CNS

Biochemistry

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

الشيت طويلة لأنها ملياانة صور.. بس سهلة وبتخلص بسرعة بإذن الله

So DON'T WORRY!!

Biochemistry of neurotransmitters

Definition of a neurotransmitter:

Neurotransmitter: a **chemical substance** that is synthesized in a neuron, then, it is released at a synapse following depolarization of the nerve terminal (usually dependent on an influx of **calcium** ions), once it is released, it binds to receptors on the postsynaptic cell inducing a signal transduction in that cell or some of them can bind to receptors on the presynaptic terminal. Resulting in a specific response.

Characteristics of a neurotransmitter: A chemical substance that:

1- Is synthesized and stored in a presynaptic neuron waiting for stimulus (the enzymes needed for its synthesis must be present in the neuron).

2- Is released at a synapse following depolarization of the nerve terminal (usually dependent on an influx of calcium ions).

3- Binds to receptors on the postsynaptic cell and/or presynaptic terminal.

4- Elicits **rapid-onset** and rapidly **reversible** responses in the target cell (activates signaling pathways).

5- Is **removed** or **inactivated** from the synaptic cleft, so that the signal is terminated.

Types of neurotransmitters:

1-Small-molecule neurotransmitters

- Biogenic amines: histamine, serotonin and catecholamines (which are epinephrine, norepinephrine, dopamine)
- Amino acids (GABA (modified glutamate), glutamate, aspartate, and glycine)
- Acetylcholine
- Purines (ATP)

2-Neuropeptides

3-Gases (nitric oxide NO, carbon monoxide CO):

Can act as neurotransmitters, but they are an exception.

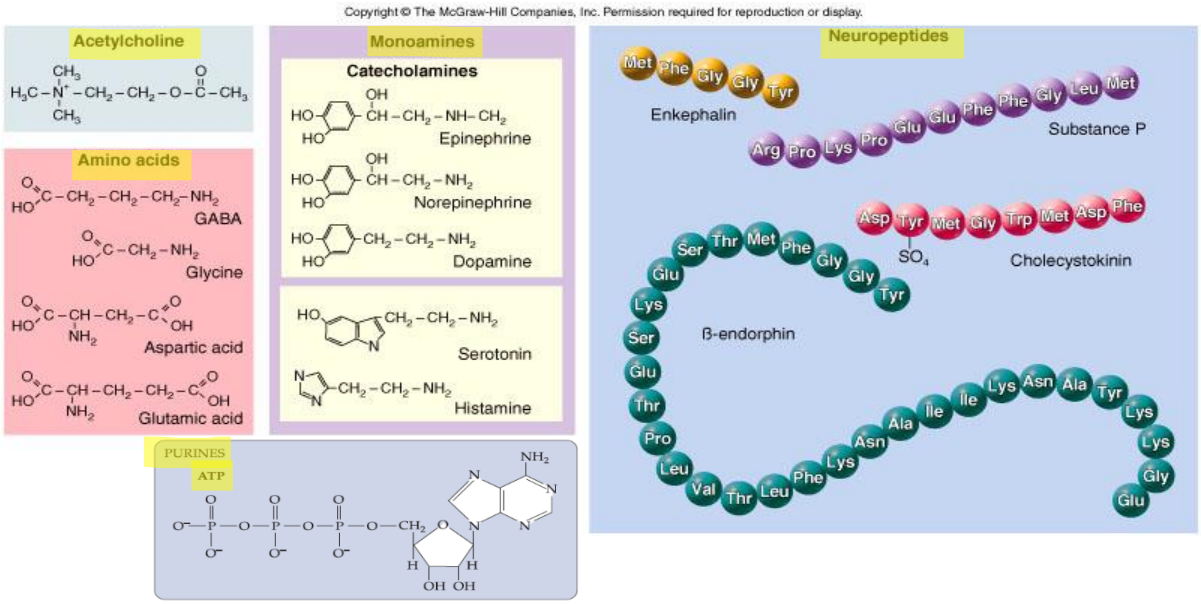
NOTE: Certain neurons might have **more than one neurotransmitter** (two or more), usually a small-molecule neurotransmitter and a neuropeptide can coexist in the same neuron.

*Example: Most spinal motor neurons contain acetylcholine and calcitonin gene-related peptide.

But usually, neurons contain one single type of neurotransmitter, such as dopaminergic neurons.

Structures of neurotransmitters:

Structures are not required.



Difference between neuropeptides and small-molecule neurotransmitters:

such as difference in structure, synthesis, action, potency, regulation, and inactivation.

DO NOT MEMORIZE, some of these differences will be explained during the lecture, but this is only for your reference.

Neuropeptides	Small-molecular neurotransmitters
Short-chain peptides (3-60 aa's), Large MW	Endogenous chemicals, Low MW
Slow-acting	Fast-acting
Slow response	Acute response
Prolonged action	Short-term response
Acts on several receptors	Acts on specific a receptor
Can change metabolism	Most do not change metabolism
Alter gene expression	Most do not change gene expression
Synthesized in the ER and Golgi apparatus	Synthesized in the cytosol of presynaptic nerves
Synthesized in low concentrations	Synthesized in high concentrations
Found allover the neuron	Found in the axon terminals of presynaptic neurons
Stored in large dense-core vesicles	Stored in small secretory vesicles
Released to the synaptic cleft along with another NT	Released individually
released at low cytosolic Ca^{2+} concentrations	released at high cytosolic Ca^{2+} concentrations
Have a different site of actions than their origin	Acts in direct apposition of to the releasing cell
Not re-taken up and not reused	Can be re-taken up and reused
Relatively more potent	Relatively less potent
Terminated when proteolytically degraded or diffused	Terminated by reuptake, taken up by glial cells, diffused, or enzyme degradation

The doctor didn't explain it, but the highlighted differences are the ones mentioned during the lecture, so you can review it after you finish the lecture.

Neuropeptides:

- **More than 50 neuropeptides (nearly 64 according to recent updates) have been described affecting a variety of functions:** Behavior, pain perception, memory, appetite, thirst, temperature, homeostasis, and sleep.

Just for extra information, these are some links for lists of neuropeptides from the doctor.

LISTS OF NEUROPEPTIDES

NEUROPEPTIDES | HUGO GENE NOMENCLATURE COMMITTEE

NEUROPEPTIDE GENE FAMILIES

LIST OF NEUROTRANSMITTER INHIBITORS AND NEUROPEPTIDES

- They can be considered **neurotransmitters** or **neurohormones**.

There is a distinction between these two terms. This depends on where they act (site of action) and how they are released:

- it is a **neurohormone** if it is released by certain neurons into the bloodstream and travels a long distance, then, exerts its effects on distant peripheral targets. It has long duration of action.

- it is a **neurotransmitter** if it functions on the **neighboring** cell (doesn't travel for a long distance but acts on the vicinity).

They are synthesized just like proteins are: so anything applies to proteins can also be applied to neuropeptides (details about their synthesis is on page 6).

- They are subject to **alternative splicing** and **protein processing.**
- They can be tissue-specific.
- Examples (to understand not to memorize): substance P/neurokinin A and proopiomelanocortin (POMC).

Since neuropeptides are made of amino acids, they are surely encoded by genes and synthesized just like proteins but in smaller molecules relative to proteins. So, here are some mechanisms that cause diversity in the neuropeptides:

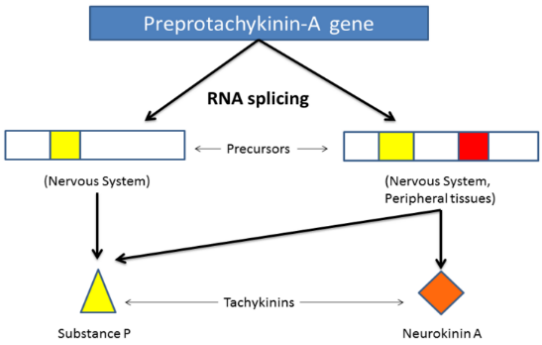
Alternative Splicing and Post-translational Modifications

1- Alternative Splicing:

mRNA alternatively spliced into exons (at the level of mRNA) → each exon will produce certain neuropeptide.

Example: substance P and other neuropeptides like neurokinin A are produced from the same gene (ex: preprotachykinin -A). And this gene, through alternative splicing, produces different mRNAs that will be translated into different neuropeptides.

Do not memorize examples.

