

Pituitary Disorders

Objectives

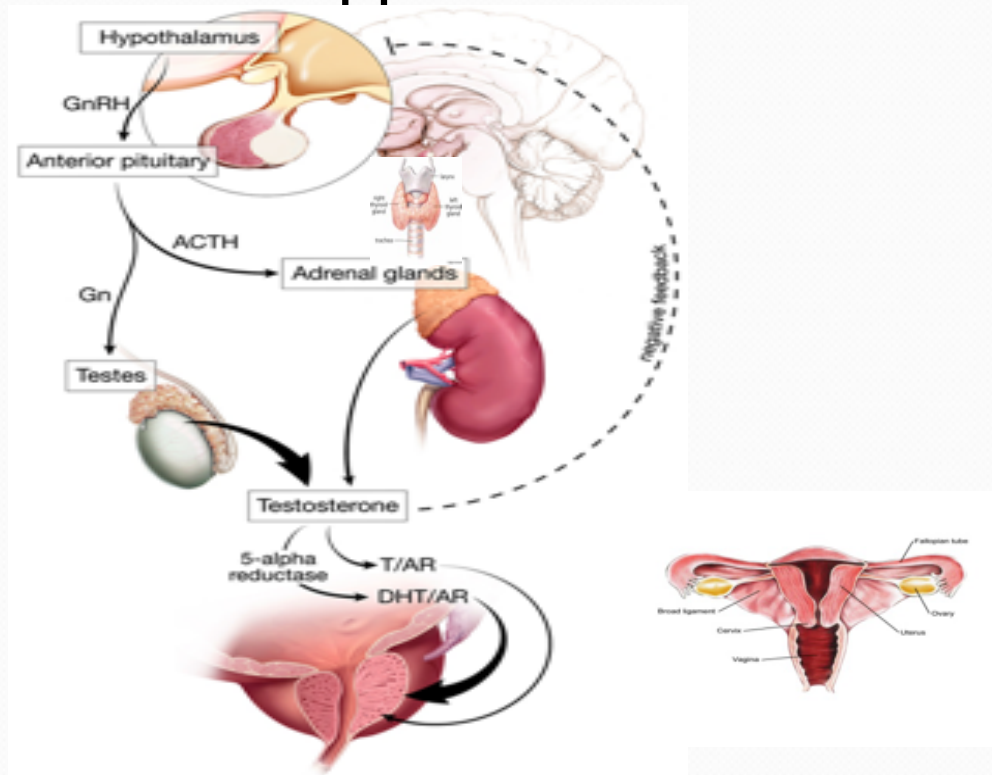
- Anatomy of hypothalamus and pituitary
- Function of hypothalamus and pituitary
- Hormones:
 - Anterior pituitary with related disorders
 - Posterior pituitary with related disorders

Hypothalamic-Pituitary Axis

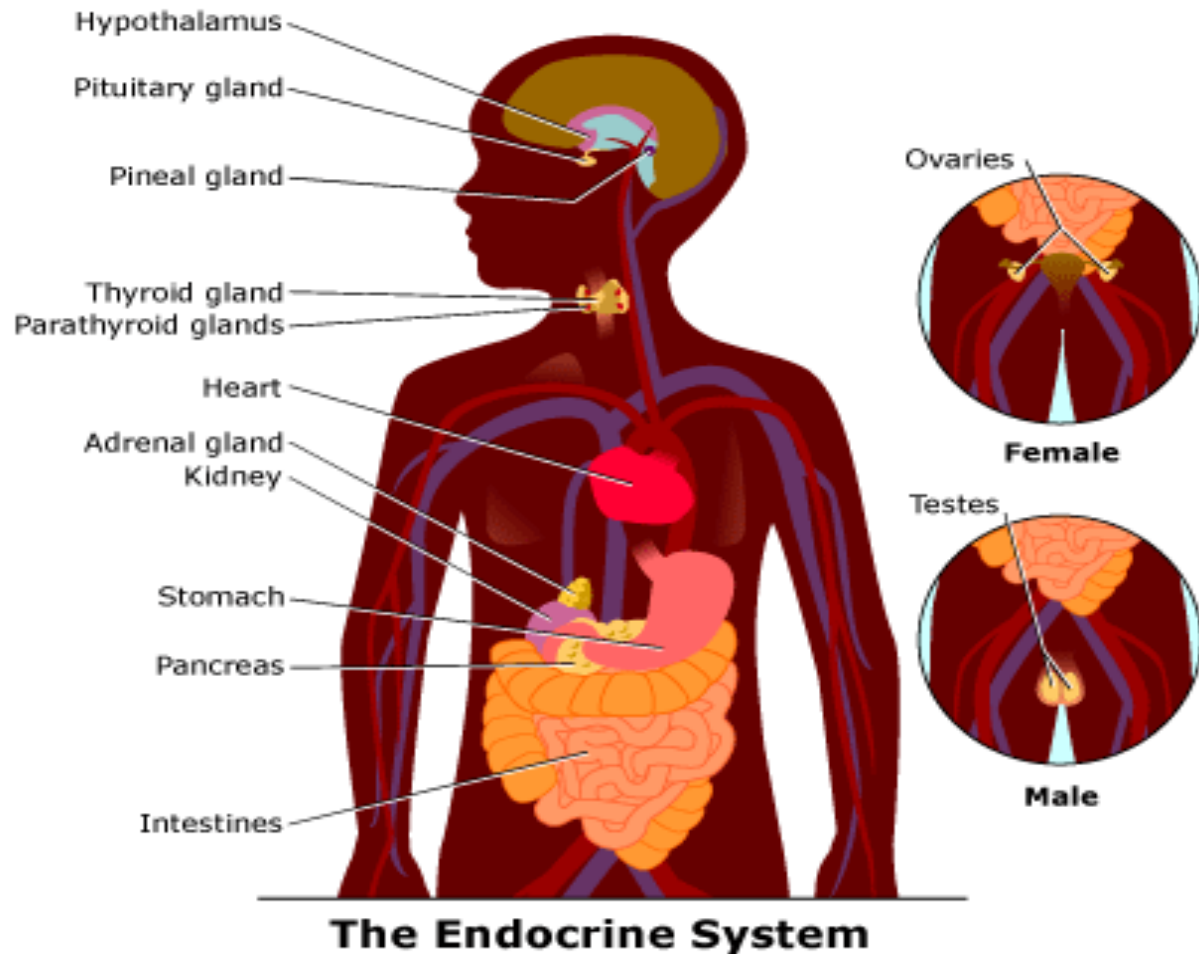
- The hypothalamus is the coordinator of Endocrine system
- Received signals from cortical brain, autonomic function, environment cues like light and temperature
- It affects function of thyroid gland, adrenal, gonads, growth, milk production and water balance

Hypothalamus-pituitary Axis

- nonendocrine functions such as temperature regulation, the activity of the autonomic nervous system, and control of appetite.



