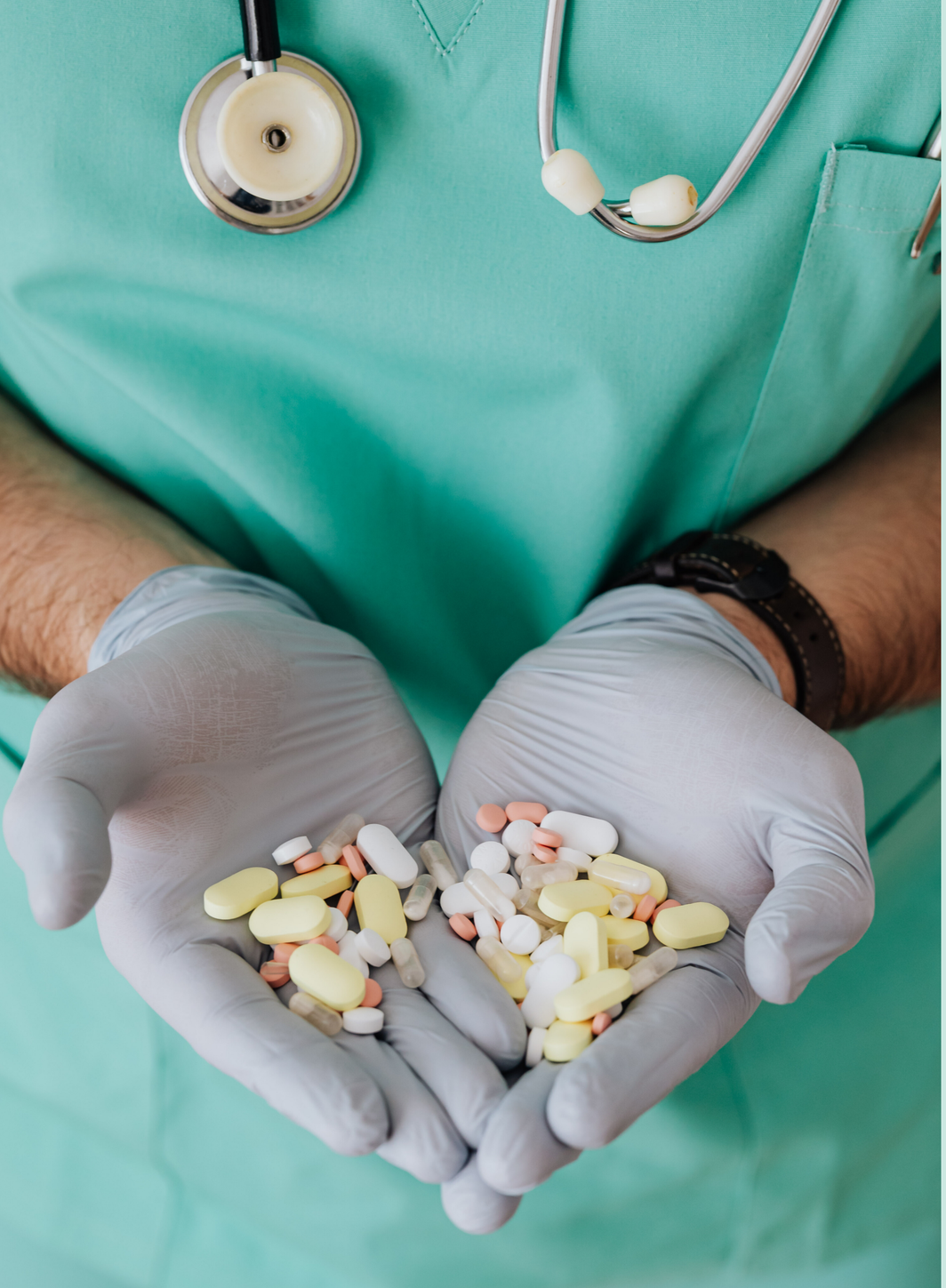

Sheet# 4

PASSION ACADEMIC TEAM YU - MEDICINE

Endocrine system

Lec. Title : Catecholamines & Thyroid Hormones

Written By : Wasan Ababneh
Mustafa Tawaha

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CATECHOLAMINES & THYROID HORMONES ARE MADE FROM TYROSINE

Catecholamines Are Synthesized in Final Form & Stored in Secretion Granules

All synthesized from Tyrosine.

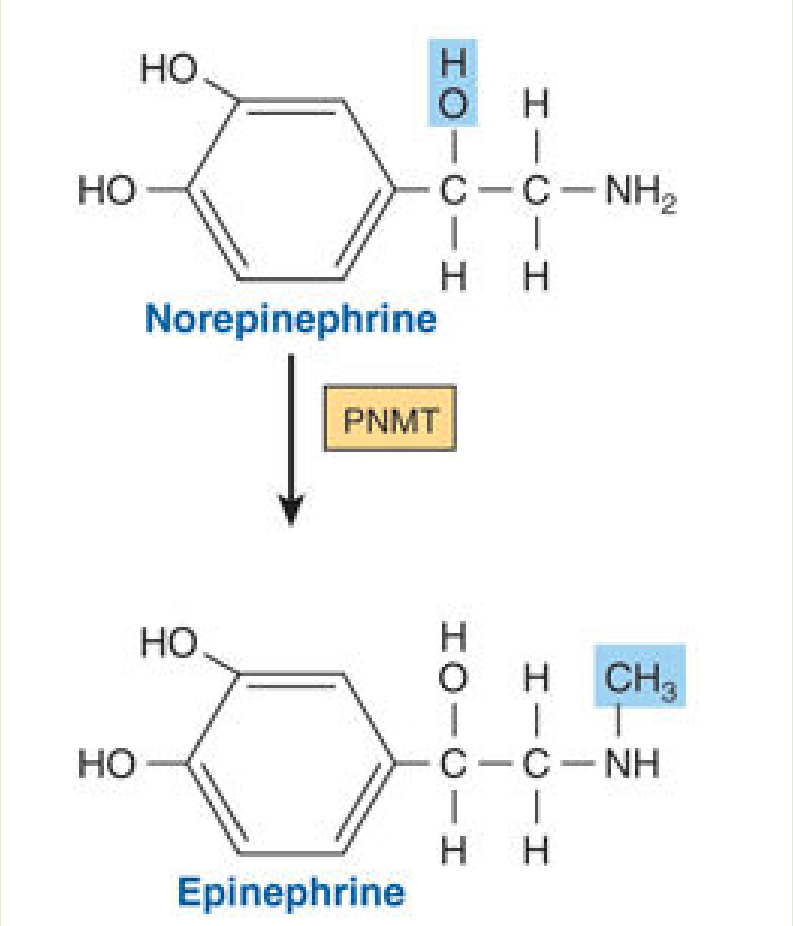
I. Dopamine - synthesized in the brain

II. Norepinephrine -methylated epinephrine- synthesized in the brain and adrenal medulla- chromaffin cells

III. Epinephrine-80% of the catecholamines in the medulla- "it is not made in extramedullary tissue"- chromaffin cells

-tyrosine can be generated from metabolism of phenylalanine ,but here phenylalanine is not considered as the precursor
The Tyrosine is considered as the precursor for these hormones

the difference between NE and Epi is just the methyl group on Epi



The conversion of tyrosine to epinephrine requires four sequential steps:

(1)ring hydroxylation;

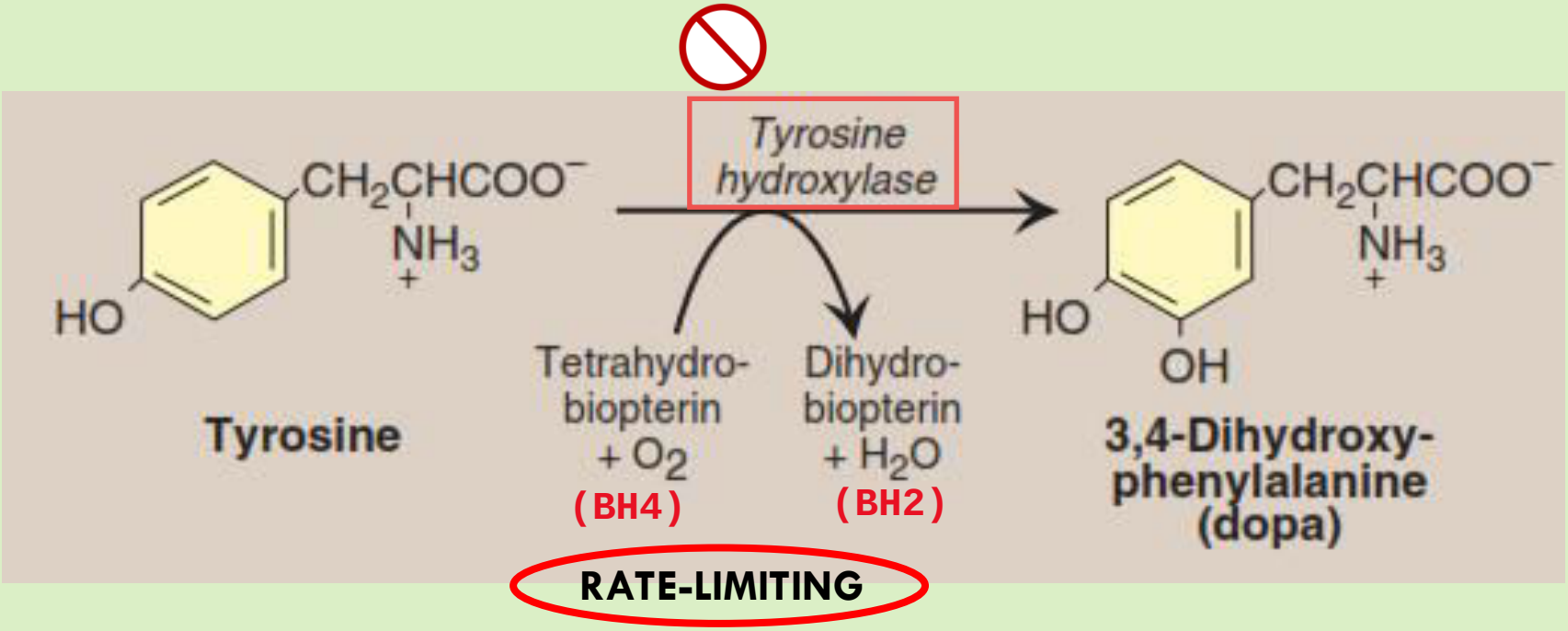
(2)decarboxylation;

(3)side-chain hydroxylation to form norepinephrine;

(4)N -methylation to form epinephrine.

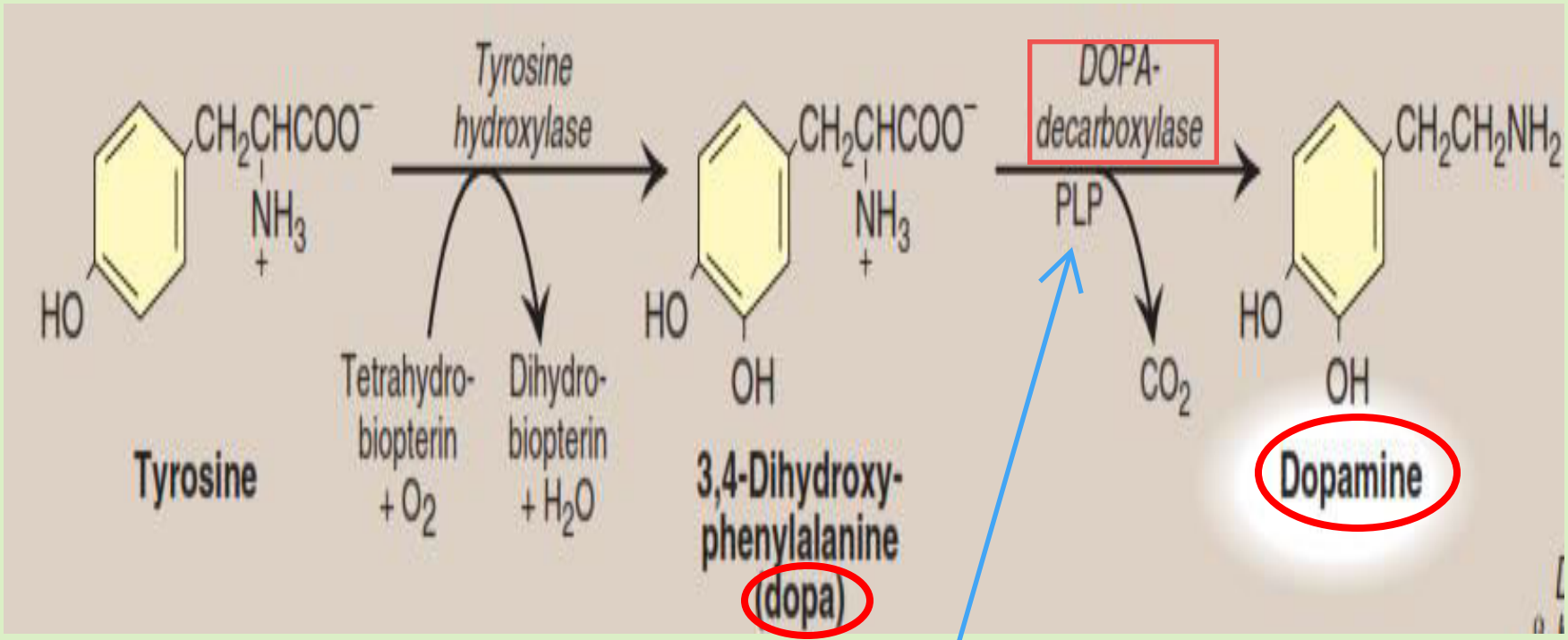
the enzymes and coenzymes in catecholamine are required

