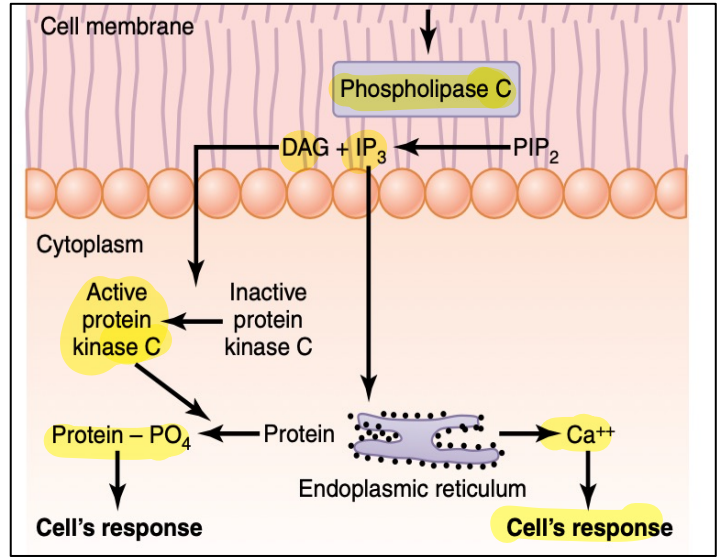
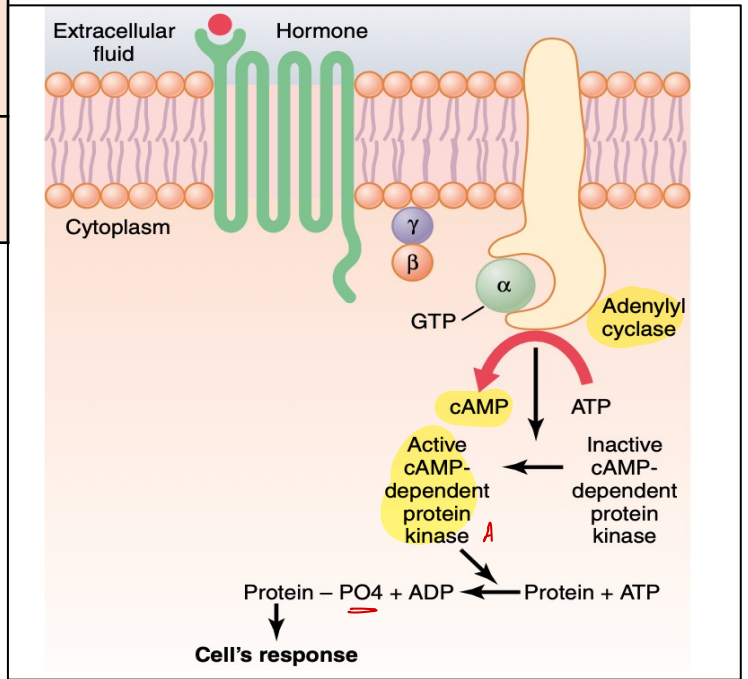
INTEGRATED ENDOCRINE SYSTEM

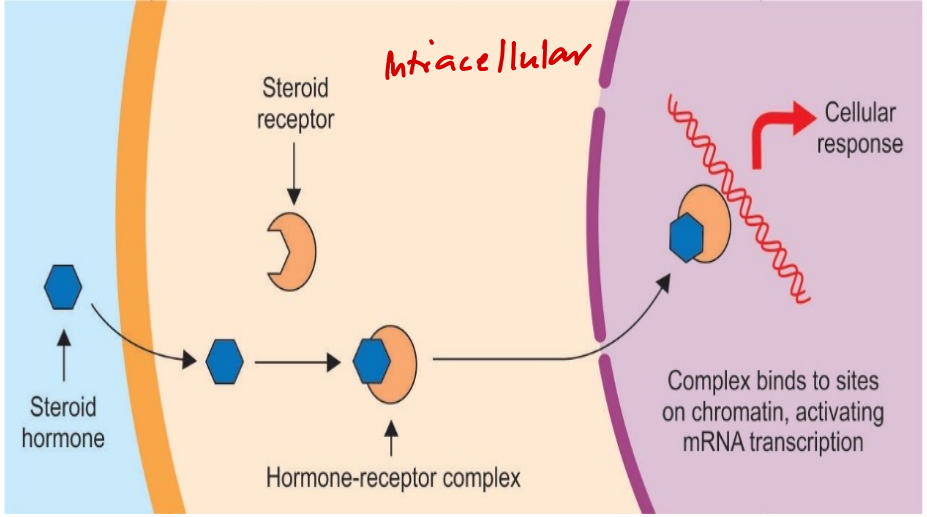
Hormone Actions

G-protein GPCR = metabotropic	Receptor and ligand	Second messenger
G_q-alpha subunit	"Hav1 M and M-GOT" H_1 α_1 V_1 M_1 M_3 AT-II · GnRH · oxytocin · TRH · Gastrin · CCK	↑IP3 ↑DAG
G_s-alpha subunit	FSH, LH, ACTH, TSH, CRH, hCG, ADH-V_2, MSH, PTH, Calcitonin, H2, Glucagon, GHRH All B receptors	↑cAMP
G_i-alpha subunit	MAD 2 somatostatin M2 α2 D2	↓cAMP
Receptor Guanyl cyclase	BAN BNP ANP NO = EDRF = arginine	↑cGMP

Glutamate	Ligand-gated ion channels: NMDA, AMPA (Ca^{2+} Na^+)
GABA	Ligand-gated: GABA A, GABA C (Cl^- influx) (B-GPCR)
Acetylcholine	Nicotinic → Ligand-gated
Norepinephrine, 5HT, Dopamine, Ach-M	GPCR (*except 5HT3 which is ligand-gated)*







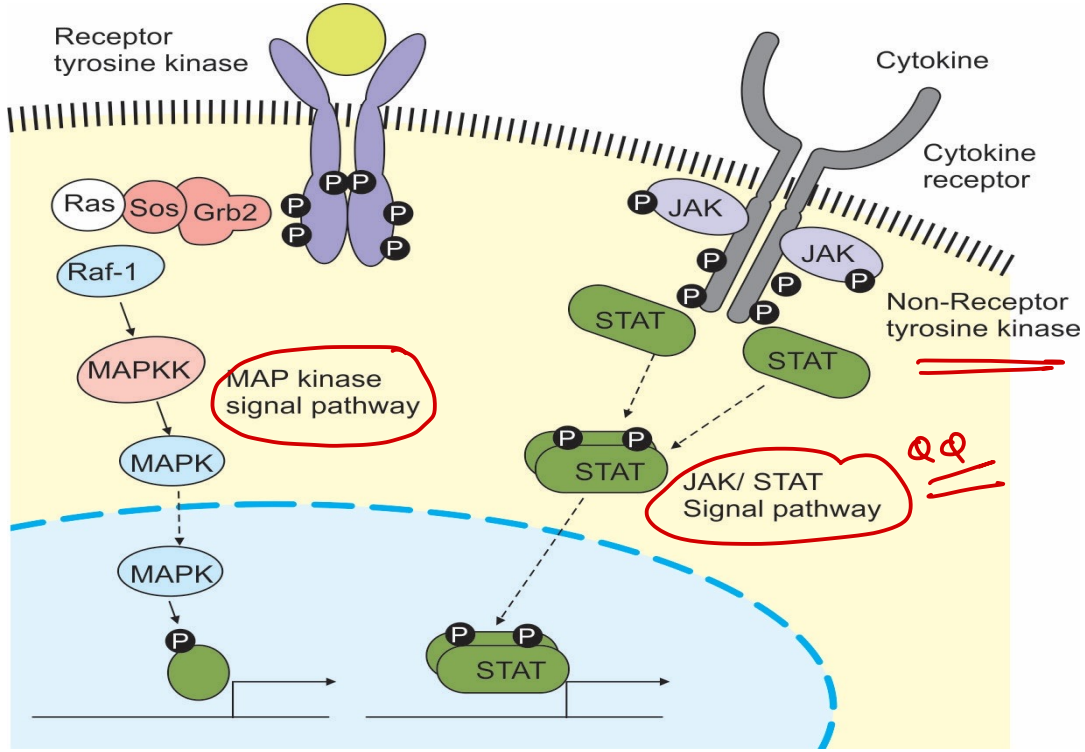
STEROIDS PREP TV

Intracellular :

Intranuclear: NEAT → Estrogen / vit A / T3 / T4

Cytoplasmic: gc / mc

Progesterone - both
vit D



INSULIN PIFE

PDGF IGF FGF EGF

PIGGLET

Eosinophils
- PRL
- GH

GM-CSF
EPO
TPO

IL-2
Leptin
adipogyles

Diabetes mellitus - Diagnosis

WHO : Symp + RBS >200

HbA1c	FBS	RBS	OGTT-75g
5.7 – 6.5 / N | IGT \ DM	100 – 126 / N | IGT \ DM	140 – 200 / N | IGT \ DM	140 – 200

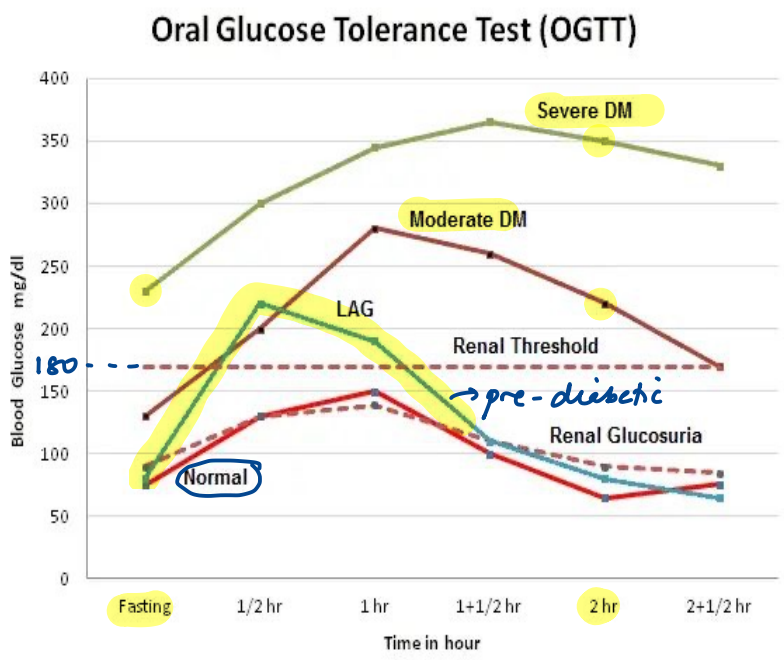
Stages of Type 1 DM
Stage 1: Auto-Ab
Stage 2: Auto-Ab + Dysglycemia
Stage 3: Auto-Ab + Dysglycemia + Symptoms

