Adrenocortical steroids and their analogues.

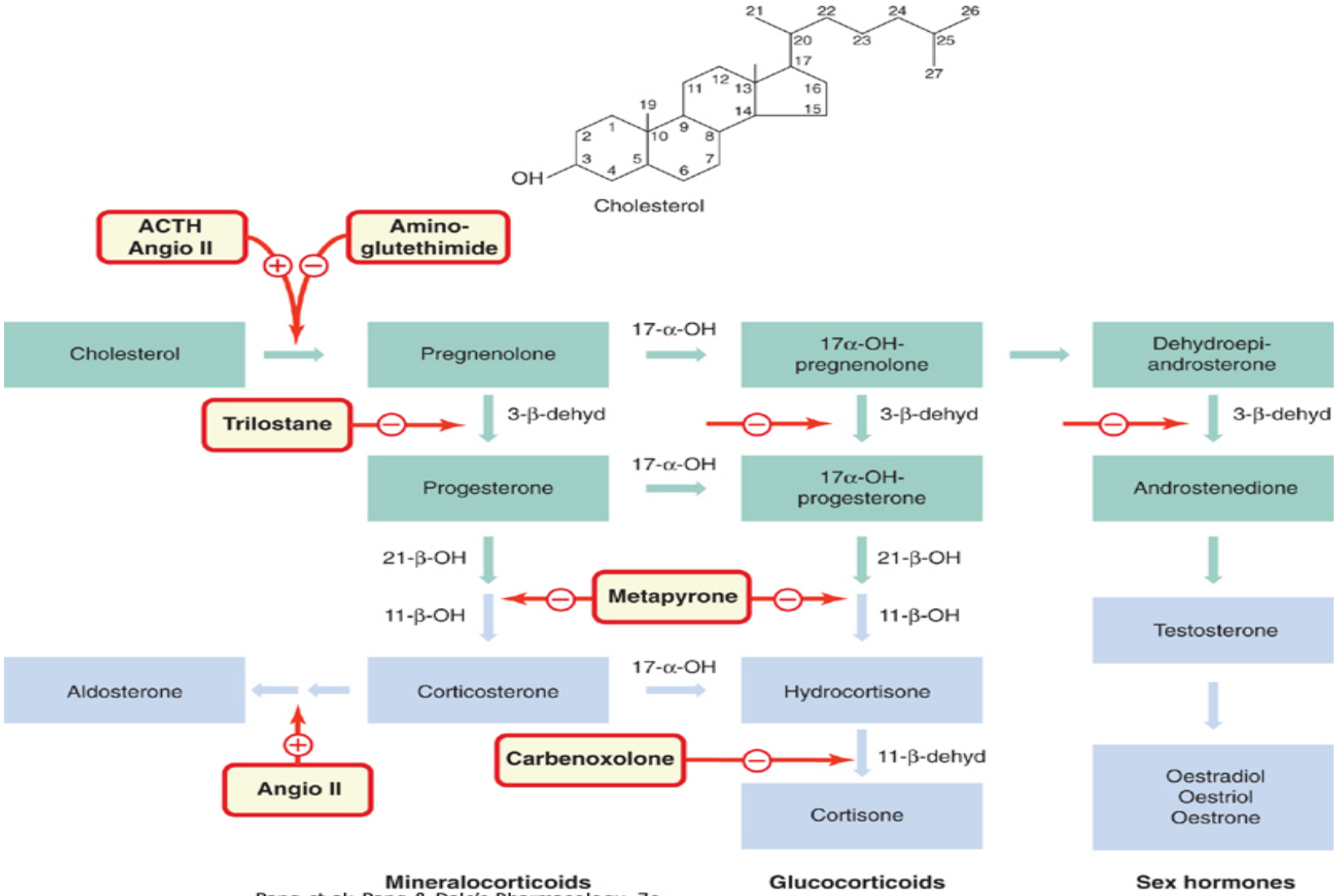
The Adrenal Cortex

- Medulla : Catecholamines
- Cortex : Adrenal steroids or Corticosteroids
- 3 concentric zones:
- zona **g**lomerulosa : mineralocortocoids
- Z **f**asciculata : glucocorticoids
- Z **r**eticularis: androgens

