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Pharmacology of hypothalamic & pituitary hormones

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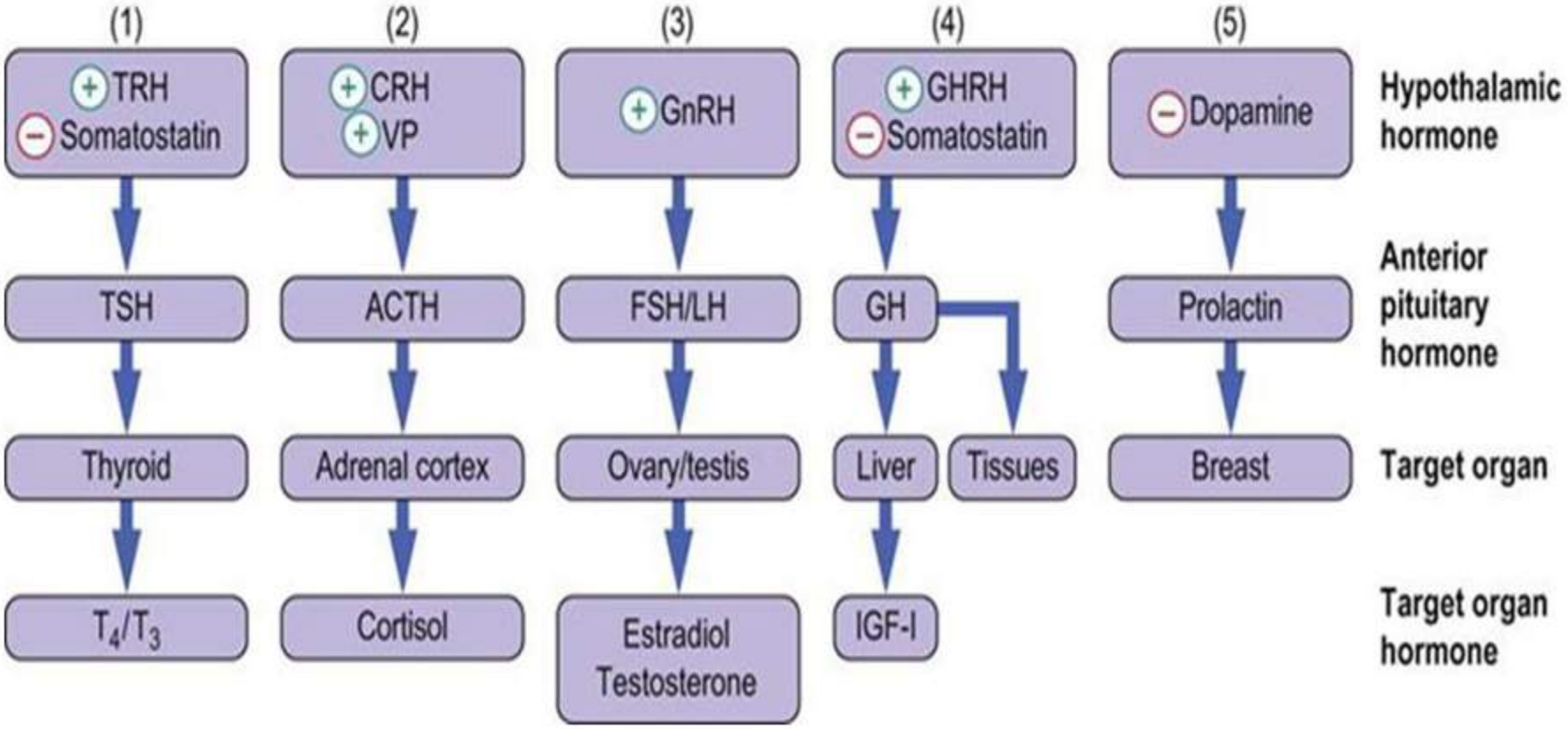
Hypothalamic & pituitary hormones

- The hypothalamus synthesize specific "releasing" or "inhibiting" factors or hormones, which stimulate or inhibit the release of **anterior Pituitary** hormones.
- The anterior Pituitary hormones (except prolactin) stimulate other endocrine glands or cells to secrete their specific hormones.
- Drugs, emotional factors, neurotransmitters and other factors can regulate the hypothalamic hormone release
- Negative feedback inhibition tightly controls hormone release from hypothalamus and pituitary gland.

Endocrine axes

There are 5 endocrine axes or pathways. Each pathway includes a hypothalamic factor(s), pituitary gland hormone(s), and the target gland (e.g. thyroid, adrenal or gonads).



Hypothalamic hormones

A- Growth hormone-releasing hormone (GHRH): used for diagnostic purposes and for treating GH deficiency.

