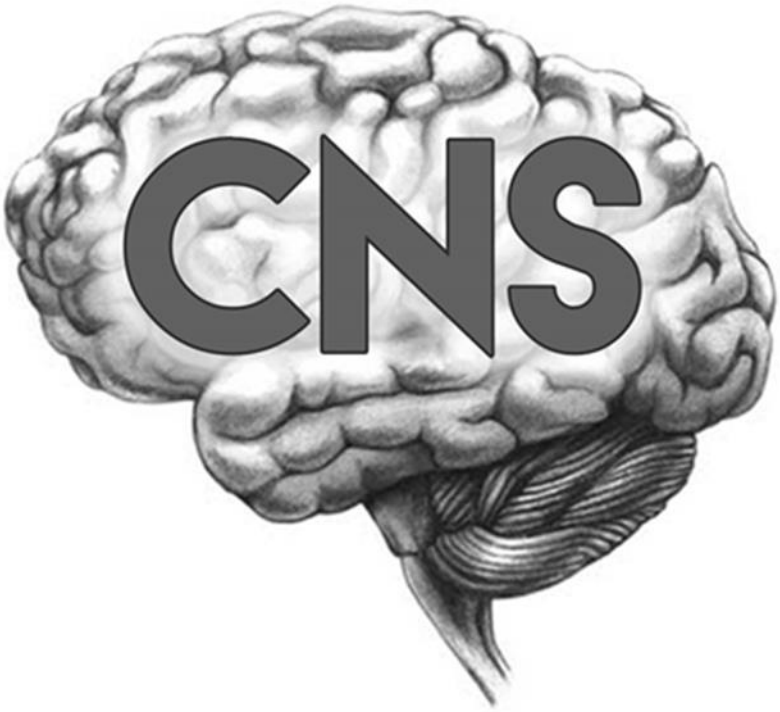

Biochemistry

☑ Sheet ○ Slide ○ Handout

Number

2

Subject

Neurotransmitters

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Date: 00/3/2017

Price:

- this sheet is written according to section 1 recording

Neurotransmitters

Neurotransmitter Definition and Characteristics:

A chemical substance that is:

- Synthesized in a neuron, packaged & stored in vesicles of different types (Enzymes needed for the synthesis must be present in the neuron)
- These vesicles are fused to the plasma membrane and neurotransmitters get released at a synapse following depolarization of the nerve terminal (usually dependent on influx of calcium ions)
- Neurotransmitters then bind to receptors on the postsynaptic cell (another neuron or a muscle cell) and/or presynaptic terminal to elicit a specific response.
- then the neurotransmitter must be inactivated by different inactivation mechanisms "enzymatic, diffusion, reuptake" depending on the neurotransmitter itself

  - There are 3 types of neurotransmitter:

1. small molecule neurotransmitter :

- derived from Amino acids, “they are AA themselves”
- can be derived from Krebs cycle and glycolytic pathways

2. **Neuropeptides** : (relatively larger neurotransmitter)
3. **Gases** : very small (nitric oxide)

- More than one transmitter (usually a small-molecule transmitter and a neuroactive peptide) coexist in many mature neurons
- so one neuron can produce different types and even different classes of neurotransmitter at the same time

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Neuropeptides:

➢ They have different actions and effects

"can control pain perception taste, behavior, appetite etc..."

- How is a neuropeptide considered neurotransmitter or a neurohormone?

- depends on where they act, if a neuropeptide acts within the vicinity "the same area" where it is released, it is considered a neurotransmitter, if its released in the blood and acts far away from its releasing site then it is considered a neurohormone.

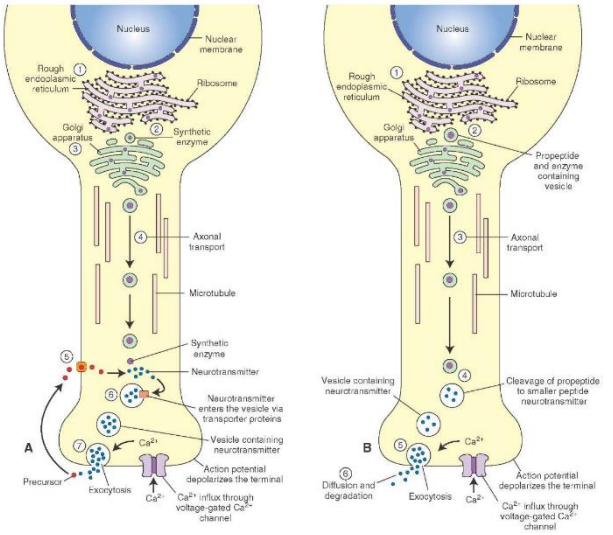
Classes of Neuropeptides:

Neuropeptide Families
Tachykinins: substance P, bombesin, substance K **Insulins**: insulin, insulin-like growth factors **Somatostatins**: somatostatin, pancreatic polypeptide **Gastrins**: gastrin, cholecystokinin **Opioids**: opiocortins, enkephalins, dynorphin

- they have similarity in structure between them yet they have different effects and receptors due to the small difference in AA sequence
- like vasopressin and oxytocin, they share the same 7 out of 9 AA yet they have different effect!
- The three glycoprotein hormones from the anterior pituitary, TSH, LH, and FSH, share a common α subunit, but have distinct β subunits.
- Opiate peptides share a common sequence, but are receptor-selective.

