ENDOCRINES

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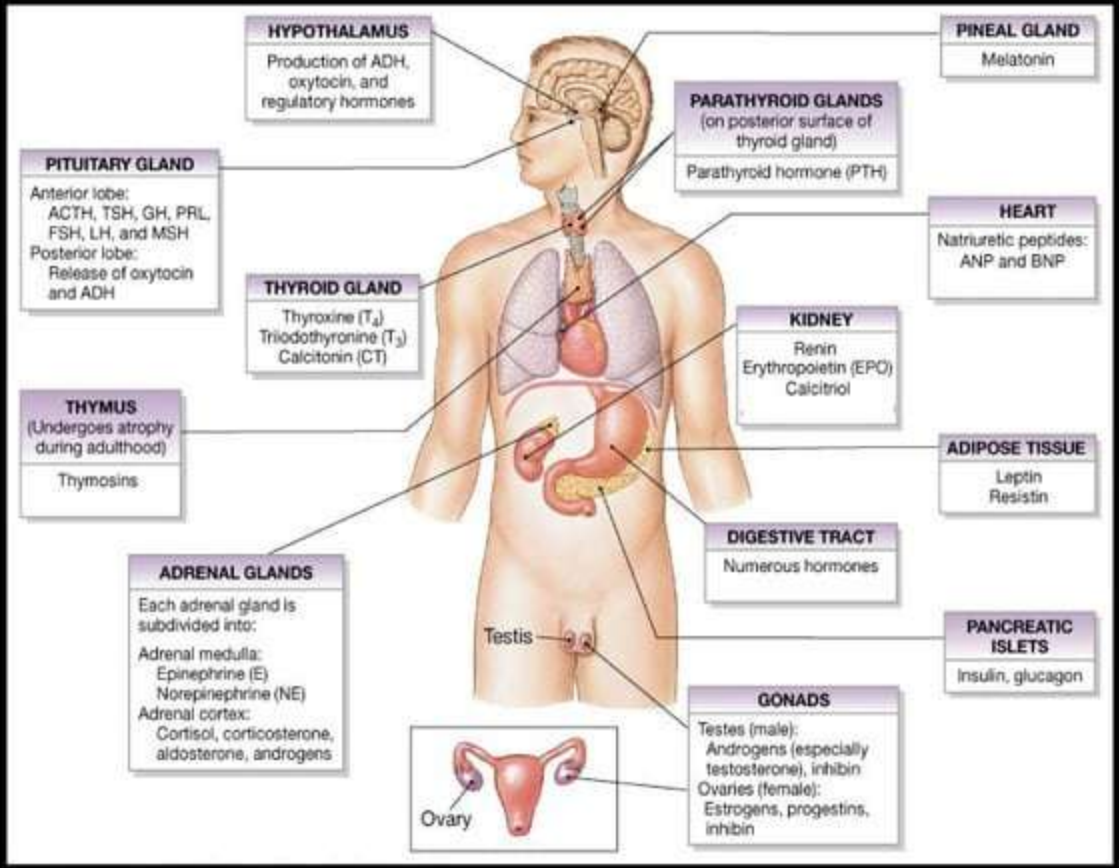
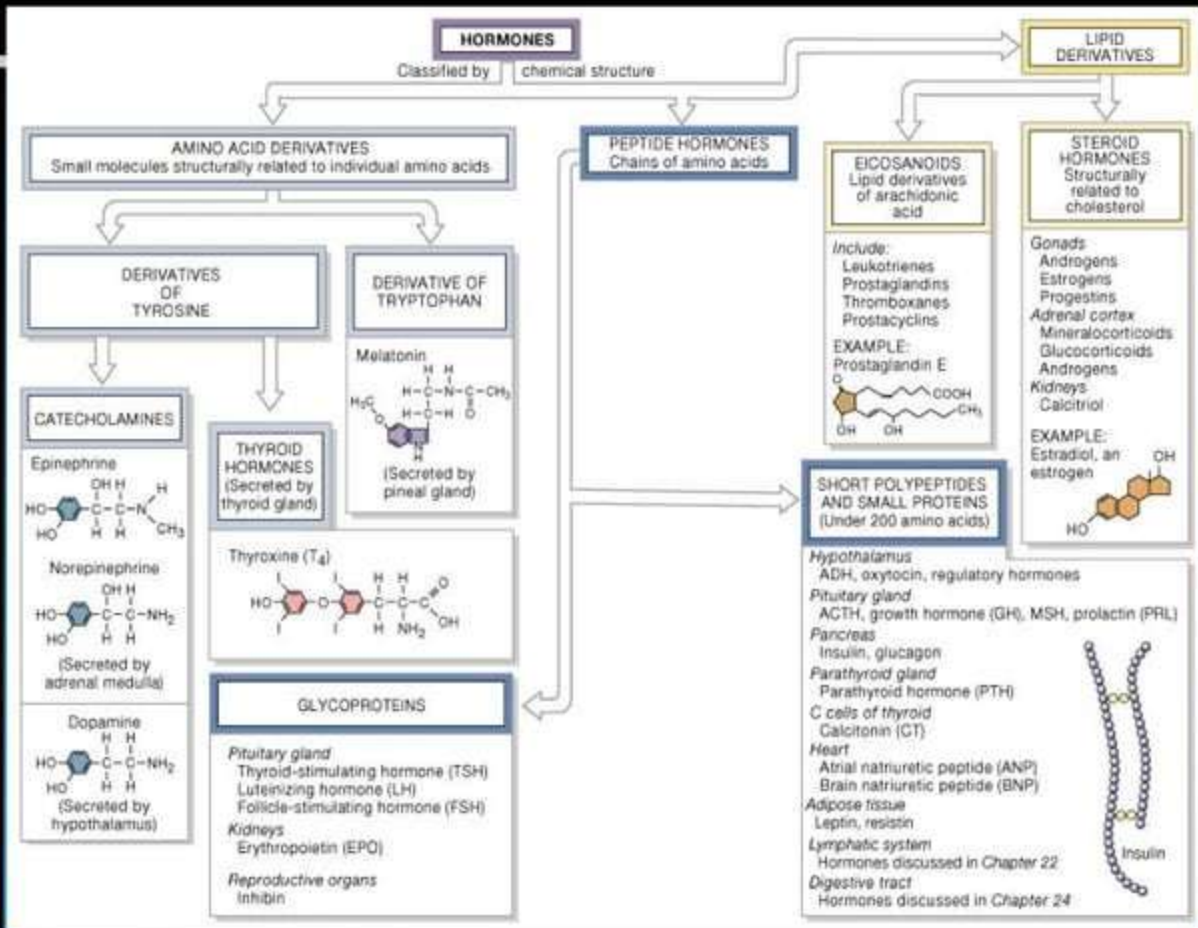
Endocrine versus Nervous system

