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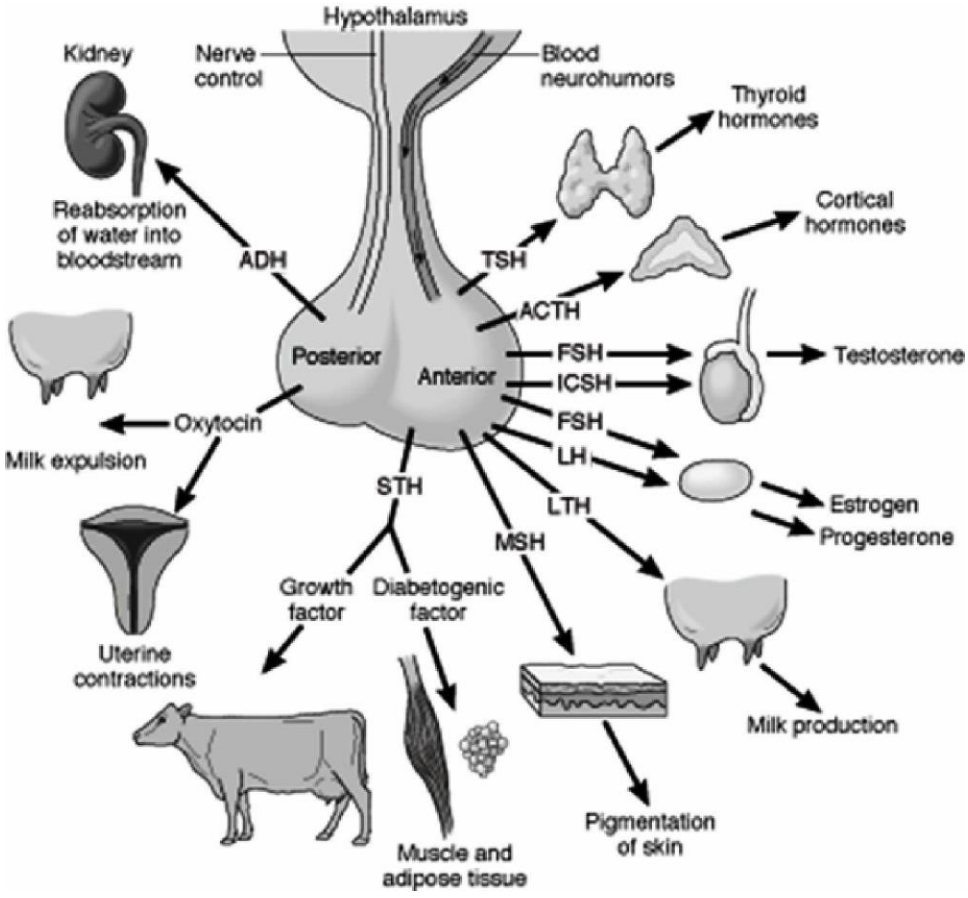
Endocrine and Reproductive System Pharmacology

I- Endocrine Pharmacology

- The endocrine system is composed of ductless glands that secrete chemical messengers called *hormones* into the blood.
- ***Hormones*** are chemical substances produced by cells in one part of the body and transported to another part of the body where they influence cellular activity.
- The endocrine system is controlled by a feedback mechanism that includes the hypothalamus, pituitary gland, and the other endocrine glands.
- Feedback mechanism may be either negative or positive. The Negative feedback mechanism are more common and work in response to low or high levels of hormone in the body, while Positive feedback mechanism occur when hormone levels continue to rise in response to stimuli.