- Mineralocorticoids : regulate water & electrolyte balance .Main endogenous form is aldosterone : sodium & water retaining
- Glucocorticoids : metabolic & regulatory effects on host defence mech. Hydrocortisone (Cortisol) main GC : used mainly as anti-inflammatory agents & immunosuppresive agents

- **Addison's disease**: deficiency in CS prod
- Excess CS prod ; excessive GC: **Cushing's Syndrome;**
- excessive MC : primary hyperaldosteronism (**Conn's syndrome**) or Secondary hyper---

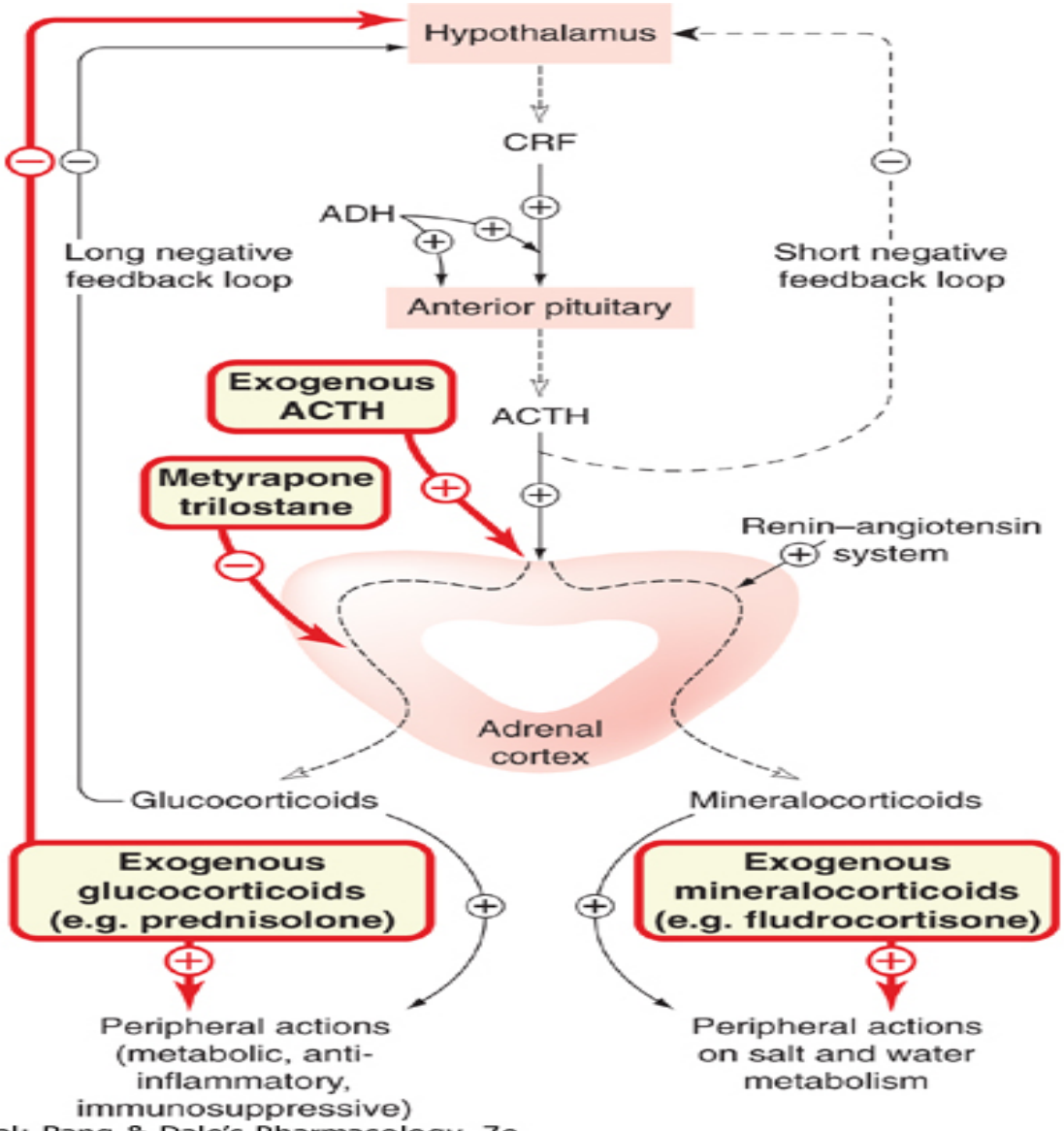
Biosynthesis of adrenocorticosteroids



Endogenous Glucocorticoids: Cortisol (Hydrocortisone)

