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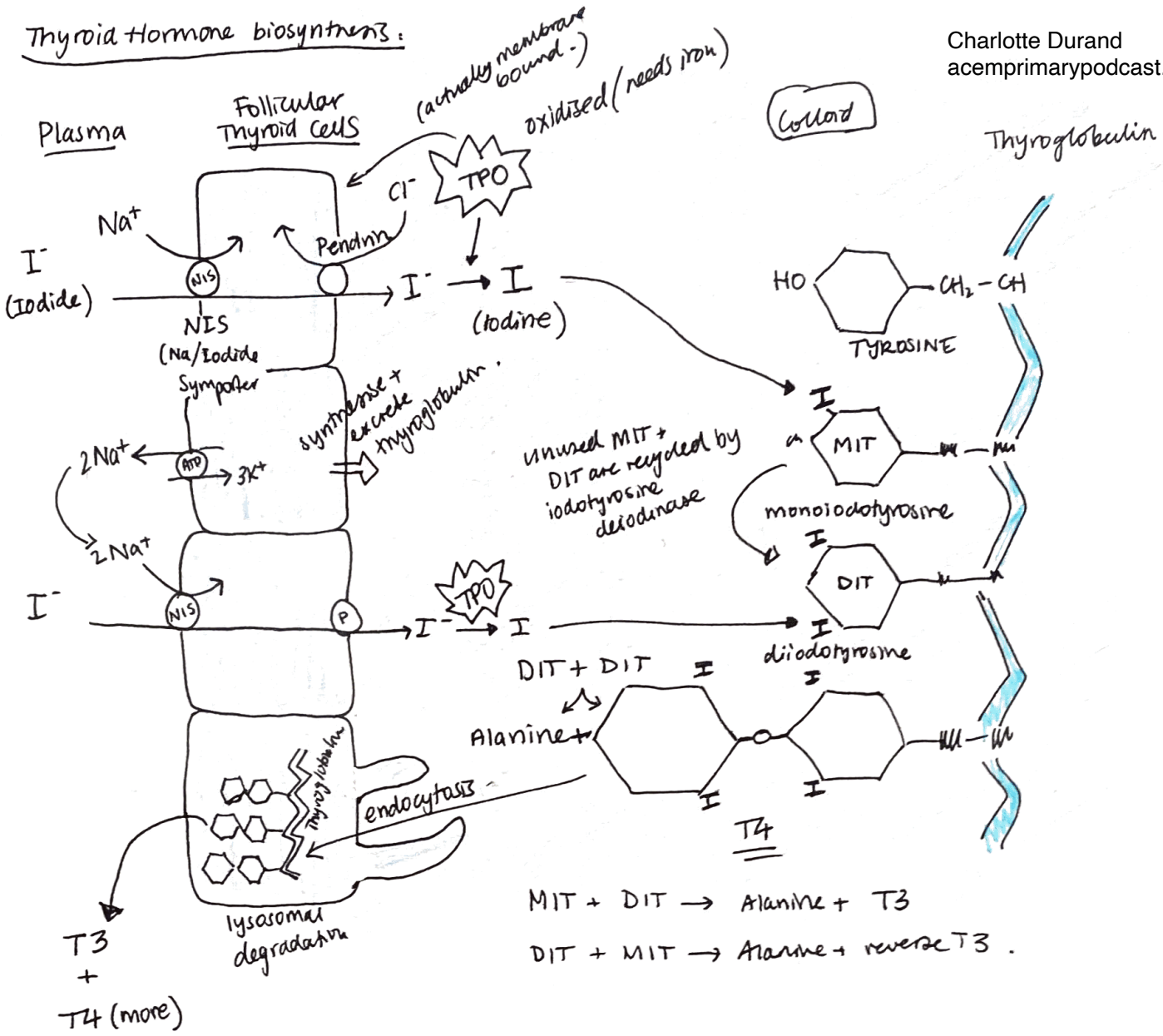
Thyroid Hormone biosynthesis:



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Thyroid gland has 2 functions – thyroid hormone production and calcitonin production
Comes from the thyroglossal duct – i.e. path from the tongue to the neck
Pyramidal lobe arises from the isthmus
One of the highest rates of blood flow per gram of tissue

colloid = "glue like"

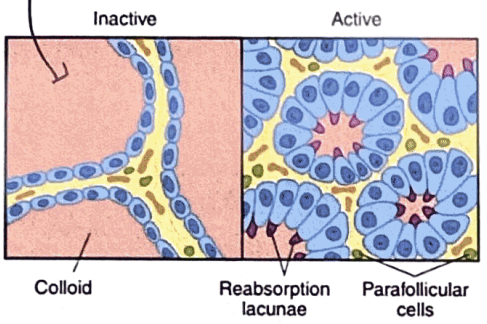

FIGURE 19–2 Thyroid histology. The appearance of the gland when it is inactive (left) and actively secreting (right) is shown. Note the small, punched-out "reabsorption lacunae" in the colloid next to the cells in the active gland.

