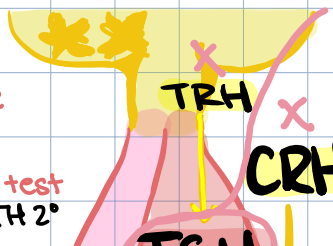
PITUITARY

Hypopituitarism: treat by replacing hormones with natural or synthetic analogs



TRH

Levothyroxine

rGH (somatotrophin)

CRH **GnRH** **GHRH** **Somatostatin** **PRH**

Dopamine

TSH

LH **FSH**

ACTH

GH

Prolactin

CRH → **ACTH** → **Cortisol**

① CRH stim test: ↑cortisol → 2°

② Dexamethasone suppression test: ↑cortisol → 1°

③ Serum ACTH test: ↑ACTH 1° ↓ACTH 2°

④ serum cortisol test (AM)

⑤ saliva cortisol test (PM)

2° hypercortisolism

Cushings Syndrome → **ACTH**

may result from overproduction of **CRH**, **ACTH**, or **cortisol**

Pasireotide ALSO inhibits release of **ACTH**

Ostreotide
Pasireotide ⊣ **GH**

Somatostatin analogs
mimic/substitute GH/IH

Pegvisomat ⊣

GH antagonist
prevents GH binding

liver, target organs

Cabergoline
Bromocriptine

Dopamine receptor agonists substitute for dopamine

Tuberinfundibular Pathway: dopaminergic pathway that turns off prolactin secretion

---

Cushing's Disease

1° hypercortisolism due to **adrenal adenoma**

target organs

Mifepristone ⊣

competitively inhibit cortisol binding to GC receptor IN target cell

Pregnancy X
induces abortion

Cortisol

Cortisol (glucocorticoid)
increases serum glucose
70% AM 30% PM

Synthetic GCs can replace **Cortisol** and/or **aldosterone** to treat adrenal insufficiency or **Addison's Disease**

(1) **Hydrocortisone**
(3.5) **Prednisone**

Eventually need **hydrocortisone** **fludrocortisone** combo

Fludrocortisone

Aminoglutethimide
Ketoconazole

inhibit synthesis of **Cortisol** by inhibiting enzymes in biosynthetic pathway

Toxicities: **anti-androgen effects** (gynecomastia)

CYP inhibition can ↑ toxicity of other drugs

BLOCK/Replace: completely block cortisol synthesis w/ high dose → replace w/ exogenous GCs

Normalization: block cortisol synthesis until normal level achieved

---

angiotensin II

ACE ↑

angiotensin I

↑

angiotensinogen

renin

aldosterone (mineral-corticoid)
reabsorption of Na^+/H_2O at distal tubules and collecting duct

K^+ excretion

1° hyperaldosteronism

aldosterone antagonists

Eplerenone
Spironolactone

ACE inhibitors

Captopril
Lisinopril

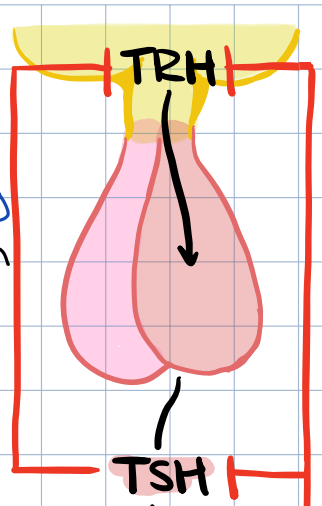
↓aldosterone
↓vasoconstriction
↓H_2O retention

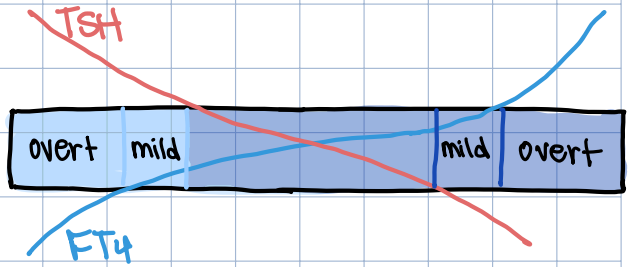
ARBs

Losartan
Valsartan

2° hyperaldosteronism

THYROID





Hypothyroid ↓HR, cold intolerance, high cholesterol | euthyroid | hyperthyroid palpitations, heat intolerance, ↓weight, ↑appetite, sweating