- Nervous system performs short term crisis management
- Endocrine system regulates long term ongoing metabolic process.
- Endocrine communication is carried out by endocrine cells releasing hormones
  - Alter metabolic activities of tissues and organs
  - Target cells
- Paracrine communication involves chemical messengers between cells within one tissue

The Endocrine System



A Structural Classification of Hormones



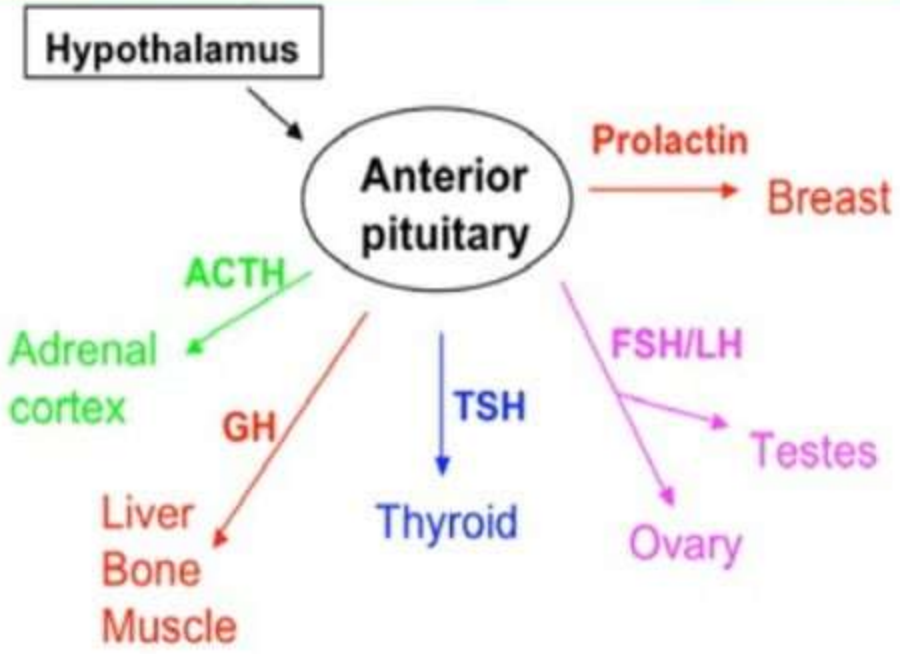
Hormones can be

- Freely circulating
- Rapidly removed from bloodstream
- Bound to transport proteins

Mechanisms of hormone action

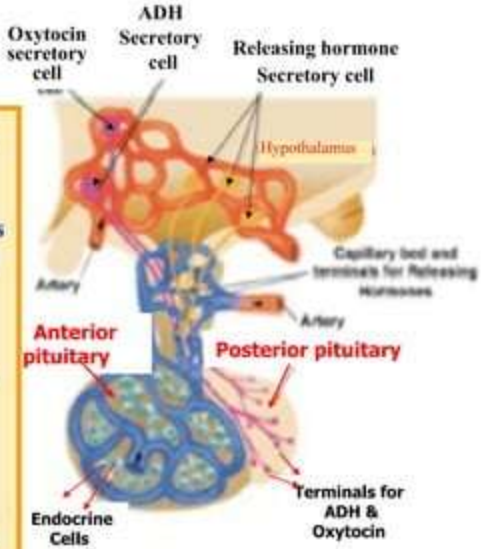
- Receptors for catecholamines, peptide hormones, eicosanoids are in the cell membranes of target cells
- Thyroid and steroid hormones cross the membrane and bind to receptors in the cytoplasm or nucleus