feedback inhibition by: catecholamines

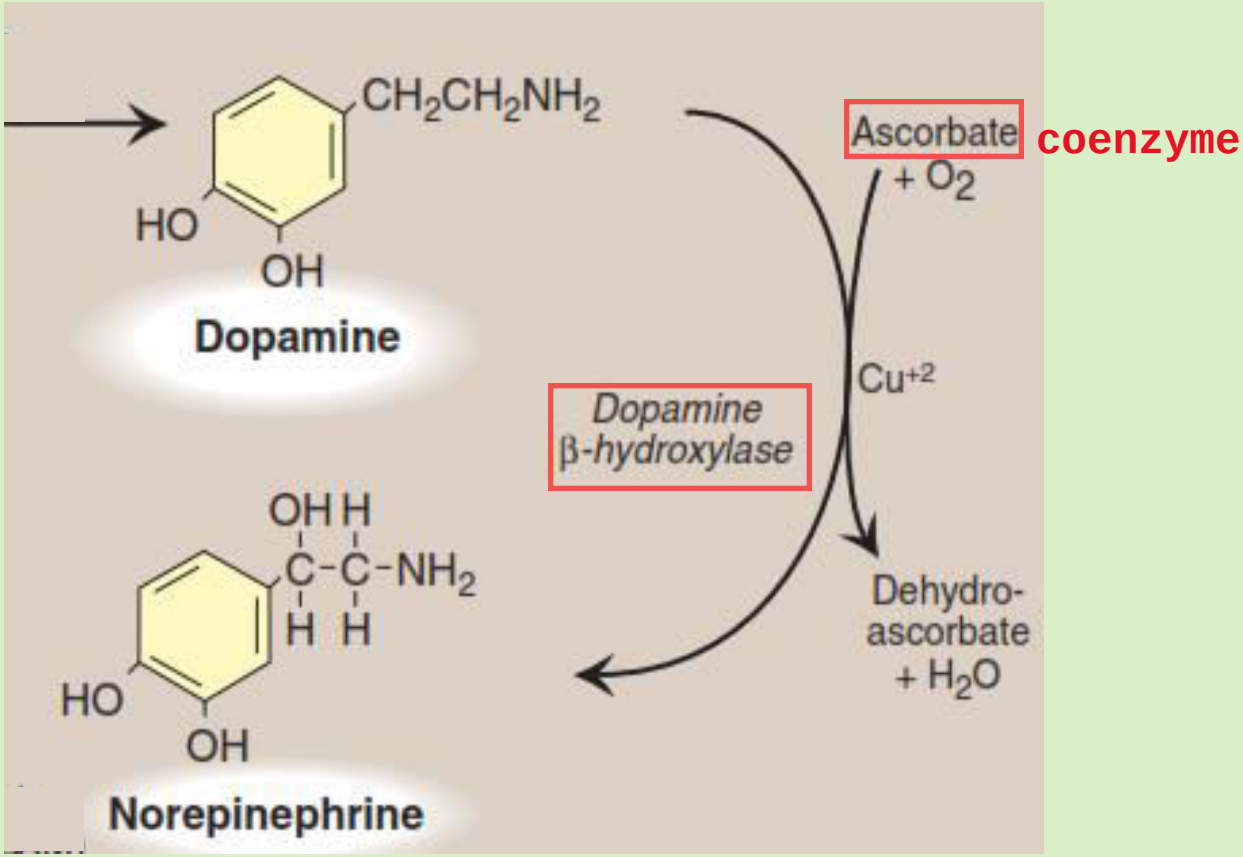


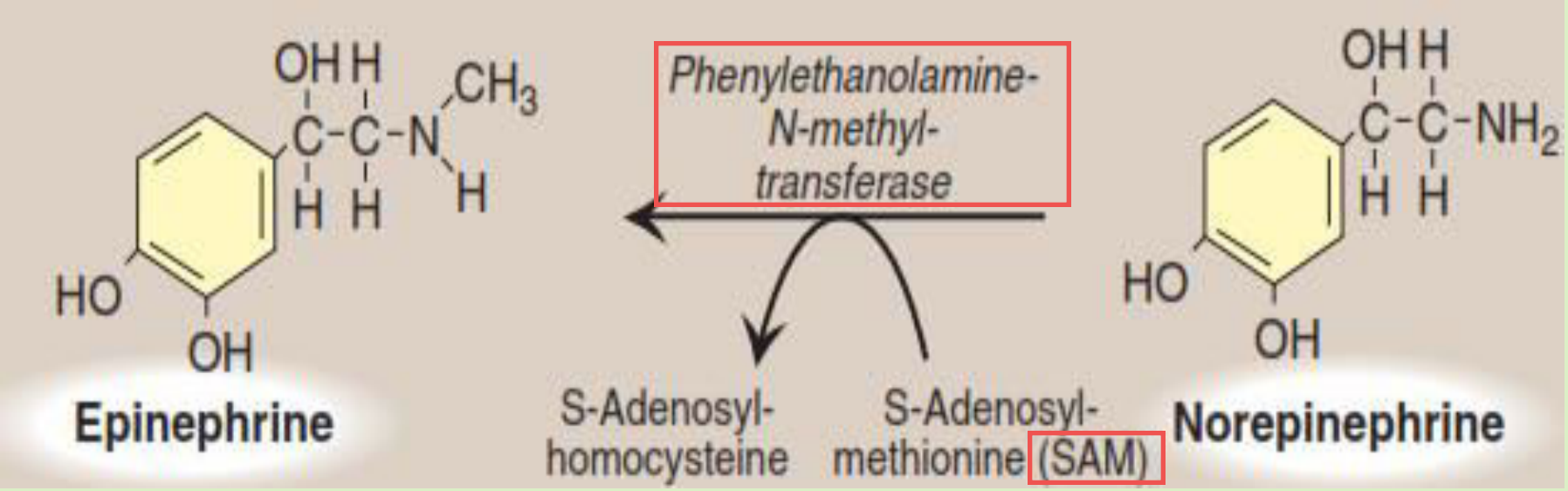
Methyldopa is effective in treating some kinds of hypertension

