

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



العلم

BIOCHEMISTRY

FINAL | Lecture 1

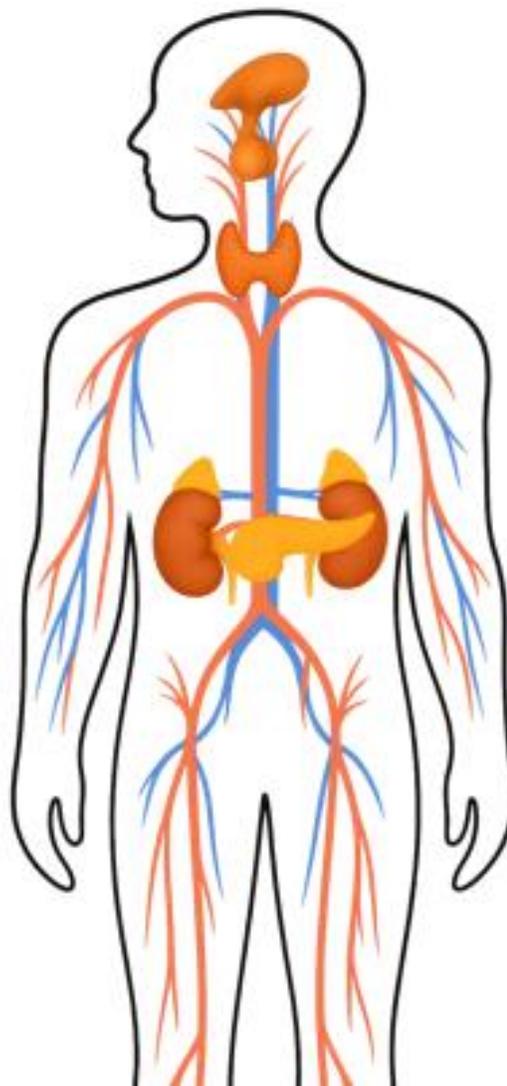
Receptor Tyrosine Kinase cascade & Hormones

Writer:

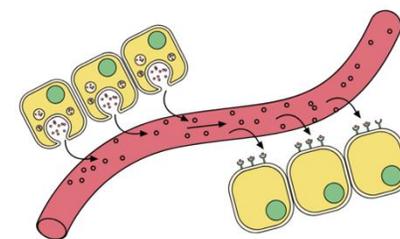
Layan Fawarseh

Reviewer:

Layan Fawarseh



اللهم جنبنا الفتن، ما ظهر منها وما بطن



الحديث الخامس والعشرون

عَنْ أَبِي ذَرٍّ رَضِيَ اللَّهُ عَنْهُ قَالَ: أَنَّ أَنَسًا مِنْ أَصْحَابِ رَسُولِ اللَّهِ ﷺ قَالُوا لِلنَّبِيِّ ﷺ يَا رَسُولَ اللَّهِ: ذَهَبَ أَهْلُ الدُّثُورِ بِالْأَجُورِ، يُصَلُّونَ كَمَا نُصَلِّي، وَيَصُومُونَ كَمَا نَصُومُ، وَيَتَصَدَّقُونَ بِفُضُولِ أَمْوَالِهِمْ، قَالَ: (أَوْ لَيْسَ قَدْ جَعَلَ اللَّهُ لَكُمْ مَا تَصَدَّقُونَ؟ إِنَّ بِكُلِّ تَسْبِيحَةٍ صَدَقَةٌ وَكُلِّ تَكْبِيرَةٍ صَدَقَةٌ وَكُلِّ تَحْمِيدَةٍ صَدَقَةٌ وَكُلِّ تَهْلِيلَةٍ صَدَقَةٌ وَأَمْرٌ بِالْمَعْرُوفِ صَدَقَةٌ وَنَهْيٌ عَنِ الْمُنْكَرِ صَدَقَةٌ وَفِي بَضْعِ أَحَدِكُمْ صَدَقَةٌ قَالُوا: يَا رَسُولَ اللَّهِ أَيَّتِي أَحَدْنَا شَهْوَتُهُ وَيَكُونُ لَهُ فِيهَا أَجْرٌ؟ قَالَ: أَرَأَيْتُمْ لَوْ وَضَعَهَا فِي حَرَامٍ أَكَانَ عَلَيْهِ وَزْرٌ؟ فَكَذَلِكَ إِذَا وَضَعَهَا فِي الْحَلَالِ كَانَ لَهُ أَجْرٌ)

النبى ﷺ قال للصحابه: أليس الله قد جعل لكم طرقاً كثيرة للصدقة؟ أي أن الصدقة ليست فقط بالمال، بل هناك صدقات كثيرة يمكن لكل مسلم القيام بها. كل مرة تقول فيها "سبحان الله" تعد صدقة لك، وكل مرة تقول "الله أكبر" تعتبر صدقة، وكل مرة تقول "الحمد لله" هي صدقة أيضاً، وكل مرة تقول "لا إله إلا الله" تعد صدقة، الأمر بالمعروف والنهي عن المنكر هما من أفعال الصدقة التي يجها الله، أيضاً كل عمل صالح يبذله الإنسان يعتبر صدقة، حتى أبسط الأشياء. سأل الصحابة النبي ﷺ هل يمكن أن يحصل الإنسان على أجر حتى في شهواته؟ فأجاب النبي ﷺ: إذا استغلها في الحرام يكون عليه وزر، وإذا استغلها في الحلال فله أجر وثواب. الحديث يشجع على الذكر المستمر ويعلم أن الأعمال الصالحة ليست مقصورة على المال فقط، وأن الله جعل لكل شخص فرصة للصدقة مهما كانت إمكانياته. كما يوضح أن الشهوات الطبيعية يمكن أن تكون سبباً للأجر إذا كانت في حدود الشرع

اللهم اجعلني من الذاكرين لك، واجعل عملي خالصاً لوجهك، وارزقني خير الدنيا والآخرة

REMEMBER FROM GENERAL BIOCHEMISTRY

- phosphorylation does not always lead to activation of proteins and enzymes but logically should lead to activation of some target proteins and inhibition of others.

62! Don't freak out – you already know most of the information on the slides. Some content is repeated, and there are many figures as well.

استعينوا بالله وبسم الله

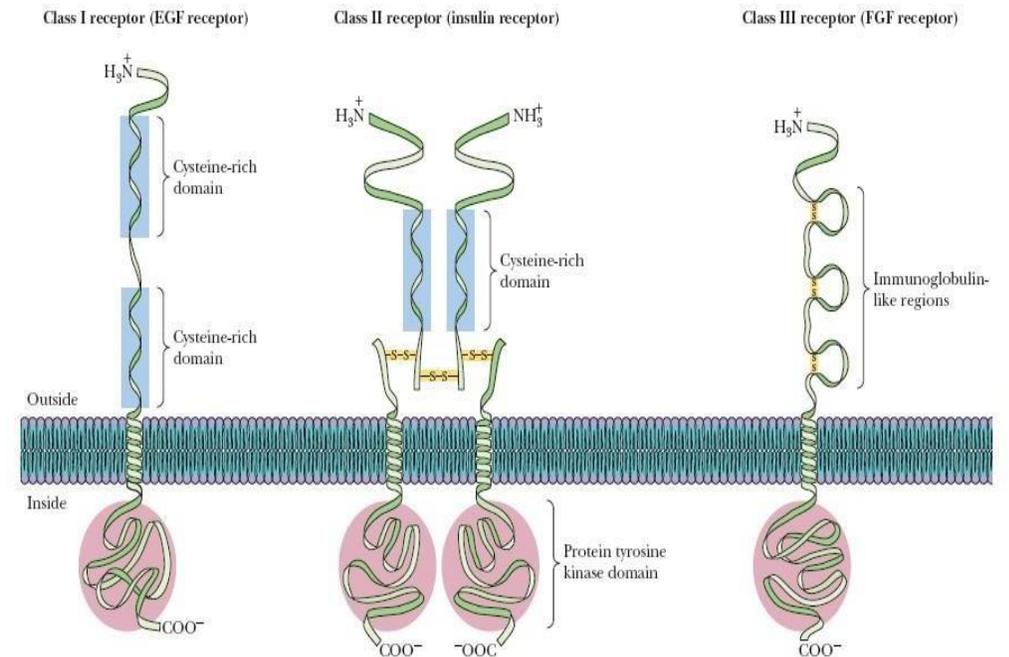


Receptor Tyrosine Kinases Cascade

These receptors are performing two functions:

1. Second Messengers **inside cells, since they are enzymes.**
2. Hormone receptor & tyrosine kinase portion: span the membrane, several subclasses (class II, Insulin R).

The receptors differ from each other as they belong to different classes either dimers, like the insulin receptor (which has a disulfide bond), or monomer receptors, where the hormone binding causes conformational changes that leads to dimerization of 2 receptors.





Second Messengers

Receptor Tyrosine Kinases

- When activated (**dimer**) → tyrosines on target proteins:
 - Alterations in membrane transport of ions & amino acids & the transcription of certain genes
- They are kinases, so their activation leads to phosphorylation of many proteins downstream this signaling process that allows for changes inside the target cells including the transcription of genes, they have tyrosine on each monomer of the dimer receptor.
 - **Dimerization all the time is necessary but not sufficient for activation (kinase activity).**
 - The way they get activated is implied in the name they adopt “Tyrosine”; where they have tyrosine on each monomer of the dimer receptor.
 - **Phospholipase C** is one of the targets
 - Insulin-sensitive protein kinase: activates **protein phosphatase 1**



Second Messengers

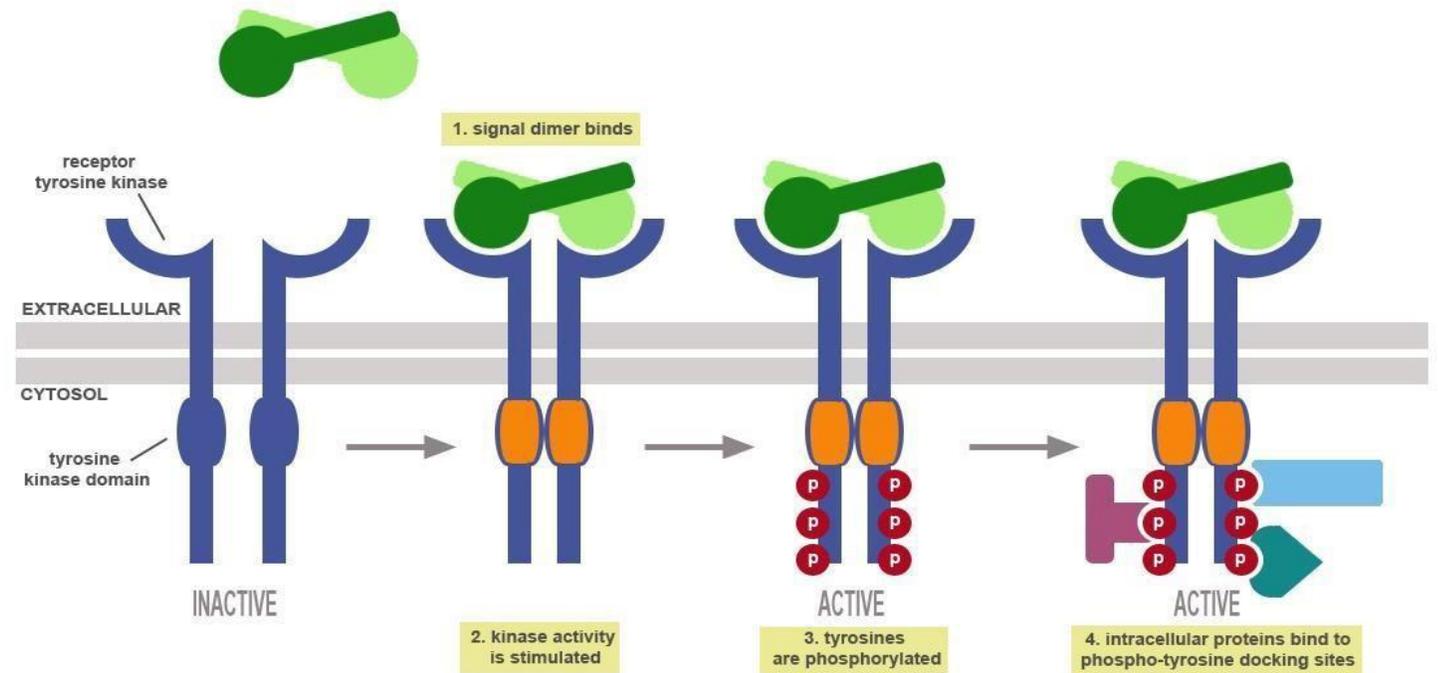
Receptor Tyrosine Kinases

1. **Hormonal binding** induces dimerization.

2. **Conformational changes** occur on each monomer that allow these tyrosines to be **phosphorylated on the same monomer and on the other monomer**, so each monomer

will be able to phosphorylate its own and the other monomer's tyrosines in what is called **auto- and cross-phosphorylation**.

- **So, dimerization is key for the activation of these receptors, however it is not enough. Full activation occurs when tyrosines are phosphorylated, and this leads to phosphorylation of target proteins and molecules.**

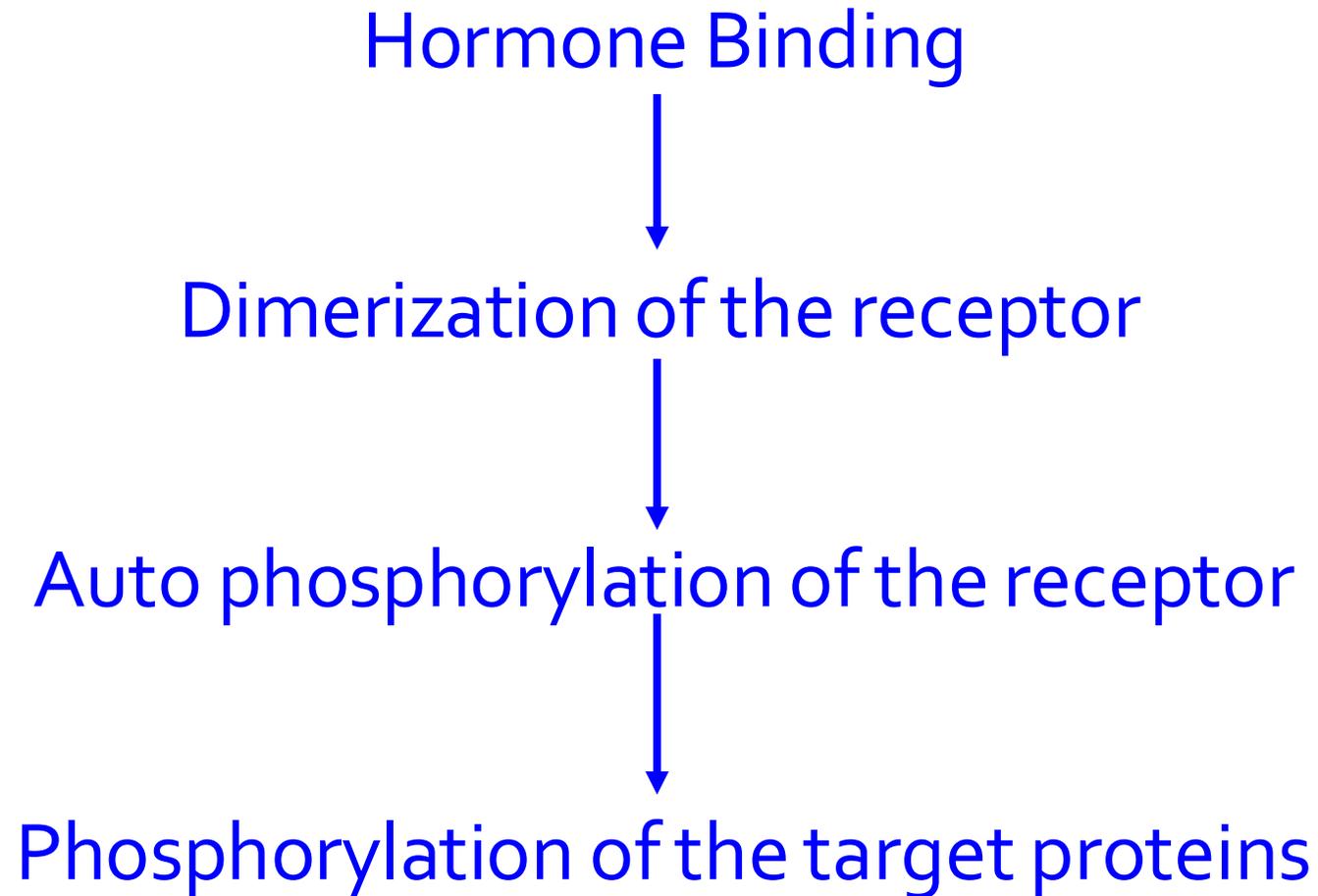




Signal Transduction through Tyrosine Kinase

Growth hormones:

- ✓ **Epidermal Growth Factor**
- ✓ **Platelet-derived growth Factor**
- ✓ **GH**
- ✓ **Insulin**





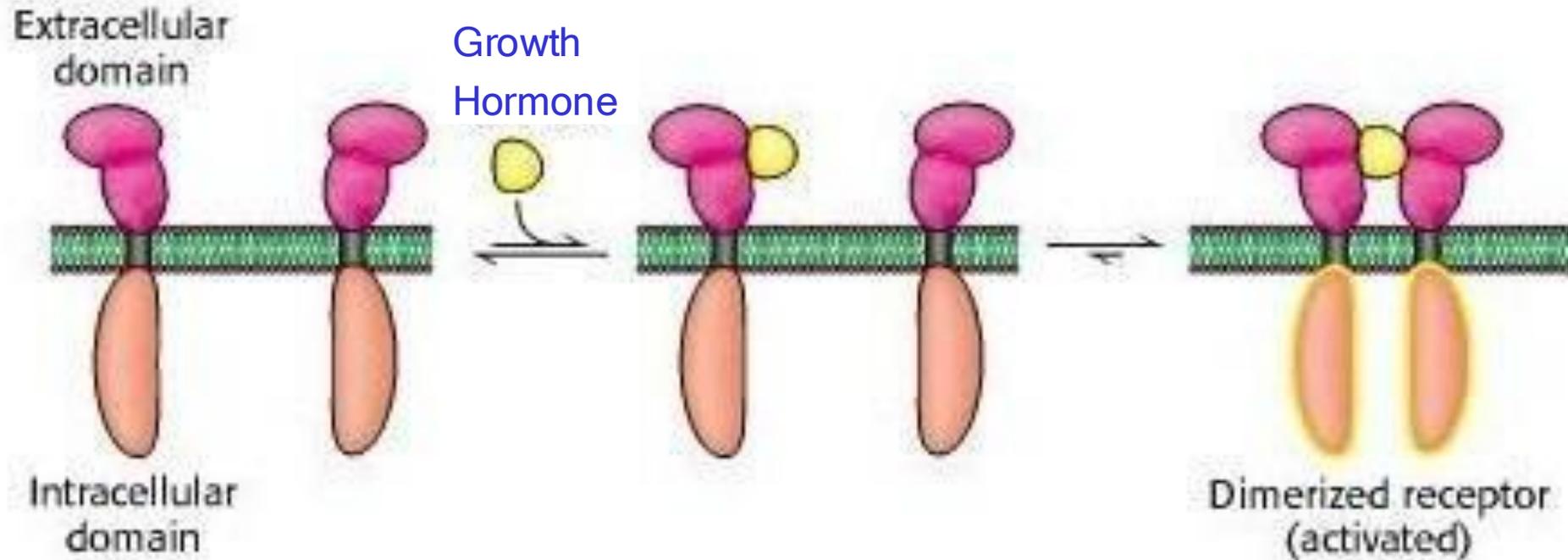
Growth Hormone dimerization

Binding of one molecule of growth hormone



Dimerization of the receptor

(B)

