PC
Pharmacology Concepts
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Steroidal Hormone Endocrine Pharmacology (Part 2)


Website

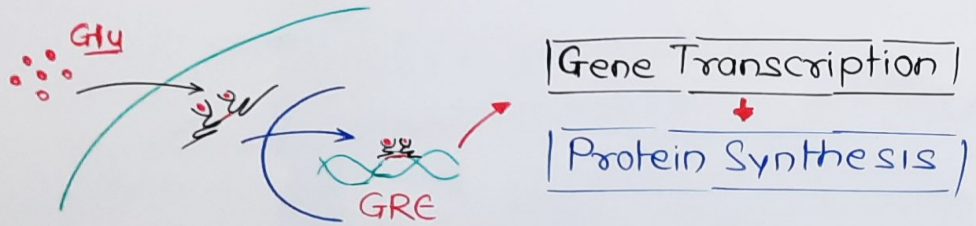

Videos

Pharmacology 2

GLUCOCORTICOID

↳ Glucocorticoid is a part of Carticosteroids, which release from adrenal cortex (Z Fasciculata).
↳ Synthesized from Cholesterol.
Cholesterol → Pregnenolone → Glu/Mineralocorticoids

MOA OF GLUCOCORTICOIDS



Actions →
- Deeper translocatn of Glu. transporter → ↓ Glu. uptake, Utelizatn
- ↑ Hepatic Gluconeogenesis → ↑ Glu. Conc.
- ↑ Protein breakdown → Amino Acid
- ↑ Hep. Glycogen synthase → ↑ deposit^{n} of Glycogen
- ↑ Lipolysis & Altered distribution of body fat
- ↑ Expression of Adr. & AT, Receptor in vessels
- ↓ Expression of POMC gene → ↓ ACTH production
- ↓ Ca^{+2} level (↓ Absorption & ↑ renal excretion)
- Maintain normal GFR
- Maintain Vascular & Myocardial tonicity
- Optimum level requir to muscular tonicity
- (+) Euphoria (CNS)
- ↑ Gastric Secretion (HCl & pepsin)
- (+) Maturation of Foetal Lungs
- "ANTI-INFLAMMATORY & IMMUNOSUPRESIVE"

Anti-inflammatory Action →

↳ (+) Annexins → ↓ PL-A_2 → ↓ PGs, LT_S & PAF
↳ (−) regulatn of COX → ↓ PG
↳ (−) regulatn of Ck gene → ↓ ILs, TNFα, Inf → ↓ T-cells
↳ ↓ Collagenase → ↓ Tissue destruction

DRUGS →

A) Short Acting – Hydrocortisone
B) Intermediate → Prednisolone, me-prednisolone, Deflazacort, Triamcinolone
C) Long → Dexamethasone, Betamethasone

Uses –

HRT = Adrenal Insufficiency, Addison's disease, Adreno-genital syndrome

Pharmacotherapy :→ Arthritidis, Collegen disease, Anaphylaxis, Autoimmune disease, Asthma, Infective disease, Eye/Skin disease, Organ transplantation, Sheptic Shock, Thyroid storm.

ADR :→ Cushing's habitus, Hyperglycemia, myopathy, Secondary infection, Delayed healing, Ulcer, Osteoporosis, Cataract, Growth retardatn, Glaucoma, Foetal Abnormalities, Psychitric disturbance,

Contraindicatn → Diabetes, HTN, Ulcer, RF, Osteoporosis, Viral/Fungal/TB infection, CHF, Psychosis.