	Type 1 DM (type 1.5)	Type 2 DM	MODY (AD)
	Latent adult Adult onset: LADA Antibodies: islet cell / anti-insulin / GAD 65 → most in ZnT8	Insulin R	"monogenic familial" MC type: 3 Gene: HNF 1α
Age of onset	childhood	adult	<25yrs ; ≥2 gener"
Habitus	lean	obese	N
Insulin levels	↓↓	↑↑ — ↓	mild ↓
B cell mass	↓↓	↑↑ — ↓	mild ↓
OHG	x role	✓	✓ SU- responsive

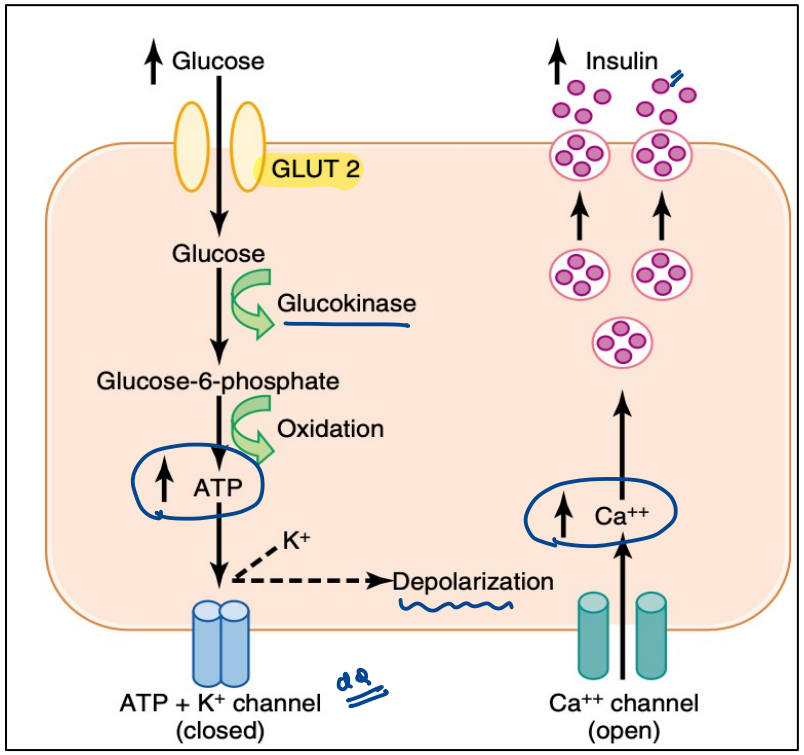
x DKA

x Auto-Ab

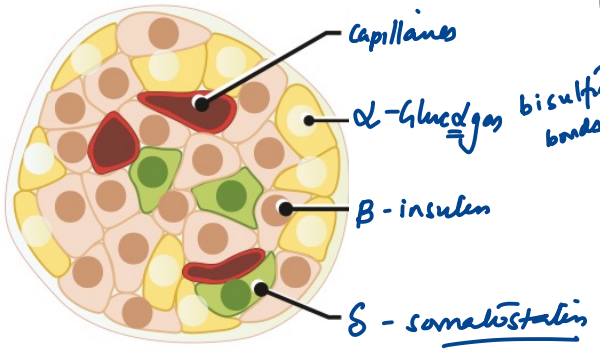
Insulin – dependent



Insulin

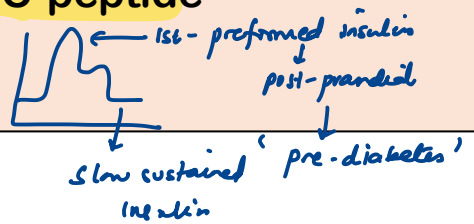


Increase Insulin Secretion	Decrease Insulin Secretion
Increased blood glucose/ FFA / AA	Decreased blood glucose / fasting
Gastrointestinal hormones (gastrin, cholecystokinin, secretin, GIP)	Somatostatin
Glucagon, growth hormone, cortisol	Leptin (adipocytes)
β-Adrenergic stimulation	α-Adrenergic activity
Insulin resistance (obesity)	



most structurally similar to IGF-1/IGF-2

Preproinsulin (RER) - signal peptide
Proinsulin (stored in secretory granules)
Insulin (51aa) and C-peptide
Biphasic release:



Metabolic syndrome: NCEP-ATP III = syn X

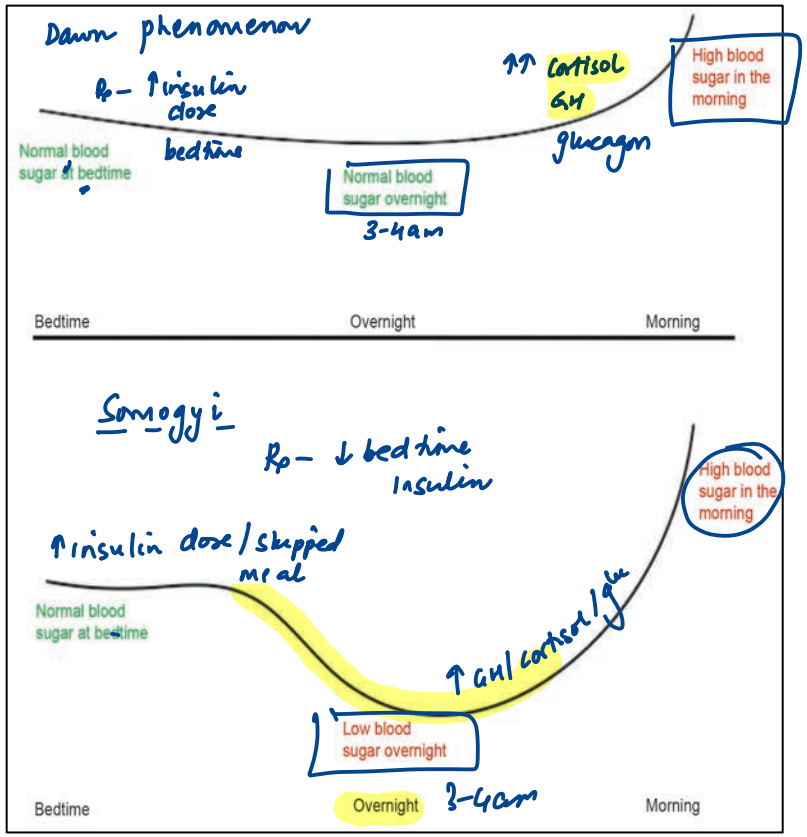
1. **Central obesity**:
   >102 cm (India-90cm) in men
   >88 cm (India-80cm) in women
2. **Elevated triglycerides**: >150 mg/dL
3. **HDL**
   < 40 mg/dL in men
   < 50 mg/dL in women.
4. **Blood pressure**: >130/85 mm Hg
5. **Fasting glucose**: >100 mg/dL

