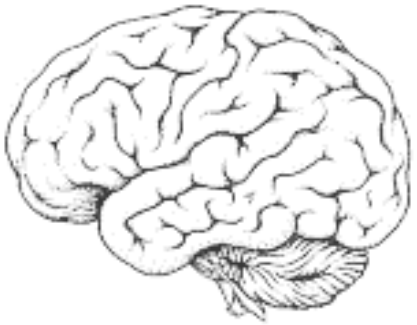
BAU-Medicine



دعاء لزميلنا رشيد ....

اللهُم اجعل الراحلين إليك في ظلٍ ظليل و اجعل عن يمينهم

و عن شمائلهم نورًا حتى تبعثهم امنين مطمئنين اللهم ارحم موتانا

و جميع موتى المسلمين

Sheet no. 1
Lecture Date: 25/2/2021
Lecture Title: Neurotransmitters
Written by: Tasnim Fadel

Boxes are part of the sheet

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Neurotransmitters

Objectives

1 . Outline the criteria that need to be met before a molecule can be classified as “neurotransmitter”

2 . Identify the major neurotransmitter types

3 . Mechanism of action of important neurotransmitters.

4 . Identify some clinical disorders that can arise as a result of disruption of neurotransmitter metabolism.

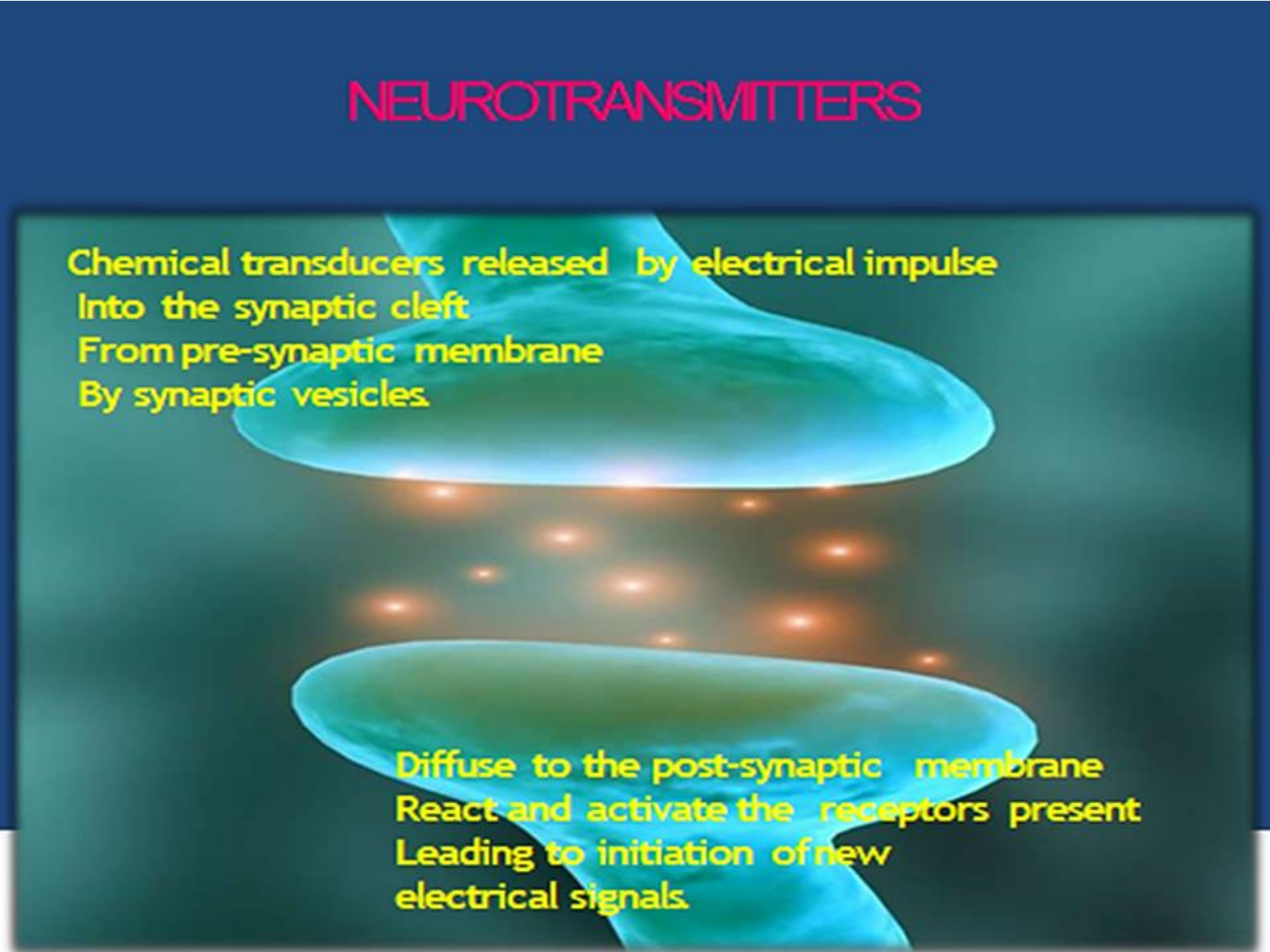
What are the Neurotransmitter Criteria ?

Neurotransmitter Criteria

Neuroscientists have set up a few guidelines or criteria to prove that a chemical is really a neurotransmitter. Not all of the neurotransmitters that you have heard about may actually meet every one of these criteria.

The chemical must be produced within a neuron. 	The chemical must be found within a neuron. 	When a neuron is stimulated (depolarized), a neuron must release the chemical. 
When a chemical is released, it must act on a post-synaptic receptor and cause a biological effect. 	After a chemical is released, it must be inactivated. Inactivation can be through a reuptake mechanism or by an enzyme that stops the action of the chemical. 	If the chemical is applied on the post-synaptic membrane, it should have the same effect as when it is released by a neuron. 

NEUROTRANSMITTERS



Chemical Synaptic Transmission

- 4 steps:
  1. Synthesis of transmitter
  2. Storage & release of transmitter
  3. Interaction of transmitter with receptor in postsynaptic membrane
  4. Removal of transmitter from synaptic cleft.

Neurotransmitters in brain

AMINES

Dopamine

Serotonin
Nor-epinephrine
Epinephrine
Acetylcholine
Melatonin
Histamine

AMINO ACIDS

Glutamic acid
GABA
Glycine
Aspartic acid

OPIOIDS PEPTIDES

Endorphin
Enkephaline

MISCELLANEOUS PEPTIDES

Bradykinin
Neuropeptide Y
Neurotensin
Bombesin

AMINES

#	NAME	ACTION
1	Noradrenaline	Excitatory & Inhibitory
2	Adrenaline	Excitatory & Inhibitory
3	Dopamine	Inhibitory
4	Serotonin	Inhibitory
5	Histamine	Excitatory

AMINO ACIDS

#	NAME	ACTION
1	GABA	Inhibitory
2	Glycine	Inhibitory
3	Glutamate	Excitatory
4	Aspartate	Excitatory

OTHERS

#	NAME	ACTION
1	Nitric oxide	Excitatory
2	Acetylcholine	Excitatory

Neurotransmitter receptors

- Once released, the neurotransmitter molecules diffuse across the synaptic cleft.

- When they “arrive” at the postsynaptic membrane, they bind to neurotransmitter receptors.

Two main classes of receptors:

1.Ligand-gated ion channels

•Transmitter molecules bind on the outside, cause the channel to open and become permeable to either sodium, potassium or chloride

2. G-protein-coupled receptors

• G-protein-coupled receptors have slower, longer-lasting and diverse postsynaptic effects. They can have effects that change an entire cell's metabolism

•or an enzyme that activates an internal metabolic change inside the cell activate cAMP activate cellular genes: forms more receptor proteins activate protein kinase: decrease the number of proteins

Excitatory neurotransmitters:

Neuron - Action potential
Muscle - Contraction
Gland - secretion

CNS

Depolarization of Post-synaptic membrane (EPSP)

Eg: Glutamate
Ach
Asparatic acid

Inhibitory neurotransmitters:

Reduce or block activity of postsynaptic cell.

