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ASSIGNMENT TITLE: ENDOCRINE AND REPRODUCTIVE SYSTEM PHARMACOLOGY

**ASSIGNMENT**

Pharmacology of the pituitary gland

**ANSWER**

**What is the Pituitary Gland?**

The pituitary is an endocrine (hormone-producing) gland that sits just beneath the base of the brain, behind the bridge of the nose. It is very small – only about the size of a pea. The pituitary gland is very important as it takes messages from the brain (via a gland called the hypothalamus) and uses these messages to produce hormones that affect many parts of the body, including stimulating all the other hormone-producing glands to produce their own hormones. For this reason, it is often referred to as the ‘master gland’.

The pituitary gland has two parts. The anterior (or front) pituitary produces hormones that affect the breasts, adrenals, thyroid, ovaries and testes, as well as several other hormones. The main glands affected by the posterior (or rear) pituitary are the kidneys.

**How Does the Normal Pituitary Work?**

The pituitary gland produces a number of hormones. Hormones are essential for many aspects of life. Some send messages to other endocrine glands to tell them to increase or decrease production of their hormones. One such example is TSH, which stimulates the thyroid to grow and produce thyroid hormones.

The main hormones produced by the pituitary are:

|  |  |
| --- | --- |
| **ACTH** | adrenocorticotropic hormone |
| **ADH** | anti-diuretic hormone, or vasopressin |
| **FSH** | follicle-stimulating hormone |
| **GH** | growth hormone |
| **LH** | luteinizing hormone |
| **PRL** | prolactin |
| **TSH** | thyroid-stimulating hormone |

Anterior pituitary hormones classifiable into:

1. somatotropins consisting of GH & Prolactin.

2. glycoproteins consisting of TSH (Thyroid stimulating hormone), FSH (follicular stimulating hormone), LH (luteinizing hormone).

3.POMC derivatives: Corticotropin (ACTH), α-MSH.

Regulators:

1. hypothalamic releasing hormones.

2.somatotropin-negative regulator of GH & thyrotropin secretion.

3. dopamine: inhibits prolactin secretion.

Posterior pituitary:

1. arginine vasopressin

2. oxytocin.

**Physiological Actions of Growth Hormone (GH)**

-In childhood: GH promotes linear growth, growth of long bones, cartilage, muscle, organ systems; it is a major determinant of adolescent growth spurt.

- In adulthood major effects are metabolic: It increases protein synthesis and bone density; promotes lipolysis and inhibits lipogenesis; promotes gluconeogenesis and glucose release; opposes insulin-induced glucose uptake in adipose tissue, reduces insulin sensitivity.

- GH is released in a pulsatile manner, mostly during sleep. Pulses are generated by interplay of GHRH and Somatostatin.

-GH secretion decreases with age.

**- Mechanism of Action:**

o Binding of GH to its receptor activates the signaling cascade mediated by receptor associated JAK tyrosine kinases and STATs.

o The effects of GH are primarily mediated by insulin-like growth factor 1 (IGF-1) , released from liver in response to GH.

**Features of Growth Hormone Deficiency**

1. In Children, results in short stature and adiposity, hypoglycemia. This is most commonly due to a deficiency of GHRH.

2. In Adults: This results in , released from liver in response to GH.

o Changes in body composition: increased generalized adiposity

o Decreased skeletal muscle mass and strength

o Decreased bone density o Cardiovascular changes; cardiac muscle atrophy, atherogenic blood lipid profile

o Fatigue, weakness, depression, overall malaise

**Pharmacology of Growth Hormone Deficiency**

Drugs Used:

o Synthetic GHRH (Sermorelin)

o Recombinant human growth hormone (Somatropin, Somatrem)

o Recombinant IGF1 (Mecasermin)

**Treatment with synthetic GHRH (Sermorelin)**

Sermorelin is used if a patient possesses defective hypothalamic release of GHRH but normally functioning anterior pituitary somatotrophs

**Treatment with Recombinant Human Growth Hormone (Somatropin, Somatrem**

**Drug Description:**

o Most cases of GH deficiency are treated with replacement recombinant human growth hormone (rhGH). They are:

(1) Somatropin (synthetic growth hormone), which is a 191-amino acid peptide, identical to the native form of hGH

(2) Somatrem, which is a 192-amino acid peptide consisting of 191aa of GH plus an extra methionine residue at the N-terminus

**Mechanism if Action:**

o It replaces GH

**Efficacy:**

Children

* Increases linear growth, weight gain to low normal range
* Increases muscle mass, organ size, RBCs

**Adults**

* Increases bone mineral density
* Normalizes body composition: decreased central adiposity
* Increases muscle mass and strength
* Improves lipid profile and cardiac function
* Improves psychological symptoms and sense of well being   
  **Side Effects**:
* Leukemia, rapid growth of melanocytic lesions
* Hypothyroidism
* Insulin resistance
* Arthralgia o Increase in cytochrome P450 activity

**Contraindications:**

* Pediatric patients with closed epiphyses
* Active underlying intracranial lesion
* Active malignancy
* Proliferative diabetic retinopathy

**Treatment with 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.

**Features of Growth Hormone Excess**

This usually results from benign tumor of the anterior pituitary.

**(1) In children**: It causes **gigantism**. This occurs before the closure of epiphyses, because excess IGF1 causes excessive longitudinal bone growth

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

This occurs after epiphyses close, because excess IGF1 although can no longer stimulate long bone growth, can still promote growth of deep organs and cartilaginous tissue. This is characterized by:

* Thickening of bones, esp. face, hands
* Large facial structure, macroglossia and hepatomegaly
* Increased soft tissue growth
* Enlarged, arthritic joints
* Headache, sleep apnea, excessive sweating o Increased risk of CV disease, GI cancers (esp. colon), reproductive disorders

**Pharmacology of Growth Hormone Excess**

Standard treatment for larger pituitary adenoma is transsphenoidal surgery to remove the tumor. Medical options for smaller adenomas are as follows:

**Drugs Used:**

* Somatostatin analogues (Octreotide, Lanreotide in Europe)
* GH receptor antagonist (Pegvisomant)
* Dopamine receptor agonist (Bromocriptine - described under hyperprolactinemia)

**Treatment with Somatostatin Analogue (Octreotide)**

**Drug Description**:

* Somatostatin analogues:
* Somatostatin physiologically inhibits GH secretion, but is rarely used clinically, since it has a very short half-life (a few minutes)
* Octreotide is a synthetic long-lasting peptide analogue of somatostatin (45 times more potent)

**Mechanism of Action:**

o It inhibits GH secretion

**Drug** **Indications**:

o Used to control pituitary adenoma growth in acromegalic patients

o Carcinoid crisis- flushing, diarrhea and all symptoms of carcinoid syndrome

o Secretory Diarrhea from vasoactive intestinal peptide-secreting tumors

o To control acute GI bleeding

**Side Effects:**

o Nausea, vomiting, abdominal cramps, GI discomfort

o Cardiac effects include sinus bradycardia and conduction disturbances

o Hypoglycemia

o Gallstone formation

**Contraindications:**

o Hypersensitivity to octreotide

**Treatment with GH Receptor Antagonist (Pegvisomant)**

**Drug Description:**

o Pegvisomant is GH receptor antagonist, recombinant protein,191 amino acids

o Has multiple polyethylene glycol (PEG) residues, which prolongs its half-life

**Mechanism of Action:**

o Pegvisomant is a competitive antagonist of GH activity

o This can bind to the transmembrane GH receptor but cannot activate subsequent intracellular signaling

o It decreases serum IGF1 levels

**Drug Indications:**

o Used for the treatment of acromegaly that is refractory to other modes of surgical, radiologic, or pharmacologic intervention.

