بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Biochemistry | Final 2

Hormones Structure By their location

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Structure of hormones by location

- Hormones can also be classified according to their **anatomical origin**.
- The major glands include the **endocrine hypothalamus, pituitary, thyroid, parathyroid, adrenal, endocrine pancreas, gonads and pineal gland**. Each produces a specific hormone that is **regulated by a specific feedback mechanism.**
- This localization is important **to define where a certain disease starts and how**.
- An example is Addison's disease, where the problem is **adrenal cortex dysfunction (Primary Adrenal Insufficiency)**. This presents with **specific lab results:↓Cortisol ↓Aldosterone ↑ACTH.** This helps differentiate **primary from secondary adrenal insufficiency.**
- In **secondary insufficiency:↓ Cortisol, ↓ACTH, Aldosterone is usually preserved.**

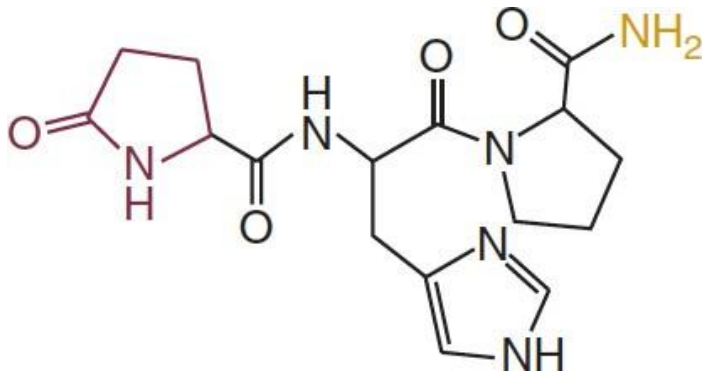
Hypothalamus

❑ Hormones that are secreted by the Hypothalamus:

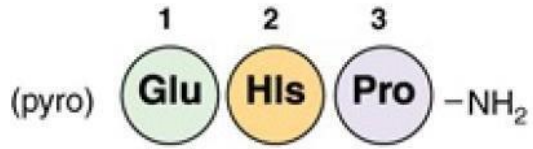
Hormone	Composition
Growth hormone releasing hormone (GHRH)	Two forms: polypeptides (40 & 44 amino acids)
Somatostatin (Growth Hormone Inhabiting Hormone)	Two forms: polypeptides (14 & 28 amino acids)
Dopamine (Prolactin Inhabiting Hormone)	Catecholamine (amino acid derivative)
Corticotropin releasing hormone (CRH)	Polypeptide (41 amino acids)
Gonadotropin releasing hormone (GnRH)	Polypeptide (10 amino acids)
Thyrotropin releasing hormone (TRH)	Polypeptide containing 3 amino acids

Hypothalamus

- This slide shows the amino acid sequence of different hypothalamus trophic hormones (I don't think that they are required for memorisation)



thyrotropin-releasing hormone, TRH.



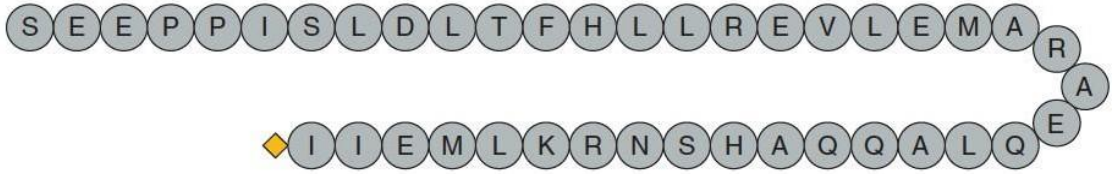
TRH

E = pyroglutamyl

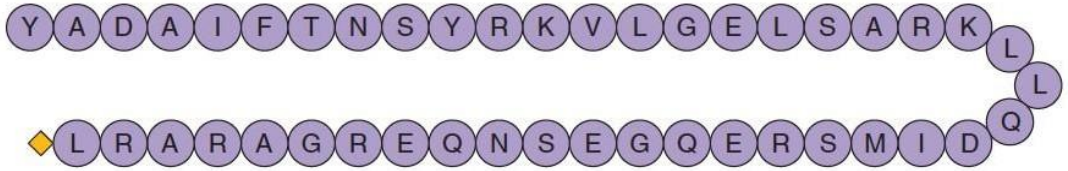
= c-terminal amide: prolinamide (TRH); glycinamide (GnRH); isoleucinamide (CRH); leucinamide (GHRH)

TRH: Thyrotrophin releasing hormone

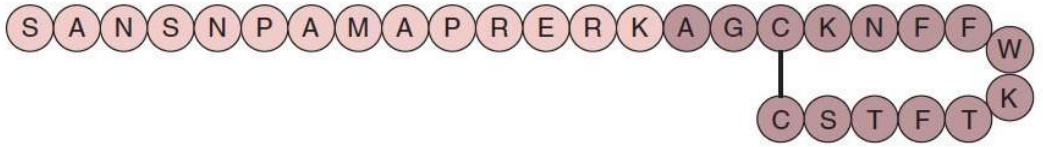
GnRH: Gondaotrophin releasing hormone



CRH: Corticotrophin releasing hormone



GHRH: Growth hormone releasing hormone



SST: Somatostatin

Nots regarding the previous Slide

- The hypothalamus produces releasing hormones and catecholamines (dopamine). These hormones are either inhibiting or releasing, to regulate the release of anterior pituitary hormones.
- Dopamine agonists are used for treating prolactinomas; an example is bromocriptine.
- GnRH has a **pulsatile release pattern**. When it is **administered continuously, its receptors are downregulated, leading to decreased FSH and LH secretion**. Therefore, GnRH agonists are used for **prostate cancer, endometriosis**, etc.
- **These hormones are very important as they are the first level of regulation**.
- Any problem in this system leads to abnormal endocrine regulation. For example, any hypothalamic lesion can cause decreased release of releasing hormones, leading to hypopituitarism.

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)
Adrenocorticotropic 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)

- The **glycoproteins** have **two main acids chains : alpha & Beta.**
- The **alpha chain is similar in its amino acids sequences between all glycoproteins.**
- The **beta** chain is different between different glycoproteins and it is what gives the glycoprotein its characteristic.

Notes Regarding the previous Slide

- As demonstrated by the amino acid sequence, these hormones are of varying length.
- TRH is pyroglutamyl-histidyl-proline amide. Pyroglutamic acid at the N-terminus is a cyclized variation of glutamic acid that protects the N-terminus from being degraded by aminopeptidases. All of them are rapidly degraded by GI processes, so they must be given parenterally if used therapeutically.
- However, synthetic analogs resistant to degradation have been developed. GnRH agonist: Leuprolide.
- TRH is identical across many species, which highlights its importance. Somatostatin exists in two forms: 14 amino acids, 28 amino acids.
- **The longer form (28 aa) is more active in the GIT (intestinal mucosa). The shorter form (14 aa) is more active in the hypothalamus, pancreas.** This demonstrates how a single gene gives rise to the same protein, but post-translational processing results in tissue-specific functions.

Notes Regarding the previous Slide

- **GH is mainly a 191-aa polypeptide**, but a **176-aa variant** might be generated by alternative splicing.
- **GH is the most abundant anterior pituitary hormone.**
- Prolactin is structurally related to GH. Therefore, both work on non-RTK JAK/STAT pathways
- The glycoproteins TSH, FSH and LH are **heterodimers (they are glycoproteins)** composed of:

1) **An identical α-subunit composed of 92 aa.**
2) **A β-subunit specific to each hormone.**

- This is why **we use the β-subunit for diagnosis, while the α-subunit is not diagnostically as useful.**
- The β-subunit determines receptor specificity for each hormone.

Notes Regarding the previous Slide

- GH is mainly a 191 a.a. polypeptide, but a 176 a.a. variant might be produced by alternative splicing, and it is the most abundant anterior pituitary hormone.
- Prolactin is structurally related to GH. Therefore, both work on non-RTK (JAK/STAT).
- The glycoproteins TSH, FSH, LH are heterodimers composed of an identical α-subunit composed of 92 a.a., and a β-chain that is specific to each one.
- This is why we use the β-subunit for diagnosis, while the α-subunit is not diagnostically useful.
- The β-subunit is also what determines the receptor specificity for each of these hormones.
- Post-translational glycosylation affects the folding, secretion, and bioactivity of these hormones.
- More highly glycosylated isoforms of FSH have shown longer T½ but lower receptor affinity (higher T½).