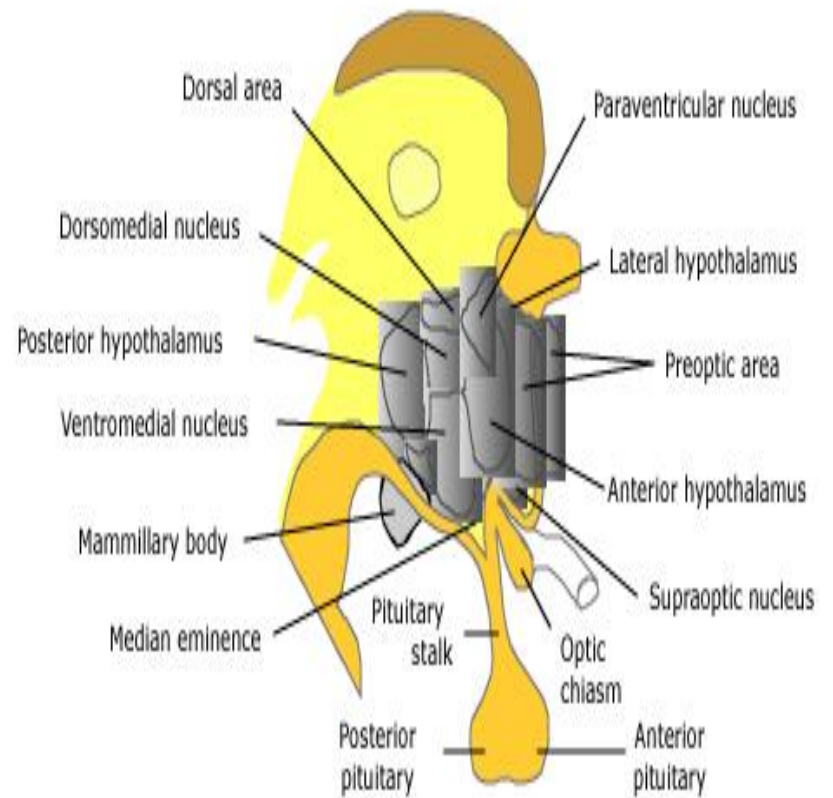
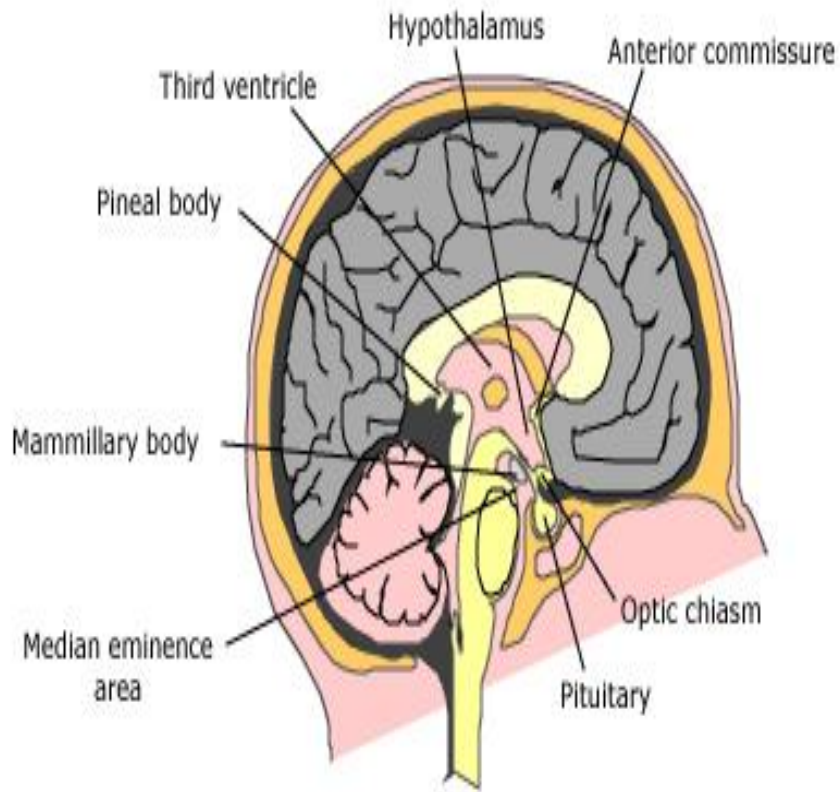
Endocrine system



Hypothalamus

- At the base of the brain, below third ventricle, above pituitary gland and optic chiasm
- Hypothalamus is connected to the pituitary gland by pituitary stalk which connect median eminence to the pituitary gland
- Multiple nuclei in anterior part producing hormones to anterior pituitary
- Paraventricular and supraoptic nuclei produce ADH to control poster pituitary function

