

Pituitary Disorders

Objectives

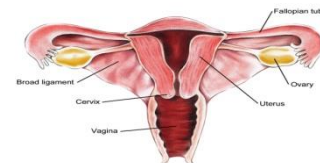
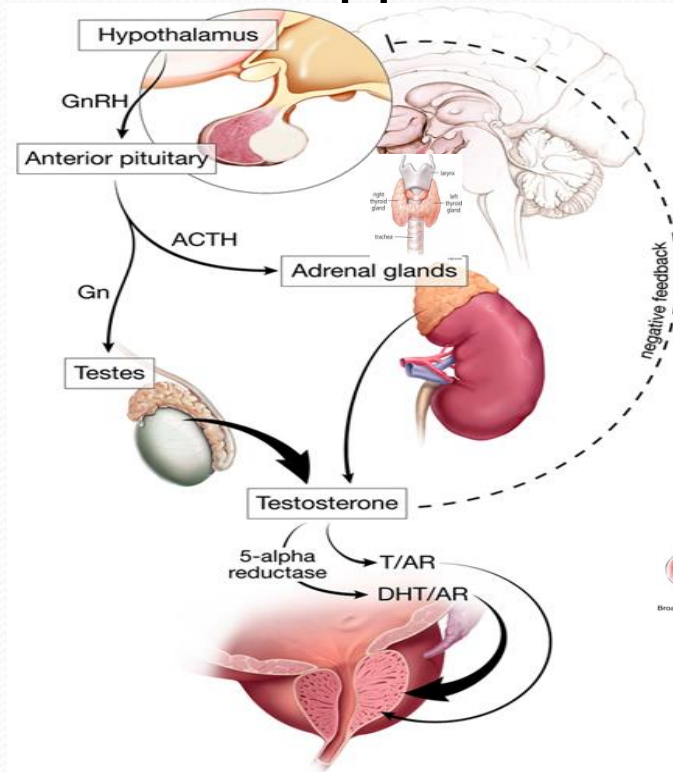
- Anatomy of hypothalamus and pituitary
- Function of hypothalamus and pituitary
- Hormones:
 - Anterior pituitary with related disorders
 - Posterior pituitary with related disorders

Hypothalamic-Pituitary Axis

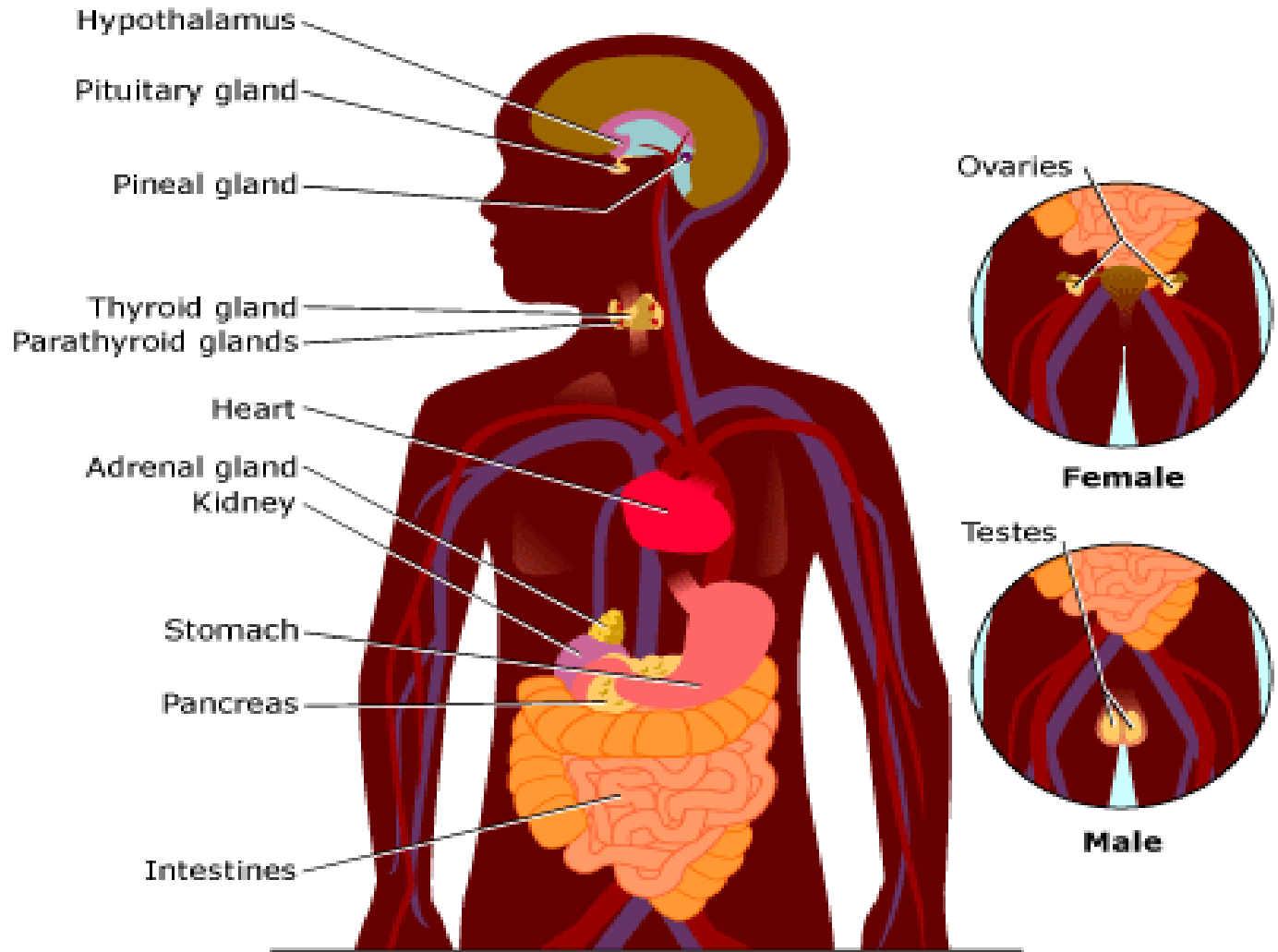
- The hypothalamus is the coordinator of Endocrine system
- Received signals from cortical brain, autonomic function, environment cues like light and temperature
- It affects function of thyroid gland, adrenal, gonads, growth, milk production and water balance

