

# **DRUGS AFFECTING REPRODUCTION**

**University Of Nairobi**

**Department Of Public Health, Pharmacology & Toxicology**

**JPT 341 Pharmacology & Toxicology**

**BVM 3<sup>RD</sup> Year Lecture Notes**

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## Lecture objectives

- By the end of this lecture the students should be able;
  - ❖ To give examples of the hormones and their analogues that affect reproduction.
  - ❖ To describe the mechanisms of action of drugs acting on reproductive systems and the resulting pharmacological effects
  - ❖ To explain how reproductive hormones are relevant in clinical vet medicine

# Lecture outline

- Introduction
- Examples of reproductive hormones/drugs
- Mechanism of action and pharmacological effects of reproductive hormones/drugs
- Application of reproductive hormones in clinical vet medicine

## Introduction

- Hormones affecting the reproductive system are either glycopeptides or steroid hormones.
- Glycopeptide(glycoprotein) hormones include those produced by pituitary, thyroid, parathyroid and Islets of Langerhans in pancreas.
- These hormones/drugs are usually given parenteral as they can be digested when given orally.

# Introduction

- The other group of reproductive hormones are steroids.
- Steroids are mainly produced from gonads (ovaries/testis) and adrenal glands (adrenal cortex).
- Most reproductive hormones are steroid hormones except a few, which are glycoproteins.
- Steroid hormones include androgens, oestrogen and progestogens.

# Introduction

- Classification of reproductive hormones/drugs
  - ❖ Hormones which influence the functions of gonads such as gonadotrophins and gonadotrophin releasing hormones.
  - ❖ Hormones/drugs which mimic gonadal functions such as sex steroids like androgens, oestrogens and progestogens.
  - ❖ Hormones/drugs that influence uterine functions including ecbolics and uterine spasmolytics.

## **Examples of reproductive hormones/drugs**

- Follicle-stimulating hormone (FSH)
- Human chorionic gonadotropin (hCG)
- Equine chorionic gonadotropin
- Estradiol esters
- Progesterone and synthetic progestins

## Examples of reproductive hormones/drugs

- Testosterone
- Prostaglandin (PG) F<sub>2a</sub> and its analogs
- Oxytocin
- Other drugs affecting reproduction

## **Follicle Stimulating Hormone and its Mechanism of action**

- FSH is a gonadotropin and has been extracted from animal pituitary glands.
- FSH interacts with FSH receptor (FSHR), which is transmembrane receptor found in the ovary, testis, and uterus.
- FSHR is a G protein-coupled receptor (GPCR).

## Mechanism of action FSH

- Binding of FSH to FSHR activates G protein, which detaches from the receptor and activates the cAMP system.
- cAMP then activates cAMP dependent protein kinases (protein kinase A) leading to protein phosphorylation and the functional effects on the ovaries, testis and uterus.

## **Functional effects and clinical application of FSH**

- The effects include follicular growth and estrogen production in the female and spermatogenesis in the male.
- FSH is used for superovulation of several domestic species and induction of fertile estrus in bitches and queens.
- Prolonged use or higher doses of FSH can cause cystic endometrial hyperplasia and follicular cysts,

## **Equine chorionic gonadotropin**

- The hormone has FSH activity in most species.
- It is used to induce ovarian follicular growth, both for superovulation and for estrus induction.

## **Human chorionic gonadotropin (hCG),**

- hCG exerts mainly luteinizing-hormone-like effects in domestic animals.
- ,
- It is used for stimulation of gonads (as a test for cryptorchidism and for the ovarian cysts treatment in cattle or dogs).
- It is also used to cause ovulation of mature ovarian follicles in cows or mares in controlled-breeding programs

## **Chorionic gonadotropin**

- Choriogonadotropin alpha stimulates late follicular maturation and resumption of oocyte meiosis, and initiates rupture of the pre-ovulatory ovarian follicle
- It binds to the Follicle stimulating hormone receptor which results in ovulation in the absence of sufficient endogenous Luteinizing hormone.
- Ovidrel is an analogue of Luteinizing Hormone (LH) and binds to the LH/hCG receptor of the granulosa and theca cells of the ovary.

# Progesterone

- Progesterone is a progestational steroid that is secreted primarily by the corpus luteum and the placenta.
- It acts on the uterus, the mammary glands, and the brain
- The hormone is required for embryo implantation, pregnancy maintenance, and the development of mammary tissue for milk production.
- Progesterone, converted from pregnenolone, also serves as an intermediate in the biosynthesis of gonadal steroid hormones and adrenal corticosteroids.

