

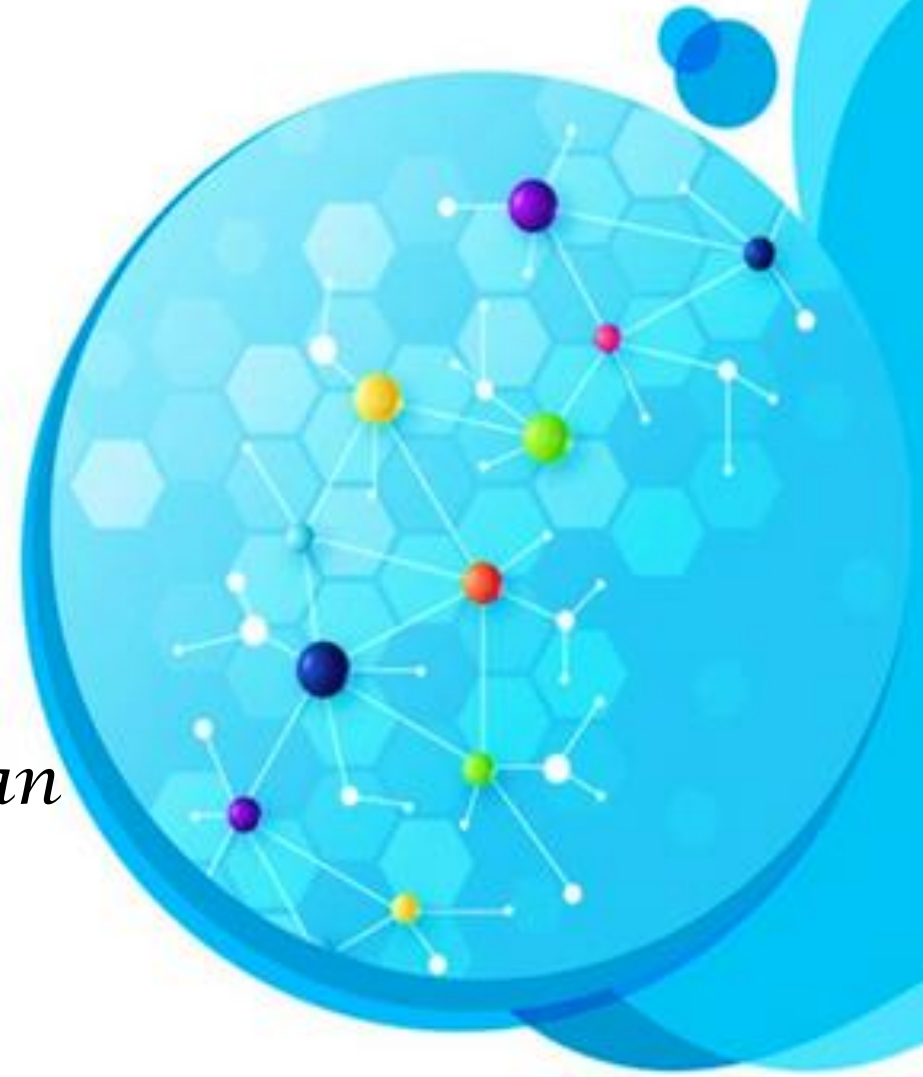
Medical Biochemistry

*Biochemistry of
neurotransmitters*

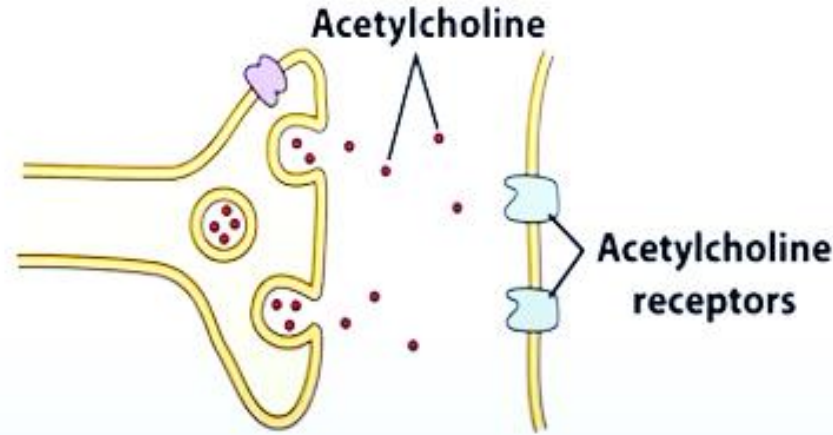
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Introduction: The definition and key characteristics neurotransmitters



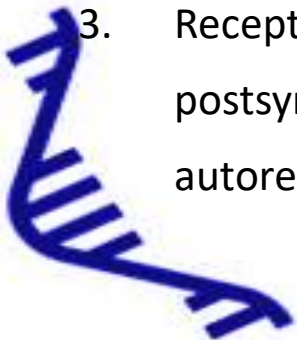
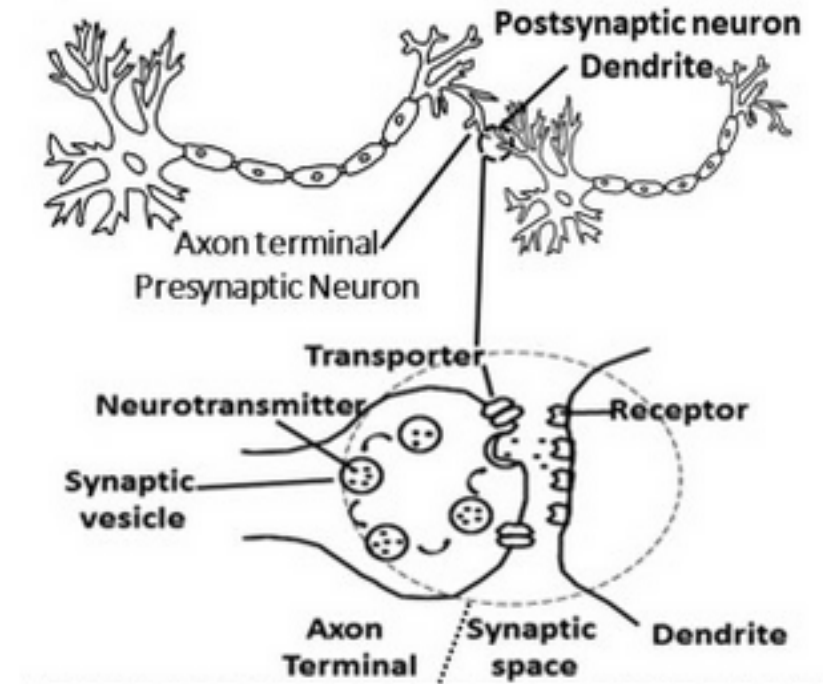
- Neurotransmitters are small molecules or peptides that mediate communication between neurons or between neurons and other target cells (e.g., muscle cells or glands).



