Endocrine Physiology
Fall 2023

Lecture 2
Part 1
Pituitary Hormones and Their Control by Hypothalamic Hormones

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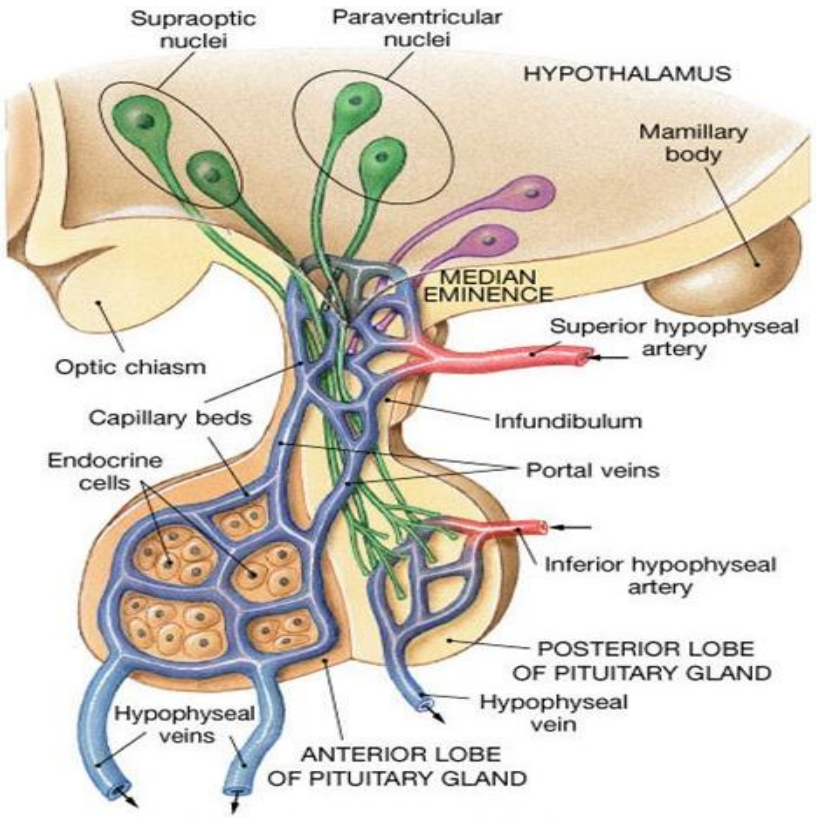
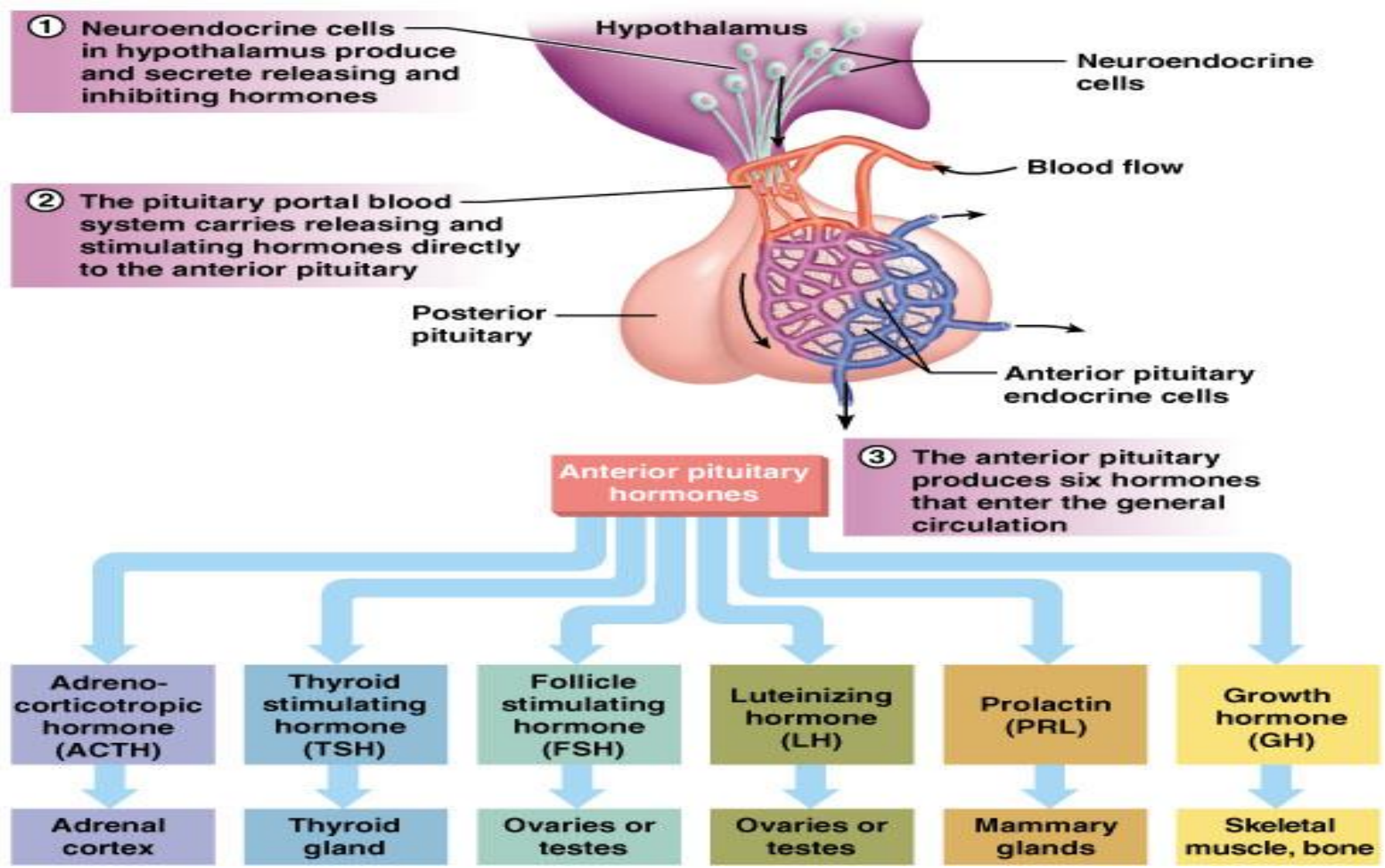
Lecture objectives