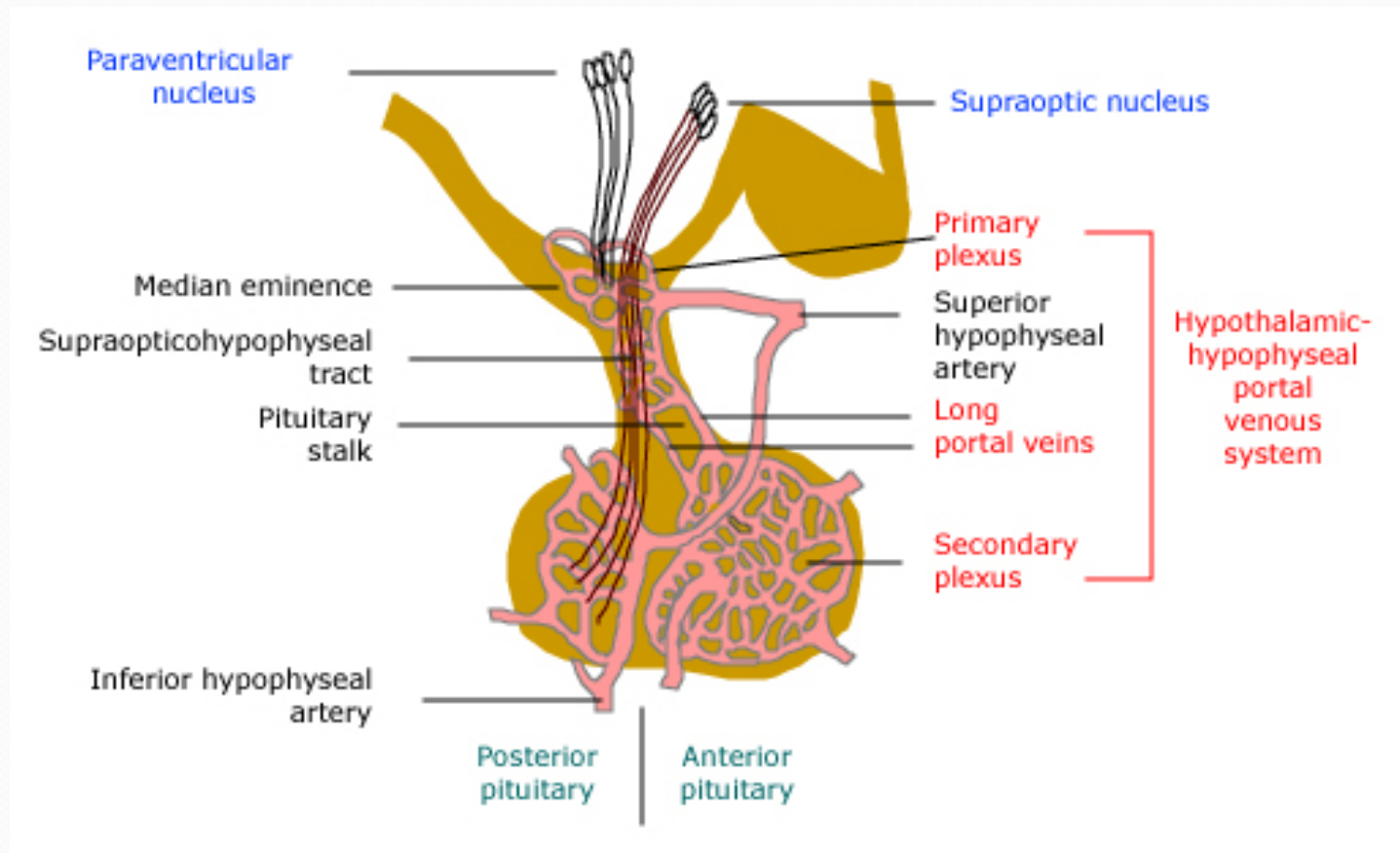
Hypothalamus



Function of hypothalamus

- Terminals of hypothalamic neurones are in the median eminence carrying the hormones through capillary plexus to the pituitary gland
- Release all the hormones to control the pituitary function beside neuroendocrine function

Hypothalamus



Major hypothalamic hormones and their effect on anterior pituitary

hormones

Hypothalamic stimulatory hormones	Pituitary hormones
Corticotropin-releasing hormone - 41 amino acids; released from paraventricular neurons as well as supraoptic and arcuate nuclei and limbic system	Adrenocorticotrophic hormone - basophilic corticotrophs represent 20 percent of cells in anterior pituitary; ACTH is product of proopiomelanocortin (POMC) gene
Growth hormone-releasing hormone - two forms, 40 and 44 amino acids	Growth hormone - acidophilic somatotrophs represent 50 percent of cells in anterior pituitary
Gonadotropin-releasing hormone - 10 amino acids; mostly released from preoptic neurons	Luteinizing hormone and follicle-stimulating hormone - gonadotrophs represent about 15 percent of anterior pituitary cells
Thyrotropin-releasing hormone - three amino acids; released from anterior hypothalamic area	Thyroid-stimulating hormone - thyrotropes represent about five percent of anterior pituitary cells
Prolactin-releasing factors - include serotonin, acetylcholine, opiates, and estrogens	Prolactin - lactotrophs represent 10 to 30 percent of anterior pituitary cells
Hypothalamic inhibitory hormones	
Somatostatin - 14 amino acids	Inhibits the release of growth hormone
Prolactin-inhibiting factors - includes dopamine	Major prolactin control is inhibitory