B- Growth hormone-inhibitory hormone (somatostatin).

Actions of somatostatin

- Inhibit secretions of: gastrin, cholecystokinin, **glucagon**, **growth hormone**, insulin, **TSH**, vasoactive intestinal peptide (**VIP**) & other hormones.
- It reduces intestinal and pancreatic secretions (↓ fluids in GIT).
- It decreases GIT motility.
- It produces **vasoconstriction** of the blood vessels.
- It decreases portal pressure.

❑ **Octeriotide** is a synthetic somatostatin **(but more powerful than the natural hormone).**

- Octeriotide has some analgesic effects (partial agonist at the mu opioid receptor).

Therapeutic uses of Octeriotide

1. Octeriotide is used for the treatment of growth hormone producing tumors (acromegaly or gigantism), when surgery is contraindicated.
2. Octeriotide is used for treating diarrhea in AIDS patients and diarrhea associated with tumors like VIPomas & carcinoid tumor .
3. Octeriotide is used in some pancreatic tumors like glucagonoma.
4. Octeriotide inhibits insulin release and protects against hypoglycemia caused by excessive doses of sulphonylureas
5. Octeriotide is infused for management of acute hemorrhage from esophageal varices in liver cirrhosis.
6. Octreoscan in nuclear medicine (Octeriotide plus radioactive isotopes) to diagnose tumors by imaging.

Adverse effects of Octeriotide

The most common adverse effects are headache, **hypothyroidism**, **cardiac conduction changes,** GIT upset, **gallstones**, reduction of insulin release, or hyperglycemia (↓glucagon release).

N.B. Diabetic patients might need **less insulin** or less oral anti-diabetics when treated with Octeriotide.

C- Thyrotropin- releasing hormone: used for diagnostic purposes
D- Corticotropin- releasing hormone: used for diagnostic purposes
E-Gonadatropin-releasing hormone (Gn-RH): used in diagnosis and treatment of hypogonadal states.
F-Prolactin release-inhibitory hormone (**dopamine**)
-**Bromocriptine** is dopaminergic agonist and used in treatment of hyperprolactinemia.

Anterior Pituitary hormones

Growth Hormone (GH)

- It is the most abundant pituitary hormone (~**40-50%** of pituitary cells are **somatotrophs**; i.e. secreting GH).
- **GH** Induces liver & other tissues to secrete **Insulin-like Growth Factor I (IGF-I)**; also called **somatomedin**.
- The effects of GH are primarily mediate by **IGF-1.**
- **Prolactin** & insulin may **stimulate** somatomedin release from liver.
- GH is released in a pulsatile manner, **mostly during sleep**. Pulses are regulated by hypothalamic hormones.
- GH secretion **decreases with age.**
- GH has potent **anti-natriuretic** properties that cause **fluid retention**

Physiological Actions of Growth Hormone (GH)

- **In childhood:** causes **linear growth** (bones, cartilage, muscles & organs)
- **In adulthood, the major effects are metabolic:**
  - **It increases protein synthesis** and **bone density**
  - It **promotes lipolysis** and **inhibits lipogenesis**
  - It promotes gluconeogenesis and glucose release.
- GH **opposes insulin actions in adipose tissue.**

Features of Growth Hormone Deficiency

1. In Children: **short stature** and **adiposity**, **hypoglycemia**. **Deficiency of Growth Hormone releasing Hormone (GHRH) is a common cause.**
2. In Adults: This results in
   - Changes in body composition: increased generalized **adiposity**
   - Decreased skeletal muscle mass and strength
   - Decreased bone density

Drugs used in Growth Hormone Deficiency

1- Synthetic GHRH **(Sermorelin)** is used if a patients defective in hypothalamic GHRH but normally functioning anterior pituitary somatotrophs.

2-Recombinant human GH **(Somatropin and Somatrem)**
They can be used for most cases of GH deficiency.

3- Recombinant **IGF1 (Mecasermin)**
Mecasermin is used for children with severe IGF1 deficiency due to mutations in the GH receptor (Laron dwarfism) or development of neutralizing antibodies against GH.

Indications of GH therapy:

1-**Growth failure** (e.g. GH deficiency, small for gestational age, **chronic renal failure, Prader-Willi** & **Turner** syndromes).

2- **Idiopathic short stature** (non GH-deficient).

3- **GH deficiency in adults**.

4- **Wasting** in **AIDS** patients .

5- **Short bowel syndrome.**

Adverse effects of GH therapy:

1. **Hypothyroidism**.
2. **Pancreatitis** and **Nevus growth**
3. **Insulin resistance** and increases the risk of diabetes.

4. **Fluid retention** →**edema**, **carpal tunnel syndrome**, **arthralgia**, **myalgia**, gynecomastia, & **pseudotumor cerebri.**

5- Increase in **cytochrome P450 activity** → drug interactions.