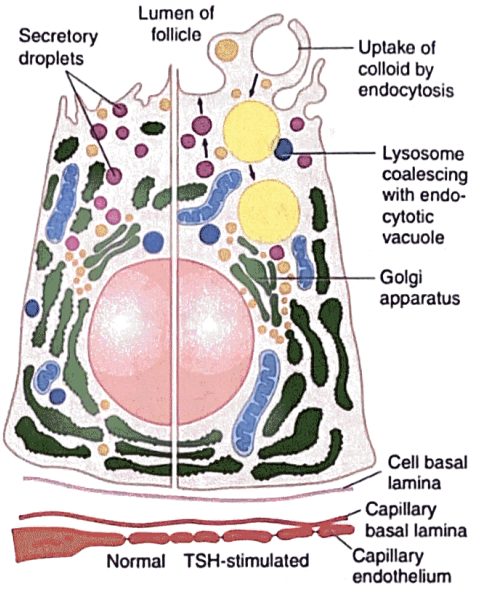

FIGURE 19–3 Thyroid cell. Left: Normal pattern. Right: After TSH stimulation. The arrows on the right show the secretion of thyroglobulin into the colloid. On the right, endocytosis of the colloid and merging of a colloid-containing vacuole with a lysosome are also shown. The cell rests on a capillary with gaps (fenestrations) in the endothelial wall.

1. Describe the key steps in synthesis of thyroid hormones

T4 (thyroxine) is secreted as the primary hormone along with lesser amounts of T3 (triiodothyroxine)
T3 has greater activity than T4 and is generated at tissues by deiodination of T4 (by D1 enzyme)
Small amounts of other stuff i.e. reverse T3 (not active) are also present

Iodine homeostasis

- Dietary iodine absorbed by intestine → enters circulation. Minimum daily intake 150microg to maintain thyroid function
- Table salt means 500 per day in most developed areas
- Taken up by thyroid and kidneys
- Some in bile/ renal excretion
- Iodine excess and deficiency both cause hypothyroidism via inhibition of function

Iodide transport across thyrocytes

- Basolateral membranes have a 2Na+ symporter (NIS)
- Secondary active transport -> Na transported out by the Na/K/ATPase
- Can generate intracellular I- concentrations that are 20-40 times the plasma concentration
- TSH influences NIS expression and retention in the basolateral membrane
- Iodide exits across the apical membrane to the colloid via **pendrin** Cl-/I- exchange (named from Pendred syndrome of thyroid dysfunction)
- NIS also in many other tissues

Synthesis of hormones

Between the thyrocyte and the colloid = organification of iodide

1. Iodide oxidised to iodine
2. Incorporated into thyroglobulin – secreted via exocytosis of granules
   - **Colloid** = reservoir of thyroid hormones (can have no iodide for 2 months before thyroid function decreases)
3. When needed, colloid internalised by thyrocytes via endocytosis and undergoes lysosomal degradation to discharge free T4 and T3
4. **Thyroid peroxidase** – membrane bound enzyme in the apical membrane of thyrocyte that mediates the oxidation and reaction of iodide with thyroglobulin

NB: Needs iron to work!

5. TPO generates reactive iodine species that can attack thyroglobulin
6. First produces MIT, then DIT
7. Then, 2 x DIT molecules undergo oxidative condensation to form T4
8. T3 is formed by MIT + DIT
9. Unused MIT/DIT are recycled by iodotyrosine deiodinase (recycling provides twice as much iodine as NIS does) T3 and T4 are resistant to this enzyme

Normal human thyroid hormone distribution is 3% MIT, 33% DIT, 35% T4 and 7% T3 traces of RT3
Secreted 80microg (103nmol) of T4, 4 migroc T3 and 2 microg RT3 per da

Four functions of thyrocytes

1. Collect and transport iodine
2. Synthesise thyroglobulin
3. Fix iodine to thyroglobulin to make hormones
4. Remove thyroid hormones from thyroglobulin

TABLE 19–1 Binding of thyroid hormones to plasma proteins in normal adult humans.

Protein	Plasma Concentration (mg/dL)	Amount of Circulating Hormone Bound (%)	
		T_4	T_3
Thyroxine-binding globulin (TBG)	2	67	46
Transthyretin (thyroxine-binding prealbumin, TBPA)	15	20	1
Albumin	3500	13	53

SYSTEMIC EFFECTS OF THYROID HOROMONES

T3 binds to TR in the nucleus which then binds to DNA via zinc fingers and increases or decreases the transcription of some genes

Calorigenesis

T4 and T3 increase O2 consumption of almost all tissues except adult brain, testes, uterus lymph nodes, spleen and anterior pituitary. Some of the effects of thyroid hormones are due to fatty acid metabolism, some are due to increased activity of membrane bound Na/K/ATPase. Effects can be still seen 6 days later

Carotenemia – thyroid hormones needed to convert carotene to vitamin A = yellow tint to skin in hypothyroidism (not sclera)

Myxedema – proteins accumulate in the skin and attract water

Heart- increases the genes for myosin hevy chains, SR Calcium ATPase, K channels, Beta adrenergic receptors. G proteins, Na/K/ATPase ↑ pulse pressure due to inotropy, ↓ peripheral resistance due to cutaneous vasodilation

4-(not B)

Brain- not directly affected by T3/T4 astrocytes convert T3 to T4 in the brain, sharp increase in brain D2 activity that can be reversed in hours by IV dose of thyroxine. CNS and basal ganglia affected in development. Thus, thyroid hormone deficiency in development causes deafness, mental delay etc.

Catecholamines- toxicity of these is increased with high T_4 levels. Effects of hyperthyroidism i.e. tremors, thyroid storms can be treated with beta blockers ↑ # & affinity of adrenoreceptors.
Does not ↑ levels of catecholamines though.

