LO1 Hormones & Signaling

GPCRs: heterotrimeric, α subunit has GTPase activity

Gαs: FSH, LH, ACTH, TSH, CRH, hCG, ADH(V_2), MSH, PTH
→ GTP bound Gαs → Adenylyl cyclase → cAMP is made → activates PKA → activates phosphorylase kinase

Gαq: GnRH, Oxytocin, ADH(V_1), TRH, Histamine, Ang II, Gastrin
→ Gαq → phospholipase C → cleaves PIP_2
PIP_2 → DAG (hydrophobic) = docking site PKC
TQ → IP_3 → binds ligand-gated Ca^{2+} channel receptor

★ IP_3, DAG, & Ca^{2+} = 2nd messengers

GPCR desensitization:
TQ
→ GRK phosphorylates receptor
→ arrestin binds to phosphorylated site
→ phosphatase removes arrestin

★ **Disorder of GPCR signaling:**
TQ ★ Pseudohypoparathyroidism type I (PHP-1a): ↑PTH, ↓Ca^{2+}
→ dz caused by maternal imprinting of gene encoding Gα = GNAS gene
can produce signaling hormone
defective Gαs ∴ PTH doesn't work

RTK

★ RTK pathways require dimerization (activates kinase function)

★ RAS-MAPK Pathway → GTP → Ras → Raf → MEK → ERK → kinases → changes protein & gene expression

★ PI-3 Kinase Pathway → protein synth & cell growth
1. insulin binds, receptor phosphorylates itself (dimerizes) = dock for IRS
2. IRS binds PI-3 kinase
3. PI3-K phosphorylates PIP_2 (P) → PIP_3
4. PIP_3 = dock for PDK1 & PKB (P)
5. PKB (P) increases GLUT4 expression = ↑glucose uptake & glycogen synthesis

RTK: IGF-1 & insulin can activate each others receptors when in excess

TGFβ = same as RTK except they phosphorylate serines & threonines instead of tyrosine

GUANYLYL CYCLASE → ANP/BNP; EDRF; NO
→ smooth muscle RELAXATION
→ GTP → cGMP activates PKG; which phosphorylates PLN
TQ → phosphorylated PLN cannot inhibit SERCA
∴ SERCA puts Ca^{2+} back to ER → ∅ calcium = Relaxation

TNF Receptors → RANK binding to RANKL → IKK phosphorylates inhibitor (IK-B) → frees NFκB to go to nucleus

TQ → when ↓Ca^{2+}, PTH binds to osteoBLASTS → which release RANK-L
RANK-L binds to RANK on osteoCLASTS → breakdown bone to ↑Ca^{2+}

STEROID HORMONE SIGNALING: cytoplasmic (intracellular) receptors
- glucocorticoid, mineralocorticoid, androgens, progesterone
→ translocates to nucleus, binds HREs & modifies gene expression

THYROID HORMONE SIGNALING: receptor is IN THE NUCLEUS !!!
★ includes estrogen receptor
HDAC → T_3 binds → HAC → transcription

TQ

LO2 immuno

Concepts	Learning Objectives	
1 Self-reactive B and T cells are generated in the bone marrow and thymus but can be eliminated by the processes of central tolerance (B and T cell strong binding of BCR and TCR, respectively, to self-Ag) and peripheral tolerance (anergy, deletion, regulation by Treg cells). *central tolerance: strong binding = apoptosis! *peripheral tolerance: anergy, deletion, Tregs	1 – Recognize the cells responsible for presenting self-Ag in the thymus to T cells. What gene/protein permits this to occur in the thymus? What signal outcome dictates where the T cell lives or dies during negative selection? (DCs; T cell: weak binding = LIVES)	6
	2 – Identify the outcome of BCR signaling that leads to survival, anergy or deletion. What happens to self-reactive B cells that are rendered anergic? (strong = death; weak = anergy; none = survival) → follicular exclusion (stay in lymph node)	7-8, 11
2 Self-reactive T cells can escape central tolerance and are controlled in the lymphoid organs and peripheral tissues by anergy (DC providing signal 1 and inhibitory molecules expressed on the T cell surface, CTLA-4 and PD-1), Treg cells ($CD4^+$ $CD25^+$ $Foxp3^+$ T cells that inhibit DC Ag presentation, T cell activation, NK and B cell functions through cell contact) and deletion (lack of costimulation/cytokines to induce Bcl-2 proteins to block apoptosis and/or Fas ligand-mediated induction of apoptosis).	1 – Identify the required signals for T cell activation (signals 1-3) and define the outcome of T cell activation if any particular signal is absent. What is DC maturation and how does it contribute to T cell activation? (DC need microbial exposure for maturation → bind TLRs; 1. Ag px 2. B7 = DC 3. cytokines; all 3 signals elicits T-cell response!)	13-15, 17-19
	2 – Distinguish between anergy, Treg regulation and deletion mechanisms of peripheral tolerance of T cells.	22-25
	3 – Recognize the steps that must occur in order for an immune response to successfully generate organ-specific damage and autoimmunity.	28-33
3 The major immune-mediated endocrine disorders are type 1 diabetes ($CD4^+$ and $CD8^+$ T cell destruction of pancreatic beta cells), Hashimoto's thyroiditis (antibody-mediated destruction of thyrocytes, ↓ thyroid hormones), Graves' disease (antibody-mediated stimulation of TSH receptor, ↑ thyroid hormones, ophthalmopathy), Addison's disease (antibody-mediated destruction of adrenal cortical cells, ↓ cortisol) and autoimmune polyendocrine syndromes (AIRE-deficient, HLA-associated and Foxp3 mutants).	1 – Recognize the key symptoms and underlying immune-mediated mechanisms associated with type 1 diabetes, Hashimoto's thyroiditis, Graves' disease, Addison's disease and APS. What type of hypersensitivity reactions are apparent in each?	36-47
	2 – Identify the genetic anomaly that is associated with the development and progression of disease in each, when noted in the discussion.	36, 38, 41, 44, 47
	3 – Identify the targets (cells, proteins, pathways) of antibodies and effector cells and how disruption by these immune responses lead to a diseased state in each of the disorders listed. What is the role of AIRE, HLA and Foxp3 in the different APS?	36, 38-45, 47