Introduction: The definition and key characteristics neurotransmitters



1. **Synthesized and Stored in Presynaptic Neurons** using specific biosynthetic pathways.
 - The enzymes required for synthesis must be present in the neuron, and the neurotransmitters are stored in synaptic vesicles to prevent degradation.
2. **Release upon Depolarization:** An action potential triggers the opening of voltage-gated calcium channels, allowing Ca^{2+} influx. This promotes vesicle fusion with the presynaptic membrane, leading to neurotransmitter release into the synaptic cleft.
3. **Receptor Binding:** The neurotransmitter binds to receptors on the postsynaptic membrane to elicit a response. It can also bind to presynaptic autoreceptors to modulate its own release.





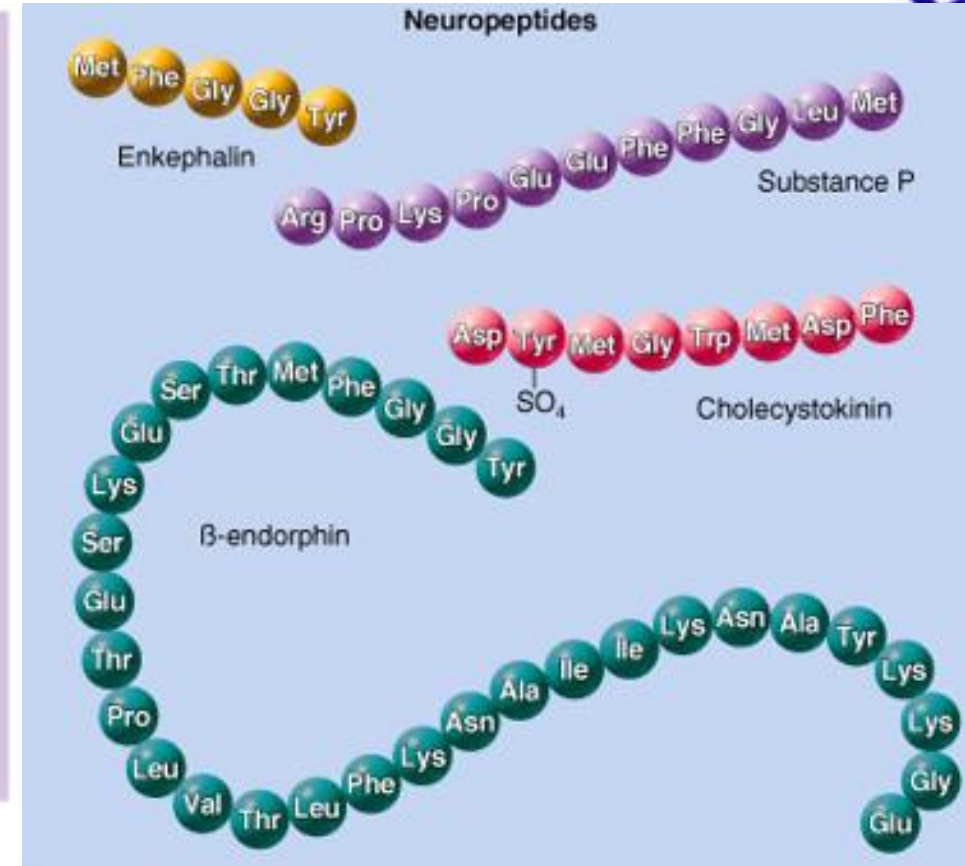
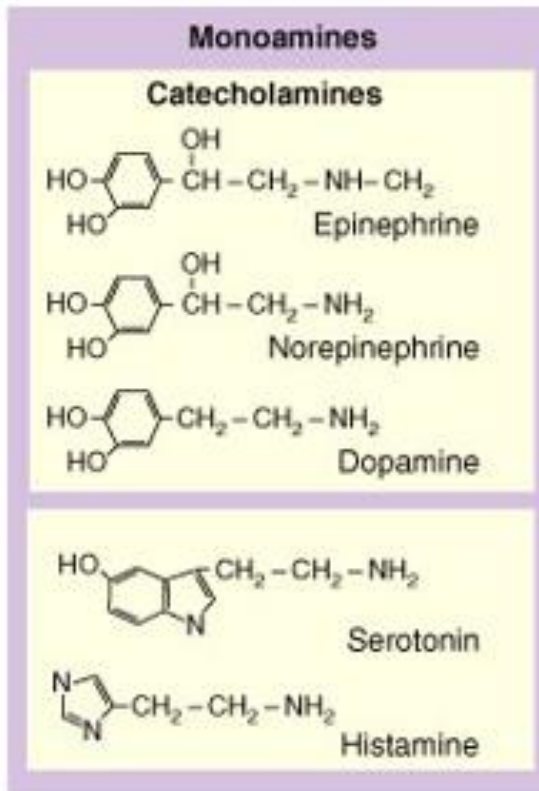
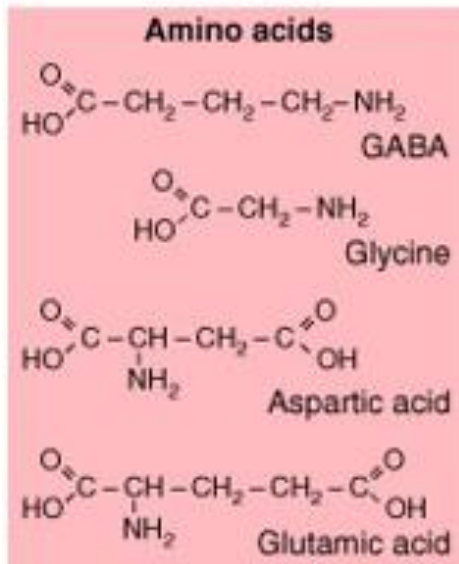
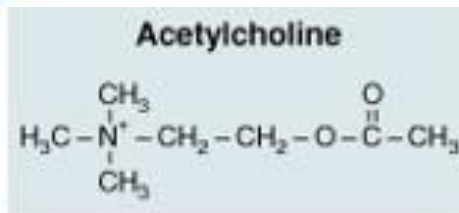
Introduction: The definition and key characteristics neurotransmitters



4. Neurotransmitter action is fast and transient.
5. Neurotransmitters are rapidly removed from the synaptic cleft to terminate signaling.
 - Mechanisms include:
 - Reuptake (e.g., serotonin reuptake by SERT transporters).
 - Enzymatic degradation (e.g., acetylcholine by acetylcholinesterase).
 - Diffusion away from the synapse.