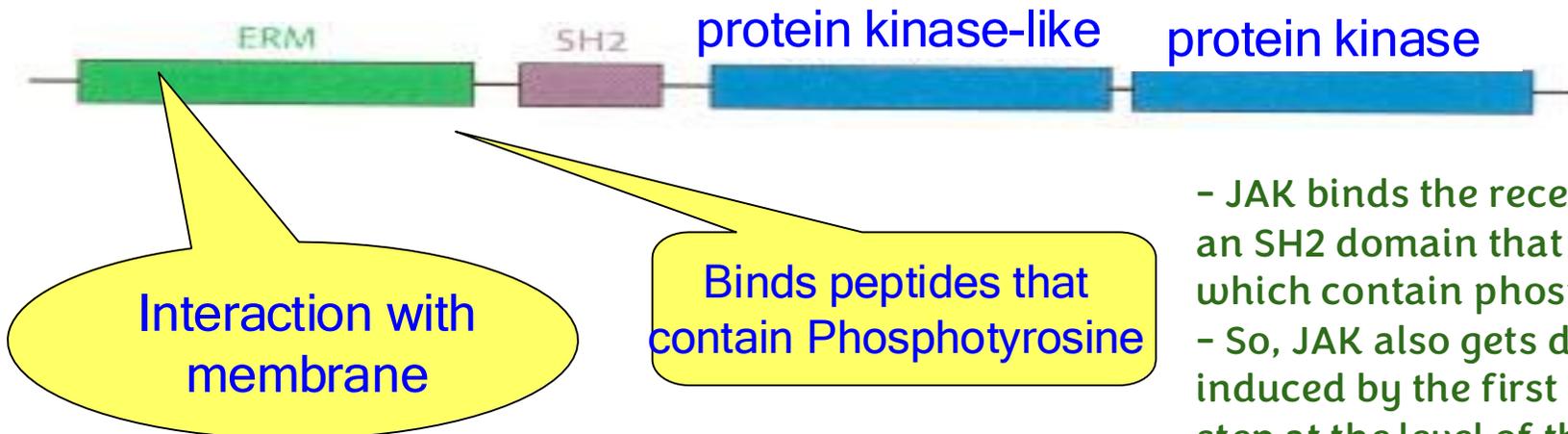




Janus



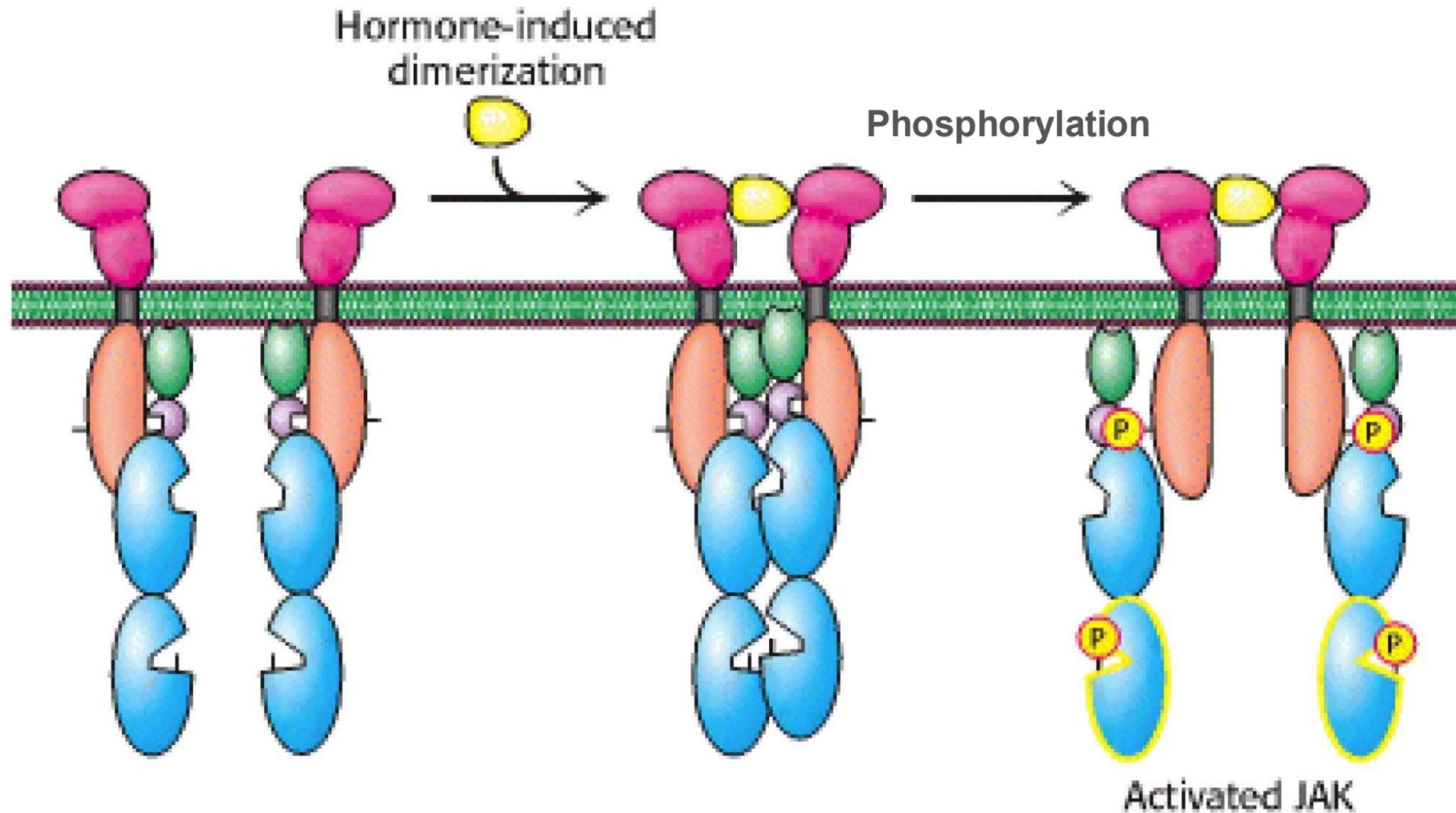
- Receptor tyrosine kinases are functioning as dimers where each monomer has an intracellular domain is attached or associated with a protein kinase called Janus Kinase 2 “JAK” that also works as a dimer.
- As a result of this dimerization step of “Receptor Tyrosine Kinase” , **JAK will also dimerize**, inducing **phosphorylation of JAK itself** by the receptor, and when JAK is phosphorylated, it is now **fully active** where it can phosphorylate other target proteins since JAK is also a kinase.



- JAK binds the receptor since it has an SH2 domain that binds peptides which contain phosphotyrosine.
- So, JAK also gets dimerized that is induced by the first dimerization step at the level of the receptor itself.



Receptor dimerization brings two JAKs together
Each Phosphorylates key residues on the other





Activated JAK 2 can Phosphorylate other substrates

- **STAT**
 - Signal Transducers & Activators of Transcription
- Regulator of transcription
- STAT Phosphorylation → **Dimerization** → Binding to specific DNA sites
- If JAK2 remains active it will produce **Cancer**

- **Activated JAK can phosphorylate other substrates including what is called the STATs (Signal Transducers and Activators of Transcription) proteins. These proteins will affect their target, as the name implies, which are genes. So they are transcription factors.**

- **Amazingly, these transcription factors also work through a dimerization process.**

- **STAT has also:**

a- **tyrosine residues to be phosphorylated by JAK.**

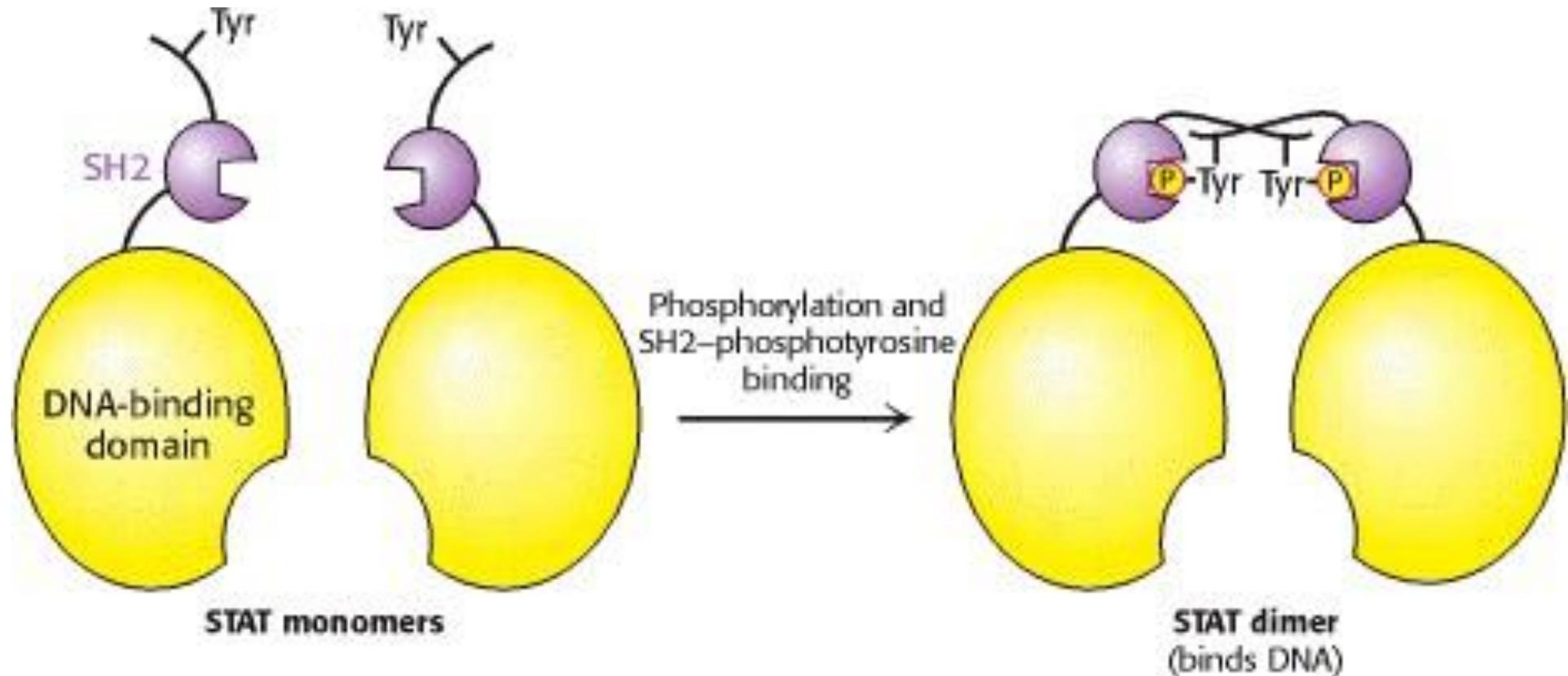
b- **SH2 domain for JAK binding.**

- **As a coupling domain, DNA-binding domain transmits the message to the genes for the transcription to start.**



STAT is phosphorylated on a tyrosine residue near the carboxyl terminus

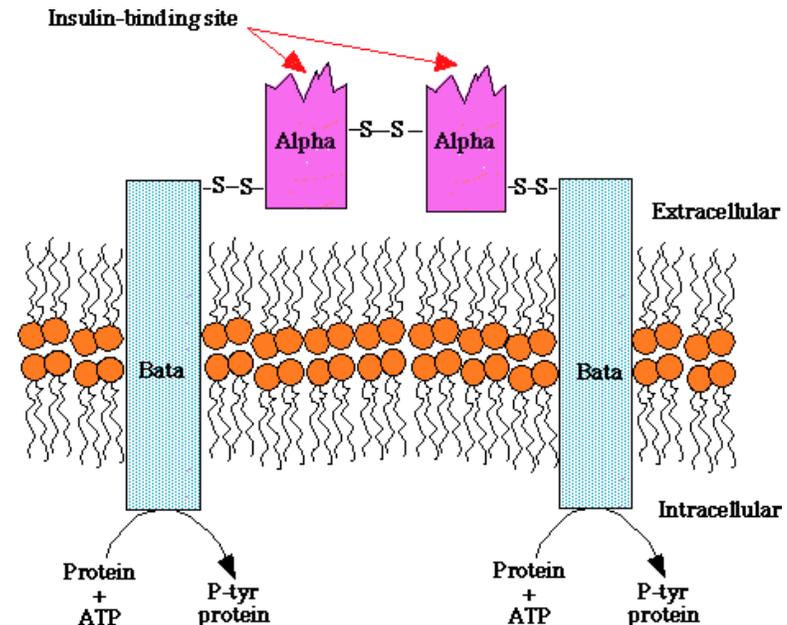
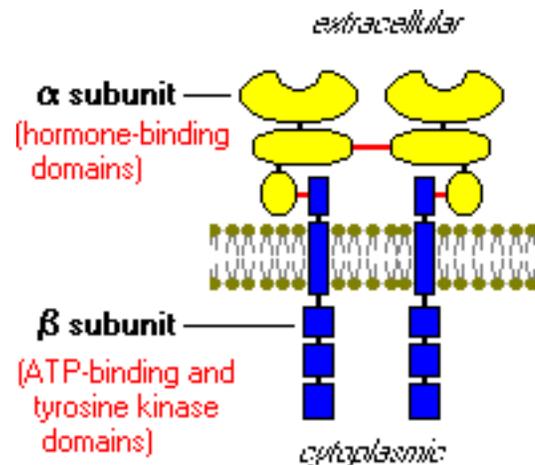
Phosphorylated tyr binds to SH2 domain of another STAT molecule





Tyrosine Kinase & other Hormones

- Insulin Receptor (class II receptor)
- Tetramer (2α ; 2β), dimer ($2\alpha\beta$ pairs)
- Connected by Disulfide bridges, although these receptors are in the dimeric form from the start, they are inactive.
- Insulin Binding → Activation of the Kinase
- Binding of the hormone to them induces conformational changes (in spite of the disulfide bridges present) that leads to partial activation. This is followed by phosphorylation that leads to full activation as discussed earlier.



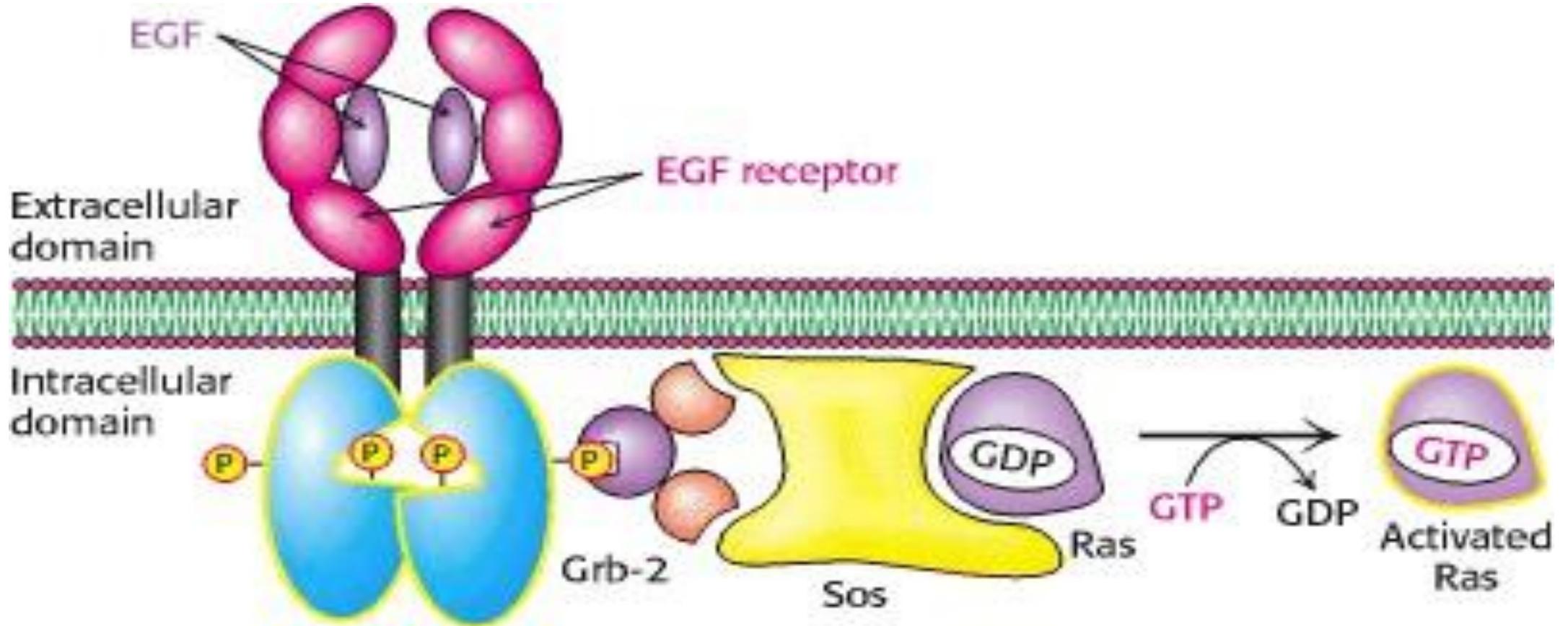


Ras is a member of small G proteins family

- Monomeric G proteins (function just like the alpha subunit of the trimeric G proteins).
- 2 forms: GDP \leftrightarrow GTP (They get activated through binding of the GTP in place of GDP and get deactivated through hydrolysis of the bound GTP)
- Smaller (1 subunit). Trimeric G proteins are membrane bound and associated to receptors while monomeric ones like **RAS are not associated with the membrane and exert their effect in the cytoplasm or the nucleus**. These proteins include several groups or subfamilies and play major role in growth, differentiation, cellular transport, motility etc...
- GTPase activity
- Many similarities in structure and mechanism with $G\alpha$
- Include several groups or subfamilies
- Major role in growth, differentiation, cellular transport, motility etc...



Ras is a member of small G proteins family





Impaired GTP_{ase} activity can lead to cancer in human

- Mammalian cells contain 3 types of Ras proteins where each is reported to have a mutation that might lead to cancer :

Mutation → Loss of ability to hydrolyze the bound GTP → Ras is locked in “ON” position → continuous stimulation of growth



Structure of hormones by location

It is not required to know all the structures as some are included only to get you exposed to them. Required structures will be pointed out.



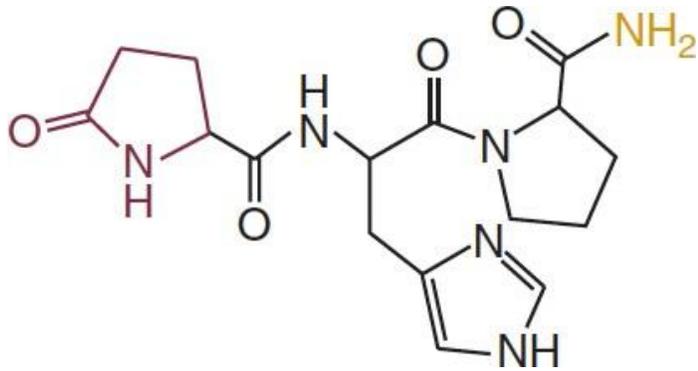
Hypothalamus

Hormone	Composition
Growth hormone releasing hormone (GHRH) - the biggest among hypothalamus hormones	Two forms: polypeptides (40 & 44 amino acids)
▪ Somatostatin, the special feature in somatostatin is that it has a disulfide bridge. As you will notice, many proteins have disulfide bonds, why? - After protein folds to its 3D structure, disulfide bonds are formed to stabilize the structure.	Two forms: polypeptides (14 & 28 amino acids)
Dopamine is the odd one (amino acid derived not a polypeptide) - <i>structure required</i> .	Catecholamine (amino acid derivative)
Corticotropin releasing hormone (CRH)	Polypeptide (41 amino acids)
Gonadotropin releasing hormone (GnRH)	Polypeptide (10 amino acids)
Thyrotropin releasing hormone (TRH) is the smallest peptide hormone	Polypeptide containing 3 amino acids

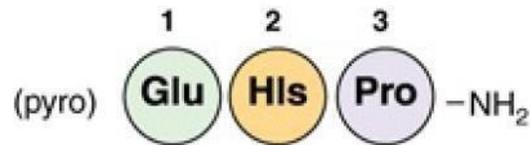
- Growth hormone and somatostatin have two forms.



Hypothalamus



thyrotropin-releasing hormone, TRH.