Axes Controlled via the Anterior Pituitary

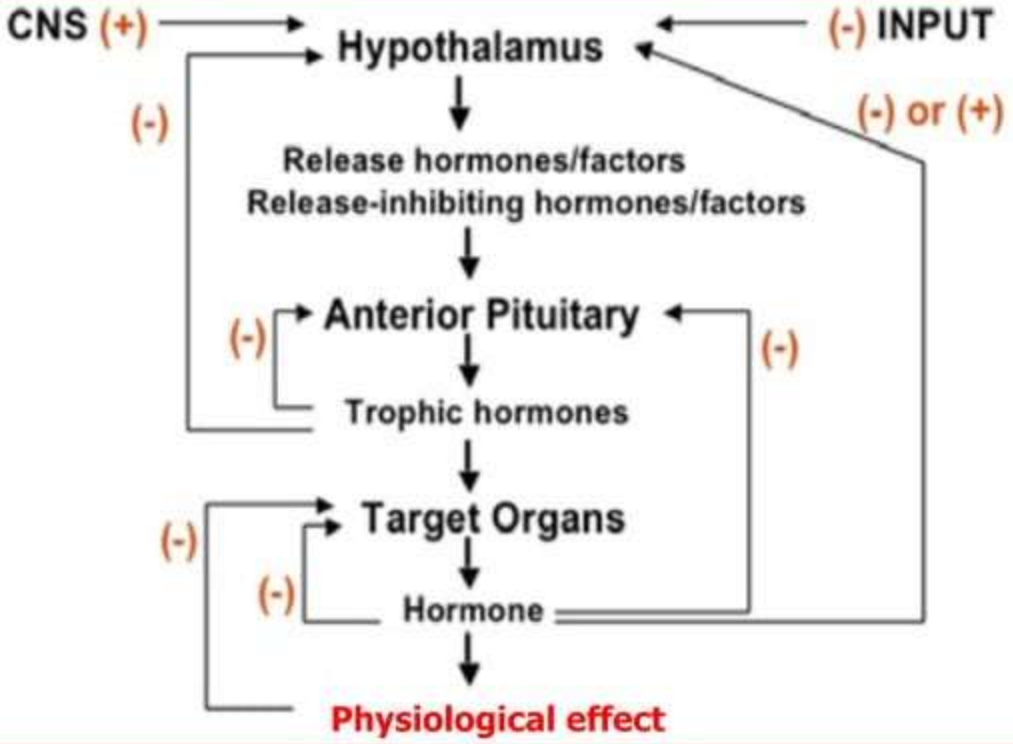


Pituitary Gland

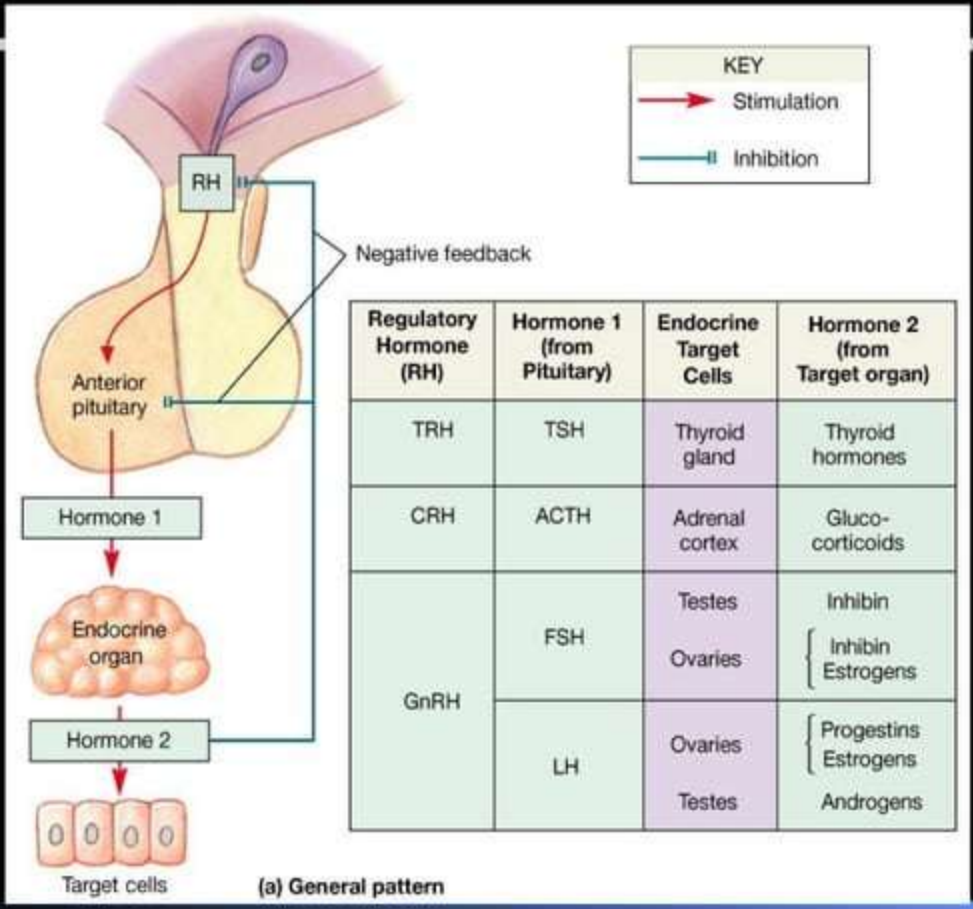
- Small round gland attached to base of brain
- Three lobes:
  - Anterior (adenohypophysis)
  - Intermediate
  - Posterior



Feedback Regulation of Hormone Release



Feedback control of Endocrine Secretion



Regulatory Hormone (RH)	Hormone 1 (from Pituitary)	Endocrine Target Cells	Hormone 2 (from Target organ)
TRH	TSH	Thyroid gland	Thyroid hormones
CRH	ACTH	Adrenal cortex	Gluco-corticoids
GnRH	FSH	Testes	Inhibin
		Ovaries	Inhibin, Estrogens
	LH	Ovaries	Progestins, Estrogens
		Testes	Androgens

