CRITERIOS PARA CLASIFICAR LAS HORMONAS

ESTRUCTURA o NATURALEZA QUIMICA

ESTRUCTURAS ANATÓMICAS DONDE SON SINTETIZADAS

UBICACIÓN CELULAR DEL RECEPTOR CON EL CUAL INTERACTUAN

SEGUNDO MENSAJERO QUE SE ORIGINA POR LA INTERACCIÓN HORMONA-RECEPTOR

3 aa
Thyroliberin (TRH)

Hypothalamus

Pituitary

Brain

TSH

Thyrotropin secretion ↑

Neurotransmitter action

α chain 92 aa
β chain 112 aa
Thyrotropin (TSH)

Adeno-hypophysis

Thyroid gland

Thyroxine

Synthesis and secretion of thyroxine ↑

A chain 21 aa
B chain 30 aa
Insulin

B cells

Pancreas

Glucose

Glycogen ↑ ↓ Glucose

Proteins ↑ ↓ Amino acids

Fats ↑ ↓ Fatty acids

Glucose uptake by cells ↑
Blood glucose ↓

Storage compounds: formation ↑ degradation ↓

29 aa
Glucagon

A cells

Pancreas

Glycogen ↓ Glucose ← Amino acids

Fats ↓ Fatty acids ↓ Ketone bodies

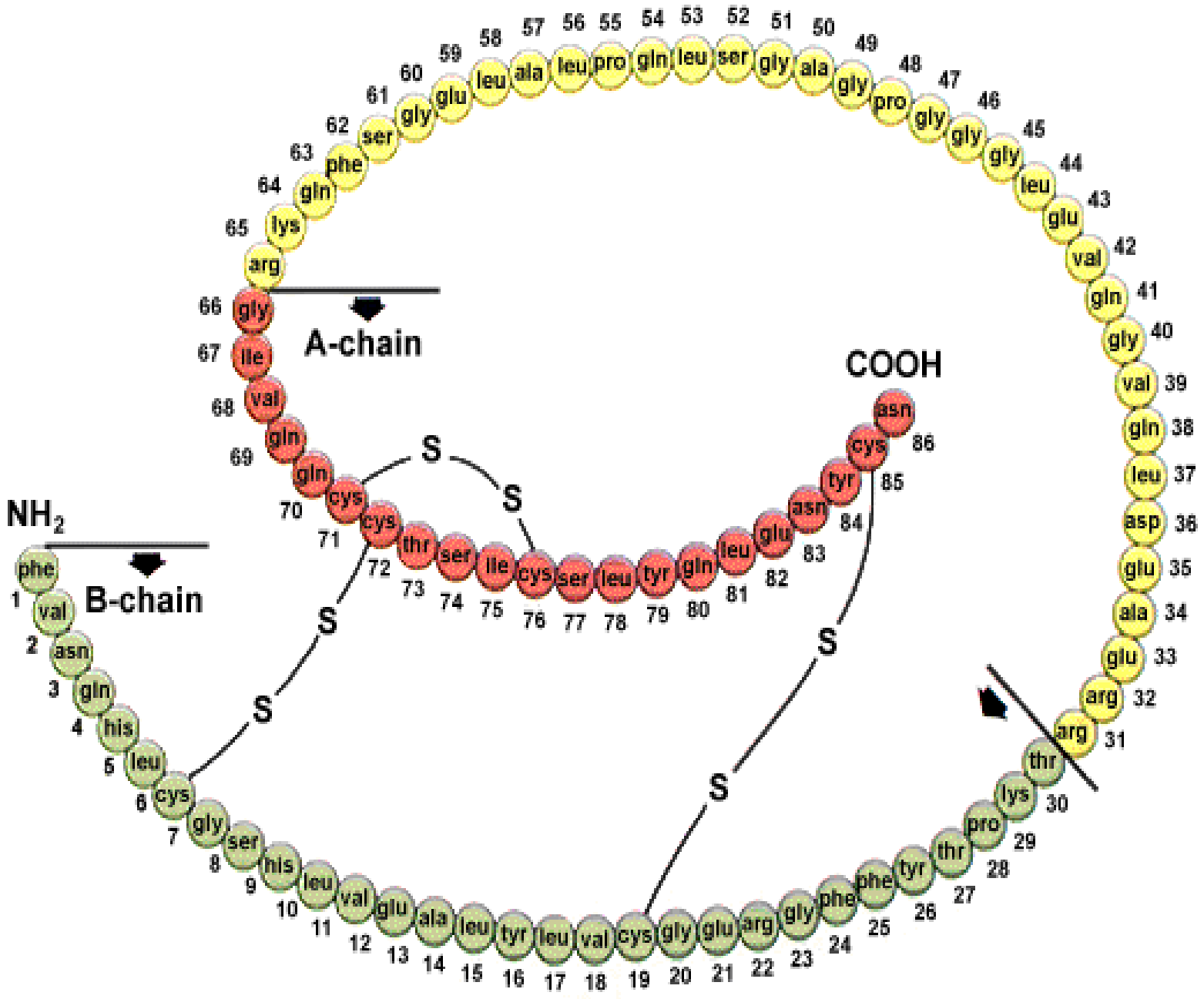
Glycogenolysis ↑

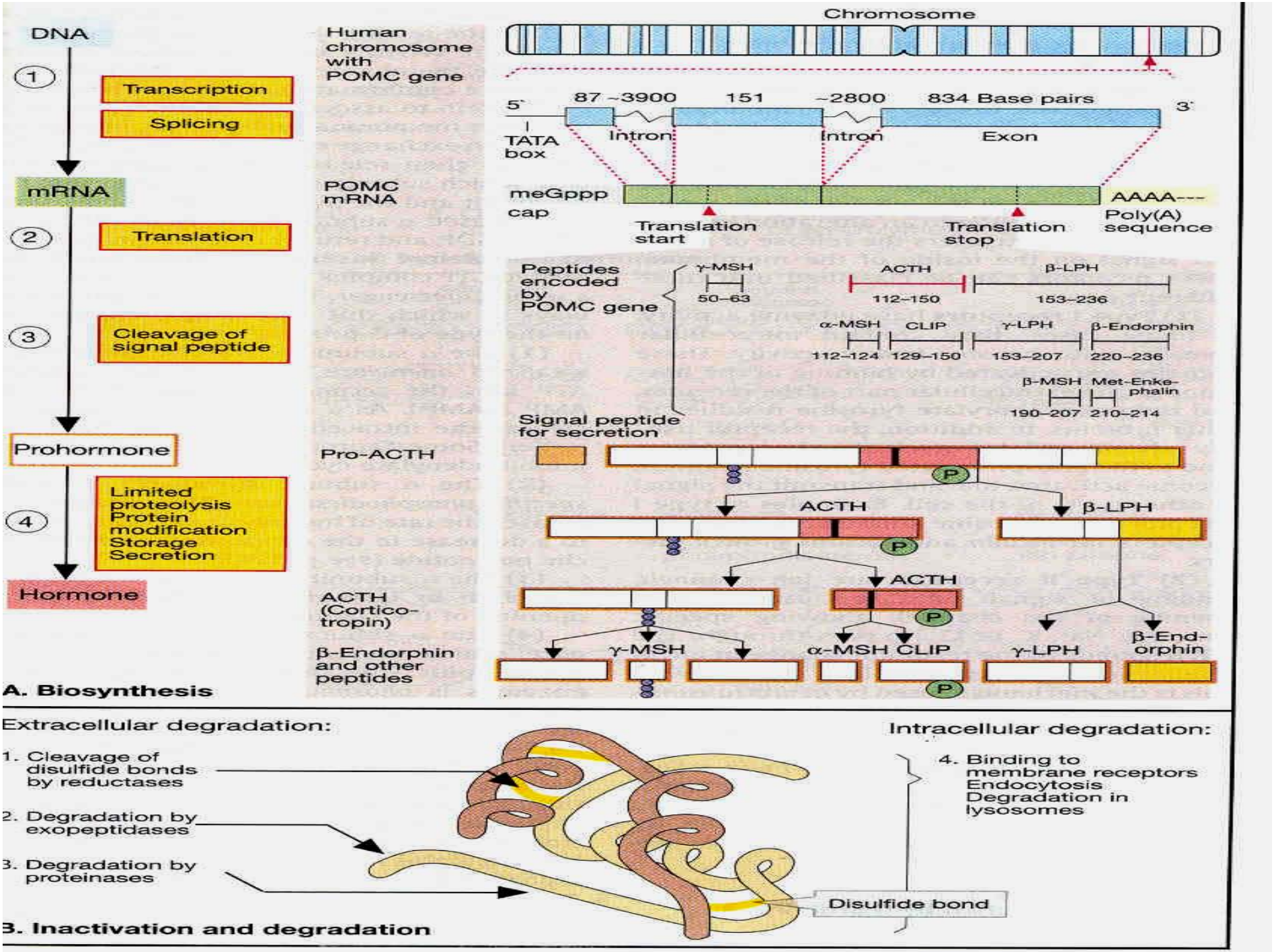
Gluconeogenesis ↑

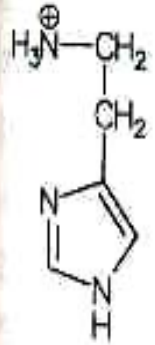
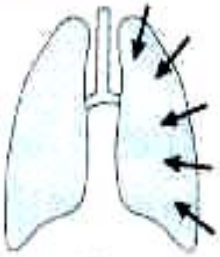
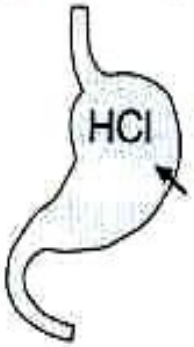
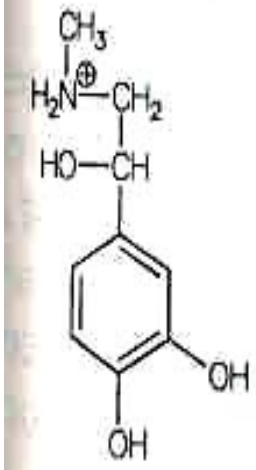
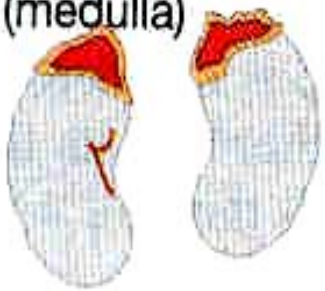
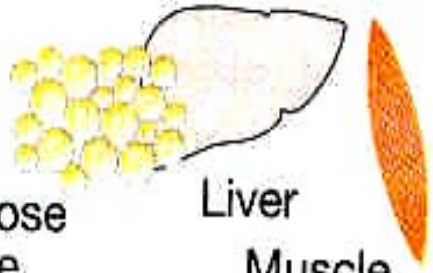
Blood glucose ↑

Ketone body formation ↑

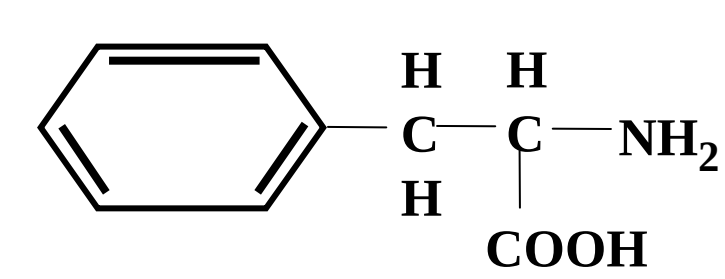
B. Peptide and proteohormons: examples


NH2
B-chain
A-chain
COOH
S
S
S
S
S
phe 1
val 2
asn 3
gln 4
his 5
leu 6
cys 7
gly 8
ser 9
his 10
leu 11
val 12
glu 13
ala 14
leu 15
tyr 16
leu 17
val 18
cys 19
gly 20
glu 21
arg 22
gly 23
phe 24
phe 25
tyr 26
thr 27
pro 28
lys 29
thr 30
arg 31
arg 32
glu 33
ala 34
glu 35
asp 36
leu 37
gln 38
val 39
gly 40
gln 41
val 42
glu 43
leu 44
gly 45
gly 46
gly 47
pro 48
gly 49
ala 50
gly 51
ser 52
leu 53
gln 54
pro 55
leu 56
ala 57
leu 58
glu 59
gly 60
ser 61
phe 62
gln 63
lys 64
arg 65
gly 66
ile 67
val 68
gln 69
gln 70
cys 71
cys 72
thr 73
ser 74
ile 75
cys 76
ser 77
leu 78
tyr 79
gln 80
leu 81
glu 82
asn 83
tyr 84
cys 85
asn 86


DNA
1
Transcription
Splicing
mRNA
2
Translation
3
Cleavage of signal peptide
Prohormone
4
Limited proteolysis
Protein modification
Storage
Secretion
Hormone
Human chromosome with POMC gene
POMC mRNA
Pro-ACTH
ACTH (Cortico-tropin)
β-Endorphin and other peptides
Chromosome
5'
87 ~3900
151
~2800
834 Base pairs
3'
TATA box
Intron
Intron
Exon
meGppp cap
AAAA---
Poly(A) sequence
Translation start
Translation stop
Peptides encoded by POMC gene
γ-MSH
50–63
ACTH
112–150
β-LPH
153–236
α-MSH
112–124
CLIP
129–150
γ-LPH
153–207
β-Endorphin
220–236
β-MSH
190–207
Met-Enke-phalin
210–214
Signal peptide for secretion
P
ACTH
β-LPH
ACTH
γ-MSH
α-MSH
CLIP
γ-LPH
β-End-orphin
A. Biosynthesis
Extracellular degradation:
1. Cleavage of disulfide bonds by reductases
2. Degradation by exopeptidases
3. Degradation by proteinases
Intracellular degradation:
4. Binding to membrane receptors
Endocytosis
Degradation in lysosomes
Disulfide bond
B. Inactivation and degradation

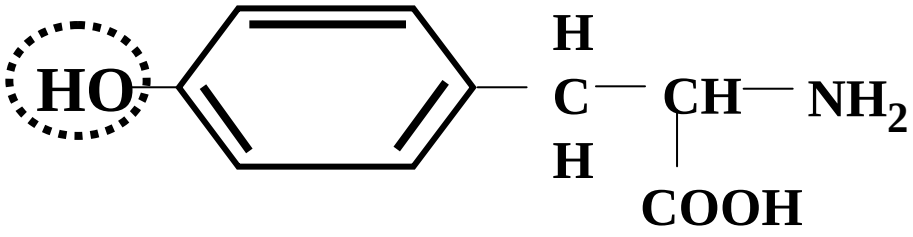
Hormone	Sites of formation	Sites of action	Actions
 **Histamine**	 Mast cell  Basophilic granulocyte	 Lungs  Stomach	Width of bronchi ↓ Capillaries: width ↑ permeability ↑ Gastric acid secretion by parietal cells ↑
 **Epinephrine**	 Adrenal glands (medulla)	 Heart  Adipose tissue, Liver, Muscle	Cardiac output ↑ Width of blood vessels ↓ Blood pressure ↑ Metabolism: Glycogenolysis ↑ Blood glucose ↑ Lipolysis ↑

Catecholamine Biosynthesis



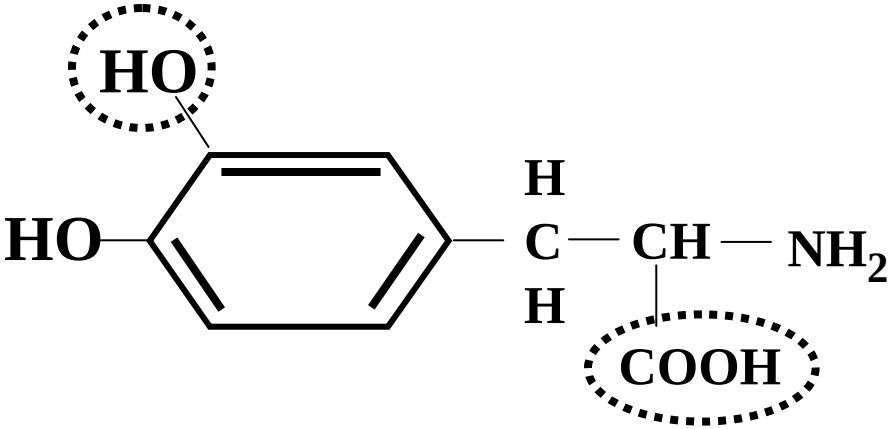
Phenylalanine

Phenylalanine hydroxylase



Tyrosine

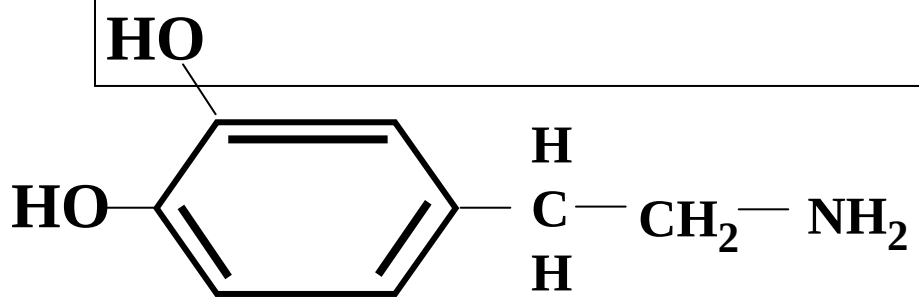
Tyrosine hydroxylase



Dopa

L-Aromatic Amino Acid Decarboxylase

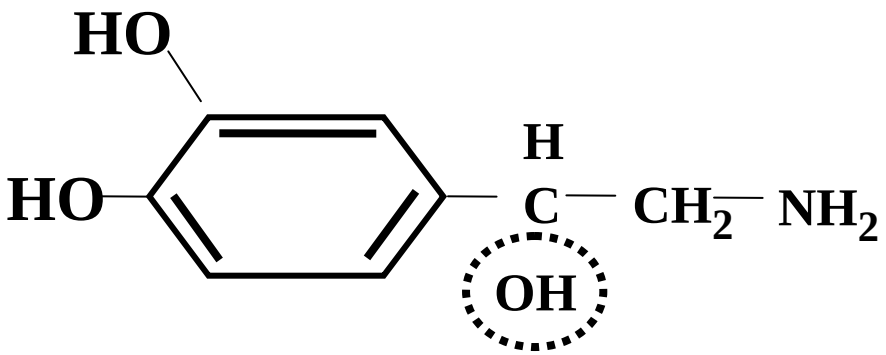
Catecholamine Biosynthesis



Dopamine

Dopamine

β-hydroxylase

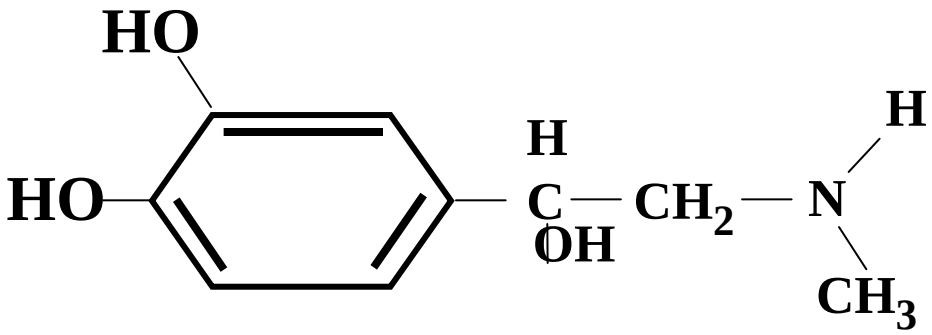


Norepinephrine

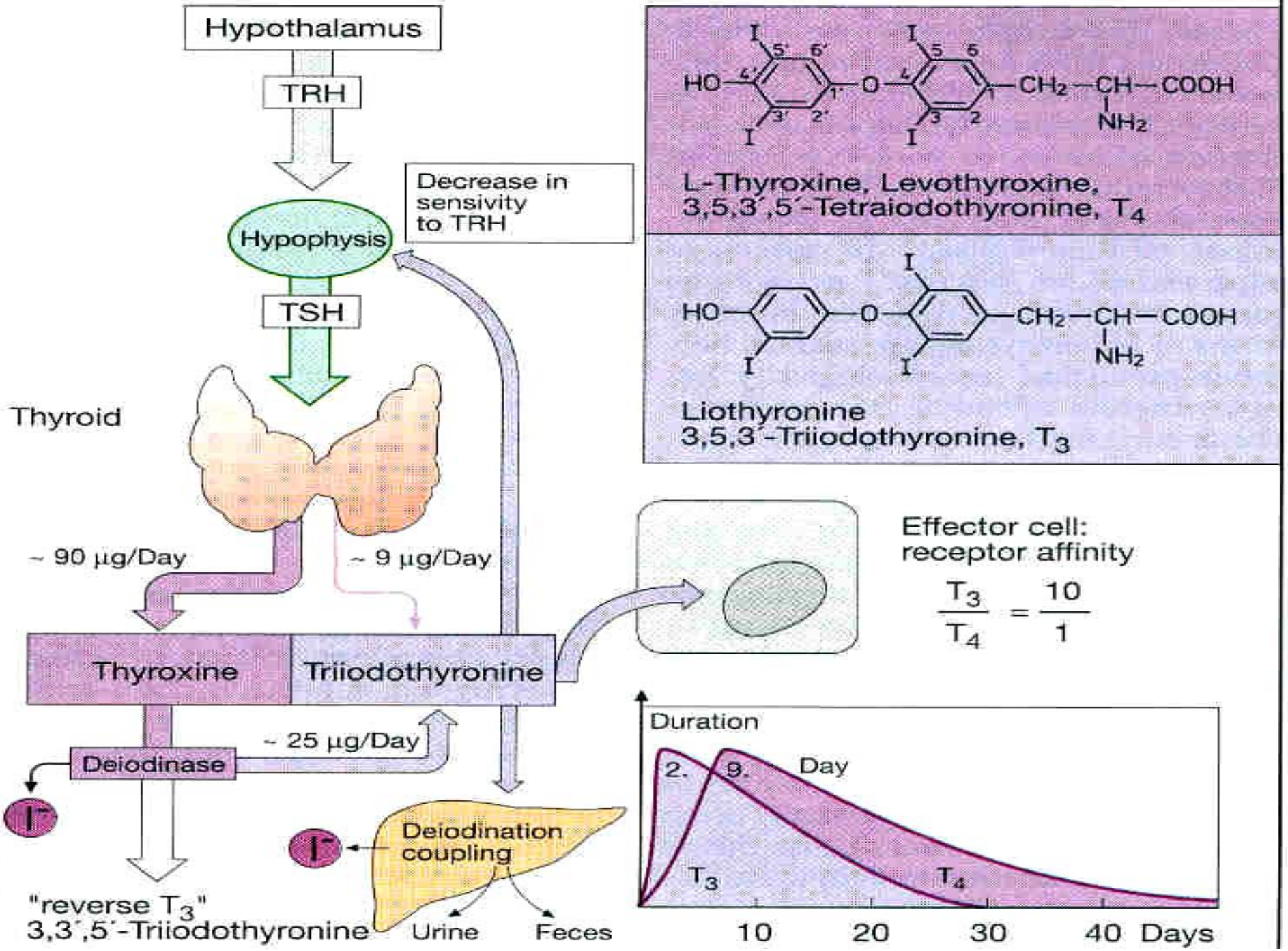
Phenylethanolamine

N-Methyltransferase

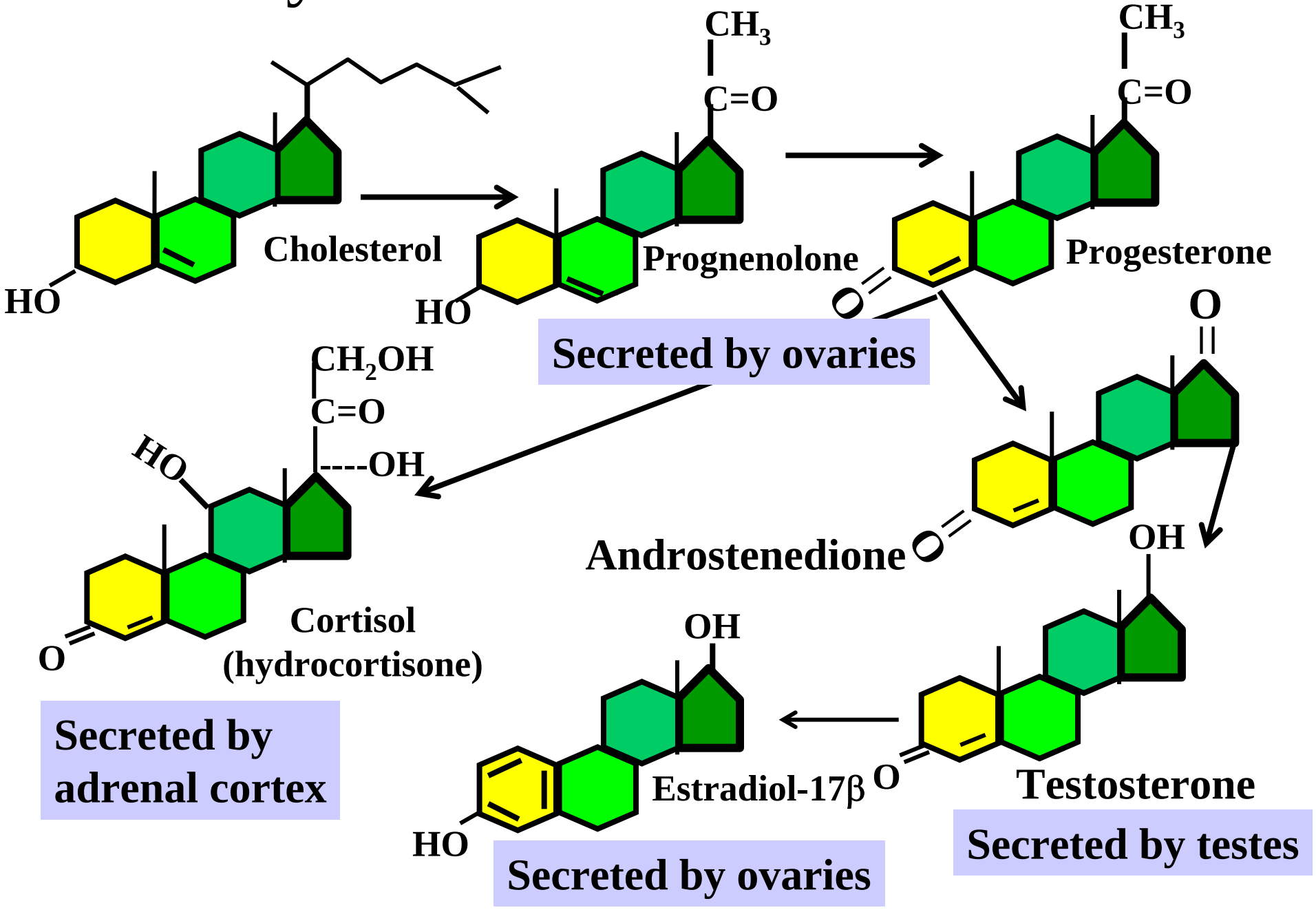
(PNMT)

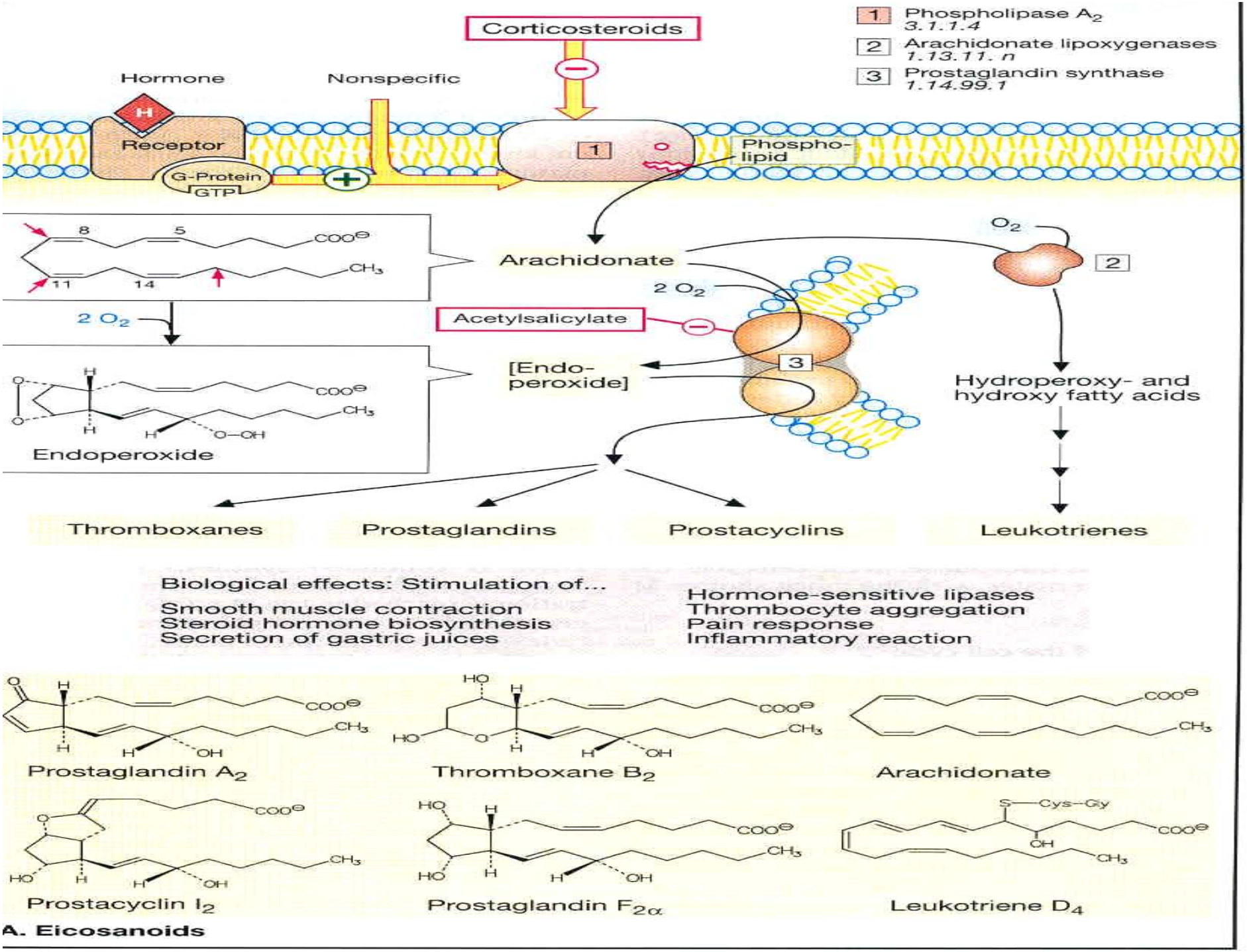


Epinephrine


Hypothalamus
TRH
Hypophysis
TSH
Thyroid
Decrease in sensivity to TRH
~ 90 µg/Day
~ 9 µg/Day
Thyroxine
Triiodothyronine
~ 25 µg/Day
Deiodinase
I⁻
I⁻
Deiodination coupling
"reverse T3"
3,3´,5´-Triiodothyronine
Urine
Feces
L-Thyroxine, Levothyroxine,
3,5,3´,5´-Tetraiodothyronine, T4
Liothyronine
3,5,3´-Triiodothyronine, T3
Effector cell:
receptor affinity
T3/T4 = 10/1
Duration
2.
9.
Day
T3
T4
10
20
30
40 Days