CNS

Hyperpolarization of Post-synaptic membrane (IPSP)

Eg: Glycine
GABA
Dopamine

Acetylcholine

- Acetylcholine is the transmitter used by motor neurons of the spinal cord
- Released at all vertebrate neuromuscular junctions
- Present in autonomic & parasympathetic neurons
- Used in many brain synapses

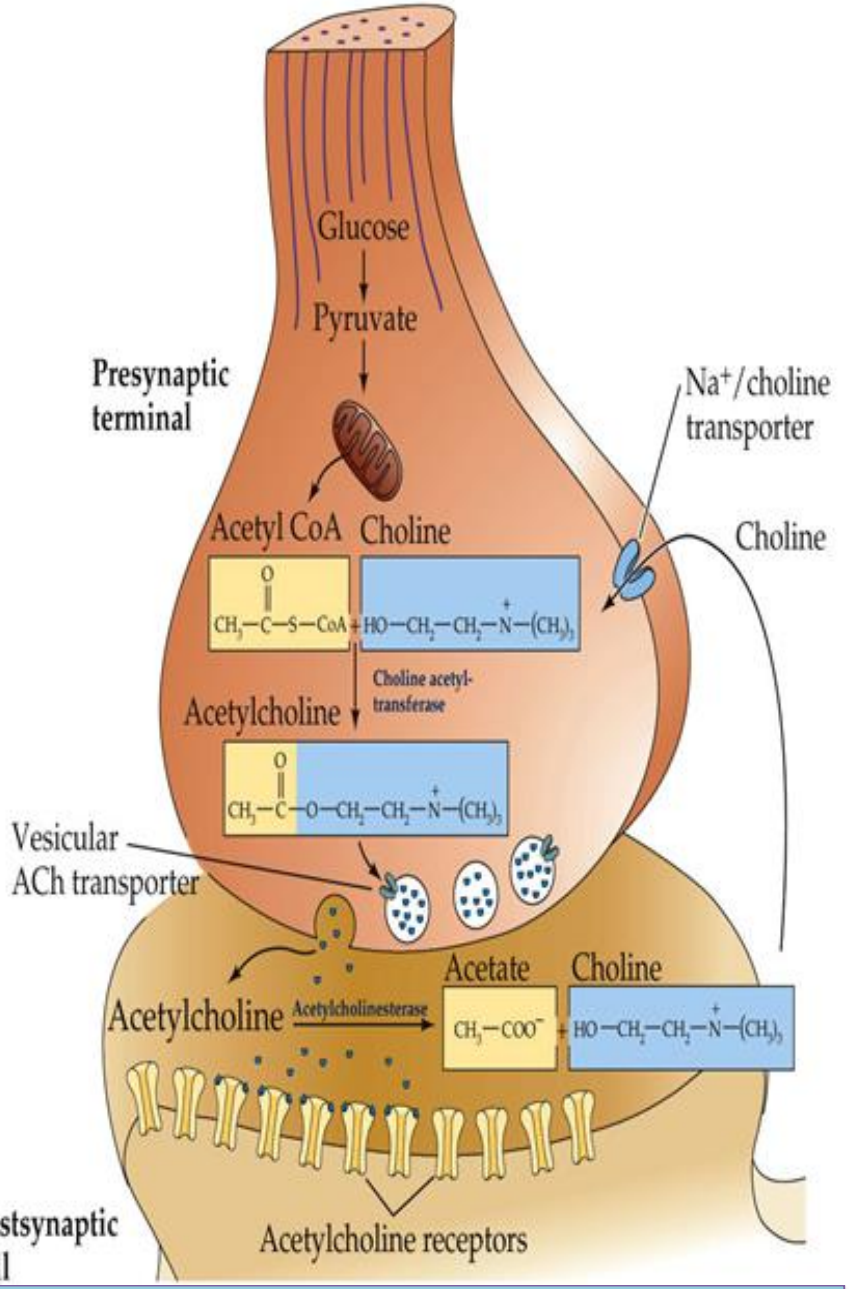
Acetylcholine (ACh)

1. Transmitter at **neuromuscular junction** and in the **CNS**
2. Plays important roles in **autonomic nervous system** (part of the PNS that maintains homeostasis in the body)
3. Synthesized from
    1. **choline** (an essential dietary component) and
    2. **acetate** (donated by acetyl coenzyme A – synthesized from glucose by choline acetyltransferase (CAT))
4. Degraded extracellularly by **acetylcholinesterase** (**AChE**)
5. **Choline** is transported back into presynaptic terminals

Acetylcholine neurotransmission

*All the organophosphorus gases inhibit AChE so:

- exacerbate the function of Ach.
- increase muscle contraction
- paralysis of respiratory muscles and suffocation.



AChE is the target of many nerve gases and insecticides

- **Indicated effects:**
  - ↪ excitation or inhibition of target organs
  - ↪ essential in movement of muscles
  - ↪ important in learning and memory

Biogenic Amine Transmitters

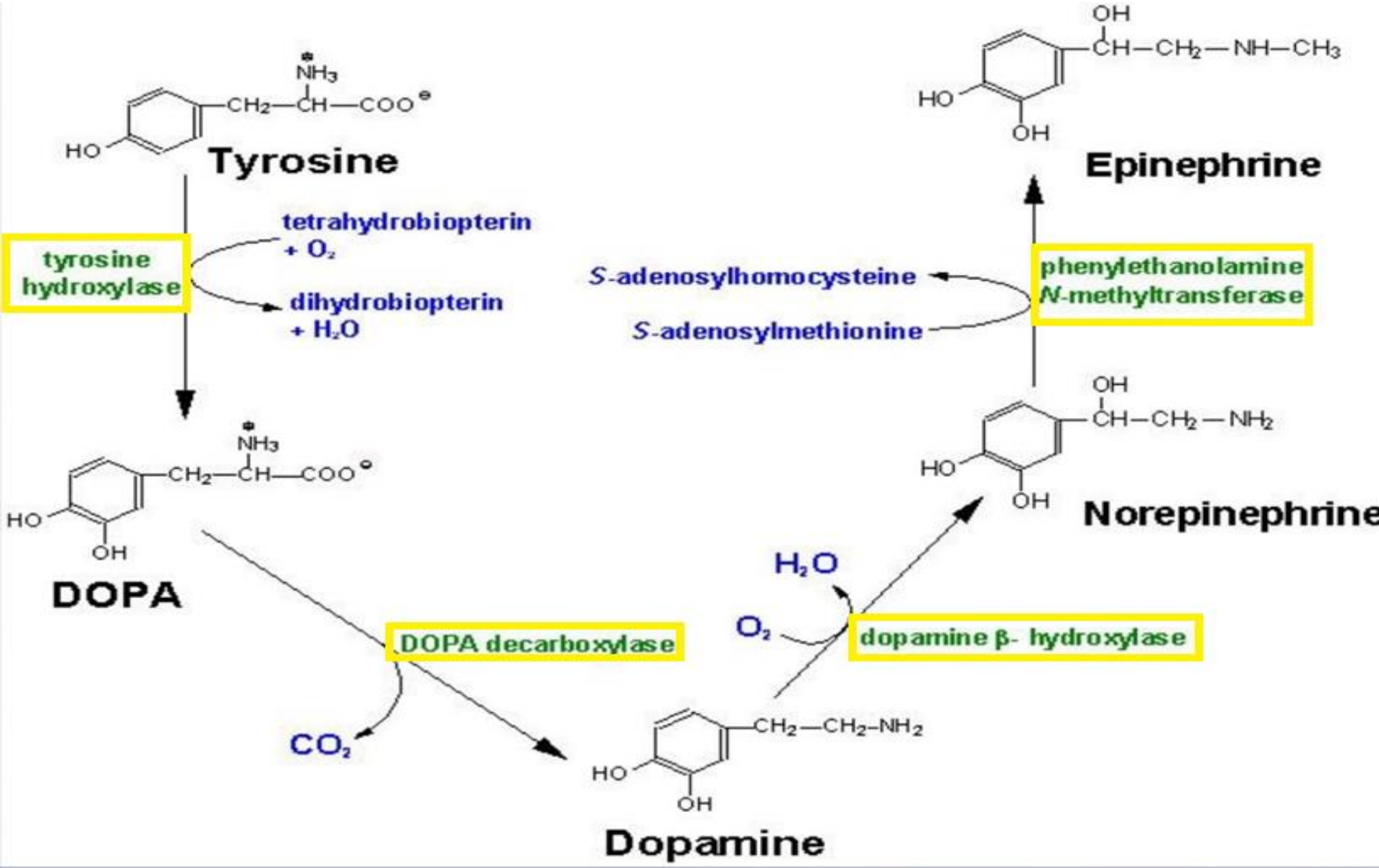
- Includes serotonin & the catecholamines (dopamine, epinephrine & norepinephrine)