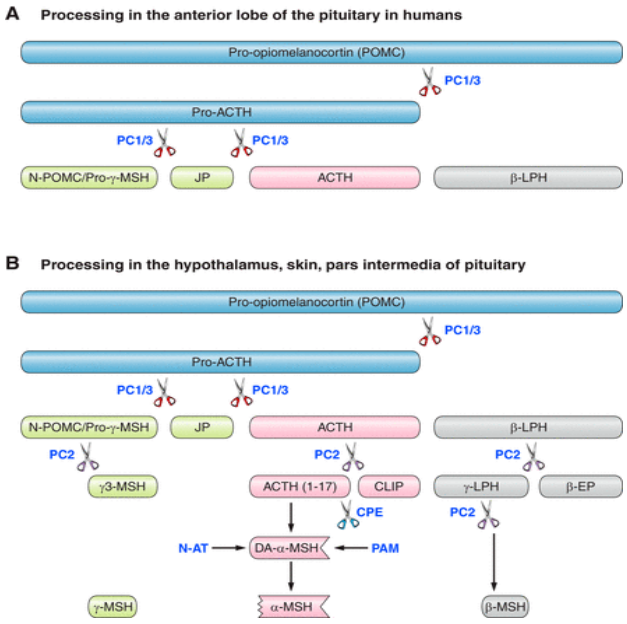


2- Post-Translational Modifications:

Modifications after protein synthesis: such as glycosylation, and proteolytic cleavage where neuropeptides are produced from a longer precursor protein (pro-peptide is cleaved into different peptides, and each one of them can act as a neuropeptide). These modifications can occur in endoplasmic reticulum, Golgi apparatus, and in vesicles.

Example: Processing of the proopiomelanocortin (POMC) precursor proceeds in an ordered, stepwise fashion (POMC is a large polypeptide that get cleaved into smaller peptides, and each one of them can act as a neuropeptide with different function). Some of the reactions are **tissue specific**. This processing results in the formation of adrenocorticotropic hormone (ACTH), corticotropin-like intermediate lobe peptide (CLIP), joining peptide (JP), lipotropin (LPH), melanocyte-stimulating hormone (MSH), and prohormone convertase (PC).

Do not memorize examples.



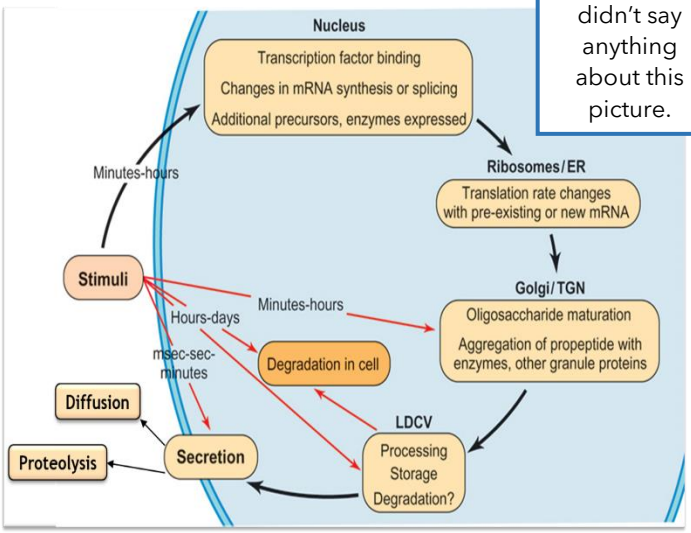
The levels of regulation of neuropeptide expression:

Transcriptional
- Transcription factors
- Histone modifications

Post-Transcriptional
Such as alternative splicing and mRNA stability
- ncRNA
- RBPs
- mRNA localization
- RNA decay

Translational
Regulation of the rate of polypeptide synthesis

Post-Translational
Modifications, processing, and protein stability
- Phosphorylation
- Ubiquitination
- Acetylation
- Glycosylation
- Protein-protein interactions

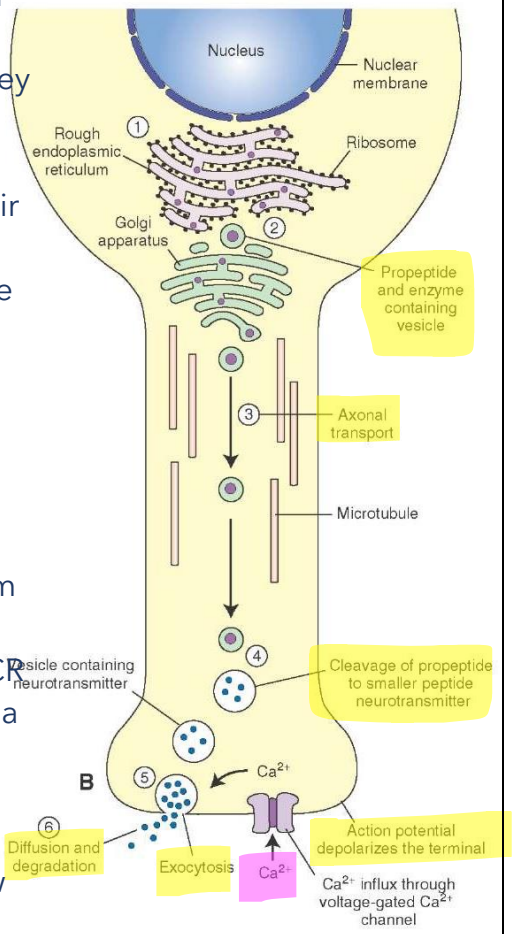


The doctor didn't say anything about this picture.

Stages of action of neuropeptides:

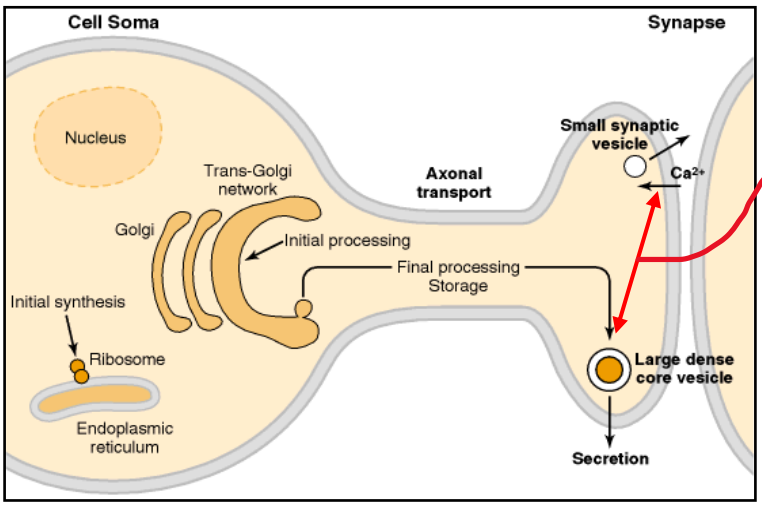
Synthesized in the cell body.

- **Synthesized in ER (1)** as pre-propeptides then propeptides, and then go into Golgi apparatus **(2)**, (synthesized as proteins on the surface of endoplasmic reticulum, then inserted into ER where they get modified, then travel to Golgi for further modification).
- **Packaging** the pro-peptide into large-dense core vesicles. They coexist with modifying enzymes in these vesicles. And during their travelling from cell body toward the terminus, they are modified further inside the vesicles. The characteristics of these vesicles are large and thick membrane.
- **Transport (via fast-axonal transport) (3):** along microtubules, during their transport proteases cleave the precursor neuropeptide into the final mature form **(4)**. Then these vesicles stay in terminals waiting for a stimulus to be released.
- **Release (exocytosis) (5):** They are released gradually over time in response to general increase in the level of intracellular calcium introduced by a stimulus.
- **Action (prolonged).** Once they release, they bind mainly to GPCR resulting in the action. Their action is prolonged (they survive for a long time), and the site of action may be on the vicinity (a neurotransmitter) or they act far away from the site of release (a neurohormone).
- **Termination (6)** by (diffusion →very low concentration→very low effect→the body can get rid of them) and degradation (by proteases released from different cells). No reuptake mechanisms.



Role of calcium Ions in neuropeptides:

influx of Ca ions→allow vesicles to fuse with presynaptic membranes→release of neurotransmitters.



Vesicles are located **further away** from the presynaptic membrane and away from the area of Ca^{2+} ions influx.