T cell Central Tolerance
$CD4^+$ & $CD8^+$ T cells are tested in the thymus for self rxtivity w/ MTECs & DCs
- TCR binds self Ag w/ high or no affinity → APOPTOSIS
- TCR binds self Ag w/ weak affinity → survive & leave

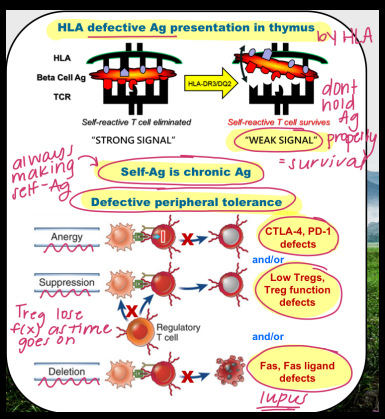
B cell Central Tolerance
- strong BCR-Ag → APOPTOSIS
- weak BCR-Ag → anergy → follicular exclusion
- Ø BCR-Ag → survival

T cell activation
1. Ag Presentation
2. B7 (CD80/86) on DC binds CD28 on T cell
3. cytokine release = differentiation

if signals 2 & 3 are absent
- (means there was no infection)
- self-Ag px = T-cell anergy

DC maturation requires microbial Ag

if that Ag was self Ag, you'd activate anergic T cells against host tissue/proteins = BAD



Peripheral Tolerance:
1. Anergy: if T cell is chronically engaging self-Ag, CTLA4 & PD1 downregulate CD80/86 on DC
2. Treg: activated by self-Ag
   - require TGFβ, IL2 via FOXP3
   - produce cytokines to turn off immune resp. (IL-10 & TGFβ)
3. deletion: Fas - FasL signal (IL-2 driven) → caspases!

In order for autoimmunity to occur:
- HLA defective → weak signal → T cells survive
- self Ag = chronic
- defective peripheral tolerance
  - CTLA/PD1 defects
  - ↓Tregs
  - Fas/FasL defect

T1D: type IV hypersensitivity
- beta cells destroyed, viral trigger (COXB)
- ↓Tregs ** defective CTLA4, chronic self-Ag, & defective HLA
  - IL6 suppresses Tregs

direct damage → Th17 cells ↑inflammation → Th1 cells ↑IL2

Hashimoto's type II hypersensitivity (CD40L rescues anergic B-cells so they can make antibodies)
- dx by autoantibodies (IgG - anergic B cells)
- killing via CTL → Fas, perforin, granzyme
- Th1 cytokines → IFN-γ & TNFα

Graves type II hypersensitivity
- NO cellular damage to thyroid!
- ↓TSH levels
- anti-TSHR IgG via Th2 response → IL-4

Addison's type III hypersensitivity
- autoantibodies against 21α hydroxylase
- MSH↑ ∴ skin darkens

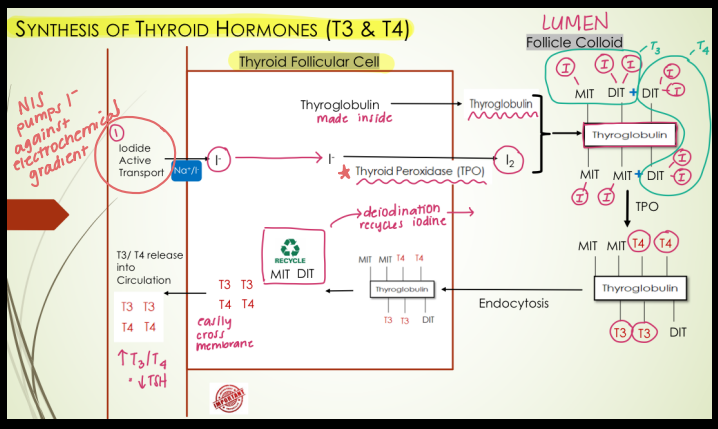
TQ

Feature	APS I	APS II	APS III (IPEX)
Age of diagnosis	Infants (rare)	Primarily adults (~20 per million pop.)	Newborn (rare)
Genes involved	Mutations of AIRE	HLA-DR3/DR4 associations	Mutations of FOXP3 (50% of cases)
Disease manifestations	• Mucocutaneous candidiasis • Hypoparathyroidism • Addison's disease HAM	• Addison's disease • Type 1 diabetes • Autoimmune thyroiditis TAT	• Enteropathy (severe diarrhea) • Dermatitis • Type 1 diabetes • Autoimmune thyroiditis • Autoimmune anemia, hepatitis, nephritis