~~2A Describe the synthesis of catecholamines and the enzymes involved on paper~~

Thyroid hormones lower circulating cholesterol levels via ↑ LDL receptor in liver

Gut – causes ↑ CHO absorption of the gut

→ promotes (N) bone growth

→ Normal CNS function.

→ Catabolic to lipid tissue.

→ Muscle breakdown

AMIODARONE & THE THYROID.

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Issues

1. Amiodarone contains iodine (40% by weight)
2. Amiodarone is structurally similar to thyroid hormones
3. Amiodarone + metabolites cause toxic destruction to thyrorid cells

Effects

Wolff-Chaikoff effect → ↑ Iodide assoc. w/ treatment causes acute inhibition of T_4 & T_3 production in first 2 wks. Thyroid can "escape" @ 2 wks.

Amiodarone Induced Hypothyroidism → usually thyroid cannot "escape".

Amiodarone Induced Thyrotoxicosis → 2 mechanisms

Type 1 – Iodide load on abnormal thyroid ⇒ ↑ synthesis of hormones (not inhibited)
- Jod-Basdow phenomenon
- Graves opthalmopathy

Type 2 – Normal thyroid subject to destructive thyroiditis.
- Release of pre-formed hormone into blood.

Insulin actions at the tissues

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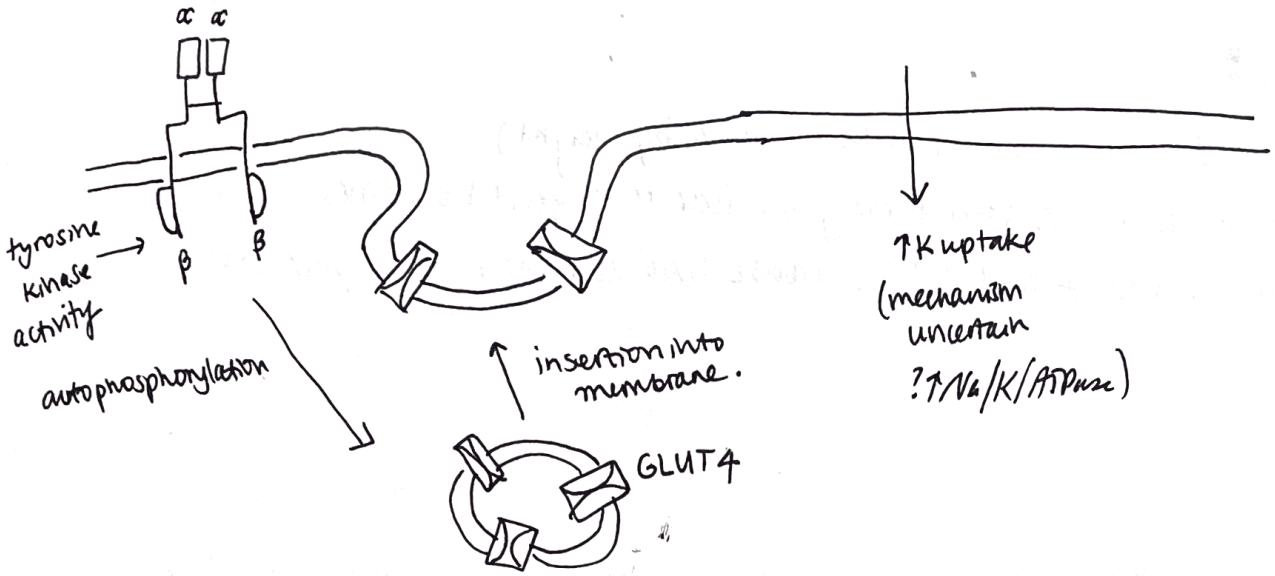

VIVA Q: what are the major factors determining plasma glucose levels? concept + 3 factors to pass.

A: CONCEPT → balance between glucose entering + leaving the plasma.

- dietary intake
- cellular use + uptake
- Hepatic → gluconeogenesis / glycogenolysis
- Renal resorption to max levels.
- Hormones — insulin / glucagon

Q: List the hormones which effect plasma glucose levels 3 to pass

↓ BSL via insulin = glucose uptake + glycogenesis + fat synthesis
IGF = similar but less

↑ BSL via catecholamines = ↑cAMP → glycogenolysis, gluconeogenesis
Glucagon = ↑cAMP as above
T4T3 = ↑ liver synth
cortisol = permissive to glucagon
GH = blocks insulin, ↓ tissue uptake.

Q: What are the pathways for glucose metabolism?

- aerobic
- anaerobic
- glycogen synthesis
- pentose pathways.