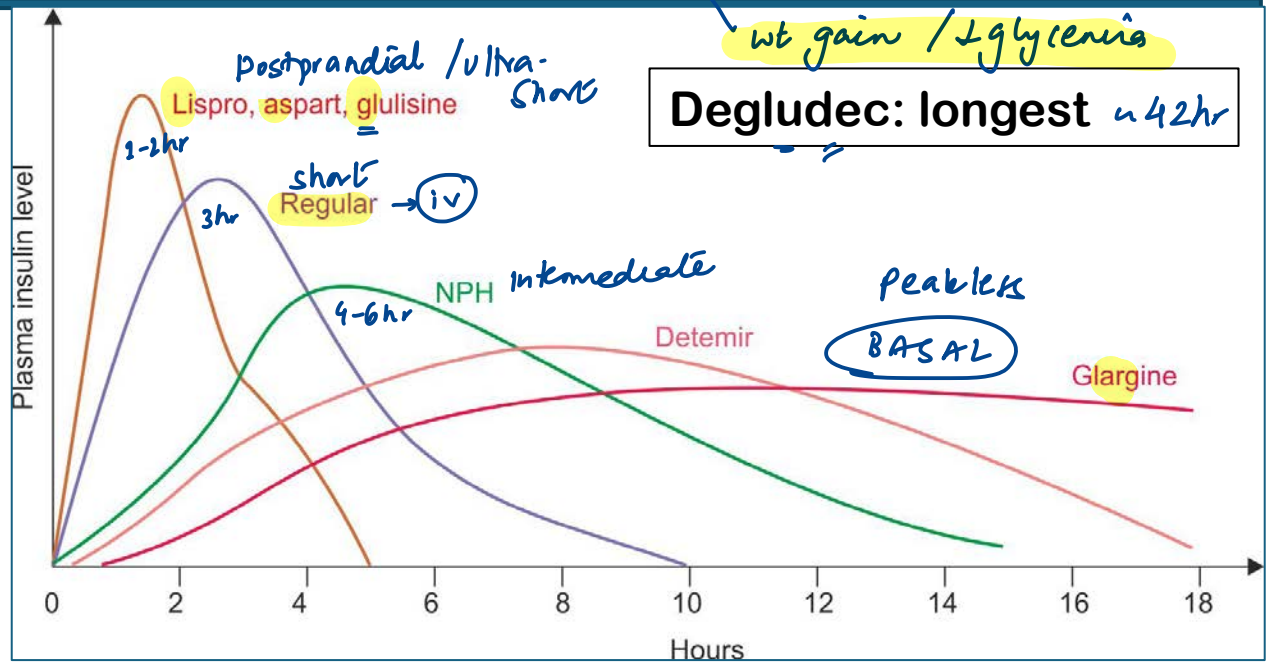
syn Z = OSA + syn X

XLDL

DM

Insulin SC injn → Lipodystrophy, ↓K+, wt gain / ↓glycemia

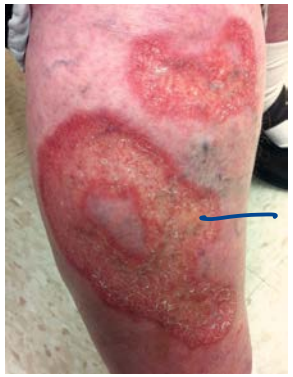




Degludec: longest ~42hr

Legacy effect / metabolic memory → early control beneficial

Affreza: Inhalational –Postprandial s/e: COPD / lung ca
Good glycemic control can reduce: microvasc complicn
Mortality: macrovasc complicn
MC microvascular complication: neuropathy
MC type: distal sm N → glove & stocking N



Necrobiosis diabeticorum

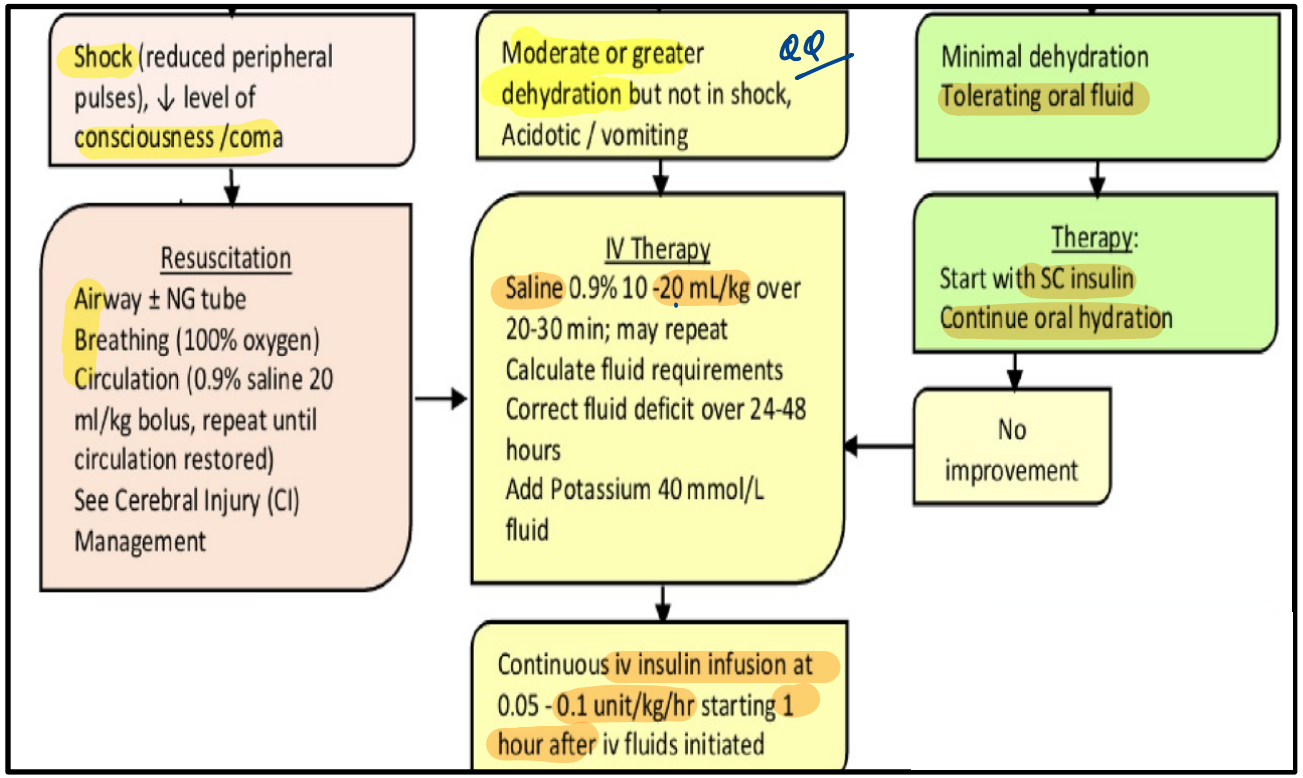
Glucagonoma → Diarrhea, Depression, DVT, DM, Necrolytic migratory erythema

Drugs causing DM:
- Steroids
- Thiazide
- Niacin
- Phenytoin
- PI
- Clozapine
- B Agonists
- IFN alpha

↑ uricemia, DM

DKA-HHS

ISPAD guidelines for DKA



- Add IV potassium if serum K ≤5.2 mEq/L
- Hold insulin for serum K <3.3 mEq/L
- Hco3 if pH <6.9

	DKA	HHS (Hyperosmolar)
Glucose	250 - 300 mg/dl	500 - 600 mg/dl
ABG	HAGMA	–
Ketones	++	–
Demographic	type 1 DM	elderly
Pathophysiology	· Stressor ++	· dehydrated
Mortality	1%	15% ∵ cerebral edema

↓ IV fluids + insulin

↓ Rx - IV fluids

OSM = 2 Na + glc/18 + BUN/2.8

K⁺ in DKA

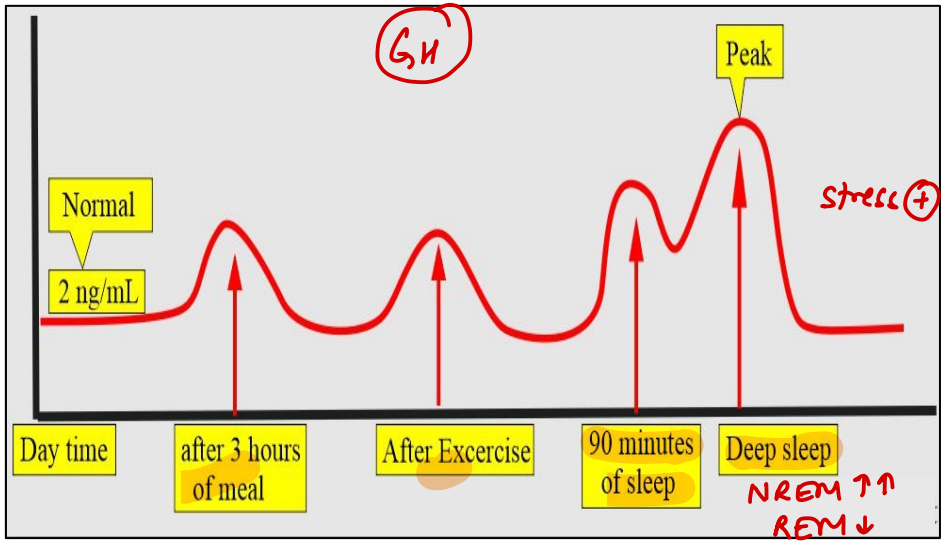
· ECF K⁺ ↑ but total body stores ↓

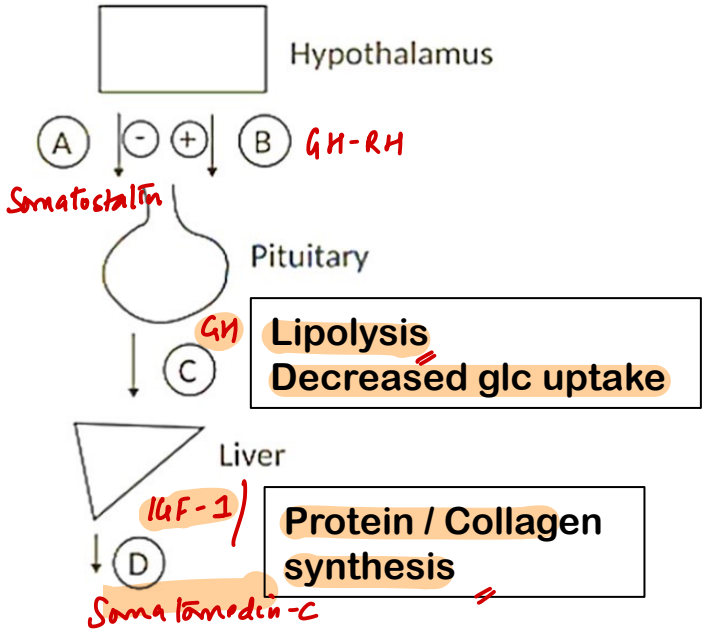
OHG

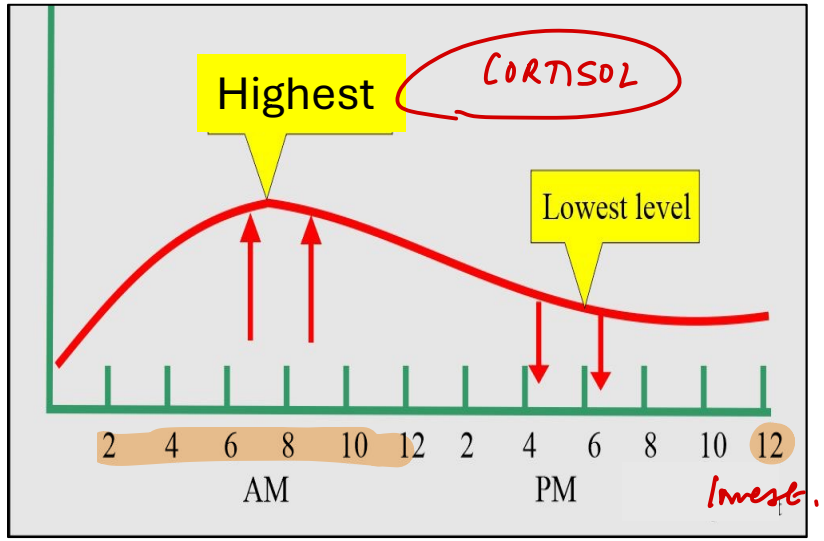
-ide – ↑insulin secr
"tide" – ⊗ wt gain / Hyglc