Feedback control of Endocrine Secretion

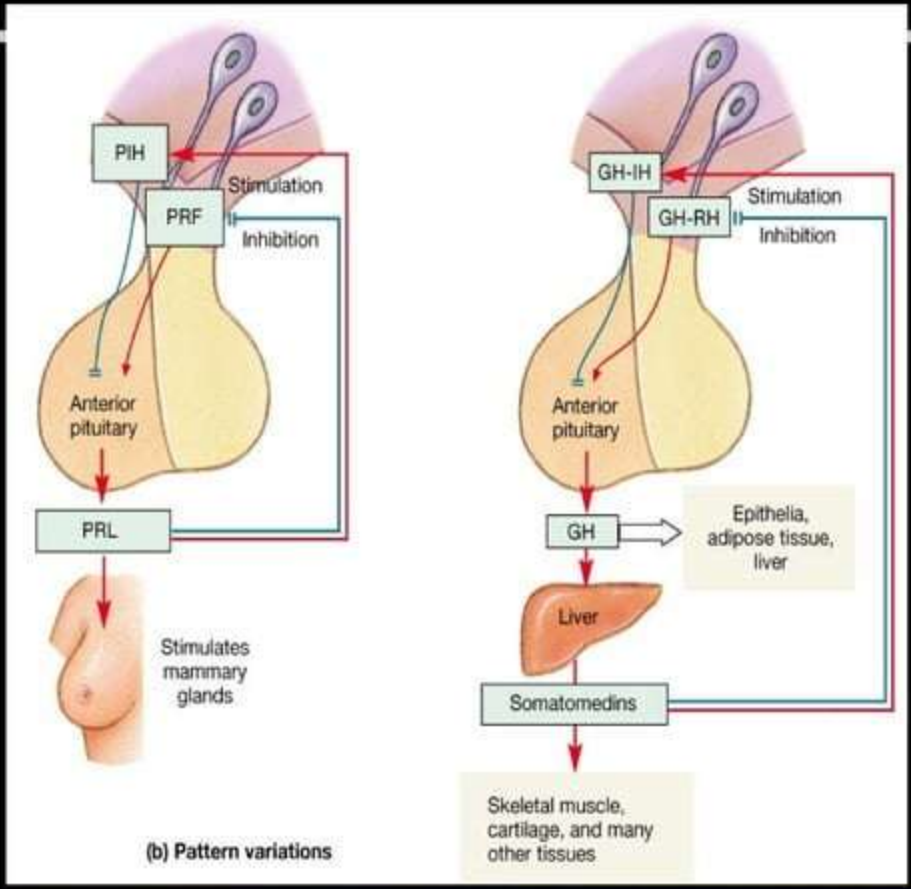


Figure 18.8b

Hormones of the Anterior pituitary

- Thyroid stimulating hormone (TSH)
  - Triggers the release of thyroid hormones
  - Thyrotropin releasing hormone promotes the release of TSH
- Adrenocorticotropic hormone (ACTH)
  - Stimulates the release of glucocorticoids by the adrenal gland
  - Corticotrophin releasing hormone causes the secretion of ACTH

Hormones of the Anterior pituitary

- Follicle stimulating hormone (FSH)
  - Stimulates follicle development and estrogen secretion in females and sperm production in males
- Leutinizing hormone (LH)
  - Causes ovulation and progestin production in females and androgen production in males
- Gonadotropin releasing hormone (GNRH) promotes the secretion of FSH and LH

Hormones of the Anterior pituitary

- Prolactin (PH)
  - Stimulates the development of mammary glands and milk production
- Growth hormone (GH or somatotropin)
  - Stimulates cell growth and replication through release of somatomedins or IGF
    - Growth-hormone releasing hormone (GH-RH)
    - Growth-hormone inhibiting hormone (GH-IH)

Hormones of the Anterior pituitary (intermediate lobe)

- May be secreted by the pars intermedia during fetal development, early childhood, pregnancy or certain diseases
- Stimulates melanocytes to produce melanin

Growth Hormone (Somatotropin)

- Most abundant pituitary hormone
- (10 - 15%)
- 21 kDa protein
- 91 amino acids
- Structurally similar to prolactin
- Half life = 20 –25 min; binds specific plasma proteins; increase half life for transport

Growth Hormone: Physiologic Effects

- **Promotes Growth**
  - Increases cell number in organs
  - Skeletal growth
  - Cartilage formation
  - Collagen biosynthesis (epiphysal plates)
  - Muscle cell growth
- **Promotes Protein Synthesis**
  - Positive nitrogen balance
  - Increases amino acid uptake
  - Decreases urea excretion
- **Carbohydrate and Lipid Metabolism**
  - Promotes fat usage
  - Switches metabolism from carbohydrate to fat
  - ↑ blood glucose (ketosis ??)
  - Exercise & Hypoglycemia ↑GH
  - ↑Fatty acid release from adipose