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A- Pituitary Gland Hormones: The pituitary gland is divided into two parts: anterior (cranial) and posterior (caudal)

- Anterior pituitary hormones used in veterinary practice include:

- **Thyroid stimulating hormone (TSH)** Dermathycin®: TSH is used for temporary supportive therapy in hypothyroidism in dogs. In actuality however, TSH is used in veterinary medicine principally as a diagnostic agent in the TSH stimulation test to diagnose primary hypothyroidism.
- **Adrenocorticotropic hormone (ACTH)** Adrenomone®: ACTH is approved for use in dogs, cats, and beef or dairy cattle for stimulation of the adrenal cortex when there is a deficiency of ACTH, and as a therapeutic agent in primary bovine ketosis (rising of ketone bodies level in blood due to hypoglycemia). In practice however, it tends to be used most often in the diagnosis of hyper- or hypoadrenocorticism (ACTH stimulation test) and to monitor the response to mitotane therapy in Cushing syndrome (Hypercortisolism). ACTH has been used for several purposes in human medicine for its corticosteroid stimulating properties, but as it must be injected, it is not commonly employed.
- **Follicle stimulating hormone (FSH) and Luteinizing hormone (LH)**: will be discussed latterly.
- **Growth hormone (GH).**GH is used to increase growth rate and feed use efficiency in livestock and increase milk production in dairy cows

-Posterior pituitary hormones used in veterinary practice include:

- **Antidiuretic hormone (ADH) or Vasopressin:** Vasopressin is used in veterinary medicine as a diagnostic agent and in the treatment of diabetes insipidus (disease characterized by the inability to concentrate urine due to insufficient amounts of ADH). In small animals.
- **Oxytocin:** In veterinary medicine, oxytocin has been used for induction or enhancement of uterine contractions at parturition, treatment of postpartum retained placenta and metritis, uterine involution after manual correction of prolapsed uterus in dogs, and in treating agalactia.

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B- ***Pancreas Hormones:*** The pancreas secretes two hormones that help regulate blood glucose:-

- **Insulin (**secreted from β cells of pancreas**)** responds to a rise in blood glucose and promotes the uptake and use of glucose for energy in cells. While **Glucagon (**secreted from α cells of pancreas**)** increases blood glucose levels by promoting the breakdown of glycogen into glucose.
- **Diabetes mellitus** is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia).

Insulin is used to treat diabetes mellitus by keeping blood glucose in the proper range

• Sources of insulin include pork, synthetic, and recombinant forms .

• Onset and duration of insulin action are controlled by modifying the regular insulin structure .

- Short-acting is used for initial treatment of diabetic ketoacidosis and keep blood glucose stable (regular crystalline insulin, semilente)
- Intermediate-acting is used to control blood glucose in uncomplicated cases of diabetes mellitus (NPH and lente)
- Long-acting is used to control blood glucose for longer periods of time, especially in cats (protamine zinc insulin and ultralente).

Oral hypoglycemic agents :- have been used with some success in animals

- Work by stimulating pancreatic beta cells to secrete insulin; therefore some pancreatic function is needed.
- Has been more successful in cats.
- An example of an oral hypoglycemic agent is glipizide.

C- Thyroid gland hormones: The thyroid gland secretes two hormones involved in metabolism:

a. Thyroxine or T_4.

b. Tri-iodothyronine or T_3.(the active form of thyroxin).

- **Hyperthyroidism** is characterized by an increased production of thyroid hormone.
- Signs of hyperthyroidism include increased thirst, weight loss, increased stool production, restlessness, and tachycardia
- Diagnosed by measuring serum total T_4 and T_3.
- Hyperthyroid animals are treated with anti-thyroid drugs or surgical removal.

Radioactive isotopes of iodine (I^{131}): destroy the thyroid gland.

- **Methimazole :** Methimazole is considered by most clinicians to be the agent of choice when using drugs to treat feline hyperthyroidism. It interferes with the incorporation of iodine in the molecules of T4 and T3.
- **Propylthiouracil (PTU):** this agent acts by two mechanisms:-

- PTU inhibits the enzyme thyroperoxidase, which normally acts in thyroid hormone synthesis to add iodide to the tyrosine residues on the hormone precursor thyroglobulin, thus forming thyroxine.
- PTU also acts by inhibiting the enzyme 5'-deiodinase (tetraiodothyronine 5' deiodinase), which converts T_4 to the active form T_3.

D- **Adrenal cortex hormones*:*** The adrenal cortex is the outer part of the adrenal gland, it produce two types of hormones those are:

a. Mineralocorticosteroids (Aldosterone)\ increase the reabsorption of sodium and water and the release (secretion) of potassium in the kidneys.
b. Glucocorticoids (Cortisol)\ regulate nutrient levels in blood (increase blood glucose levels).