- All catecholamines are synthesized from the amino acid, tyrosine.

Summary of Catecholamine Synthesis

- All catecholamines have a catechol nucleus & a 3,4-dihydroxylated benzene ring
- The 1st enzyme, tyrosine hydroxylase, converts tyrosine to L-dihydroxyphenylalanine (L-DOPA)
- L-DOPA is a precursor for all catecholamines
- The 2nd step converts L-DOPA to dopamine & CO_2
- The 3rd step converts dopamine to norepinephrine
- The 4 th step converts norepinephrine to epinephrine

Catecholamine Synthesis

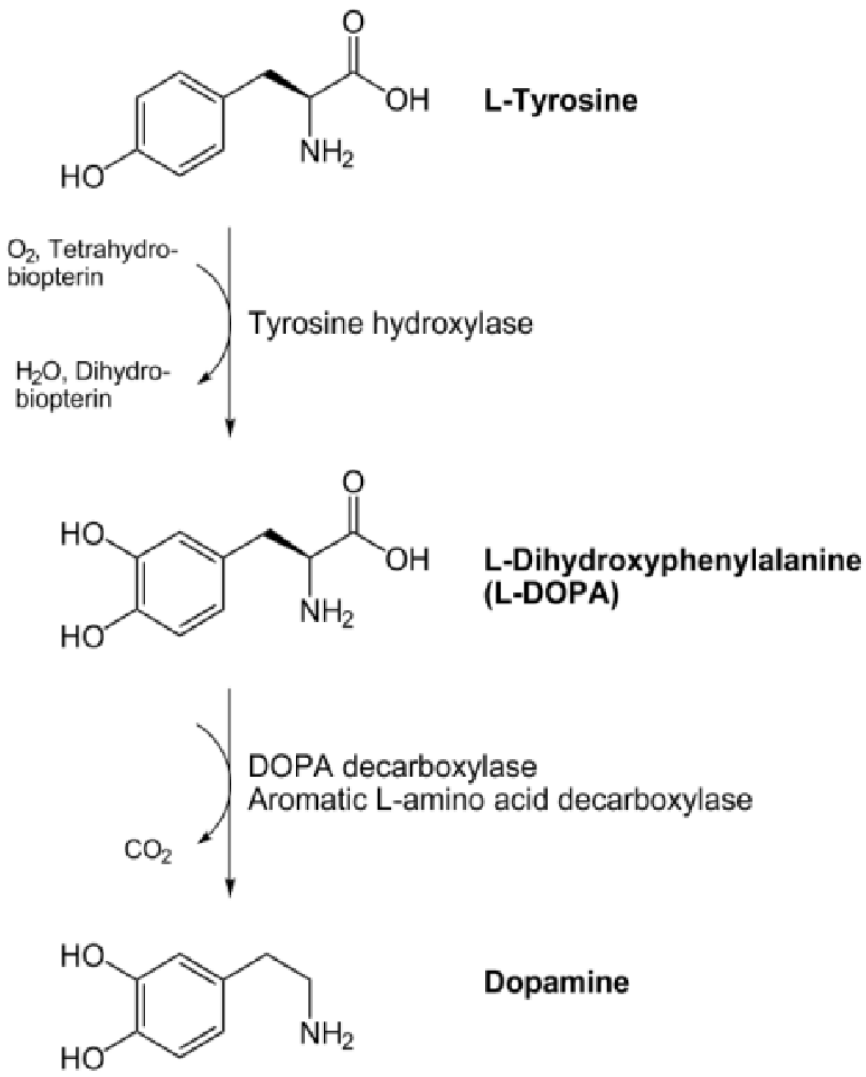


Epinephrine (adrenalin)

- Present in brain at lower levels than NE
- Adrenal production is part of stress response
- Adrenal gland is the primary source
- Formed by PNMT (phenylethanolamine-n-methyltransferase)
  - Endogenous cortisol increases PNMT

epinephrine & cortisol are the stress hormones.

Dopamine -



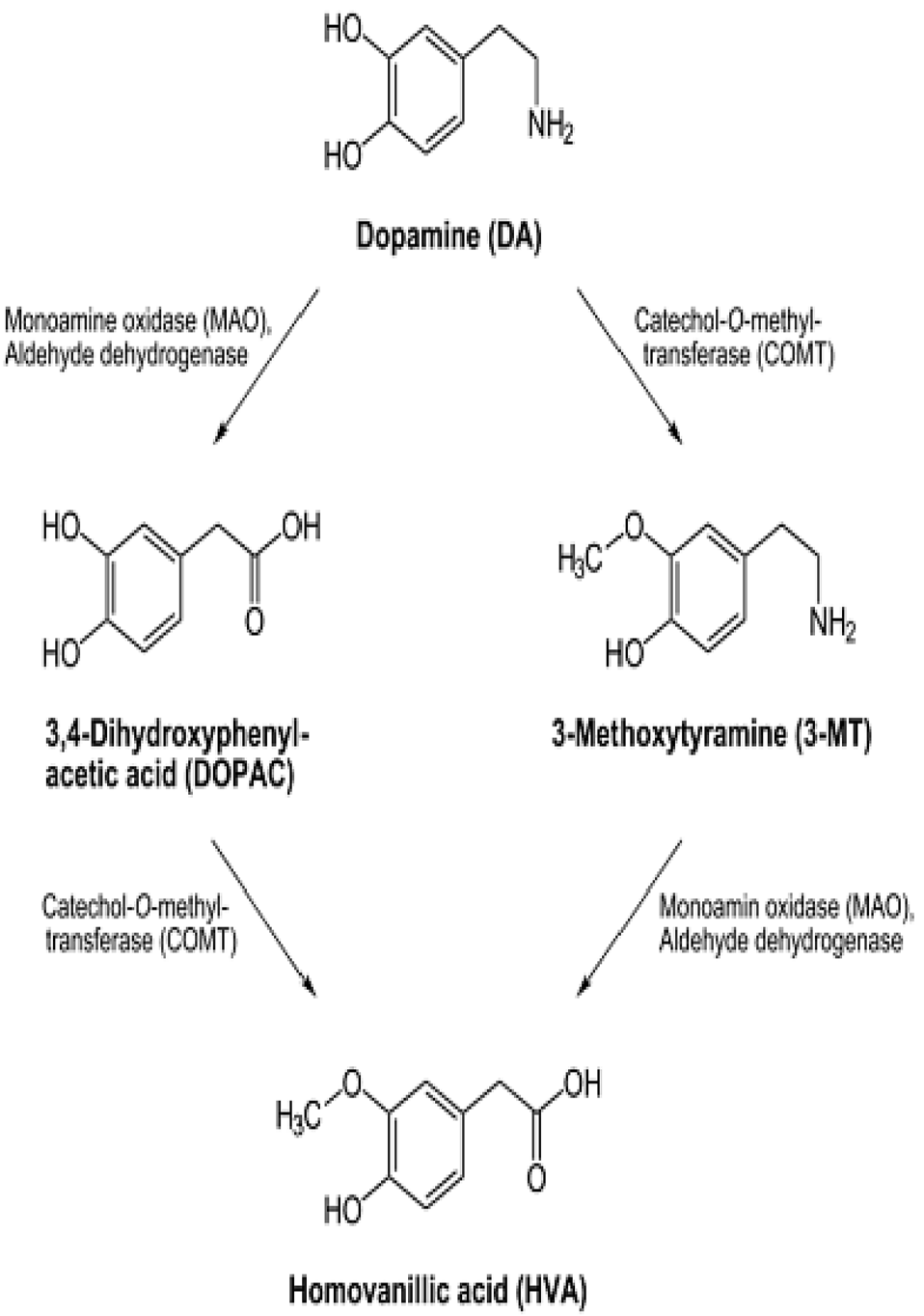
- DOPA is converted so rapidly into Dopamine that DOPA levels are negligible in the brain
- Rate of synthesis is regulated by
  - Catecholamine acting as inhibitor of TH
  - Availability of BH_4 (Tetrahydrobiopterin)
  - Presynaptic DA receptors
  - Amount of activity in nigrostriatal pathway