Notes Regarding the previous Slide

- This is clinically important in menopausal females, where the loss of ovarian feedback (reduced estrogen) leads to increased FSH and LH secretion (inhibition is removed).

- The gonadotrophs are working at maximum capacity, resulting in **altered processing and a shift in the glycoforms of the hormones.**

- **This can affect immunoassay accuracy.**

- Changes in branching/size of the carbs can alter the **interaction between antibodies and the protein.**

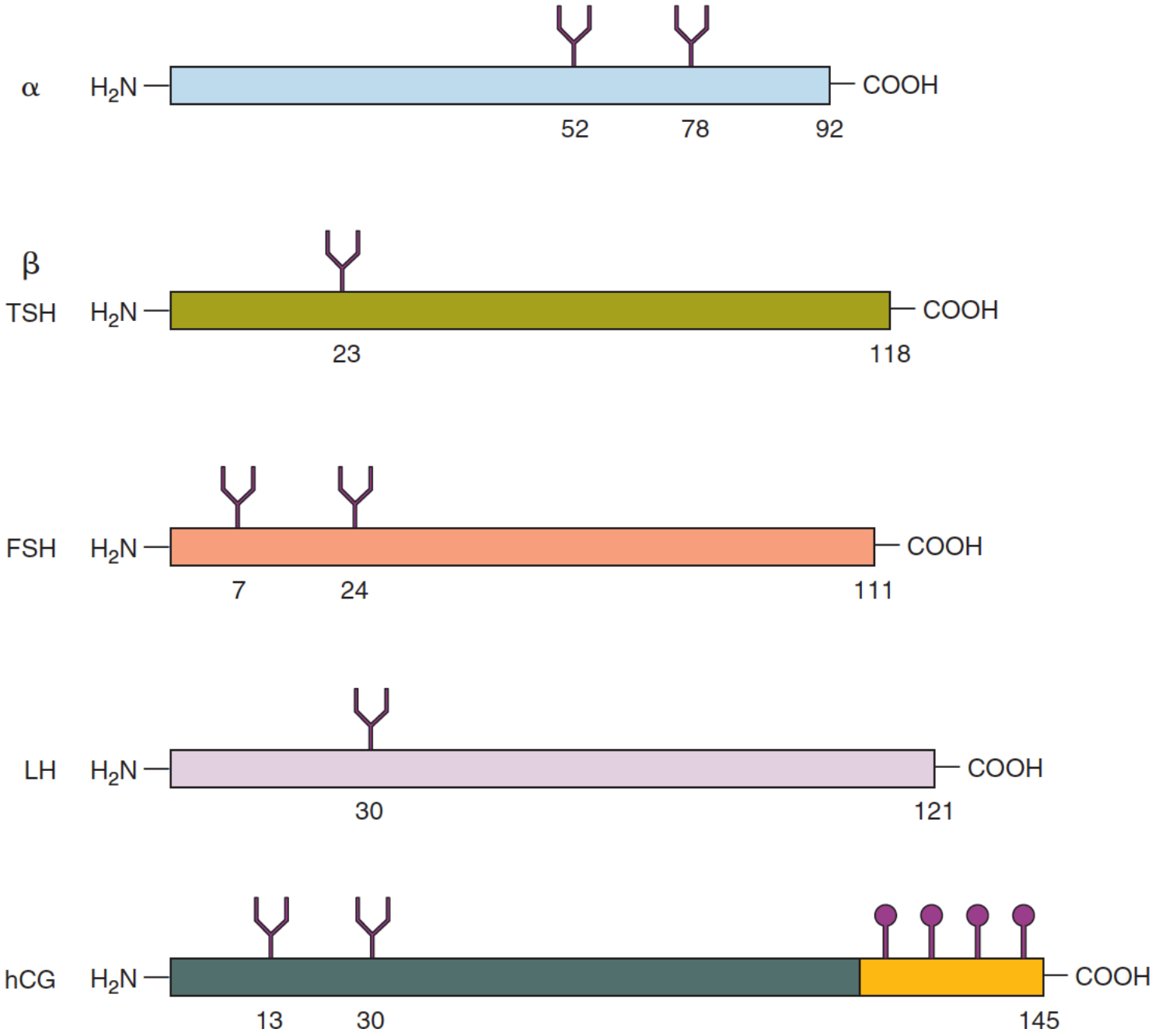
- This can overestimate or underestimate [hormone levels].

- Summary :

- **Menopause** → ↓ **estrogen** → the normal negative feedback on the pituitary is lost.
- Therefore, the pituitary ↑ **FSH and** ↑ **LH**.
- Because gonadotroph cells are producing these hormones at very high rates, their **processing/glycosylation changes**.
- FSH and LH are **glycoprotein hormones**, meaning they have carbohydrate (sugar) chains attached to them.
- Changes in these sugar chains can change how the hormones interact with **antibodies used in immunoassays**.
- Therefore, laboratory tests may **overestimate or underestimate FSH/LH levels**

Anterior pituitary

- N-glycosylation (Asn) vs. O-glycosylation (ser)



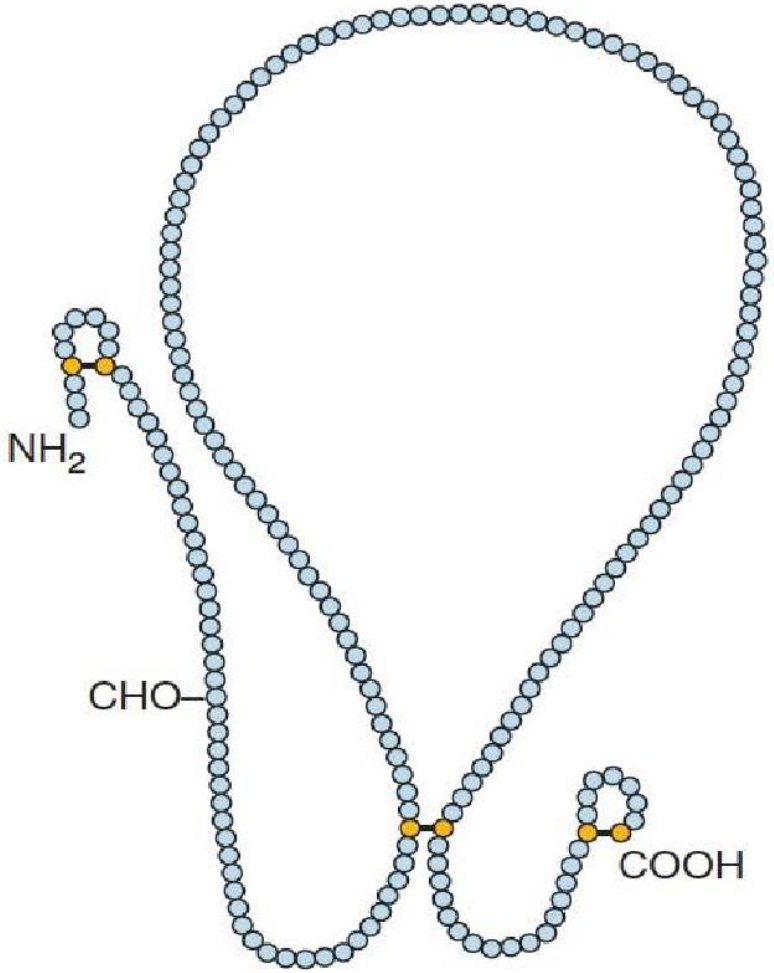
Anterior pituitary, Glycosylation

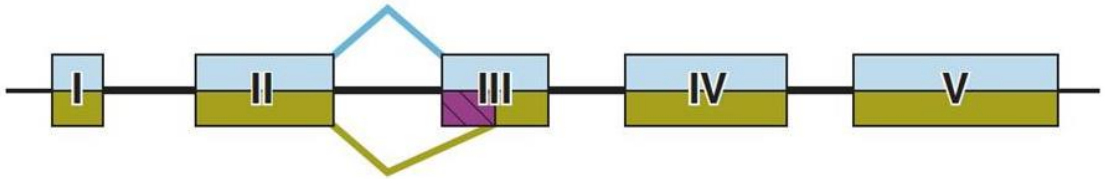
- **Glycosylation** is a critically **important post-translational modification** for anterior pituitary Glycoprotein hormones. Two main types exist:
  - **N-glycosylation on *asparagine* residues and mainly happens in the RER (rough endoplasmic reticulum).**
  - **O-glycosylation on *serine/threonine* residues and mainly happens in the Golgi apparatus.**