- Describe the anatomic connections between the hypothalamus and the pituitary gland and the functional significance of each connection. “(Review)
- Describe the hypophysiotropic hormones released by the hypothalamus , their mechanism of action. and the effect of each on anterior pituitary function
- Identify different cell types of the anterior pituitary gland, hormones released by different cell of anterior pituitary and their target peripheral glands or tissue.
- Understand the function of hormones derived from proopiomelanocortin (POMC) and how they are involved in regulating skin coloration.
- Describe the effects of hypersecretion or hyposecretion of anterior pituitary gland on function of target endocrine glands and its consequences on growth and development , sexual maturity and other body functions.

Hypothalamic Hypophysial portal system and hypothalamic hypophysial tract



Anterior pituitary hormones



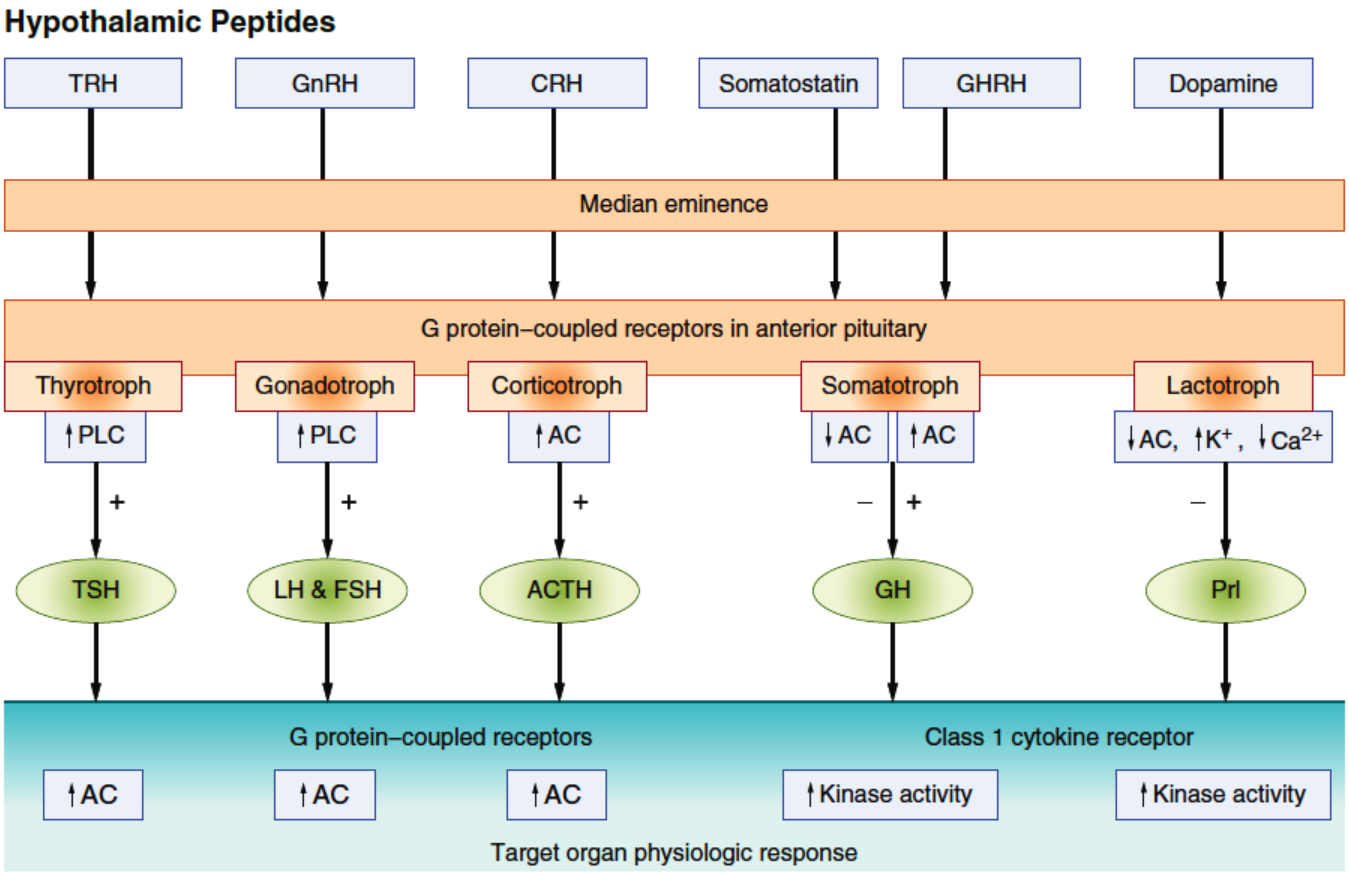
Adenohypophysis Cells & Hormones

Cell	Hormone	Chemistry	Physiologic Actions
Corticotropes	Adrenocorticotropic hormone (cortico-tropin; ACTH)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (thyro-tropin; TSH)	Glycoprotein having two subunits, α (89 amino acids) and ß (112 amino acids)	Stimulates production of thyroid hormones, T4 and T3, by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein having two sub-units, α (89aa) and ß (115aa)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
Gonadotropes	Lutenizing hormone (LH)	Glycoprotein having two sub-units, α (89aa) and ß (115aa)	Causes ovulation and formation of corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Mammotropes, Lactotropes	Prolactin (PRL)	Single chain of 198 amino acids	Essential for milk production by lactating mammary gland
Somatotropes	Growth hormone (somatotropin; GH)	Single chain of 191 amino acids	Stimulates postnatal body growth; stimulates secretion of IGF-1; stimulates triglyceride lipolysis; inhibits actions of insulin on carbo-hydrate and lipid metabolism

Hypophysiotropic Hormones : Hypothalamic hormones regulating pituitary gland secretion