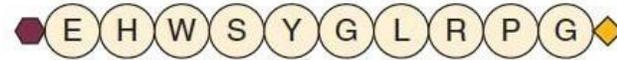
TRH

● (E) = pyroglutamyl

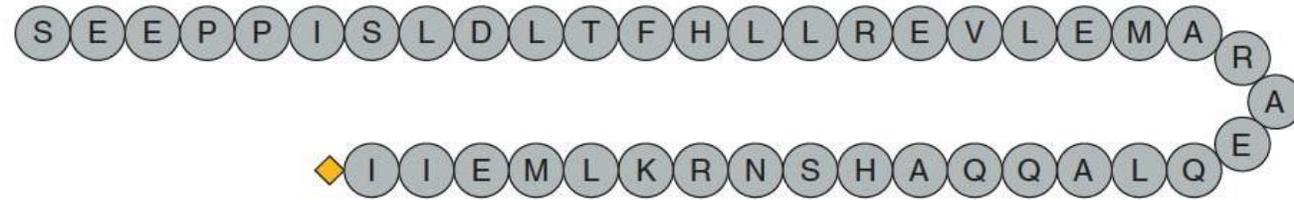
○ ◆ = c-terminal amide: prolinamide (TRH); glycynamide (GnRH); isoleucinamide (CRH); leucinamide (GHRH)



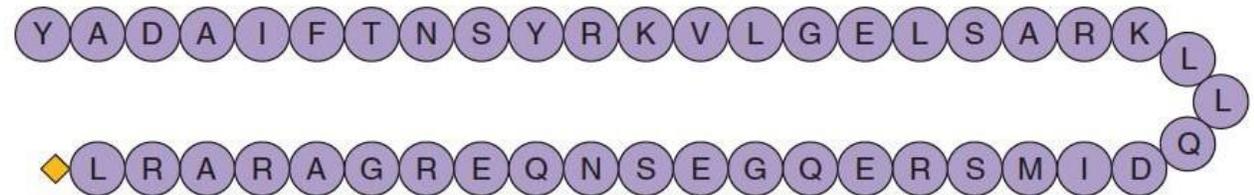
TRH: Thyrotrophin releasing hormone



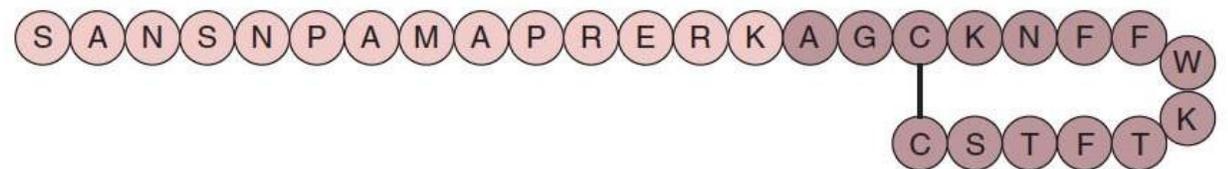
GnRH: Gondaotrophin releasing hormone



CRH: Corticotrophin releasing hormone



GHRH: Growth hormone releasing hormone



SST: Somatostatin



Anterior Pituitary

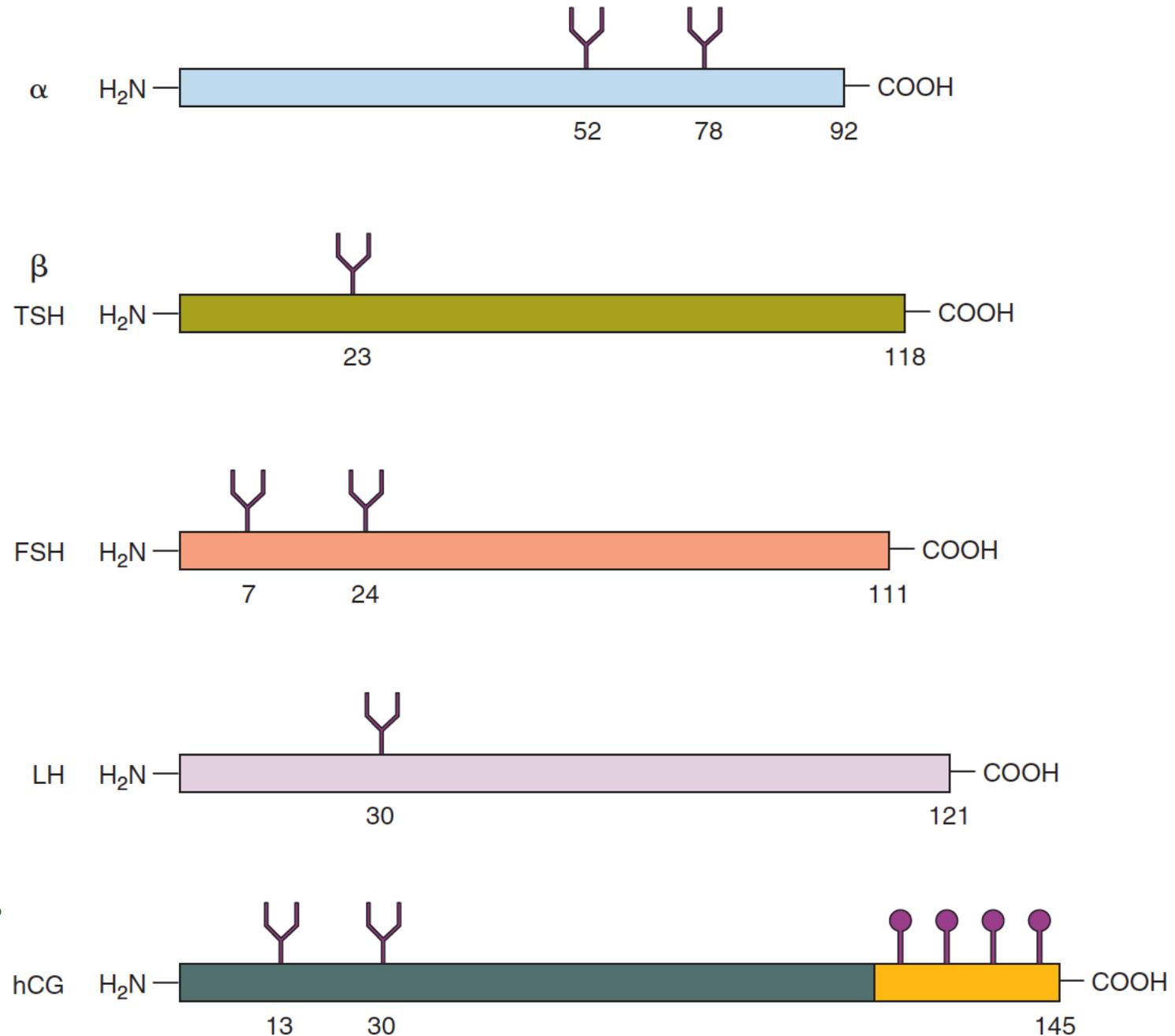
Hormone	Composition
Growth hormone (somatotropin, GH)	Straight-chain protein: two forms (191 aa) and (176 aa)
Prolactin (PRL)	Straight-chain protein (198 aa)
Adrenocorticotrophic hormone (ACTH)	Small polypeptide (39 aa)
Follicle-stimulating hormone (FSH)	2-chain glycoprotein: (α , 92 aa; β , 111 aa)
Luteinizing hormone (LH)	2-chain glycoprotein: (α , 92 aa; β , 116 aa)
Thyrotropic hormone (TSH)	2-chain glycoprotein: (α , 92 aa; β , 112 aa)

- FSH, LH, and TSH are 2 subunit proteins consisting of α and β subunits connected by a disulfide bridge.
 - The α subunit in these proteins are identical indicating that it has only a structural role, while the β subunits are different indicating that it has a functional role.
- hCG (human chorionic gonadotropin) has O-glycosylated region, this hormone is produced by placenta during pregnancy, it shares the alpha subunit with anterior pituitary hormones.



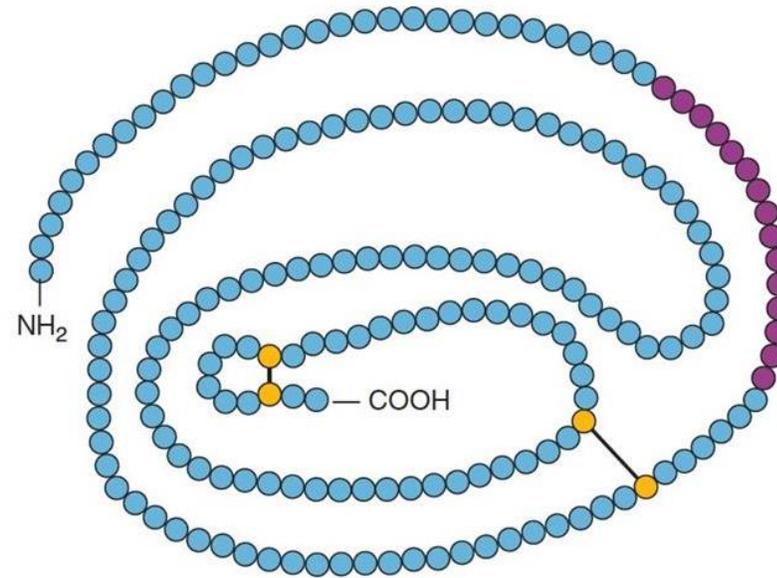
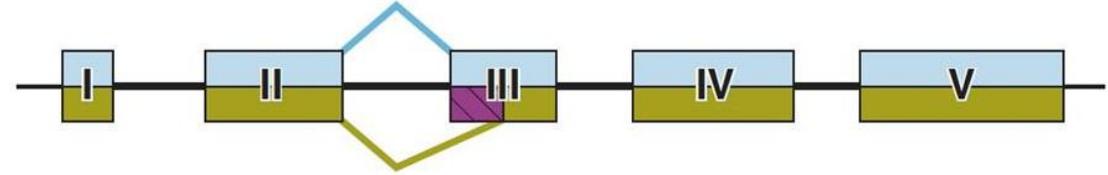
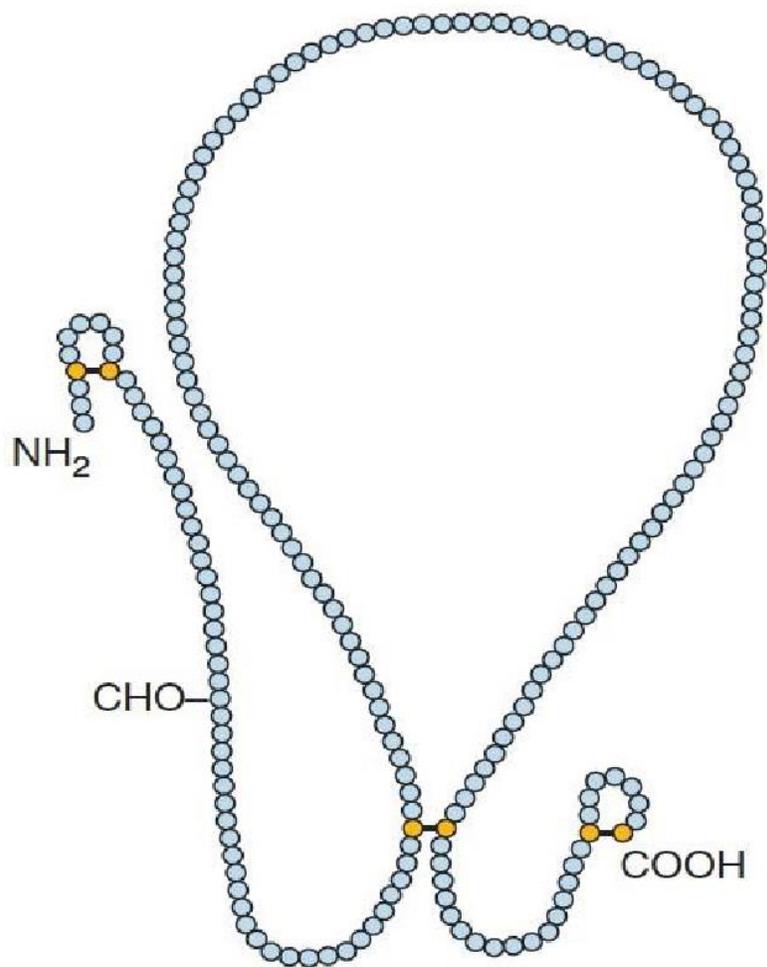
Anterior pituitary

- N-glycosylation (Asn)
vs. O-glycosylation (ser)
- All anterior pituitary gland hormones are N-glycoproteins (except for prolactin – not glycosylated).
- The glycosylation of the proteins gives them a greater binding ability since it makes them more viscous and stickier.

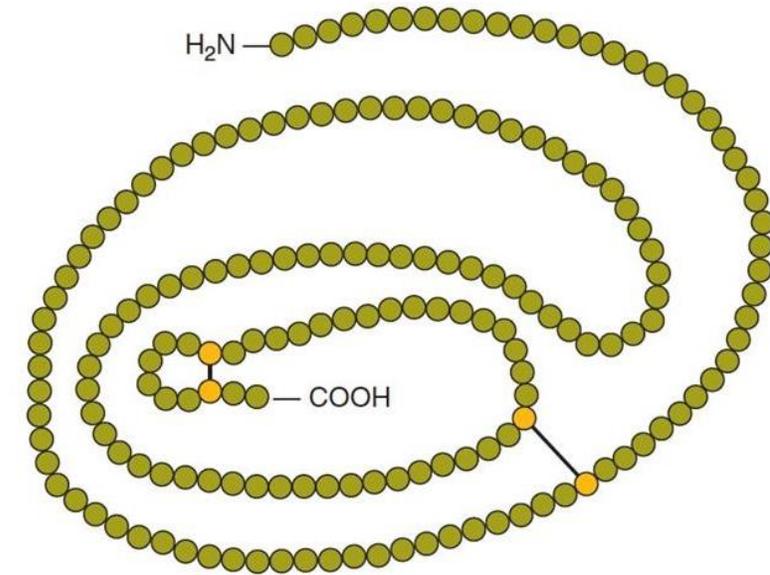




Anterior pituitary – GH & prolactin



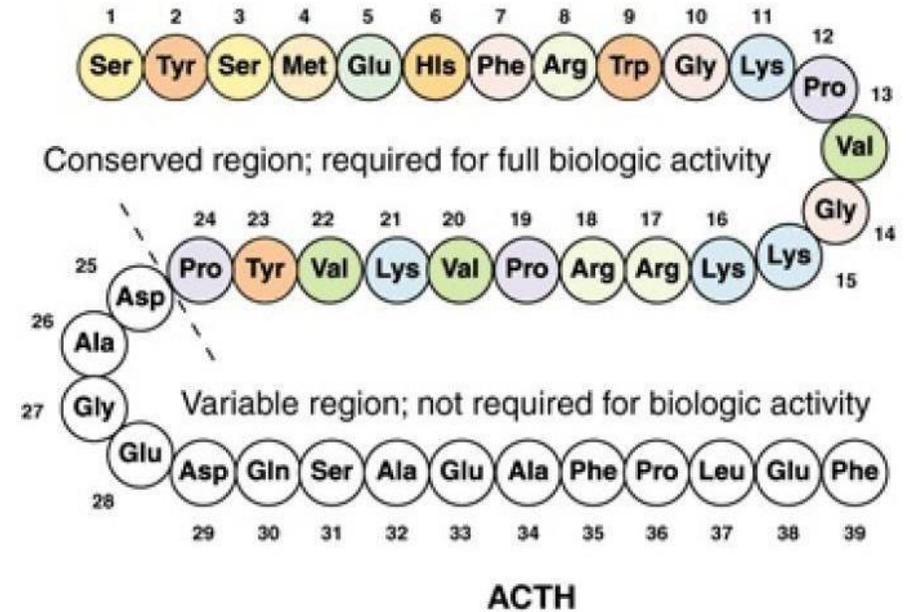
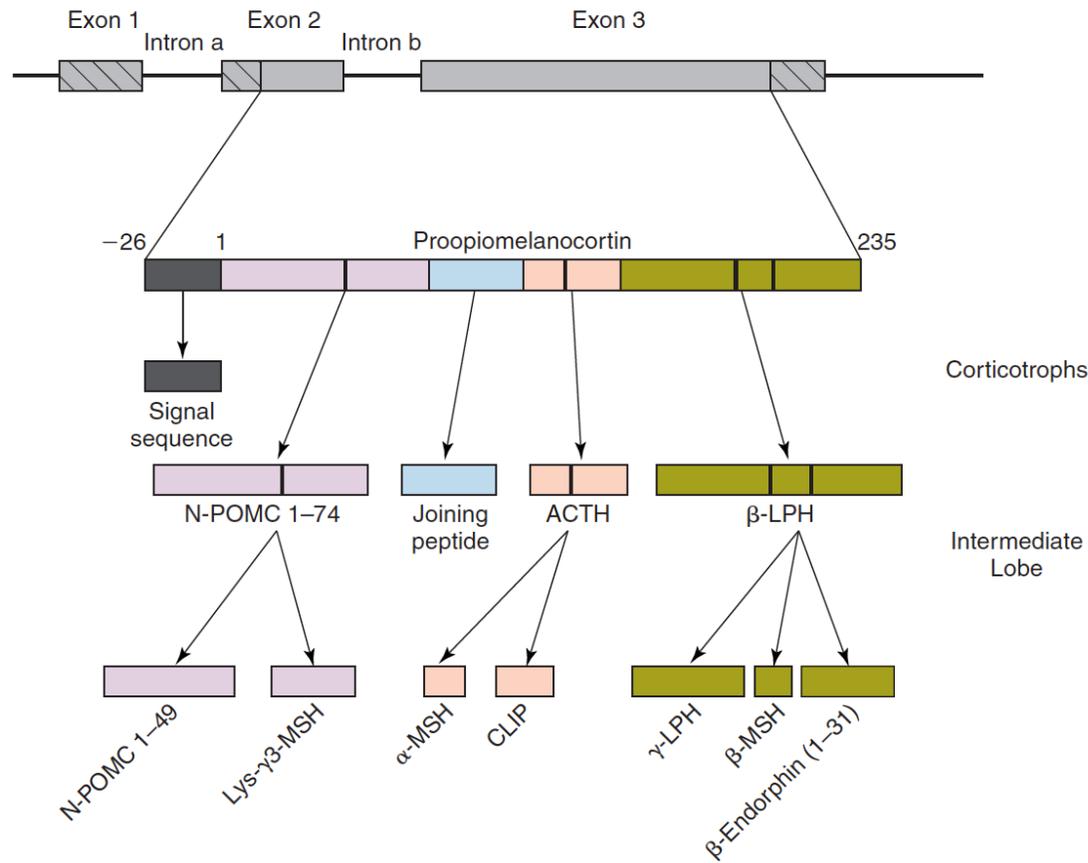
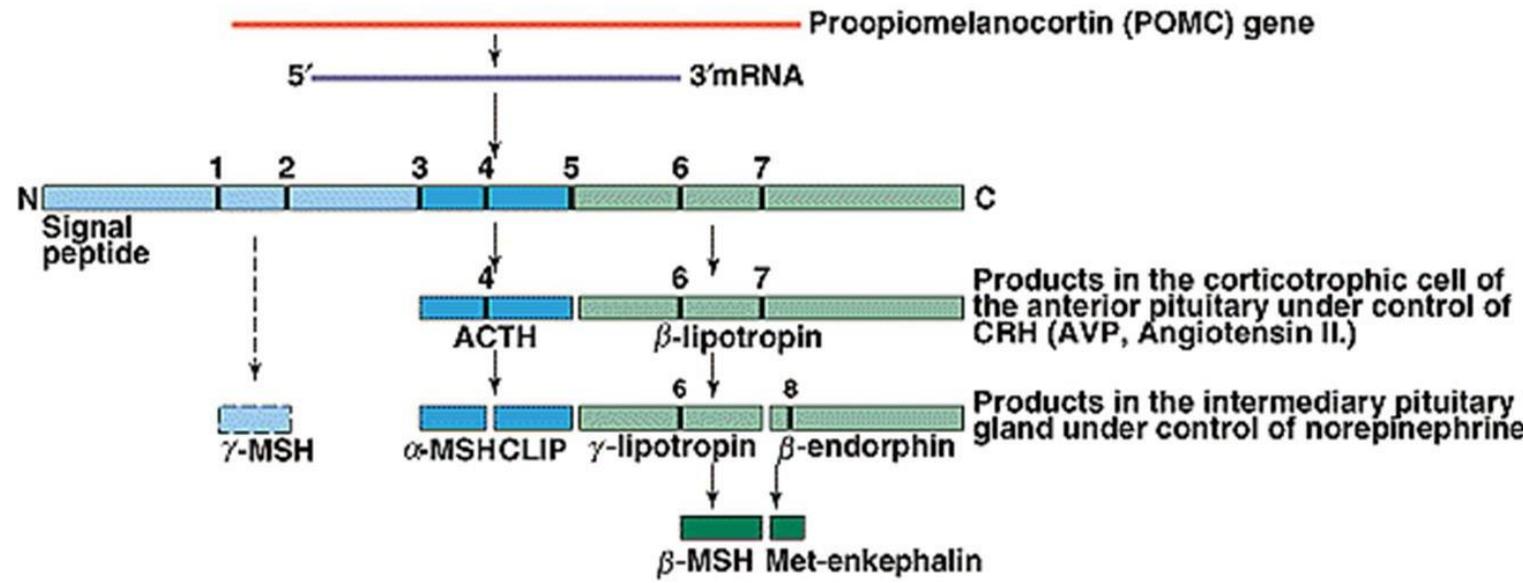
22K-GH
191aa



20K-GH
176aa



Anterior pituitary – Proopiomelanocortin (POMC)