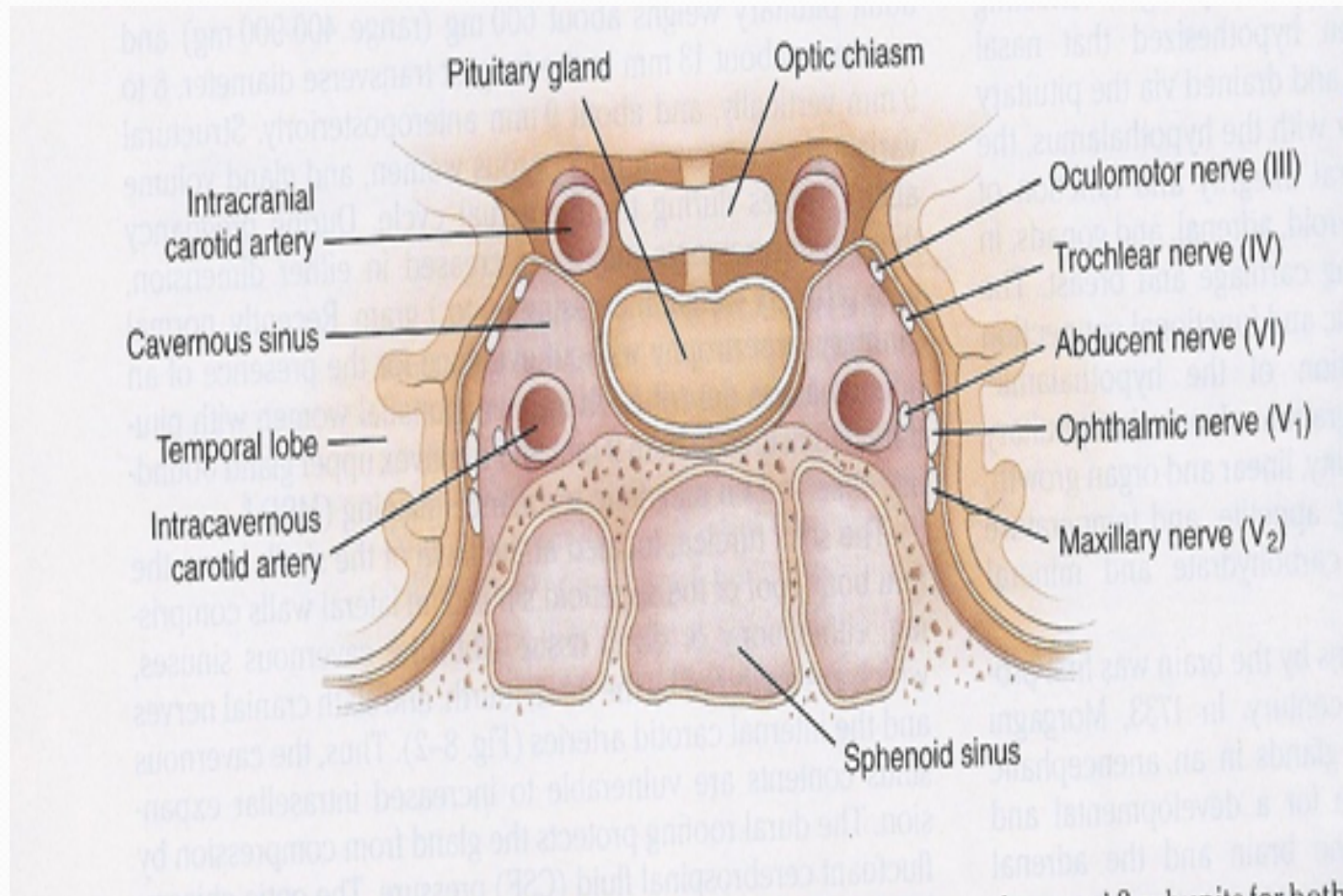
Pituitary Development

- Anterior pituitary is recognizable by 4- 5th wk of gestation
- Full maturation by 20th wk
- From Rathke's pouch, Ectodermal evagination of oropharynx
- Migrate to join neurohypophysis
- Portion of Rathke's pouch →→ Intermediate lobe
- Remnant of Rathke's pouch cell in oral cavity →→ pharyngeal pituitary
- Lies at the base of the skull as sella turcica
- Roof is formed by diaphragma sellae
- Floor by the roof of sphenoid sinus

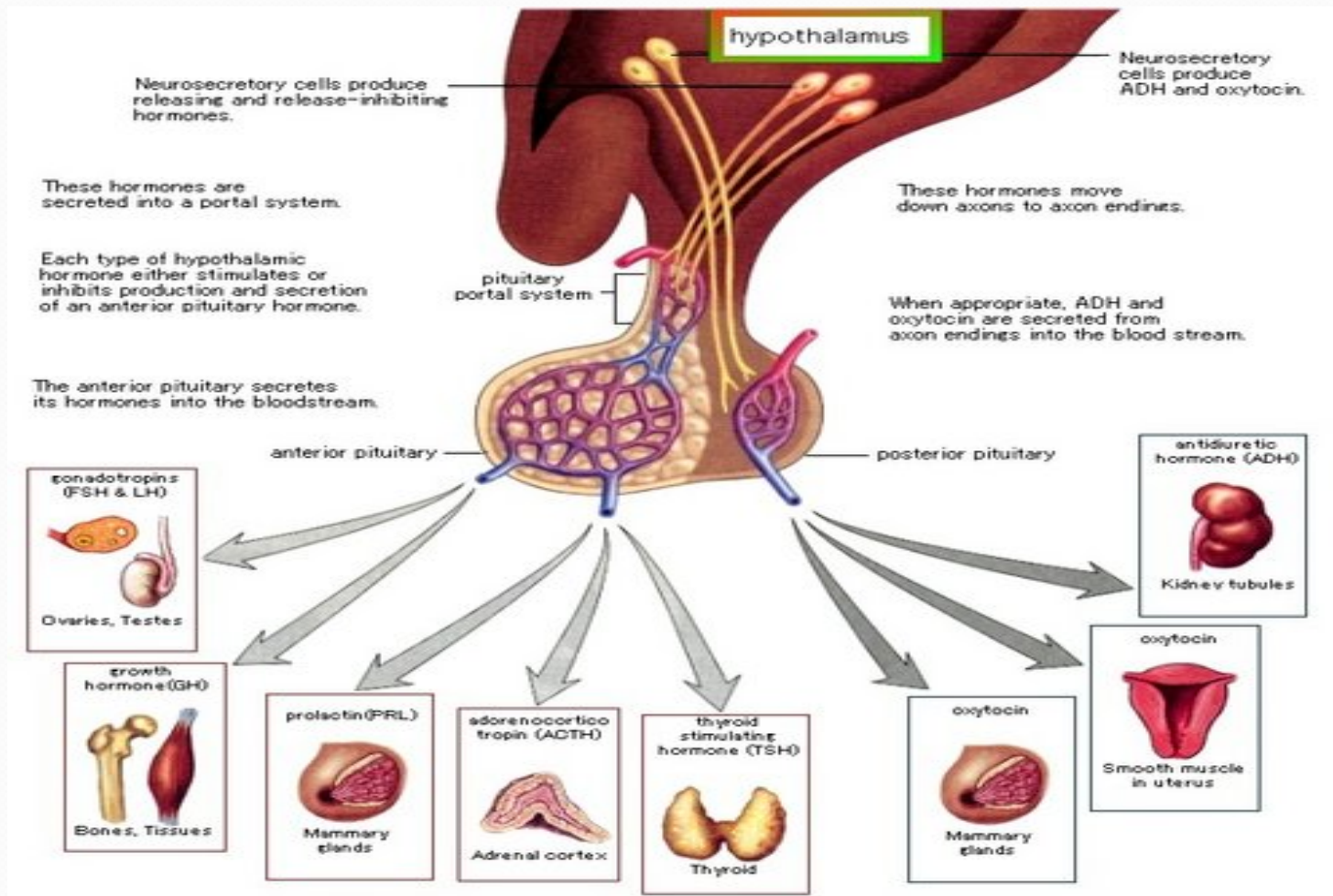
Pituitary Development

- Pituitary stalk and its blood vessels pass through the diaphragm
- Lateral wall by cavernous sinus containing III, IV, VI, V₁, V₂ cranial nerves and internal carotid artery with sympathetic fibers. Both adjacent to temporal lobes
- Pituitary gland measures 15 X 10 X 6 mm, weighs 500 mg but about 1 g in women
- Optic chiasm lies 10 mm above the gland and anterior to the stalk
- Blood supply : superior, middle, inferior hypophysial arteries (internal carotid artery) running in median eminence from hypothalamus
- Venous drainage: to superior and inferior petrosal sinuses to jugular vein