Types of neurotransmitters



- **Small-molecule**
 - Amines (Biogenic Amines) (epinephrine, dopamine, histamine, etc.)
 - Amino acids (glutamate, aspartate)
 - Acetylcholine (ACh)
- **Neuropeptides**
- **Gases (nitric oxide)**



Neurotransmitters

Neuropeptides



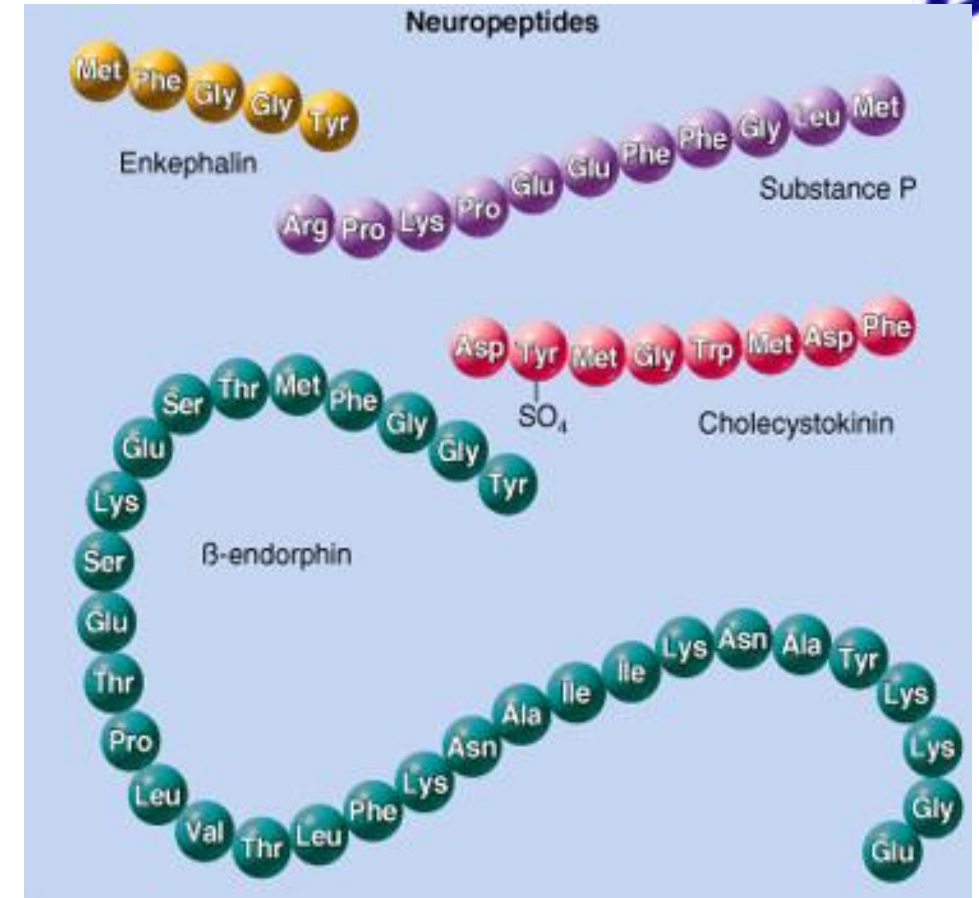
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What are Neuropeptides?

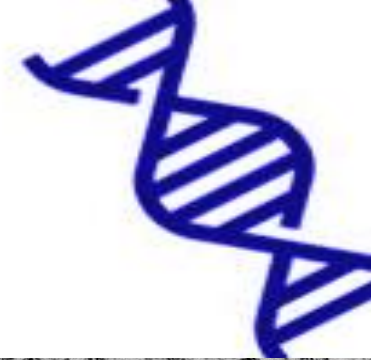


- Neuropeptides are larger molecules compared to small-molecule neurotransmitters (like dopamine or serotonin).
- They are composed of 3 or more amino acids and typically act through G-protein coupled receptors (GPCRs).
- There are a great many different neuropeptides.
- Synthesis and Storage: Neuropeptides are synthesized in the cell body (not in the nerve terminal) and transported in dense-core vesicles to the synaptic terminal, where they are released.

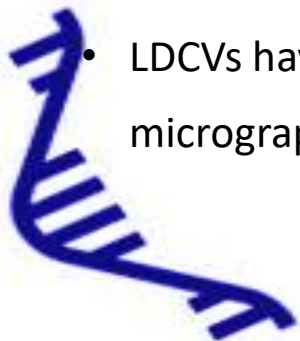
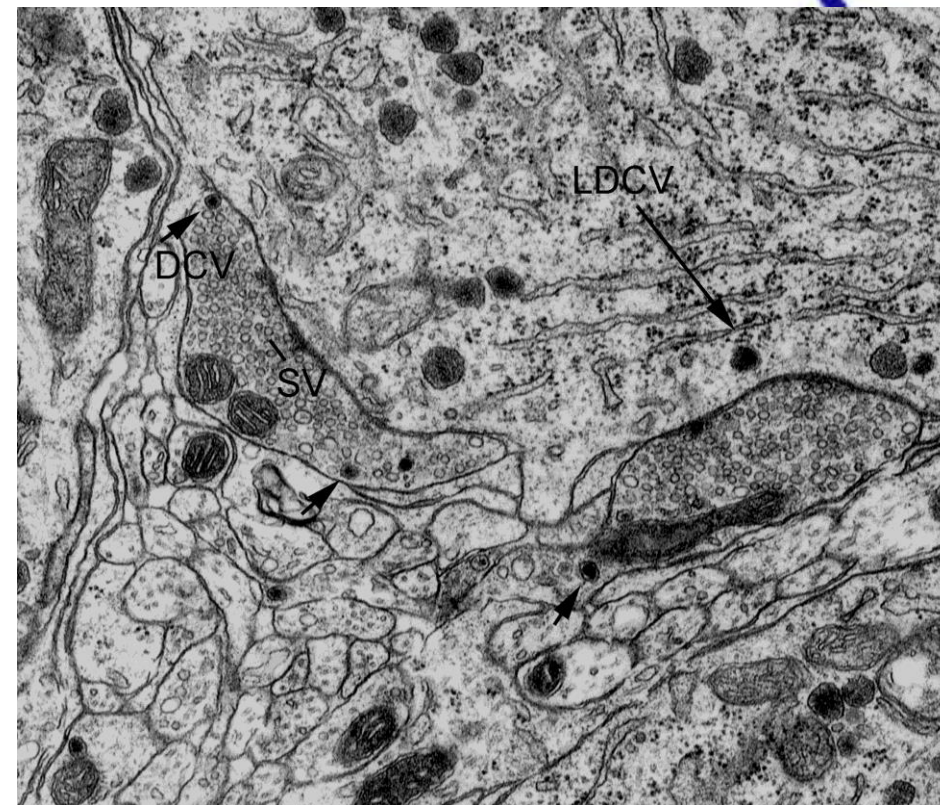




Large dense core vesicles (LDCVs)



- **LDCVs** are lipid vesicles in neurons and secretory cells which may be filled with neuropeptides.
- LDCVs release their content through exocytosis similar to synaptic vesicles.
- One key difference between synaptic vesicles and LDCVs is that protein synaptophysin (synaptic vesicle trafficking, exocytosis, and neurotransmitter release) which is present in the membrane of synaptic vesicles is absent in LDCVs.
- LDCVs have an electron dense core which appear as a black circle in micrographs obtained with transmission electron microscopy.

