Endocrine pharmacology

Endocrine pharmacology

The endocrine system is controlled by two parts of the brain: The Pituitary gland and the Hypothalamus. • This system coordinates the various functions of our body by transmitting information in the form of biochemicals between individual cells and tissues of the body. • The messengers called as HORMONES.

• FUNCTIONS: Maintain Internal Homeostasis, Support Cell Growth, Coordinate Development , Coordinate Reproduction, fertility, sexual function AND Facilitate Responses to External Stimuli.

3. **Anterior Pituitary • Somatotrophs** :

Growth hormones • Thyrotrophs TSH • Gonadotrophs : • Lactotrophs : Prolactin • Corticotrophs Posterior pituitary • Oxytocin • Antidiuretic hormone

4. **CONTENTS • Growth Hormone •**

Prolactin • Sex Hormones • Oral Contraceptives • Corticosteroids

5. **GROWTH HORMONE • Water**

soluble hormone ; hence cannot diffuse through lipid bilayer of PM. • They bind to Receptors protruding from target cell surface(integral transmembrane proteins) They act as 1st messengers->produce 2nd messengers inside the cell, leads to hormone stimulated responses. • General mechanism of water soluble hormone : Hormone-Rc complex G Protein(Activated) Adenylyl cyclase converts ATP Cyclic AMP Protein kinases Cellular proteins/enzymes (activation/inactivation) Reactions that produces physiological responses. • Examples that follows this MOA: ADH, TSH, ACTH, Glucagon, Epinephrine. ACT ACT ACT PHOSPHORYLATES

6. **• Most abundant**

anterior pituitary hormone.

• Secreted by Somatotrophs, AP Cells.

• Somatotropins stimulates tissues to secrete Insulin like growth factors(IGF) That produces hormones which stimulates general body growth and regulate aspects of metabolism.

• Due to the alternative splicing of GH gene, anterior pituitary secrets homogenous mixture of GH peptides that circulates in blood(protein bound) to a corresponding extracellular domain of GH receptor.

7. **Secretion and regulation •**

Secretion is high in children , reaches maximum levels at puberty.

• GH and its peripheral factors(IGF-1) acts in negative feedback loop to suppress GH secretion. IGF inhibits the GH secretion through direct effect on the pituitary gland.

• Somatostatin(SST) and ghrelin also acts by negative regulation.

• SST synthesized by neurons, Neuro endocrine cells in GI tract and pancreas as prohormone precursor.

• It exerts its effect by binding to GPCR and activating Gi > Inhibits cAMP Accumulation > Activate K+ Channels and Tyrosine phosphates.

• SST Receptor subtypes: SSTR2 and SSTR5 are most important for regulation of GH Secretion. -They have direct effect on somatotrophs in pituitary -indirect effect is mediated via GHRH neurons

• Several Neurotransmitters,

Drugs, Metabolites, Other stimuli modulate release of GHRH or SST and Affect the GH secretion.

• Dopamine, 5-HT, α2-Agonist Stimulate GH release (Hypoglycemia, Exercise, stress, emotional excitement, ingestion of protein rich meals also stimulates GH release) • B-Agonist, free fatty acids, IGF-1 and GH itself inhibits the release. • GHRH and SST acts on somatotrophs in anterior pituitary to regulate growth hormone secretion. • SST inhibits GHRH release, GH has direct effects on target tissues , exerts indirect effect by stimulating release of IGF-1. • Gastric peptide Ghrelin Enhances GH release.

10. **Molecular and cellular** action •

GH receptor - widely distributed, belongs to cytokine Rc superfamily. • Extracellular domain (single membrane spanning region) where GH binds and an intracellular domain which mediates the signal transduction. • A single GH molecule binds to 2 identical receptor(activates them) thus forming ligand occupied receptor dimer(LORD) which brings intracellular domains into close proximity activate cytosolic components(important for cell signaling) • The LORD doesn't have tyrosine kinase activity (But provides docking sites for 2 molecules of JAK 2) • Juxta position of 2 JAK 2 molecules brings about trans phosphorylation and auto activation of JAK2 which further mediates downstream signaling events.

11. **Pegvisomant- Recombinant pegylated**

variant of human GH, with mutations , has high affinity for GHRc.

12. **Physiologic Effects of** Growth Hormone

• Stimulate longitudinal growth of bones, increases bone mineral density after growth ceases and epiphyses have closed.

• Stimulate myoblast differentiation(in experiment animals) increases muscle mass (in human with GH deficiency) , increases GFR

. • Stimulate preadipocyte differentiation into adipocytes.

• Acts directly on adipocytes increases lipolysis . On hepatocytes it stimulates Gluconeogenesis (mediated by IGF-1)

• USFDA approved a NDA for recombinant human IGF-1 to treat short stature in patients resistane to GH.