Pituitary Development



Hormonal regulation



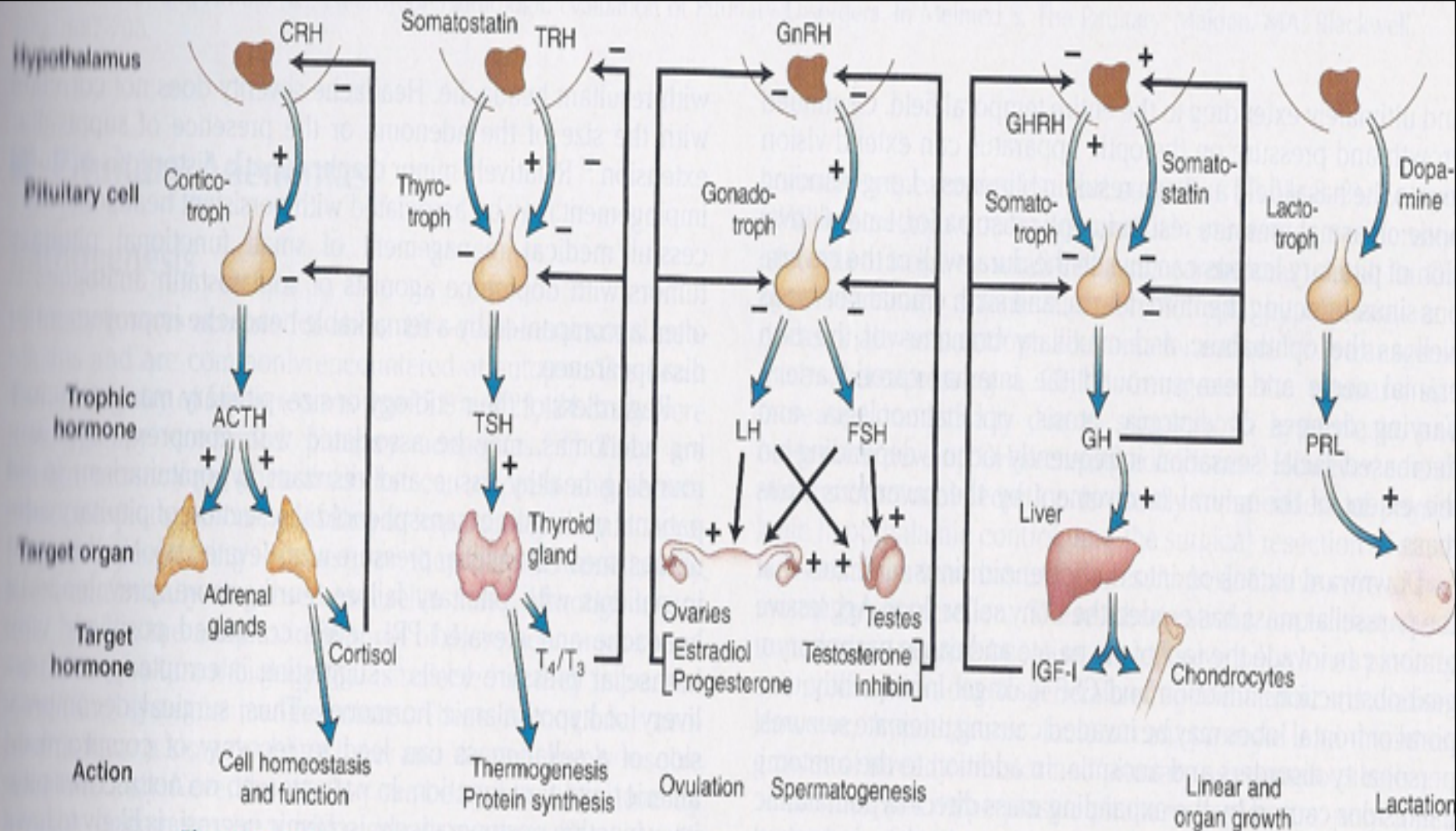


Figure 8-6 • Control of hypothalamic-pituitary target organ axes. ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; T_3 , triiodothyronine; T_4 , thyroxine; TRH, thyrotrophin-releasing hormone; TSH, thyroid-stimulating hormone. Adapted from Melmed S, Mechanisms for pituitary tumorigenesis. The plastic pituitary. J Clin Investigation 2003 112:1603-1618.

Anterior Lobe

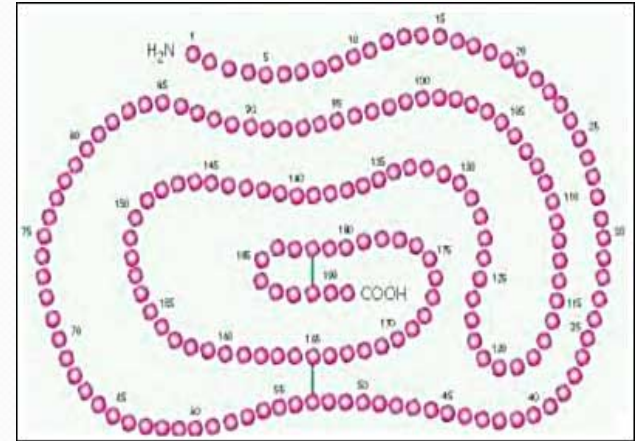
- Growth hormone (GH)
- Gonadotrophs (LH/FSH)
- TSH
- Prolactin
- Corticotropin (ACTH)