- The hypothalamus regulates the adrenal cortex by secreting releasing hormones for ACTH, which stimulates the adrenal cortex.

- **Adrenocortical insufficiency (Addison's disease)** is a progressive condition associated with adrenal atrophyis in which the adrenal gland produces insufficient amounts of steroid hormones (glucocorticoids and often mineralocorticoids).

- Treatment involves a long-acting mineralocorticoid and corticosteroids .

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Fludrocortisone:

- Fludrocortisone is used in small animal medicine for the treatment of Addison's disease.
- It has also been suggested to be used as adjunctive therapy in hyperkalemia.
- Additionally in humans, fludrocortisone has been used in salt-losing congenital adrenogenital syndrome and in patients with severe postural hypotension.

- **Hyperadrenocorticism (Cushing's disease):** is characterized by excessive glucocorticoid production due to prolonged administration of adrenocortical hormones, adrenocortical tumors, or pituitary disorders.
- Treatment involves destroying part of the adrenal cortex.

- **Mitotane:**

- An adrenal cytotoxic agent, also it inhibits adrenocortical function without causing cell destruction.
- In veterinary medicine, mitotane is used primarily for the medical treatment of pituitary-dependent hyperadrenocorticism (PDH).principally in the dog.
- It has also been used for the painkilling treatment of adrenal carcinoma in humans and dogs.

- **Ketoconazole:**

- An imidazole antifungal agent, but it also blocks the enzymes needed to produce steroid compounds.
- It used clinically for the medical treatment of hyperadrenocorticism in dogs (and sometimes cats).

- **Selegiline:**

- Monoamine oxidase inhibitor (MAO inhibitor).
- It approved for use in dogs only for the treatment of Cushing's disease.
- in Canada it is also approved for the treatment of Canine Cognitive Dysfunction (so- called old dog dementia).
- In humans, selegiline's primary indication is for the adjunctive treatment of Parkinson's disease.

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II- Reproductive Pharmacology

- Reproductive system is responsible for the process of producing offspring, consequently mentainance of species.
- Male reproductive system, and composed from:-
  - Testes, epididymis, ductus deferens, accessory sex glands, urethra, penis.
  - Sperm are produced in the seminiferous tubules of the testes.
- Female reproductive system, and composed from:-
  - Ovaries, uterine tubes, uterus, cervix, vagina, and vulva.
  - Ova are produced in the Graafian follicle of the ovary.

So that the drugs of reproductive system are divided to:-

I- ***Gonadotropines:*** Gonadotropins are hormones that stimulate the gonads they are glycoprotines in their nature, and they secreted from pituitary gland and from placenta too (in case of pregnancy).

- **Gonadotropins include:-**

1- Follicular stimulating hormone (FSH): is a hormone synthesized and secreted by the anterior pituitary gland. FSH regulates the development, growth, pubertal maturation, and reproductive processes of the animal body.

Effects of FSH in Females:-

- FSH stimulates the growth and recruitment of immature ovarian follicles in the ovary. As the follicle matures, one becomes dominant.

Effects of FSH in males:-

- FSH enhances the production of androgen-binding protein by the Sertoli cells of the testes, and is critical for spermatogenesis.

Pharmacological Uses of FSH:-

- The exogenous FSH used as a supplemental source of FSH when there is a general deficiency in cattle, horses, swine, sheep and dogs.
- Its primary use in veterinary medicine has been to induce follicular growth for the purposes of super-ovulation and out-of-season breeding.
- *FSH effect is simulated by the use of Pregnant Mare Serum Gonadotropin (PMSG).*

Pregnant mare serum gonadotropin (PMSG) ; is produced by endometrium of the mare during pregnancy and

- Usually obtained from serum obtained from serum of pregnant mare at 50-80 days of gestation .
- The most predominant hormone in PMSG is FSH. So that it used to get the effect of FSH.
- It used to produce estrus and ovulation in mares and as a follicle stimulant in many species.