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3. Describe the physiology of insulin effects on adipose/muscle/liver
   Half life of insulin is 5 minutes in circulation – binds to receptors, internalised

Adipose
- Increased glucose entry
- Increased fatty acid synthesis
- Increased glycerol phosphate synthesis
- Increased triglyceride deposition
- Activation of lipoprotein lipase
- Inhibition of hormone sensitive lipase
- Increased K uptake

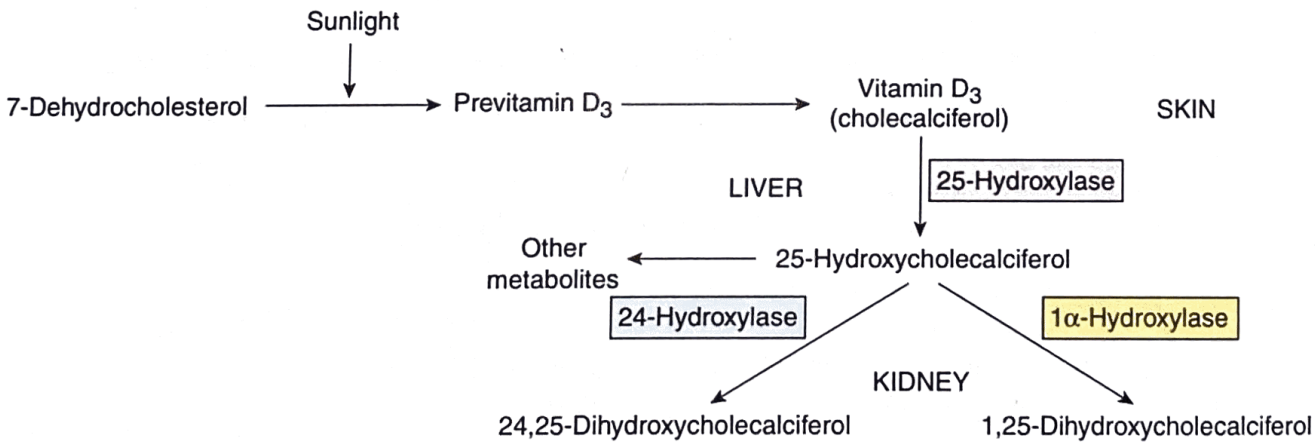
Muscle
- Increased
  - Glucose entry
  - Glycogen synthesis
  - Amino acid uptake
  - Protein synthesis in ribosomes
  - Ketone uptake
  - K uptake
- Decreased protein catabolism
- Release of gluconeogenic amino acids

Liver
- Decreased ketogenesis
- Increased protein synthesis
- Increased lipid synthesis
- Decreased glucose output from decrease in gluconeogenesis, increased glycogen synthesis and increased glycolysis

VIVA Q: What are ketone bodies? How are they produced & metabolized?
→ Acetoacetate, β-hydroxybutarate, acetone
substrate → acetyl CoA & fatty acids
site → mitochondria
citric acid cycle → oxidation of fatty acids
Liver metabolism, excreted in urine + breath.
Tissue metabolism; $CO_2 + H_2O$.

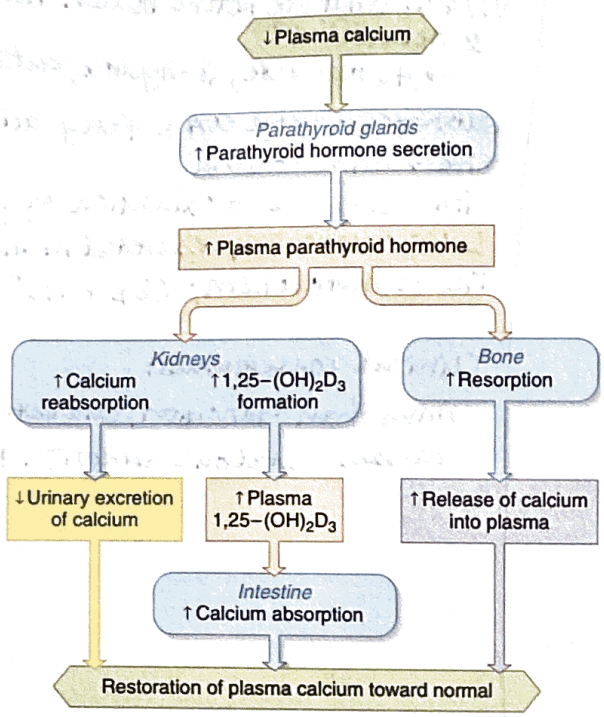
Clinical consequences:
Arises from starvation, diabetes, ETOH.
causes metabolic acidosis. Nausea.

4. Describe how calcium homeostasis is achieved – on paper
5. Role of vitamin D



1,25 dihydroxycholecalciferol (1,25-(OH)2D3 also made in placenta, skin keratinocytes and macrophages.
Stimulates expression of gene products involved in calcium transport and handling
Receptor is a transcription regulator in bound form e.g. Calbindin-D
Causes increased absorption from small intestine
Increased synthetic activity of osteoblasts (and therefore also osteoclasts)
Necessary for normal calcification of matrix (i.e. deficiency causes rickets)
Regulated somewhat by calcium and phosphate levels ie hen hyperglycaemic, less potent form is produced by kidneys