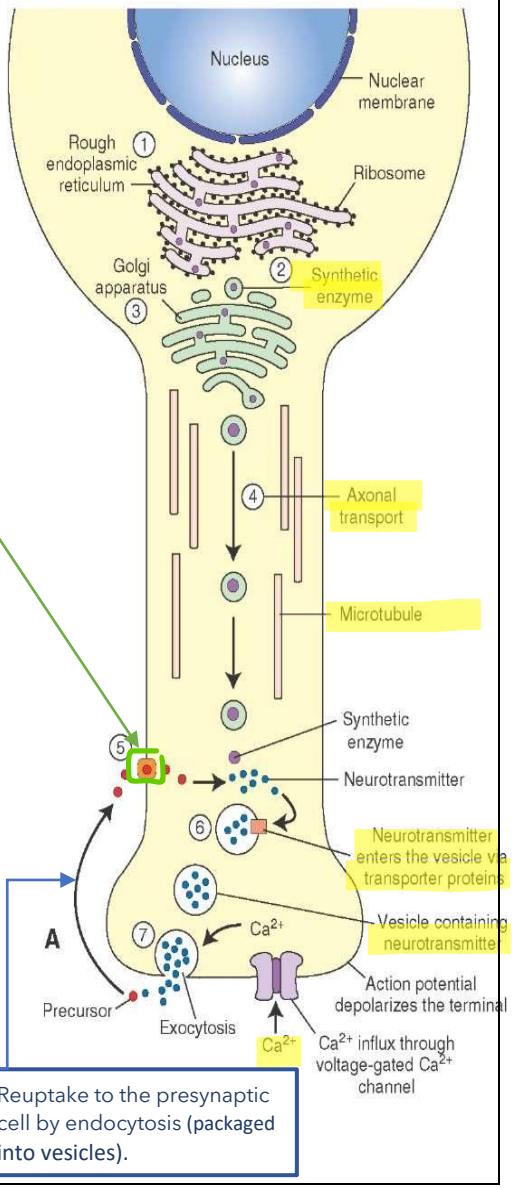
Ca^{2+} ion influx can be from external of internal sources and at **lower concentrations than required for small-molecule neurotransmitters.**

Small-molecule neurotransmitters:

Synthesized in the nerve terminal not the cell body.

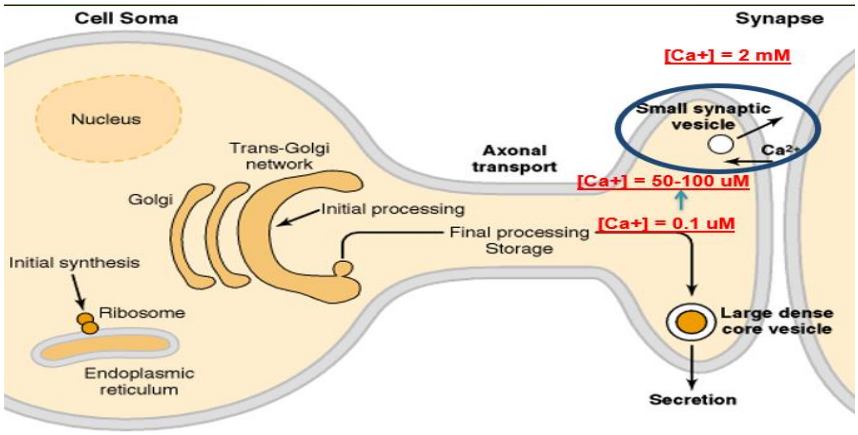
Stages of synthesis and action:

- Synthesis of **the enzymes** in ER (1) and Golgi apparatus (2) where they are modified (3) (enzymes responsible for synthesizing the small-molecule neurotransmitters not the neurotransmitters themselves).
- Transport of **soluble** enzymes via slow axonal transport via microtubules – without vesicles along the microtubules-(4) (Remember: neuropeptides→via fast axonal transport)
- Neurotransmitter precursors are taken up into the cells via transporter proteins located in the plasma membrane of the nerve terminal (5), and the neurotransmitter is synthesized in the **cytosol** of presynaptic nerve terminal and then packaged in **small synaptic vesicles** which will wait for calcium influx near the plasma membrane of nerve terminal (6). (Remember: neuropeptides are synthesized by ER and Golgi apparatus in the cell body, unlike small-molecule neurotransmitters which are synthesized in the cytosol of presynaptic neurons).
- Release is stimulated by brief pulses each time an action potential triggers the influx of calcium. (Remember: neuropeptides need lower concentration of calcium influx)
- Action (short) on presynaptic or postsynaptic neuron, (remember: prolonged action in neuropeptides)
- Termination by diffusion (diffusion out of the synaptic cleft), re-uptake(by glial cells or post-synaptic neurons) or enzymati inactivation (chemically modified)
(remember: no reuptake mechanism in neuropeptides).

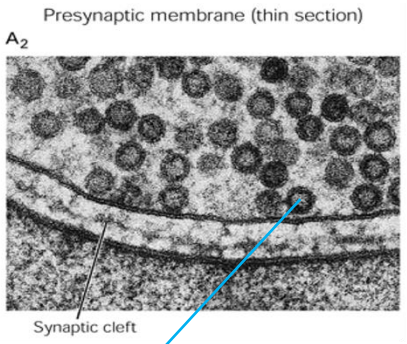


Reuptake to the presynaptic cell by endocytosis (packaged into vesicles).

Role of calcium Ions in small-molecule neurotransmitters:



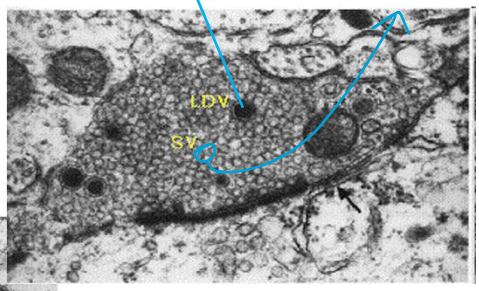
Vesicles are located near the presynaptic membrane and the area of Ca^{2+} ions influx (unlike neuropeptides' vesicles which are located further away from the area of calcium influx).

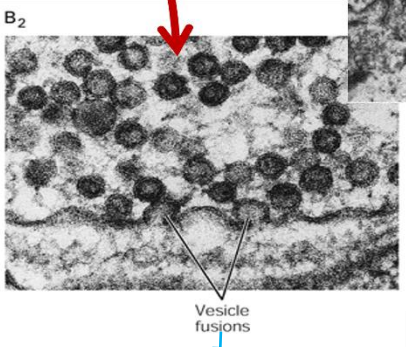


Vesicles are waiting near the plasma membrane for calcium influx. Calcium binds with proteins present on the vesicle's membrane, so these proteins fuse with proteins on plasma membrane of presynaptic neuron.

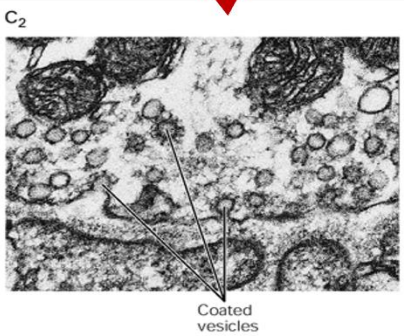
Large dense vesicles

Small vesicles





Vesicle fusions and then release.