Posterior Lobe

- Oxytocin
- Vasopressin

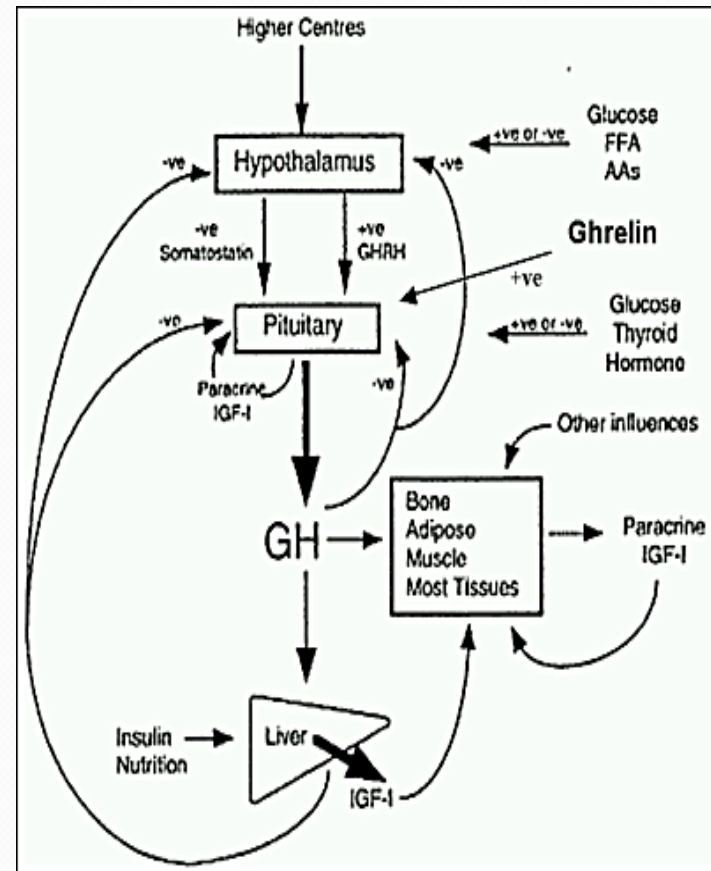
Growth hormone

- Polypeptide hormone
- Somatotrophs of anterior pituitary
- Action is mediated by IGF-I
- Half life is 20-50 mins
- Has a binding protein: GHBP
- Pulsatile secretion: variable level in the blood
- Binds to its receptor on cell-surface: cytokine receptor
- Lack intrinsic enzyme activity
- Has similar receptor structure to others: leptin, IL-2, PRL
- Controlled by HP and peripheral factors
- **GHRH stimulates it, somatostatin inhibits**



Growth hormone

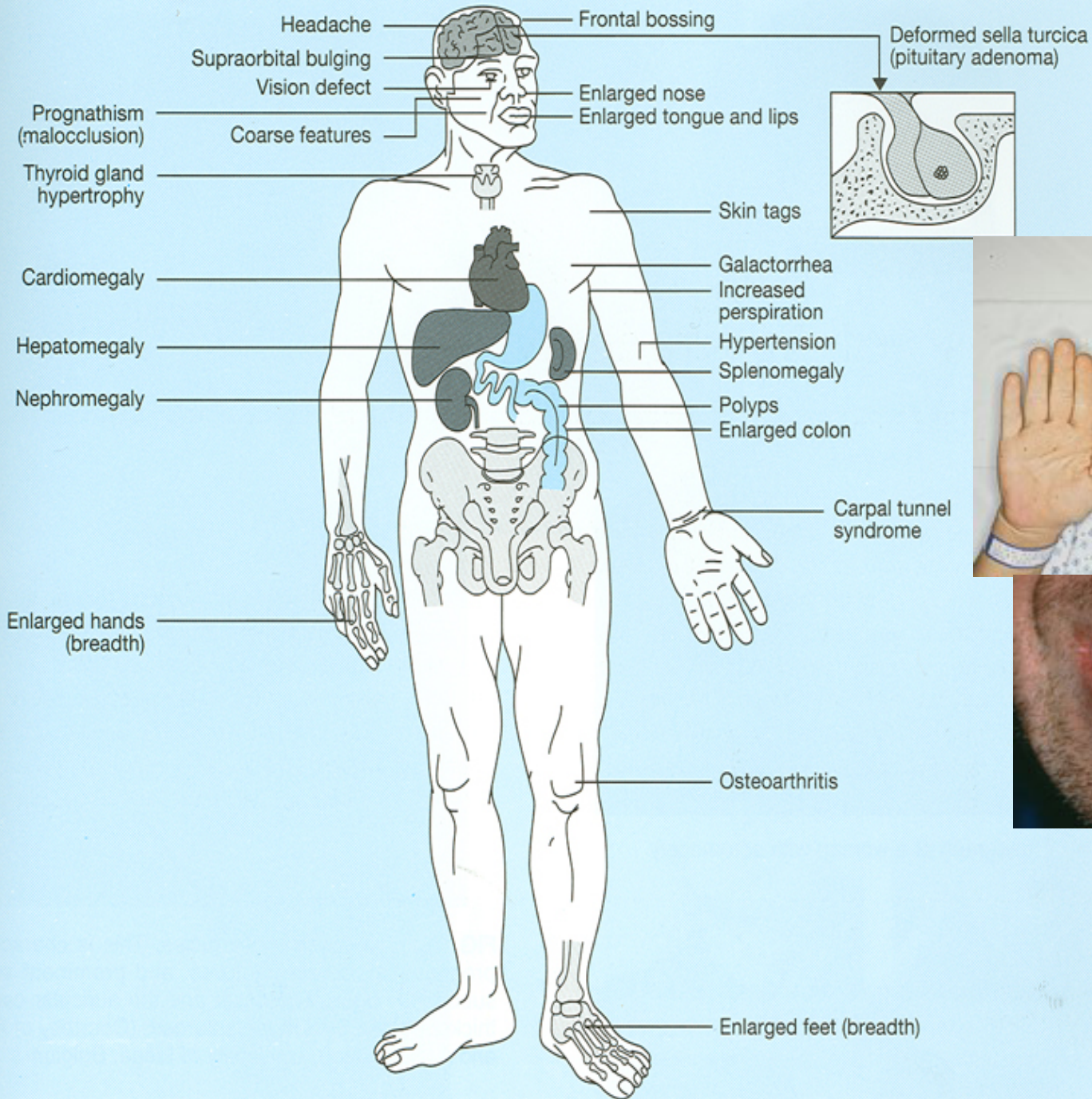
- **↑↑ GH:**
- **Physiologic:**
sleep, exercise, stress, fasting
- **Pathologic:**
Liver cirrhosis, AN, CRF, starvation
- **Pharmacologic:**
Estrogen, ACTH, ADH, GHRH, Ghrelin
dopamine agonist, K infusion, serotonin
arginin
- **↓↓ GH:**
- **Physiologic:**
↑glucose, ↑ FFAs,
- **Pharmacologic:**
Somatostatin, GH, GC, PG
- **Pathologic:** ↑ or ↓ T₄,
Obesity



