Endocrine system

Sheet 3

Pharmacology

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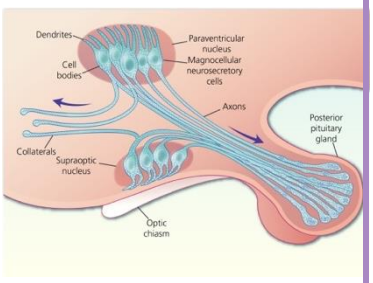
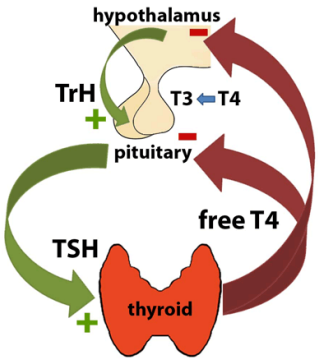
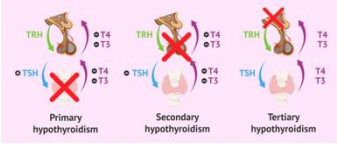
المحاضرة سهلة -نسبيًا-، بشوف لو ترجع بعد دراسة فسيو٣و٤أحسن -لو لسا مادرستهم- ويعطيكم العافية، بالتوفيق.



- Hypothalamic hormones
  - The Hypothalamus synthesizes and releases **ADH & Oxytocin (Neurohormones)** and by the neuro-secretory axons they reach **Posterior pituitary**, where they are stored and get releases when needed
  - The Hypothalamus regulates the synthesis and release of hormones of the **Anterior pituitary**, via regulatory hormones reaching AP through network of capillaries (Namely, **portal system**)
    - AP's hormones Under **Stimulatory** control by the hypothalamus:
      - ACTH (Adrenocorticotropic hormone), TSH (Thyroid-stimulating hormone), LH (Luteinizing hormone) and FSH (Follicle-stimulating hormone)
    - AP's hormones Under **Stimulatory** and **Inhibitory** control by the hypothalamus: GH (Growth hormone), PRL (Prolactin) and MSH (Melanocyte stimulating hormone)
- General characteristics of hypothalamic hormones:
  - TRH, CRH, GHRH, GHIH, GnRH, Dopamine (DA)
  - They are small peptides and polypeptides (Except for **Dopamine** being an Amino acid derivative) of low M.W.
  - Needed in very low concentrations (pg) (10^{-12}g!!)
  - Have short $t_{1/2}$
  - Act on receptors on **plasma membrane**.

- TRH=Thyroid releasing hormone (**Protirelin**)
  - Tripeptide, synthetic analogs are available.
  - Effective orally and I.V.
  - Stimulates TSH synthesis and release in the anterior pituitary gland.
    - MOA:
      - Activation of phospholipase C to increase intracellular IP3 and DAG.
    - Also, TRH has been found to increase **PRL release** through 2^{nd} messenger $\boldsymbol{Ca}^{++}$.
  - Mainly used:
    - As a diagnostic tool or for diagnostic purposes in what came to be known as **TRH test** to assess the function of TSH producing cells in the anterior pituitary.





- To treat certain cases of hypothyroidism, namely, TERTIARY hypothyroidism which is accompanied with TRH deficiency -Provided that the anterior pituitary and thyroid are OKAY-
  - Dose:
    - 50μg **I.V.**, 5mg **orally**, maximum response in 15-30 minutes, duration of action 2-4 hrs.