- Not stored in adrenal
- Secretion under circulating ACTH , pulsatile fashion
- ACTH sec under CRF from hypothalamus & Vasopressin from post pit
- HPA axis

Regulation of synthesis & secretion of adrenal corticosteroids



Cortisol …PK:

- N adults (no stress) : 10-20 mg/day
- Circadian rhythm
- In plasma - 90% bound to CBG ,rest free ;albumin bound =free
- CBG ↑ in pregnancy, Estrogens, hyperthyroidism
- CBG ↓ in hypotyhroidism, genetic defects & hypoprotenemias
- Normally T1/2 – 60-90 min ,
- 20% converted to cortisone . Mostly metabolized in liver – 1/3 cortisol excreted in urine ;

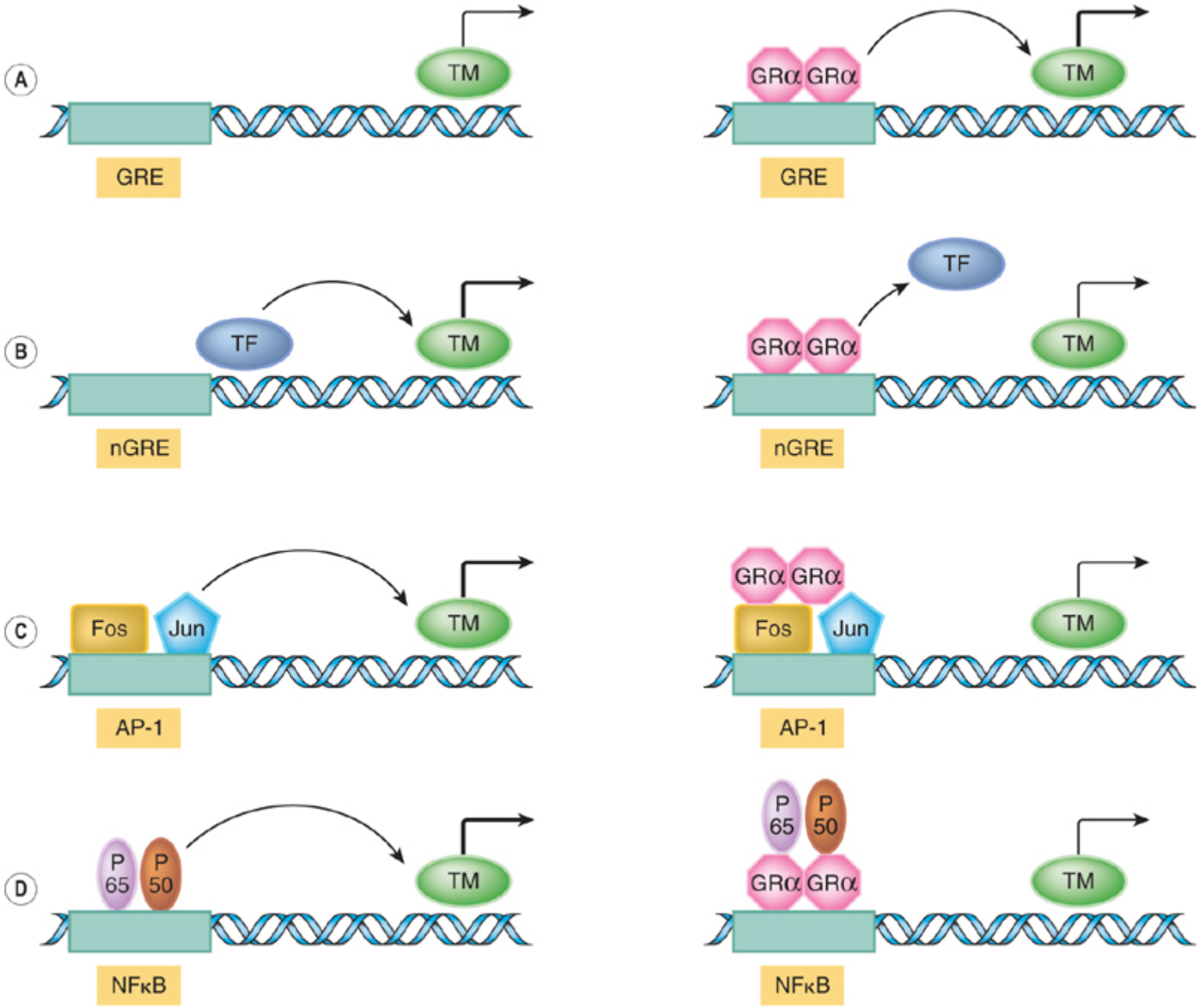
Cortisol….MOA

- Glucocorticoid Receptors : Nuclear R superfamily
- Control gene expression thru complex transcriptional control mechanism mainly thru Glucocorticoid response elements (GRE)
- Other transcp factors –Ap1 & NF-kB
- These trans factors have imp role in regulation of GF,pro-inflamm cytokines : mediate anti-growth,anti-inflamm & immunosuppressive effects of GC.

Cortisol … MOA…

- Effects of GC mainly d/t proteins synth from mRNA transcribed from target genes

- Some effects of GC are due to binding to Aldosterone R (AR)



- GC also triggers imp signal transduction events while still in cytosolic compartment : eg initial feedback inhibition of pituitary ACTH within minutes, release of protein annexin 1 ,a potent inhibitor of leukocyte trafficking & other biological axns.: can happen v rapidly (**imp. in anti-inflammatory effects).**
- Mainly d/t direct effects on cell membrane R for hormones or non-genomic effects of the GR

Glucocorticoids..

Physiological Effects

- General: Widespread effects

  - mainly by direct actions

  - *permissive effects :* required for normal fnctions eg vascular and Bronchial sm ms response to CA is ↓ in absence of cortisol.

Metabolic Effects…

Carbohydrates & Protein metabolism: Dose related effects

- stimulate gluconeogenesis & glycogen synth
- ↑ S. glucose levels: stimulate insulin rel.
- Inhibit uptake and utilisation of glucose: causes a tendency to hyperglycaemia.
- Promote deposition of glycogen in liver. Mobilize AA by inhibiting protein synthesis in muscle ,connective ts,& skin
- Cause of serious A/E of CS