Agent	Mechanism of action	Side effects
Sulfonylureas Chlorpropamide, Glipizide, Glyburide **Meglitinides** Repaglinide, Nateglinide	Increases insulin secretion by inhibiting B-cell K+ ATP channels	Hypoglycemia , Weight gain Safe in renal failure (Max-Glipizide/ Glicazide) Chlorpropamide: SIADH / cholestatic jaundice / disulfiram like rxn
Biguanides Metformin	Stimulates AMP kinase, decreasing insulin resistance	Lactic acidosis, Weight loss, Vit B12 deficiency, Diarrhea · CI in renal failure Max reduction in HbA1c
Thiazolidinediones Pioglitazone, Rosiglitazone	Activates transcription regulator PPAR-g, decreasing insulin resistance	Weight gain, Heart failure, Hepatotoxic, Fractures, CME Risk of bladder cancer - Pio MI- Rosi
GLP-1 agonists – wt loss Exenatide, Liraglutide, Tirazepatide-SC Semaglutide-Oral / SC → Ozempic **DPP4 inhibitors : ORAL** – Wt neutral Sitagliptin, Saxagliptin, Linagliptin	Increases glucose-dependent insulin secretion, decreases glucagon secretion, delays gastric emptying Useful in CV risk mortality GLP-2 agonist: Teduglutide GLP-1 + GLP-2 agonist: Dapiglutide	Inj Mounjaro Max wt loss GLP-1 + GIP ⊕ Increase satiety, Weight loss Pancreatitis, MTC – GLP-1 ⊕ Nasopharyngitis- DPP4 ⊖ GLP1- safe in renal failure except: Exenatide DPP4 - CI in renal failure except: Linagliptin CYP metabolized: Saxagliptin
Amylin Analogue Pramlintide	Decreases glucagon secretion, delays gastric emptying	Increase satiety ↓ type 1 DM
α-glucoside inhibitors Acarbose , Miglitol, Voglibose	Reduces intestinal disaccharide absorption	Diarrhea, Flatulence CI in IBD
SGLT2 Inhibitors Canagliflozin, Dapagliflozin Sotagliflozin: SGLT-1 / 2 ⊖	Increases renal glucose excretion Useful in CV risk mortality ↓ intravas volume Only if eGFR >20	Urinary tract infections, Fournier gangrene, Polyuria Weight loss, Fractures Euglycemic ketoacidosis Sx SGLT2 ⊖ stopped 2-3d prior
Bromocriptine, bile acid sequesterant (colesevalam), ranolazine		fta → glc Metab modulator

Hormone-Graphs





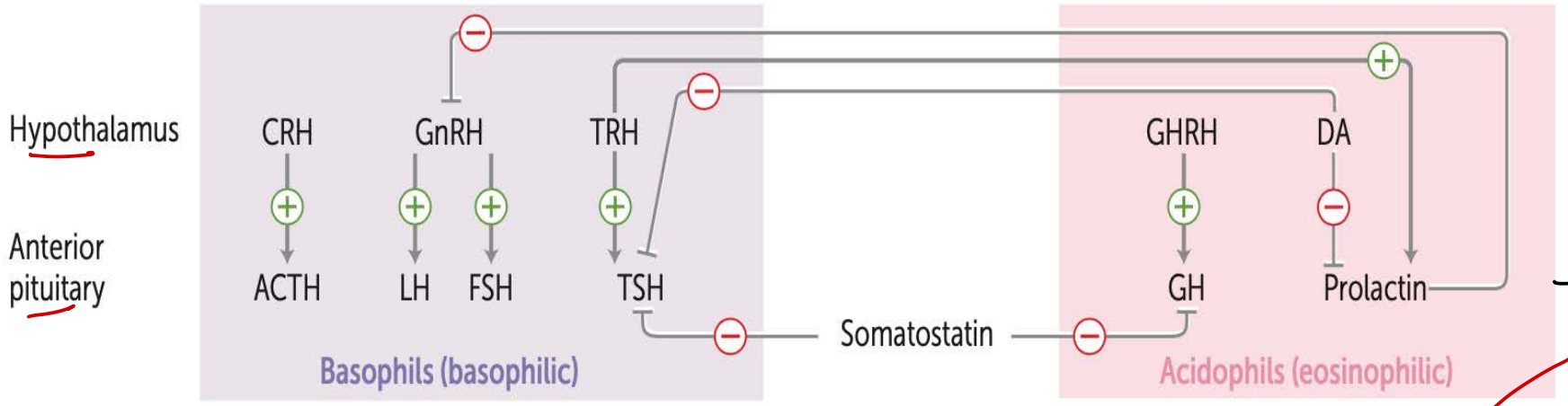


Autocrine + IL-2 CMI M2

Paracrine Histamine acts H2 → H+ ↑ /NO

Endocrine - blood vessels

Pituitary hormones



aa
Dopamine ⊖ → PRL ⊖ → GnRH
↑⊕
TRH

Stalk: trauma / Sx / RT / LCH / germinomas / lymphocytic hypophysitis
transection
post pit ← ADH, oxytocin / PRL ↑
(SAD POX)

Hypopituitarism + Hyperprolactinemia + Central Diabetes Insipidus

Triphasic response: DI → SIADH (Shred TT) → DI permanent

GnRH agonists-Goserelin, Nafarelin, Leuprolide

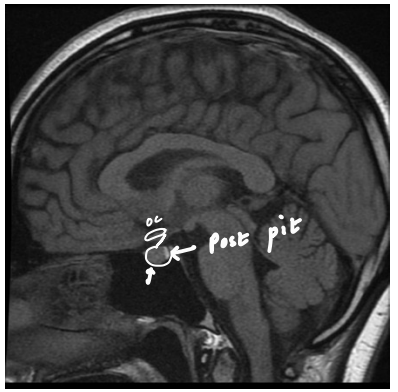
Continuous : flare → ↓↓ FSH/LH – Uses : endom/ fibroid / E-hyperplasia / Ca prostate / PP

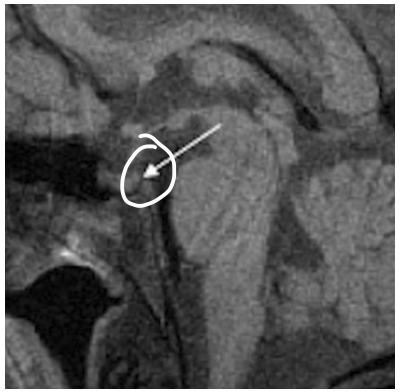
Pulsatile: ↑↑ → use : infertility / delayed puberty

GnRH antagonists-Ganirelix, Cetrorelix

GHRH analog- Tesamorelin ⊖ HIV ass lipodystrophy

Mecasermin: rIGF-1 → Laron dwarfism (GH-R resistance)





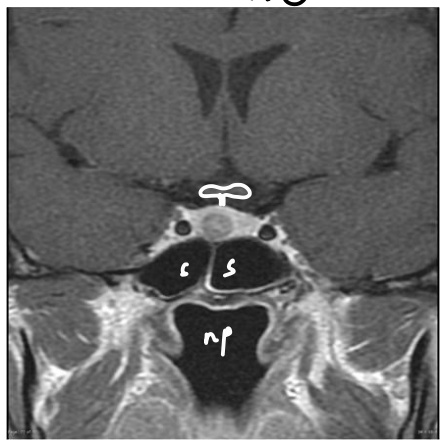
Post pit hot spot absent

Anterior Pituitary

GH ↑ < Gigantism / Acromegaly

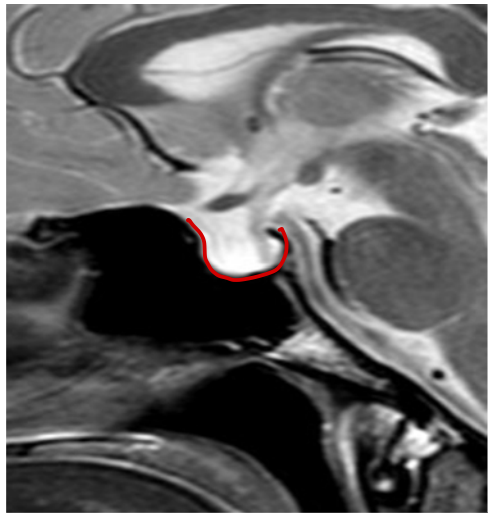
Amenorrhea, infertility, galactorrhea ↑PRL