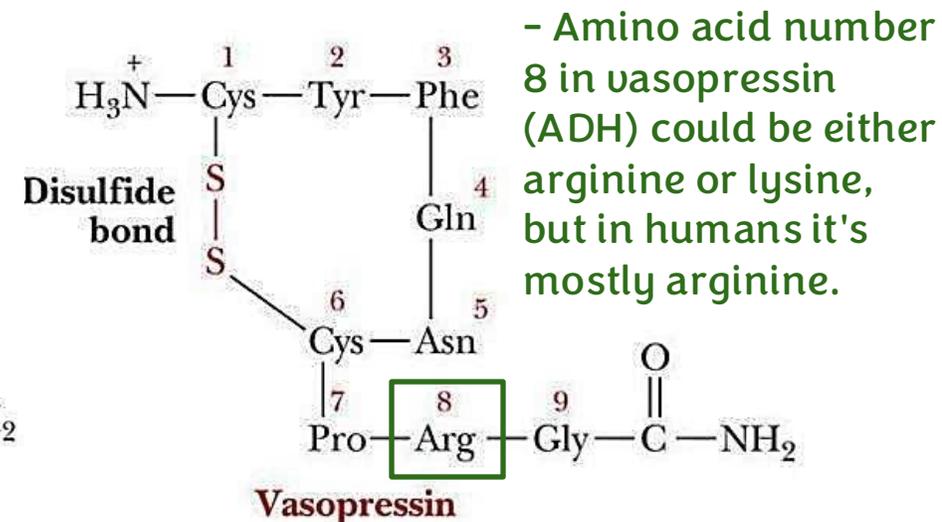
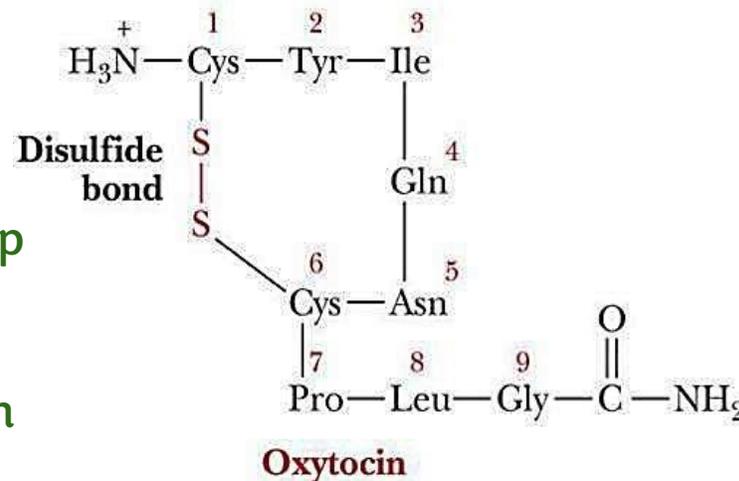


Posterior pituitary

- Posterior pituitary gland stores two hormones; oxytocin and antidiuretic hormone (ADH) where both contain 9 amino acids with one disulfide bridge. They are identical in 7 of these amino acids, and differ in amino acids number 3 and 8. - **structure required**

Hormone	Composition
Oxytocin	Polypeptide containing 9 amino acids
Antidiuretic hormone (ADH; vasopressin)	Polypeptide containing 9 amino acids; two forms: arginine-ADH (most common in humans) and lysine-ADH

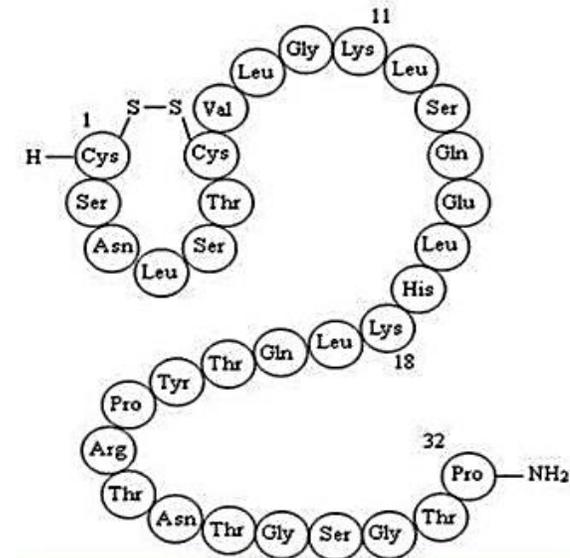
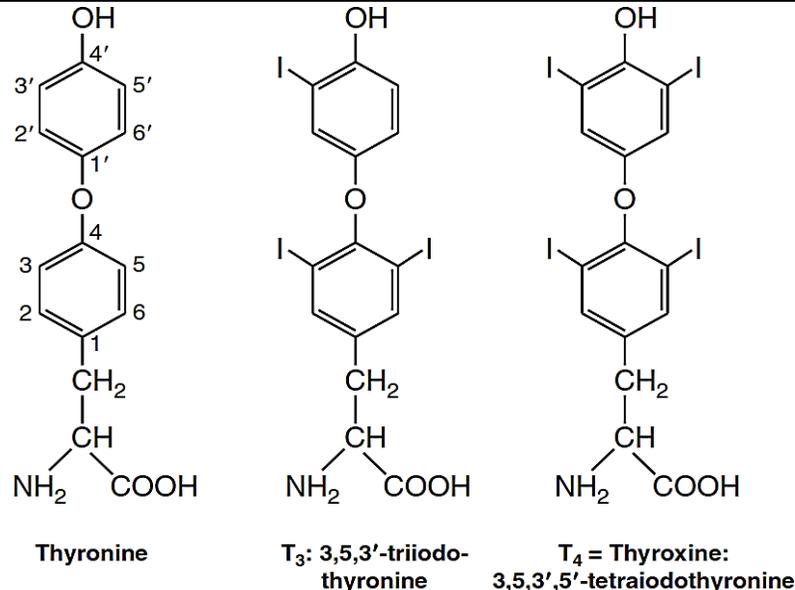
- These two hormones have two different functions, but the similarity in structure could make an overlap in their function.
- In regular cases, carboxyl group is found at the C-terminal, but here there is an amide group where the process of amidation at the C-terminal protects the hormone from degradation.





Thyroid

Hormone	Composition
Thyroxine (tetraiodothyronine, T4) and triiodothyronine (T3), Thyroid hormones are derivatives of tyrosine - structure required . They are made by connecting two tyrosine molecules together.	Amino acid derivative
Calcitonin (thyrocalcitonin) is a polypeptide hormone that has an amide linkage at its C terminal (the last amino acid), contributes to Ca⁺² homeostasis in the body	Polypeptide containing 32 amino acids

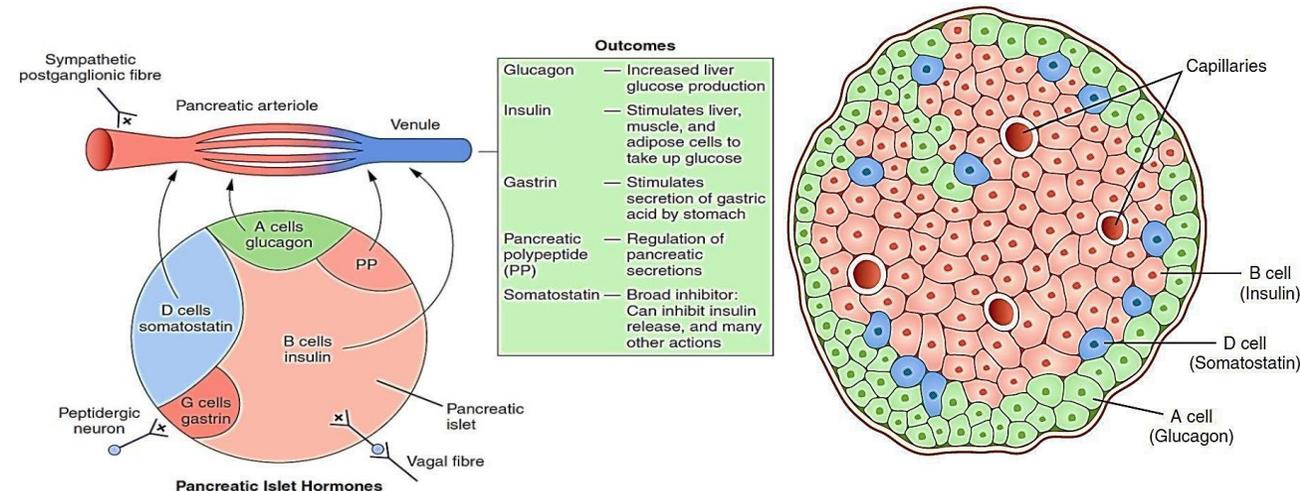




Pancreas

Hormone	Composition (amino acids)
Insulin	51
Glucagon	29
Somatostatin	37
Pancreatic polypeptide (PP)	14
Gastrins	34, 17, 14

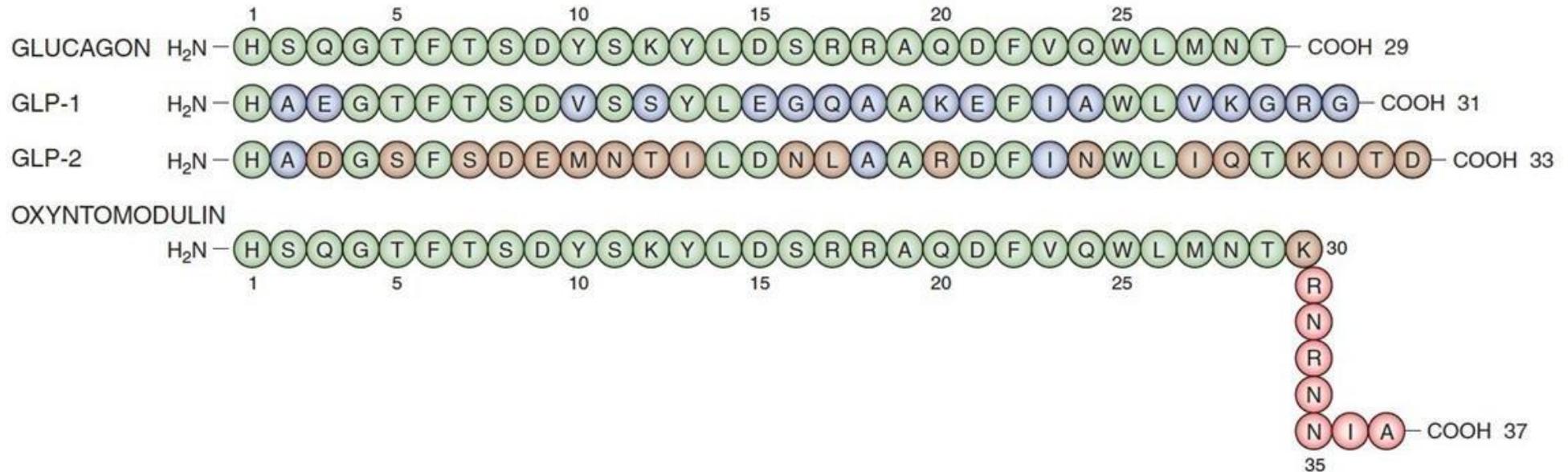
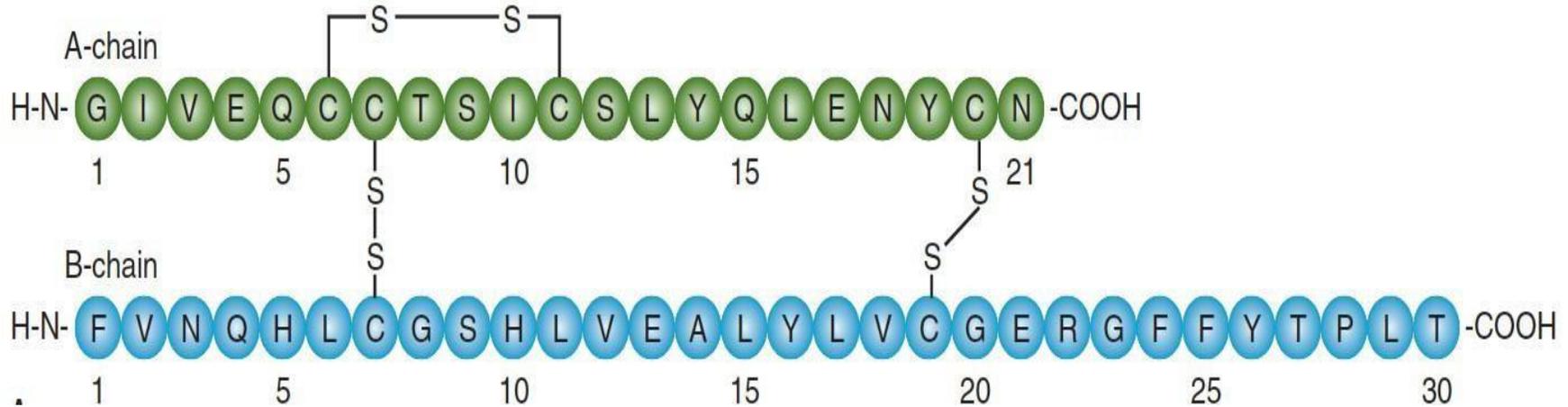
- Insulin is a bigger hormone compared to glucagon. ***Insulin structure recognition is required***
- Insulin has only one form while glucagon is polymorphic; the first is pancreatic glucagon (29 aa) and the other is glucagon like peptides (GLPs) (31, 33 aa) and oxyntomodulin (37 aa) which are secreted by the intestinal cells.
- Insulin consists of two subunits (A and B subunits) connected with 3 disulfide bridges: 2 disulfide bridges between A and B subunits + 1 disulfide bridge internal in the A subunit.





Pancreas

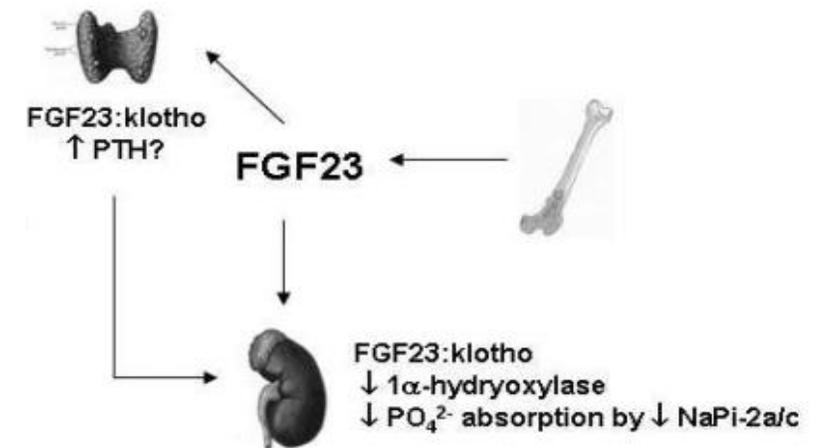
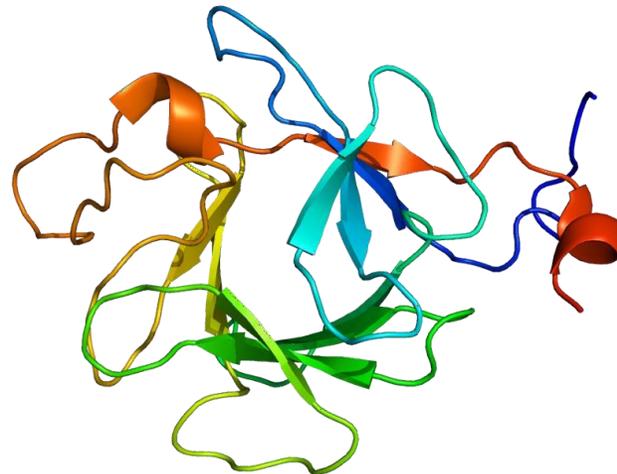
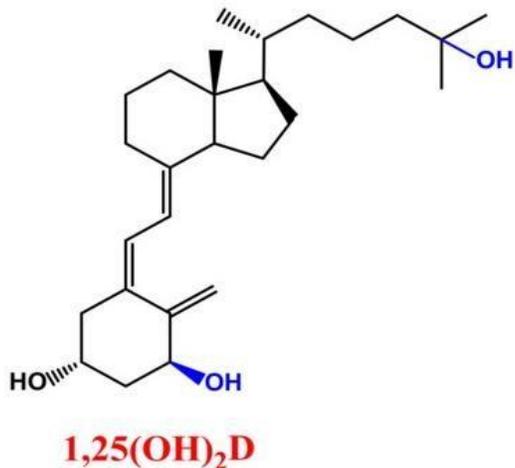
Primary structure of insulin: Amino acid sequence of the A-chain and B-chain of one insulin molecule.





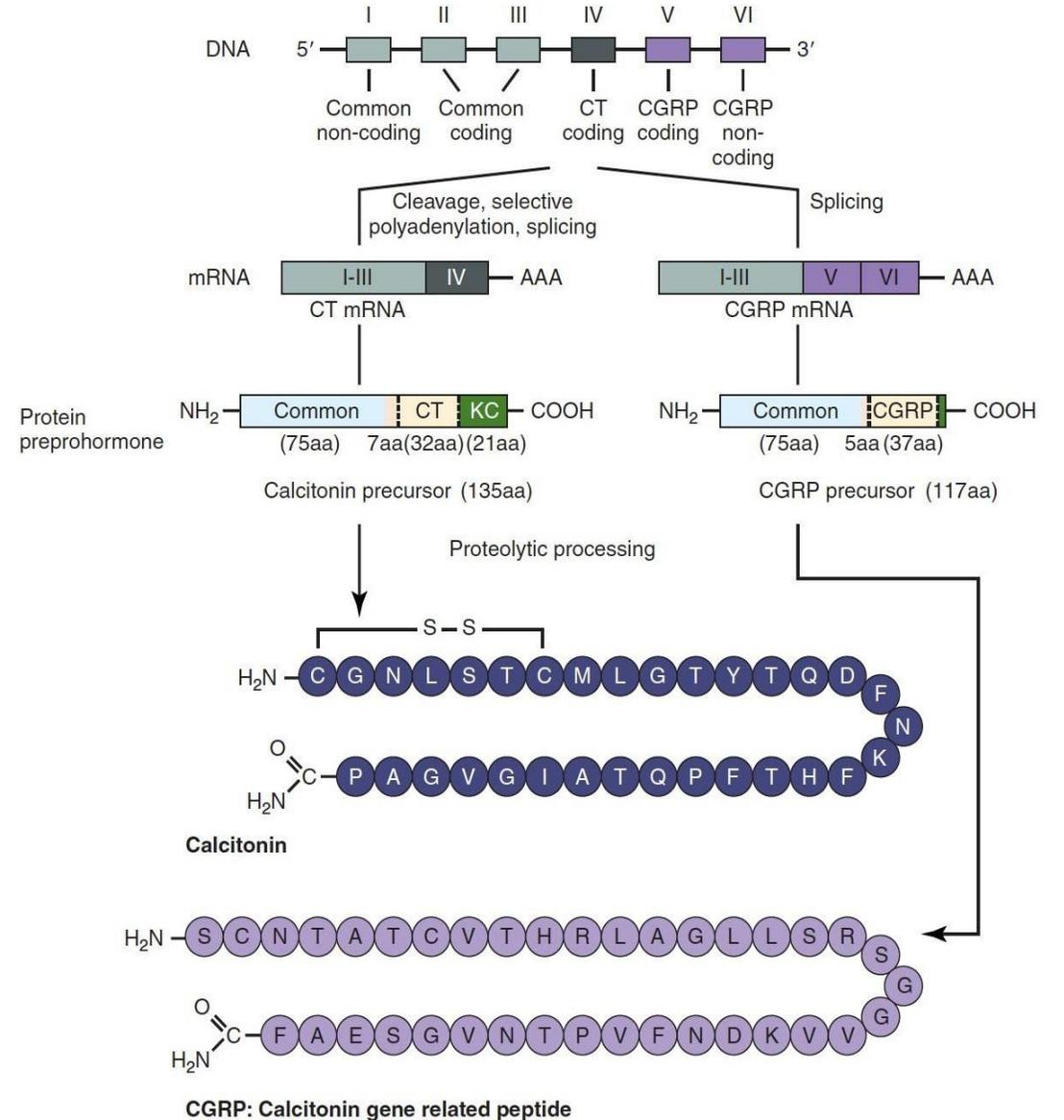
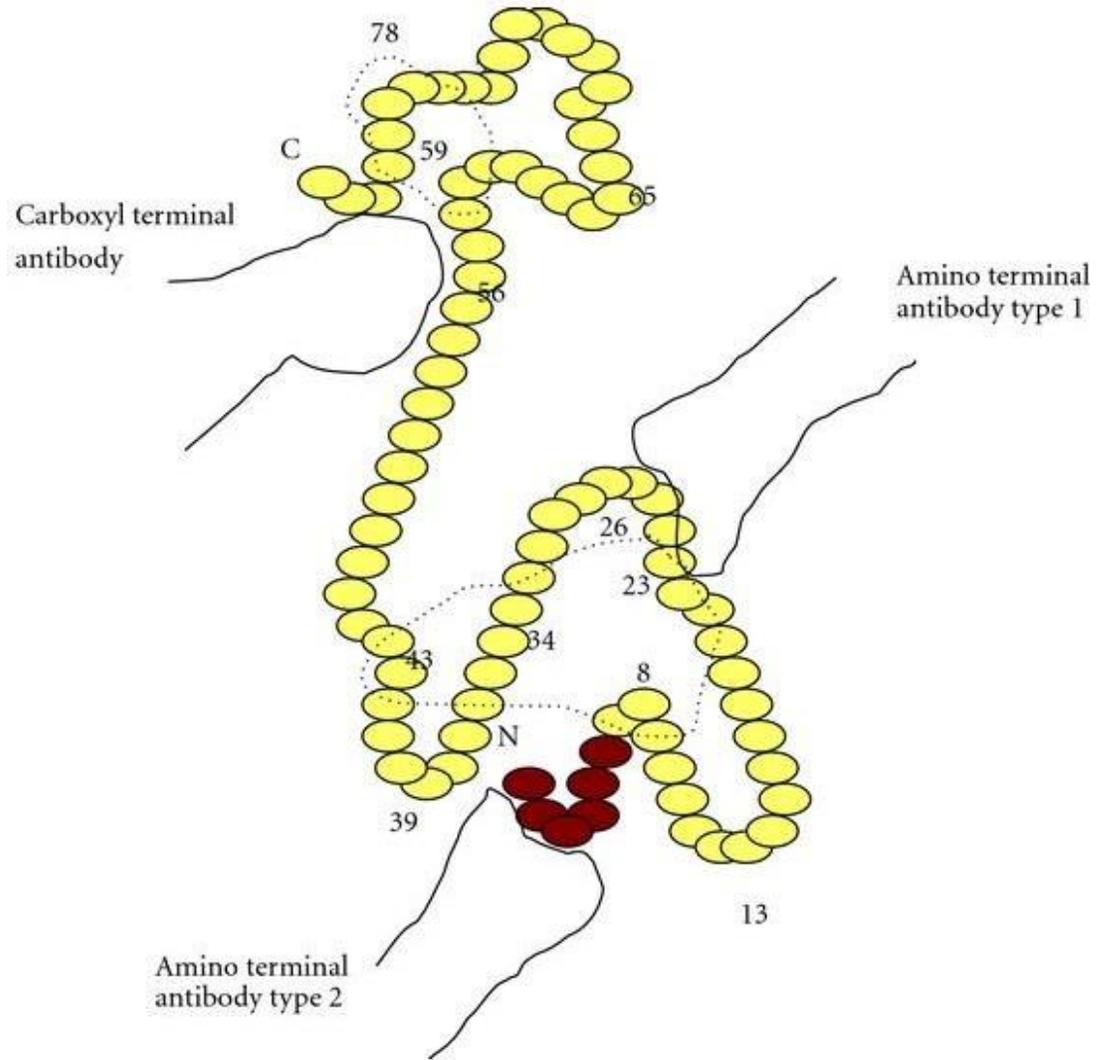
Calcium Regulating Hormones