6. What are the bodies responses to hypocalcaemia/hypercalcaemia
Hypocalcaemia



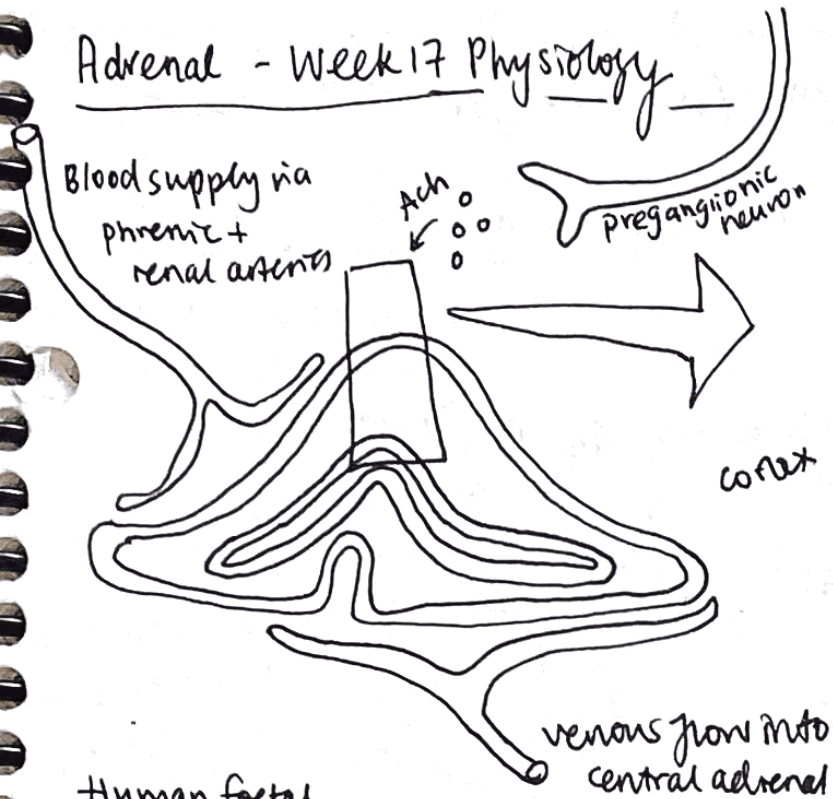
Hypercalcaemia
Mild – asymptomatic

7. Calcitonin
Calcium lowering hormone from parafollicular cells in the thyroid called clear cells or C cells
Secreted in response to higher plasma calcium levels
Also stimulated by heaps of other hormones ESPECIALLY gastrin i.e. really high in Zollinger Ellison syndrome and pernicious anaemia
Receptors in bone and kidneys
Lowers phosphate too
Inhibits the action of osteoclasts
Potentially important in young person development and prevents bone troubles in pregnant women

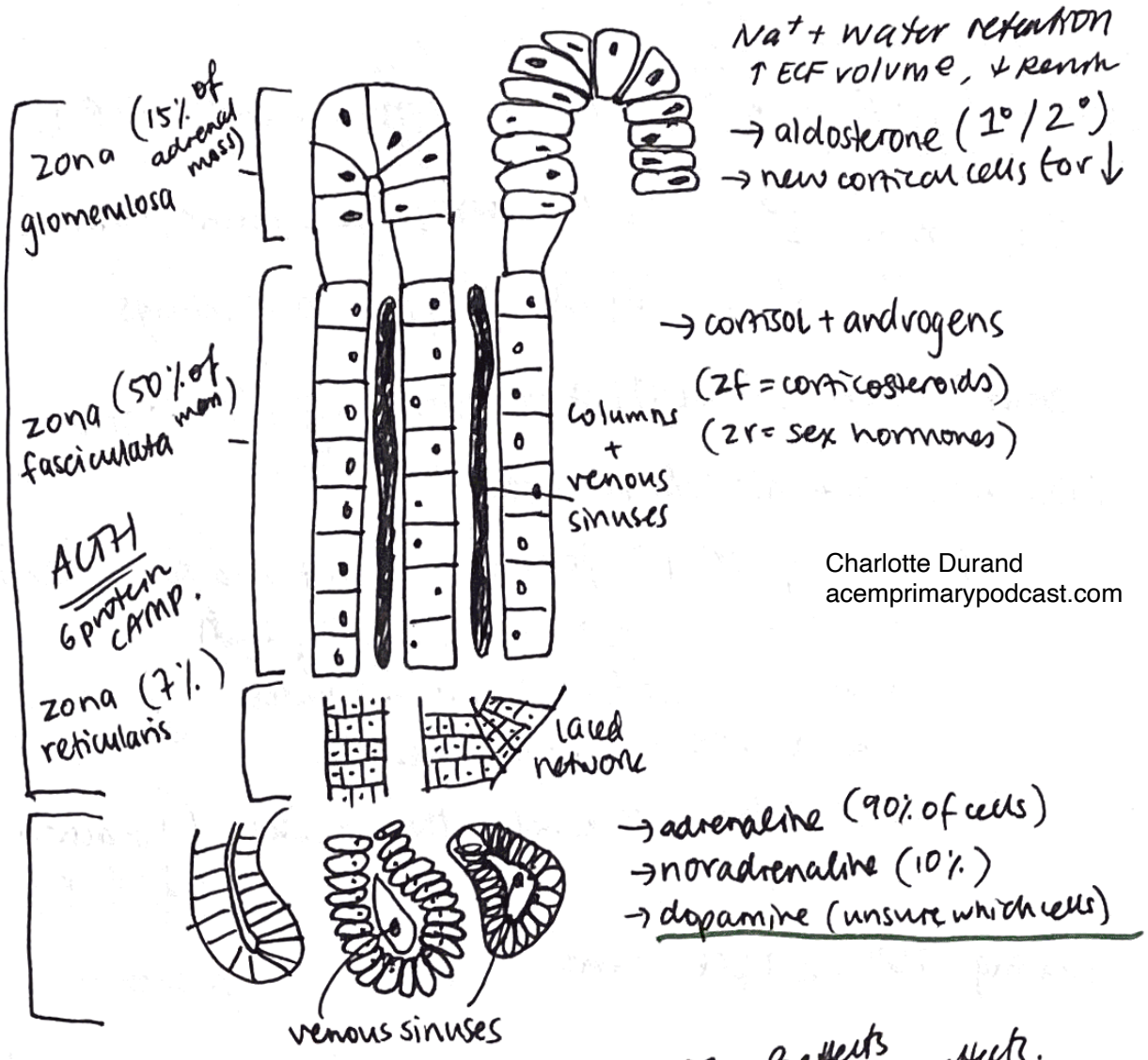
8. A note on hypocalcaemic tetany with hyperventilation
Calcium bound by plasma proteins
When a patient hyperventilates = blows off CO2 = higher plasma pH (resp alkalosis)
Higher pH = more ionized plasma proteins = more anions to bind with Calcium