13. **Clinical disorders • GH**

deficiency in children leads to short stature, Turner's syndrome, Prader-willi syndrome, Chronic renal insufficiency. • GH deficiency in adults leads to decrease in muscle mass, decreased bone density, impaired psychosocial function. • Increases mortality rates after Heart surgery or abdominal surgery, acute respiratory failure. Treatment • Recombinant GH Replacement therapy- Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope etc • Derivative of GH- Somatrem (used in children with deficiency) Dose : 40 µg/kg/day – Subcutaneously in evening. Turner's syndrome : 50 µg/kg ; IGF-1 levels are monitored for initial responses and compliance SIDE EFFECTS: intra cranial HT with papilledema, visual changes,headache, nausea/vomiting, Leukamia(some children), Type 2DM. In Adults: Peripheral edema, Carpal tunnel syndrome, Arthralgias, Myalgias.

14. prolactin

It is structurally related to GH.

• Secreted by Lactotrophs of anterior pituitary. With other hormones it initiates milk production in mammary glands.

• Serum levels remains low in normal males throughout life and somewhat in females.

• Prolactin levels rise markedly during pregnancy reach maximum at term and decline thereafter unless the mother breast feeds the infant.

• Only after mammary glands primed by Estrogen, Progesterone, glucocorticoids, hGH , thyroxin and insulin exert permissive effects, prolactin brings about milk secretion.

• Ejection of milk from mammary glands depends on Oxytocin hormone(released from posterior pituitary)

• **Suckling/Breast manipulation**

stimulates circulating prolactin levels, rises 10-100 folds within 30 minutes.

• Prolactin inhibiting hormone- Dopamine inhibits release of prolactin(D2 receptor) each month just before the menstruation begins , the secretion of PIH diminishes and prolactin level rises(not enough to stimulate milk production)

• Suckling action involves decreased secretion of dopamine by tuberoinfundibular neurons and possibly increased release of factors that stimulate prolactin and reduction In hypothalamic secretion of PIH.

• Prolactin is also synthesized by decidual cells near the end of luteal phase of menstrual cycle and early in pregnancy.

• Factors influencing prolactin secretion are similar to those that affect GH secretion : Sleep, stress, Hypoglycemia, Exercise, Estrogen.

. **Molecular and cellular** action

• Prolactin receptor is encoded by single gene alternative splicing gives multiple forms of receptors (soluble forms in circulation with extracellular domain)

• Membrane bound prolactin receptor structurally related to GHRc (But it has no GH like activity) , Cytokines and uses similar signaling mechanisms. • Prolactin lacks intrinsic tyrosine kinase activity.

• Upon binding of prolactin to the receptor , it undergoes conformational changes and leads to JAK kinase activation . Activation of JAK 2 leads to phosphorylation , dimerization, Nuclear translocation of transcription factor STAT5.

. **Physiological effect: Prolactin plays**

an important role in inducing growth and differentiation of the ductal and lobuloalveolar epithelium which is essential for lactation. Prolactin Excess:

• Hyper prolactinemia (common endocrine abnormality) caused by prolactin-secreting pituitary adenomas, it also results from hypothalamic or pituitary disease that interfere with delivery of inhibitory dopaminergic signals

• Primary hyperthyroidism with increased TRH levels, Renal failure.

• Hyper secretion in males : Erectile dysfunction(impotency)

• Hyper secretion in females : Galactorrhea (inappropriate lactation) , Amenorrhea(Absence of menstrual cycle) and infertility

18. **Treatment: Trans sphenoidal**

surgery, Radiation, Dopamine receptor agonist(suppress prolactin production via D2 receptor) 1.BROMOCRIPTINE (D2 receptor Agonist):

• Semisynthetic ergot alkaloid

• Inhibits spontaneous and TRH induced prolactin release.

• Acts on D1 receptor to lesser extent.

• Normalizes serum prolactin levels in 70-80% patients and decrease the tumor size in 50% patients.

• Side effects : Nausea, Vomiting, headache, Postural hypotension, Nasal congestion, CNS effects(psychosis, hallucinations,nightmares/insomnia-less frequent)

• 7% dose reaches systemic circulation due to extensive first pass metabolism.

• Used in Management of acromegaly, at high conc-Parkinson’s disease

.PERGOLIDE (Ergot derivative) •

FDA approved – Treatment of Parkinson's disease and hyper prolactinemia. • Side effects are same as of bromocriptine.

• Dose – Once a day : 0.025mg bed time gradually increasing to 0.5mg. 3.CABERGOLINE (ergot derivative)

• High affinity and greater sensitivity for D2 Receptor. 4 times more potent than bromocriptine, half life is 65 hours.

• FDA approved for the treatment of hyperprolactinemia.

• Lower tendency to cause side effects(Hypotension and dizziness) 4.QUINAGOLIDE

• Non ergot D2 Receptor agonist, half life is 22 hours, Dose : 0.1- 0.5mg

• Not approved by FDA.

- SEXHORMON

and progestins (steroid hormones)

• In women they control ovulation, cyclical preparation of the reproductive tract for fertilization and implantation and metabolic actions.