PRL: < >200 – PRLoma; 40-200 – 2° causes
RULE OUT:
TSH
RFT
UPT
Drugs D2⊖ < Typical AP; Antiemetics - Metoclop ✓BBB; Verapamil
H2⊖



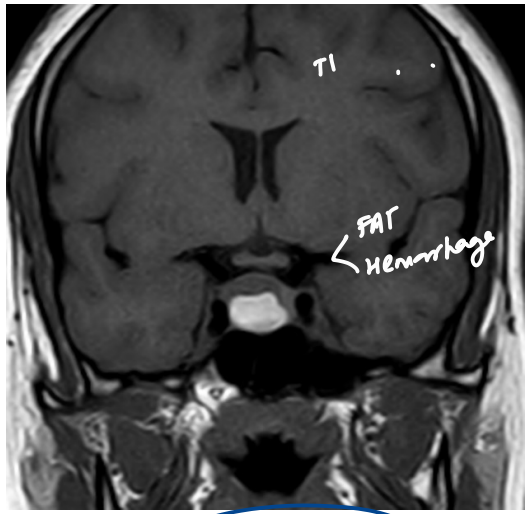
IOC - MRI Sella (c+)
- micro adenoma - <10mm
- macro adenoma - >10mm
↳ compression Sx ✓ suprasellar
Rx - Medical My - D⊕ < Cabergoline = DOC
Bromocriptine (ergot) < VC ♡ valve fibrosis

Post-partum Failure to lactate, Amenorrhea, Fatigue, Hypoglycemia (Hypo-pit)
PRL / GH/ TSH

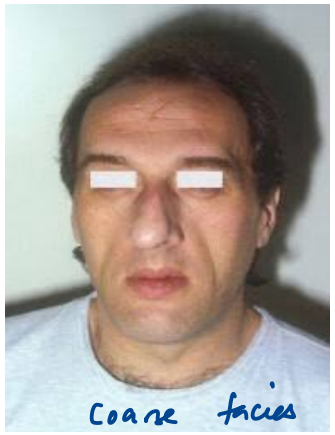


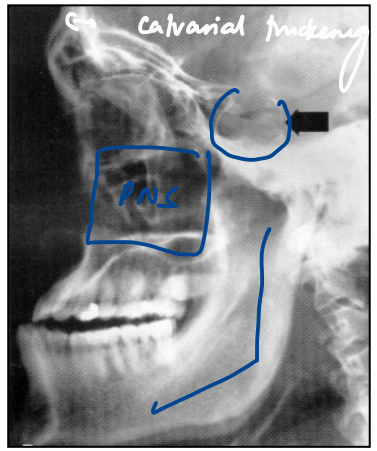
IOC

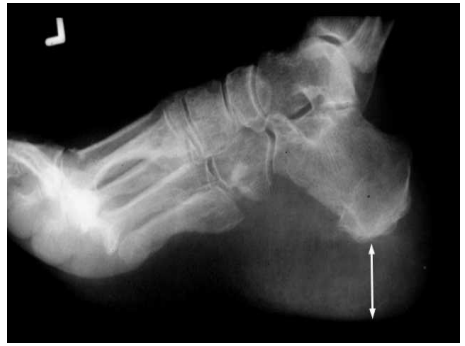
Sudden headache, visual deficit
Pre-existing adenoma
↓
'Shock'



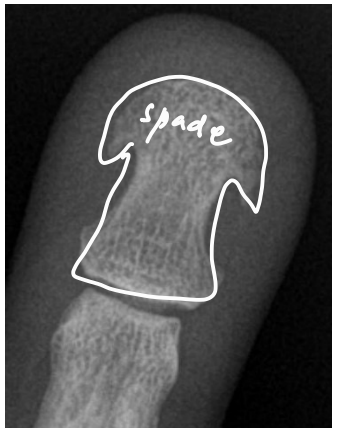
Pit apoplexy







Heel pad ↑↑ ≥25mm



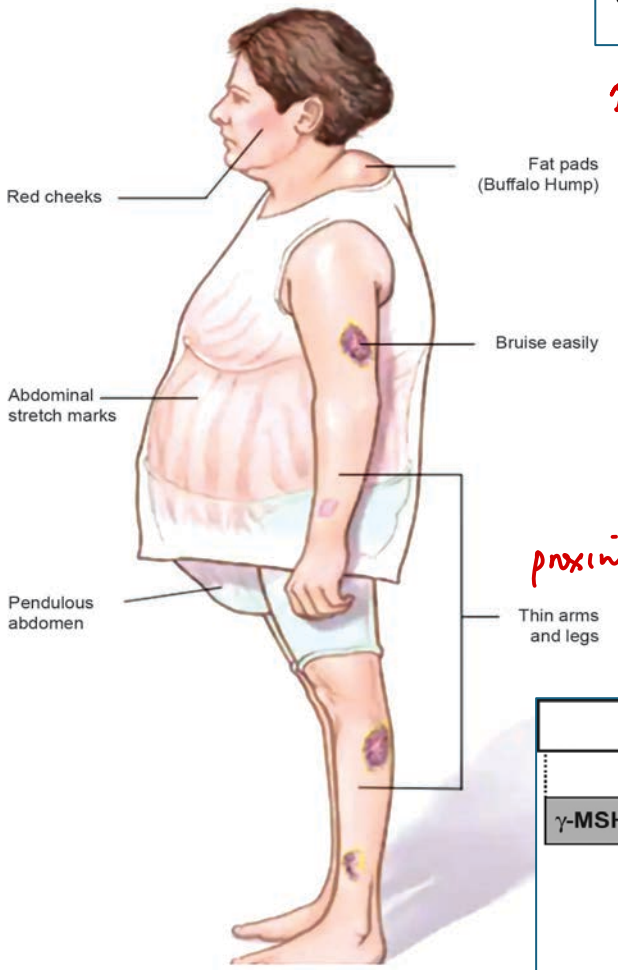
Insulin tolerance test

Sheehan Sx
MRI - Empty sella Sx

Insulin - ↓glc - GH↑ (N) ACTH↑

Initial: IGF-1 ↑↑
Confirmatory: OGTT < GH ↓ (N) ; GH ↑↑ - acromegaly
Management: Surgical
Unresectable: Octreotide → ✗ → Pegvisomant ✓ visual c/o ; GH-R ⊖

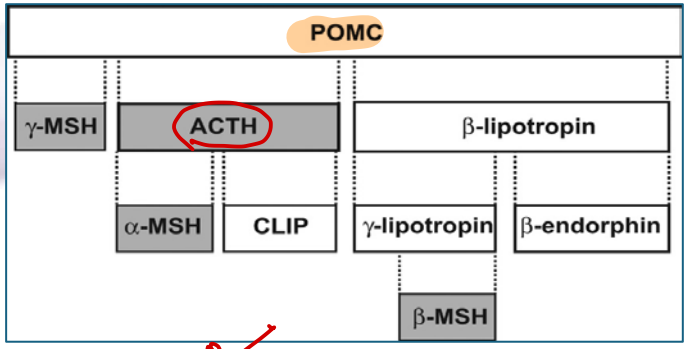
CUSHING SYNDROME



"A BIG FIB"

↑ apetite
Insulin R
BP ↑
Gluconeog ↑
DM
Permissive actim
BP
+cortisol
Epi
Dose
- Fibroblast ↓ wound healing
- IL-2 ↓
- Bone - o'blast ↓

proximal myopathy.



CUSHING SYNDROME:
MCC: exogenous steroid. Next: cortisol
IOC to confirm- 1. Midnight ↓ cortisol
2. 24hr ↓ cortisol 3. Low dose D. (1mg dexa ovr) → cortisol ↓
Cushing (N) (↑) =

ACTH

Low
↓
adrenal adenoma / hyperplasia
IOC → CECT Abdo

High
↓
High dose DMS: 2mg 6hly x48hrs

Supress
↓
Pit adenoma
IOC - MRI sella
↓ ×
IPSS - Inf petrosal sampl
Central ACTH >2x peripheral

Not supressed
↓
Ectopic
Carcinoid
Small cell Ca lung
IOC - DOTANOC PET > CECT

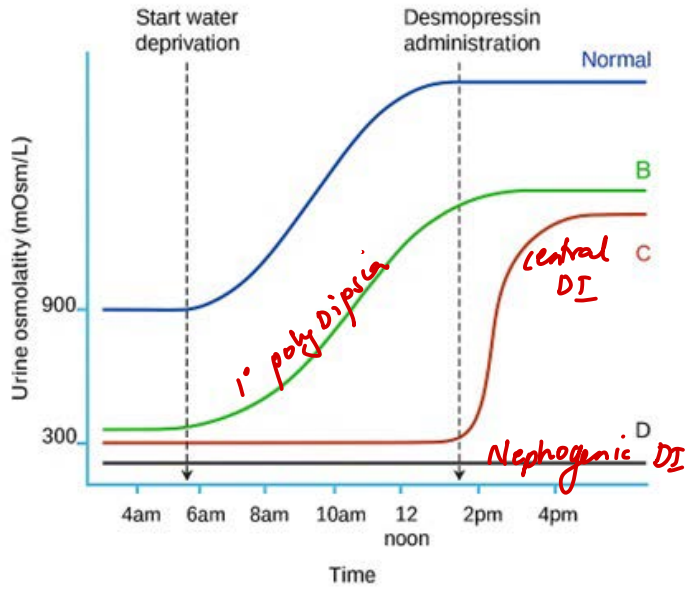
Neutrophil: ↑ (chemotaxis ⊖)
Eosinphil: ↓
Lymphocytes: ↓

~~CD~~ Nelson syndrome: Hyperpigmentation + Headache/visual symptoms
H/o B/L adrenalectomy for Cushing syndrome