## **Pharmacological actions of progesterone**

- The ovary then produces progesterone, preventing the release of further eggs and priming the lining of the womb for a possible pregnancy.
- Progesterone shares the pharmacological actions of the progestins.
- It binds to the progesterone and estrogen receptors. Target cells include the female reproductive tract, mammary gland, hypothalamus, and pituitary.

## Pharmacological actions of progesterone

- Once bound to the receptor, progestins like Progesterone slows the frequency of release of gonadotropin releasing hormone (GnRH) from the hypothalamus and inhibit the pre-ovulatory LH surge.
- Progesterone acts to maintain the pregnancy and stimulates the growth of mammary alveolar tissue and relaxes uterine smooth muscle. It has little estrogenic and androgenic activity

## Pharmacological action of Estradiol

- Estradiol enters target cells such as female organs, breasts, hypothalamus, pituitary and interacts with a target cell receptor.
- When the estrogen receptor has bound its ligand it can enter the nucleus of the target cell, and regulate gene transcription which leads to formation of messenger RNA.
- The mRNA interacts with ribosomes to produce specific proteins that express the effect of estradiol upon the target cell.

## Pharmacological action of Estradiol

- Estrogens increase the hepatic synthesis of sex hormone binding globulin (SHBG), thyroid-binding globulin (TBG), and other serum proteins and suppress follicle-stimulating hormone (FSH) from the anterior pituitary

# Testosterone

- Testosterone is a steroid sex hormone found in both men and women. In men, testosterone is produced primarily by the Leydig (interstitial) cells of the testes when stimulated by LH.
- It stimulates spermatogenesis, promote physical and functional maturation of spermatozoa, maintain accessory organs of the male reproductive tract.
- It also support development of secondary sexual characteristics, stimulate growth and metabolism throughout the body and influence brain development by stimulating sexual behaviors and sexual drive.

## Pharmacological action of testosterone

- The effects of testosterone in humans and other vertebrates occur by way of two main mechanisms: by activation of the androgen receptor (directly or as DHT), and by conversion to estradiol and activation of certain estrogen receptors.
- Free testosterone (T) is transported into the cytoplasm of target tissue cells, where it can bind to the androgen receptor, or can be reduced to 5 $\alpha$ -dihydrotestosterone (DHT) by the cytoplasmic enzyme 5 $\alpha$ -reductase. DHT binds to the same androgen receptor.

## **Pharmacological action of testosterone**

- In women, testosterone is produced by the ovaries (25%), adrenals (25%) and via peripheral conversion from androstenedione (50%).
- In women, it maintain libido and general wellbeing and exerts a negative feedback mechanism on pituitary release of LH and follicle-stimulating hormone (FSH).
- In males and females, it plays key roles in health and well-being with enhanced libido, energy, immune function, and protection against osteoporosis.

## Prostaglandin (PG) F<sub>2α</sub> and its analogs

- *Dinoprost tromethamine* is the tromethamine (THAM) salt of the naturally occurring PGF<sub>2α</sub>.
- The pharmacologic effects of PGF<sub>2α</sub> include stimulation of myometrial activity, relaxation of the cervix, inhibition of steroidogenesis by CL, and can potentially lyse CL.
- Dinoprost binds to the PGF<sub>2α</sub> receptors and stimulates myometrial contractions in a gravid uterus and these are similar to the contractions that occur during labor.

## Prostaglandin (PG) F<sub>2α</sub> and its analogs

- These contractions may cause abortion and uterine response to PGF<sub>2α</sub> increase gradually throughout pregnancy. Dinoprost also facilitates cervical dilatation.
- *Dinoprostone* is also a naturally occurring PGF<sub>2α</sub> with important effects in labour.
- It also stimulates osteoblasts to release factors which stimulates bone resorption by osteoclasts. It is used to prepare the cervix for labour and to induce labour.

## Prostaglandin (PG) F<sub>2α</sub> and its analogs

- *Carboprost tromethamine* is another synthetic prostaglandin.
- It binds to the PGF<sub>2α</sub> E2 receptor, causing myometrial contractions, and the induction of labour or the expulsion of the placenta.
- In laboratory animals and in humans large doses of the drug can raise blood pressure, probably by contracting the vascular smooth muscle.