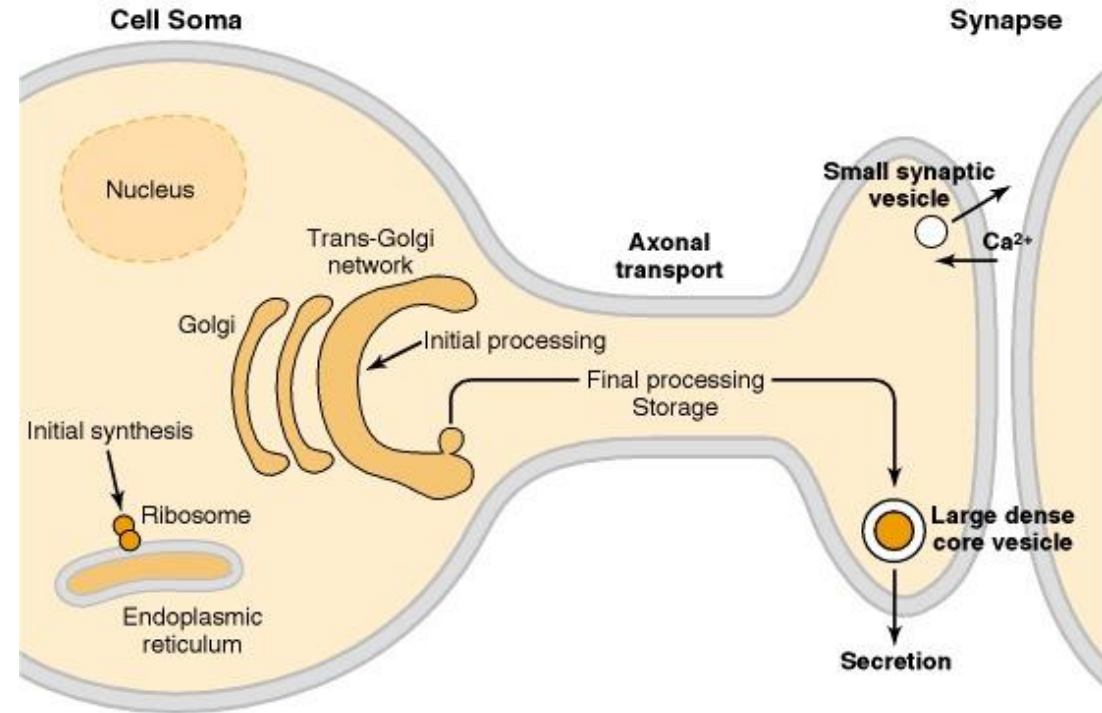




Intracellular pathway of bioactive peptide biosynthesis, processing and storage



- Step 1: Transcription & Translation
- The initial product is a **large precursor protein (prepropeptide)**.
- **Step 2:** The **signal peptide** of the prepropeptide is cleaved in the **endoplasmic reticulum (ER)**, generating a **propeptide**.



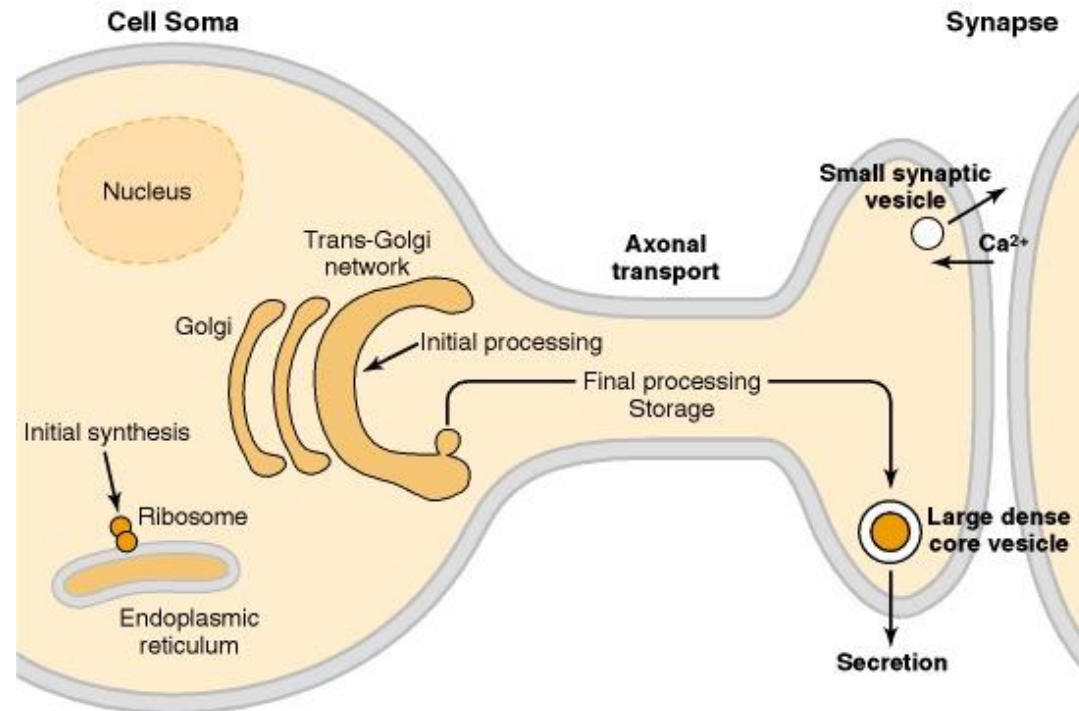
Step 3: Post-Translational Modifications in the Golgi

Amidation, acetylation, sulfation, and glycosylation → Increases peptide stability and receptor binding affinity.

Cleavage by prohormone convertases (PC1 & PC2) → Produces smaller bioactive peptides.

Cysteine bridge formation → Stabilizes peptide structure.