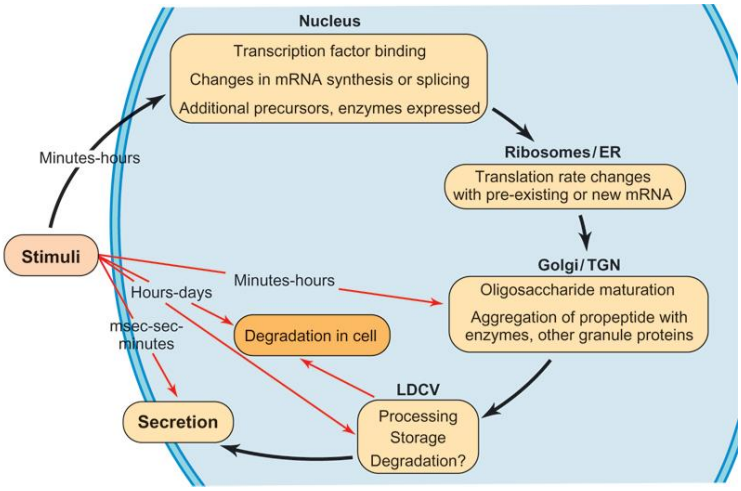
Stages of action of Neuropeptides:

- Synthesis (in ER and Golgi apparatus)
- Packaging into **large-dense core vesicles** (with modifying enzymes)
- Transport (fast-axonal transport) to the **periphery**
    - During the transport, proteases cleave the precursor neuropeptide into the final mature form.



- Release:
  - They are released gradually over time in response to general increases in the level of intracellular calcium.
- Action (prolonged) "because they are stable"
- Termination by diffusion and degradation

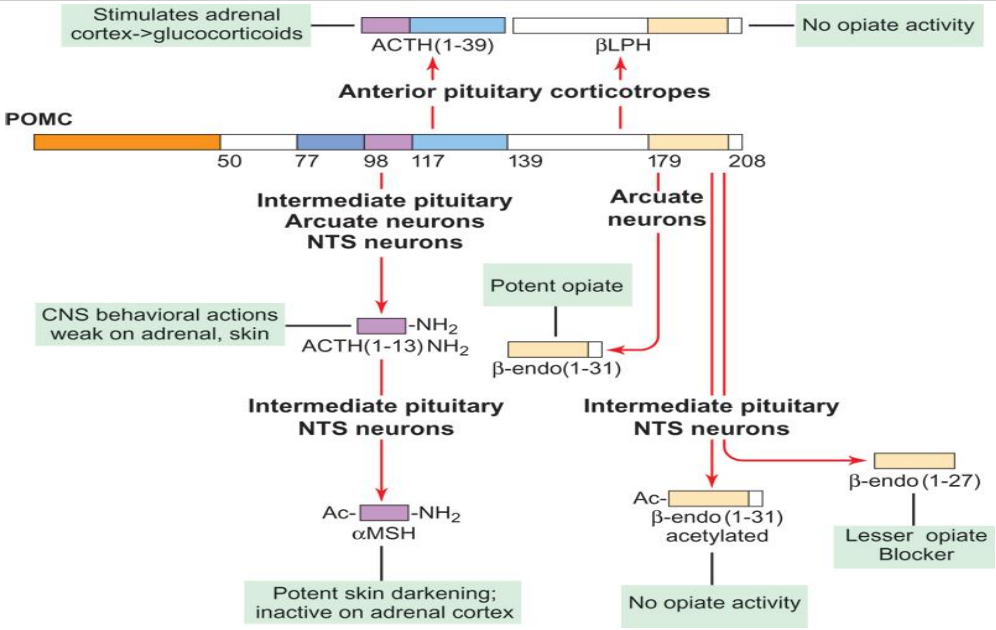
Levels of regulation of synthesis:



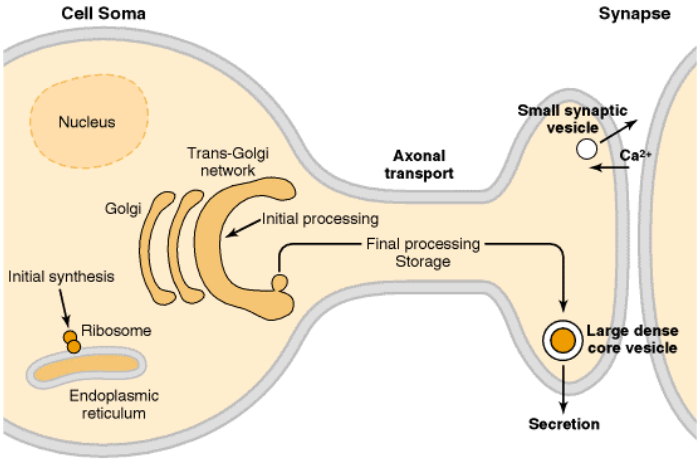
a. Expression
b. Transcription
c. alternative splicing (post transcriptional regulation):
   - ❖ Alternatively spliced mRNA produces different types of neuropeptides ex: substance p & neurokinin
d. post translational level: one large polypeptide includes different types of neuropeptides
   - ❖ ex: POMC (Pro-opiomelanocortin) cleaved to several types of hormones
e. packaging inside vesicles
f. enzymatic degradation

Processing of the POMC precursor proceeds in an ordered, stepwise fashion, Some of the reactions are tissue specific.