**Side Effects:**

o Increased pituitary adenoma size

o Elevated serum aminotransferase levels

**Contraindications:**

o Hypersensitivity to pegvisoment

**Physiological Actions of Gonadotropins**

The gonadotroph cells in the pituitary secrete two types of gonadotropins in response to pulsatile GnRH:

o **LH** (Luteinizing hormone)

o **FSH** (Follicle-stimulating hormone)

**In Women:**

The main function of FSH is ovarian follicle development. In the follicular stage of the menstrual cycle, LH stimulates androgen production in the ovary (Thecal cells), whereas FSH stimulates conversion of androgens to estrogens (Granulosa cells). In the luteal phase, estrogen and progesterone production is primarily controlled by LH, and during pregnancy controlled by hCG (human chorionic gonadotropin) produced by the placenta.

**In Men:**

FSH primarily regulates spermatogenesis. LH stimulates production of testosterone by the testicular Leydig cells. In Sertoli cells, FSH produces androgen binding protein, which helps to maintain high testicular levels of testosterone.

**Drugs Used:**

**Stimulation**

o Gonadotropins (human menopausal gonadotropins or menotropins, human chorionic gonadotropin or hCG, Urofollitropin, Follitropin)

o Gonadotropin Releasing Hormone (GnRH) or its analogue Gonadorelin with short-half life (4 minutes)- pulsatile form

**Inhibition**

o Synthetic analogs of GnRH with longer half-lives – continuous form (Goserelin, Histrelin, Leuprolide, Nafarelin, Triptorelin)

o GnRH receptor antagonists (Ganirelix, Cetrorelix, Abarelix)

**Stimulation of the Gonadal Axis by Gonadotropins**

**Drug Description:**

o Menotropins are obtained from the urine of menopausal women and contain FSH and LH

o hCG is a placental hormone and an LH agonist

o Urofollitropin is purified FSH isolated from the urine of postmenopausal women

o Follitropin is a recombinant from of human FSH

**Mechanism of Action:**

o Replaces FSH and LH

**Drug Indications:**

o Ovulation induction (in women) in hypogonadotropic hypogonadism, polycystic ovary syndrome, obesity

o Controlled ovarian hyperstimulation in assisted reproductive technology procedures (example IVF)

o Infertility in male hypogonadotropic hypogonadism

**Side Effects:**

o Ovarian hyperstimulation syndrome (associated with ovarian enlargement, ascites, hydrothorax, hypovolemia, sometimes resulting in shock)

o Increase in multiple pregnancies (15-20% chance)

o Increased risk of gynecomastia in men

o Ovarian cancer

o Ovarian cysts and hypertrophy

**Contraindications:**

o Any endocrine disorder other than anovulation (eg thyroid or adrenal dysfunction)

o Primary gonadal failure

o Pituitary tumors or sex-hormone dependent tumors

o Ovarian cyst or enlargement

o Pregnancy

**Stimulation of the Gonadal Axis by GnRH Agonist (Pulsatile)**

o Pulsatile GnRH secretion or short-half life GnRH analogue Gonadorelin (half-life ~4 minutes) can stimulate the gonadotroph cells to produce and release LH and FSH (Stimulation of gonadal axis): mimicking physiology.

o Used mostly in diagnosis of hypogonadism and occasionally to stimulate ovulation or to treat infertility in men.

**Inhibition of the Gonadal Axis by GnRH Agonist (Sustained)**

**Drug Description:**

o Goserelin, Histrelin, Leuprolide, Nafarelin, Triptorelin are synthetic analogs of GnRH

o More potent and longer-lasting than native GnRH or gonadorelin

o Long half-life (~3hours)

**Mechanism of Action:**

o Sustained, nonpulsatile administration of GnRH or GnRH analogs with long half-life desensitizes the GnRH receptors and inhibits the release of FSH and LH in both men and women - (Inhibition of gonadal axis). o Produces biphasic response:

1. first there is a transient (7-10 days) increase in gonadal hormone levels (flare) – agonist effect

2. followed by a long-lasting suppression of gonadotropins and gonadal hormones inhibitory action

