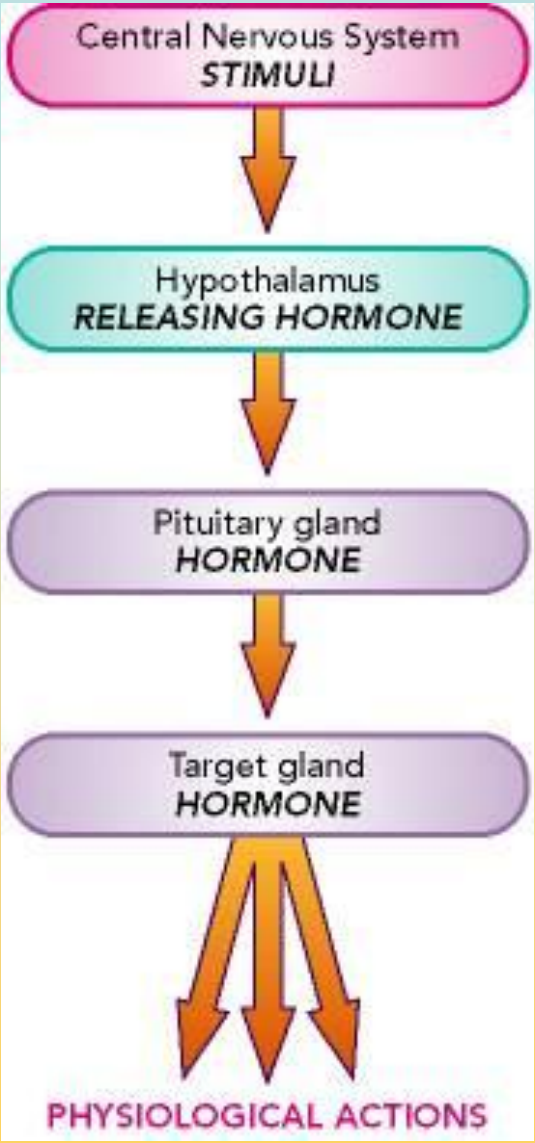
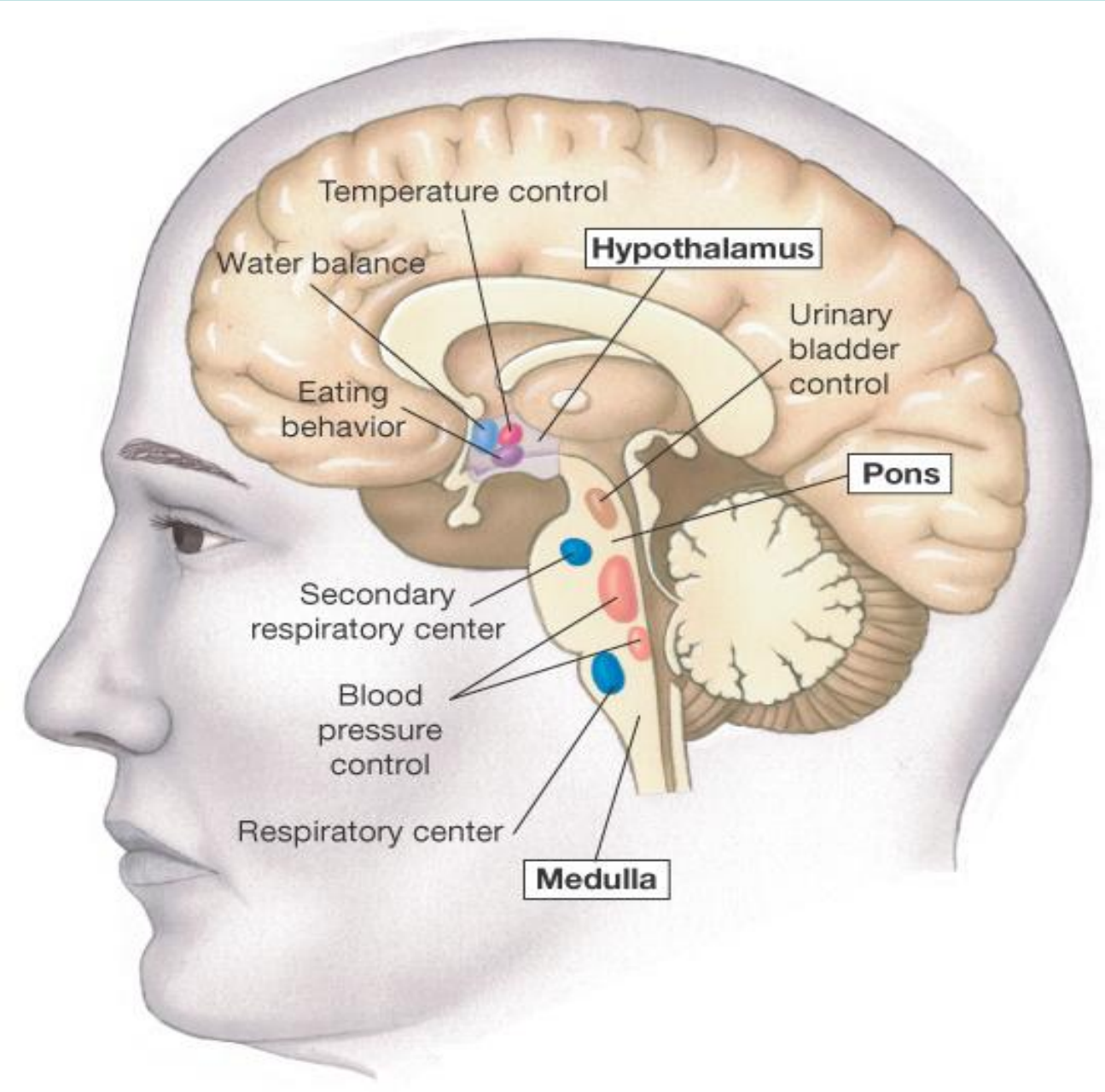
The hierarchy of the hormone system



Neuroendocrine messengers

	Neurotransmitter (Present in Nerve Endings)	Hormone Secreted by Neurons	Hormone Secreted by Endocrine Cells
Dopamine	+	+	+
Norepinephrine	+	+	+
Epinephrine	+		+
Somatostatin	+	+	+
Gonadotropin-releasing hormone (GnRH)	+	+	+
Thyrotropin-releasing hormone (TRH)	+	+	
Oxytocin	+	+	+
Vasopressin	+	+	+
Vasoactive intestinal peptide	+	+	
Cholecystokinin (CCK)	+		+
Glucagon	+		+
Enkephalins	+		+
Pro-opiomelanocortin derivatives	+		+
Other anterior pituitary hormones	+		+

Autonomic control centers in the brain



HYPOTHALAMUS

- Integrates functions that maintain chemical and temperature homeostasis.
- Controls the release of hormones from the anterior and posterior pituitary.
- Functions with the limbic system.