Biosynthesis of Steroid Hormones




1 Phospholipase A2 3.1.1.4
2 Arachidonate lipoxygenases 1.13.11. n
3 Prostaglandin synthase 1.14.99.1
Corticosteroids
Hormone
Nonspecific
H
Receptor
G-Protein
GTP
1
Phospho-lipid
Arachidonate
2 O2
O2
2
Acetylsalicylate
3
[Endo-peroxide]
Endoperoxide
Hydroperoxy- and hydroxy fatty acids
Thromboxanes
Prostaglandins
Prostacyclins
Leukotrienes
Biological effects: Stimulation of...
Smooth muscle contraction
Steroid hormone biosynthesis
Secretion of gastric juices
Hormone-sensitive lipases
Thrombocyte aggregation
Pain response
Inflammatory reaction
Prostaglandin A2
Thromboxane B2
Arachidonate
Prostacyclin I2
Prostaglandin F2α
Leukotriene D4
A. Eicosanoids

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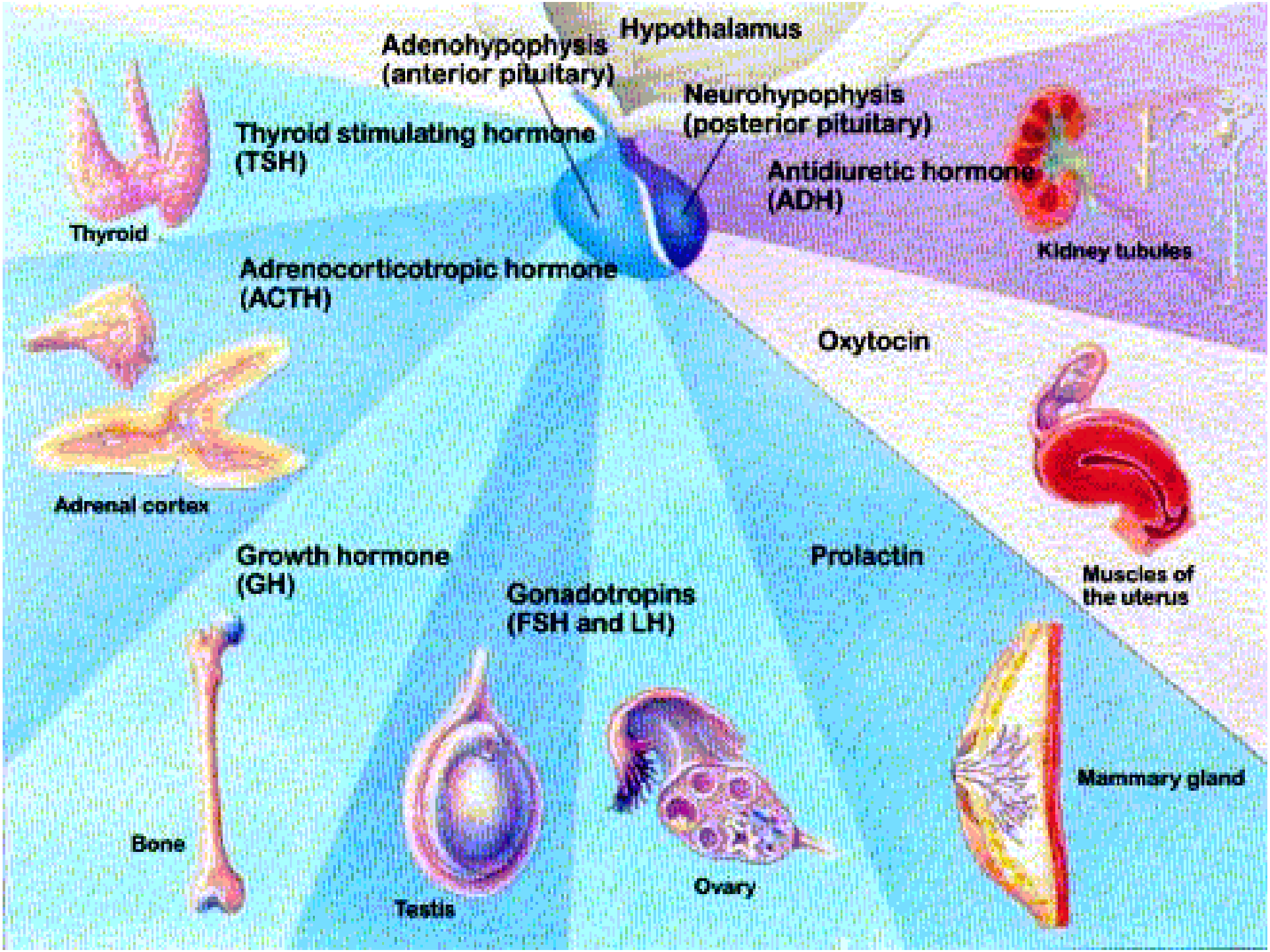
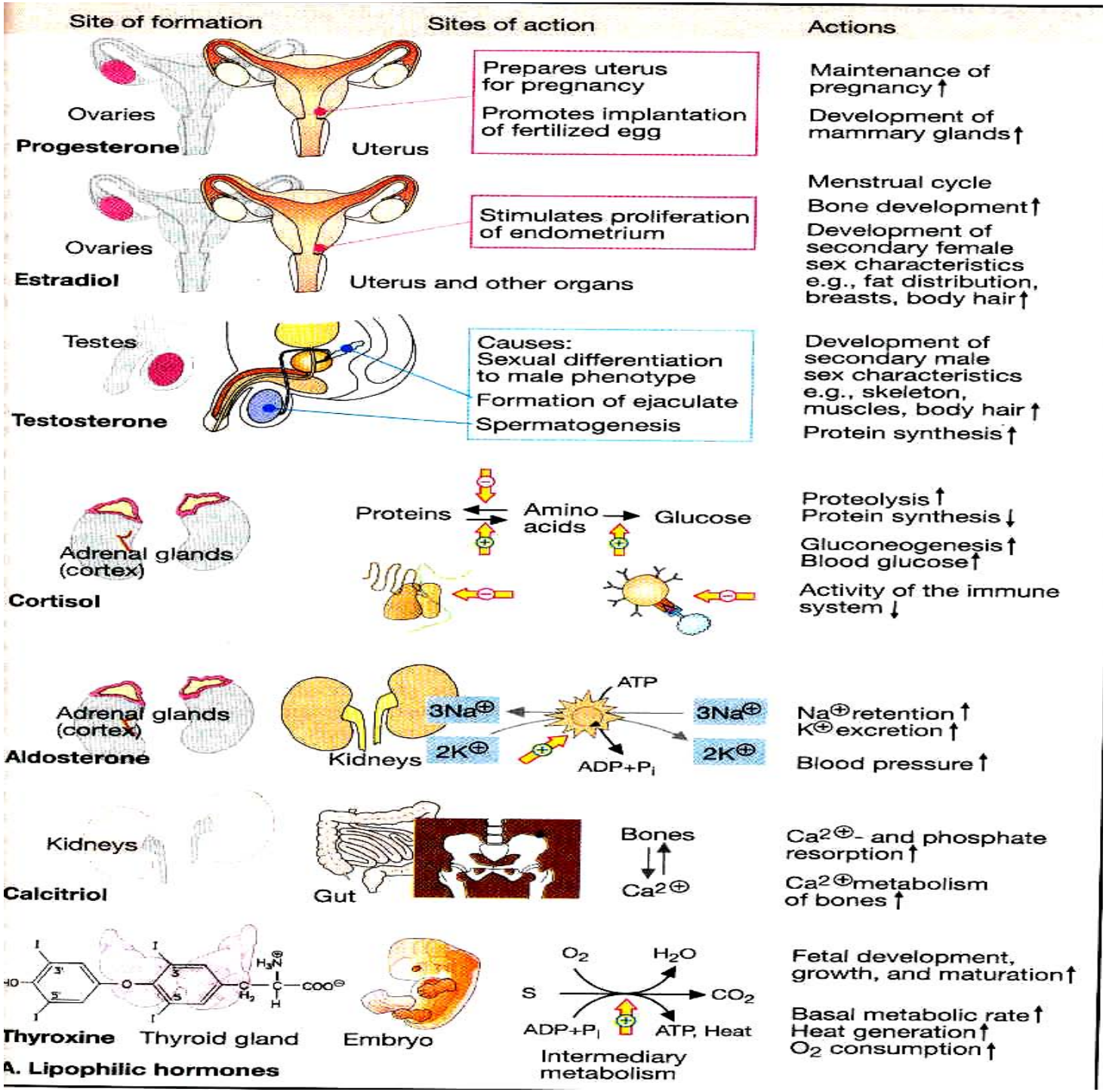

Hypothalamus
Adenohypophysis
(anterior pituitary)
Neurohypophysis
(posterior pituitary)
Thyroid stimulating hormone
(TSH)
Antidiuretic hormone
(ADH)
Thyroid
Kidney tubules
Adrenocorticotropic hormone
(ACTH)
Oxytocin
Adrenal cortex
Growth hormone
(GH)
Gonadotropins
(FSH and LH)
Prolactin
Muscles of
the uterus
Mammary gland
Bone
Testis
Ovary


Site of formation
Sites of action
Actions
Ovaries
Progesterone
Uterus
Prepares uterus for pregnancy
Promotes implantation of fertilized egg
Maintenance of pregnancy ↑
Development of mammary glands ↑
Ovaries
Estradiol
Uterus and other organs
Stimulates proliferation of endometrium
Menstrual cycle
Bone development ↑
Development of secondary female sex characteristics e.g., fat distribution, breasts, body hair ↑
Testes
Testosterone
Causes:
Sexual differentiation to male phenotype
Formation of ejaculate
Spermatogenesis
Development of secondary male sex characteristics e.g., skeleton, muscles, body hair ↑
Protein synthesis ↑
Adrenal glands (cortex)
Cortisol
Proteins
Amino acids
Glucose
Proteolysis ↑
Protein synthesis ↓
Gluconeogenesis ↑
Blood glucose ↑
Activity of the immune system ↓
Adrenal glands (cortex)
Aldosterone
Kidneys
3Na⊕
2K⊕
ATP
ADP+Pi
Na⊕ retention ↑
K⊕ excretion ↑
Blood pressure ↑
Kidneys
Calcitriol
Gut
Bones
Ca2⊕
Ca2⊕- and phosphate resorption ↑
Ca2⊕ metabolism of bones ↑
Thyroxine
Thyroid gland
Embryo
Fetal development, growth, and maturation ↑
O2
H2O
S
CO2
ADP+Pi
ATP, Heat
Intermediary metabolism
Basal metabolic rate ↑
Heat generation ↑
O2 consumption ↑
A. Lipophilic hormones

Sistema endocrino

Aporta mecanismos para la comunicación entre células y órganos

El término “ENDOCRINO” se refiere al proceso de secreción de sustancias “HORMONAS” que ejercen acciones regulatorias en células distintas a las que la producen

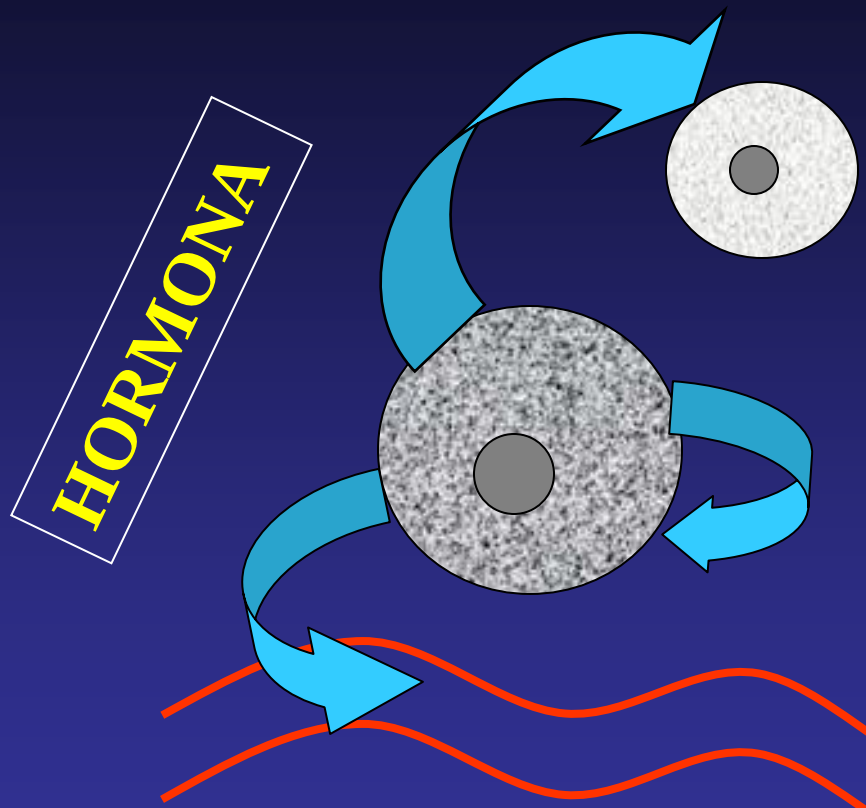
Sistema endocrino

Existen tres formas de comunicación celular

La hormona liberada por una glándula actúa en forma:

- Endocrina
- Paracrina
- Autocrina

Mecanismo Paracrino
Actúa sobre células vecinas



Mecanismo Autocrino
Actúa sobre la misma célula

Mecanismo Endocrino
Actúa a distancia a través del torrente sanguíneo sobre órganos o tejidos

Sistema endocrino

Para actuar, una hormona debe unirse a sitios específicos de otras células llamados "RECEPTORES"

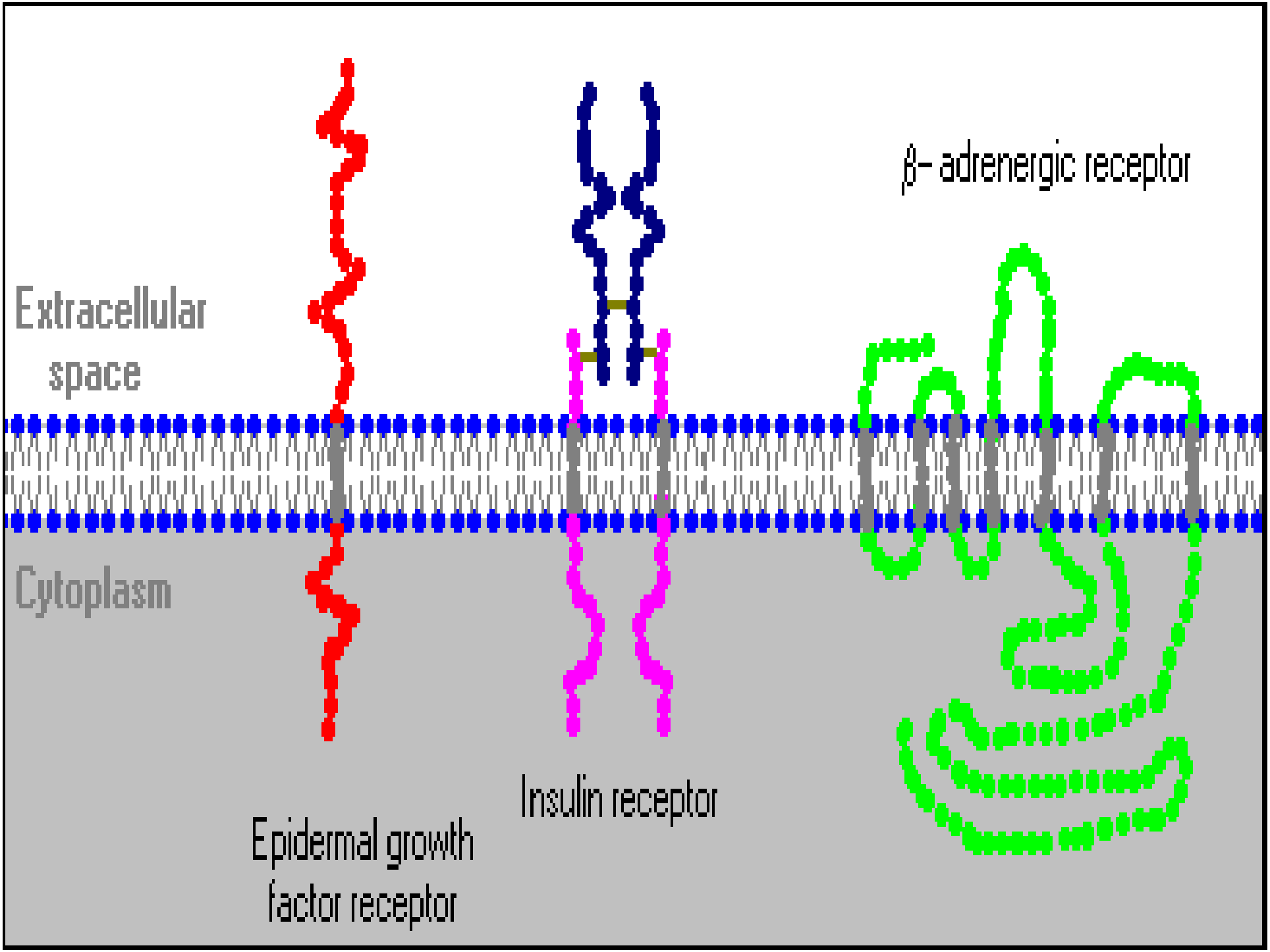
Tienen dos funciones:

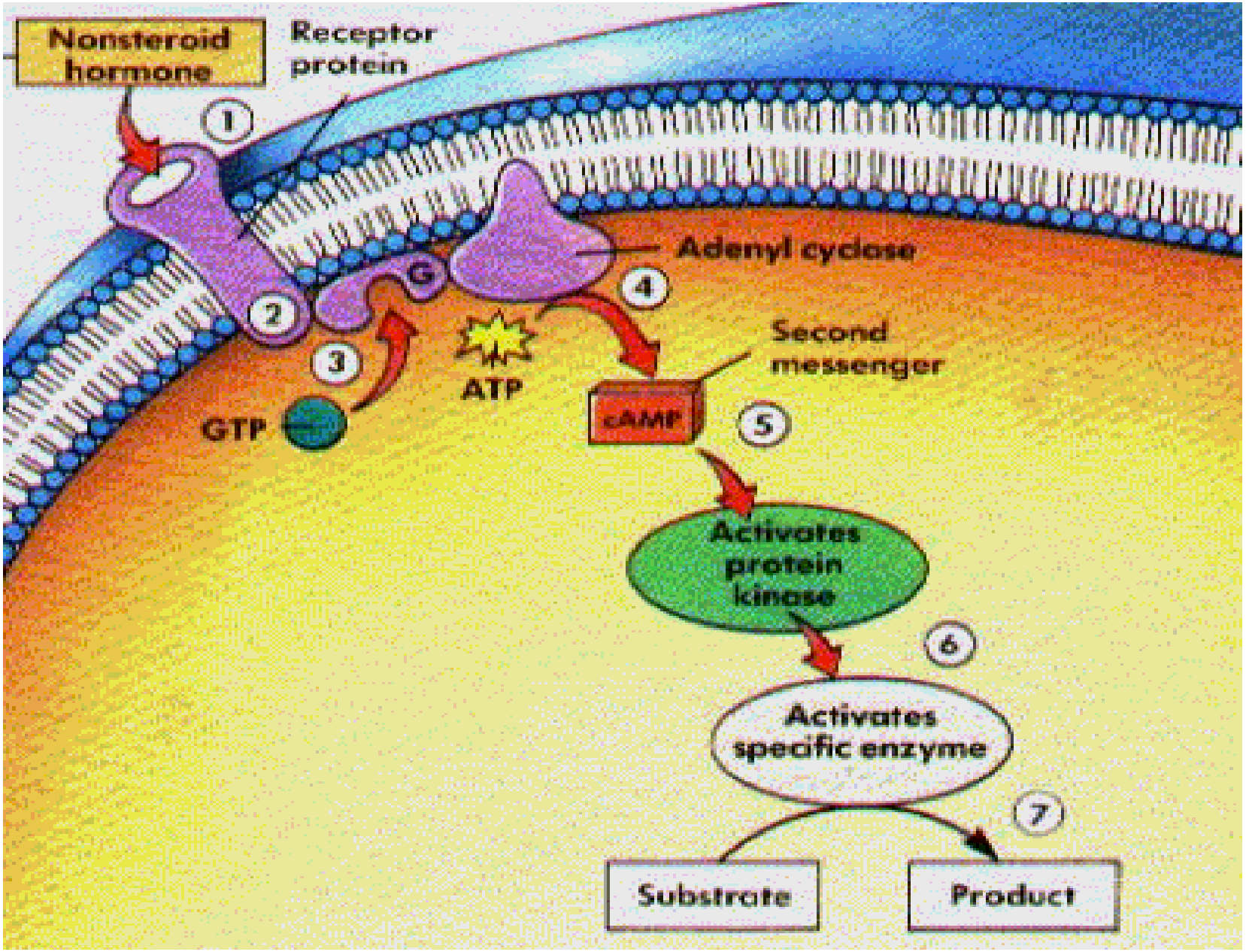
- distinguir la hormona de cualquier otra sustancia circulante
- debe ser capaz de transmitir la información hormonal al núcleo celular y promover una acción específica

RECEPTORES DE MEMBRANA

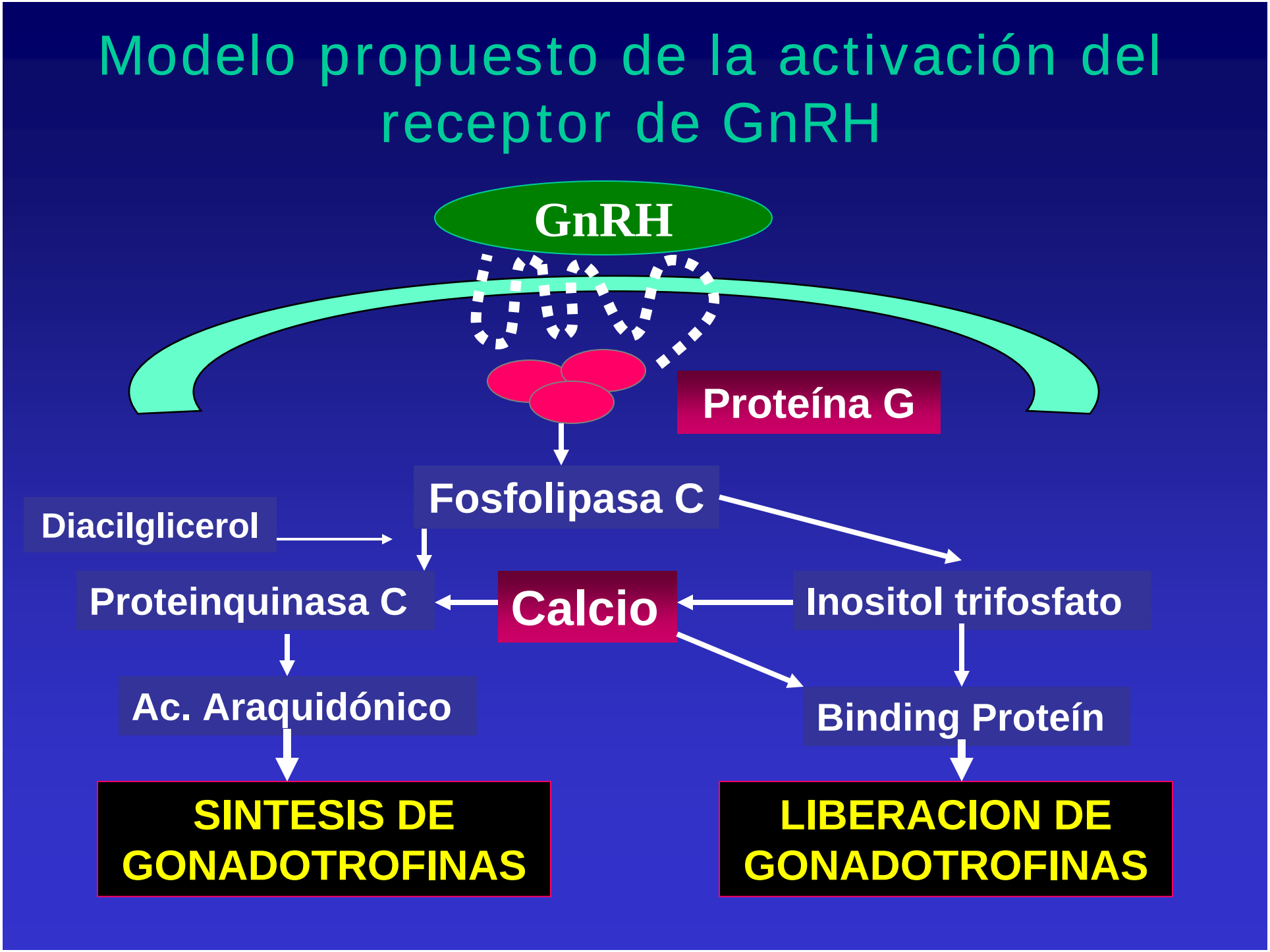
En general, para todas las hormonas proteicas

- Actúan sobre un receptor de membrana específico
- Activa una serie de eventos y a través del segundo mensajero, alcanza el núcleo


β- adrenergic receptor
Extracellular space
Cytoplasm
Insulin receptor
Epidermal growth factor receptor


Nonsteroid hormone
Receptor protein
1
Adenyl cyclase
2
G
4
3
ATP
Second messenger
GTP
cAMP
5
Activates protein kinase
6
Activates specific enzyme
7
Substrate
Product

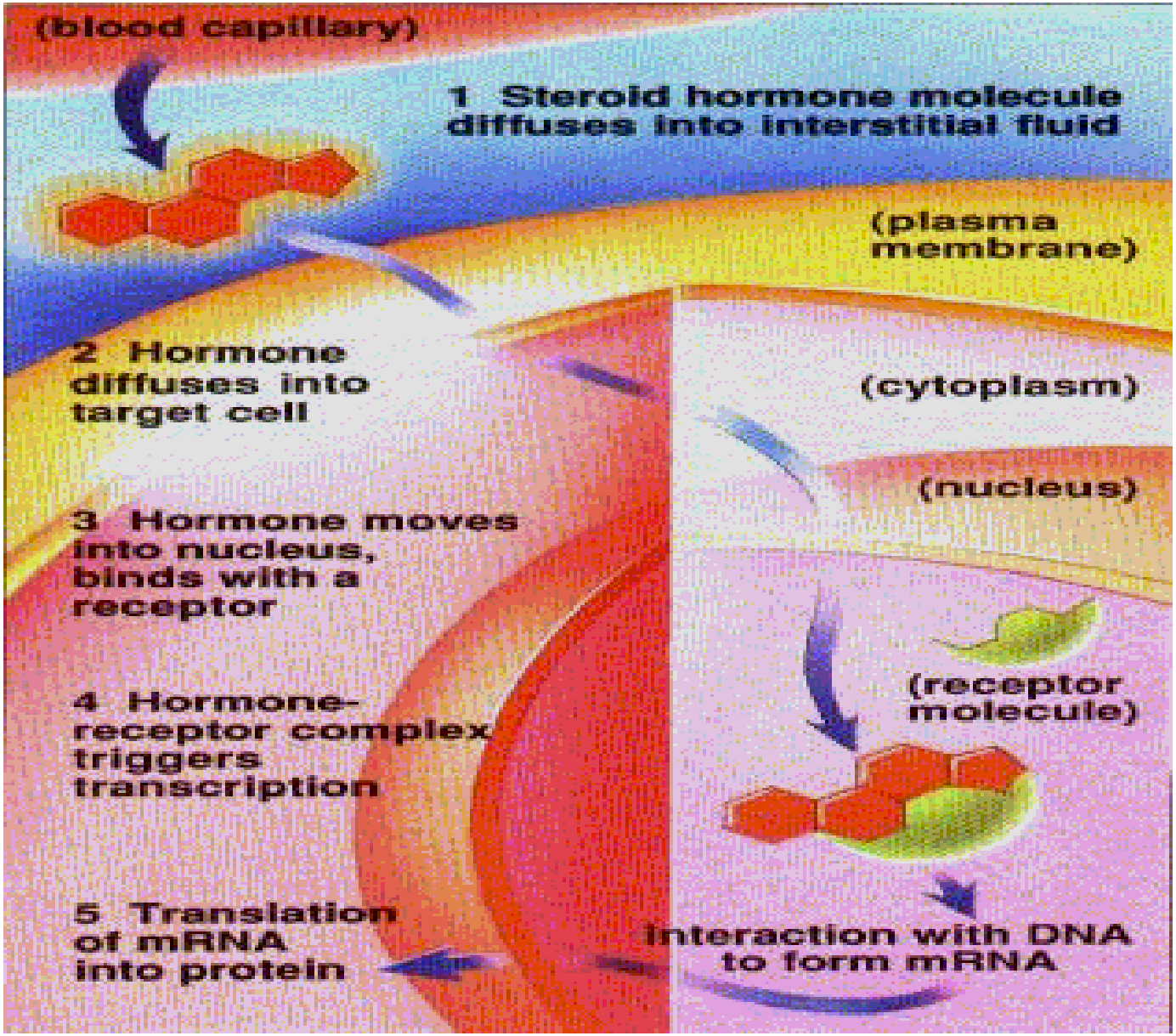
Modelo propuesto de la activación del receptor de GnRH

