PATHOPHYSIOLOGY OF THE ENDOCRINE SYSTEM

Introduction

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The endocrine system consists of the endocrine glands that are either macroscopic structures or small clusters of cells or single cells dispersed in other non-endocrine tissues. The endocrine glands produce hormones and release then in the blood. By the blood, the hormones are distributed throughout the body and are transported to their target tissues (note: differentiate endocrine secretion = in the blood – the topic of this chapter; exocrine secretion = in an organ cavity or on the body surface; paracrine secretion = in a tissue to influence the cells in the proximity; lymphocrine = in the lymph; autocrine = the cell influences itself by its own product).

The role of the endocrine system is to control homeostatic mechanisms (in cooperation with the nervous and immune systems).

There is a tight cooperation between the endocrine and nervous system. The endocrine glands are controlled by the nervous system - innervation of the glands (in addition to other regulatory mechanisms – see below). Furthermore, the nervous system has receptors for hormones, and thus, its function (end even morphology) is influenced by hormones. Many hormones play also a role of neurotransmitters (noradrenalin, dopamine etc.). Some structures of the nervous system are endocrine glands, such as the hypothalamus and, epiphysis.

Hormones

Hormones are released from the gland into the blood that transports them throughout the body. The role of hormones is to transfer information. Hormones act on their target tissues via specific receptors (superficial on the cell membrane, cytosolic, nuclear). If the cell does not have a receptor sensitive to a particular hormone, it cannot respond to its presence. There can be several types of hormones for a certain hormone or a group of hormones of certain family. Individual receptor types can have a different sensitivity to different hormones of the family (e.g. different response to epinephrine and norepinephrine), can be expressed by different cells and can mediate different effects of the hormone on the target tissues. These facts are of importance for different manifestations of abnormal sensitivity or receptors. (see below).

Classification of hormones according to their chemical structure

- steroids
- aminoacid derivates
- peptides

- fatty acid derivates

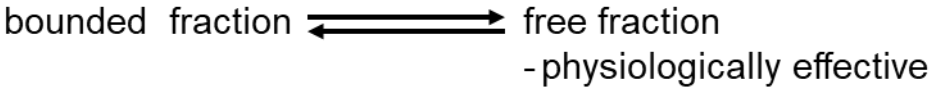
Chemical structure of hormones is related to character of their metabolism, i.e. their synthesis, inactivation, degradation and elimination.

Protein binding of hormones

Some hormones (e.g. thyroid hormones, steroids) are, in part, in the plasma bounded on plasmatic proteins. There are either specific proteins for specific hormones (e.g. thyroxine-binding globulin = TBG, cortisol-binding globulin = CBG) or the hormones can bind also on albumin.

The free fraction is physiologically effective. Free hormone molecules can penetrate the tissue and bind on their receptors. Free fraction is also involved in the feedback regulations of hormone production. On the other hand, free fraction is available to elimination processes (inactivation, degradation, renal excretion).

Protein-bounded fraction is physiologically ineffective, but it is protected from elimination. Thus, it represents a reserve of the hormone ready to quickly replenish the free fraction. There is a balance between the free and protein-bounded fraction. If the free fraction drops it is replenished by release of the molecules from the protein binding.



Changes of binding protein amount (i.e. their binding capacity) can be manifested by changes of total hormone concentration in the blood. However, changes of the free fraction level, leading to change of intensity of the hormone's impact on the tissues, occur rather during rapid changes of binding capacity (that must be saturated first after its rapid increase, or that is not capable of binding all hormone molecules in the case if its sudden reduction). In long-term states, a new balance is established at normal level of the free fraction of the hormone that ensures adequate effect of the hormone on the target tissues (therefore, there are usually no signs of hyper- or hypofunction of the hormone, although its total level is out of the normal range). The reason is that the free fraction, but not the bounded fraction, ensures feedback control of hormone production.