**Drug Indication:**

o To keep the LH surge low in controlled ovarian hyperstimulation that provides multiple mature oocytes for assisted reproductive technologies (like IVF)- [leuprolide, nafarelin]

o Endometriosis & Uterine fibroids [leuprolide, nafarelin, goserelin]

o Adjunctive in prostate cancer [leuprolide, goserelin, histrelin, triptorelin]

o Central precocious puberty [leuprolide, nafarelin]

o Others include: advanced breast & ovarian cancer, amenorrhea and infertility in women with polycystic ovary disease

**Side Effects:**

o Hot flashes, sweats, headache (menopausal symptoms)

o Osteoporosis

o Urogenital atrophy

o Temporary worsening of precocious puberty during the initial weeks of treatment

**Contraindications**:

o Hypersensitivity to GnRH or GnRH analogs

o Pregnancy

o Breast feeding

**Inhibition of the Gonadal Axis by GnRH receptor Antagonists**

**Drug Description:**

o Ganirelix, Cetrorelix and Abarelix are used to inhibit gonadal axis

o Ganirelix and Cetrorelix produce immediate antagonistic effect, and so their duration of administration during IVF is shorter compared to GnRH agonists.

**Mechanism of Action:**

o They function as competitive antagonists of GnRH receptors o Inhibits the secretion of FSH and LH in a dose dependent manner o Does not produce the flare effect (increased FSH/LH) as GnRH agonists

**Drug Indications:**

o Ganirelix and Cetrorelix - keeps LH surge low in controlled ovarian hyperstimulation in in IVF, resulting in improved rates of implantation and pregnancy

o Abarelix - used metastatic prostate cancer in patients with extensive metastases or tumor encroaching on the spinal cord

**Side Effects:**

o Ovarian hyperstimulation syndrome

o QT interval prolongation (abarelix)

o Ectopic pregnancy, thrombotic disorder, spontaneous abortion (ganirelix)

o Anaphylaxis (cetrorelix)

**Contraindications:**

o Pregnancy, lactation, ovarian cysts or enlargement not due to polycystic ovarian syndrome o Primary ovarian failure   
o Thyroid or adrenal dysfunction

o Vaginal bleeding of unknown etiology

**Regulation of Prolactin Secretion**

Lactotrophs of the anterior pituitary produce and secrete prolactin. Prolactin release is inhibited by dopamine, secreted by hypothalamus and increased by Thyrotropin-releasing hormone or TRH. Prolactin does-not stimulate hormone secretion in its target organ (mammary gland) and so there is no negative feedback regulation. Increased estrogen levels during pregnancy stimulate prolactin release. Suckling provides a powerful stimulus for prolactin release.

**Physiological Actions of Prolactin**

Prolactin regulates mammary gland development, milk protein biosynthesis and secretion. Increased prolactin inhibits GnRH release and thus the hypothalamic-pituitary-gonadal axis and estrogen synthesis, thereby suppressing ovulation during lactation.

**Disorders of Hypothalamic-Pituitary-Prolactin Axis**

**Features of Hyperprolactinemia**

Hyperprolactinemia occurs more commonly due to prolactin secreting adenomas. Hyperprolactinemia produces

o A syndrome of amenorrhea and galactorrhea, infertility in women

o Loss of libido and infertility in men

o In large tumors it can cause visual changes due to compression of the optic nerves

**Pharmacology of Hyperprolactinemia**

Drugs Used: o

Dopamine Receptor Agonists Bromocriptine, Cabergoline, Pergolide; (Quinagolide is approved in Europe, not available in USA)

**Prolactin Deficiency:**

o No preparation of prolactin is available to treat these patients

**Treatment with Dopamine Receptor Agonists**

**Drug Description:**

o Bromocriptine, Cabergoline, Pergolide, Quinagolide are synthetic dopamine receptor agonists.

o High affinity to dopamine D2 receptors

**Mechanism of Action:**

o They inhibit pituitary prolactin release

o GH release is reduced in patients with acromegaly, although less effectively

**Side Effects:**

o Orthostatic hypotension

o Cerebral vascular accident, seizure, acute myocardial infarction (Bromocriptine)

o Arrhythmia, myocardial infarction, heart failure (Pergolide)

o Pulmonary fibrosis and pleural effusion (Cabergoline)

