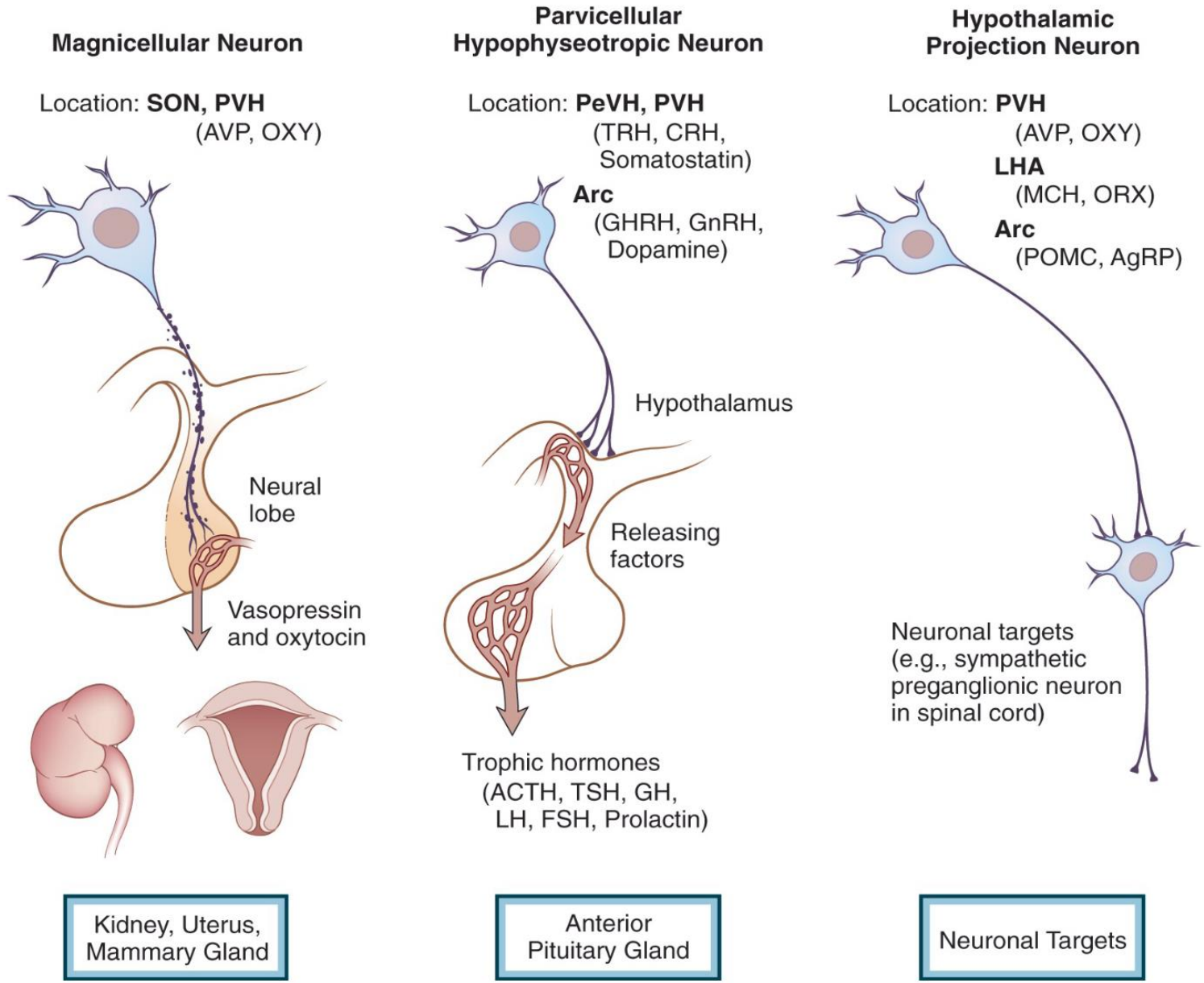
Physical Activity and Health Promotion

Costanzo Giulio Moretti
Unit of Endocrinology
University of Rome TorVergata
St John Calibita Hospital Tiber Island Rome
Section of Reproductive Endocrinology

Lesson 2
Neuroendocrinology

https://www.endocrinologiamoretti.it

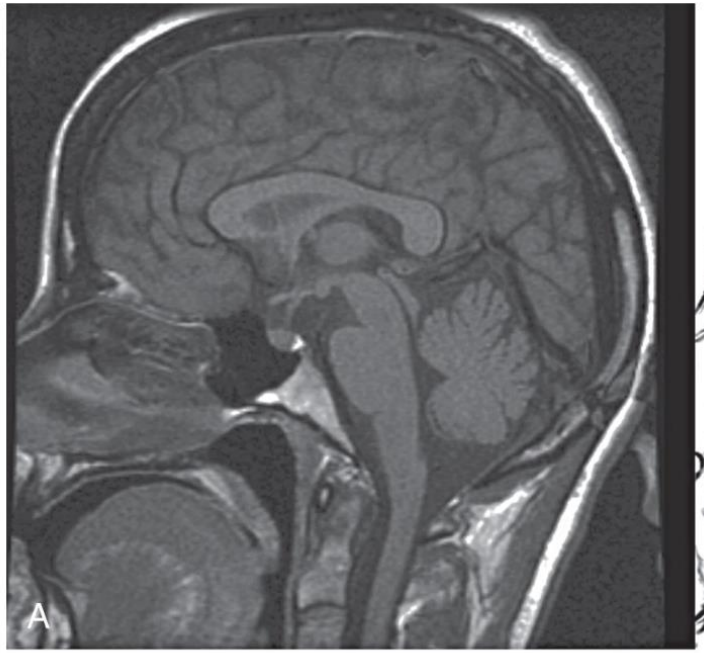

Magnicellular Neuron
Location: SON, PVH
(AVP, OXY)
Neural lobe
Vasopressin and oxytocin
Kidney, Uterus, Mammary Gland
Parvicellular Hypophyseotropic Neuron
Location: PeVH, PVH
(TRH, CRH, Somatostatin)
Arc
(GHRH, GnRH, Dopamine)
Hypothalamus
Releasing factors
Trophic hormones
(ACTH, TSH, GH, LH, FSH, Prolactin)
Anterior Pituitary Gland
Hypothalamic Projection Neuron
Location: PVH
(AVP, OXY)
LHA
(MCH, ORX)
Arc
(POMC, AgRP)
Neuronal targets
(e.g., sympathetic preganglionic neuron in spinal cord)
Neuronal Targets

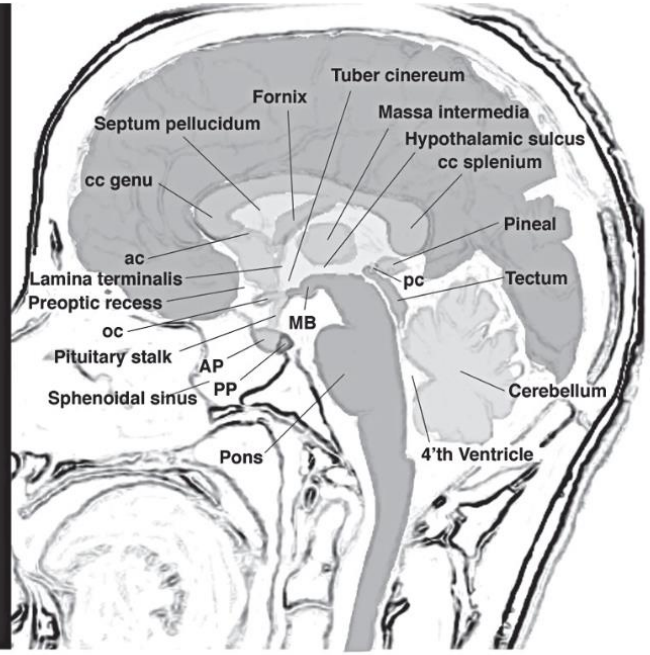
Hypothalamic-Pituitary Unit

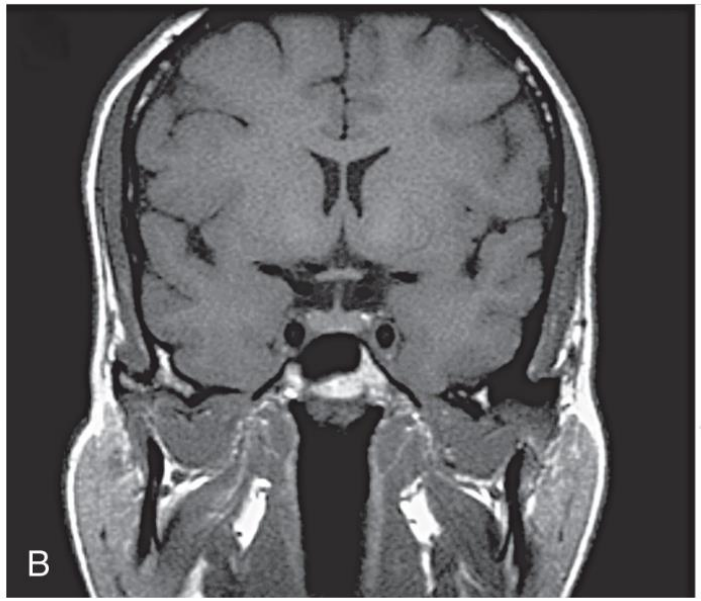
The hypothalamus is one of the most evolutionarily conserved and essential regions of the mammalian brain. Indeed, the hypothalamus is the ultimate brain structure that allows mammals to maintain homeostasis, and destruction of the hypothalamus is not compatible with life.

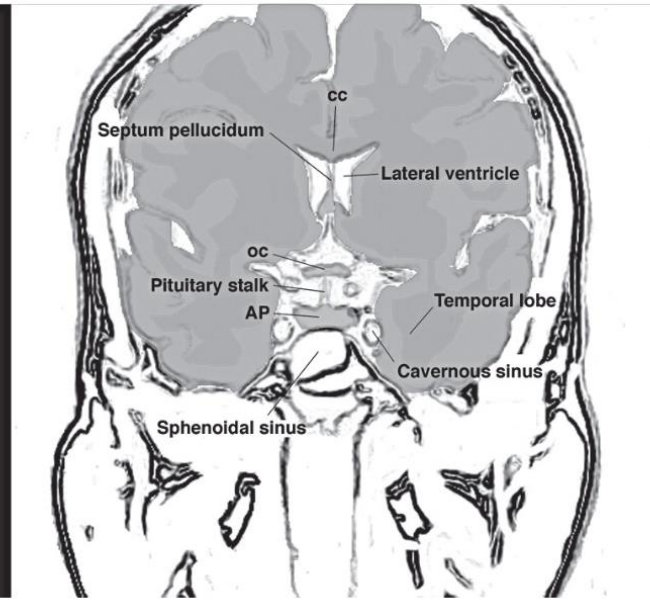
The hypothalamus receives sensory inputs from the external environment (e.g., light, nociception, temperature, odorants) and information regarding the internal environment (e.g., blood pressure, blood osmolality, blood glucose levels).

The hypothalamus integrates diverse sensory and hormonal inputs and provides coordinated responses through motor outputs to key regulatory sites. These include the anterior pituitary gland, posterior pituitary gland, cerebral cortex, premotor and motor neurons in the brain stem and spinal cord, and parasympathetic and sympathetic preganglionic neurons.