Hormone	Predominant hypothalamic localization	Structure	Actions on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Paraventricular	Peptide consisting of 3 amino acids	Stimulates secretion of TSH by thyrotropes; stimulates expression of genes for α and ß subunits of TSH thyrotropes; stimulates synthesis of PRL by lactotropes
Gonadotropin-releasing hormone (GnRH)	Arcuate	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Paraventricular	Single chain of 41 amino acids	Stimulates secretion of ACTH by corticotropes; stimulates expression of gene for POMC in corticotropes
Growth hormone-releasing hormone (GHRH)	Arcuate	Single chain of 44 amino acids	Stimulates secretion of GH by somatotropes; stimulates expression of gene for GH in somatotropes
Growth hormone-inhibiting hormone (somatostatin)	Anterior periventricular	Single chain of 14 amino acids	Inhibits secretion of GH by somatotropes
Prolactin-inhibiting hormone (PIH)	Arcuate	Dopamine	Inhibits biosynthesis and secretion of PRL by lactotropes

Mechanism of action of hypothalamic and pituitary hormones



Pituitary disorders : Hypersecretion

- Pituitary adenomas are tumors of the anterior pituitary.
- Most pituitary tumors are slow-growing and benign. They are classified based on size or cell of origin
- Prolactinomas are the most common
- GH-secreting adenomas can be associated with acromegaly or bone and soft tissue overgrowth in adults and gigantism in children.
- ACTH-releasing adenomas are associated with excess cortisol production or Cushing disease
- Thyrotropin-secreting tumors are rare and are frequently large when diagnosed.

Panhypopituitarism

- Panhypopituitarism means decreased secretion of all the anterior pituitary hormones.
- Congenital hypopituitarism means the pituitary did not develop normally before birth.
- Acquired hypopituitarism refers to damage to the pituitary during or after birth
- Acquired can result from
  - Head trauma , surgery
  - Severe blood loss and decreased blood flow (ischemia of the pituitary)
  - Ischemic damage to the pituitary gland or hypothalamic-pituitary stalk during the peripartum period , the period shortly before or during ao after delivery ((Sheehan syndrome).
  - **Craniopharyngioma** a rare type of brain tumor derived from pituitary gland embryonic tissue that occurs most commonly in children, but also affects adults.

Panhypopituitarism

- **The general effects of adult panhypopituitarism are**
  - Hypothyroidism
  - Adrenal insufficiency
  - Hypogonadism
  - Loss of lactation in lactating mothers .
  - Diabetes insipidus due to loss of ADH

- **Pediatric Hypopituitarism**
  - GH deficiency cause growth retardation, short stature leading to dwarfism
  - Hypogonadism and impaired fertility Hypoglycemia
  - Adrenal crisis due Adrenal insufficiency
  - Diabetes insipidus due to loss of ADH

EVALUATION OF ANTERIOR PITUITARY FUNCTION

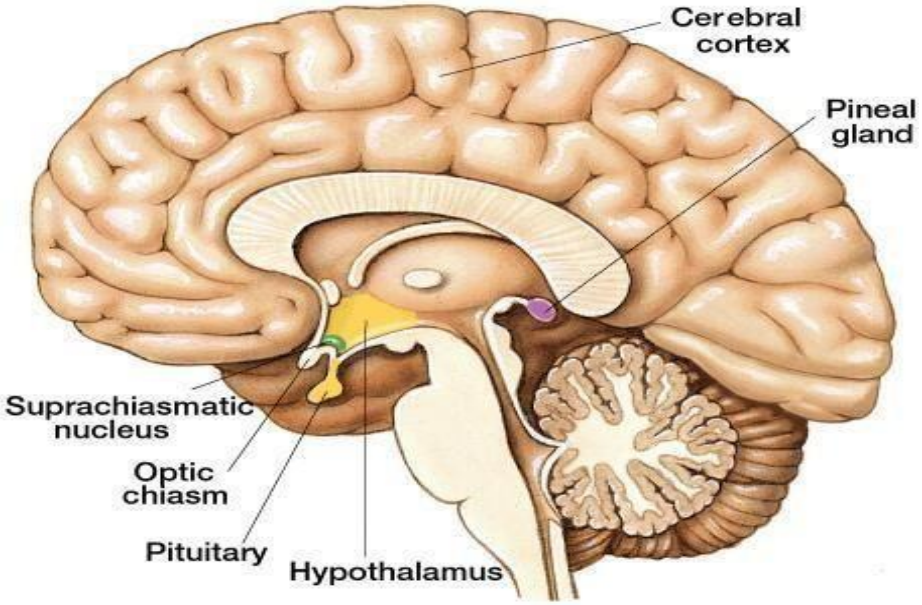
- Measurements of anterior pituitary hormone concentrations and hormones of the respective target gland hormone levels are used to assess the functional status of the system.
- For example, paired measures of TSH and thyroid hormone, FSH and estradiol, and ACTH and cortisol are used to evaluate the integrity of the respective systems.
- In addition, stimulation and inhibition tests can be used to assess the functional status of the pituitary gland.
- These tests are based on the normal physiologic feedback mechanisms that control tropic hormone release.
- For example, administration of the amino acid arginine can be used to elicit an increase in GH release in patients with suspected GH deficiency.
- For example (Low dose Dexamethasone suppression test)

