Pharmacology - ES

Done By

Dana Obeidat

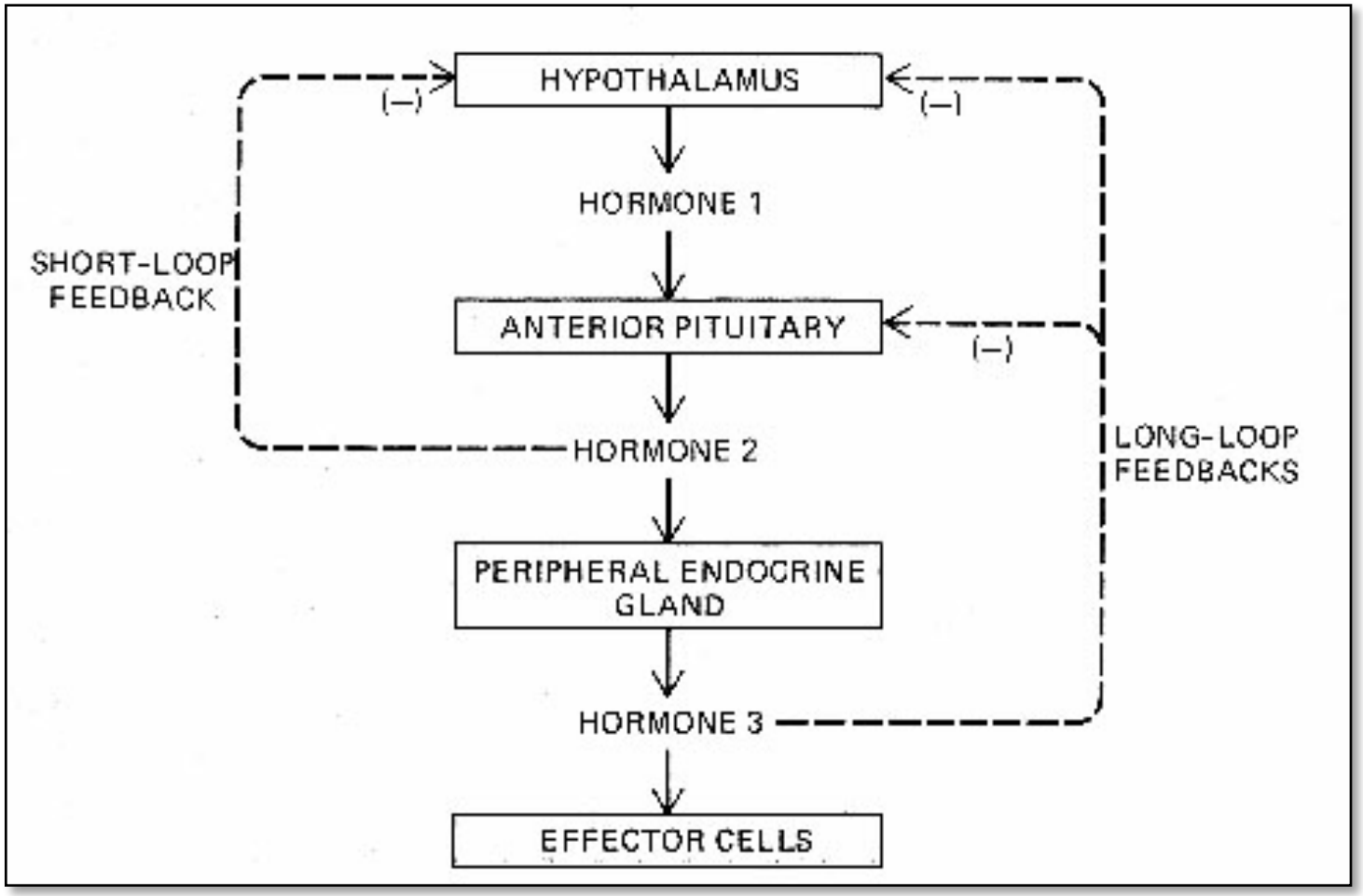
Corrected By

Samah Freihat

النادي الطلابي
كلية الطب

Lecture 2

Feedback control



Recap: Notice that there's 2 loops that discribe the negative feedback control of the Hypothalamus-Pituitary secretions:
First: the **short loop** where accumulation of **hormone 2** will lead to inhibition of the **hypthalumus (–ve feedback mechanism)**.
secondly: the **long loop** where accumulation of **hormone 3** will lead to inhibition of both **hypo thalumus and pituitary** secretions.