Metabolic Effects …

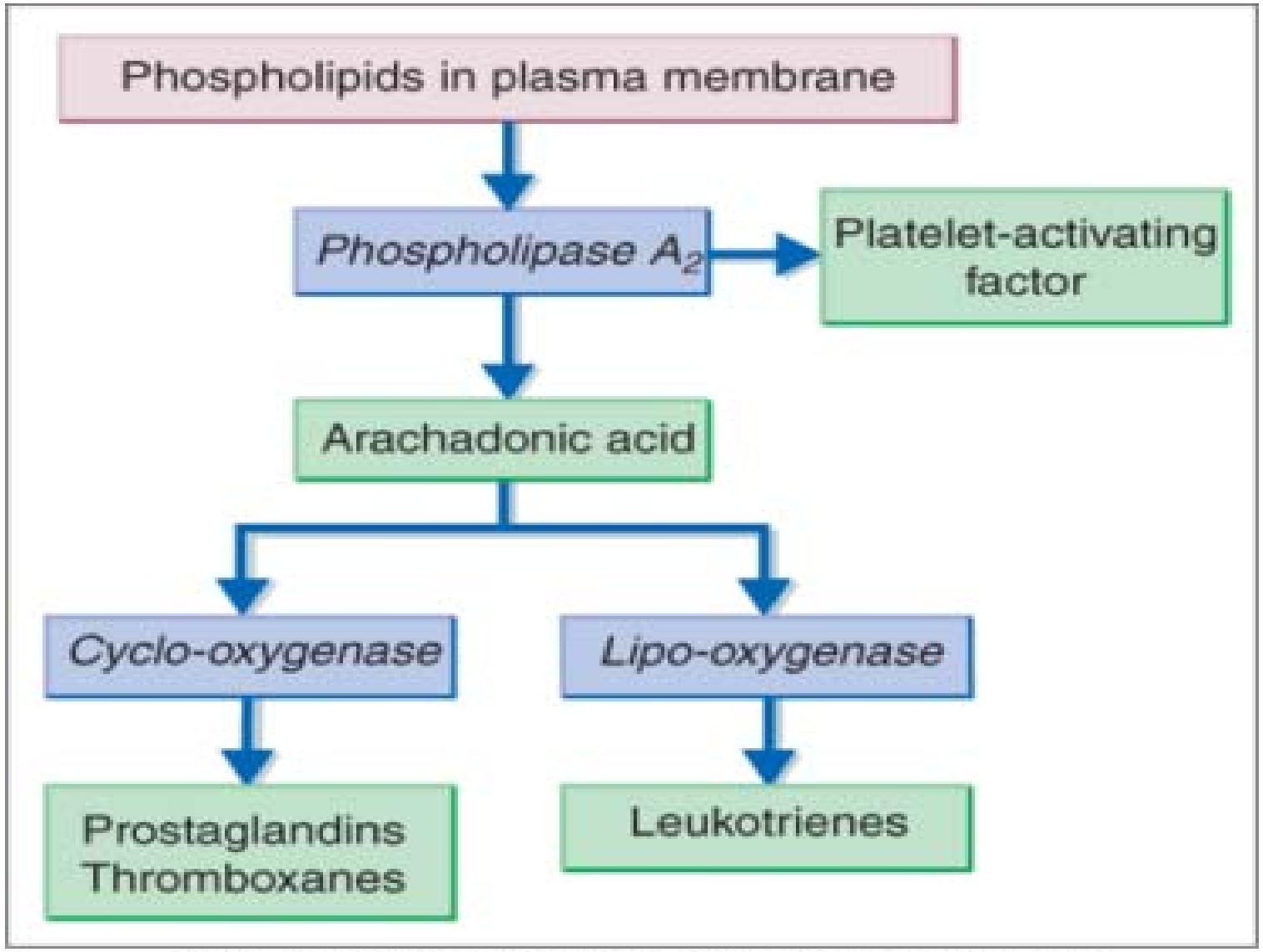
- ***Lipids*:** a permissive effect on lipolytic effects of GH, thyroxine & adrenaline.
- Mobilize FFA , but glucose utilization by both adipose ts & muscle is inhibited : ↑in deposition of fats.
- Long term admn causes a redistribution of fat, from peripheral stores towards central locations : centripetal obesity : d/t differential sensitivity of adipocytes to insulin .

Catabolic & antianabolic effects

- CS have catabolic and antianabolic effects in lymphoid & connective ts, ms, peripheral fat & skin.
- Leads to A/E during use : ↓ms mass, weakness, thinning of skin. In bones- osteoporosis . ↓growth in children.

Anti-inflammatory & Immunosuppresive effects

- Glucocorticoids : anti-inflamm agent *par excellence*
- Inhibit both early & late manifestations of inflamm
- **Reverse virtually all types of inflamm rxn : invading pathogens/chemical/physical stimuli/hypersensitivity or autoimmune ds**.
- Supress CMI as well as humoral immunity



Action on the *mediators* of inflammatory and immune response

- In macrophages, monocytes endothelium & fibroblasts induce formation of annexin-1 (lipocortin-1) which inhibits phospholipase-A2 : anti-inflamm action.
- ↓ production of prostanoids owing to ↓ expression of cyclo-oxygenase-2
- ↓ generation of many cytokines, IL-1 to IL-6, IL-8, TNF-α, cell adhesion factors and GM-CSF, & ↓ generation of induced nitric oxide: supress CMI & also humoral immunity
- ↓ histamine release from basophils and mast cells
- ↓ IgG production

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- increased synthesis of anti-inflammatory factors such as IL-10, IL-1-soluble receptor and annexin-1
- ***Overall effects***: **↓ in the activity of the innate and acquired immune systems, but also ↓ healing and diminution in the protective aspects of the inflammatory response**.