ANDROGENS

↳ Male sex hormone, which causes 2° sex charecters in castrated male.
↳ Testosterone (testicular hormone) is the prime male hormone, produce 5-12 mg daily
↳ It's endocrine functn was estabilised in 1849 by Berthold. Synthetically – 1935

Cholesterol → "Testosterone" → Dihydro testo (More Active)
5-α-Redutase

Ad. Cortex
↳ Dihydroepiandrosterone
Androstenedione
0.25 – 0.5 mg/day
Weak Androgen
potency = 1/20 – 1/30

Testo → Androsterone (1/10 activity) → Urine

MOA = T → DHT → AR → Gene transcription

AR_1 & AR_2 → Genital & Muscle & Bone (* 5αR_1)
(• 5-α-R_2 * Finasteride

Biological Actions →

A) Androgenic Action :→ All changes during puberty
↳ Growth of Genital parts ↳ Hair distributn
↳ Development of 2° sex charecters

B) Testes → At normal → Spermatogenesis & maturatn of spermatozoa
At High dose → testicular Atrophy (due to ↓Gn release)

c) Skeletal Muscle/ Bone → Growth & Strength
↳ Anabolic function

D) Erythropoiesis → ↑ Erythropoietin production

P'KINETICS = Orally inactive (High 1st pass metabolism)
Duration of action - short after im injection, so Slowly absorbed ester salt are used by this route
↳ Metabolite are excreted through urine
↳ 98% protein binding (SHB Globulin)

Uses - HRT (Hypogonadism)
↳ Testicular failure
↳ AIDS Related muscle wasting
↳ Male infertility

ADR - ↳ In Female → Male like charecters
↳ Oligozoospermia – testicular Atrophy
↳ Salt Retention & Oedema
↳ Hepatic carcinoma & jaundice
↳ Gynacomastia in children & Liver failure patient due to peripheral conversion → Oestrogen

ANTI ANDROGENS

FINASTERIDE

Testosterone —(5α-Reductase-2)→ DHT → Androgenic Effects

Prostate & Hair follicle

- It decreases the prostate size & ↑ urine flowrate in 50% of patients with BHP
- Beneficial effects on BHP – 6 months (5mg)
- withdrawal of drug → Regrowth of prostate so continue the therapy – maintain for 3 years
- But lesser effective as compared to surgery & α_1 blockers
- Finasteride – ↓ static component of obstruct^n
  α_1-blockers – ↓ Dynamic component
  Combinat^n → Greater Symptomatic relief
- Also useful in male pattern Baldness, though hair follicle have 5α reductase type 1, in such subject promote hair growth & prevent hair loss

Pkinetic → Orally effective, Metabolized by liver, & excreted through urine & faeces

ADR – Impotancy, Gynaecomastia

FLUTAMIDE

- Non-steroidal AR Antagonist with no other hormonal activity
- Flutamide → 2-hydroxy Fl. —X— AR on acessory sex organ & pituitary ⇝ ↑ LH Secretn
- Monotherapy ⇝ ↑ plasma testosterone level so used only in conjuctn with GnRH Agonist to supress the LH & testosterone secretn or used along with "Combined Androgen blockade (CAB) therapy. – For metastatic carcinoma of prostate

BICALUTAMIDE :- More potent & longer durat^n over than "Flutamide"

- use → Prostate Cancer, as a part of CAB

ADR – Hot Flashes, Chills, Oedema, Loose stool

bw- better tolarated & less hepatotoxic than Flutamide

Clink the icon → Video Lectures Website/Notes

ESTROGENS

↳ Female Sex Hormone, release from Ovaries

↳ In 1900, it was established that Ovaries control the reproductive function through hormonal mech.

↳ Allen & Doisy (1923) - found that alc. extract of ovaries can induce estrus in rodent

↳ 1929 - pure active Estradiol

Natural Estrogen - "Estradiol" - synthesized in graafian follicle, Corpus luteum & placenta from Chol.