Growth Hormone Action

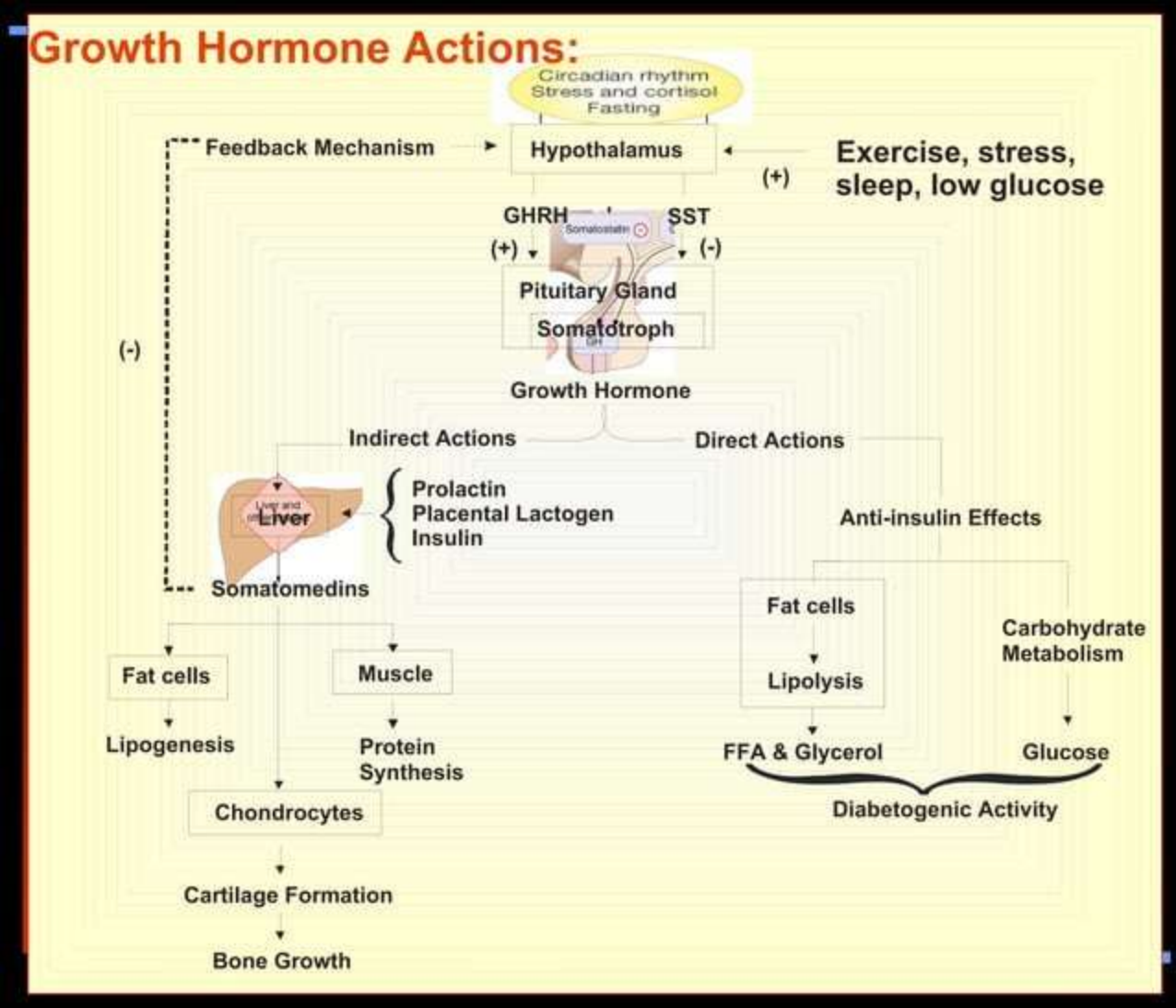
Growth Hormone Action

- Increased fat metabolism
- Collagen biosynthesis
- Fountain of youth?

Growth Hormone Action

- Synthesized and stored in Anterior Pituitary
  - Somatatrophs (specialized cells in AP)
- Most functions via **somatomedins**
  - Group of peptide hormones produced predominantly in liver: **insulin-like growth factors (IGF)**
  - IGF–1: homologous to insulin; binds to specific IGF-1 receptor; widely distributed; IGF-1 also produced in bone (controlled by parathyroid hormone and pGE2)
  - IGF-2: produced in fetal tissue; important in fetal development; in adults important in brain, liver and kidney function; converted to IGF-1; binds IGF-1 receptor

Growth Hormone Actions:



Growth Hormone Release

Release- **pulsatile**

6–8 discrete pulses/day

Distribution of pulses varies with age

Most pronounced pulse: just after onset of deep sleep

Children: 50 –75% GH released during sleep

Adolescents: ↑ secretion during waking hours

Growth Hormone Plasma Levels

- Mid-fetal life: 150 ng/ml
- Children: 5-10 ng/ml
- Adults: 2-5 ng/ml
- Elderly: <2 ng/ml

Other Hormones Affecting Growth

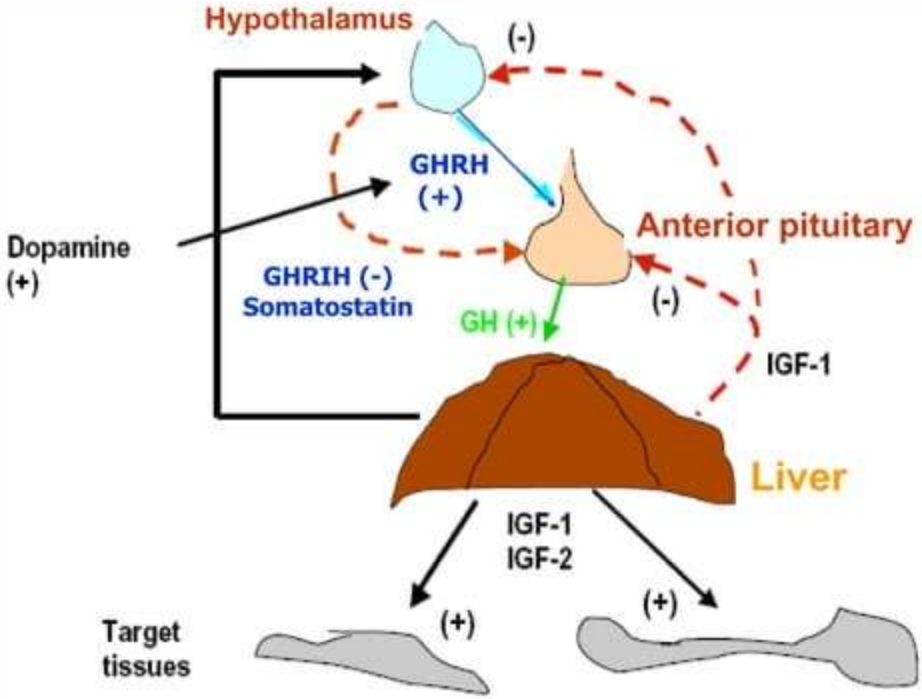
- Prolactin: stimulates IGF-1
- Insulin: stimulates IGF-1
- Thyroid Hormone
- Glucocorticoids
- Estrogen
- Testosterone

Control of Growth Hormone Release

Hypothalamus

- **Growth Hormone Releasing Hormone (GHRH):**
  - Stimulates GH release
  - Release is pulsatile
  - Can be used in diagnosis of GH deficiency
  - Binds to specific receptors on somatotrophs in anterior pituitary
- **Somatostatin (GHRIH):**
  - Blocks GH release from somatotrophs
  - Widely distributed outside hypothalamus
  - Inhibits a variety endocrine and exocrine glands
  - ↓insulin levels
  - Affects other axes