ACTH, adrenocorticotropic hormone; CLIP, corticotropin-like intermediate lobe peptide; JP, joining peptide; LPH, lipotropin; MSH, melanocyte-stimulating hormone; PC, prohormone convertase.



Role of calcium influx in the release of these neuropeptides:



- You have to know that the site of vesicles fusing with plasma membrane and releasing the neuropeptides can be far away from where Ca influx takes place, which is different in the case of small molecule neurotransmitter, “we will talk about it later”.
- the source of Ca itself can either be **external** or **internal** like Ca store inside the cell, so when these stores release the Ca ion the vesicles will be fused and neuropeptides will be released

Small Molecule Neurotransmitters:

Stages of Action:

- The enzymes responsible for synthesis of small molecule neurotransmitter are synthesized in cell body and then they are transported by microtubules to periphery by either slow or fast axonal transport (while neuropeptides vesicles are fast axonal transport)
- Synthesis of these neurotransmitter takes place in the **periphery,** then the get packaged inside vesicles "synaptic vesicles", waiting for Ca influx to be released
- once released, their action is short due to their short half life
- they can be inactivated after being released by diffusion, enzymatic reactions or by reuptake into the presynaptic cells
- so these presynaptic cells can take up these neurotransmitter again, which has important implication **therapeutically!**
- Ca influx will induce fusion of vesicles containing the neurotransmitters occur near the site of influx (which is different from the neuropeptides as we mentioned before),
- vesicles line up near the plasma membrane waiting for Ca influx to fuse with the membrane releasing neurotransmitter
- once released, reuptake occurs by endocytosis back to the presynaptic cell

- Why would Ca induce fusion of vesicles to plasma membrane?
  - beacuse Ca is required for the interaction between different proteins that exists on the plasma membrane and the synaptic vesicles
  - so Ca level goes up allowing these interactions to occur between vesicles and membrane
  - another mechanism for fusion not mentioned in the slides, which is that these vesicles bind to microtubules and then they jump from microtubules to the actin on plasma membrane, but there is a gap or empty region between the actin and the membrane , when the Ca increase inside the cell, the actin cytoskeleton move and interact with the plasma membrane allowing for the vesicles to get near the plasma membrane so that they fuse and release the neurotransmitter

Role of Vitamin and vitamin derivatives "cofactors" in regulating the synthesis of small molecule neurotransmitter

- S-adenosylmethionine for (methyl transfer)
- Pyrodoxal phosphate (vitaminB6) transamination, decarboxylation
- Tetrahydrobiopterin (BH4) involved in synthesis of catecholamines

☆ Catecholamines (Tyrosine derived neurotransmitters):

"They are called catecholamines because they contain a Catechol ring"

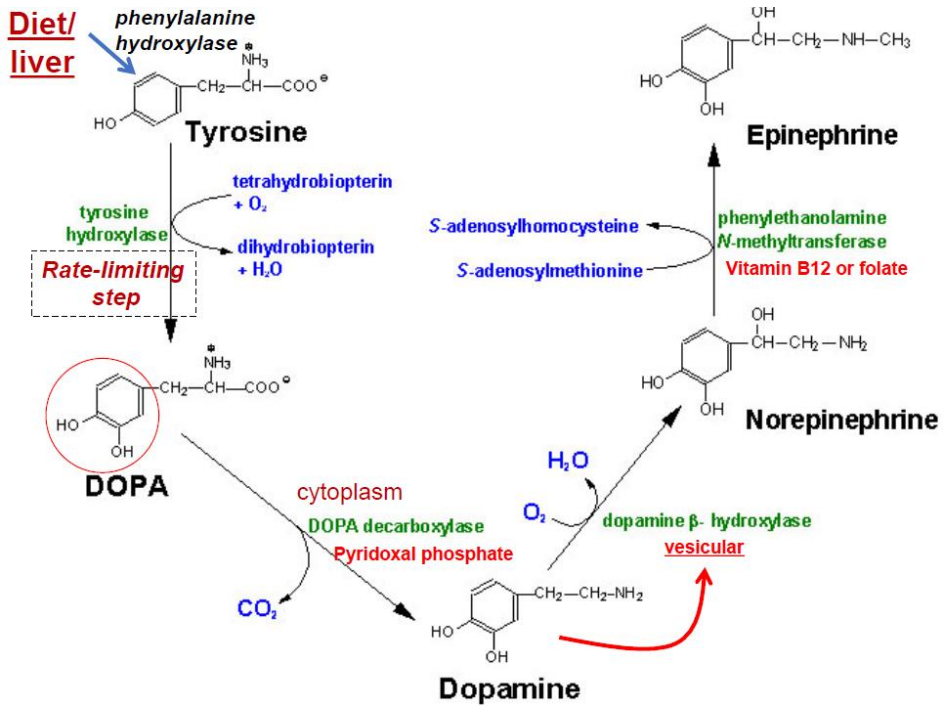
((Dopamine, Epinephrine and Norepinephrine))

Synthesis: *(very important)*

- Synthesized from tyrosine (hence called tyrosine derived)
- tyrosine is hydroxylated in a rate limiting step reaction catalyzed by **tyrosine hydroxylase** which needs (THBP) as a cofactor, producing DOPA
- DOPA is then decarboxylated by Vit B6 producing **dopamine** "which is a stimulant",
- *The earlier two reaction occur in the cytoplasm*
- Then the dopamine is packaged into vesicles, inside these vesicles dopamine is converted to **norepinephrine**
- So norepinephrine synthesis is **vesicular!**
- then norepinephrine again leaks out to the cytoplasm and converted to epinephrine via methyltransferase which requires (s-adenosylmethionine)