**Contraindications**:

o Hypersensitivity to ergot derivatives

o Uncontrolled hypertension

o Toxemia of pregnancy (Bromocriptine)

**Vasopressin:**

* + Peptide hormone
  + Released by posterior pituitary in reaction to:
    - Rising plasma tonicity
    - Decreasing blood pressure
  + Antidiuretic properties
  + Vasopressor properties
  + Vasopressin deficiency:  diabetes insipidus
* **Structure:**
  + Nonapeptide
* **Pharmacokinetics:**
  + Routes of administration:
    - IV, intramuscular, intranasal
  + Half-life: 20 minutes
  + Renal and hepatic catabolism
  + Minimal vasopressin excreted unchanged in the urine
* **Pharmacodynamics:**
  + Receptor types:
    - V1-- vascular smooth muscle (vasoconstriction)
    - V2 -- renal tubule cells: antidiuresis
      * Mechanism:
        + (1) increased water permeability
        + (2) increased collecting tubule water resorption
    - Extrarenal V2 receptors--promote coagulation factor VIIIc and von Willebrand factor release.
  + Desmopressin acetate (DDAVP, 1-desamino-8-D-arginine vasopressin)
    - Synthetic vasopressin derivative
    - Long-acting
    - Limited V1receptor activity
    - Significant antidiuretic/vasopressor ratio compared to vasopressin
* **Clinical Use:** 
  + Vasopressin and desmopressin: alternative treatment for pituitary diabetes insipidus
  + Nocturnal enuresis (desmopressin at bedtime) -- mechanism: reduced night urine production
  + IV vasopressin: may be effective in managing esophageal variceal bleeding and colonic diverticular leading
* **Toxicity**:
  + Vasopressin (not desmopressin): vasoconstriction -- cause issues in patients with coronary vascular disease
  + Unusual side effects include: agitation, allergic reactions, abdominal cramping, headache, nausea

**Oxytocin:**

* + Levels:
    - Physiologic levels:cause milk ejection in lactating women
    - Pharmacological doses:
      * Induce uterine contraction/maintain labor
  + **Chemistry**:  oxytocin
    - 9-amino acid peptide
  + **Pharmacokinetics**:  oxytocin
    - IV administration for labor stimulation
    - Nasal spray: postpartum lactation induction
    - Catabolism: renal and hepatic
    - Half-life: (circulating) 5 min.
  + **Pharmacodynamics**:
    - Influences ionic currents in myometrial smooth muscle:  uterine contraction
    - Uterine sensitivity to oxytocin: ­ increases in pregnancy
    - Inhibition of oxytocin-induced myometrial uterine contraction:
      * Magnesium sulfate
      * β-adrenergic receptor agonists
      * Inhalation anesthetics
    - Promotes myoepithelial cell contraction (surrounding mammary alveolar) :   milk ejection
    - Normal lactation requires oxytocin
* **Clinical Uses:** 
  + Diagnostic Applications:
    - Checking placental circulatory reserve:
      * IV oxytocin near-term:  uterine contractions:  decrease fetal blood supply:   fetal heart rate response monitored (abnormal response may suggest intrauterine growth retardation; may suggest advisability of cesarean section
  + **Therapeutic Uses:**
    - Labor induction
    - Promoting dysfunctional labor
    - When early vaginal delivery is required
    - Rh factor concerns, maternal diabetes, preeclampsia
    - Uterine inertia
    - Incomplete abortion
    - Control of postpartum uterine bleeding
    - Enhance impaired milk ejection (nasal Route of Administration)
* **Toxicity**:
  + Serious toxicity: rare
  + Reported adverse reactions include: hypertensive reactions, uterine rupture, water intoxication, fetal death, afibrinogenemia
* **Contraindications:** 
  + Fetal distress, abnormal fetal presentations, factors predisposing to uterine rupture
* **Thyrotropin-releasing hormone,TRH**
  + Tripeptide
  + Location: hypothalamus (and other brain regions)
  + TRH:   portal venous system:   pituitary stimulation:  thyroid-stimulating hormone (TSH, thyrotropic) production:  thyroid-stimulation and release:   thyroxine (T4) and triiodothyronine
  + TRH stimulation of thyrotropin:
    - Blocked by thyroxine
    - Enhanced by thyroxine deficiency
* **Chemistry/pharmacokinetics:** 
  + Glu-His-Pro-NH2
  + IV administration
  + Plasma half-life: 4-5 minutes
* **Pharmacodynamics**:
  + Hyperthyroidism: serum thyrotropin level reduced
  + Primary hypothyroidism:
    - Thyrotropin levels: high
    - Enhanced thyrotropin response to TRH
  + Secondary (pituitary) hypothyroidism:
    - Thyrotropin serum levels: low (by sensitive TSH assay) or "inappropriately normal"
    - TSH often does not increase after TRH
  + Tertiary (hypothalamic) hypothyroidism:
    - Serum thyrotropin levels: normal or low
    - Thyrotropin response to TRH: normal or attenuated
  + TRH infusion:
    - Increased prolactin released by the pituitary
    - No effect on growth hormone or ACTH
    - Pituitary tumors:

Some pituitary tumors:

* + - * 1. Release growth hormone in response to TRH (acromegaly).
        2. Release ACTH in response to TRH (Cushing's disease).
        3. Failure to release prolactin (prolactinoma).

**Thyrotropin, TSH**

* + Anterior pituitary hormone.
  + Thyroid function regulation involves stimulation of thyroxine and triiodothyronine production and release.
* **Chemistry**:
  + Consists of two peptides (A and B) with associated carbohydrate side chains
  + Therapeutic thyrotropin:
    - Source:  Recombinant human TSH
    - TSH-b subunit provides thyroid specificity since TSH-a subunit is nearly identical to a subunit of FSH, LH, hCG.
* **Pharmacokinetics:** 
  + Route of Administration:
    - Intramuscular
    - Subcutaneous
  + Half-life: one-hour
  + Renal degradation
* **Pharmacodynamics:** 
  + Thyrotropin :   thyroid cell adenylyl cyclase activation→ increased cyclic AMP production: → increased iodine uptake:  →increased thyroid hormone production
* **Clinical Use:** 
  + Diagnostic/therapeutic:
    - Possible diagnostic use in a metastatic thyroid carcinoma.
    - Possibly effective therapeutic stimulation of radioactive iodine uptake for treatment of metastatic thyroid carcinoma.

Adrenocorticotropin (corticotropin, ACTH )

**ACTH**

* + Peptide hormone;
  + Synthesis site: anterior pituitary
  + Major endocrine function: stimulation of cortisol synthesis and release from adrenal cortices
  + Synthetic corticotropin-derivative use clinically to assess adrenocortical status
    - Reduced adrenocortical response to corticotropin administration:  adrenocortical insufficiency
* **Chemistry:  ACTH**
  + Single 39-amino acid peptide
    - Amino acids 1-24: required for full biological activity
    - Amino acids 25-39: species specificity
  + Synthetic, human ACTH1-24: cosyntropin
* **Pharmacokinetics:  ACTH**
  + Porcine and synthetic corticotropin: well absorbed following intramuscular administration
  + Corticotropin: no oral administration due to GI proteolysis
  + half-life: < 20 minutes
  + Tissue concentration: in liver and kidney
* **Pharmacodynamics: ACTH**
  + ACTH stimulates adrenal cortex to produce glucocorticoid, mineralocorticoid, and androgen.
  + ACTH increases cholesteryl esters activity (cholesterol:  pregnenolone step: rate-limiting in steroid hormone production)
  + ACTH promotes adrenal hypertrophy and hyperplasia
  + Corticotropin may cause increased in skin pigmentation
* **Clinical Use: ACTH**
  + ACTH adrenal stimulation: inadequate response in adrenal-insufficiency
  + Cosyntropin may be used rule out adrenal-insufficiency
  + Differentiation of "late-onset" (non-classic) congenital adrenal hyperplasia from states of ovarian hyperandrogenism
  + Therapeutics: no advantage over direct glucocorticoid administration