Hypothalamus-pituitary Axis

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



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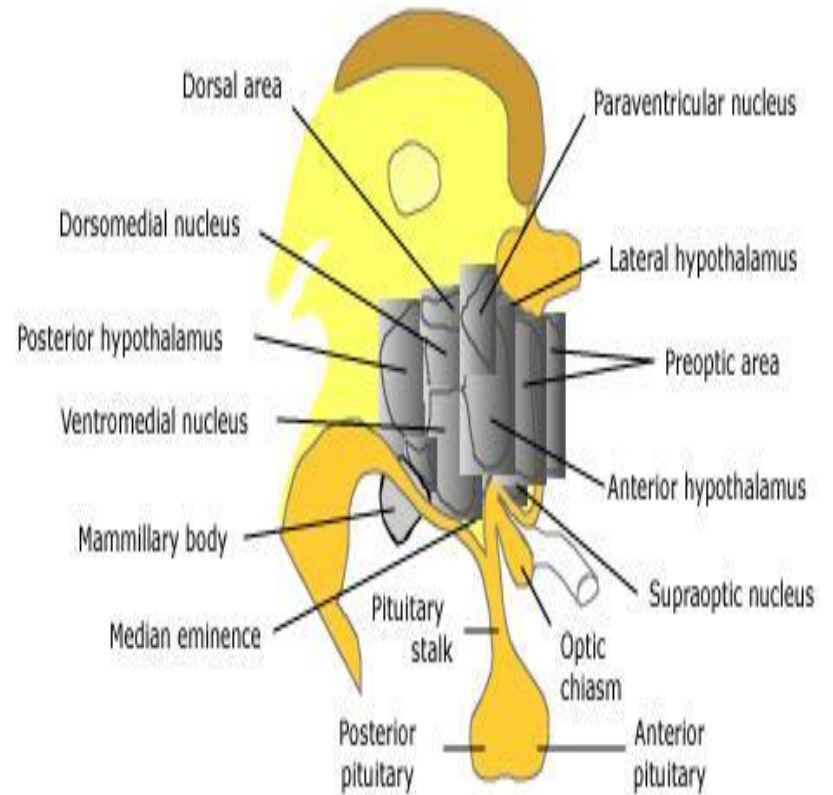
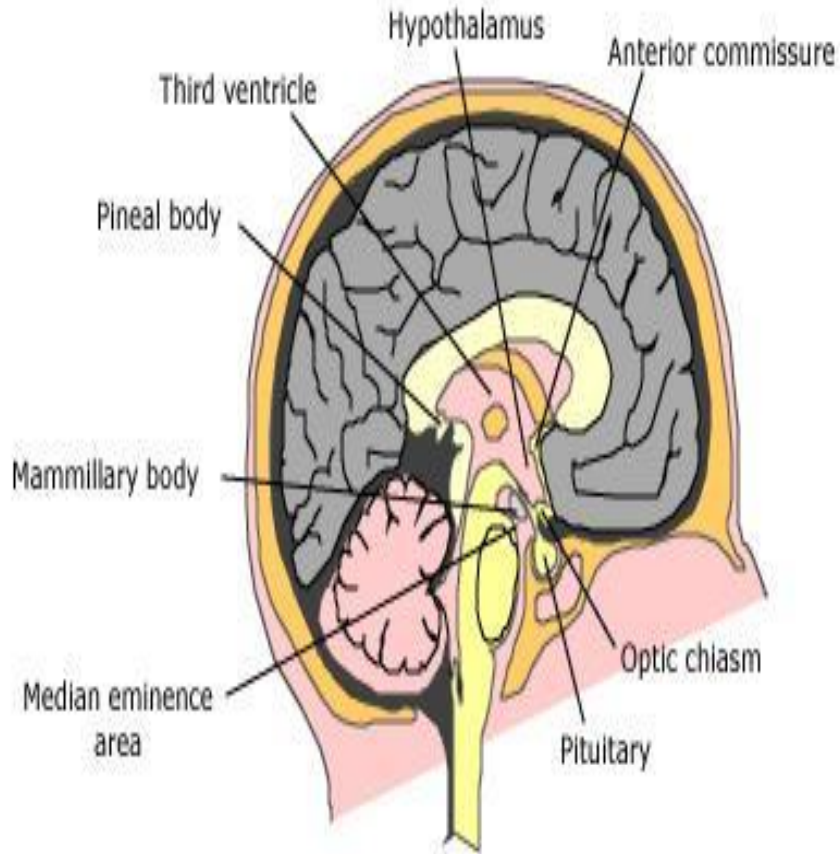