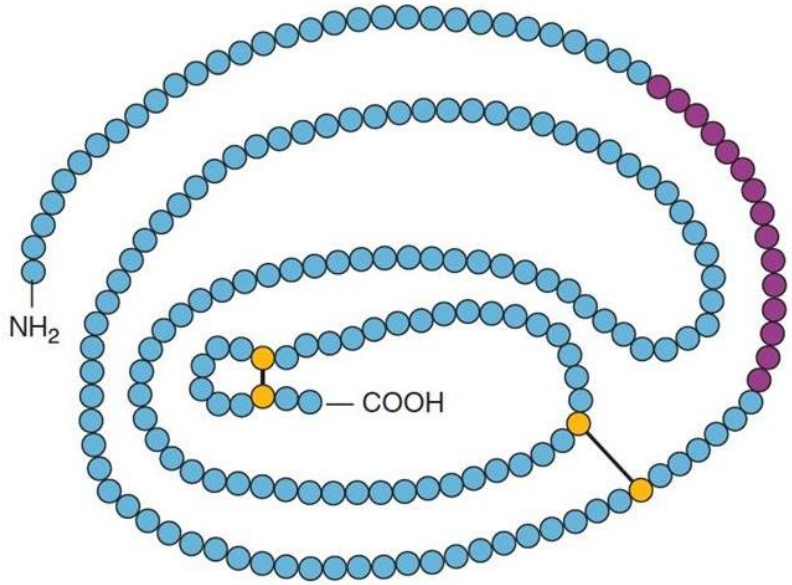
- N-glycosylation is important for protein **folding, intracellular trafficking and secretion.**
- The glycan compositions **vary and might include sialic acid, fucose, galactose, and N-acetylglucosamine, all affecting half-life and receptor activity.**
- Sialic acid addition (sialylation) **significantly increases T½ by reducing liver clearance.**
- The liver has **asialoglycoprotein receptors, which, as the name implies, bind to glycoproteins with no/low sialic acid residues.**

- **Sialylation** decreases the **biological activity of the hormones.**
- **Glycosylation** is important clinically **because some patients with pituitary adenomas might present with normal hormone levels but abnormal bioactivity due to differences in glycosylation patterns.**
- Certain immunoassays might **not detect all isoforms, which might result in false-negative results.**
- A patient presents with **normal hormone levels** but symptoms of **hyperfunction**: the **glycosylation pattern blocked antibodies from binding to these results. (Antibodies are our way of measuring hormones levels).**
- A patient with normal levels but symptoms of **hyposecretion**: the **glycosylation pattern changed the activity and clearance of the hormone.**

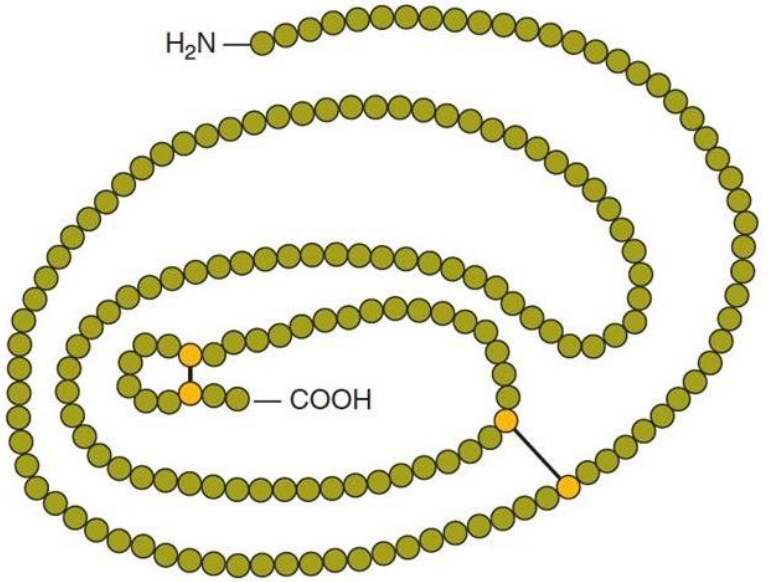
Anterior pituitary – GH & prolactin







22K-GH
191aa



20K-GH
176aa

Anterior pituitary – GH & prolactin

- GH and prolactin are structurally related. **Both are single-chain polypeptides of approximately the same weight.**
- They share a **common 4-helix bundle structure (anti-parallel helices)**, which is characteristic of the cytokine/hematopoietic protein family.
- This explains why **high levels of prolactin can have growth-promoting effects.**
- As was mentioned in the previous slide, **GH has multiple isoforms,** the most abundant being the **191 a.a. form, with the 176 a.a. form produced by alternative splicing and having reduced bioactivity.**
- Very important: ***GH can't be glycosylated in humans [no sites for such glycosylation], but prolactin can be glycosylated, which results in longer T½ but reduced activity.***
- Intramolecular disulfide bonds between cysteine residues are essential for maintaining the protein's 3D structure.
- Important for synthetic GH somatropin – to have the correct structure.
- This explains why patients with **GH deficiency respond to these drugs, while patients with GH receptor mutations (a condition known as Laron syndrome) don't respond.**
- They have ↑ GH but ↓ IGF-1 (produced by the liver in response to the GH).

Side Note

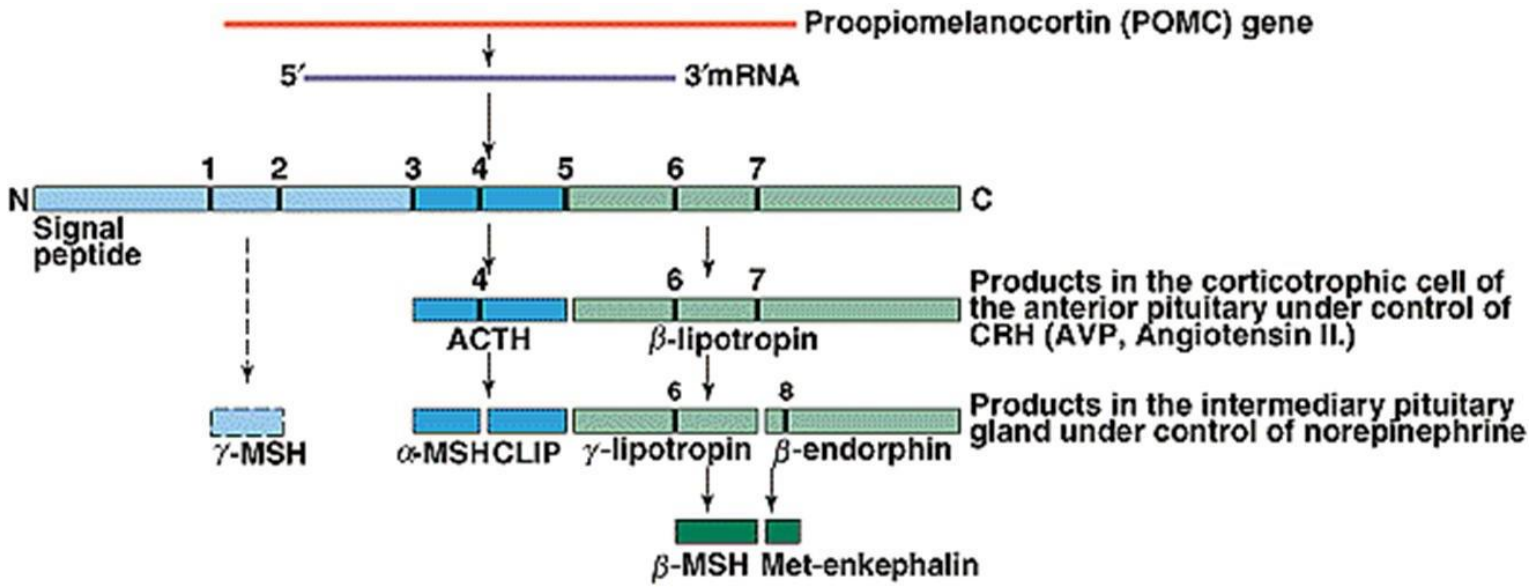
- **All proteins have 3 levels of structure:**