2- **Luteinizing hormone (LH):** is another gonadotropin which synthesized and secreted by the anterior pituitary gland, and its effects on Reproductive system include:-

Effects of LH in Females:-

- In the female, an acute rise of LH (the LH surge) triggers ovulation.

Effects of LH in Males:-

- In the male, where LH had also been called **Interstitial Cell Stimulating Hormone** (**ICSH**), it stimulates Leydig cell production of testosterone.

Pharmacological Uses of LH analogs:-

- *In females*:-
- It used to treat inactive ovaries.
- Also LH used in treatment of Nymphomania (Cystic ovaries).
- *In males*:-
- LH analogs are used to stimulate releasing of testosterone from testis.

- Also they used to diagnose or treating of cryptochidism (failure of the testis to move, or "descend," during fetal development from an abdominal position).
- LH effect is simulated by the use of Human Chorionic Gonadotropin (HCG).

Human chorionic gonadotropin (HCG): A gonad-stimulating polypeptide secreted by the placenta, chorionic gonadotropin is obtained from the urine of pregnant women. HCG mimics quite closely the effects of luteinizing hormone (LH), but also has a little FSH-like activity.

- It used to treat cystic ovaries in cattle.
- To detect cryptorchidism in dogs.
- To get infertile bitches to cycle.
- And to induce ovulation in breeding mares.

- **Gonadotropin-releasing hormone (GnRH),** is a tropic peptide hormone responsible for the release of FSH and LH from the anterior pituitary. GnRH is synthesized and released from neurons within the hypothalamus.

- GnRH is used to treat follicular cysts in cattle.
- Also for estrus synchronization in cattle.
- And to induce estrus in small animals.

II- Sex Hormones or Sex Steroids :- Sex steroids, also known as gonadal steroids, they steroid hormones which made by the gonads (ovaries or testes), by adrenal glands, or by conversion from other sex steroids in other tissue such as liver or fat. Sex steroids play important roles in inducing the body changes known as primary sex characteristics and secondary sex characteristics.

1- **Androgens:** Steroid hormones that are secreted primarily by the testis, and *testosterone* is the principal androgen secreted. Its primary function is to regulate the differentiation and secretory function of male sex accessory organs. Androgens also possess protein anabolic activity that is manifested in skeletal muscle, bone, and kidneys. As a class, androgens are reasonably safe drugs, having limited and relatively predictable side effects.

Testosterone (testosterone cypionate, enanthate, and propionate):

- Made in the interstitial cells of the testes .
- Used to treat conditions such as infertility and hypogonadism, produce estrus detectors, and for testosterone-responsive urinary incontinence in dogs.
- High and long periods of usage cause oligospermia and sterility in males.

- **Anti-androgens:**

- Compounds those are capable of preventing or inhibiting the biologic effects of androgens.
- They used as an antineoplastic agent and palliative, adjuvant hormonal therapy in prostate cancer.
- Example: Spironolacton, Ketoclonazole and finasteride.

2- Estrogens: Steroid hormones that are secreted primarily by the Ovary. They promote female sex characteristics and stimulate and maintain the reproductive tract.

Estradiol: Estradiol is a naturally occurring steroidal estrogen. the indications for the use of estradiol include:-

- Induction of estrus during the non-breeding or breeding seasons and to enhance the mare's uterine defense mechanism.
- Estradiol cypionate has also been used as an abortifacient agent in cattle, cats and dogs.
- To correct anestrus (absence of heat period) in the absence of follicular cysts in some cases.
- To treat cattle having persistent corpus luteum due to certain causes.
- To expel purulent material from the uterus in pyometra of cows.
- To stimulate uterine expulsion of retained placentas and mummified fetuses.
- Main side effects include: prolonged estrus, genital irritation, decreased milk flow, precocious development and follicular cysts may develop after estrogen therapy.

- **Anti-estrogens:**

- Substances that block the activity of estrogens.
- Antiestrogens may stop some cancer cells from growing and are used to prevent and treat breast cancer. They are also being studied in the treatment of other types of cancer.
- Example: Tamoxifen.