Cholesterol → Estradiol ⇌ Estrone → Estriol

Estradiol → Most potent for Estrogen R

- In female - 10 - 100 ug/day depends on phase
- In Male - 2-20 ug/day from extra gonadal tissue

Mode of Action :→ Through Estrogen Receptor

↓

Gene Transcription

Location :→ Female reproductive Organs, breast, Liver, Pituitary, bone, BV, Heart, CNS & hormone responsive breast carcinoma cells

ERα → Uterus, Vegina, breast, bone, BV, hypothalamus

ERβ → Prostate glands & Ovaries

↳ Estradiol ⇒ have equal affinity to both ERα & ERβ

1) Sex Organ → Developement of female sex organ - vegina, uterus, & fallopian tube.
→ Proliferatn of Endometrium; at modest dose it may cause Endometrium hypertrophy & delayed menstruatn
→ it augment rhythmic contractn of the f. tube & uterus & induce watery alkaline sec. from cervix (this is favorable to sperm penetration.

2) 2° sex character in female

3) Metabolic Effects - Anabolic effects (lesser than testost.)
↳ Important in maintaining bone mass
↳ Na^+/water Retention ↳ ↑ BP in long term
↳ ↓ LDL & ↑ HDL & TG ↳ ↑ blood Coagulatn (II, VII, IX, X)
↳ + NO Synthase & PGI_2 Productn → Vasodilation

Uses = HRT Birth Control Pills, Veginitis, Hypogonadism in female, Dysmenorrhoea Acne, Prostate Carcinoma,

ADR - Loss of libido, Gynaecomastia, Irregular menstrual cycle after menopause, ↑ Incidence of breast cancer, Gallstone, Migrane, epilepsy

ANTI ESTROGEN

CLOMIPHENE CITRATE – Bind into both ERα & ERβ

↳ Trans – Enclomiphene → pure ER Antagonist
↳ Cis → Zuclomiphene & Rac. → Weak Agonistic Action
↳ Clomiphene → block FBS → ↑ GnRH ⇝ ↑ GnH (FSH/LH) ⇝ Ovulation

Uses – used in infertility (50mg OD, after 5th Day)
→ to aid in vitro fertilization
→ In men, used in oligozoospermia

Selective Estrogen Receptor Downregulator

↳ FLUVESTRANT "SERDs" – Antagonist

Use – Treatment of Locally advance or metastatic ER positive breast cancer in post menopausal women. (Not responding to temoxifen)

MOA → Inhibits ER dimerization & prevent the interactn with DNA & Receptor degradatn in enhanced.

Selective Estrogen Receptor Modulators (SERMs)

↳ TEMOXIFEN CITRATE
↳ chemically related to clomiphene

Action – 1) Potent ER Antagonist in breast carcinoma cells, blood vessels & at peripheral cells
2) Partial Agonist in uterus, bone, liver & pituitary
↳ ↓ breast cancer cells
↳ (+) Endometrial proliferatn, ↓ Gn & prolectin level in post menopausal women
↳ Improve the bone density
↳ ↓ TC & LDL (No effect on HDL & TG)
↳ ↑ the risk of Deep vein thrombosis

Aromatase Inhibitor

↳ LETROZOLE
↳ Anastrozole

Androstandione → Estrone
Testosterone → Estradiol

Ring A Aromatizatn

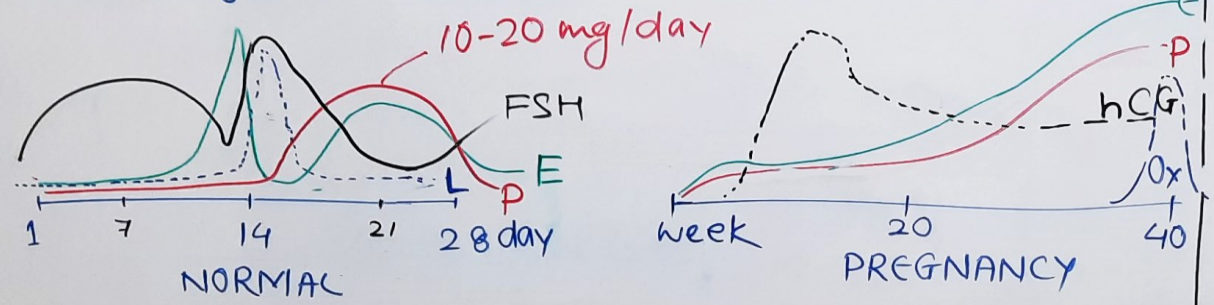
Use = In breast cancer

PROGESTINS

↳ These are substances which convert the estrogen primed proliferative endometrium to secretory & maintain pregnancy after conception.