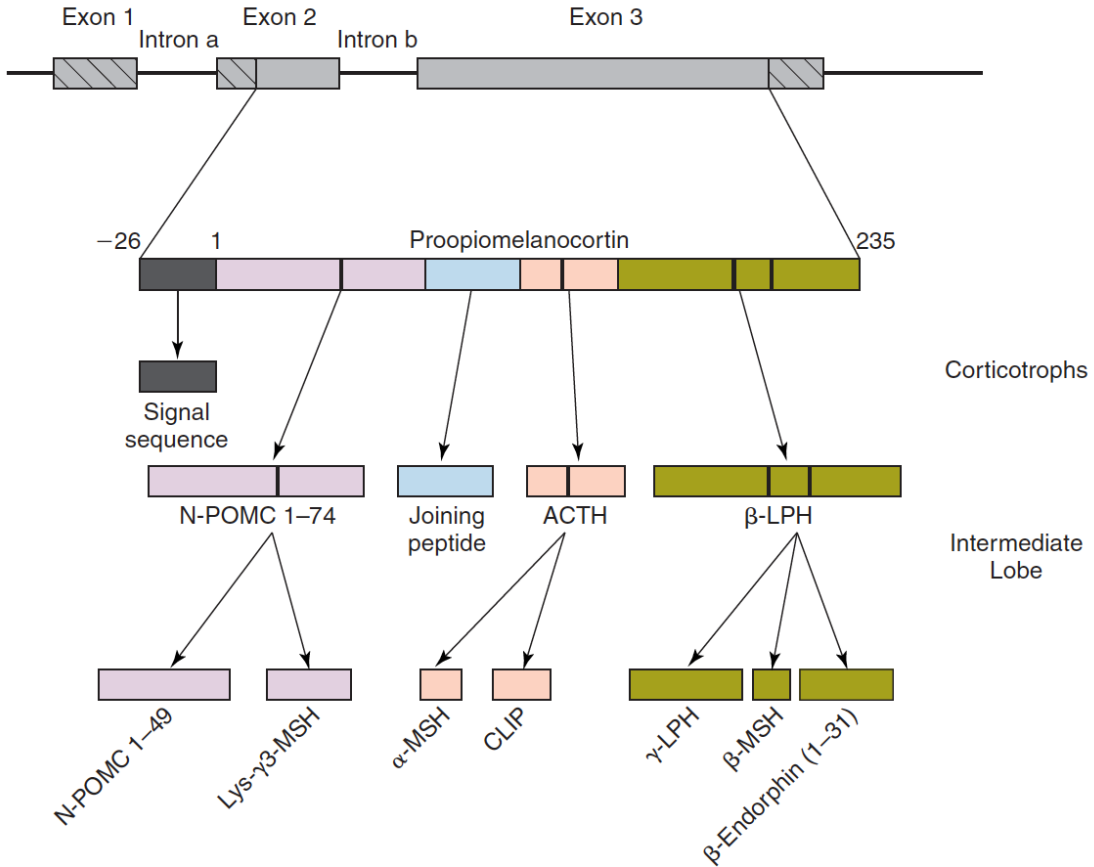
1) Primary – which is the number and sequence of amino acids.
2) Secondary – which is the localized organization of the amino acids in the polypeptide chain.
3) Tertiary – which is the final 3D structure.

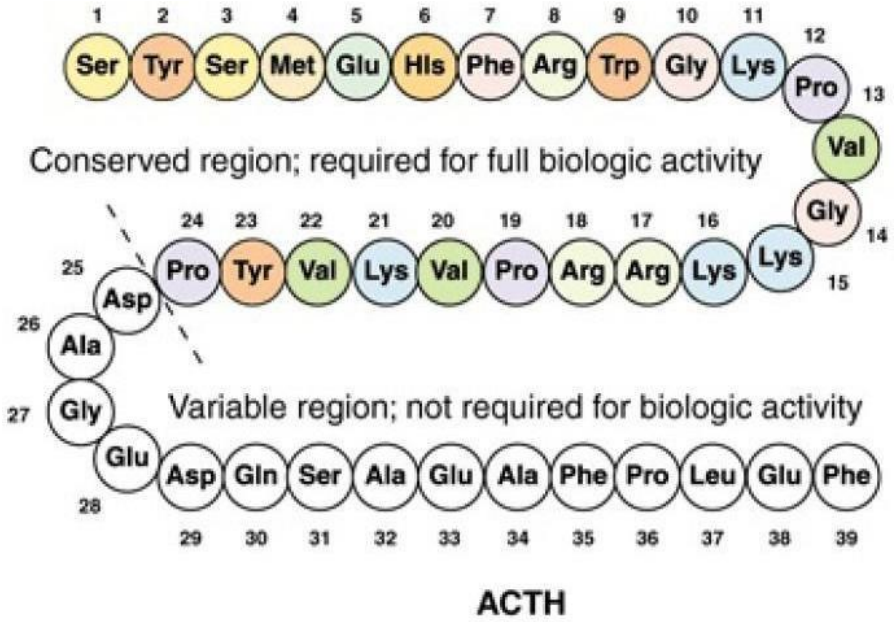
- Some proteins with multiple polypeptides have quaternary structure.

- The secondary structure is formed by the α-carbon with the amino nitrogen and carboxyl carbon, resulting in hydrogen bonds and local arrangement of the backbone, leading to formation of α-helix, β-pleated sheets, loops, etc.

Anterior pituitary – Proopiomelanocortin (POMC)







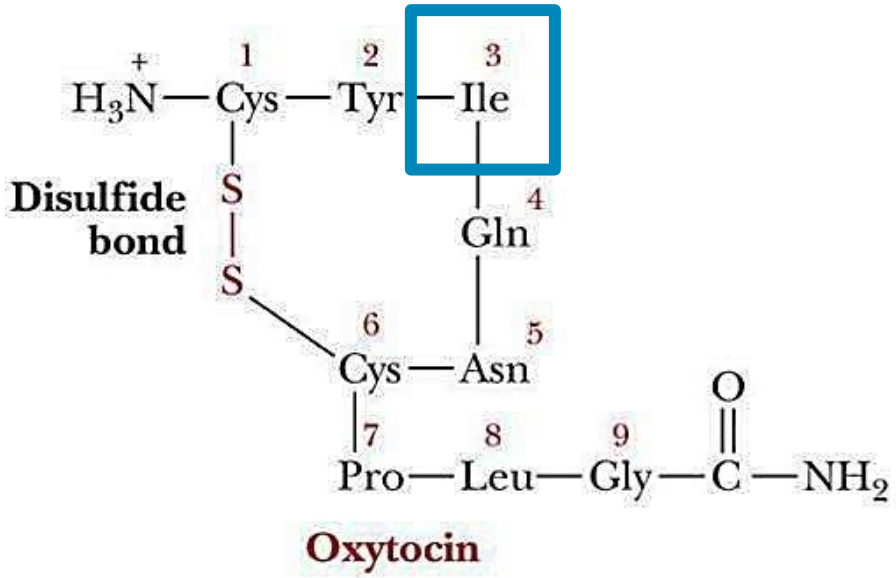
ACTH

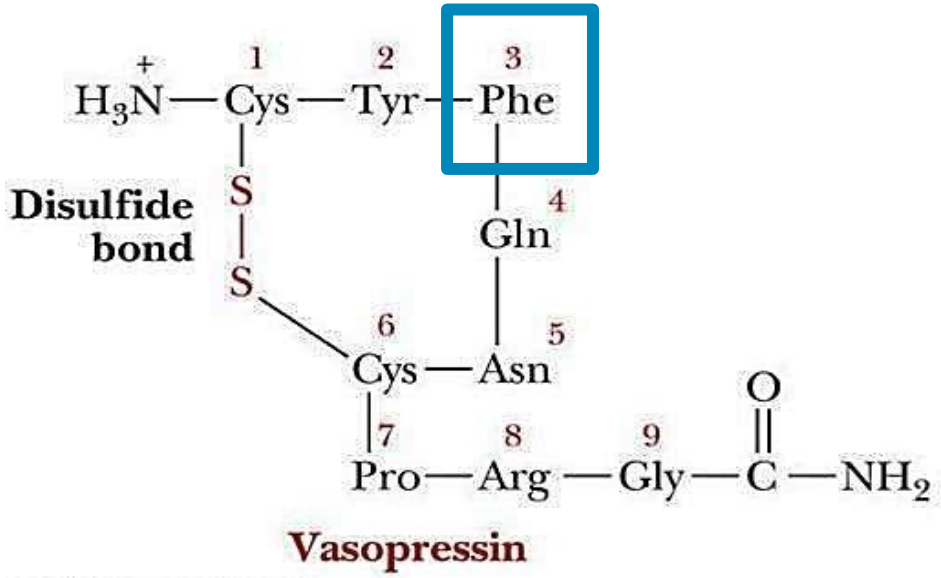
Notes Regarding the previous slide

- POMC is a prohormone that is **processed in a tissue-specific manner to produce multiple peptides which belong to the POMC family.**
- The POMC gene is located on chromosome 2, and it encodes a 241 a.a. precursor synthesized in the anterior pituitary, hypothalamus and other tissues (lung, GIT, placenta…).
- In the anterior pituitary, prohormone convertase 1 (PC1/3) cleaves POMC, **primarily into ACTH (39 a.a.), β-lipotropin (β-LPH), which is 91 a.a., and N-terminal peptide (NPP).**
- In the **hypothalamus and skin, a different form of the enzyme, PC2, cleaves POMC into:**
  - ***α-MSH and corticotropin-like intermediate peptide (CLIP) from ACTH.***
  - ***β-LPH into β-endorphin, γ-LPH and β-MSH.***
- This tissue-specific processing demonstrates how the same gene produces different hormones in different tissues.