3- Progesterone: Steroid hormone that secreted primarily by the Ovary (Corpus luteum), placenta and adrenal glands. It decreases uterine activity when a female is in estrus or pregnant.

Medroxyprogesterone Acetate (MPA):

- Synthetic **Progestins**. (A group of compounds similar in effect to progesterone).
- Decreases uterine activity when a female is in estrus or pregnant.
- Progestins are used in dogs to block estrus.
- Progestins are used in cattle to synchronize breeding and birth cycles.
- Progestins may be used to treat behavior problems and some forms of dermatitis.
- Other similar drugs are: Megestrol acetate, Altrenogest and Melengestrol.
- Side effects include: Increased appetite and/or thirst, depression, lethargy, personality changes, adrenocortical depression, mammary changes (including enlargement, milk production, and neoplasms), diabetes mellitus, pyometra and temporary inhibition of spermatogenesis.

- **Anti-progesterones (Anti-progestins):**

- Substances that prevent cells from making or using progesterone.
- Antiprogestins are used for contraception, labour induction, and treatment of endometriosis and breast cancer.
- Example: Mifepristone.

Drugs Affecting uterine Motility:

We can divide the drugs which effect on the uterine muscle motility to stimulants or relaxants:-

Uterine Muscles Stimulants:

Oxytocin:

- Stimulates uterine smooth muscle contraction, effect is Ca^{+2} dependent.
- It used for Induction of labor, augmentation of labor and therapeutic abortion.
- Side Effects include:-

a. Mother: Uterine hyperactivity, uterine rupture, hypotension, tachycardia.

b. Fetus: Hypoxia, acidosis.

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Prostaglandins (PGs):

- Also they increase Ca^{+2} ion concentration, and that leads to increase uterine muscle contractions.
- PGE_2 and $PGf_{2\alpha}$ are the two PGs whom used for increase uterine muscle contractions.
- $PGf_{2\alpha}$ causes lysis of the corpus luteum, which initiates a new estrus cycle (Naturally).
- In small animals, prostaglandins are used to treat pyometra, cause abortion, and induce parturition
- In cattle, prostaglandins are used for estrus synchronization and inducing uterine contractions to facilitate emptying of the uterus (pus or fetus)
- In horses, prostaglandins are used for estrus synchronization too.
- Side effects include: Uterine hyper tonus sweating, increased respiration, mild abdominal discomfort, uneasiness and defecation may be seen after PGs injection.

Ergot alkaloids (Ergonovine, Methyl ergonovine):

- Alpha-adrenergic agonists
- Increase uterine smooth muscle contraction.
- It has a medical use in obstetrics to facilitate delivery of the placenta and to prevent bleeding after parturition by causing smooth muscle tissue in the blood vessel walls to narrow, thereby reducing blood flow.

Uterine Muscles Relaxants:

- **B2- adrenergic agonists (Albuterol, Salbutamol):**

- To Arrest premature labor.
- Side effects include: Tachycardia and hypotension in mother and fetus, nausea and vomiting, Hyperglycemia.

- **Magnesium Sulfate**:

- Antagonizes the action of Ca, results in smooth muscle relaxation consequently it delay or prevent premature parturition.
- Side effects include: Skin flushing, nausea, headache, palpitation, decreased reflexes.

Higher doses: respiratory depression and cardiac arrest CNS depression in fetus (rare).

- **Cyclooxygenase (COX) Inhibitors (In particular *Endomethacin*):**

- Prevent synthesis and release of PGs, which are endogenous stimulants.
- They Delay or prevent premature parturition.
- Side effects include: Anorexia, nausea, headache, confusion, bone marrow depression. In fetus may cause premature closure of the ductus arteriosus, and pulmonary hypertension.

- **Calcium Channel Blockers (Niphedipine):**

- They close Ca^{+2} channels leading to decrease uterine muscles contractions.

Ethanol:

- Inhibits both ADH and Oxytocin release. Also has a beta-adrenergic stimulating effect as well as direct inhibitory action on uterine muscle. Might seem an ideal agent. However, because it can cause CNS depression in fetus, is not used much anymore.