• Estrogens in males have effects on bone, spermatogenesis and behavior.

• Estrogen and progestins are used in menopausal hormone therapy(MHT) and contraception in women.

• Estrogen and progestin antagonists are also available.

ESTROGEN

Steroidal and non steroidal compounds. The most potent naturally occurring estrogen in humans for both estrogen receptor α and β are 17 β- estradiol, estrone, estriol.

• They all contain a phenolic A ring with OH group at C3 and β-OH or ketone in 17th position of ring D.

• Phenolic ring is responsible for selective high affinity for both receptors.

• Diethyl stilbestrol, structurally similar to estradiol(trans), high affinity, same potency but longer half life.

• Non steroidal compounds with estrogenic or anti estrogenic activity : Flavones, isoflavones(genistain), coumestan derivatives, DES, Bisphenol A, Genistein.

• Synthetic: Pesticides, Plasticizers etc

• Steroidal: Estradiol, Estradiol Valerate, Ethinyl estradiol, Mestranol, Estrone sulfate, Equlin

22. **Biosynthesis: • Androstenedione/testosterone ->**

Aromatization of ring A, Catalyzed by Aromatase(CYP19) an enzyme found in ovarian granulosa cells, testicular Sertoli and Leydig cells, adipose stroma, placental syncytiotrophoblast, preimplantation blastocysts, bone, various brain regions, and other tissues.

• Ovaries are the principal source of circulating estrogen in premenopausal women. Gonadotropins, acting via receptors that couple to the Gs-adenylyl cyclase–cyclic AMP pathway, increase the activities of aromatase and the cholesterol side-chain cleavage enzyme. The ovary contains the type I isoform of 17 β-hydroxysteroid dehydrogenase, which favors the production of testosterone and estradiol from androstenedione and estrone, respectively. In the liver, the type II isoform oxidizes circulating estradiol to estrone, which then is converted to estriol.

• These estrogens

are excreted in the urine along with their glucuronide and sulfate conjugates. In postmenopausal women, the principal source of circulating estrogen is adipose tissue stroma, where estrone is synthesized from dehydroepiandrosterone (DHEA) secreted by the adrenals.

• In men, the testes produce estrogens but extragonadal aromatization of circulating androstenedione and DHEA accounts for most circulating estrogens.

• Local production of estrogens by the aromatization of androgens may play a causal role in the development or progression of diseases such as breast cancer. Estrogens also may be produced from androgens by CYP19 in the central nervous system (CNS) and other tissues and exert local effects near their production site (e.g.,in bone they increase bone mineral density).

24. **Physiological and Pharmacological** Action

• Estrogens in girls cause growth and development of the vagina, uterus, and fallopian tubes, and contribute to breast enlargement, molding the body contours, shaping the skeleton, and causing the pubertal growth spurt of the long bones and epiphyseal closure.

• Growth of axillary and pubic hair, pigmentation of the genital region, and the regional pigmentation of the nipples and areolae that occur after the first trimester of pregnancy are also estrogenic actions.

• Estrogens also play developmental roles in males. In boys, estrogen deficiency diminishes the pubertal growth spurt and delays skeletal maturation and epiphyseal closure so that linear growth continues into adulthood.

• Estrogen deficiency in men leads to elevated gonadotropins, macro orchidism, and increased testosterone levels and also may affect carbohydrate and lipid metabolism and fertility.

25. **Metabolic effects • Estrogens**

Estrogen increase bone mass, largely by decreasing the number and activity of osteoclasts, thereby decreasing bone desorption.

• ↑ high-density lipoprotein (HDL) levels and ↓ the levels of low- density lipoprotein (LDL)

. • increase biliary cholesterol secretion and decrease bile acid secretion, leading to increased saturation of bile with cholesterol that results in gallstone formation in some women receiving estrogens.

• estrogens increase plasma levels of corticosteroid-binding globulin (CBG), thyroxine-binding globulin (TBG), and sex hormone–binding globulin (SHBG), which binds both androgens and estrogens.

• Estrogens slightly increase coagulation factors II, VII, IX, X, and XII, and decrease the anticoagulation factors protein C, protein S, and antithrombin III.

. **Mechanism of action** :

• ERα is expressed most abundantly in the female reproductive tract— especially the uterus, vagina, and ovaries—as well as in the mammary gland, hypothalamus, endothelial cells, and vascular smooth muscle.

• ERβ is expressed most highly in the prostate and ovaries, with lower expression in lung, brain, bone, and vasculature.

• ligand-activated transcription factors that increase or decrease the transcription of target genes.

• the hormone binds to an ER in the nucleus, change in ER conformation dissociates heat-shock proteins, causes receptor dimerization, which increases receptor binding to DNA.

• ER dimer binds to estrogen response elements (EREs), located in the promoter region of target genes.

• The ER/DNA complex recruits a cascade of coactivators and other proteins to the promoter region of target genes.

