Physical Activity and Health Promotion

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Lesson 4
Pituitary physiopathology

Steps in Expression of a Protein-Encoding Gene

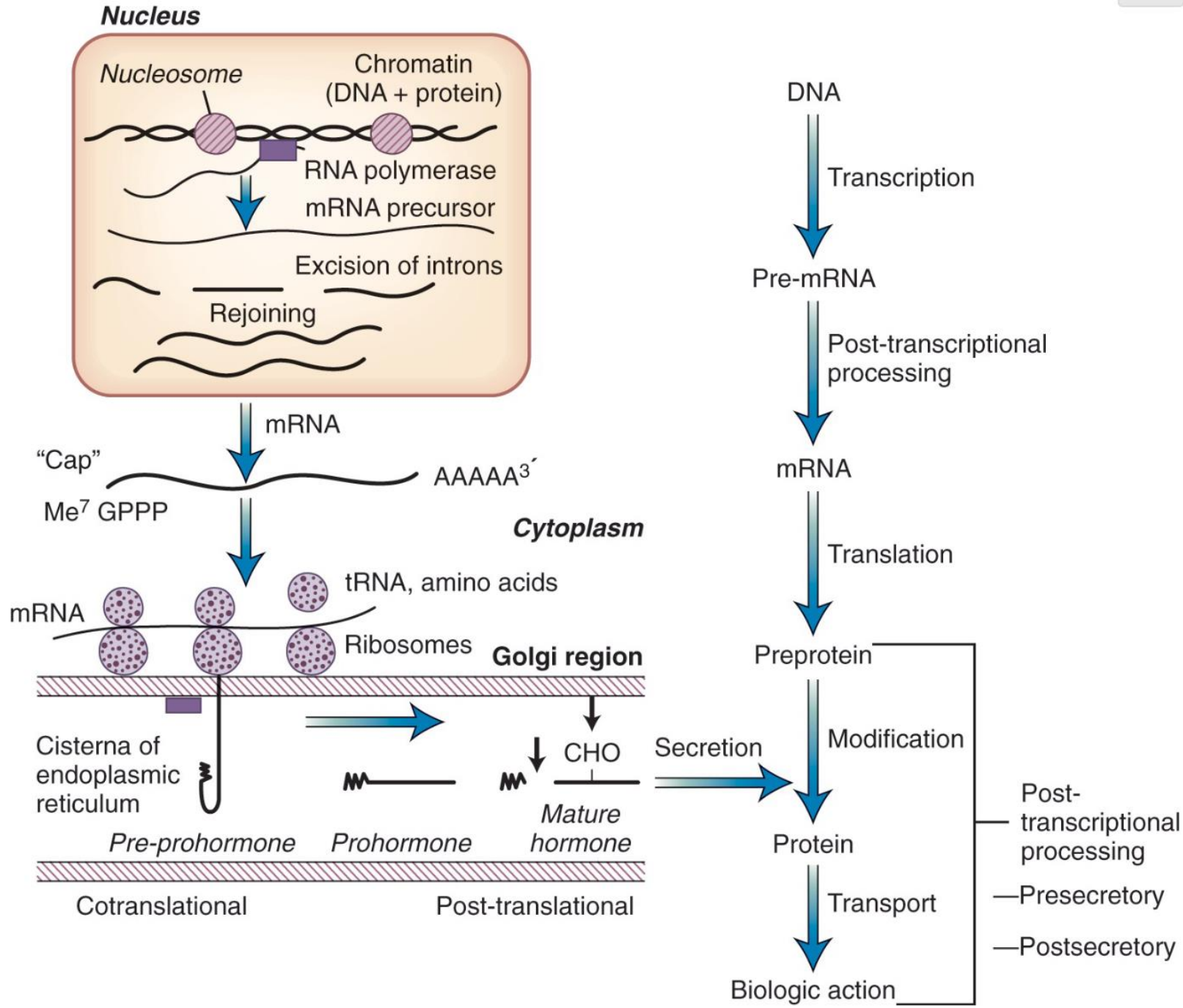
Rearrangements and transpositions of DNA segments. These processes occur over eons in evolution, with the exception of uncommon mechanisms of somatic gene rearrangements such as rearrangements in the immunoglobulin genes occurring during the lifetime of an individual.

Transcription. Synthesis of RNA results in the formation of RNA copies of the two gene alleles and is catalyzed by the basal RNA polymerase II–associated transcription factors.

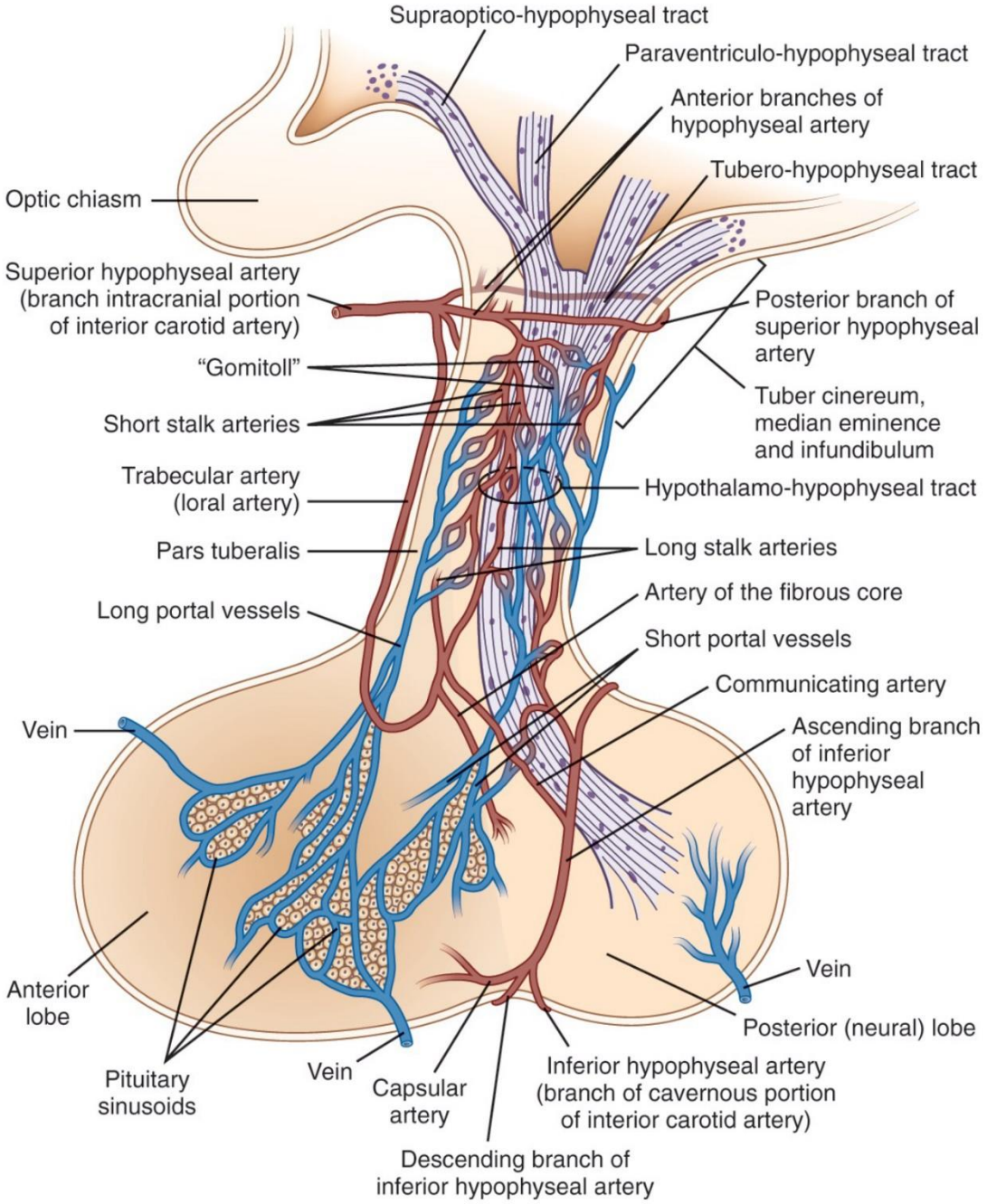
Post-transcriptional processing. Specific modifications of RNA include the formation of messenger RNA (mRNA) from the precursor RNA by way of excision and rejoining of RNA segments (introns and exons) and the modification of the 3′ end of the RNA by polyadenylation and of the 5′ end by addition of 7-methylguanine caps.

Translation. Amino acids are assembled by base pairing of the nucleotide triplets (anticodons) of the specific "carrier" amino-acylated transfer RNAs to the corresponding codons of the mRNA bound to polyribosomes and are polymerized into polypeptide chains.

Post-translational processing and modification. Final steps in protein synthesis may involve one or more cleavages of peptide bonds, which result in the conversion of biosynthetic precursors (prohormones) to intermediate or final forms of the protein; derivatization of amino acids (e.g., glycosylation, phosphorylation, acetylation, myristoylation); and folding of the processed polypeptide chain into its native conformation.


Nucleus
Nucleosome
Chromatin
(DNA + protein)
RNA polymerase
mRNA precursor
Excision of introns
Rejoining
mRNA
"Cap"
AAAAA3´
Me7 GPPP
Cytoplasm
tRNA, amino acids
mRNA
Ribosomes
Golgi region
Cisterna of
endoplasmic
reticulum
CHO
Secretion
Mature
hormone
Pre-prohormone
Prohormone
Cotranslational
Post-translational
DNA
Transcription
Pre-mRNA
Post-transcriptional
processing
mRNA
Translation
Preprotein
Modification
Protein
Transport
Biologic action
Post-
transcriptional
processing
—Presecretory
—Postsecretory

The pituitary gland is situated within the sella turcica. Its name derives from the Greek *ptuo* and Latin *pituita*, “phlegm,” reflecting its nasopharyngeal origin



The pituitary gland comprises the predominant anterior lobe, the posterior lobe, and a vestigial intermediate lobe. The gland is situated within the bony sella turcica and is overlain by the dural diaphragma sella, through which the stalk connects to the median eminence of the hypothalamus. The adult pituitary weighs approximately 600 mg (range, 400 to 900 mg) and measures approximately 13 mm in the longest transverse diameter, 6 to 9 mm in vertical height, and about 9 mm anteroposteriorly. Structural variation may occur in multiparous women, and gland volume also changes with the menstrual cycle. During pregnancy, size may be increased in any dimension, and pituitary weight increases up to 1 g.