## Oxytocin

- Oxytocin induces labor by enhancing uterine contractions during labor.
- It has specific receptors in the uterine muscle lining and the receptor concentration increases during pregnancy reaching a maximum in early labor at term.
- Oxytocin binds the oxytocin receptor causing an increase in intracellular  $Ca^{2+}$  ions levels and activates myosin light chain kinase.

# Oxytocin

- Thus oxytocin-oxytocin receptor interaction induces uterine contractions during parturition and of milk ejection
- The uterine motility depends on the formation of the contractile protein actomyosin under the influence of the  $\text{Ca}^{2+}$ -dependent phosphorylating enzyme myosin light-chain kinase.

## Specific drugs affecting reproduction

- *Cyproterone* is an antiandrogen, which suppresses the actions of testosterone (and its metabolite dihydrotestosterone) on tissues.
- It acts by blocking androgen receptors and prevents androgens from binding to them suppressing LH and thus reducing testosterone levels.
- The direct antiandrogenic effect of cyproterone is blockage of the binding of dihydrotestosterone to the specific receptors in the prostatic carcinoma cell.

## Specific drugs affecting reproduction

- *Cyproterone* also exerts a negative feed-back effect on the hypothalamo-pituitary axis.
- The effect is due to inhibiting the secretion of LH leading to reduction in testicular testosterone production.
- *Cyproterone* is used for the palliative treatment advanced prostatic carcinoma.

## Specific drugs affecting reproduction

- *Tamoxifen* are selective estrogen receptor modulators (SERMs).
- The drug has both estrogenic and antiestrogenic effects.
- *Tamoxifen* has the same nucleus as diethylstilbestrol and possesses an additional side chain which accounts for its antiestrogenic activity.

## Specific drugs affecting reproduction

- *Tamoxifen* binds to estrogen receptors (ER), inducing a conformational change in the receptor.
- This results in a blockage or change in the expression of estrogen dependent genes.
- With prolonged binding of tamoxifen to the nuclear chromatin, DNA polymerase activity is reduced.
- Impaired thymidine utilization and blockade of estradiol uptake ensues causing decreased estrogen response.

## Specific drugs affecting reproduction

- Tamoxifen may bind with different estrogen receptors, ER-alpha or ER-beta.
- The binding produces both estrogenic and antiestrogenic effects.
- *Tamoxifen* is indicated for the treatment of metastatic breast cancer in women and men

## Specific drugs affecting reproduction

- *Toremifene* is a nonsteroidal triphenylethylene derivative which is a selective estrogen receptor modulator (SERM) that is structurally related to tamoxifen.
- The drug is also an estrogen agonist for bone tissue and cholesterol metabolism but is antagonistic on mammary and uterine tissue.
- Toremifene binds to estrogen receptors and may exert estrogenic, or antiestrogenic, or both activities.

## **Specific drugs affecting reproduction**

- The antitumor effect of toremifene in breast cancer is believed to be mainly due to its antiestrogenic effects.
- The drug competes with estrogen for binding sites in the cancer cells, blocking the growth-stimulating effects of estrogen in the tumor.
- Toremifene is used for the treatment of metastatic breast cancer in postmenopausal women.

## Specific drugs affecting reproduction

- *Toremifene* is currently under investigation as a preventative agent for prostate cancer in men with high-grade prostatic intraepithelial neoplasia and no evidence of prostate cancer.

## Specific drugs affecting reproduction

- *Ergot alkaloids* are got from the fungi *Claviceps purpuria* and include ergotoxin, ergotamine and ergotamine.
- *Ergonovine*, like other ergot alkaloids, produces arterial vasoconstriction by stimulating  $\alpha$ -adrenergic and serotonin receptors. It is a less potent vasoconstrictor than ergotamine
- It directly stimulates the myometrium and increases its force and frequency of contractions.

## **Specific drugs affecting reproduction**

- With normal doses, these contractions precede periods of relaxation; with larger doses, basal uterine tone is elevated and these relaxation periods will be decreased.
- Contraction of the uterine wall around bleeding vessels at the placental site produces hemostasis. Ergonovine also induces cervical contractions.
- The sensitivity of the uterus to the oxytocic effect is much greater toward the end of pregnancy. The ecboic actions of ergonovine are greater than its vascular effects.

