Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a group of rare autosomal recessive disorders caused by a genetic defect of one of the enzymes that is involved in the production of adrenal hormones.

Overview

There are two types of CAH due to a deficiency in the enzyme 21-hydroxylase:

Classic CAH — a more severe form that is classified as a rare disorder and is typically identified at or soon after birth.

Non-classic CAH — a milder, later-onset form that is more common than classic CAH.

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

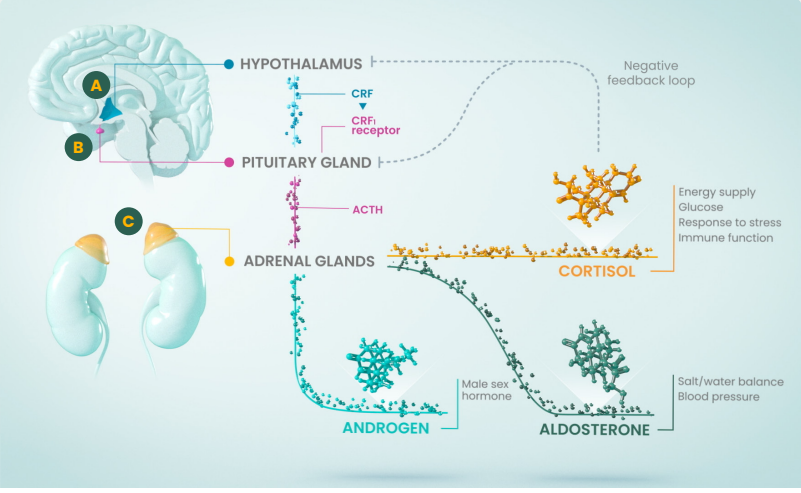
The HPA axis, consisting of the hypothalamus, pituitary gland, and adrenal glands, is a component of the neuroendocrine system. It regulates a complex set of hormone interactions through a "checks and balances" system, enabling the body to maintain homeostasis and respond to stress.

The HPA axis consists of the:

A. Hypothalamus — produces corticotropin releasing factor (CRF), which acts on receptors in the pituitary

B. Pituitary gland — regulated by CRF to secrete adrenocorticotropic hormone (ACTH)

C. Adrenal glands — stimulated by ACTH to produce multiple steroid hormones, including cortisol, aldosterone, and androgens.



The 21-hydroxylase enzyme is responsible for converting steroid precursors into steroid hormones, such as cortisol and aldosterone. These hormones are necessary for several important processes in the body, including response to stress and regulation of salt and water.

Cortisol is part of a negative feedback loop to the hypothalamus and pituitary gland that "feeds back" or modulates CRF and ACTH release to signal that levels are sufficient in order to maintain homeostasis or balance in the system.

Approximately up to
30,000 people
in the U.S. &
50,000 people
in Europe have classic CAH due to 21-OHD deficiency.[1, 2]

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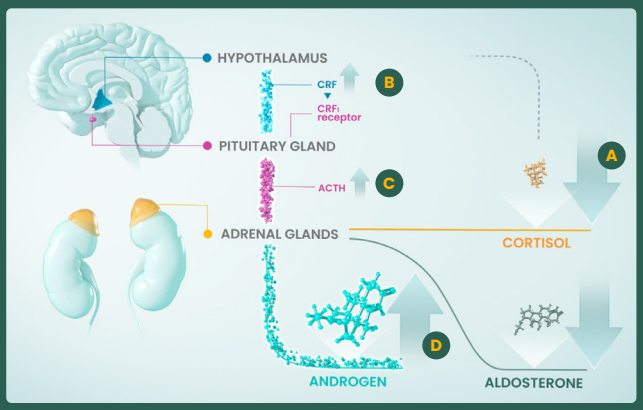
Classic CAH: Disruptions in the HPA Axis

~95% of CAH cases
are caused by a mutation
in the gene *CYP21A2*.[1]

The *CYP21A2* gene encodes the 21-hydroxylase enzyme. Mutation of this gene causes 21-hydroxylase deficiency (21-OHD), with clinical presentation determined by the severity of the resulting deficiency. In classic CAH, this severe enzyme deficiency can lead to an inability of the adrenal glands to produce cortisol and, in some cases, aldosterone.