Biological Rhythms and Pineal gland

- Many body functions exhibit rhythmic changes during the 24 hours period of the day.
- The most common type is the circadian rhythm, which cycles approximately once every 24 h.
- Examples Waking and sleeping, body temperature, hormone concentrations in the blood.
- Your circadian rhythm is a 24-hour biological cycle characterized by sleep-wake patterns.
- Daylight and darkness help dictate your circadian rhythm.
- Light exposure stops the release of melatonin, and in turn, this helps control your circadian rhythms.
- Melatonin secretion is low during the daylight hours and high during dark periods, which
- has some influence over your reaction to photoperiod (the length of day versus night).
- .

What is the neural basis of body functions biological rhythms

- The suprachiasmatic nucleus of the functions as the principal pacemaker, or time clock, for circadian rhythms
  The pacemaker receives input from the retina s and many other parts of the nervous system, and these inputs mediate the entrainment effects exerted by the external environment.
- The pacemaker sends out neural signals to other parts of the brain, which then influence the various body systems, activating some and inhibiting others.
- One output of the pacemaker goes to the pineal gland, a gland within the diencephalon that secretes the hormone melatonin.



Endocrine Physiology Fall 2023

Lecture 2

Part 2

Functions of prolactin and hormonal regulation of lactation

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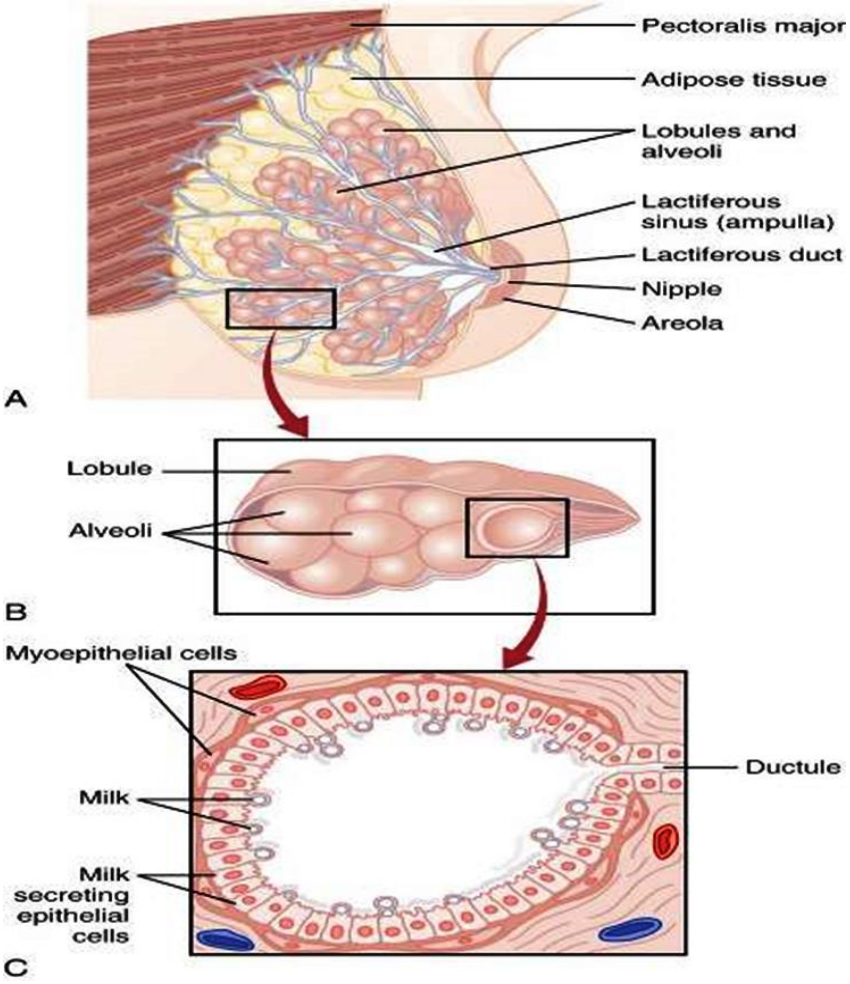
Lecture objectives