Posterior pituitary

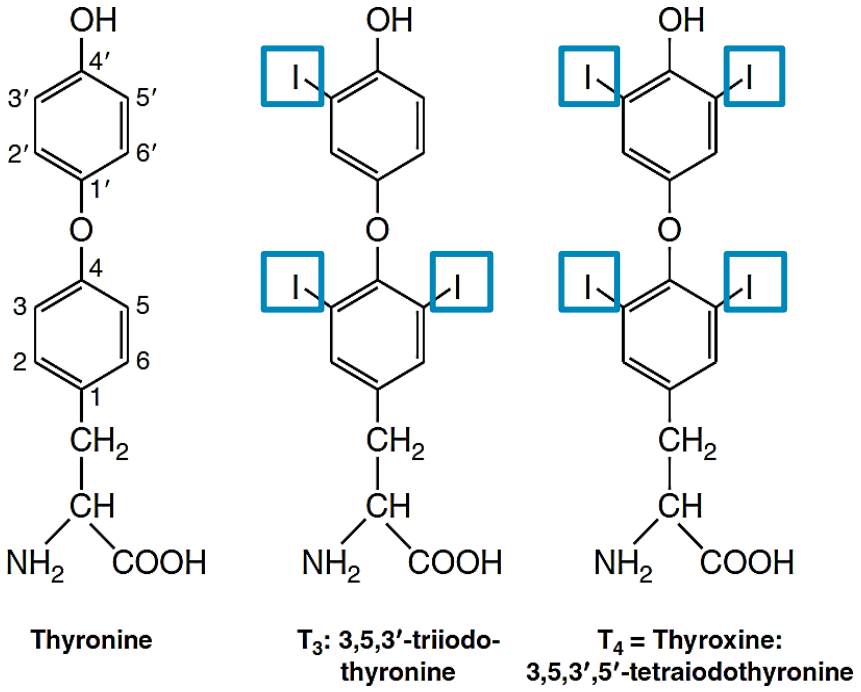
Hormone	Composition
Oxytocin	Polypeptide containing 9 amino acids
Antidiuretic hormone (ADH; vasopressin)	Polypeptide containing 9 amino acids; two forms: arginine-ADH (most common in humans) and lysine-ADH





Thyroid

Hormone	Composition
Thyroxine (tetraiodothyronine, T4)and triiodothyronine (T3)	Amino acid derivative
Calcitonin (thyrocalcitonin)	Polypeptide containing 32 amino acids

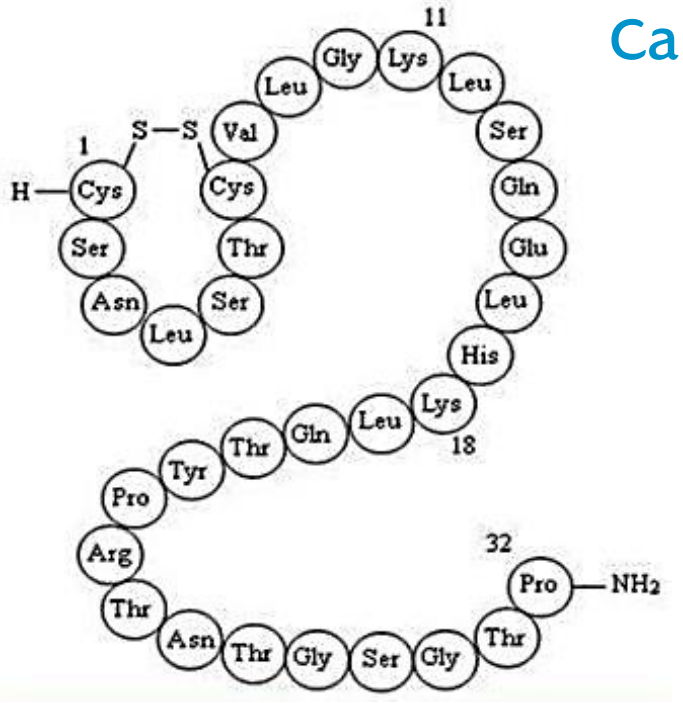


Thyronine

T_3: 3,5,3′-triiodo-thyronine

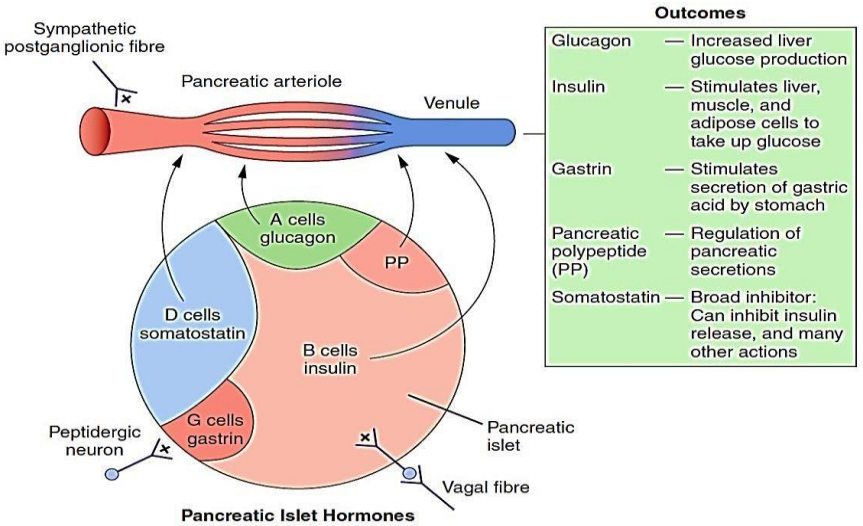
T_4 = Thyroxine: 3,5,3′,5′-tetraiodothyronine