Posterior Pituitary

Polydipsia-Polyuria – DM

	SIADH	Central DI	Nephrogenic DI (ADH → R)	Primary polydipsia
Urine Osm	↑↑	↓	↓	↓
Plasma Osm	↓↓	↑	↑	↓
Serum Na	↓↓ Euvolemic Hypo Na	↑	↑	↓ – (N)
Uric acid (∝ ADH)	↓	↑	↓	(–)
Diagnosis	Water loading test: ADH high	Water deprivation test: Osm low	Water deprivation test: Osm low	Water deprivation test: Osm >600 mosm/kg
Management	Fluid restrict ↓ Vaptans V2 (–)	Desmopressin	THIAZIDES; Li induced – Amiloride	Stop drinking H2O



D/D: (CSW)
Hypovolemic HypoNa + SAH
High BNP → Natriuresis → Increased Urinary Na+

Na-Cl (–) → diuresis → ↓GFR → RAAS ↑↑ → AT-II → PCT ↑HCO_3 reabs ↑H_2O "

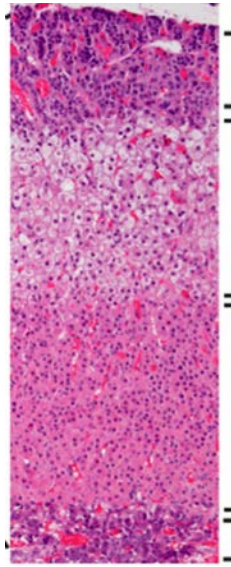
Barter-Schwartz Criteria for SIADH:
- Clinically Euvolemic (aldosterone ↓, ANP)
- Low Serum Osmolality <275
- Urine Osmolality >100 or Urine Na+ > 40meq/L
- Absence of Any Renal, Thyroid disease, diuretic use
- Correction with fluid restriction

Hypothyroid

ADH: V1- VC
V2 < AQP2 – CD, ↑vWF·f8
V3- ↑ACTH

SIADH causes: Chlorpropamide, Oxcarbamazepine, Cyclophosphamide, Vincristine, SSRI, Small cell ca lung, Pneumonia, Encephalitis

ADRENAL INSUFFICIENCY



Glomerulosa – MC ← RAAS

Fasciculata – gc

Reticulata – sex steroids

← ACTH

Medulla → Epi/NE ← N_N Ach (PNMT)

Rx → Hydrocortisone (gc/mc) 20mg/d / 10mg – 5mg – 5mg

- Dexa
- Beta } longest
- Triamcinolone

gc only.

IOC:
COSYNTROPIN TEST = ACTH stimulⁿ

HIGH CORTISOL (N)

LOW CORTISOL <20ug/dl → confirmed

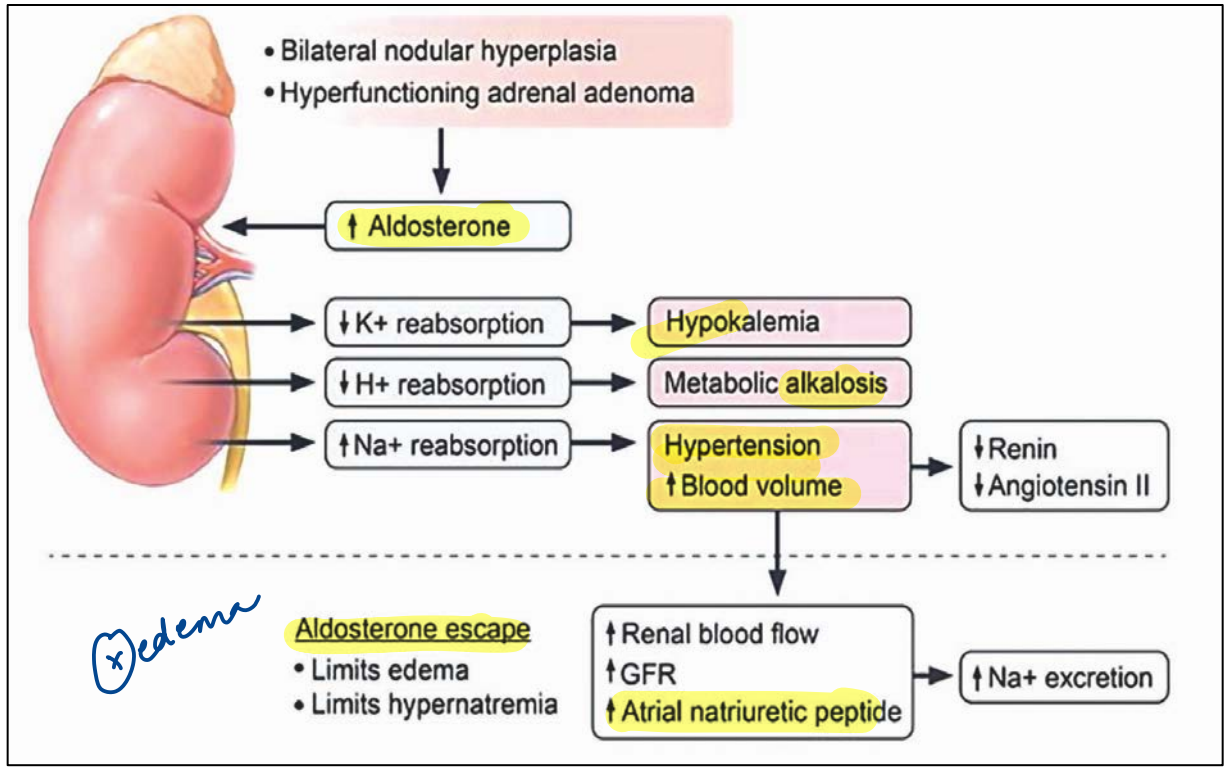
ACTH

LOW → 2° adrenal insuff

HIGH → 1° adrenal inf.

Primary versus central adrenal insufficiency		
	Primary	**Secondary**
Most common cause	**Autoimmune/ Granulomatous** (Addison → TB/Histopl)	**Chronic glucocorticoid therapy** (3°)
Cortisol	↓	↓
ACTH	↑	↓ QQ
Aldosterone	↓ QQ	N
Clinical features	• Severe symptoms • **Hyperpigmentation** QQ • Hyperkalemia / ↓↓ Na^+ acidosis	• Less severe • No hyperpigmentation • No hyperkalemia

HYPERALDOSTERONISM

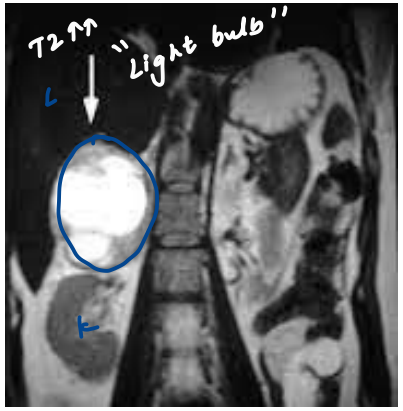


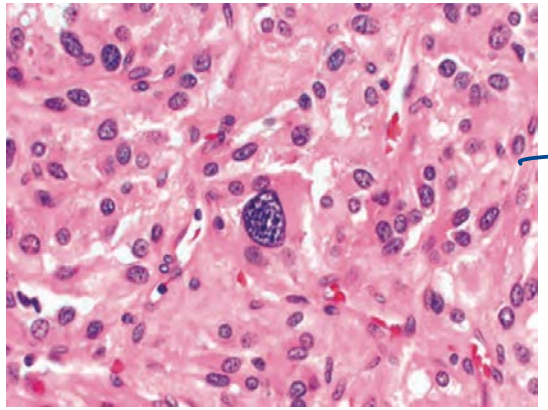
Hypertension + hypokalemia + alkalosis

↑Renin ↑Aldosterone	↓Renin ↑Aldosterone	↓Renin ↓Aldosterone
· Reninoma · Malignant hyptn/ RAS	Adrenal adenoma/ hyperplasia II Conn's Sx	· Liddle Sx · SAME II BMSD liquorice → Cortisol (gc/mc) ↓ → Cortisone (gc) · CAH 11 / 17 αH

Pheochromocytoma

Headache / Sweating / Palpitation ↑↑ Epi / NE
Initial Ix- Urine VMA / metanephrine
Confirm Ix- Plasma metanephrine
Best to localize- MRI
Biopsy/ FNAC- NO
Best for mets- MIBG (I-131)
Best for extraadrenal pheo- DOPA-PET
MC site for extradrenal pheo- organ of Zuckerkandl
Rule of 10 :
-Extradrenal/ No hypertension/ Children
-B/L But 50% in Syndromic → NF1 / VHL / MEN2a / MEN 2b / SDH
-Malignant But 40% in familial
-Familial (25%)
Treatment: Prep: α-blocker (1st) Phenoxybenzamine → β-blockers.
Intra-op: Nicardipine, Nitroprusside, Phentolamine
x β-blockers