Tyrosine-Derived Neurotransmitters

Type of small-molecule neurotransmitters

(Dopamine, norepinephrine, and epinephrine) → The catecholamines

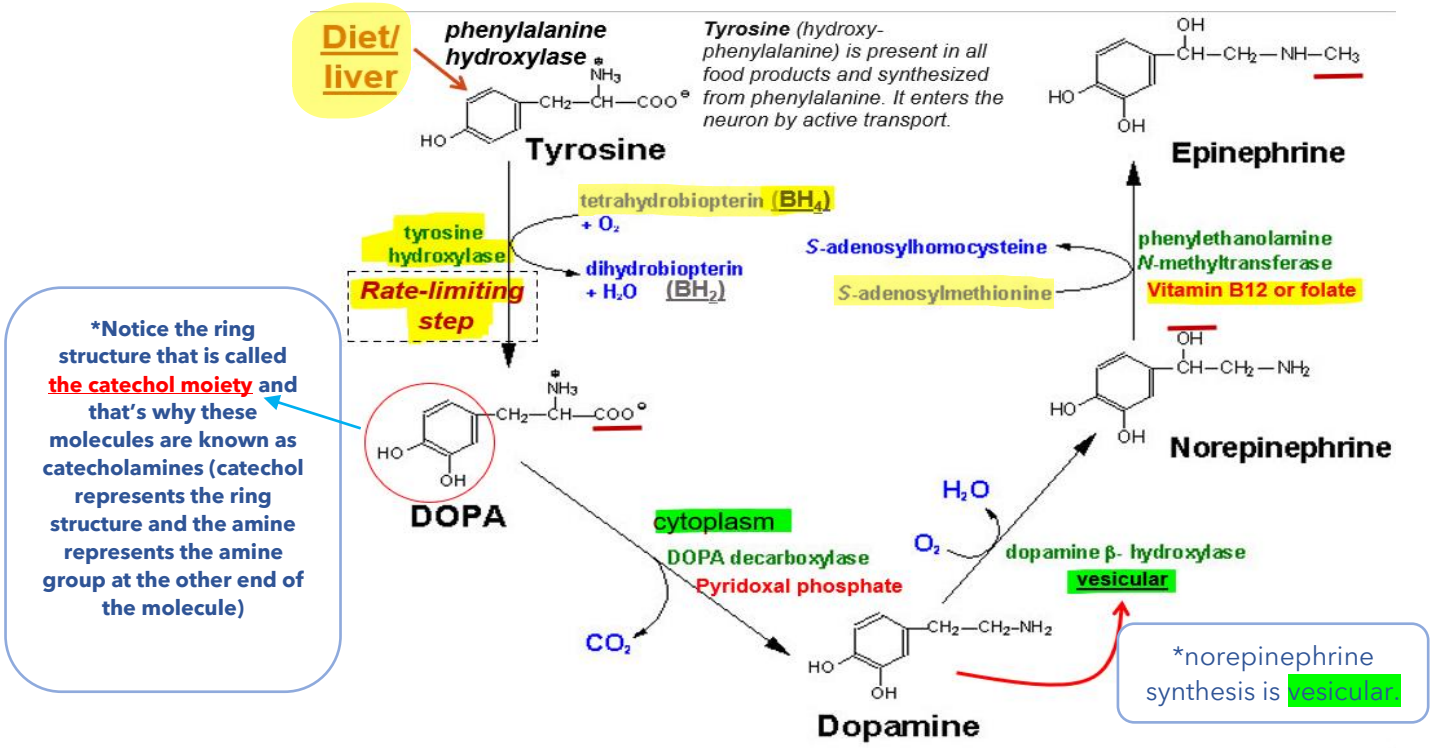
Steps of synthesis (they are synthesized sequentially).

1- Tyrosine is converted into DOPA by an enzyme known as **tyrosine hydroxylase**. This step requires **BH4** as a cofactor, this is the **rate-limiting step (the committed step: once dopa is synthesized, the synthesis of any of these three neurotransmitters must be continued)**. The source of tyrosine is either from the diet, synthesis in the liver or from hydroxylase phenylalanine.

2- DOPA is then converted into dopamine via decarboxylation by DOPA decarboxylase. This reaction requires **pyridoxal phosphate (vitamin b6)** and occurs in the **cytosol**.

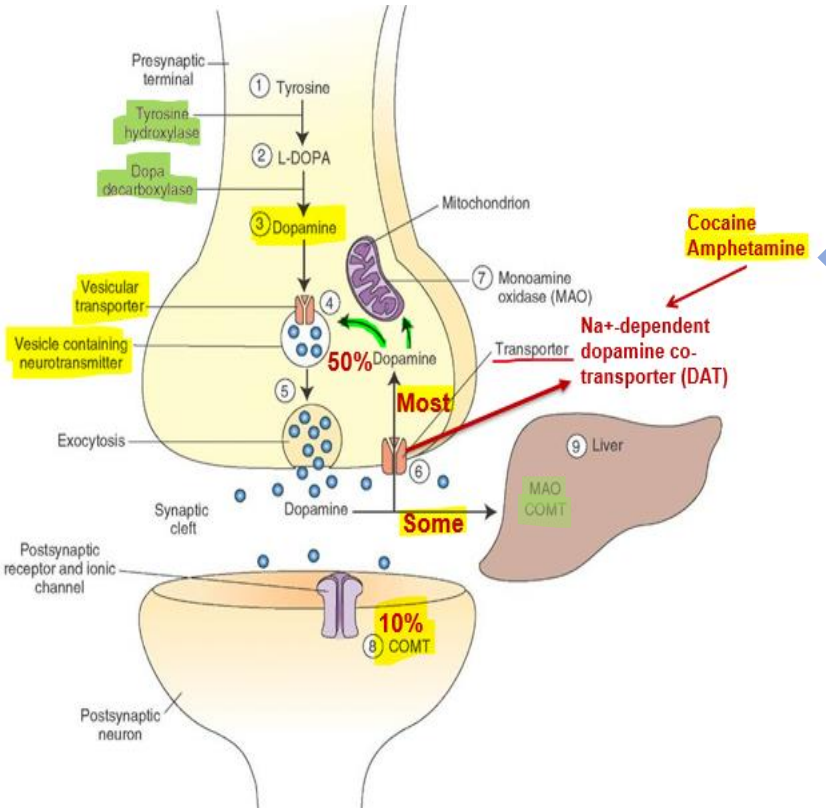
3- Dopamine can be converted into norepinephrine by dopamine β hydroxylase. This step occurs in the **vesicles**.

4- Norepinephrine can be **methylated** to get converted into epinephrine. This step requires more than one cofactor: S-adenosylmethionine and **vitamin B12 or folate(B9**), occurs in the **cytosol.**



- **Role of cofactors (important)**
  - S-adenosylmethionine (methyl transfer)
  - Pyridoxal phosphate (vitamin B6): transamination, decarboxylation
  - Tetrahydrobiopterin (BH4), which is synthesized from guanosine.

1- Dopamine:



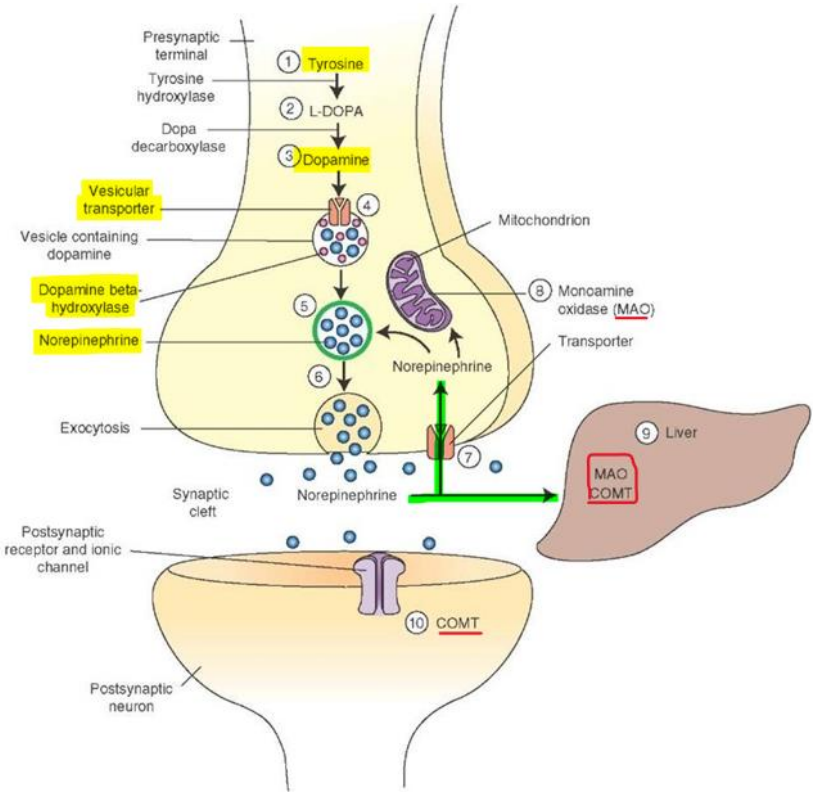
***Effect of cocaine and amphetamine** blocks the dopamine transporter, inhibiting reuptake of dopamine from the synaptic cleft into the pre-synaptic axon terminal, so that it stays for a longer period in the synapse and stimulates the postsynaptic neuron for a longer time, and this explains the feel of awaking and excitement produced by cocaine.

