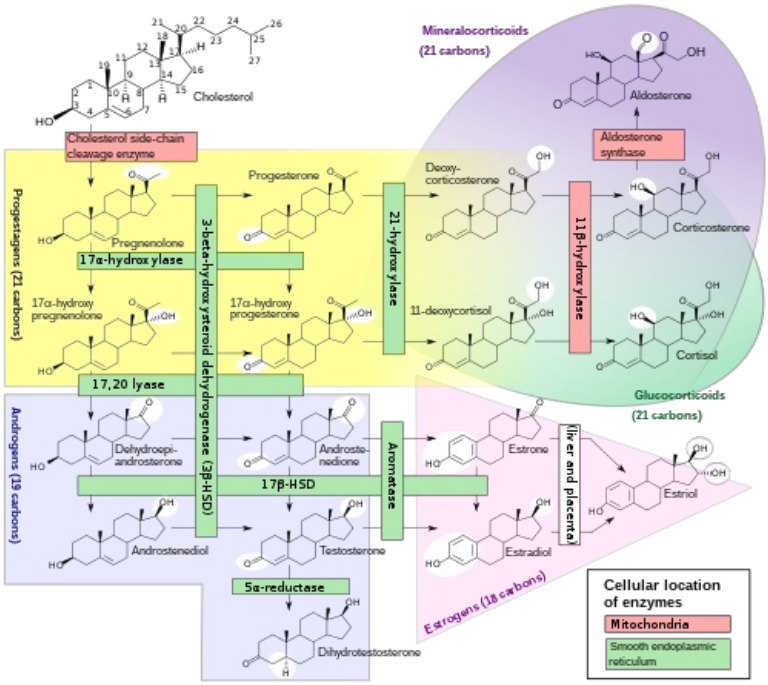
Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH, formerly *adrenogenital syndrome*) is a group of autosomal recessive inherited steroid hormone synthesis disorders caused by the absence of any of the five essential enzymes. Enzymatic block leads to a deficiency of part of the spectrum of steroid hormones and an excess of another group of hormones due to overproduction of ACTH in the release of feedback. The clinical picture is specific for each type of enzymatic defect. The most common is 21-hydroxylase deficiency (CYP21 gene). Failure to recognize and treat severe forms of CAH leads to salt wasting syndrome, hyponatremia, hyperkalemia, dehydration and hypotension.

Enzymes involved in the production of steroid adrenal cortex hormones: *SCC / 20,22-desmolase, 17-alpha-hydroxylase / 17,20-desmolase, 21-alpha-hydroxylase, 11-beta-hydroxylase, aldosterone synthetase* .

Adrenal function and its disorders



The adrenal medulla and cortex are 2 histologically and functionally different parts, which are derived from different germinal tissues in embryonic development.

Adrenal medulla

- comes from ectoderm , developmentally cleaves from nervous tissue; functionally it is close to the sympathetic nerve ganglia;
- produces catecholamines : adrenaline, noradrenaline;
- Hyperfunctional tumor - pheochromocytoma .

Adrenal cortex

- it is formed together with gonads from a common mesodermal base;
- produces steroid hormones :
  1. mineralocorticoids - aldosterone ,
  2. glucocorticoids - cortisol ,
  3. sex hormones - androgens , (less) estrogens;
- the common precursor is cholesterol ;
- the renin-angiotensin system regulates aldosterone production;
- Adrenocorticotropic hormone (ACTH) controls the synthesis and secretion of glucocorticoids and adrenal androgens.

Adrenal disorders in children

Congenital adrenal hyperplasia (CAH)

- a group of congenital enzymatic disorders of steroidogenesis , which lead to a deficiency of a part of the spectrum of steroid hormones and due to feedback through ACTH to overproduction of other steroids.

Adrenal insufficiency

- reduced ability to synthesize and secrete steroid hormones;
- congenital (acquired) or acquired causes (adrenal bleeding, infections, autoimmune diseases - Addison's

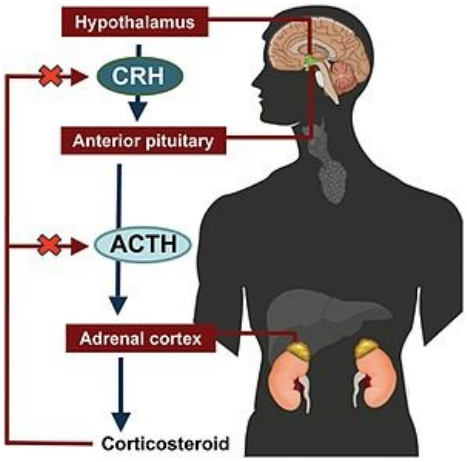
disease).

Overproduction of adrenal hormones

- adrenal cortex tumor or central overproduction of ACTH (Cushing's disease).

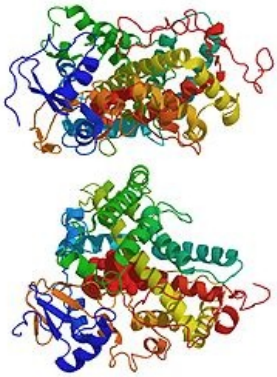
21-hydroxylase deficiency

- 95% of CAH patients have 21-hydroxylase deficiency;
- in the Czech Republic frequency 1:10 000;
- severe secretion of cortisol and aldosterone , ACTH output increases → production of adrenal metabolites with androgenic activity;
- clinical manifestations depend on the type of gene mutation that determines the residual activity of the enzyme:



Axis hypothalamus (CRH) - hypophysis (ACTH) - adrenal cortex (kortisol, androgens).