The **posterior pituitary gland**, in contrast to the anterior pituitary, is directly innervated by supraopticohypophyseal and tuberohypophyseal nerve tracts of the posterior stalk. Hypothalamic neuronal lesions, stalk disruption, or direct systemically derived metastases are often associated with reduced secretion of vasopressin/ADH (diabetes insipidus) or oxytocin or both.

Hormone-secreting cell types of the anterior pituitary gland

The **hypothalamus** contains nerve cell bodies that synthesize **hypophysiotropic releasing and inhibiting hormones** as well as the **neurohypophyseal hormones** of the posterior pituitary (vasopressin and oxytocin). Five distinct hormone-secreting cell types are present in the **mature anterior pituitary gland**:

- **1**

Corticotroph cells express pro-opiomelanocortin (POMC) peptides including adrenocorticotropic hormone (ACTH, also called *corticotropin*).

- **2**

Somatotroph cells express growth hormone (GH, also called *somatotropin*).

- **3**

Thyrotroph cells express the common glycoprotein α-subunit (αGSU) and the specific β-subunit of thyroid-stimulating hormone (TSH, also called *thyrotropin*).

- **4**

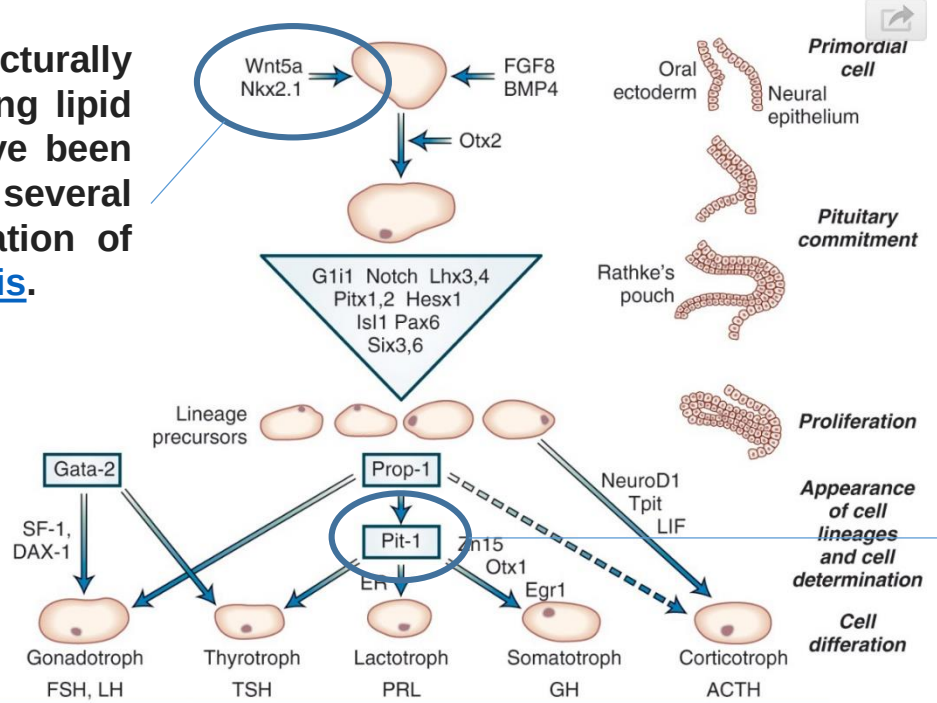
Gonadotrophs express the α- and β-subunits for both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

- **5**

Lactotrophs expresses prolactin (PRL).

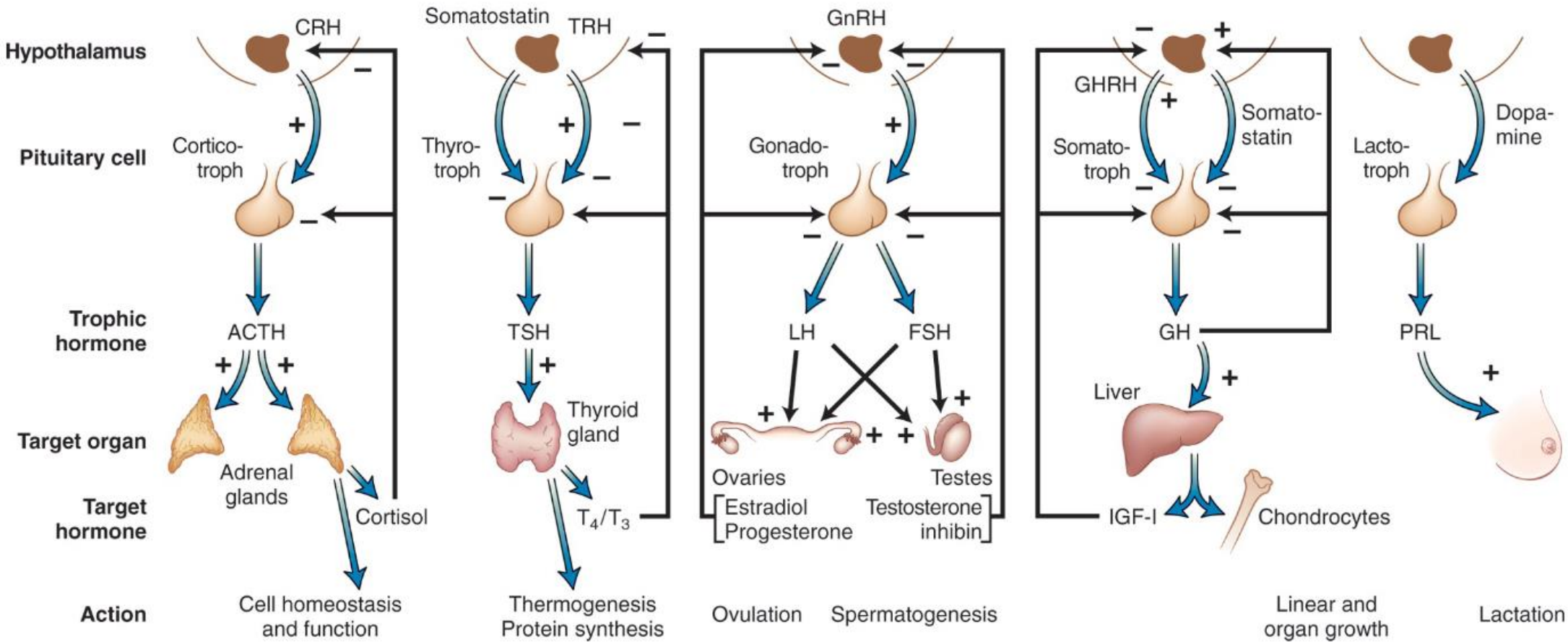
Each cell type is under highly specific signal controls that regulate its differentiated gene expression.

The WNT gene family consists of structurally related genes that encode secreted signaling lipid modified glycoproteins. These proteins have been implicated in oncogenesis and in several developmental processes, including regulation of cell fate and patterning during embryogenesis.



Fetal appearance	12 weeks	12 weeks	12 weeks	8 weeks	8 weeks
Hormone	FSH LH	TSH	PRL	GH	POMC
Chromosomal gene locus	β-11p; β-19q	α-6q; β-1p	6	17q	2p
Protein	Glycoprotein α, β Subunits	Glycoprotein α, β Subunits	Polypeptide	Polypeptide	Polypeptide
Amino acids	210 204	211	199	191	266 (ACTH 1–39)
Stimulators	GnRH, estrogen	TRH	Estrogen, TRH	GHRH GHS	CRH, AVP gp-130 cytokines
Inhibitors	Sex steroids, inhibition	T3,T4, Dopamine, somatostatin glucocorticoids	Dopamine	Somatostatin, IGF activins	Glucocorticoids
Target gland	Ovary, testis	Thyroid	Breast, other tissues	Liver, bones, other tissues	Adrenal
Trophic effect	Sex steroid Follicle growth Germ cell maturation M, 5–20 IU/L F (basal) 5–20 IU/L	T4 Synthesis and secretion	Milk production	IGF-I production, growth induction, insulin antagonism	Steroid production
Normal range	M, 5–20 IU/L F(basal) 5–20 IU/L	0.1–5 mU/L	M <15; F <20 μg/L	<0.5 μg/L	ACTH, 4–22 pg/L

PIT1 is a pituitary-specific transcription factor responsible for pituitary development and hormone expression in mammals and is a member of the POU family of transcription factors that regulate mammalian development.


Hypothalamus
Pituitary cell
Trophic hormone
Target organ
Target hormone
Action
CRH
Cortico-troph
ACTH
Adrenal glands
Cortisol
Cell homeostasis and function
Somatostatin
TRH
Thyro-troph
TSH
Thyroid gland
T_4/T_3
Thermogenesis Protein synthesis
GnRH
Gonado-troph
LH
FSH
Ovaries
Testes
Estradiol Progesterone
Testosterone inhibin
Ovulation
Spermatogenesis
GHRH
Somato-troph
Somato-statin
GH
Liver
IGF-I
Chondrocytes
Linear and organ growth
Lacto-troph
Dopa-mine
PRL
Lactation

Pituitary Blood Supply

The pituitary gland enjoys an abundant blood supply derived from several sources. The superior hypophyseal arteries branch from the internal carotid arteries to supply the hypothalamus, where they form a capillary network in the median eminence, external to the blood-brain barrier. The long and short hypophyseal portal vessels originate, respectively, from infundibular plexuses and from the pituitary stalk. These vessels form the hypophyseal-portal circulation, the predominant blood supply to the anterior pituitary gland. They deliver hypothalamic releasing and inhibiting hormones to the trophic hormone–producing cells of the adenohypophysis without significant systemic dilution, allowing the pituitary cells to be sensitively regulated by timed hypothalamic hormone secretion. Vascular transport of hypothalamic hormones is also locally regulated by a contractile internal capillary plexus (*gomitoli*) derived from stalk branches of the superior hypophysial arteries.

Lactotroph Cells Prolactin

Lactotroph cells comprise 15% to 25% of functioning anterior pituitary cells. Their absolute number does not change with age, but lactotroph hyperplasia occurs during pregnancy and lactation and resolves within several months after delivery. Most PRL-expressing cells appear to arise from GH-producing cells. Ablation of somatotrophs by expression of GH–diphtheria toxin and GH–thymidine kinase fusion genes inserted into the germline of transgenic mice eliminates most lactotrophs, suggesting that the majority of PRL-producing cells arise from postmitotic somatotrophs.