The Hypothalamic-Hypophyseal Portal System

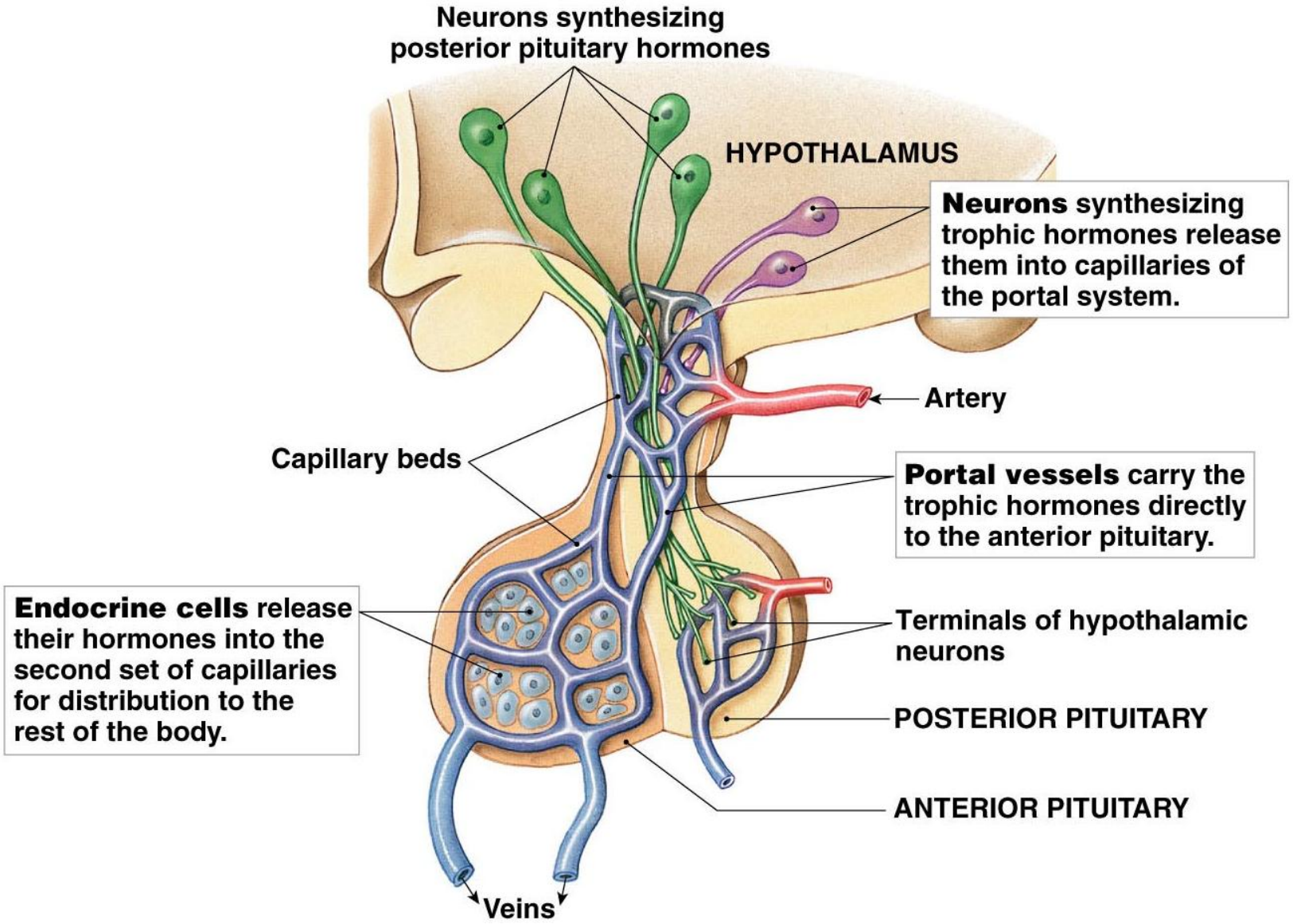


Figure 7-16

HYPOTHALAMUS

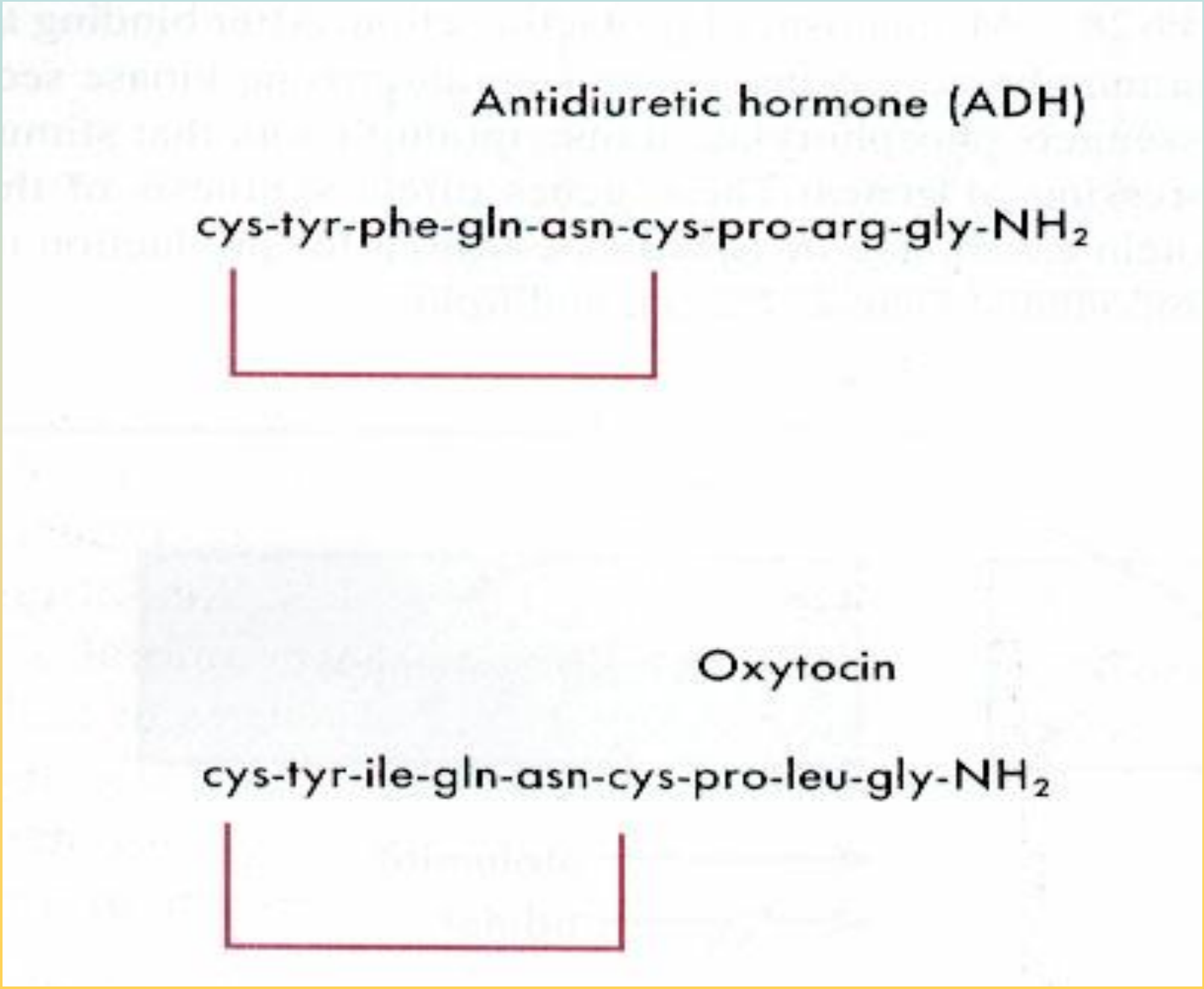
Synthesizes & releases hypophysiotropic hormones:

- Thyrotropin-releasing hormone (TRH)
- Corticotropin-releasing hormone (CRH)
- Gonadotropin-releasing hormone (GnRH)
- Growth hormone-releasing hormone (GHRH)
- Growth hormone-inhibiting hormone (GHIH)
- Prolactin-releasing factor (PRF)
- Prolactin-inhibiting hormone-PIH (Dopamine)

POSTERIOR PITUITARY

- **Hormones synthesized in the hypo-thalamus (SON and PVN) are transported down the axons to the endings in the posterior pituitary.**
- **Hormones are stored in vesicles in the posterior pituitary until release into the circulation.**
- **Principal Hormones: Vasopressin and Oxytocin.**

Structures of ADH and Oxytocin



ANTERIOR PITUITARY HORMONES

Synthesis of different anterior pituitary hormone is by different cell populations

Corticotrophs - ACTH (Corticotropin)

Lactotrophs - Prolactin

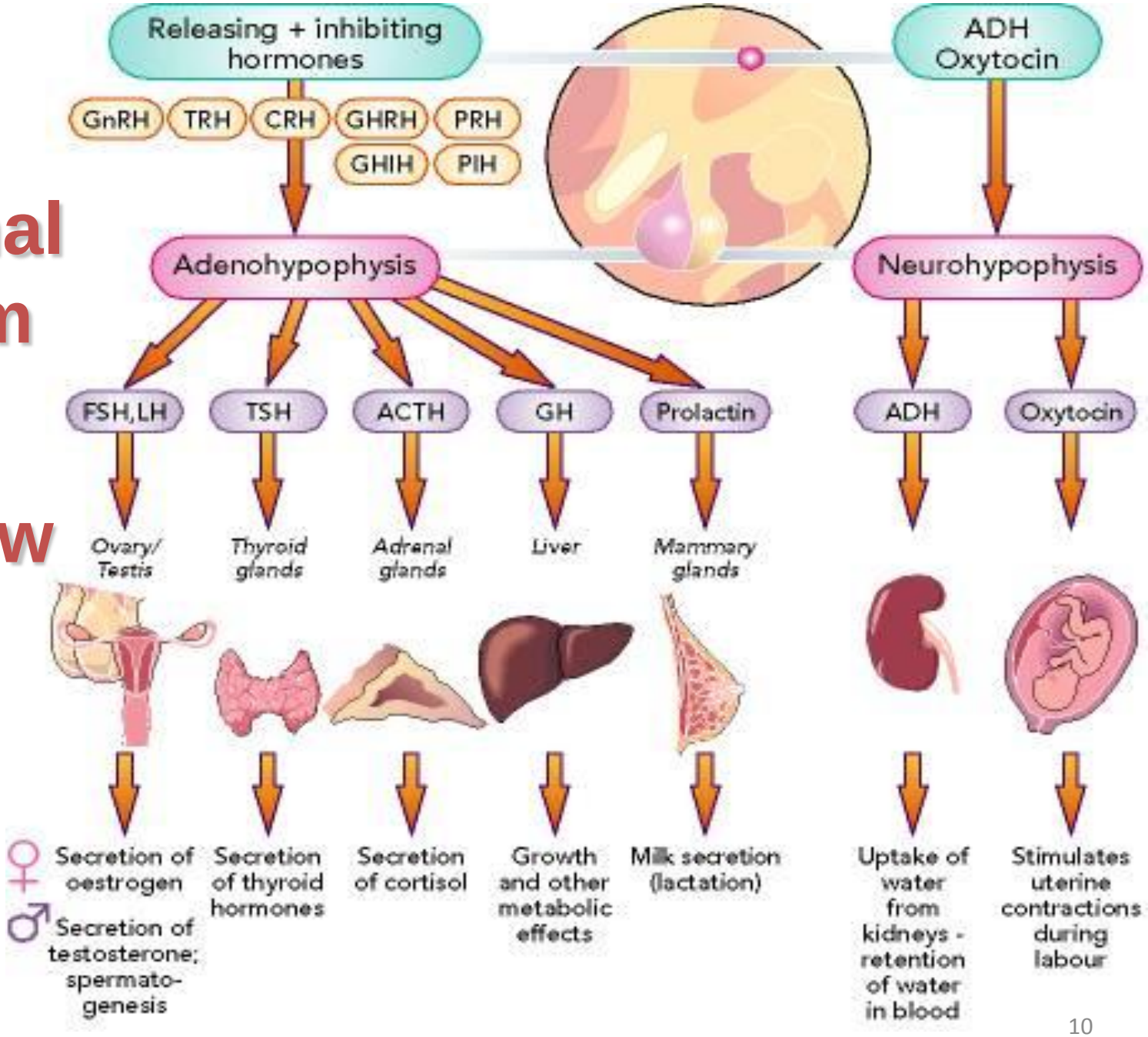
Somatotrophs - Growth Hormone

Thyrotrophs - TSH (Thyrotropin)