Acromegaly

- 98% GH pituitary adenoma
- 1/3 of all functional pituitary adenomas
- Stimulates growth of skin, connective tissue, cartilage, bone, and viscera
- Nitrogen retention, insulin antagonism, and lipogenesis





Risks of Long Term Excess GH

- Arthropathy
- Neuropathy
- Cardiomyopathy
- Respiratory obstruction
- Diabetes Mellitus
- Hypertension:
 - exacerbates cardiomyopathy
 - NOT Reversible
- increased risk of tumors:
 - leiomyomata
 - colon polyps

Reduced overall survival by an average of 10 years

Diagnosis of acromegaly

- GH, IGF-I
- Oral glucose tolerance testing
- To assess excess GH secretion

Treatment

- Goal: lower the serum insulin-like growth factor to normal for age/gender
- Surgically accessible micro- or Macroadenomas:
 - Transsphenoidal surgery
- 2nd Line therapy: Somatostatin analogs or Dopamine agonists
- 3rd Line therapy: Somatostatin receptor antagonist
- Last resort: Radiation

Growth hormone deficiency



- Diagnosis in children and adult



Diagnosis of GH-deficiency and management

- GH, IGF-I level
- Dynamic testing: clonidine stimulation test, glucagon stimulation, exercise testing, arginine-GHRH, insulin tolerance testing
- X-ray of hands: delayed bone age
- In Adult: Insulin tolerance testing, MRI pituitary to rule out pituitary adenoma
- Management: GH replacement

Cortisol under ACTH

- Stable circadian rhythm

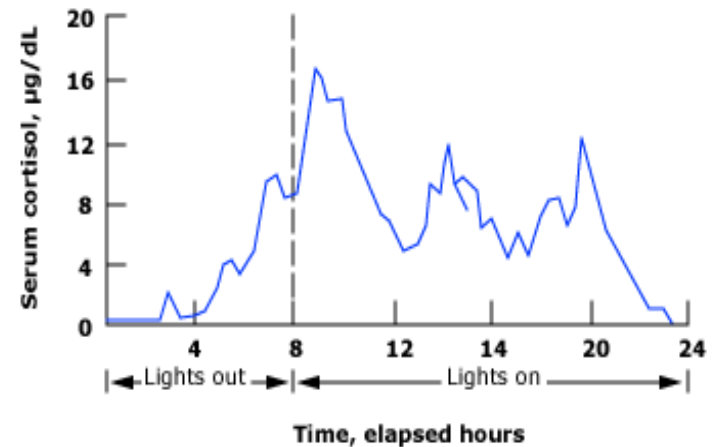
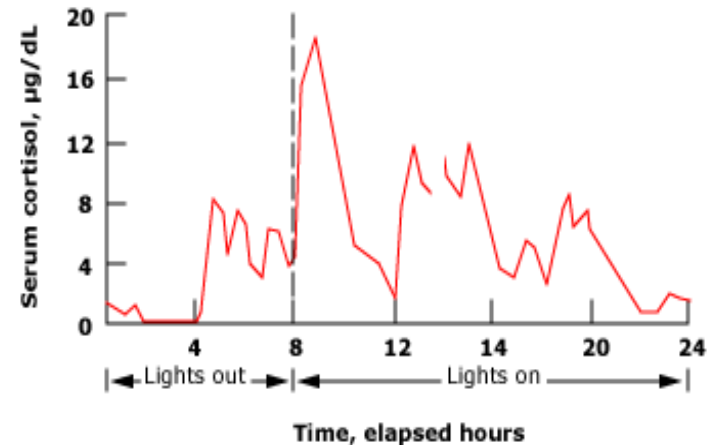
- Altered by:

Physical stress

Psychological stress

CNS and pituitary disorder

liver and renal failure



Cushing's Disease



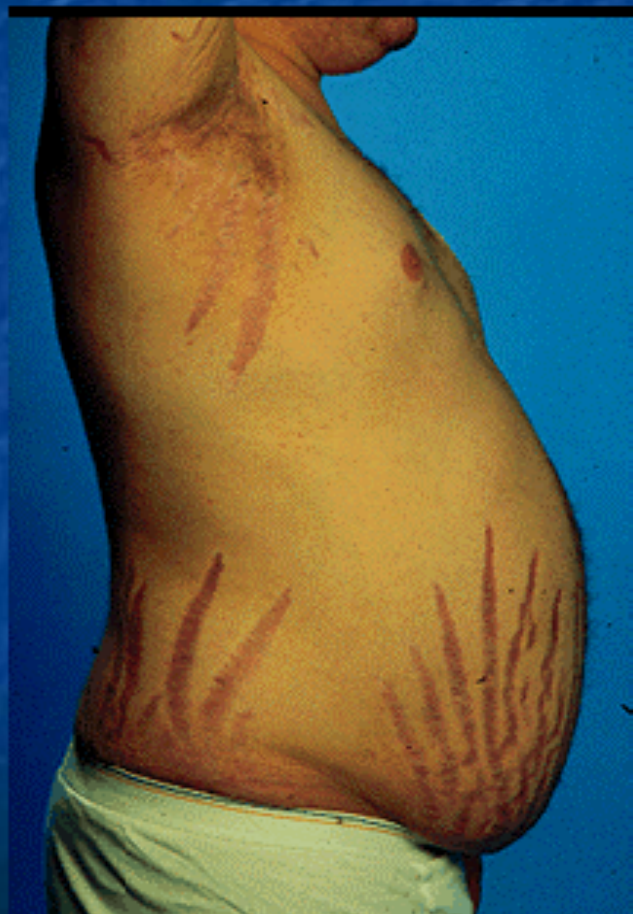
- High ACTH leads to excess glucocorticoid
- Incidence may be 5-25 per million
- Women are 3-8X more likely than men

Cushing's disease

- Centripetal obesity
- Moon face; buffalo hump
- Skin atrophy
- Easily bruised
- Striae
- Cutaneous fungal infections
- Hyperpigmentation
- Oligo or amenorrhea
- Hirsutism and Virilization with adrenal tumors



Cushing's Disease



- Proximal muscle wasting & weakness
- Osteoporosis
- Glucose intolerance
- HTN, hypokalemia
- Thromboembolism
- Depression, Psyc
- Infection
- Glaucoma