- Review the anatomy of the mammary gland
- Describe the structure of prolactin and identify the pituitary cells which synthesis it
- List the primary hormones involved in breast
- development
- List the main function of prolactin and in its role lactation
- List other hormones need for milk synthesis in mammary gland
- Discuss the carnages in female hormone hormones levels that cause the initiation of lactation after delivery
- Describe milk let down reflex and

The mammary gland



Breast Development : Hormonal Regulation

- Development in breast at puberty is mainly due high levels of estrogens
- Estrogens released by the ovaries during the monthly female menstrual cycle stimulate growth of the breasts' *mammary glands* plus the deposition of fat to give the breasts mass
- More growth occurs during the high-estrogen state of pregnancy: , High levels of estrogen during pregnancy cause further development of the duct system and full development of glandular tissue and the glands are ready for milk production
- Final development of the breasts into milk-secreting organs also requires *progesterone.*
- *Growth hormone, prolactin,* and *insulin also contribute to the development of the duct system of the mammary gland*

Prolactin

- A polypeptide hormone synthesized and secreted by lactotrophs in the anterior pituitary gland
- The lactotrophs account for approximately 15–20% of the cell population of the anterior pituitary gland,
- This increases dramatically in response to elevated estrogen levels, particularly during pregnancy.
- Prolactin levels are higher in females than in males
- Plasma concentrations of prolactin are highest during sleep and lowest during the waking hours

Actions of prolactin

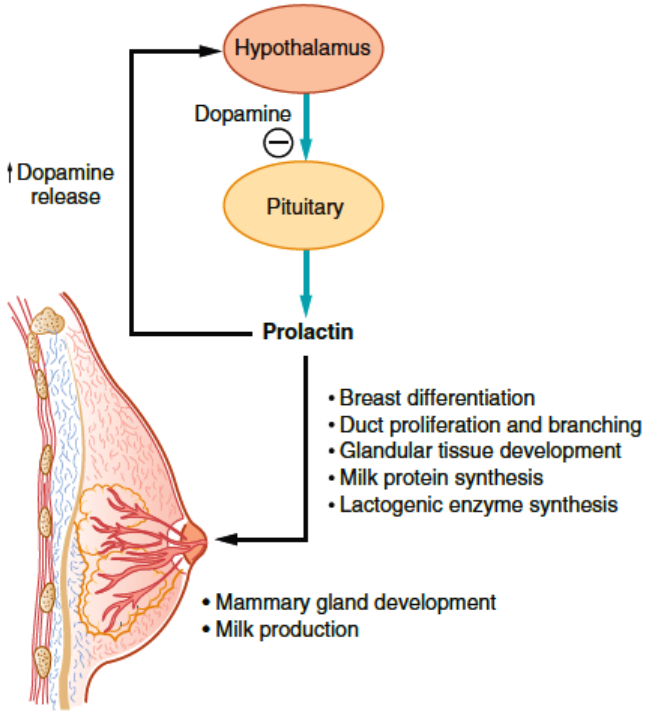
- Stimulates development of breast including growth and development of the mammary gland tissue and ductal proliferation
- These actions are enhanced by estrogen during pregnancy.
- Stimulates milk production in the breast by
  - stimulates glucose and amino acid uptake by mammary gland cells
  - Causes synthesis of the milk proteins β-casein and α-lactalbumin, the milk sugar lactose, and milk fats by the mammary epithelial cells
  - *Growth hormone, cortisol, parathyroid hormone,* and *insulin.* These hormones are necessary to provide the amino acids, fatty acids glucose, and calcium required for the formation of milk.
  - Inhabits gonadotropin-releasing hormone (GnRH) during pregnancy leading to amenorrhea
- Inhibits spermatogenesis in males (by decreasing GnRH) when secreted in large amounts (Pituitary adenoma)
- modulates reproductive and parental behavior

