# PATHOPHYSIOLOGY OF ENDOCRINE SYSTEM

# The adrenal glands

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The adrenal glands are a pair of endocrine glands located at the upper pole of the kidneys. It consists of cortex and medulla, which produce hormones of different chemical structure, different effects and mechanisms of regulation. Thus, they are in fact two endocrine structures joined into one anatomically defined organ, but forming within its internal structure two bounded parts.

## The adrenal cortex

The adrenal cortex forms the external part of the adrenal glands. It produces mineralocorticoids, glucocorticoids and androgens. All adrenal cortex hormones are based on steroid chemical structure.

**Structure and functional organization of the adrenal cortex**
The adrenal cortex has 3 layers producing hormones in different combinations. The layers are listed here from the surface towards the medulla:

- zona glomerulosa – mineralocorticoids
- zona fasciculata – glucocorticoids, androgens
- zona reticularis – androgens, glucocorticoids

**Hormones of the adrenal cortex**
C19 steroids:
– Dehydroepiandrosterone, androstenedione - androgenic activity
– Oestrogens are formed in the blood from androstenedione.
C21 steroids:
– Mineralocorticoid and glucocorticoid activity – for different hormones in different proportions
– According to the predominant character of the activity, we divide C21 steroids into:
  - Glucocorticoids: cortisol, corticosterone
  - Mineralocorticoids: aldosterone, deoxycorticosterone (only 3% of activity of aldosterone)

### Glucocorticoids

The major human glucocorticoid is cortisol. Another is corticosterone.

**Effects of glucocorticoids**
Glucocorticoids act on a variety of tissues and processes in the body. They are the main hormones of the resistance phase of the stress response. Therefore, their role is to prepare

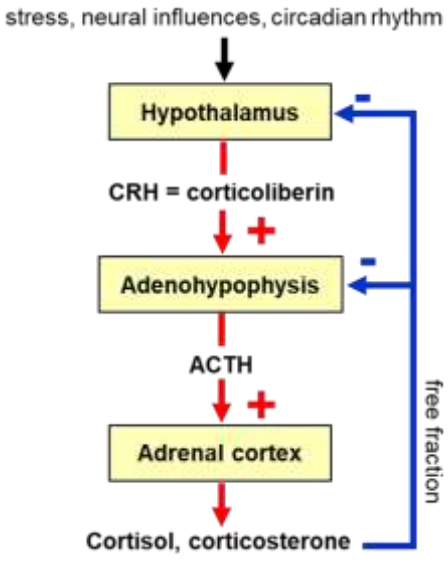
the organism and its internal environment for the threat and increased physical activity associated with the fight-flight response. In this respect, a number of effects are important and necessary for dealing with an acute threat and for the survival of an immediate threat. In the long run, however, they can be harmful to the body and lead to damage (see pathophysiology of stress). The effects of glucocorticoids in individual components of the organism and its function are:

- Metabolism
  - The increase of glycaemia is induced by stimulation of gluconeogenesis (the formation of glucose from non-sugar sources) and by reducing the utilization of glucose in the muscles. Stimulation of glycogen synthesis has the opposite effect. Overall, however, the hyperglycaemic effect of glucocorticoids clearly predominates.
  - Stimulation of protein catabolism - provides amino acids for gluconeogenesis, participates in the effect of glucocorticoids on muscles and connective tissues (see below).
  - Stimulation of lipolysis - provides fatty acids as a source of energy to save glucose.
- Immune system
  - Anti-inflammatory (↓ expression of pro-inflammatory cytokines) and immunosuppressive effects → therapeutic use of glucocorticoids
- Blood:
  - Increased blood clotting to reduce blood loss in case of injury.
- Connective tissue:
  - Reduction of collagen production
  - Resorption predominates over osteogenesis in bone.
- Cardiovascular system:
  - Increased cardiac output
  - Increased peripheral resistance
  - These two factors lead to an increase in blood pressure.
- Kidneys:
  - Increased glomerular filtration
  - Weak mineralocorticoid effect
- CNS
  - Influence on behaviour and emotions
  - Suppression of neurogenesis

**Regulation of glucocorticoid secretion**

Glucocorticoid secretion is controlled by the hypothalamic-adenohypophysis axis.

Glucocorticoids belong to the main stress hormones and their levels rise during the stress response. Basal glucocorticoid level has marked circadian rhythmicity with a maximum in the morning, a gradual decrease during the day and a low level at night. In the feedback regulation, the free fraction (see below) of glucocorticoids is involved.