- **Synthesis:** dopamine is produced **from tyrosine in the nerve terminal**, then it is transported into the small secretory vesicles where it can be converted into the other catecholamines. They are stored in the vesicles waiting the influx of calcium ions to induce the fusion and their release.
- **Fate:**
  - most of the released dopamine can be taken up again by the presynaptic neuron(reuptake) where they undergo inactivation in cytosol or repackaged into small secretory vesicles (50%).
  - 10% are used by the postsynaptic neuron.
  - The rest is either:
    1- degraded by certain enzymes to inactive molecules (removed enzymatically by monoamine oxidase or methyltransferase enzyme).
    2- diffuse out of the synaptic cleft to be eliminated by the liver.

2- Norepinephrine:

- **Synthesis**: is vesicular
  The dopamine is transported into vesicles that will fuse with other vesicles containing the enzymes required for the conversion into norepinephrine. And these vesicles fuse with the plasma membranes releasing norepinephrine.
- **Fates** of norepinephrine after release (**same as dopamine):**

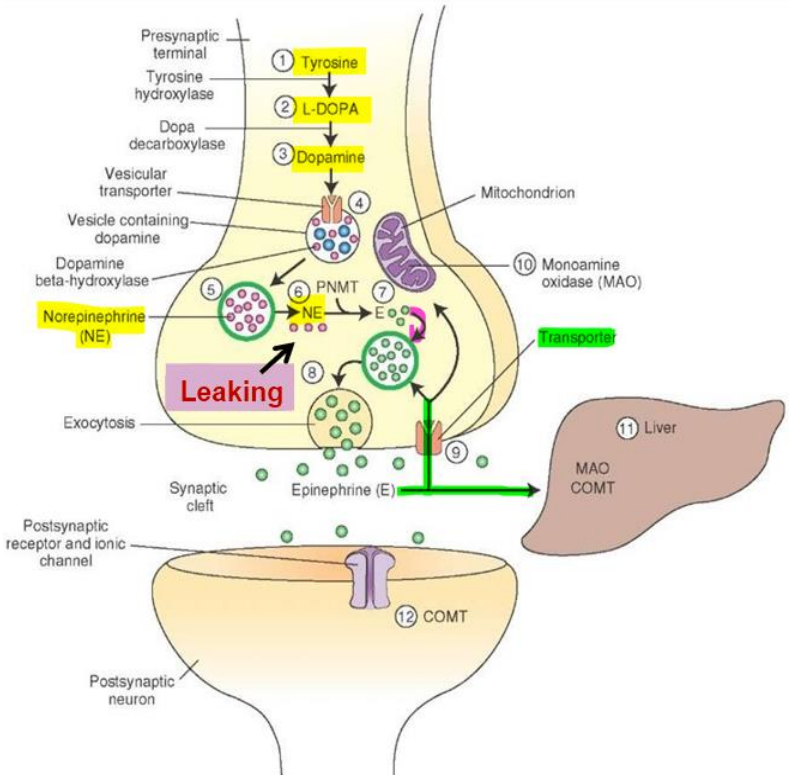
1. taken up (reuptake) by presynaptic or postsynaptic neurons (predominantly the presynaptic)
2. inactivated enzymatically by Monoamine oxidase (MAO) or methyltransferase
3. diffusion



3- Epinephrine:

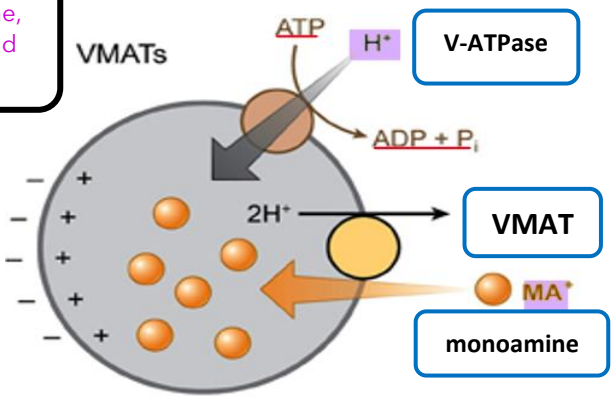
- **Synthesis**: Norepinephrine leaks out of the vesicles to the cytosol, and then it is converted in the cytosol into epinephrine by a methyltransferase. Then, epinephrine gets packed into vesicles, waiting for calcium influx which helps the fusion of vesicles and release of epinephrine.

- **Fate**: Then most of it, is taken up by presynaptic cells, some of it by postsynaptic or become enzymatically inactivated by monoamine oxidase or methyltransferase.



Packaging into vesicles:

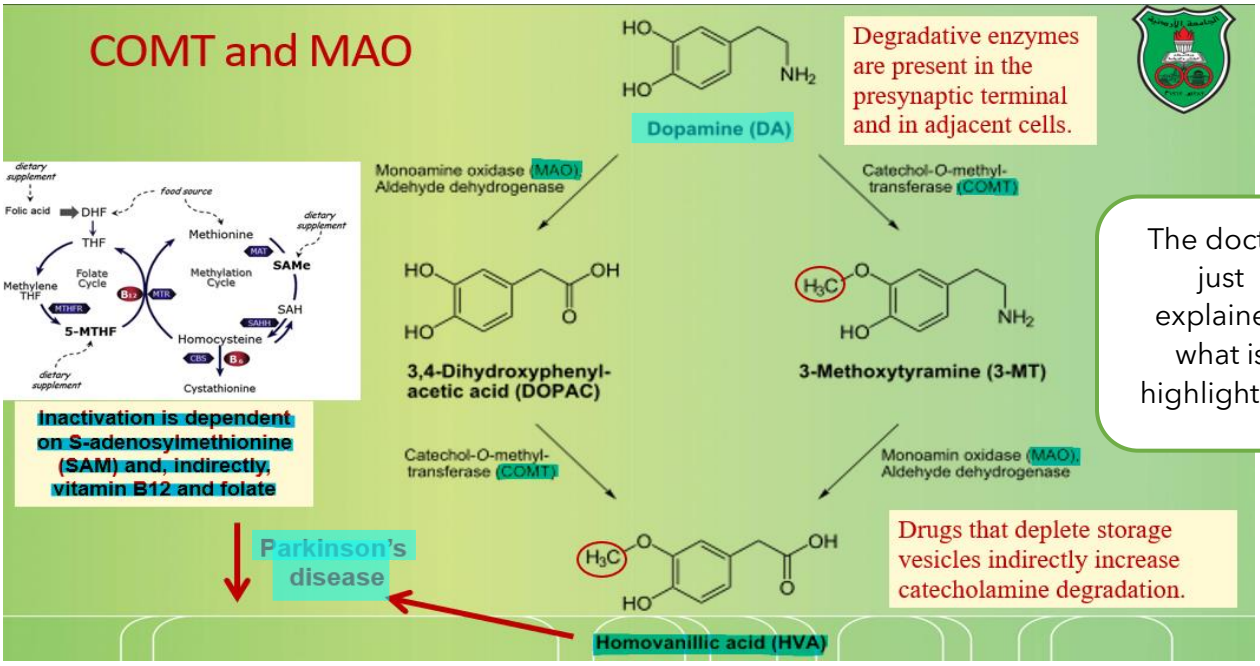
Not norepinephrine, only dopamine and epinephrine



The catecholamines **(dopamine and epinephrine)** are transported into vesicles by an ATP-dependent process linked to a proton pump.

- Protons are pumped into the vesicles by a vesicular ATPase (V-ATPase).
- The protons then exchange for the positively charged catecholamine via the transporter VMAT (vesicular monoamine transporter).
- Targeting VMATs causes depletion of the neurotransmitters:
  - This exchanger is a target for certain drugs (VMAT inhibitors→monoamines can't enter the vesicles→they stay for a longer time in the cytosol→undergo enzymatic inactivation by monoamine oxidase (MAO) and mythel transferase.

Enzymatic Inactivation (COMT and MAO):



The doctor just explained what is highlighted.

Dopamine and other monoamines such as norepinephrine and epinephrine can be enzymatically inactivated: We have two enzymes: (refer to the picture above)

1- The monoamine oxidase MAO

2- The catechol-O-methyl transferase COMT: This enzyme requires S- adenosylmethionine (SAM). Synthesis of SAM depends on vitamin b12 and folate, **that's why inactivation is dependent on SAM, vitamin B12 and folate.**

The inactivation requires both of them sequentially **regardless of their order** (it doesn't matter if MAO or COMT acted first). Eventually, the final product is the homovanillic acid (HVA). The decrease in the level of homovanillic acid is associated with Parkinson's disease, so it's an indicator and a marker for Parkinson's disease.