Cushing's disease

- Upper body obesity with thin arms and legs
- Buffalo Hump
- Red, Round Face
- High Blood Sugar
- High Blood Pressure
- Vertigo
- Blurry Vision
- Acne
- Female Balding
- Water Retention
- Menstrual Irregularities
- Thin Skin and Bruising
- Purple Striae
- Poor Wound Healing
- Hirsutism
- Severe Depression
- Cognitive Difficulties
- Emotional Instability
- Sleep Disorders
- Fatigue



Diagnosis of cushing's disease

- 24 hr urine free cortisol
- Overnight 1 mg dexamethasone suppression testing
- ACTH level and Pm cortisol
- MRI pituitary: for pituitary adenoma

Treatment

- Transsphenoidal surgery
- Pituitary irradiation
- Adrenalectomy (Surgical, Mitotane)
 - **Nelson's Syndrome:** expanding intrasellar tumor and hyperpigmentation
- Pregnancy:
 - 1st Trimester: Surgery
 - 2nd Trimester: Adrenal Enzyme Inhibitors vs. surgery
 - 3rd Trimester: Early delivery, enzyme inhibitors until lung maturity

Thyrotropin-secreting Adenoma

- <1% of all hyperthyroidism cases
- 25% of adenomas secrete other hormones
- Goiter, visual defects, menstrual irreg, galatorrhea

Lab:

Normal or High TSH

High total and free T4 and High T3

MRI

TSH –secreting adenoma

- Mild signs and symptoms of hyperthyroidism:
 - Palpitations, tremor, weight loss, diarrhoea, heat intolerance, irregular period in female, excessive sweating
 - Signs: tachycardia, tremor, warm skin, goiter sometimes

Treatment

- Transsphenoidal surgery
 - 1/3 Cure
 - 1/3 improvement
 - 1/3 no change
- Dopamine Agonist
- Somatostatin Analogue (Octreotide)
 - Works so well, may give before surgery
 - Nausea, diarrhea, bloating, glu intolerance, cholelithiasis
- Do NOT use antithyroid therapy



Hyperprolactinemia

■ Causes:

- 1. disruption of dopamine (tumor, trauma, infiltrative lesions)
- 2. hypothyroid (increases TRH)
- 3. estrogen increase (pregnancy)
- 4. chest wall burns – neuronal effect like suckling
- 5. chronic renal failure, returns to nml after transplant
- 6. drugs (verapamil, H2 blockers, estrogens, opiates, dopamine receptor antagonists, reserpine, amethyldopa)

Prolactinomas



- Most common functional pituitary tumor
- 10% are lactotroph and somatotroph such as GH producing
- Presents with amenorrhea and infertility
- Prolactinomas lose TRH response
- Microadenomas <10mm on MRI
- Macroadenomas >10mm

Symptoms

- Premenopausal women:
 - Hypogonadism, amenorrhoea or oligomenorrhoea, infertility, Galactorrhoea
- Men: hypogonadotropic hypogonadism, decreased libido, infertility, galactorrhoea, Gynecomastia

Treatment Pregnancy Not Desired

- Treat only if symptomatic
 - (HA, vision changes)
- Dopamine agonist (Bromocriptine)
 - 1.25mg qhs 1 wk, then BID
 - If intolerant with nausea, may give vaginally
 - Not recommended for breastfeeding
- Transspenoidal surgery if unsuccessful

Gonadotroph adenoma

- Usually considered non-functioning
 - Secrete inefficiently, variably
- Presents with neurologic symptoms
- Difficult to Diagnose
 - Rule out other adenomas
 - Prepubertal girls= breast devel, vag. Bleeding
 - Premenopausal= amenorrhea, oligo

Gonadotroph adenoma vs. menopause and ovarian failure

- High FSH with low LH
- High serum free alpha subunit
- High estradiol, FSH, thickened endometrium and polycystic ovaries

Treatment of non-functioning anterior pituitary gonadotrophin macroadenoma

- Transsphenoidal surgery
- +/- Radiation

Hypopituitarism

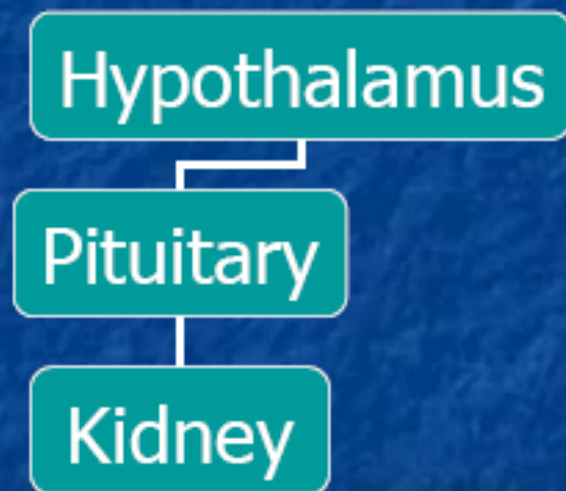
- 76% tumor or treatment of tumor
 - Mass effect of adenoma on other hormones
 - Surgical resection of non-adenomatous tissue
 - Radiation of pituitary
 - Check hormones 6 mos after and then yearly
- 13% extrapituitary tumor
 - Craniopharyngioma
- 8% unknown
- 1% sarcoidosis
- 0.5% Sheehan's syndrome

Infiltrative Lesions

- Hereditary Hemochromatosis
 - Fe deposition in pituitary
 - Gonadotropin deficiency most common
 - Tx repeat phlebotomy
- Pituitary Apoplexy
 - Sudden hemorrhage into pituitary
 - Severe, sudden HA; diplopia; hypopituitarism
 - Sudden ACTH def. is life-threatening hypotension
 - Tx: surgical decompression

Central Diabetes Insipidus

- Polydipsia and Polyuria (2-15 Liters/day)
- Abrupt onset
- 30-50% are idiopathic
 - Dec. production by hypothalamus
- Surgery or Trauma
- Rare with Sheehan's
 - Mild, undetectable degree



Dx of Central DI

- Water Deprivation test:
 - Restrict p.o. fluids or administer hypertonic saline to increase serum osmolality to 295-300 mosmol/kg (nml: 275-290)
 - Central DI: urine osmolality still low and returns to normal after administer vasopressin
 - Nephrogenic DI: exogenous vasopressin does not alter urine osmolality much

Treatment of Central D.I.

- DDAVP (Desmopressin Acetate)
 - Synthetic analog
 - Not catabolized by vasopressinase
 - No vasopressor action
 - Administered intranasally (rec.) or p.o.
 - Titrate 10-20ug qd or bid
 - Safe in pregnancy and breastfeeding