9. Hypercalcaemia associated with malignancy
20% of hypercalcaemic pts with cancer have bone mets
Erosion of bone via prostaglandins from tumour = release of calcium
Humoral hypercalcaemia of malignancy happens through PTHrP

Adrenal - Week 17 Physiology



Human foetal adrenals = v. different
secretes some androgens that Δ to oestrogen by placenta.



Na^+ + water retention
↑ ECF volume, ↓ renin
→ aldosterone (1°/2°)
→ new cortical cells for ↓

→ cortisol + androgens
(zf = corticosteroids)
(zr = sex hormones)

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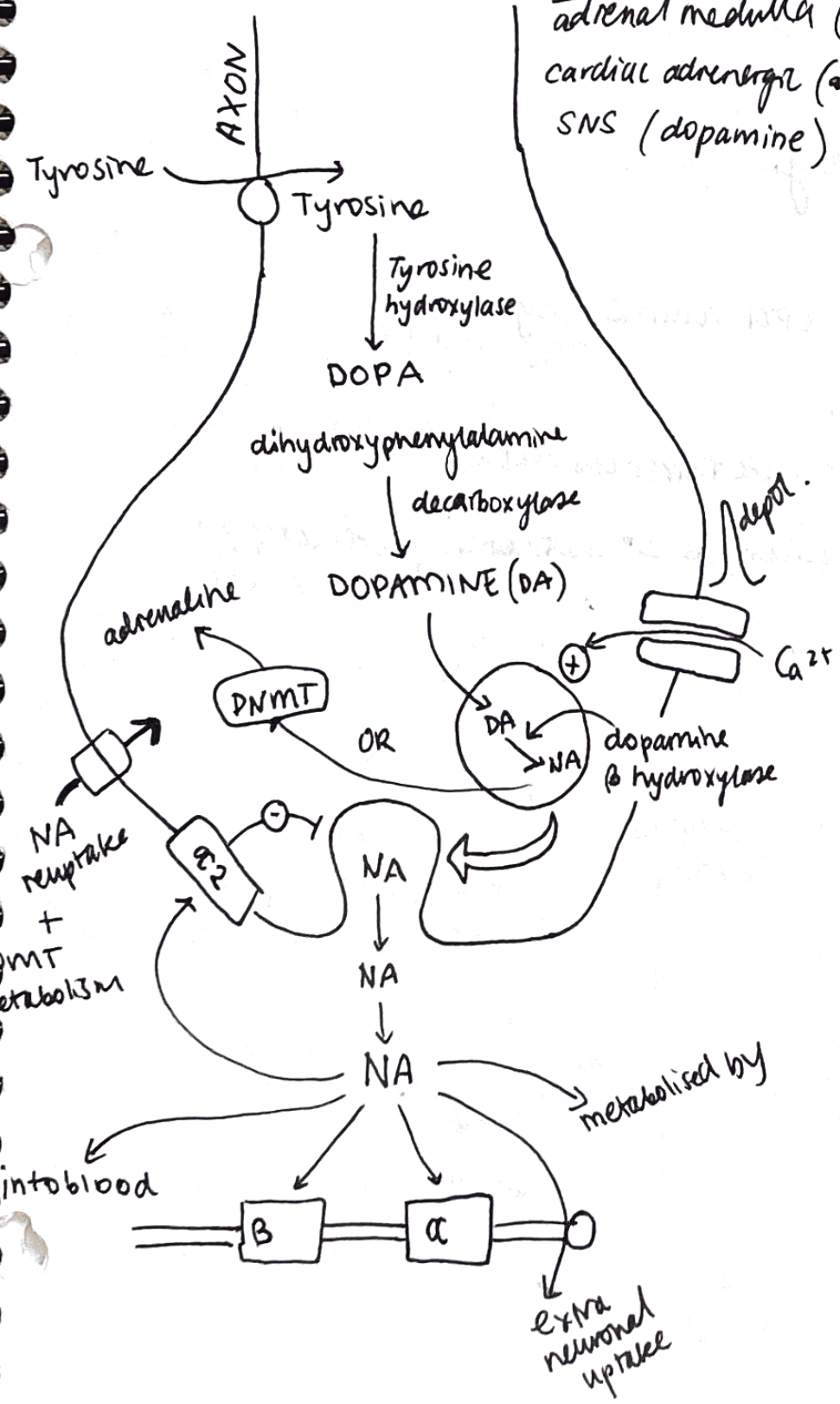
→ adrenaline (90% of cells)
→ noradrenaline (10%)
→ dopamine (unsure which cells)

Synthesis of catecholamines



SITES
adrenal medulla (Dop/NA/Adren)
cardiac adrenergic (adrenaline)
SNS (dopamine)

Adrenaline / Noradrenaline

low [] = β effects
↑ [] = alpha effects.