**Glucocorticoid metabolism**

In plasma, glucocorticoids are free and bound to proteins. The specific binding protein is transcortin (CBG).

The biological half-life is in the order of tens of minutes (cortisol: 60-90 min, corticosterone: 50 min). Inactivation of glucocorticoids takes place in the liver. Therefore, in liver disease, the elimination of glucocorticoids is slowed down.

**Hypersecretion (hyperfunction) of glucocorticoids**

Elevated level of glucocorticoids for any reason leads to their excessive effect on tissues. The manifestation is a set of symptoms called Cushing's syndrome.

Cushing's syndrome has a number of possible causes:

- Iatrogenic - therapeutic administration of glucocorticoids for their anti-inflammatory effects, one of the most common causes of elevated level of glucocorticoids (or their analogues).
- Cushing's disease - not to be confused with the term Cushing's syndrome, it is only one of its causes, see below
- Ectopic ACTH secretion (e.g. small cell lung carcinoma)
- Primary hypercorticalism - see below

***Cushing's disease***

= hypersecretion of ACTH in the adenohypophysis stimulating the adrenal cortex to overproduce glucocorticoids

Causes: adenoma in the adenohypophysis, corticoliberin hypersecretion in the hypothalamus (corticoliberin stimulates production of ACTH in the adenohypophysis)

High ACTH level increases glucocorticoid secretion and leads to bilateral hyperplasia of the adrenal cortex.

In the case of an adenohypophyseal tumour, compression of the normal pituitary tissue can lead to a decrease of production of other adenohypophyseal hormones.

***Primary hypercorticalism***

= hypersecretion of glucocorticoids by tumour (most often adenoma, less often carcinoma) of adrenal cortex regardless of regulatory mechanisms and requirements of the organism.

High glucocorticoid level feedback suppresses the secretion of corticoliberin and ACTH. Therefore, unlike Cushing's disease, ACTH level is low in primary hypercorticalism. This leads to atrophy of the zona fasciculata and reticularis of the adrenal cortex over a prolonged period (the same occurs with prolonged administration of exogenous corticoids - see also below).

***Manifestations of Cushing's syndrome***

- Hyperglycaemia - Glucocorticoids increase glycaemia by stimulating gluconeogenesis and reducing glucose utilization. They basically induce a state of insulin resistance with hyperinsulinemia, i.e. a special type of diabetes = steroid diabetes (because it is induced by glucocorticoids, i.e. hormones of a steroid nature).
- Muscle atrophy - It is the result of protein catabolism. The patient has weaker limbs.
- Central obesity (abdomen, moon face)
  - compensated by muscle atrophy and bone mass loss, so the weight gain is only slight
  - mechanism of origin: increased appetite, hyperinsulinemia
- Reduced collagen production - deteriorated connective tissue quality, including skin components, red-violet skin striae.

- Bone mass reduction - Decreases the formation of bone matrix components, reduces the absorption of calcium in the intestine. The result is hypocalcemia and stimulation of parathyroid hormone secretion, which then promotes the release of calcium from the bones.
- Poor wound healing - a consequence of reduced collagen production and suppression of inflammation
- Anti-inflammatory effects, reduced immunity - reduced resistance to infections
- Hypertension - Probably due to hypervolemia caused by the mineralocorticoid effects of glucocorticoids.
- Mental changes = steroid encephalopathy - emotional lability, depression, anxiety, cognitive impairment, sleep disorder

**Lack of glucocorticoids**

Insufficient secretion of glucocorticoids may occur alone while maintaining normal secretion of other adrenal cortex hormones (selective glucocorticoid deficiency), or it is part of general adrenal cortex hypofunction (Addison's disease), when in addition to glucocorticoids there is also a lack of other adrenal cortex hormones, especially aldosterone (Addison's disease - further in the chapter on mineralocorticoids).