Causes of Hyperprolactinemia

PHYSIOLOGIC
1.Pregnancy 2.Lactation 3.Stress 4.Sleep 5.Coitus 6.Exercise

PATHOLOGIC
Hypothalamic-Pituitary Stalk Damage
1.Tumors: craniopharyngioma, suprasellar pituitary mass extension, meningioma, dysgerminoma, hypothalamic metastases 2.Granulomas 3.Infiltrations 4.Rathke's cyst 5.Irradiation 6.Trauma: pituitary stalk section, sellar surgery, head trauma
Pituitary
1.Prolactinoma 2.Acromegaly 3.Macroadenoma (compressive) 4.Idiopathic 5.Plurihormonal adenoma 6.Lymphocytic hypophysitis or parasellar mass 7.Macroprolactinemia
Systemic Disorders
1.Chronic renal failure 2.Polycystic ovary syndrome 3.Cirrhosis 4.Pseudocyesis 5.Epileptic seizures 6.Cranial irradiation 7.Chest: neurogenic chest wall trauma, surgery, herpes zoster

Causes of Hyperprolactinemia

PHYSIOLOGIC

1.Pregnancy
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4.Sleep
5.Coitus
6.Exercise

PHARMACOLOGIC

Neuropeptide

Thyrotropin-releasing hormone

Drug-Induced Hypersecretion

Dopamine Receptor Blockers

1.Phenothiazines: chlorpromazine, perphenazine
2.Butyrophenones: haloperidol
3.Thioxanthenes
4.Metoclopramide

Dopamine Synthesis Inhibitors

α-Methyldopa

Catecholamine Depletors

Reserpine

Cholinergic Agonist

Physostigmine

Opiates and Opiate Antagonists

1.Heroin
2.Methadone
3.Apomorphine
4.Morphine

Antidepressants

1.Tricyclic antidepressants: chlorimipramine, amitriptyline
2.Selective serotonin reuptake inhibitors: fluoxetine

Antihypertensives

1.Labetalol
2.Reserpine
3.Verapamil

H_2 Antihistamines

1.Cimetidine
2.Ranitidine

Estrogens

1.Oral contraceptives
2.Oral contraceptive withdrawal

Anticonvulsant

1.Phenytoin

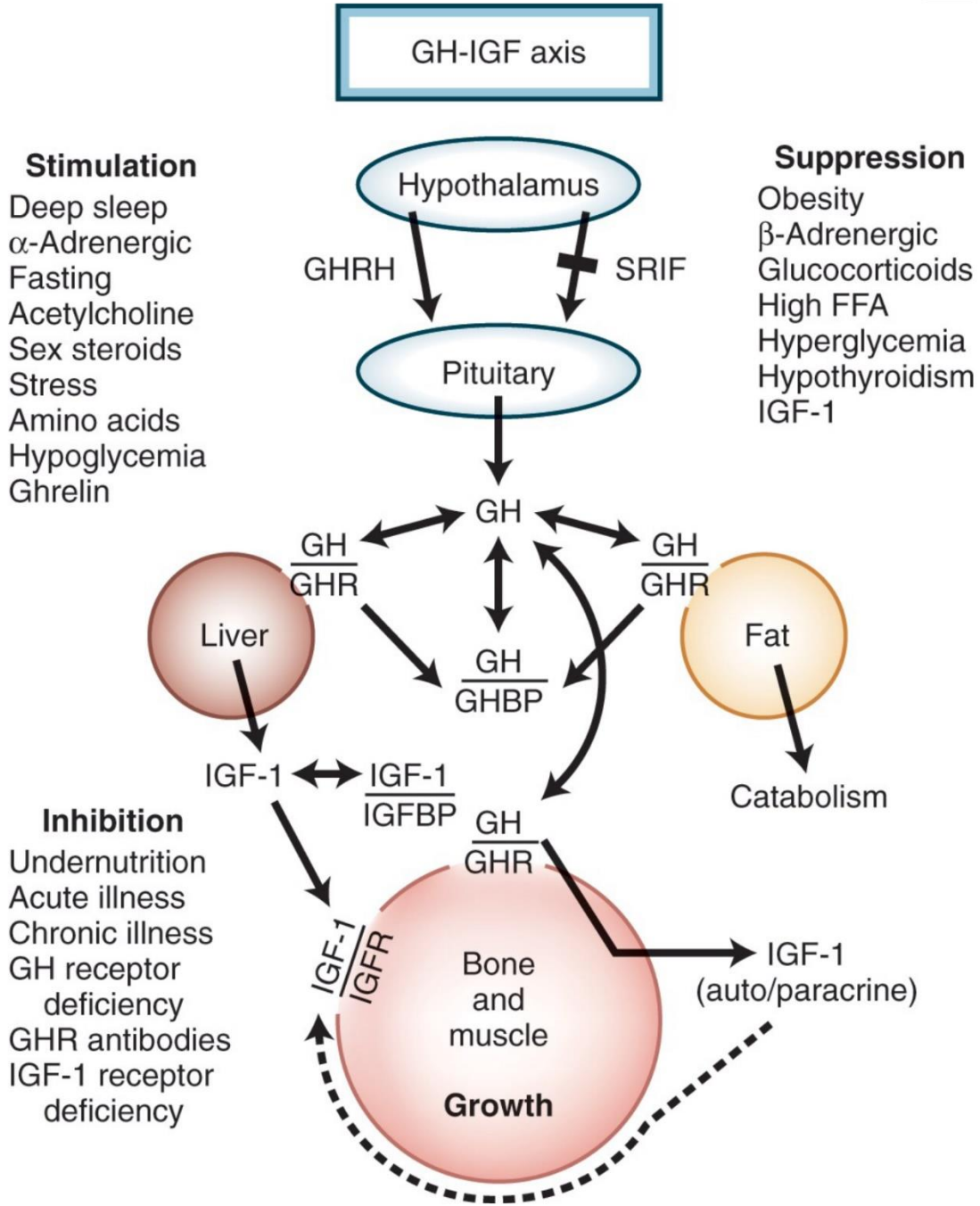
Anesthetics

Neuroleptics

1.Chlorpromazine
2.Risperidone
3.Promazine
4.Promethazine
5.Trifluoperazine
6.Fluphenazine
7.Butaperazine
8.Perphenazine
9.Thiethylperazine
10.Thioridazine
11.Haloperidol
12.Pimozide
13.Thiothixene
14.Molindone

Somatotroph Cells Growth Hormone

Mammosomatroph cells expressing both PRL and GH arise from the acidophilic stem cell and immunostain mainly for PRL. Somatotrophs are located predominantly in the lateral wings of the anterior pituitary gland and comprise between 35% and 45% of pituitary cells. These ovoid cells contain prominent secretory granules up to 700 µm in diameter. Juxtanuclear Golgi structures are particularly prominent, with secretory granules in formation. The gland contains a total of 5 to 15 mg of GH.


GH-IGF axis
Stimulation
Deep sleep
α-Adrenergic
Fasting
Acetylcholine
Sex steroids
Stress
Amino acids
Hypoglycemia
Ghrelin
Hypothalamus
GHRH
SRIF
Pituitary
Suppression
Obesity
β-Adrenergic
Glucocorticoids
High FFA
Hyperglycemia
Hypothyroidism
IGF-1
GH
GH/GHR
GH/GHR
Liver
Fat
GH/GHBP
IGF-1
IGF-1/IGFBP
Catabolism
Inhibition
Undernutrition
Acute illness
Chronic illness
GH receptor deficiency
GHR antibodies
IGF-1 receptor deficiency
GH/GHR
IGF-1/IGFR
Bone and muscle
Growth
IGF-1 (auto/paracrine)

Growth Hormone Secretagogues and Ghrelin

Nutrition plays a major role in GH regulation. Chronic malnutrition and prolonged fasting increase GH pulse frequency and amplitude

Obesity decreases basal and stimulated GH secretion, insulin-induced hypoglycemia stimulates GH, and hyperglycemia inhibits GH secretion. However, chronic hyperglycemia is not associated with low GH levels, and, in fact, poorly controlled diabetes is associated with increased basal and exercise-induced GH levels.

Central glucoreceptors appear to sense glucose fluctuations, rather than absolute levels. High-protein meals and intravenous administration of single amino acids (including arginine and leucine) stimulate GH secretion.

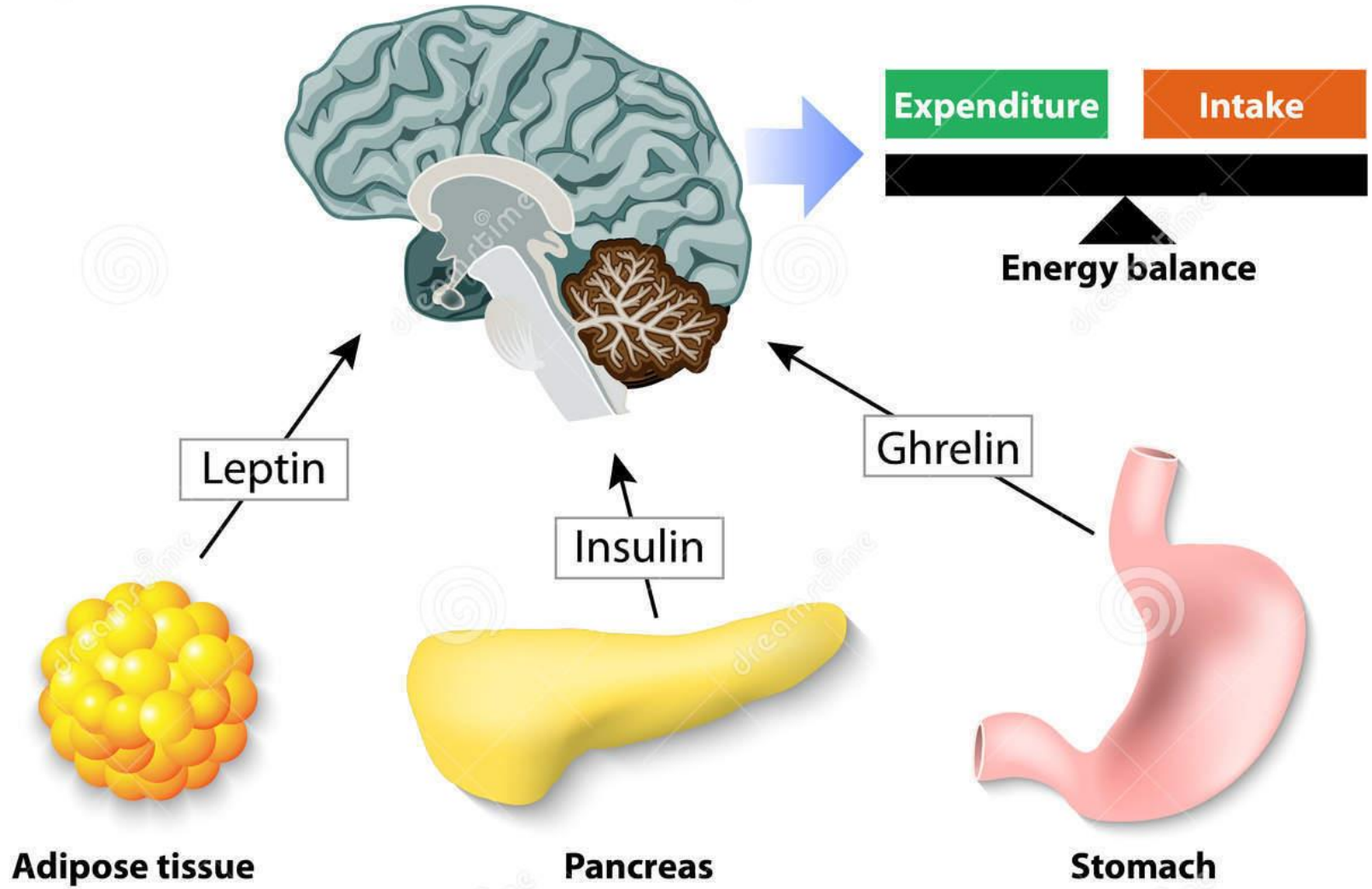
Increased **serum free fatty acids** blunt the effects of arginine infusion, sleep, dopa, and exercise on GHRH-stimulated GH release.