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Actions on *inflammatory cells* include

- ↓ egress of neutrophils from blood vessels and thus increase the no. of N in circuln.
- ↓ activation of macrophages and mast cells d/t decreased transcription of the genes for cell adhesion factors and cytokines
- ↓ overall activation of T-helper (Th) cells, ↓ clonal proliferation of T cells, and a 'switch' from the Th1 to the Th2 immune response
- ↓ fibroblast function, less production of collagen and glycosaminoglycans, and thus ↓ healing and repair
- ↓ activity of osteoblasts but increased activation of osteoclasts and therefore a tendency to develop osteoporosis.

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Glucocorticoids: other effects

- *Hypothalamus* and *anterior pituitary gland*: a negative feedback action resulting in reduced release of endogenous glucocorticoids
- *Cardiovascular system*: stimulate CO , reduced vasodilatation, decreased fluid exudation.
- Increase no. of RBCs ,platelets & N in circ but decrease lympho, E & Basophils. Show marked lytic effects on malignant lymphtic ts,
- *Musculoskeletal*: decreasing osteoblast and increasing osteoclast activity
- CNS: mild euphoria, insomnia,anxiety, seizure threshold decreased.

Glucocorticoids: other effects..

- Calcium & other electrolyte metab: GC also ↓intest absb of Ca & increase excretion thru kidneys .Cause loss of osteoid ;vertebrae & ribs show ↑resorption. Also ↑ axn of PTH.
- Imp physiological role in fetal lung development : surfactant
- ↓secretion of GH

Synthetic CS

Synthetic steroids developed to separate GC axn from MC axn : BUT not able to separate anti-inflamm axn of GC from metabolic axns

CS may be administered orally, systemically or intra-articularly; given by aerosol into the respiratory tract, administered as drops into the eye or the nose, or applied in creams or ointments to the skin.

- Topical administration: ↓ systemic toxic effects .

Compound	Relative affinity for receptor[a]	Approximate relative potency in clinical use		Duration of action after oral dose[b]	Comments
		Anti-inflammatory	Sodium retaining		
Hydrocortisone	1	1	1	Short	**Drug of choice for replacement therapy (cortisol)**
Cortisone	Prodrug	0.8	0.8	Short	Cheap; inactive until converted to hydrocortisone; not used as anti-inflammatory because of mineralocorticoid effects
Deflazacort	Prodrug	3	?	Short	Must be converted by plasma esterases into active metabolite Similar utility to prednisolone
Prednisolone	2.2	4	0.8	Intermediate	**Drug of choice for systemic anti-inflammatory and immunosuppressive effects**
Prednisone	Prodrug	4	0.8	Intermediate	Inactive until converted to prednisolone
Methylprednisolone	11.9	5	Minimal	Intermediate	Anti-inflammatory and immunosuppressive

Compound	Relative affinity for receptor[a]	Approximate relative potency in clinical use		Duration of action after oral dose[b]	Comments
		Anti-inflammatory	Sodium retaining		
Triamcinolone	1.9	5	None	Intermediate	Relatively more toxic than others
Dexamethasone	*7.1*	*27*	*Minimal*	*Long*	**Anti-inflammatory and immunosuppressive, used especially where water retention is undesirable (e.g. cerebral oedema); drug of choice for suppression of adrenocorticotrophic hormone production**
Betamethasone	5.4	27	Negligible	Long	-same-
Fludrocortisone	3.5	15	150	Short	Drug of choice for mineralocorticoid effects
Aldosterone	0.38	None	500	-	Endogenous mineralocorticoid

Therapeutic uses: General principles

1. Analyze risk-benefit ratio in each patient
2. Determine appropriate dose by trial & error & re-evaluate periodically in each patient
3. A single large dose or a short course upto 2 week is usually without harm .Beyond 2 weeks ,there are time & dose related increases in severe ADRs
4. GC are neither specific nor curative, only palliative ,except for use in replacement

General principles….

5. Stopping CS suddenly after prolonged therapy- adrenal insufficiency. Always taper the dose slowly .
6. . At times of stress supplementary CS therapy must be given for (2- 10 times increased dose for 24-72 hrs
7 Alternate day therapy ,
8 Pulse therapy

Therapeutic uses

A) **Endocrinal Uses**.