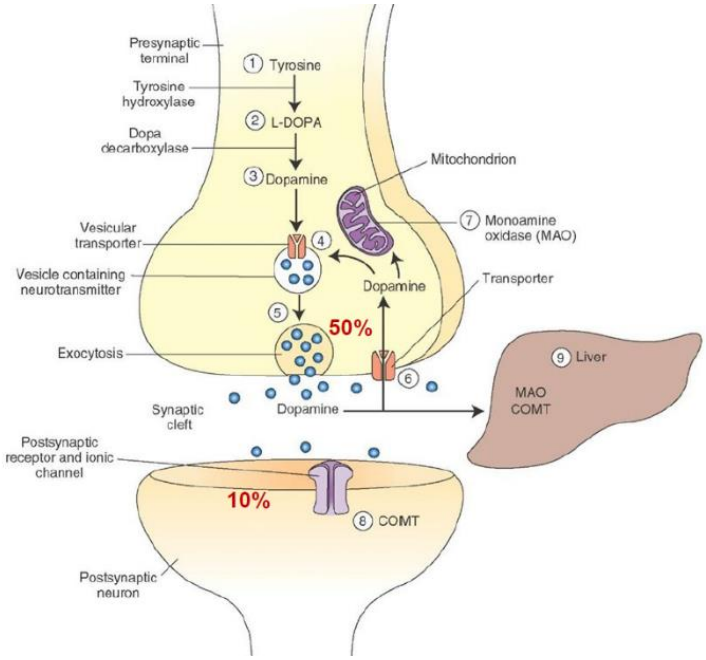
"epinephrine synthesis is cytoplasmic!"

- Then it gets packaged inside synaptic vesicles.

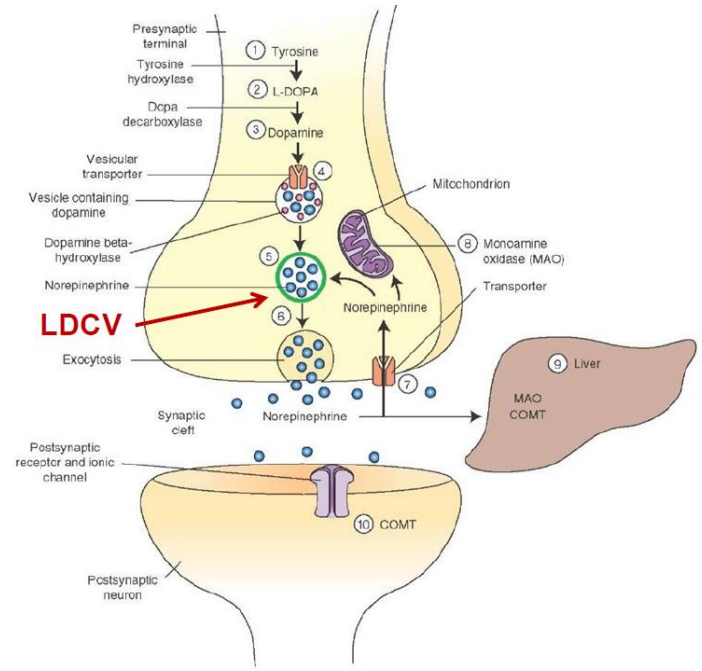


Inactivation mechanisms:

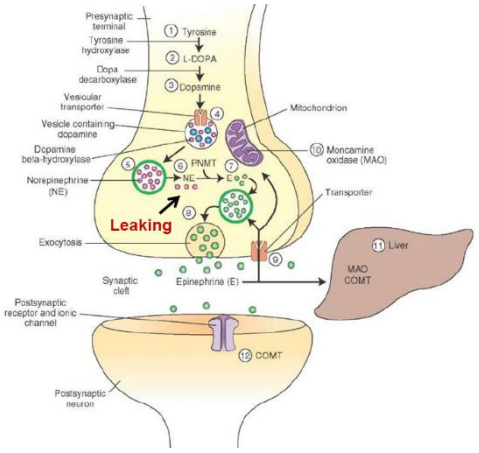
- **Dopamine:**
  - Dopamine is inactivated enzymatically by Mono-Amine-Oxidase **"MAO"** or Catecholamine Methyl-Transferase **"COMT"** Catechol-O-methyltransferase,
  - 50% of it is reuptaken by the <u>presynaptic</u> neuron, and packaged inside vesicles (recycled).
  - and some of it is taken by the <u>postsynaptic</u> cell or neuron



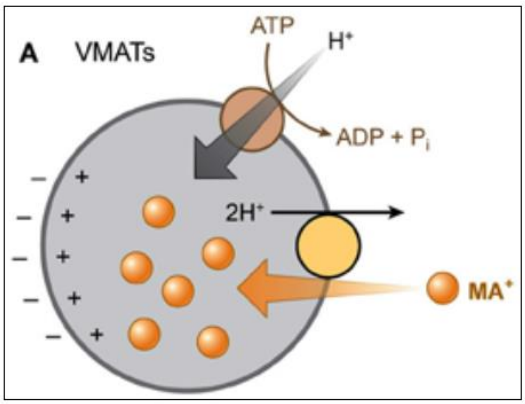
- **Norepinephrine:**
  - Norepinephrine inactivation is by diffusion, MAO, or reuptake in pre- and post- synaptic cells