AIRE = autoimmune regulator
IPEX = Immune dysregulation, enteropathy, polyendocrinopathy, X-linked syndrome (also APS III)

PDD

L03/04 Thyroid Disorders



- ★ TSH: β subunit = biologic specificity (same α as TSH & LH)
- ★ TSH receptor: G_{as} → cAMP
- ★ thyroid hormone: T_3 more active, T_4 more abundant
  - regulated by hypothalamus - ant. pituitary
- ★ TPO: ① iodine oxidation ② binding TG ③ coupling thyrosyl residues
- ★ transport of thyroid hormones: thyroxine-binding globulin (TBG)
  - ↓TBG: testosterone, liver failure
  - ↑TBG: estrogen (pregnancy)

★ Iodine deficiency:
① ↓thyroid hormone synth.
② ↑MIT : DIT
③ ↑TSH

Iodine excess
① blocks NIS, thyroid hormone release
→ dysfunction

★ T_3 ↑basal metabolic rate by ↑Na^+/K^+ ATPase (explains why hypothyroid = hypoventilation)
∴ ↑ tissue oxygen consumption → increases 2,3-DPG → ↑ventilation

↑C.O. by upregulating β₁ adrenergic receptors of heart

↑bone growth, synergy w/ GH ; ↓brain development → Øthyroid hormone prenatally = Cretinism

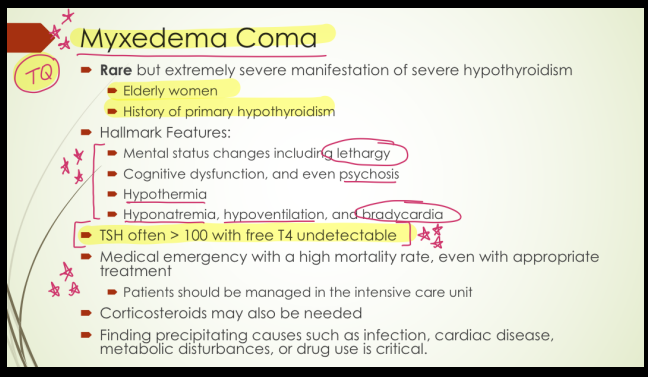
Repro f(x):
- ↓thyroid hormone = delayed puberty, anovulation, & infertility
- ↑hyperthyroidism = ↑aromatization of androgens → gynecomastia

Table 9-8 Factors Affecting Thyroid Hormone Secretion

Stimulatory Factors	Inhibitory Factors
TSH	I^- deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I^- intake (Wolff-Chaikoff effect)
	Perchlorate; thiocyanate (inhibit Na^+-I^- cotransport)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

TQ ★ Pt px w/ suspected thyroid dysfunction → GET TSH LEVEL → esp. 1° hypothyroidism → like hashimoto
most useful single screening test for hyperthyroidism
- ↑TSH: 1° hypothyroid or 2° hyperthyroid
- ↓TSH: 1° hyperthyroid or pituitary hypofunction

T_3 levels = suspected HYPERthyroidism; Øaccurate for hypo



TQ ★ 75 yo female w/ Hx of Hashimoto's has lethargy, hyponatremia, HR: 45, temp: 96.5°F
Dx: MYXEDEMA COMA

HYPERTHYROID

- heat intol., weight loss, tachycardia/AFib, hyperreflexia (1st sx in elderly)
- ★ thyroid storm: emergency
  → tach (>140), delirium, fever (104°-106°)
  "pt w/ grave's dz underwent hip replacement (stress)" = ↑response to catecholamines
- MC ★ Graves: IgG that activates TSH receptor (TQ)
  ↓TSH ; ↑T_3/T_4
  exophthalmos & goiter
  → ↑retroorbital C.T. & adipose bc ↑GAGs → Δ osmotic pressure
- ★ Toxic multinodular goiter/adenoma → secretes thyroxine
  insidious onset
- ★ Early thyroiditis (starts hyper → hypo)
  follows viral illness / pregnancy
- ★ Radioiodine uptake thyroid scan:
  → High uptake of radioidine → Graves, toxic multinodular adenoma bc indicates de novo synth. of T_3/T_4
  → Low uptake → preformed T_3/T_4 causing hyperthyroidism (damage to thyroid or exogenous)

PHARM of HYPOTHYROID

★ LEVOTHYROXINE (synthetic T_4)

→ SE: nervousness, heat intol., palpitations → start LOW & go SLOW!