Abuse of Growth hormone

- The classic form of "abuse" of human GH are **athletes** or **bodybuilders**.
- GH is abused to reverse aging and maintain youth.
- No good evidence exists that human GH actually works in these setting.

The human disease acromegaly suggests that long-term abuse of GH could result in facial disfigurement, sleep apnea, **hypertension**, **osteoarthritis**, **cardiomyopathy**, and a possible increased risk of malignancy (e.g. leukemia).

- GH affects normally and abnormally growing blood cells in vitro and in animal experiments, but the clinical data in humans do not indicate a direct cauaslity between GH & induction of tumor growth.

- GH may increase the spread of malignant melanoma.

Growth Hormone Excess

This usually results from benign tumor of the anterior pituitary.

(1) In children: It causes **gigantism**.

(2) In adults: It causes **acromegaly**.

Drugs Used:

1.Somatostatin analogues: **Octreotide**, or **Lanreotide** (Longer acting).

2. GH receptor antagonist (**Pegvisomant**).

3. Dopamine receptor agonist (**Bromocriptine**).

Other anterior pituitary hormones

- TSH: used for diagnostic purposes
- ACTH: used for diagnostic purposes
- FSH, LH: used for diagnosis and treatment of disease related to genital system and infertility.
- Prolactin: It causes milk production.

Posterior pituitary hormones

These hormones are synthesized in the hypothalamic neurons and stored in posterior pituitary to be released.

1-Oxytocin

Pharmacological effects:

1- It stimulates uterine smooth muscles causing contraction of gravid uterus.

2- It causes ejection of milk from lactating breast in response to suckling.

3- It relaxes vascular smooth muscles, ↓ BP → reflex tachycardia.

Therapeutic Use:

Natural **oxytocin** or synthetic **syntocinon** can be used by injection (I.V. infusion and I.M.) for:

1. Induction and maintenance of labor in certain conditions.
2. Control of postpartum bleeding & **uterine hypotonia**.

➢ Oxytocin can be given **intranasal.**

Side effects of oxytocin:

1. Very strong uterine contraction may cause **rupture of the uterus** (if there is obstruction during delivery). Uterine rupture may cause pelvic hematoma, fetal or maternal death.

- **Oxytocin** is **contraindicated** in suspected cases of obstructed labor like cephalo-pelvic disproportion (contracted pelvis), uterine scars, and uterine abnormalities.

2. **Anaphylactic reactions**.
3. **Convulsions**.
4. Nausea and **vomiting**.

Oxytocin antagonist

- **Atosiban** is a new oxytocin receptor antagonist that relaxes the uterus (tocolytic), it is approved to prevent **premature labor**.

2-Antidiuretic hormone (ADH) or vasopressin

Actions

- **V1 receptors:** contraction of vascular and non-vascular smooth muscles
- **Renal V2 receptors**: **increases water reabsorption** (anti-diuretic effect).
- **Extra-renal V2 receptors: release of coagulation factors.**

➢ Deficiency in ADH causes diabetes insipidus (polyurea and polydipsia, and dehydration) but excess secretion of ADH can cause water retention.

Therapeutic uses

A- **V1**-receptor-mediated therapeutic applications (smooth m contraction):

1. Postoperative **paralytic ileus.**
2. Control of bleeding from **esophageal varices.**
3. **Decrease the risk of bleeding**, in portal hypertension, during abdominal surgery.

B- **V2-**receptor-mediated therapeutic applications:

Desmopressin is a synthetic vasopressin (selective V2-receptor agonist)

It is given **I. V.**, **S.C**. or **intranasal** route for:

1.Treatment of central diabetes insipidus.

2. Treatment of bleeding disorders due to defects in coagulation factors.

3. Primary nocturnal enuresis.

4. Post-lumbar puncture headache because water retention will facilitate rapid fluid equilibration in the CNS.

Adverse reactions:

1. **Hypertension** (Large doses).
2. Coronary vasospasm, **angina**, and even infarction
3. **Hyponatremia** and water intoxication.
4. Marked **pallor** of the face and skin (severe vasoconstriction).
5. **Hypersensitivity** reactions as urticaria, fever and bronchospasm.

Precautions and contraindications of vasopressin

1. Hypertension
2. Coronary artery diseases
3. Heart failure
4. Edema.
5. Epilepsy
6. Migraine.

Vasopressin antagonists

- **Conivaptan** and **Tolvaptan** are new vasopressin receptor antagonists that are approved for **treatment of hyponatremia** and **acute heart failure.**
- These drugs are called aquaretic drugs as they increase water (but not sodium) in urine.
- They are useful in elderly patients.


Thank
you