Regulation of GH (Somatotropin) Release



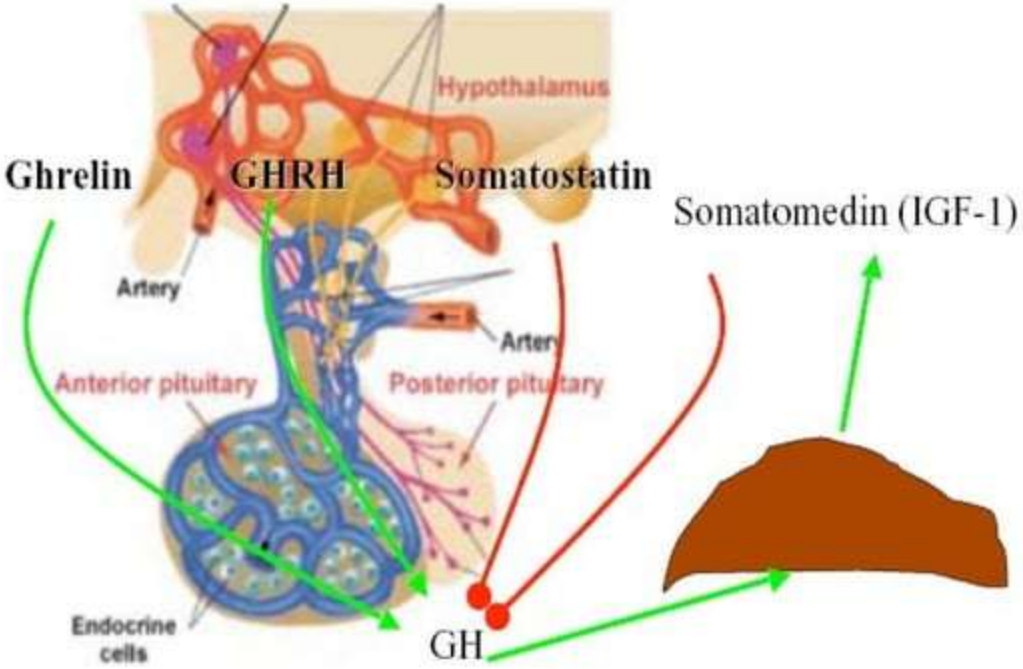
Ghrelin

- So-called "hunger hormone" discovered in 1999
- Produced in fundus of stomach and arcuate nucleus of hypothalamus
- Stimulates GH release in anterior pituitary via separate mechanism to GHRH, utilizes the Growth Hormone Secretagogue Receptor
- Important in hippocampus neurotrophy (learning effects)
- Increases food intake and fat mass-part of reward circuit (comfort food)
- Sleep increases levels (while lowering leptin levels)

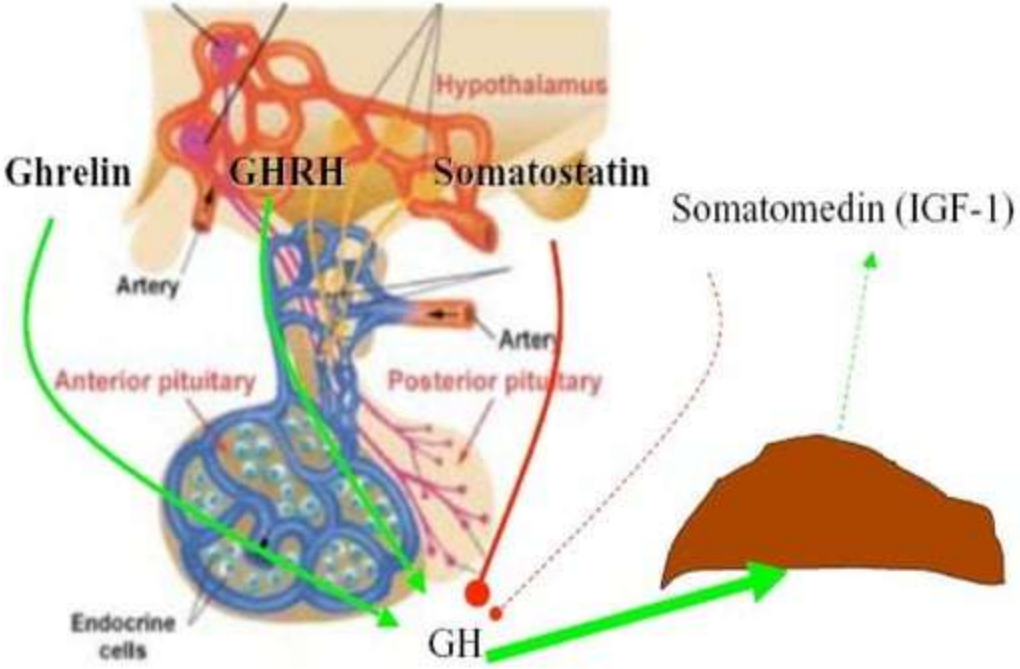
Ghrelin

- Disrupted ghrelin circadian rythmn in obese
- Promotes lung growth and development in the fetus
- Prader-Willi Syndrome characterized by high fasting levels
- Can be severely affected by gastric bypass surgery
- Obestatin is a converse hormone generated by differential splicing of ghrelin precursor
- Anti-obesity vaccine?