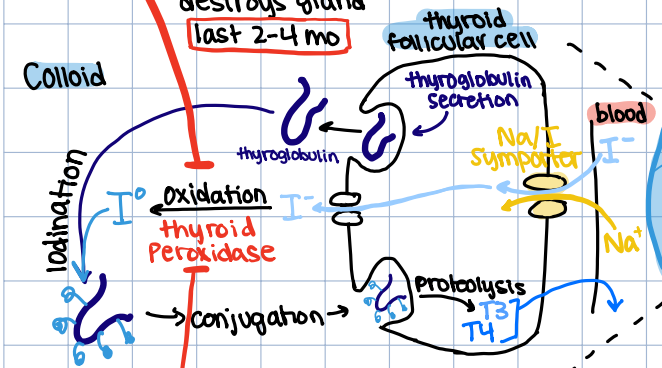
2° Hyperthyroidism: ↑TRH/TSH secretion
- pituitary tumor, radiation/surgery

1° Hyperthyroidism: ↑T3/T4 secretion

Graves Disease - autoantibody mimics action of TSH

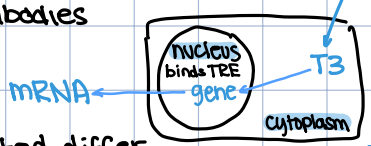
Severe: potassium iodide + other drugs
- inhibits TPO by ↑oxidized iodine
- (Wolff-Chaikoff) lasts 7-10 days

Radioactive Iodine (I^{131})
- accumulates, kills cells and destroys gland
- last 2-4 mo



Thioamides: MOA 1 direct inhibitors (lasts years)
- **Propylthiouracil** during pregnancy. ALSO inhibits D2 deiodinase
- **Methimazole** (can be used after 1st tri)
- MOA 2: ↓secretion of auto-antibodies immunosuppression

T4 → (D2 deiodinase) → T3



The genes that are regulated differ among target cell types, producing distinct effects

1° Hypothyroidism: ↓T3/T4 secretion
- **Levothyroxine (T4)** - long half life
- **Lyothyronine (T3)** - hard to dose (varies)
- PK issues: ferrous sulfate and BABAs interfere w/ absorption. Take 1hr before or 3hr after.

Causes:
- Autoimmune (Hashimotos): spontaneous auto-antibodies destroy thyroid gland
- Iatrogenic: post surgery/radiation
- Iodine deficiency: prevents maturation release of TH
- drug-induced: AMIODARONE. Inhibits D2.

2° Hypothyroidism: ↓TRH/TSH secretion
- hypothalamic/pituitary disease

TARGET TISSUES

Heart: ↑cardiac Sensitivity to SNS by ↑number, affinity of β adrenergic receptors and ↑ response to catecholamines.
- hypothyroid → ↓cardiac output
- hyperthyroid → heart palpitations

Atenolol, metoprolol, propranolol

Nervous system promote normal brain development (fetal brain)
- TH produces reelin → ECM protein involved in neuronal migration
- T3 ↑reelin during development → proper 3D structure of brain

Fetal CNS developmental disorders if hypothyroid

Lipoprotein Stimulate formation of LDL receptors to draw more LDL out of circulation.
- Hypothyroid → CAD and hypercholesterolemia

Gut associated w/ Carbohydrate absorption

Adipose stimulate lipolysis

Muscle increase protein breakdown

Thermoregulation Stimulate oxygen consumption by metabolically active tissues and ↑metabolic rate

Mitochondria produce ATP: glycolysis produces pyruvate → TCA extracts energy as $NADH$ and $FADH_2$ → oxidative phos. produces H^+ gradient → ATP BUT TH ↑UCP creating Heat.