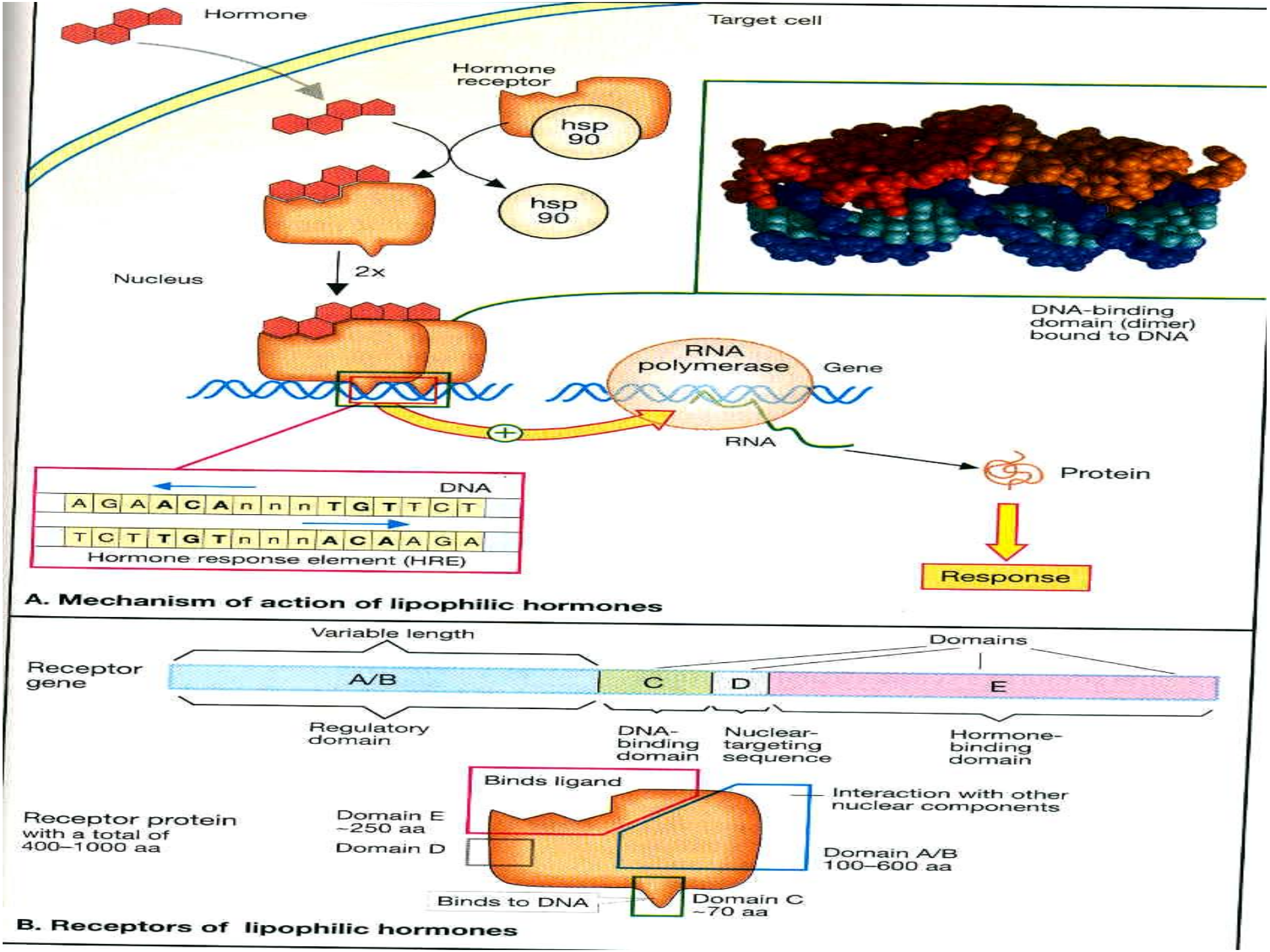


RECEPTORES NUCLEARES

Familia de receptores nucleares:

- Hormonas esteroideas (sexuales y adrenales)
- Hormonas tiroideas
- 1,25-dihidroxicolecalciferol
- Acido retinoico


(blood capillary)
1 Steroid hormone molecule diffuses into interstitial fluid
(plasma membrane)
2 Hormone diffuses into target cell
(cytoplasm)
(nucleus)
3 Hormone moves into nucleus, binds with a receptor
(receptor molecule)
4 Hormone-receptor complex triggers transcription
5 Translation of mRNA into protein
Interaction with DNA to form mRNA


Hormone
Target cell
Hormone receptor
hsp 90
hsp 90
Nucleus
2x
DNA-binding domain (dimer) bound to DNA
RNA polymerase
Gene
RNA
Protein
DNA
A G A A C A n n n T G T T C T
T C T T G T n n n A C A A G A
Hormone response element (HRE)
Response
A. Mechanism of action of lipophilic hormones
Variable length
Domains
Receptor gene
A/B
C
D
E
Regulatory domain
DNA-binding domain
Nuclear-targeting sequence
Hormone-binding domain
Binds ligand
Interaction with other nuclear components
Receptor protein with a total of 400–1000 aa
Domain E ~250 aa
Domain D
Domain A/B 100–600 aa
Binds to DNA
Domain C ~70 aa
B. Receptors of lipophilic hormones

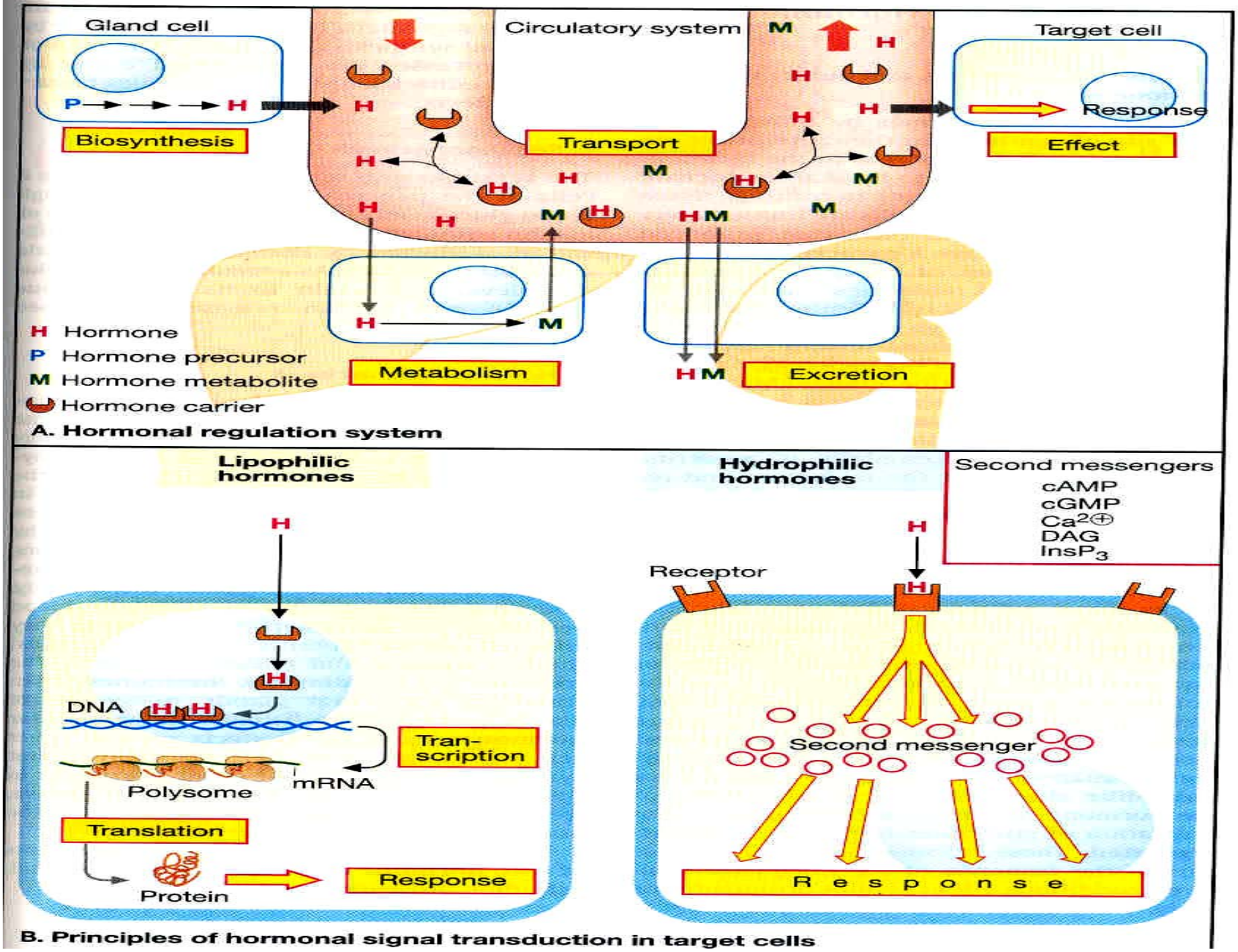
Sistema endocrino

TRANSPORTE HORMONAL

- Las hormonas solubles en agua son transportadas en el plasma en solución y no requieren de un mecanismo específico

- Las hormonas insolubles requieren de proteínas de transporte

- La mayoría de las hormonas actúan sobre la célula en estado libre, por lo cual las proteínas sirven de reservorio hormonal


Gland cell
P
H
Biosynthesis
Circulatory system
Transport
Target cell
Response
Effect
Metabolism
Excretion
H Hormone
P Hormone precursor
M Hormone metabolite
Hormone carrier
A. Hormonal regulation system
Lipophilic hormones
Hydrophilic hormones
Second messengers
cAMP
cGMP
Ca2⊕
DAG
InsP3
Receptor
DNA
Tran-scription
mRNA
Polysome
Translation
Protein
Response
Second messenger
R e s p o n s e
B. Principles of hormonal signal transduction in target cells

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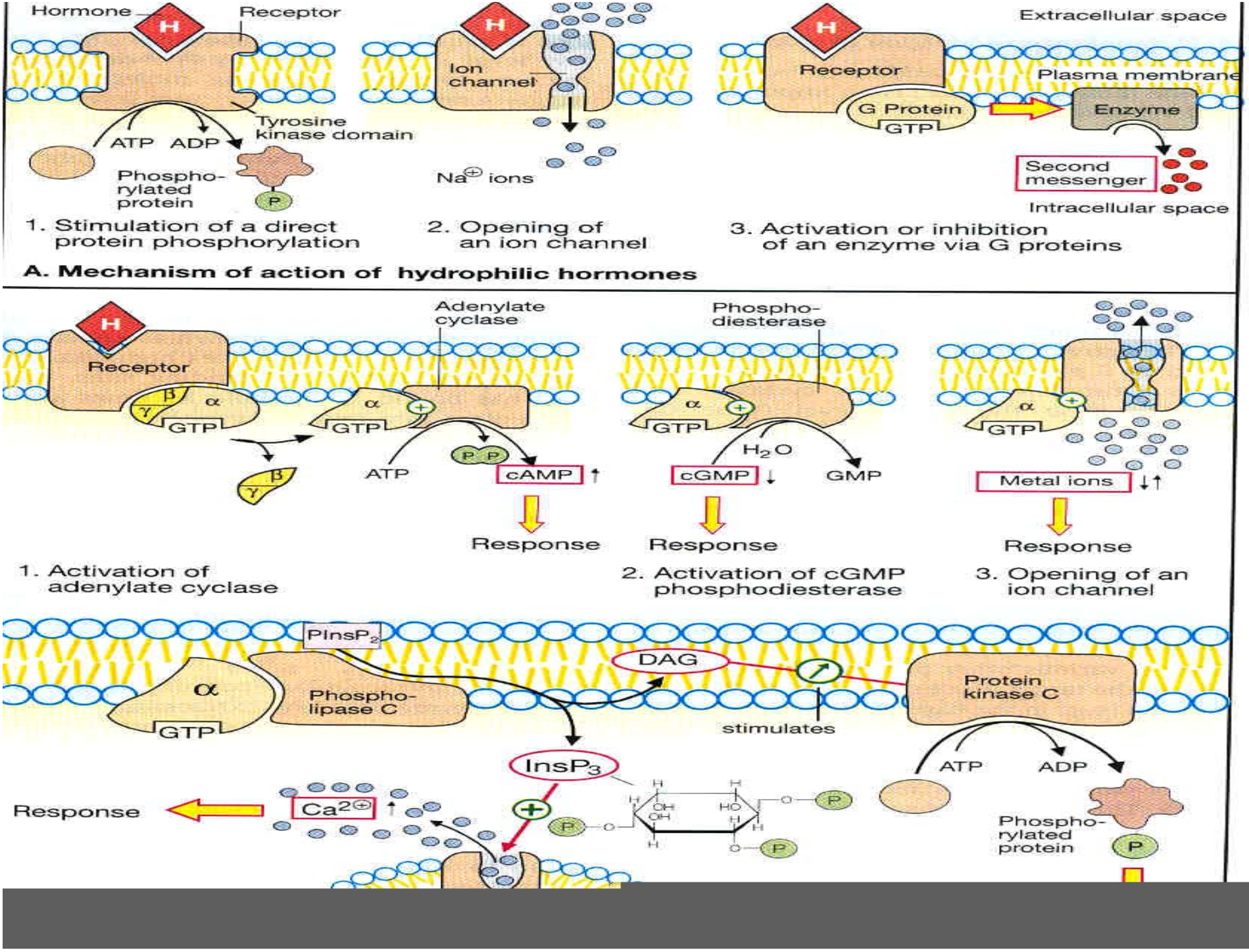
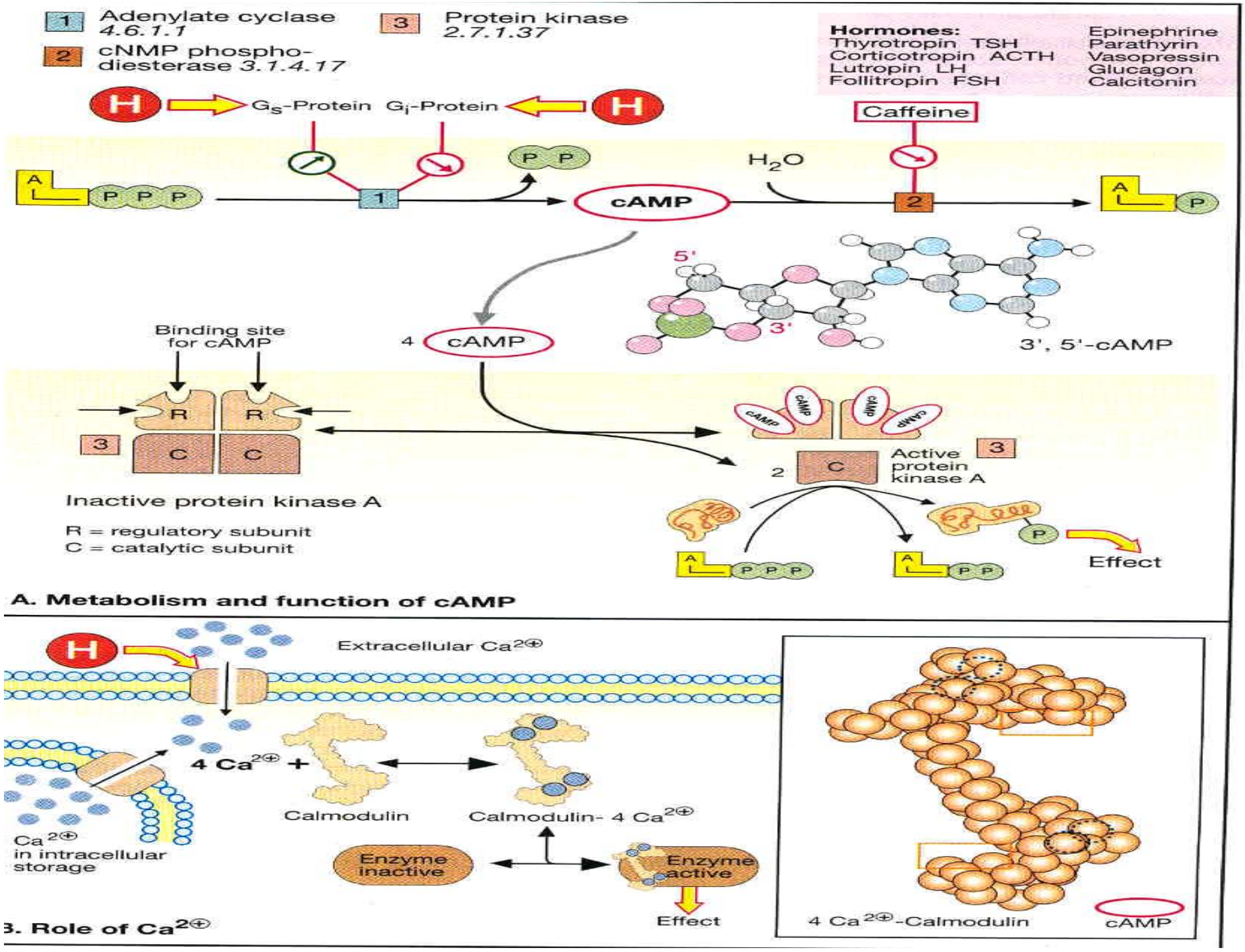

Hormone
Receptor
H
Tyrosine kinase domain
ATP
ADP
Phospho-rylated protein
P
1. Stimulation of a direct protein phosphorylation
Ion channel
Na⊕ ions
2. Opening of an ion channel
Extracellular space
Receptor
Plasma membrane
G Protein
GTP
Enzyme
Second messenger
Intracellular space
3. Activation or inhibition of an enzyme via G proteins
A. Mechanism of action of hydrophilic hormones
Adenylate cyclase
Receptor
β
γ
α
GTP
ATP
P P
cAMP
Response
1. Activation of adenylate cyclase
Phospho-diesterase
H2O
cGMP
GMP
Response
2. Activation of cGMP phosphodiesterase
Metal ions
Response
3. Opening of an ion channel
PInsP2
DAG
Protein kinase C
stimulates
Phospho-lipase C
InsP3
Ca2⊕
Response
ATP
ADP
Phospho-rylated protein
P

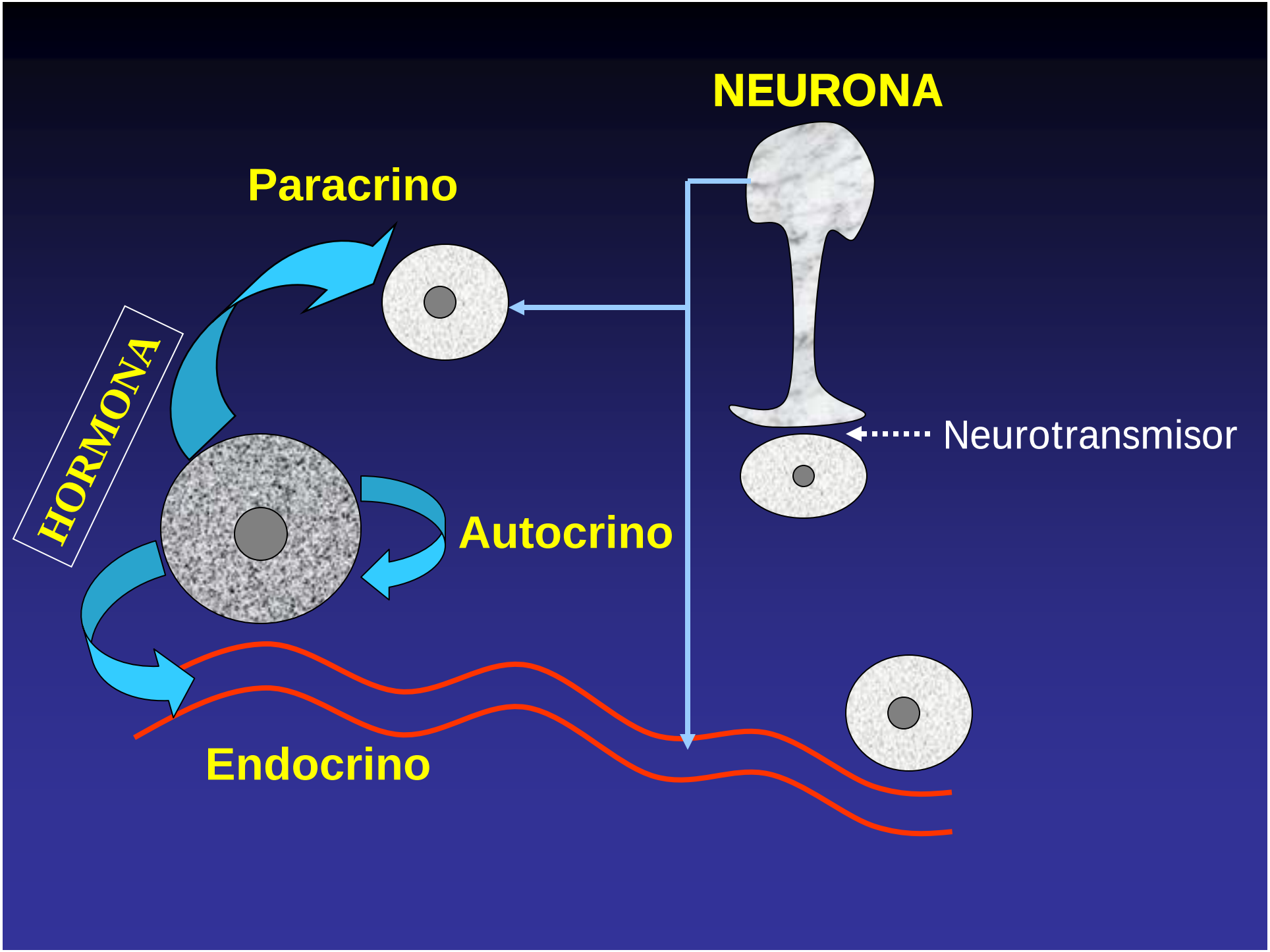

1 Adenylate cyclase 4.6.1.1
2 cNMP phospho-diesterase 3.1.4.17
3 Protein kinase 2.7.1.37
Hormones:
Thyrotropin TSH
Corticotropin ACTH
Lutropin LH
Follitropin FSH
Epinephrine
Parathyrin
Vasopressin
Glucagon
Calcitonin
H
Gs-Protein
Gi-Protein
H
Caffeine
ATP
1
cAMP
H2O
2
AMP
5'
3'
3', 5'-cAMP
Binding site for cAMP
4 cAMP
R
R
3
C
C
Inactive protein kinase A
R = regulatory subunit
C = catalytic subunit
cAMP
cAMP
cAMP
cAMP
2
C
Active protein kinase A
3
ATP
ADP
Effect
A. Metabolism and function of cAMP
H
Extracellular Ca2⊕
4 Ca2⊕ +
Calmodulin
Calmodulin- 4 Ca2⊕
Ca2⊕ in intracellular storage
Enzyme inactive
Enzyme active
Effect
4 Ca2⊕-Calmodulin
cAMP
3. Role of Ca2⊕

Integración neuro-endocrina

Los sistemas nervioso y endocrino son los mediadores principales de la adaptación fisiológica al estrés

Hay tres tipos de interacción neuroendocrina

- Regulación hipotalámica de la hipófisis
- Respuesta combinada neuro-endocrina a estímulos
- Control neural de la secreción endocrina


NEURONA
Paracrino
HORMONA
Neurotransmisor
Autocrino
Endocrino

Funciones del sistema endocrino

- Mantenimiento del Medio Interno
- Producción de energía, utilización y almacenamiento
- Respuesta a situaciones de estrés
- Crecimiento y Desarrollo
- Reproducción sexual