PHARM of HYPERTHYROID

- ★ Methimazole → inhibit TPO → can be used 2nd/3rd trimester
- PTU → inhibit TPO AND inhibit peripheral conversion $T_4 \rightarrow T_3$ → can use 1st trimester
  - → SE: AGRANULOCYTOSIS (fatal)
- ★ Potassium iodide → overwhelms symporter (Wolff-Chaikoff)
  - ↓thyroid size & vascularity before surgery
  - Ø pregnancy
- ★ RAI → destroy follicular cells
  - tx thyrotoxicosis
- ★ thiocyanate/perchlorate → competitive inhibitors of NIS
  - SE: aplastic anemia
- ★ BETA BLOCKERS: PROPRANOLOL → inhibits $T_4 - T_3$ peripheral conversion & control tachycardia (Amiodorone & glucocorticoids also do this)
- ★ Aspirin/NSAIDs: ↓TBG binding = ↑free T_3/T_4 ∴ Ø given in thyrotoxicosis
- ★ Amiodorone: causes hyperthyroid: iodine concentration or hypothyroid: blocks $T_4 - T_3$ peripheral conversion

LO5 Pituitary Axis

Hypothalamus → regulates ANS & Limbic system

★ HPA connects autonomic, nervous, & endocrine systems via NEUROENDOCRINE CELLS (functional link = median eminence between hypothalamus & pituitary)

★ ANATOMY: pituitary gland connected to hypothal via infundibulum

- ★ sella turcica of sphenoid
- ★ CN, optic nerve, ICA, & cavernous sinus

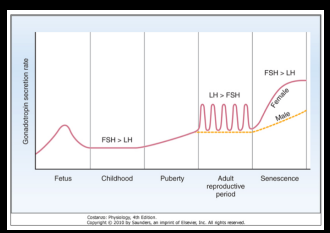
→ CLINICAL CORRELATE: traumatic head injury

Triphasic Response → @posterior pituit. bc it relies on axon transport (?)

1. ØADH (DI)
2. ↑↑ADH (SIADH)
3. ↓ADH (DI)

2 parts:

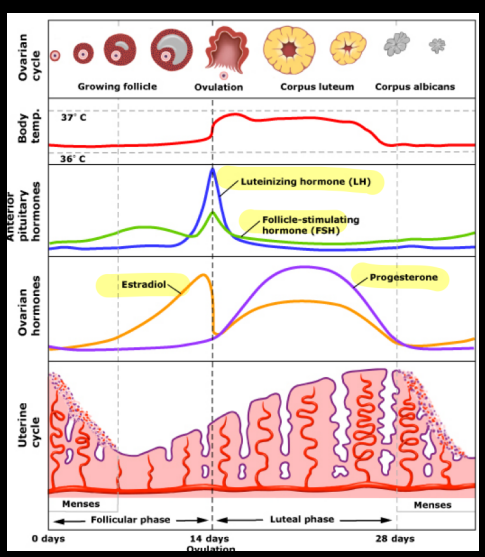
- anterior pit: derived from pharynx (endocrine tissue)
- posterior pit: from neuroectoderm (neuroendocrine tissue)



HORMONE FAMILIES:

1. TSH, LH, TSH → same α subunit, different β ("β = Biologically specific") [also HCG]
2. ACTH & MSH → derived from POMC
3. GH & PRL → direct organ action, Ø messengers
   - ★ dopamine inhibits prolactin! → antipsychotic = ↓dopamine = ↑prolactin
   - ★ TRH stimulates prolactin → 1° Hypothyroid = ↑prolactin = ↓GnRH = ↓TSH & LH = infertility
   - ★ prolactin inhibits GnRH → Ø ovulation

galactorrhea & infertility → tx prolactinoma w/ dopamine agonist = BROMOCRIPTINE ★★



GnRH → FSH (low freq) & LH (high freq) → determines onset of puberty

★ PULSATILE

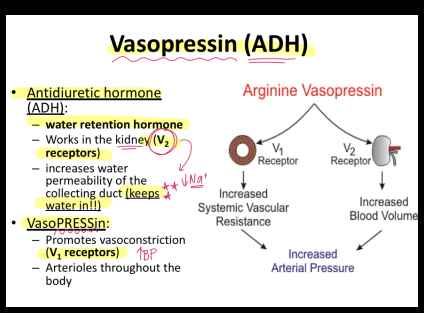
- ⊕ feedback: mid-cycle to promote LH surge
- ⊖ feedback: women = estrogen & progesterone reg. men = testosterone by inhibin

IN MEN:

- ★ LH = Leydig cells produce testosterone
- ★ FSH = Sertoli cells produce SPERM

POSTERIOR PITUITARY → oxytocin & ADH

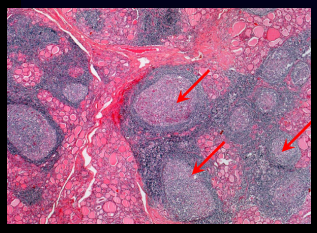
- oxytocin → milk ejection
- ADH → increase BP by retaining H_2O & vasoconstrict