The Endocrine System

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

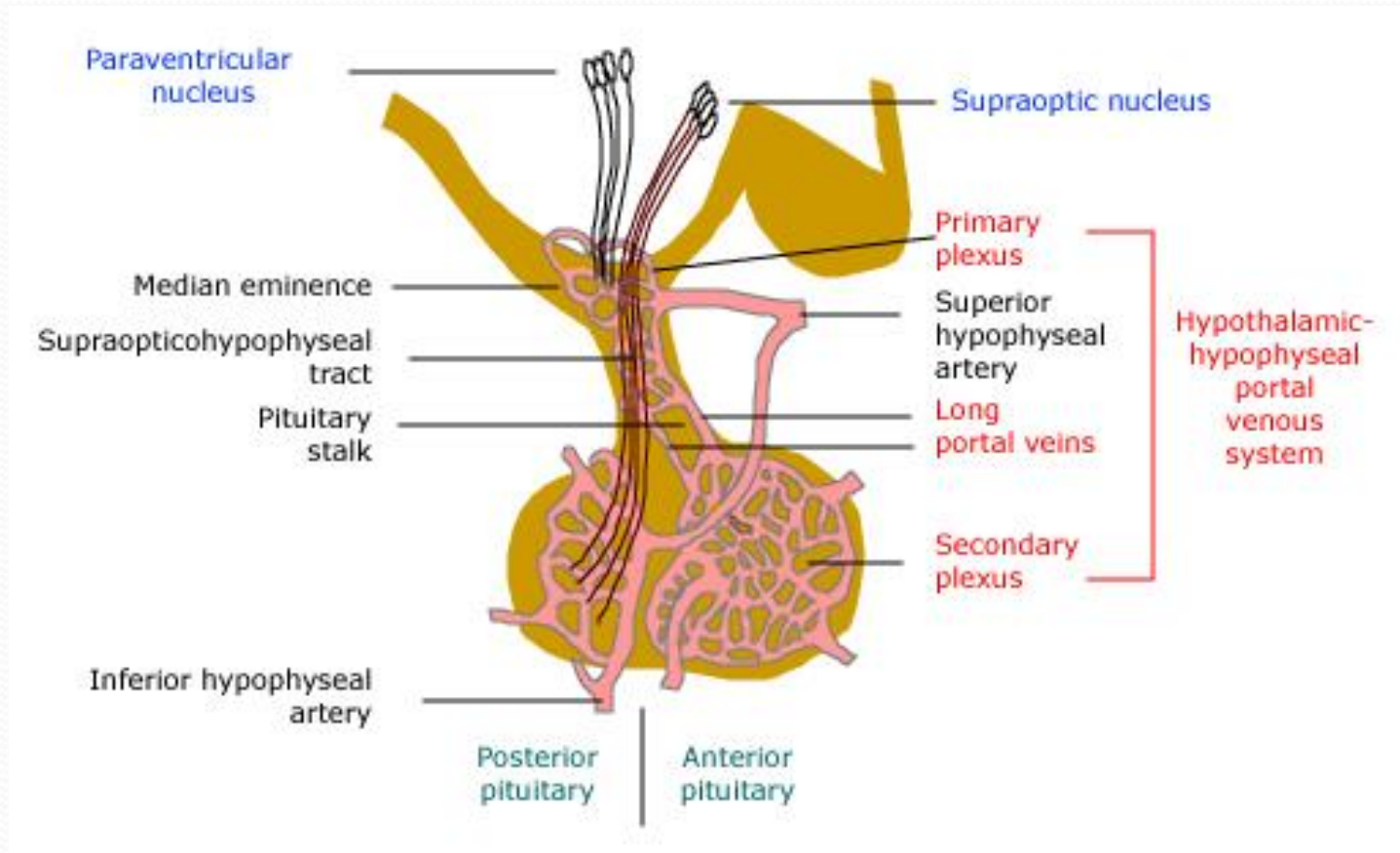
Hypothalamus



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

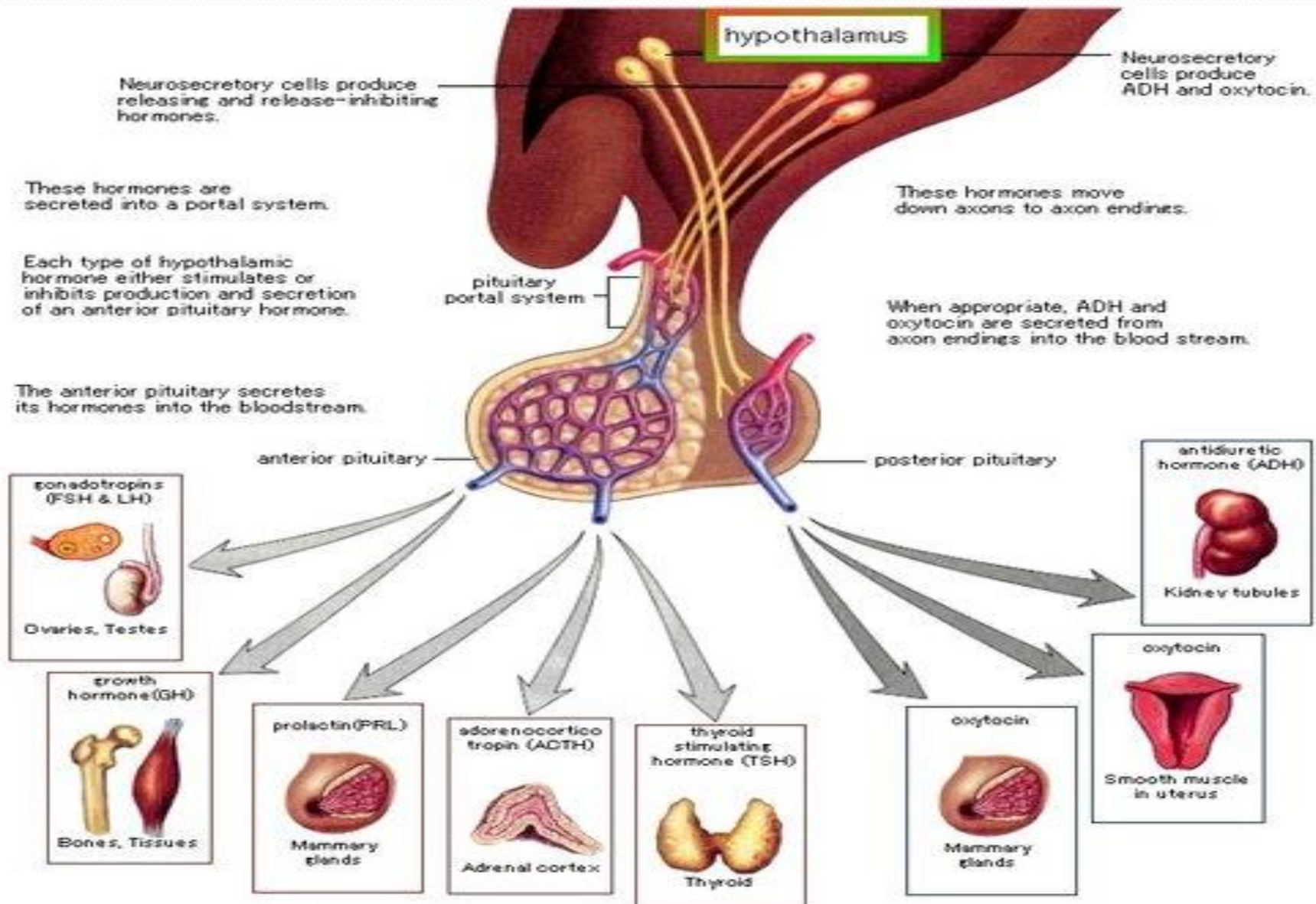
Hypothalamus



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



Neurosecretory cells produce releasing and release-inhibiting hormones.

Neurosecretory cells produce ADH and oxytocin.

These hormones are secreted into a portal system.


These hormones move down axons to axon endings.

Each type of hypothalamic hormone either stimulates or inhibits production and secretion of an anterior pituitary hormone.

When appropriate, ADH and oxytocin are secreted from axon endings into the blood stream.


The anterior pituitary secretes its hormones into the bloodstream.

gonadotropins (FSH & LH)



Ovaries, Testes

growth hormone (GH)




Bones, Tissues

prolactin (PRL)




Mammary glands

adrenocortico tropin (ACTH)




Adrenal cortex

thyroid stimulating hormone (TSH)




Thyroid

antidiuretic hormone (ADH)