Regulation

Tyrosine hydroxylase (It's involved in the rate limiting step; that's why it's under regulation)

Short-term

- Inhibition by free cytosolic catecholamines, which compete with BH_4 binding to the enzyme.
- Activation by depolarization, which activates several protein kinases including PKC, PKA, Ca^{2+}-calmodulin–dependent kinases that phosphorylate tyrosine hydroxylase (details are not important). This makes the enzyme bind more tightly to BH4 and, consequently, less sensitive to end-product inhibition.

Long-term

- (Also applied to dopamine β-hydroxylase)
- Prolonged sympathetic neuronal activity increases the amounts of tyrosine hydroxylase and dopamine β–hydroxylase mRNAs (increases gene expression)

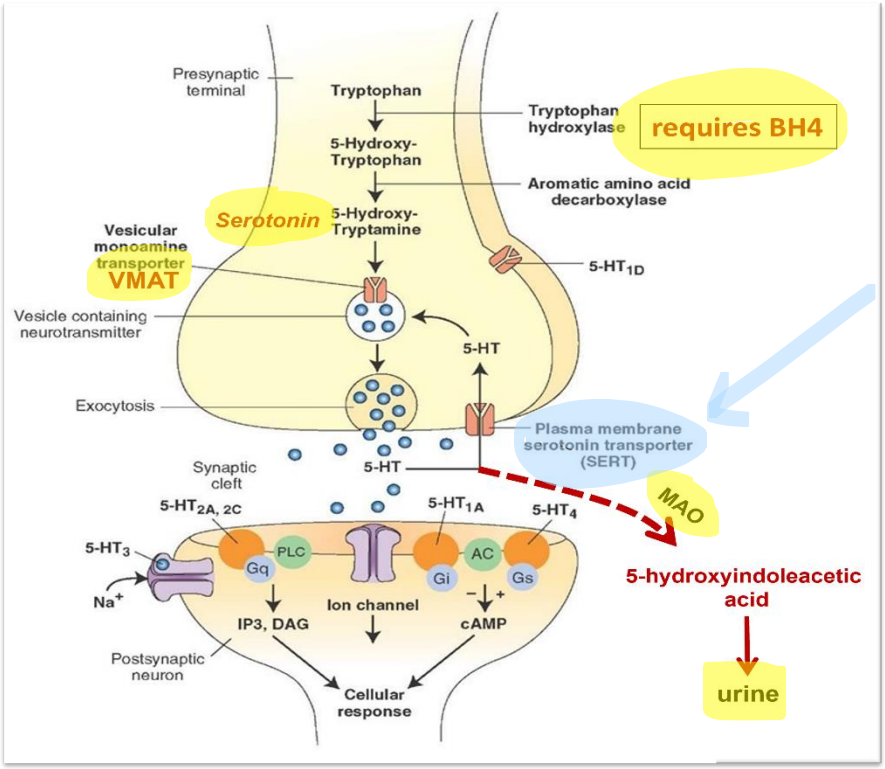
→ regulation at the gene level

Tryptophan-Derived Neurotransmitters

(Serotonin and Melatonin)

1- Serotonin

Serotonin is packaged into vesicles by VMAT.

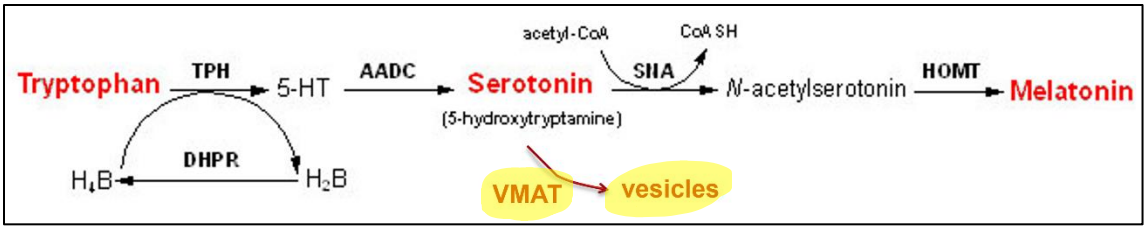


Antidepressants, called selective serotonin reuptake inhibitors (SSRIs) like Prozac® inhibit the reuptake process resulting in prolonged serotonin presence in the synaptic cleft.

2- Melatonin

Serotonin is synthesized in the pineal gland and serves as a precursor for the synthesis of melatonin, which is a neurohormone involved in regulating:

- sleep patterns
- seasonal and circadian (daily) rhythms; people who travel for long distances are advised to take melatonin
- dark-light cycle



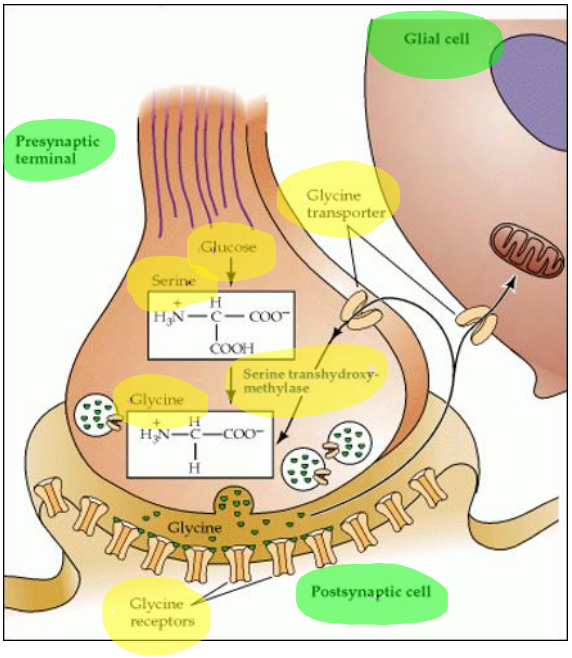
Amino acid-based neurotransmitters

(Glycine, Glutamate, Aspartate ,GABA and Histamine)

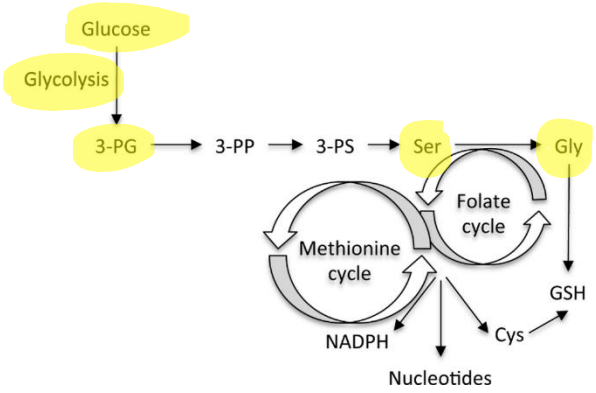
1- Glycine

A major inhibitory neurotransmitter

- **Synthesis**: from serine-by-serine hydroxymethyltransferase through 3-phosphoglycerate.
- **Removal**: by its own high-affinity transporter *(reuptake on presynaptic terminal's and glial cell's membranes)*



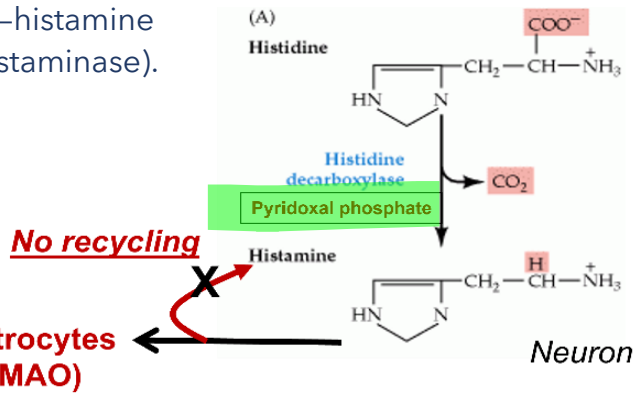
It has its own receptors.



2- Histamine

- It does not penetrate the blood-brain barrier and, hence, must be synthesized in the brain.
- **Synthesis**: Decarboxylation of histidine
- **Removal**:
  1- Enzymatically; inactivated by two enzymes—histamine methyltransferase and diamine oxidase (histaminase).
  2- By neighbouring Astrocytes (MAO)

- It's packaged into vesicles by VMAT
- NO RECYCLING to presynaptic membrane



Pyridoxal phosphate needed as co-factor.