Metabolism

- In primates and human
– HVA major metabolite
- Accumulation of HVA in brain or CSF used as index of function of dopaminergic neurons

- One of the causes of hypertension is: pheochromocytoma
- The diagnostic test for this tumor is : 24-hour urine collection for the end product ⟶ HVA.

(for primary or unknown cause of hypertension)



Removal of Catecholamines

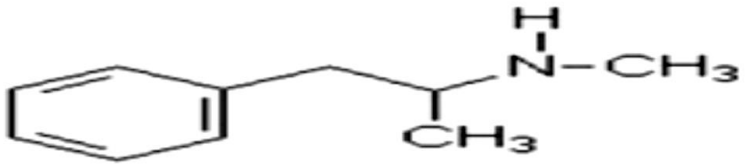
- All three catecholamines are removed by selective reuptake by the presynaptic axon terminals
- They are either reused or degraded by monoamine oxidase (MAO)
- Amphetamines and cocaine block the reuptake of catecholamines, thereby prolonging their synaptic action

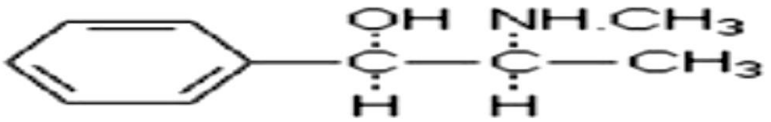
to stay awake for 24 to 36 hours (especially amphetamines.)

Close Cousins?

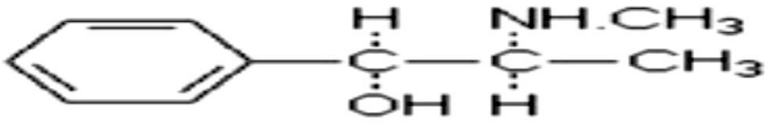
Amphetamine

Methamphetamine





Ephedrine



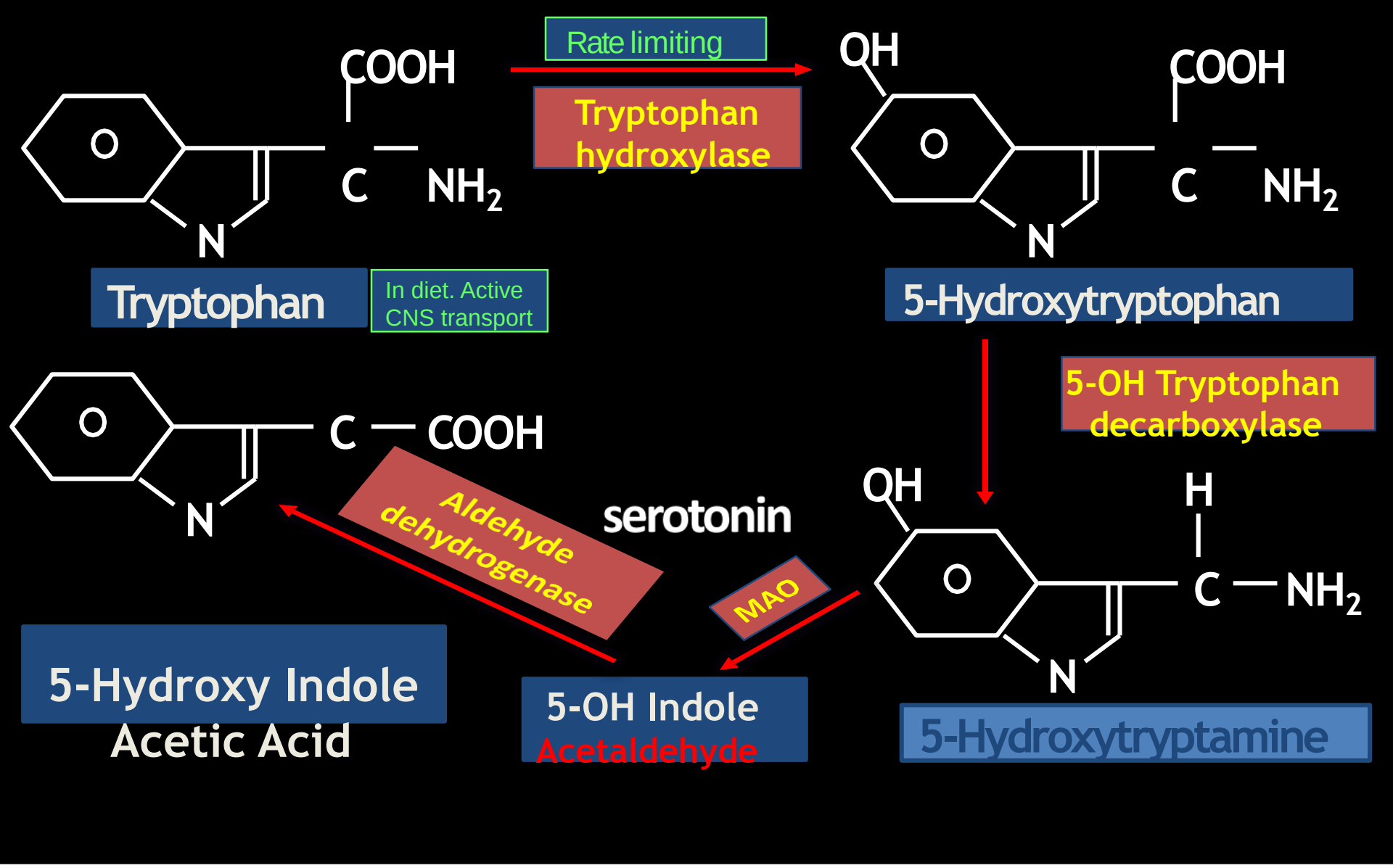
Pseudoephedrine

*All of these are stimulants (sympathomimetics) found in energy drinks.