PRESENT IN ALL TISSUES

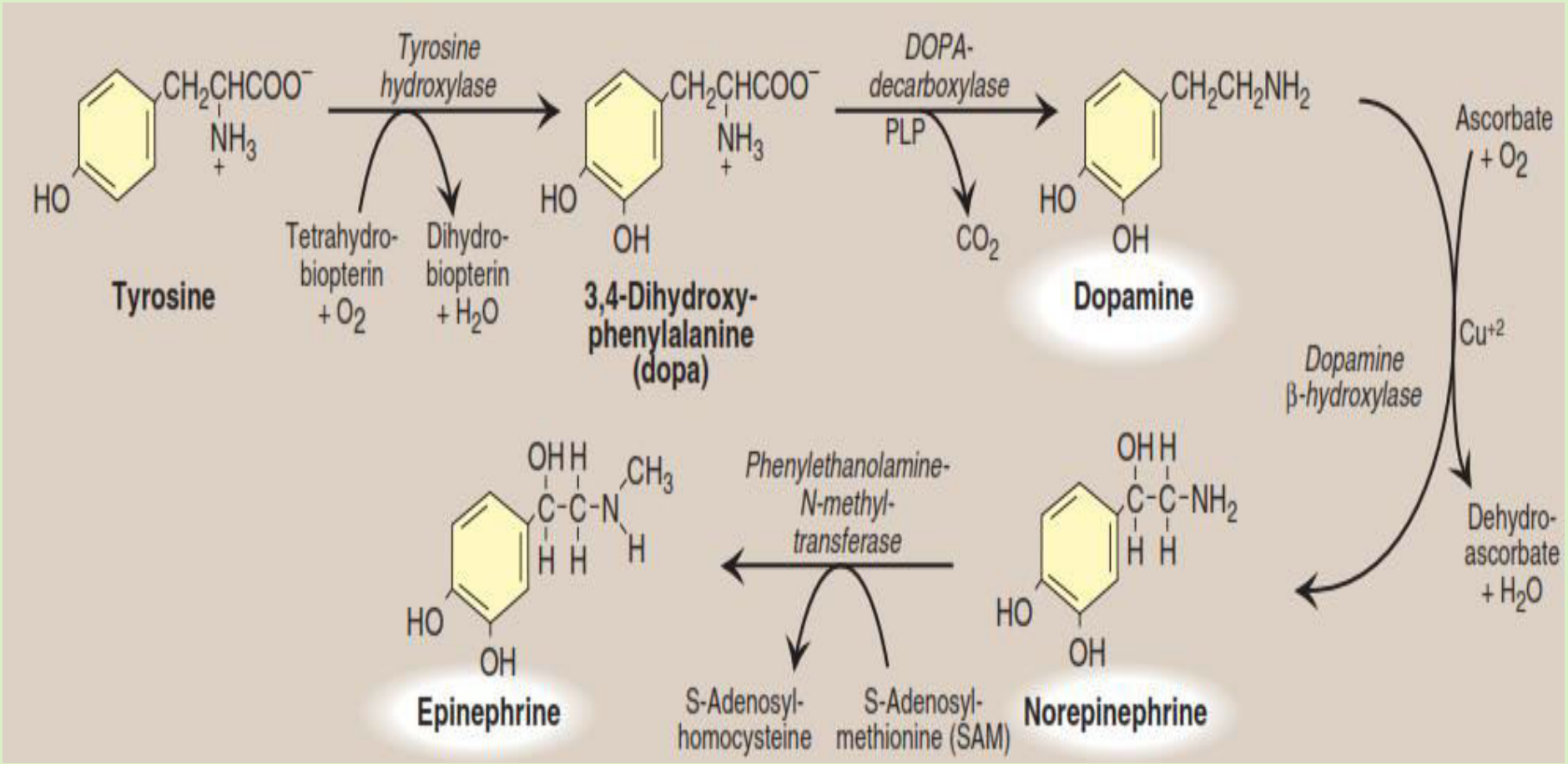


PLP: Pyridoxal phosphate ,
REQUIRED AS CARBON CARRIER


CH2CH2NH2
HO
OH
Dopamine
Ascorbate
+ O2
coenzyme
Cu+2
Dopamine
β-hydroxylase
OH H
C-C-NH2
H H
HO
OH
Norepinephrine
Dehydro-
ascorbate
+ H2O



coenzyme:the carbon donor


Tyrosine
Tyrosine hydroxylase
Tetrahydro-biopterin + O2
Dihydro-biopterin + H2O
3,4-Dihydroxy-phenylalanine (dopa)
DOPA-decarboxylase
PLP
CO2
Dopamine
Ascorbate + O2
Cu+2
Dopamine β-hydroxylase
Dehydro-ascorbate + H2O
Norepinephrine
Phenylethanolamine-N-methyl-transferase
S-Adenosyl-homocysteine
S-Adenosyl-methionine (SAM)
Epinephrine

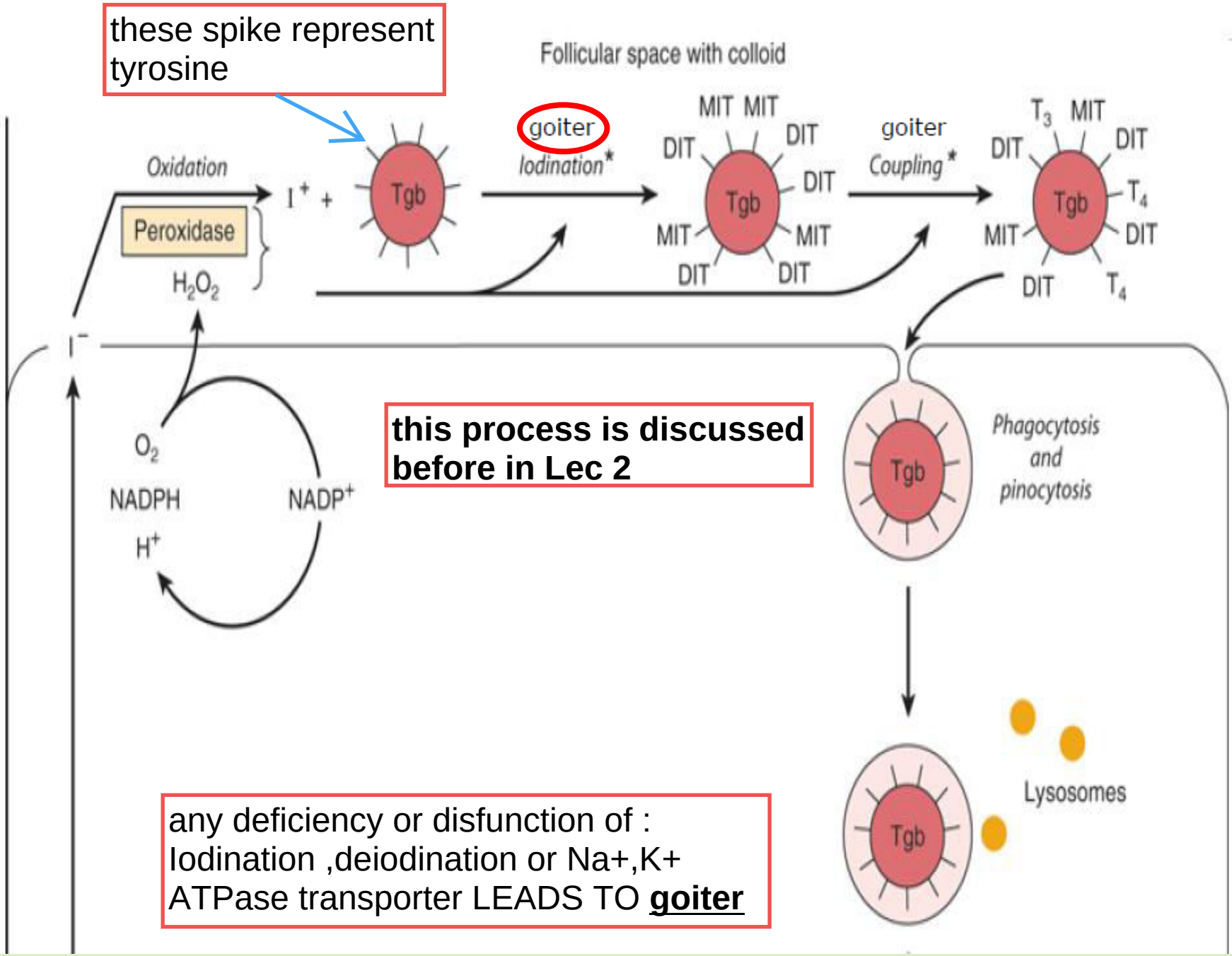
Parkinson disease, a neurodegenerative movement disorder, is due to insufficient dopamine production as a result of the idiopathic loss of dopamine-producing cells in the brain. Administration of L-DOPA (levodopa) is the most common treatment.

