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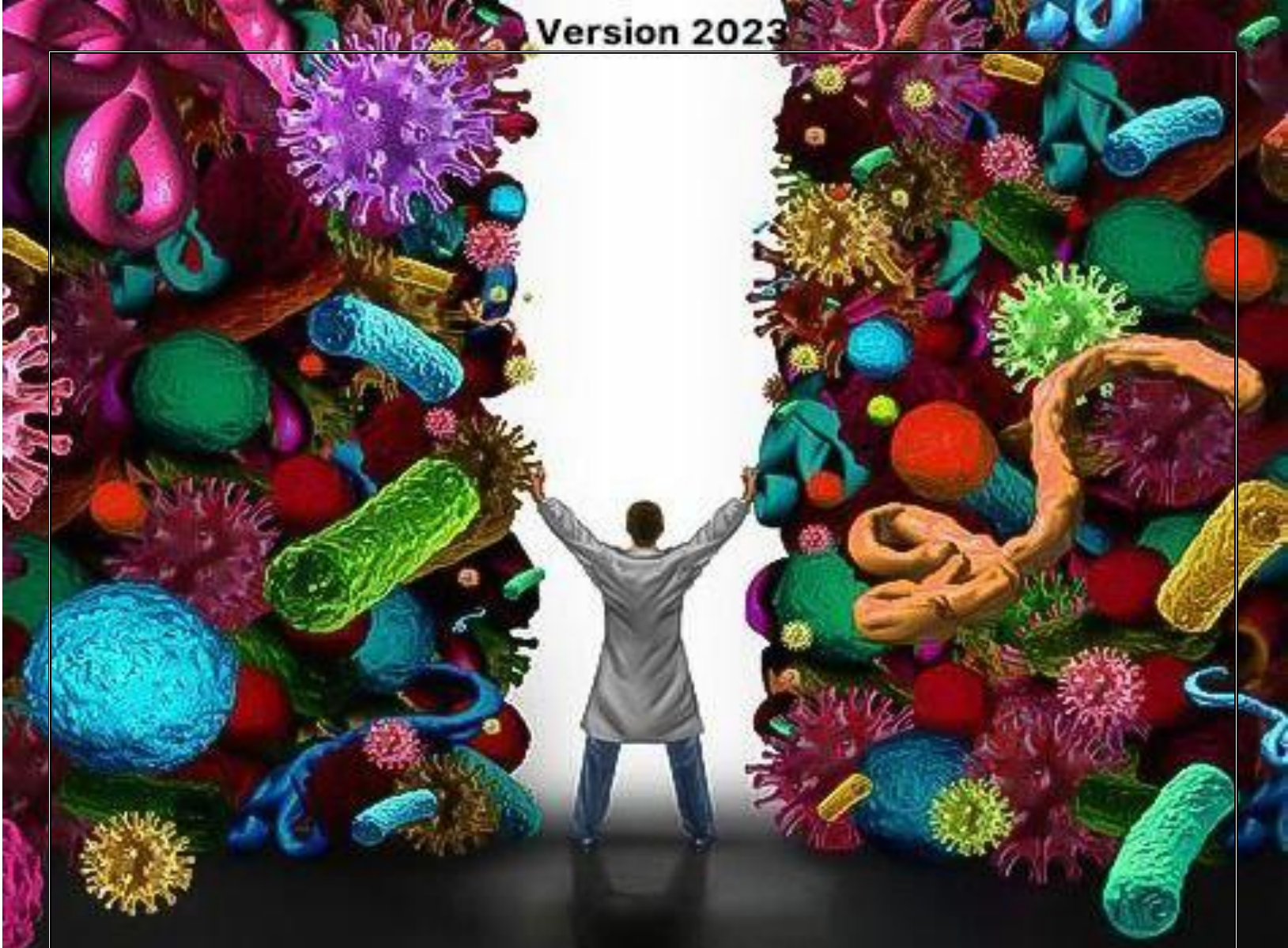

Endocrine Pharmacology

SUMMARY

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Hypothalamic & Ant.Pit Hormones