27. **Pharmacokinetics • estrogens are**

Estrogens are available for oral, parenteral, transdermal, or topical administration(estrogen alone or in combination with a progestin)

• Oral route : high doses must be used due to first-pass metabolism.

• Transdermal administration of estradiol provides slow, sustained release of the hormone, systemic distribution, and more constant blood levels than oral dosing.

• Estrogens undergo rapid hepatic biotransformation, with a plasma t1/2 measured in minutes.

• Estradiol is converted primarily by 17β-hydroxysteroid dehydrogenase to estrone, which undergoes conversion by 16α-hydroxylation and 17-keto reduction to estriol, the major urinary metabolite. A variety of sulfate and glucuronide conjugates also are excreted in the urine.

• Estrogen conjugates also undergo enterohepatic recirculation.

ADVERS EFFECT

Increased incidence of vaginal and cervical adenocarcinoma was noted in female offspring of mothers who had taken diethylstilbestrol.

• Estrogen use during pregnancy also can increase the incidence of nonmalignant genital abnormalities in offspring.

. • Estrogen in postmenopausal women increases the risk of endometrial carcinoma by 5–15-fold

. • Oral estrogens significantly increase the risk of thromboembolic disease in healthy women.

• Nausea and vomiting occur in some women but often disappear with time.

• Estrogens may cause severe migraine in some women.

• Estrogens also may reactivate or exacerbate endometriosis

Therapeutic uses

components of combination oral contraceptives and for MHT.

• Estrogen therapy in postmenopausal women : amelioration of vasomotor symptoms and the prevention of bone fractures/ Osteoporosis and urogenital atrophy.

• Vaginal Dryness and Urogenital Atrophy.

• Estrogen treatment in the failure of ovarian development.

• Selective estrogen receptor modulators : TAMOXIFEN, RALOXIFENE, AND TOREMIFENE , Their pharmacological goal is to produce beneficial estrogenic actions in certain tissues (e.g.,bone, brain, and liver) but antagonist activity in others (e.g.,breast and endometrium).

• Antiestrogens: CLOMIPHENE AND FULVESTRANT These compounds are pure antagonists in all tissues. Clomiphene is approved for the treatment of infertility in an ovulatory women; fulvestrant is used to treat breast cancer in women with disease progression after tamoxifen.

30. **PROGESTINS • The progestins**

The progestins are widely used with estrogens for MHT and other situations in which a selective progestational effect is desired.

• Progesterone is secreted by the corpus luteum during the second half of the menstrual cycle under the stimulus of LH. Pharmacological actions:

• Progesterone produced in the luteal phase of the cycle decreases the frequency of GnRH pulses.

• Progesterone decreases estrogen-driven endometrial proliferation and induces a secretory endometrium.

• Mammary gland development requires both estrogen and progesterone. During pregnancy, luteal phase of the cycle, progesterone acts with estrogen to induce proliferation of the acini of the mammary gland

• **Progesterone increases** basal body temperature by about 0.6°C at midcycle when ovulation occurs. • Progesterone also increases the ventilatory response of the respiratory centers to CO2 and leads to reduced arterial and alveolar CO2 in the luteal phase of the menstrual cycle and during pregnancy.

• Progesterone increases basal insulin and postprandial insulin levels but does not normally alter glucose tolerance.

• Progesterone and analogs increase LDL and cause either no effect or modest reduction in serum HDL levels.

• Progesterone also may diminish the effects of aldosterone in the renal tubule.

Mechanism of Action •

A single gene encodes two isoforms of the PR, PRA and PRB , by differential use of two distinct estrogen-dependent promoters.

• Upon progesterone binding, the receptors form homo- and heterodimers that bind with high selectivity to progesterone response elements located on target genes.

• Transcriptional activation by PR occurs primarily by recruitment of co- activators that recognize the activated PR conformation.

• Progesterone antagonists also facilitate receptor dimerization and DNA binding, but antagonist-bound PR preferentially interacts with corepressors.

Pharmacokinetics • Progesterone undergoes

rapid first-pass metabolism. • Progesterone also is available in oil solution for injection, as a vaginal gel, and as a slow-release intrauterine device for contraception. • Esters are available for intramuscular administration. • The elimination t1/2 of progesterone is : 5 minutes; the hormone is metabolized primarily in the liver to hydroxylated metabolites and their sulfate and glucuronide conjugates, which are eliminated in the urine. • The synthetic progestins have much longer half-lives. • Metabolism of synthetic progestins is primarily hepatic, and elimination is generally in the urine as conjugates and various polar metabolites.

34. **Therapeutic uses: • The**

two most frequent uses of progestins are for contraception, either alone or with an estrogen, and in combination with estrogen for hormone therapy of postmenopausal women. • Progestins also are used for secondary amenorrhea, abnormal uterine bleeding in patients without underlying fibroids or cancer, luteal-phase support to treat infertility, and premature labor. • Progestins are used diagnostically to test for estrogen secretion and for responsiveness of the endometrium. • Progestins are highly efficacious in decreasing the occurrence of endometrial hyperplasia and carcinoma caused by unopposed estrogens. • Progestins are also used for metastatic endometrial carcinoma. Megestrol acetate is used as a second-line treatment for breast cancer.

