Title: Sheet 2 – Hypothalamus and pituitary 2

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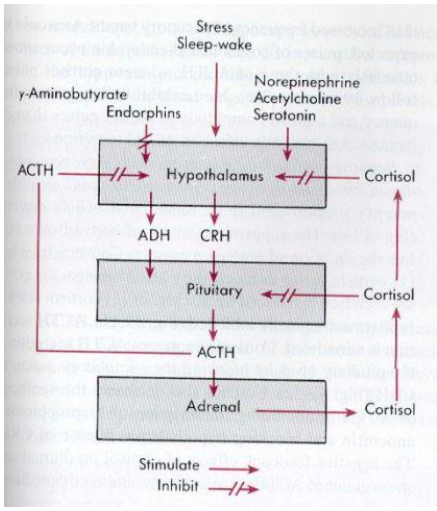
Addison's Disease (1:27)

- Disease in which patients lack cortisol from the zona fasciculata in the adrenal cortex, and thus lack negative feedback that usually suppresses ACTH production.
- **Result**: overproduction of ACTH.
- Due to the overproduction of ACTH, some substances/products will increase in the body, one of them being **MSH → Skin color will darken**.
- **Note**: the *zona fasciculata* constitutes the middle zone of the adrenal cortex, sitting directly beneath the zona glomerulosa.

ACTH and its Regulation (3:08)



- **ACTH** stimulates production of glucocorticoids from the adrenal cortex.
- **Acts on the adrenal cortex to:**
  - Stimulate growth of the cortex (trophic action)
  - Stimulate steroid hormone synthesis
- **Lack of negative feedback from cortisol** results in aberrantly high ACTH, and elevated levels of other adrenal corticosteroids, such as adrenal androgens.
- **Stimulation of release of ACTH**: CRH (Corticotropin-releasing hormone) and ADH (Vasopressin), Stress, Hypoglycemia (notice the figure on the right).
- **The diagram on the right** demonstrates the effect of ACTH on the production of cortisol.
  - **Stress and sleep-wake cycles** stimulate the hypothalamus → **CRH** is secreted → Stimulates the **anterior pituitary** → **ACTH** is secreted from the anterior pituitary → **ACTH** affects the **adrenal gland** and stimulates the release of **cortisol** → Cortisol accumulates and is responsible for **the feedback inhibition** (affecting both the hypothalamus and anterior pituitary gland).

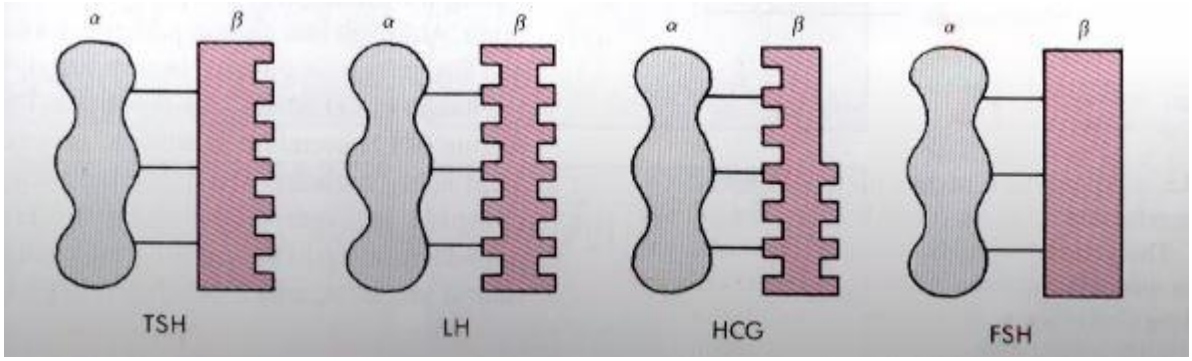
- **Circadian pattern** of release of ACTH and cortisol
  - ✓ Cortisol levels are highest in the early morning, following ACTH release**.**
  - ✓ Depends on sleep-wake cycle (jetlag can result in alteration of the pattern).
- Cortisol opposes the circadian pattern of growth hormone secretion, which occurs in the early hours of sleep. So, by getting enough sleep, we are able to maintain balance between the level of **cortisol** and **growth hormone.**
- **To treat patients having adrenocortical insufficiency** (low ACTH) it's easier and less expensive to use glucocorticoid replacement therapy than it is to use ACTH (Use of ACTH (Acthar) is restricted to diagnosis).

Gonadotropins (8:29)

- Follicle-stimulating hormone (FSH), luteinizing hormone(LH), human chorionic gonadotropin (hCG) ''produced by the placenta after implantation'' and TSH

Note: The professor included TSH amongst gonadotropins, but according to Guyton, and other trusted internet sources, it is not identified as one.

- They have α and β subunits, each subunit encoded by a different gene.
  - ✓ a subunit is identical in all of the previously stated hormones.
  - ✓ b subunit is unique (So it provides biological specificity).
- Glycoprotein hormones (TSH, LH, FSH and hCG) contain two subunits, a **common** α subunit and a **distinct** β subunit (It differs from one hormone to another).