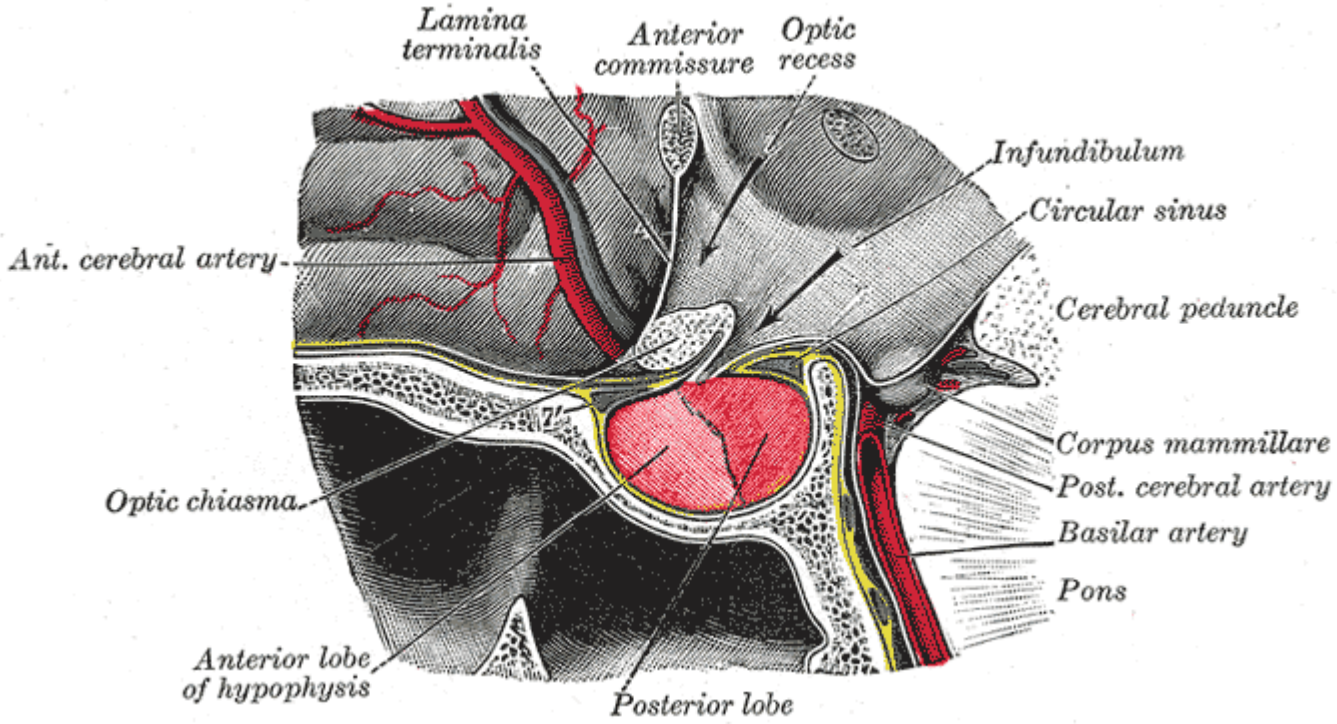




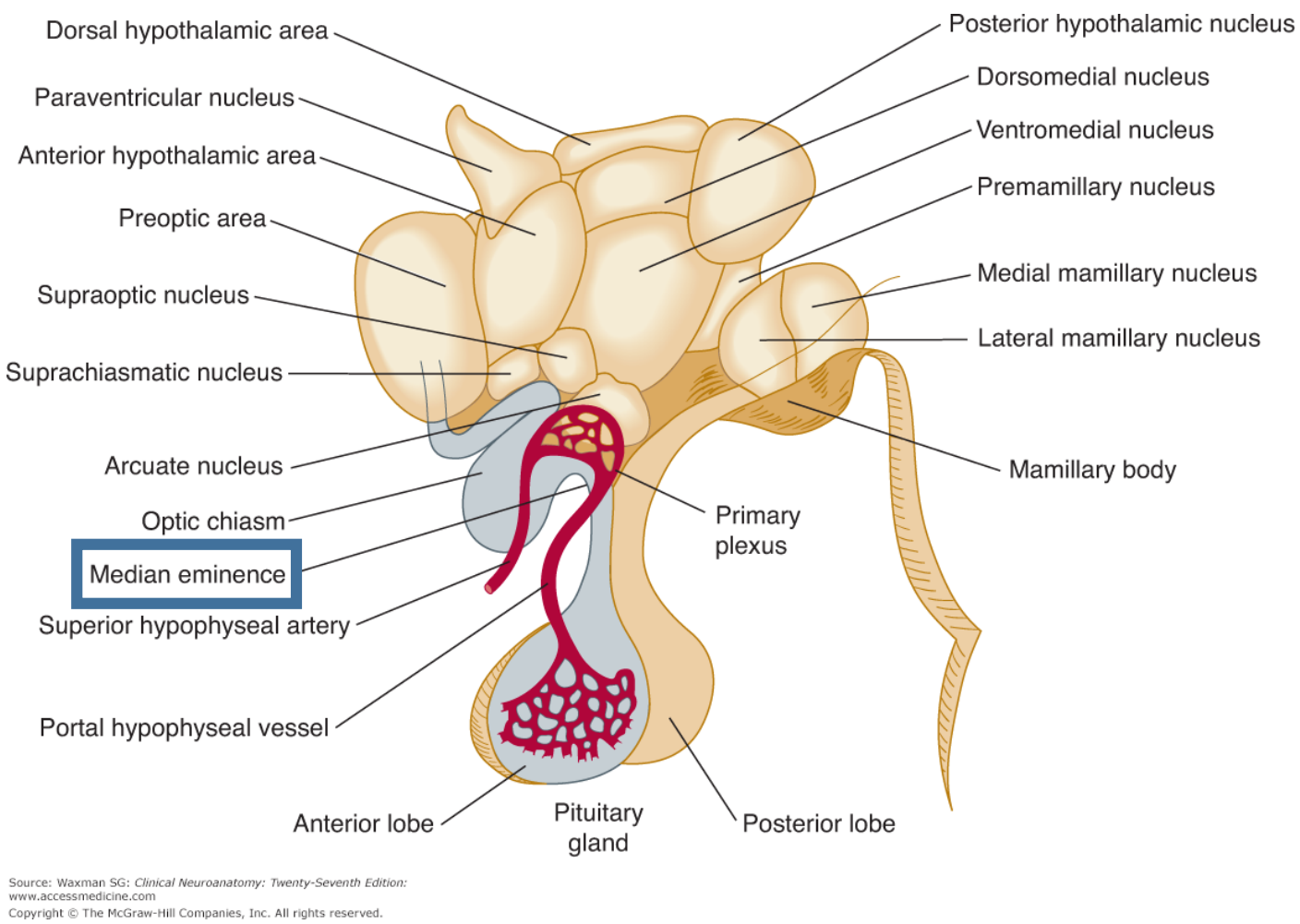
The pituitary gland is regulated by three interacting elements:

- hypothalamic inputs (releasing factors or hypophyseotropic hormones)
- feedback effects of circulating hormones
- paracrine and autocrine secretions of the pituitary itself.

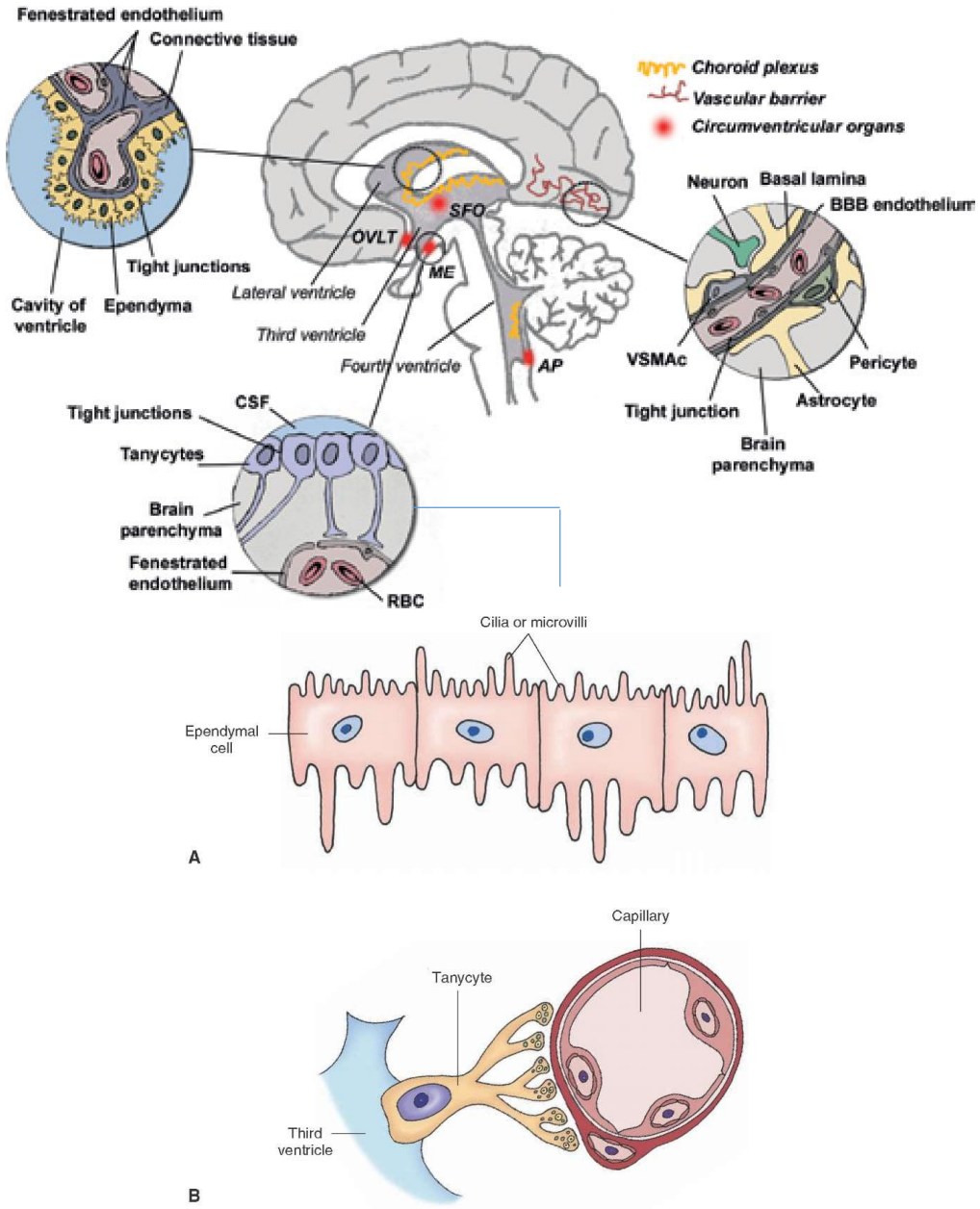
In humans, the pituitary gland (hypophysis) can be divided into two major parts, the adenohypophysis and the neurohypophysis, which are easily distinguishable on T1-weighted magnetic resonance imaging (MRI). The anterior and intermediate lobes of the pituitary derive from a dorsal invagination of the pharyngeal epithelium, called *Rathke's pouch*, in response to inductive signals from the overlying neuroepithelium of the ventral diencephalon.



The pituitary gland lies in the sella turcica ("Turkish saddle") of the sphenoid bone and underlies the base of the hypothalamus. In humans, the base of the hypothalamus forms a mound called the *tuber cinereum*, the central region of which gives rise to the median eminence. The anterior and intermediate lobes of the pituitary derive from a dorsal invagination of the pharyngeal epithelium, called *Rathke's pouch*, in response to inductive signals from the overlying neuroepithelium of the ventral diencephalon. During development, precursor cells within the pouch undergo steps of organ determination, cell fate commitment to a pituitary phenotype, proliferation, and migration.



The median eminence is the functional link between the hypothalamus and the anterior pituitary gland. It lies in the center of the *tuber cinereum* and is composed of an extensive array of blood vessels and nerve endings

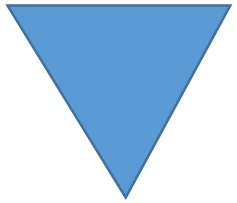


The median eminence (ME) is the functional connection between the hypothalamus and the pituitary gland

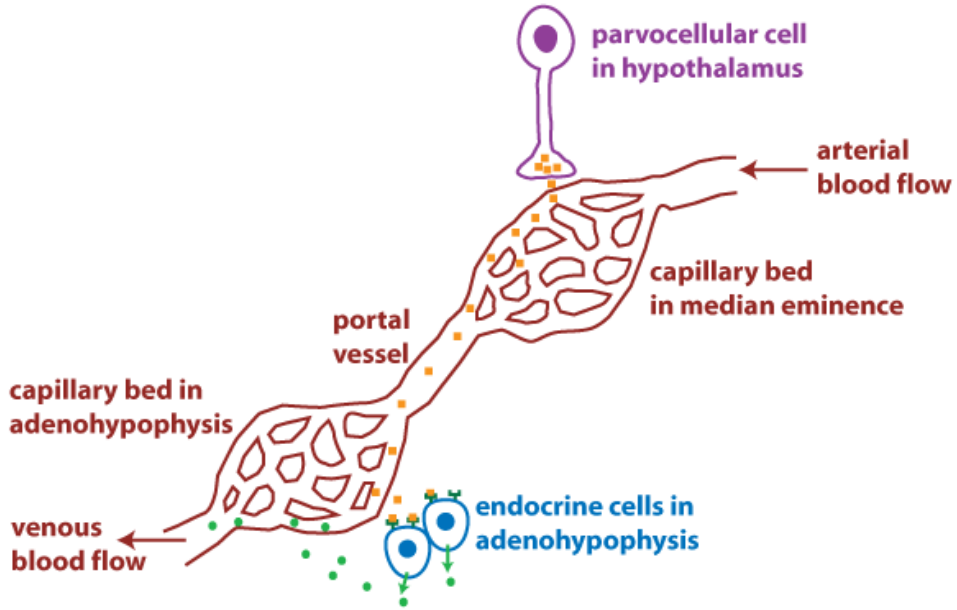
Three distinct compartments of the median eminence are recognized: the **innermost ependymal layer**, the **internal zone**, and the **external zone**. Ependymal cells form the floor of the third ventricle and are unique in that they have microvilli rather than cilia. Tight junctions at the ventricular pole of the ependymal cells prevent the diffusion of large-molecular-weight substances between the cerebrospinal fluid (CSF) and the extracellular space within the median eminence. The ependymal layer also contains specialized cells, called ***tanycytes***, that send processes into the other layers of the median eminence. Tight junctions between tanycytes at the lateral edges of the median eminence likely prevent the diffusion of releasing factors back into the medial basal hypothalamus