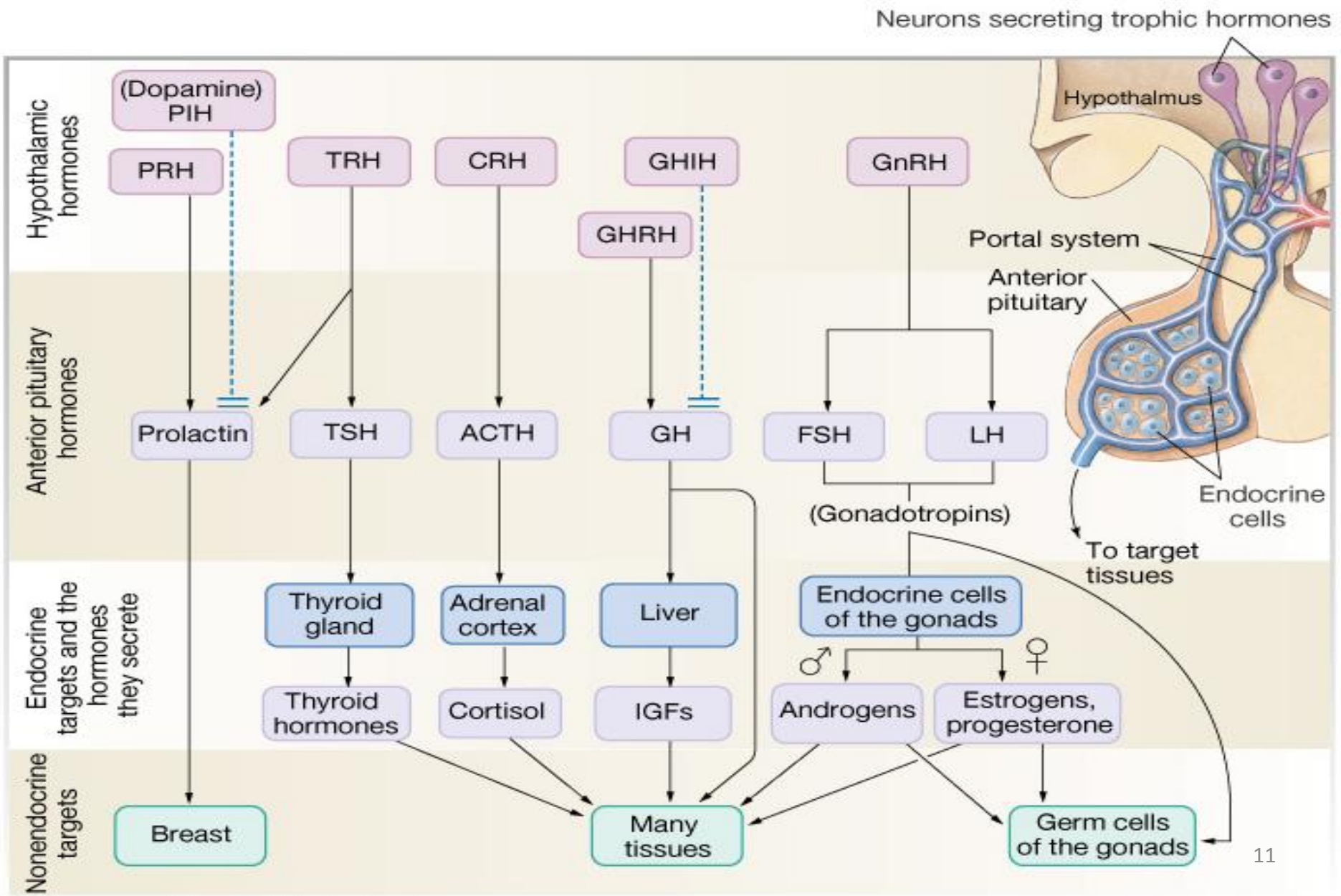
Gonadotrophs - FSH, LH (Gonadotropins)

The hormonal system

An overview



Hypothalamic-Anterior pituitary Axis



Hypothalamic Hormones

Hypophysiotropic Hormones

- **GHRH**

  ↑Growth of Somatotrophs → ↑GH

  Precursor: 108 a.as → GHRH 44 a.as (1-29 full activity)

- **Smoatostatin**

  ↓GH, TSH, insulin, glucagon, gastrin, secretin, and VIP secretion.

  Source: hypothalamus, pancreatic islet D cells, Gastro-intestinal mucosa, thyroid C cells.

  Precursor: 116 a.as → somatostatin 14 (hypothalamus)

  somatostatin 28 (gut).

Hypophysiotropic Hormones … Continue

- **Dopamine**

  Primary PRL inhibitory hormone (Primary Control).

  Hypothalamic lesions, stalk section increases PRL.

  GABA, cholinergic pathway ↓PRL.
- **PRL Releasing Factors**

  TRH ↑ PRL (physiology?).

  PRL increases during sleep, stress, suckling (not mediated by TRH).

  VIP, serotonergic pathway increases |PRL.
- **TRH**

  Tripeptide.

  Precursor: 242 a.a5. (six copies TRH)

  ↑TSH secrection (thyrotropin).

Hypophysiotropic Hormones … Continue

- **Corticotropin-Releasing Hormone (CRH)**

  41 a.as (precursor 196 a.as)

  ↑ACTH and POMC

  Half-life: 60 min

  ADH, angiotensin II potentiate CRH-mediated secretion of ACTH.

  Secreted also from placenta (↑ during pregnancy and delivery).

- **Gonadotropin-Releasing Hormone (Gn RH)**

  ↑ gonadotropin secretion (LH + FSH) in testis and ovary.

  Linear decapeptide, precursor 92 a.as. (GnRH + 56 a.as GnRH associated peptide)

Mechanism of Action of Hypothalamic Stimulatory Hormones

- **Half-life**

  Short except CRH
- **Secretion**

  Immediate secretion from secretory granules
- **Receptors**

  Plasma-membrane receptors

  Feedback regulation is due in part to changing no. of receptors (↑ thyroid hormone → ↓ no. TRH receptors.
- **Post-receptor signaling**

  PI, Adenylate Cyclase, ↑ intracellular calcium

  TRH and GnRH: activate both systems, IP_3, DAG, cAMP

  CRH and GHRH: ↑cAMP

Mechanism of Action of Hypothalamic Inhibitory Hormones

- **Not well understood.**

- **Somatostatin and Dopamine:**

  Inhibit adenylate cyclase via G-protein (Gi).

  Inhibit secretion induced by cAMP analogues: do not act exclusively by reduction of intracellular cAMP.

Physiology of Control of Anterior Pituitary Hormones

Release of Hypothalamic Hormones

- **Regulation of Secretion**

  Negative feedback by T_3/T_4 (Closed-loop system).

  Direct or indirect feedback loop.

  Open loop from neurotransmitters from higher centers (response to stress, exercise, temp.).
- **Positive feedback loop**

  Estrogen on LH in mid menstrual cycle.
- **Pulsatile**

  Crucial to function (GnRH at puberty).

Release of Hypothalamic Hormones ….Continue

- **Circadian rhythm**

  Role of pineal gland:

  Neural connection between retina and pineal gland → ↑ melatonin

  Melatonin rises at night: the increase declines with age (triggers the onset of puberty).

  Effect through N-acetyltransferase.

Anterior Pituitary Hormones

ACTH, GH, PRL, TSH, LH and FSH

- Conticotropin related peptides: ACTH, LPH, MSH, endorphins.
- **GH, PRL** (with hCG): polypeptide hormones with sequence homology.
- **LH, FSH, TSH**: (Glycoproteins, two subunits, with structural similarities)

GH (Growth Hormone)

Biosynthesis

Pre-GH (28,000) → GH (21,500), 2 -S-S- linkages, 191 a.as.

Function

Indirect effects (through IGF-1)

Expansion of chondrocytes

↑ linear growth

↑ DNA synthesis in cartilage, collagen synthesis

↑ Body weight

Direct effects (antagonize insulin)

↑ lipolysis

↓ glucose uptake

↑ amino acid transport

↑ protein synthesis

↑ IGF production (liver)

Growth Hormone …

Measurement

2 ng/ml (400 mg/d for adult, 700 mg/d for young)

t½ 20-50 min

Secretion

Major systems: GHRH, Somatostatin (episodic)

Neural control: sleep

Stress: ↑ GH

Metabolic Control

Cortisol excess, hypo- and hyperthyroidism blunt GH response to stimuli)

Neuropharmacological agents: depaminergic, serotonergic, α-adrenergic ↑GH.

Growth Hormone …

Evaluation

- **Basal levels:**
  low

- **Provocative tests:**
  GHRH – Arg test
  Insulin – induced hypoglycemia

Growth Hormone …

Mechanism of Action

GH

- Receptors: age 7 months
- Soluble TK
- Binding: dimerization, recruitment of TK, JAK-2
- GH causes down-regulation of receptors

IGF-1

- IGF-1 receptors: similar to insulin (intrinsic TK)

Prolactin

Biosynthesis

Precursor (40,000-50,000) → PRL (198 a.as, MW 22,000)

Function

↑ Lactation in postpartum

During pregnancy: PRL (+ estrogen, progesterone, hPL, insulin, thyroid hormone, cortisol), additional breast development, milk.

Pregnancy: Estrogen blunts PRL on lactation

↑ PRL → hypogonadism

(↓ LH, FSH pulsatile secretion , ↓LH surge)

Prolactin …

Measurement

400 mg/d, 15-20 ng/ml (♀ 13 ng/ml, ♂ 5 ng/ml)

Secretion

Dopamine: ↓ PRL (dopamine agonists e.g. bromocriptine).

Pregnancy and Lactation: ↑ PRL up to 10 times.

TRH and VIP: ↑ PRL (thyroid hormones blunt TRH)

Episodic: Peak 4-7 am

Stress: (exercise, hypoglycemia, M1) ↑PRL

E_2 ↑, glucocorticoids ↓ PRL.

Mechanism of Action

Like GH, soluble TK

ACTH and Related Peptides

Biosynthesis

POMC → ACTH (39 a.as.), α,β, and γ MSH, β-endorphin (from β-Lipotropin), N-terminal fragment.