- **Gonadotrophs**: cells in the anterior pituitary that produce LH and FSH.
- Synthesis and secretion of LH and FSH are stimulated by GnRH (major effect on LH).
- **FSH secretion is controlled by inhibin** (A hormone secreted by the granulosa cells in the ovaries of women, and it inhibits the secretion of FSH).
- The pulsatile secretion of **GnRH** and **inhibin** controls secretion of LH and FSH.

LH/FSH (11:21)

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

Regulation of LH/FSH (12:58) -Contraception-

- Negative feedback
  - ✓ **Testosterone** from Leydig cells (its synthesis is stimulated by LH)→ Leads to feedback inhibition of GnRH production from hypothalamus, and it down-regulates GnRH receptors.

- ✓ **Progesterone**:
  - Its accumulation will lead to negative feedback on the GnRH secretion from the hypothalamus → This leads to suppression of ovulation (basis for oral contraceptives).
  - It also provides negative feedback on the secretion of LH from the anterior pituitary.
  - So, progesterone works at both levels of the pituitary and the hypothalamus.
- **Dopamine, endorphin, and prolactin** inhibit GnRH release by negative feedback. (Prolactin inhibition affords post-partum contraceptive effect)
- Overproduction of prolactin via pituitary tumor can cause amenorrhea and infertility– shuts off (inhibits) GnRH
  - ✓ **Treated with bromocriptine (dopamine agonist)**
  - **Dopamine** inhibits prolactin secretion → No accumulation of prolactin → This affects the negative feedback that affects GnRH → GnRH is now released and is no longer inhabited by prolactin → Stimulates LH secretion → Ovulation
  - ✓ Surgical removal of pituitary tumor
- Positive feedback
  - ✓ In the late follicular phase of the ovarian cycle, **high plasma concentration of Estradiol** stimulates GnRH and LH secretion, which will trigger ovulation.

Hypothalamic Regulatory Hormones (16:37)

- Five peptides isolated from the hypothalamus regulate release of one or more pituitary hormones. In addition, dopamine released from the hypothalamus inhibits prolactin production.

- **Somatostatin (17:20)**
  - ✓ Somatostatin (or somatotropin release–inhibiting factor [SRIF]) is a 14 amino acid peptide, although a **28 amino acid form also exists.**
  - ✓ Somatostatin inhibits the secretion of many hormones, including GH.
  - ✓ It inhibits the secretion of GH, TSH, Prolactin, ACTH, Insulin, Glucagon, Pancreatic polypeptide and Gastrin.
  - ✓ Not useful for therapy (clinically) because it inhibits the production of many hormones, which makes it non-specific and non-effective. In order to use a substance for therapy, it should be specific primarily (but we can use somatostatin for diagnosis).

- **Thyrotropin-Releasing Hormone (18:28)**
  - ✓ Thyrotropin-releasing hormone (or **protirelin**) consists of **three amino acids.**
  - ✓ TRH (**Relefact TRH**) is used in tests, to distinguish primary from secondary hypothyroidism (not useful clinically).

- **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, approximately every 2 hours.
  - ✓ The pituitary gland responds to these regular pulses by producing LH and FSH.

Posterior pituitary hormones (19:37)

- The posterior pituitary gland is considered as a protrusion of the hypothalamus.
- Hormones of the posterior pituitary gland are hormones that are originally synthesized in the hypothalamus and are STORED in the posterior pituitary.
- ADH and Oxytocin are both synthesized in the cell bodies of hypothalamic neuron
  - ✓ **ADH**: supraoptic nucleus
  - ✓ **Oxytocin**: paraventricular nucleus
- Both are synthesized as preprohormones and processed into nonapeptides (Peptides that consist of nine amino acids).
- They are released from the termini in response to an action potential which travels from the axon body in the hypothalamus.

Oxytocin (21:03)

- **stimulates myoepithelial contractions** in 1- The **uterus during parturition** and in 2- The **Mammary gland during lactation**
- Stimulates milk ejection from **lactating mammary gland**
  - ✓ **Suckling** is the major stimulus for the release of milk. How?
  - ✓ Sensory receptors in the nipple are connected to nerve fibers to the spine, then impulses are relayed through the brain to PVN (paraventricular nucleus) where cholinergic synapses fire on oxytocin neurons and stimulate its release.
- **Uterine contractions**
  - ✓ Reflexes originating in the cervix, vagina and uterus stimulate oxytocin synthesis and release through neural input to the hypothalamus → Oxytocin is then stored in the posterior pituitary, to be released.
  - ✓ During the process of ovulation, plasma levels of oxytocin increase. (This occurs in response to a signal that induces myoepithelial contractions).

ADH: conserves body water and regulates tonicity of body fluids (23:30)

- Also known as **vasopressin** (AVP)
- Regulated by osmotic and volume stimuli.
- Water deprivation increases osmolality of plasma which activates hypothalamic osmoreceptors to stimulate ADH release → This conserves water and returns the plasma osmolality back to normal.