Paraventricular Nucleus	Arcuate Nucleus
Magnicellular Division	Acetylcholine
Angiotensin II Cholecystokinin (CCK) Dynorphins Nitric oxide (NO) Oxytocin Vasopressin (AVP)	γ-Aminobutyric acid (GABA) Agouti-related peptide (AgRP) Cocaine- and amphetamine-regulated transcript (CART) Dopamine Dynorphin Endocannabinoids Enkephalins Galanin Galanin-like peptide (GALP) Glutamate Gonadotropin-releasing hormone (GnRH) Growth hormone–releasing hormone (GHRH) Kisspeptins Melanocortins (ACTH, α-MSH, β-MSH, γ-MSH) Neurokinin B (NKB) Neuromedin U Neuropeptide Y (NPY) Neurotensin Nociceptin/orphanin FQ (OFQ) Opioids (β-endorphin) peptides Pancreatic polypeptide Prolactin Pro-opiomelanocortin Pyro-glutamyl-RFamide peptide (QRFP) Somatostatin Substance P
Parvicellular Divisions	
γ-Aminobutyric acid (GABA) Angiotensin II Atrial natriuretic factor (ANF) Bombesin-like peptides Cholecystokinin (CCK) Corticotropin-releasing hormone (CRH) Dopamine Endocannabinoids Enkephalins Galanin Glutamate Interleukin-1 (IL-1) Neuropeptide Y (NPY) Neurotensin Nitric oxide (NO) RFamide–related peptides (RFRP) Somatostatin Thyrotropin-releasing hormone (TRH) Vasopressin (AVP) Vasoactive intestinal peptide (VIP)	

Neurotransmitters and Neuromodulators in the Paraventricular Nucleus and the Arcuate Nucleus of the Hypothalamus

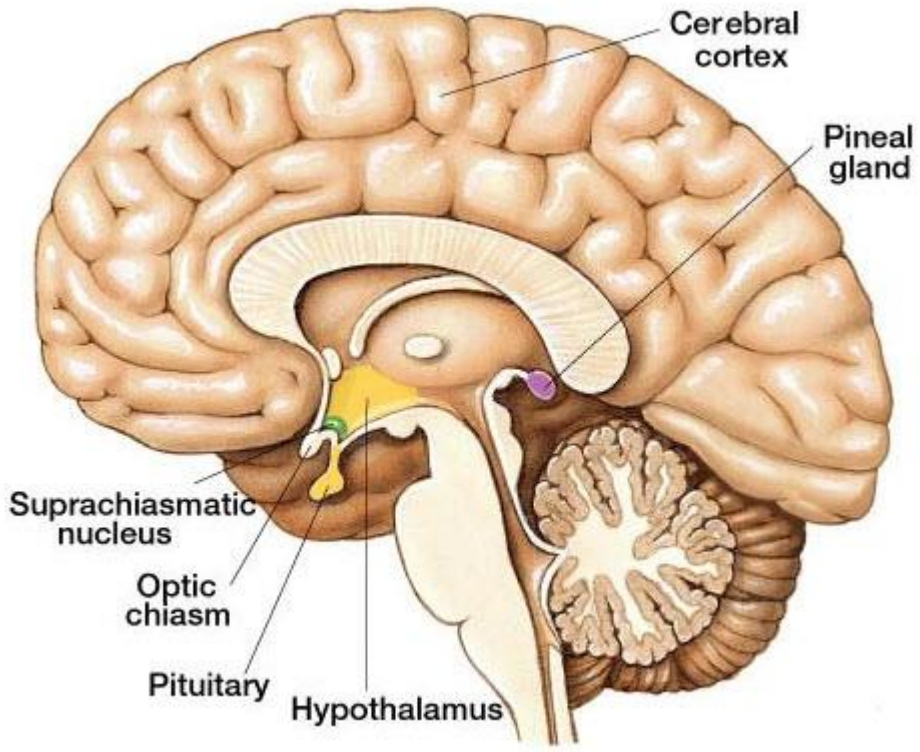


The axon terminals are in close association with a capillary plexus, and they secrete substances **into the hypophyseal veins and thence into the general circulation**



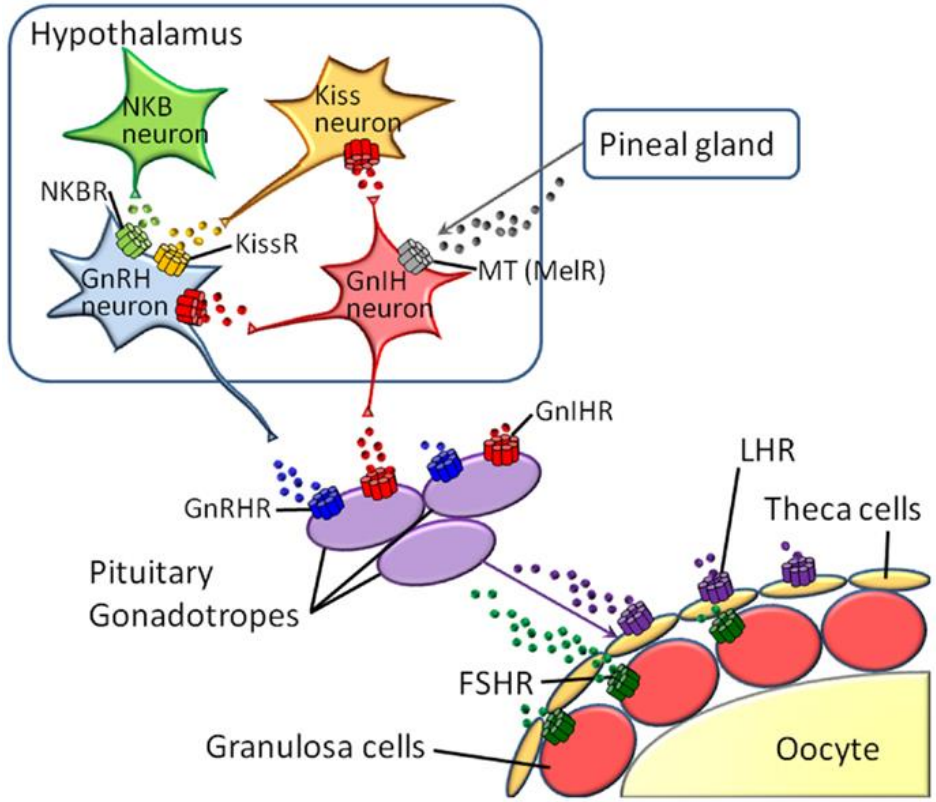
The pineal gland

The pineal gland is both an endocrine organ and a CVO; it is derived from cells located in the roof of the third ventricle and lies above the posterior commissure near the level of the habenular complex and the sylvian aqueduct. The gland is composed of two cell types, pinealocytes and interstitial (glial-like) cells. Histologic studies suggest that the pineal gland cells are secretory in nature, and indeed the pineal is the principal source of melatonin in mammals



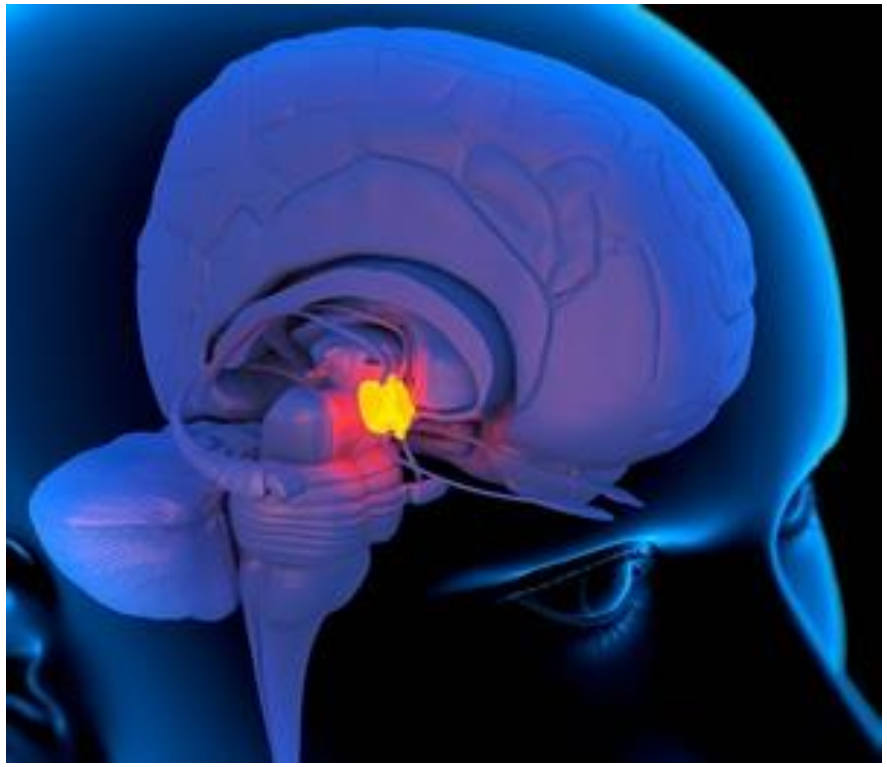
The pineal is an epithalamic structure and consists of primordial photoreceptive cells. The gland retains its light sensitivity in lower vertebrates such as fish and amphibians but lacks direct photosensitivity in mammals and has evolved as a strictly secretory organ in higher vertebrates

Melatonin regulates the reproductive axis, including gonadotropin secretion and the timing and onset of puberty



Hypophyseotropic Hormones and Neuroendocrine Axes

Pituitary secretion is controlled by hypothalamic hormones released into the portal circulation. All of the principal hypothalamic-pituitary regulating hormones are peptides, with the notable exception of dopamine, which is a biogenic amine and the major prolactin-inhibiting factor



General Features of Hypothalamic Function

- Controls visceral activity
- Output of emotions from limbic system
- Neural and endocrine functions exerted via axonal pathways and vascular system
- Functions include self-preservation (such as eating and drinking) and preservation of the species (reproduction)
- Involved in water balance, food intake, endocrine control, reproduction, sleep, behavior, output of endocrine system

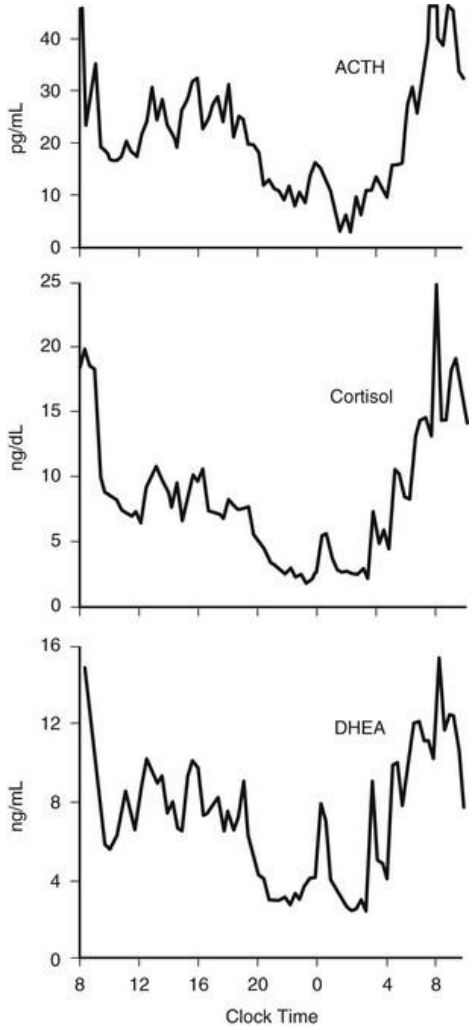
Hypophyseotropic Hormones and Neuroendocrine Axes

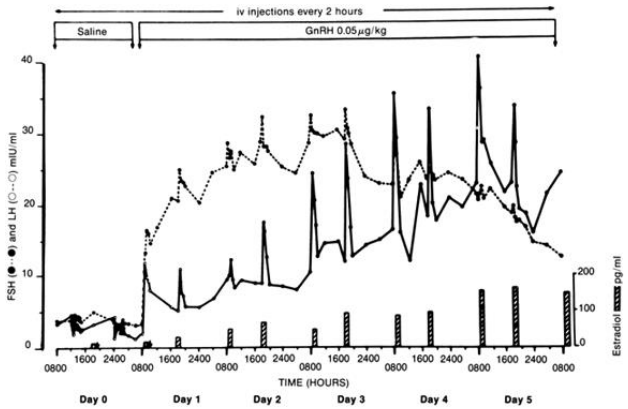
Secretion of the releasing hormones is regulated by neurotransmitters and neuropeptides released by a complex array of neurons synapsing with hypophyseotropic neurons. Control of secretion is also exerted through **feedback control** by hormones such as glucocorticoids, gonadal steroids, thyroid hormone, anterior pituitary hormones (**short-loop feedback control**), and hypophyseotropic factors themselves (**ultrashort-loop feedback control**)