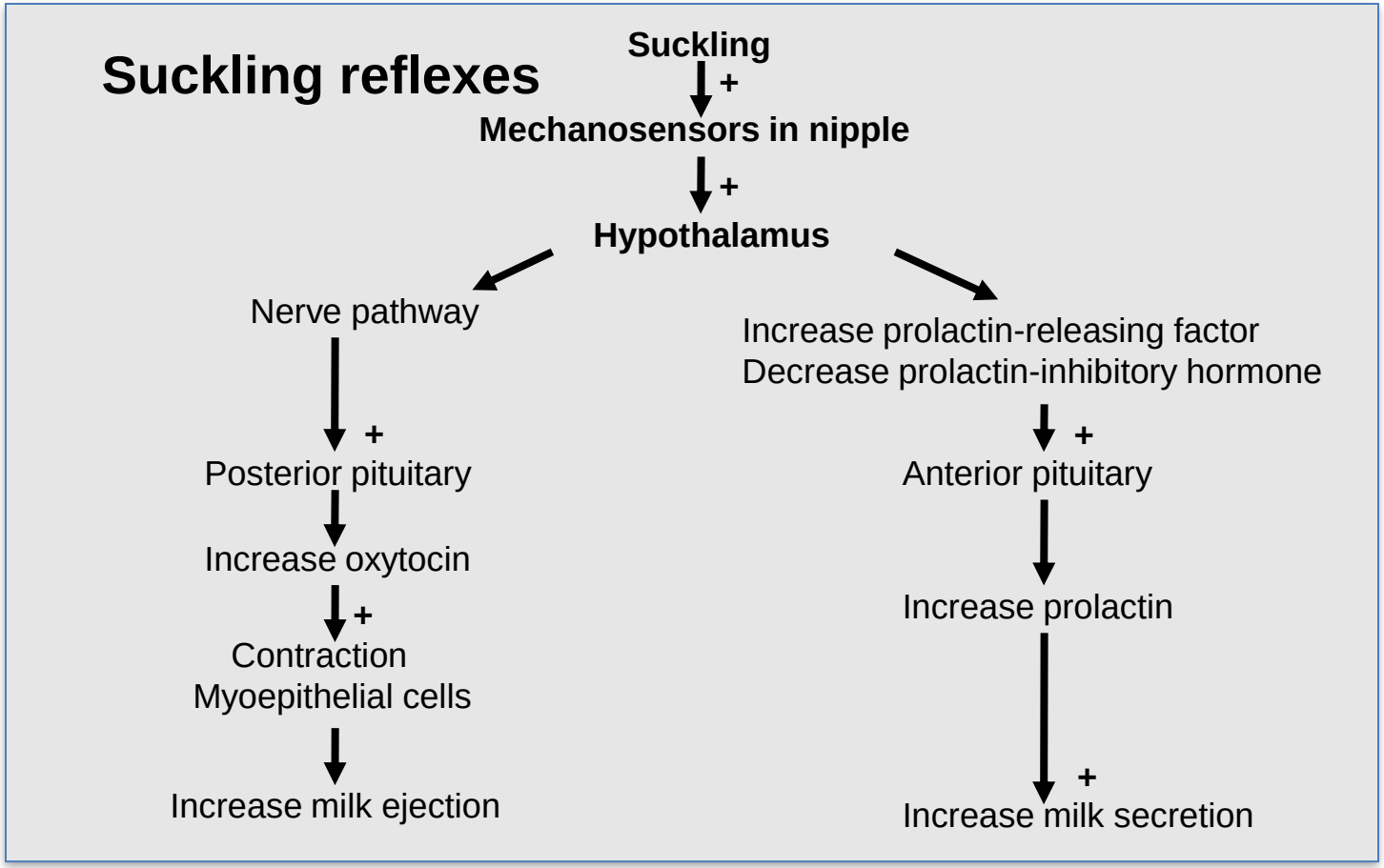
Physiologic effects of prolactin and its regulation b y dopamine

Prolactin release is predominantly under negative feedback control by hypothalamic dopamine.