  Gametogénesis - Coito - Fertilización
  Sustento fetal y del recién nacido

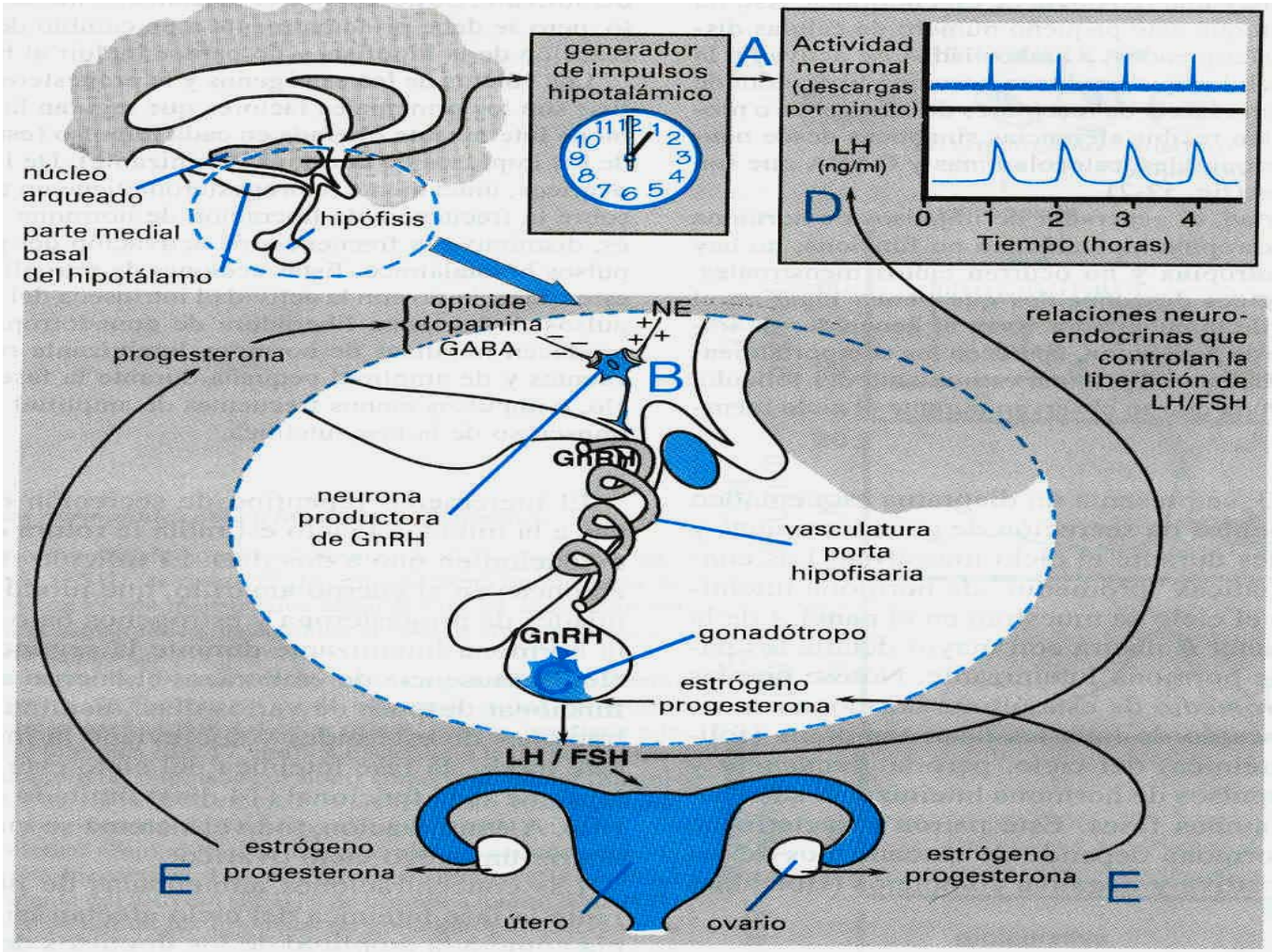
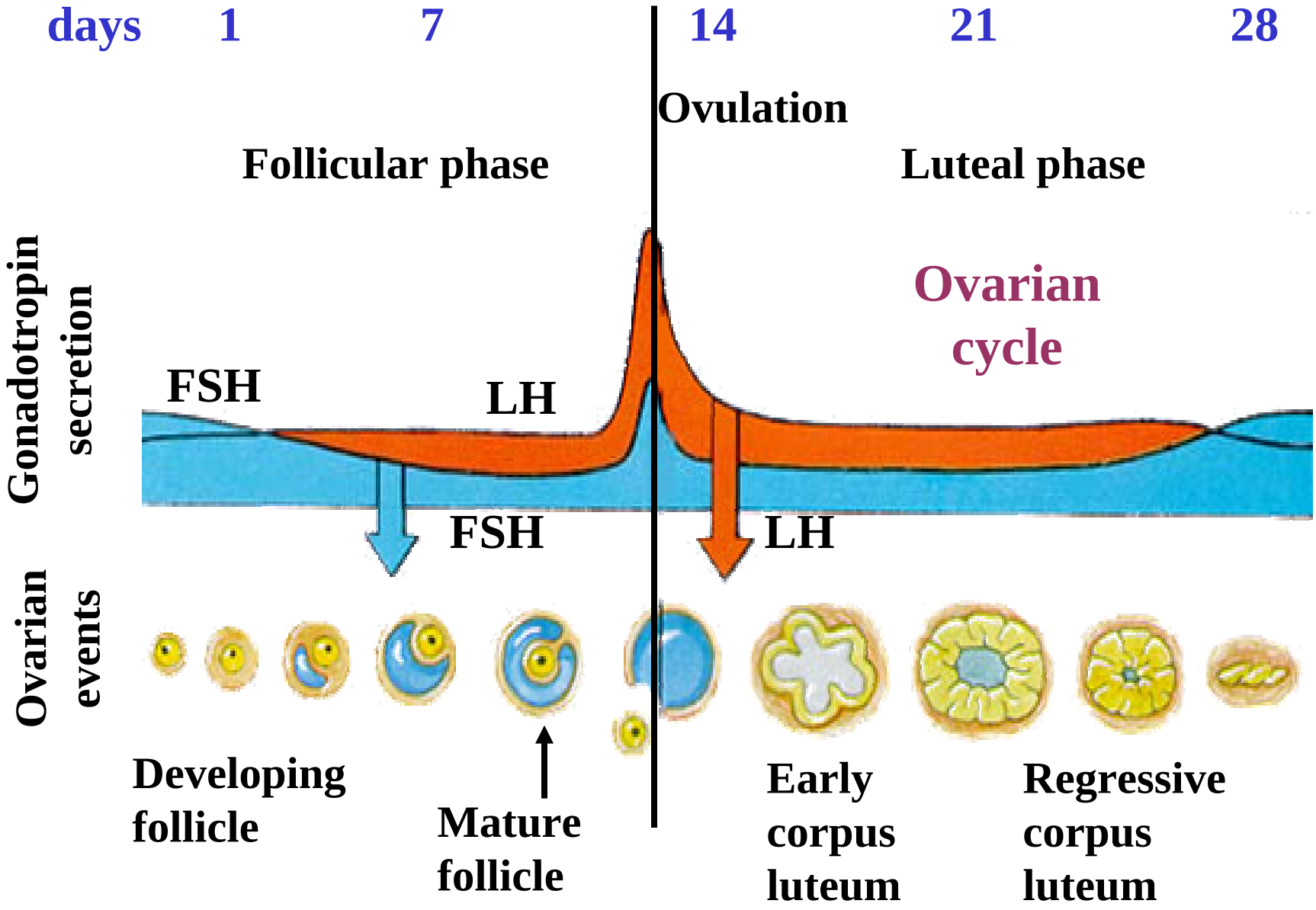
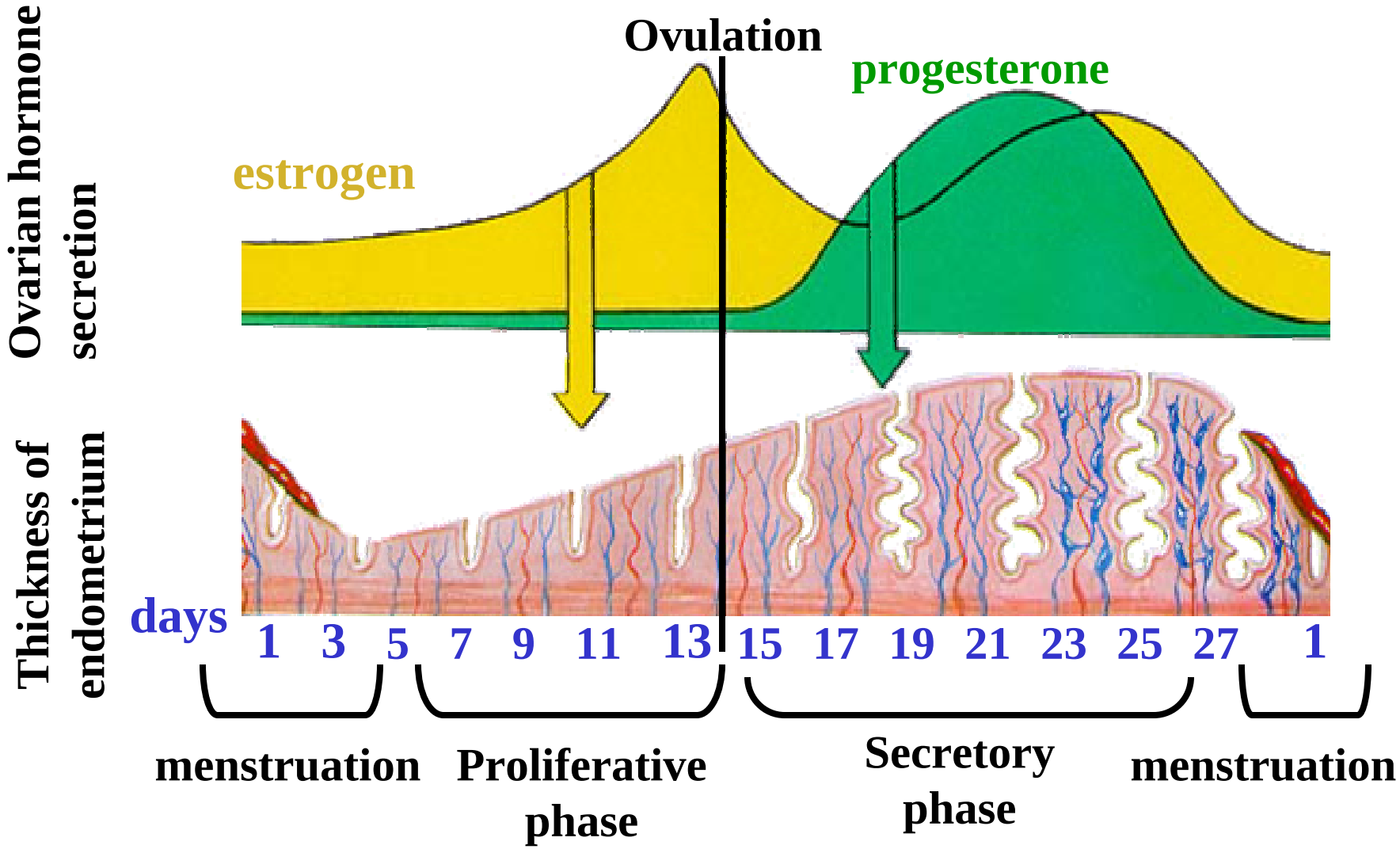


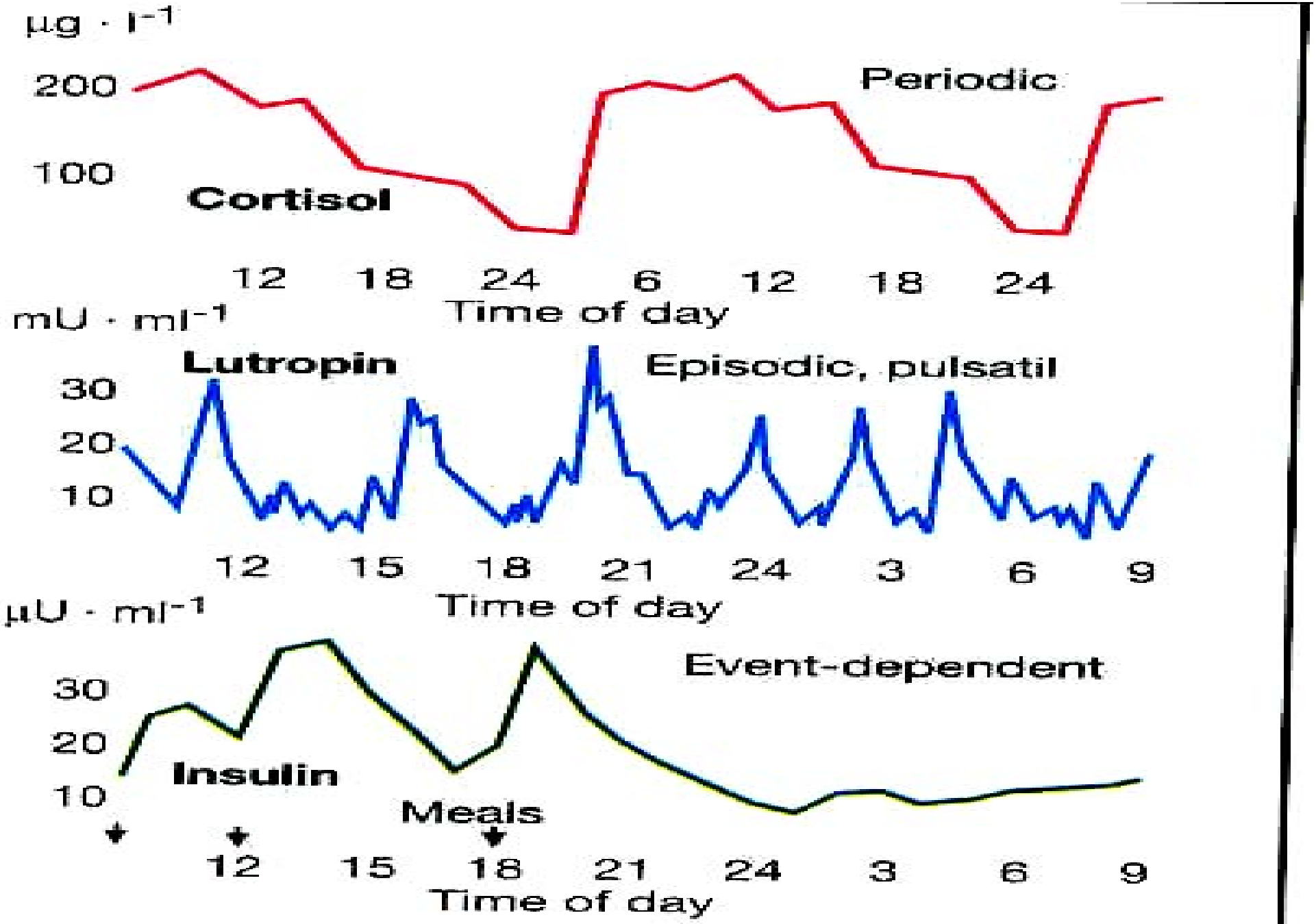
Fig. 57-2. Control neuroendocrino de la secreción de gonadotropina en mujeres.

El generador de impulsos hipotalámico localizado en el núcleo arqueado del hipotálamo funciona como un "reloj" neuronal que se activa a intervalos regulares cada hora **(A)**. Esto da por resultado liberación periódica de hormona liberadora de gonadotropina (GnRH) a partir de neuronas que contienen dicha hormona, hacia la vasculatura porta hipotalámica-hipofisaria **(B)**. Las neuronas que contienen hormona liberadora de gonadotropina **(B)** reciben impulsos aferentes inhibidores provenientes de neuronas productoras de opioides, dopamina y ácido γ-aminobutírico (GABA), y estímulos aferentes estimulantes desde neuronas noradrenérgicas. Los impulsos de hormona liberadora de gonadotropina desencadenan la liberación intermitente de hormonas luteinizante (LH) y estimulante del folículo (FSH) a partir de gonadótropos hipofisarios **(C)**, lo cual origina un comportamiento plasmático pulsátil **(D)**. La hormona estimulante del folículo y la hormona luteinizante regulan la producción ovárica de estrógenos y progesterona, que ejercen controles de retroalimentación **(E)** (véanse más detalles en el texto y en la fig. 57-3).

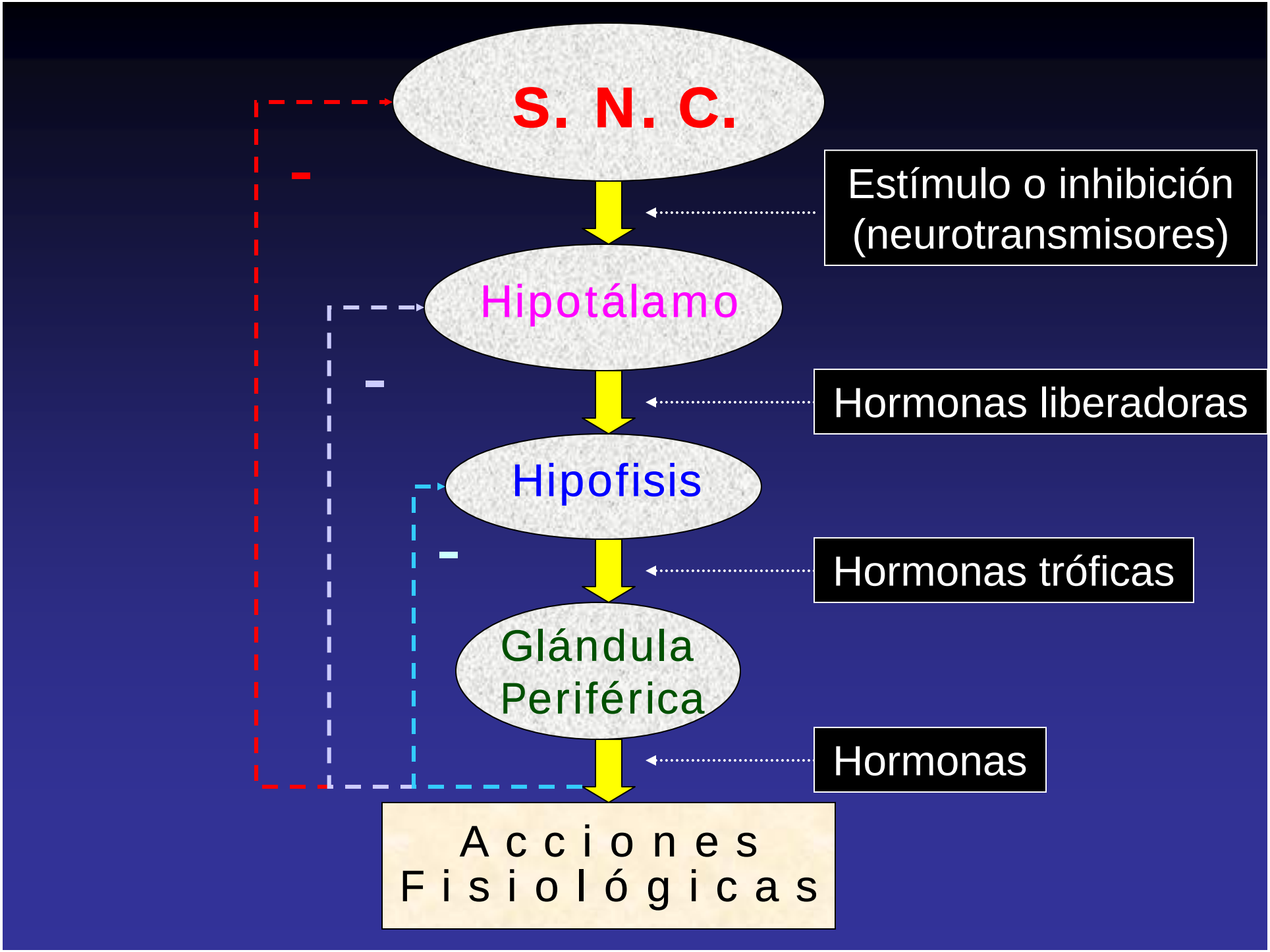

days
1
7
14
21
28
Ovulation
Follicular phase
Luteal phase
Gonadotropin secretion
Ovarian cycle
FSH
LH
FSH
LH
Ovarian events
Developing follicle
Mature follicle
Early corpus luteum
Regressive corpus luteum

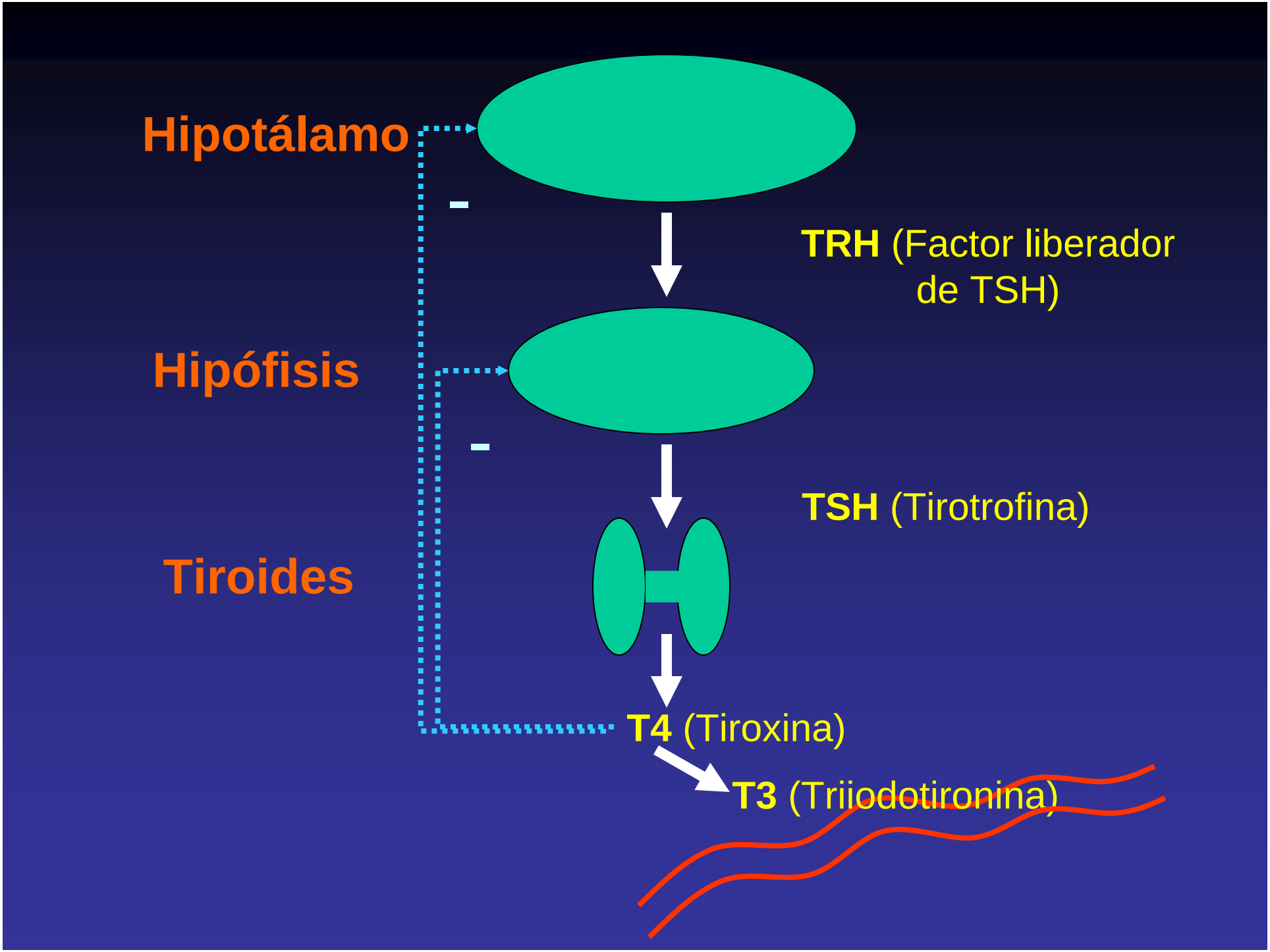
Menstrual Cycle

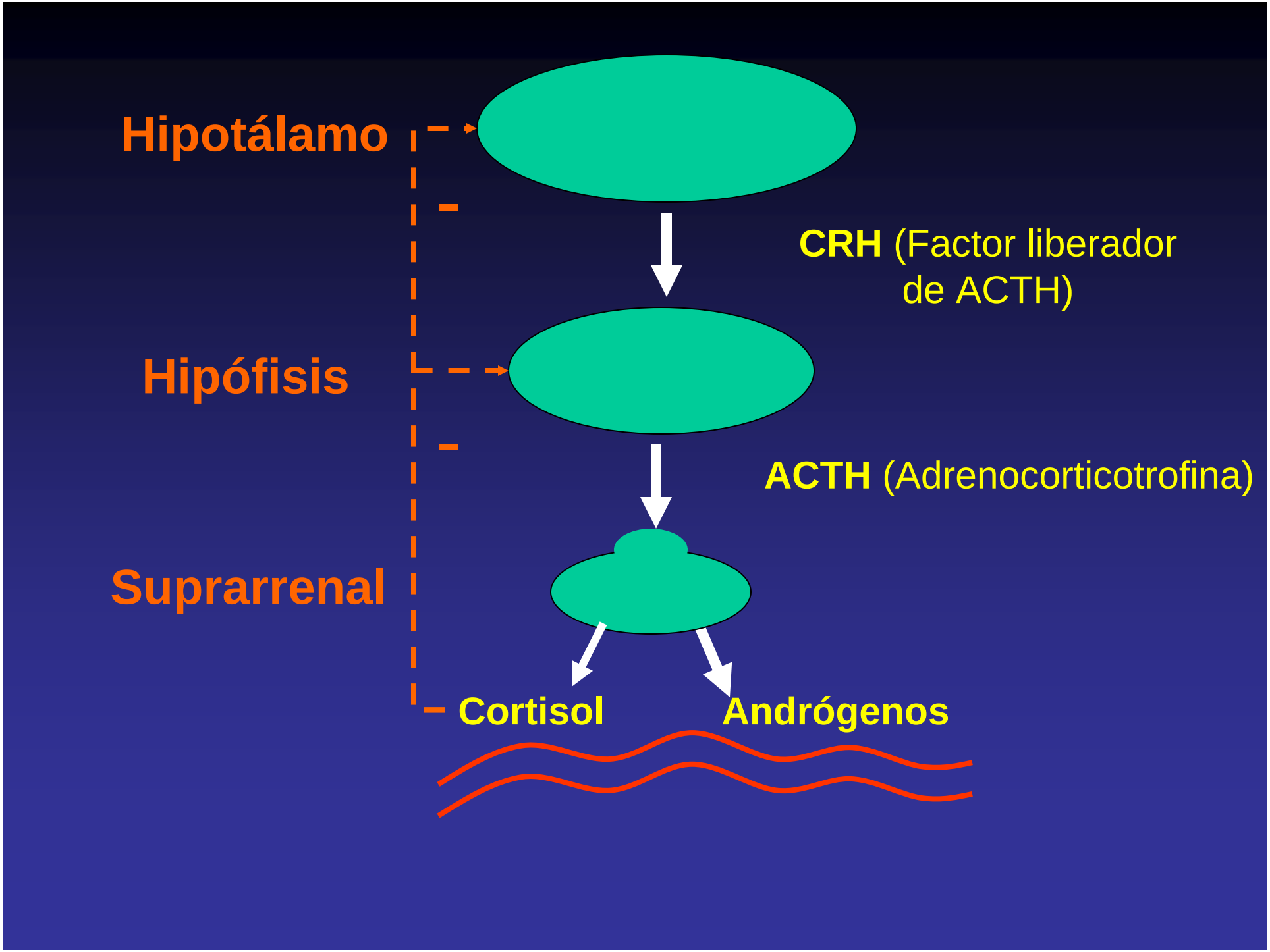


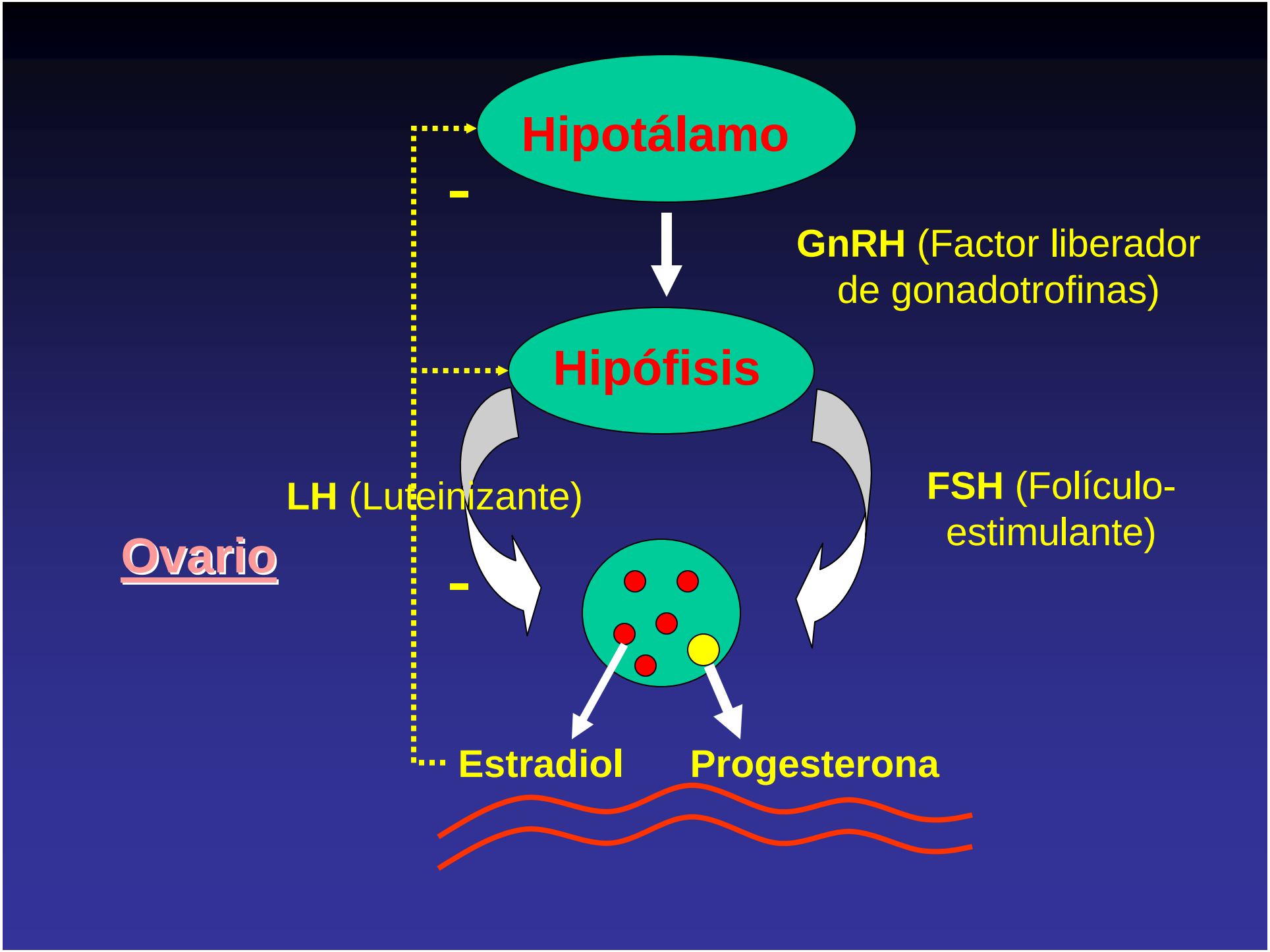


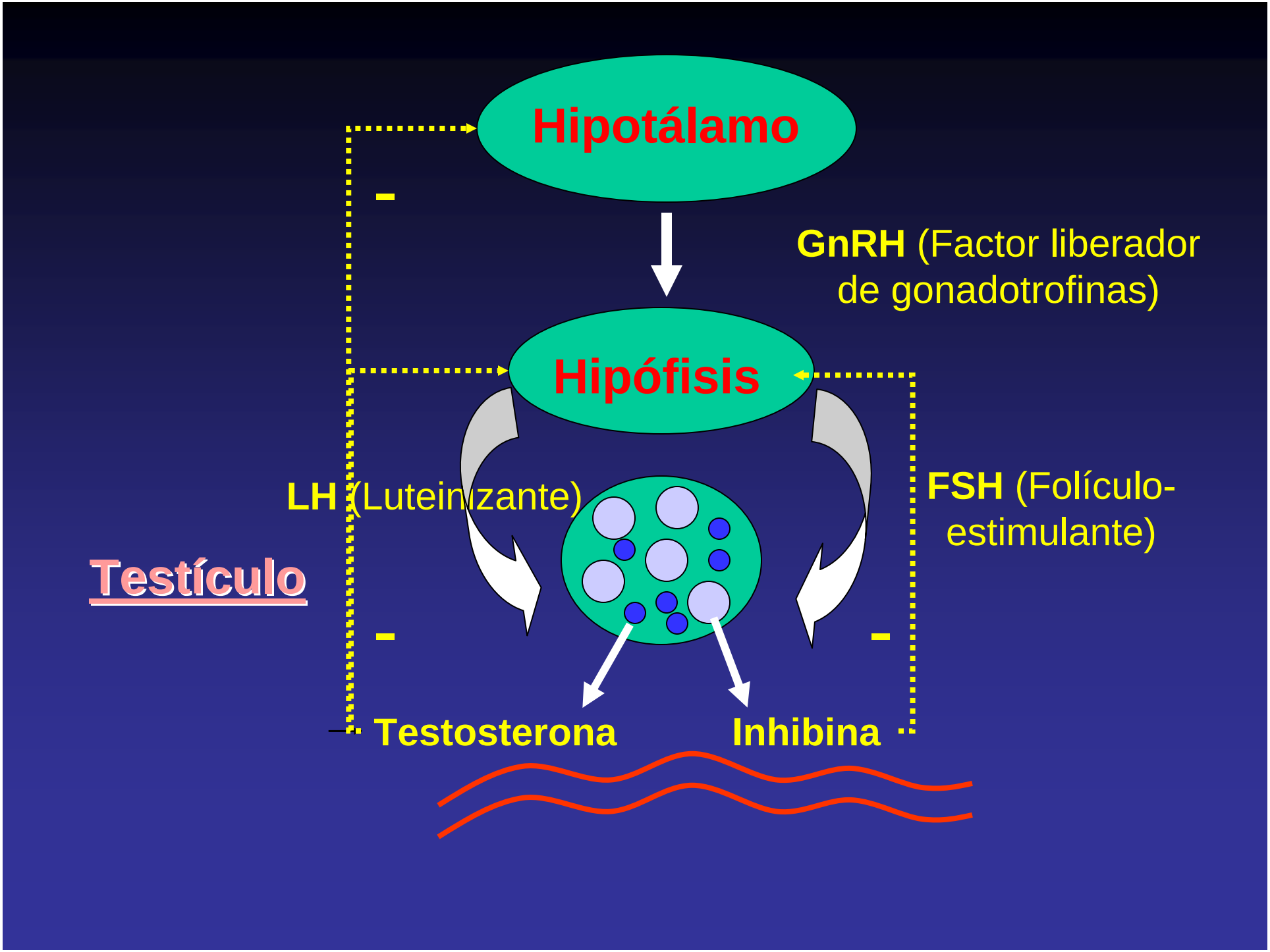
3. Plasma level dynamics


S. N. C.
Estímulo o inhibición (neurotransmisores)
Hipotálamo
Hormonas liberadoras
Hipofisis
Hormonas tróficas
Glándula Periférica
Hormonas
Acciones Fisiológicas