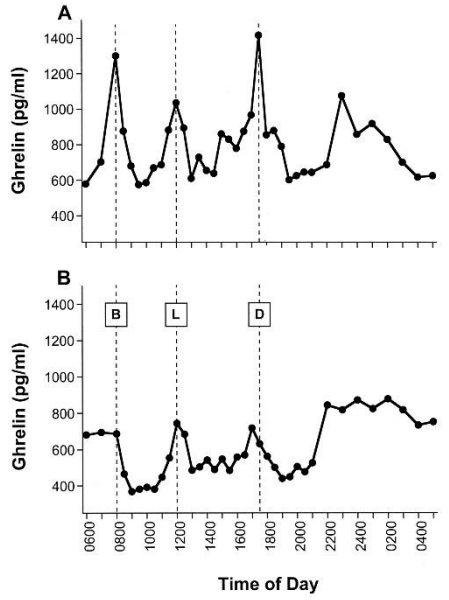
Endocrine Rithms

Virtually all functions of living animals (regardless of their position on the evolutionary scale) are subject to periodic or cyclic changes, many of which are influenced primarily by the nervous system

Period	Length of the cycle
Circadian	About a day (24 hr)
Diurnal	Exactly a day
Ultradian	Less than a day (i.e., minutes or hours)
Infradian	Longer than a day (i.e., month or year)
Mean	Arithmetic mean of all values within a cycle
Range	Difference between the highest and lowest values
Nadir	Minimal level (inferred from mathematical curve fitting calculations)
Acrophase	Time of maximal levels (inferred from curve fitting)
Zeitgeber	“Time-giver” (German); the external cue, usually the light-dark cycle that synchronizes endogenous rhythms
Entrainment	The process by which an endogenous rhythm is regulated by a zeitgeber
Phase shift	Induced change in an endogenous rhythm
Intrinsic clock	Neural structures that possess intrinsic capacity for spontaneous rhythms; for circadian rhythms, these are located in the suprachiasmatic nucleus





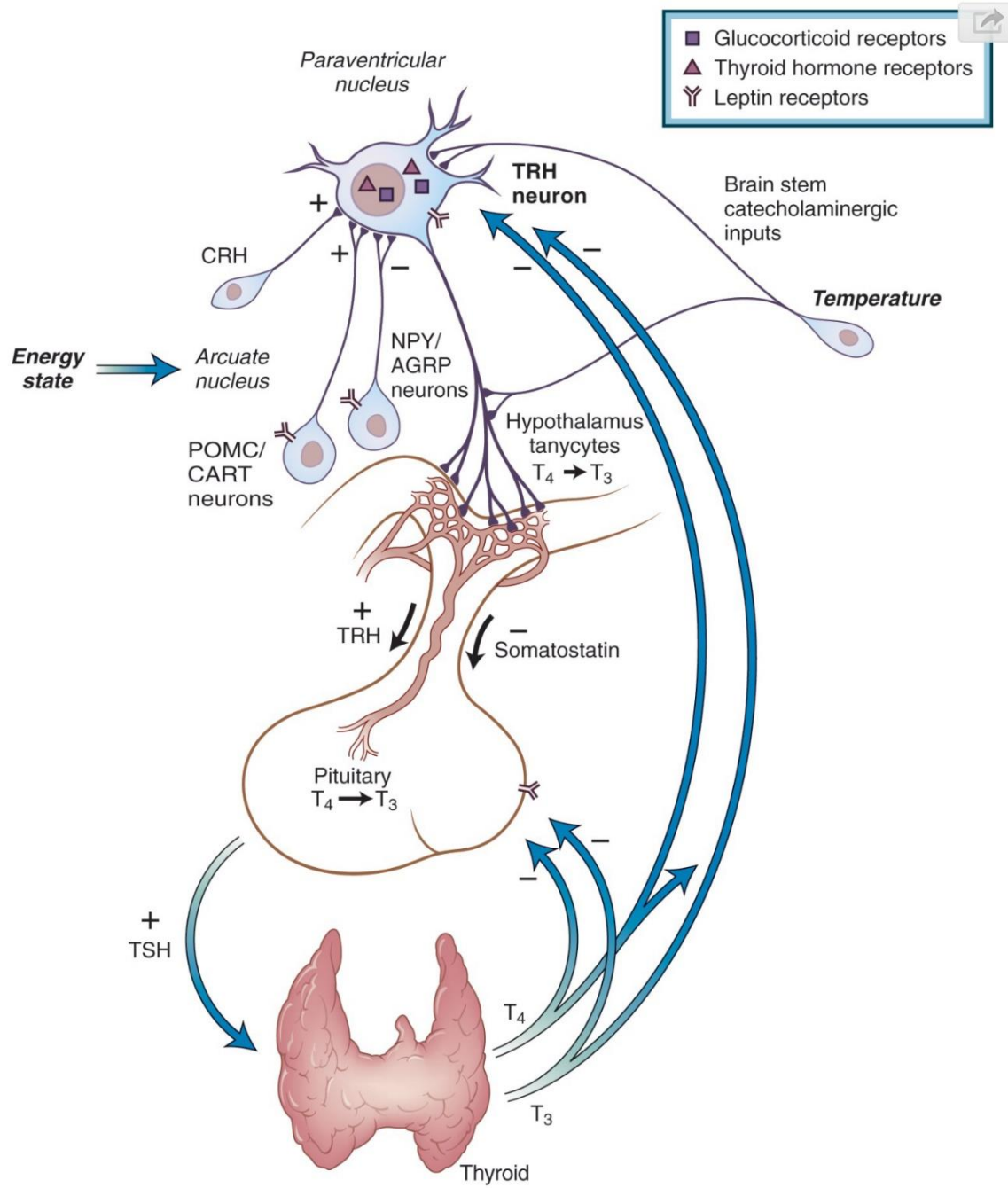


Thyrotropin releasing hormone

TRH, the smallest known peptide hypophyseotropic hormone, is the tripeptide pyroGlu-His-Pro-NH_2. Six copies of the TRH peptide sequence are encoded within the human TRH pre-prohormone gene.

TRH is a phylogenetically ancient peptide that has been isolated from primitive vertebrates and even from invertebrates. TRH is widely expressed in both the CNS and periphery in amphibians, reptiles, and fishes but does not stimulate TSH release in these poikilothermic vertebrates. Therefore, TRH has multiple peripheral and central activities and was co-opted as a hypophyseotropic factor midway during the evolution of vertebrates, perhaps specifically as a factor needed for coordinated regulation of temperature homeostasis.

TRH is also a potent PRF. The time course of response of blood PRL levels to TRH, the dose-response characteristics, and the suppression by thyroid hormone pretreatment (all of which parallel changes in TSH secretion) suggest that TRH may be involved in the regulation of PRL secretion.


Glucocorticoid receptors
Thyroid hormone receptors
Leptin receptors
Paraventricular nucleus
TRH neuron
Brain stem catecholaminergic inputs
CRH
Temperature
Energy state
Arcuate nucleus
NPY/ AGRP neurons
POMC/ CART neurons
Hypothalamus tanycytes $T_4 \rightarrow T_3$
TRH
Somatostatin
Pituitary $T_4 \rightarrow T_3$
TSH
T_4
T_3
Thyroid

Corticotropin releasing hormone

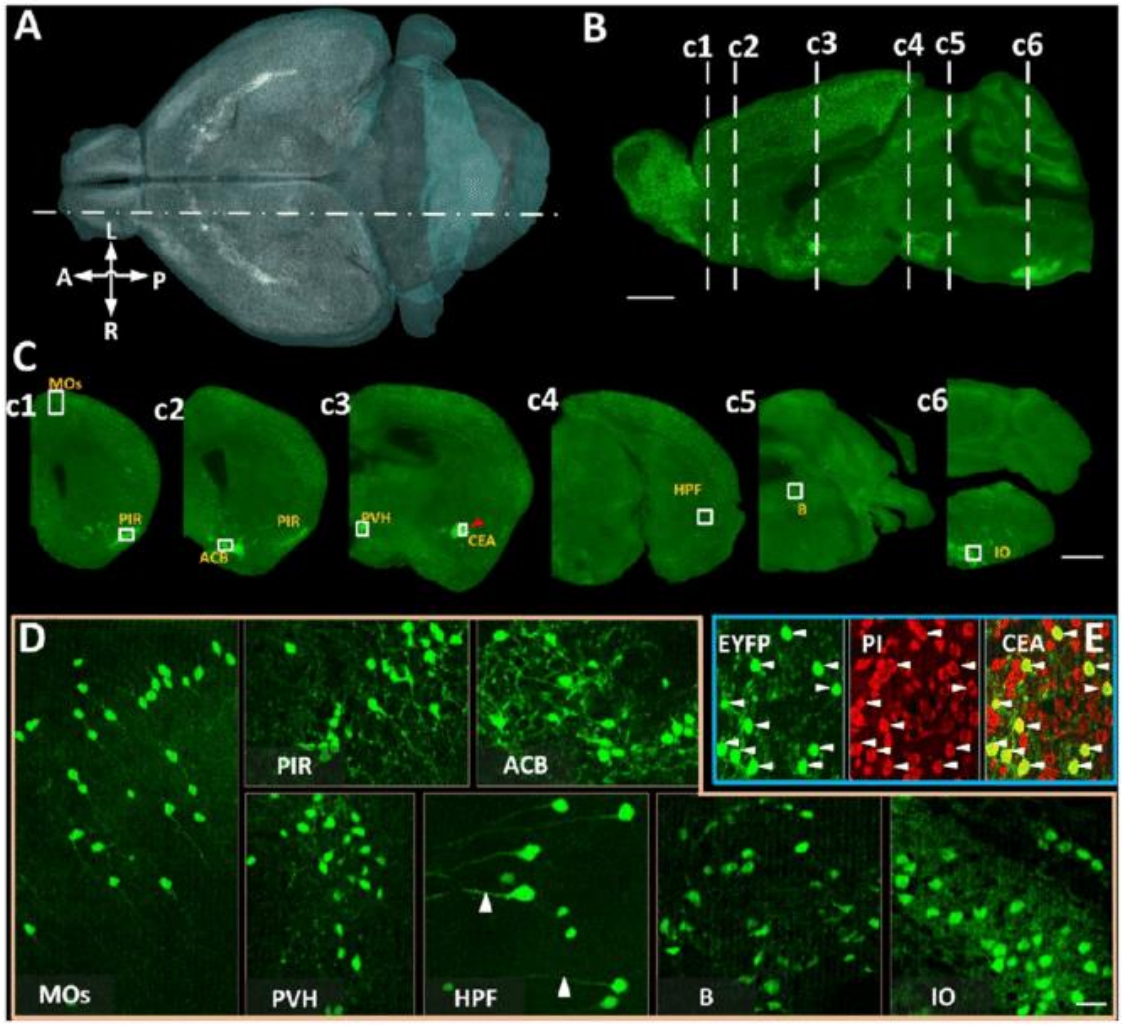
The CRH system in the CNS is vitally important in the behavioral response to stress. This complex system includes not only nonhypophyseotropic CRH neurons but also three CRH-like peptides (urocortin, urocortin 2 or stresscopin-related peptide, and urocortin 3 or stresscopin), at least two cognate receptors (CRH-R1 and CRH-R2), and a high-affinity CRH-binding protein, each with distinct and complex distributions in the CNS.