Kidney tubules

oxytocin



Smooth muscle in uterus

oxytocin



Mammary glands

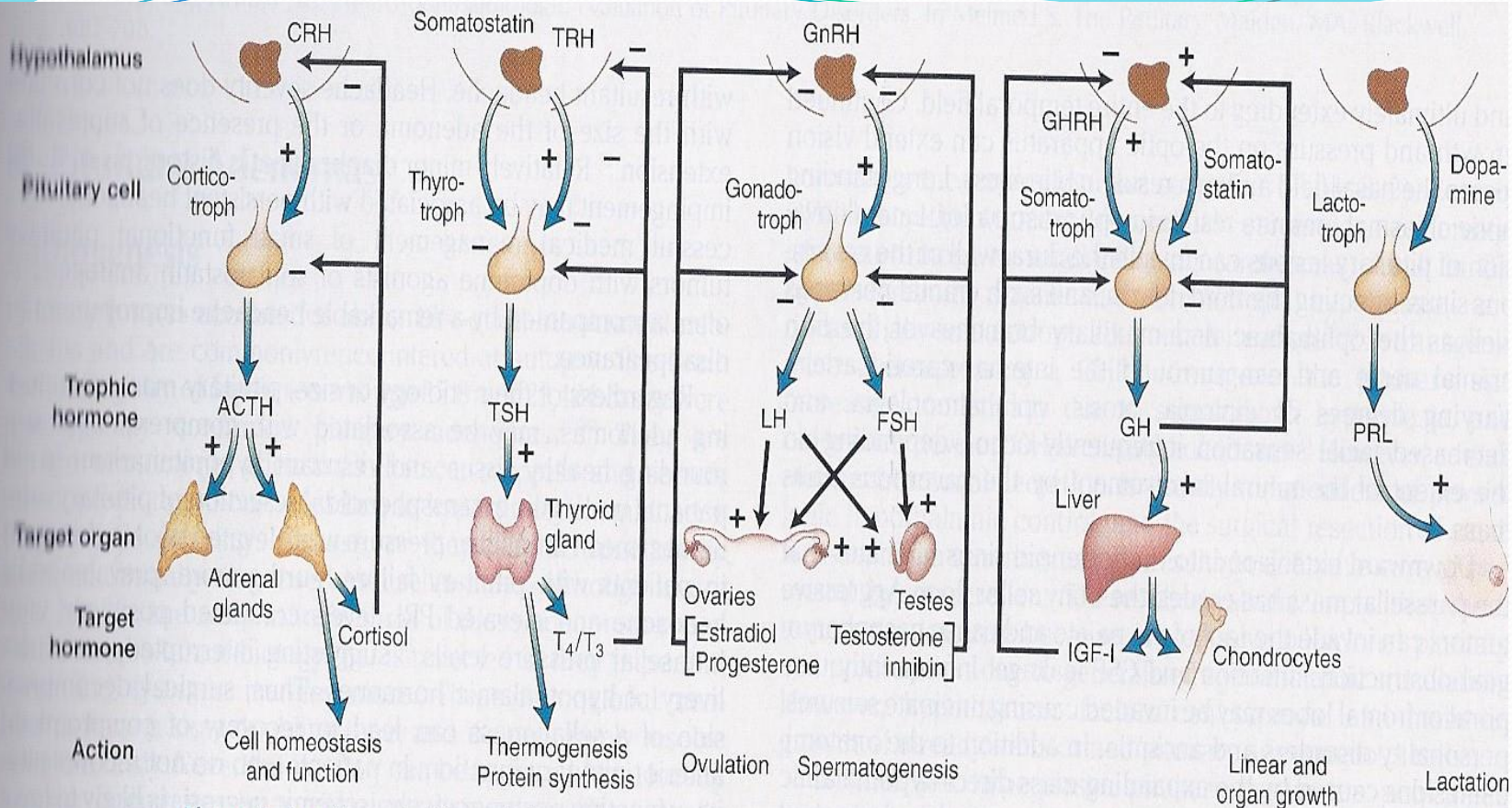


Figure 8-6 ■ Control of hypothalamic-pituitary target organ axes. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; 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

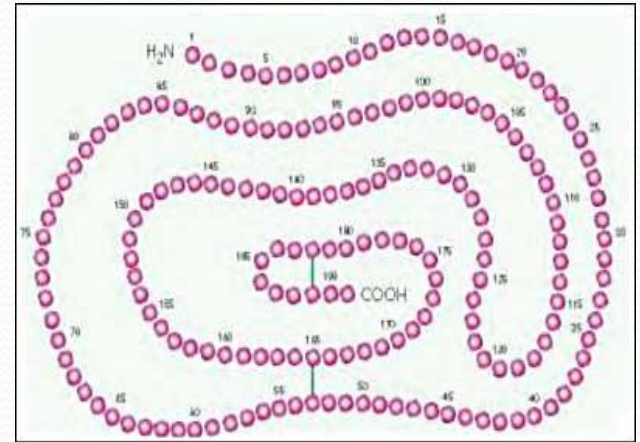
- Growth hormone (GH)
- Gonadotrophs (LH/FSH)
- TSH
- Prolactin
- Corticotropin (ACTH)