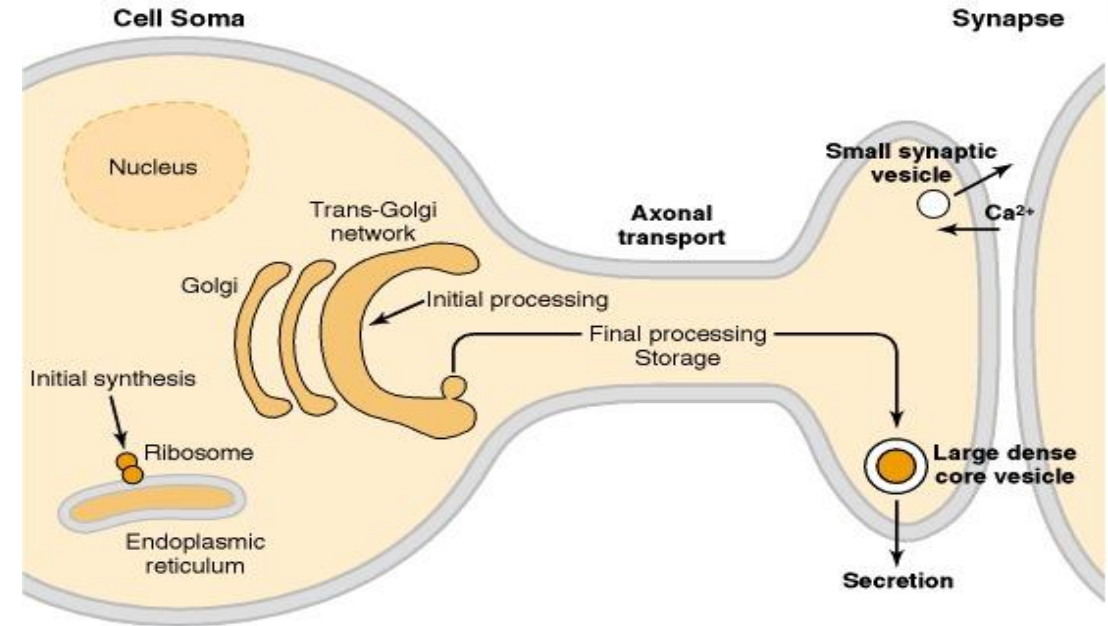
Intracellular pathway of bioactive peptide biosynthesis, processing and storage



- **Step 4:** The processed bioactive peptides are packaged into **large dense-core vesicles (LDCVs)**.
- **Step 5:** LDCVs are transported along the axon via **fast axonal transport** (kinesin-dependent, microtubule-mediated) to **synaptic terminals** or **neurosecretory regions**.

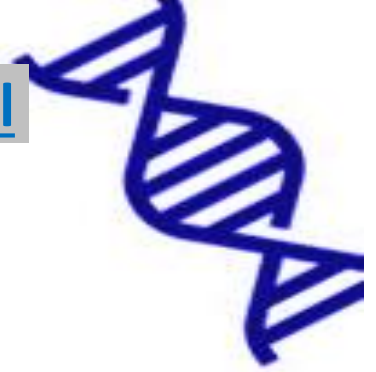
Intracellular pathway of bioactive peptide biosynthesis, processing and storage

- **Step 6: Secretion is calcium-dependent,**
- **Step 7: Neuropeptides bind to G-protein-coupled receptors (GPCRs) on target cells.**
- **Step 8: They are *not rapidly recycled* like classical neurotransmitters but instead are degraded by peptidases.**





Neuropeptides: Secretion is calcium-dependent, but unlike classical neurotransmitters



- Conventional neurotransmitters are secreted from small secretory vesicles (SSVs) after cytosolic $[Ca^{2+}]$ transiently reaches concentrations of 50 to 100 μM , while peptides are released from LDCVs at lower concentrations of cytosolic $[Ca^{2+}]$.
- Conventional neurotransmitter release is thought to occur very close to the site of Ca^{2+} entry, while neuropeptides are typically released at a distance from the site of Ca^{2+} entry.
- Diffuse over longer distances
- Have a longer duration of action compared to small neurotransmitters.





Neuropeptides

- Neuropeptides can function as either neurotransmitters or neurohormones, depending on where they are released.
 - Neurohormones are secreted into the bloodstream to act at distant targets.
 - Neurotransmitters are released at synapses to affect local postsynaptic neurons.

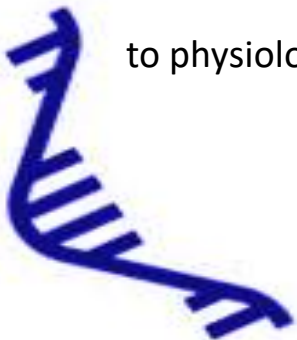




Vasopressin



- Vasopressin, the first neuropeptide to be identified.
- A 9-amino acid peptide synthesized in hypothalamic neurons and released from the posterior pituitary.
- Synthesis and Processing:
 - Derived from preprovasopressin.
 - Packaged into large dense-core vesicles (LDCVs).
- Release:
 - Released into the bloodstream or synaptic cleft in response to physiological stimuli.
- Mechanism of Action:
 - Binds to V1a, V1b, and V2 receptors (GPCRs).
 - Regulates water retention, blood pressure, and in the regulation of complex social cognition and behaviour
- Why a Neuropeptide?:
 - Peptide structure.
 - Synthesized in neurons and packaged in LDCVs.
 - Acts as a neuromodulator in the brain.





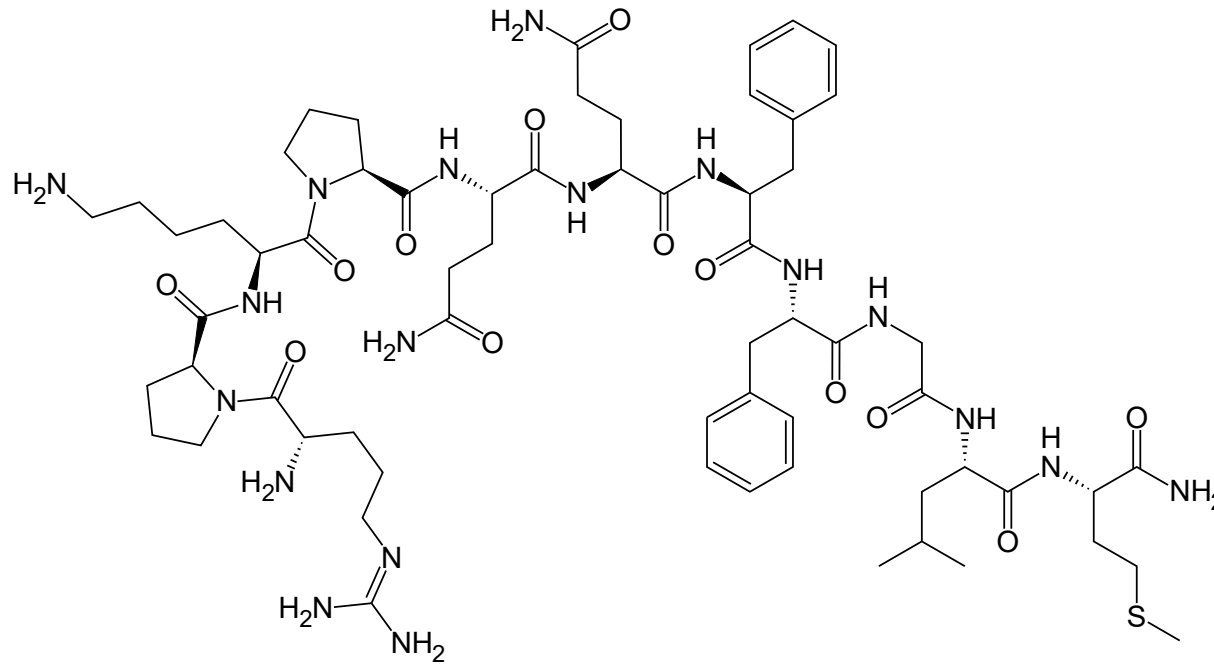
Galanin: A Multifunctional Neuropeptide



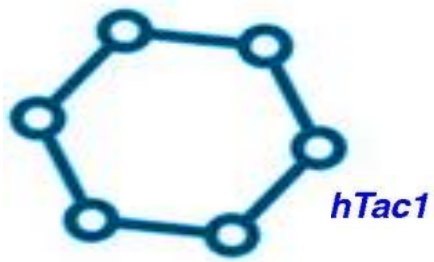
- Structure:
 - 30-amino acid peptide
 - Derived from preprogalanin (123 amino acids).
- Distribution:
 - Widely expressed in the brain, spinal cord, and gut.
- Galanin is implicated in a wide range of biological functions, including:
 - Pain perception
 - Regulation of sleep and wakefulness.
 - Cognition (learning and memory).
 - Modulation of mood and emotional responses.



