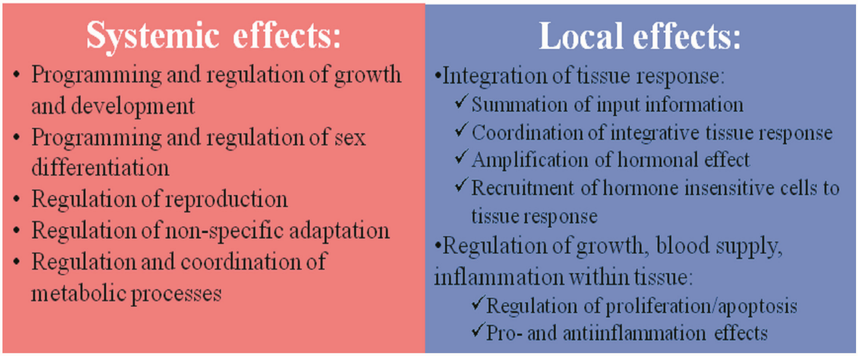


Fig. I-2-2. Differences between systemic and local effects of hormones

Hormone-producing cells

Hormones can be secreted by the cells with different specialization levels (Fig. I-2-3):

- Endocrine cells
- Cells with mixed functions
- Effector cells

Each endocrine gland usually secretes several types of hormones (see Appendix A). It is also important to note that hormones with the same structure as the hormones produced by the endocrine glands can be produced locally in effector cells and tissues in normal conditions and after tumor development (see Appendices B and C).

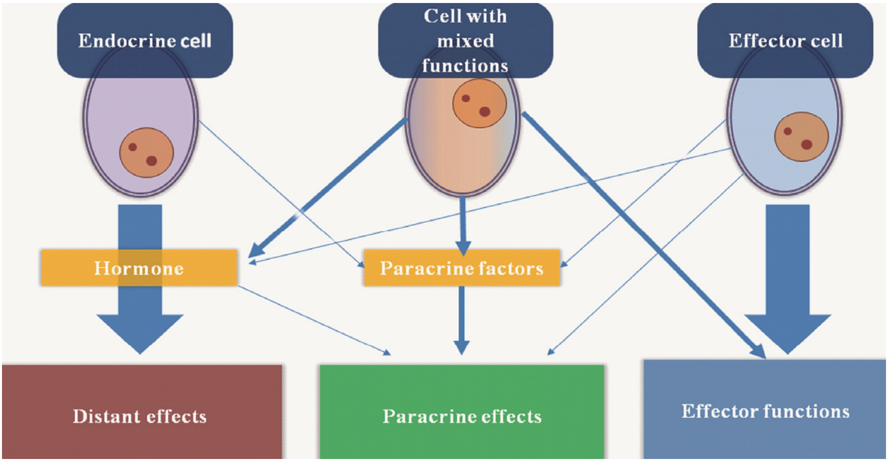


Fig. I-2-3. Hormone-producing cells – each with different degrees of specialization

Endocrine cells

Endocrine cells are highly specialized for the production of hormones and are able to secrete a number of paracrine factors (e.g., the cells of endocrine glands).

Cells with mixed functions

In addition to the production of hormones and paracrine factors, this type of cell has additional effector functions (for example, Sertoli cells secrete estrogens, activin, inhibin, and other hormones, while being responsible for the maintaining of spermatogenesis).

Effector cells

Effector cells are specialized for separate physiological functions, but are able to secrete hormones and paracrine factors (for example, adipocytes – which are specialized for lipid metabolism – secrete hormones such as leptin, adiponectin, resistin, and other factors participating in the systemic regulation of lipid metabolism and eating behavior (see Appendix D).

Endocrine cells may combine in various ways:

- they may be incorporated in non-endocrine organs as individual cellular elements
- they may form groups of cellular elements to be a part of glands with mixed endocrine and exocrine secretion
- they may form a separate organ; i.e., an endocrine gland

Endocrine glands

Endocrine glands (Fig. I-2-4) consist of cellular elements of different embryonic origin; in lower invertebrates, however, different types of endocrine cells do not always join together into a single organ (Fig. I-2-5, Fig. I-2-6). Organization of several endocrine cells in a gland facilitates the information exchange via paracrine signalling. The biological significance of this integration of endocrine cells is to increase control over the information network and effector functions (Fig. I-2-4).