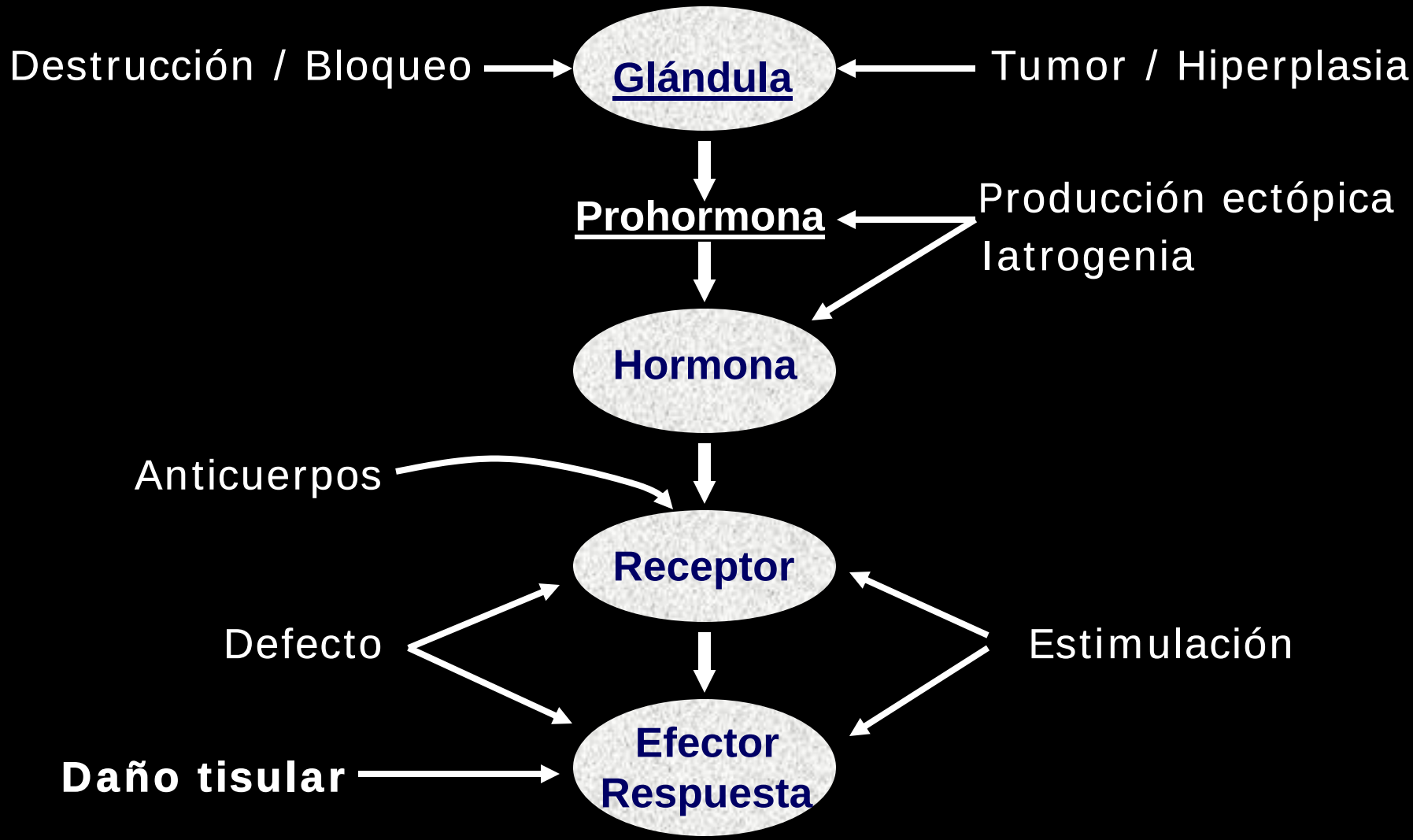

Hipotálamo
-
TRH (Factor liberador de TSH)
Hipófisis
-
TSH (Tirotrofina)
Tiroides
T4 (Tiroxina)
T3 (Triiodotironina)


Hipotálamo
CRH (Factor liberador de ACTH)
Hipófisis
ACTH (Adrenocorticotrofina)
Suprarrenal
Cortisol
Andrógenos

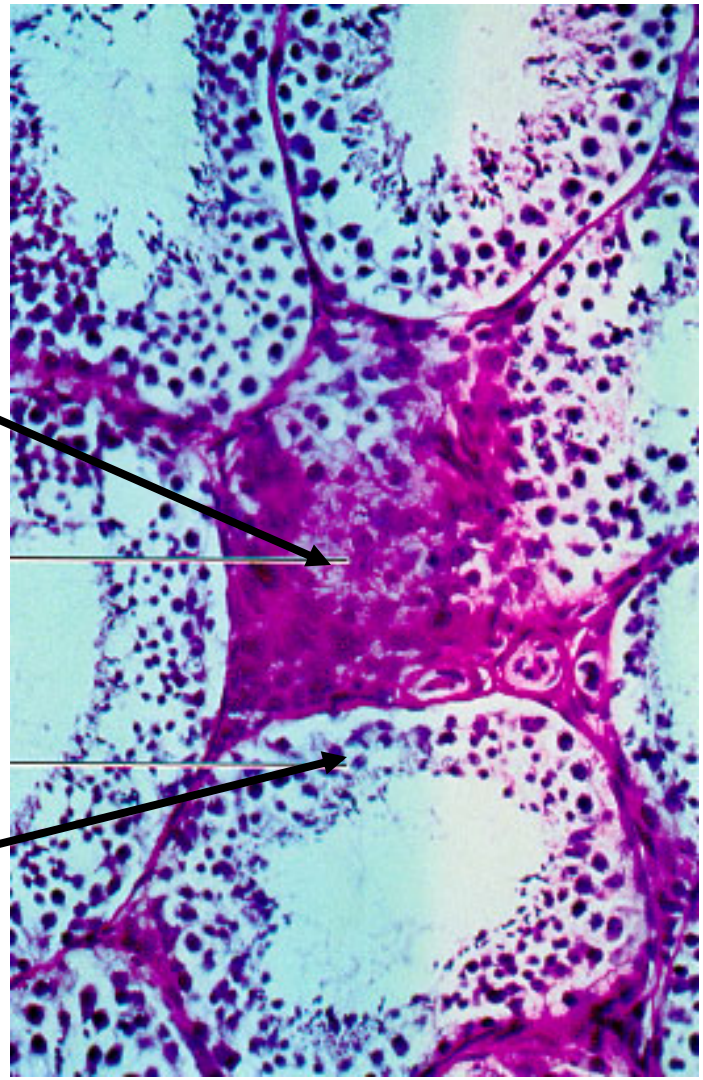

Hipotálamo
-
GnRH (Factor liberador de gonadotrofinas)
Hipófisis
LH (Luteinizante)
FSH (Folículo-estimulante)
Ovario
-
Estradiol
Progesterona


Hipotálamo
GnRH (Factor liberador de gonadotrofinas)
Hipófisis
LH (Luteinizante)
FSH (Folículo-estimulante)
Testículo
Testosterona
Inhibina

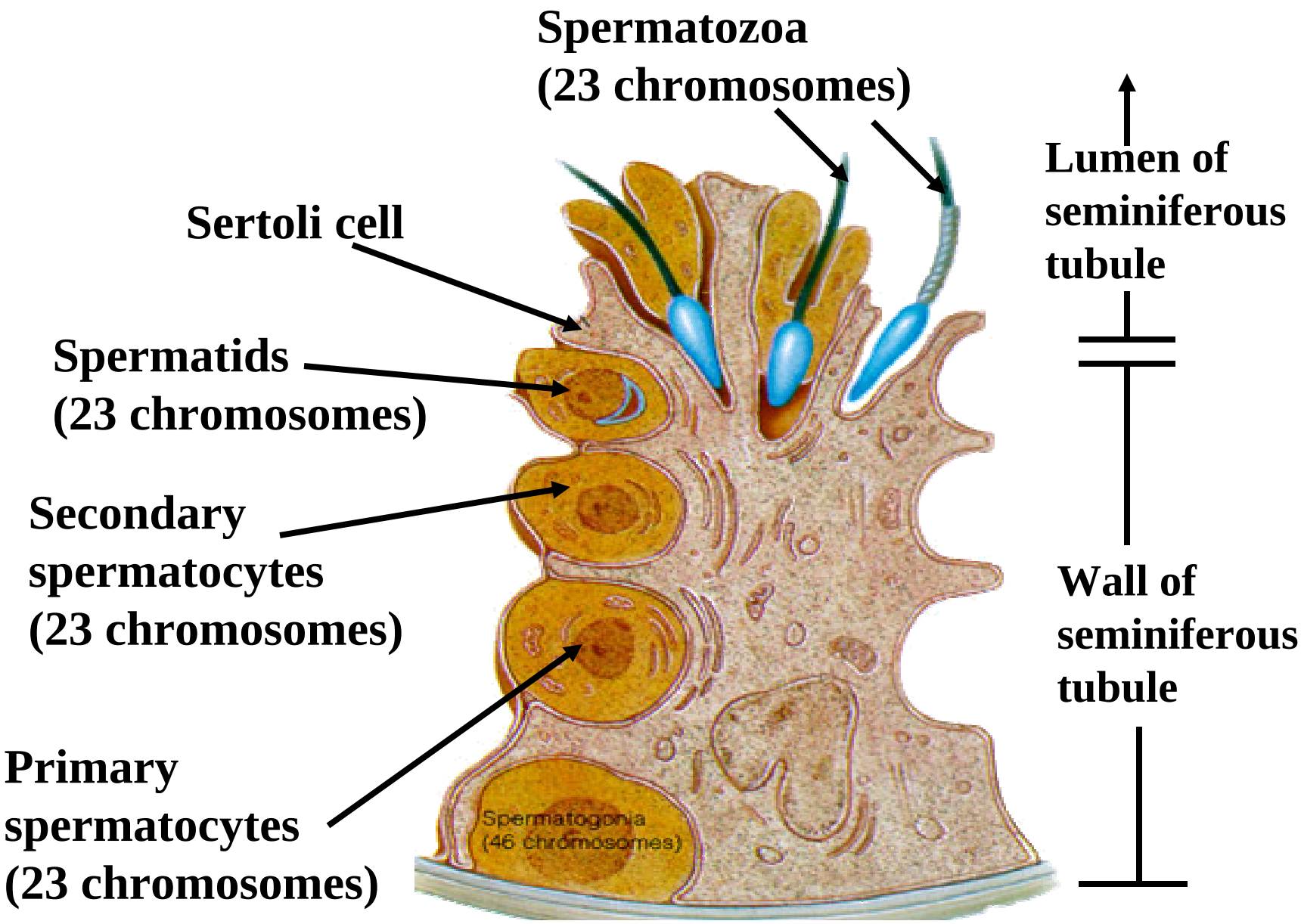
Causas de hipo e hiper función del sistema endocrino

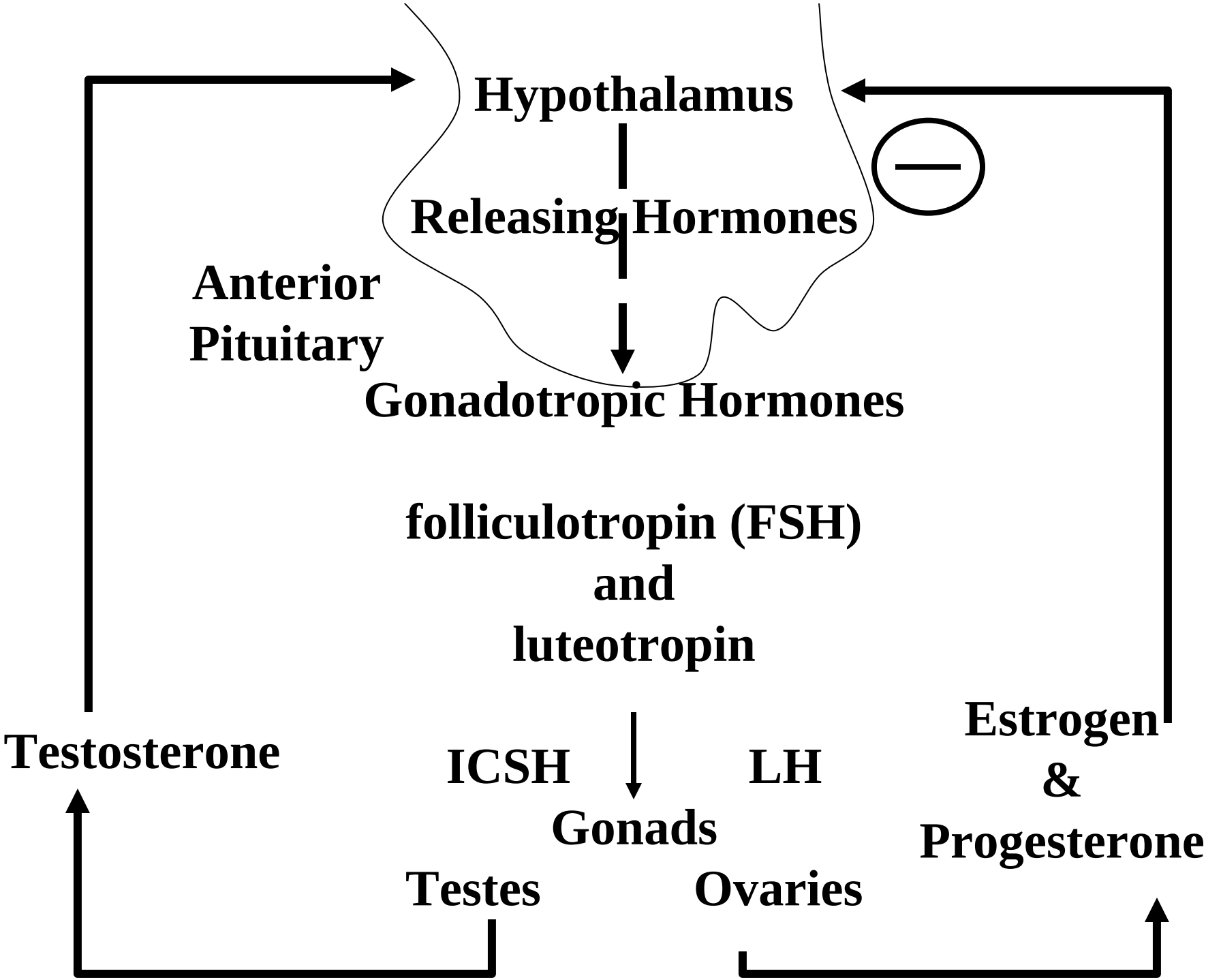


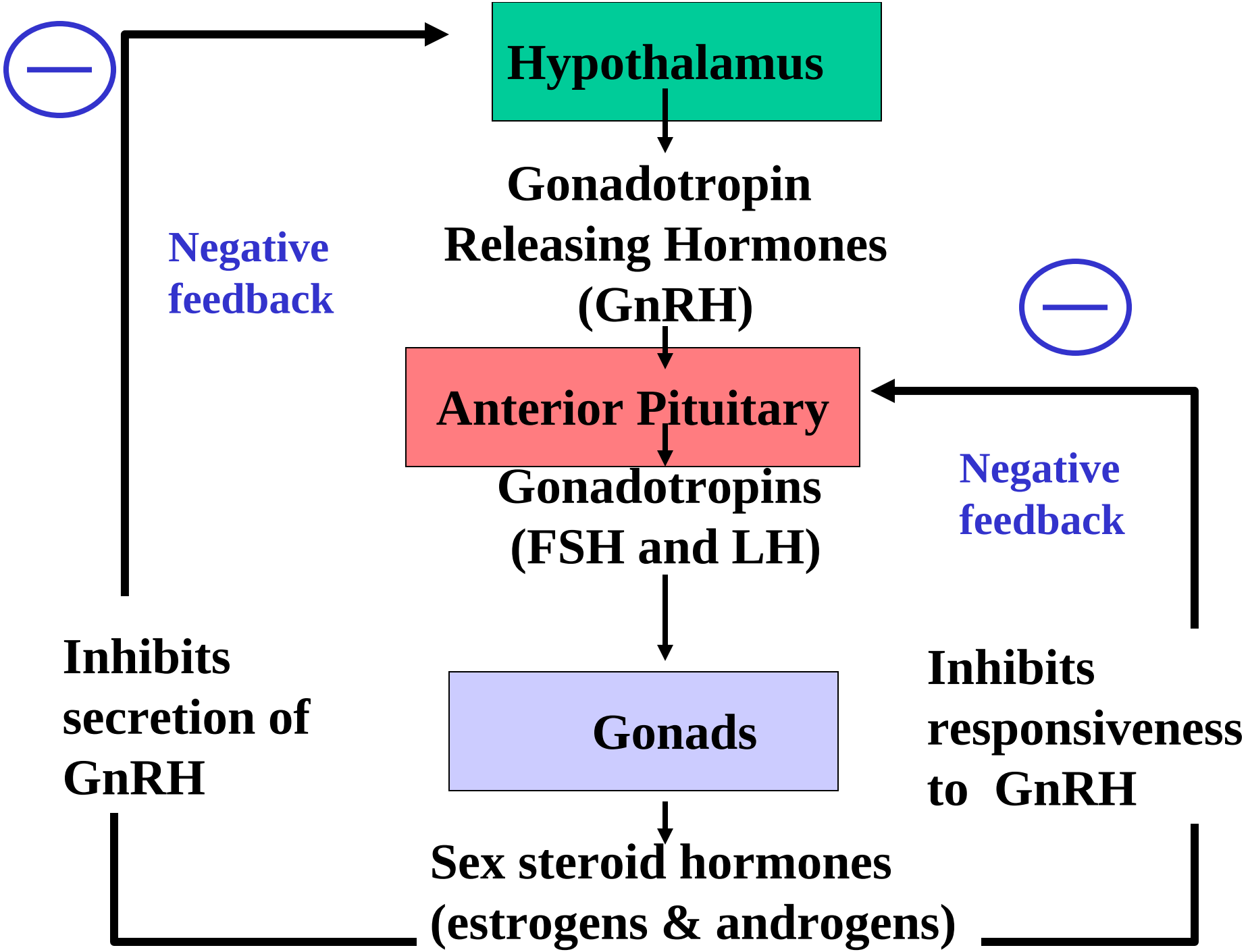
Interstitial tissue with Leydig cells



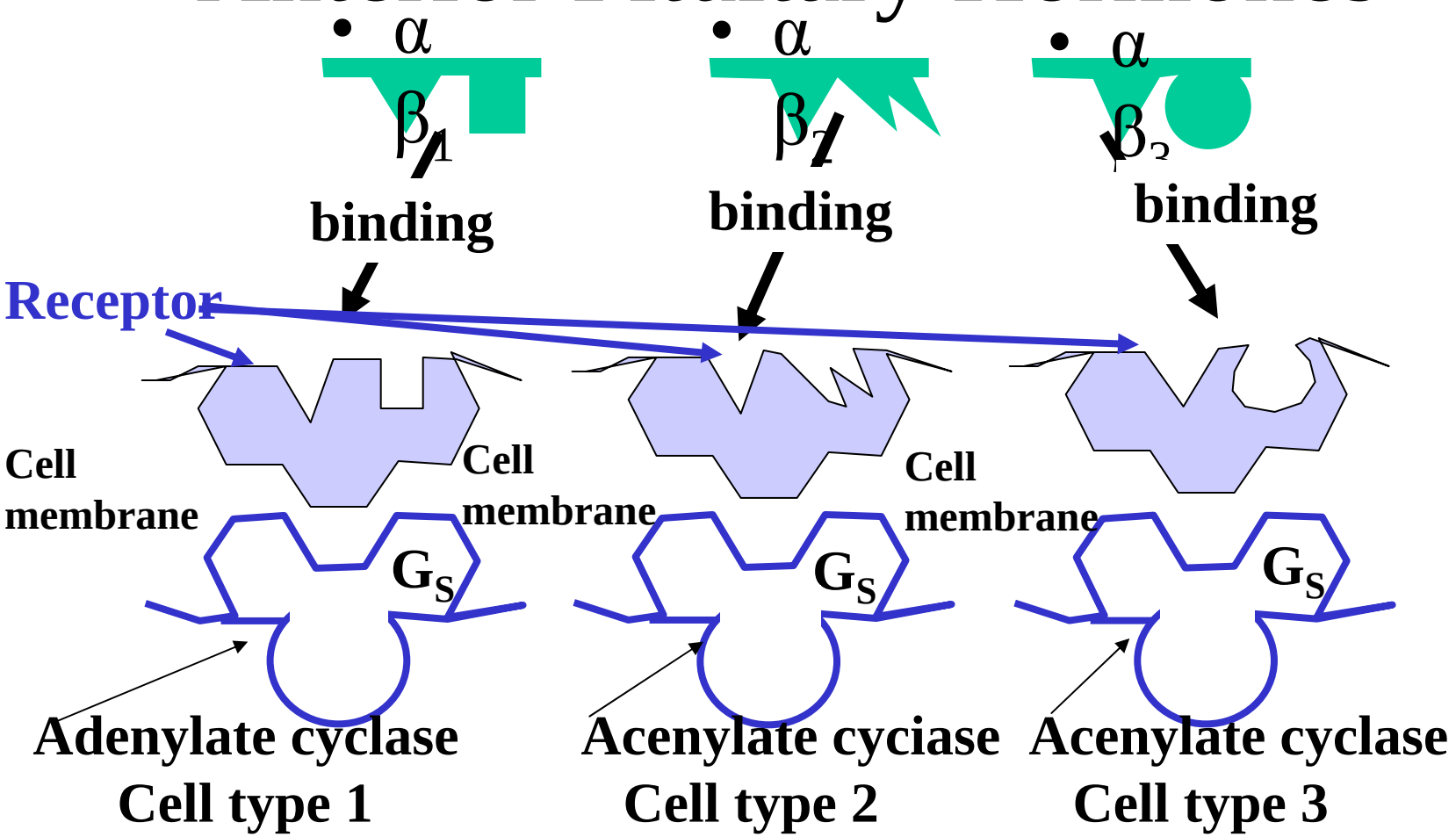
Seminiferous tubule


Spermatozoa
(23 chromosomes)
Lumen of seminiferous tubule
Sertoli cell
Spermatids
(23 chromosomes)
Secondary spermatocytes
(23 chromosomes)
Primary spermatocytes
(23 chromosomes)
Wall of seminiferous tubule
Spermatogonia
(46 chromosomes)


Hypothalamus
Releasing Hormones
Anterior Pituitary
Gonadotropic Hormones
folliculotropin (FSH) and luteotropin
Testosterone
ICSH
LH
Gonads
Estrogen & Progesterone
Testes
Ovaries


Hypothalamus
Gonadotropin Releasing Hormones (GnRH)
Anterior Pituitary
Gonadotropins (FSH and LH)
Gonads
Sex steroid hormones (estrogens & androgens)
Negative feedback
Inhibits secretion of GnRH
Negative feedback
Inhibits responsiveness to GnRH