Function

↑glucocorticoids and androgens (adrenal cortex)

↑ cholesterol → pregnenolone

Measurement

5-52 Pg/ml, $t_{½}$ (7-12 min)

Secretion

CRH →↑ ACTH (pulsatile, diurnal rhythm –peak before awakening)

Stress →↑ ACTH

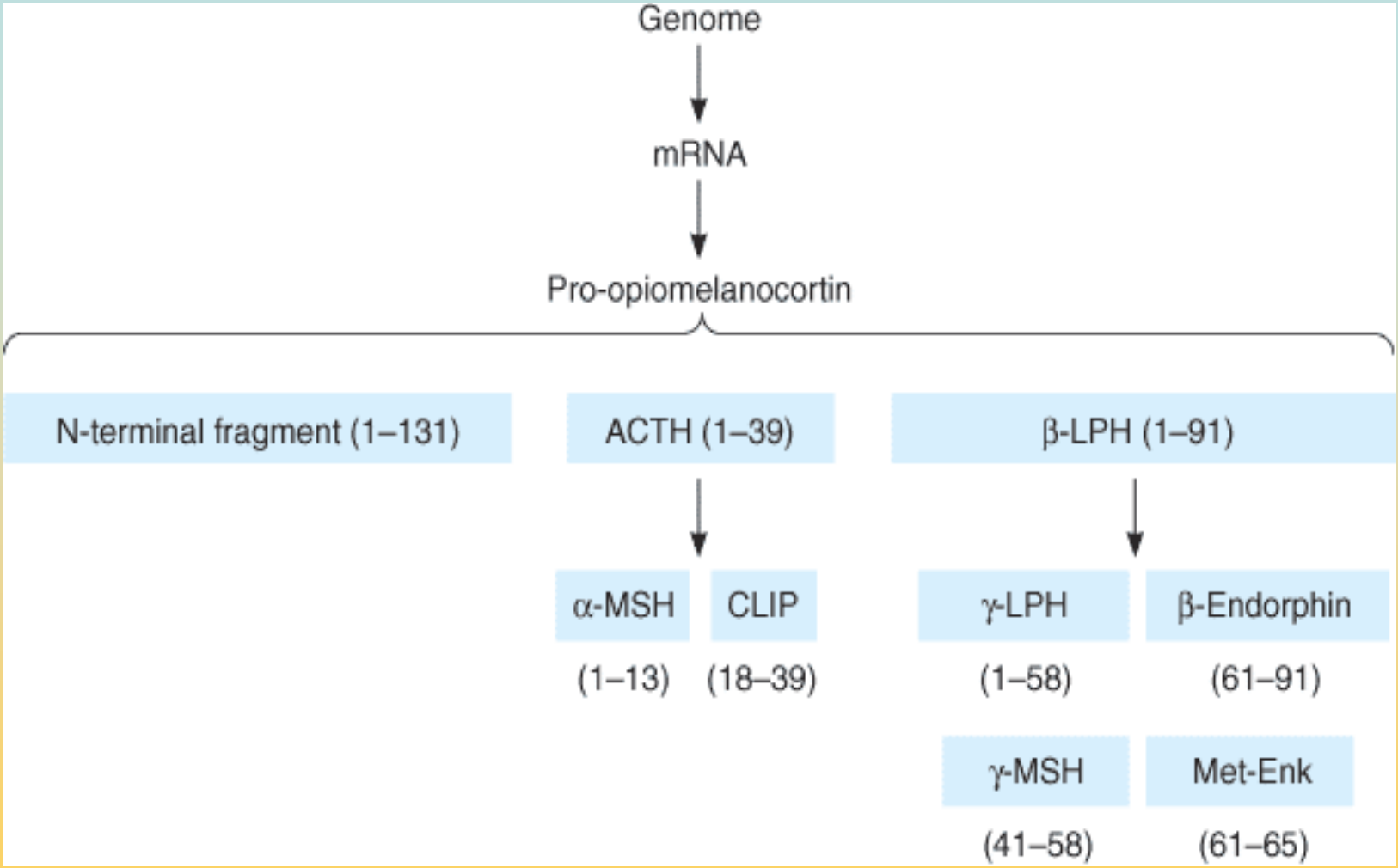
Negative feedback: at the level of hypothalamus and pituitary

"Slow feedback"

"Fast feedback"

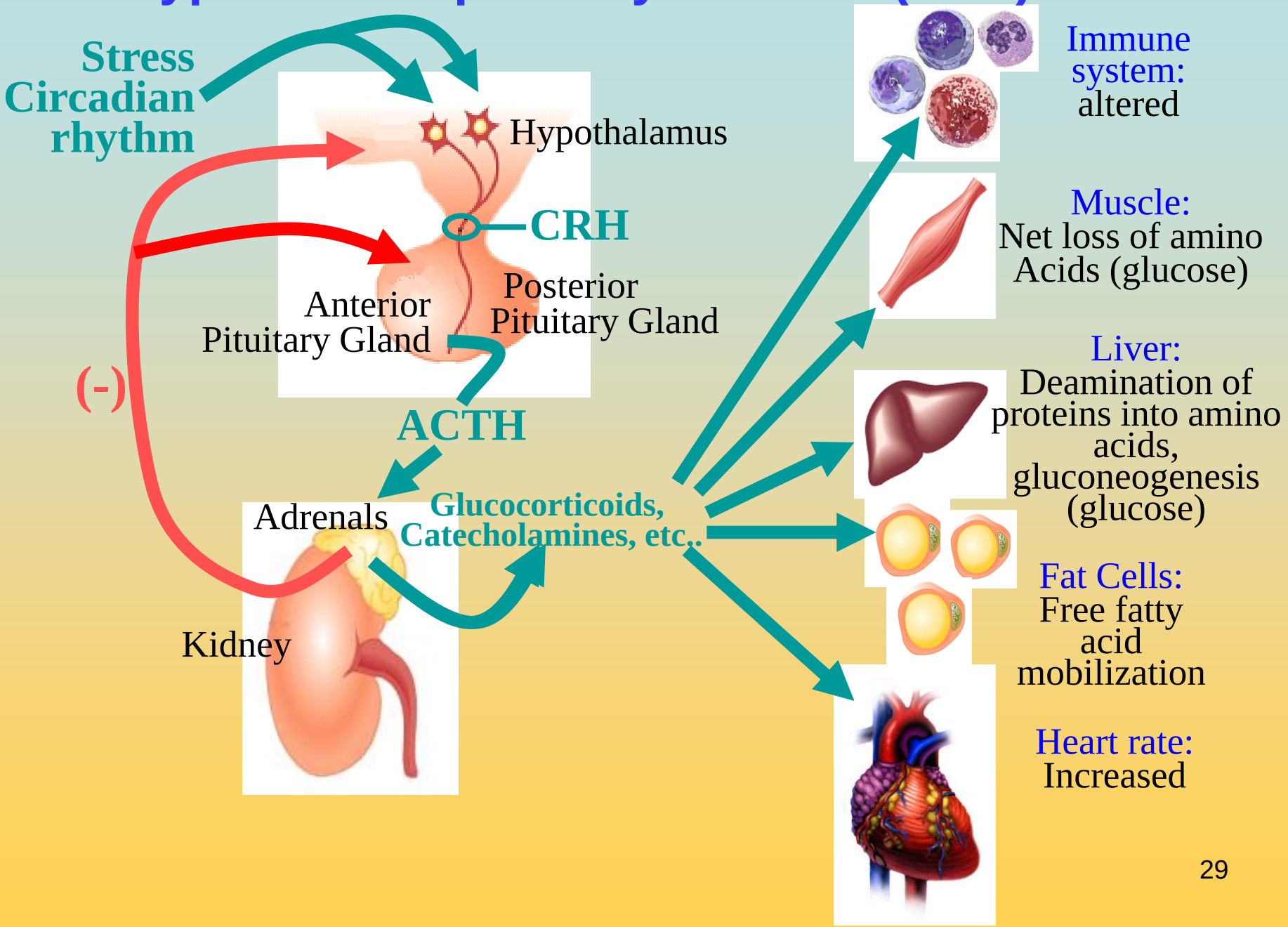
ACTH inhibits its own secretion (short loop)

ACTH synthesis

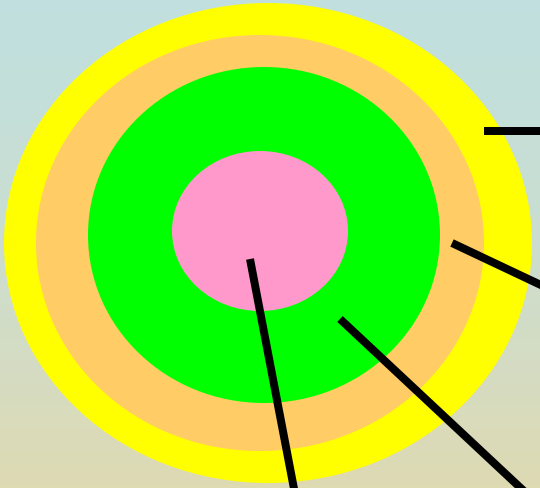


Processing and cleavage of pro-opiomelanocortin (POMC)

Hypothalamopituitary adrenal (HPA) axis



Adrenals



CORTEX

Zona Glomerulosa

Mineralocorticoids (Aldosterone)

Na+, K+ and water homeostasis

Zona Fasciculata

Glucocorticoids (Cortisol)

Glucose homeostasis and many others

Zona Reticularis

Sex steroids (androgens)

Medulla: "Catecholamines"

Epinephrine, Norepinephrine, dopamine

TSH (Thyroid Stimulating Hormone)

Structure

Glycoprotein, two subunits α,β, MW 28,000

α Subunit: (similar to LH and FSH) and to hCG.

β Subunit: different (hormone specificity)

Function

Thyroid: ↑ iodine uptake, hormone synthesis and release.

