ENDOCRINE
PHARMACOLOGY

02

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HYPOTHALAMIC HORMONES

- **Hypothalamus → ADH & Oxytocin → neuro-secretory axons** (neurohormone) **→ Posterior pituitary (**stored there**).**
- **Hypothalamus → Hormones → network of capillaries (portal system) →Anterior pituitary.**
- **ACTH, TSH, LH, FSH (stimulatory control)**
- **GH, PRL** is inhibited by dopamine**, MSH,** it protects the skin from UV & makes skin darker **(stimulatory and inhibitory control)**

- **General characteristics of hypothalamic hormones:**

TRH, CRH, GHRH, GHIH, GnRH, Dopamine (DA)

- **Small peptides and polypeptides (except DA** which is an AA derivative**) of low M.W.**
- **Needed in very low concentrations (pg).**
- **Have short t1/2.**
- **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.**
- **MOA: Activation of phospholipase C to increase intracellular IP3 & DAG**
- **Also, TRH has been found to increase PRL release through 2nd messenger Ca++**

- **Mainly used:**
  - **As a diagnostic tool (TRH test)** to assist the function of TSH producing cells in the anterior pituitary.
  - **To treat certain cases of hypothyroidism.** (TRH deficiency with normal thyroid).
  - **Dose: 50 µg I.V, 5 mg orally, maximum response in 15-30 min, DOA 2-4 hrs**

➢ CRH=Coricotropin Releasing Hormone

- ❖ **41 A.A peptide stimulates synthesis and release of ACTH, stress ↑ CRH release.**
- ❖ **Diagnostic use (CRH test).**

➢ GHRH (Hexarelin, Sermorelin)

- ❖ **40 A.A peptide, synthetic preparations are available.**
- ❖ **Diagnostic use and in the management of certain cases of dwarfism (it is given SC).**

➢ GHIH (Somatostatin)

- ❖ **14 A.A peptide**
- ❖ **↓ secretion of GH, ACTH, TSH, Insulin, Glucagon, Gastrin, Serotonin**
- ❖ **Its effects on blood glucose levels are dose dependent.**
  - **Low doses → hypoglycemia (↓ glucagon secretion).**
  - **High dose → hyperglycemia (↓ insulin secretion).**

Octreotide (given S.C) & Lanreotide (given I.M) Synthetic analogs to somatostatin with longer t1/2 are mainly used in the management of:

- ❖ **Acromegaly** (excess production of GH)
- ❖ **Carcinoid syndrome** → tumor affecting enterochromaffin cells in intestine with excess release of serotonin leading to severe diarrhea, (somatostatin analogs inhibit serotonin).
- ❖ **Insulinomas** increase insulin even after your blood sugar is low**, gastrinomas** increase in gastrin secretion**.** (Somatostatin inhibits insulin & gastrin release).
- ❖ **Esophageal varices** extremely dilated veins in the lower esophagus, they are most often a consequence of portal hypertension. (Somatostatin increase platelet aggregation)
- ❖ **Diabetes mellitus**→ (they are under clinical evaluation due to somatostatin side effects)

➢ **Major side effects: Gall bladder stone formation and platelet abnormalities.**

PITUITARY HORMONES

ANTERIOR PITUITARY HORMONES

- **Simple peptides: ACTH, MSH** is produced by the hypothalamus and the skin.
- **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 → ↓ Anterior Pituitary Hormones except PRL**
- **Hypothalamic stimulation → ↑ Anterior Pituitary Hormones except PRL** (because prolactin is inhibited by dopamine which has different and additional routes to reach the anterior pituitary than other hormones)

- **TSH**
  - **↑ T3 & T4 through ↑ cAMP, ↑ Iodine uptake** (only needed by thyroid gland to synthesize hormones)
  - **↑ iodination and hydrolysis of thyroglobulin**
  - **diagnostic use** or to assess the function of the thyroid gland.
- **ACTH**
  - **Derived from larger precursor (Pro-opiocortin)**
  - **↑ cortisol release**
  - **Undergoes circadian rhythm.**
  - **Acthar and Cosyntropin (tetracosactrin; Cortrosyn) are synthetic analogs.**

- **Uses:**
  - **Diagnostic use (given I.V or I.M)** to assist the function of cortisol releasing cells in adrenal gland.
  - **Certain cases of adrenal insufficiency**

- **Growth hormone (Somatropin)**
  - **Species specific Synthesized**, animal insulin for example (beef or pig). Pig insulin differs from human insulin in 1 AA (less allergy), not used on humans only for research.
  - **MOA unclear, its effects believed to be mediated through IGFs (Somatomedins) which are formed in the liver, kidneys, muscles, and other tissues.**
  - **GH stimulates growth of soft tissues and bones.**
  - **↑ lipolysis - ↑ gluconeogenesis & ↓ glucose utilization (diabetogenic effect)**
  - **PRL-like activity** (similar structure)

  - **Factors ↑ GH release:**
    - **Sleep, Arginin, Insulin, Hypoglycemia**

When we give arginine or insulin if there is an increase in GH release then there is no problem.