Calcitonin

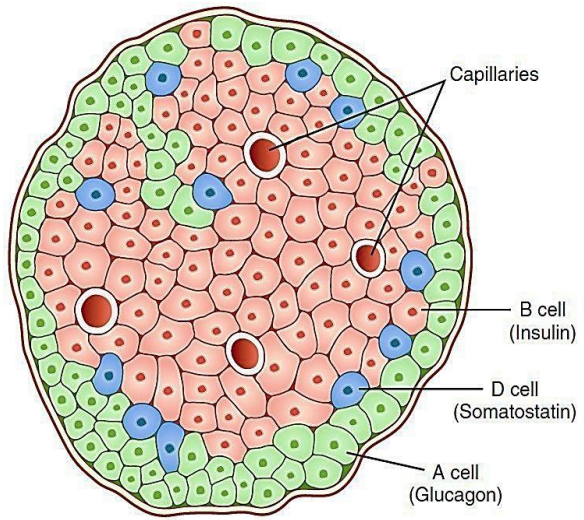


Pancreas

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



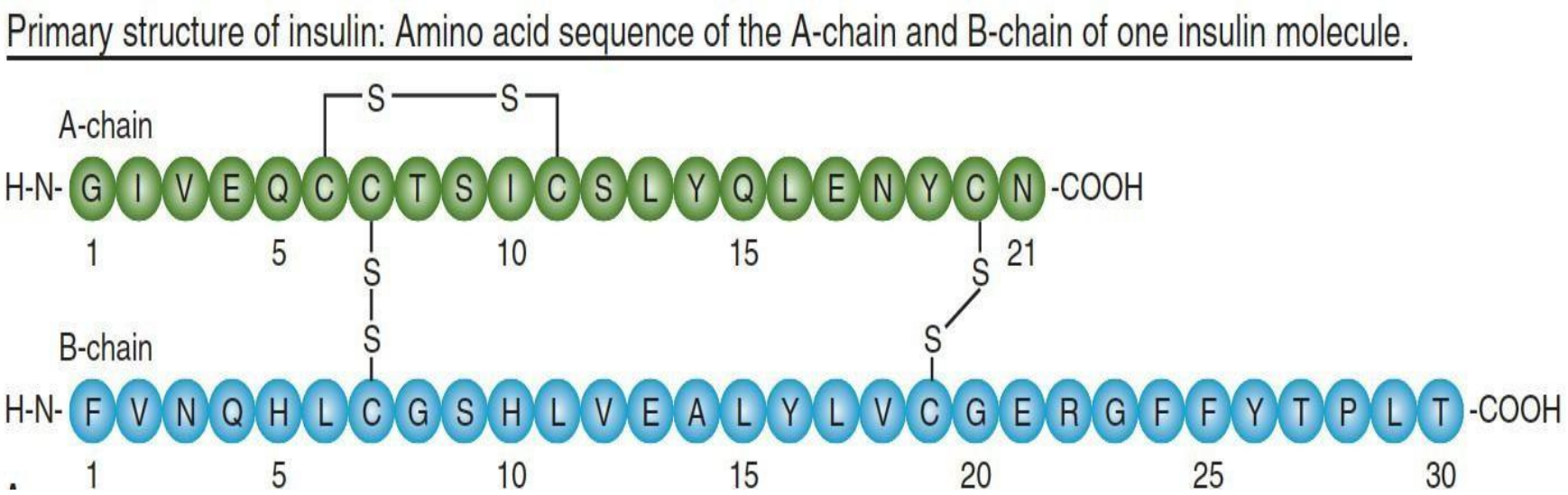
Pancreatic Islet Hormones

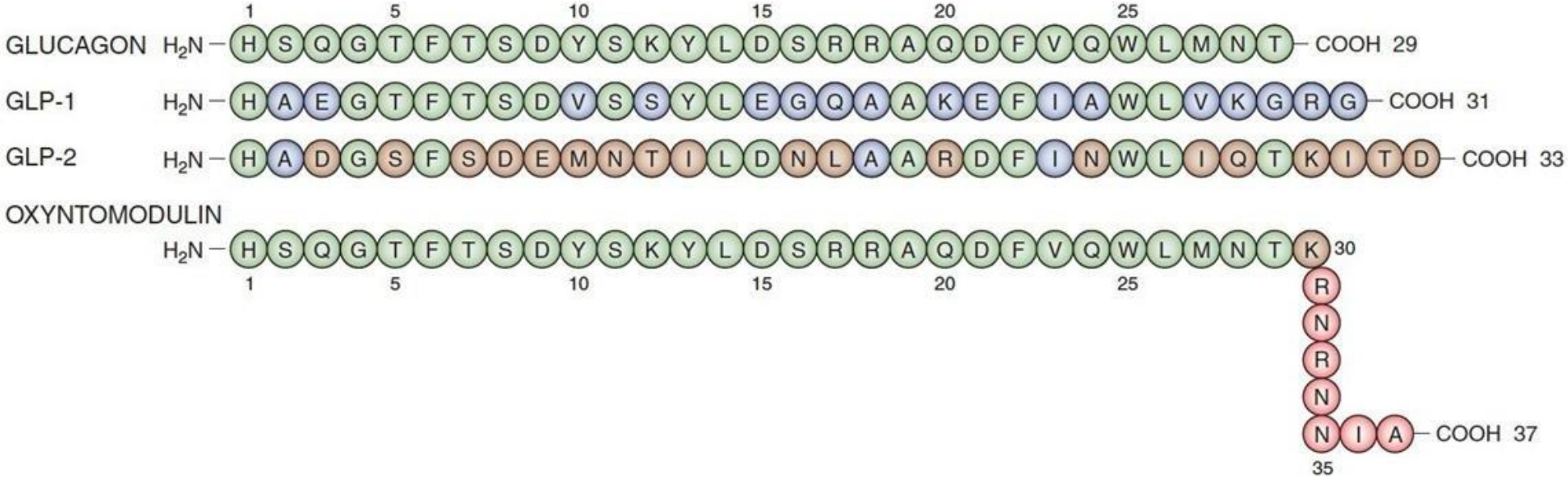


Pancreas

- The endocrine pancreas, represented by islets of Langerhans, produces the hormones mentioned in the previous slide.
- The intestinal L-cells produce the incretin hormone GLP-1, which is functionally integrated with the pancreatic physiology (decrease glucagon secretion and stimulates insulin secretion).
- Another incretin hormone that is related is GIP, which is produced by K-cells.
- GLP-1 has 30-31 a.a. and accounts for the majority of post-prandial insulin secretion, suppresses glucagon, induces satiety, and delays gastric emptying. It is rapidly degraded by DPP-4 found in the circulation, with a T½ of 1-2 mins. Synthetic GLP-1 agonists resist DPP-4 degradation (Ozempic).
- The insulin-glucagon balance is important for glucose homeostasis, and in diabetes this balance is disrupted.

Pancreas


Primary structure of insulin: Amino acid sequence of the A-chain and B-chain of one insulin molecule.
A-chain
H-N- G I V E Q C C T S I C S L Y Q L E N Y C N -COOH
1 5 10 15 21
S S S S S S
B-chain
H-N- F V N Q H L C G S H L V E A L Y L V C G E R G F F Y T P L T -COOH
1 5 10 15 20 25 30


GLUCAGON H2N- H S Q G T F T S D Y S K Y L D S R R A Q D F V Q W L M N T -COOH 29
GLP-1 H2N- H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R G -COOH 31
GLP-2 H2N- H A D G S F S D E M N T I L D N L A A R D F I N W L I Q T K I T D -COOH 33
OXYNTOMODULIN H2N- H S Q G T F T S D Y S K Y L D S R R A Q D F V Q W L M N T K R N R N N I A -COOH 37
1 5 10 15 20 25 30 35

Pancreas (notes regarding previous slide)

- Insulin is a heterodimeric protein made of 51 amino acids. The A chain has 21 amino acids with an intrachain disulfide bond, and a B chain with 30 amino acids with 2 interchain disulfide bonds. It is an anabolic hormone promoting glucose uptake, glycogen synthesis, lipogenesis and protein synthesis.
- It is synthesized as preproinsulin, with a 23 a.a. pre/leader sequence that directs the protein to the RER, where it is cleaved to proinsulin. *(biologically inactive but has a slight anti-inflammatory and vasodilatory effect)*

- Proinsulin has a connecting peptide (C-peptide), which connects the A and B chains. It is secreted in an equimolar manner (1:1), which allows for assessment of β-cell function, where low levels indicate insulin insufficiency (T1DM), while normal or high levels indicate T2DM. C-peptide is cleaved by PC1/3 and PC2, along with carboxypeptidase E in Golgi.

- Synthetic insulins are often modified to alter pharmacokinetics, an example is insulin lispro, has a reversed proline^{28} and lysine^{29} residues at positions 28 and 29 in the B chain, reducing the hexamer formation, meaning more of insulin is available as monomers upon injection. *(Usually human insulin forms hexamers (6 insulin molecules) via zinc and H-bonds, which have to disassociate)*

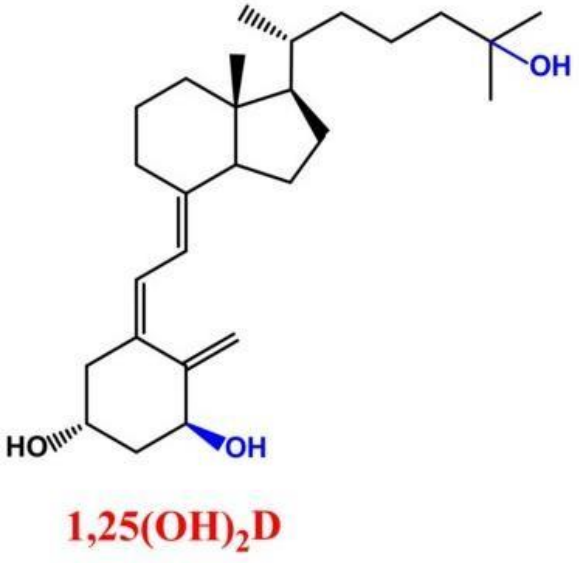
- Glucagon is a 29 a.a. hormone that opposes insulin's effects by promoting glycogenolysis, gluconeogenesis, and lipolysis.