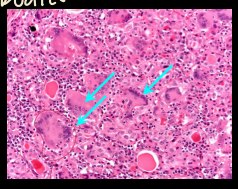


LOU 107 THYROID GLAND PATHOLOGY

HYPOTHYROID

- ★ Cretinism: hypothyroid baby → skeletal & brain development problems
  - → short stature, umbilical hernia, protruding tongue
- TQ ★ Hashimoto Thyroiditis
  - → anti-TPO or anti-Thyroglobulin
  - ★ Destruction → lymphocytic infiltrate & large, active germinal centers
    - → $CD8^+$ cytotoxic T-cell mediated
  - ★ HLA DR3 & DR5
  - ★ Painless
- TQ ★ Granulomatous Thyroiditis = PAINFUL — trigger: - viral infx
  - Early = HYPER; Later = HYPO + antithyroid antibodies
  - ★ multinucleated giant cells



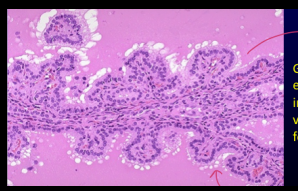


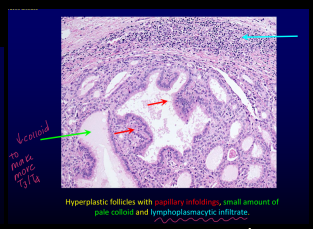
★ Hypothyroidism

- Deficiency of thyroid hormone
- Structural or functional derangement that reduces thyroid hormone production
- Symptoms: Fatigue; loss of energy, lethargy; weight gain; decreased appetite; cold intolerance; dry skin; hair loss; sleepiness; depression, etc — dry skin, hair loss, depression
- Signs: Slowed speech and movements; nonpitting edema (myxedema), brittle, straw-like hair; periorbital puffiness; macroglossia; goiter (simple or nodular); etc
- Elevated TSH, low T_4, or FTI (if normal free T_4 or FTI, mild or subclinical) — ↓T_3/T_4, ↑TSH
- Thyroid hormone replacement (Levothyroxine)

HYPERTHYROID

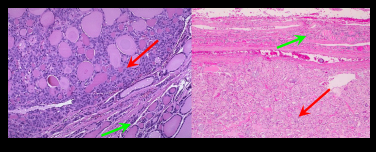
- ★ multinodular goiter - repeated hyperplasia & degeneration
  - usually normal T_3/T_4; thyroglobulin may ↑
  - ★ irregularly enlarged follicles
  - Ex: TOXIC multinodular goiter = Plummer syndrome
    - → somatic mutations of TSH R
- ★ Subacute lymphocytic (painless) thyroiditis
  - = transient HYPERthyroidism; ↑T_3 & T_4; resolves itself
- ★ Thyrotoxicosis = hypermetabolic state
  - ↑T_3 & T_4 (preformed); ↓TSH
  - can be caused by: ① Graves ② Hyperfunctional multinodular goiter ③ Hyperfunctional thyroid adenoma
  - weight loss, ↑appetite; Afib, HTN
  - ★ star gazing & lid lag due to overstimulation of sympathetics
- ★ Thyroid storm = EMERGENCY
  - pt w/ thyrotoxicosis (esp. Graves) undergoes any stress or cessation of antithyroid meds
- ★ Apametic Hyperthyroidism
  - older pts w/ cardial complications/arrhythmias
  - can result in osteoporosis
  - ↑T_3 & T_4 ↓TSH
- ★ Graves Disease
  - TRIAD: ① diffuse thyroid enlargement
    - ② opthalmopathy → exopthalmos
    - ③ pretibial myxedema
  - TQ ↑T_3/T_4 ↓TSH
  - ★ HISTO: intact follicles, hyperplasia & hypertrophy of follicular cells, & pale colloid w/ scalloped margin
    - → increased VOLUME of extraocular muscles & retro-orbital CT; including adipocytes & ECM
      - + inflammation & T-cell infiltration





NEOPLASMS

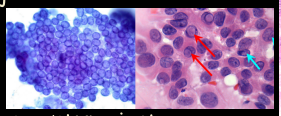
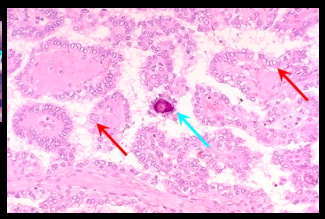
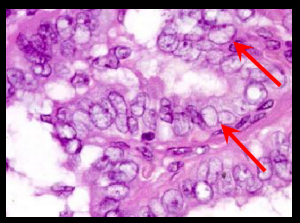
- ★ Adenomas: benign w/ follicular differentiation
  - Ø invasion, Ø nuclear fxs BUT need to submit entire capsule
  - ★ 20-50yr old women
  - ★ closely packed follicles → compress normal thyroid



- ★ Thyroid carcinoma

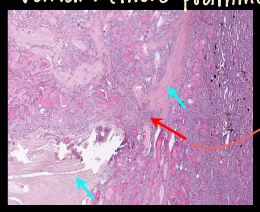
MC ① Papillary carcinoma RF: radiation & Hashimoto's