Bone promote normal growth and development

TH ↑RANKL expression → osteoclast activation

REPRODUCTIVE

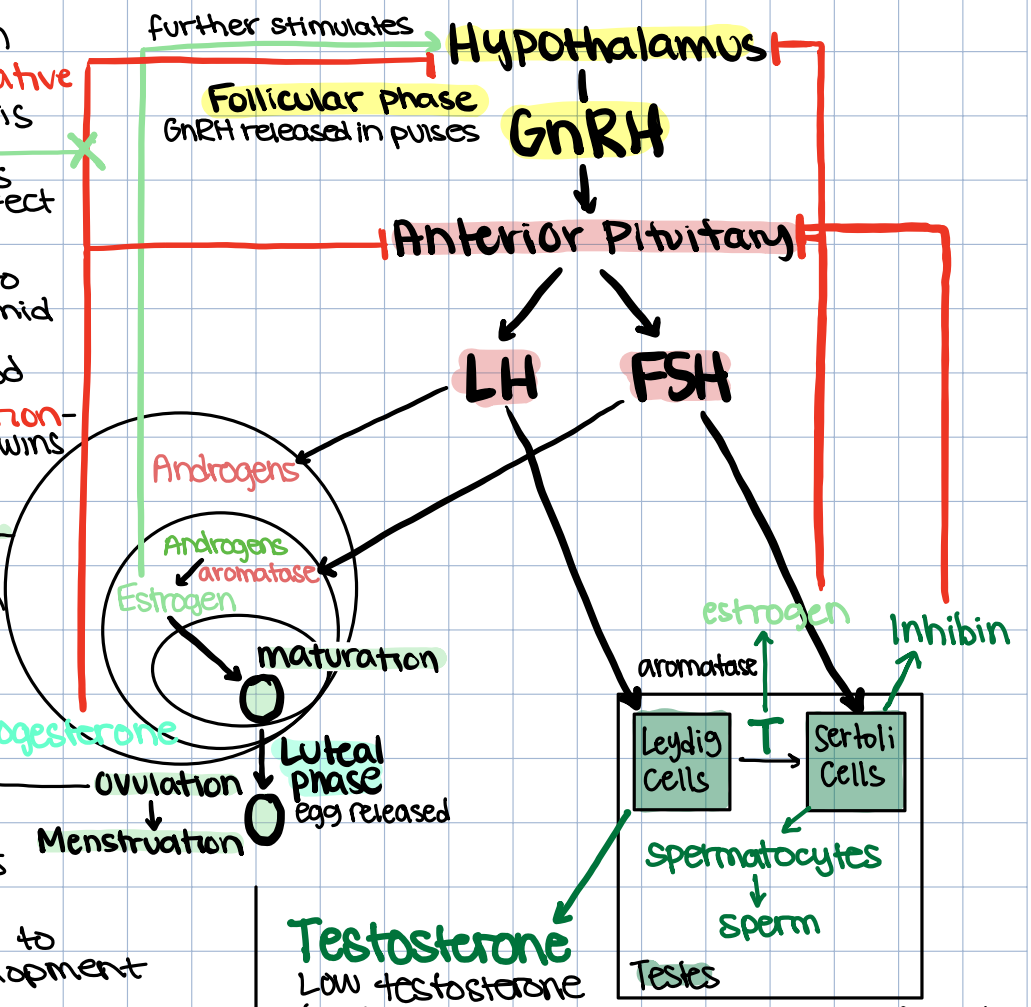
FEMALE INFERTILITY

ovulatory dysfunction

IF caused by ↑estrogen → negative feedback shuts down HPG axis

Clomiphrene disinhibits axis through anti-estrogenic effect
- administered during follicular phase (day 3–7) to promote FSH/LH release mid cycle.

Toxicities: anti-estrogenic – mood swings, hot flashes. Superovulation – cramps, ectopic preg, fraternal twins. ↑RISK OF VTE – estrogen increases clotting proteins



Step 1: downregulate GnRH receptors and inhibit gonadotropin release

Leuprolide **Goserelin** — GnRH agonists — menopause sx

Constant stimulation exhausts receptors → desensitization → long-term ↓in GnRH signaling

Step 2: use synthetic hormones to promote ovulation

rFSH → estradiol measured to determine follicular development

hCG → mimics LH surge stimulating ovulation → intercourse/insemination

Gender Affirming

Female → Male
- Stop menses
- induce virilization (hair, voice, contours)

↓

Androgens

Testosterone
- inhibits the female HPG axis at level of hypothalamus/pituitary
- Stimulates androgen receptors in various tissues to produce masculinization.
  - ↳ could take up to 5 years for desired masculinization
- muscle mass, fat redistribution, facial hair

Male → Female
- induce feminization (hair, contours)

↓

Androgen Suppressors

Leuprolide **Goserelin** inhibit GnRH

Anti-Androgens

Spironolactone

Flutamide

Estrogens

Ethinyl estradiol - stimulates estrogen receptors in various tissues to produce feminization. Effects could take 3 yrs.
- breast growth, ↓sperm production, ↓testicular volume, ↓muscle mass and strength

MALE INFERTILITY

Testosterone

Low testosterone is the primary cause of hormonal infertility

1° hypogonadism → treat with testosterone

IF 2° hypogonadism

① Clomiphene removes negative feedback inhibition of testosterone synthesis

② hCG and FSH then can directly stimulate testosterone synthesis

Anastrozole to treat Obesity-associated male infertility. Functions as aromatase inhibitor
- ↳ found largely in peripheral adipose tissue. ↑estrogen.