- **Replacement therapy** for patients with adrenal failure. **Acute adrenal insufficiency** (*Addisonian Crisis)*. Life threatening emergency : Severe hypotension, hyponatremia, hyperkalemia, dehydration , weakness, lethargy, GIT distress.
- Trt: hydrocortisone 100 mg IV bolus ,then by infusion at rate of 100mg TDS & D-NS infusion, Rx for ppting factors eg infection,trauma..

Replacement therapy..

- **Chronic adrenal insufficiency**(**Addison's ds**) : CF: weakness,lethargy,fatigue, hypotension,wt loss, hyperpigmentation. Minor stressful event can ppt ac adrenal insuff

  - Hydrocortisone 20-30 mg/day . May also require fludrocortisone . Synthetic GC -No

- **Congenital adrenal hyperplasia** : d/t reduced cortisol synth. Trt: Hydrocortisone oral

B. **Diagnostic use..**

- **Dexamethasone suppression test**

  for diagnosing Cushing's syndrome : pt given 1mg dexa Po at 11 PM & cortisol measured at 8AM .Suppr of pl cortisol to less than 5microgm/dl :pt does not have Cushing's syndrome.

Therapeutic uses in Non –endocrine diseases: Pharmacotherapy

1. Collagen vascular ds: SLE, PAN, sarcoidosis , polymyositis, giant cell erteritis, rheumatoid arthritis , tendonitis,etc
2. Renal diseases : nephrotic synd
3. Allergic disease:
4. Bronchial asthma :inhalational steroids: beclomethasone, budesonide , flunisolide, fluticasone

Therapeutic uses in Non –endocrine diseases: Pharmacotherapy….

5. Infectious diseases: AIDS with PCP, HiB meningitis,sepsis
6. Eye diseases : uveitis, conjuctivitis, choroiditis (CI in herpes simplex keratitis)
7. Skin diseases: ointments
8. Gastrointestinal diseases: IBD
9. Hepatic diseases: Autoimmune chronic active hepatitis

Therapeutic uses in Non –endocrine diseases: Pharmacotherapy…..

10. Malignancies: ALL, lymphomas
11 Cerebral edema :
12 Thrombocytopenia
13 Autoimmune destruction of RBCs
14 Organ transplantation
15 Spinal cord injury
16 Misc conditions/ds

Toxicity of CS

Seen mainly after prolonged systemic use (beyond 2 weeks) as anti-inflammatory or immunosuppressive agents but not usually following replacement therapy.