35. **Oral contraceptives • These**

These are hormonal preparations used for reversible suppression of fertility.

• In the earlier part of 20th century, methods of contraception used (condoms, diaphragms, spermicidal creams, foam tablets, etc.)

• These also have higher failure rate.

• Oral contraceptives are medicines taken by mouth to help prevent pregnancy

. • They are also known as “birth control pills”.

• Oral contraceptives

are widely used worldwide and have had a revolutionary impact by providing a convenient, affordable, and reliable means of contraception.

• In addition to contraceptive actions, these agents have substantial health benefits. • Birth control (contraceptive) medications contain hormones (estrogen and progesterone, or progesterone alone).

• Estrogens : Ethinyl estradiol, Mestranol

• Progesterones: Norethynodrel, Norethindrone Norethindrone acetate, Norgestimate Desogestrel, Ethynodiol diacetate Norgestrel, Levonorgestrel,Drospirenone

. **Combination oral contraceptives** :

• The most frequently used are combination oral contraceptives containing both an estrogen and a progestin.

• Their theoretical efficacy is considered to be 99.9%.

• Ethinyl estradiol and mestranol are the two estrogens used (with ethinyl estradiol being much more frequently used).

• The progestins have varying degrees of androgenic, estrogenic, and antiestrogenic activities that may be responsible for some side effects.

• Combination oral contraceptives are generally provided in 21-day packs with an additional 7 pills containing no active hormone.

• For monophasic agents, fixed amounts of the estrogen and progestin are present in each pill, which is taken daily for 21 days, followed by a 7-day "drug-free" period.

. **• The biphasic**

and triphasic preparations provide two or three different pills containing varying amounts of active ingredients, for different days in the 21-day cycle.

• The FDA recently approved a levonorgestrel–ethinyl estradiol combination that is taken continuously for the full 90 days, eliminating any menstrual periods.

• The estrogen content ranges from 20 to 50 μg; most contain 30–35 μg. Preparations containing ≤35 μg of an estrogen are termed "low- dose" pills.

• Additional options include a once-monthly medroxy progesterone– estradiol cypionate injectable , an ethinyl estradiol– norelgestromin(the active metabolite of norgestimate) patch applied weekly, and an ethinyl estradiol–etonogestrel(the active metabolite of desogestrel) flexible vaginal ring used for 3 weeks (followed by a removal for 1 week that leads to menstrual bleeding).

40. **Progestin-only contraceptives : •**

Progestin-only contraceptives are only slightly less efficacious than combination oral contraceptives, with theoretical efficacy of 99%.

• Specific preparations include the “minipill” : low doses of progestins (e.g.,350µg of norethindrone or 75 µg of norgestrel) taken daily without interruption.

• Subdermal implants of 216 mg of norgestrel for slow release and resultant long-term contraceptive action .

• crystalline suspensions of MPA for intramuscular injection of 150 mg of drug, which provides effective contraception for 3 months.

• An intrauterine device that releases low amounts of progesterone locally is available for insertion on a yearly basis. Contraceptive action probably is due to local effects on the endometrium

41. **Postcoital or emergency**

contraceptives : • The FDA has approved two preparations for postcoital contraception.

• PLAN-B is two doses of the “minipill” (0.75 mg levonorgestrel per pill) separated by 12 hours. • Will soon be available without a prescription for women 18 years old and older.

• PREVEN is two 2-pill doses of a high-dose oral contraceptive (0.25 mg of levonorgestrel and 0.05 mg of ethinyl estradiol per pill) separated by 12 hours.

• The first dose of such preparations should be taken within 72 hours after intercourse, and this should be followed 12 hours later by a second dose.

• These treatments reduce the risk of pregnancy following unprotected intercourse by approximately 60–80%.

42. **Mechanism of Action •**

Combination oral contraceptives : act by preventing ovulation.

• Plasma LH and FSH levels are suppressed, the midcycle surge of LH is absent, endogenous steroid levels are diminished, and ovulation does not occur.

• The combination synergistically decreases plasma gonadotropin levels and suppresses ovulation more consistently than either alone.

• Oral contraceptives exert hypothalamic and pituitary effects. Progesterone diminishes the frequency of GnRH pulses, and oral contraceptives also decrease pituitary responsiveness to GnRH.

• Estrogens also suppress FSH release from the pituitary during the follicular phase of the menstrual cycle, which likely contributes to the lack of follicular development in oral contraceptive users.

• Progestin also leads to a thick, viscous mucus that reduces sperm penetration and induces an endometrium that is not receptive to implantation.