Hormone	Composition
Parathyroid hormone (PTH)	Polypeptide 84 amino acids
Vitamin D is a steroid and a derivative of cholesterol. - Vitamin D structure recognition is required	Steroid
Calcitonin is produced by the thyroid.	Polypeptide 32 amino acids
Fibroblast Growth Factor 23 is the biggest protein hormone.	Protein 251 amino acids





Calcium Regulating Hormones

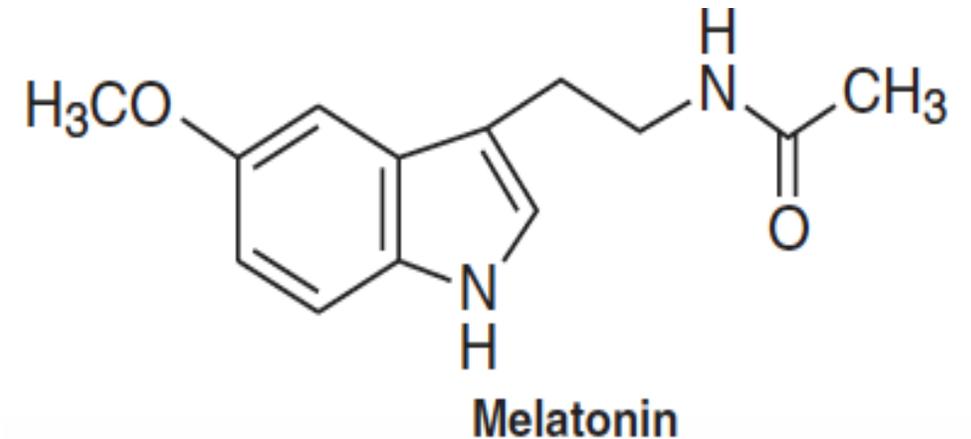




Pineal Gland Hormones

Hormone	Composition (amino acids)
Melatonin	Indolamine (N-acetyl-5- methoxytryptamine)

- Melatonin is an amino acid derived hormone made from tryptophan.- ***Melatonin structure recognition is required.***
- It's responsible for the control of circadian rhythm (your daily cycle like sleeping waking etc.).

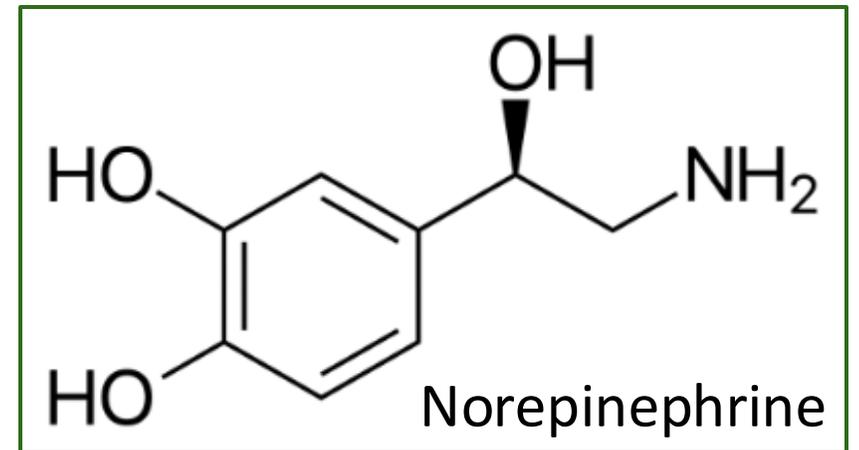




Adrenal and Sexual Glands' Hormones

Hormone	Composition (amino acids)
Group of hormones	steroids
Norepinephrine	Amino acid derivative

- Most of these hormones are steroids.
- Norepinephrine is an amino acid derivative (tyrosine). - ***Norepinephrine structure recognition is required***





Synthesis and Degradation of hormones

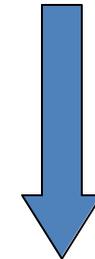
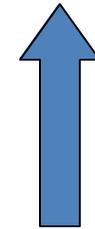
according to the receptor location (intracellular vs extracellular).



Chemistry of Hormones

- **Steroids:** steroid hormones are synthesized from cholesterol. They are divided into categories according to the number of carbon atoms.
 - Small molecules - nitric oxide NO
 - Amino acid derivatives
 - Thyroid hormones
-
- Catecholamines
 - Proteins and peptides
 - FA derivatives - eicosanoids

Receptor inside
the cell
(Intracellular
receptors)

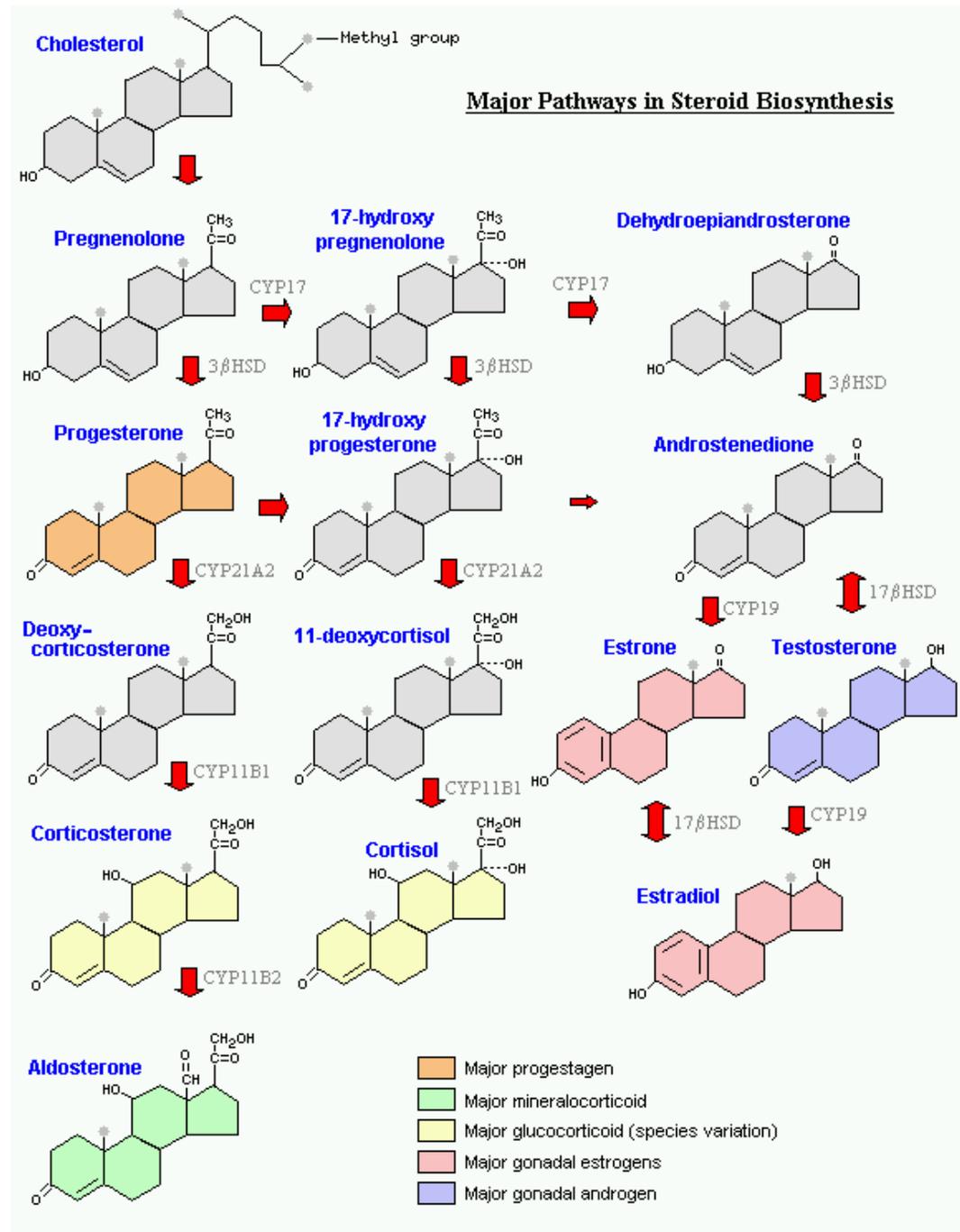


Surface receptor
(Extracellular
receptors)



Steroid hormone synthesis

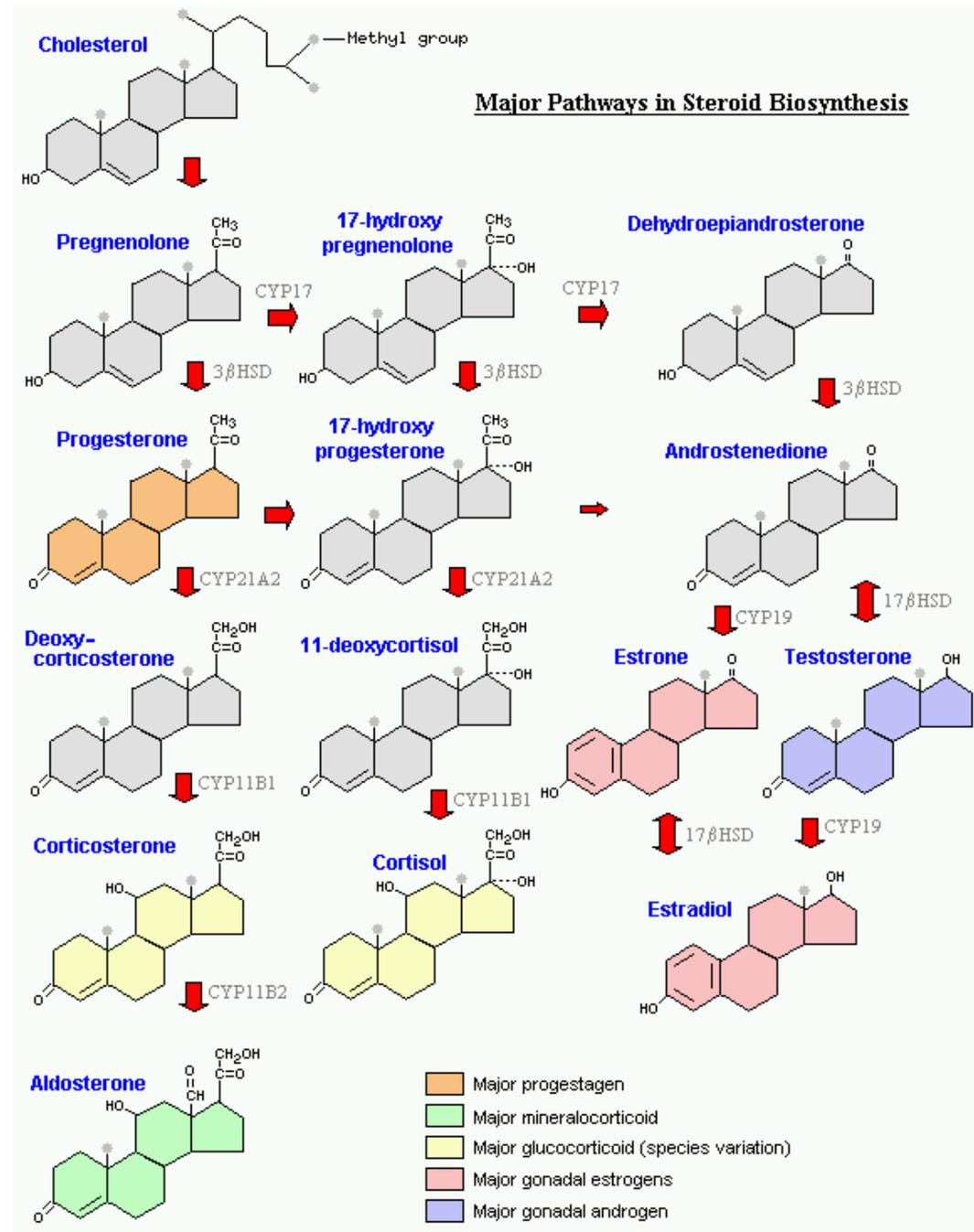
- C21:
 - Progesterone: directly from pregnenolone
 - Cortisol & Aldosterone: from progesterone





Steroid hormone synthesis

- C19
 - Testosterone: from progesterone or pregnenolone
 - 2c shortage
- C18 (estrogen): from testosterone through aromatase
 - Cleaves C18
 - Reduction



Steroid hormone

- Minimal **differences** found between the steroid hormones (in the number of carbons and some simple modifications like hydroxylation) but still are able to induce huge functions
- **Cholesterol** is not a steroidal hormone. It is a lipidic structure composed of 27 carbons. The structure contains four fused rings [three six membered cyclohexane rings (a, b, c), and one five membered cyclopentane ring (d)].
- We can synthesize cholesterol in our body from acetyl-CoA and the synthesis occurs in the liver. However, we cannot breakdown the fused rings after they are synthesized.
- Even though, **the body discards this sterane or steroid ring through the liver by hydroxylation and conjugation with glucuronides or sulphates**. So, it will be secreted with the bile. Also, some are being secreted **through urine** as unchanged hormones or their metabolites.



Steroid hormone breakdown

- Steran core cannot be cleaved
- In the liver: hydroxylation and conjugation with glucuronides or sulphates
- Urinary excretion:
 - ✓ Of metabolites
 - ✓ Of unchanged hormones

This slide is a summary of the previous slide (:

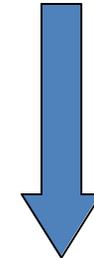
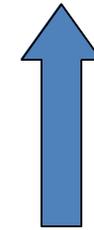


Chemistry of Hormones

- Steroids
- **Small molecules - NO**
- Amino acid derivatives
 - Thyroid hormones

- Catecholamines
- Proteins and peptides
- FA derivatives - eicosanoids

Receptor inside the cell

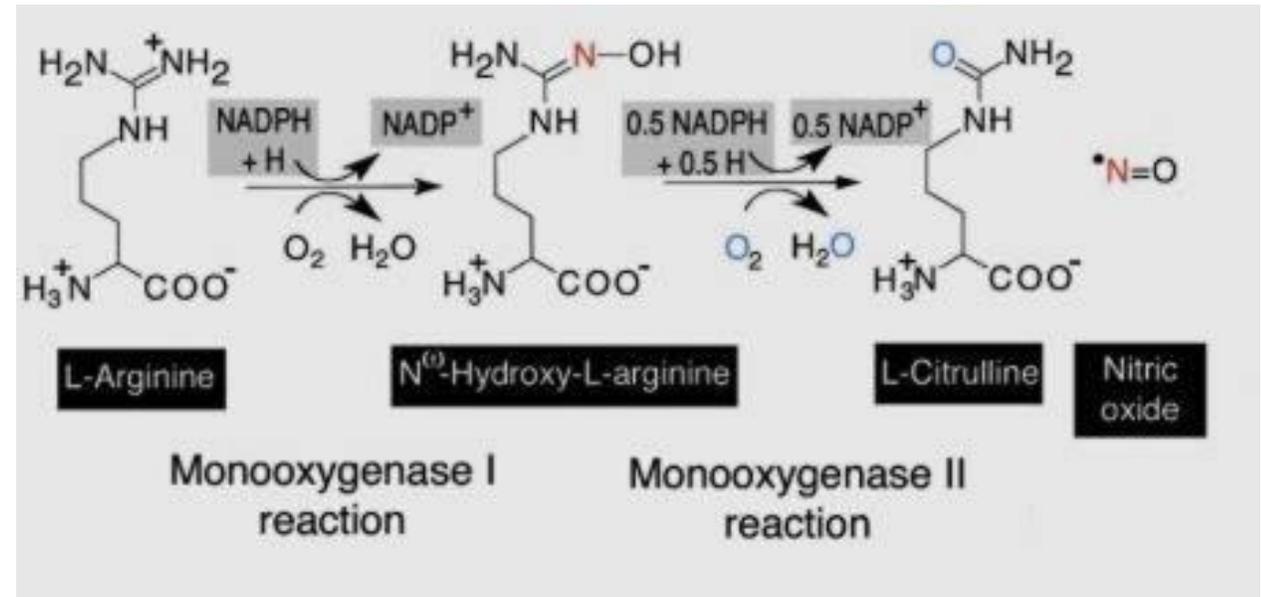
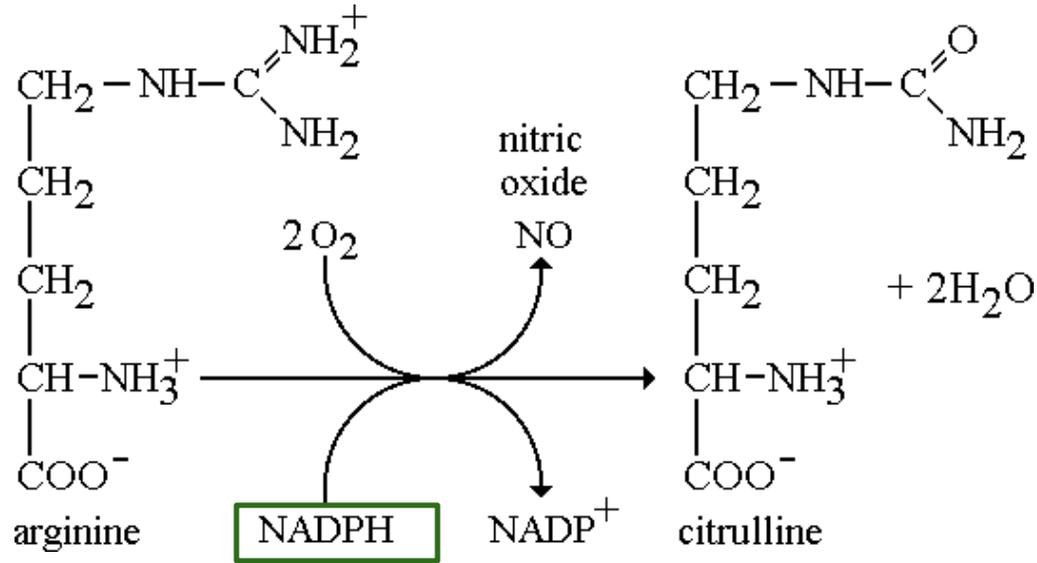


Surface receptor

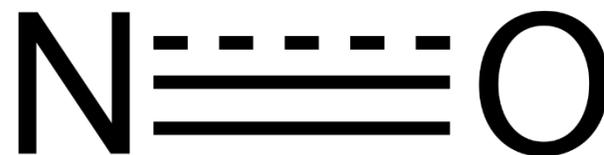


Nitric oxide (NO)

NO: synthesized by NO-synthase as a byproduct of the reaction that converts arginine (a basic amino acid) to citrulline (another basic amino acid)



This reaction is dependent on NADPH, so is considered a reduction reaction catalyzed by NO-synthase.