Suckling stimulates the release of prolactin by releasing the tonic inhibition of dopamine.

Prolactin inhibits its own release by stimulating dopamine(feed back regulation)
The release of prolactin in response to suckling is neuroendocrine reflex




Suckling reflexes
Suckling
+
Mechanosensors in nipple
+
Hypothalamus
Nerve pathway
+
Posterior pituitary
Increase oxytocin
+
Contraction
Myoepithelial cells
Increase milk ejection
Increase prolactin-releasing factor
Decrease prolactin-inhibitory hormone
+
Anterior pituitary
Increase prolactin
+
Increase milk secretion

Control of prolactin secretion

- Prolactin release is predominantly under tonic inhibition by dopamine derived from dopaminergic (D2) neurons of the hypothalamus.
- D2 inhibition of lactotroph release of prolactin is mediated by D2 Gαi protein–coupled receptors.
- Prolactin release is affected by :
  - suckling of breast during lactation increase prolactin secretin
  - increased levels of ovarian steroid hormones, primarily estrogen.
- This surge in prolactin release in response to a suckling stimulus is mediated by a decrease in the amount of dopamine released at the median eminence, relieving the lactotroph from tonic inhibition.
- Estrogen stimulates growth of the lactotrophs during pregnancy as well as prolactin gene expression
- TRH has identified as potential prolactin-releasing factors

Regulation of Prolactin Secretion

Factors that Increase Prolactin Secretion

- Estrogen (pregnancy)
- Breast-feeding
- Sleep
- Stress
- TRH

Factors that Decrease Prolactin Secretion

- Dopamine
- Bromocriptine (dopamine agonist)
- Somatostatin
- Prolactin by negative feedback by increasing dopamine release

Initiation of Lactation after Delivery

- The breasts enlarge during pregnancy in response to high circulating levels of estrogens, progesterone, prolactin, and possibly hCG.
- Prolactin and estrogen synergize in producing breast growth, but estrogen antagonizes the milk-producing effect of prolactin on the breast
- During pregnancy , high levels of estrogen and progestogen inhibits lactation
- Some milk is secreted into the ducts as early as the fifth month, but the amounts are small compared with the surge of milk secretion that follows delivery
- After expulsion of the placenta at parturition, the levels of circulating estrogens and progesterone abruptly decline.
- The drop in circulating estrogen initiates lactation.
- Suckling not only evokes reflex oxytocin release and milk ejection, it also maintains and augments the secretion of milk because of the stimulation of prolactin secretion it produces

Disorders of prolactin secretion

- Hyposecretion (*Prolactin deficiency)*
  - Infarction of pituitary (Sheehan's syndrome)
  - Drugs Dopamine agonist
- Hypersecretion : Caused by
- Hypothalamic damage (due to loss of the tonic "inhibitory" control by dopamine)
- a hormone-producing pituitary adenoma
    - Prolactinomas are the most common tumors of pituitary gland
    - Usually benign neoplasm.
- Patients with a prolactinoma present with
  - elevated levels of prolactin (hyperprolactinemia)
  - excessive secretion of milk (galactorrhea)
  - reproductive dysfunction including loss of libido , amenorrhea
  - In males, prolactinomas may cause infertility by producing hypogonadism due to inhibition of GnRH. can be treated with bromocriptine, which reduces prolactin secretion by acting as a dopamine agonist.

Mechanism of prolactin on breast and mammary glands

- The effects of prolactin on the breast and mammary gland are mediated by a cytokine cell membrane receptor
- Hormone receptor biding that stimulates the *Janus kinase* (*JAK*) and signal transducer and activator of transcription (STAT) pathway
- Commonly known as the *JAK*/STAT signaling pathway
- Progesterone produce by the placenta during pregnancy interferes with prolactin binding to the receptors on the alveolar cells within the breast, thereby directly suppressing milk production during pregnancy
- High levels of prolactin during lactation and as lactation continues, suppresses **ovulation** because prolactin inhibits GnRH secretion by the hypothalamus and FSH and LH secretion by the anterior pituitary.
- Although not 100% effective, breastfeeding is method of contraception and family spacing in some regions of the world.