Serotonin

Found in banana and milk

- Derived from the amino acid, tryptophan
  - Belongs to a group of compounds called indoles
  - Serotonergic neurons are found in the brainstem
  - Involved in regulating attention & other complex functions



5-hydroxy indole acetic acid an end product in tryptophan metabolism & also used for 24-hour urine collection … INDICATION FOR SERATONIN

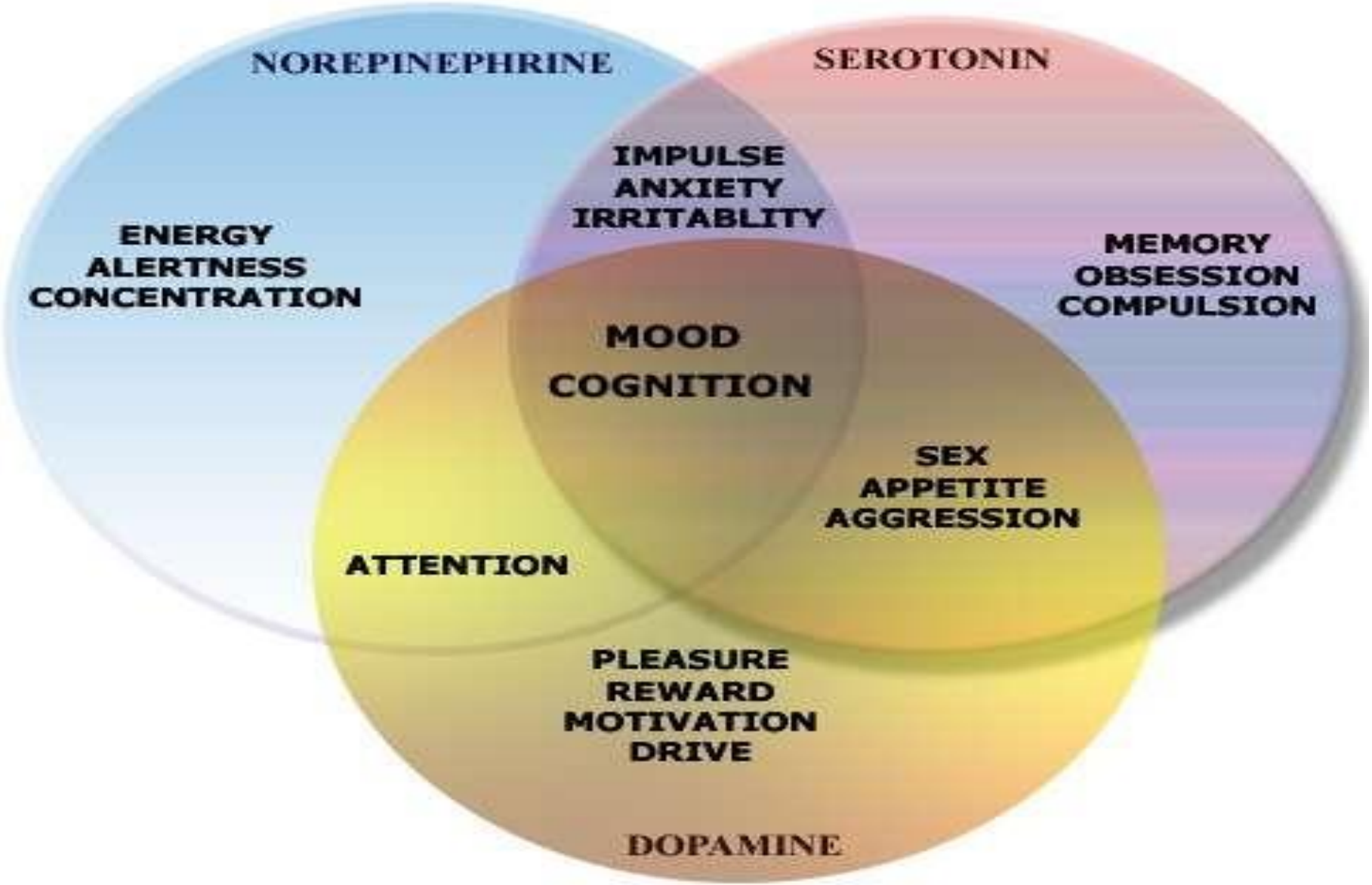
Serotonergic Neurons

- Use serotonin (5-HT) as a neurotransmitter
  - Because tryptophan comes from the diet, serotonergic neurons can be quickly affected by dietary deficiencies in tryptophan
- Removal:

– Selective reuptake by the presynaptic axon terminals

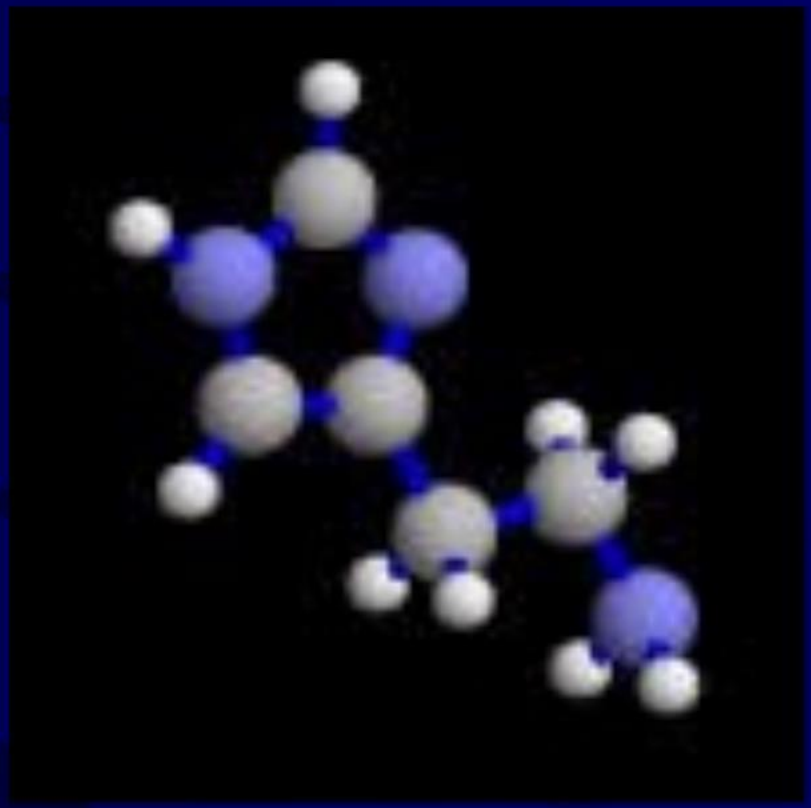
– Either reused or degraded by MAO

Amine Neurotransmitters



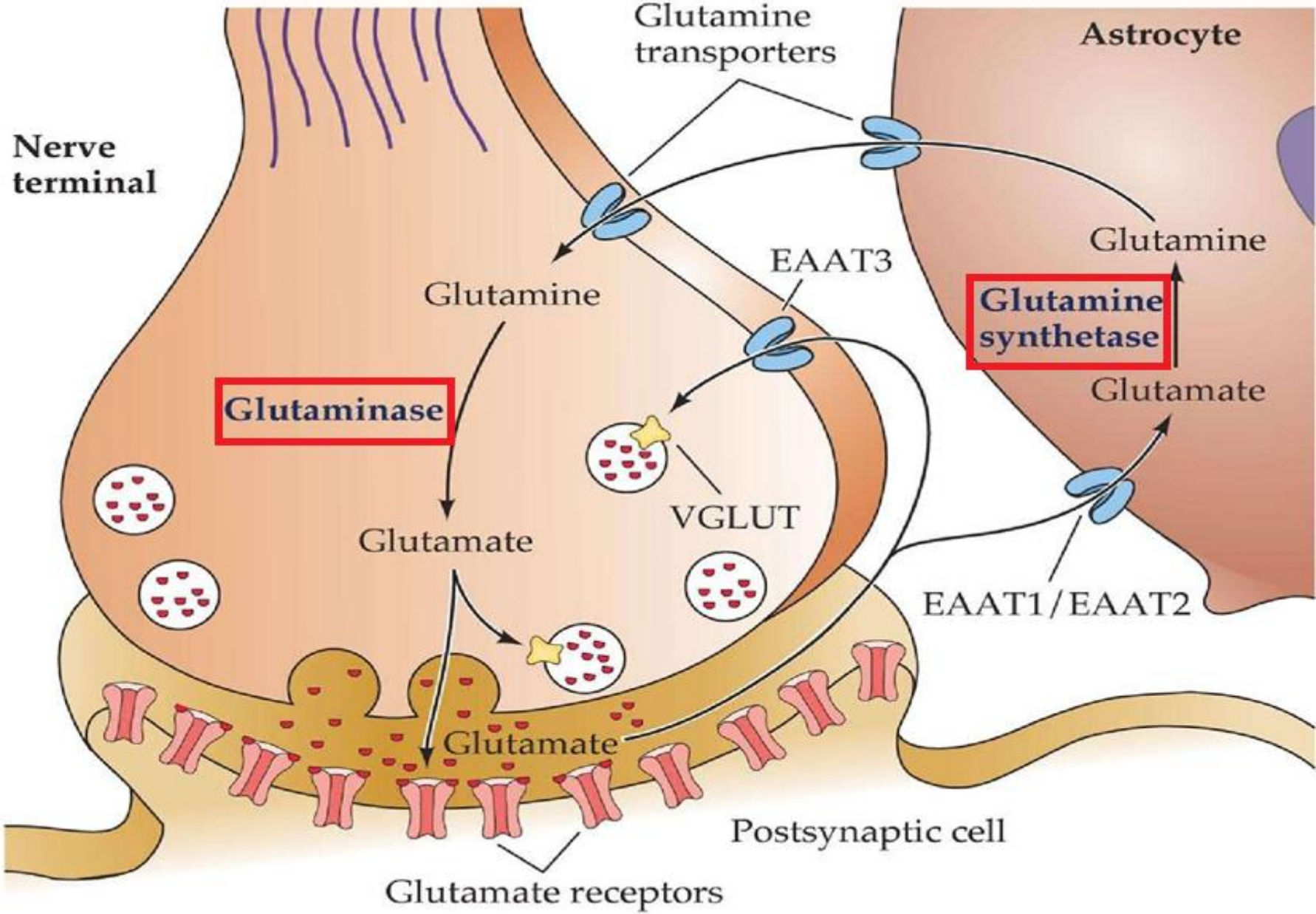
Histamine

- Acts as a local hormone (autocoid)
  - Involved in control of blood vessels*Vasodilator, inflammatory response, etc.
  - Also acts as a neurotransmitter in invertebrates

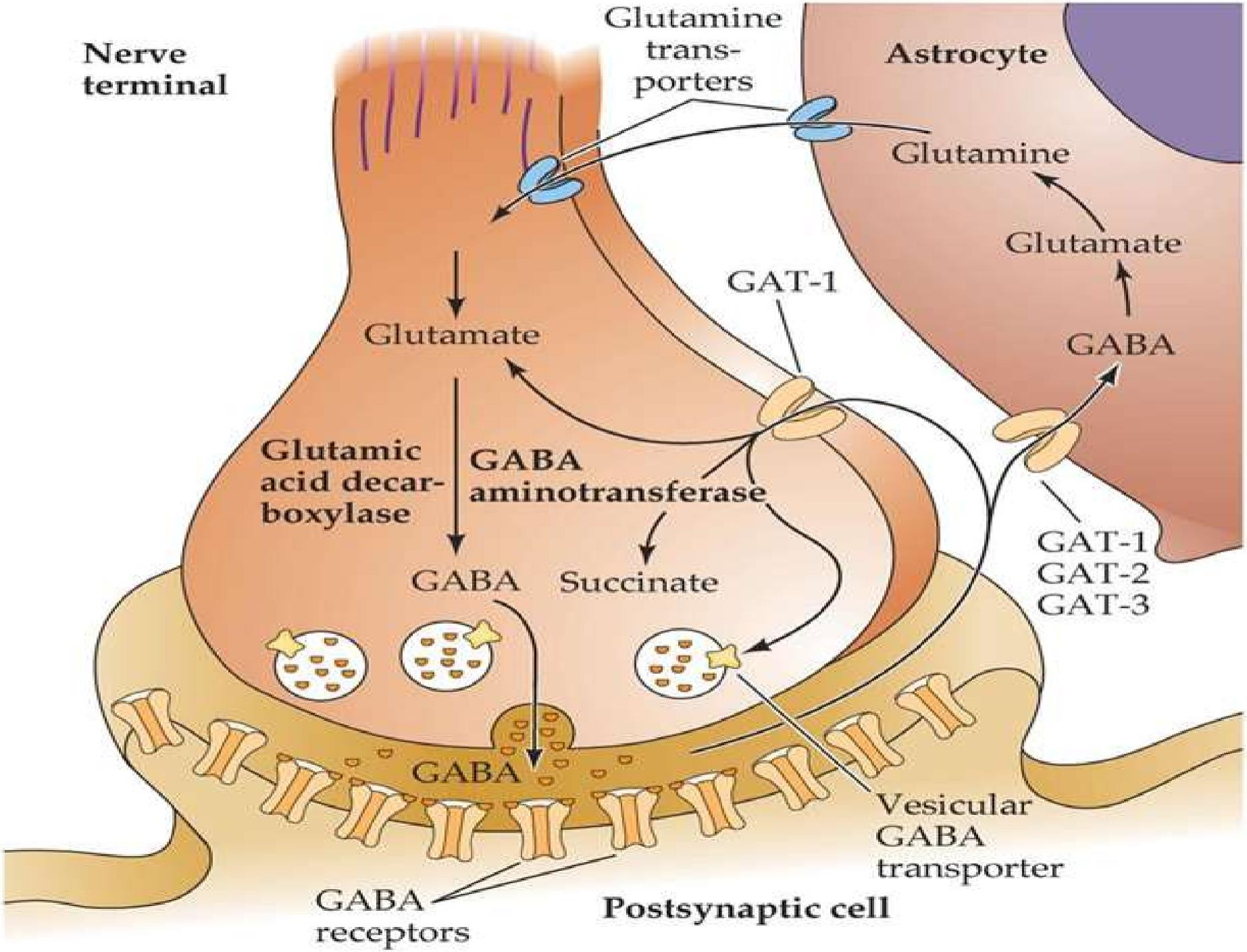


Amino Acid Transmitters

- Unlike acetylcholine & biogenic amines, these are universal parts of cells
- Glycine & glutamate are common parts of proteins
- GABA
  - is synthesized from glutamate
  - is a major inhibitory transmitter at many sites in brain
- Common amino acids act as transmitters in some neurons, not in others



Excitatory amino acid transporter 2 (EAAT2)


Nerve terminal
Glutamine trans-porters
Astrocyte
Glutamine
Glutamate
GAT-1
GABA
Glutamate
Glutamic acid decar-boxylase
GABA aminotransferase
GAT-1
GAT-2
GAT-3
GABA
Succinate
GABA
Vesicular GABA transporter
GABA receptors
Postsynaptic cell