Time course of hormone effects

The onset of hormone effect after the gland stimulation is quite variable. It depends on processes that must happen between the gland activation signal and hormone release (just a release of pre-synthetized hormone, initiation of hormone synthesis...), hormone distribution and also on the character of cell response and complexity of the signalling pathway (e.g. effects mediated by gene expression take more). For instance, adrenaline effect onset is within seconds, while effects of thyroid hormones became fully apparent within days.

Persistence of hormone effects is also diverse. It depends on the character and mechanism of the effects and strongly on biological half-time of the hormone. The effect of catecholamines fades away within several minutes after termination of their release. The effect of thyroidal hormones persists for days or weeks.

Time course of hormone secretion (including their potential circadian rhythmicity) and their biologic half-time should be considered when taking blood samples for hormone level examination and when interpreting the results. In hormones having a rapid and marked

oscillations of their levels during the day or in dependence on functional state of the organism (not only physiological responses to stimulation but also in pathological states), the current level does not need to be an indicator of the overall situation. Adrenaline is a good example. Its level can rise significantly within a short time in a healthy organism in response to stress stimuli. On the other hand, paroxysmal dramatic release of catecholamines from the pheochromocytoma (see pathophysiology of the adrenal medulla) is difficult to be detected by one blood sample due short half-time of catecholamines. Therefore, assessment of whole-day production of catecholamines by measurement of their metabolites in urine is used.

Inactivation/elimination of hormones

After gland stimulation and elevation of hormone levels, they should return to their basal values to ensure normal function of the system and maintenance of regulatory and information role of the hormones. Changes of processes of inactivation or elimination of hormones in pathologic states could lead to changes of hormone levels and thereby to inadequate effects on their target tissues.

Mechanisms of hormone inactivation and elimination are:

- proteolysis
- oxidation
- conjugation in the liver
- urine excretion
- antihormones (antibodies) – They play a role rather as a pathological factor - a hormone is inactivated by an autoantibody.

General effects of hormones

1) Organization – The hormone influences growth, development and functional organization of certain structure (tissue, organ).

   In some cases, these effects can apply or be of special importance only during certain phases of ontogenetic development. Lack or excess of the hormone in such period can have permanent consequences that cannot be corrected later by subsequent normalization of hormone levels (critical developmental periods).

   For example: The role of thyroidal hormones in the CNS development; lack of thyroidal hormones in childhood leads to so called cretinism (short growth, mental retardation) while hypothyroidism occurring in adulthood has different features (see pathophysiology of the thyroid gland).

   Or: Different effects of growth hormone shortage or excess before and after ossification of the growth cartilages.

   Or: Different impacts of shortage or excess of sex hormones during different phases of ontogenetic development.

2) Activation – The hormones activate (modulate) certain function of the tissue or organ at that moment.

Regulations in the endocrine system

Function of the endocrine glands is controlled by following mechanisms:

- Neural control (innervation of the gland)

- Simple or complex negative feedback (oscillations due to delay in information and signal transmission and reaction time is characteristic; the amplitude of the oscillations decreases consecutively and the system tends to stabilize; on the other hand, permanently stable hormone level can be a manifestation of some disorder – e.g. continual autonomous hypersecretion of a hormone by a tumour without any response to control mechanisms leads to permanently elevated hormone levels; reduced functional capacity of a damaged gland producing insufficient hormone amount although working at maximum of its residual capacity leads to permanently low hormone level)
- Positive feedback – e.g. oxytocin secretion during delivery (this kind of regulation has to be terminated, otherwise it would lead to system instability and damage of the organism; in this example, the cycle is interrupted at the moment of foetus birth terminates mechanical stimulation)
- Control by another hormone (e.g. hypothalamus – pituitary – peripheral gland axis)

In many cases, more regulatory mechanisms and involved.
Changes and disorders of the regulatory mechanisms are important causes of function disorders of the endocrine glands.
It is important to note that even **physiological regulatory mechanisms** triggered by pathological factors or under pathological conditions can **play a significant role in pathogenesis of diseases** (e.g. secondary hyperaldosteronism)!