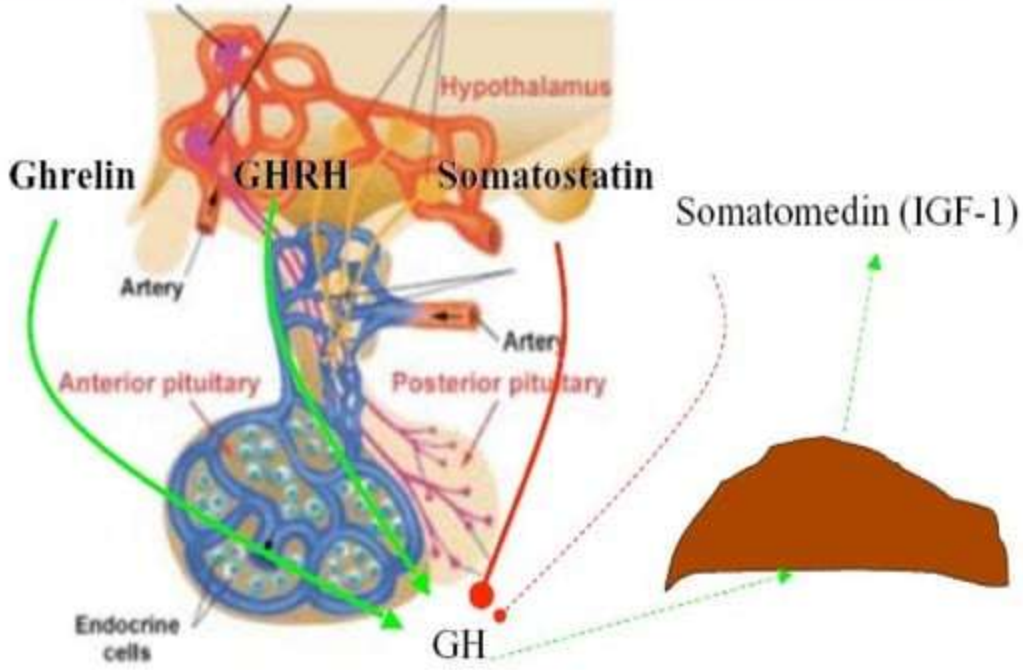
Hypothalamic Pituitary GH Axis



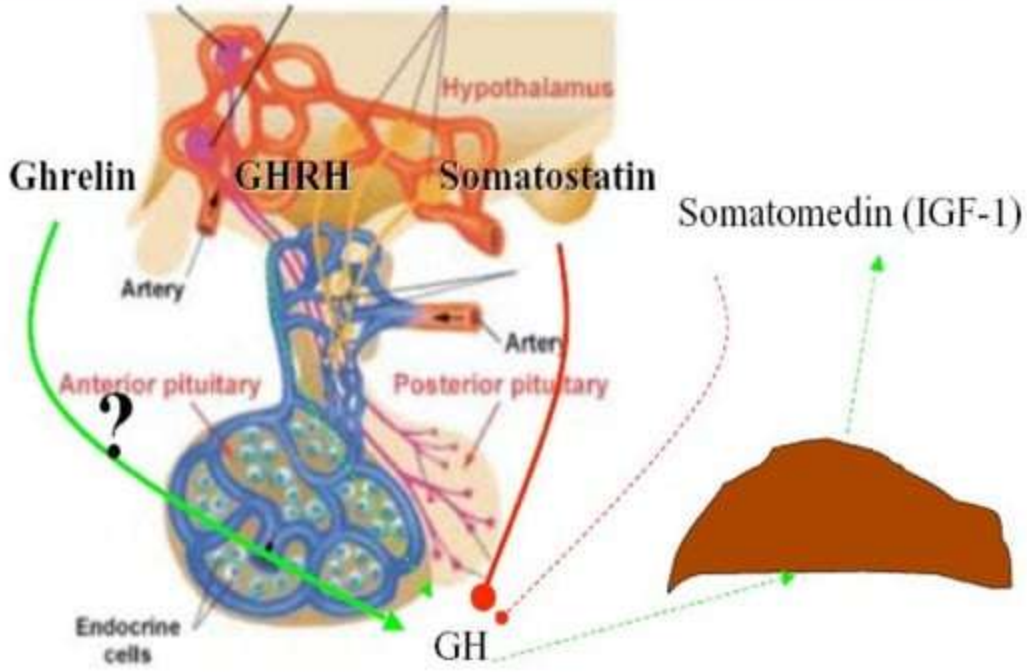
GH Insensitivity (Laron dwarfism)



Secondary Deficiency



Tertiary Deficiency



Regulation of GH Release

- **Stimulation of GH secretion**
  - ↓ blood glucose
  - ↑ blood amino acids (arginine, leucine- from high protein meal)
  - GHRH, TRH, ADH, glucagon, dopamine, uncontrolled diabetes
  - Drugs: dopamine agonists-bromocriptine, insulin, glucagon
  - Exercise, stress, sleep, fever, puberty
- **Inhibition of GH secretion**
  - Somatostatin; IGF-1 (feedback inhibition); hypothyroidism
  - Increased blood glucose
  - Dopamine antagonists, chlorpromazine
  - Emotional deprivation in children, aging

Therapeutic Uses of Growth Hormone

Source:

- **Human**: use stopped in 1985; contamination with slow virus-

  Creutz Feldt Jakob disease
- **Synthetic**: recombinant growth hormone (Somatrem)

Used diagnostically and therapeutically

Anterior Pituitary Abnormalities

Hypopituitarism

- Children: failure of pituitary to develop (hypopituitary dwarfism)

Hyperpituitarism (oversecretion)

Example: ↑↑ GH => Acromegaly

Therapeutic Uses of Growth Hormone

Hypopituitary dwarfism: failure of pituitary to develop; diagnosed by failure to produce GH in response to insulin, arginine, sleep, levodopa; treat with rGH (somatropin, somatrem)→ increases growth; can exacerbate diabetes. Sermorelin-synthetic GHRH

Acromegaly: excessive GH release (95% pituitary tumors); disproportionate growth of bones and tissues

Treatment: -Surgery to remove tumor

-GH receptor antagonist (pegvisomant); normalizes IGF-1 levels

-Somatotstatin agonists (octreotide)

-Dopaminergic agonist (bromocriptine): inhibits GH release caused by tumor *(negative feedback?)*

Somatostatin Analogs

SST-14 Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys

Octreotide D Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr

- Analogs have different receptor binding profiles to SST
- Reduce GH release and decrease adenoma size
- Significant effects on thyrotropin release
- Can lead to gallstones and mess up glycemic control
- Difficult to administer
- Interfer with cytokine production potential anti-inflammatory effects.