## Specific drugs affecting reproduction

- Terbutaline is a relatively selective beta2-adrenergic and appears to have a greater stimulating effect on beta-receptors of the bronchial, vascular, and uterine smooth muscles (beta2 receptors) than on the beta-receptors of the heart (beta1 receptors).
- The pharmacological effects include relaxation of smooth muscle and inhibition of uterine contractions. The drug may also have some cardiostimulatory effects and CNS stimulation.

## Specific drugs affecting reproduction

- The pharmacologic effects of terbutaline are due to stimulation of  $\beta_2$ -adrenergic receptors on outer membrane of myometrial cell and activates adenyl cyclase that increase the level of cAMP.
- This decreases intracellular  $Ca^{2+}$  ions concentration leading to a decrease of uterine contractions. The drug causes uterine relaxation.
- Also used acute IV and sub-Q therapy in selected women to inhibit uterine contractions in preterm labor and prolong gestation when beneficial.

## **Specific drugs affecting reproduction**

- Ergotamine (ergonovine) are also indicated for uterine involution especially in excessive bleeding.
- It may be indicated in metritis causes due to infection where it is given together with antibiotics.

# **Application of reproductive hormones in clinical veterinary medicine**

## **Gonadotrophin releasing hormones (Gonadorelin)**

- Luteinization of cystic follicles.
- Induction of ovulation
- Stimulation of follicular development in the absence of a functional oestrus.

## **Gonadotrophins (FSH, LH, HCG and PMSG)**

- Achieving ovulation in mares.
- Treatment of cryptorchidism in foal and yearling.
- Assisting in deficiencies in sperm production and sex drive in the stallion.
- Failure of lactation after farrowing.

## **Androgens (methyltestosterone and testosterone propionate)**

- Alopecia of hormonal origin in male small animals.
- Cryptorchidism not responding to gonadotrophins.
- Deficient sex drive in adult studs using testosterone.
- Control of mammary tumors in the bitch.
- Pseudopregnancy in the bitch using testosterone.
- Oestrus suppression in bitch and queen cat using testosterone.

## **Androgens (methyltestosterone and testosterone propionate)**

- Control of mammary tumors in the bitch.
- Pseudopregnancy in the bitch using testosterone.
- Oestrus suppression in the bitch and queen cat using testosterone.

## **Antiandrogens (Delmadinone acetate)**

- Controlling hypersexuality in male, cat and dogs
- Relieving prostatic hypertrophy
- Certain behavioral problem such as aggression

## **Oestrogens (oestradiol monobenzoate, dienogest and stilboestrol dipropionate)**

- Treatment of vaginal discharges associated with irregular cycles and of anoestrus or suboestrus in cattle
- Removal of retained placenta and mummified foetus.
- Treatment of chronic metritis and pyometra.
- Treatment of excessive libido in young dogs
- Fattening steers or as growth promoters.

## Anti-oestrogens (Clomiphene) and Progestogens

- *Clomiphene* is used to treat un-ovulatory infertility.
- *Progestogens*
  - ❖ To maintain pregnancy in habitual and threatened abortion and control of oestrus in cow/sow.
  - ❖ Suppression or deferment of oestrus in bitches and queen cat (Progesterone acetate).
  - ❖ Induction of oestrus with ovulation in ewes

## **Ecbolics**

- Ergot alkaloids and analogues
  - ❖ used in cases of prolonged parturition when presentation is normal and cervix is open.
  - ❖ Used in flaccid post-parturient uterus which is not contracting.
  - ❖ Used in post parturient haemorrhage.

# Ecbolics

- Oxytocin
  - ❖ Used for speeding expulsion of fetuses/feotus in uterine inertia when presentation is normal.
  - ❖ Assist in expulsion of placenta debris and involution of the uterus after birth.
  - ❖ Management of functional agalactia in sows.

## Ecbolics

- **Prostaglandin (PGF<sub>2α</sub>/PGE<sub>2</sub>) and its analogs**
  - ❖ Induction of abortion due to their powerful effect on uterine contractions in last third trimester in human.
  - ❖ Used to induce early parturition.
  - ❖ *Cloprostenol* and *fluprostenol* are luteolytic effect and are used for control of oestrus in cow/mare.
  - ❖ *Prostalene* is PGF<sub>2α</sub> analogue used for induction of oestrus in the mare

## Uterine spasmolytics

- *Isoxuprine* is a mixed  $\beta$  adrenergic drug used to relax the myometrium in domestic species.
- *Clenbuterol* is  $\beta_2$ -adrenergic agonist is a bronchodilator and myometrial relaxant. It is used in case of overdose with ecbolics.

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