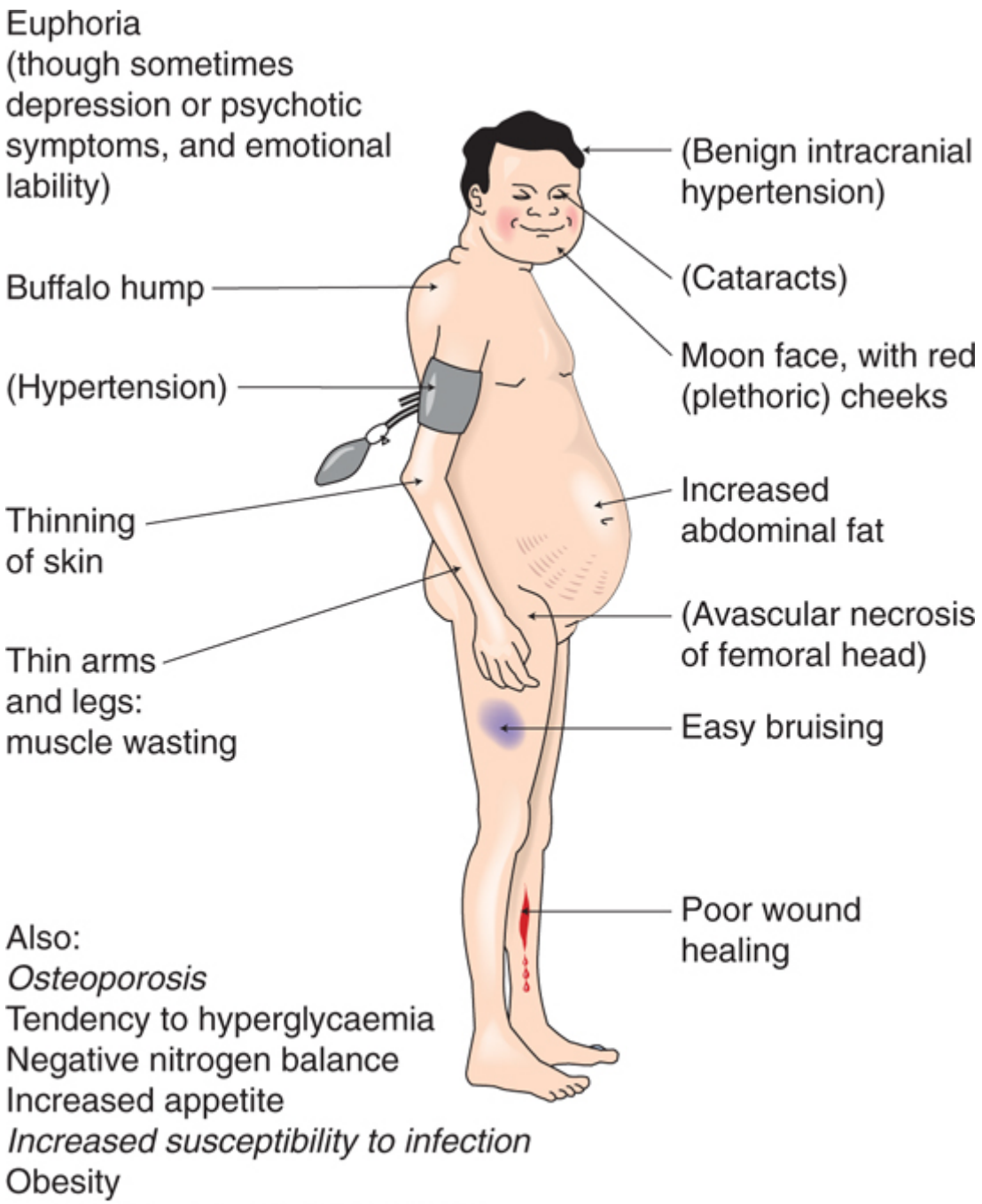
Metabolic effects : iatrogenic Cushing ‘s syndrome

Toxicity

1. Immune response: increased susceptibility to infections
2. Risk of peptic ulcers
3. Myopathy & muscle wasting
4. Osteoporosis
5. Hyperglycemia
6. Behavioral changes: hypomania or acute psychosis

Toxicity…

- Cataracts (posterior subcapsular), glaucoma
- Regulation of growth & development
- Fluid & electrolyte balance: Na ,water retention,HT, hypokalemia,
- HPA Axis suppression
- Misc.: acne, thinning of skin, purple striae. Hirsutism, menstrual abnormalities, wt gain, pancreatitis.



Contraindications

All are relative

1. Peptic ulcer
2. DM
3. HT
4. Osteoporosis
5. TB & other inf
6. Psychosis
7. Epilepsy
8. CHF
9. RF

Absolute CI

HS keratitis, Cushing's Synd

Mineralocorticoids

- Aldosterone: promote reabsb of Na from distal part of DCT & CT and increases K^+ and H^+ efflux into the tubules
- Binds to mineralocorticoid R in cytoplasm of target cells. acts on intracellular receptors that modulate DNA transcription, causing synthesis of protein mediators
- Metab similar to cortisol,excreted in urine.

Mineralocorticoids…

- **Fludrocortisone** : Given orally 0.1 mg 2-7 times weekly used in to produce a mineralocorticoid effect.
- used together with a glucocorticoid in replacement therapy.
- **Aldosterone antagonist** Spironolactone: for primary aldosteronism 50-100 mg/day . Also used for hirsutism in females , diuretic
- Eplerenone: HT

Antagonists of Adrenocortical agents

- Aminoglutethimide: in Ca breast with dexa to reduce estrogen prod .NOT used now
- Ketoconazole: antifungal: used for Cushing's synd
- Metyrapone: used in adrenal fnction tests
- Abiraterone: newer, studied for refractory prostate Ca
- **Mifepristone:** (RU 486): pharmacologic antagonist at steroid R . Uses: Inoperable pt with ectopic ACTH secretion or adrenal Ca.

Strong Antiprogestin activit: **mainly used in termination of pregnancy**