Posterior Lobe

- Oxytocin
- Vasopressin

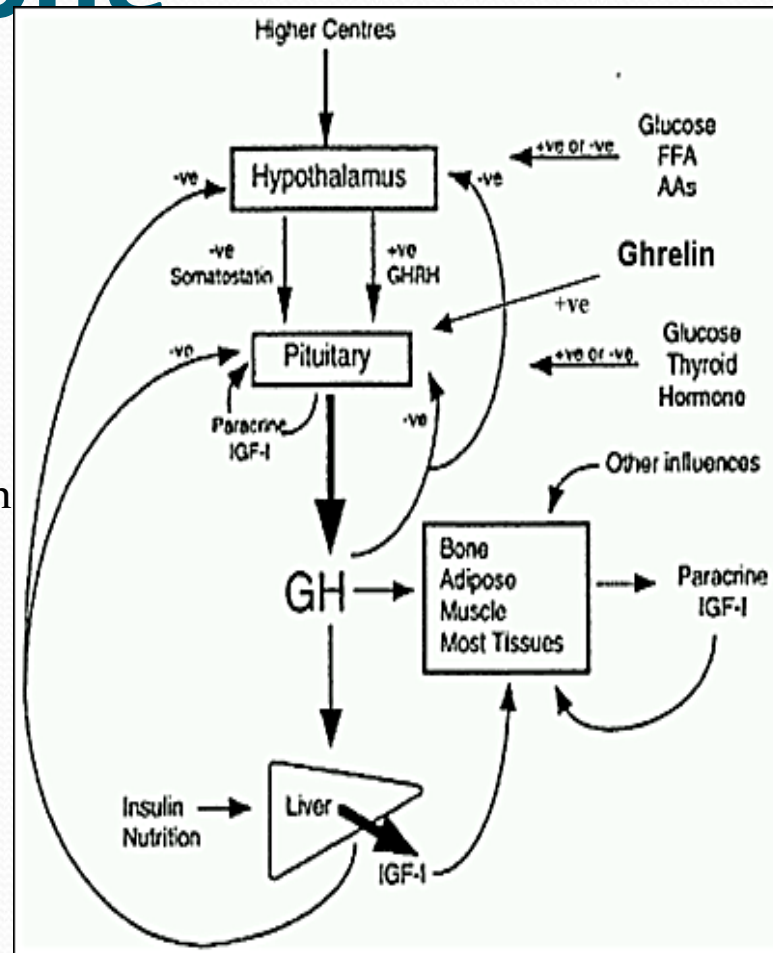
Growth hormone

- Polypeptide hormone
- Somatotrophs of anterior pituitary
- Action is mediated by IGF-I
- Half life is 20-50 mins
- Has a binding protein: GHBPs
- 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

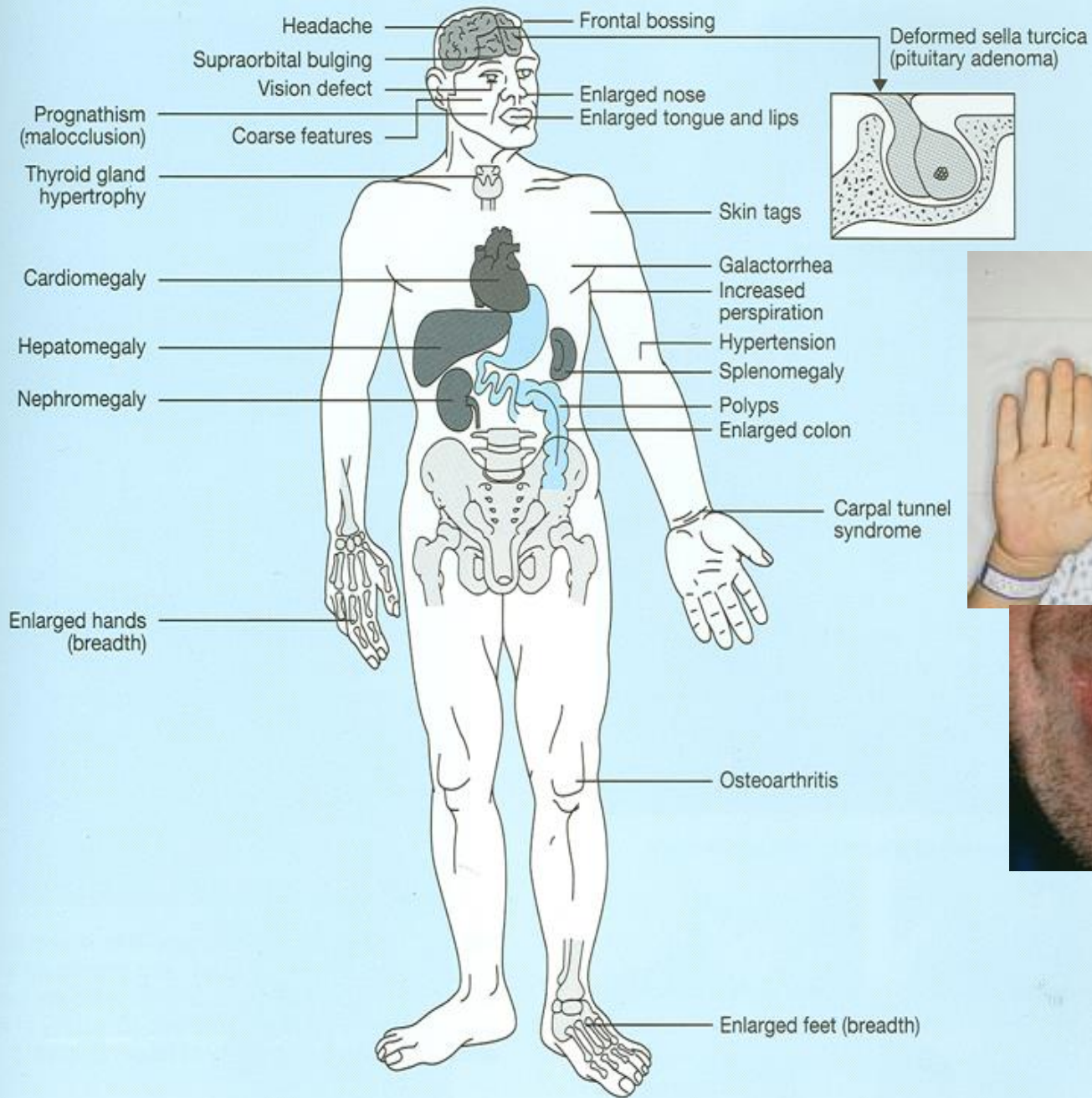
- **↑↑ GH:**
- **Physiologic:**
sleep, exercise, stress, fasting
- **Pathologic:**
Liver cirrhosis, AN, CRF, starvation
- **Pharmacologic:**
Estrogen, ACTH, ADH, GHRH, Ghrelin
dopamine agonist, K infusion, serotonin
arginin
- **↓↓ GH:**
- **Physiologic:**
↑glucose, ↑ FFAs,
- **Pharmacologic:**
Somatostatin,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