Hormone	Function	Regulation	Use
TRH (protirelin)	-Promotes secretion of TSH -Promotes release of Prolactin	-Activation of PLC to increase IP3& DAG -Increase PRL release through 2nd messenger Ca2	- As diagnostic tool (in TRH test) - Treat certain cases of hypothyroidism
CRH	- stimulate synthesis and release of ACTH	-stress increases CRH release which is reflected on ACTH release and hence cortisol synthesis and release	-Diagnostic use CRH test to assist ACTH releasing test
GHRH (HEXARELIN, SERMORELIN)	-stimulate release of GH	-Given S.C	- Diagnostic use and in the management of certain cases of dwarfism
GHIH (somatostatin)	-decrease release of GH,ACTH,TSH, SEROTONIN,GASTRIN, INSULIN,GLUCAGON	-Effect on blood dose dependent -L.D>> hypoglycemia --H.D>>hyperglycemia	-Octreotide & Lanrotide : -Acromegaly -Carcinoid syndrome -Insulinomas ,Gstrinomas -Esophageal varices -DM S.Fs: Gallbladder stone & platelet abnormalities
TSH	-Increase TH synthesis and release of T3&T4	-Works through elevation of intracellular CAMP and increasing iodine uptake	- Diagnostic use to assess the function of thyroid gland
ACTH (Acthar& cosyntropin)	-It increases synthesis and Release of cortisol from adrenal gland	- Undergoes circadian rhythm (higher during night and lower during day)	- Diagnostic use - Certain cases of adrenal insufficiency

GH **somatropin**	- Stimulates growth of soft tissue and bones -increases lipolysis, gluconeogenesis and decrease glucose utilization -PRL-like activity	- MOA unclear -Its effects belived to be through IGFs -Factor In. release: - Sleep,Arginine,Insulin,Hypo-Glycemia, B-adenergic antagonist, Clonidine, Bromocriptine and levodopa in normal individuals - Factor dec. release: Bromocrptine in acromegalics Somatostatin synthetic analogs	- GH replacement therapy: - GH-replacement therapy with S.C or I.M recombinant human GH preparations such as Somatropin & Somatrin -Mecasermin -Mecasermin rinfabate
Prolactin	- In males: -Increase testosterone production π testes and hence spermatogenesis -If PRL INC.>>>>Dec. LH& FSH consequently impotency & infertility -In females: -Breast development -Lactation -If PRL INC.>>>>Dec. LH&FSH consequently galactorrhea and amenorrhea syndrome	- Dopamine the major regulator of Prolactin -GH-like activity -Factors In. release: Pregnancy, Sleep, Nursing, Stress, TRH, Estradiol, DA antagonist, Methyldopa, Reserpine, Diazepam, Opiates. -Factor dec. release: DA angonists , Amorphine,Clonidine, MAO inhibitors(pargyline).	SIDE NOTE - Bromocriptine& Cabergolin: Hyperprolactinemia -Suppression of lactation - Acromegaly -Parkinson's disease -DM2 -Bromocriptine is given orally S.Fs: RARE -pulmonary fibrosis -confusion -hallucinations -MI

Thyroid Gland Hormones

Drug	MOA	Uses	Side effects	Notes
T_3&T_4	T4>>T3 in target cell in cytoplasm -T3 binds nuclear receptor protein	-promote growth&development - INC. BMR -INC. O2 consumpti.. -INC.general metabo. -INC.CHO metabol.. -INC.Lipolysis -INC.lipid breakdow. -INC.GIT motility -INC.β-adrenergic re. -DEC.cholesterol B.L		T3>> POTENT T4>> Binding protein
Thyroid USP (bovine, ovine, porcine) oral	Taken π thyroid gland of animal like pigs or sheep and make tablets out of them	Treat hypo-thyrodism	Allergy is frequent	-Iodine tablets shouldn't exceed specific percentage
Thyroid extract (Thyroglobulin) oral		Treat hypo-thyrodism	Allergy less frequent here	
-l- thyroxine sodium; synthetic T4, oral **- Liotrix, synthetic T4 & T3 (4:1), oral**		Treat hypo-thyrodism		
-Liothyronine sodium, synthetic T3, oral & I.V		Treat hypo-thyrodism		$T_{1/2}$ approximately one day
Propranolol		controls the manifestations of thyrotoxicosis		-β-blocker - It is NOT an anti-thyroid drug