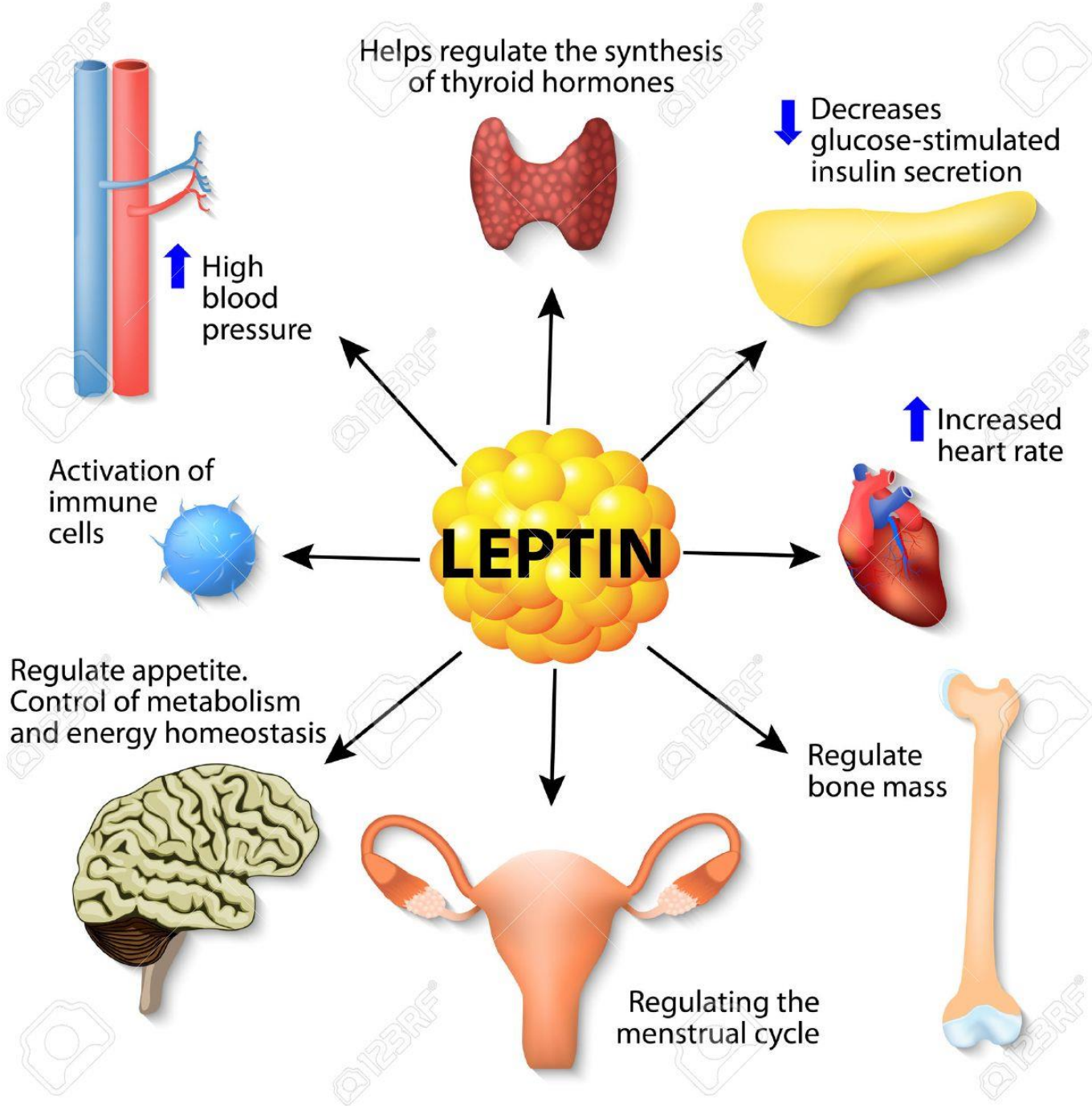
Leptin plays a key role in regulation of body fat mass, regulating food intake and energy expenditure, and may act as a metabolic signal to regulate GH secretion. Leptin- and neuropeptide Y–producing hypothalamic neurons synapse with somatostatin neurons, and antisera to neuropeptide Y and somatostatin reverse starvation-induced GH release.

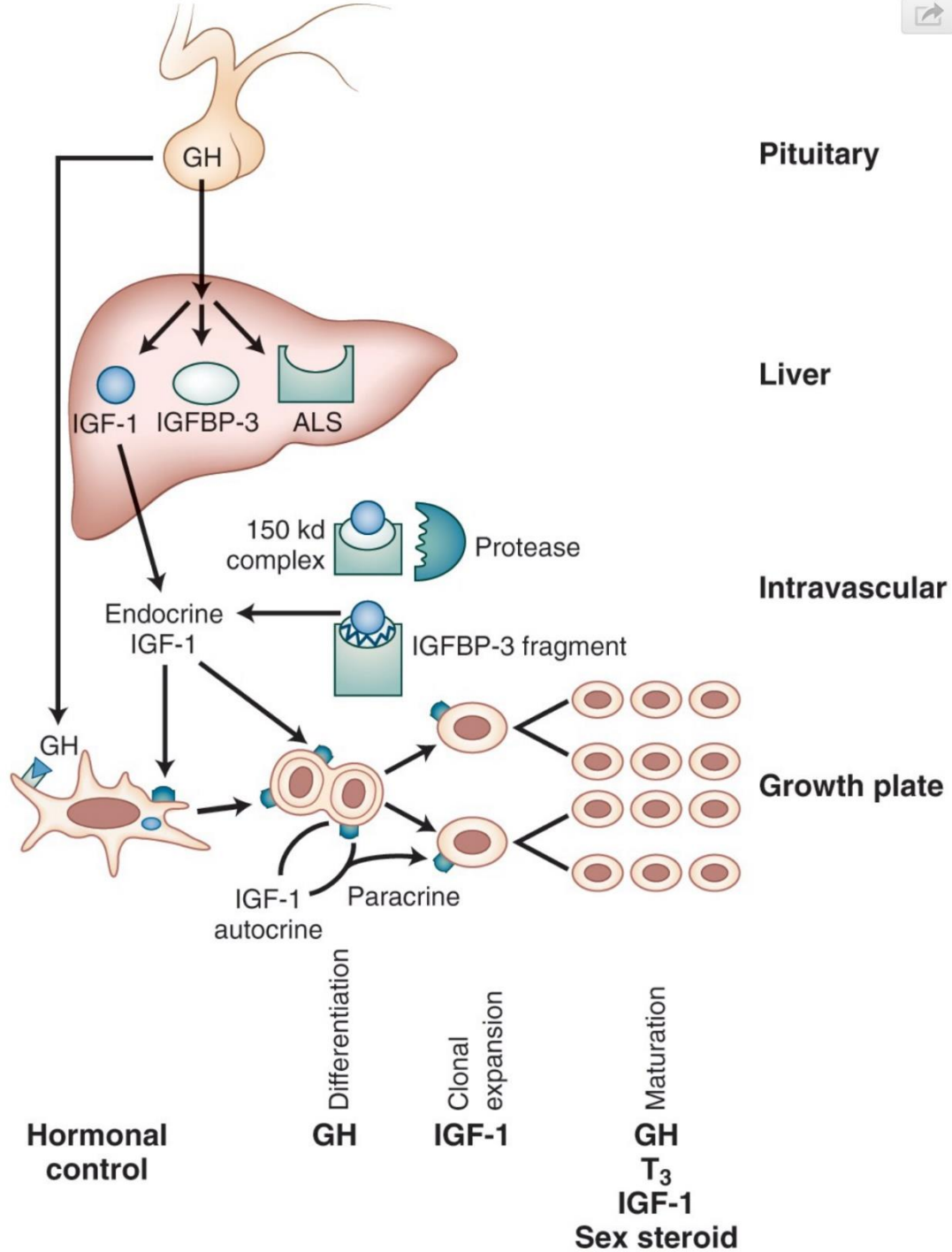
The isolation of **ghrelin** implicated an additional control system for regulation of GH secretion. Ghrelin is a 28-amino-acid peptide that binds the GHS receptor[172] to induce hypothalamic GHRH and pituitary GH. Ghrelin is synthesized in peripheral tissues, especially in gastric mucosal neuroendocrine cells, as well as centrally in the hypothalamus. Ghrelin administration dose-dependently evokes GH release and also induces food intake

