DRUGS AFFECTING REPRODUCTION

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JPT 341 Pharmacology & Toxicology
BVM 3RD 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 Langern 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) $F_{2a}$ 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 5α-dihydrotestosterone (DHT) by the cytoplasmic enzyme 5α-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$_{2\alpha}$ and its analogs

- *Dinoprost tromethamine* is the tromethamine (THAM) salt of the naturally occurring PGF$_{2\alpha}$.

- The pharmacologic effects of PGF$_{2\alpha}$ include stimulation of myometrial activity, relaxation of the cervix, inhibition of steroidogenesis by CL, and can potentially lyse CL.

- Dinoprost binds to the PGF$_{2\alpha}$ receptors and stimulates myometrial contractions in a gravid uterus and this are similar to the contractions that occur during labor.
Prostaglandin (PG) F$_{2\alpha}$ and its analogs

• These contractions may cause abortion and uterine response to PGF$_{2\alpha}$ increase gradually throughout pregnancy. Dinoprost also facilitates cervical dilatation.

• *Dinoprostone* is also a naturally occurring PGF$_{2\alpha}$ 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$_{2\alpha}$ and its analogs

- *Carboprost tromethamine* is another synthetic prostaglandin.

- It binds to the PGF$_{2\alpha}$ 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 is 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 ca2+ ions levels and activates myosins 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 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 ecbolic 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 ca2+ 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, dienoetrol 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 foetuses/foetus 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.
Ecboics

- Prostaglandin (PGF$_{2\alpha}$/PGE$_2$) 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$_{2\alpha}$ analogue used for induction of oestrus in the mare
Uterine spasmolytics

- *Isoxuprine* is a mixed β adrenergic drug used to relax the myometrium in domestic species.

- *Clenbuterol* is β₂-adrenergic agonist is a bronchodilator and myometrial relaxant. It is used in case of overdose with ecbolics.
References

• Veterinary applied Pharmacology and Therapeutics. G.C. Brander, D.M. Pugh and R.J. Bywater


• DrugBank: http://www.drugbank.ca/drugs/