. **Progestin-only contraceptives • Progestin-only**

Progestin -only pills and levonorgestrel implants are highly efficacious for contraception. • The pills block ovulation in only 60–80% of cycles, • Effectiveness is thought to be due largely to local effects in the cervix and uterus, such effects also account for the efficacy of intrauterine devices that release progestins. • Depot injections of MPA yield plasma levels of drug high enough to prevent ovulation in virtually all patients, presumably by decreasing the frequency of GnRH pulses.

44. **Adverse effects: Cardiovascular Effects** :

• There is a 28% increase in relative risk for venous thromboembolism, but the estimated increase is very small because these events are rare in women without other predisposing factors. • The incidence of hypertension is much lower with low-dose preparations. Cancer : • Combined oral contraceptives may increase the risk of cervical cancer by about twofold, but only in long-term users with human papilloma virus infection. • There are reported increases in the incidence of hepatic adenoma and hepatocellular carcinoma in oral contraceptive users : very rare

45. **Metabolic and Endocrine**

Effects : • In women who smoke, the ethinyl estradiol in oral contraceptives appears to cause a dose-dependent increase in several serum factors that may shift the hemostatic profile toward a hypercoagulable condition. • oral contraceptives may increase hepatic synthesis of a number of serum proteins, including CBG, TBG, and SHBG. • Miscellaneous Effects : Nausea, edema, and mild headache occur in some individuals. Some patients may experience breakthrough bleeding during the 21-day cycle when the active pills are being taken. Acne and hirsutism are thought to be mediated by the androgenic activity of the 19-nor progestins.

46. **• Amenorrhea becomes**

common after a year or more of use. • Mood changes and weight gain also have been reported. • Decreases in HDL levels and increases in LDL levels and decreased bone density. • Norethindrone implants may be associated with infection, local irritation, pain at the insertion site, and rarely, expulsion of the inserts. Headache, weight gain, mood changes, and acne occur in some patients. Contraindications: the presence or history of thromboembolic disease, cerebrovascular disease, myocardial infarction, coronary artery disease, or congenital hyperlipidemia;known or suspected carcinoma of the breast, carcinoma of the female reproductive tract, or other hormone- dependent/responsive neoplasias; abnormal undiagnosed vaginal bleeding; known or suspected pregnancy; and past or present liver tumors or impaired liver function.

47. **Corticosteroids • These are**

a class of steroid hormones that are produced in the adrenal cortex, it includes synthetic analogues of these hormones. • The term ‘corticosteroid’ or ‘corticoid’ includes natural gluco- and mineralo-corticoids and their synthetic analogues. • Two main classes of corticosteroids: glucocorticoids and mineralocorticoids. • They are involved in a wide range

of physiological processes, including stress reponse, immune response, regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

48. **Biosynthesis • The corticoids**

(both gluco and mineralo) are 21 carbon compounds having a cyclopentanoperhydro-phenanthrene (steroid) nucleus. • They are synthesized in the adrenal cortical cells from cholesterol. • Since adrenal cortical cells store only minute quantities of the hormones, rate of release is governed by the rate of biosynthesis. • Hydrocortisone—10–20 mg daily (nearly half of this in the few morning hours), Aldosterone — 0.125 mg daily.

49. **Mineralocorticoid actions : •**

The principal mineralocorticoid action is enhancement of Na+ reabsorption in the distal convoluted tubule in kidney. • Its deficiency results in decreased maximal tubular reabsorptive capacity for Na+ . • Dilutional hyponatraemia →excess water enters cells →cellular hydration: decreased blood volume and raised haematocrit. Hyperkalaemia and acidosis. • These distortions of fluid and electrolyte balance progress and contribute to the circulatory collapse. • The action of aldosterone is exerted by gene mediated increased transcription of m-RNA in renal tubular cells which directs synthesis of proteins.

50. **• Synthesis of**

β subunit of amiloride sensitive Na+ channel is also induced. • Because of the time taken to induce protein synthesis, aldosterone action has a latency of 1–2 hours. • aldosterone rapidly induces phosphorylation and activation of amiloride sensitive Na+ channel. • The main adverse effect of excessive mineralocorticoid action is fluid retention and hypertension. • Natural and some of the synthetic glucocorticoids have significant mineralocorticoid activity responsible for side effects like edema, progressive rise in BP, hypokalemia and alkalosis. • The diuretic induced hypokalemia is aggravated by

mineralocorticoid excess. • Aldosterone has been shown to promote CHF associated myocardial fibrosis and progression of the disease

51. **Glucocorticoid actions: Carbohydrate and**

protein metabolism: • Promote glycogen deposition in liver(by inducing hepatic glycogen synthase and promoting gluconeogenesis), inhibit glucose utilization by peripheral tissues, increased glucose release from liver : hyperglycaemia. • They also cause protein breakdown and amino acid mobilization from peripheral tissues. The amino acids so mobilized funnel into liver →used up in gluconeogenesis, excess urea is produced → negative nitrogen balance. • Glucocorticoids are thus catabolic. Their function appears to be aimed at maintaining blood glucose levels during starvation.