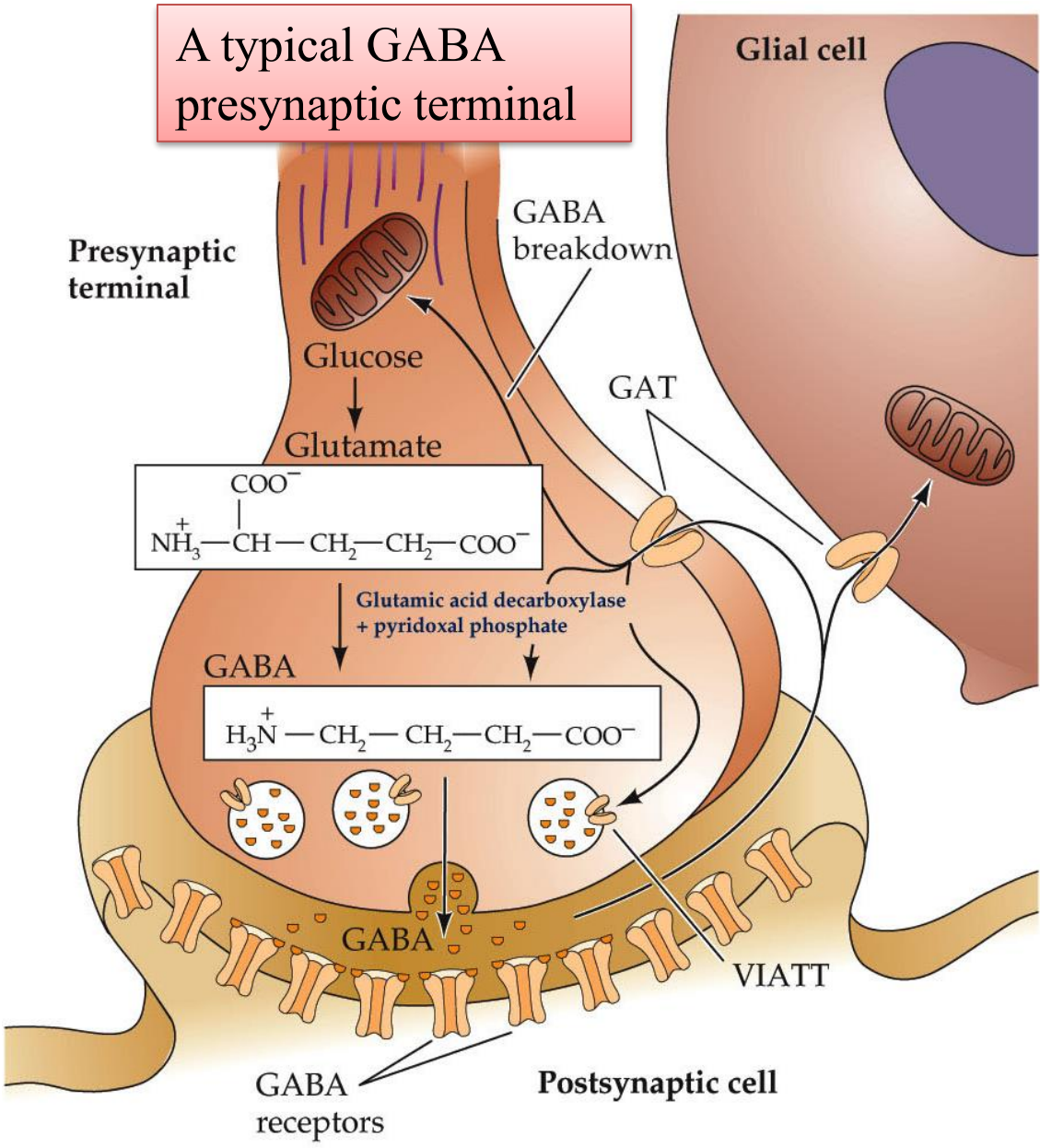
Whereas glutamate is the principal excitatory neurotransmitter, GABA is the principal inhibitory neurotransmitter in the brain

GABA aminotransferase needs pyridoxal phosphate as a co-enzyme.

GABA overlaps with succinate and alpha ketoglutarate

succinate & alpha ketoglutarate → parts of CAC

glucose is precursor of glutamate & glutamine



Summary of GABA synthesis, release, reuptake, degradation

1. GABA is formed by removal of carboxyl group of glutamate, by the enzyme GAD
2. GABA is packaged into synaptic vesicles by VIAAT and released by depolarization
3. GABA may be taken up by nerve terminal by GAT proteins for repackaging into synaptic vesicles
4. GABA may be taken up by glial cells, where it undergoes reconversion to glutamate (amine group is transferred to α-ketoglutarate, generating glutamate and succinic semialdehyde)
5. Glutamate is transported back into nerve terminal, where it serves as precursor for new GABA synthesis

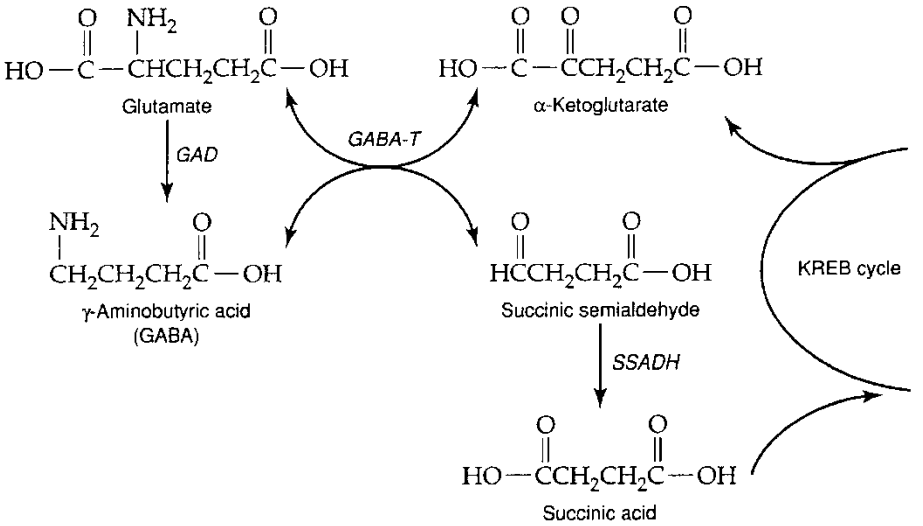
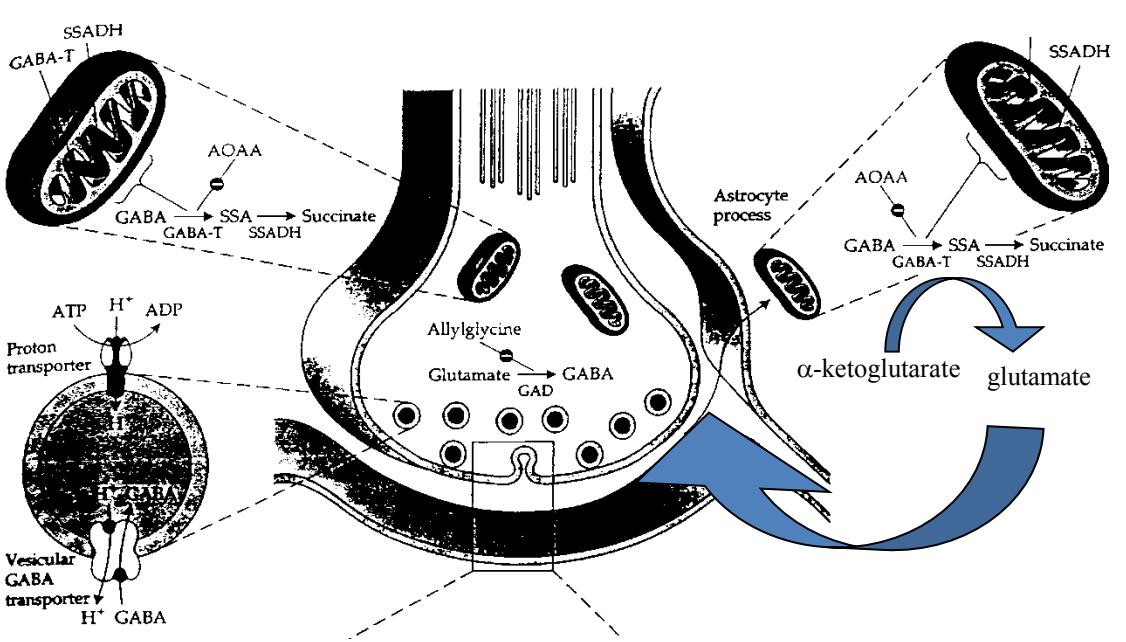
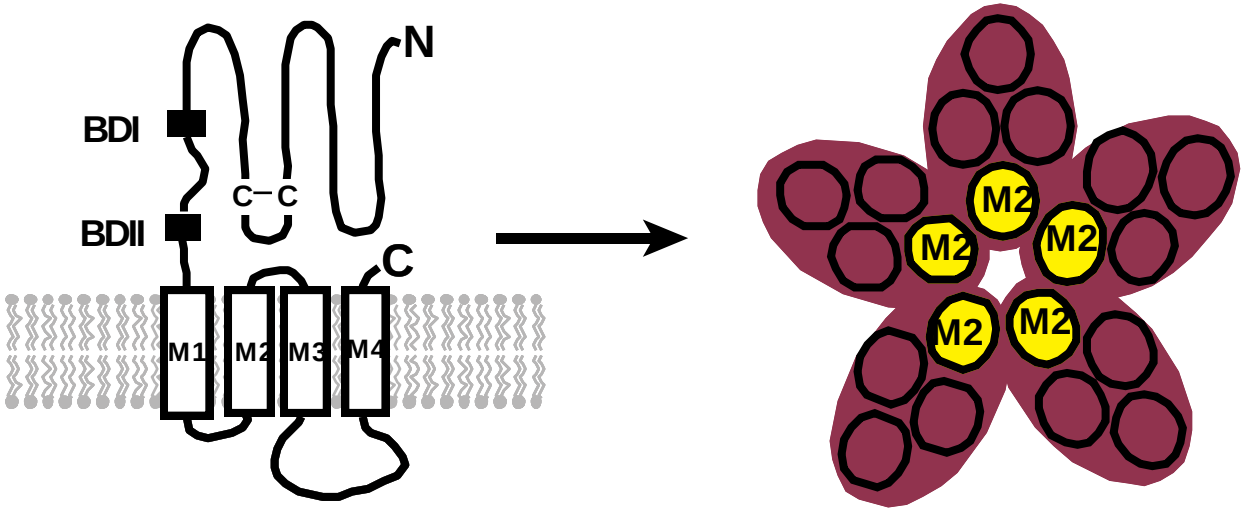