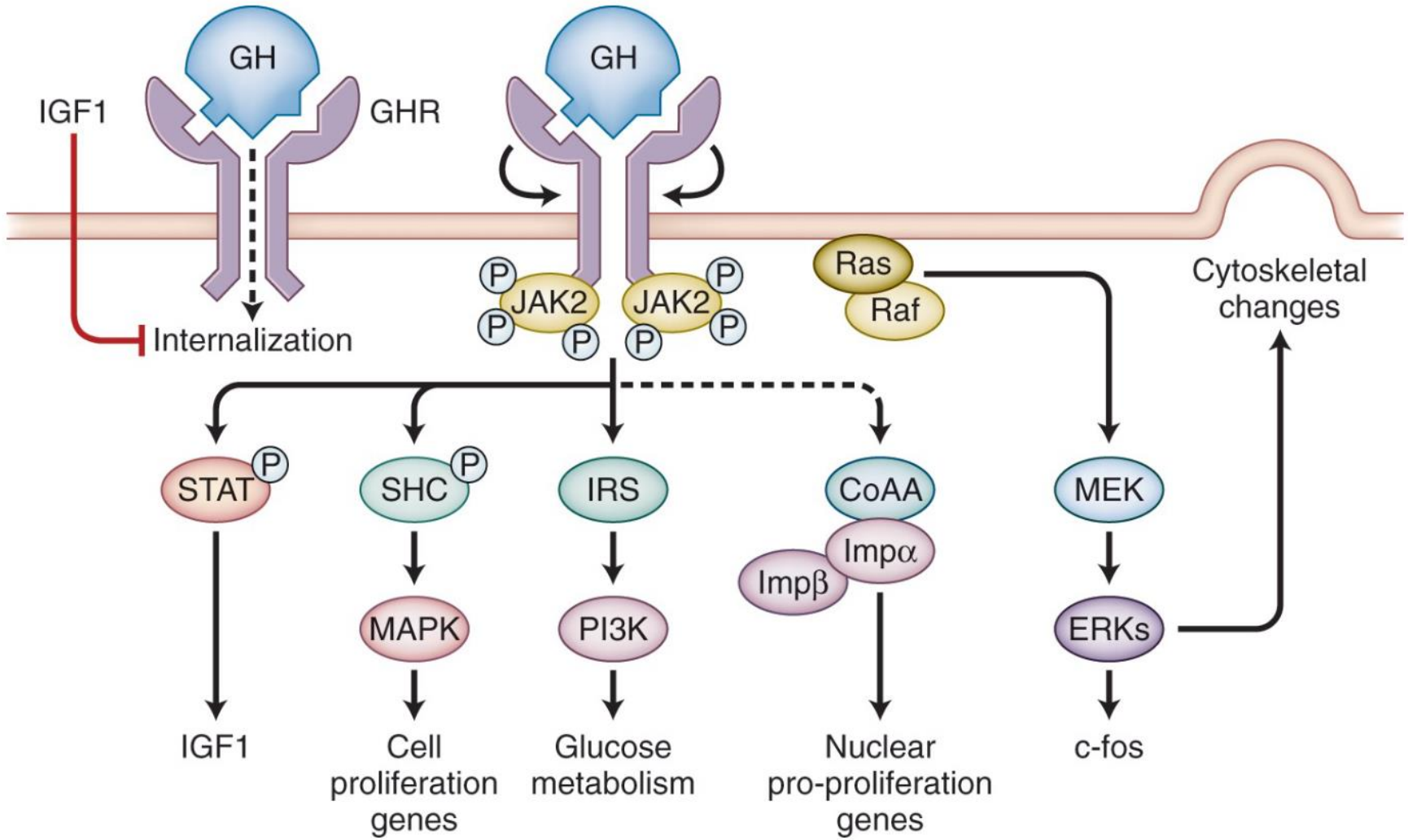
LEPTIN & GHRELIN

CONTROL OF FOOD INTAKE




Helps regulate the synthesis of thyroid hormones
Decreases glucose-stimulated insulin secretion
High blood pressure
Increased heart rate
Activation of immune cells
LEPTIN
Regulate appetite. Control of metabolism and energy homeostasis
Regulate bone mass
Regulating the menstrual cycle


GH
Pituitary
IGF-1
IGFBP-3
ALS
Liver
150 kd
complex
Protease
Intravascular
Endocrine
IGF-1
IGFBP-3 fragment
GH
Growth plate
IGF-1
autocrine
Paracrine
Differentiation
Clonal
expansion
Maturation
Hormonal
control
GH
IGF-1
GH
T3
IGF-1
Sex steroid


GH
GH
IGF1
GHR
Internalization
P
JAK2
JAK2
P
Ras
Raf
Cytoskeletal
changes
STAT
SHC
IRS
CoAA
Impα
Impβ
MEK
MAPK
PI3K
ERKs
IGF1
Cell
proliferation
genes
Glucose
metabolism
Nuclear
pro-proliferation
genes
c-fos

Secretion of Growth Hormone in Adults

Interval	Young Adult	Fasting	Obesity	Middle Age
24-hr Secretion (μg/24 hr)	540 ± 44	2171 ± 333	77 ± 20	196 ± 65
Secretory bursts (no. in 24 hr)	12 ± 1	32 ± 2	3 ± 0.5	10 ± 1
GH burst (μg)	45 ± 4	64 ± 9	24 ± 5	10 ± 6

Adult Somatotropin Deficiency

Clinical Consequence	Effect of GH Replacement
Body Composition	
General and central adiposity	Decrease
Reduced lean mass	Increase
Reduced bone mass	Increase
Function	
Reduced exercise capacity	Improve
Muscle weakness	Increase
Impaired cardiac function	Improve
Hypohidrosis	Increase

Quality of Life	
Low mood	Improve
Fatigue	Improve
Low motivation	Improve
Reduced satisfaction	Improve
Cardiovascular Risk Profile	
Abnormal lipid profile	Improve
Insulin resistance	No change
Increased inflammatory markers	Decrease
Intimal media thickening	Decrease

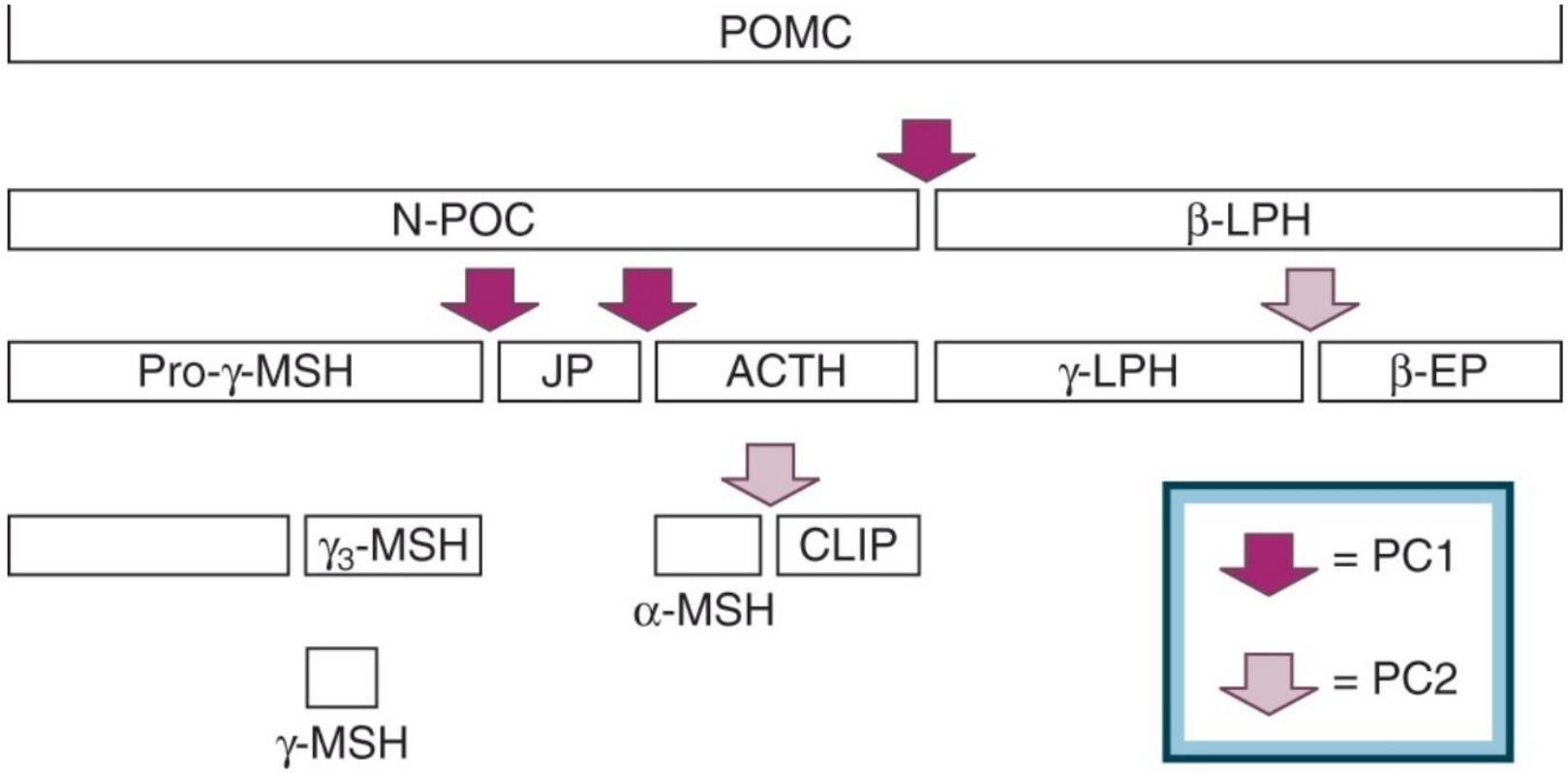
GH and Sports

The public policy issues regarding GH abuse in competitive sports have received much attention. GH has been widely abused by athletes to enhance performance. Whether persistent GH use is accompanied by increased muscle strength is unclear. A systematic review concluded that claims of GH enhancement of physical performance are not supported by the scientific literature evaluating effects on aerobic capacity, strength, and power and that more research is needed to conclusively determine the effects of GH on athletic performance. A recent double-blind, placebo-controlled study reported that GH enhances sprint capacity, but not aerobic capacity, strength, or power, in recreational athletes.

Corticotroph Cells and Adrenocorticotropic Hormone (ACTH)

- The hypothalamic-pituitary-adrenal (HPA) axis plays a critical role in maintaining homeostasis and in mounting an appropriate response to stress.
- Key components of the stress response are aimed at providing adequate amounts of glucocorticoids that exert vital pleiotropic effects on energy supply, fuel metabolism, immunity, and cardiovascular function.
- Corticotrophs are clustered mainly in the central median pituitary wedge. They are large, irregular cells, and their ultrastructural features include prominent neurosecretory granules (150-400 nm), endoplasmic reticulum, and Golgi bodies.
- These cells produce the POMC gene products, including ACTH(1-39), β-lipotropin, and endorphins.