- **Epinephrine:**
  - same mechanism of inactivation as norepinephrine



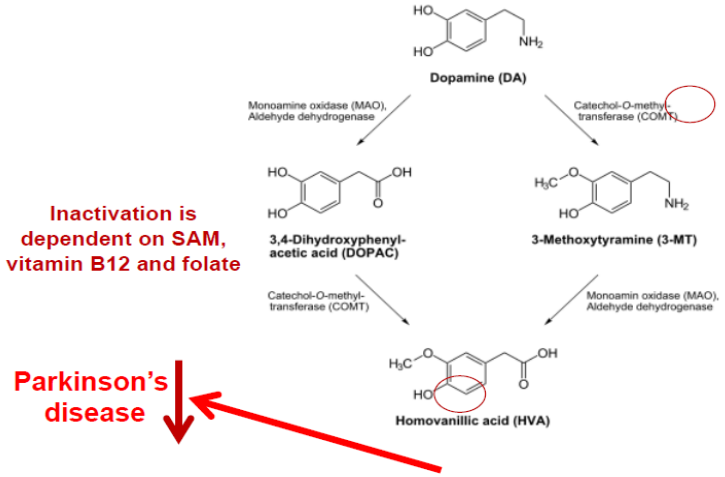
Packaging into vesicles:



- Packaging inside the vesicles happens via ATP dependent process linked to a proton pump
- So a proton gets in the vesicle which requires ATP, then the transporter (vesicle monoamine transporter) exchanges this proton for catecholamine

Enzymatic inactivation process is done by two enzymatic reactions:

- MAO and COMT



- Doesn't matter which one happens is first but both of them are required !
- The final product is **homovanillic** acid, its level is reduced in Parkinson's disease which considered a marker for the disease

- Remember: The rate limiting step reaction (tyrosine hydroxylase)

Regulation:

- short and long term regulation for the enzyme
- Long term regulation is by gene expression which takes hours
- Short term regulation is either by:
  a. inhibition of the enzyme “by the free cytosolic catecholamine”, so when we have high levels of these neurotransmitter the enzyme will be inhibited
  b. or the enzyme can be **activated** by depolarization which allows for the tight binding to BH4

EXTRANOTE

Treatment for ADD is by dopamine “to give the patient a stimulant”, and also amphetamine

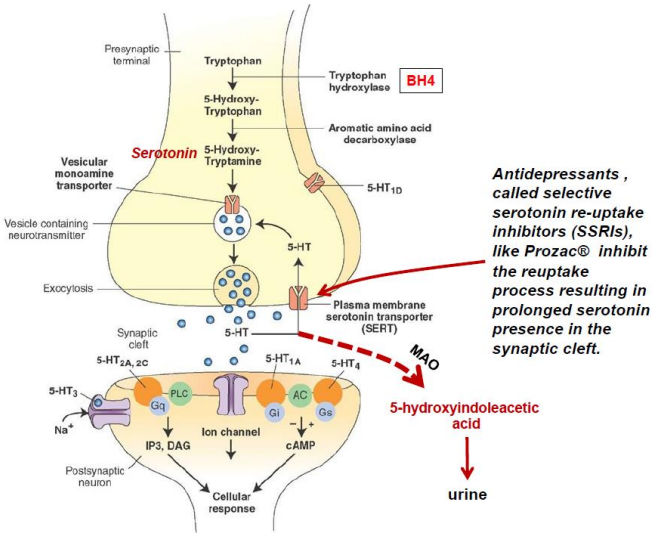
attention deficit disorder (ADD)

any of a range of behavioral disorders occurring primarily in children, including such symptoms as poor concentration, hyperactivity, and impulsivity

Other types of neurotransmitters:

Serotonin & melatonin:

Serotonin:



- Serotonin synthesis occurs inside the cytosol ➔ packaged inside vesicles ➔ Ca influx produces depolarization ➔ release
- Once they're outside, they get inactivated by reuptake in presynaptic cell, diffusion or enzymatic inactivation by MAO
- Serotonin is responsible for happiness and relaxation.
- So depressed people are giving a drug that inhibit serotonin reuptake, (SSRIs) which keeps the serotonin in the CNS for a long time
- In the US a drug named **Prozac** “an SSRI” is giving in a ridiculous way to anyone who thinks he’s depressed!

Melatonin:

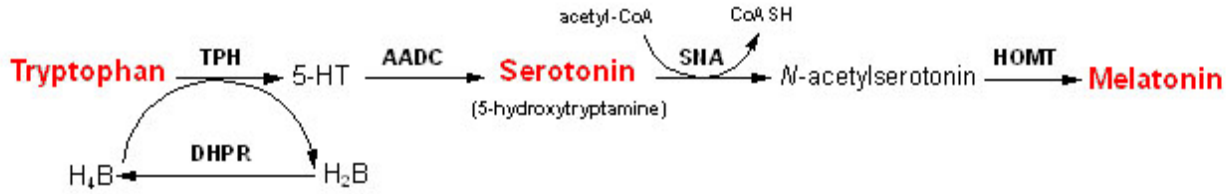
- Serotonin is the precursor for melatonin, which is responsible for regulating:

I. sleep pattern,
II. circadian and seasonal rhythm
III. dark-light cycle

People who travels to a far-away places might suffer from "jet lag", so they're advised to take melatonin to regulate and balance their circadian rhythm

Jet Lag:

Extreme tiredness and other physical effects felt by a person after a long flight across several time zones.