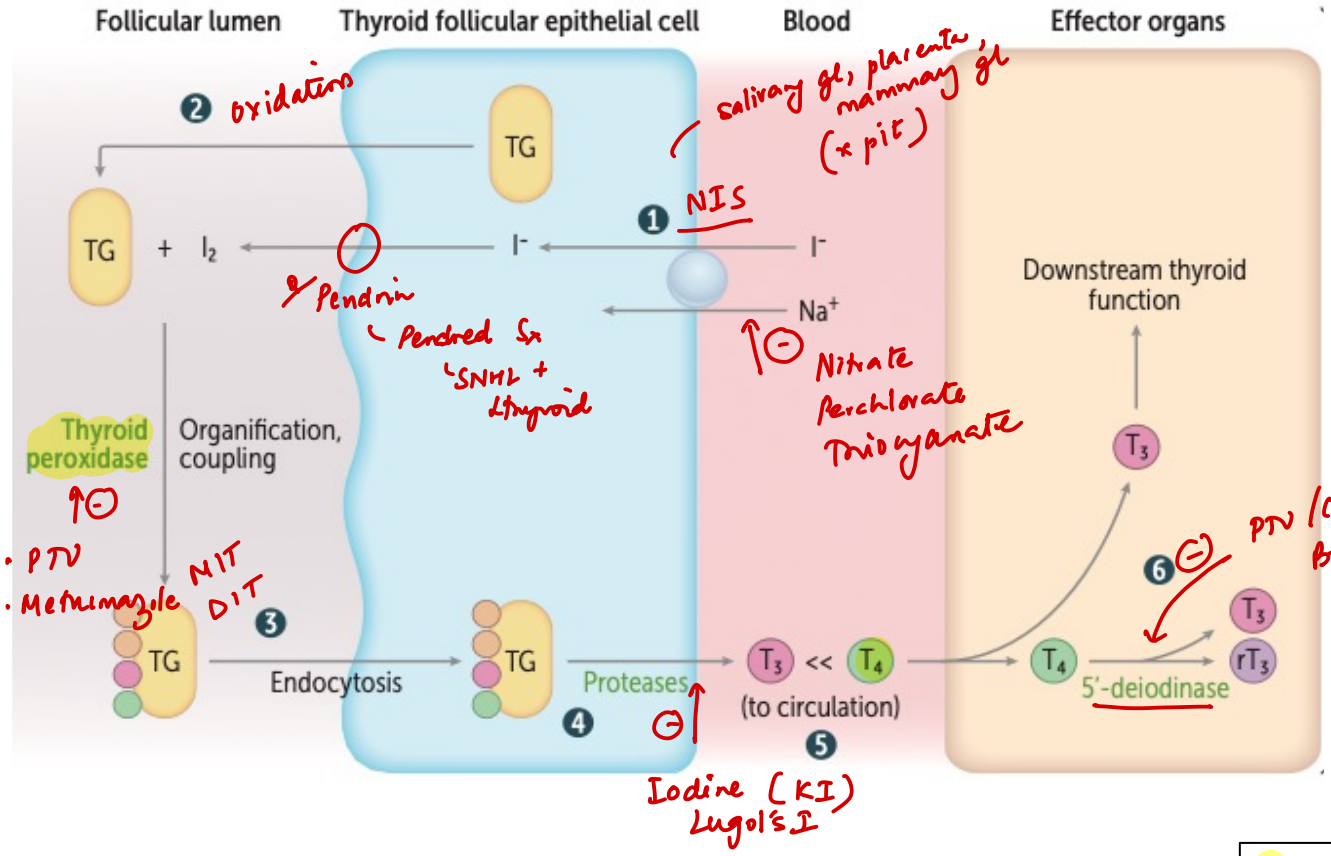
Carcinoid tumor

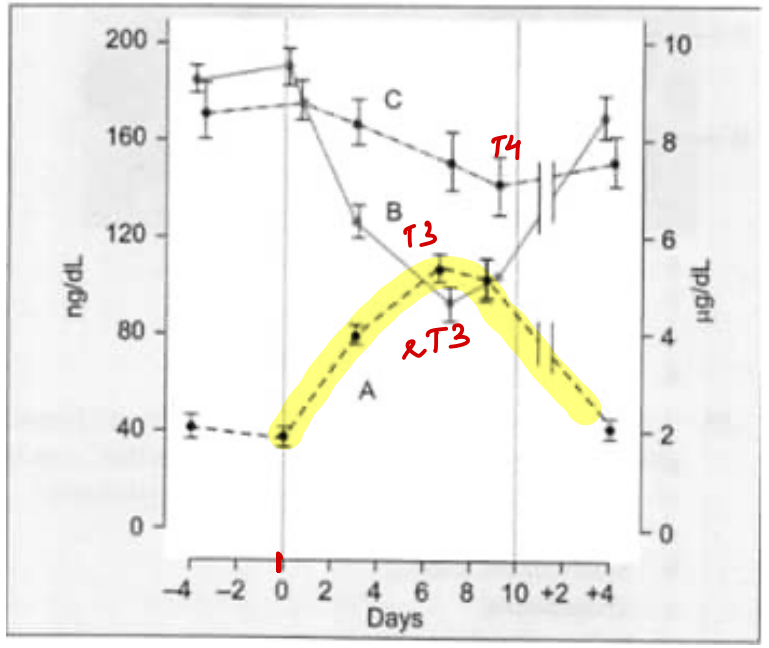
5-HT

Origin: APUD = Kulthinsky cells
MC site: Appendix > Ileum
Urinary: 5-HIAA
Skin flushing
Heart valve disease (tricuspid)
Intestinal diarrhea
Vasospasm
Asthma
Rx: Surgery (x) → octreotide
Telotristat- tryptophan hydroxylase (-)
Rule of 1/3: Mets, 2nd malignancy, multiple

MC site of carcinoid Sx
Liver mets

Thyroid hormone



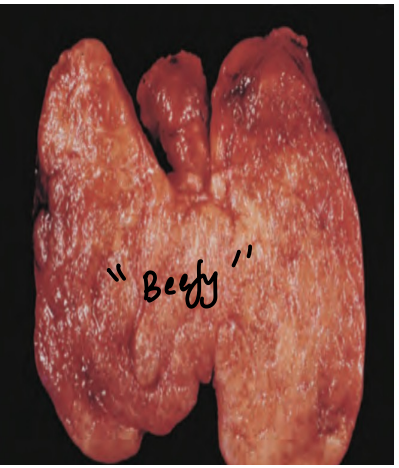


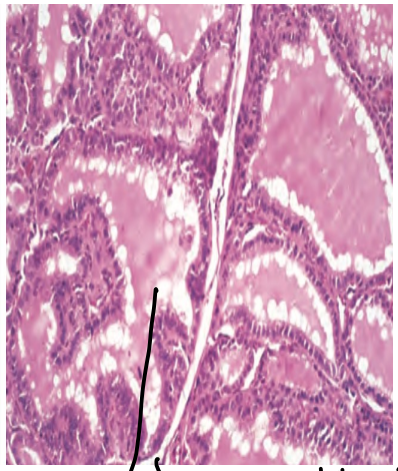
- **Brain maturation**
- **Bone O'clast +**
- ↑ β_1 receptors in heart
- **Basal metabolic rate** ↑ (via ↑ Na^+/K^+-ATPase)
- **Blood sugar** ↑ (↑ glycogenolysis, gluconeogenesis)
- **Break down lipids** ↑ (↑ lipolysis)
- **Babies**: stimulates surfactant synthesis

Graves Disease

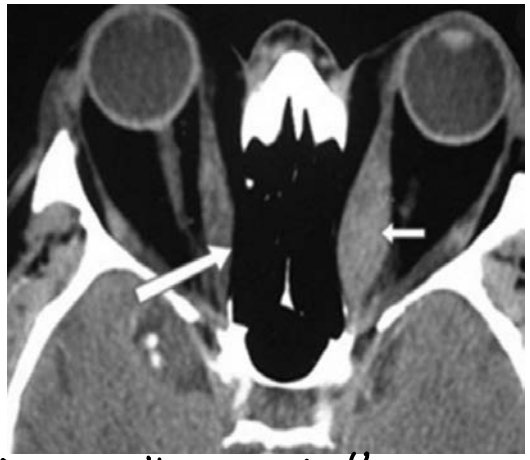
type II / III hypersensitivity
anti-TSH(R) - TSI / LATS

↑fibroblasts ↑GAG.

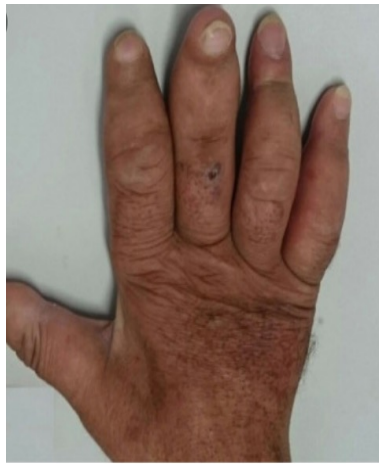




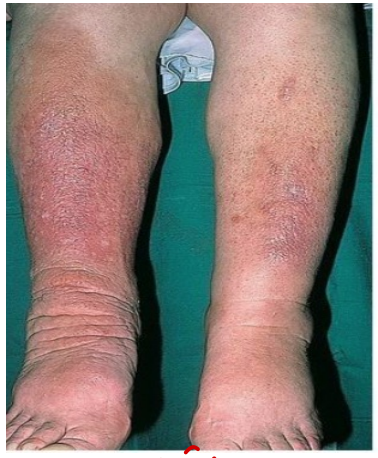
↳ "scalloping" of colloid



"coca cola"

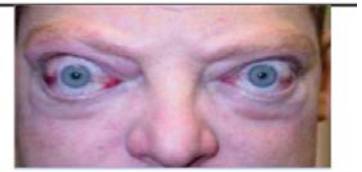
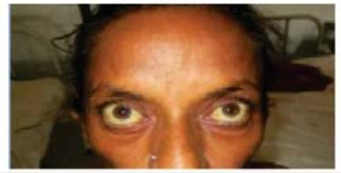
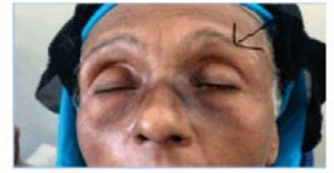
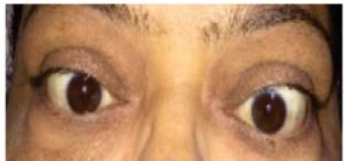


thyroid acropachy



pretibial myxedema
↳ Graves ↑↑ specific

1-Only signs
2-Soft tissue involvement
3: Proptosis
4: Extraocular muscle involvement IM SLO
5: Corneal involvement
6: Sight loss (optic nerve involvement) 00 (severe)