The CRH peptides signal by binding to CRH-R1 and CRH-R2 receptors that couple to the stimulatory G protein (G_s) and activate adenylyl cyclase. Two splice variants of the CRH-R2 receptor that differ in their extracellular N-terminal domain, termed CRH-R2αand CRH-R2β, have been found in both rodents and humans, and a third N-terminal splice variant, CRH-R2γ, has been reported in the human

CRH, urotensin, and sauvagine are potent agonists of CRH-R1; urocortin is a potent agonist of both receptors; and urocortins 2 and 3 are specific agonists of CRH-R2. CRH-activation of the HPA axis is mediated exclusively through CRH-R1 expressed in the corticotroph. CRH neurons projecting to the median eminence are found mostly in the PVH, although most hypothalamic nuclei contain some of these neurons

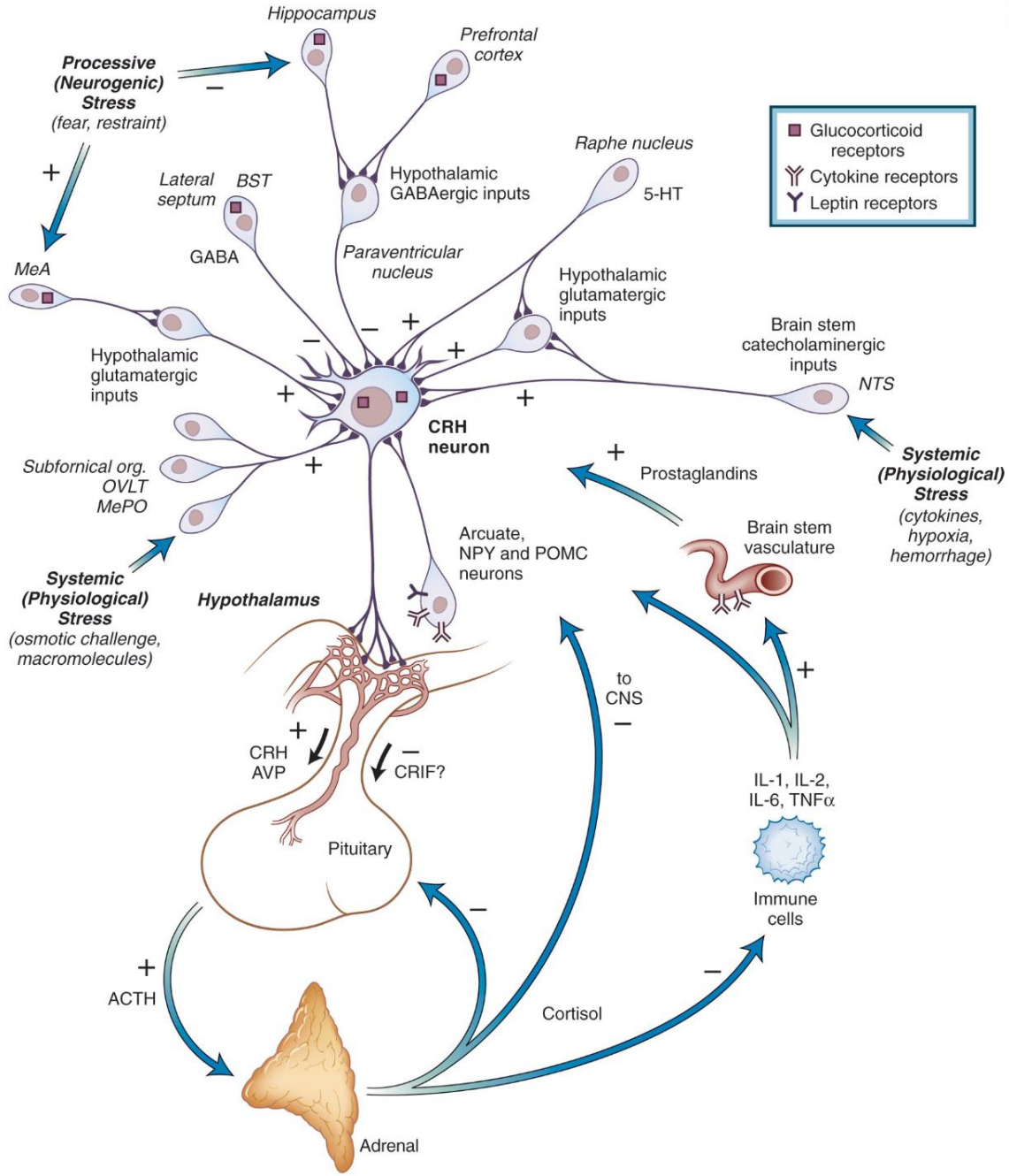
Terms like *neurogenic*, *emotional*, or *psychological stressors* involve, in addition, nociceptive or somatosensory pathways as well as cognitive and affective brain centers

Distribution of CRH neurons in brain



CRH neurons projecting to the median eminence are found mostly in the PVH, although most hypothalamic nuclei contain some of these neurons. Some CRH fibers in the PVH also project to the brain stem, and nonhypophyseotropic CRH neurons are abundant elsewhere, primarily in limbic structures involved in processing sensory information and in regulating the autonomic nervous system. Sites include the prefrontal, insular, and cingulate cortices; amygdala; substantia nigra; periaqueductal gray; locus ceruleus; nucleus of the solitary tract; and parabrachial nucleus

Administration of CRH to humans causes prompt release of ACTH into the blood, followed by secretion of cortisol


Hippocampus
Prefrontal cortex
Processive (Neurogenic) Stress
(fear, restraint)
Raphe nucleus
Lateral septum
BST
Hypothalamic GABAergic inputs
5-HT
GABA
Paraventricular nucleus
MeA
Hypothalamic glutamatergic inputs
Hypothalamic glutamatergic inputs
Brain stem catecholaminergic inputs
NTS
CRH neuron
Systemic (Physiological) Stress
(cytokines, hypoxia, hemorrhage)
Prostaglandins
Subfornical org.
OVLT
MePO
Arcuate, NPY and POMC neurons
Brain stem vasculature
Systemic (Physiological) Stress
(osmotic challenge, macromolecules)
Hypothalamus
to CNS
CRH
AVP
CRIF?
IL-1, IL-2, IL-6, TNFα
Pituitary
Immune cells
ACTH
Cortisol
Adrenal
Glucocorticoid receptors
Cytokine receptors
Leptin receptors

CRH and related peptides : extrapituitary functions

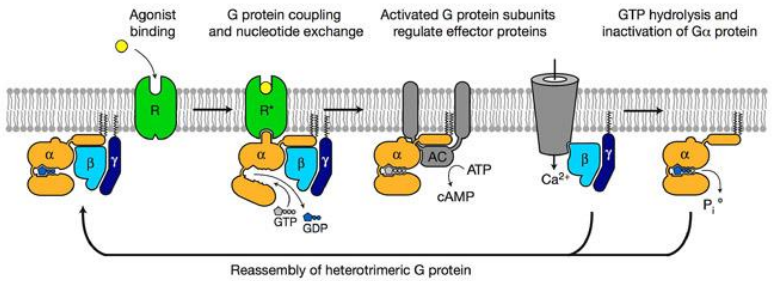
CRH and the urocortin peptides have a wide range of biologic activities in addition to the hypophyseotropic role of CRH in regulating ACTH synthesis and release. Centrally, these peptides have behavioral activities in anxiety, mood, arousal, locomotion, reward, and feeding and increase sympathetic activation. Many of the non hypophyseotropic behavioral and autonomic functions of these peptides can be viewed as complementary to activation of the HPA axis in the maintenance of homeostasis under exposure to stress. In the periphery, activities have been reported in immunity, cardiac function, gastrointestinal function, and reproduction

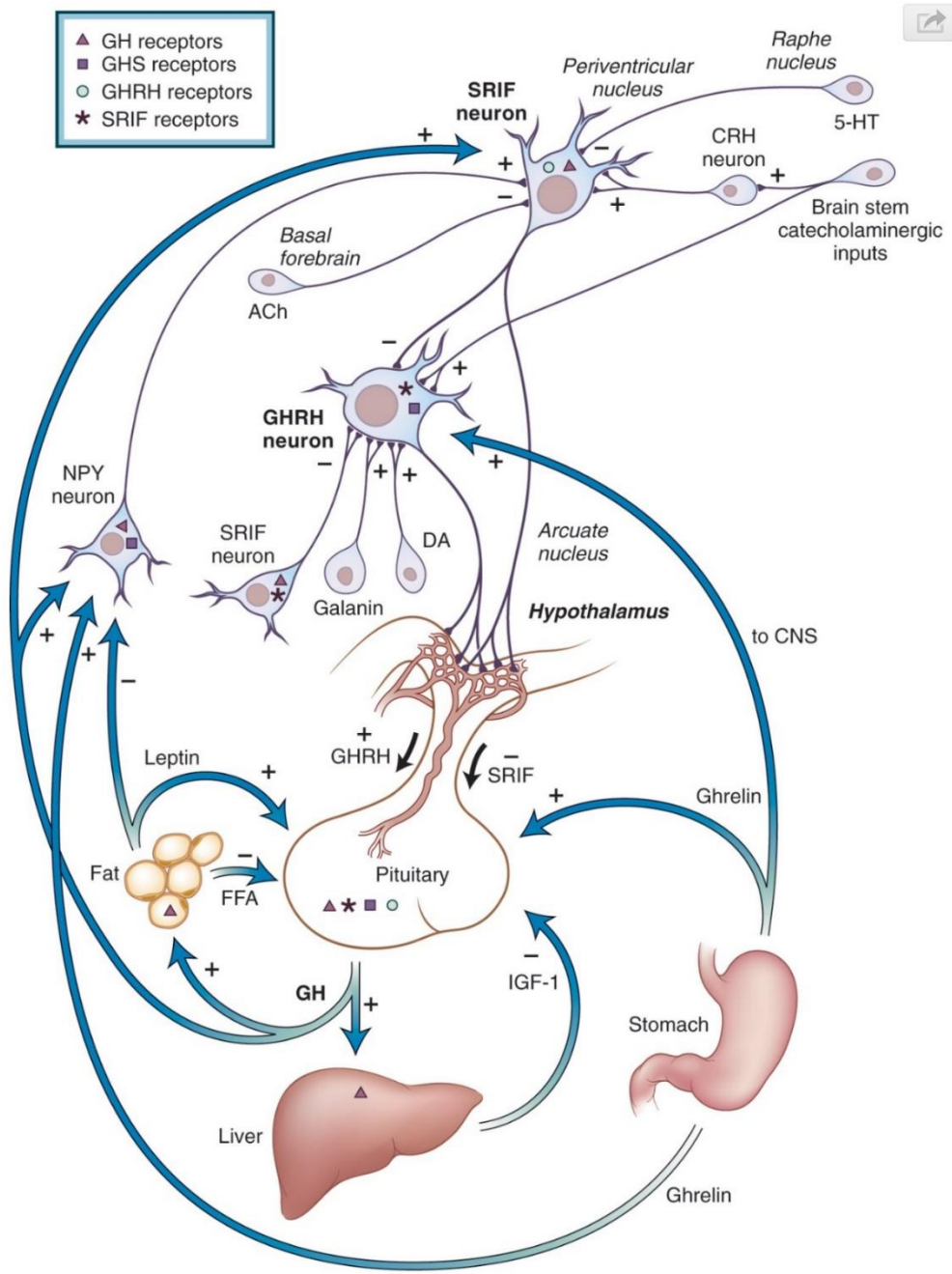
Growth Hormone releasing hormone

GH stimulates the release of GH from the pituitary. GH is released episodically, follows a circadian rhythm, responds rapidly to stress, and is blocked by pituitary stalk section.

Two principal molecular forms of GHRH occur in the human hypothalamus: GHRH(1-44)-NH_2 and GHRH(1-40). As with other neuropeptides, the various forms of GHRH arise from post-translational modification of a larger prohormone. GHRH-containing nerve fibers that terminate adjacent to portal vessels in the external zone of the median eminence arise principally from within, above, and lateral to the infundibular nucleus in human hypothalamus, corresponding to rodent arcuate and ventromedial nuclei

The GHRH receptor is a member of a subfamily of G protein–coupled receptors that includes receptors for VIP, pituitary adenylyl cyclase–activating peptide, secretin, glucagon, glucagon-like peptide 1, calcitonin, parathyroid hormone or parathyroid hormone–related peptide, and gastric inhibitory polypeptide. GHRH elevates intracellular cAMP by its receptor coupling to a stimulatory G protein (G_s), which activates adenylyl cyclase, increases intracellular free Ca^{2+}, releases preformed GH, and stimulates GH mRNA transcription and new GH synthesis.

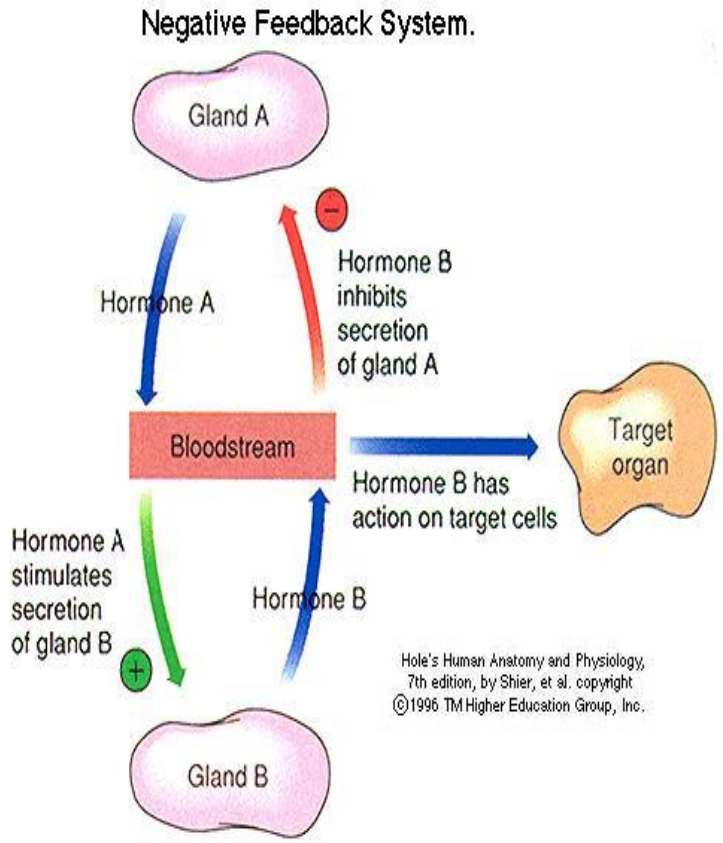



GH receptors
GHS receptors
GHRH receptors
SRIF receptors
SRIF neuron
Periventricular nucleus
Raphe nucleus
5-HT
CRH neuron
Brain stem catecholaminergic inputs
Basal forebrain
ACh
GHRH neuron
NPY neuron
SRIF neuron
DA
Galanin
Arcuate nucleus
Hypothalamus
to CNS
Leptin
GHRH
SRIF
Ghrelin
Fat
FFA
Pituitary
GH
IGF-1
Stomach
Liver
Ghrelin