Addison's Disease

- Disease in which patients **lack cortisol** from zona fasiculata **(Part of the adrenal cortex)** , and thus **lacks negative feedback** that suppresses ACTH production. **Which will lead to accumulation of ACTH, and therefore accimulation of MSH which will cause skin pigmentation.**
- Result: **overproduction of ACTH**
- **Skin color will darken**

The zona fasciculata constitutes the middle zone of the adrenal cortex, sitting directly beneath the zona glomerulosa.

Regulation of ACTH

- ACTH stimulates production of glucocorticoids from the adrenal cortex.
- **Which lead to** Stimulation to release
  - **CRH and ADH**
  - **Stress**
  - **Hypoglycemia**
- **CRH** and **ADH** both synthesized in hypothalamus

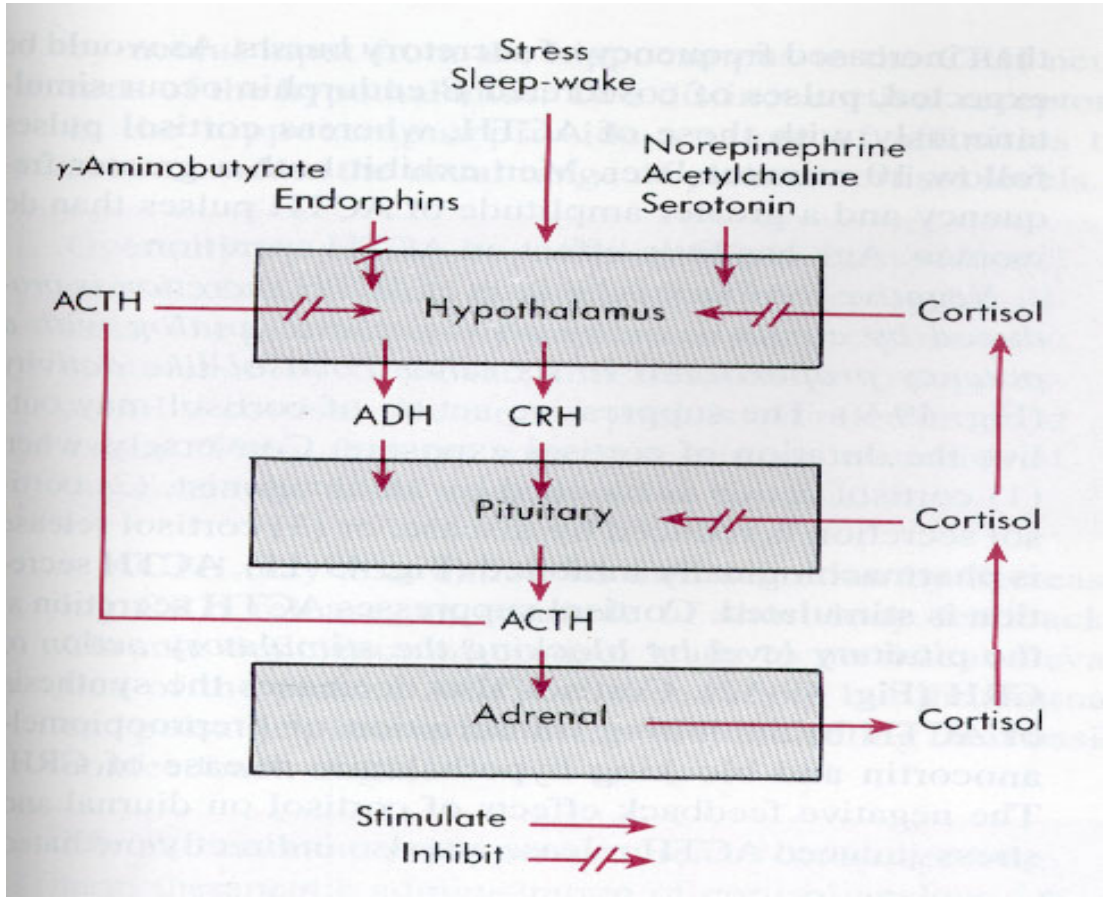
Vasopressin, also known as **antidiuretic hormone** (**ADH**)

Corticotropin-releasing hormone (**CRH**)

ACTH

- **Circadian pattern of release**
  - Highest levels of cortisol are in early AM following ACTH release
  - Depends on sleep-wake cycle, jet-lag can result in alteration of pattern
- **Opposes the circadian pattern of growth hormone secretion**
- **While the Secretion of Growth hormone is highest at the early sleep hours , the secretion of Cortisol is highest after a long night of sleep (At early morning hours) 6:00 – 8:00 AM**

Regulation of ACTH



This diagram summarize the effect of ACTH on the secretion of Cortisol.
1- waking up or Stress will stimulate the Hypothalumus to secrete CRH.
2- CRH will stimulate the Ant. Pituitary gland to secrete ACTH.
3- ACTH will stimulate the Adrenal cortex to produce Cortisol.
4- Accumulation of this cortisol will act in a negative feedback control system, inhibiting the secretions of both the Hypothalumus and the pituitry gland.