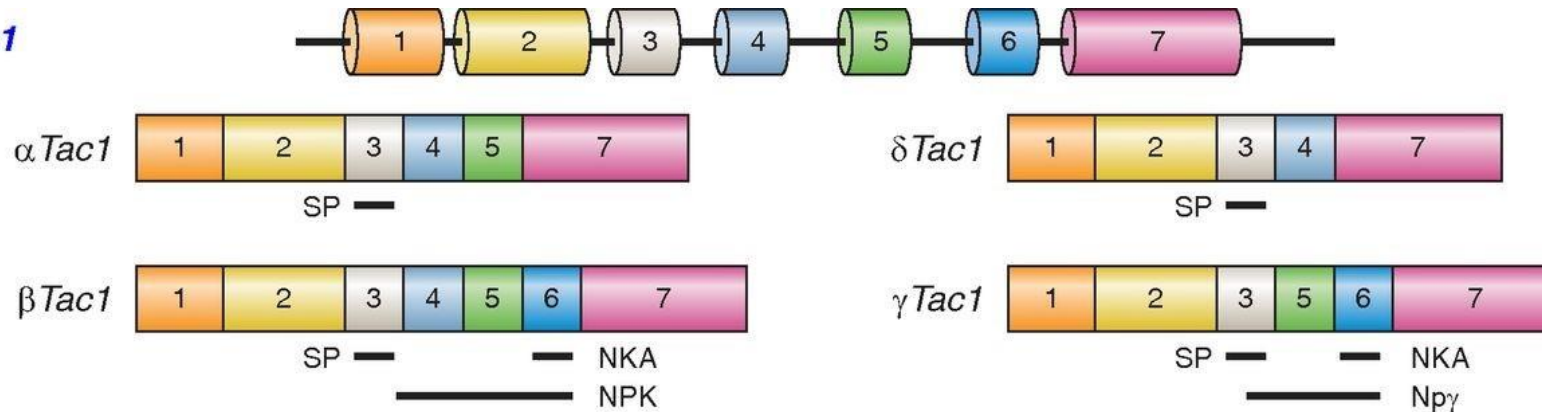
Substance P: A Member of the Tachykinin Family



- Substance P is an 11-amino acid neuropeptide.
- It is widely distributed in the central and peripheral nervous systems and plays a key role in pain signaling, inflammation, and other physiological processes.
- Amino acid sequence: Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂.



Substance P Synthesis



1. Gene & Precursor:

1. Encoded by **TAC1 gene**, producing **Preprotachykinin-A (PPT-A)**.

2. Processing:

1. PPT-A undergoes **cleavage & amidation** to form active **Substance P (11 aa)**.

3. Storage & Release:

1. Stored in **dense-core vesicles** and **released upon neuronal stimulation**.

4. Receptor Binding:

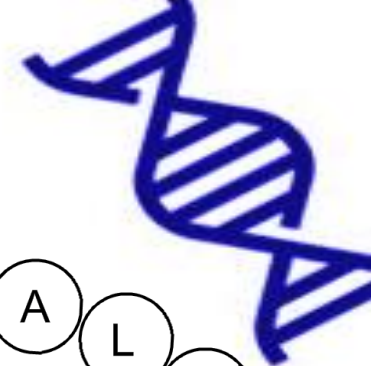
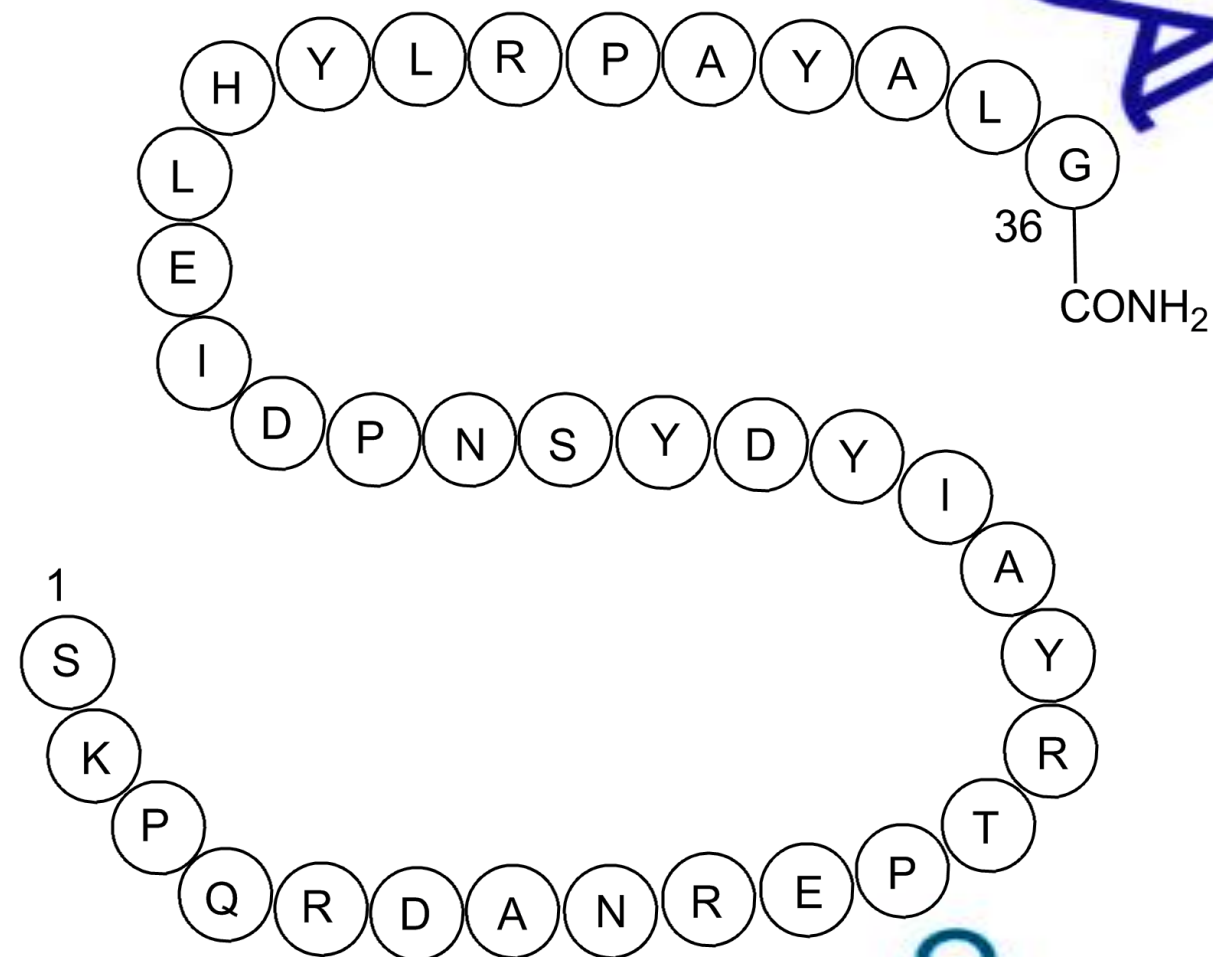
1. Binds to **NK1 receptors**, mediating **pain, inflammation, vasodilation, and stress responses**.