Other Factors Influence the secretion of Growth Hormone

Physiologic	Hormones and Neurotransmitters	Pathologic
Stimulatory Factors		
Episodic, spontaneous release Exercise Stress Physical Psychological Slow-wave sleep Postprandial glucose decline Fasting	Insulin hypoglycemia 2-Deoxyglucose Amino acid infusions Arginine, lysine Neuropeptides GHRH Ghrelin Galanin Opioids (μ-receptors) Melatonin Classic neurotransmitters α_2-Adrenergic agonists β-Adrenergic antagonists M1 cholinergic agonists 5-HT1D-serotonin agonists H1-histamine agonists GABA (basal levels) Dopamine (? D2 receptor) Estrogen Testosterone Glucocorticoids (acute)	Acromegaly TRH GnRH Glucose Arginine Interleukins 1, 2, 6 Protein depletion Starvation Anorexia nervosa Renal failure Liver cirrhosis Type 1 diabetes mellitus
Inhibitory Factors*		
Postprandial hyperglycemia Elevated free fatty acids Elevated GH levels Elevated IGF1 (pituitary) REM sleep Senescence, aging	Glucose infusion Neuropeptides Somatostatin Calcitonin Neuropeptide Y (NPY†) CRH† Classic neurotransmitters $\alpha_{1/2}$-Adrenergic antagonists β_2-Adrenergic agonists H1 histamine antagonists Serotonin antagonist Nicotinic cholinergic agonists Glucocorticoids (chronic)	Acromegaly L-Dopa D2R DA agonists Phentolamine Galanin Obesity Hypothyroidism Hyperthyroidism

CRH, Corticotropin-releasing hormone; DA, dopamine; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF1, insulin-like growth factor type 1; REM, rapid eye movement; TRH, thyrotropin-releasing hormone.

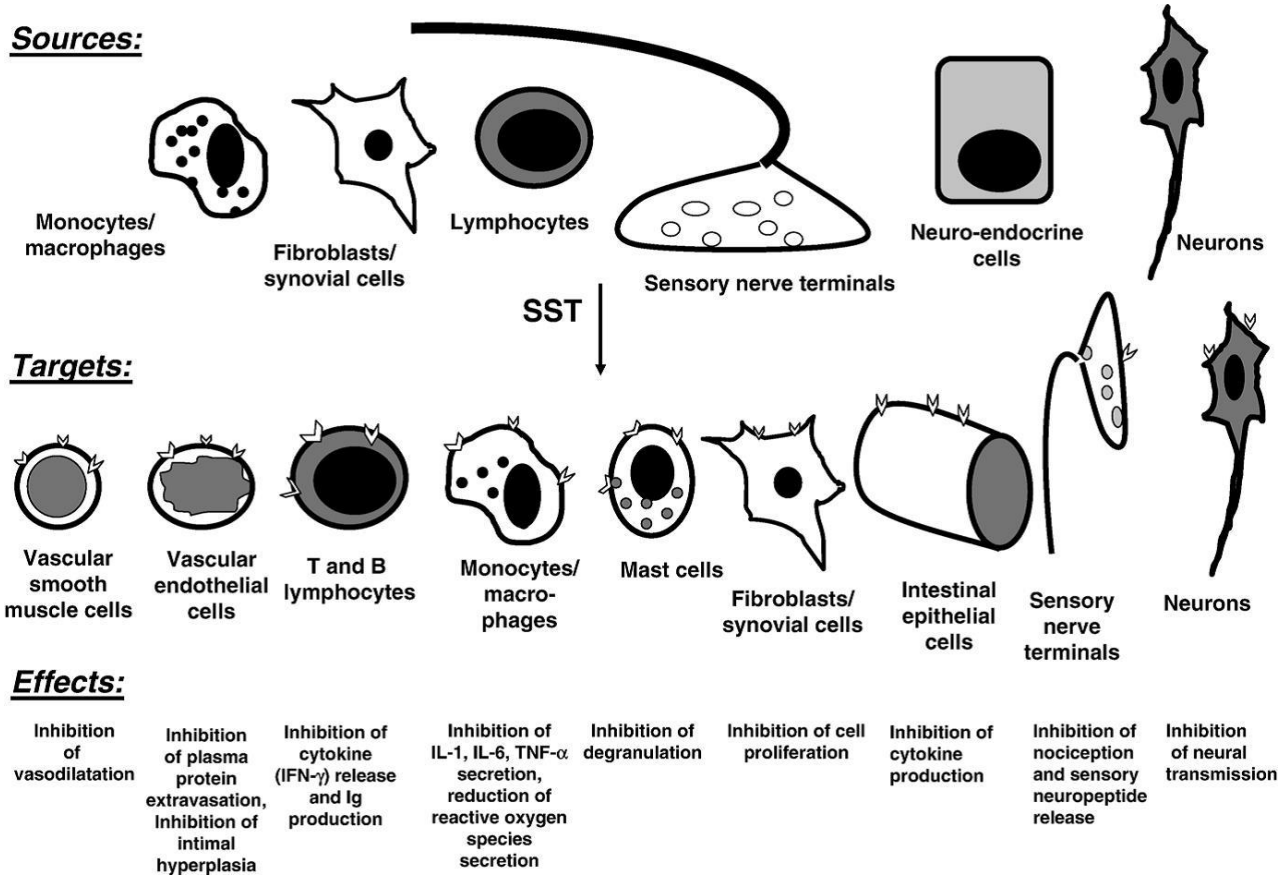


- **The daily GH secretion rate varies over 2 orders of magnitude, from a maximum of almost 2.0 mg/day in late puberty to a minimum of 20 µg/day in older or obese adults. The neonatal period is characterized by markedly amplified GH secretory bursts followed by a prepubertal decade of stable, moderate GH secretion of 200 to 600 µg/day. There is a marked increase in daily GH secretion during puberty that is accompanied by a commensurate rise in plasma IGF1 to levels that constitute a state of physiologic hypersomatotropism.**

- **GH secretion in young adults exhibits a true circadian rhythm over a 24-hour period, characterized by a greater nocturnal secretory mass that is independent of sleep onset**

Somatostatin

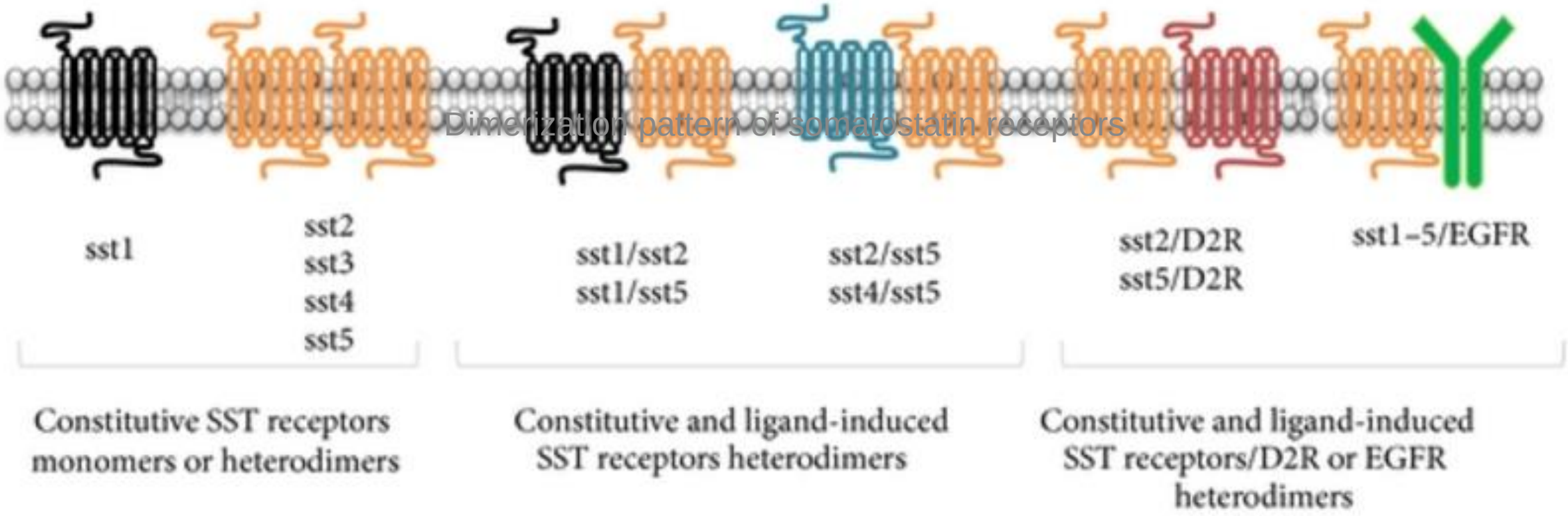
Somatostatin (SST-14/SST-28) is a peptide responsible for the inhibition of GH secretion by pituitary somatotrophs and of insulin secretion by pancreatic islet extracts



Somatostatin receptors

Five somatostatin receptor subtypes (SSTR1 to SSTR5) have been identified by gene cloning techniques, and one of these (SSTR2) is expressed in two alternatively spliced forms. These subtypes are encoded by separate genes located on different chromosomes; they are expressed in unique or partially overlapping distributions in multiple target organs; and they differ in their coupling to second-messenger signaling molecules and therefore in their range and mechanism of intracellular actions. The subtypes also differ in their binding affinity to specific somatostatin analogues. Certain of these differences have important implications for the use of somatostatin analogues in therapy and in diagnostic imaging.