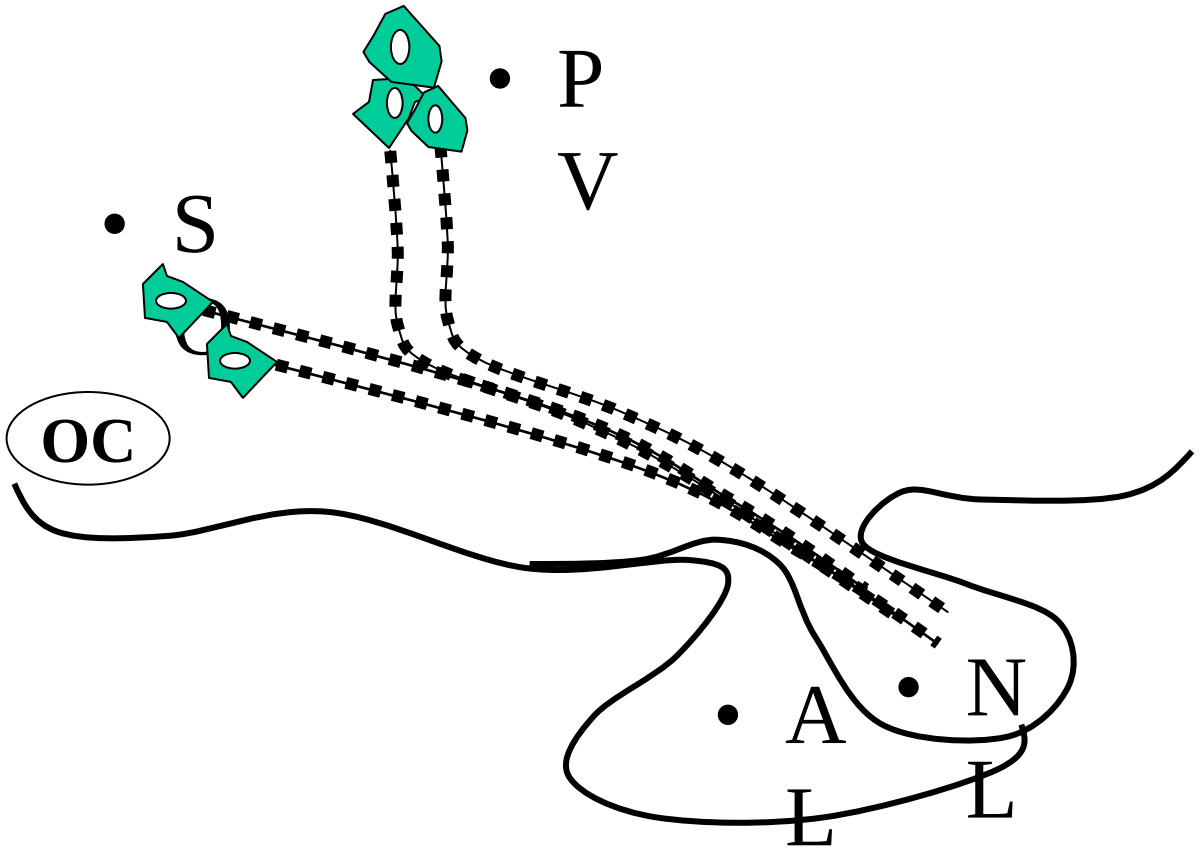
Anterior Pituitary Hormones

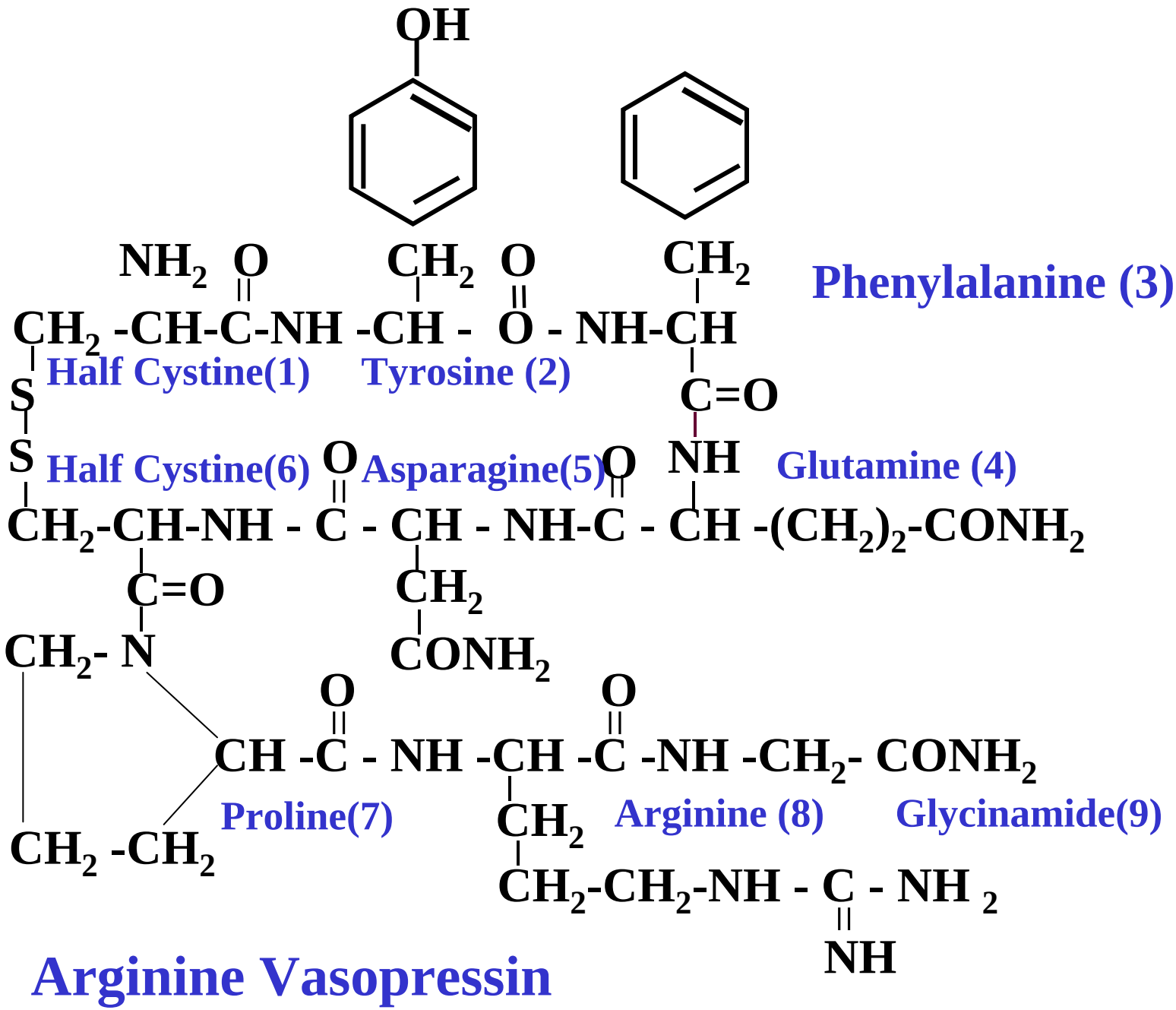


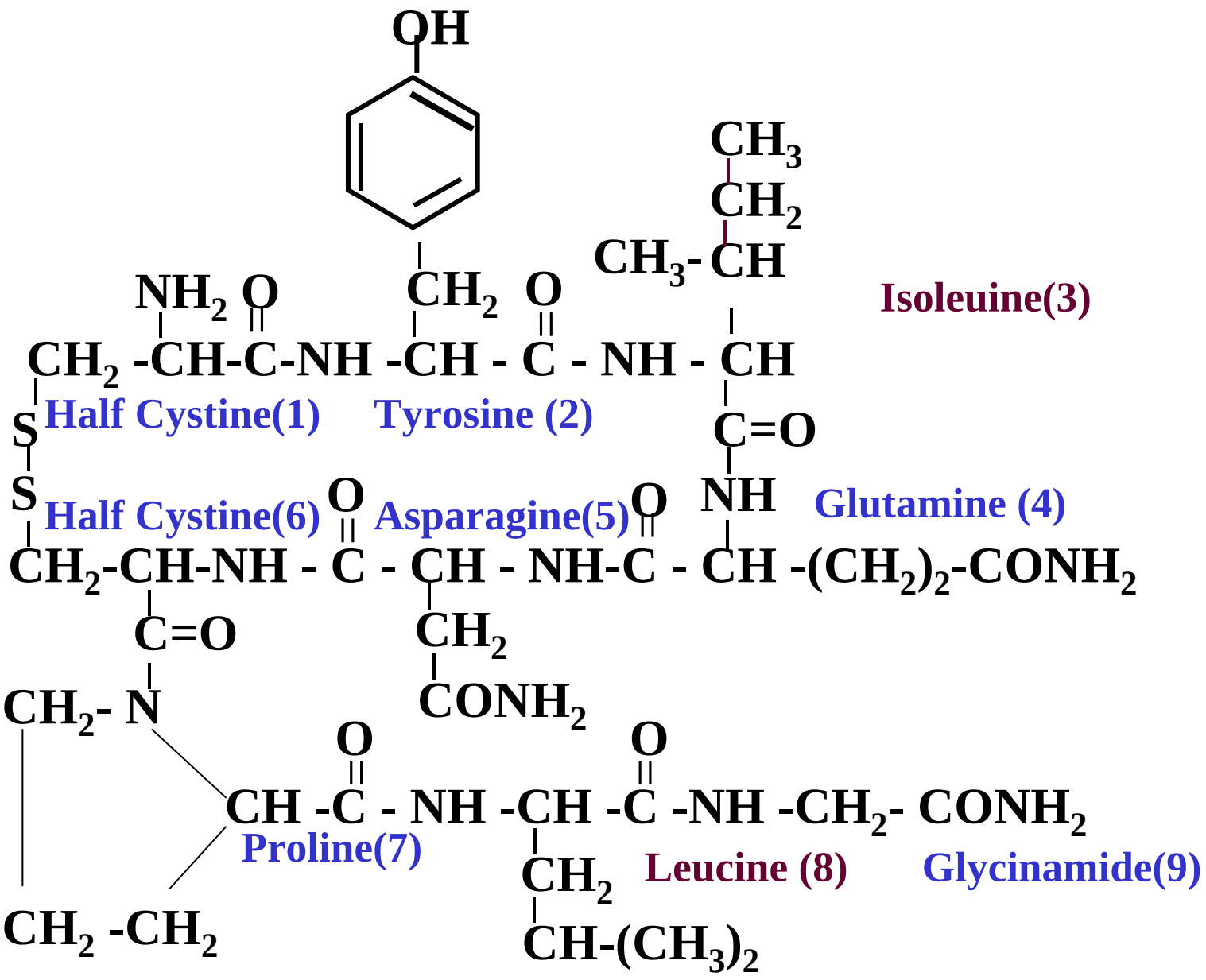
How anterior pituitary hormones that share a similar subunit (TSH,FSH, LH) specify receptors on different cell types.

Neurohypophysis

The hormones (ADH & Oxytocin) are nonapeptides (9AA). They are produced in the hypothalamus & transported down axon tracts to the pars nervosa for storage




Phenylalanine (3)
Half Cystine(1)
Tyrosine (2)
Half Cystine(6)
Asparagine(5)
Glutamine (4)
Proline(7)
Arginine (8)
Glycinamide(9)
Arginine Vasopressin


OH
CH3
CH2
CH3- CH
Isoleuine(3)
NH2 O
CH2 O
CH2 -CH-C-NH -CH - C - NH - CH
Half Cystine(1)
Tyrosine (2)
C=O
S
S
Half Cystine(6)
O
Asparagine(5)
O
NH
Glutamine (4)
CH2-CH-NH - C - CH - NH-C - CH -(CH2)2-CONH2
C=O
CH2
CH2- N
CONH2
O
O
CH -C - NH -CH -C -NH -CH2- CONH2
Proline(7)
CH2
Leucine (8)
Glycinamide(9)
CH2 -CH2
CH-(CH3)2

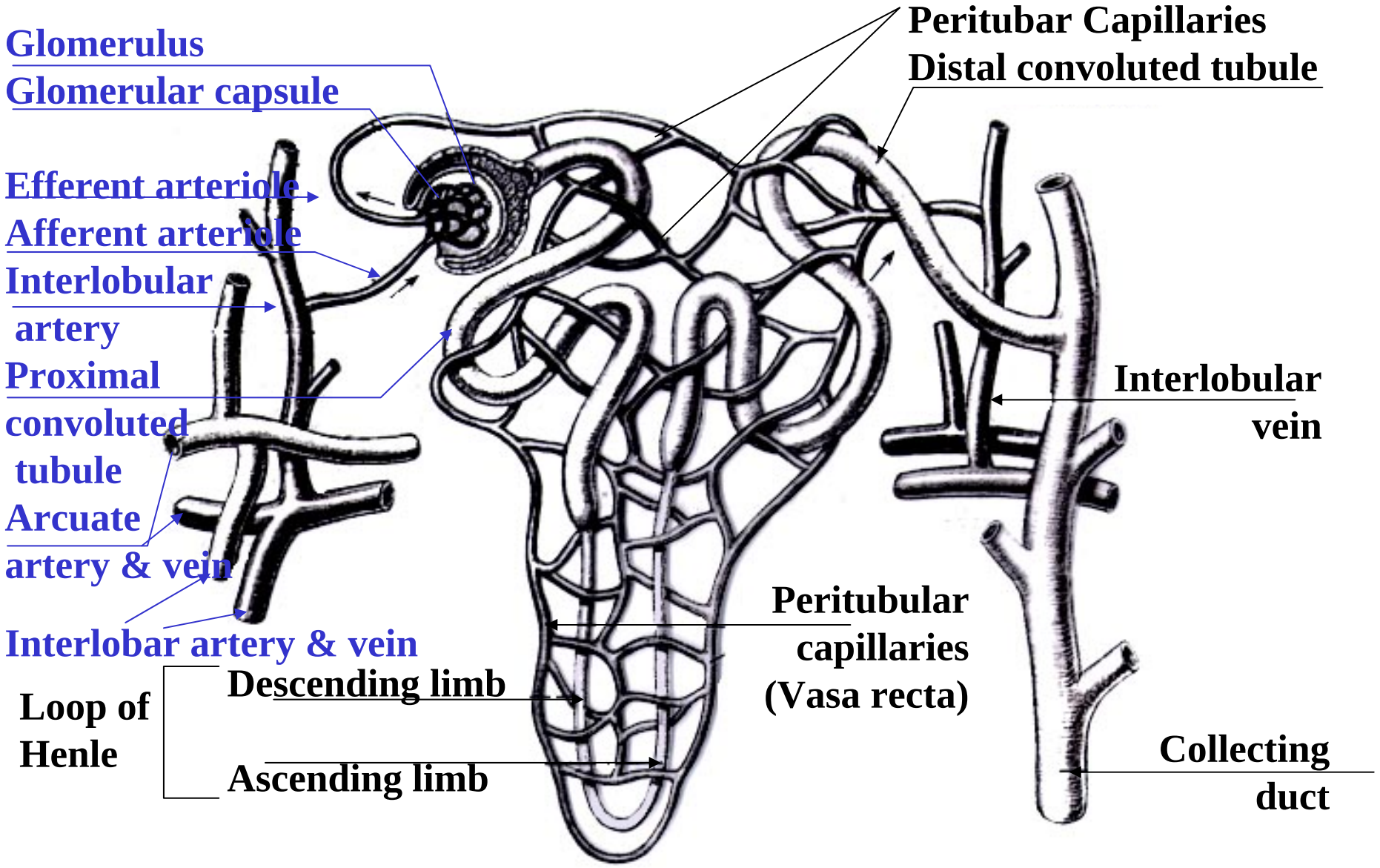
Oxytocin

Antidiuretic Hormone (ADH) Vasopressin

- Chemistry: Produced by the supraoptic nuclei of hypothalamus. Circulating concentration of 1-2 picograms/ml (10^{-12} gms); half-life of 18 minutes.
- Biologic Actions:
- 1. H_2O reabsorption by distal tubule and collecting ducts of the kidneys.
- 2. Vasopressor effect: ↑blood pressure.

Antiduretic Hormone (ADH) Vasopressin

- Mechanisms of Action:
- cAMP in kidney tubules.
- ↑ pore size; ↑ permeability.
- Mechanisms of Release :
- Osmoreceptors



The Nephron Tubule and Its Associated Blood Vessels

Stimuli Affecting ADH Release

- Increase Release
- 1. ↑ effective osmotic pressure of plasma
- 2. ↓ extracellular fluid volume
- 3. Pain, emotion, "stress", exercise
- 4. Morphine, nicotine, barbiturates

- Decrease Release
- 1. ↓ effective osmotic pressure of plasma
- 2. ↑ extracellular fluid volume
- 3. Alcohol-vasodilation of afferent arteriole & ↓ permeability of collecting tubule

Stimuli Affecting ADH Release

- Deficiency Effect:
- Diabetes Insipidus

- Oxytocin

- Biologic Actions
- 1. Uterine Contractility
- a) Parturition
- b) Female orgasm
- 2. Milk Ejection

Thyroid Gland

- Structure:

  The thyroid consists of two lobes lying on either side of the trachea and connected by a thin isthmus of tissue. It weights 20-30 grams, and is one of the most sensitive organs of the body. It increases in size at puberty; during pregnancy; and during prolonged stress. The lobes contain many single cell layered follicles.

Thyroid Gland

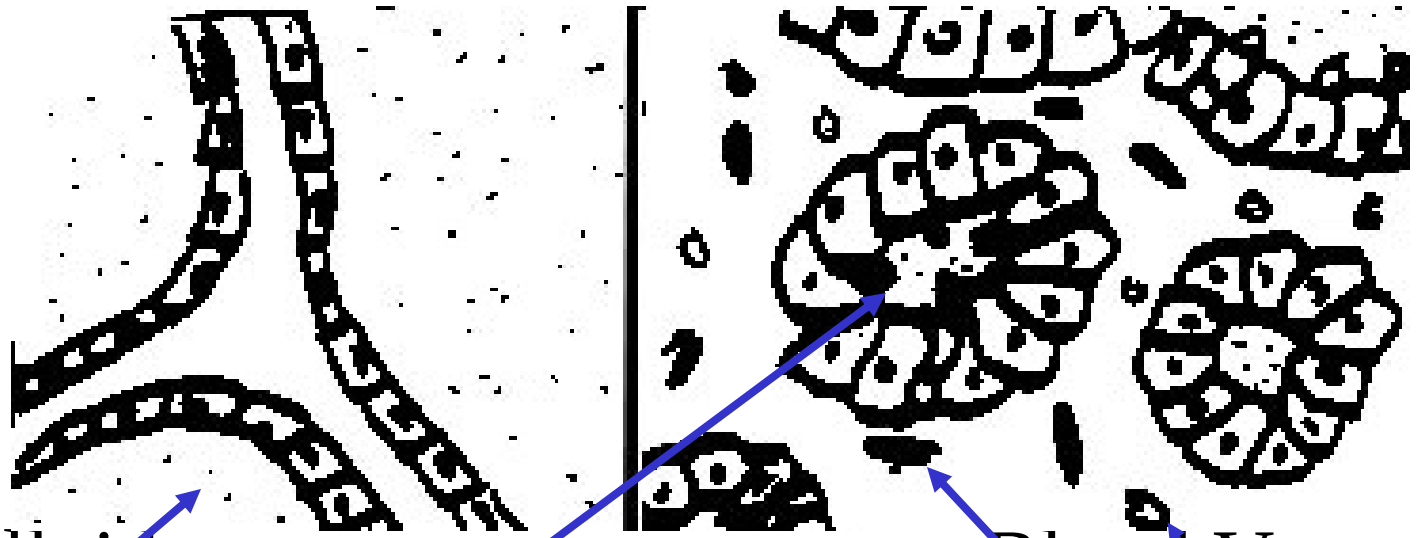
- Chemistry:
- The gland produces three hormones:
- 1) 3,5,3',5'-tetraiodothyronine T_4
- 2) 3,5,3'-triiodothyronine T_3
- 3) Calcitonin
- T_4 & T_3 are produced by follicular cells by the iodination of tyrosine. Most adults secrete about 80 ug of T_4 and 40ug of T_3 per day. The thyroxine is bound in peptide linkage to thyroglobulin for storage in the colloid. Upon stimulation, the complex is reabsorbed into the follicular cells & hydrolyzed (thyroglobulin is removed). It enters the blood where it binds with plasma binding proteins (thyroxine binding globulin TBG, or albumin).

Thyroid Gland

- Iodide trapping:
- The thyroid actively concentrates I” from the circulation by a process known as iodide pump. The ratio of iodides in the thyroid to plasma is the (T/S) ratio. These pumps can be blocked by ouabain.

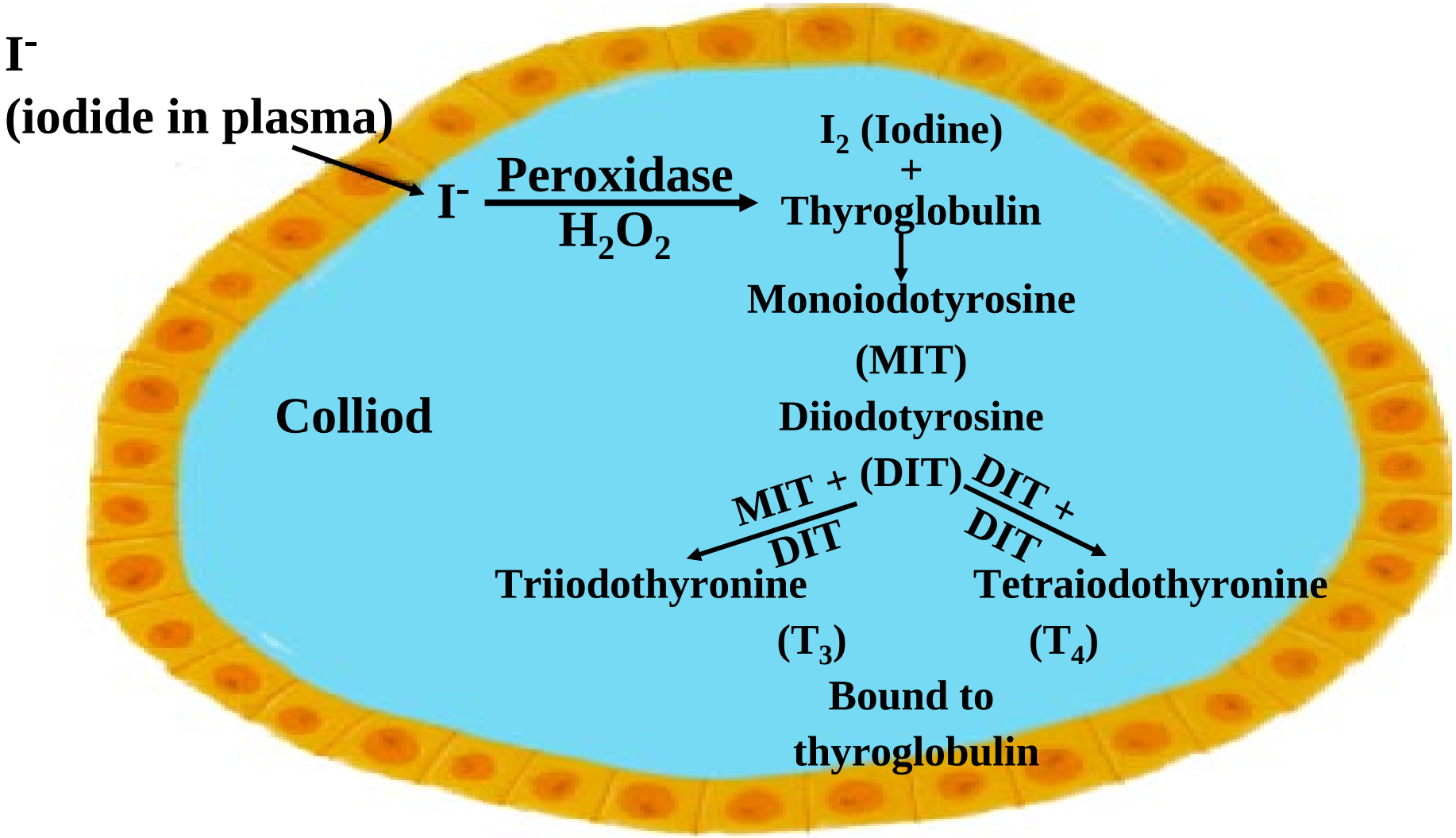
Thyroid Histology

- Inactive Active

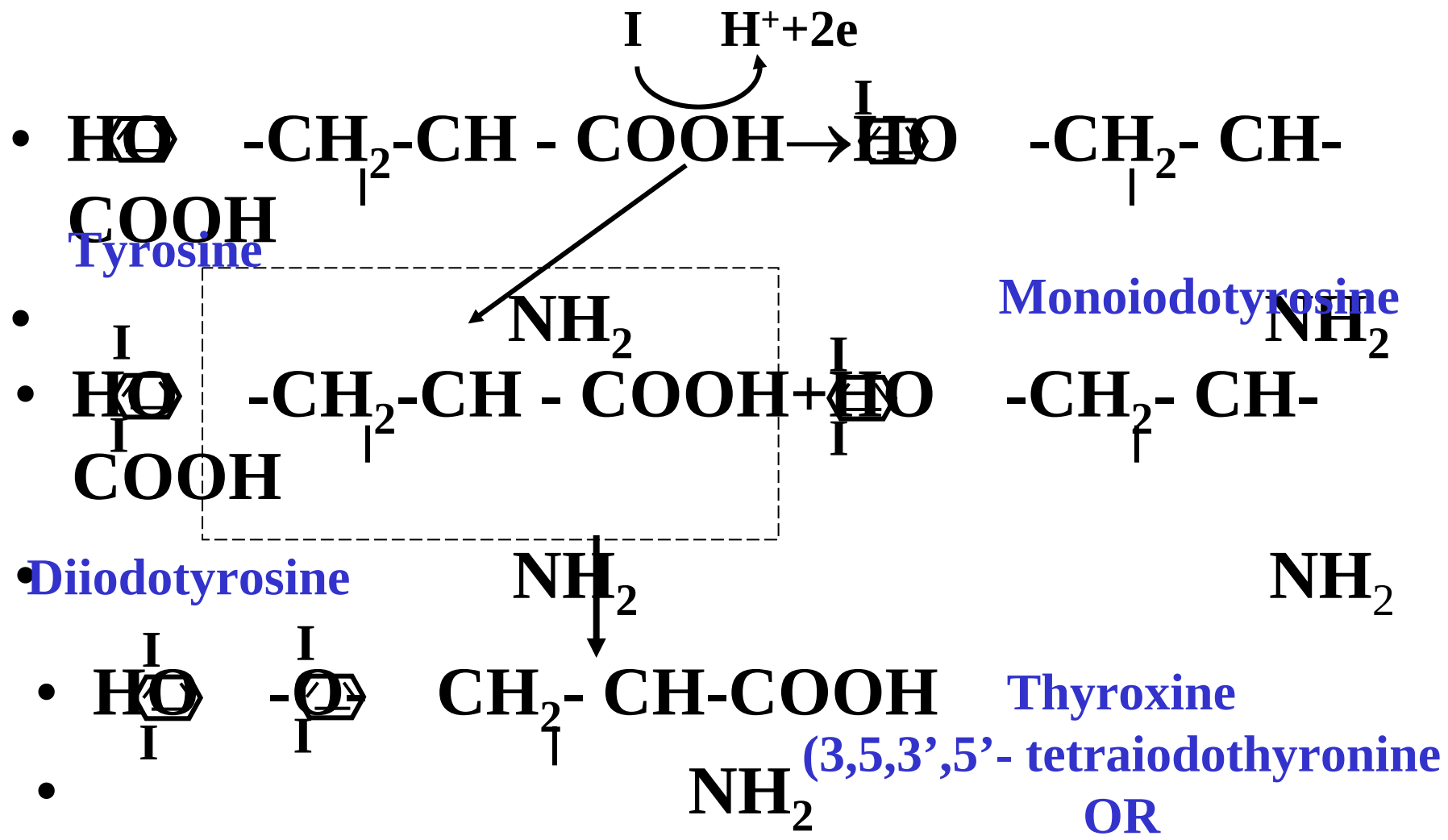


- Colloid Blood V.
- Reabsorption Parafollicular
- lacunae cells

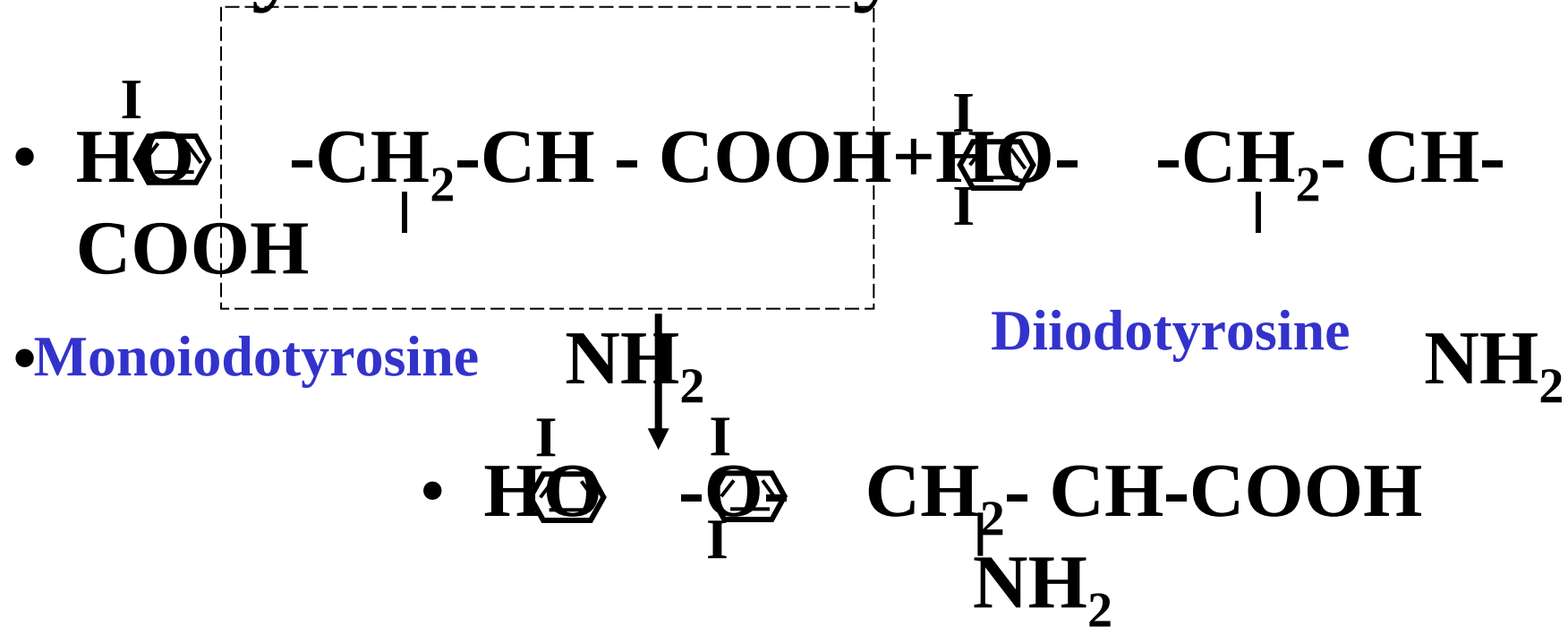
Production of Thyroid Hormones
Thyroid follicle



Biosynthesis of Thyroid Hormones



Biosynthesis of Thyroid Hormones



Biologic Actions for Thyroxine

- 1. Calorigenic (thermogenesis)
- ↑ O_2 consumption
- 2. Growth effects
- 3. Protein metabolism
- 4. Fat metabolism
- 5. Carbohydrate metabolism
- Calorigenic Effect:
- ↑ liver, kidney, skeletal muscle, cardiac muscle, gastric mucosa, and diaphragm.
  ACTH acts as a synergist to thyroxine.

Biologic Actions for Thyroxine

- No Affect:
- Brain, retina, anterior pituitary, spleen, testes, and lungs
- BMR - Basal Metabolic Rate:
- The rate of O_2 consumption at rest.
- Kcal heat produced/sq. meter body surface/hr.
  - OR
- Volume O_2 consumed/sq. meter body surface/hr.
- RQ - Respiratory Quotient:
- Molar ratio of CO_2 produced to O_2 consumed.