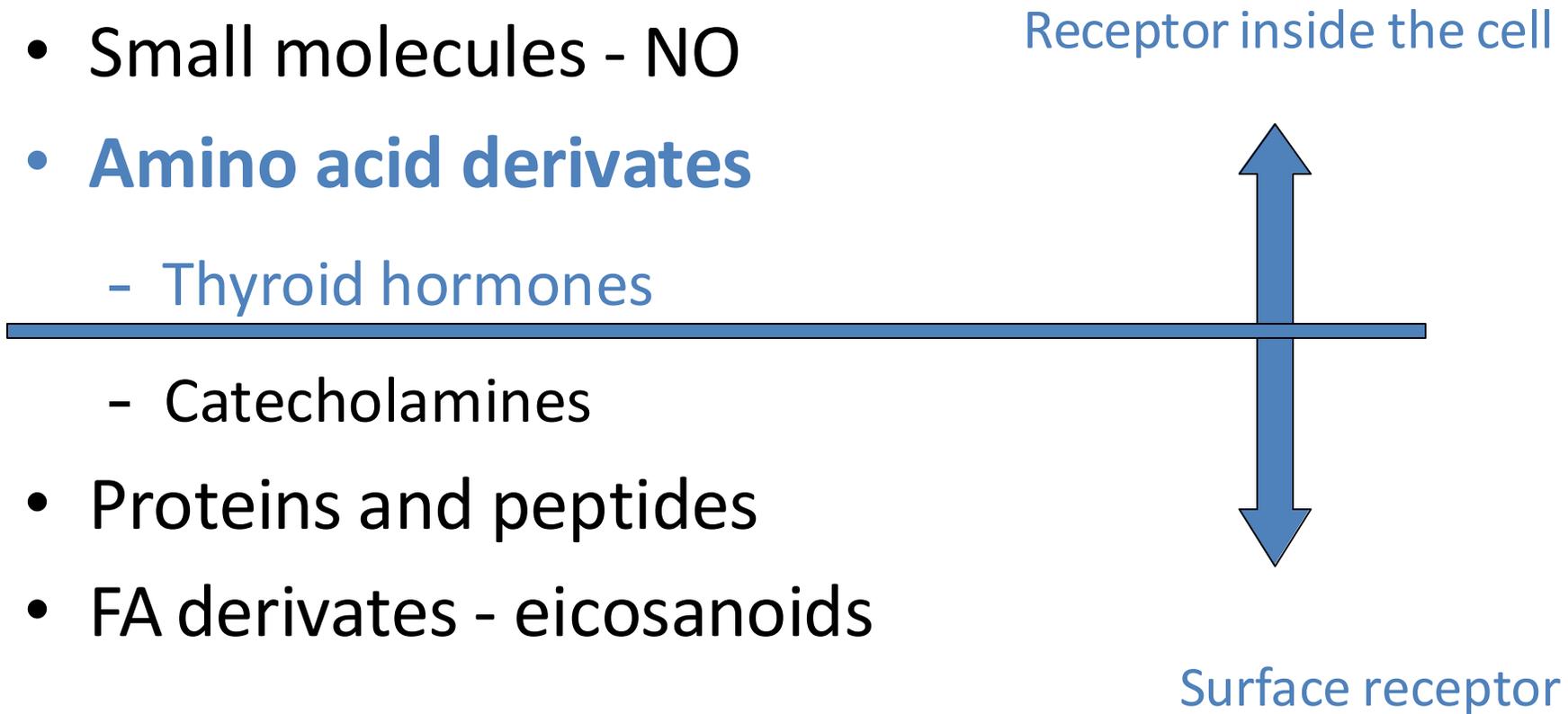
Nitric oxide synthase isozymes

- The nitric oxide has many function in the body, and there are 3 isoforms of NO-synthase (NOS):
 - ✓ In neurons (NOS-I): neurotransmission.
 - ✓ In macrophages (NOS-II): **because it has free radicals, it can** kills bacteria.
 - ✓ Endothelial (NOS-III): **(by cascade)** smooth muscle → **cGMP** as a **second messenger** → vasodilation
- Clinical correlation:
 - ✓ Nitrates in the treatment of angina or myocardial infarction through its **immediate secretion by the endothelial cell**. This is why drugs like trinitroglycerin which is composed of glycerin and 3 nitrous groups can help in this situation (vasodilator).
 - ✓ Refractory hypotension during septic shock



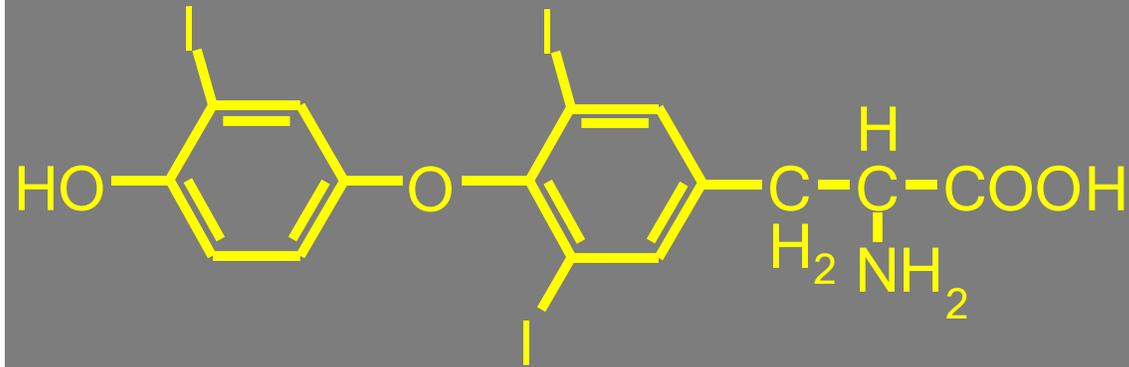
Chemistry of Hormones

- Steroids
- Small molecules - NO
- **Amino acid derivatives**
 - Thyroid hormones
 - Catecholamines
- Proteins and peptides
- FA derivatives - eicosanoids

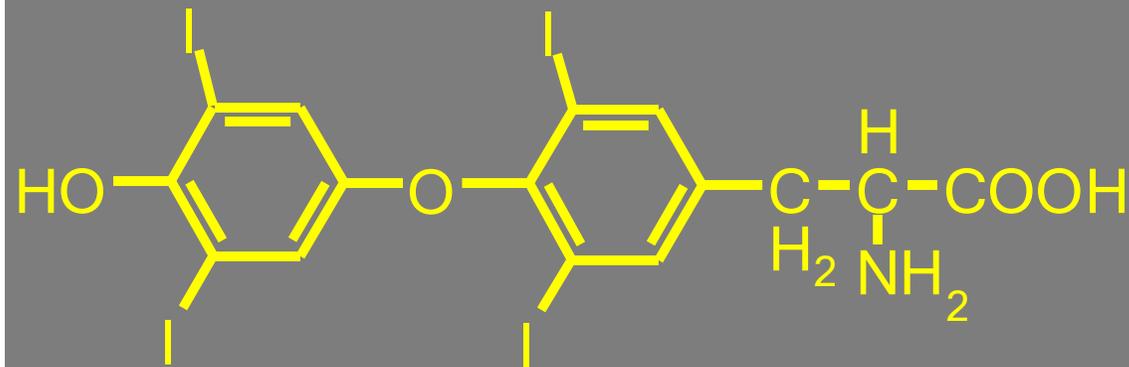




Thyroid hormones



Triiodothyronine (T3)



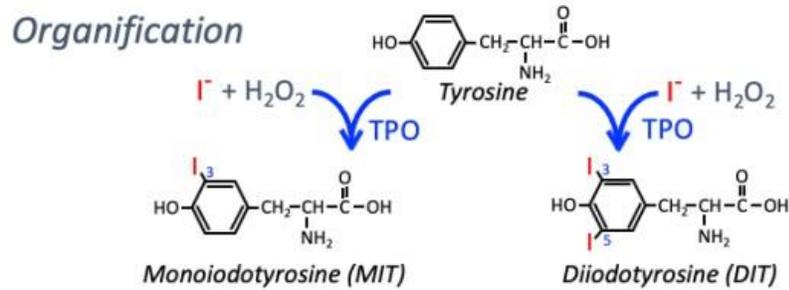
Thyroxine (T4)

Thyroid hormones synthesis

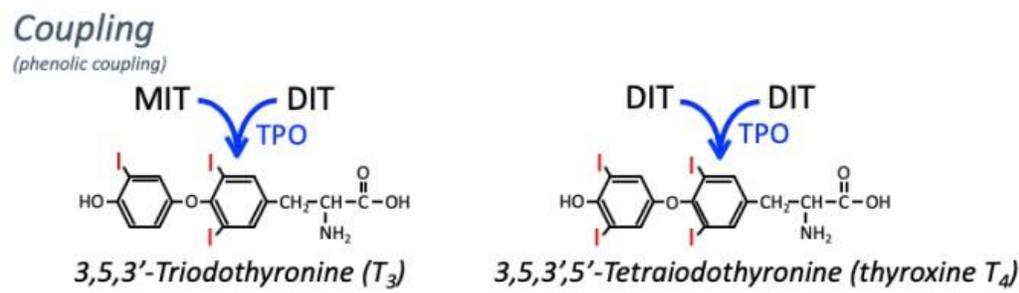
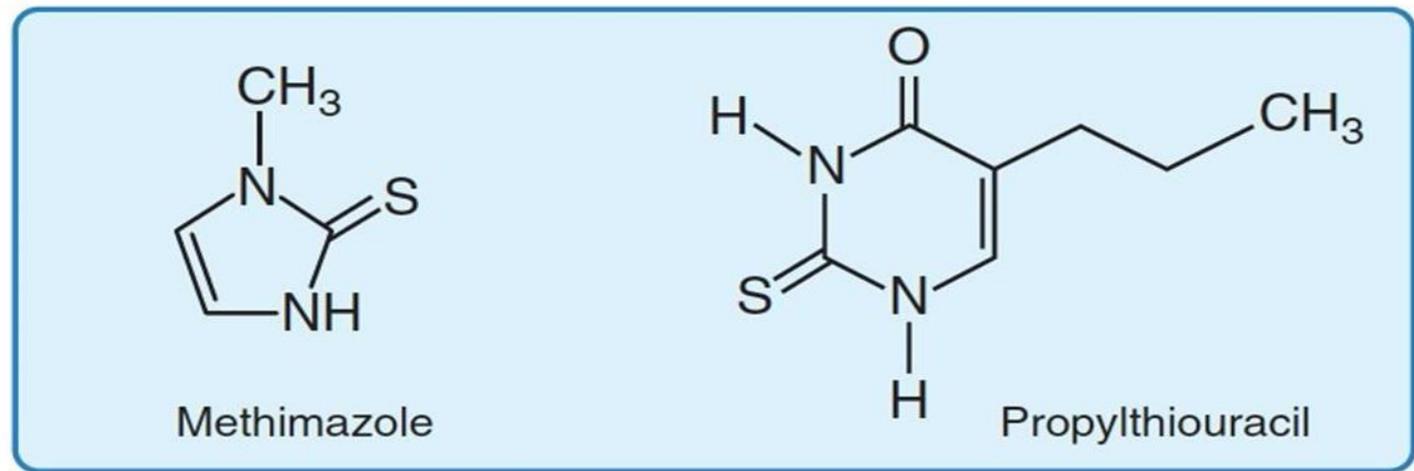
- It is synthesized from tyrosine. The starting point is phenylalanine that is hydroxylated through phenylalanine hydroxylase to form tyrosine. Then modification occurs on tyrosine to produce the functioning T3 and T4 through iodination using thyroid peroxidase.
- Thyroid peroxidase will oxidize the iodide (I^-) to iodine (I_2) and then it will catalyze iodination of tyrosine forming Monoiodotyrosine (MIT) by adding one iodine atom or diiodotyrosine (DIT) by adding two iodine atoms.
- This occurs with the help of thyroglobulin protein.
- Thyroid peroxidase also couples two molecules of tyrosine, (if MIT was coupled with DIT, T3 will be formed, and if DIT gets coupled with DIT, T4 will be formed) inside the thyroid gland.
- Note that MIT can't be coupled with another MIT.
- Please memorize the inhibitors and their effect on each step by looking at the slides.
- Cyanide & perchlorate are toxic substances that limits iodine uptake from bloodstream.
- The thiocyanate generated during detoxification of cyanide in the body is believed to interfere with iodine uptake because of its structural similarity.



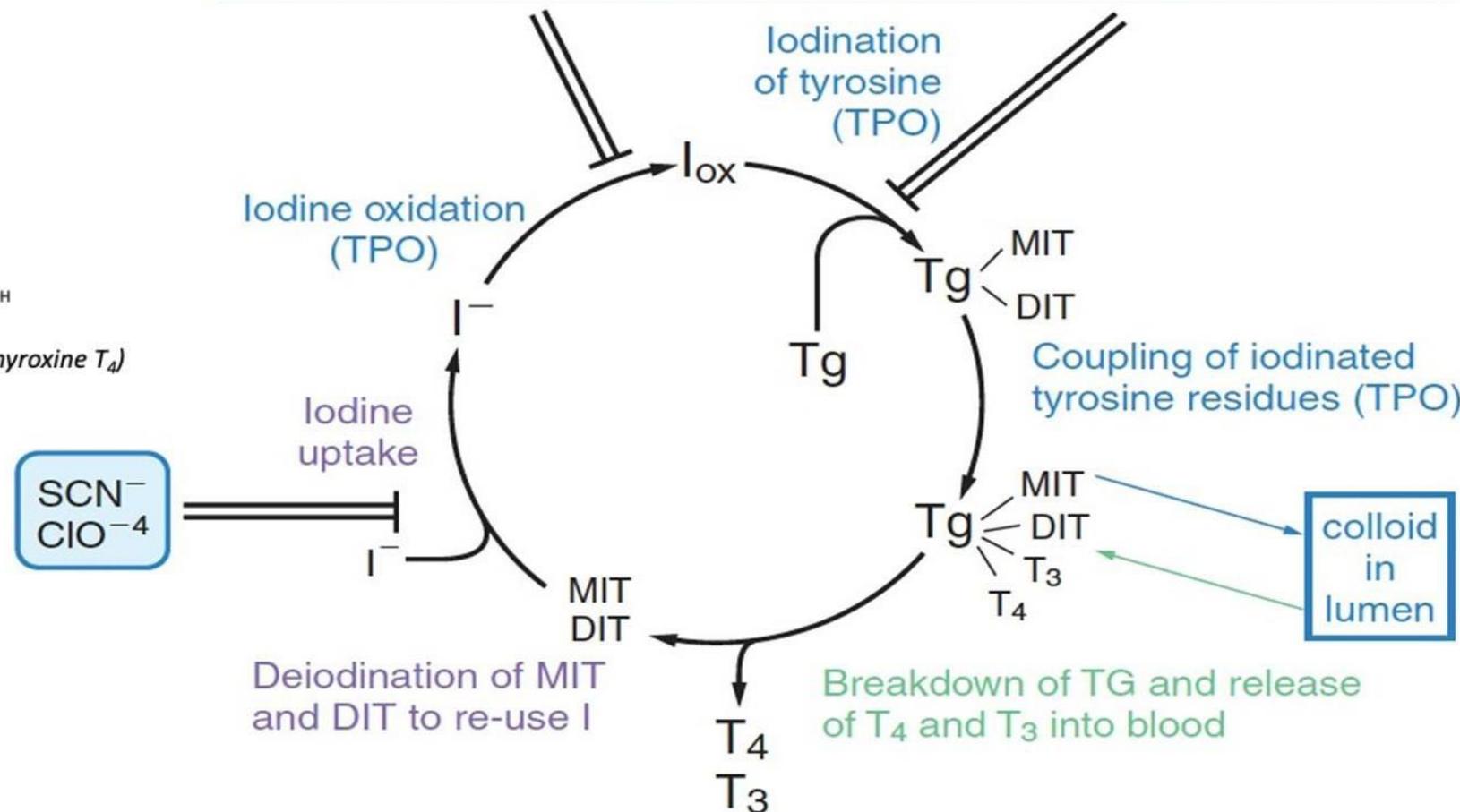
Thyroid hormones



Inhibitors of TPO
Methimazole
PTU



- ✓ TPO, thyroid peroxidase;
- ✓ Tg, thyroglobulin;
- ✓ MIT, monoiodotyrosine;
- ✓ DIT, diiodotyrosine;
- ✓ SCN⁻, thiocyanate;
- ✓ ClO⁻⁴, perchlorate.