↑ gland size (↑ mRNA and protein synthesis), ↑ cAMP

Measurement

Normal range 0.5-4.7 μU/ml; $t_{½}$ 50-60 min

Secretion

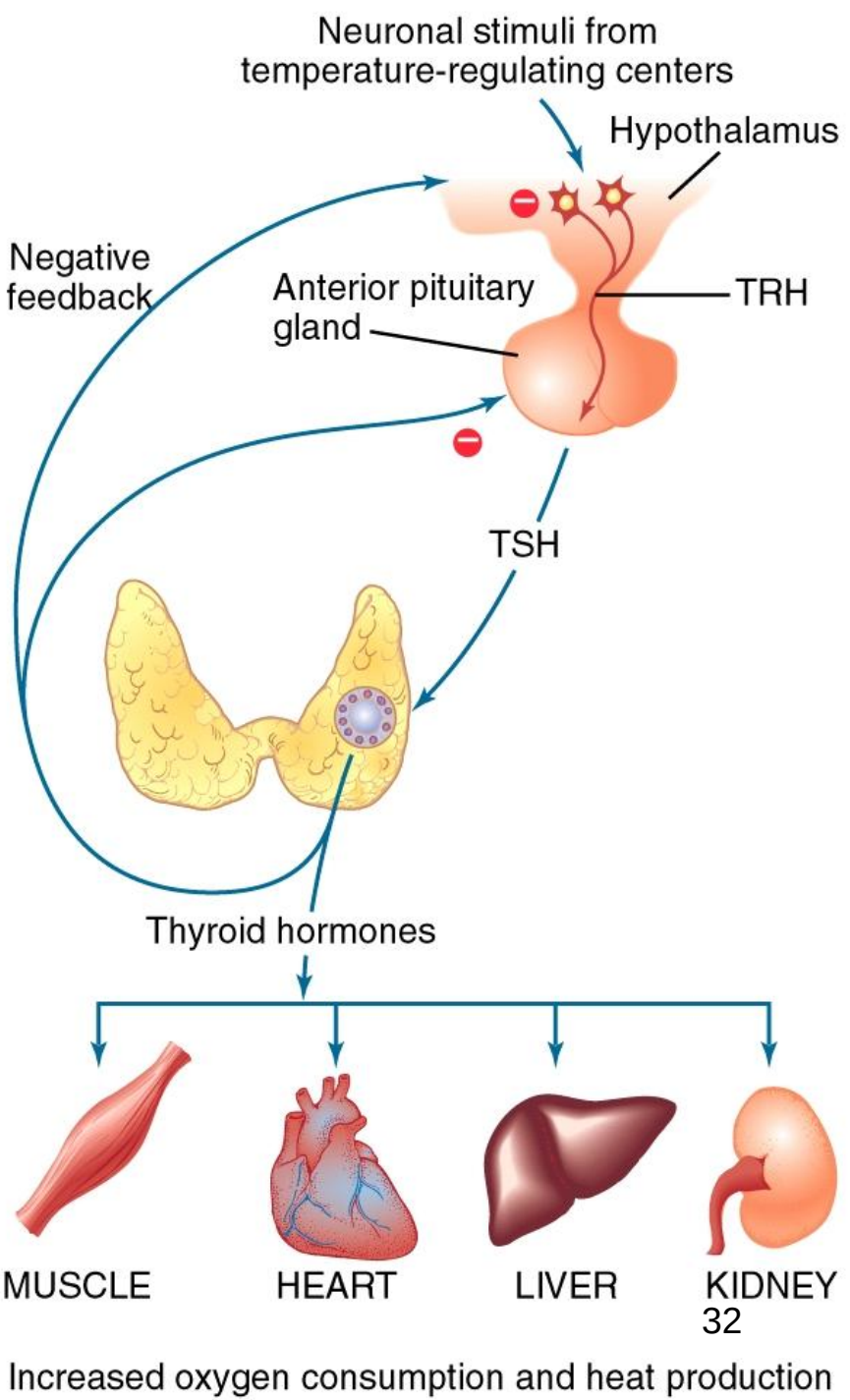
TRH stimulates TSH synthesis and release.

Somatostatin: ↓ TSH.

Negative Feedback Inhibition :by thyroid hormone (pituitary and hypothalamus levels), ↓ number of TRH receptors, mRNA for TRH synthesis.

Hypothalamothyroid axis

- Tissues become sensitive to epinephrine
- Increase cellular respiration, O_2 use and metabolism
- Heat is generated
- Thermoregulation
- Growth and development



Gonadotropins (LH, FSH)

Biosynthesis

Glycoproteins, α and β subunits, MW 30 KDa

hCG: activity resembles LH

hMG (human menopausal gonadotropin): FSH-like activity.

Function

↑ sex steroids ↑ gametogenesis

♂ LH ↑T (Leydig cells). In Sertoli FSH ↑ androgen binding protein

Spermatogenesis requires LH + FSH

♀ LH ↑ E_2 and progesterone (ovary)

LH surge → ovulation

FSH → development of ovarian follicle

LH + FSH ↑ E_2 production by ovarian follicle.

Measurement

LH + FSH low before puberty, elevated in postmenopause.

Puberty: nocturnal ↑ LH (boys), cyclic FSH + LH (girls)

LH + FSH: vary in menstrual cycle.

Gonadotropins (LH, FSH) …

Secretion

LH + FSH under GnRH

Puberty: LH + FSH, leptin

Episodic secretion, pulsatile GnRH, pulsatile LH + FSH

Positive feedback:

$E_2 \rightarrow \uparrow$ LH + FSH surge; Progesterone augments E_2 effect.

Negative feedback:

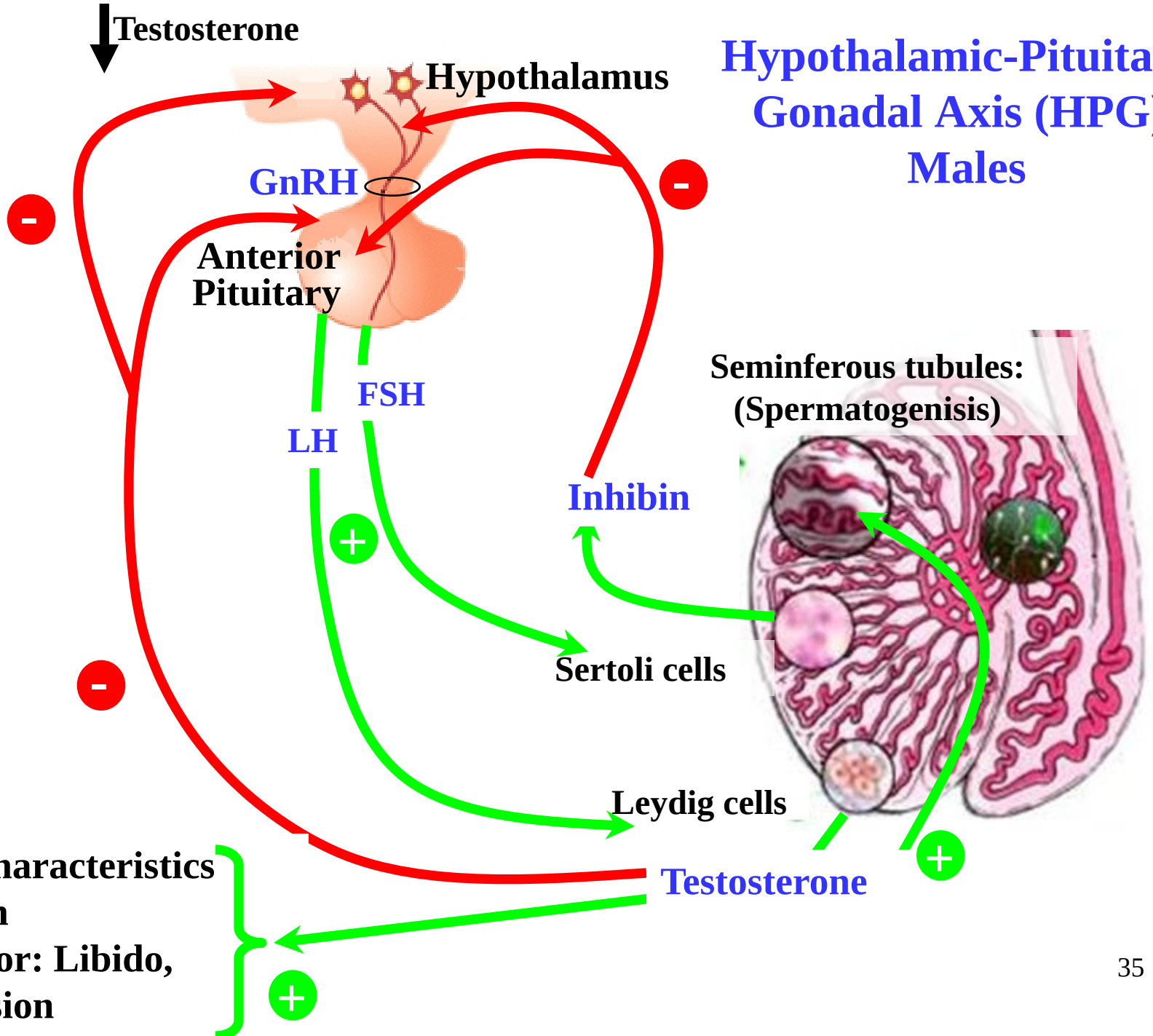
In Women: Primary gonadal failure (Menopause)
↑ LH + FSH