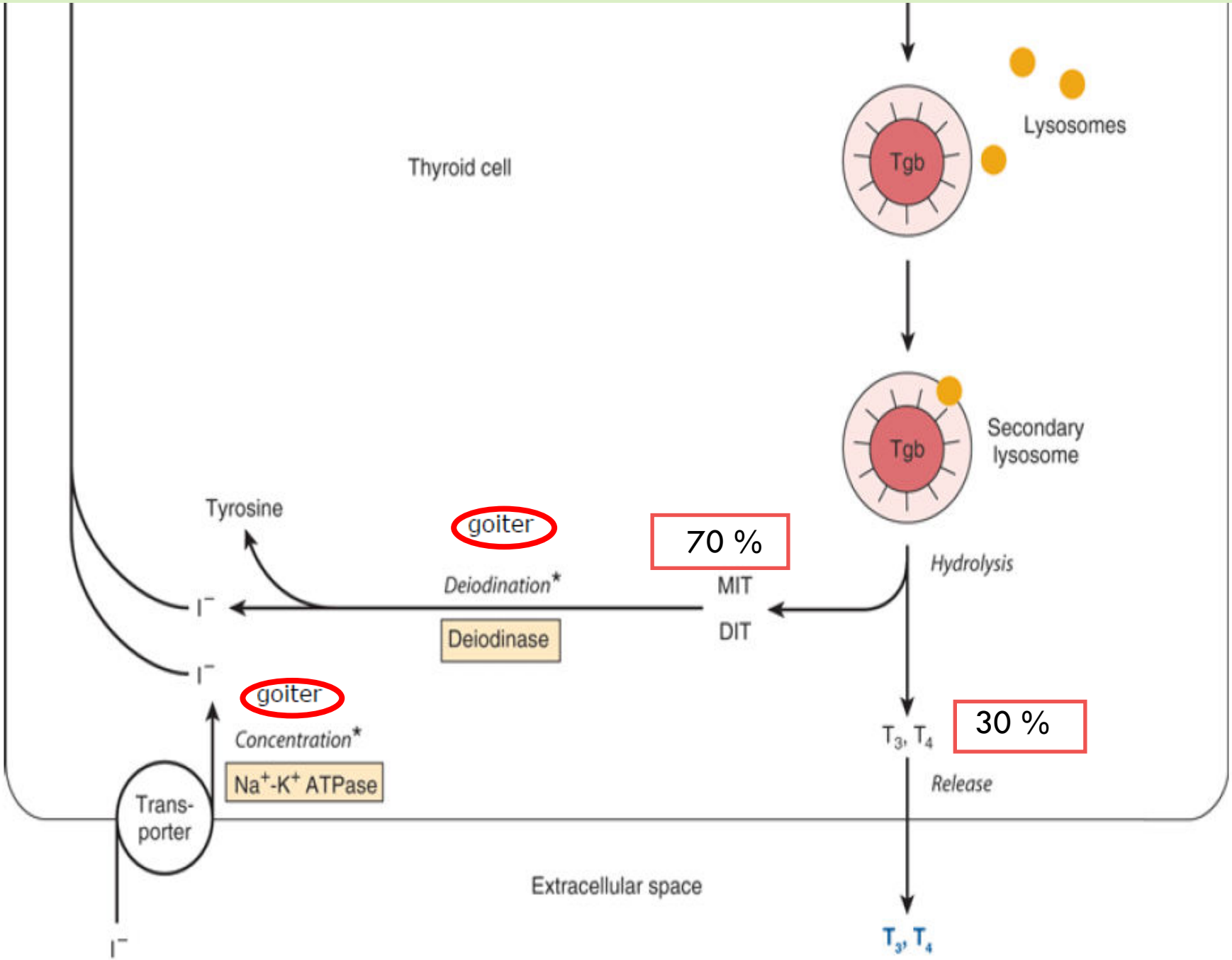
T3 & T4 Illustrate the Diversity in Hormone Synthesis

triiodothyronine (T3)

tetraiodothyronine (thyroxine; T4)

- Synthesized as part of a very large precursor molecule (thyroglobulin)
- Stored in (colloid)
- Peripheral conversion of T4 to T3 , active hormone.


these spike represent tyrosine
Follicular space with colloid
Oxidation
Peroxidase
H_2O_2
I^+ +
Tgb
goiter
Iodination*
MIT MIT
DIT
DIT
DIT
MIT
MIT
DIT
DIT
goiter
Coupling*
T_3 MIT
DIT
DIT
T_4
MIT
DIT
DIT
T_4
I^-
O_2
NADPH
H^+
$NADP^+$
this process is discussed before in Lec 2
Phagocytosis and pinocytosis
Lysosomes
any deficiency or disfunction of : Iodination ,deiodination or Na+,K+ ATPase transporter LEADS TO goiter


Thyroid cell
Lysosomes
Tgb
Tgb
Secondary lysosome
Tyrosine
goiter
70 %
Deiodination*
MIT
DIT
Deiodinase
Hydrolysis
I⁻
I⁻
goiter
Concentration*
Na⁺-K⁺ ATPase
Trans-porter
T3, T4
30 %
Release
Extracellular space
I⁻
T3, T4

Thyroglobulin (large prohormone)

- It is a large iodinated, glycosylated protein.
- Carbohydrate 8–10%
- Iodide 0.2–1%.
- Composed of two large subunits.
- Contains 115 tyrosine residues (potential site of iodination.

rich in tyrosine

- T4 :T3 ratio is about 7:1

Iodide Metabolism

The thyroid is able to concentrate I– against a strong electrochemical gradient.

through

Na+ -K+ ATPase-dependent thyroidal I– transporter.