Because of this deficiency, low levels of cortisol impair the body's ability to respond to stress, which might bring on an adrenal crisis, causing extreme weakness, low blood pressure, shock, and even death.



The CYP21A2 mutation blocks production of the 21-hydroxylase enzyme, leading to little or no cortisol production (A).

Lack of cortisol feedback within the HPA axis triggers:

(B) the hypothalamus to increase secretion of CRF,

(C) the pituitary gland to increase secretion of ACTH,

(D) leading to overproduction of androgen.

CAH Screening

Newborn screening is essential to diagnose and promptly treat the potentially life-threatening complications of CAH due to 21-OHD that can present with salt wasting adrenal crisis in the first few weeks of life. While affected female infants may be identified at birth based on atypical genitalia, affected male infants may not be readily identified without screening.

Newborn screening for CAH caused by 21-OHD is mandated in all 50 U.S. states and at least 12 other countries.[3]

Dried blood samples are collected on filter paper to measure the level of the hormone 17-hydroxyprogesterone (17-OHP).

While 17-OHP levels above 1000 ng/dL are considered diagnostic, most affected infants have levels well above 5000 ng/dL.

Genetic testing can help confirm the diagnosis but is not used as a first-line diagnostic test because of the complexity of the CYP21A2 mutation.

CAH Presentation

Symptoms of Classic CAH

At birth:

- Salt wasting adrenal crisis if affected infants are not diagnosed and treated early
- Females may have atypical genitalia, resulting from high levels of androgens in utero
- High androgen levels do not affect the sexual differentiation of males

During childhood:

- Advanced growth
- Risk of early puberty, which can result in premature closure of the growth plates
  - » This can lead to a reduction in final adult height that is below genetic potential

In adolescence and adulthood:

- Females can experience irregular menstrual periods, facial hair, acne, and other male-pattern characteristics due to high androgen levels
- Males can develop testicular adrenal rest tumors (TARTs)

Symptoms of Non-Classic CAH

- Later onset
- Can vary from person to person
- Generally milder versions of the symptoms associated with classic CAH
- May only require a low dose of glucocorticoids or no treatment at all if there are minimal symptoms

Classic CAH Treatment Options

There are currently
no non-steroidal U.S. FDA-approved treatments
for classic CAH.

For more than 60 years, corticosteroids, such as glucocorticoids and mineralocorticoids, have been the standard of care for classic CAH. Mineralocorticoids are prescribed to treat the aldosterone deficiency, while glucocorticoids are prescribed to treat the cortisol deficiency and to also stimulate cortisol feedback on the hypothalamus and pituitary to reduce high ACTH levels in an attempt to control androgen excess.

The dose and duration of glucocorticoids required to suppress ACTH in order to control androgen levels are often well above what is needed for replacement dosing to treat the cortisol deficiency. The result is an undesirable trade-off of trying to balance the negative effects of too much glucocorticoids with the negative effects of too much androgen.

Glucocorticoid Excess

Long-term, chronic exposure to greater than physiologic dosing of glucocorticoids can cause:

- Metabolic issues
- Bone loss and increased risk of fractures
- Growth impairment
- Increased risk of infections
- Increased risk of cardiovascular disease

Androgen and ACTH Excess

Long-term exposure to high androgen levels can cause:

- Accelerated growth before puberty
- Premature closure of growth plates
- Early puberty
- Shorter adult height
- Excessive hair growth and menstrual irregularity in females
- Female infertility
- TARTs in males
- Male infertility issues

References

1. National Organization for Rare Disorders. Congenital adrenal hyperplasia. Accessed Feb. 1, 2022. https://rarediseases.org/rare-diseases/congenital-adrenal-hyperplasia/. **2.** The World Bank. Population, total – European Union, United States, China. Accessed December 18, 2020. https://data.worldbank.org/indicator/SP.POP.TOTL?locations=EU-US-CN. **3.** Trapp CM, Speiser PW, Oberfield SE. Congenital adrenal hyperplasia: an update in children. *Curr Opin Endocrinol Diabetes Obes.* 2011;18(3):166-170. doi:10.1097/MED.0b013e328346938c.

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