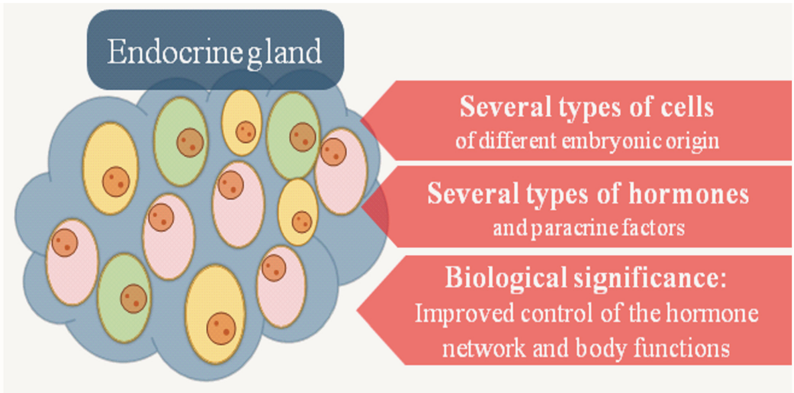


Fig. I-2-4. Endocrine gland

The formation of endocrine glands is the result of an evolutionary adaptation. In elasmobranchs, for example, interrenal tissue (a homologue of the mammalian adrenal cortex) is, as its name implies, located between the kidneys; while chromaffin tissue (a homologue of the adrenal medulla) consists of small islets scattered over the surface of the kidneys. In the course of evolution, interrenal tissue became combined with chromaffin tissue in urodele amphibians. Subsequently, this process continued until distinct adrenal glands evolved in higher vertebrates (Fig. I-2-5).

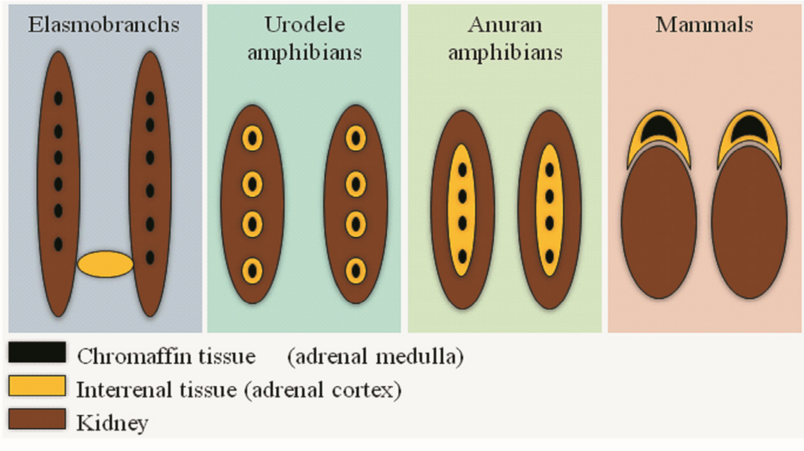


Fig . I-2-5. Evolution of the adrenal glands of vertebrates

One of the examples of the glands with cells of different embryonic origin is pituitary gland. The anterior and posterior lobes of the pituitary gland develop from different embryonic progenitor cells, i.e. from the ectoderm of the pharynx (Rathke's pouch) and the neural ectoderm of the neural tube, respectively (Fig. I-2-6). The somatotrophs, lactotrophs, thyrotrophs, and gonadotrophs of the anterior pituitary develop from the dorsoventral area of the Rathke's pouch, while the corticotrophs of the anterior pituitary and the cells of the intermediate pituitary are derived from its distal part that is in close contact and is fused with the neurohypophysis. Sequential action of transcription factors *Prop-1* and *Pit-1* induces the development of somatotrophs and lactotrophs of the anterior pituitary. It affects the differentiation of thyrotrophs as well. The differentiation of gonadotrophs is regulated by transcription factors *Prop-1* and *SF-1*.