Neurokinin 1 receptor (NK1R) is a G protein coupled receptor



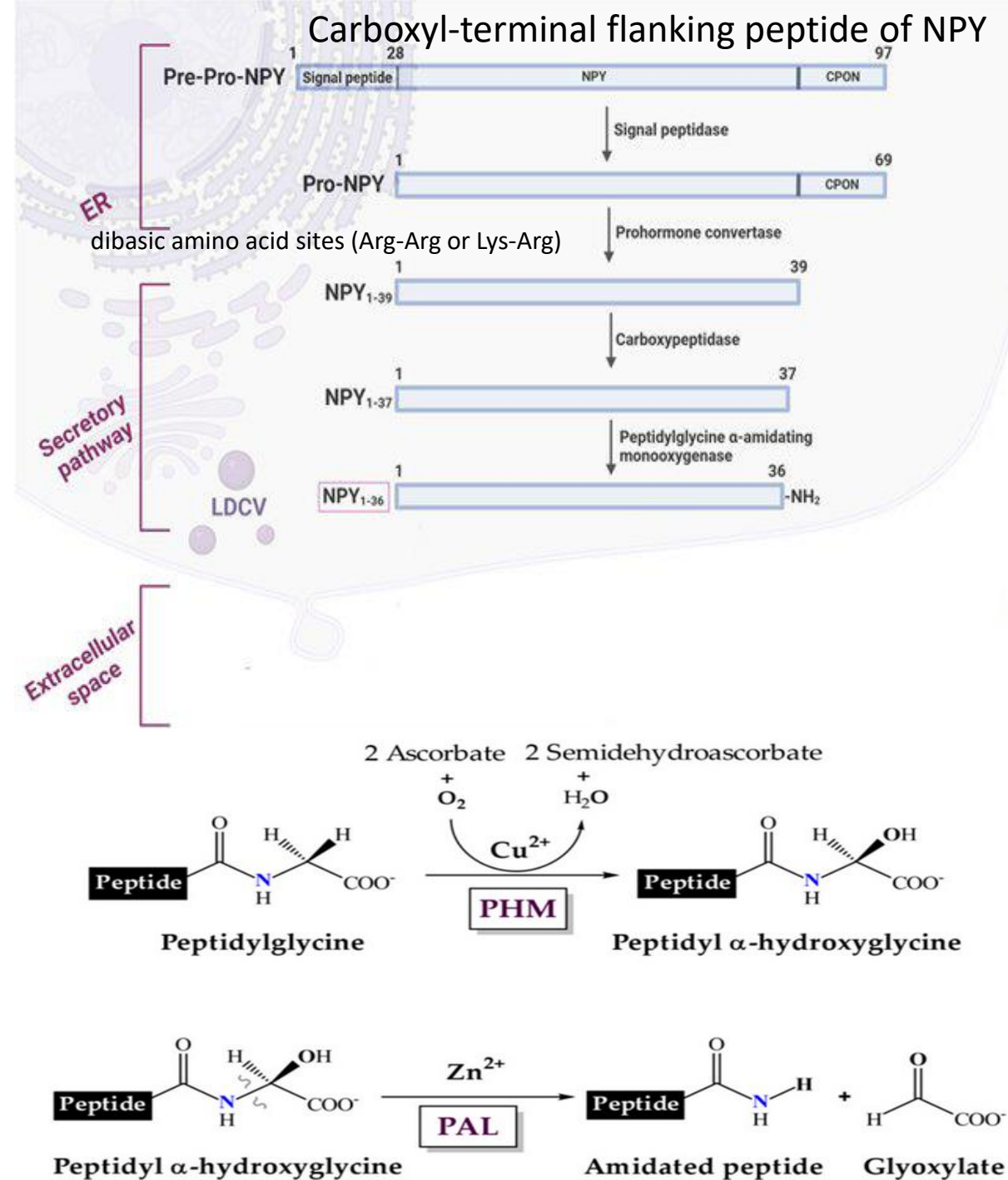
Neuropeptide Y

- **Neuropeptide Y (NPY)** is a **36-amino acid neuropeptide** found abundantly in the **central and peripheral nervous systems**.
- NPY exerts its effects via **G-protein-coupled receptors (GPCRs)** called **Y receptors** (Gi/o).
- NPY primarily functions in **appetite regulation**, and augments the vasoconstrictor effects of norepinephrine



Synthesis of NPY

- NPY is initially synthesized as a 97-amino acid precursor called Pre-Pro-NPY.
- In the **ER**, the signal peptide is cleaved, producing **Pro-NPY**.
- Pro-NPY (~69 amino acids)** is cleaved by **prohormone convertase**.
- The newly generated NPY(1–39) still contains extra C-terminal basic residues. Which removed by Carboxypeptidase E (CPE), generating NPY(1–37).
- Hydroxylation of the terminal glycine by peptidylglycine α -hydroxylating monooxygenase (PHM).
- Cleavage of hydroxylated glycine by peptidyl- α -hydroxyglycine α -amidating lyase (PAL), leaving an amide (-NH₂) group on the new C-terminal residue.





Opioid peptides

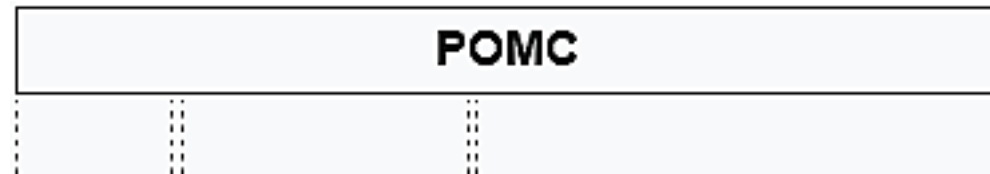
- **Opioid peptides** are a specific class of **neuropeptides**.
- They are neuropeptides that **bind to opioid receptors** (μ , δ , and κ receptors) in the brain and peripheral nervous system.
- Endogenous opioid peptides are classified into three categories, namely endorphins, enkephalins, and dynorphins.