Dimerization pattern of somatostatin receptors

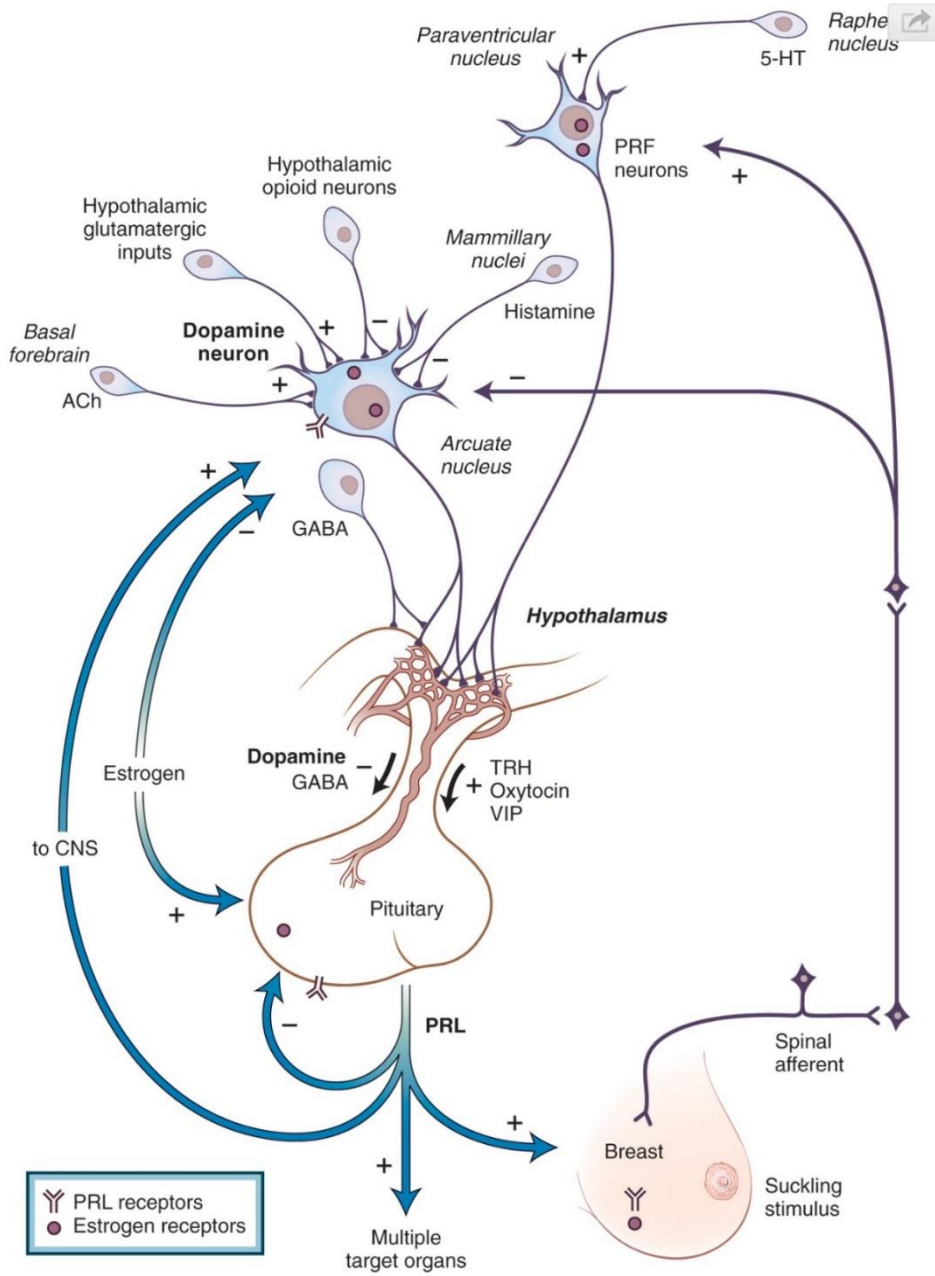


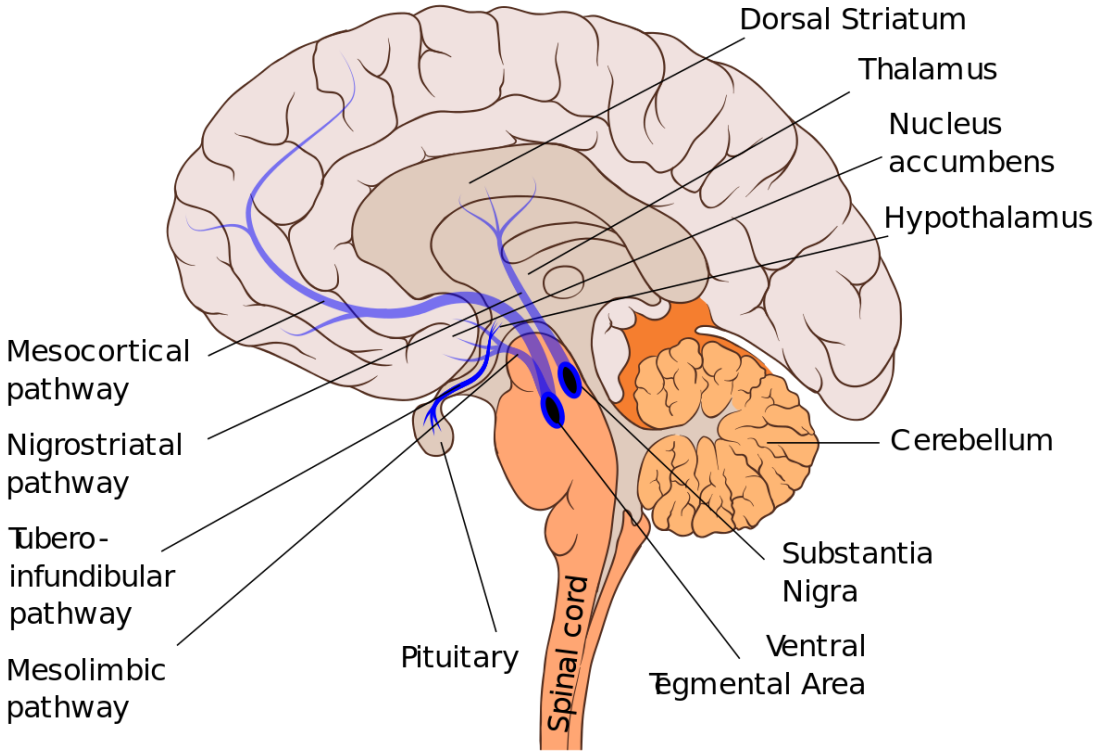
Biologic Actions of Somatostatin Outside the Central Nervous System

Hormone Secretion Inhibited (by Gland)	Other Gastrointestinal and Extragastrointestinal Actions Inhibited
Pituitary gland	Gastric acid secretion
GH, thyrotropin, ACTH, prolactin	Gastric and jejunal fluid secretion
Gastrointestinal tract	Gastric emptying
Gastrin	Pancreatic bicarbonate secretion
Secretin	Pancreatic enzyme secretion
Gastrointestinal polypeptide Motilin Glicentin (enteroglucagon) Vasoactive intestinal peptide Pancreas Insulin Glucagon Somatostatin Genitourinary tract Renin	Stimulates intestinal absorption of water and electrolytes
	Gastrointestinal blood flow
	AVP-stimulated water transport
	Bile flow
	Extragastrointestinal Actions
	Inhibits the function of activated immune cells
	Inhibition of tumor growth

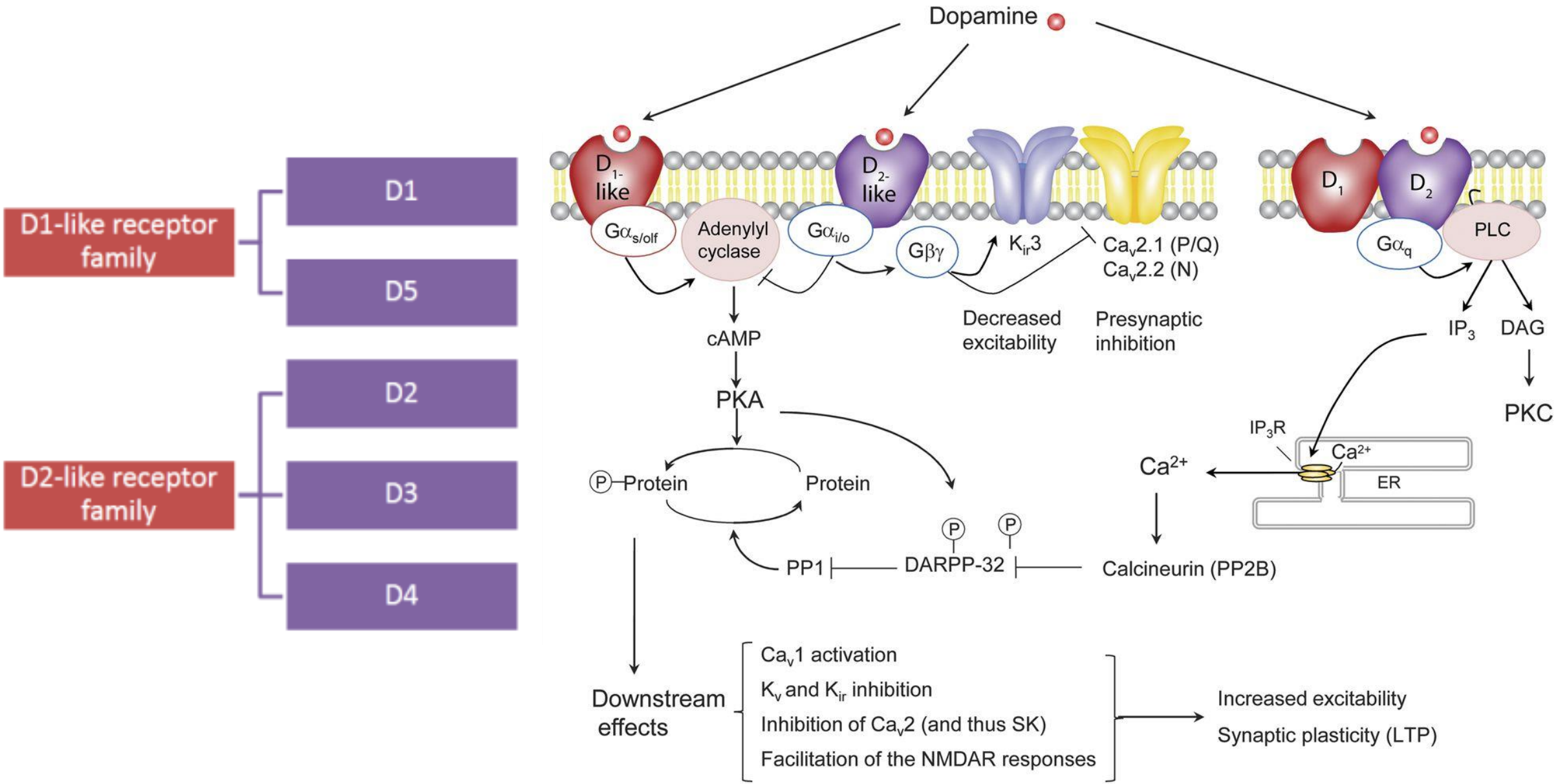
Prolactin-Regulating Factors

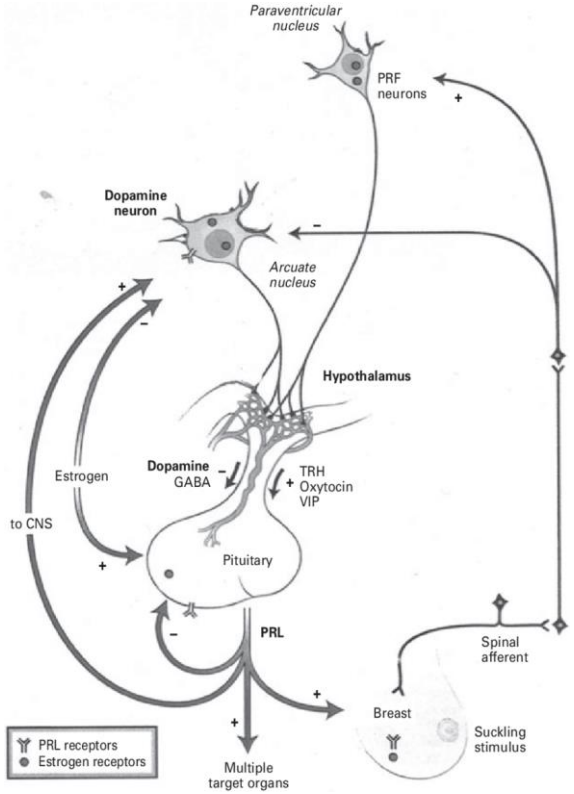
Destruction of the stalk median eminence or transplantation of the pituitary gland to ectopic sites causes a marked constitutive increase in PRL secretion, in contrast to a decrease in the release of GH, TSH, ACTH, and the gonadotropins. Many lines of evidence indicate that dopamine is the principal physiologic PIF released from the hypothalamus.


Paraventricular nucleus
+
5-HT
Raphe nucleus
PRF neurons
+
Hypothalamic opioid neurons
Hypothalamic glutamatergic inputs
Mammillary nuclei
Histamine
Basal forebrain
ACh
Dopamine neuron
+
–
+
–
–
Arcuate nucleus
+
–
GABA
Hypothalamus
Estrogen
Dopamine
GABA
–
+
TRH
Oxytocin
VIP
to CNS
+
Pituitary
–
PRL
+
+
Spinal afferent
Breast
Suckling stimulus
PRL receptors
Estrogen receptors
Multiple target organs



Tuberoinfundibular dopamine neurons (TIDA) are considered to be the major source of dopamine to the anterior lobe through the long portal vessels originating in the median eminence, dopamine can also reach the anterior lobe from the neural and intermediate lobes by the interconnecting short portal veins. Central dopamine can indirectly affect PRL secretion by altering the activity of inhibitory interneurons that synapse on the TIDA neurons.


D1-like receptor family
D1
D5
D2-like receptor family
D2
D3
D4
Dopamine
D1-like
D2-like
Gαs/olf
Adenylyl cyclase
Gαi/o
Gβγ
Kir3
Cav2.1 (P/Q)
Cav2.2 (N)
D1
D2
Gαq
PLC
cAMP
Decreased excitability
Presynaptic inhibition
IP3
DAG
PKC
PKA
IP3R
Ca2+
ER
P
Protein
Protein
PP1
DARPP-32
Calcineurin (PP2B)
Downstream effects
Cav1 activation
Kv and Kir inhibition
Inhibition of Cav2 (and thus SK)
Facilitation of the NMDAR responses
Increased excitability
Synaptic plasticity (LTP)