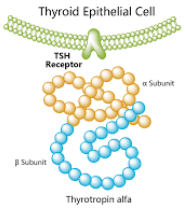
- CRH=Corticotropin releasing Hormone
  - It's the central hormone of the "Flight and fight"/Stress response.
    - **41 a.a** peptide stimulates synthesis and release of **ACTH**.
    - CRH release is **elevated** during **Stress** ↑
  - Diagnostic use (**CRH test** to assess ACTH producing cells)
- GHRH=Growth hormone releasing hormone (Hexarelin, sermorelin)
  - **40 a.a**, synthetic preparations are available.
  - Diagnostic use & in the management of certain cases of dwarfism. (**It is given SC**)
    - As it can be used to manage GH deficiency in patients with hypothalamic dysfunction
- GHIH (Somatostatin)
  - 14 a.a peptide
  - ↓ Secretion and synthesis of GH, ACTH, TSH, Insulin, Glucagon, Gastrin, serotonin. (From GI module we know it has a sorta "all rounded" inhibitory effect)
  - Its effects on blood glucose are **dose dependent.**
    - **Low dose ➔ hypoglycemia** (↓ glucagon secretion)
    - **High dose ➔ hyperglycemia** (↓ insulin secretion)
      - Thus, it has a role in the management of DM.
    - Why don't we just use it? The natural somastatin is characterized by a short $t_{1/2}$ lower than 5 minutes.
      - We have synthetic analogs that have a longer duration of action. (Ex: Octreotide)
- Octreotide (Given **S.C**) & Lanreotide (Given I.M)
  - Synthetic analogs to somatostatin with longer $t_{1/2}$ and are mainly use in the management of:
    - **Acromegaly (Excess production of growth hormone in adults)**
    - **Carcinoid tumor**
      - A tumor affecting the interchromatin cells of the intestines ➔ Characterized by the excessive production of **serotonin** and can eventually lead to severe manifestation of ➔ **Intractable diarrhea**.
        - Since octreotide is a synthetic analog of somatostatin, thus, **it inhibits serotonin release** and therefore, it can be used here.
    - Insulinomas, gastrinomas
      - Since it and other analogs inhibit Insulin & Gastrin production/release.
    - Esophageal varices
      - It promotes platelet aggregation ➔ It could eliminate the bleeding that occurs in the varicose veins which affect the esophagus.
    - ?? Diabetes mellitus
      - They are still **under clinical evaluation** because of the side effects that are produced, particularly on platelets.

- **Major side effects**: Gallbladder stone formation and platelet abnormalities**.**

- Pituitary hormones
  - Anterior Pituitary Hormones could be chemically classified into:
    - **Simple peptides**
      - ACTH
      - MSH
    - **Proteins**
      - GH
      - PRL
    - **Glycoproteins**
      - LH
      - FSH
      - TSH
  - Posterior Pituitary Hormones
    - **Simple peptides** (9 a.a)
      - ADH (Vasopressin)
      - Oxytocin
    - Hypothalamic hormones regulating the anterior pituitary hormones reach the anterior pituitary through a network of capillaries (Portal system).
    - whereas ADH and oxytocin reach the posterior pituitary via neurosecretory axons.

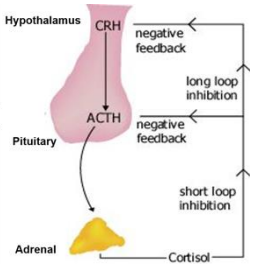
- Anterior pituitary hormones
  - Hypothalamic lesion or removal ➔ ↓ Ant. Pit H's **except PRL**
  - Hypothalamic stimulation ➔ ↑ Ant. Pit H's **except PRL**
    - That gives you an idea that prolactin is mainly under the (↓) **inhibition by the hypothalamus** through a hormone or substance that **inhibits the release and synthesis of prolactin** from AP, namely, **Dopamine**.

- **TSH=Thyroid stimulating hormone (Glycoprotein)**



  - It's only needed by the thyroid gland.
  - ↑ T_3 & T_4(Stimulates some steps of the synthesis of such hormones) through ↑ **intercellular cAMP, ↑ Iodine uptake ➔ Storing them in the thyroid**
  - Since TSH is a glycoprotein, it has α *and* β subunits ➔ Thus, it could be used as a **diagnostic tool** to assess the function of the thyroid.

- ACTH



  - Derived from larger precursor (pre-opiocortin)
  - ↑ **Cortisol synthesis and release** from the adrenal gland
  - Undergoes circadian rhythm.
    - It has a diurnal variation, aka:
      - It has a **higher** production and release during the **Day**
      - It has a **lower** production and release during the **night**
      - Thus, this (Circadian rhythm) is reflected also on cortisol's levels.
      - This has a clinical significance ➔ Because whenever we use hormones in HRT, we try as much as possible to mimic physiology.
  - **Acthar and Cosyntropin** (Tetracosactrin; Cortrosyn)
    - Are **synthetic analogs** to ACTH.

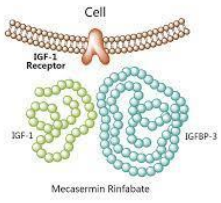
- Uses:
  - (Mainly)Diagnostic use (Given **I.V** or **I.M**)
    - Assess the functions of cortisol secreting cells from the adrenal gland.
  - Management of certain adrenal insufficiency ➔ Provided the adrenal gland is okay.