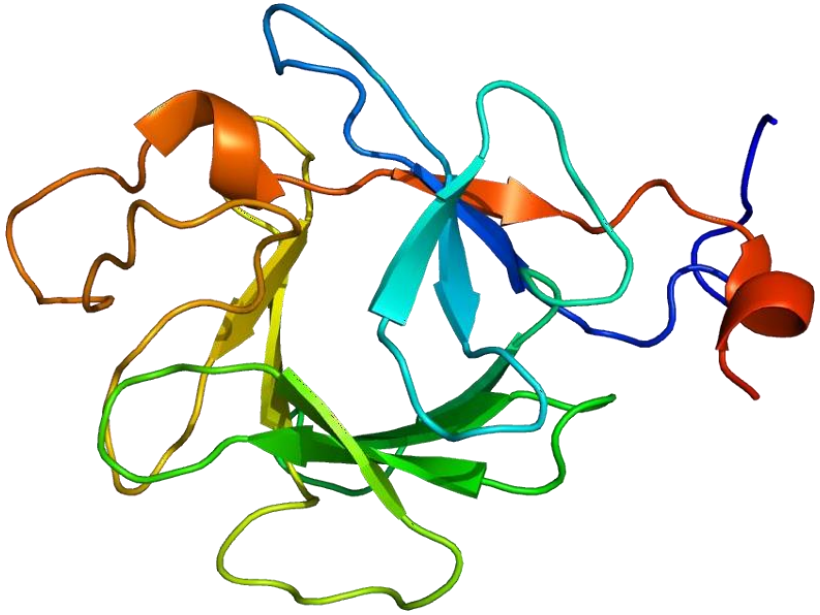
- Somatostatin is produced by delta cells of the pancreas and inhibits insulin and glucagon secretion in a paracrine manner.

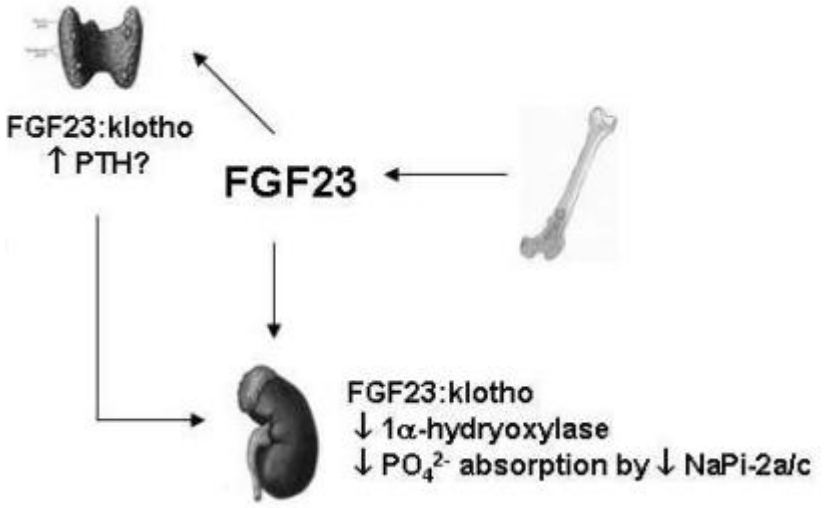
- Pancreatic polypeptide is secreted by PP cells, and regulates exocrine and endocrine secretion and suppresses appetite.

Calcium Regulating Hormones

Hormone	Composition
Parathyroid hormone (PTH)	Polypeptide 84 amino acids
Vitamin D	Steroid
Calcitonin	Polypeptide 32 amino acids
Fibroblast Growth Factor 23	Protein 251 amino acids