Thionamides **(Methimazole, Carbimazole, Propylthiouracil)**	-Inhibitors to thyroid perioxidase enzyme - Interfere with oxidation, iodination, and coupling reactions -Probyl. >> Decrease peripheral de-iodination Of T4	-Inhibit production of thyroid hormones	- Allergy - Hepatic dysfunction. Agranulocytosis - Methimazole is teratogenic - Propylthiouracil Not teratogenic can be used in pregnancy	-Methi. > Carbi. > Propyl. All effective orally - Carbimazole (pro-drug) is converted to Methimazole (more potent) - Delayed onset of action (12-18 hrs) - Prolong Rx (12-18 months) - Side effects - High relapse rate
Iodide	↓ oxidation ↓ release of T4, T3	-Inhibition of T3 & T4 release and synthesis	- Allergy	Widely used before thyroid surgeries to ↓ vascularity of the thyroid gland
Radioactive iodine=RAI (131I)	-Inhibition of T3 & T4 release and synthesis	-Treatment of thyrotoxicosis -Diagnostic use (small dose) -- Rx of hyperthyroidism and Grave's disease (intermediate dose) - Rx of thyroid Ca (large doses)	hypothyroidism is dose dependent -Pulmonary fibrosis -Teratogenicity and carcinogenicity	Contraindications: pregnancy (absolute), ophthalmopathy (relative-RAI Therapy may cause or worsen this condition).
Lithium carbonate	Has similar MOA to iodide	- Inhibits release of T3 and T4 **-treat manic depressive psychosis**	**-Nausea, diarrhea, drowsiness, blurred vision Ataxia, tinnitus and diabetes insipidus**	**-Oral and S.R tab** **-Narrow therapeutic window**
Iodinated contrast media (Ipodate)		-Inhibit peripheral conversion of T4 to T3 -Inhibit release of T4 & T3	**Allergic reactions**	**Given orally** **Contain iodine**

Parathyroid Gland & Ca+2 Met.

Drug	Function	Regulation
PTH	-Maintenance of calcium and phosphate homeostasis (bone, intestine, kidney) by: mobilization of calcium from bone, reabsorption of calcium from kidney and enhancing intestinal calcium absorption indirectly by activating release of vit D3	Secretion stimulated by low concentration of free Ca+2 and inhibited by high conc. Of it. - Little if any regulation by PO4 (2-). - PTH sec.: 3.5<plasma Ca2+<5.5
Vitamin D3	-Maintenance of calcium and phosphate homeostasis (bone, intestine, kidney) by: Enhancing intestinal calcium and phosphate absorption, mobilization of calcium and phosphate from bone, reabsorption of calcium and phosphate from kidney	-Synthesis of 1,25(OH)2D3 is activated by PTH
Calcitonin	-Maintenance of calcium, phosphate, magnesium homeostasis (bone, kidney) - Antagonist of PTH -regulating bone remodeling	- Secretion stimulated by high concentration of free Ca+2 - synthesized and released from para-follicular cells of thyroid

Rx of hypo-parathyroidism:

-Vitamin D, Calcifediol, Calcitriol, Ergocalciferol, α-Calcidol, Dihydrotachysterol...

-Ca++ supplement, Ca++ rich diet, Ca++ salts (carbonate, gluconate, chloride...)

-Thiazide diuretics

-Teriparatide (synthetic rPTH)-recently approved in the management of osteoporosis; given SC

-Rx of hyperparathyroidism:

- Low Ca++ diet

- Na+ phosphate

- Steroids … Prednisolone Dec. Ca2+ absorption

- Calcitonin

- Surgery (best Rx)

- Cinacalcet (calcimimetic)

Drugs effective in the management of hypercalcemia:

- Diuretics

-Plicamycin

- Biophosphonates, Etidronate, Pamidronate...

Rx of Paget's disease:

-Salmon calcitonin

-Biophosphanates, Etidronate, alendronate, residronate, pamidronate

مما قِيلَ في وصف النبي ﷺ:

كان هيّن المؤنة، ليّن الخلق، كريم الطبع، جميل المُعاشرة، طلق الوجه بسّامًا، متواضعًا من غير ذلّة، جوادًا من غير سرف، رقيق القلب، رحيمًا بكل مسلم خافض الجناح للمؤمنين، ليّن الجانب لهم."