3- Glutamate and Aspartate

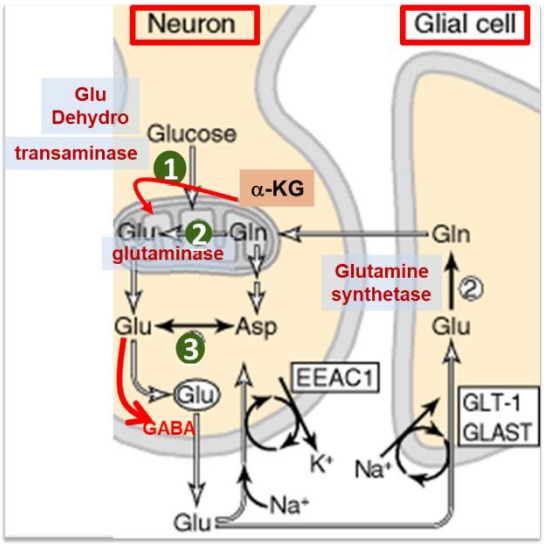
- Nonessential amino acids
- Do not cross BBB
  - must be synthesized in neurons (internal synthesis in CNS)
- Main synthetic compartments
  - neurons
  - glial cells
- Both are excitatory neurotransmitters.

- **Synthesis of Glutamate**

  Sources:

  1. Glycolysis → Krebs cycle → dehydrogenation and transamination of α-ketoglutarate
  2. Glutamine (deamination) by glutaminase
  3. Aspartate (transamination)

- **Removal**
  - Reuptake: Excitatory amino acid carrier-1 (EAAC1)
  - Glial cells: Glutamate transporter-1 (GLT-1) and glutamate–aspartate transporter (GLAST)

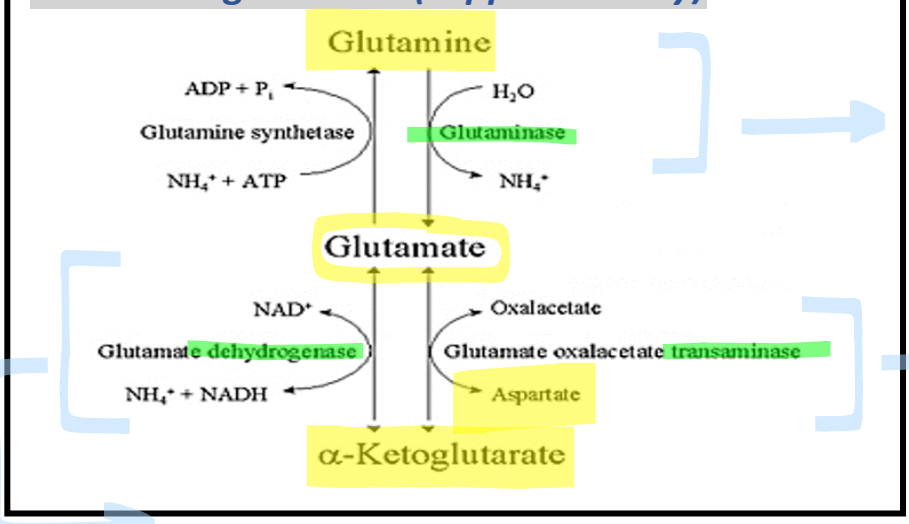


Names of transporters are not important, just focus on the mechanism of transport.

Glutamate is transferred into glutamine in glial cells then it is taken up by the presynaptic neuron and the cycle continues (recycling).

extra

Sources of glutamate *(supplementary)*



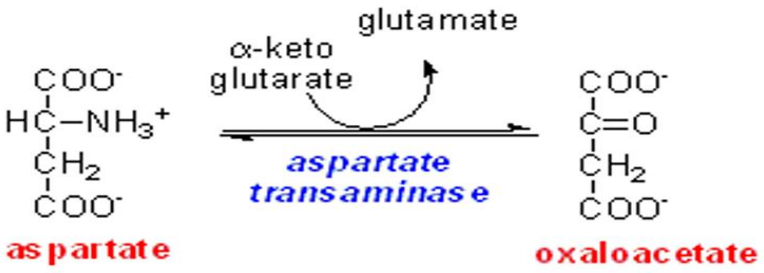
Deamination

Transamination

Dehydrogenation

Aspartate

- Not really considered as a neurotransmitter (controversy)
- Note: A vesicular uptake mechanism for aspartate has not yet been demonstrated, somewhat weakening the case for considering aspartate to be a neurotransmitter
- Precursor: 1- Oxaloacetate (transamination)
  2- α-ketoglutarate (//)
  3- Glutamate (//)



4- Gamma- aminobutyric acid (GABA)

- The MAJOR neurotransmitter
- GABA is present in high concentrations (millimolar) in many brain regions.
  - These concentrations are about 1,000 times higher than concentrations of the classical monoamine neurotransmitters in the same regions.
- The GABA shunt is a closed-loop process with the dual purpose of producing and conserving the supply of GABA. Because its needed in high concentrations.

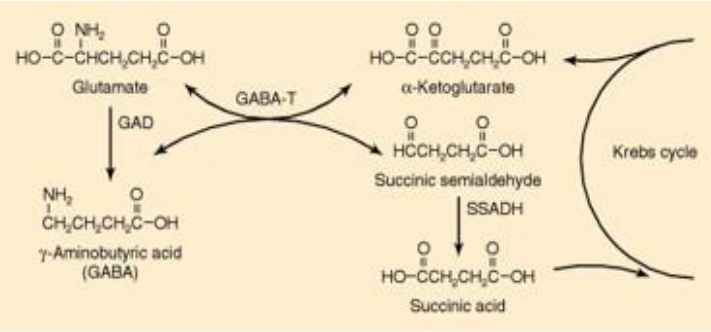
GABA shunt

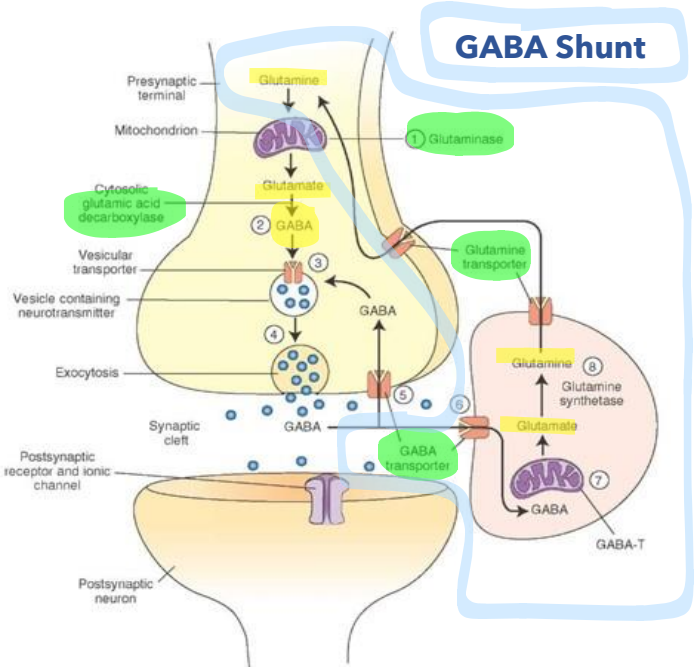
1- Gln → Glu by glutaminase.
2- Glu → GABA by glutamate decarboxylase (GAD), which requires pyridoxal phosphate (vitamin B6).
3- GABA is stored in vesicles until released upon a signal.
4- GABA is either

   a. taken up into the presynaptic terminal and repackaged

   b. goes into the GABA Shunt where it is taken up into the glia and converted to Glu.

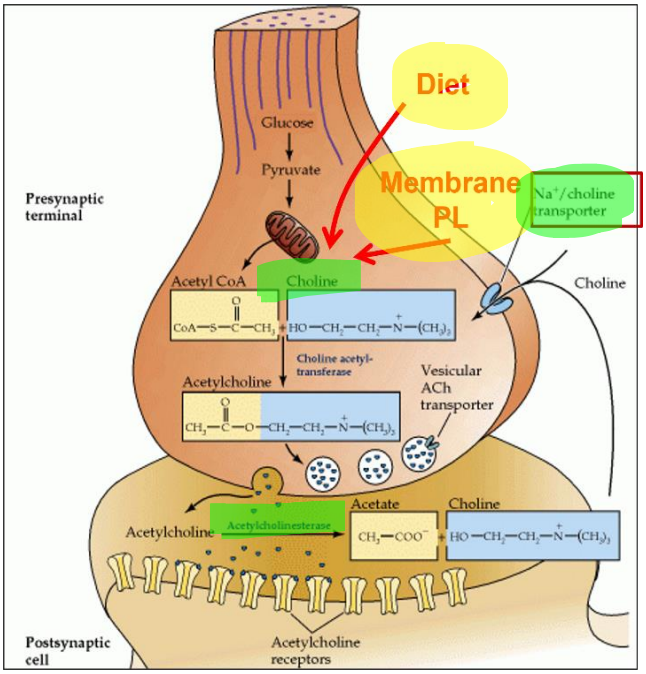
      - Glu is converted into Gln, which is transported into the neighboring nerve terminals to synthesize Glu.