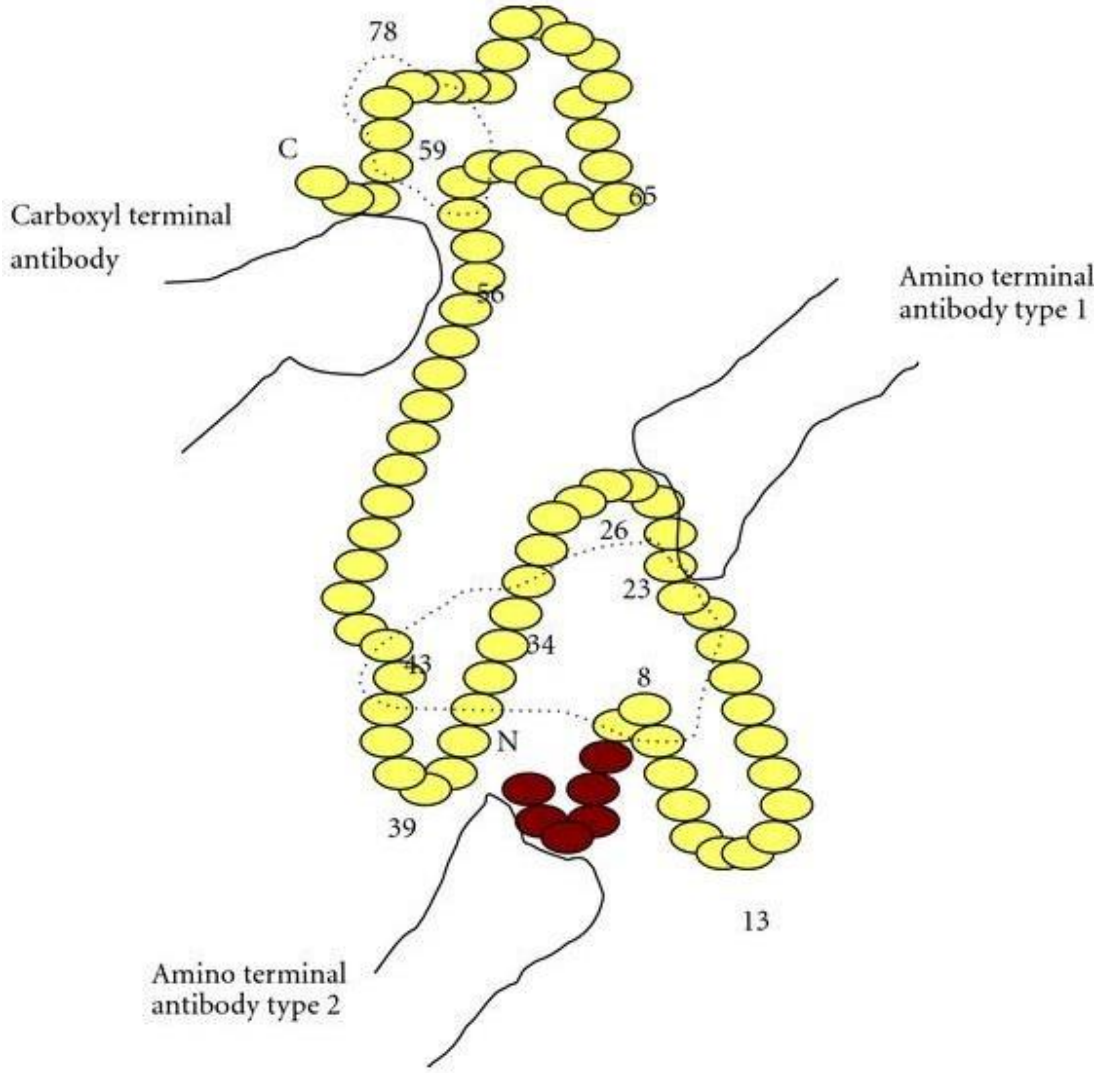


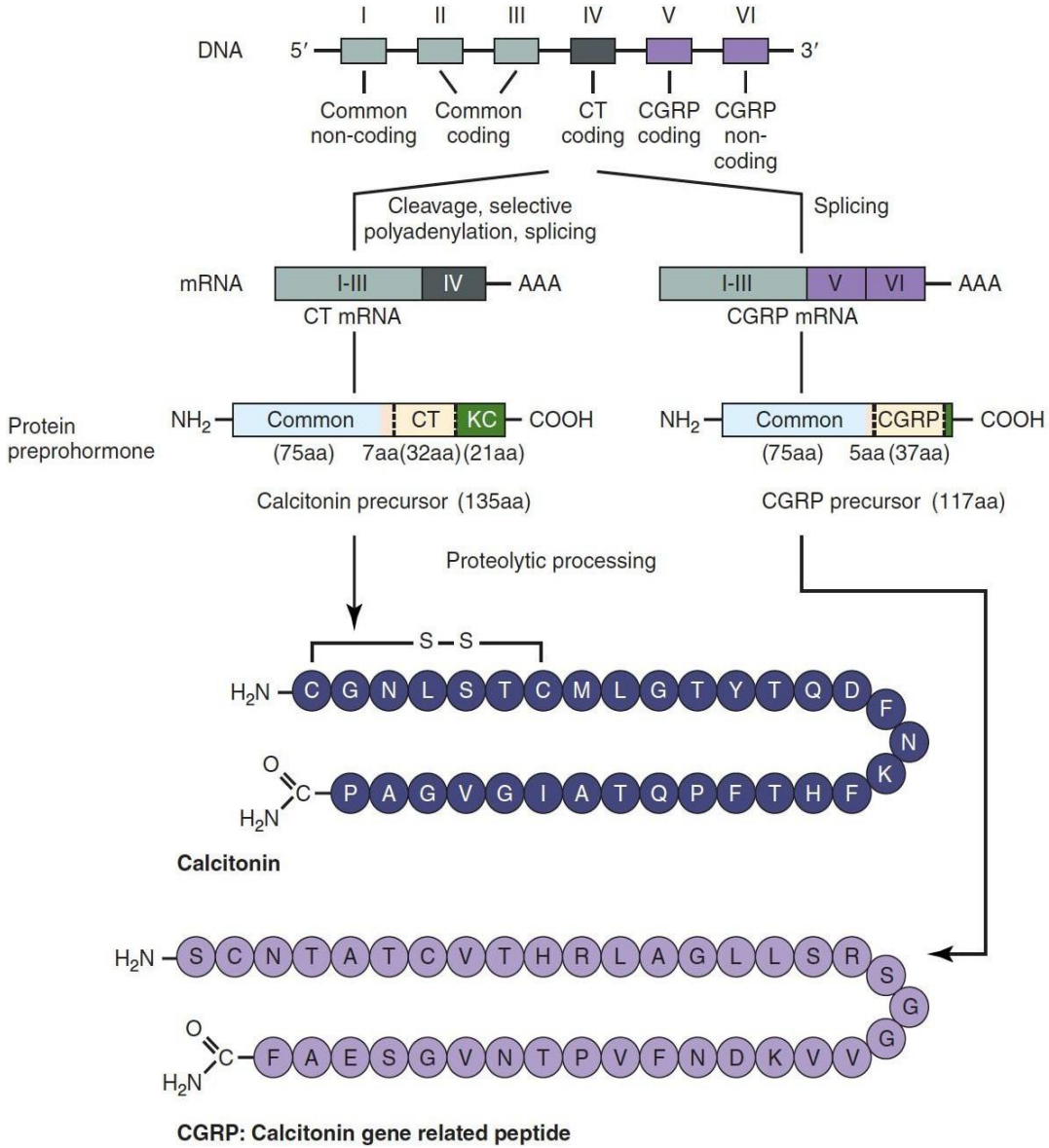


Calcium Regulating Hormones

- Calcium homeostasis is regulated by the 4 major hormones mentioned above.
- PTH is an 84 a.a hormone secreted by chief cells in the PT gland.
- It is the primary hormone to raise serum Ca^{+2} by increasing Ca^{+2} reabsorption with increased phosphate excretion, increasing bone resorption, and indirectly increasing Ca^{+2} absorption from the intestines by activating vit.D
- Vit. D (calcitriol / 1,25-dihydroxycholecalciferol) is a steroid hormone derived from cholesterol. Its synthesis requires 25 hydroxylation in the liver, and 1 hydroxylation in the kidney; this 1 hydroxylation is stimulated by PTH.
- It increases Ca^{+2} and phosphate absorption from the intestines.FGF-23 is a 251 a.a bone-derived hormone, secreted by osteocytes and osteoblasts. It targets the kidney and stimulates phosphate excretion, and it suppresses the enzyme 1-hydroxylase which reduces activation of vit. D, and also stimulates 24-hydroxylase, to get more 24,25(OH)2D which is inactive.
- Elevated levels of FGF-23 lead to hypophosphatemia, seen in X-linked hypophosphatemia caused by mutation in a gene located on the X-chromosome which helps break down and control FGF23.
- **Primary hyperparathyroidism → ↑PTH, ↑Ca^{+2}**
- **Vit. D deficiency → ↑PTH, ↓vit. D**

Calcium Regulating Hormones





Calcium Regulating Hormones

- Ca^{+2} homeostasis is maintained by a negative feedback loop:

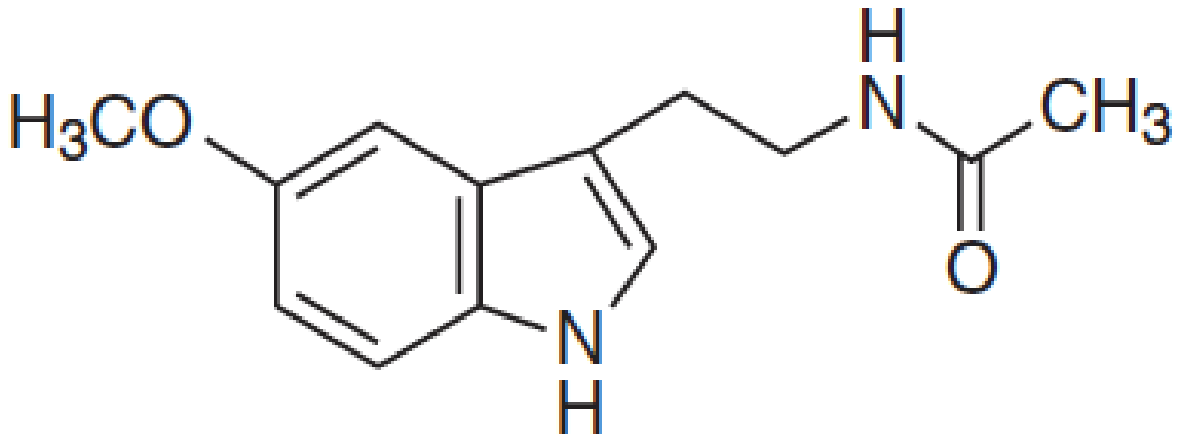
- Low Ca^{+2} stimulates PTH secretion, which acts on kidneys, bones, and GIT (indirectly), to raise Ca^{+2} levels.
- The raise in Ca^{+2} level leads to PTH suppression. This regulation is essential because Ca^{+2} is important for muscle contraction, neural transmission, coagulation (clotting factor 4), and bone health.

- Phosphate homeostasis is less regulated, but it is important for bone mineralization and cellular metabolism.
- Both PTH and FGF23 have the same effect on phosphate, but opposing effects on vit. D.

- Secondary hyperparathyroidism seen in CKD is managed by vit. D and phosphate binders.

Pineal Gland Hormones

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



Melatonin

Adrenal and Sexual Glands' Hormones

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

رسالة من الفريق العلمي:

لقاء مهم بين د.إياد قنيبي و أ .أيمن عبلي عن جريمة سبّ الله و الدين، تجدونه الآن على يوتيوب.

هذه الحلقة ليست موجّهة فقط لمن يقع في هذه الجريمة الشنيعة، بل كذلك لمن حوله، وللمجتمع الذي تحوّل، بشكل أو بآخر، إلى بيئة خصبة لانتشارها والتساهل معها.

لأنّ خطورة هذه الظاهرة لا تكمن فقط فيمن يرتكبها، بل أيضًا في التطبيع معها، والسكوت عنها، وفقدان الشعور بخطورتها و خطورة مآلاتها.

#تعظيم_الرب_والدين

https://youtu.be/2UkbCb8oNgA?si=50ByTaYERjJgnMbF

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 7; Last Note	**The longer form (28 aa) is more active in the GIT. The shorter form (14 aa) is more active in the hypothalamus, pancreas and intestinal mucosa.**	**The longer form (28 aa) is more active in the GIT (intestinal mucosa). The shorter form (14 aa) is more active in the hypothalamus, pancreas.**
	Slide 3 ; Last Note	In **secondary insufficiency:↓ Cortisol, ↑ACTH, Aldosterone is usually preserved.**	In **secondary insufficiency:↓ Cortisol, ↓ACTH, Aldosterone is usually preserved.**
V1 → V2			