POMC Processing



Several post-translational POMC modification steps are required for polypeptide hormone secretion. POMC proteolytic processing occurs at Lys-Arg or Arg-Arg residues by enzymes called *prohormone convertases* (PCs), which are a superfamily of subtilisin/kexin proteinases

Biologic Actions of POMC-Derived Peptides

1. **ADRENAL ACTION**

Full-lenght ACTH is the only POMC-derived peptide with adrenocorticotropic function and it is the ligand of the melanocortin receptor type 2 receptor (MC2R). MC2R activation results in production of adrenal glucocorticoids, androgenic steroids and, to a lesser extent, mineralcorticoids

2. **SKIN PIGMENTATION**

Melanocyte stimulation occurs through activation of MC1R. ACTH, β-lipotropin and γ-LPH produced from the corticotrophs share a common heptapeptide sequence that is required to activate MC1R. These peptides are responsible for inducing skin pigmentationin Addison's disease.

3. **APPETITE REGULATION**

POMC-derived peptides, and in particular α-MSH, play a critical role in central regulation of appetite. The melanocortin system mediates feed-back suppression of appetite by leptin trough activation of MC3R and MC4R by αMSH in the hypothalamus. Genetic and pharmachologic abrogation of the melanocortin system causes profound obesity.

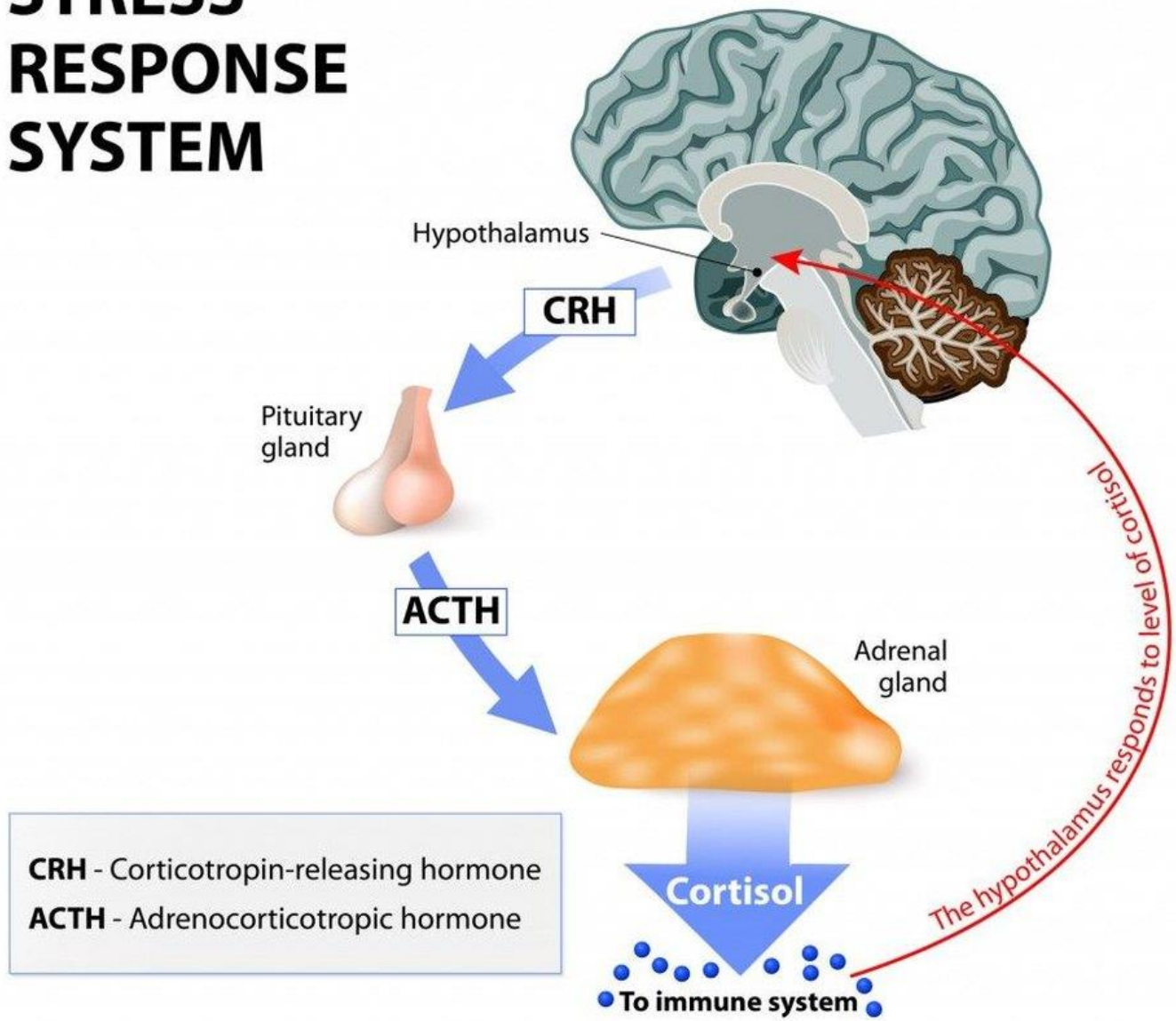
4. **IMMUNE MODULATION**

αMSH influences the inflammatory process by modulating the function of antigen-presenting cells and T cells. It suppresses fever induced by IL-6 and inhibits macrophage function and leucocite migration

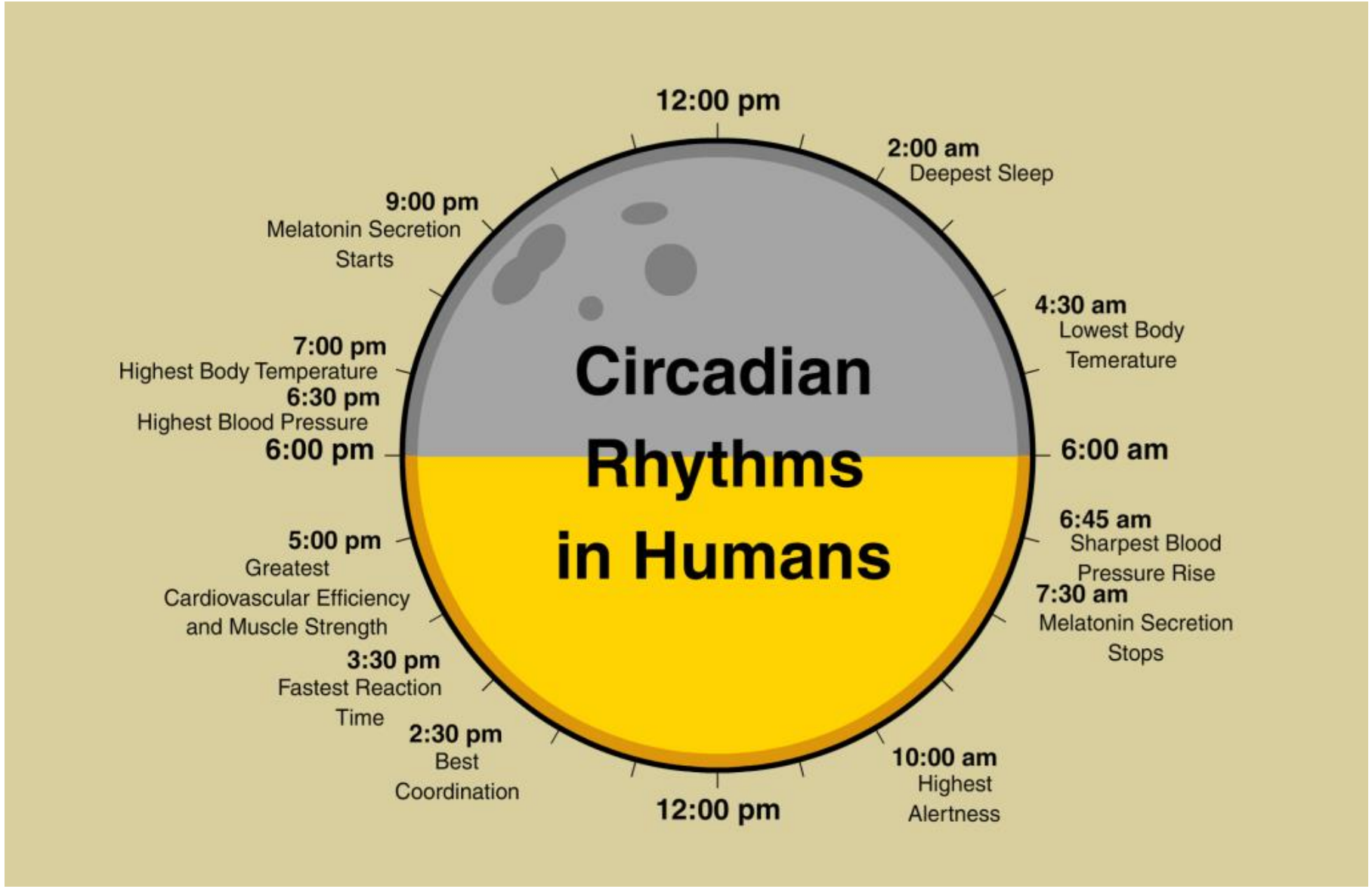
5. **ANALGESIA**

β-endorphin produced by corticotrophs exerts a potent analgesic effect through opiate receptors