52. **Fat metabolism: They**

promote lipolysis due to glucagon, growth hormone, Adr and thyroxine. Calcium metabolism : Glucocorticoids inhibit intestinal absorption and enhance renal excretion of Ca2+. Loss of osteoid indirectly results in loss of Ca2+ from bone, producing negative calcium balance. Water excretion : Hydrocortisone and other glucocorticoids, but not aldosterone, maintain normal g.f.r. In adrenal insufficiency, the capacity to excrete a water load is markedly reduced. CVS : Glucocorticoids restrict capillary permeability, maintain tone of arterioles and myocardial contractility. They also play a permissive role in development of hypertension, Adrenal insufficiency is attended by low cardiac output, arteriolar dilatation, poor vasoconstrictor response to Adrenaline and increased permeability of capillaries. These changes along with hypovolemia (due to lack of mineralocorticoid) are responsible for cardiovascular collapse.

53. **Skeletal muscles: Optimum**

level of corticosteroids is needed for normal muscular activity. Weakness occurs in both hypo- and hypercorticism, but the causes are different. Hypocorticism: diminished work

capacity and weakness are primarily due to hypodynamic circulation. Hypercorticism: excess mineralocorticoid action →hypokalaemia →weakness; Excess glucocorticoid action →muscle wasting and myopathy →weakness. CNS : Mild euphoria is quite common with pharmacological doses of glucocorticoids. Glucocorticoids also maintain the level of sensory perception and normal level of excitability of neurones. Stomach : Secretion of gastric acid and pepsin is increased—may aggravate peptic ulcer. Inflammatory responses : inflammatory response is suppressed by glucocorticoids. The cardinal signs of inflammation—redness, heat, swelling and pain are suppressed.

54. **Mechanism of action: •**

Corticosteroids penetrate cells and bind to a high affinity cytoplasmic receptor protein. • A structural change occurs in the steroid receptor complex that allows its migration into the nucleus and binding to glucocorticoid response elements (GRE) on the chromatin. • Transcription of specific m-RNA →regulation of protein synthesis. • This process takes at least 30–60 min. • The overall effect is catabolic, i.e. inhibition of protein synthesis. This may be a consequence of steroid directed synthesis of an inhibitory protein.

55. **• The glucocorticoid**

receptor (GR) is very widely distributed .It has been cloned and its structure determined. It is made up of 800 amino acids. • Several coactivators and corepressors modulate the interaction of liganded GR with the GREs, altering the intensity of response. • Some actions of corticoids are exerted more rapidly (like inhibition of ACTH release from pituitary). These may be mediated by a cell membrane receptor or a different mechanism not involving protein synthesis.

56. **Pharmacokinetics: • All natural**

and synthetic corticoids, except DOCA are absorbed and are effective by the oral route. • Hydrocortisone undergoes high first pass metabolism, has low oral: parenteral activity

ratio. Oral bioavailability of synthetic corticoids is high. • The corticosteroids are metabolized primarily by hepatic microsomal enzymes. The metabolites are further conjugated with glucuronic acid or sulfate and are excreted in urine. • The plasma t½ of hydrocortisone is 1.5 hours However, the biological t½ is longer because of action through intracellular receptors and regulation of protein synthesis. • Phenobarbitone and phenytoin induce metabolism of hydrocortisone, prednisolone and dexamethasone, etc. to decrease their therapeutic effect

57. **1. Hydrocortisone (cortisol): •**

Acts rapidly but has short duration of action. In addition to primary glucocorticoid, it has significant mineralocorticoid activity as well. • Replacement therapy—20 mg morning + 10 mg afternoon orally. • Shock, status asthmaticus, acute adrenal insufficiency—100 mg i.v. bolus + 100 mg 8 hourly i.v. infusion. • Topically and as suspension for enema in ulcerative colitis. 2. Prednisolone: • It is 4 times more potent than hydrocortisone, also more selective glucocorticoid, but fluid retention does occur with high doses. • Has intermediate duration of action. • Used for allergic, inflammatory, autoimmune diseases and in malignancies: 5–60 mg/day oral, 10–40 mg i.m., intraarticular; also topically.

58. **3. Methylprednisolone : •**

Slightly more potent and more selective than prednisolone. • 4–32 mg/ day oral. Methylprednisolone acetate has been used as a retention enema in ulcerative colitis. • high dose methylprednisolone (1 g infused i.v. every 6–8 weeks) active rheumatoid arthritis, renal transplant, pemphigus, etc. with good results and minimal suppression of pituitary adrenal axis. 4. Triamcinolone : • Slightly more potent than prednisolone but highly selective glucocorticoid • 4–32 mg/day oral, 5–40 mg i.m., intraarticular injection. Also used topically.