Metabolic: glycogenolysis
↑ metabolic rate
mobilisation of FFA's
↑ lactic acid.

CVS: Vasoconstriction + dilation
↑ HR ↑ strength.

α1: constriction (NORAD)
α2: mixed SMC effects (AD)
β1: ♡ inotropy ↑ chronotropy, irritability
β2: Dilation of SMC (airway), liver + muscle vessel dilatation.
β3: lipolysis, detrusor relaxation.

↑ alertness

differences:

- BP
- HR
- CO
- TPR

Aldosterone ⟹ Na^+ + H_2O retention, expanded ECF & shuts off stimulus for renin release.

↑ secretion: 1° → stress hormone, low pressure/volume via hormone mech's.

2° → CCF, cirrhosis, nephrosis, drugs

Stimulation = ① ACTH from pituitary / ② renin from kidney via Ang II / ③ ↑ K^+

MOA: ~~reabsorbtion~~ mineralocorticoid

↑ Na^+ resorption (2° from kidney but also saliva + colon)

→ acts on principal cells of collecting ducts

→ Na exchange for K^+ & H^+ in tubules

→ K^+ diuresis & ↓pH of urine

→ 10–30mins to develop then peaks (1st action via ↑ insertion of ENAC; 2nd via ↑ synthesis of ENAC)

causing ↑BP via ↑ECF volume

Mechanism of thirst

Under control of osmoreceptors in anterior pituitary

Sense osmolality of body fluids.

Water intake ↑ by: ↑plasma osmotic pressure, ↓ECF volume, psychology

↓ECF volume → drinking mediated by RAAS.

~~Renin act~~ AT II acts on diencephalon to stimulate thirst centres

High protein diet = thirsty b/c of renal osmotic diuresis 2° metabolic products.

Week 17 Physiology – Calcium Homeostasis

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NORMAL VALUES

Young adult = 1100g of calcium (99% in skeleton)

Diet ≈25mmol

Total body phosphorus 500 – 800g

HYPOPARATHYROIDISM

↓ in Ca^{2+} = net excitatory effect on muscles i.e tetany & ↑ excitability

↑PO_4 = ↓Ca^{2+} = negative feedback

Thyroid & parathyroid

posterior thyroid

superior poles

inferior poles

Note on MAGNESIUM

Req'd for normal PTH secretory response.

Impaired PTH release can cause ↓Ca^{2+} seen in Mg^{2+} deficiency.

↓Ca^{2+}

↑PO_4 = ↑ PTH due to binding Ca^{2+} = ↓Ca^{2+}

calcitonin

t½ 10–30mins

Inhibits bone resorption

(from chief cells)

Parathyroid hormone (PTH)

t½ 10mins

Feedback:

Membrane Ca^{2+} receptor + G protein

$1,25(OH)_2D_3$ ↓ preproPTH mRNA

Mg^{2+} req'd for PTH secretion

cleaved into fragments by Kupffer cells

cleared by kidneys.

↑resorption + mobilisation

↑PO_4

↑Ca^{2+}

↓PO_4

25 OH_2CC

(N) = 0.03mg/mL

(from vit-D)

1, 25 - Dihydroxycholecalciferol (calcitriol)

to blood plasma

mobilises calcium from bone

500mmol/day in & out

Bone

Exchangeable zone

100mmol

Ca^{2+}

Ca^{2+}

Phosphorus absorbed in gut - duodenum & small intestine

Vit D ⊕ ↑blasts action

PTH binds to osteoblasts NOT clasts

Bone remodelling via resorption + deposition

moves only 7.5mmol/day

Stable 27,200 mmol

↑urinary phosphate excretion

Kidney

regulates ↑Ca^{2+} absorption from intestine via TRPV6

Intestine

absorbed by ⊕ intracellular Calbindin-D

as Ca^{2+} ↑ this inhibits 1,25-dhcc.

~3mg

Phosphorus also held in bone...

85–90% in the skeleton!

vit D ⊕ ↑resorption

↓excretion

Plasma Ca^{2+} filtered by kidneys

99% reabsorbed

urine 2.5mmol

Phosphorus filtered by kidney & 85–90% reabsorbed by Na^+ dependent active transport

Absorbs 15mmol

Secretes 12.5mmol

Glucocorticoids ↓Ca^{2+} by inhibiting osteoclast action + formation.

oestrogens inhibit action of cytokines on osteoclasts.