- **β-adrenergic antagonists, Clonidine, Bromocriptine and Levodopa in normal individuals**

- **Factors ↓ GH release:**
  - **Bromocriptine in acromegalics**
  - **Somatostatin synthetic analogs**

Bromocriptine lowers GH only when there is over secretion (acromegaly)

And increase GH in normal individuals. (Dopamine agonists in general have the same effect).

❖ **Disorders affecting GH secreting cells:**

1. **Hypersecretion → Gigantism** (children)**, Acromegaly** (adults)

❖ **Rx:**

➢ **Surgery** (intranasal to remove tumors if there is a good outcome may be a complete cure)

➢ **Somatostatin synthetic analogs**

➢ **DA agonists (Bromocriptine; Cabergoline) and**

➢ **Pegvisomant (GH-receptor antagonist, given SC, major side effects include abnormal liver enzymes and some reports indicated increased growth of GH-secreting pituitary tumors)**

2. **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.**

❖ **In adults Not so common but it may lead to a higher level of body fat, especially around the waist, anxiety, and depression, decreased sexual function and interest, fatigue, less muscle.**

➢ **Rx of dwarfism → GH replacement therapy**

➢ **Rx of GH deficiency in adults → loss of weight, good sleep, high protein low carbohydrate diet, exercises ± GH replacement therapy** (lifestyle modification)

GH replacement therapy

➢ **GH-replacement therapy with S.C** (subcutaneous) **or I.M** (intramuscular) **recombinant human GH preparations:**

- **Somatropin (Humatrope)**
- **Somatrem (Protropin)**

❖ If given subcutaneously→everyday till puberty. (Preferable at night)
❖ If given IM→2 or 3 times a week. (More convenient and lead to better results)

➢ **Mecasermin (recombinant human IGF-1).**

❖ In certain cases, it is believed that the problem is from GH deficiency, but GH levels are normal, they don't respond to HRT, it was found out that the deficiency is from IGF-1.

- ❖ **mecasermin rinfabate (recombinant human IGF-1 +IGF binding protein-3 (IGFBP-3), given SC in dwarf with IGF-1 deficiency not responding to GH, hypoglycemia is a major side effect.**
- ❖ **Mecasermin rinfabate is like Mecasermin in that both drugs contain recombinant DNA origin insulin-like growth factor 1 (IGF-1). Mecasermin rinfabate however, is already bound to recombinant DNA origin insulin-like growth factor binding protein 3 (IGFBP-3). The binding of IGF-1 to IGFBP-3 is said to extend the half-life and reduce the clearance of IGF-1 in patients with growth hormone resistant syndromes and low levels of IGFBP-3 though this may represent <500 patients worldwide.**

✓ **Both mecasermin and mecasermin rinfabate are usually given SC**

Side effects of synthetic rHGH (recombinant human growth hormone) **products:**

- ❖ **Water retention, the development of antibodies to HGH, insulin resistance and diabetes, hypertension, carpal tunnel syndrome, abnormal bone growth, reduced life span, disturbed insulin metabolism, leukemia, overgrowth of connective tissue, and tumors, intracranial pressure with papilledema**

➢ **Prolactin (PRL)**

Anterior Pituitary & Placenta

- ❖ **Dopamine (DA)**
- ❖ **Has GH-like activity**
- **In ♂s:**
  - ❖ **PRL increases testosterone production by testes** (14 days treatment) **and hence spermatogenesis but ↑ PRL → ↓ LH & FSH → ♂ impotency & infertility.**

It increases sexual desire & help in ejaculation.

- **In ♀s:**
  - ❖ **Breast development (puberty; pregnancy)**
  - ❖ **Lactation**
  - ❖ **↑ PRL → ↓ LH & FSH (galactorrhea amenorrhea syndrome)**

Side note: galactorrhea is a milky nipple discharge unrelated to the normal milk production of breast-feeding. amenorrhea: the absence of menstruation.

- **Factors/drugs ↑ PRL:**
  - **Pregnancy, sleep, nursing, stress (surgery, exercise)**
  - **TRH, Estradiol, DA antagonists (antipsychotics= phenothiazines and haloperidol; metoclopramide...)**
  - **Methyldopa, reserpine, diazepam, opiates, meclizine, imipramine…**
- **Factors/drugs ↓ PRL: DA agonists (Bromocriptine, pergolide, levodopa) apomorphine, clonidine, MAO inhibitors (pargyline)**

➢ **Clinical uses to dopamine agonists:**

- **Bromocriptine, Cabergolin…**

1. **Hyperprolactinemia in ♂s and ♀s irrespective of its causes (drug of choice)** its common in men to become infertile due to high prolactin but it can happen in females, also it may not affect the sexual function and just be a normal increase.
2. **Suppression of lactation.** (Drugs of choice to a breastfeeding mother that lost her child).
3. **Acromegaly.**
4. **Parkinson's disease** (deficiency of dopamine release in nervous system)
5. **Cushing's syndrome** (Dopamine agonists have been found to inhibit ACTH release)
6. **DM type II Dopamine agonists are given orally.**

- **Side effects:**
  - **Rare, pulmonary fibrosis; confusion; hallucinations; MI…**

V2

Everything that was added is Highlighted.