- Growth hormone (Somatropin)
  - Species specific. The chemical structure of GH in humans is completely different to that of animals. Thus, any GH of animalic origin is ineffective.
    - Unlike insulin for example, which has a chemical structure so similar to that of a pig's, cow (Difference of 3 AA) or any porcine source.
  - MOA: **Unclear,** its effects are believed to be mediated through **IGFs (Somatomedins)** which are formed in the liver, kidneys, muscles and other tissues.
  - GH stimulates growth of soft tissue and bones
  - ↑ Lipolysis
  - ↑ **Gluconeogenesis** & ↓ Glucose utilization ➔ Diabetogenic effect.(elevate blood sugar level).
  - **PRL -like activity** (They have a somewhat identical chemical structure)
- Factors ↑ **GH** release:
  - **Sleep** (Release and synthesis of GH are maximal during the night ➔ That's why we advise children advised to sleep early ➔ To maximize their growth.), **Arginine**, **Insulin** and **Hypoglycemia/**
  - β-adrenergic antagonists
  - Clonidine
  - ***DA* agonists**: Bromocriptine & Levodopa in **normal individuals**.
- Factors ↓ **GH** release:
  - **Bromocriptine (It's the most prominent one out of DA agonists)** in **acromegalics**.
    - It's still not well understood why such a paradoxical effect is taking place...
  - Somatostatin synthetic analogs.
- Disorders affecting GH secreting cells:
  - Hypersecretion of GH ➔ Gigantism (Children), Acromegaly (Adults)
    - R_x:
      - Surgery:
        - At the very late stages, no matter what you do, it doesn't matter, the patient wouldn't survive, surgical removal of the pituitary and replacement of other hormone would save him.
      - Somatostatin synthetic analogs (Ex: Octreotide) ➔ ↓ synthesis and release of GH.
      - **DA agonists** (Ex: Bromocriptine: Cabergoline) ➔ ↓ synthesis and release of GH. Only in acromegalics)
      - **Pegvisomant** (GH receptor antagonist, given **SC**, **major side effects** include:
        - Abnormal liver enzymes
        - Some reports indicate increased growth of GH-secreting pituitary tumors.
        -

- Hyposecretion of GH ➔
    - In **children** it leads to **dwarfism** manifested by a very short trunk, short neck, shortened arms and legs, average-size hands and feet, broad rounded chest…
        - R_x of **dwarfism** ➔ GH replacement therapy. (Highly successful in children)
    - In **adults(**It's not that much common**)** leads to a higher level of body fat, especially around the waist, anxiety and depression, decreased sexual function and interest, fatigue, less muscle…
        - R_x of GH deficiency in adults ➔ (Lifestyle modification) Loss of weight, good sleep, high protein-low carbohydrate diet, exercises ± GH replacement therapy (Not that much frequently because it's associated with severe side effects, particularly on the cardiovascular system.)

- GH replacement therapy
    - **Highly successful** in treating dwarfism in **children**.
    - GH-replacement therapy is given in 2 forms:
        - I.M (3 injections per week)
        - S.C (Taken on daily basis)
            - **It's better than I.M**, not only because it's **easier** than I.M or because the patient can do it himself, rather, as we knew from before, GH release is maximal during the night, so, reaching a maximal release everyday would certainly have a better impact than only 3/week.
                - **For how long** does the child need to take it? ➔ Until the growth (Epiphysial) plate closes.
    - Recombinant human (As we discussed before, no animal GH is effective. Thus, we resort to recombinant technology) GH preparations:
        - Somatropin (Humatrope)
        - Somatrem (Protropin)

- **Mecasermin (Recombinant human IGF-1)**



    - There were certain cases of growth deficiency believed to be due to growth hormone deficiency but **weren't responding to GH HRT!** ➔ Later, it was found that they are **deficient in IGF.**
    - Mecasermin rinfabate (Recombinant human IGF-1 + **IGF** binding protein-3=IGFBP-3 (To extend duration of action of Mecasermin))
        - For whom is it given? Given by **SC** for a dwarf with IGF-1 deficiency not responding to GH.
        - Major side effect is hypoglycemia.