STRESS RESPONSE SYSTEM



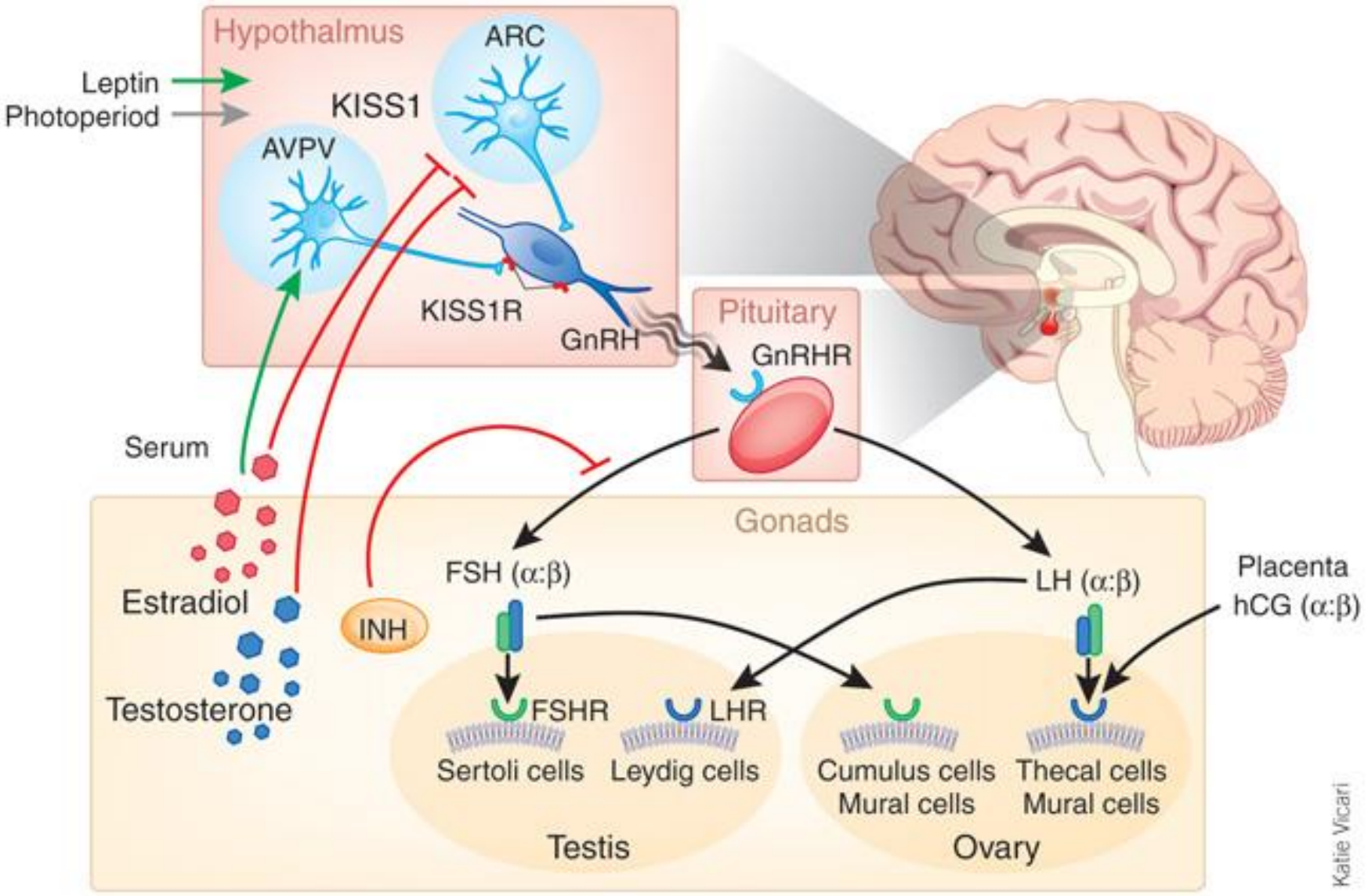
The **circadian rhythm** is based off of a 24 hr clock that tells our bodies when to sleep and regulates other physiological processes



Gonadotroph Cells LH/FSH

Gonadotroph cells secreting FSH and LH comprise 10% to 15% of the functional anterior pituitary cells. Two classes of secretory granules are evident : large (350 to 450 nm) and small (150 to 250). The granules are packaged in vesicles. LH secretory granules often accumulate peripherally and their Golgi structure may be less prominent. FSH and LH function to regulate gonadal steroid hormone biosynthesis and to initiate and maintain germ cell development, in concert with peripheral hormones and paracrine soluble factors.

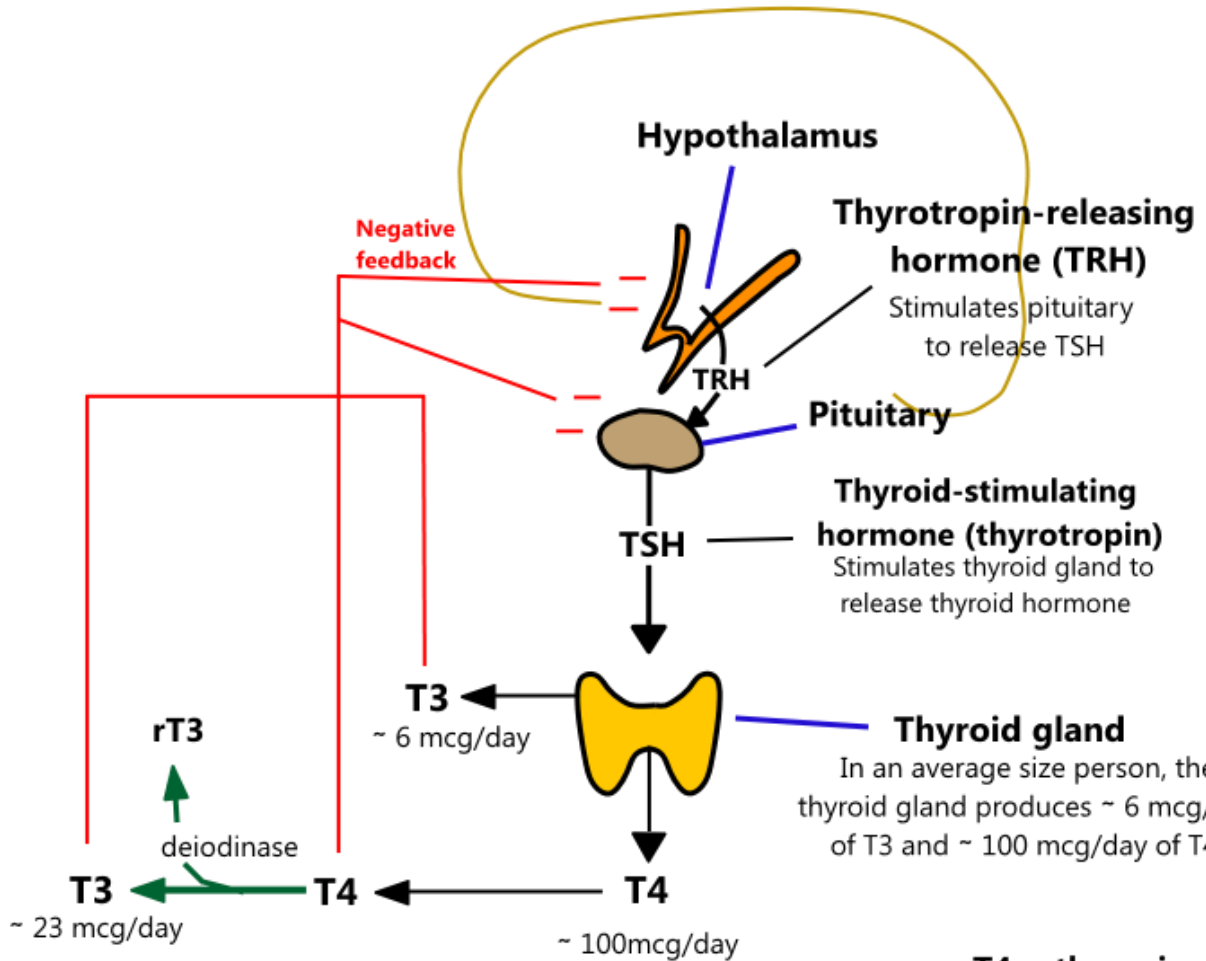
Hypothalamic GnRH neurons and regulation of LH/FSH secretion



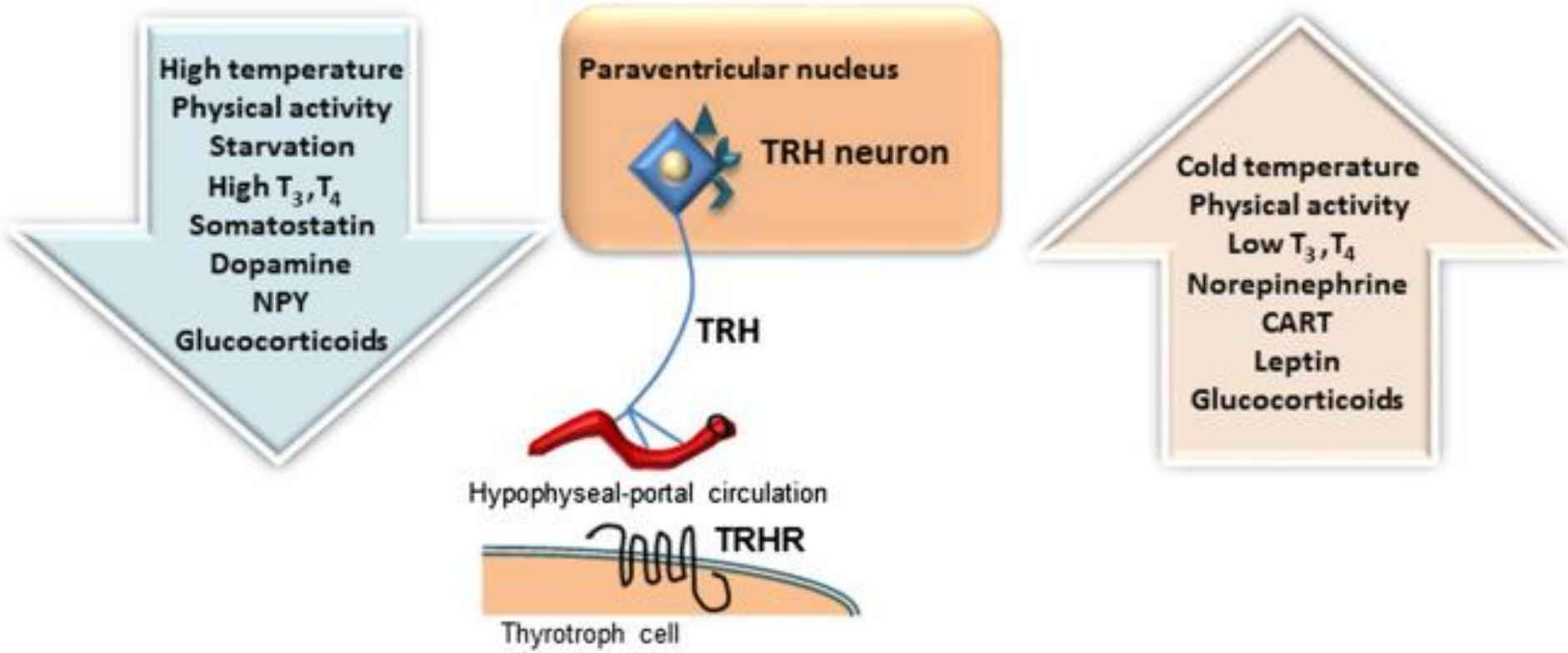
Thyrotroph Cells Thyroid-Stimulating hormone

The hypothalamic-pituitary thyroid system plays a critical role in development, growth and cellular metabolism, with thyroid hormone availability and action controlled by complex mechanisms at the tissue level. Thyrotroph cells comprise approximately 5% of the functional anterior pituitary cells and are situated predominantly in the anteromedial areas of the gland. They are smaller then the other cell types, irregularly shaped with flattened nuclei and relatively small secretory granules ranging from 120 to 150 μm. TSH is a glycoprotein hormone comprising a heterodimer of noncovalently linked α- and β-subunits