The T:S ratio in humans on a normal iodine diet is about 25:1

stimulated by TSH

which means all iodine is concentrated in thyroid gland

Thyroperoxidase, a tetrameric protein requires hydrogen peroxide as an oxidizing agent. (thiourea drugs are inhibitors)

The coupling of two DIT molecules to form T4 —or of an MIT and DIT to form T3 —occurs within the thyroglobulin molecule.

DIT + DIT = T4
DIT + MIT = T3

A deiodinase removes I– from the inactive mono and diiodothyronine molecules in the thyroid.

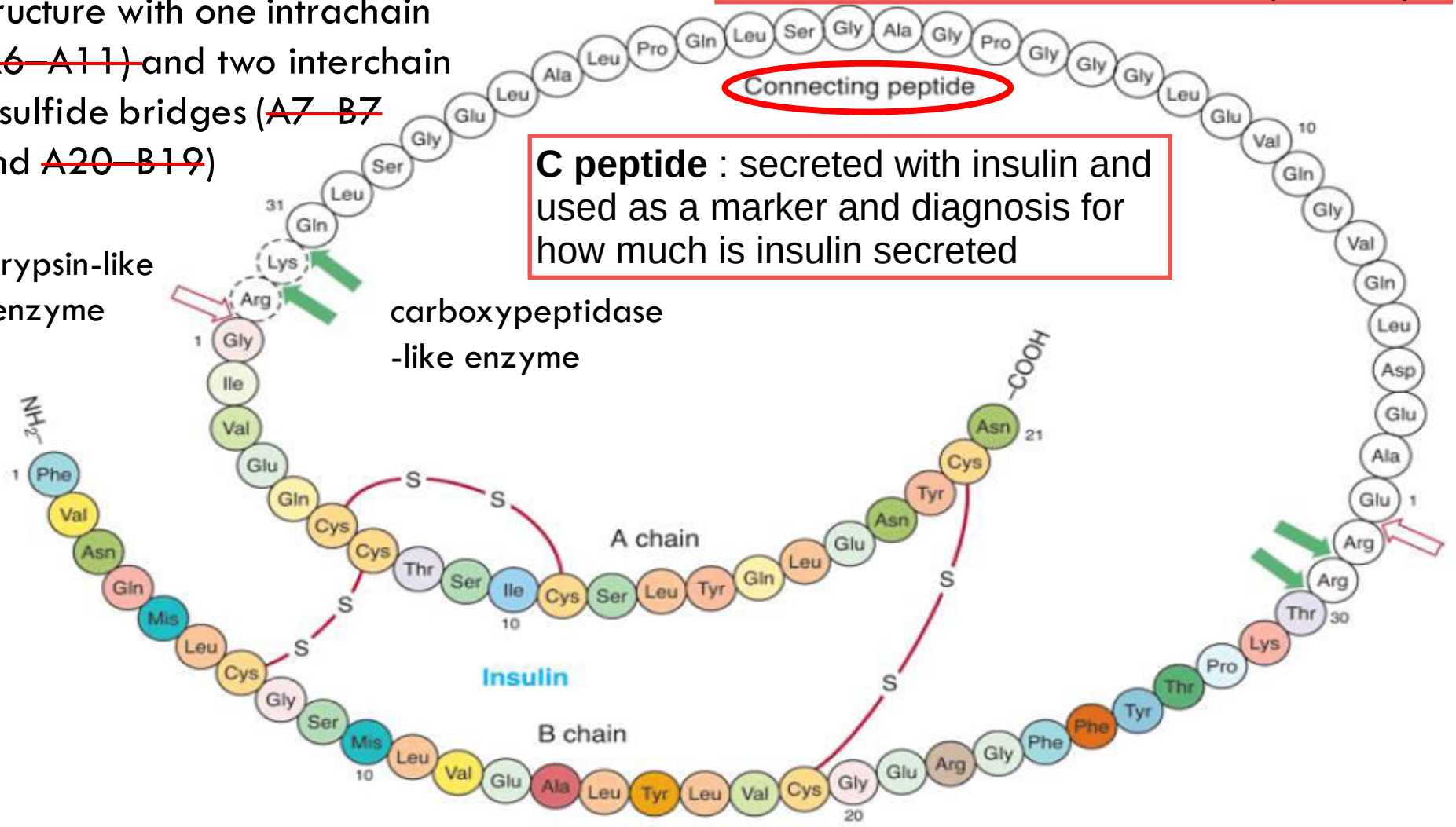
A peripheral deiodinase in target tissues such as pituitary, kidney, and liver selectively removes I– from the 5' position of T4 to make T3

Several Hormones Are Made from Larger Peptide Precursors

Insulin Is Synthesized as a Preprohormone & Modified Within the Beta Cell

Insulin has an AB heterodimeric structure with one intrachain ~~(A6–A11)~~ and two interchain disulfide bridges (~~A7–B7~~ and ~~A20–B19~~)

interchain : between 2 diff. chains(A and B)
intrachain: between same chain (A chain)