DM

A disease characterized by high blood sugar level

A metabolic disorder manifested by abnormalities in CHO, lipid and protein metabolism

Diabetes is a major cause of heart disease and stroke

Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults

	Type 1 DM	**Type 2 DM**
Age	Most commonly occurs in childhood or adolescence mainly (10-14) but may occur at any age	Usually discovered accidentally after the age of 30-40 yrs
Ketoacidosis	Often patients present with ketoacidosis	Rare (unless of certain circumstances of unusual stress)
Symptoms	Weight loss easy fatigability, polyuria, polydipsia, polyphagia.	mild polyuria and fatigue
management	Diet + Insulin therapy	Diet + exercise ± Oral hypoglycemic agents ± Insulin
Special Characteristics	downhill course-severe type of DM (mortality is high)	Patients are obese more commonly in females as compared to males. Strong family history (genetic background) Insulin levels can be high, normal or low

Symptoms: Early→ Polyuria, Polydipsia, Polyphagia and

Ketoacidosis (ketoacidosis only in type one)

Late →Atherosclerosis & IHD, Retinopathy Nephropathy and neuropathy

Diagnosis:

Random blood sugar (RBS)

Fasting blood sugar

Glycosylated hemoglobin (HbA1c)

Glucose tolerance test

Insulin

Protein consists from two chains a (21 amino acid) b (30 amino acid)

Synthesis of insulin:

Preproinsulin →(In RER) Proinsulin →(In golgi) insulin + c-peptide

Proinsulin has 1/10 potency of insulin

c-peptide has no insulin-like activity

secretion of insulin

Ca^{+2} dependent & the major regulator is glucose level

Factors that increase insulin release:	**Factors that decrease insulin release**
β- adrenergic, cholinergic drug	α-adrenergic, anticholinergics
sulfonylureas	phenytoin; alloxan; streptozotocin
GH, glucagon, ACTH	
Glucose, amino acid, fatty acid	

Insulin MOA

Insulin binds to its receptor leading to phosphorylation of insulin receptor complex (1) which in turn starts many protein kinases activation cascades (2). These include: **translocation of Glu transporter-4** to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis

Insulin effect

increasing in	decreasing in
glucose uptake or transport into muscles & adipocytes	glycogenolysis
glucose oxidation by muscles	hepatic gluconeogenesis
hepatic glycogen synthesis and storage	lipolysis
a.a uptake and protein synthesis by muscles and liver	ketogenesis

Insulin absorption

Highest absorption at abdomen > arm > buttocks > thigh

Increased by exercise depth of injection and dose

Metabolized in liver, muscles and kidney

Doses vary between patients

Side effects of insulin

Hypoglycemia & sympathetic activity

Lipodystrophy (loss of fat at the site of injection)

Allergy

Induration

Insulin preparation

Ultra-rapid onset; very short acting	DOA
Insulin Lispro **Insulin Aspart** **Insulin Glulisine**	3-4
Rapid onset & short acting	**Nearly 8 hours(important)**
Crystalline zinc	5-8
Insulin zinc prompt (Semilente)	12-16
Intermediate onset & action	**Nearly 24 hours(important)**
Insulin zinc suspension (Lente)	18-24
Isophane insulin suspension (NPH, humulin)	20-28
Slow onset & action	**Nearly 36 hours(important)**
Protamine zinc suspension	24-36
Extended insulin zinc suspension (Ultralente)	24-36
Insulin Glargine (peakless)	24-36
Insulin Detemir(peakless)	24-36
Mixed insulins	
Intermediate & short	20-24
Intermediate & long	22-24

They are given s.c except for regular insulin, insulin Glulisine & insulin Aspart (SC & I.V)

Advantages of peakless insulins over intermediate-acting insulins:

a- Constant circulating insulin over 24hr with no peak

b- Safer than NPH & Lente insulins due to reduced risk of hypoglycemia

c- Clear solution that does not require resuspension before administration

	MOA	Side effects	Examples	Uses
biguanides	Decrease: CHO absorption hepatic gluconeogenesis glucagon release Increase: peripheral utilization of glucose glycolysis response to insulin	1-Nausea & vomiting 2- metallic taste 3-Abdominal pain and diarrhea 4-Hypoglycemia (rare) 5-Lactic acidosis 6-**Decrease vitamin B12 absorption**	Metformin	Type 2 DM Obesity (↓ fat deposition) polycystic ovarian syndrome (decrease androgens)
Sulfonylureas	**On pancreas** 1-Increase insulin release **(major MOA)** (Receptor-mediated effect) 2-Increase no. of β-cells 3-decrease glucagon release **on peripheral cells** 1-increase no. of insulin receptors 2-sensitivity to insulin effect 3-increase insulin binding to its receptors & affinity to its receptors **on liver** 1-decrease hepatic gluconeogenesis **Others** increase somatostatin release	1- **Hypoglycemia** 2-nausea and vomiting, dizziness 3-Allergy 4-Agranulocytosis 5-Hepatic dysfunction	First generation, DOA Tolbutamide 6-12 Chlorpropamide 24-72 Tolazamide 12-16 Acetohexamide 12-18 The shortest DOA from FG →Tolbutamide The longest →Chlorpropamide The only one without active metabolite in **FG** is Tolbutamide **Second generation** **DOA metabolic fate** Glyburide 20-24 ± Glipizide 14-16 - Gliclazide 10-15 - Glimeperide 18-22 ±	DM Nocturnal enuresis (Glyburide increases ADH release)
α glucosidase inhibitors	Decease CHO absorption Decrease fasting and postprandial hyperglycemia **Decrease** insulin secretion and spare β cell	Abdominal pain and diarrhoea	Acarbose	Type 2 DM before or with meals Reduce incidence or risk of atherosclerosis in diabetics Could be given with insulin and sulfonylureas

Prandial glucose regulators	Increase insulin release (similar to sulfonylureas)	Hypoglycemia is infrequent	Repaglinide	Taken before meals Could be taken with metformin or insulin
Thiazolidinediones (TZD)	Peroxisome Proliferator-Activated Receptors agonist (γ isoform) Increase sensitivity of peripheral tissues to insulin Decrease insulin resistance decrease glucose exit or output from the liver		Pioglitazone	NIDDM (DM 2) for patients with ↑ insulin levels which are believed to be responsible for ↑ B.P↑ lipids and atherosclerosis in patients with insulin resistance
Incretin mimetic drugs	DPP-4 inhibitors (an enzyme that metabolizes GIP + GLP) increase blood levels of GLP-1, GIP increase insulin and C-peptide decrease glucagon level	Hypoglycemia is infrequent	Sitagliptin	Reduce glucose blood level and HbA1c levels Orally Could be taken with metformin or sulfonylureas
analogs to GLP-1	increase insulin decrease glucagon blood levels	Hypoglycemia is infrequent	Exenatide	adjunct therapy to metformin, sulfonylureas in type 2D.M Obesity **S.C** 60 min before a meal
Aldose reductase (AR) inhibitors	It prevents the transformation of glucose to fructose to Sorbitol		Epalrestat	to improve diabetic polyneuropathy Orally effective
Amylin mimetic drugs	It reduces the production of glucose by the liver by inhibiting the action of glucagon and diminishes postprandial glucose fluctuations		Pramlintide	type II DM **subcutaneous**

	Amylin's physiological effects mimic in part those of GLP-1 decreasing glucagon secretion from pancreatic alpha cells &delays gastric emptying and likely possesses a central effect to enhance satiety (هاي النقطة مكتوبة عند ال amylin ف كتبتها احتياطا)			
Inhibitors of subtype 2 sodium-glucose transport protein in the kidney	Block the transporter responsible for glucose reabsorption in the kidney		Canagliflozin	decrease the incidence of heart attacks and strokes in patients with type II DM orally along with metformin ± sulfonylureas
Bromocriptine	A sympatholytic D2-dopamine agonist Reduces plasma glucose, triglycerides and Free Fatty Acid Increases hypothalamic dopamine levels and inhibits excessive sympathetic tone within CNS	nausea		within 2 h of awakening
Somatostatin	In low doses decreases glucagon release			

Others:

- Role of ACEI's, ARB's, Statins

Role of Glucagon in diabetics

Pancreatic transplantation and gene therapy

About sulfonylureas

How they increase insulin production: receptors found on beta cells linked to ATP-ase sensitive K+ ion channel then, receptors found on beta cells linked to ATP-ase sensitive K+ ion channel

Ca ++ binds to Calmodulin which activates kinases that cause exocytosis of insulin-containing secretory granules

-**Propranolol (important),** sulfa drugs, oral anticoagulants, aspirin...etc increase sulfonylureas activity

Drugs ↓ blood glucose levels: **β-blockers**, salicylates, indomethacin, naproxin, alcohol, sulfonamides, clofibrate, anabolic steroids, lithium, Ca++, ampicillin, bromocriptine