- In adults



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

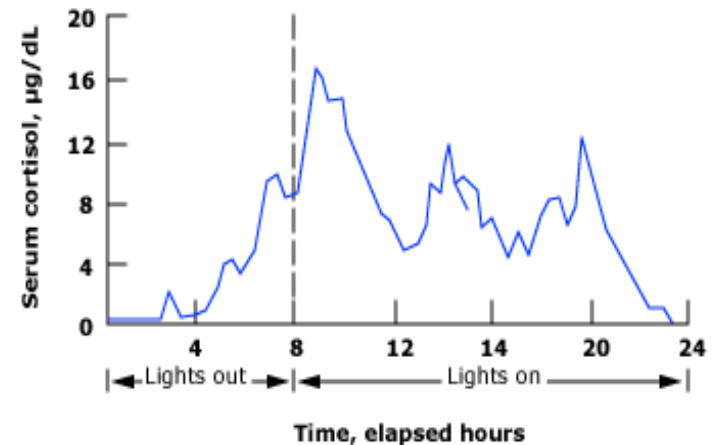
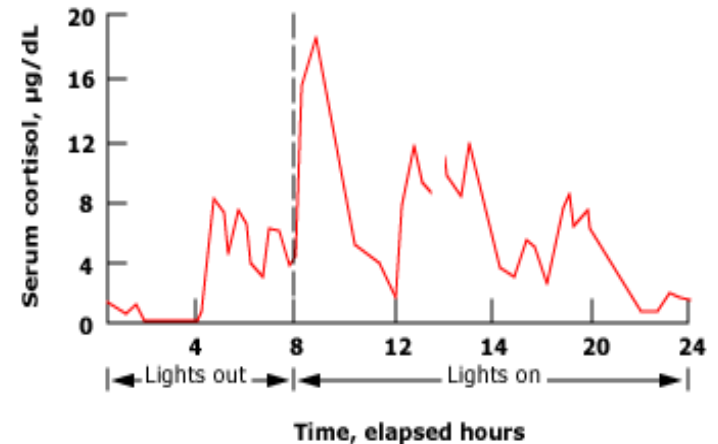
- Altered by:

Physical stress

Psychological stress

CNS and pituitary disorder

liver and renal failure



Cushing's Disease

- High ACTH leading
- More common in females 3-8 times than in men
- Generally not common : 5-25 per million

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

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
- Transsphenoidal 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

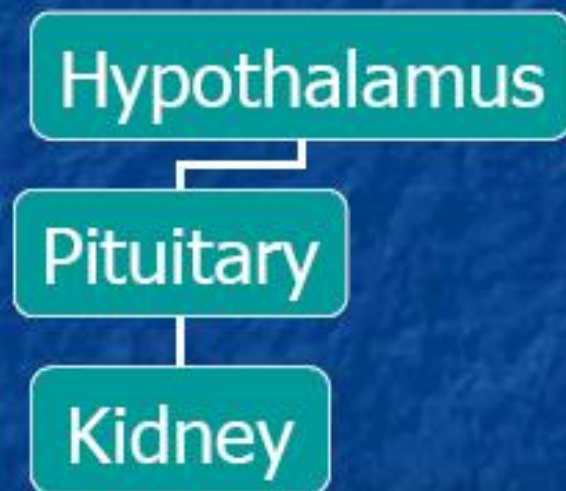
- 76% tumor or treatment of tumor
 - Mass effect of adenoma on other hormones
 - Surgical resection of non-adenomatous tissue
 - Radiation of pituitary
 - Check hormones 6 mos after and then yearly
- 13% extrapituitary tumor
 - Craniopharyngioma
- 8% unknown
- 1% sarcoidosis
- 0.5% Sheehan's syndrome

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