Diseases and function disorders of the endocrine structures

Causes of diseases and function disorders of the endocrine glands

- Developmental anomaly (as a consequence of any teratogenic factors, including genetic disorders)
- Mutations of genes encoding peptide hormones, enzymes important for hormone synthesis, receptors
- Injuries
- Inflammations
- Tumours
- Vascular disorders (ischemia, haemorrhage)
- Iatrogenic (states after surgical ablation of the gland, hormone administration)
- Disorders of gland regulation
- Trophic changes (e.g. as a consequence of long-term disorder of regulation – long-term lack of stimulation can lead to gland parenchyma atrophy and to reduction of its functional capacity, when resuming the stimulation, the atrophic gland is not capable of adequate increase of hormone production until the re-emerging stimulation leads to a recovery of its state and normalization of its functional capacity)

Classification of endocrine gland disorders

In the hypothalamus – pituitary – peripheral gland axis:

- **Primary** – disorder affects primarily the peripheral gland; increase or decrease of its hormone production is the primary change, while changes of higher-level hormones (hypothalamic, pituitary) are then just secondary responses in the frame of negative feedback control.

- **Secondary** – the disorder affects the adenohypophysis; change of certain (or several) anterior pituitary glandotropic hormone induces a change of function of the respective peripheral gland.
- **Tertiary** – the disorder affects the hypothalamus, change of secretion of hypothalamic statin or liberin (or disorder of more of them) leads to change of adenohypophysis activity and thereby to change of production of the relevant pituitary glandotropic hormone (or hormones). The change of its level leads then to a change of function of relevant peripheral gland.

For details see pathophysiology of the hypothalamus – pituitary system.

In general:

- **Primary** – the disorder is a consequence of the disease or damage of the gland itself.
- **Secondary** – the gland is not damaged, but it reacts on pathological conditions changing factors and parameters of homeostasis that regulate the gland function.

Example: Primary hyperaldosteronism is a consequence of the adrenal cortex tumour producing excessive amounts of aldosterone without respecting need of the organism and regulatory signals. Secondary hyperaldosteronism is a consequence e.g. of decreased renal perfusion due to renal artery stenosis, left heart failure or other pathological conditions. Decreased renal perfusion leads then to activation of the renin – angiotensin – aldosterone system (see physiology) that is a normal regulatory mechanism ensuring, under other conditions, an expedient and adequate response of the organism to loss of fluids and hypovolemia. In the case of above-mentioned renal artery stenosis and heart failure, such secondary hyperaldosteronism aggravates the situation and participates in development of a complex pathological state.

Among secondary disorders, we rank also changes of hormone elimination that lead to changes of the hormone level when, in fact, the gland works correctly.

Classification of diseases and disorders of the endocrine system from the function point of view

- Eufunction = function of the gland remains normal (e.g. small tumour in the gland without endocrine activity, if sufficient amount of functioning gland parenchyma is preserved; damage of one adrenal gland, because one healthy adrenal gland is enough to maintain normal quantities of the hormone)
- Hyperfunction = gland function (or hormone effect) is increased
- Hypofunction = gland function (or hormone effect) is decreased
- Dysfunction = combination of hyper- and hypofunction of several hormones produced by one gland (e.g. adenohypophysis)

Mechanisms of change of function of the endocrine gland

- Change of hormone synthesis, secretion or distribution

  This group includes among others damage of the gland leading to reduced functional capacity of its parenchyma, disorders of metabolic pathway of hormone synthesis (usually hereditary enzymopathies), lack of essential compounds (iodine for thyroidal hormones), tumours having endocrine activity, uncontrolled hormone release from damaged gland cells etc.
- Disorder of hormone degradation or excretion

It depends on way and place of hormone elimination. E.g. enzymatic defects, liver diseases (steroid hormones are inactivated in the liver).