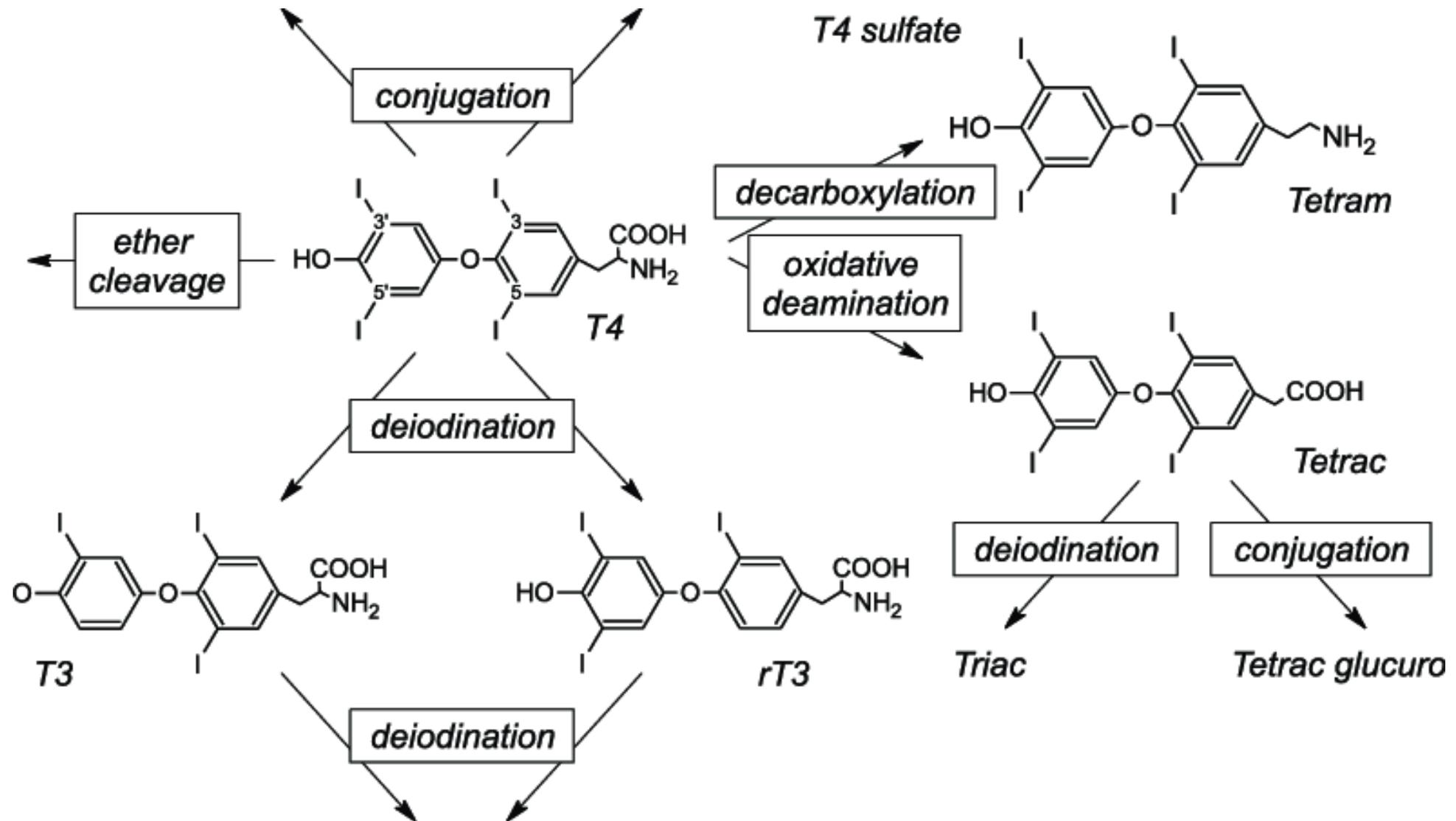


Thyroid hormones degradation

- Deiodinase is an enzyme that removes iodine, converting T4 to T3 which is the active form, found normally in lower concentration than T4 and have a lower half life.
- How can the body get rid of T4?
 1. Deiodination by the deiodinase enzyme converting it to T3
 2. Conjugation directly into the bile
 3. Any modification to its structure will inactivate it: removing carboxyl group from the backbone of tyrosine or by oxidative deamination (removing the amino group) will end the effect of hormone.
- How can the body get rid of T3?
 - By deiodination making it inactive then through bile or other mechanisms



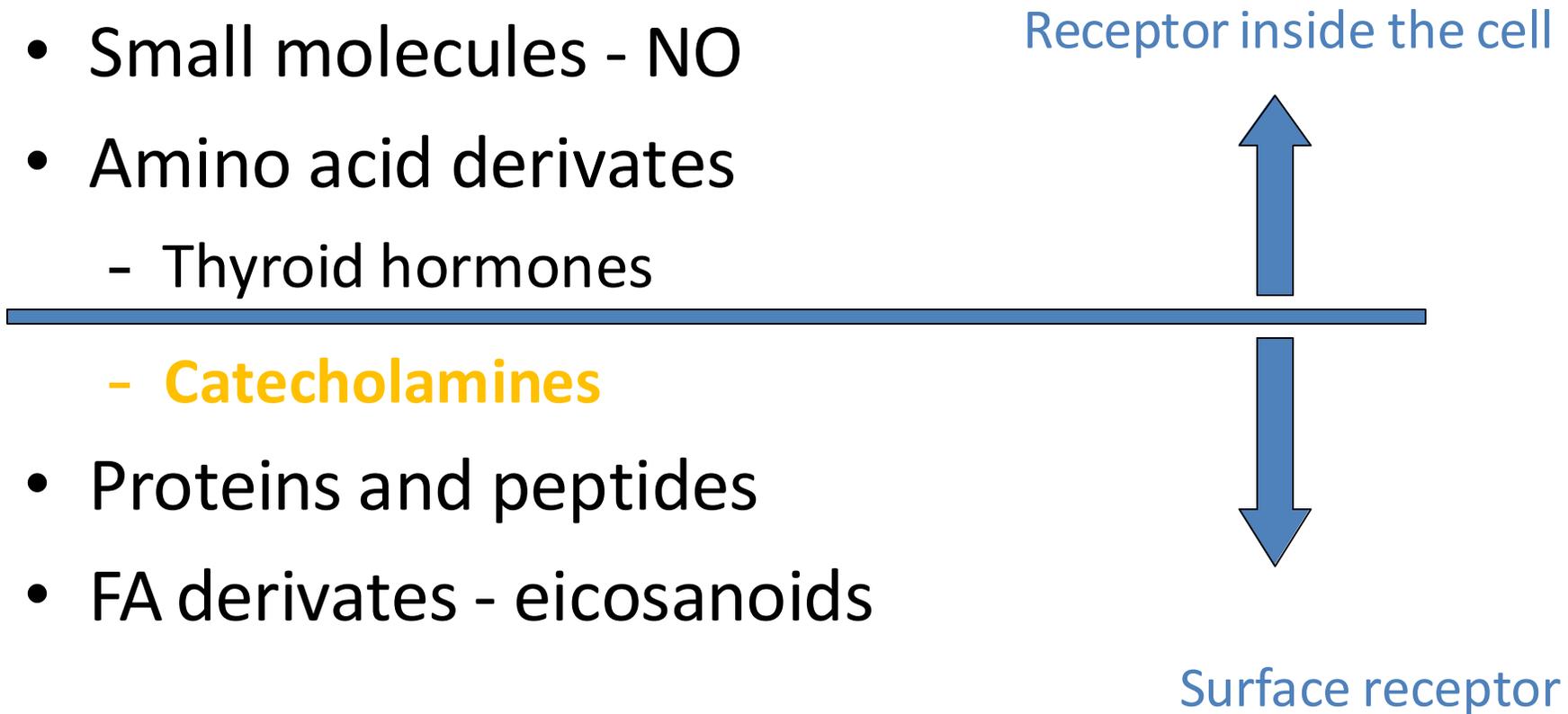
Thyroid hormones degradation





Chemistry of Hormones

- Steroids
- Small molecules - NO
- Amino acid derivatives
 - Thyroid hormones
 - **Catecholamines**
- Proteins and peptides
- FA derivatives - eicosanoids





Catecholamine synthesis

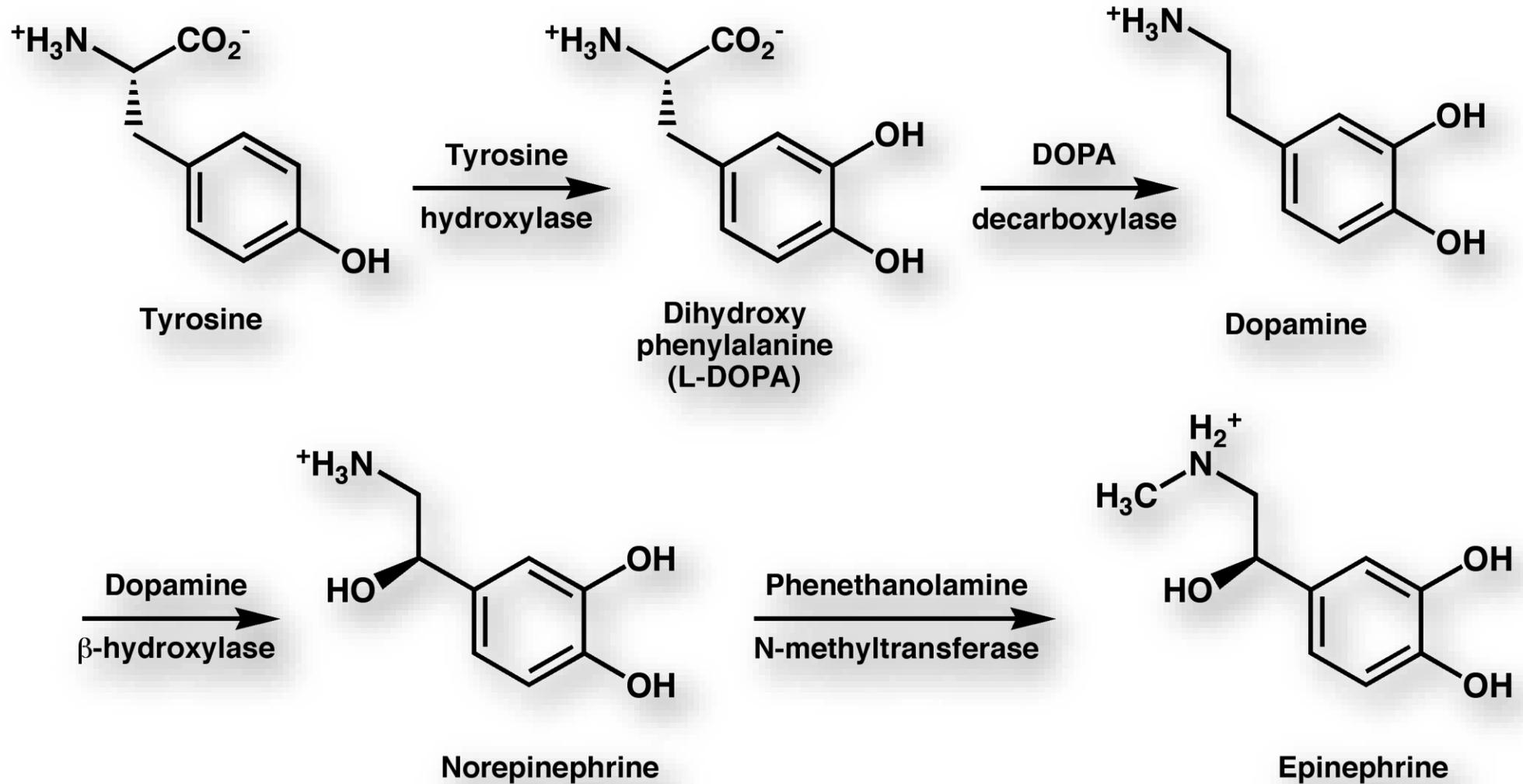
- Substrate = Phe or Tyr
- Possess a catechol ring (benzene ring holding two adjacent hydroxyl groups). Modification of tyrosine by carboxylation leads to production of molecules that holds one amino group, this is why these molecules are named monoamines (MA).
- Synthesis located in: adrenal medulla, nerve tissue (norepinephrine).
- Products:
 - Dopamine, adrenaline (hormones)
 - Noradrenaline (neurotransmitter)

Catecholamine synthesis

- The reaction starts with phenylalanine, which is hydroxylated by phenylalanine hydroxylase (if this enzyme is deficient the patient will suffer from phenylketonuria) to produce tyrosine.
- Again the tyrosine is hydroxylated by tyrosine hydroxylase producing dihydroxy phenylalanine (L-DOPA).
- Now a decarboxylation reaction (by decarboxylase enzyme) removes the carboxyl group producing dopamine.
- The dopamine may produce norepinephrine by hydroxylation and then methylation reaction will produce epinephrine by methyltransferase enzyme.



Catecholamine synthesis

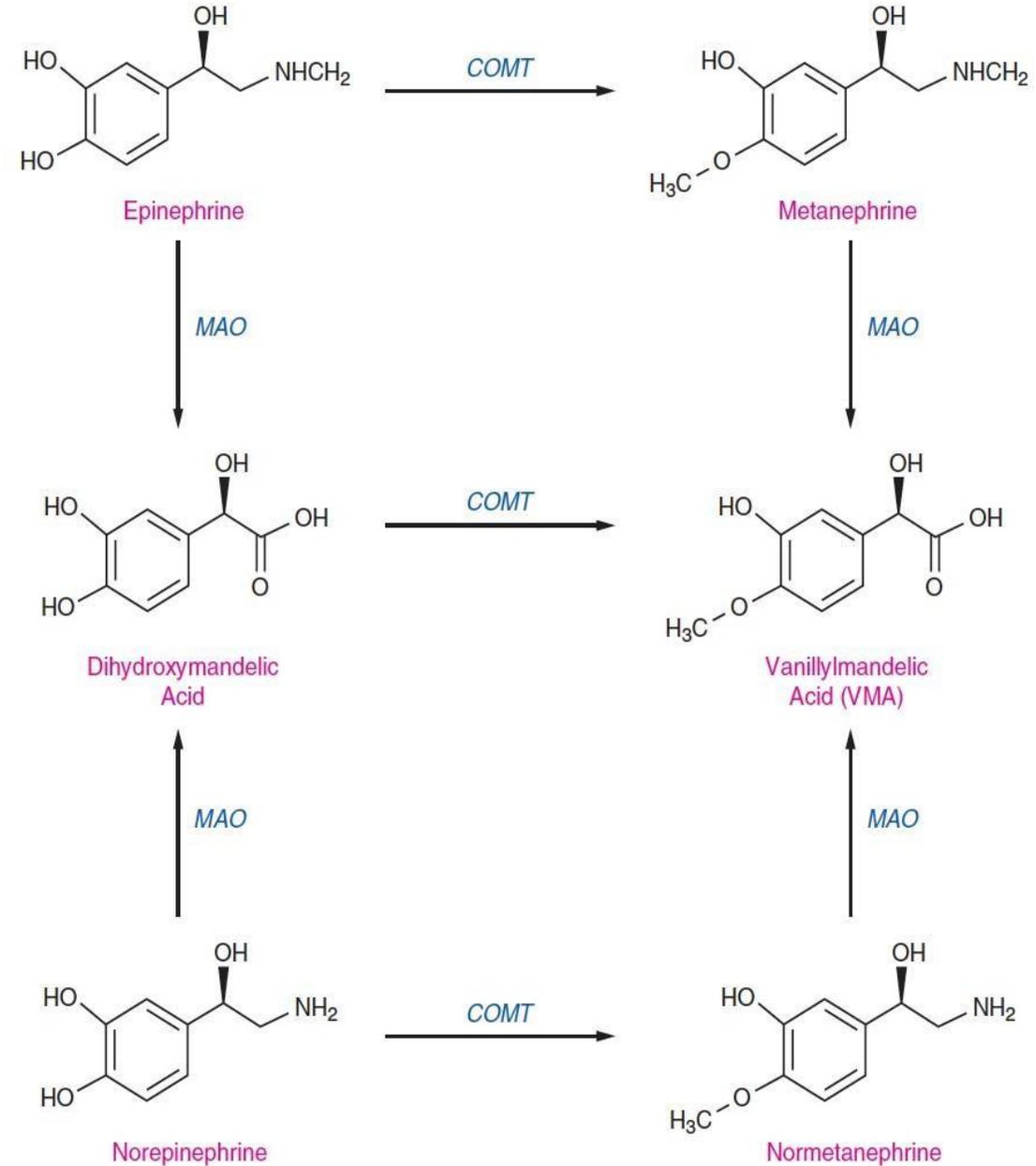
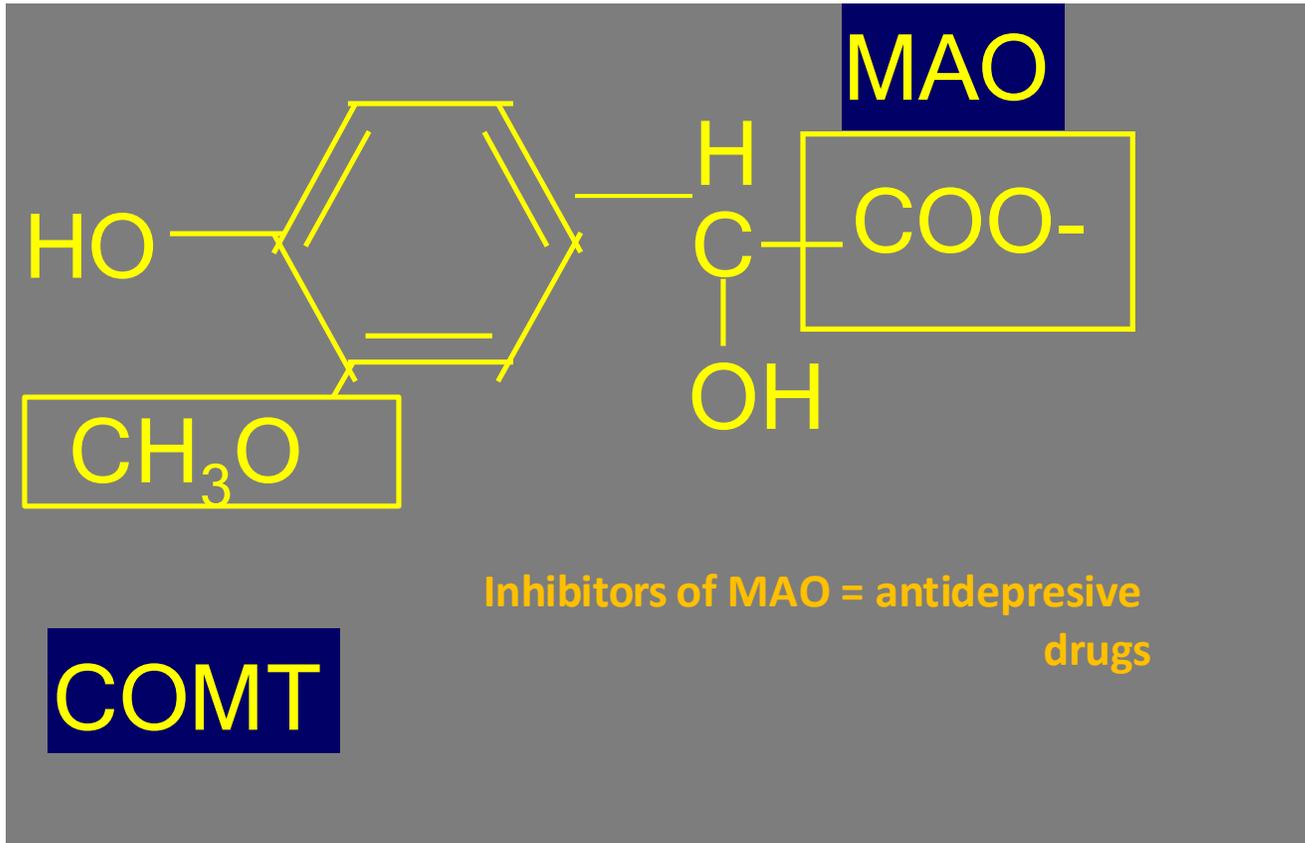


Catecholamine breakdown

- To degrade catecholamine molecules, we either:
 - Acting on the catechol ring by COMT enzyme (catechol O-methyl transferase)
 - Or, removing the (amino group) by monoamine oxidase
- So, there are two enzymes:
 - 1) monoamine oxidase (MOA): removes the amino group by an oxidation reaction (oxidative deamination).
 - Clinically, MAO inhibitors are used as antidepressants.
 - 2) COMT: by transferring a methyl group to the hydroxyl group.