Drugs ↑ blood glucose levels: **β-blockers**, thiazides and loop diuretics Glucocorticoids Oral contraceptive drugs Ca++ channel blockers Phenytoin, morphine, heparin Nicotine, clonidine, diazoxide H2 -receptor blockers

لتسهيل الحفظ

الي بناخذهم s.c هم analogs to GLP-1 و Amylin mimetic drugs

الي بيقللو من atherosclerosis هم α glucosidase inhibitors و TZD والي بحمي من stroke & heart attack هو الInhibitors of subtype 2 sodium-glucose transport protein in the kidney

اما في حالات ال obesity بنعطي biguanides و GLP-1 analogs

:من وصف الرافعي للنبي ﷺ
مَن رآه بديهةً هَابه، ومن خالطه معرفةً أحبَّه، لا يحسب جليسُه أن أحدًا أكرم عليه منه، ولا يطوي عن أحدٍ من الناسِ بِشْرَه، قد وسع الناس بَسطه وخُلُقه، له نورٌ يعلوه، كأن الشمسَ تجري في وجهه.
(يَا أَيُّهَا الَّذِينَ آمَنُوا صَلُّوا عَلَيْهِ وَسَلِّمُوا تَسْلِيمًا) ﷺ

Adrenal steroids

Drug	MOA	Uses	Side effects	Notes
Aldosterone	- Synthesized and released: -Inc.in plasma conc. of ANG3 -Inc.in plasma ANG2 -Inc. in K+ blood level -ACTH -Dec. ECF or blood volume ;metabolic acidosis	-Acts on distal convoluted tubules in kidney: -Inc. reabsorption of Na+>HP.T -Inc. excretion of K+&H+>Hypo-kalemia& metabolic alkalosis -Inc. EC volume -Inc. BP		- Synthesis from cholesterol -Disorders affecting ALD Release: - Hypoaldosteronism Manifested π hypotension, hypovolemia, Hyperkalemia and Metabolic acidosis Rx: Fludrocortisone-Hyperaldosteronsim
Cortisol				- Circadian rhythm -synthesized from cholesterol
Metyrapone (Metopirone)	-11β-hydroxylase inhibitor --Steroid synthesis Inhibitor	-Diagnostic tool (metyrapone test) -management of Cushing's syndrome		

Glucocorticoid preparations:

Short acting:

Cortisol

Cortisone

Corticosterone

Fludrocortisone

Intermediate acting:

Prednisone

Prednisolone

Methylprednisolone

Triamcinolone

Beclomethasone

Long acting:

Betamethasone

Dexamethasone

Clinical uses Vs Side effects:

- Adrenal insufficiency
- Inflammatory conditions
- Allergic reactions
- Immunosuppressant effect
- Many eye, ear, and skin diseases
- Hypercalcemia associated with……

- Suppression of hypothalamic-pituitary-adrenal axis
- Cushing's syndrome
- Salt & water retention, edema, ↑ BP, obesity
- Peptic ulcer disease and GIT ulcerations
- Osteoporosis
- Diabetes mellitus
- ↑ incidence of viral and fungal infections
- ↓ wound healing and skin atrophy and myopathy
- Suppression of growth of children – Cataract

Pharmacological effects/side effects:

On proteins	On CHO	On lipids	On electrolytes	Anti-inflammatory effect	Immunosuppressant effect	Antiallergic effect	CNS manifestations
↑ Catabolism ↓ anabolism- Osteoporosis; steroid myopathy; delayed wound healing; delayed peptic ulcer healing	↑ blood sugar level (↑ gluconeogenesis; ↓ peripheral utilization of glucose)	↑ lipolysis Fat redistribution	Aldosterone-like effect ↓ Ca++ absorption from intestine ↑ Ca++ excretion by kidney ↑ uric acid excretion	-Inhibits phospholipase A2 -inhibit neutrophil and macrophage function - Inhibition of platelet activation factor (PAF)- Inhibition of tumor necrosis factor or receptor (TNF; TNR) - Inhibition of nitric oxide reductase	↓ initial processing of Ag ↓Ab formation ↓ effectiveness of T-lymphocytes ↓ lymphocyte induction & proliferation ↓ lymphoid tissue including leukemic lymphocytes (antileukemic effect)	Suppress allergic response ↓ histamine release ↓ eosinophils	Euphoria Psychosis