- Side effects of synthetic rHGH (Recombinant human growth hormone)
    - **Usage of IGF-1 have very severe side effects**; however, they aren't that much common in the dwarf child because usually only small doses are given. We usually don't use pharmacological or high doses.
    - Water retention
    - The development of antibodies to HGH
    - Insulin resistance & Diabetes
    - Hypertension
    - Carpal tunnel syndrome
    - Abnormal bone growth

- Reduced life span (Many reports saying that administering GH to adults with GH deficiency could lead to decrease or reduction of lifespan)
- Disturbed insulin metabolism
- Leukemia
- Overgrowth of connective tissue and tumors
- ↑ Intracranial pressure with **papilledema**

- **Prolactin (PRL)**
  - **Produced by: Ant. Pit; Placenta**
  - Dopamine is a major regulator of prolactin synthesis and release by the anterior pituitary. In order to increase prolactin ➔ We have to inhibit dopamine.
  - Has GH-like activity (Due to the similarity of chemical structure with GH).
  - In ♂s
    - Normally, normal levels of PRL have a role in the sexual function of the male as PRL increases testosterone production by testes and hence spermatogenesis, **BUT ↑ PRL, high levels of prolactin, hyperprolactemia usually leads to➔** ↓ LH & FSH ➔ ♂ impotency & infertility.
  - In ♀s
    - Prolactin's role is much more obvious in females where it's very essential to.
      - Breast development (Puberty; Pregnancy)
      - Lactation (Synthesis of milk is the function of prolactin. Ejection of milk from breast during breast feeding is the function of oxytocin)
    - **↑ PRL ➔** ↓ LH & FSH ➔ Galactorrhea (Milky discharge from the nipple) amenorrhea (Loss of menses) syndrome
- Factors/Drugs ↑ PRL:
  - Pregnancy, sleep, nursing, stress (Surgery, exercise)
  - TRH, Estradiol, DA antagonists (Antipsychotics=Phenothiazines and haloperidol; metoclopramide...)
  - Methyldopa, resprine, diazepam, opiates (Addicts to opiates don't get pregnant easily because of opiates' effect on prolactin release and synthesis), meclizine, imipramine...
- Factors/Drugs ↓ PRL:
  - DA agonists:
    - Again, why not just use dopamine? ➔ It doesn't enter the CNS
    - **Bromocriptine**
      - Clinical uses:
        - The drug of choice for the management **hyperprolactemia** in ♂s and ♀s irrespective of its causes.
          - Sometimes, there can be cases of infertility from the male side rather than the female's, it could be due to a little elevation of PRL without affecting the sexual function of the male.
          - In cases of infertility, both should be tested with respect to their hormones related to fertility.
          - In such cases of hyperprlocatemia, management with DA agnonist is so easy, especially, with bromocriptine which is highly effective.

- Suppression of lactation
  - **ONLY** If there was any indication to suppress lactation, Bromocriptine is given.
    - If the fetus died in utero after delivery ➔ The lady would still have high production of milk.
    - If there was a severe cracking of the nibble or an abscess forming next to breast due to severe inflammation.
- **Acromegaly**
- Parkinson's disease (Some types of Parkinson's are characterized by dopamine deficiency and excessive Acetylcholine production)
- DM type II
  - The exact MOA is little bit complex. It acts at the level of hypothalamus ➔ Changing the circadian rhythm of food intake by the hypothalamus ➔ ↓ Sympathetic activity ➔ serotonin activity ↓ ➔ ↓ Blood glucose level ➔ ↑ sensitivity of peripheral tissue to insulin

- Bromocriptine is given **orally**
- Side effects:
- **RARE.** Pulmonary fibrosis; confusion; hallucination; MI...

- **Pergolide**
- **Levodopa**

- Apomorphine
- Clonidine
- MAO inhibitors (pargyline)

Test your knowledge

1) Which of the following is wrong about hyperprolactinemia?

a) In males it causes impotence
b) Over-stress could cause levels of prolactin to increase
c) Responsible for half of the cases of infertility in females
d) Treated with Dopaminergic agonists
e) Non of the above

2) Which of the following sentence is true?

a) Highest levels of cortisol are at night following ACTH release
b) Cortisol release is same as the circadian pattern of growth hormone secretion

c) Lowest levels of cortisol are in early AM following ACTH release Cortisol release
d) Opposes the circadian pattern of growth hormone secretion
e) None of the above

3) Secreted by the posterior pituitary gland

a) ACTH
b) ADH
c) LH
d) FSH
e) None of the above
f) All the above

4) False statement about prolactin

a) Prolactin acts with other hormones on the mammary gland during pregnancy to develop lactation and after birth to maintain it
b) Hyperprolactinemia causes impotence in men
c) Hyperprolactinoma causes amenorrhea and infertility in women
d) Decreases during stress

5) Maximum level of Growth Hormone at

a) An hour after the onset of sleep
b) An hour before waking up
c) During the day
d) None of the above

Thank you

1)C 2)D 3)B 4)D 5)A