In men: Primay gonadal failure with low T
↑ LH + FSH

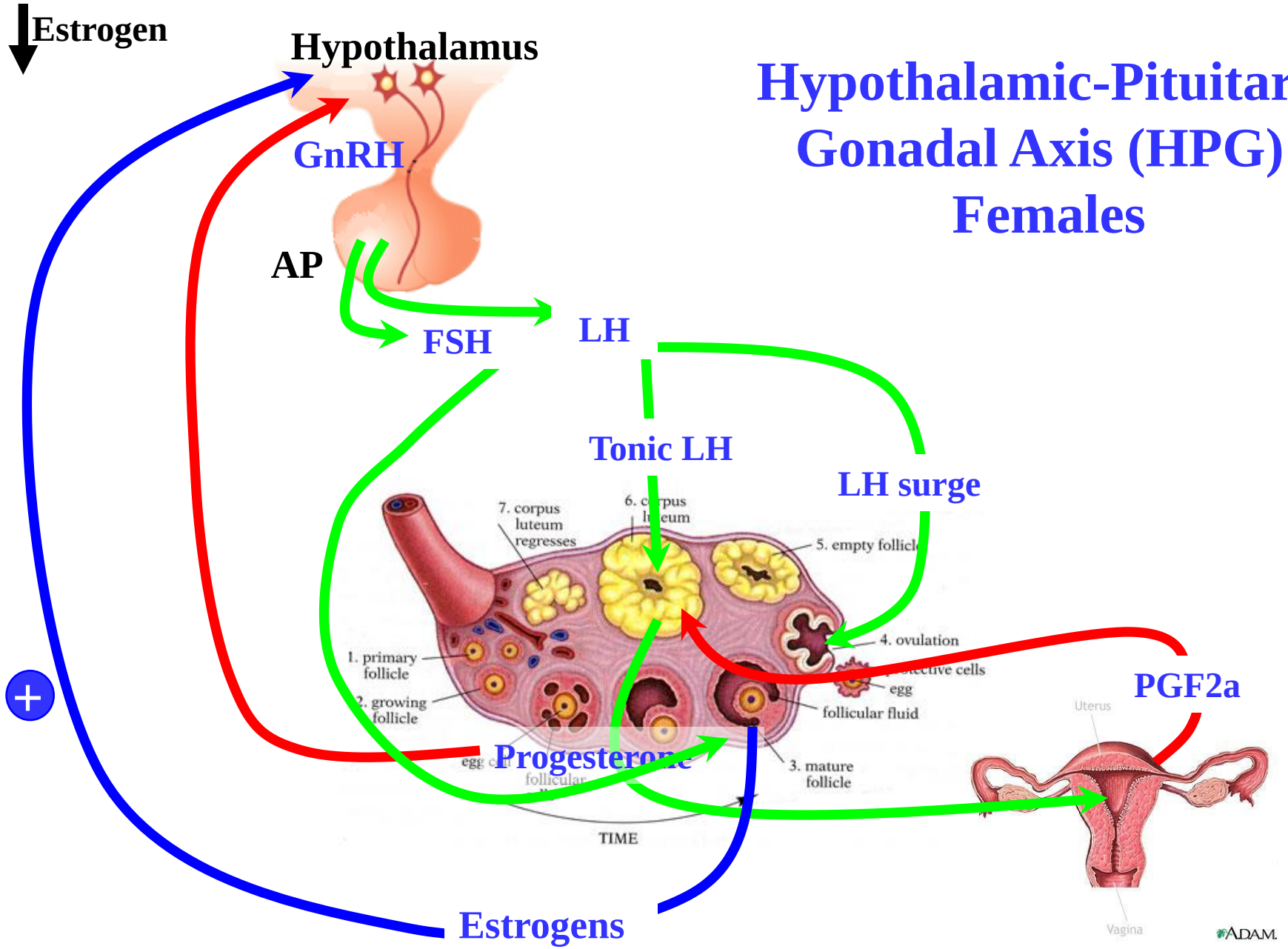
↑ inhibin → ↓ FSH

Castration: ↑FSH + LH

Hypothalamic-Pituitary-Gonadal Axis (HPG): Males



Hypothalamic-Pituitary-Gonadal Axis (HPG): Females

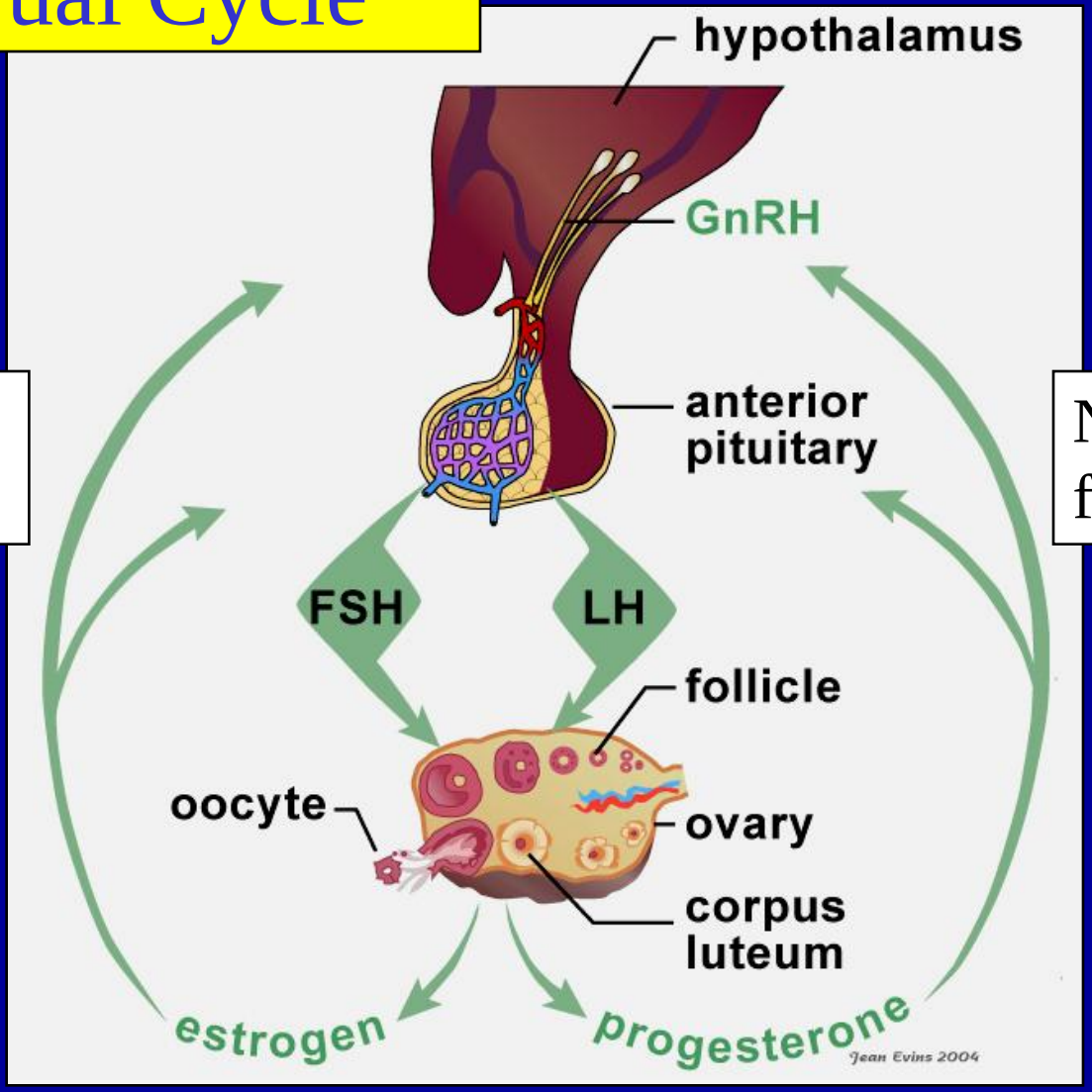


Menstrual cycle

The cyclic buildup and break-down of the endometrium as the uterus prepares monthly for a blastocyst

Hormones and Menstrual Cycle

Negative feedback

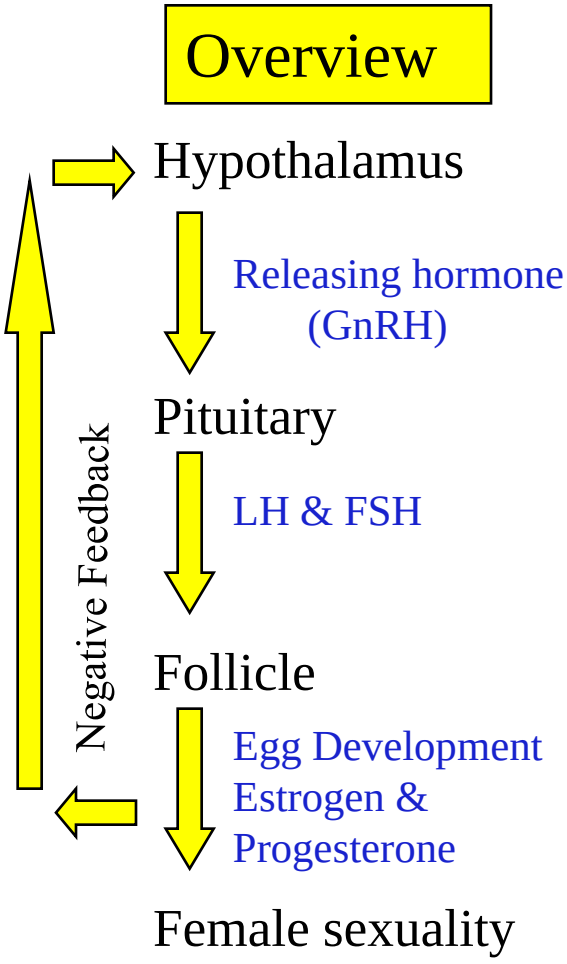


Negative feedback

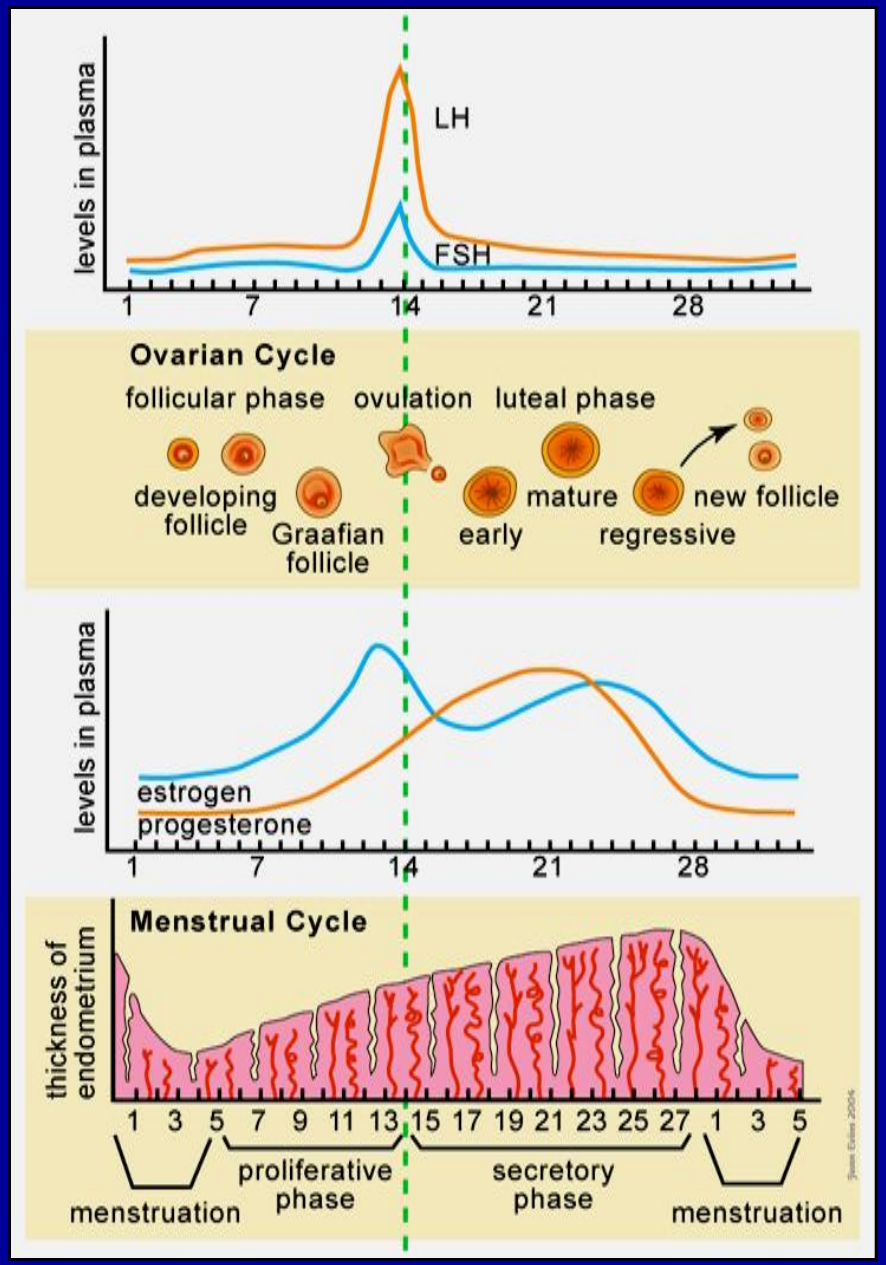
Based on: Mader, S., *Inquiry Into Life*, McGraw-Hill