Thyrotropin - 2

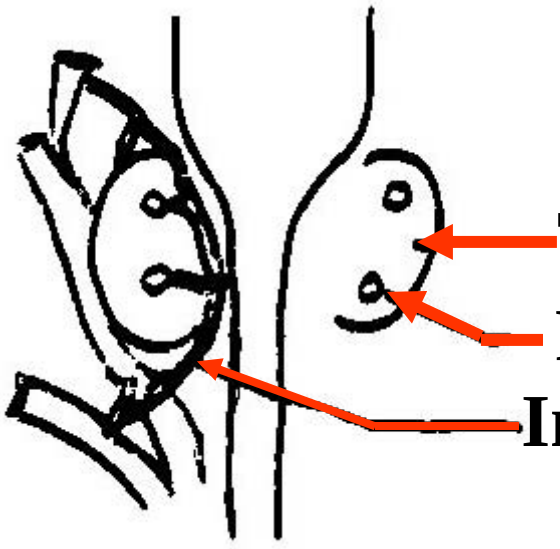
- III. Regulation of Release
  - A. Stimulation (via thyrotropin releasing hormone)
  - Negative Feedback
  - 1) ↓ thyroxine
  - 2) ↓ body temperature
  - B. Inhibition
  - 1) ↑ serum thyroxine
  - 2) ↑ body temperature

Thyrotropin - 2

- IV. Assay Methods
  - A. Bioassay
  - 1)↑height of secretory epithelium
  - 2) Number of colloid droplets in cells
  - 3) Iodine depletion in 1-day old chicks
  - 4) Uptake of radioactive iodine

  - B. Radioimmunoassay

Parathyroid Glands

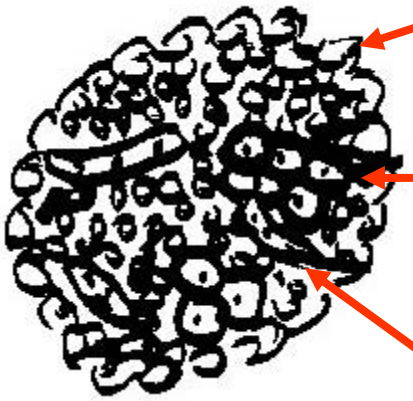


Thyroid

Paralhyroid

Inferior thyroid artery

Histology



Chief cells

Oxyphil

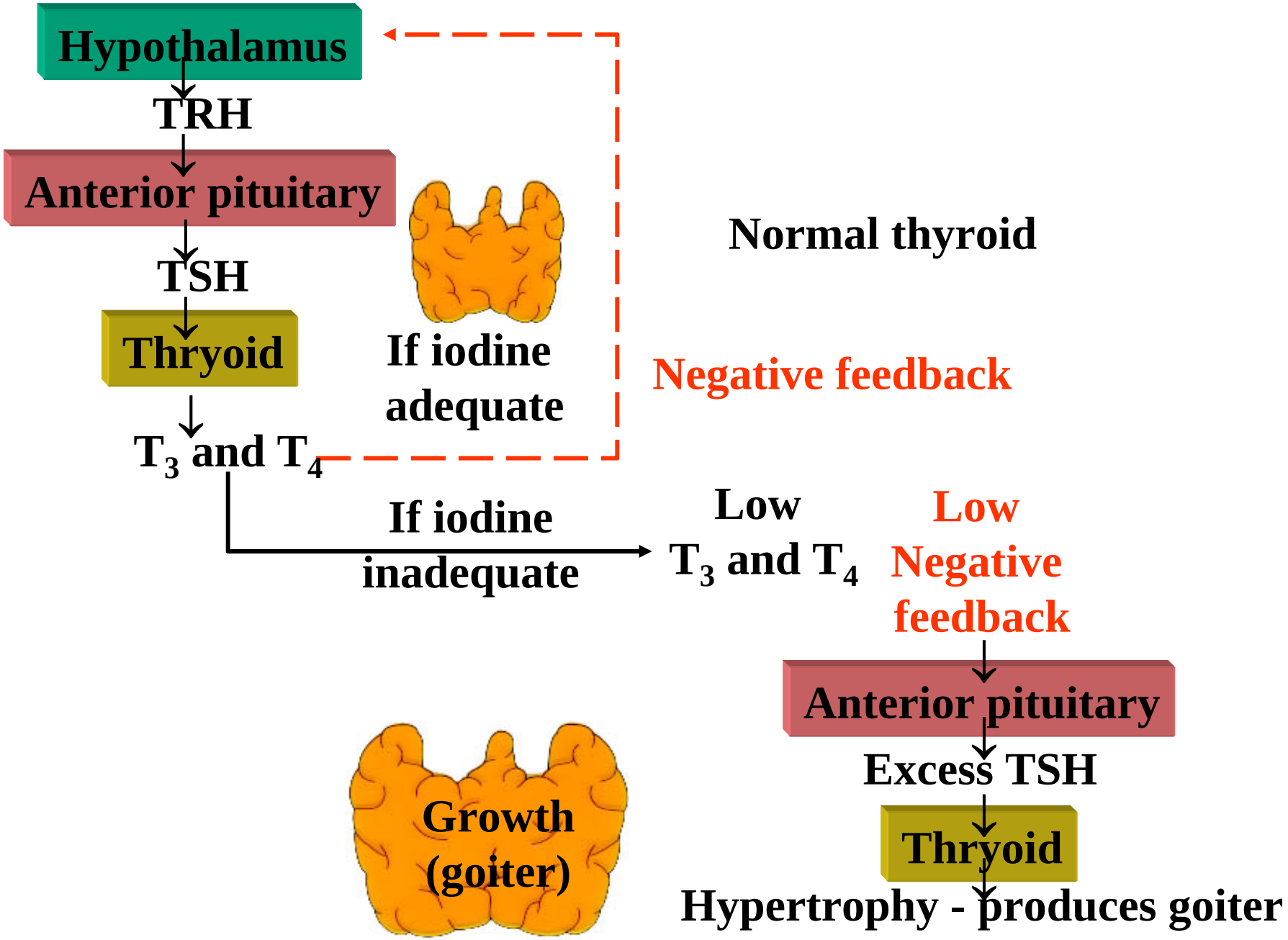
Red Blood Cells

Parathyroid Gland

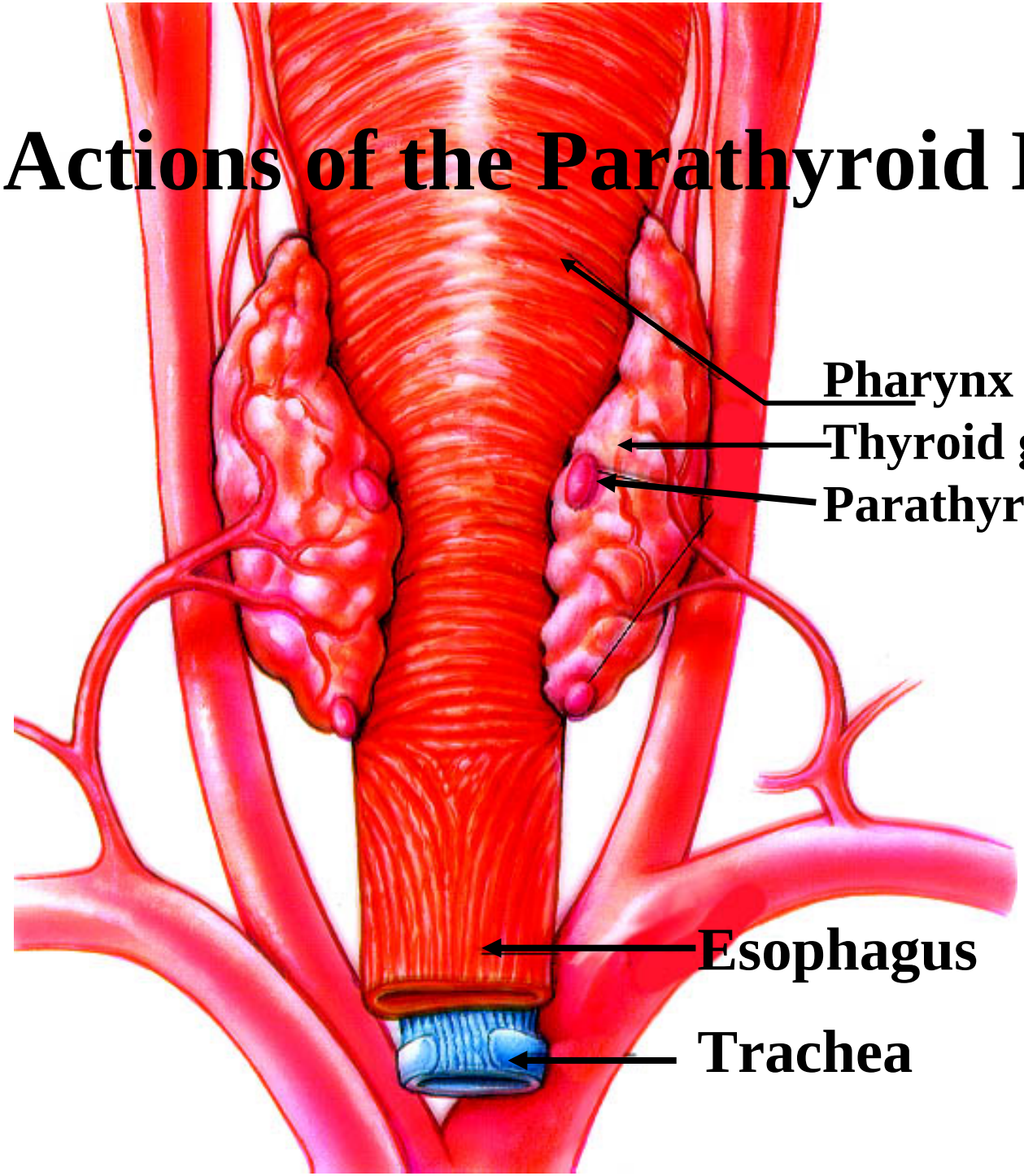
- Hormone-Chemistry
- PTH (parathyroid hormone) is a linear peptide with
- mole wt. of 9,600 and 84AA. Synthesized from pre-
- pro-PTH (115AA) → pro-PTH (90AA) → PTH
- (84 AA). Secreted by chief cells. Half life 3-4 mins.
- Biologic Actions
- 1. ↑renal tubular reabsorption of calcium
- 2. ↑renal tubular excretion of phosphates
- 3. stimulates the removal of calcium from the bone
- 4. ↑formation of 1,25-dihydroxycholecalciferol

Parathyroid Gland (cont.)

- Calcium Metabolism
- Normal plasma levels 9-11 mg%
- Hydroxgapatite
- Calcium requirements:
- 1gm/day: 2gm/day pregnancy
- Calcium functions:
- 1. Co-factor for coagulation of blood
- 2. Coupling factor for muscle contraction
- 3. Controls permeability and electrical properties of cell membranes
- 4. Bone formation


Hypothalamus
TRH
Anterior pituitary
TSH
Thryoid
T_3 and T_4
If iodine adequate
Normal thyroid
Negative feedback
If iodine inadequate
Low T_3 and T_4
Low Negative feedback
Anterior pituitary
Excess TSH
Thryoid
Hypertrophy - produces goiter
Growth (goiter)

Actions of the Parathyroid Hormone



Deficiency Effects of Ca^{++}

- 1. ↓serum calcium; which causes:
- a) anorexia
- b) tetany
- c) rickets
- 2. ↑ urinary excretion of Ca^{++}
- 3. ↓ urinary excretion of phosphates

Phosphate Metabolism

- Normal levels: 3 - 4.5 mg % adult
- 5 - 7 mg % children
- Functions:
- 1. PH buffer (pk = 6.9)
- 2. Metabolism
- 3. Nucleic acids
- 4. Phspholipids of cell membranes

Mechanisms of Hormonal Action (via cAMP)

- 1. Bone
- Enzyme & acid secretions of osteoclast cells
- a) Proteolytic enzymes-dissolve organic matrix
- b) acids (citric & lactic) - free bone salts
- 2. Kidneys
- ↑ phosphate excretion
- Regulation of Release
- Negative feedback with plasma [Ca^{++}]

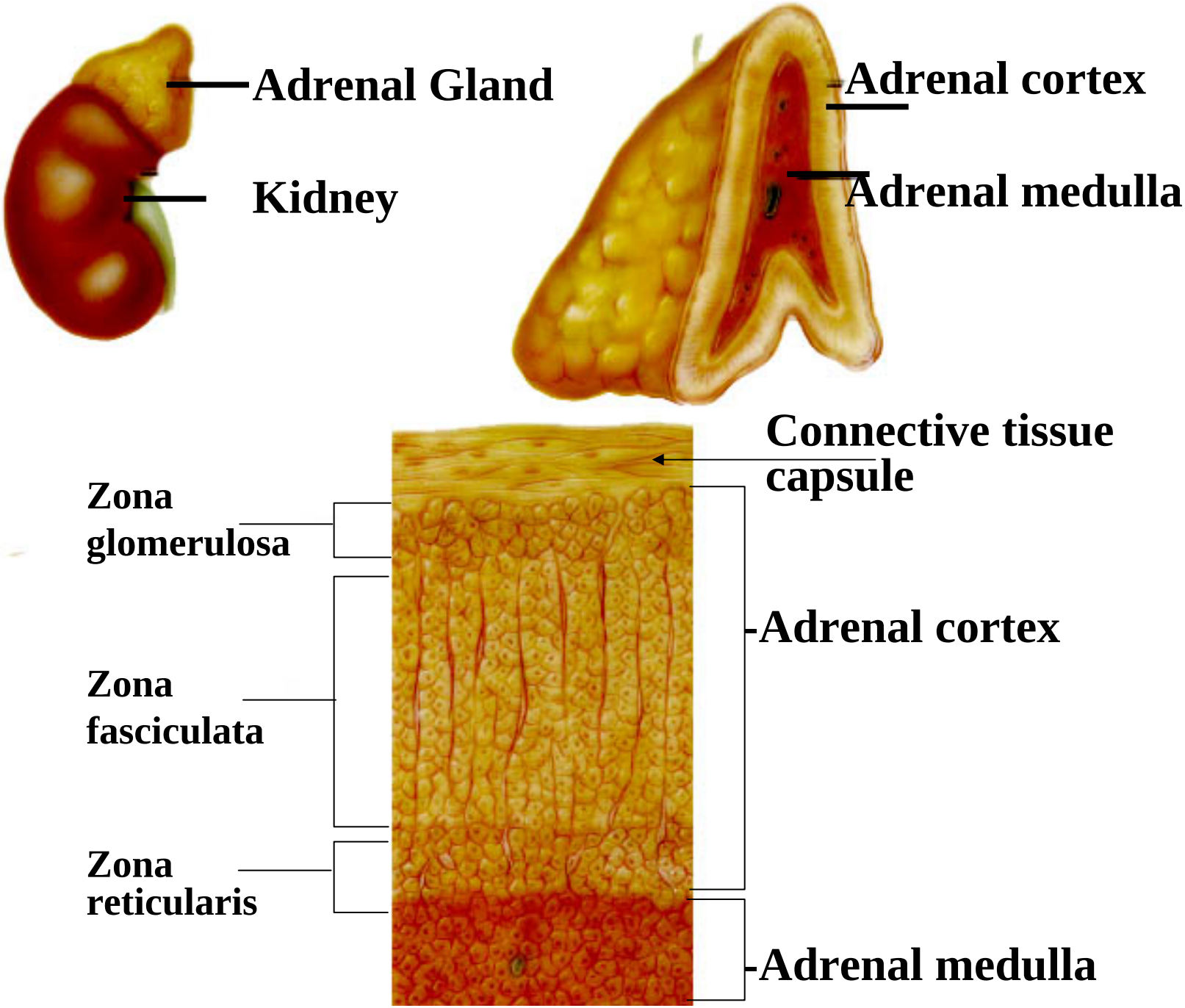
Adrenal Glands

Histology

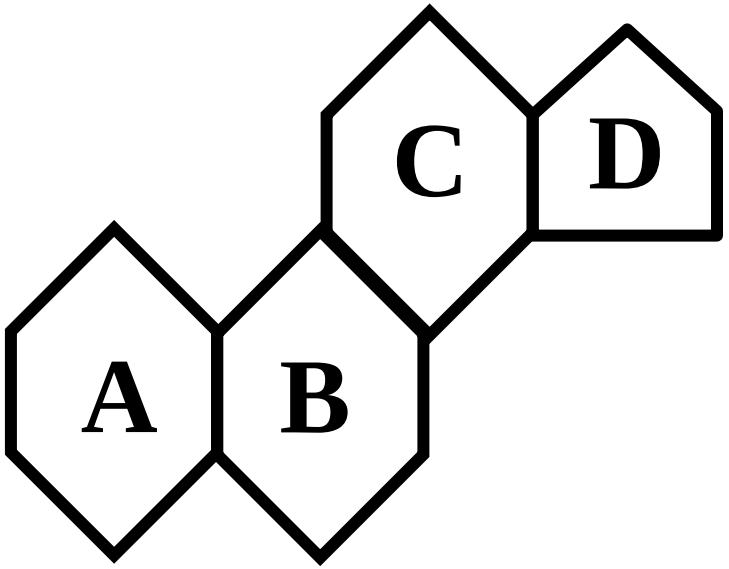
- A. Cortex (Corticosteroids)
- Derived from lateral mesoderm in association with developing gonads.
- Coats:
- 1. Zona glomerulosa - mineralcorticoids
- 2. Zona fasciculata - glucocorticoids
- 3. Zona reticularis - sex steroids
- B. Medulla (catecholamines)
- derived from neural crest cells along with the sympathetic ganglia.

Steroid Hormones

- These are tetracyclic ring compounds.
- Their structures are:
- “cyclopentano-perhydro-phenanthrene rings”
- that is,
- 3, hydrogenated phenathrene rings (A, B, &C)
- 1,5-carbon cyclopentane ring (D)

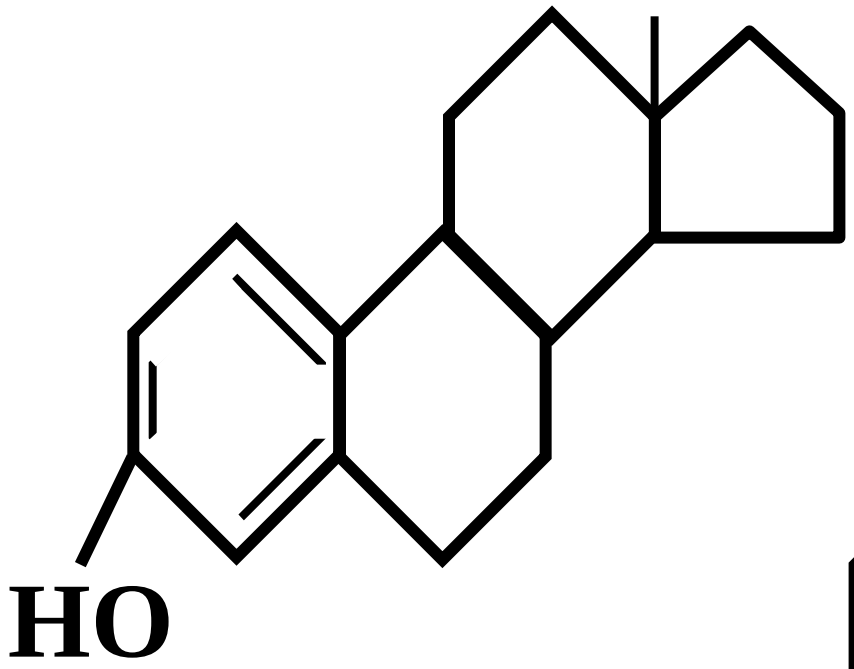

Adrenal Gland
Kidney
Adrenal cortex
Adrenal medulla
Connective tissue capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Adrenal cortex
Adrenal medulla

Steroid Hormones

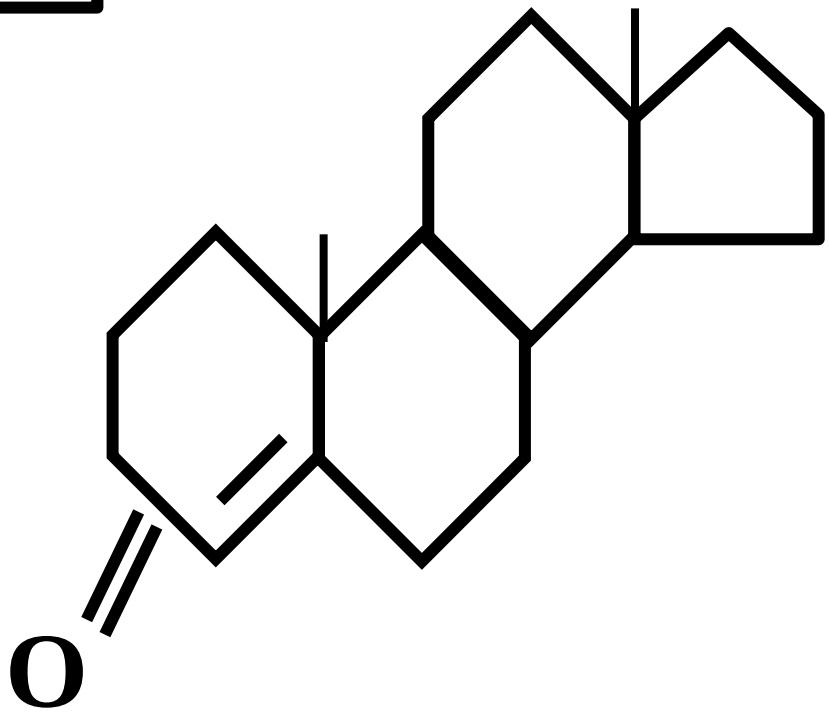


- Tetracyclic Ring Nucleus
- “Cyclopentano perhydro phenanthrene ring”
- 3 hydrogenated phenanthrene rings (A,B,C)
- One, 5-carbon cyclopentane ring (D)

C-18 (Estrogens)

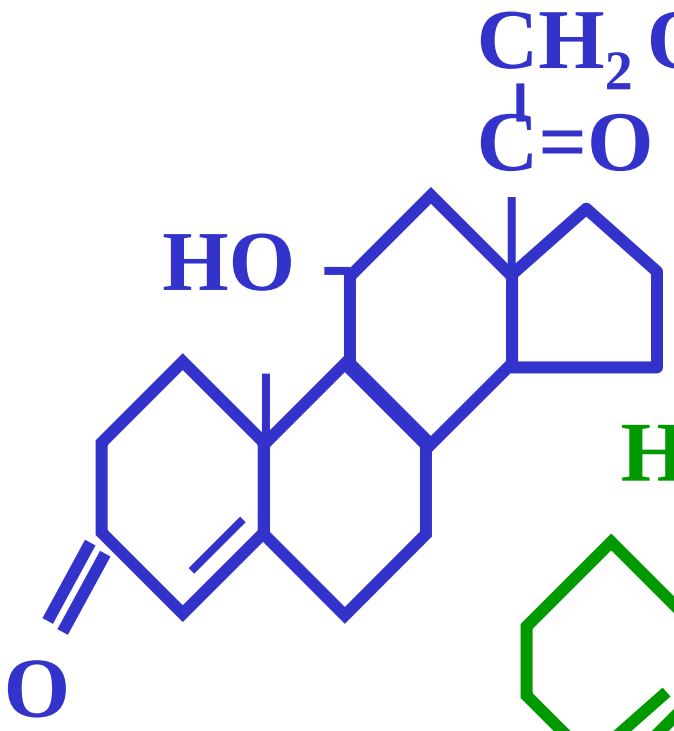


C-19 (Androgens)



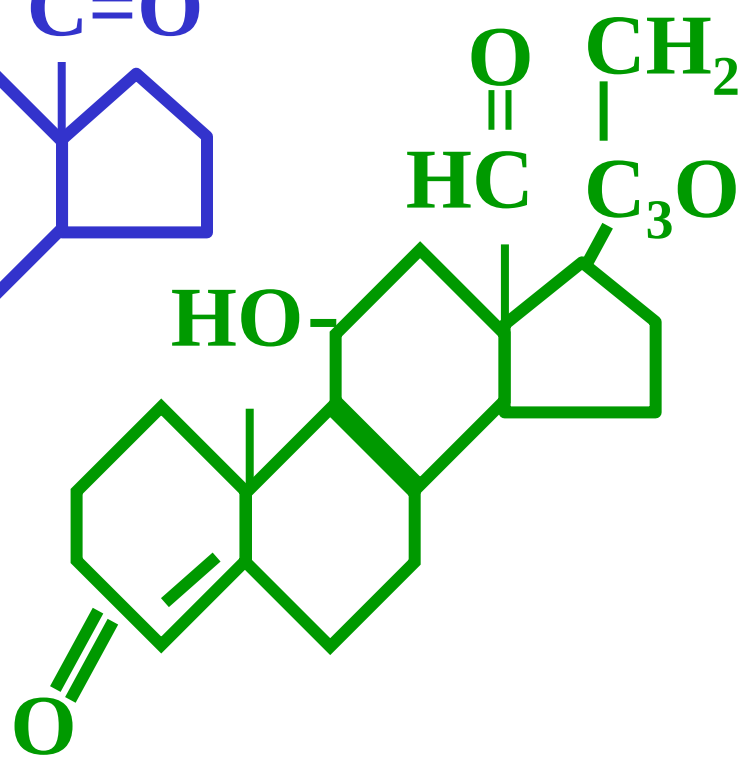
C-21

Glucocorticoids



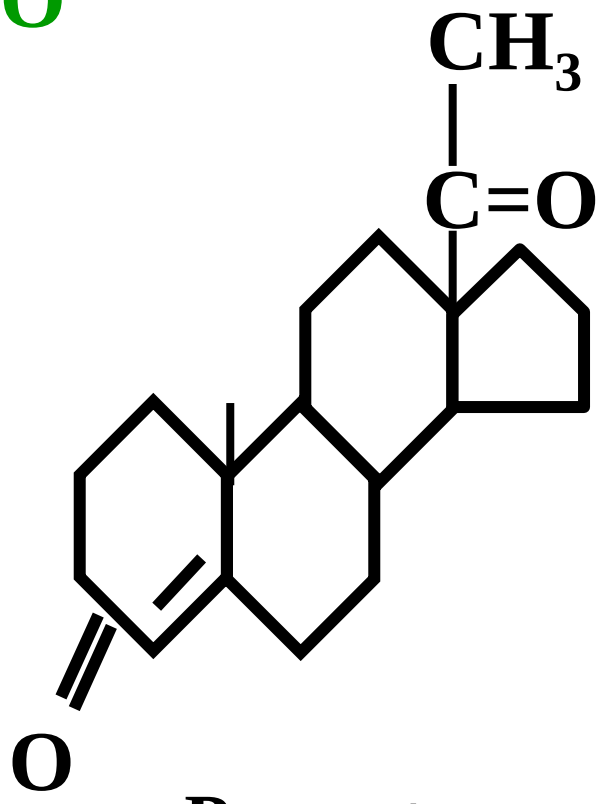
Cortisol

Mineralocorticoids



Aldosterone

Progestogens



Progesterone

Types

- C-18 steroids (estrogens):
- They have 3 double bonds in ring A.
- C-19 steroids (androgens):
- Those with keto groups at the 17th C are called
- 17-ketosteroids. Others have -OH groups at the
- 17th position.
- C-21 steroids (progestogens, mineralcorticoids, and glucocorticoids)

Adrenal Cortex-Mineralocorticoids (Zona Glomerulosa)

- Biologic Actions: (Aldosterone)
- Acts on distal tubules, collecting ducts, salivary
- glands, sweat glands, and the mucosa of the G.I.
- tract to cause:

  1. ↑ Reabsorption of sodium
  2. ↑ Excretion of potassium
  3. ↑ Absorption of sodium by gut
  4. ↑ Reabsorption of chlorides (secondarily to Na^+)

  Note: ↓ Plasma [K^+] causes ↑ tubular secretion of H^+

Adrenal Cortex-Mineralocorticoids (Zona Glomerulosa)

- Mechanisms of Action:
- Aldosterone activates the genetic synthesis of
- enzymes which:
- 1. Permeability of cells to Na^+ (permease hypothesis)
- 2. Acts directly to ↑ the activity of the sodium pump located on the serosal side of the target cell.

Glucocorticoids
(Zona Fasciculata)

- Biologic Actions: (Cortisol)
- 1. ↑ blood glucose by ↑ activity of glucose-6 -phosphatase (G ← G-6-phosphate)
- 2. ↑ protein and fat catabolism
- 3. ↑ gluconeogenesis
- 4. ↑ resistance to stress
- 5. ↑ overall number of WBC (↑ neutrophils; ↓ basophils and eosinophils)
- 6. Stabilizes the membranes of lysosomes
- Note: 1 and 3 have anti-insulin affects.

Glucocorticoids
(Zona Fasciculata)

- Pharmacologic Effects:
- 1. Anti-inflammatory agents
- 2. Anti-allergic effects
- 3. Inhibits ACTH release (at high concentrations)
- 4. Inhibits growth (↓ STH release)
- 5. Cushing's Syndrome:
  - a) ↑ protein catabolism (depletion)
  - b) Therefore, thin skin & subcutaneous tissues
  - c) Poor wound healing
  - d) Redistribution of fat (face, neck, abdomen)

Glucocorticoids
(Zona Fasciculata)

- Mechanisms of Action:
- 1) Same as mineralocorticoids (via protein synthesis)
- 2) Modulate the number of receptor sites for hormones
- 3) Inhibit prostaglandin synthesis by ↓ phospholipase activity

Glucocorticoids
(Zona Fasciculata)

- Regulation of Release:
- 1) Negative feedback with ACTH which acts via cAMP
- 2) Stress (neurohumoral)

Adrenal Sex Steroids

- A. Androgens (dehydroepiandrosterone)

- Biologic Actions:
- Less potent than testosterone in masculinizing
- effects and the promotion of protein anabolism and
- growth

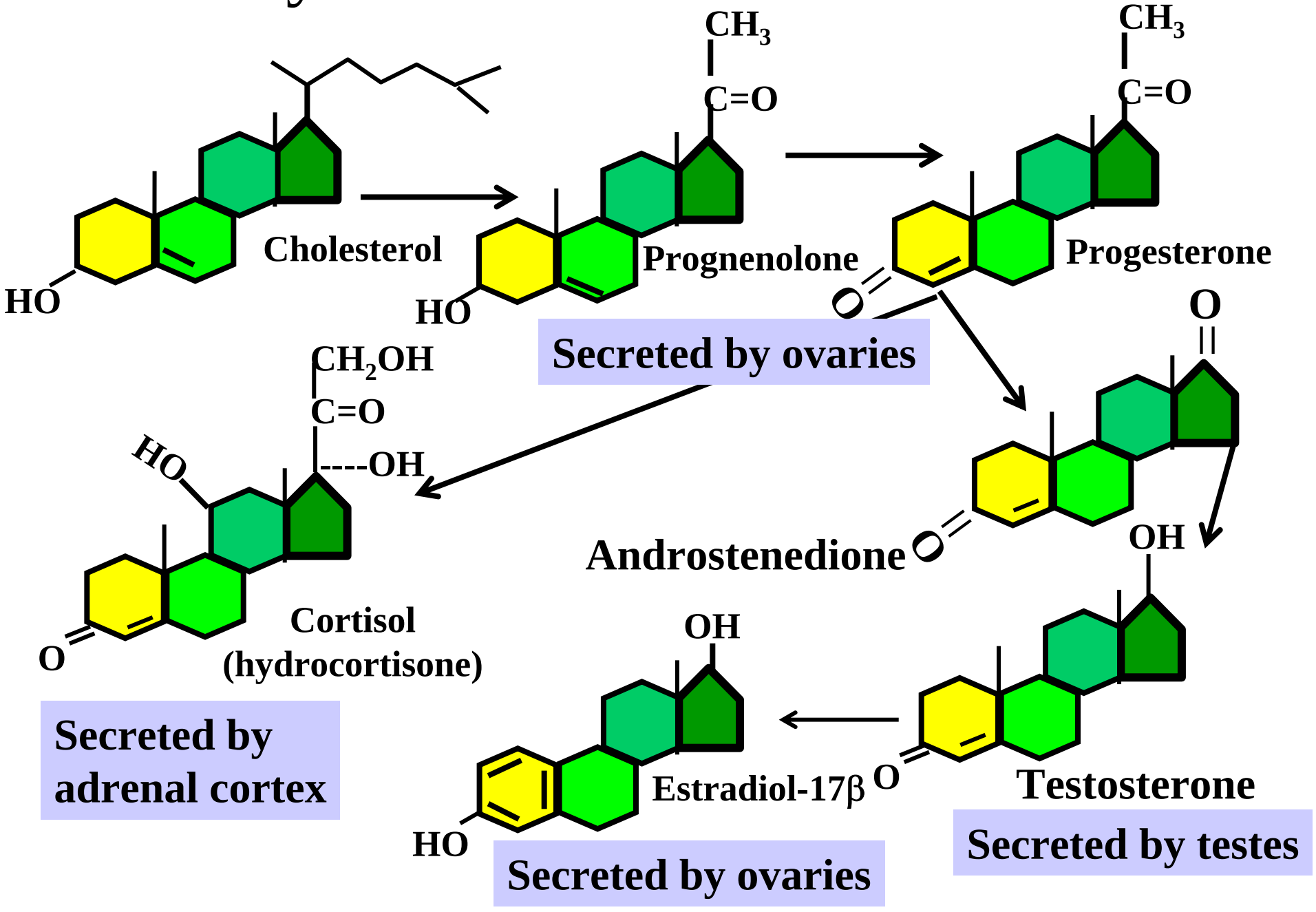
Adrenal Sex Steroids

- Oversecretions:
- 1. Precocious pseudopuberty in prepuberal boys.
- 2. Accentuation of existing characteristics in men.
- 3. Pseudohermaphroditism in genetically female fetuses.
- 4. Masculinization in pre and post puberal females.