Opioid peptides

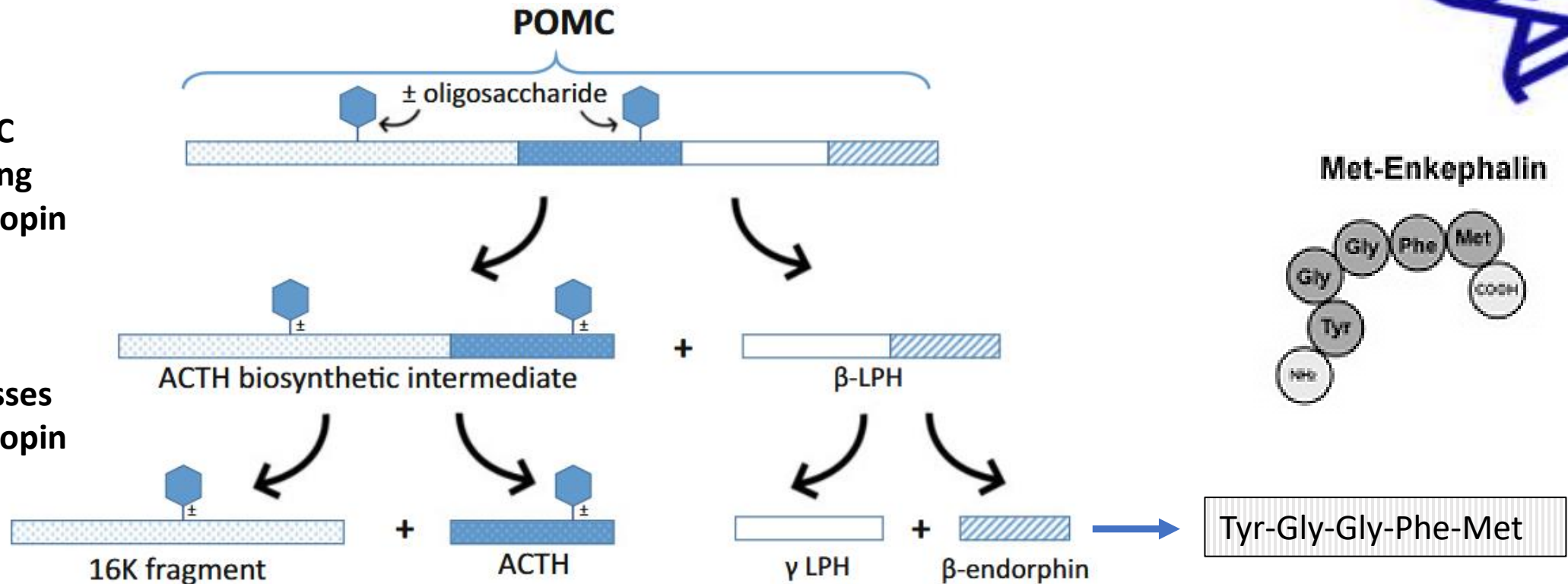
- The Opioid peptides are endogenously produced by peptidases digestion of larger precursor proteins, namely proopiomelanocortin (endorphins), proenkephalin (enkephalins) and prodynorphin (dynorphins).



Opioid peptides: Synthesis is sequential

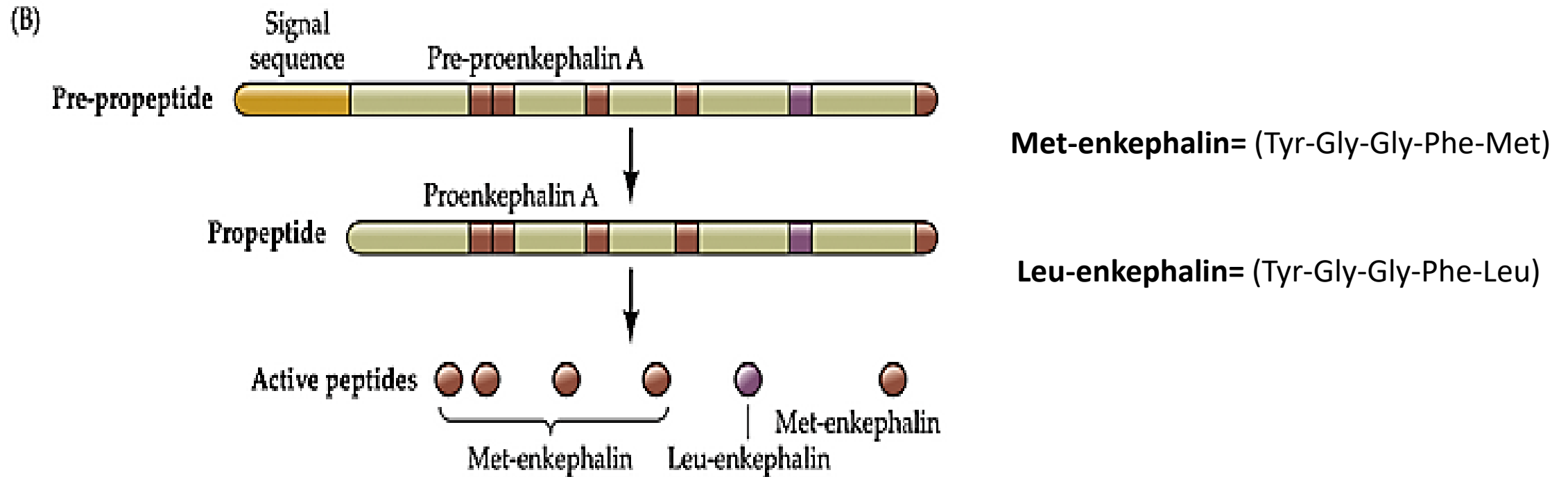
PC1 initiates POMC cleavage, generating ACTH and β -Lipotropin

PC2 further processes ACTH and β -Lipotropin into β -Endorphin



- At anterior pituitary, proopiomelanocortin (POMC) is processed in corticotrophs to generate mainly ACTH and β -lipotropin.
- The further processing of β -lipotropin gives rise to β -endorphin (61–91 aa), which in turn may yield [Met]-enkephalin.

Enkephalins



- Enkephalins are **endogenous pentapeptides that act as relatively weak analgesics by activating opioid receptors, particularly the delta-receptors.**
- Proenkephalin is processed into multiple opioid peptides, including Met-enkephalin and Leu-enkephalin.
- Processing occurs in the Golgi & secretory vesicles via prohormone convertases (PC1/PC2) and carboxypeptidase E.



Thanks Part 1



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