Staring look — Stellwag sign	
Absent creases in the forehead on superior gaze — Jofroy sign	
Hyperpigmentation of the superior eye folds — Jellnick sign	
Loss of the lateral third of eyebrows — Hertoge sign	
Retraction of upper eye lid — Dalrymple sign	
Lid lag of the upper eyelid on downward gaze — Von Graffe sign	
Inability to converge — Mobius sign	

Treatment

Management of Graves

RADIO-IODINE ABLATION (TOC)

I-131 – β + γ rays

except

- pregnancy
- severe TED

DRUGS

Pregnancy

- PTU – safe in preg (1st T) – agranulocytosis, hepatotoxic
- Methimazole – teratogenic (2nd / 3rd T)

SURGERY

severe TED (orbital decomp)

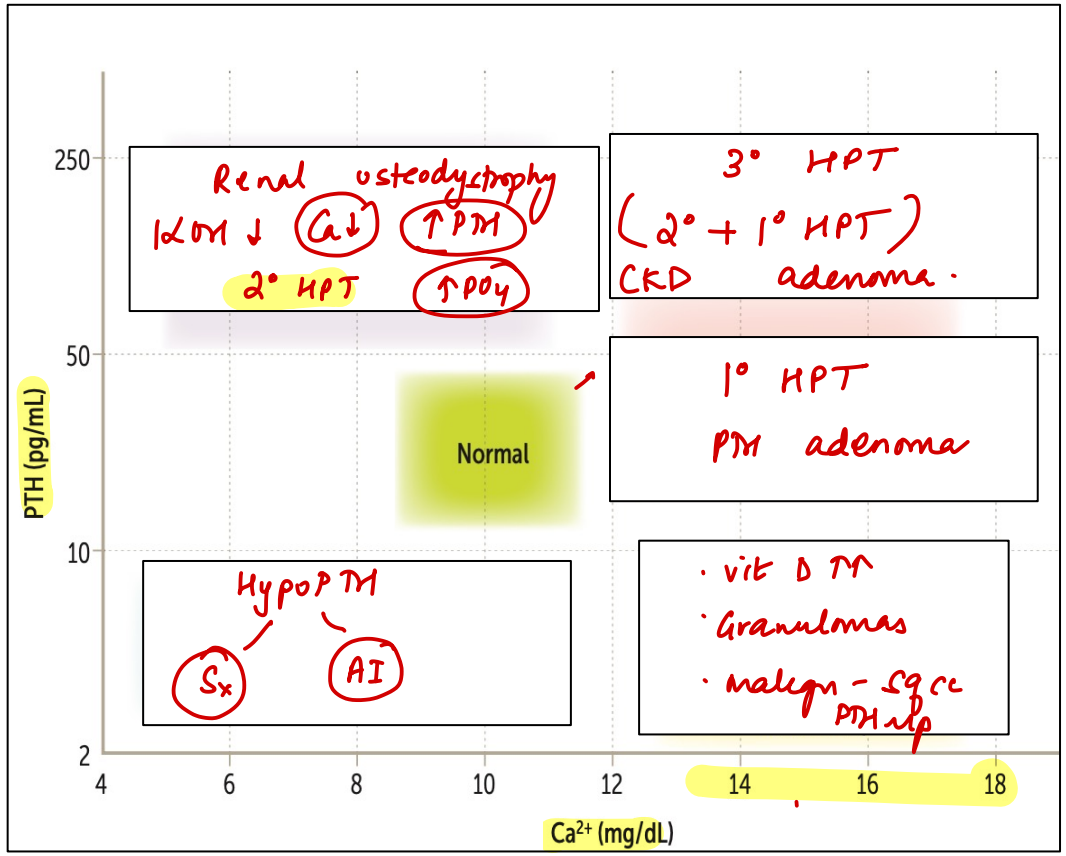
Thyroid storm

- Beta blockers (1st line) – MHR / A.Fib; Asthma ± Verapamil
- PTU – T4 → T3 ×
- Glucocorticoids
- Sodium iodide
- If asthma + A-fib: Verapamil

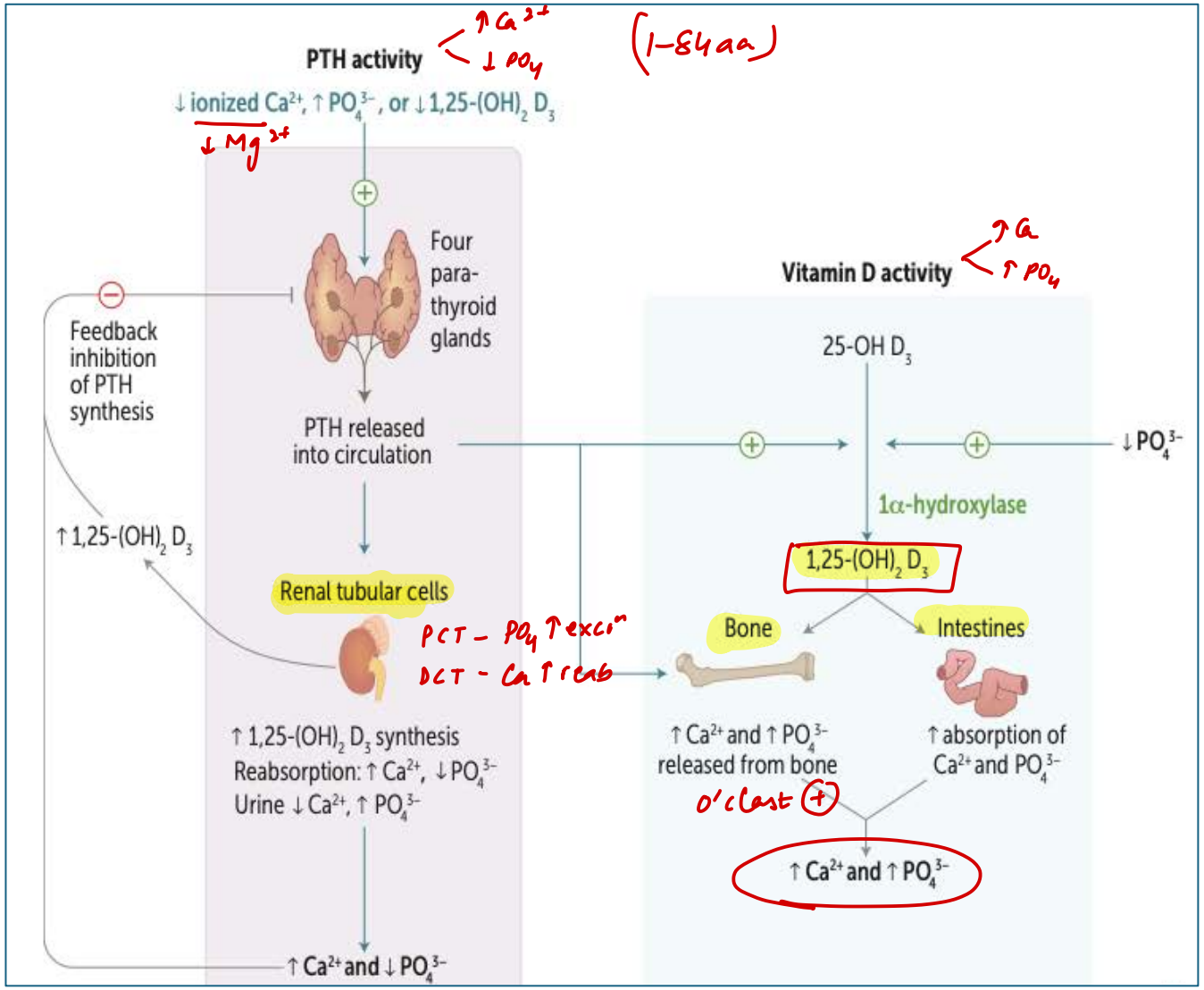
Myxedema coma

IV T3 and/or L-thyroxine (T4)
IV Hydrocortisone
0.9% NaCl if Na^+ < 120 mEq/L
Treat hypothermia (temperature < 35 °C)

Parathyroid and calcium



↑ Serum Ca^{2+} → stimulation of parafollicular (C) cells of the thyroid → ↑ calcitonin
Inhibits osteoclastic bone resorption



Intermittent/ 1-34 aa chain PTH:
Teriparatide
O' blast +

Hypercalcemia

Confirm hypercalcemia
- Repeat testing
- Correct for albumin concentration or measure ionized calcium

Measure **PTH** level

High-normal or elevated PTH (**PTH-dependent**)

- **Primary (or tertiary) hyperparathyroidism**
- **Familial hypocalciuric hypercalcemia**
- **Lithium**

Suppressed PTH (**PTH-independent**)

- **Malignancy**
- **Vitamin D toxicity**
- **Granulomatous diseases**
- **Thiazides**
- **Milk-alkali syndrome**
- **Thyrotoxicosis**
- **Vitamin A toxicity**
- **Immobilization**

	PTH	Ca	U_{CA}
↑HPT	↑	↑	↑
FHH	↑	↑	↓

Management:
Severe (Calcium > 14 mg/dL) or Symptomatic
- **Normal saline hydration plus calcitonin**
- **Avoid loop diuretics unless volume overload (heart failure) exists**

Long-term treatment: Bisphosphonate

NDI
- ↑Ca^{2+}
- ↓K^+
- Li
- Demeclocycline