***Selective glucocorticoid deficiency***

Causes:

- Lack of ACTH (secondary disorder) - usually part of panhypopituitarism (the selectivity of glucocorticoid deficiency in this context is understood within the hormones of the adrenal cortex only)
- Corticoliberin deficiency (tertiary disorder) - leads to ACTH deficiency
- Condition after long-term corticosteroid therapy (or by analogy after elimination of the cause of primary hypercorticalism): Higher levels of glucocorticoids reduce ACTH production via negative feedback and thus reduce its trophic action on the zona fasciculata and reticularis of the adrenal cortex, which may atrophy and reduce their functional capacity. If corticosteroids are abruptly discontinued (or the cause of primary hypercorticalism is remedied), there is a risk of transient hypofunction and glucocorticoid deficiency because the atrophic cortex is unable to respond immediately to renewed ACTH stimulation by adequately increasing glucocorticoid production. The condition resolves after ACTH stimulation adjusts the adrenal cortex trophic (even after a number of weeks).
- ACTH receptor disorder - an inherited disorder, the adrenal cortex is insensitive to ACTH. Glucocorticoid production is therefore reduced. ACTH level, on the other hand, is increased by feedback controls.
- Defects of enzymes for glucocorticoid synthesis (11-hydroxylase, 21-hydroxylase, 3β-hydroxydehydrogenase, 17-hydroxylase) mean the inability of the adrenal glands to form glucocorticoids, while the synthesis of other types of corticoids is preserved. Mutations in the relevant genes are the base, and the disorder is therefore hereditary and congenital. Congenital absence of glucocorticoids accompanied by a feedback increase in ACTH level leads to congenital hyperplasia of the adrenal cortex with overproduction of dehydroepiandrosterone and androstenedione = **adrenogenital syndrome** (see also pathophysiology of the reproductive system).

Symptoms:

- Weakness, fatigue, weight loss

- Tendency to hypoglycaemia, especially during starvation (reduced gluconeogenesis does not allow to supplement glycaemia from non-sugar sources in the period without regular food intake of carbohydrates)
- Reduced resistance to stressors, reduced load tolerance, imbalance in the body easily goes into shock.
- In the case of secondary and tertiary glucocorticoid deficiency, the hyperpigmentation typical of primary adrenal disorders is absent.

## Mineralocorticoids

The major human mineralocorticoid is aldosterone.
The role of aldosterone is to maintain levels of sodium and potassium and to regulate water excretion. Aldosterone increases the resorption of sodium in the kidneys, sweat, saliva and gastrointestinal secretions. It increases the excretion of potassium and $H^+$ (promotes alkalosis) by exchanging for sodium ions. Excretion or, conversely, greater water retention is associated by osmotic mechanisms with the effect of aldosterone on sodium metabolism.
Normal values:

- Natremia: 130 - 148 mmol/l
- Kalemia: 3.8 - 5.1 mmol/l

**Regulation of aldosterone secretion** is ensured by several mechanisms:

1) Feedback effect of levels of sodium and potassium: increase of $K^+$ (even small changes), decrease of $Na^+$ (up to more significant changes) stimulate aldosterone secretion
2) Renin - angiotensin - aldosterone system (complex feedback reaction)
   Renin is a proteolytic enzyme that converts angiotensinogen to angiotensin I. It is then converted by angiotensin converting enzyme (ACE) to angiotensin II, which has both vasoconstrictive effects and stimulates aldosterone secretion.
   Renin secretion is stimulated by:
   - decrease in intraarteriolar pressure in the area of juxtaglomerular cells - in hypoperfusion of the kidney
   - decrease in the supply of $Na^+$ and $Cl^-$ to the distal tubulus
   - prostaglandins
   - sympathetic nerve system and circulating catecholamines

   Renin secretion is inhibited by:
   - angiotensin II (feedback)
   - increase in intraarteriolar pressure in the area of juxtaglomerular cells

   The role of this system in hypovolemia is to retain water in the body and maintain blood pressure and perfusion of organs.
3) ACTH has a transient stimulatory effect (1-2 days) on aldosterone secretion (this effect is partially limited by a decrease in renin due to hypervolemia) and a permanent effect on deoxycorticosterone. Therefore, in pituitary disorders, basal aldosterone secretion is normal, but there is no increase in stress.
4) Atrial natriuretic peptide (ANP) inhibits renin secretion, reduces the sensitivity of the zona glomerulosa to angiotensin II.

**Hyperaldosteronism**

***Primary hyperaldosteronism = Conn's syndrome***

Cause: adenoma or bilateral hyperplasia of the adrenal cortex

High aldosterone level increases $Na^+$ and water retention, decreases $K^+$ and $H^+$ excretion, reduces renin level.