TQ
- RET, RAS, BRAF, NTRK1
- NUCLEAR FEATURES!
  - → overlapping nuclei, clear chromatin, intranuclear inclusions & longitudinal grooves
- ⊕thyroglobulin
  - → follicular variant, tall cell variant, & diffuse sclerosing variant (more psammoma)

⊕Psammoma Bodies

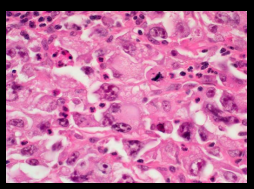
② Follicular Carcinoma RF: radiation & PTEN mutation
- PAX-8-PPARγ, PTEN, RAS/PI3K
- older women
- w/ capsular or vascular invasion
- ∅ nuclear elements



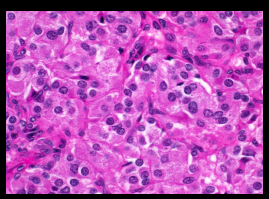
→ busted through collagen capsule = FOLLICULAR

③ Anaplastic (undifferentiated) carcinoma FATAL
- older people
- ⊕keratin & vimentin, p53 & PAX8
- ⊖thyroglobulin
- N-RAS & BRAF mutations

pleiomorphic w/ necrosis →



④ Medullary Carcinoma NEUROENDOCRINE from C cells
- MEN 2A/2B syndrome
- ⊕calcitonin & chromogranin A; ⊖thyroglobulin
- activating mutation on RET
- AMYLOID deposits! CONGO RED



→ "salt & pepper nuclei" = punctuate chromatin

L08 Hypothalamic & Pituitary Dysfunction

- Apply knowledge of function of pituitary hormones to diagnosis of hyper/hypo-secretion
- Recognize clinical presentation of syndromes of hormone hyper/hypo-secretion
- Discuss causes of syndromes of pituitary hormone hyper/hypo-secretion
- Apply knowledge of feedback mechanisms of H-P axis to serologic diagnosis of hormone hyper/hypo-secretion
- Recognize presentation and causes for diabetes insipidus
- Recognize features of SIADH

HYPOPITUITARISM

qIs 2° f secondary

- Invasive – space occupying lesions – macroadenoma, craniopharyngioma
- Infarction
  - Sheehan syndrome
    - Pituitary necrosis following postpartum vascular instability or hemorrhage
    - Hypotension and vasospasm in hypophysial arteries
    - Clinical features depend on extent of damage – need ≥ 75% destruction
    - Failure to lactate (severe), more insidious is menstrual irregularities
    - Can take years to diagnose

hypophysial arteries damaged = infarction (>75%)

  - Pituitary apoplexy = EMERGENCY
    - Hemorrhagic infarction of a pituitary tumor
    - Fulminant clinical syndrome – severe headache, visual impairment, visual issues, meningismus, altered level of consciousness
    - Can be fatal; treat with steroids and transsphenoidal sellar decompression

infarction of pituitary tumor

Blood in the brain = stroke that can't @pituitary

DIABETES INSIPIDUS (DI): DILUTE POLYURIA

- Increased fluid ingestion – primary polydipsia psych conditions
  - Mild serum osmolality decrease, large volume urine, eventually decreased response to ADH with decreased aquaporins (thus recovers shortly after polydipsia resolves)
- Decreased synthesis of ADH – central DI
  - Damage to neurons – tumor, trauma, surgery
  - Familial
  - Granulomatous disease or autoimmune inflammatory
  - DI (axonal shock)/SIADH (leaking of ADH)/DI (stress depletion) – brain trauma
  - Increased metabolism of ADH – effect of pregnancy osmostat and increased breakdown
- Decreased end-organ response – nephrogenic DI @kidneys! V2 doesn't work
- Diagnose with dehydration test → withhold water
- Imaging – MRI
- Treatment of central DI that can't keep up with water intake
  - DDAVP synthetic vasopressin
  - Treat underlying cause

ADH pee out all water

SIADH: SYNDROME OF INAPPROPRIATE ADH PRODUCTION

too much ADH

hold onto water

- Decreased plasma osmolality due to increase in water retention, and subsequent increase in sodium loss in urine excreting (sodium out @water
  - Hypo-osmolality doesn't stimulate lack of thirst efficiently, which leads to continued intake of fluids, making the process worse
- Inappropriate concentration of urine due to increase in ADH
  - Inappropriately normal or increased urine osmolality
- Clinical euvolemia
- Decreased serum sodium with increased sodium excretion HYPONATREMIA
  - Increased FeNA (fractional excretion of sodium)
- Treatment:
  - Find the underlying cause and treat it
  - Water restriction
  - If severe, treat with hypertonic saline to increase sodium
  - Vaptans – for euvolemic or hypervolemic hyponatremia due to SIADH, CHF, chirrhosis
    - V1a, V2 non-selective receptor antagonists - conivaptan
    - V2 selective receptor antagonists – tolvaptan