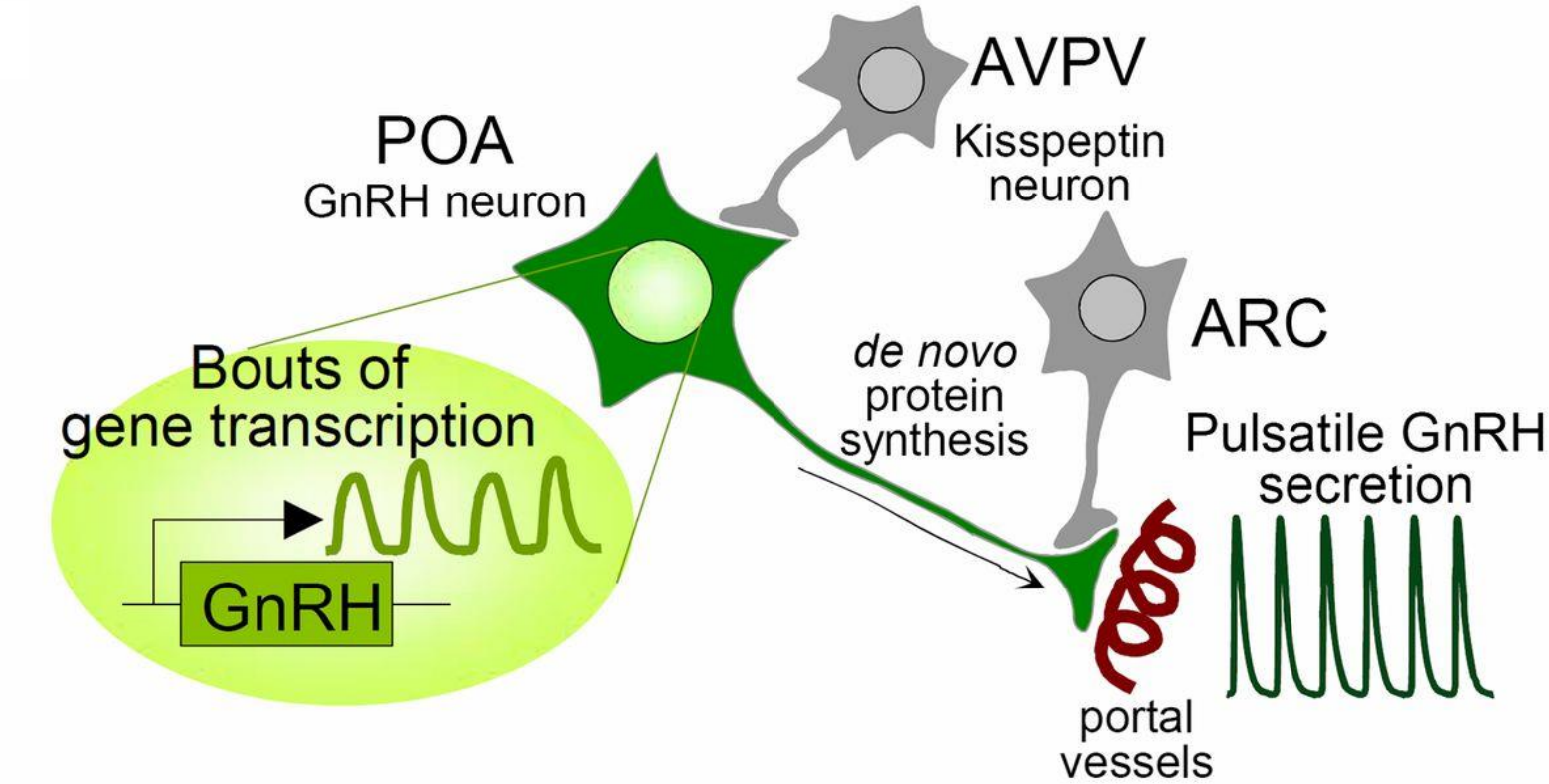
Although tonic suppression of PRL release by dopamine is the dominant effect of the hypothalamus on PRL secretion, a number of stimuli promote PRL release, not merely by disinhibition of PIF effects but by causing release of one or more neurohormonal PRFs. The most important of the putative PRFs are TRH, oxytocin, and VIP, but AVP, angiotensin II, NPY, galanin, substance P, bombesin-like peptides, and neurotensin can also trigger PRL release under different physiologic circumstances. TRH has already been discussed. In humans, there is an imperfect correlation between pulsatile PRL and TSH release, suggesting that TRH cannot be the sole physiologic PRF under basal conditions.

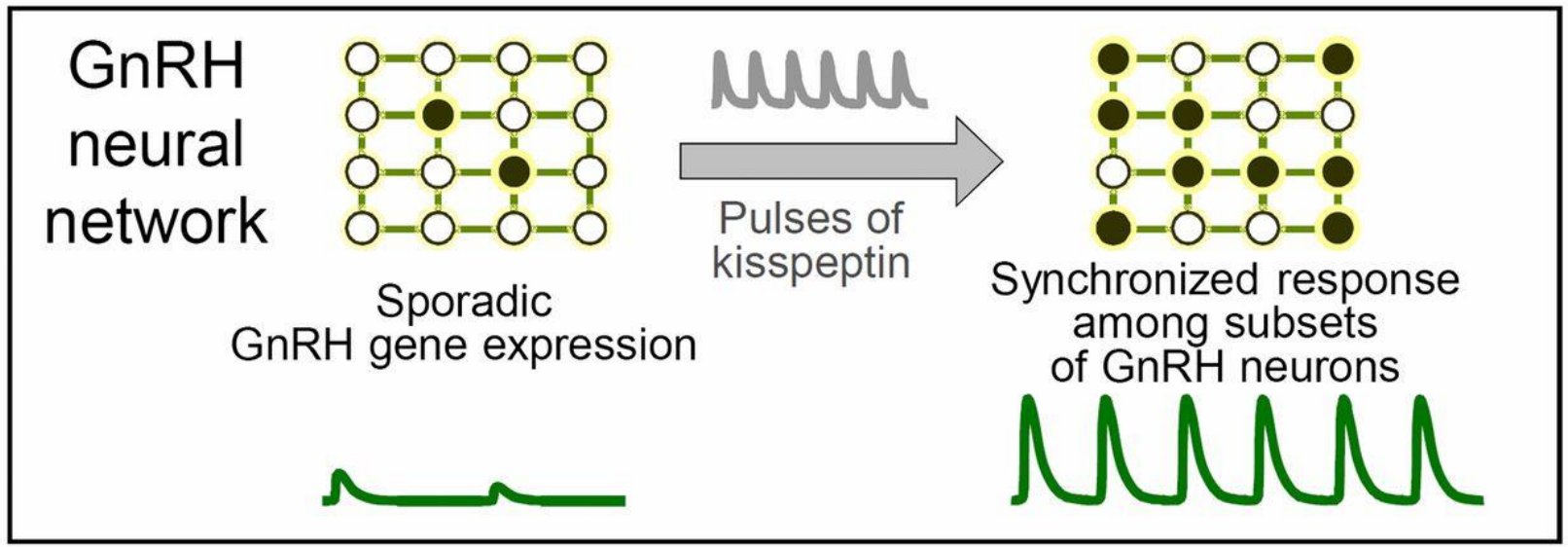
Gonadotropin-Releasing Hormone and Control of the Reproductive Axis

GnRH is a 10-amino-acid hypothalamic neuropeptide that controls the function of the reproductive axis. It is synthesized as part of a larger precursor molecule that is enzymatically cleaved to remove a signal peptide from the N-terminus and GnRH-associated peptide (GAP) from the C-terminus

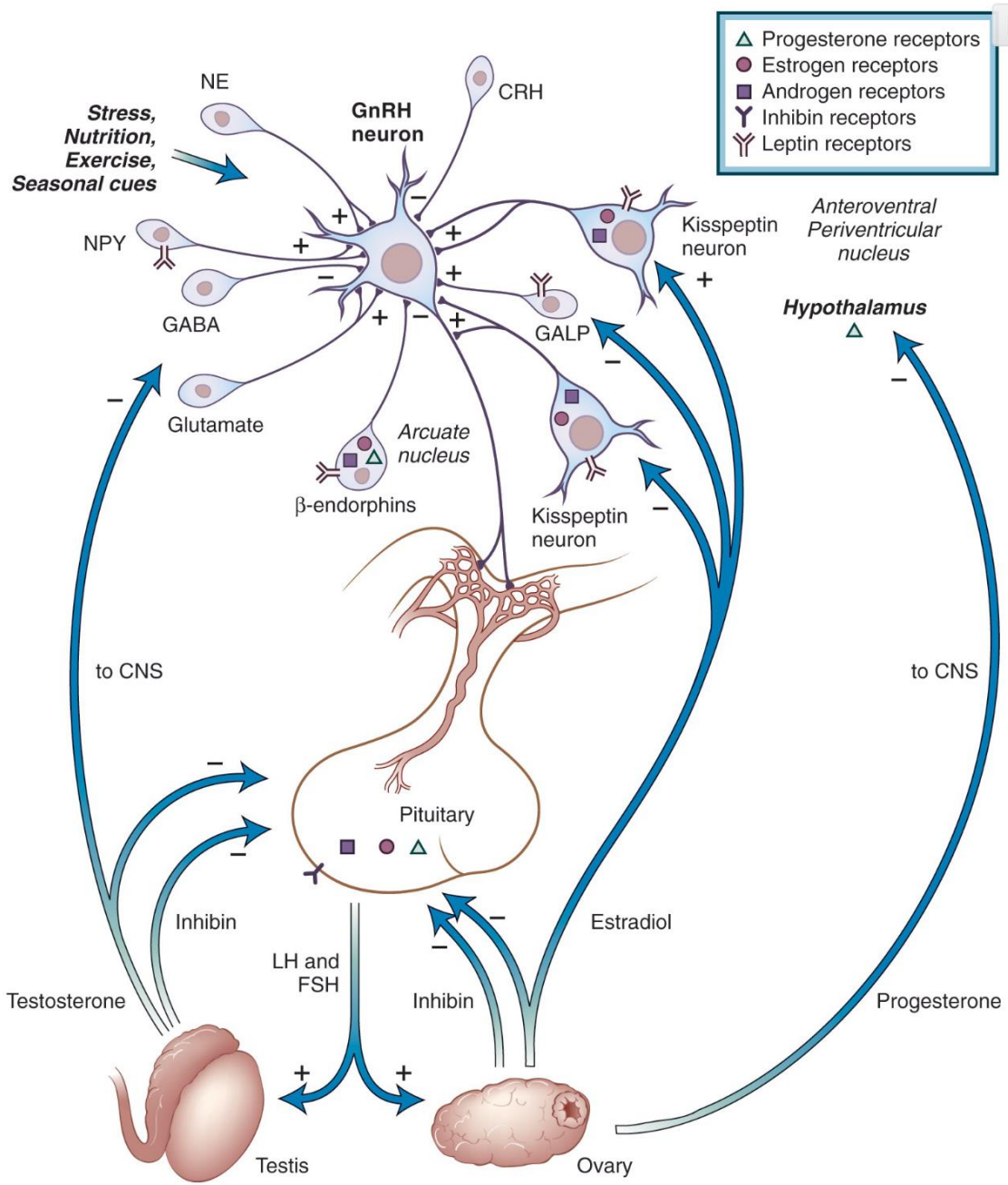
Two genes encoding GnRH have been identified within mammals.[315,316] The first, *GNRH1,*encodes a 92-amino-acid precursor protein. This is the form of GnRH that is found in hypothalamic neurons and serves as a releasing factor to regulate pituitary gonadotroph function.[317] The second GnRH gene, *GNRH2,* encodes a decapeptide that differs from the first by three amino acids.[318] This form of GnRH is found in the midbrain region and serves as a neurotransmitter rather than as a pituitary releasing factor

GnRH binds to a membrane receptor on pituitary gonadotrophs and stimulates synthesis and secretion of both LH and FSH. The GnRH receptor is a seven-transmembrane-domain G protein–coupled receptor, but it lacks a typical intracellular C-terminal cytoplasmic domain.[321] Under physiologic conditions, GnRH receptor number varies and is usually directly correlated with the gonadotropin secretory capacity of pituitary gonadotrophs.


AVPV
Kisspeptin neuron
POA
GnRH neuron
ARC
de novo protein synthesis
Bouts of gene transcription
GnRH
Pulsatile GnRH secretion
portal vessels


GnRH neural network
Sporadic GnRH gene expression
Pulses of kisspeptin
Synchronized response among subsets of GnRH neurons

The pulsatile nature of GnRH stimulation of the pituitary leads to the release of distinct pulses of LH into the peripheral circulation.


Progesterone receptors
Estrogen receptors
Androgen receptors
Inhibin receptors
Leptin receptors
NE
Stress,
Nutrition,
Exercise,
Seasonal cues
GnRH
neuron
CRH
NPY
GABA
Glutamate
Arcuate
nucleus
β-endorphins
GALP
Kisspeptin
neuron
Anteroventral
Periventricular
nucleus
Hypothalamus
Kisspeptin
neuron
to CNS
to CNS
Pituitary
Inhibin
LH and
FSH
Testosterone
Inhibin
Estradiol
Progesterone
Testis
Ovary

Feedback Regulation

Steroid hormone receptors are abundant in the hypothalamus and in many neural systems that impinge on GnRH neurons, including noradrenergic, serotoninergic, β-endorphin–containing, and NPY neurons. Early studies identifying regions of the brain that bind labeled estrogens showed that in rodents the preoptic area and the VMH had the highest concentrations of estrogen receptors in the brain. Further localization studies, identifying estrogen receptors by immunocytochemistry or in situ hybridization, confirmed the strong presence of estrogen receptors in the hypothalamus and in brain areas with abundant connections to the hypothalamus, including the amygdala, septal nuclei, bed nucleus of the stria terminalis, medial part of the nucleus of the solitary tract, and lateral portion of the parabrachial nucleus.

Summary

- Hormone production from the hypothalamus and pituitary gland is highly dependent upon negative feed-back from the relevant end-organs.
- Hormones from the hypothalamus and pituitary gland are peptides synthesized by specific neuroendocrine cells
- The hypothalamus and anterior pituitary function regulates severale endocrine end-organs