Symptoms:
- Hypertension
- Oedema - usually not large, because hypervolemia from fluid retention increases the secretion of ANP (atrial natriuretic peptide), which increases the excretion of $Na^+$ and with it also water. This partially compensates the accumulation of water caused by aldosterone alone.
- Hypernatremia is not usually present for two reasons: 1) aldosterone retains not only $Na^+$ but also water, 2) the action of ANP compensates $Na^+$ retention.
- Hypokalaemia - causes extrasystoles, U wave occurrence and low T wave on the ECG, muscle weakness to paralysis of the respiratory muscles (!), paralytic ileus, rhabdomyolysis, damage of the renal tubules
- Alkalosis - the possibility of increasing neuromuscular excitability

***Secondary hyperaldosteronism***
It can arise for various reasons from several mechanisms. However, the disorder is not directly in the adrenal glands.
Mechanisms of origin:
1) Activation of the renin - angiotensin - aldosterone system by renal hypoperfusion caused from various causes:
   a) Hypovolemia due to fluid loss (dehydration, bleeding) leads to a decrease in renal perfusion and thus to an increase in renin production. By this mechanism, the organism saves water in a situation of its lack and it is an effective compensatory mechanism.
   b) Hypovolemia from fluid transfer to other compartments (oedema of various types and origins, ascites, etc.)
   c) Renal artery stenosis
   d) Heart failure - decreased cardiac output reduces perfusion of organs, including kidneys.
2) Hyponatremia or hyperkalemia stimulates aldosterone secretion.
3) Bartter's syndrome - production of renin by tumour
4) Disorder of elimination of aldosterone by the liver
   - In liver disease
   - Secondary hyperaldosteronism then contributes to the development of hepatic oedema.

Secondary hyperaldosteronism may then contribute to the worsening and development of complications of the primary disease. In heart failure, it causes water retention, hypervolemia, thereby increasing the volume load of the heart and worsening the accumulation of blood in front of the failing ventricle. In damage of the renal artery and renal function disorder, it is one of the mechanisms of renal hypertension and renal oedema development. In more extensive or generalized oedemas or ascites, secondary hyperaldosteronism increases water retention and thus promotes fluid accumulation in tissues or body cavities, thus, it is involved in a vicious circle.

**Hypoaldosteronism**
Causes of hypoaldosteronism can be congenital or acquired.

*Congenital hypoaldosteronism*

- Mutations in the gene encoding 18-hydroxylase or 18-dehydrogenase, i.e. the enzymes necessary for aldosterone synthesis: There is a defect in aldosterone synthesis with preserved production of glucocorticoids.
- Pseudohypoaldosteronism - In its congenital form, it is a disorder of the aldosterone receptor. Manifestations are the same as in hypoaldosteroteronism, but aldosterone level is high.
- Congenital adrenal hypoplasia - Leads to congenital Addison's disease, where there is a lack of aldosterone and glucocorticoids.

*Acquired hypoaldosteronism*

- Hyporenin hypoaldosteronism - A disorder of the juxtaglomerular apparatus that produces insufficient amount of renin.
- Pseudohypoaldosteronism - In its acquired form, it is the inability of kidneys to respond to aldosterone when the tubules are damaged.
- Acquired form of Addison's disease from damage of the adrenal cortex for various reasons. There is a lack of aldosterone and glucocorticoids (see below).

***Addison's disease***

Causes:

Addison's disease occurs when 80-90% of the tissue (functional capacity) of the adrenal cortex is damaged. The adrenal cortex has a large functional reserve. Therefore, minor damages do not result in corticoid deficiency.

- autoimmunity - one of the most common causes nowadays
- Infections – e.g. adrenal tuberculosis was a common cause in the past
- haemorrhage - in meningococcal sepsis
- ischemia - in shock
- congenital hypoplasia

Consequences:

- Decreased aldosterone secretion
  - The most serious consequence
  - Potassium retention, sodium and water loss
- Decreased glucocorticoid secretion
  - reduced resistance to stressors
- Reduction of adrenal androgen secretion
  - It is not a serious problem in these circumstances.
- Increase in ACTH - Induced via feedback regulation due to low level of glucocorticoids. Increased production of its precursor proopiomelanocortin also leads to hyperpigmentation.

*Chronic Addison's disease*

Loss of sodium and water leads to hypovolemia. The result is a tendency to hypotension, including orthostatic hypotension. At the same time, glomerular filtration decreases and ADH secretion increases. This somewhat reduces water loss. Sodium loss is therefore relatively higher than water loss, so hyponatremia occurs. Hyperkalaemia due to potassium retention means a risk of arrhythmias. Lack of glucocorticoids is manifested by fatigue, loss of appetite,

weight loss, or a tendency to hypoglycemia during starvation. Hyperpigmentation is also a manifestation.

