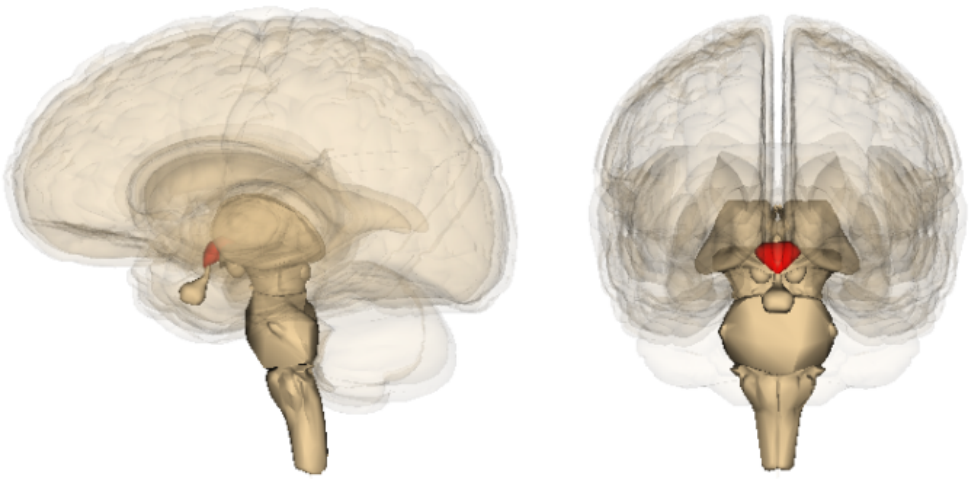
Hypothalamic–Pituitary–Gonadal (HPG) Axis Differentials

See online here

The endocrine system of the body consists of endocrine glands that produce metabolic changes through the secretion of chemicals called hormones. The Pituitary gland is considered the 'Master' gland of the body. Hormones produced by different endocrine glands have a different mechanism of action. The hypothalamic-pituitary-gonadal axis is a system of interrelated endocrine glands that work like a single entity with a series of communications that regulate hormone secretion between them.



The Hypothalamus

The hypothalamus, in the base of the brain, controls many functions in the body. It also affects sections of various endocrine glands. As part of its role in the hypothalamic-pituitary-gonadal axis, the hypothalamus secretes GnRH that travels to the anterior pituitary gland via the hypophyseal portal system.

Other hormones secreted from the hypothalamus include thyrotropin-releasing hormone, corticotrophin-releasing hormone, and growth-releasing hormone, all of which exert their effects on the pituitary gland.

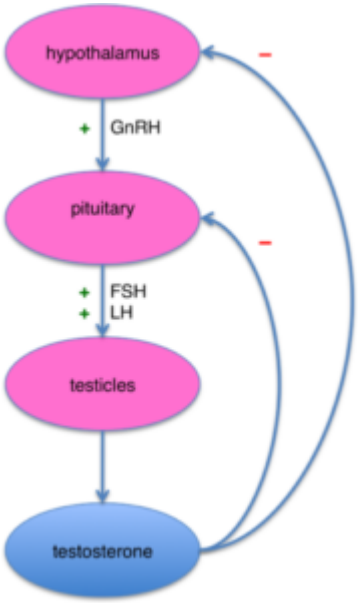
The Pituitary Gland

Under the influence of GnRH, the **pituitary gland** itself controls the secretion of gonadotropic hormones, such as LH and FSH, that exert the final effects of the axis.

Similarly, other endocrine glands, like the **adrenals** and **thyroid** **glands, are also activated by hormones from the pituitary gland, which include** thyroid stimulating hormones and adrenocorticotropic hormone.

Like other stimulating hormones, the pituitary gland also produces inhibitory hormones or factors to help regulate hormone levels in the body through **positive and negative feedback mechanisms**.

Hypothalamic–Pituitary–Gonadal (HPG) Axis



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The hypothalamic-pituitary-gonadal axis (HPG axis) includes the **hypothalamus**, **pituitary gland**, and **gonadal glands** working together in a loop, regulating hormone production. These glands work as if they are a single entity.

The downstream products of the hypothalamic-pituitary-gonadal pathway are regulated through the **negative feedback mechanism**. **Spermatogenesis**, which is the production of sperm in the testes, is stimulated by the gonadotropin-releasing hormone (GnRH) from the arcuate nucleus in the hypothalamus.