Adrenocortical insufficiency

It is easier and less expensive to treat patients having **adrenocortical insufficiency** (lower level of cortisol) with **glucocorticoid replacement** therapy than it is to use ACTH.
Therefore, use of ACTH (*Acthar) is restricted to diagnosis.* (here we only use ACTH for diagnosis)

ACTH

Summary

- **Acts on adrenal cortex**
  - stimulates **growth of cortex** (trophic action)
  - Stimulates **steroid hormone** synthesis. **Especially the cortisol**

- **And Lack of negative feedback from cortisol results in aberrantly high ACTH, elevated levels of other adrenal corticosteroids like adrenal androgens. >> elevated adrenal androgens**

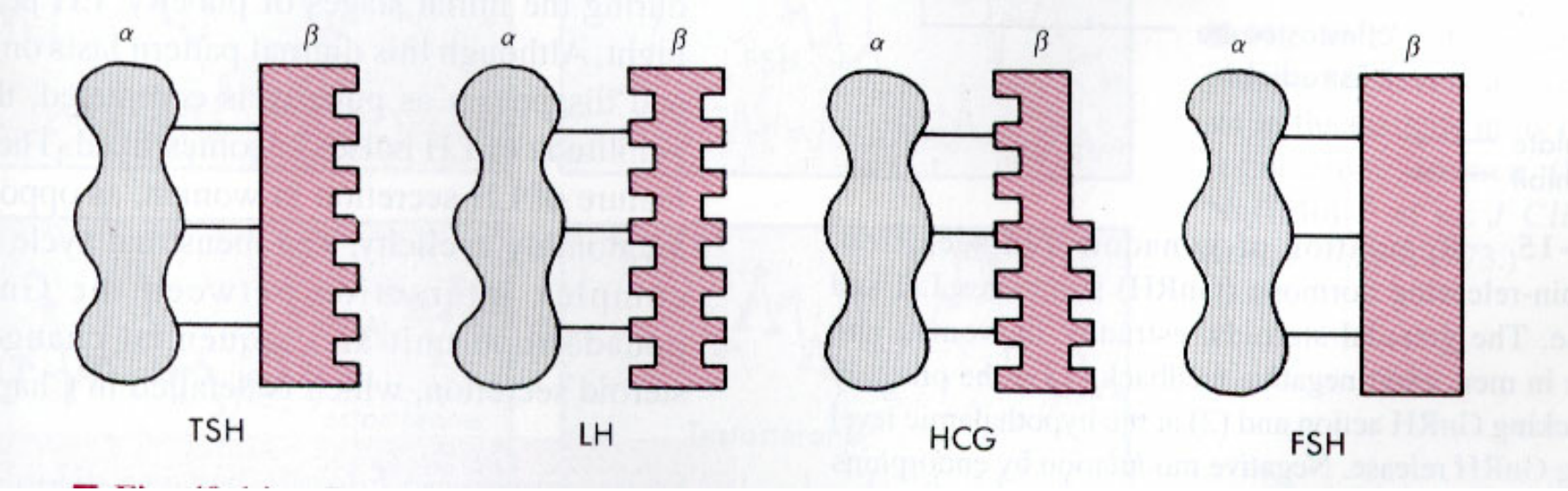
Gonadotropins

1. Follicle-stimulating hormone (**FSH**),
2. luteinizing hormone(**LH**),
3. human chorionic gonadotropin (**HCG**)
4. **TSH**

- And they have
  - (Alpha) and (Beta) subunits
  - Each subunit encoded by different gene
- **(Alpha) subunit**is identical for all hormones
- **(Beta) subunit** are unique and provide biological specificity

Glycoprotein hormones

- **Glycoprotein hormones contain two subunits, a common α subunit and a distinct β subunit: TSH, LH, FSH and hCG.**



Gonadotrophs

- Cells in anterior pituitary that **produce LH and FSH**
- Synthesis and secretion are **stimulated by GnRH**– major effect on LH
- FSH secretion controlled by **inhibin**
- Pulsitile secretion (Like pulses) of GnRH and inhibin cause distinct patterns of LH and FSH secretion.
- Both Inhibin and GnRH are released from the hypothalumus and control the secretions of the Gonadotrophs, specificly GnRH stimulate the secretion of LH while inhibin control the secretion of FSH.