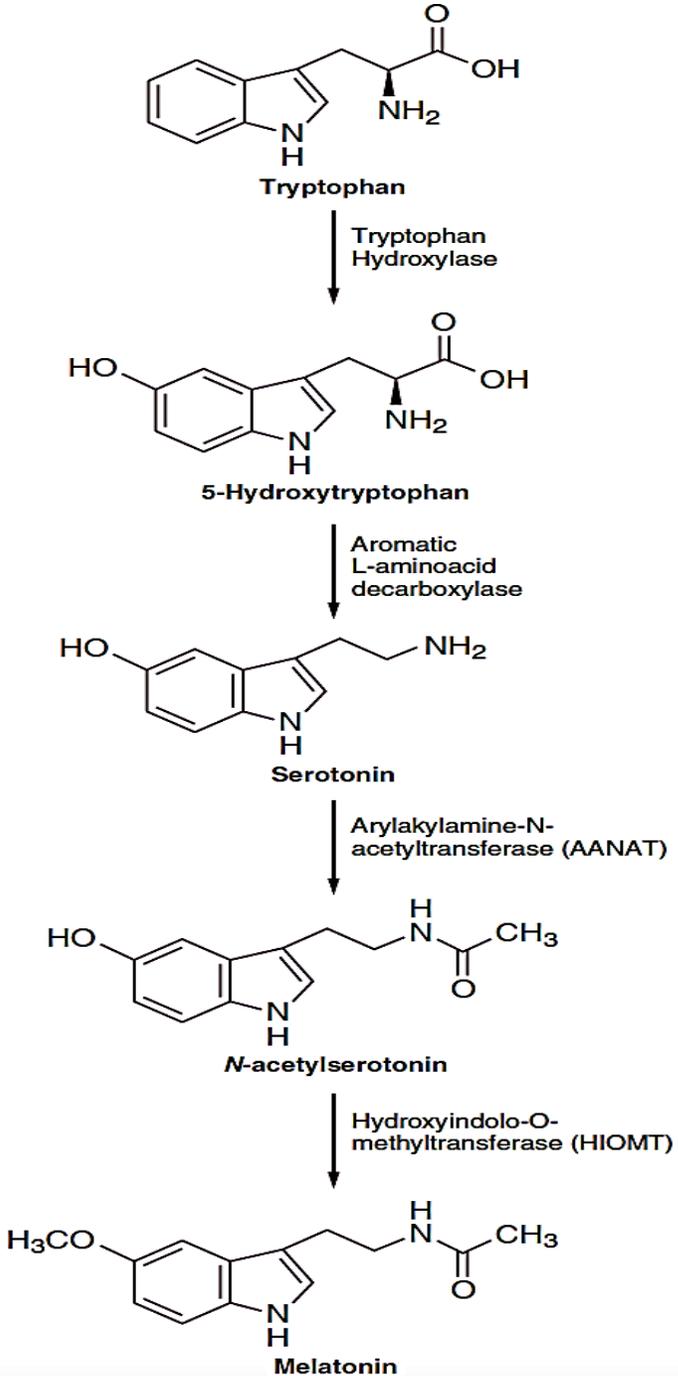
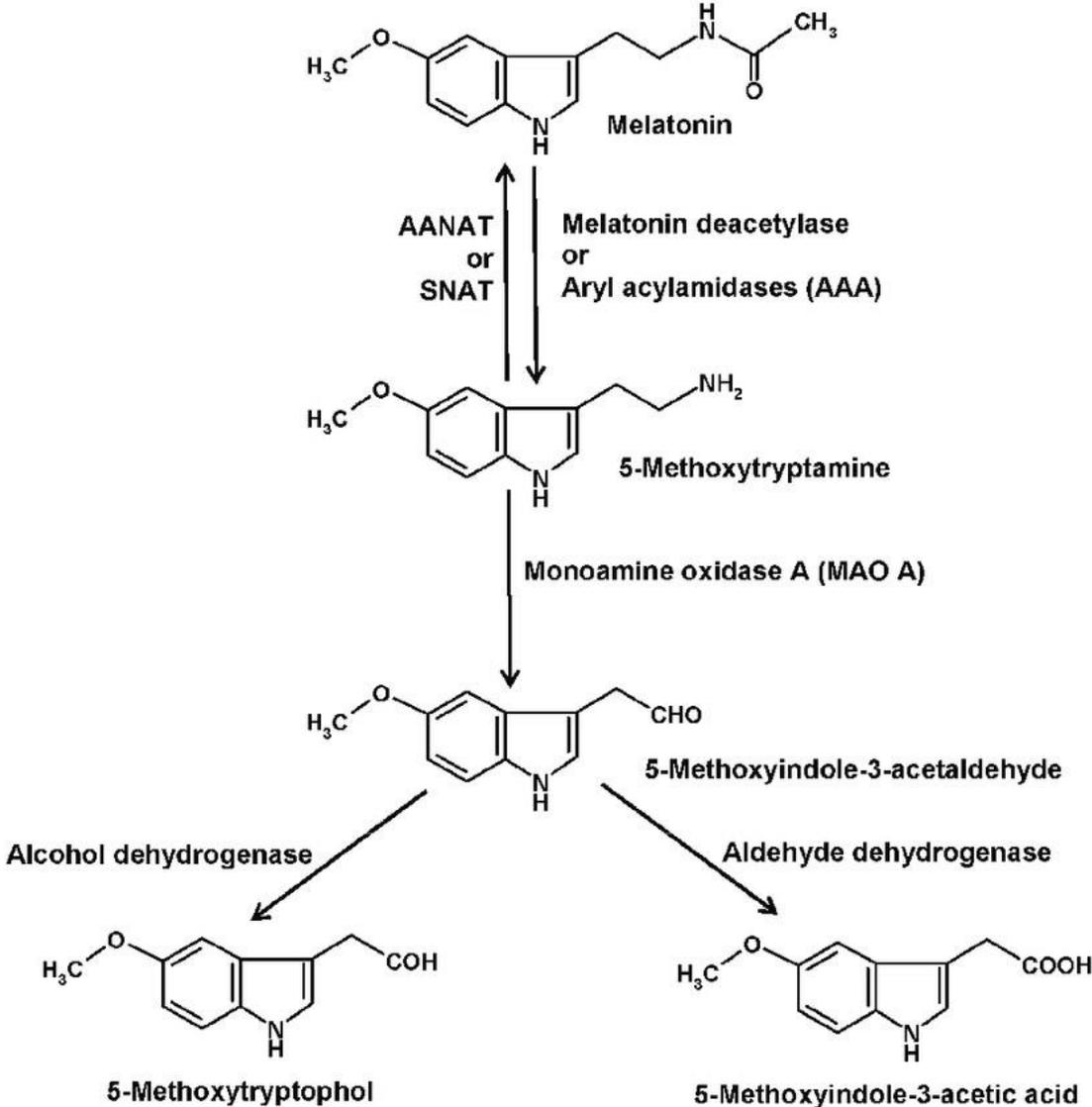
Catecholamine breakdown



Melatonin

- **The synthesis of the melatonin** starts with tryptophan amino acid by hydroxylation reaction to produce (5- hydroxytryptophan), then decarboxylation of the backbone of the amino acid to produce serotonin (5-hydroxytryptamine), then by acetylation to the backbone of serotonin that will produce the (N-acetyl serotonin), followed by methyl group transfer to indole ring of serotonin that eventually produces melatonin.
- **To degrade melatonin**, we delete what was added, for instance: (acetyl group) or amino group by the MAO enzyme (MAO acts on any amino acid derivative).

Melatonin



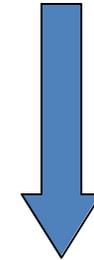
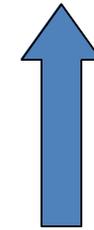


Chemistry of Hormones

- Steroids
- Small molecules - NO
- Amino acid derivatives
 - Thyroid hormones

- Catecholamines
- **Proteins and peptides**
- FA derivatives - eicosanoids

Receptor inside the cell



Surface receptor



Protein and peptide hormones

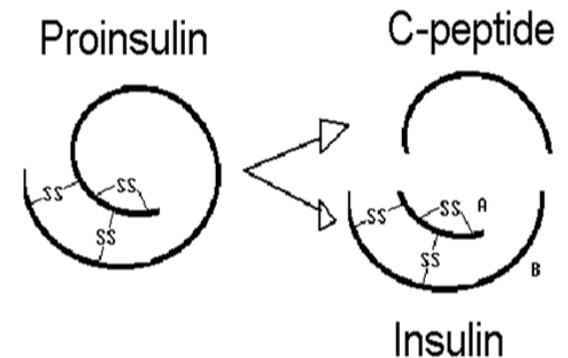
- CNS mediators: neuropeptides, opioids
- Hypothalamic releasing hormones and pituitary peptides
- **polypeptides like:** Insulin and glucagone
- Growth factors: IGF, CSF, EPO ... and many others



General steps of peptide synthesis

“Precursor Polypeptides”

- They share the same synthetic pathway: Gene transcription → mature mRNA translation → signaling peptide → to ER → cleavage of signal peptide → modifications in Golgi (forming disulfide bridges) → secreted out
- Expression of “pre-pro” protein, most of them are produced as proprotein (requires one modification to be active) or preproproteins (requires two modifications to be active).
- Transport to ER
- Splitting the signaling sequence
- Cleavage to definite peptide(s) and final modification in Golgi
 - Proinsulin to insulin
 - Proopiomelanocortine (POMC) to MSH and ACTH

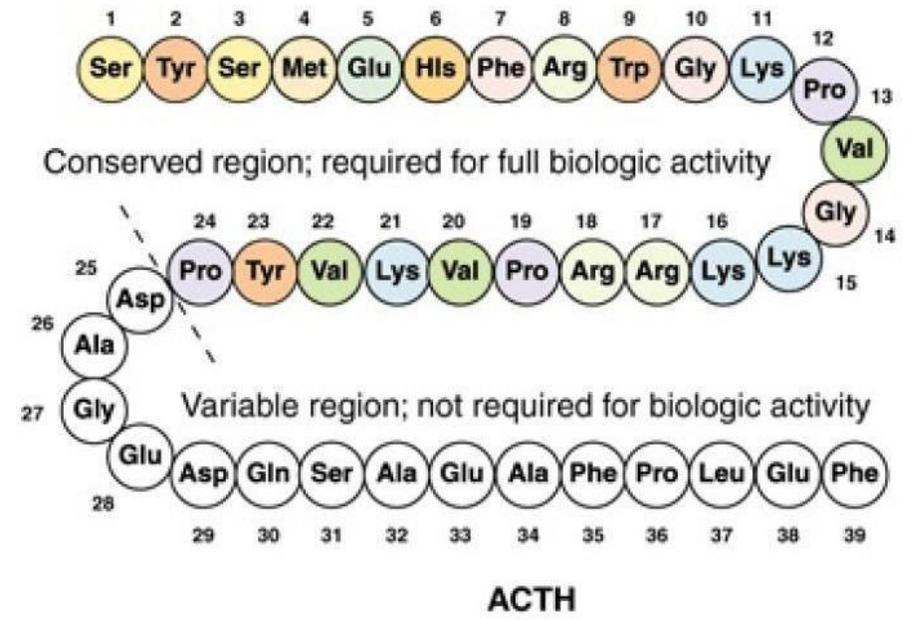
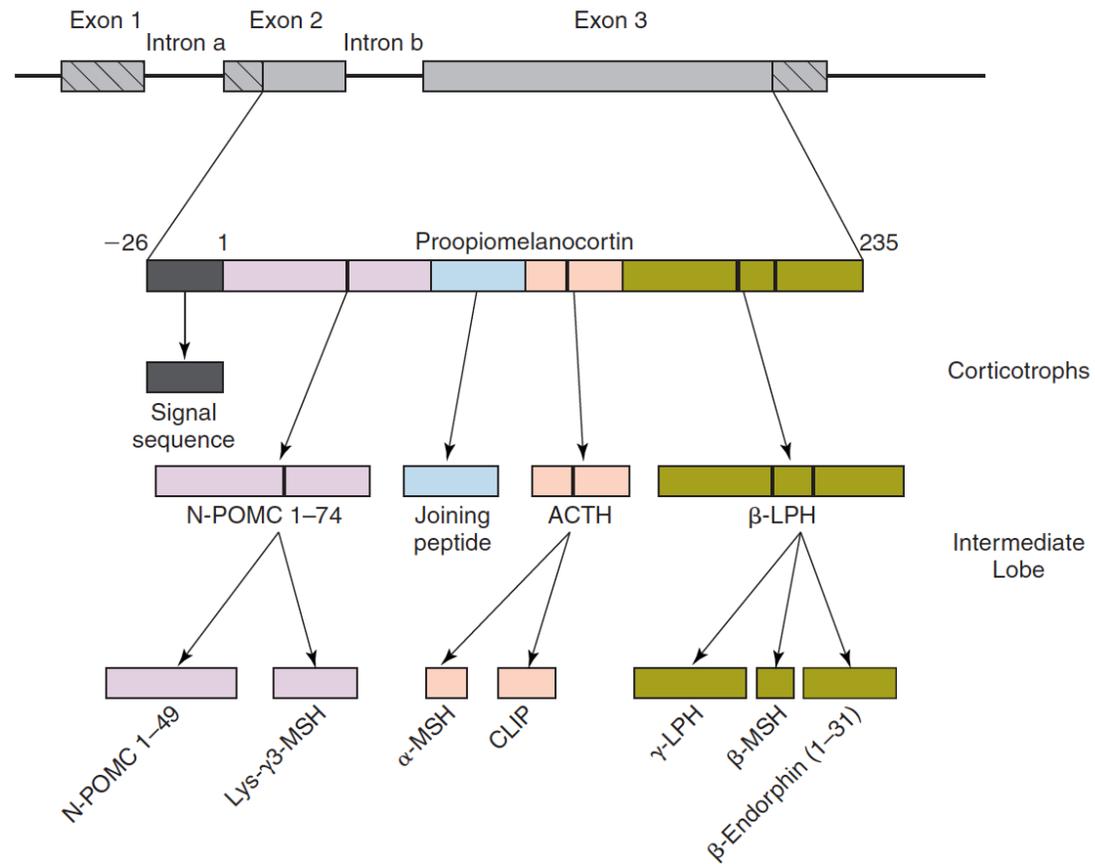
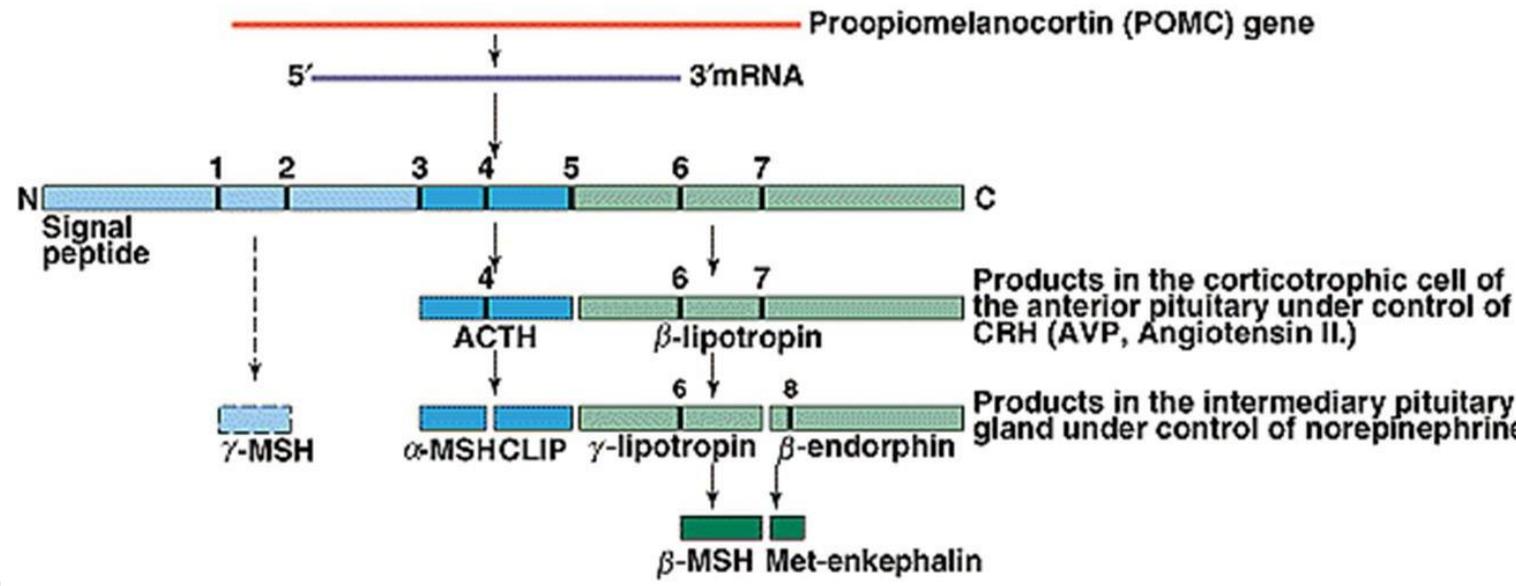


Proteins and peptides

- General steps of peptide synthesis
 - A. Synthesis from a Precursor Polypeptide
 - a. Expression of “pre-pro” protein
 - b. Transport to ER (due to a signaling sequence)
 - c. Splitting the signaling sequence
 - d. Cleavage to definite peptide(s) and final modification in Golgi
 - Examples include preproinsulin to insulin, where it includes splitting off the signal peptide and forming 3 disulfide bonds between A and B chains and hydrolysis of specific peptide bonds resulting in removal of one C peptide per insulin molecule. So, you may know the insulin concentration by measuring C peptide concentration.
 - B. Synthesis of a large protein producing many functioning proteins:
 - Examples include Proopiomelanocortin (POMC) to MSH and ACTH



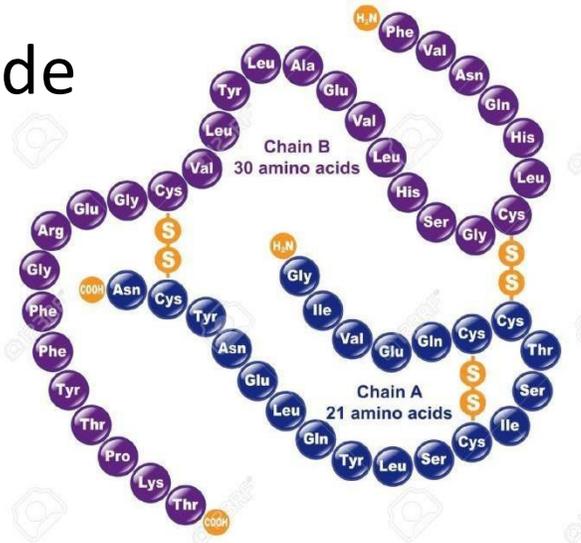
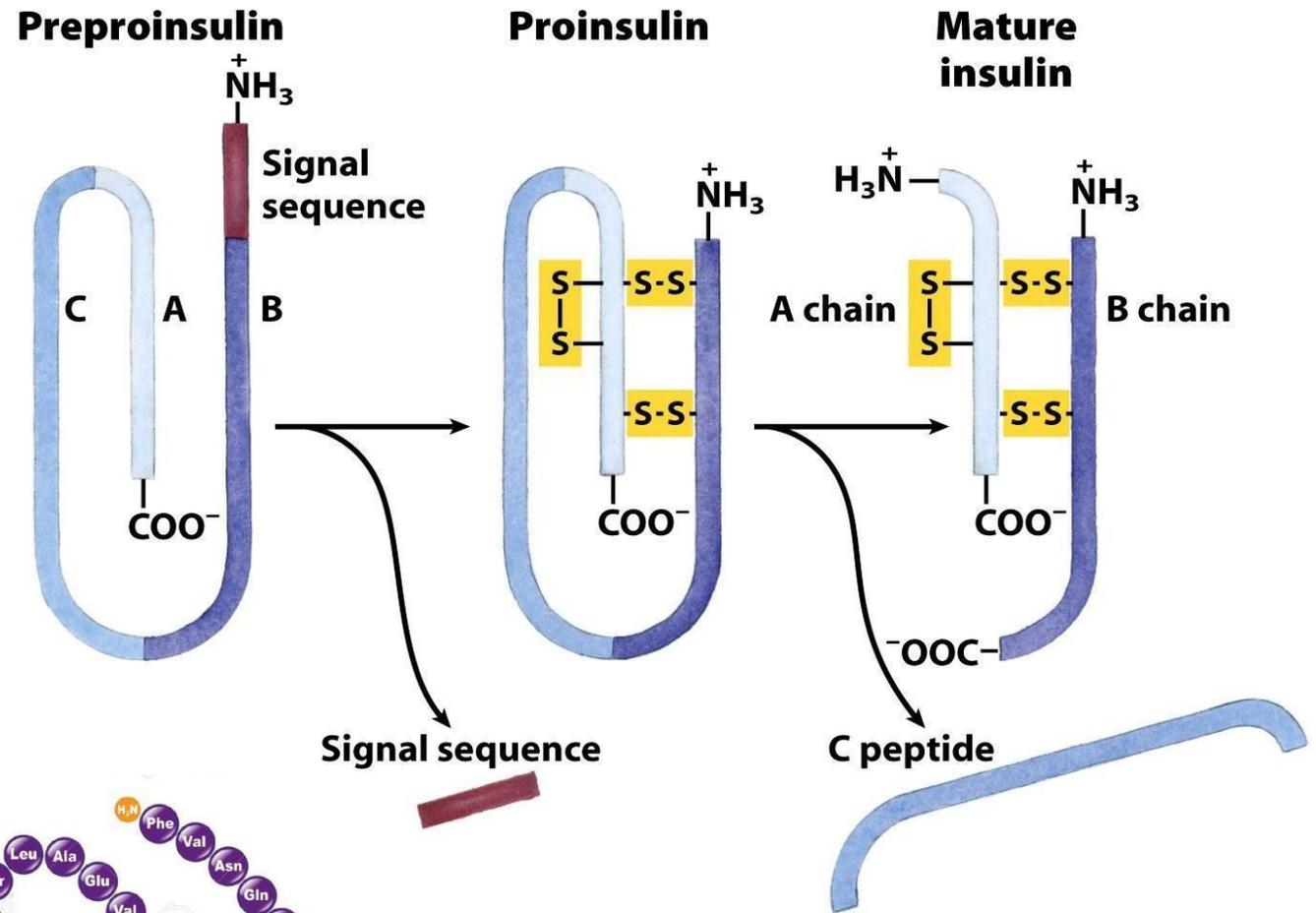
Proopiomelanocortin (POMC)





Insulin

- A larger precursor preproinsulin
 - ✓ 23 aa signal sequence
 - ✓ 3 disulfide bonds
- Proinsulin
 - ✓ Removal of the C peptide
- Mature insulin
 - ✓ A and B chains





Degradation of peptide hormones

- Lysosomal after endocytosis of complex hormone-receptor (Endocytosis of complex hormone-receptor then joining with a lysosome which contains proteases)
- Chemical modification (liver): rearrangement of S-S bridges, followed by cleavage of the peptide
- Renal excretion of small peptides

Biochemistry Quiz 3