❁ Glutamate & Aspartate

- Amino acids can also work as neurotransmitter, examples are:
  - ➢ Glutamate and aspartate & glycine

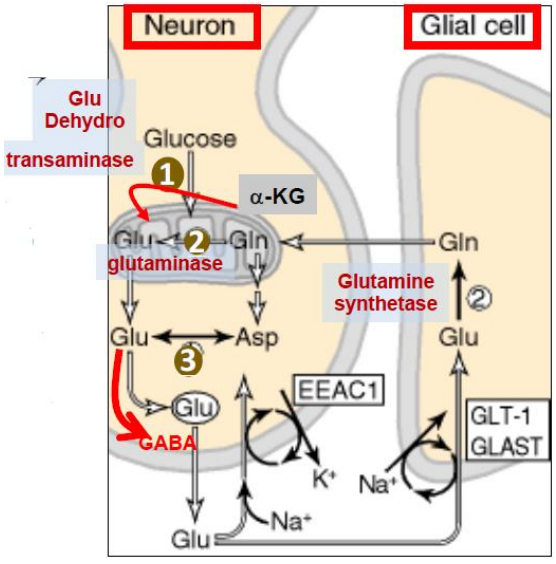
- Glutamate and aspartate are Nonessential amino acids, they do not cross BBB, So they must be synthesized in neurons or glial cells,
- Both are excitatory neurotransmitters

❁ Glutamate

Synthesis of glutamate:

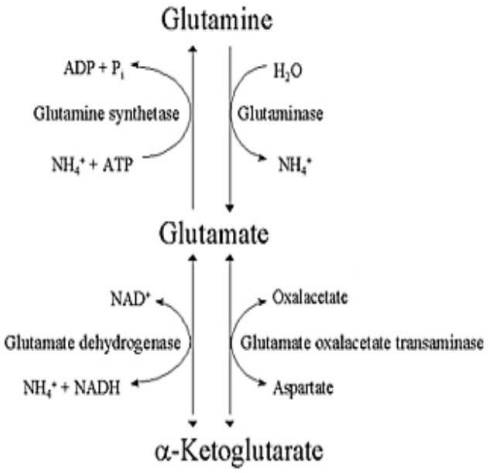
- we have 3 sources:

1. Glycolysis → krebs cycle → transamination (or dehydration) of α-ketoglutarate to glutamate
2. Glutamine deamination
3. Transamination of aspartate



Inactivation of glutamate:

- Once released, it can be reuptaken by presynaptic cells, or by glial cells
- Inside the glial cells glutamate can't be released, rather it gets converted to **glutamine**, and glutamine can then be released out of the glial cells, then it's taken up by presynaptic cells and gets packaged there and so on...

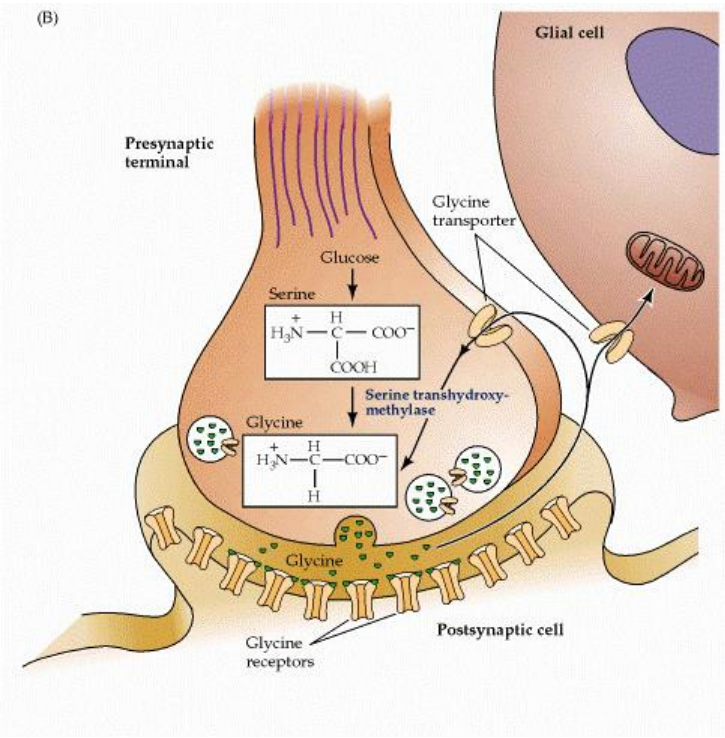


- So this is a **salvage mechanism**, which means a pathway by which we can save the source of glutamate in order not to synthesize it again! (recycling)

Aspartate:

- it's not know till now whether aspartate is a neurotransmitter or not because receptor for it has not been discovered yet!
- but if it was a neurotransmitter, it also gets reuptaken by presynaptic cells, released in the same mechanism, and it can be synthesized by transamination reaction from **oxaloacetate**, (intermediate of Krebs cycle)

Glycine:

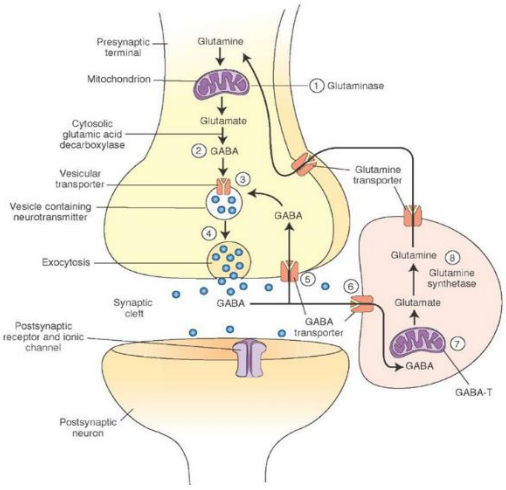


- Synthesized from serine by serine hydroxymethyl transferase through 3-phosphoglycerate •
- *The major inhibitory neurotransmitter in the spinal cord*

GABA:

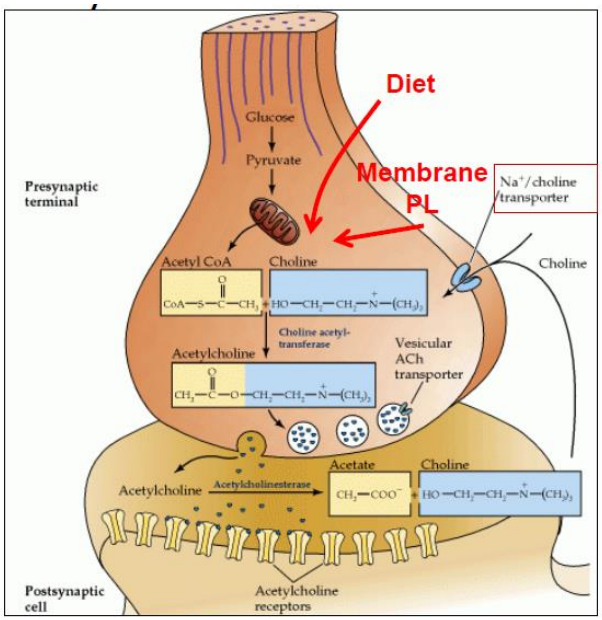
- Present in high concentrations (millimolar) in many brain regions.
- Glutamate is α-decarboxylated forming GABA via glutamate decarboxylase (GAD), which requires pyridoxylphosphate (vitaminB6).

GABA shunt:



- A mechanism by which cells don't lose GABA, because it's needed in high concentrations,
- So it's taken up by glial cells and converted to glutamate (which cannot be released by cells) so it gets converted to glutamine then realesed and taken by presynaptic cells to sunthesize GABA once again (cycle)
- GABA is either taken up into presynaptic terminal and re-packaged OR goes into the GABA Shunt

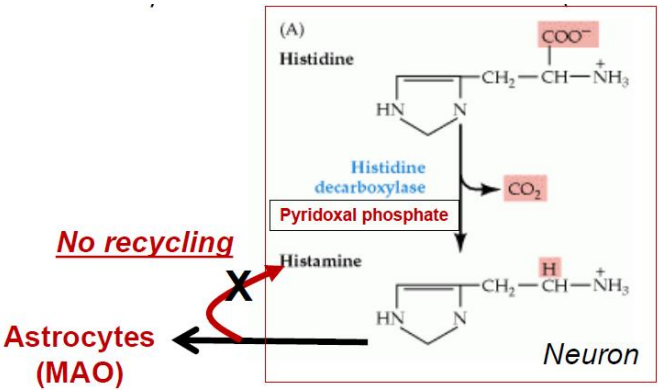
❁ Acetylcholine:



- Synthesized from acetylcoenzyme-A(derived from Krebs cycle) + choline (derived from phosphatidylcholine in plasma membrane)
- Once released, it gets inactivated by <u>acetylcholinesterase</u>
- Chemical weapons produced by using **serine** gas which inhibits this esterase, which leads to convulsions and paralysis due to high levels of acetylcholine which in the end results in death!☠

❁ Histamine:

- Histamine is synthesized from histidine by (histidine decarboxylase)



- Once released, there is no mechanism for reuptake, rather it's taken by astrocytes that have MAO for inactivation

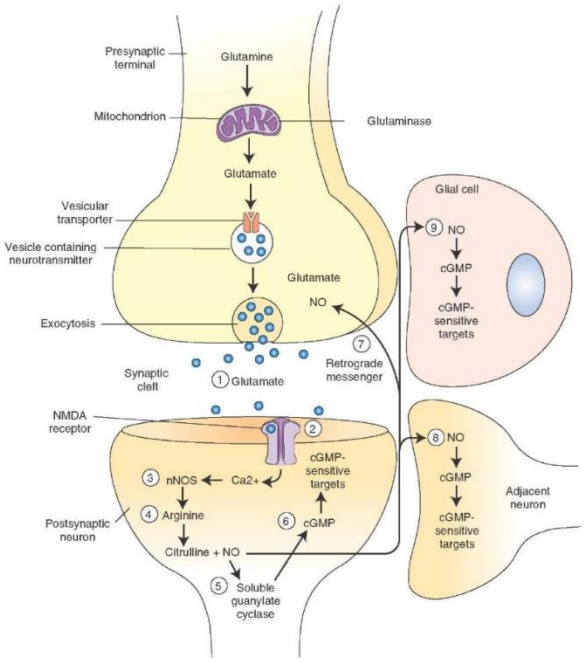
Gas neurotransmitters:

❖ NO (Nitric Oxide)

((Different from all other neurotransmitters!))