LH/FSH

- LH and FSH are pituitary hormones secreted in pulsatile fashion approximately every 2 hours.
- In women before menopause, this pattern is superimposed on much larger changes that occur during the normal **menstrual cycle**..
- **FSH** is released in substantial amounts during the **follicular phase of the menstrual cycle,** Also Required for proper development of **ovarian follicles** and for estrogen synthesis from granulosa cells of the ovary

Regulation of LH/FSH

- Contraception (prevention of pregnance/ تحديد النسل) depends on the accumulation of progesteron that acts on inhibiting the secretions of Gonadotrophs.
- **Negative feed-back**:
  - **Testosterone** from Leydig cells– synthesis stimulated by LH, feedsback to inhibit GnRH production from hypothalamus and down-regulates **GnRH** receptors
  - **Progesterone**– suppresses ovulation, basis for oral contraceptives. Works at both the level of pituitary and hypothalamus.
- **Dopamine**, **endorphin**, and **prolactin** inhibit GnRH release.
  - Prolactin inhibition affords post-partum contraceptive effect
- **Overproduction of prolactin** via pituitary tumor can cause amenorrhea– **shuts off GnRH**
  - Infertility caused by overproduction of prolactin is Treated with **bromocryptine** (**dopamine agonist**) because dopamine inhibits the secretion of Prolactin.
  - Surgical removal of pituitary tumor.

Regulation of LH/FSH

- **Positive feedback**
  - **Estradiol** at high plasma concentrations in late follicular phase of ovarian cycle stimulates **GnRH** and **LH** surge >> triggers ovulation.

HYPOTHALAMIC REGULATORY HORMONES

- **Five peptides** isolated from the hypothalamus regulate release of one or more pituitary hormones. In addition, **dopamine** released from the hypothalamus **inhibits prolactin production.**
- Remembre: Dopamine agoinsts are used to treat accumulation of prolactin.

Somatostatin

- Produced from the hypothalumus.

- Somatostatin (or somatotropin release–inhibiting factor [SRIF]) occurs primarily as a 14–amino acid peptide, although a 28–amino acid form also exists

- **Somatostatin inhibits the secretion of many substances** in addition to growth hormone.

- **Not useful clinically** (that's because it inhibits many hormones not only Prolactin so we prefer to use a drug with higher specificty, however we can use it in diagnosis)

- Inhibition of secretion of Growth hormone, Thyroid-stimulating hormone, Prolactin, ACTH, Insulin, Glucagon, Pancreatic polypeptide, Gastrin.

Thyrotropin-Releasing Hormone

- The hypothalamus releases thyrotropin-releasing **hormone** (**TRH**), which stimulates the pituitary gland to release thyroid-stimulating **hormone** (TSH)
- TRH, or **protirelin** (a synthetic analogue of the TRH), consists of three amino acids.
- Not used as a treatment but TRH (*Relefact TRH) is used for* tests to distinguish primary from secondary hypothyroidism.
- Remember that: Primary hypothyroidism is due to disease in the thyroid while Secondary hypothyroidism which is less common is due to pituitary or hypothalamic disease.

Gonadotropin-Releasing Hormone

GnRH (gonadorelin, luteinizing hormone–releasing hormone)

- Is a decapeptide that **stimulates production of LH and FSH**. It is released in bursts from the hypothalamus at regular intervals, about every 2 hours.
- The pituitary gland responds to these regular pulses by producing LH and FSH

Posterior pituitary hormones: ADH (AVP) and Oxytocin

- The posterior pituitary gland can be considered as a protrusion continuous from the hypothalamus, and as you even the hormones secreted from it are synthesized in the hypothalamus and stored at the posterior pituitary.
- Both are synthesized in the cell bodies of hypothalamic neurons
- ADH: **supraoptic nucleus**
- Oxytocin: **paraventricular nucleus**
- Both are **synthesized as pre-pro-hormones** and **processed into nonapeptides** (nine amino acids**).**
- They are **released** from the termini i**n response to an action potential** which travels from the axon body in the hypothalamus. - to axon terminals in the posterior pituitary gland -

Oxytocin:

➢stimulates myoepithelial contractions

- In uterus during parturition
- In mammary gland during lactation

➢milk ejection from lactating mammary gland

- **suckling is major stimulus for release.**
- sensory receptors in nipple connect with nerve fibers to the spine, then impulses are relayed through brain to PVN where cholinergic synapses fire on oxytocin neurons and stimulate release.

➢uterine contractions

- Reflexes originating in the cervical, vaginal and uterus stimulate oxytocin synthesis and release via neural input to hypothalamus
- Increases in plasma at time of ovulation

ADH:
conserve body water and regulate tonicity of body fluids

- Also known as **vasopressin**
- Regulated by osmotic and volume stimuli.
- Hypovolemia stimualte ADH secretion
- Water deprivation **increases osmolality** of plasma which activates hypothalmic osmoreceptors to **stimulate ADH release.** So ADH conserve body water by reducing the loss of water in urine decreasing osmolarity.