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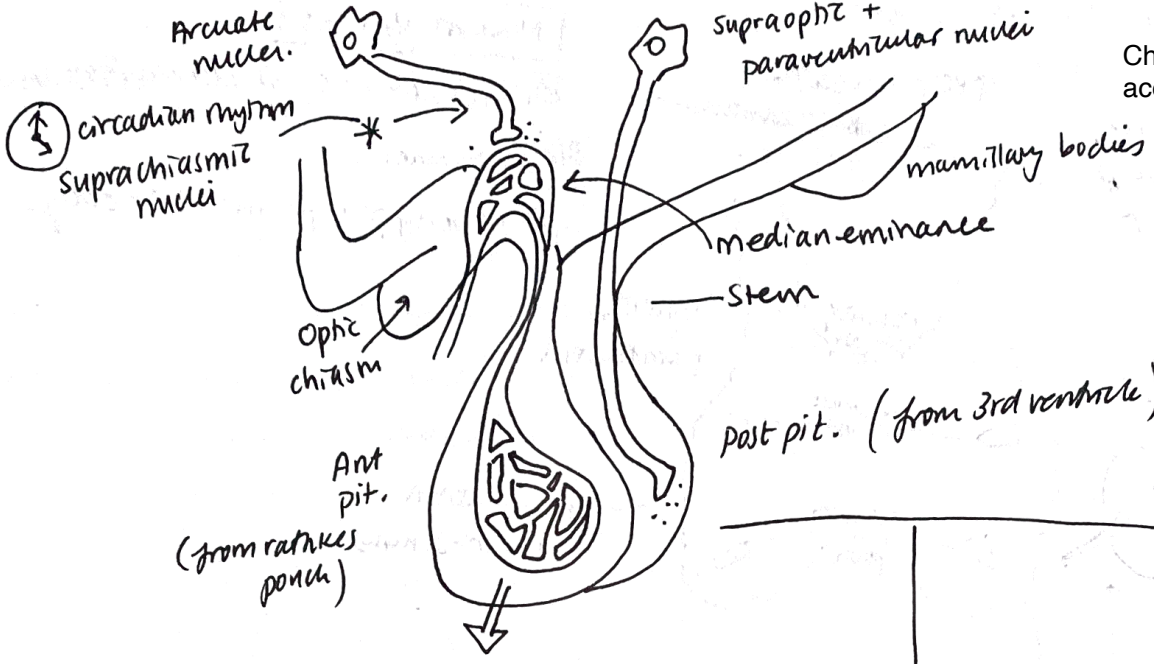

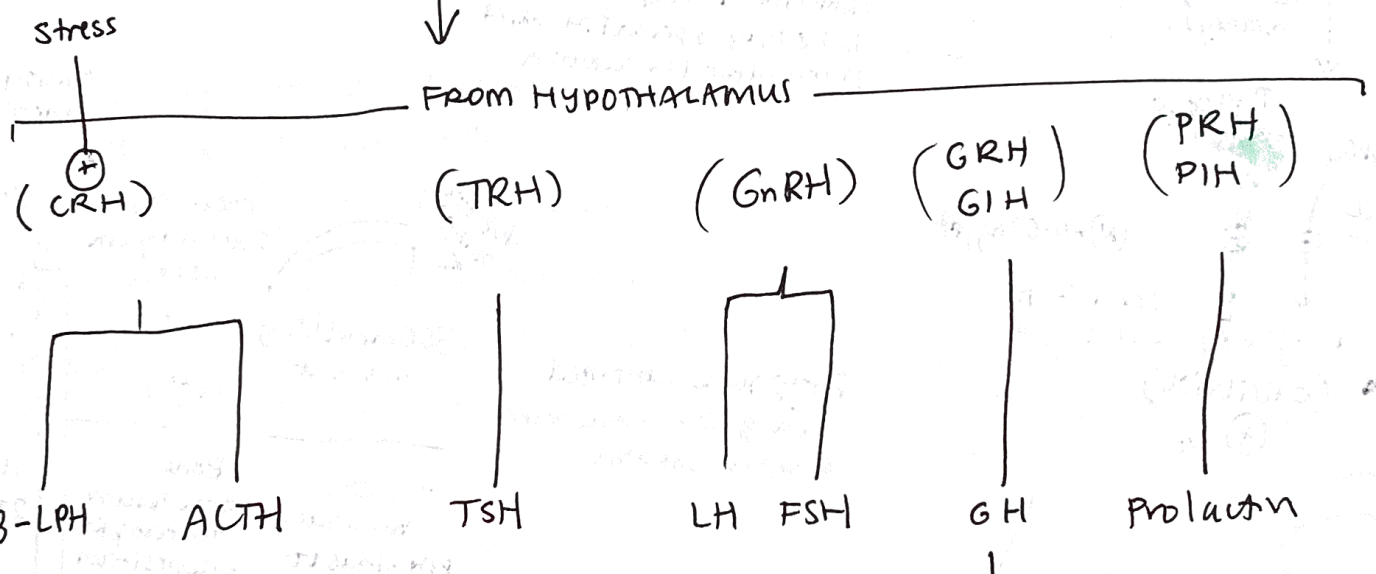

VIVA Q: What are the clinical effects of anterior pituitary insufficiency.

IGF-1

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Glucocorticoids

What are the physiological effects?

VASCULAR: permissive effect on catecholamines → pressor response.

METABOLIC: ↑BGL via gluconeogenesis + glycogenolysis.
Lipolysis + FFA mobilisation
Free water excretion

IMMUNE: ↓ inflammation, ↓ allergic response, ↓ lymphocyte activity

HAEM: ↑ PLT, ↑ RBCs, ↑ Neutrophils

CNS: Irritability, EEG slowing, inability to concentrate.

How is secretion regulated?

- Basal secretion + stress response both depend on ACTH
- Free glucocorticoids negatively feedback @ pituitary + hypothalamus level.
  Via effect on DNA.
- Circadian rhythm important. ~75% of cortisol in the morning.