Prolactin

-Structure similar to GH

-Glycoprotein hormone

-Synthesized and stored in **lactotrophs**

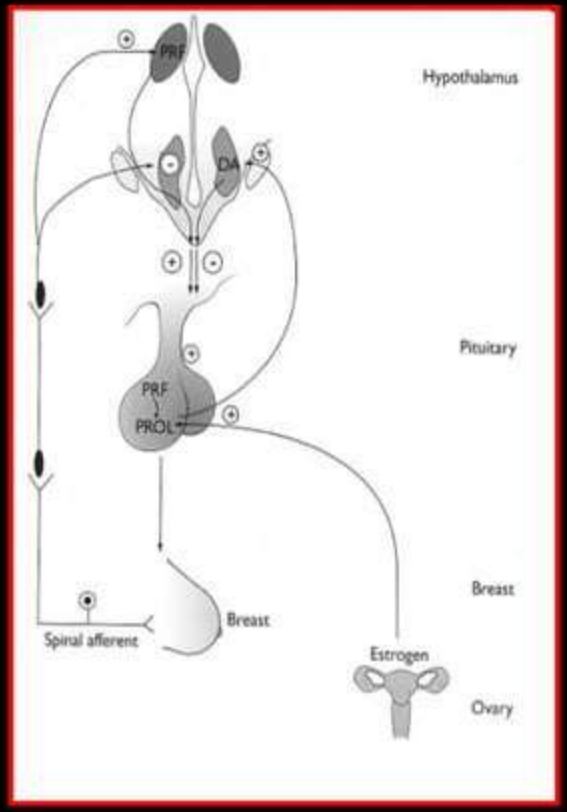
-Principally responsible for lactation

-Effects on gonads- species specific

-Concentration increases 20 –40x during pregnancy

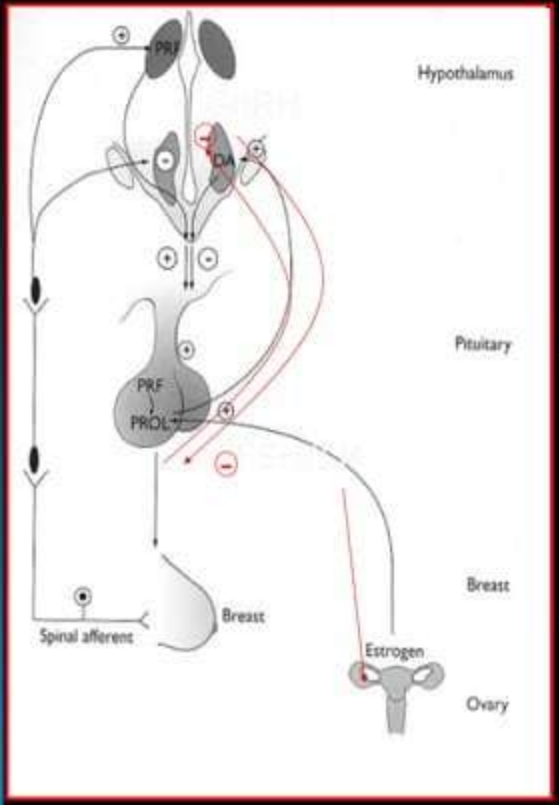
-Mechanism of action- binds to cell surface receptors

Prolactin regulation



- Prolactin is under tonic inhibitory control by the hypothalamus through release of dopamine
- Increased levels of estrogen in pregnancy induce release of prolactin
- Suckling overrides dopamine's inhibitory control through neurogenic signals from the breast.
- Suckling increases prolactin levels markedly (100 fold increase within 30 min of breast feeding)

Increased Prolactin during nursing



- Increased levels of prolactin in nursing mothers decrease the release of GnRH from the hypothalamus (by negative feedback inhibition)
- This causes a corresponding decrease in release of LH and FSH ("gonadotropins") resulting in <u>suppression of ovulation</u>
- This provides a natural form of contraception while a mother is breast feeding.

Regulation of Prolactin Secretion

- **Hypothalamus**

  -Prolactin releasing hormone (PRH)

  -Prolactin release inhibitory hormone (PRIH) (dopamine); Unique- HT influence primarily negative
- **Pregnancy and Nursing:** increase prolactin secretion
- **Drugs**:

  Dopamine antagonists (ex., opiates, barbituates, antipsychotics)- *increase* prolactin secretion

  Dopamine agonists (ex., levodopa, bromocriptine); MAO inhibitors (block dopamine metabolism)

  decrease prolactin secretion

Physiological Effects of Prolactin

-Growth and development of breasts during pregnancy

-Maintains lactation (in presence of estrogens, progesterone, insulin and corticosteroids)

-Blocks effects of FSH and LSH; initially prevents lactation

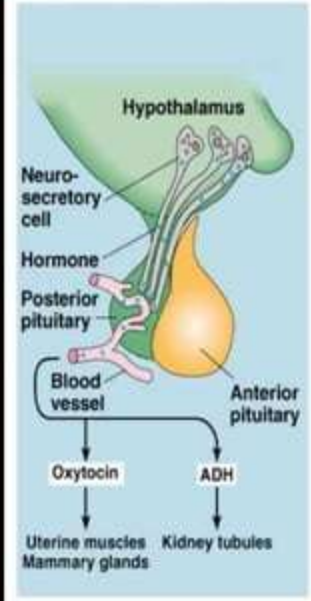
Therapeutic Uses of Prolactin

No known therapeutic use of prolactin

Prolactin hypersecretion (pituitary tumors):

- Treatment:
  - Decrease dopamine turnover
  - **Bromocriptine** (dopamine agonist)

Major Hormones of the Posterior Pituitary



Hormone	Target	Effects
Antidiuretic hormone (vasopressin)	Renal tubule	Increased renal absorption of water, excretion of concentrated urine and fluid conservation
Oxytocin	Breast, Uterus	Contraction of myoepithelial cells of mammary gland milk ducts – forces milk from alveoli of breast (oxytocin release stimulated by suckling) -can also induce contraction of pregnant uterus (but not main stimulus of parturition)

NEXT CLASS ON THYROID HORMONES

& ANTITHYROID DRUGS