How does the gonadal axis work?

The hypothalamus secretes **GnRH** in a pulsatile fashion. GnRH travels down to the **anterior pituitary gland** and binds to the pituitary gland's receptors.

LH (luteinizing hormone) and **FSH** (follicle-stimulating hormone) are released from the pituitary gland. Both these hormones enter the **bloodstream** and flow to the **testes,** where the LH stimulates the **Leydig cells** to produce **testosterone**, which acts on the **Sertoli cells** and stimulating **sperm production**.

LH binds the **LH receptors** and promotes the conversion of **cholesterol** to **pregnenolone** through **protein kinase activity**. Pregnenolone is a precursor of testosterone. **Testosterone** is also required for other important biological processes, like

the development of primary and secondary sexual characteristics, increasing libido, and epiphyseal closure.

FSH stimulates the **Sertoli cells** to produce **androgen binding globulin (ABG)** and **inhibin**. **ABG** binds to **testosterone** from the **Leydig cells** and keeps it available in the **seminiferous tubules** and **other target tissues**.

Inhibin has more of a negative feedback role; it helps regulate **spermatogenesis** and inhibit **FSH, LH,** and **GnRH** production.

Raised testosterone levels in the blood stimulate the release of inhibin, which causes negative feedback on the pituitary and hypothalamus, decreasing the production hormones in the pituitary gland.

Inhibiting the **aromatase** enzyme increases FSH production, suggesting that FSH regulation depends more on estradiol than testosterone.

In females

GnRH promotes the **release of LH and FSH,** which act on the **ovaries** and produce **estrogen** and **inhibin**. A decrease in testosterone and DHEA, with raised estrogen, leads to female **primary sexual characteristics** in the fetal stage. Later, in puberty, female **secondary sexual characteristics** occur.

Estrogen regulates the menstrual cycle, and **inhibin** inhibits the hormone, **activin**, which usually stimulates **GnRH production**.

LH surge promotes **ovulation,** and **estradiol** promotes the **growth of the endometrium**. Increased levels of estrogen and inhibin produce **negative feedback** changes on the pituitary and hypothalamus.

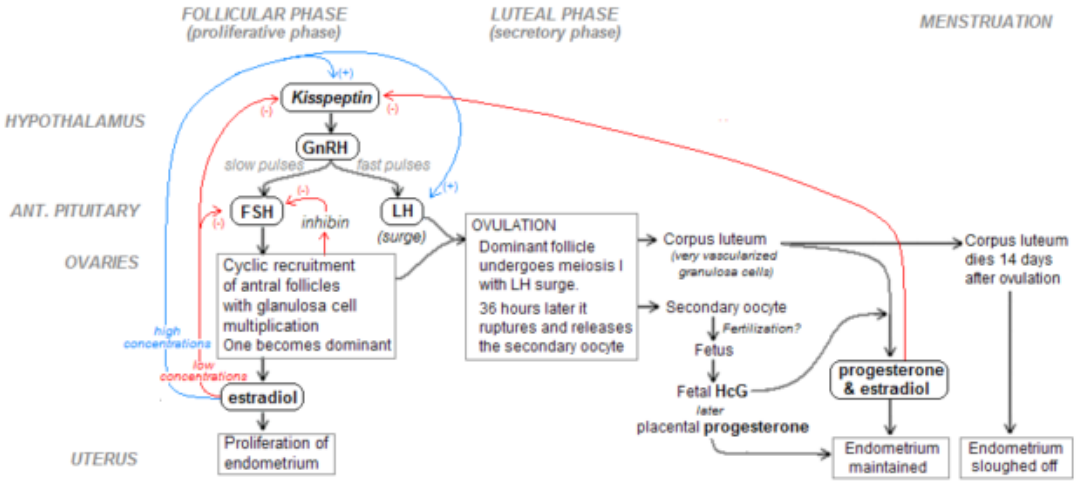

Image: “Menstrual cycle and hormonal changes.” by Npatchett. License: CC BY-SA 3.0

Role of Androgen-Binding Protein (ABP)

ABP is synthesized by **Sertoli cells** and is later secreted in the **seminiferous tubules**. This binds to testosterone and maintains a high concentration of testosterone in the testes. The concentration of testosterone is approximately 50 times higher in the testes than in the blood.