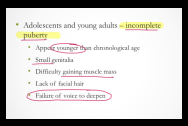
resolve hypo natremia

- Recognize clinical features of male hypogonadism in kids & adults
- Distinguish between primary and secondary hypogonadism
- Recommend treatment strategies/testosterone replacement for hypogonadism
- Discuss risks and benefits of testosterone replacement therapy

L09 Hypogonadism: def: ↓ in one or both of 2 major functions of testis: ① sperm production ② testosterone production

★ clinical features of male hypogonadism

★ KIDS

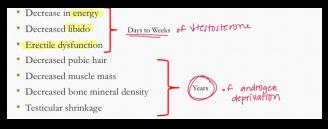


→ PE: Boys should be @least Tanner stage 1 by 14 y/o (TQ)

Hypogonad BEFORE puberty: leggy, small firm testes, gynecomastia

Hypogonad AFTER puberty: normal body, testes ↓size if 1°

★ ADULTS



1° Hypogonadism @testes ∴ ↑FSH & LH, LOW sperm count

- usually seminiferous tubule damage
- gynecomastia due to ↑aromatase

EX: Klinefelters (XXY) → firm / rubbery testes

Mumps

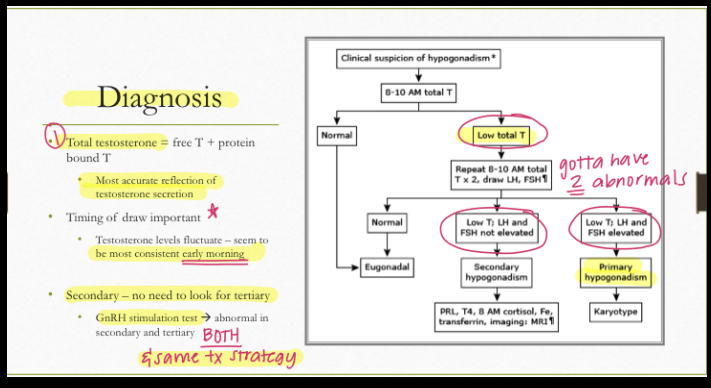
2° Hypogonadism @HPA ∴ ↓testosterone, ↓LH & FSH (or normal)

- testosterone & sperm count = proportionately low

EX: Kallmann syndrome → can't secrete GnRH; cleft lip; anosmia, cryptorchidism

Prader-Willi Syndrome → Paternal imprinting problem → delayed/incomplete puberty, infertility, cryptorchidism

Hemochromatosis
Sarcoidosis
Craniopharyngioma
→ Acquired



DIAGNOSIS

→ total testosterone → Early morning (8am) (TQ?)

if 2°: GnRH stimulation test

older men = more consistent throughout the day

TREATMENT

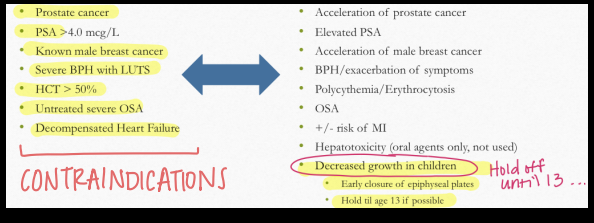
★ ONLY men who are hypogonadal

- testosterone DEFICIENT
- Ø sperm count alone

] Need SXS AND labs

→ IM testosterone w/ thick ass needle → recheck 2-3 mos → then 6-12 mos

RISKS / BENEFITS



BENEFITS →

- Development and maintenance of secondary sexual characteristics
- Increase libido
- Increased muscle strength
- Increased bone density
- Improvement in subclinical depression
- +/- cognitive benefits

L10 Path Pituitary, Hypothal, & Pineal Gland

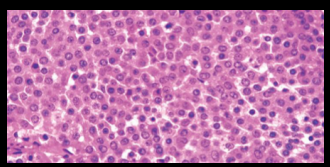
ANTERIOR PITUITARY

* transcription factors:
  - PIT1 : somato, lacto, thyrotrophs
  - SF-1 : gonadotrophs (&GATA2)
  - T-PIT : corticotrophs

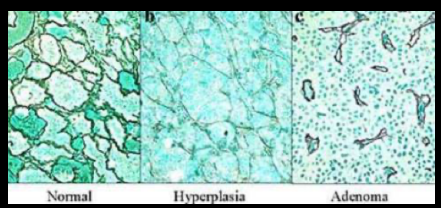
PITUITARY ADENOMAS

* Most common cause of hyperpit is pituitary adenoma

TYPES
1. Functioning : Hormone excess → Hyperpituitarism
2. Nonfunctioning
   - PX: Mass effects
     - erode through bone
     - * visual field defects → BITEMPORAL HEMIANOPSIA (TQ)
   - Hypopituitarism
     - compression → destruction of normal pituitary



* Histo: uniform, polygonal cells in SHEETS
* (TQ) NO RETICULIN MESHWORK (distinguishes from hyperplasia)



FUNCTIONING

PROLACTINOMA

* two types:
  1. ML sparsely granulated (chromophobic) w/ juxtanuclear PIT-1
  2. densely granulated (acidophilic) w/ cytoplasmic PIT-1