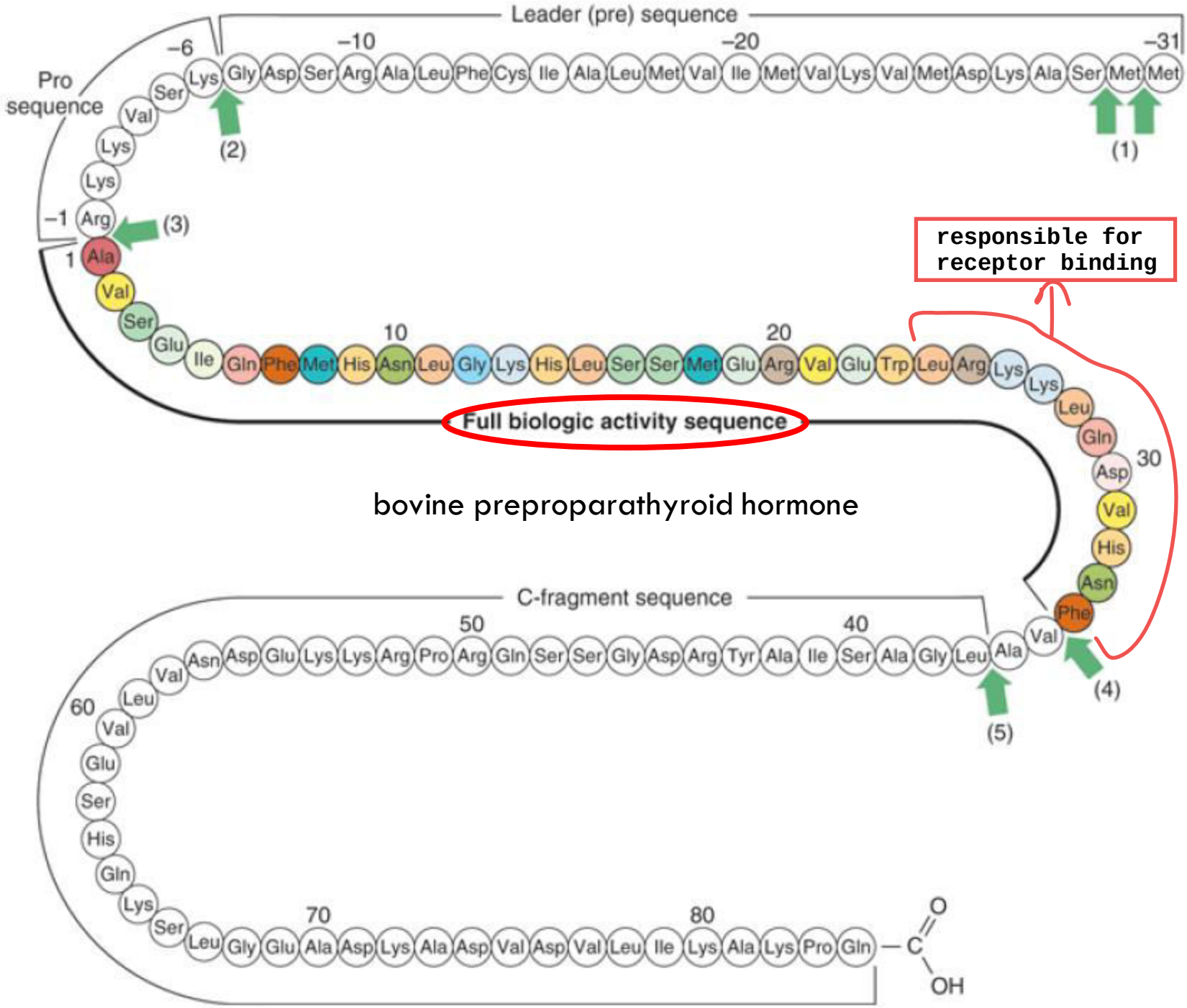


Parathyroid Hormone (PTH) Is Secreted as an 84-Amino-Acid Peptide

The immediate precursor of PTH is **proPTH:** highly basic hexapeptide amino terminal extension.

The immediate precursor for proPTH is the 115-amino-acid **preproPTH** (having an additional hydrophobic 25-amino-acid amino terminal extension)

PTH$\overset{\text{amino acids}}{(1\text{–}34)}$ has full biologic activity, and the region $(25\text{–}34)$ is primarily responsible for receptor binding



bovine preproparathyroid hormone

The biosynthesis of PTH and its subsequent secretion are regulated by the plasma ionized calcium (Ca^{2+})

An acute decrease of Ca^{2+} results in a marked increase of PTH mRNA, and this is followed by an increased rate of PTH synthesis and secretion.

A number of proteolytic enzymes, including cathepsins B and D, have been identified in parathyroid tissue.

Cathepsin B cleaves PTH into two fragments: PTH 1–36 and PTH37–84 .

PTH37–84 is not further degraded;
PTH1–36 is rapidly cleaved into di- and tripeptides.

active one

Most of the proteolysis of PTH occurs within the gland

Some studies suggested PTH, once secreted, is proteolytically degraded in other tissues, especially the liver, by similar mechanisms.

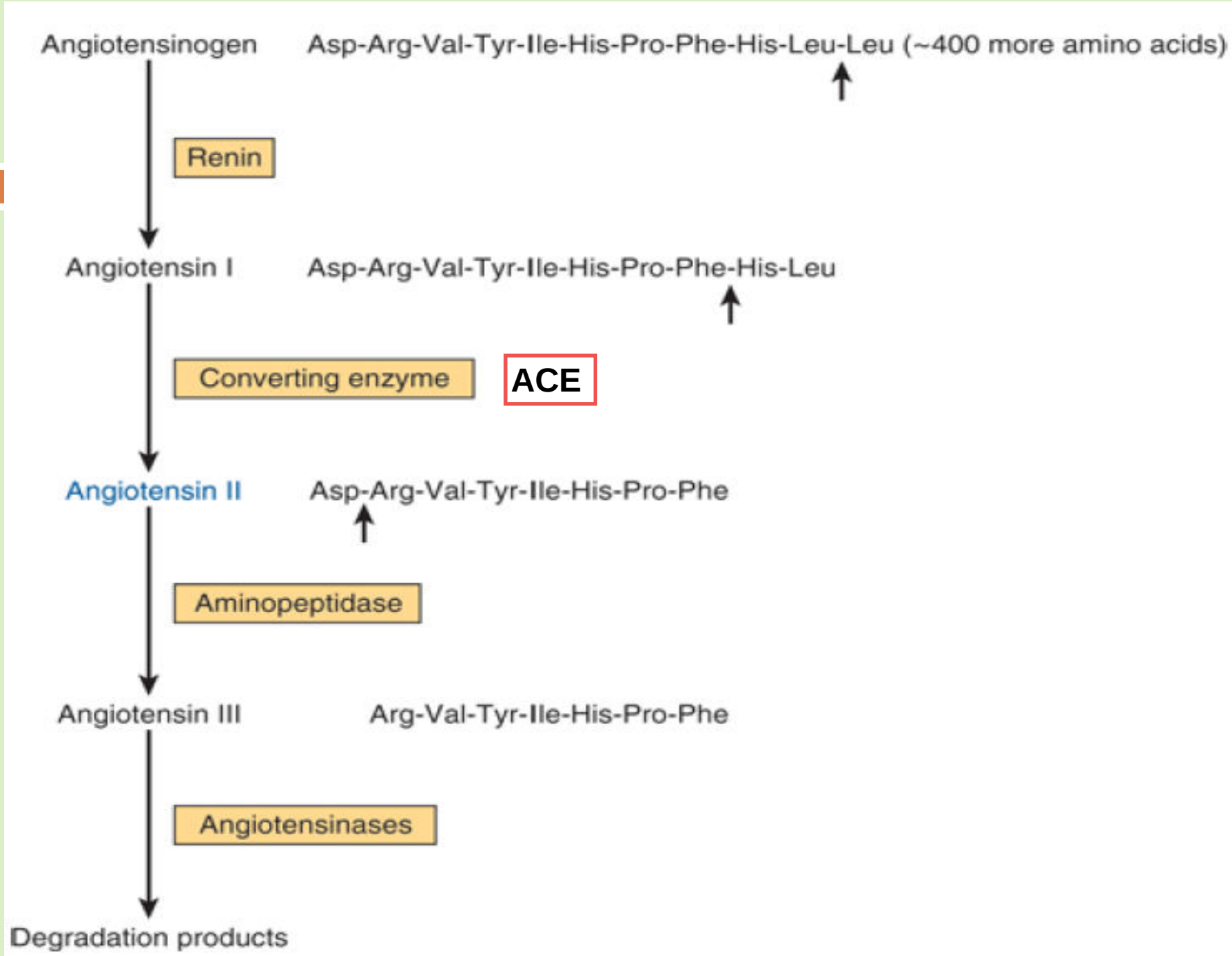
Angiotensin II Is Also Synthesized from a Large Precursor