- How?

- Glutamate is released from a presynaptic cell, acts on a postsynaptic cell (NMDA receptors),
- influx of Ca activates NO synthase (NOS), which forms NO from arginine
- NO stimulates guanylate cyclase forming cGMP, which results in a physiological response!
- NO can be released from the postsynaptic cell, diffuse to the neighboring cells,
- And/or the presynaptic cell itself! (this is known as the **retrograde messenger!)**



- The half-life for NO is only 2-4 s, so it is short distanced
- *NO is inhibited by hemoglobin and other heme proteins which bind it tightly!*

Is NO a neurotransmitter?

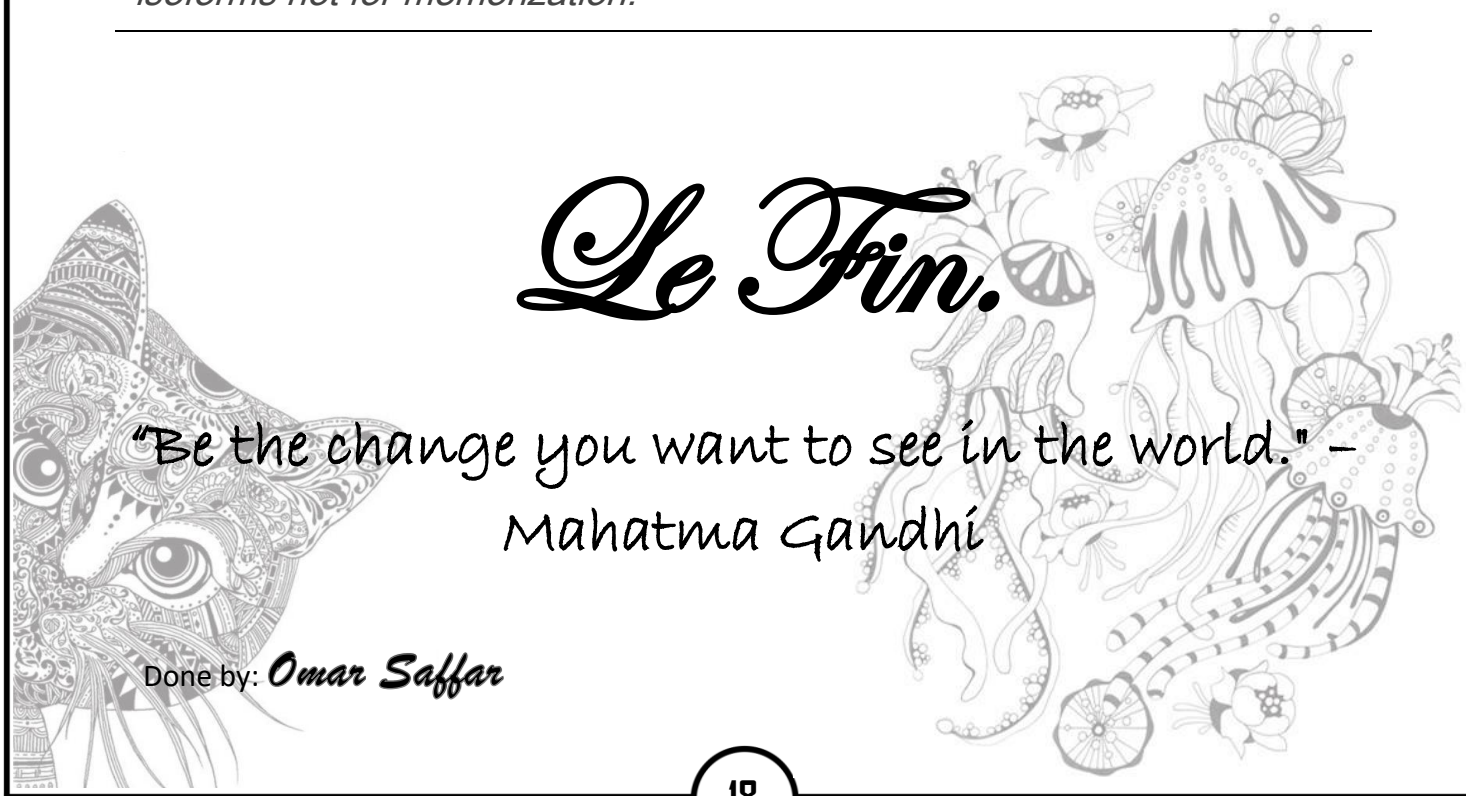
Yes, it is neurotransmitters but:

1. it's not stored in vesicles rather it diffuses out of the cell
2. not Ca dependent
3. inactivated by passive diffusion
4. decays spontaneously
5. doesn't interact with a receptor, rather works inside the cell on guanylate cyclase
6. act as retrograde messenger

So it's different from classical neurotransmitters

❖ NO synthase has 3 **isoforms** which exists in different types of cells but all of them require BH2 as a cofactor and NADPH as a coenzyme.

"isoforms not for memorization!"



Le Fin.

"Be the change you want to see in the world." – Mahatma Gandhi

Done by: **Omar Saffar**