DIABETES

excessive discharge of urine

Mellitus

due to high serum glucose → decreases reabsorption of Na^+ and H_2O → ↑urine volume

Type 1: treat with insulin

Bolus: meals

- Rapid acting: Aspart, Glulisine, Lispro
- Short acting: Insulin Regular

Basal

- Intermediate: NPH
- Long acting: Glargine, Detemir

used in combination

1. basal/bolus regimen
   - before meals
   - before bed (useful in preventing ketoacidosis or hypoglycemia during fasting)
2. Single formulation - not as accurate, but better compliance
   - taken on regular sched.
3. Glucose pumps use ONLY short-acting

Type 2

↓serum glucose or ↑insulin production

Metformin first line

gluconeogenesis inhibitor to prevent synthesis of NEW glucose molecules

- cleared renally → accumulates in patients w/ renal impairment.

Toxicities: lactic acidosis - doesn't cause problem but exacerbates.

Contraindicated: liver failure, respiratory insuff, alcoholism

Pioglitazone

enters nucleus of target to ↑expression of glucose transporters

Interactions:

BABAs ↓absorption
gemfibrozil ↓ metabolism

Acarbose: α-glucosidase inhibitor

blocks breakdown of saccharides in intestines

- not absorbed. Stays in gut.

Toxicities: diarrhea, flatulence, abdominal pain

Insipidus

due to loss of kidney control

PP → CENTRAL → ADH → NEPHROGENIC → H_2O

- ↓ADH secretion
- **Desmopressin**: ADH analog

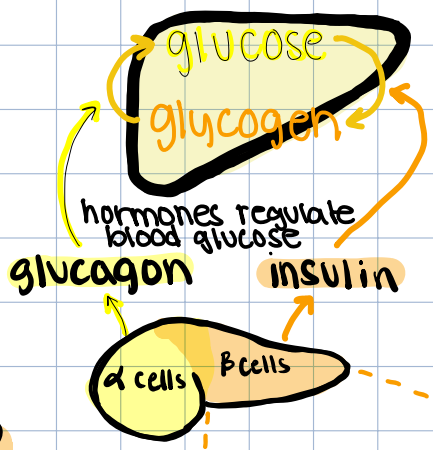
NEPHROGENIC: insensitive to ADH

Diuretics: induce volume depletion, and increase water reabsorption

- Hydrochlorothiazide and Amiloride - K^+ sparing

NSAIDs: reduced Lithium filtration by inhibiting PGD

- Indomethacin ↑Na/H_2O reabsorption



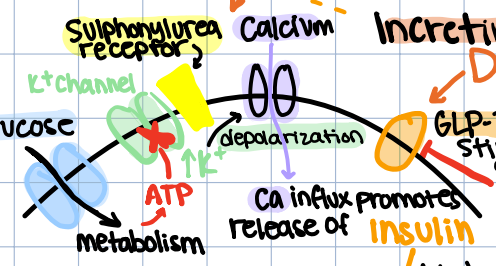
Secretagogues

block K^+ channel independent of glucose by activating receptor

- Tolbutamine - 1st gen
- Glyburide - 2nd gen more potent

Toxicities: leukopenia, thrombocytopenia

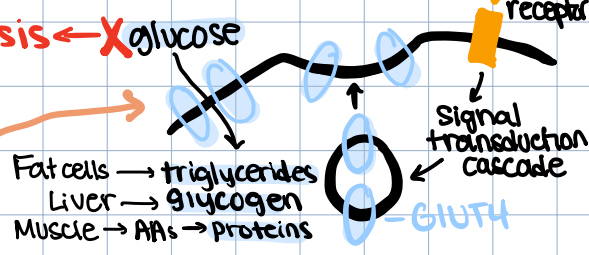
- CYP inhibitors ↑ hypoglycemia risk (amiodarone)



Incretin modulators

Dulaglutide
IM, weekly
GLP-1 incretin that stimulates insulin secretion

DPP-4 ⊤ **Sitagliptan**
oral, daily



Canagliflozin: SGLT2 inhibitor

block glucose transport protein in PCT → excretion of glucose in urine

Toxicities: UTI bacteria colonize glucose rich GU tract