Metabolic fate of testosterone

1. Binds to androgen receptors in the target tissues
2. Converted to DHEA–dihydrotestosterone at the target tissues by the action of 5-alpha-reductase
3. Or converted to estradiol by the action of aromatase

Primary sexual characteristics: include the growth and development of the testes and penis in males.

Secondary sexual characteristics: include the development of facial and pubic hair, increased muscle mass and voice changes, as well as the development of the larynx.

Maturation of HPG axis in males

GnRH secretion starts in the intrauterine life in the fetal stage of life. This leads to primary sexual characteristics. Its production decreases in the neonatal period and in the childhood stage until **puberty,** when the pulsatile secretion of GnRH occurs and testosterone is produced. Secondary sexual characteristics are produced in the body after puberty until the adult stage of life, the production of GnRH and testosterone increases and, in the latter part of adulthood, it starts decreasing.

Hypothalamic–Pituitary–Gonadal (HPG) Axis Differentials

If there is a **disturbance** of the hypothalamic-pituitary-gonadal (HPG) axis, the development of sexual characteristics is **delayed,** leading to many different **complications** in males and females. It can be due to a **central cause**, such as pituitary or hypothalamic disturbances, or **local primary diseases of the gonads**.

The disturbances are associated with several disorders, including:

1. Hypospadias
2. Micropenis
3. Cryptorchidism
4. Mumps
5. Drug or alcohol abuse

Diagnosing **hypogonadism** should include the following tests:

1. FSH level
2. LH level
3. Prolactin level
4. Estradiol levels
5. Seminal fluid examination
6. Thyroid function test
7. Karyotyping

If a clear diagnosis cannot be made, then **testicular tissue testing** (testicular biopsy) and **LH releasing hormone stimulation tests** should be completed.

Hypogonadism

Female hypogonadism

Causes of hypogonadism in females are almost the same as those of males, except that instead of **Klinefelter's syndrome**, **Turner syndrome** occurs. Turner syndrome characteristics include short stature, webbed neck, high arch palate, short fourth metacarpals, and wide-spaced nipples.

Male hypogonadism

Primary hypogonadism or hypergonadotrophic variety

The source of this type of hypogonadism is within the gonads. The pituitary and hypothalamus function normally. **Causes of primary hypogonadism include:**

1. Genital trauma
2. Autoimmune destruction
3. Mumps orchitis
4. Side effects of drugs, such as cyclosporine or chemotherapeutic agents
5. Congenital disorders (Klinefelter's syndrome or bilateral anorchia)

Secondary hypogonadism or hypogonadotropic variety

Secondary hypogonadism occurs because of decreased pituitary or hypothalamic secretions, leading to the decreased growth of gonads and other characteristics.

Causes include:

1. Idiopathic causes
2. The post-infectious state of CNS
3. Prolactinoma
4. Damage to the hypothalamus or pituitary via radiation, tumor, or infiltrative trauma
5. Hereditary hemochromatosis
6. Congenital disorders, such as Kallman's syndrome
7. Side effects of drugs, such as opiates, glucocorticoids, or Lueprolide (used to treat prostate cancer)

Signs and symptoms of hypogonadism

Hypogonadism can begin during fetal development, before puberty, or in adulthood. Signs and symptoms of the disease depend on when the condition develops.

During fetal development:

Impaired growth of external sex organs occurs during fetal development, leading to any of the following:

- Female genitals
- Ambiguous genitals — genitals that are neither clearly male nor clearly female
- Underdeveloped male genitals

At Puberty:

Delayed puberty or lack of normal development, causing:

- Decreased muscle mass development
- The voice does not deepen
- Impaired body hair growth
- Impaired growth of the penis and testicles
- Excessive growth of the arms and legs in relation to the trunk of the body
- Development of breast tissue (gynecomastia)

In adulthood:

Hypogonadism may alter physical masculine characteristics and impair normal reproductive function.

Signs and symptoms may include:

- Erectile dysfunction
- Infertility
- Decreased beard and body hair growth
- Decreased muscle mass
- Development of breast tissue (gynecomastia)
- Loss of bone mass (osteoporosis)

As testosterone decreases, men have symptoms similar to post-menopausal females, including fatigue, decreased sex drive, difficulty concentrating, and hot flashes.

References

How the Gonadal Axis Works via geekymedics.com

Hypogonadism via medlineplus.gov

Male hypogonadism via mayoclinic.org

Notes