The renin-angiotensin system is involved in the regulation of blood pressure and electrolyte metabolism (through production of aldosterone).

we call it angiotensiogen rather than proangiotensin

Angiotensin II, an octapeptide made from angiotensinogen

Angiotensinogen, a large $\alpha 2$ -globulin made in liver, is the substrate for renin, an enzyme produced in the juxtaglomerular cells of the renal afferent arteriole.


Angiotensinogen
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu (~400 more amino acids)
Renin
Angiotensin I
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu
Converting enzyme
ACE
Angiotensin II
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe
Aminopeptidase
Angiotensin III
Arg-Val-Tyr-Ile-His-Pro-Phe
Angiotensinases
Degradation products

Angiotensin-converting enzyme (ACE), a glycoprotein found in lung, endothelial cells, and plasma, removes two carboxyl terminal amino acids from the decapeptide angiotensin I to form angiotensin II in a step that is not thought to be rate-limiting.

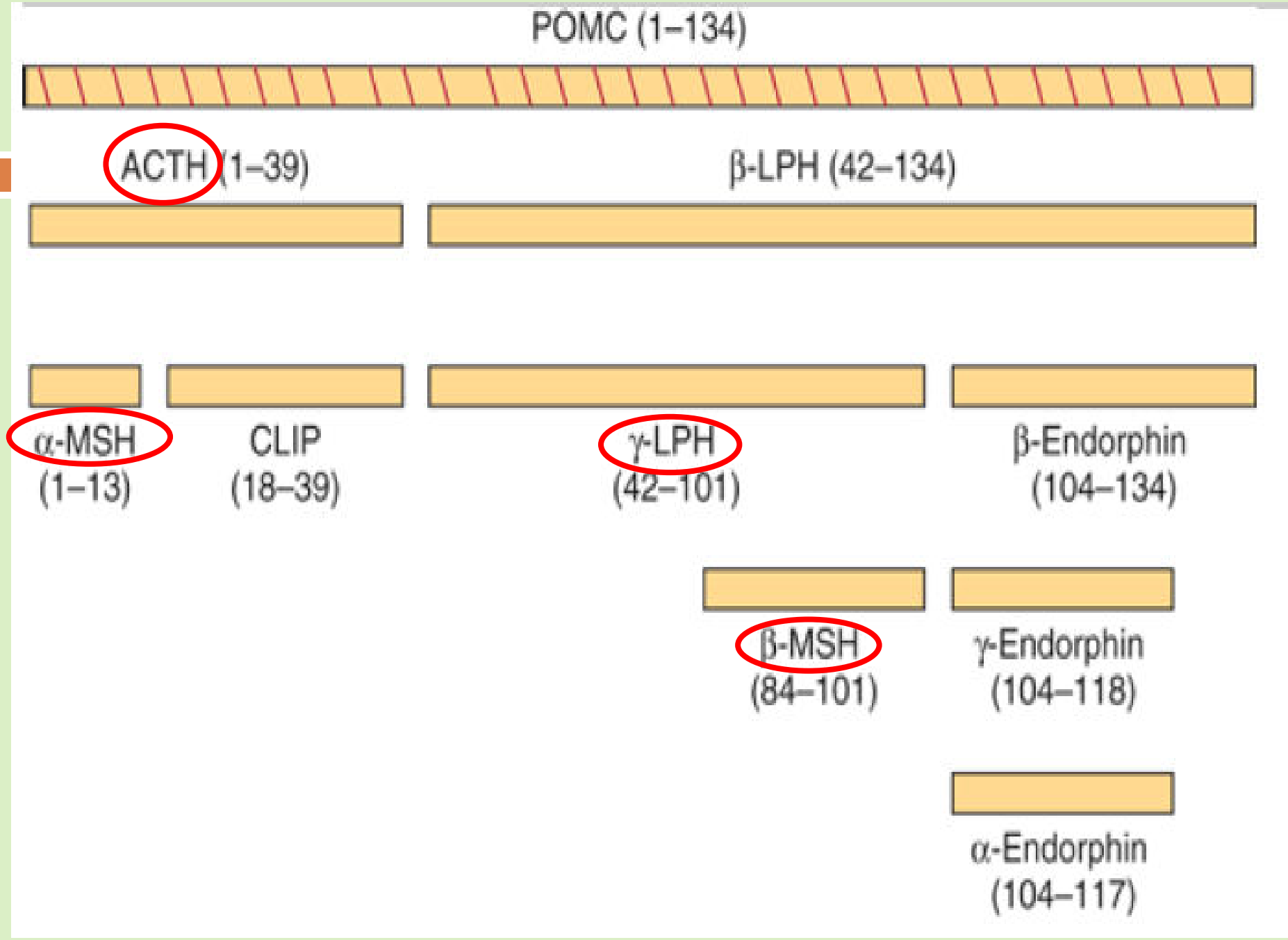
Complex Processing Generates the Pro-Opiomelanocortin (POMC) Peptide Family

The POMC family consists of peptides that act as hormones (ACTH, LPH, MSH)

Thers that may serve as neurotransmitters or neuromodulators (endorphins)

POMC is synthesized as a precursor molecule of 285 amino acids and is processed differently in various regions of the pituitary.

Mutations of the -MSH receptor are linked to a common, early-onset form of obesity. This observation has redirected attention to the POMC peptide hormones.


POMC (1–134)
ACTH (1–39)
β-LPH (42–134)
α-MSH (1–13)
CLIP (18–39)
γ-LPH (42–101)
β-Endorphin (104–134)
β-MSH (84–101)
γ-Endorphin (104–118)
α-Endorphin (104–117)