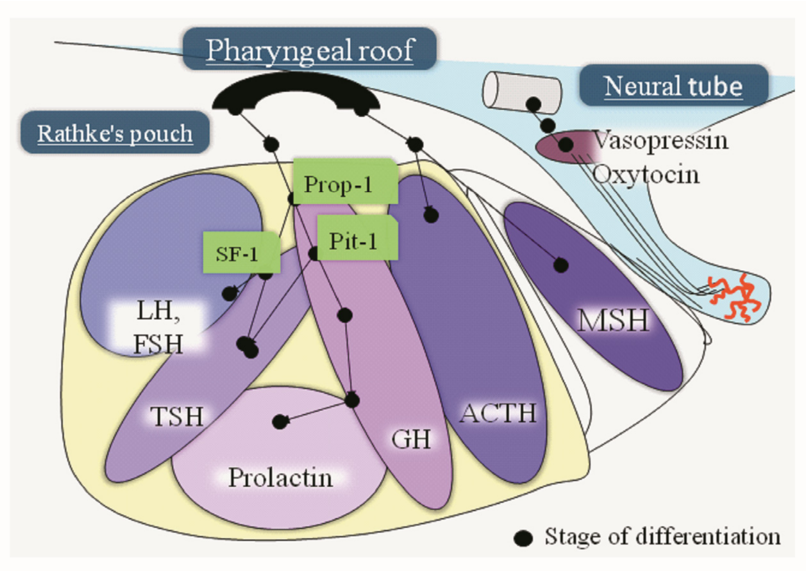


Fig. I-2-6. Mammalian pituitary embryogenesis and the topography of hormone-producing cells

- *Prop-1* is a transcription factor that regulates the production of *Pit-1*
- *Pit-1* is a transcription factor of the pituitary gland
- *SF-1* is Steroidogenic Factor 1

Hormone names and abbreviations are given in Appendix A.

Hormone functions

The functions of hormones can be divided into two different groups:

- Effector functions:
  Control of external[1] structures that support the vital functions of the body

[1] In relation to the hormonal system

- Signalling functions:
  Coordination of the informational network inside and outside of the endocrine system

The signalling role of hormones is realized within the relevant vertical/horizontal axis or between the axes. Appendix H presents the main (but not all) effector and signalling functions of the most studied hormones.

Effector functions

These functions are related to the hormone action on the target tissues, which is directly involved in the regulation of metabolism and the maintenance of physiological processes. Effector functions of hormones may be irreversible (e.g. they are often morphogenic in early ontogenesis) or reversible, (regulatory). Examples of such functions are the morphogenetic and regulatory action of androgens on the development and function of the prostate and other male reproductive organs; reversible stimulation of gluconeogenesis by glucocorticoids in the liver; etc.

Signalling functions

Signalling functions of hormones include maintaining/regulating the activities of both its hormonal axis and the hormone network as a whole. Such informative and coordinating properties of hormones are also involved in the coordination of other signalling systems (e.g. the nervous and immune systems). Androgens, for example, besides the abovementioned effector functions, are components of the reproductive hormone axis and regulate its activity. They inhibit the secretion of pituitary gonadotropins and hypothalamic gonadoliberin and in this manner control their own blood levels by a negative feedback mechanism. However, androgens also affect the production of hormones of other axes (e.g., of atrial natriuretic peptide, secreted by the heart, which stimulates natriuresis and diuresis, by engaging in the regulation of water-salt balance) and male-specific brain development, thus adapting the function of the CNS to the needs of males. In general, the regulatory influence of a hormone on its own axis is stronger than its regulatory influence on the other axes.

The ratio of the effector and information functions in different groups of hormones can vary considerably. Hypothalamic-pituitary hormones often have more pronounced information functions, while hormones produced by the peripheral glands and cells with endocrine secretion demonstrate comparable effector and information functions.

CHAPTER THREE

STRUCTURAL AND FUNCTIONAL ORGANIZATION OF THE ENDOCRINE SYSTEM

Tissue levels that determine the specificity and strength of the hormonal signal

Structures involved in the formation, transduction, and realization of hormonal signals can be divided into:

- Ones that define the specificity of the signal:
  - ✓ hormone structure
  - ✓ receptor structure and activated cascades of intracellular messengers
- Ones that regulate the signal's strength

The specificity of the signal is determined by the structure of a hormone (which depends on the producing cell/gland), on the one hand; and by its receptor apparatus (which depends on the target tissue), which binds the ligands of a particular structure/class/superfamily, on the other. However, in different targets, even the same receptors can cause different effects due to the activation of different intracellular cascades. These mechanisms allow a hormone to elicit a tissue-specific response to each of the signals.

The range of target tissues is individual for each hormone. Depending on the intensity of hormone action, such tissues may be categorized as follows:

- Hormone-dependent tissues (e.g., the prostate), where the lack of a hormone leads to the atrophy of those tissues, and
- Hormone-sensitive tissues, where hormone functioning acts to regulate a number of metabolic/growth processes but does not determine the vitality of the organ.