*Addisonian crisis*
= life-threatening exacerbation of Addison's disease.
Severe hypovolemia can lead to shock. Hyperkalemia causes arrhythmias, including ventricular fibrillation! Renal failure results from renal hypoperfusion. In the blood, hyponatremia is diagnosed with hyperkalemia, hypoglycemia, increased creatinine and increased urea.

### Androgens

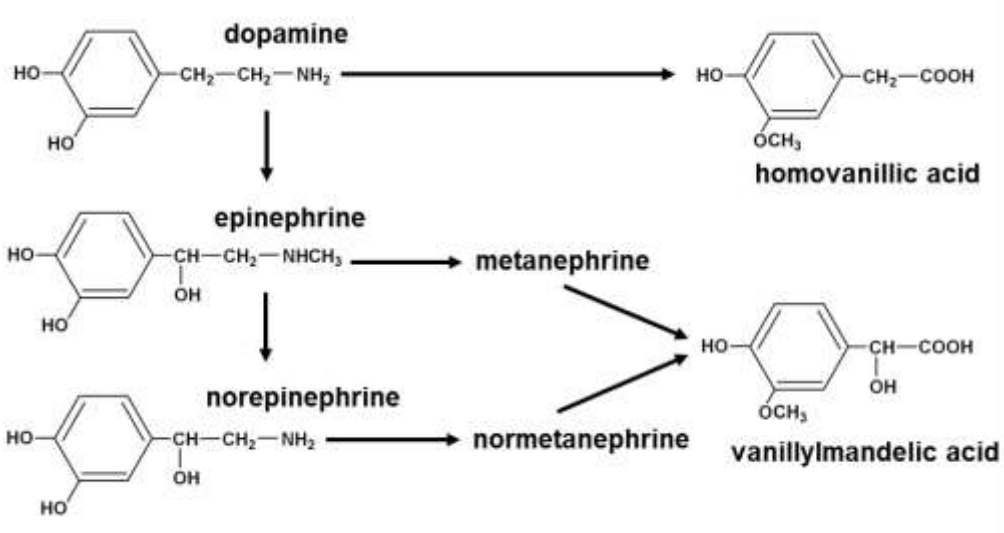
Hypersecretion of androgens by the adrenal cortex can be a source of their excess with appropriate consequences not only in adult men but also in women, prepubertal boys and men after castration. The normally functioning adrenal glands also maintain some, although reduced, androgen level in men after castration.

**Causes of hypersecretion of androgens by the adrenal cortex**
- Adenoma of the adrenal cortex
- Adrenogenital syndrome - the inability of glucocorticoid synthesis due to a genetically determined and thus congenital enzymatic defect leads to an increase in ACTH through feedback reaction. ACTH induces congenital adrenal hyperplasia with overproduction of dehydroepiandrosterone and androstenedione.

**Decreased androgen secretion by the adrenal cortex**
In the destruction of the adrenal cortex, when the reduction of adrenal androgen secretion is part of hypocorticalism. However, the lack of aldosterone and glucocorticoids has significantly more serious consequences.
See sex hormone pathophysiology for details.

## Adrenal medulla

The adrenal medulla is the inner part of adrenal glands. Produces catecholamines: adrenaline (epinephrine), noradrenaline (norepinephrine) and dopamine. Most is adrenaline, least is dopamine.



After stimulation, catecholamines are secreted into the blood very quickly and their effect therefore starts within seconds. Also, their half-life in the blood is short (2 min).

**Regulation of adrenal medulla function**

The adrenal medulla is stimulated by the sympathetic nervous system. Thus, the activation occurs simultaneously with the activation of the sympathetic nervous system. Also, the effects of adrenal medulla hormones are similar to those of the sympathetic nervous system. We are therefore talking about the so-called sympathoadrenal system. The catecholamines of the adrenal medulla, especially adrenaline, are the main hormones of the acute phase of stress. The adrenal medulla, unlike other tissues, is innervated by the preganglionic sympathetic fibre. This led to the hypothesis that the adrenal medulla is actually an enlarged sympathetic ganglion that lost axons and released catecholamines into the blood instead of into the synaptic cleft.

**Effects of adrenaline and noradrenaline**

Adrenaline and noradrenaline act on target tissues through adrenergic receptors (see physiology). Adrenaline flushed into the blood from the adrenal medulla normally reaches the threshold of its effects, while noradrenaline acts more as a mediator of postganglionic sympathetic fibres.