1. **Classical form**
   - with *salt-wasting*
     - zero 21-hydroxylase activity
     - boys: salt crisis in the 2nd to 4th week of life (hyponatremia, hyperkalemia, hypoglycemia), severe condition, sudden death
     - girls: virilization of the external genitalia (high levels of androgens *in utero* , evaluation according to the Prader scale), salt crisis, severe condition, sudden death
   - *simple virilising*
     - 1% 21-hydroxylase activity
     - boys: *pseudopubertas praecox isosexualis* aged 2–5 years (genital enlargement, pubic hair grows, testes remain childish)
     - girls: virilization of the external genitalia, *pseudopubertas praecox heterosexualis* ,
     - growth acceleration and acceleration of bone maturation → low final height
2. *late-onset*
   - 20-50% 21-hydroxylase activity
   - boys: clinically dumb
   - girls: hirsutism , cycle disorders, infertility.


Teoretical 3D structure 21-hydroxylase.

Laboratory diagnostics

- elevated 17-hydroxyprogesterone (17-OHP);
- low cortisol, high ACTH;
- synactene test;
- full-area neonatal laboratory screening (17-OHP from a dry drop) - captures the classic form with a salt disorder.

Therapy

- acute condition: hydrocortisone 50–100 mg iv, parenteral rehydration, ionogram correlation, prevention of hypoglycemia;
- long-term treatment of the classic form: substitution of hydrocortisone and mineralocorticoid → suppression of ACTH overproduction;
- in girls with virilization of the external genitalia, surgical correction;
- with a positive family history - prenatal treatment of the fetus with dexamethasone from the 8th week of pregnancy, in female fetuses until delivery (prevention of virilization).

17α-hydroxylase deficiency

Přehled syntézy steroidních hormonů.

- the adrenal gland produces only mineralocorticoid precursors, lacking cortisol, androgens and estrogens ;
- boys: insufficient virilization of the external genitalia in utero, with a complete block of the girl's external genitalia with a blind-ended vagina, testes intra-abdominally;
- lack of pubertal development;
- hypokalaemia, borderline hypernatraemia, hypertension (due to increased levels of mineralocorticoids);
- in stressful situations, cortisol deficiency shock;
- diagnosis mostly on the basis of accidentally detected hypertension or for incoming adolescence .

11-hydroxylase deficiency

It causes insufficient production of cortisol and aldosterone , increased production of androgens and 11-deoxycortisol and 11-deoxycorticosterone, which have mineralocorticoid effects. Virilization and the development of mineralocorticoid hypertension occur . The therapy is based on the administration of glucocorticoids (without mineralocorticoids).

3βHSD deficiency

This is a very rare disorder in which cortisol and aldosterone are not produced enough. The resulting androgens are weak and therefore there is only slight virilization.

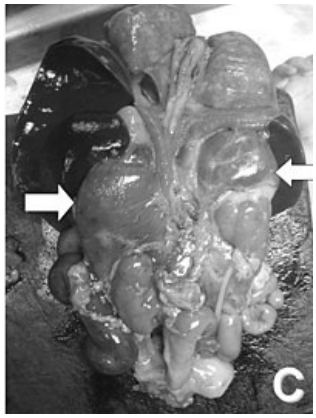
Adrenogenital syndrome

Adrenogenital syndrome from estrogen overproduction

- This form is very rare. It is always caused by a tumor of the adrenal cortex (cancer , adenoma). It most commonly occurs in adult men who develop gynecomastia , testicular atrophy, and impotence . The affected boy develops *pseudopubertas praecox heterosexualis* before puberty .

Adrenogenital androgenic syndrome

- **Acquired** - the cause is a tumor of the adrenal cortex (carcinomas , adenomas). It occurs most often in children. *Pseudopubertas praecox isosexualis develops* in affected boys before puberty, and *pseudopubertas praecox heterosexualis* develops in affected girls before puberty . In adult women, masculinization (virilization), hirsutism (excessive hair loss in women caused by endocrine disorders), clitoral hypertrophy, voice thickening and amenorrhea (lack of menstruation) occur.
- **Congenital** (or congenital adrenal hyperplasia , CAH) - is caused by a deficiency of an enzyme that metabolizes steroids . Most often, in about 90% of cases, it is a deficiency of 21-hydroxylase (= P450 C21). The second most common is 11β-hydroxylase deficiency. Lack of other enzymes (3β-hydroxysteroid dehydrogenases - 3βHSD, 17/17, 20 lyases, enzymes involved in SSC - StAR and P450 SSC , P450-oxidoreductase) is rare.



Post-mortem kids adrenal glands with CAH

Due to the absence of one of the previous enzymes, hypocortisolism (reduced cortisol production) develops, which causes increased ACTH production in the pituitary gland (the pituitary gland wants to increase cortisol levels). This leads to bilateral hyperplasia of the adrenal cortex (therefore in this case the *adrenogenital syndrome* is otherwise called *congenital adrenal hyperplasia*). More ACTH causes more steroids that are not affected by enzyme deficiency.

Deficiencies of 21-hydroxylase, 11β-hydroxylase and 3βHSD (basic forms of CAH) distinguish between classical and non-classical forms . Classical forms have a more difficult course and appear after birth or in childhood. Non-classical forms are less severe, may be asymptomatic, or may manifest during adolescence or adulthood.

Cortisol deficiency can cause an adrenal crisis .

Links

related articles

- Sexual development disorders • Puberty • Pubertas praecox • Pubertas tarda

Reference

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