59. **5. Dexamethasone : •**

Very potent and highly selective glucocorticoid. long-acting,causes marked pituitary-adrenal suppression. • It is used for Inflammatory and allergic conditions 0.5–5 mg/day oral. • For shock, cerebral edema, etc. 4–20 mg/day i.v. infusion or i.m. injection is preferred. It can also be used topically. 6. Betamethasone : • Similar to dexamethasone . • 0.5–5 mg/ day oral, 4–20 mg i.m., i.v. injection or infusion, also topical.

60. **7. Desoxycorticosterone acetate**

(DOCA)

It has only mineralocorticoid activity.

Used occasionally for replacement therapy in Addison's disease: 2–5 mg sublingual, 10–20 mg i.m. once or twice weekly. 8. Aldosterone :

It is the most potent mineralocorticoid.

Not used clinically because of low oral bioavailability and difficulties in regulating doses.

61. **Uses: Replacement therapy : •**

Acute adrenal insufficiency - In emergency conditions Hydrocortisone or dexamethasone are given i.v., first as a bolus injection and then as infusion, along with isotonic saline and glucose solution.

Chronic adrenal insufficiency (Addison's disease) : Hydrocortisone given orally is the most commonly used drug along with adequate salt and water allowance. patients who continue to excrete excess Na+ need additional mineralocorticoid.

Congenital adrenal hyperplasia (Adrenogenital syndrome) : familial disorder due to genetic deficiency of steroidogenic enzymes, mostly 21-hydroxylase. hydrocortisone 0.6 mg/ kg daily in divided doses round the clock to maintain feed back suppression of pituitary.

62. **Pharmacotherapy (for non endocrine** diseases) Arthritides :

Rheumatoid arthritis: Corticosteroids are indicated only in severe cases as adjuvants to NSAIDs.

Osteoarthritis: It is treated with analgesics and NSAIDs; systemic use of corticoids is rare.

Rheumatic fever: Corticoids are used only in severe cases with carditis and CHF with the aim of rapid suppression of symptoms, because they act faster than aspirin.

Gout:Corticoids (short course) should only be used in acute gouty arthritis when NSAIDs have failed to afford relief and colchicine is nottolerated. (they are uricosuric—use in chronic gout is not recommended)

Collagen diseases : •

Most cases of systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis, nephrotic syndrome, glomerulonephritis need corticosteroid therapy.

They may be life saving in these diseases. Severe allergic reactions :

Corticoids may be used for short periods in anaphylaxis, angioneurotic edema, urticaria and serum sickness. Autoimmune diseases :

Autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, active chronic hepatitis respond to corticoids :Prednisolone

. **Bronchial asthma : •**

Systemic corticosteroids are used only for Status asthmaticus, Actue asthma exacerbation, Severe chronic asthma not controlled by inhaled steroids and bronchodilators.

Eye diseases :

Corticoids are used in a large number of inflammatory ocular diseases—may prevent blindness. allergic conjunctivitis, iritis, iridocyclitis, keratitis. Skin diseases :

Topical corticosteroids are widely employed and are highly effective in many eczematous skin diseases.

Systemic therapy is needed (may be life-saving) in pemphigus vulgaris, exfoliative dermatitis, Stevens-Johnson syndrome and other severe afflictions.

Intestinal diseases : •

Ulcerative colitis , Crohn's disease, coeliac disease are inflammatory bowel diseases with exacerbations and remissions.Corticoids are indicated during acute phases. Malignancies : • Corticoids are an essential component of combined chemotherapy of acute lymphatic leukaemia, Hodgkin's and other lymphomas. Organ transplantation and skin allograf • High dose corticoids are given along with other immunosuppressants to prevent the rejection reaction.

Adverse effects : Mineralocorticoid :

Sodium and water retention, edema, hypokalaemic alkalosis and a progressive rise in BP. These are now rare due to availability of highly selective glucocorticoids. Gradual rise in BP occurs due to excess glucocorticoid action as well.

Glucocorticoid - Cushing's habitus: characteristic appearance with rounded face, narrow mouth, supraclavicular hump, obesity of trunk with relatively thin limbs.

Fragile skin, purple striae—typically on thighs and lower abdomen, easy bruising, telangiectasis, hirsutism.

Hyperglycaemia, may be glycosuria, precipitation of diabetes.

Muscular weakness: proximal (shoulder,arm, pelvis, thigh) muscles are primarily affected. Myopathy occurs occasionally.

Delayed healing:

of wounds and surgical incisions.

Glaucoma: may develop in susceptible individuals after prolonged topical therapy.

Growth retardation: in children occurs even with small doses if given for long periods.

Psychiatric disturbances: mild euphoria frequently accompanies high dose steroid treatment. This may rarely progress to manic psychosis. Nervousness, decreased sleep and mood changes.

CONTRAINDICATIONS :

Peptic ulcer, Diabetes mellitus, Hypertension, Viral and fungal infections Tuberculosis and other infections, Osteoporosis, Herpes simplex keratitis Psychosis, Epilepsy, CHF, Renal failure.