Adrenal Sex Steroids

- Regulation of Release
  ACTH not LH or ICSH
- B. Estrogens ?
- Not clear whether “estrogens” are
- produced in the adrenals, or if the adrenal
- androgen androstenedione is converted into
- estrogen in the circulation. Ovariectomized
- females R_x with ACTH have ↑ estrogen.

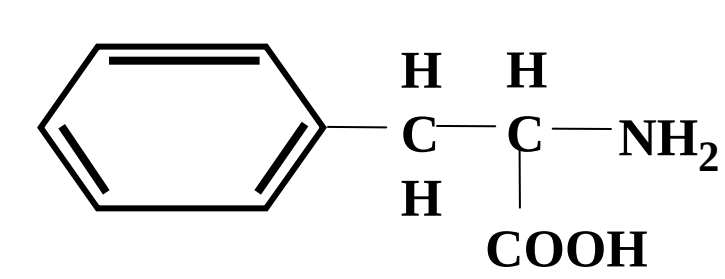
Biosynthesis of Steroid Hormones



Adrenal Medulla

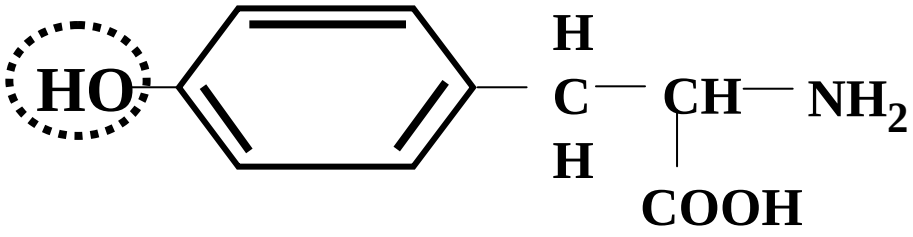
- It is composed of irregular strands and masses of
- cells separated by sinusoidal vessels.
- Cells:
- 1. Chromaffin
- 2. Sympathetic ganglia
- 3. Stilling cell
- Hormones: (Catecholamines)
- 1. Epinephrine (A-cells)
- 2. Nor-epinephrine (N-cells)

Catecholamine Biosynthesis



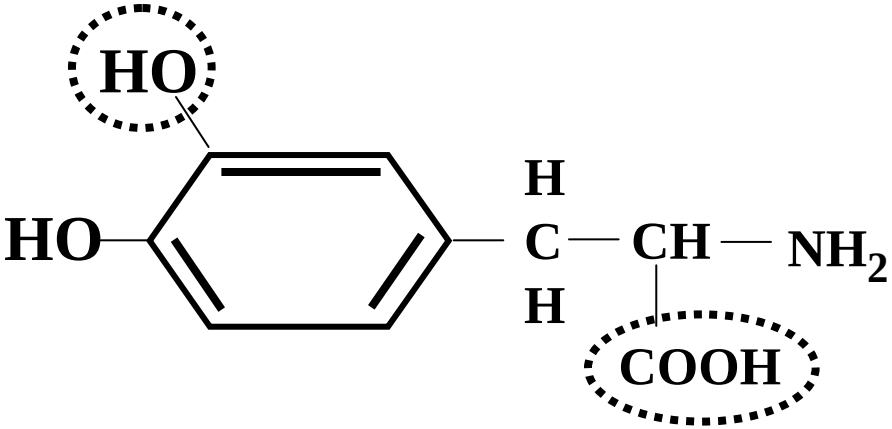
Phenylalanine

Phenylalanine hydroxylase



Tyrosine

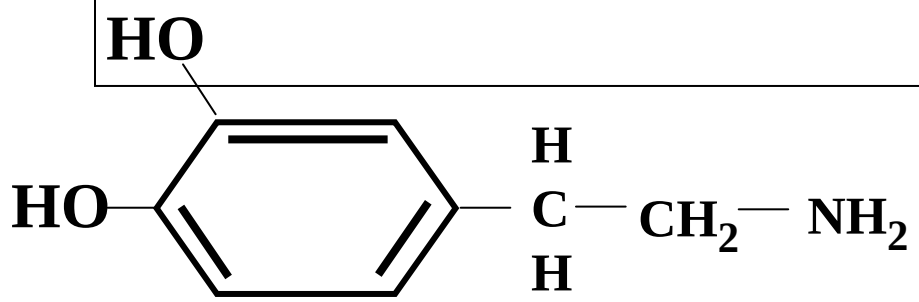
Tyrosine hydroxylase



Dopa

L-Aromatic Amino Acid Decarboxylase

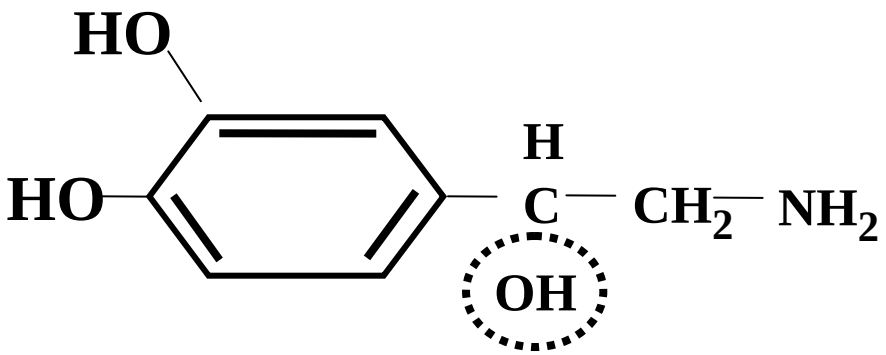
Catecholamine Biosynthesis



Dopamine

Dopamine

β-hydroxylase

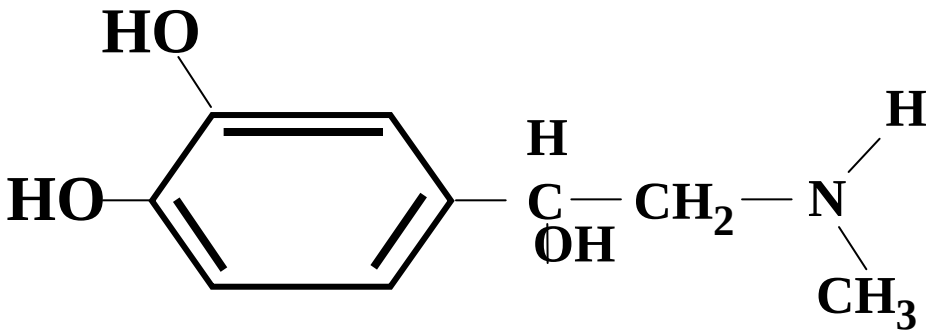


Norepinephrine

Phenylethanolamine

N-Methyltransferase

(PNMT)



Epinephrine

Contrasted Actions of Epinephrine and Norepinephrine

The Adrenal Medulla : Chromaffin Tissue

Table 10-1

Cardiovascular

FUNCTION	EFFECT		RELATIVE ACTIVITY
	EPINEPHRINE	NOREPINEPHRINE	E/N°
Peripheral resistance	Decreased	Increased	-
Systolic B.P.	Increased	Increased	0.5
Diastolic B.P.	No effect	Increased	-
Heart Rate	Increased	Slightly Increased	20
Cardiac output	Increased	No Change	-
Blood vessels in denervated limb	Vasodilation	Vasoconstriction	-
Coronary vessels	Vasodilation	Vasodilation	-
Pulse Rate	Increased	Decreased	-
Eosinophil count	Increased	No effect	-
Net peripheral vascular effect	Vasodilation	Limited vasodilator actions; over-all vasoconstriction	-

Blood Flow through Individual Organs

	EFFECT		RELATIVE ACTIVITY
FUNCTION	**EPINEPHRINE**	**NOREPINEPHRINE**	**E/N°**
Skeletal muscle	**100% increase**	**Unaltered or decreased**	**-**
Liver	**100% increase**	**No material effect**	**-**
Brain	**20% increase**	**Slight decrease**	**-**
Kidney	**40% decrease**	**20% decrease**	**2**

Respiratory System

FUNCTION	EFFECT: EPINEPHRINE	EFFECT: NOREPINEPHRINE	RELATIVE ACTIVITY: E/N°
Bronchial muscle	Inhibition	Inhibition	20

Carbohydrate Metabolism

FUNCTION	EFFECT: EPINEPHRINE	EFFECT: NOREPINEPHRINE	RELATIVE ACTIVITY: E/N°
Blood Sugar	Increased	Increased	4

Eye

FUNCTION	EFFECT: EPINEPHRINE	EFFECT: NOREPINEPHRINE	RELATIVE ACTIVITY: E/N°
Pupillary dilators	Excitation	Excitation	15

Intestine

FUNCTION	EFFECT		RELATIVE ACTIVITY
	EPINEPHRINE	NOREPINEPHRINE	E/N*
Small	Inhibition	Inhibition	2
Large	Inhibition	Inhibition	1

Genital System

FUNCTION	EFFECT		RELATIVE ACTIVITY
	EPINEPHRINE	NOREPINEPHRINE	E/N°
Nonpregnant Uterus (rat, cat)	Inhibition	Inhibition	100

Eye

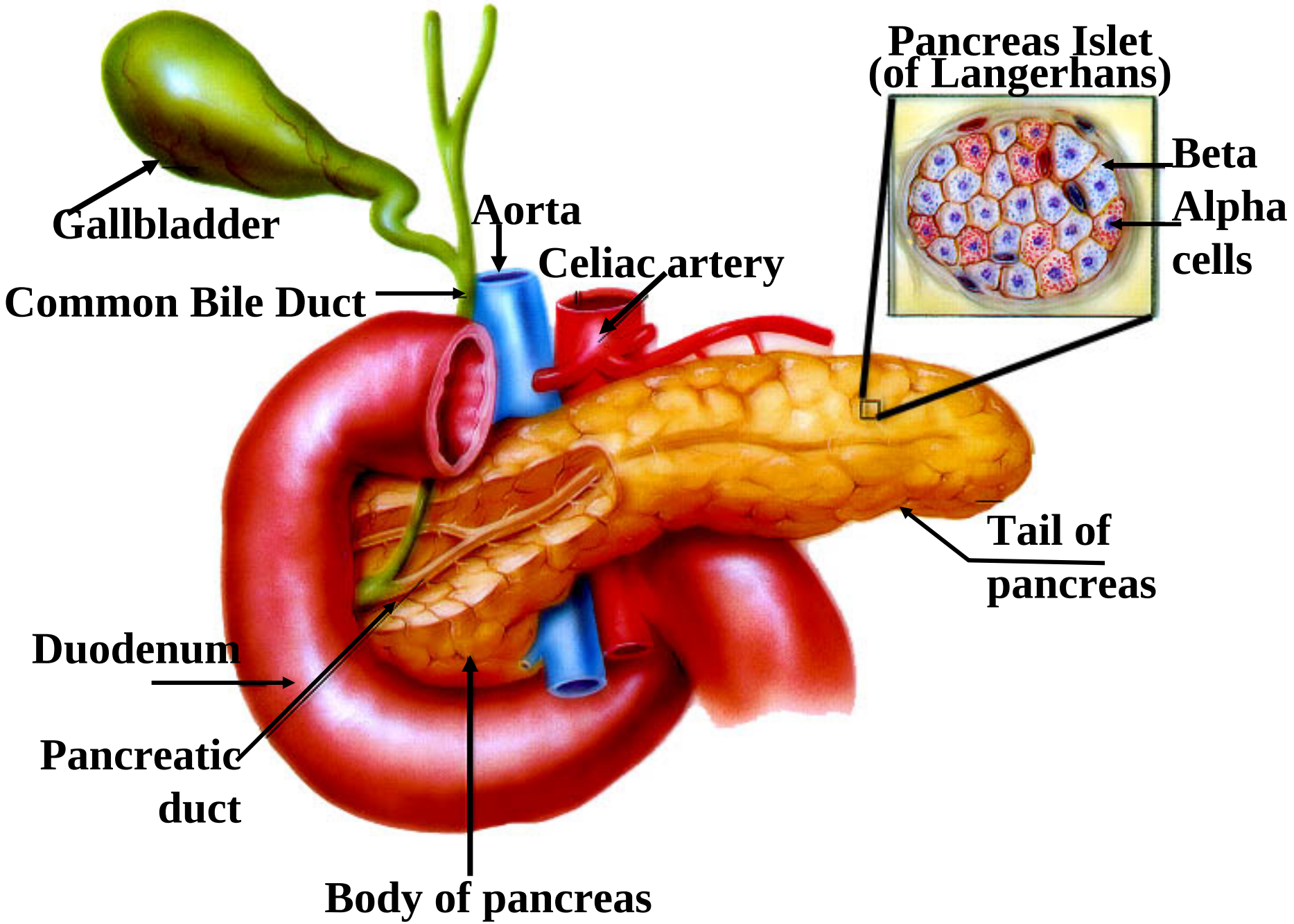
FUNCTION	EFFECT		RELATIVE ACTIVITY
	EPINEPHRINE	NOREPINEPHRINE	E/N°
Central Nervous System (man)	Mental state	Anxiety	-

Pancreas

- Structure:
- About 98% of the pancreas consist of non-endocrine secreting tissue. This is the acinar tissue which secretes the pancreatic juices. Scattered throughout the pancreas are the Islets of Langerhans which produce 4 peptides having hormonal activity.

Pancreas

- Cell types & Hormones:
- A(alpha) = 20% of granulated cells - glucagon
- B(beta) = 70% of granulated cells - insulin
- D(delta) = 1-8% of granulated cells - pancreatic somatostatin
- Fourth cell type - pancreatic
- polypeptides

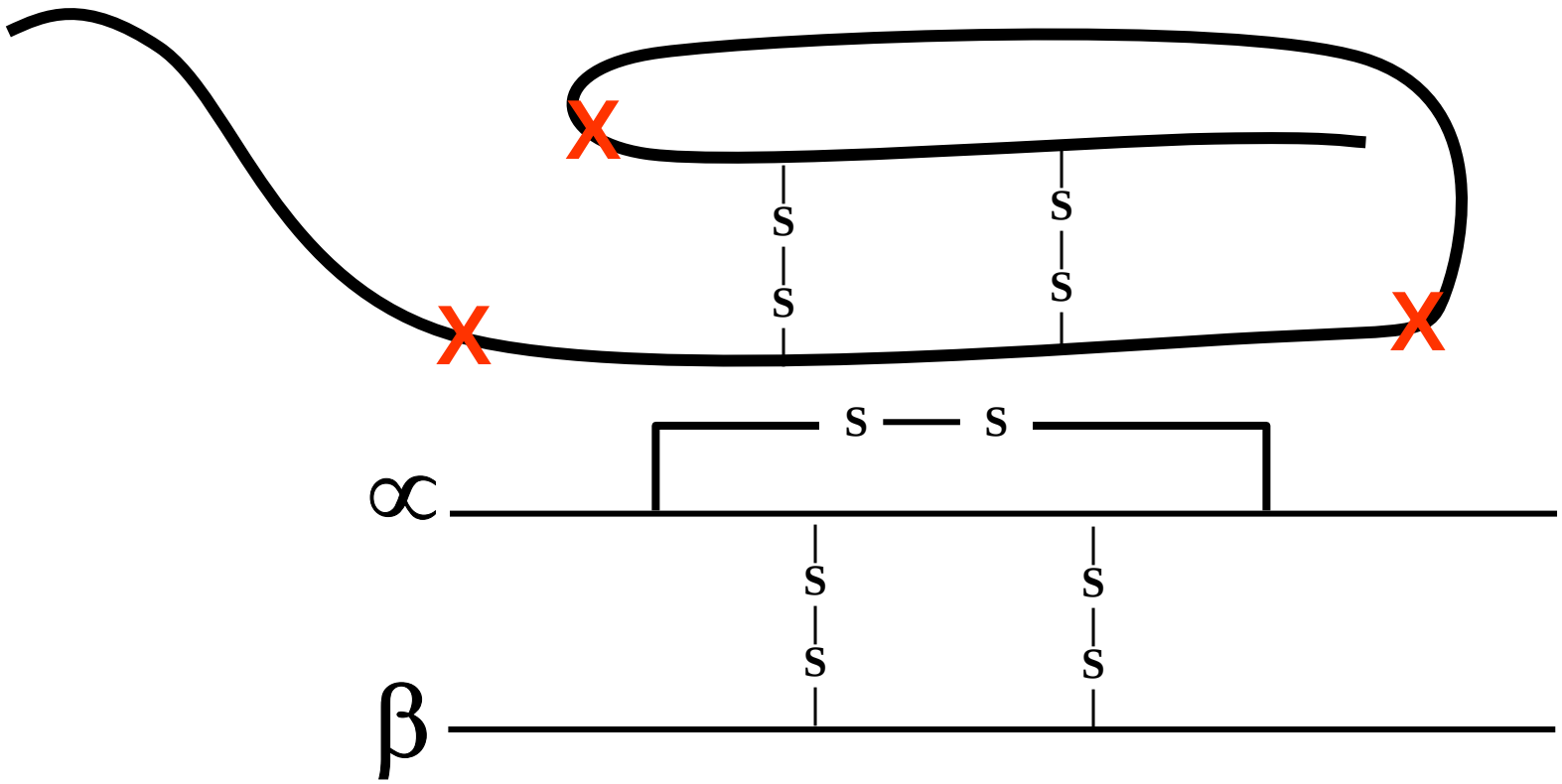

Pancreas Islet
(of Langerhans)
Beta
Alpha
cells
Gallbladder
Aorta
Celiac artery
Common Bile Duct
Tail of
pancreas
Duodenum
Pancreatic
duct
Body of pancreas

Insulin

- Chemistry:
- Polypeptide containing 2 chains linked by disulfide bonds.
- Alpha chain - 21AA
- Beta chain - 30AA
- The AA composition from other species can cause antibody production, however, the titer usually remains low. Pork insulin differs from human insulin by one AA
- Circulating half-life of 5 minutes.

Insulin Biosynthesis

- Insulin is produced in the endoplasmic reticulum of the beta cells. It is packaged into membrane-bound granules in the Golgi complex, then becomes attached to the cell membrane until secreted by exocytosis. It is synthesized as a single chain called pre-proinsulin (107AA).
- Twenty three AA are removed from C-terminal & the resultant molecule folds in & forms disulfide bonds. This is pro-insulin (84AA). The connecting peptides then break off leaving the A&B chains -insulin. Within the beta cells, insulin complexes with zinc. The # of granules in the cells denote the amount of insulin in the cells. The granules are depleted as insulin is secreted. It has a circulating half-life of 5 minutes



Biologic Action:

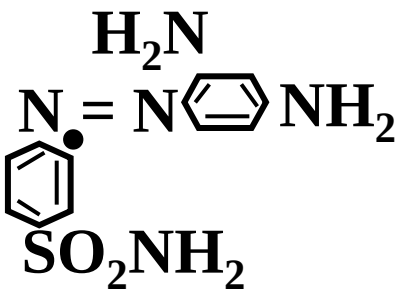
It acts on the cell membrane to ↑ permeability to glucose. It, therefore, acts to ↓ the level of blood glucose. (Helps maintain level between 80 & 120mg %).

Insulin Substitutes (oral)

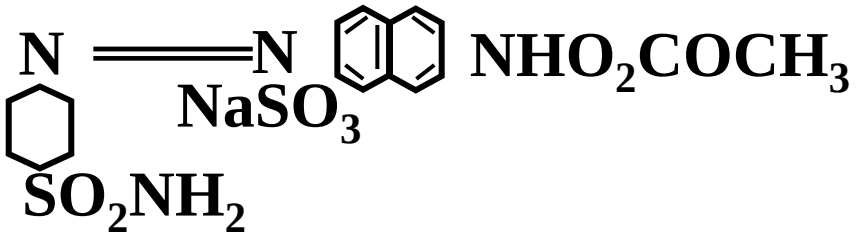
- 1. Sulfonamides - ↓ level of blood glucose
- 2. Tolbutamide - stimulates release of insulin
- 3. Biguanides - ↓gluconeogenesis in the liver

Oral Insulin Substitutes

- 1. Sulfonamides
- Amides of p-aminobenzenesulfonic acid.
- They are bacteriostatic in low concentration; bactericidal in high concentrations.

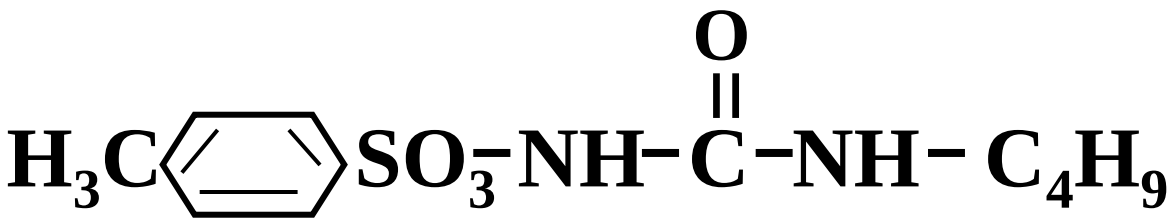


- Prontosil



Neoprontosil

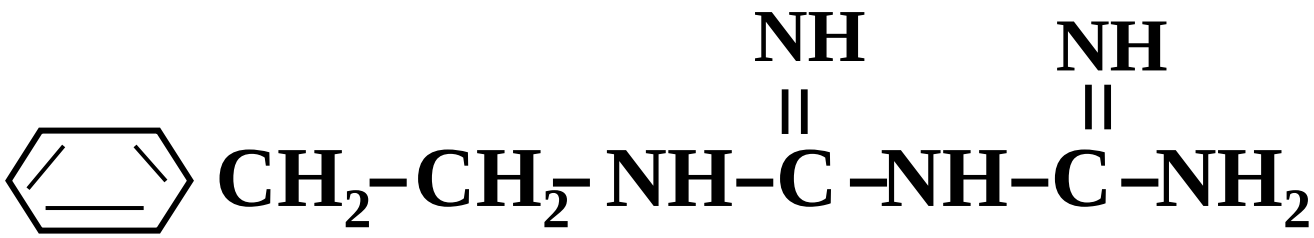
A) Sulfonylurea compounds (Tolbutamide - Orinase)



- Tolbutamide

- They stimulate the pancreas to release insulin.

B) Phenformin compounds (Biguanide)



- Phenformin

- They supplement the effect of insulin upon the peripheral utilization of glucose.
- They act by favoring anerobic glycolysis instead of the more insulin-dependent aerobic pathway.

Effects of Insulin Deficiency

- 1. Hyperglycemia
- 2. Glycosuria
- 3. ↓Glycogenesis
- 4. ↑ formation of ketone bodies
- 5. ↓ PH (acidosis then coma)

Effects of Insulin Deficiency - Treatment

- A. Diabetic Coma - injection of insulin & glucose.
- The glucose shifts system from fat to glucose metabolism
- B. Diabetes Mellitus (No national registry: NIH projections)
- 1. Undiagnosed: 8 million
- 2. Diagnosed: 8 million
- 3. Non-insulin dependent: 7.5 million
- 4. Insulin- dependent: 800,000

Effects of Hyperinsulinism

- Insulin Shock - overexcitability of brain followed by coma.

Differential Diagnosis

Diagnostic Factors	Hyperglycemia (Diabetic Coma)	Hyperinsulinism
History:		
food intake	normal or excessive	may be insufficient
insulin	insufficient	excessive
onset	gradial: days	sudden (1-2-days)
Physical Exam:		
appearance	extremely ill	very weak
skin	dry & flushed	moist & pale
infection	frequent	absent
fever	frequent	absent

Differential Diagnosis

Diagnostic Factors	Hyperglycemia (Diabetic Coma)	Hyperinsulinism
Gastrointestinal:		
mouth	**dry**	**drooling**
thirst	**intense**	**absent**
hunger	**absent**	**occasional**
vomiting	**common**	**rare**
Pain, abdominal	**frequent**	**absent**
skin	**dry & flushed**	**moist & pale**
infection	**frequent**	**absent**
fever	**frequent**	**absent**

Differential Diagnosis

Diagnostic Factors	Hyperglycemia (Diabetic Coma)	Hyperinsulinism
Respiration	Exaggerated,air hunger	Normal or shallow
Breath	Acetone odor	Acetone odor, rare
Blood Pressure	Low	Normal
Pulse	Weak & rapid	Full & bounding
Eyeballs	Soft	Normal
Vision	Dim	Diplopia
Convulsions	None	In late stages
Response to Treatment	Gradual, 6 to 12 hrs. after use of insulin	Rapid following carbohydrate administration

Pathophysiology of the Endocrine Pancreas

- Disease / Etiology
- Type I (Insulin-Dependent)
  Juvenile-onset diabetes.
- Viral-induced β-cell destruction.
  Cytotoxic autoantibodies to
  β-cell lead to β-cell destruction.

Pathophysiology of the Endocrine Pancreas

- Type II (Noninsulin-Dependent Diabetes Mellitus, NIDD) Adult (Maturity) Onset Diabetes.
- Decreased capacity of pancreatic β-cells to compensate for underlying insulin resistance by increased secretion of insulin.

Pathophysiology of the Endocrine Pancreas

- Insulin resistance (4, 11, 14, 41)
  Type A. Decrease in insulin receptor and/or affinity.
  Point mutation in insulin receptor prevents processing of the receptor precursor [30, 74].
  Defect in glucose transport effector system (glucose transporter proteins) [21, 29].

Pathophysiology of the Endocrine Pancreas

- Impaired expression of receptor tyrosine kinase activity [26, 47, 66].

- Type B. Receptor blocked by circulatory antibodies to the receptor.

Pathophysiology of the Endocrine Pancreas

- Leprechaunism

  An autosomal recessively inherited disorder of insulin function that leads to severe intrauterine growth retardation, characteristic dysmorphic features, and a disturbed glucose homeostasis.
- The process underlying this disease is a malfunctioning of the insulin receptor.

Pathophysiology of the Endocrine Pancreas

- Mutant Insulin Structures

  Defect in primary structures of insulin B chain at one or more positions [71].

  Familial Hyperproinsulinemia.

  B-C proinsulin: mutation at the cleavage site between the B chain and the connecting (C)peptide.

  A-C proinsulin: mutation at the cleavage site between the A chain and the connecting (C) peptide.

Pathophysiology of the Endocrine Pancreas

- Islet Cell Tumors[a]

  Insulinoma. Excess insulin secretion from β-cell pancreatic tumor.

  Glucagonoma syndrome. Excess glucagon secretion from α-cell pancreatic tumor.

  Somatostatinoma. Excess glucagon secretion from D-cell pancreatic tumor.

---

[a]No pathological condition or tumor has been reported which solely secretes PP, although very high levels of the peptide are often found in pancreatic disease states, exocrine and endocrine.

Pathophysiology of the Endocrine Pancreas

Hypoglycemic Disorders

Hypoglucagonesmia (isolated glucagon deficiency). Possibly due to autosomal recessive inheritance [61].

Hyperinsulinemia (β-cell tumor) [73].

No pathological condition or tumor has been reported which solely PP, although very high levels of the peptide are often found in pancreatic disease states, exocrine and endocrine.

Glucagon

- Chemistry:
- Straight chain polypeptide of 29 AA and mole wt. of 3,485.
- Biologic Actions:
- 1. Stimulates an ↑ in the blood glucose level
- 2. ↑ contractility of the heart
- 3. Stimulates secretion of STH

Glucagon

- Mechanism of Action:
- A. Acts on the liver to cause:
- 1. Glycogenolysis
- 2. Gluconeogenesis
- 3. Lipolysis
- B. ↑ plasma level of glucose by ↑ active phosphorylase which catalyzes the formation glucose-1-phosphate from glycogen.

Glucagon

Regulation of Release

- Stimulated:
  - 1. Amino acids
  - 2. Cortisol
  - 3. Exercise
  - 4. Starvation
- Inhibitors:
  - 1. Glucose
  - 2. Somatostatin
  - 3. Insulin

Mean Rates of Insulin & Glucagon Delivery