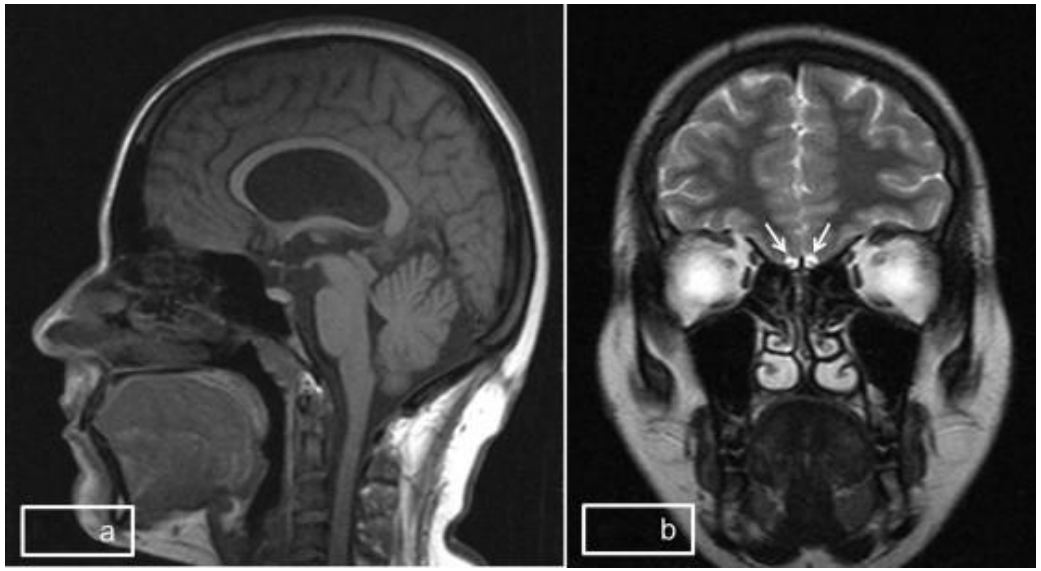
Hypothalamic-pituitary-thyroid axis



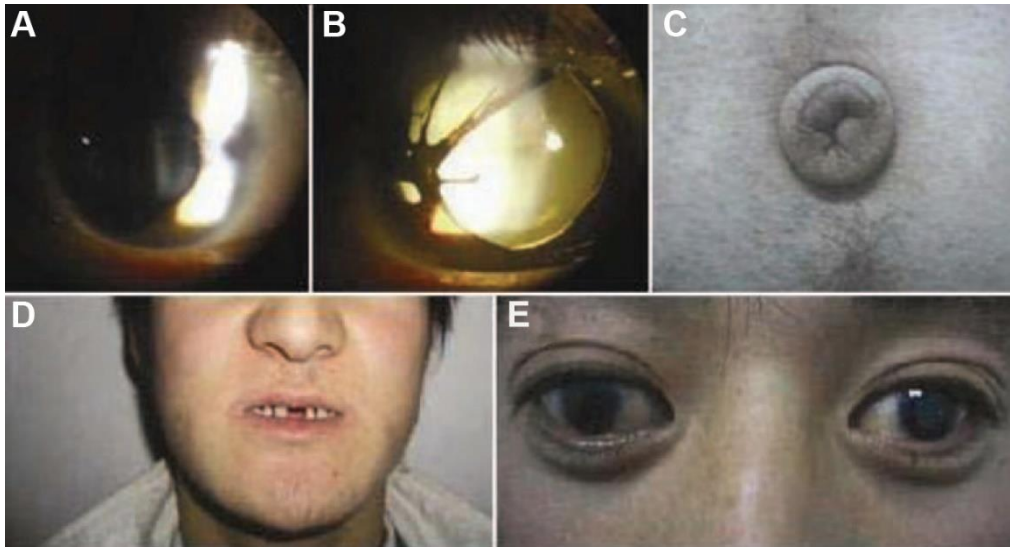
T4 = thyroxine
T3 = triiodothyronine
rT3 = reverse T3


High temperature
Physical activity
Starvation
High T_3, T_4
Somatostatin
Dopamine
NPY
Glucocorticoids
Paraventricular nucleus
TRH neuron
TRH
Hypophyseal-portal circulation
TRHR
Thyrotroph cell
Cold temperature
Physical activity
Low T_3, T_4
Norepinephrine
CART
Leptin
Glucocorticoids

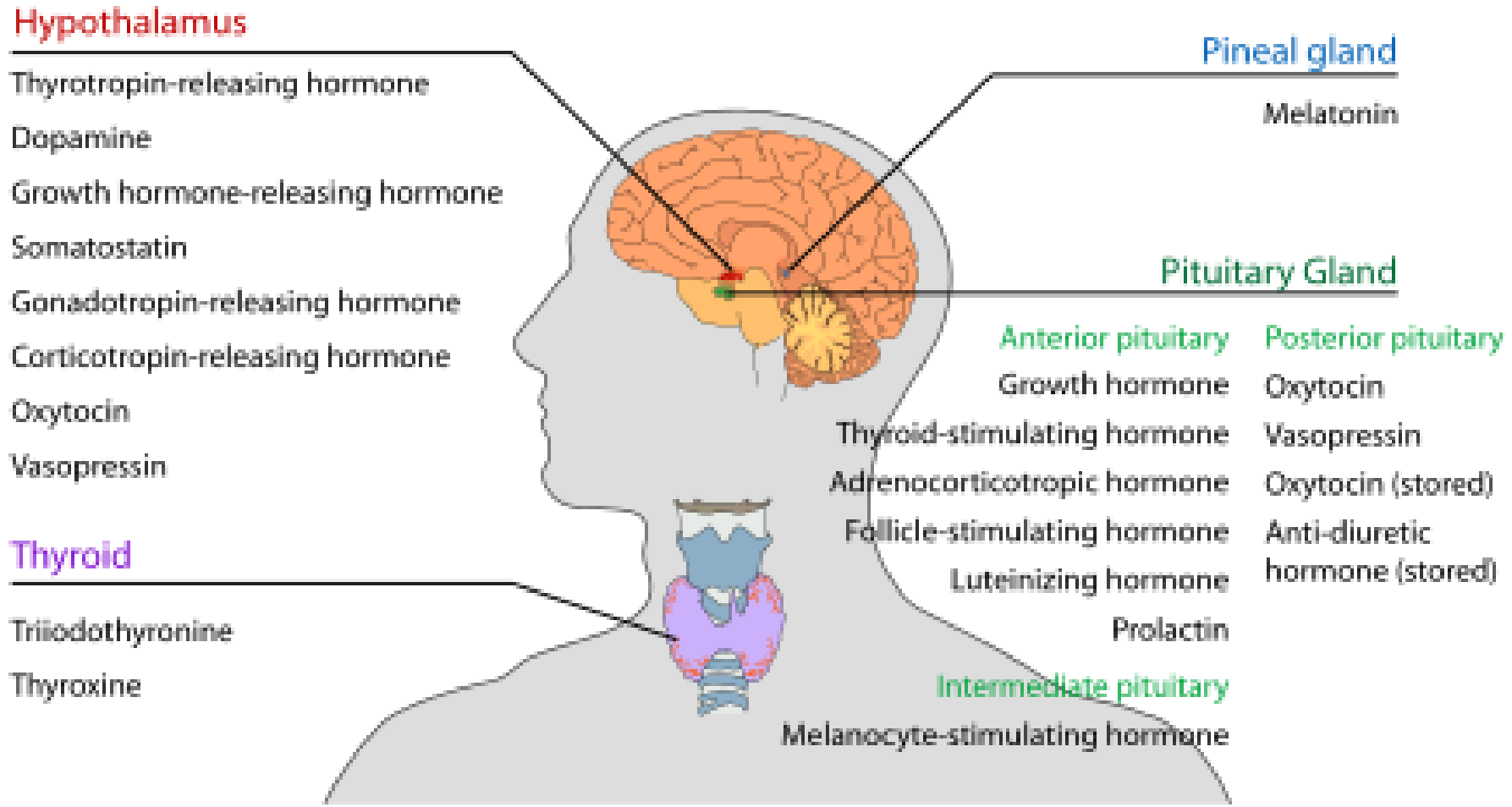
Gene	Chromosome	Pituitary Deficiency	MRI Findings	Associated Malformations	Inheritance M
POU1F1[†]	3p11	GH, PRL, ± TSH	Normal or hypoplastic anterior pituitary		Recessive, dominant
PROP1[‡]	5q35	GH, PRL, TSH, LH, FSH, ± ACTH	Normal, hypoplastic, hyperplastic, or cystic anterior pituitary		Recessive
HESX1[§]	3p21	GH, PRL, TSH, LH, FSH, ACTH, posterior defects	Hypoplastic or hyperplastic anterior pituitary	Septo-optic dysplasia	Recessive
PITX2	4q25	GH, PRL, TSH, FSH, LH	Normal or ectopic posterior pituitary	Rieger syndrome	Dominant
LHX3	9q34	GH, PRL, TSH, LH, FSH	Hypoplastic or hyperplastic anterior pituitary	Stubby neck with rigid cervical spine	Recessive
LHX4	1q25	GH, TSH, ACTH	Hypoplastic anterior pituitary, ectopic posterior pituitary		Dominant
TPIT	1q23	ACTH	Normal		Recessive
OTX2		GH, TSH, ACTH	Hypoplastic anterior pituitary, ectopic posterior	Eye malformations	Dominant/Negative



Septo-optic dysplasia (SOD), also known as **de Morsier syndrome**, is a condition characterised by optic nerve hypoplasia and absence of septum pellucidum and, in two-thirds of patients hypothalamic-pituitary dysfunction.



SUMMARY


Hypothalamus
Thyrotropin-releasing hormone
Dopamine
Growth hormone-releasing hormone
Somatostatin
Gonadotropin-releasing hormone
Corticotropin-releasing hormone
Oxytocin
Vasopressin
Thyroid
Triiodothyronine
Thyroxine
Pineal gland
Melatonin
Pituitary Gland
Anterior pituitary
Growth hormone
Thyroid-stimulating hormone
Adrenocorticotropic hormone
Follicle-stimulating hormone
Luteinizing hormone
Prolactin
Intermediate pituitary
Melanocyte-stimulating hormone
Posterior pituitary
Oxytocin
Vasopressin
Oxytocin (stored)
Anti-diuretic hormone (stored)