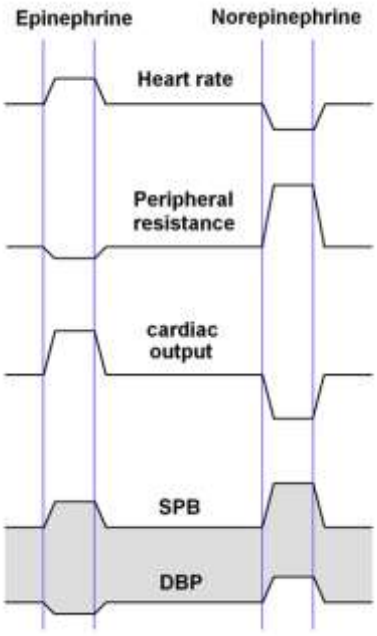
The basic effects of adrenaline and noradrenaline on the **heart** isolated from other regulatory influences are identical. This is the effect:

- positively inotropic = increase in contraction force
- positively chronotropic = increase in heart rate
- positively dromotropic = increase in excitation conduction velocity
- positively bathmotropic = increase of myocardial excitability (therefore under the influence of adrenaline the occurrence of extrasystole increases)

The result is an increase in cardiac output.

Adrenaline and noradrenaline have a different **effect on blood vessels**.

Noradrenaline generally induces vasoconstriction and thus an increase in peripheral resistance. Adrenaline ensures the redistribution of blood flow to organs whose activity is necessary during acute stress (in a state of acute danger), on the contrary, it restricts blood flow in organs that are not vital at that moment - causes vasodilation e.g. in muscles, vasoconstriction in the GIT. Because vasodilation predominates, the result is a decrease in overall peripheral resistance.




Therefore, adrenaline and noradrenaline have different effects on blood pressure. Adrenaline increases systolic blood pressure by increasing the stroke volume by its positive inotropic effect and reduces diastolic blood pressure by reducing peripheral resistance. These changes in blood pressure are observed, for instance, during physical activity in a healthy individual (see Letunov´s test). The increase in heart rate due to the effect of adrenaline is maintained.

Noradrenaline increases systolic blood pressure with a positive inotropic effect and diastolic blood pressure by increasing peripheral resistance. An increase in systolic and diastolic pressure will reduce the heart rate via baroreceptors.
Adrenaline and noradrenaline also have metabolic effects. They stimulate glycogenolysis and lipolysis, increase metabolic turnover. They belong to the hyperglycemic hormones.

**Effects of dopamine**
Dopamine acts on its target tissues via dopaminergic receptors (see physiology).
- It has a positive inotropic effect.
- Induces vasodilation in the kidneys and mesenterium, elsewhere it causes vasoconstriction.
- Increases systolic blood pressure but does not change diastolic pressure.
- Increases natriuresis probably by inhibiting the renal $Na^+/K^+$-ATPase (pump).

**Adrenal insufficiency**
There is no apparent separate adrenal medulla insufficiency syndrome. Lacking secretion of adrenal medulla hormones is compensated by sympathetic activity. Adrenal insufficiency is therefore rather part of the dysfunction of the autonomic nervous system. It is manifested e.g. by orthostatic hypotension.

**Adrenal medulla hyperfunction**
Pheochromocytoma is an adrenal medulla tumour leading to hyperfunction of the adrenal medulla. It relieves catecholamines into the blood in paroxysms. In most cases, noradrenaline predominates. Adrenaline dominates in about 10% of cases.
Manifestations are paroxysms of severe hypertension, palpitations, anginal chest pain, headache, anxiety and hyperglycemia.
Acute complications: intracranial haemorrhage from severe hypertension, myocardial infarction, arrhythmia (bathmotropic effect of catecholamines).
Chronic complications: nephropathy, retinopathy, cardiomyopathy - basically complications of hypertension
If the pheochromocytoma produces adrenaline, manifestations are attacks of hypotension (especially diastolic) with marked tachycardia and large systolic-diastolic difference and arrhythmias.

Detecting the increase of catecholamines themselves in the blood during an attack is problematic (short persistence of high catecholamine levels in the blood). Therefore, vanillylmandelic acid is determined in urine collected for 24 hours. This examination is an indicator of daily catecholamine production.

**Denervation hypersensitivity** is an increase in the sensitivity of tissues to catecholamines after removal (damage) of their sympathetic innervation. Low level (or absence) of noradrenaline stimulation from sympathetic endings leads to tissue sensitization. These then react more intensively to circulating catecholamines originating from the adrenal medulla.