Acetylcholine

- **Synthesis**:
  1- Choline (source: diet +membrane phospholipid) + acetyl coenzyme-A by choline acetyltransferase in the cytoplasm.
  2- Transported into and stored in small secretory vesicles.
- **Removal**:
  1- Enzymatically inactivated; hydrolysis by acetylcholinesterase (Main mechanism)
  2- Reuptake



اللهم صلّ على سيدنا محمد

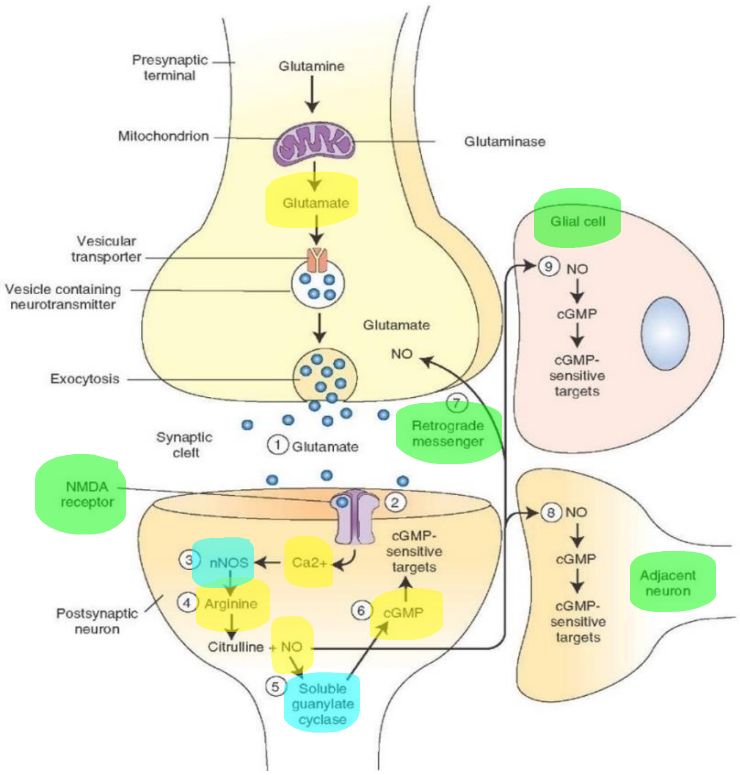
Gases

Nitric oxide (NO)

- NO has a half-life of 2-4 seconds.
- It's is inhibited by hemoglobin and other heme proteins which bind it tightly.

Synthesis and its pathway:

- Glutamate is released from presynaptic neuron (1) and acts on The N-methyl-D-aspartate (NMDA) receptors located on the post-synaptic neuron (2)
- Ca^{2+} enters the postsynaptic neuron activating nitric oxide synthase (NOS) (3), which forms NO from arginine (4).
- NO stimulates guanylate cyclase forming cGMP (5), which results in a physiological response (6)
- NO can diffuse out (INACTIVATION)
    - to the presynaptic terminal (retrograde messenger) (7) prolonging effect
    - into adjacent neurons (8) and glial cells (9) stimulating guanylate cyclase
    - or it binds to different proteins



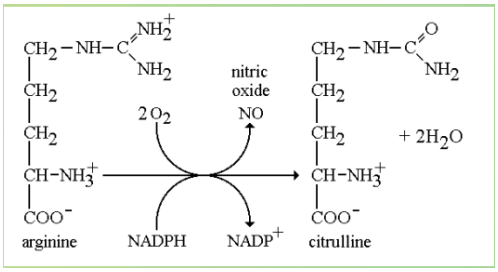
Is NO a neurotransmitter?

Yes, but:

- It is synthesized in the post synaptic neuron.
- It is not stored in vesicles.
- It is not released by calcium-dependent exocytosis (it diffuses)
- Its inactivation is passive (there is no active process that terminates its action)
    - It decays spontaneously
- It does not interact with receptors on target cells
    - Its sphere of action depends on the extent to which it diffuses, and its action is not confined to the conventional presynaptic-postsynaptic direction.
- NO acts as a retrograde messenger and regulates the function of axon terminals presynaptic to the neuron in which it is synthesized.

NO synthase (important)

- **Isoform I (nNOS or cNOS) → the same mentioned in this lecture.**
  - Neurons and epithelial cells
  - activated by the influx of extracellular calcium
- **Isoform II (iNOS)**
  - Macrophages and smooth muscle cells
  - induced by cytokines
- **Isoform III (eNOS)**
  - Endothelial cells lining blood vessels → VASODILATOR
  - activated by the influx of extracellular calcium



All three isoforms require BH2 or BH4 as a cofactor (both are correct because they both go through the same cycle of synthesis) and nicotinamide adenine dinucleotide phosphate (NADPH) as a coenzyme.

PAST PAPERS

1. **An excitatory neurotransmitter that leaks to the cytosol to be converted to another neurotransmitter, can be recycled through a presynaptic neuron transporter, and degraded by the liver or presynaptic enzymes is:**
   a. Gama-aminobutyric acid
   b. Glycine
   c. Norepinephrine
   d. Serotonin
   e. Acetylcholine

2. **Deficiency of vitamin B6 (pyridoxal phosphate) will result in the impairment of all the following pathways EXCEPT:**
   a. DOPA to dopamine
   b. Norepinephrine to epinephrine
   c. Aspartate to glutamate
   d. Tryptophan to serotonin
   e. Histidine to histamine

3. **The 'retrograde' mechanism of NO (nitric oxide) means:**
   a. It is produced in the post-synaptic neuron.
   b. It regulates the pre-synaptic neuron.
   c. It activates guanylyl cyclase.
   d. It diffuses to nearby cells.
   e. It binds to post-synaptic receptors.

4. **Which is true about neuropeptides and small transmitters:**
    a. Both released by vesicular mechanism
    b. Both synthesized in cell body of presynaptic cell
    c. Both can be released from a site far away from the site of Ca entry
    d. Both induce a signal that can be terminated by reuptake

5. **A neurotransmitter that is not deactivated by MAO:**
    a. GABA
    b. Histamine

6. **SAM is used in all of the following except**:
    a. N-methyl trans
    b. Deamination
    c. Methylation of phosphodylether …
    d. COMT

7. **TRUE about Histidine to histamine reaction:**

- Requires pyridoxal phosphate

8. **Can't cross BBB:**

- Glutamate

9. **The indicator of Parkinson's disease is:**

- homovanillic acid

10. **Which one of the following is WRONG about glutamate:**

- Cannot be synthesized inside neurons

11. **Which one of the following is WRONG about catecholamine synthesis**

- Dopamine and norepinephrine have vesical synthesis

1- C
2- B
3- B
4- A
5- A
6- B

USMLE Question:

A 43-year-old man is being evaluated for occasional retrosternal chest pressure that develops with moderate exertion and sometimes occurs when resting. He does not use alcohol, tobacco, or illicit drugs. The patient has an extensive family history of coronary artery disease. His temperature is 36.7 C (98 F), blood pressure is 124/72 mm Hg, pulse is 81/min, and respirations are 14/min. Physical examination shows no abnormalities. Coronary angiography shows mild luminal irregularities but no significant obstructive lesions. Acetylcholine infusion during the procedure results in dilation of epicardial coronary vessels. A reaction involving which of the following amino acids is most likely responsible for the observed dilation?

A) Arginine

B) Aspartate

C) Glutamate

D) Tyrosine

E) Tryptophan

* Answer A: Nitric oxide is synthesized from arginine by nitric oxide synthase. As a precursor of nitric oxide, arginine supplementation may play an adjunct role in the treatment of conditions that improve with vasodilation, such as stable angina.

لَا يُكَلِّفُ اللَّهُ نَفْسًا إِلَّا مَا آتَاهَا

سَيَجْعَلُ اللَّهُ بَعْدَ عُسْرٍ يُسْرًا