Negative Feedback & Homeostasis

Negative feedback effects of estrogen and progesterone are the prime homeostatic mechanisms maintaining female sex characteristics at a relatively constant level

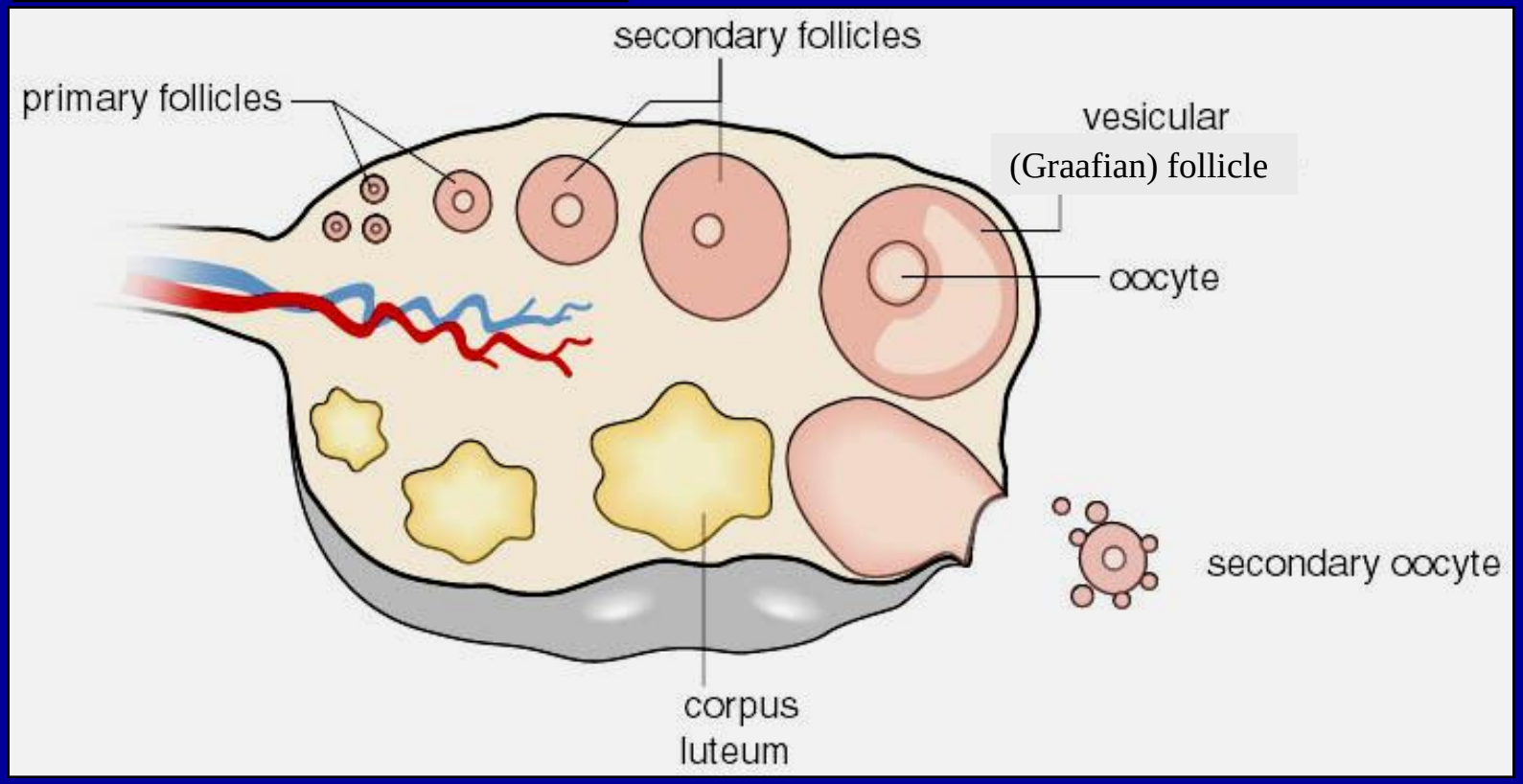


Hormonal Regulation of Ovarian and Uterine Cycles



Based on Mader, S., *Inquiry*, Wm. C. Brown Publishers

Ovulation



Based on: Mader, S., *Inquiry Into Life*, McGraw-Hill

Hormones and Menstrual Cycle

Pituitary produces FSH and LH

↓

FSH and LH cause follicle to develop and release egg

↓

Follicle produces estrogen and progesterone

↓

Estrogen and progesterone thicken endometrium to prepare for implantation of fertilized egg and suppress production of FSH and LH

↓ ↓

Egg not fertilized Egg fertilized

If the Egg is Fertilized

Fertilized egg implants in endometrium

Embryo sends out hormonal message to the old follicle (corpus luteum) to let it know an embryo is present

Old follicle continues to produce estrogen and progesterone to maintain endometrium

If the Egg is Not Fertilized

Unfertilized egg does not implant

No hormonal message is sent to the old follicle and it stops production of estrogen and progesterone

Without estrogen and progesterone, the endometrium breaks down and the menstrual flow occurs

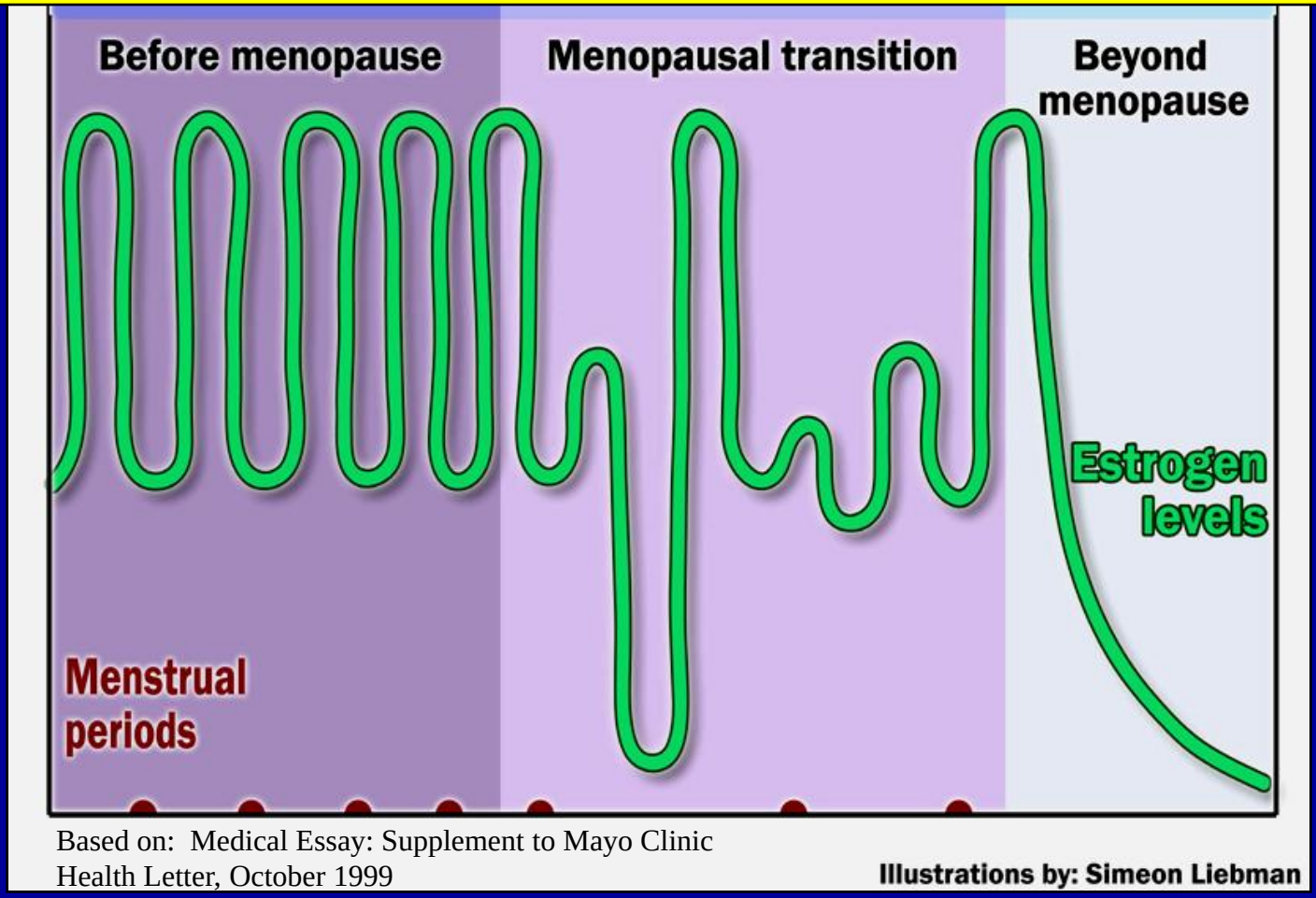
Menopause

- In a woman's 40s, estrogen production declines
- Symptoms of early menopause (perimenopause) appear and may last for 5 years
- Eventually estrogen production stops, menstrual cycle stops and woman enters menopause
  - Average age to enter menopause is 51

Symptoms of Early Menopause

- Hot flashes
- Dry skin
- Brittle hair
- Insomnia
- Vaginal dryness
- Mood swings

Changing hormone levels with menopause



The uneven rising and falling of hormone levels during perimenopause may be responsible for menstrual irregularities and other problems associated with menopause.