The regulation of the strength of the hormonal signal involves hormone-producing elements, the systems of transport and metabolism of the signalling molecules, as well as the receptor level. Hormone-producing activity of the cells is typically regulated by direct and feedback interactions among the hormones of one of the vertical[2] or horizontal[3] axis. The concentration of hormone-binding proteins, along with the expression of receptors and metabolic enzymes, are under more complex multi-hormonal control. Due to the multilevel regulation of hormone biodynamics and direct/feedback interactions, the strength of the hormonal signal is under closed loop control, and the blood concentration of the substance is maintained at a constant level.

An endocrine circuit (Fig. I-3-1), in the most general terms, includes:

- Central elements of the endocrine axis, which define the specificity and strength of the signal:
  - endocrine gland or hormone-producing cells/tissues (the production of hormones with a specific structure)
  - sensitive cells/tissues (the receptors recognizing a specific group of hormones)
- Organs regulating the strength of a hormonal signal:
  - organs producing specific transport proteins that determine the blood concentration of free hormone (mainly, the liver)
  - tissues in which hormone metabolism/inactivation/excretion occurs (the liver; kidneys; etc.)
- Regulatory systems of all the above-mentioned components of the endocrine circuit (the brain; other endocrine glands; excretory organs; etc.).

All components of this system are targets for hormonal regulation. Their interactions enable the maintenance of the concentration of hormones at a relatively constant level and allow the system to function as a closed circuit (where all the elements are balanced). Because of that, the system is able to return to its initial status after suffering any disturbing effects of any nature. The mutations of different elements of the endocrine circuit prevent from this returning (see Appendix I).

Thus, the blood concentration of hormones is an integral indicator of the activity of the endocrine circuit that includes the rate of hormone

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[2] In the case of the axes involving the hypothalamus-hypophysis-peripheral gland

[3] E.g., for the axes, involving hormones regulating carbohydrate and lipid metabolism

production and its metabolic clearance rate (as determined by the rate of metabolism, the availability and concentration of transport proteins, receptor density, and by available regulatory control of all these processes).

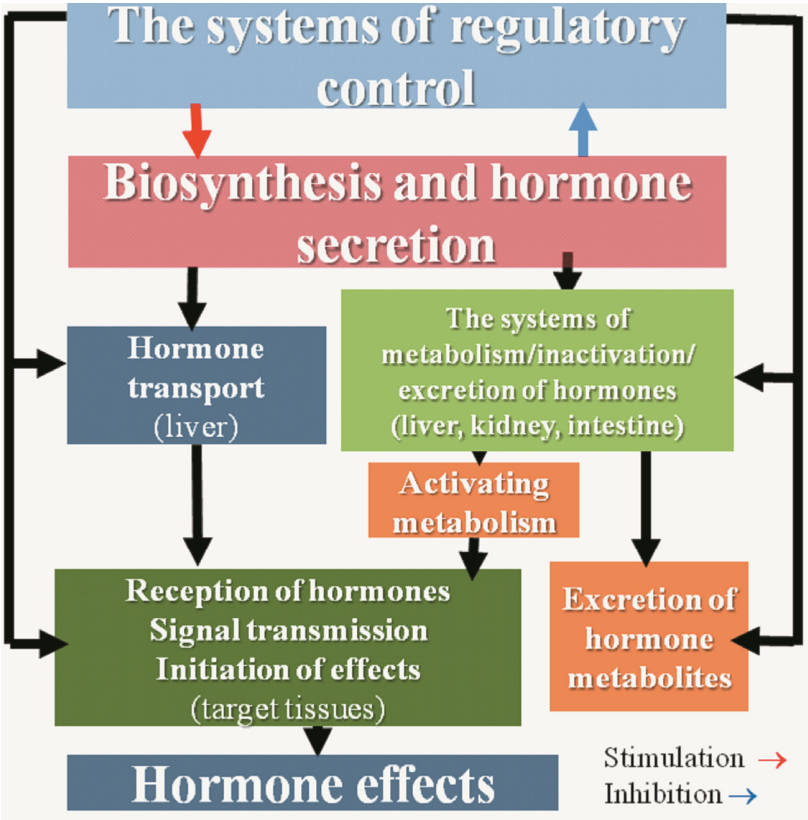

Fig. I-3-1. Physiological organization of the endocrine circuit