↳ Progesterone was isolated in 1929 & clinically - 1950s

↳ Natural progestin, secreted by carpus luteum



MODE OF ACTION : (+) Progesterone Receptor (PR-A & PR-B)

↳ Female genital tract, breast, CNS, Pituitary

BIOLOGICAL ACTIONS - Major function - preparatn of uterus for nidation & maintenance of pregnancy,

↳ ↓ Uterine motility

↳ ↓ T-cell mediated immunity, prevent reject

1) **Uterus** ⇒ Bring the secretory changes in estrogen primed endometrium :- hypermia, tortocity & ↑ Secretn

Continued Actn - bring about decidual changes in endometrium :- Stroma enlarge, spongy, glands atrophy & ↓ sensetivity of myometrium to oxytocin

2) **Cervix** - watery to viscid to prevent sperm penetration

3) **Vegina** - change in veginal mucosa in pregnacy

4) **Breast** - (+) proliferation of Acini in the mammary glands

5) **CNS** - Sedation & Mood changes

6) **Body temp** - slightly rise (0.5°C)

7) **Respiratn** - (+) Respiration

8) **Metabolism** - impaired Glucose tolerance

9) **pituitary** - Administratn of progesterone during follicula phase → ↓↓ ovulation

Uses - # Oral Contraceptive

HRT # Dysfunctional uterine bleeding

Endometriasis # Endometrial carcinoma

Threatened abortion

P'kinetic → Orally inactive due to high 1st pass metaboli

- sm (for orally special formulation), im. in oily solutn
- t1/2 = 5-7 min, completely metabolized in liver
- pregnanediol → Excreted through urine

Micronized oily suspension - Geletin capsule → Abs through lymphatic system.

OXYTOCIN

UTERINE STIMULANTS - OXYTOCICS, ABROFACIENTS

→ Drugs ⇒ "Oxytocin," Desamino-Oxytocin
⇒ Ergot alkaloids, PGs (PGE_2, $PGF_{2\alpha}$), Quinine

↳ They increase the uterine motility, especifically at term

"Oxytocin" ⇒ Nonapeptide posterior pituitary hormone

↳ 1909 - Pituitary Extract → used in Labour
↳ 1953, Vigneaud → Seperated - ADH & Oxytocin
↳ Arg-Vasopressin (AVP; ADH) & Oxytocin - Synthesized in Hypothalamic nerve cell bodies (supra optic & paraventricular nuclei) ⇝ transported down the axon & stored in nerve ending within Neurohypophysis

MOA :→ (+) Oxytocin Receptor (GqPCR) on Myometrium

UTERUS

(+) ↑ Uterine Motility
(+) ↑ Release of PGs from endometrium
(+)

BREAST - Contracts the myoepithelium of mammary alveoli and force milk to ejection

CVS = Higher dose - Vasodilation, Fall in BP, - Reflex Tachy cardia

Kidney - At higher dose → ADH like action

BIOLOGICAL ROLE - ↳ Labour
↳ Milk ejection Reflex
↳ Peptide neurotransmitter

P'kinetic = Orally inactive, Adm via I.M. or I.V.
Rapidly degraded in Liver & Kidney, $t_{1/2}$ = 6 - 12 min
in pregnant placenta produce Oxytocinase to metabolize the oxytocin

USES ⇒ ↳ Induction of Labour
↳ Uterine inertia
↳ Postpartum haemorrhage in hypertensive women
↳ Breast engorgement

ADR - ↳ Maternal & Foetal Soft tissue injury
↳ Water intoxicatn (ADH like action)

DESAMINO-OXYTOCIN"

↳ Buccal Formulation
↳ Similar as Oxytocin