Pituitary and Hypothalamic Disorders

- **Etiology**

  Pituitary adenomas

- **Manifestations**

  a. Pituitary hypersecretion
  b. Pituitary insufficiency
  c. Visual field defects
  d. Diabetes isipidus

Hypopituitarism

Primary: destruction of anterior pituitary.

Secondary: deficiency of hypothalamic stimulatory factors

Etiology: "nine I's"

1. **Invasive:** large pituitary adenomas
2. **Infarction:** Ischemic damage to pituitary, necrosis in diabetes mellitus.
3. **Infiltrative:** Sarcoidosis (hypothalamus and pituitary), Hemochromatosis: Iron storage disease

Hypopituitarism ….

4. **Injury:** Severe head trauma
5. **Immunologic:** Lymphocytic hypophysitis: in pregnancy + postpartum.
6. **Iatrogenic:** Surgical + radiation
7. **Infectious:** tuberculosis, syphilis, mycotic infections.
8. **Idiopathic:** autosomal, X-linked inheritance
9. **Isolated:** deficiency in GH, ACTH, Gonadotropin, TSH, PRL, Multiple hormone (Pit-1, Prop-1).

Clinical Features of Hypopituitarism

Pituitary insufficiency: gradual, initial: GH, gonadotropin followed by TSH then ACTH, finally PRL.

Symptoms

↓ **GH:** decreased growth in children, ↓ muscle mass ↑ body fat

Hypogonadism: amenorrhea, impotence and infertility, in children: no advance to puberty.

↓ **TSH:** hypothyroidism, cold intolerance, anemia, mental dullness.

↓ **ACTH:** adrenocortical insufficiency, hypotension, shock, cardiovascular collapse.

Disorders of Oversecretion

Due to Adenomas

Arise in Pituitary: Lack of suppression of hypothalamic hormones.

Incidence: Prolactinomas 60%

↑ GH 20%

↑ ACTH 10%

↑gonadotropins (unusual)

Pituitary Adenomas
1. Prolactinomas

Clinical Features

- **Galactorrhea**

- **Gonadal dysfunction**

  ♀ Amenorrhea, oligomenorrhea with anovulation infertility.

  ↑ PRL inhibits (pulsatile LH and FSH, LH surge, positive feedback of E_2 on gonadotropins).

  ♂ Galactorrhea, hypogonadism, ↓ libido, ↓ T impotence, infertility (↓ sperm count).

Pituitary Adenomas
1. prolactinomas …

- **Diagnosis**

  Basal PRL > 200ng/ml → prolactinomas

  20-100 ng/ml → MRI required

- **Treatment**

  Surgical

  Dopamine Agonists (bromocriptine)

  Radiotherapy.

Pituitary Adenomas
2. Acromegaly and Gigantism

- **Etiology**

  Primary pituitary adenoma

  Gs mutation ↑ cAMP (in 40% GH – adenomas)

  Ectopic GHRH

  Ectopic GH (few lung tumors)

- **Pathophysiology**

  Acromegaly in adults

  Gigantism in childhood and adolescence

  Deleterious effects: due to excessive IGF-I.

Pituitary Adenomas
2. Acromegaly and Gigantism ….

- **Clinical Features**

  Hyperinsulinemia

  Acromegaly: Enlargement of hands, feet and facial features , Hypertrophy of the heart, hypertension

- **Diagnosis**

  High basal GH levels 10-500ng/ml (normal 1-5ng/ml)

  Oral glucose suppression test: negative

  IGF-I measurement

  Tumor localization.

- **Treatment**

  Surgical treatment, Radiotherapy.

  Medical treatment: somatostatin analogs (octreotide)

Pituitary Adenomas
3. Cushing's Disease

- **Pathology**

  ACTH – secreting pituitary tumors

  Adrenal: hyperplasia of zona reticularis /fasciculata normal zona glomerulosa.

- **Pathogenesis**

1. ↑ ACTH, bilateral adrenocortical hyperplasia, hypercortisolism.
2. ACT H and cortisol circadian: absent
3. ACTH and cortisol response to stress: absent.
4. Negative feedback of ACTH by glucocorticoids: abnormal
5. GH, TSH, LH, FSH: subnormal response to stimulation.

Pituitary Adenomas

3. Cushing's Disease …

Clinical Features

Symptoms of hypercortisolism and adrenal androgen excess.

Obesity, hypertension, glucose intolerance, moon faces.

gonadal dysfunction (amenorrhea or impotence).

Cushing's disease 8:1 female /male

Ectopic ACTH 3:1 male/female

Diagnosis

↑ cortisol levels

Abnormal negative feedback by dexamethasone

ACTH levels

Treatment

Surgical, Radiotherapy, chemical

Posterior Pituitary: Neurohypophysis

Oxytocin

- Contraction of smooth muscle

  uterus: during labor

  mammary gland: milk ejection

Vasopressin (ADH)

- Kidney (V2 receptors): Water reabsorption (aquaporin-2 channels)
- Vasoconstriction (V1 receptors): ↑ BP
- Potentiate CRH on ACTH: (V3 receptors)

Posterior Pituitary: Neurohypophysis

- **Half-life:**

  5 min

- **Mechanism of Action:** G Protein

  Oxytocin and ADH (V1 receptors): PI, Ca^{++}

  ADH (V2 receptors): cAMP

Control of ADH Secretion

- ↑ Osmolality:

  ↑ ADH (H_2O retention) → ↓ Osmolality
  (Osmoreceptors of hypothalamus) → ↓ ADH

- ↓ Blood Volume: ↑ ADH

- Hemorrhage: ↑ ADH (baroreceptors)

- CNS (Stress, vomiting, …): ↑ ADH

Control of Oxytocin Secretion

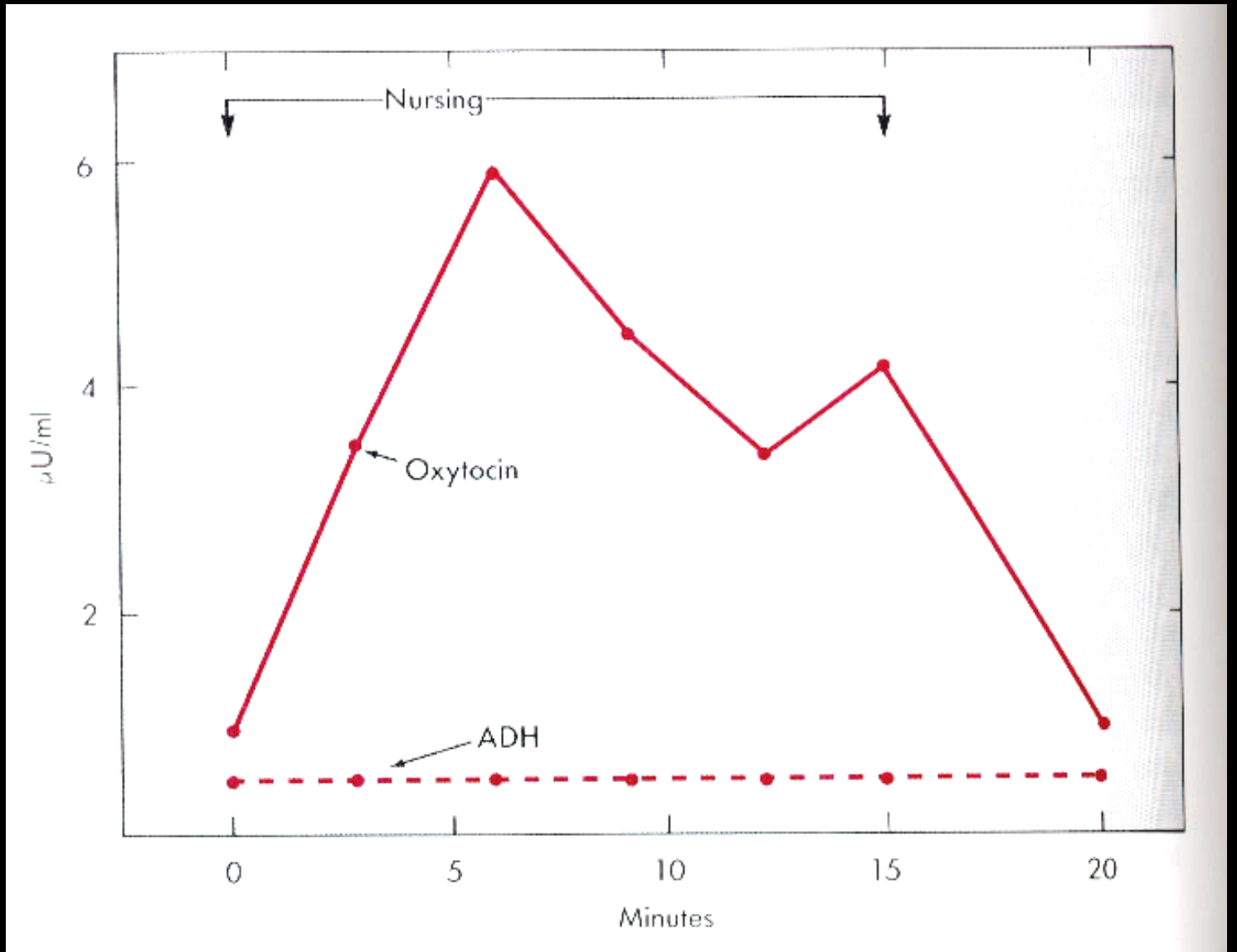
Elevated during Parturition and Lactation

- During Parturition: Vaginal stimulation,

  ↓ progesterone (Progesterone blocks uterus response to oxytocin), Positive feedback.
- Suckling (sight sound of infant) →

  ↑ oxytocin → milk ejection.
- Stress → ↓ oxytocin → ↓ flow of milk

Oxytocin secretion is stimulated by nursing



Disorders of Posterior Pituitary

Diabetes insipidus

Deficient ADH action

very dilute urine (20 liters)

Types

1. Central Diabetes Insipidus: pituitary and hypothalamic disorders (no ADH secretion)
2. Nephrogenic Diabetes Insipidus: no renal response to ADH (Chronic renal disease, defects of aquaporin-2 gene, drugs: lithium carbonate)

Syndrome of Inappropriate Secretion of ADH (SIADH)

- Ectopic ADH (Pancreatic or Duodenal tumors)

- Tuberculosis and Pneumonia ↑ ADH
  - Hyponatremia, plasma Osmolality < 280 mosm/kg.
  - Urine inappropriately concentrated.