  → PIT-1, ER-α

* dystrophic calcification

DDx: lactotroph hyperplasia → w/ any interference in dopamine
- Ex: trauma, antidopaminergics, and ANY MASS in SUPRASELLAR COMPARTMENT

GROWTH HORMONE ADENOMA

* two types:
  1. densely granulated (acidophilic)
     - ⊕GH
  2. Sparsely granulated (chromophobic)
     - ⊕cytokeratin
* sausage fingers & cardiomegaly

Adenoma Type	Hormone	Transcription Factor	Morphologic Variant	Associated Syndrome
Somatotroph adenoma	GH GH GH, PRL (in same cells) GH, PRL (in different cells)	PIT-1 PIT-1 PIT-1, ERα PIT-1, ERα	Densely granulated adenoma Sparsely granulated adenoma Mammosomatotroph adenoma Mixed somatotroph-lactotroph adenoma	Gigantism (children) Acromegaly (adults)

CORTICOTROPH ADENOMA usually microadenoma

* Hypercortisolism
  - Cushing syndrome: clinical manifestations of hypercortisolism
  - Cushing dz: hypercortisolism due to ↑ACTH
* Nelson Syndrome:
  - develop large pituitary adenoma after removal of adrenal glands (loss of ⊖feedback)
* Histo → BASOPHILIC (densely granulated)
  - PAS⊕ due to POMC breakdown
  - crook cell adenoma

NONFUNCTIONING → Null cell type: Ø staining & chromophobic
→ Silent: ⊕ staining but clinically nonfunctional

GONADOTROPH ADENOMA (produce FSH & LH)
* MC NONfunctioning pituitary adenoma ??
paradoxical hypogonadal A(x) ??

this ?

→ Sxs due to mass effect → HA, vision disturbances
may cause hypopit due to compression → BUT elevated prolactin

PITUITARY CARCINOMA

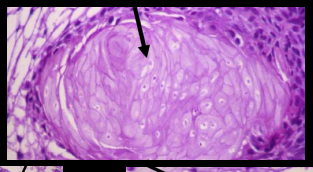
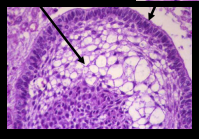
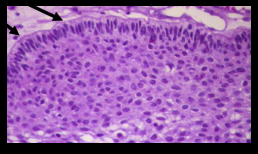
MC acquired by SPORADIC MUTATION
→ GNAS mutation (α subunit of G_s protein)
TQ
* somatotroph (MC) & corticotroph
→ USP8 (ubiquitin-specific protease-8)
* corticotroph

HYPOPITUITARISM → 75% lost; usually ↓TSH first sign

QI's causes: TUMORS (press on normal pituitary), TBI, pituitary apoplexy, Rathke cyst

HYPOTHALAMIC SUPRASELLAR TUMORS → gliomas & craniopharyngiomas

* craniopharyngiomas:
① Adamantinomatous (children)
- cystic, may contain thick cholesterol-rich fluid "machine-oil"
** TQ
* mutation in CTNNB1 (beta-catenin) → activates WNT
* Histo: "stratified squamous w/ peripheral palisading"
"stellate reticulum"
"wet keratin" & calcification

② Papillary (adults)
* mutation in BRAF
* Histo: squamous epithel. w/ fibrovascular cores

PINEAL GLAND

→ pinealoma
- pineocytoma → rosettes w/ fibrillar zones surrounded by neoplastic nuclei
→ germ cell tumors (MC)
- clear cells w/ lymphocyte infiltration

WANG THYROID PQs

I

✓ 1. E
✓ 2. D
✓ 3. D
✓ 4. C
✓ 5. A
✓ 6. A
✓ 7. E (↓TSH)
✓ 8. B
✓ 9. A
✓ 10. E
✓ 11. B ["proptosis" = Graves → inc. volume of retroorbital CT]
✓ 12. E
13. ~~E~~ B ["staring gaze" = thyrotoxicosis → Hyper-SNS = sup. tarsal muscle↑]
✓ 14. E
✓ 15. E
✓ 16. E
✓ 17. C apathetic hyperthyroid ↑T_3 ↓TSH
✓ 18. A
✓ 19. B
✓ 20. C

II

✓ 1. A
✓ 2. C
✓ 3. B
✓ 4. C
✓ 5. E
✓ 6. A → follicular adenoma
7. ~~A~~ D
✓ 8. A
✓ 9. E
✓ 10. D
✓ 11. C [papillary → multifocal ∴ tx w/ total thyroidectomy]
✓ 12. E
✓ 13. D
✓ 14. E
✓ 15. C
✓ 16. C
✓ 17. D
✓ 18. D
✓ 19. D
✓ 20. A

Pathogenesis

- Papillary carcinomas: RET-PTC, RAS, BRAF, NTRK1
- Follicular carcinomas: PAX8-PPARγ, PTEN, RAS/PI3K

(totally different morphologies)

- Medullary carcinomas: Germline RET mutation in MEN 2A and 2B, (exon 10 and 11 in 2A; exon 16 in 2B)