- Exogenous origin of the hormone
  - Therapeutic hormone administration: Substitution therapy should theoretically induce normal level of the hormone; however, exact dosage could be problematic e.g. due to changing needs of the organism or circadian rhythmicity of some hormones. Another situation is therapeutic induction of hormone hyperfunction to achieve its therapeutic effect (e.g. glucocorticoids for their anti-inflammatory effect).
  - Intake of hormones or substances with similar effects in the food (e.g. phytoestrogens).
  - Abuse of e.g. anabolic hormones.
- Ectopic secretion of hormones
  Secretion by tissue having endocrine activity out of the gland (small cell lung carcinoma, gland tissue in the teratoma, ectopic goitre)
- Changes of target tissue sensitivity
  - Disorders of receptors for the hormone – They could be either reduction (partial or complete insensitivity) or increased receptor sensitivity. They can affect not only the peripheral target tissues of the hormone (e.g. disorders for thyroid hormone receptors, peripheral diabetes insipidus – see chapters on these hormones) but also receptors involved in the feedback control of hormone production (this leads then to change of its production; e.g. disorders for thyroid hormone receptors, changes of sensitivity of the parathyroid glands to calcium – see chapters on these hormones). The consequences depend on the particular situation – i.e. whether there is changed sensitivity in one or both roles (response in the periphery or feedback regulation). It is also important whether there is a complete or partial insensitivity (if some level of sensitivity is preserved and if it affects also feedback control hypersecretion of the hormone can at certain level compensate for reduced tissue sensitivity; in fact, a new balance with higher hormone level ensuring normal intensity of target tissue stimulation is established). In the case of existence of more receptor types for the hormone, the manifestations depend on the type that is affected (mediating certain effects on certain tissues) and on types working normally. Disorders of receptor functions can be caused by their blockade or stimulation by various substances (hormone analogs, medicaments, poisons, anti-receptor antibodies...), by disorder of receptor structure (mutation in the receptor encoding gene – inactivation = reduced sensitivity, activation = increased sensitivity).
  - Change of cell response to the hormone can also be due to disorders of some components of signalling pathway mediating the cell response on receptor stimulation.
  - Damage of the target tissue that is not capable of adequate response to stimulation by the hormone.

General manifestations of the endocrinopathies

Manifestations of the endocrinopathies result from hormone effects on their target tissues and, in general, can be characterized as either insufficient or excessive effects of the hormones. Due to different effects of individual hormones, manifestations of individual endocrinopathies are also different. Particular manifestations of some endocrinopathies can also depend on ontogenetic development stage (age of the patient) in which the disorder occurs or during which it continues (it is obvious e.g. in thyroidal, sex hormones and growth

hormone – see also organization effects of hormones). With some simplification, we can name some more general features of endocrinopathies:

- Metabolic disorders – many hormones play an important role in metabolism regulation.
- Disorders of growth and development – some hormones have direct and specific effects on growth and development (growth hormone, sex hormones, thyroidal hormones). Nevertheless, metabolic disorders and impacts of endocrinopathies on overall health state of the patient could also negatively influence both growth and development of the individual.
- Changes of the body weight– some hormones lead to an increase, others to a decrease of the body weight. The causes are: metabolic effects of the hormones and also the impact of endocrinopathy on the general health of the patient.
- Disorders of sexual functions – it deals mainly with sex hormone imbalances but also in this case, general metabolic and health state of the individual plays a role.
- Mental changes – due to direct effect of some hormones on the brain and its function, the impact of the disease and difficulties accompanying it on emotional state of the patient.
- Skin changes
- Decline in physical fitness, fatigue
- Trophic changes

Neurosecretion

= production of hormones by the neurones

Hormones produced by the brain:

- Central neurotransmitters that play a role of hormones elsewhere (dopamine, noradrenalin...)
- Neuropeptides - bradykinin, neuropeptide Y, bombesin, insulin, endogenous opioids, DSIP, substance P, calcitonin, cholecystokinin, melatonin, VIP, neurotrophic factors...
- Real neurohormones - statins, liberins, oxytocin, vasopressin, melatonin

Disorders of neurosecretion:

- Syndrome of inappropriate ADH secretion (SIADH), central diabetes insipidus
- Pre-menstruation syndrome, post-climacteric tension
- Fröhlich's syndrome, Laurence-Moon-Biedl's syndrome, Prader-Willi's syndrome
- Disturbances of hypothalamic statins and liberins secretion