Figure 7–8. The GABA shunt. This metabolic pathway traces the synthesis and degradation of the neurotransmitter pool of GABA. GAD, glutamic acid decarboxylase; GABA-T, GABA transaminase; SSADH, succinic semialdehyde dehydrogenase.

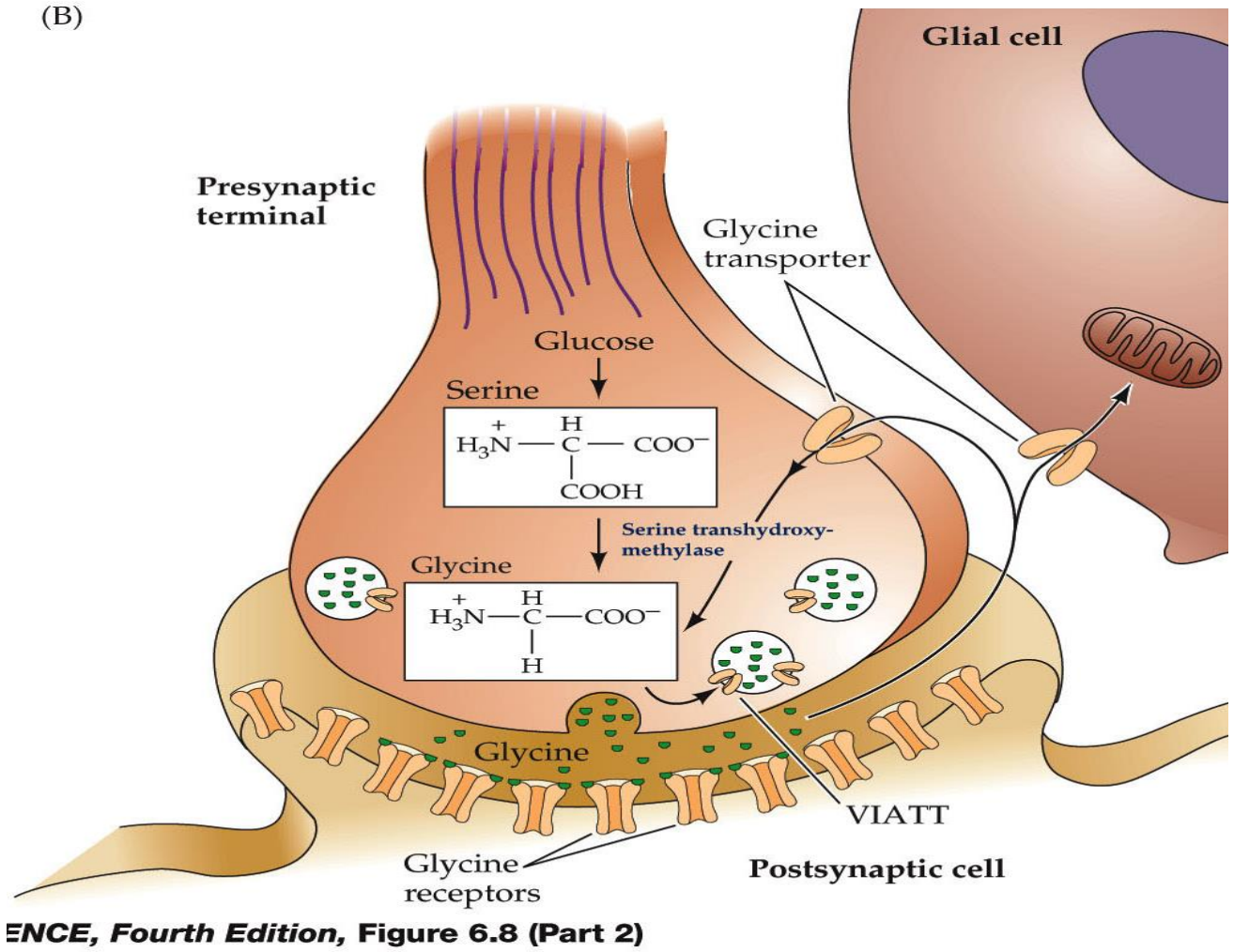


Pentameric structure of $GABA_A$ receptors



$GABA_A$ receptors belong to the 'ligand-gated ion channel superfamily', which also includes nicotinic acetylcholine receptors, glycine receptors, and the 5-HT_3 serotonin receptor.

Glycine neurotransmission



ENCE, Fourth Edition, Figure 6.8 (Part 2)

vesicular inhibitory amino acid transporter, VIAAT

Summary of Glycine synthesis, release, reuptake, degradation

1. Glycine is synthesized from serine by SHMT
2. Glycine is packaged into synaptic vesicles by VIAAT (same transporter as for GABA)
3. Glycine is removed from synapse by GLYT1 (glial, for clearance from synapse), and GLYT2 (neuronal, for re-uptake and packaging).
4. Glycine is cleaved by the glycine cleavage system

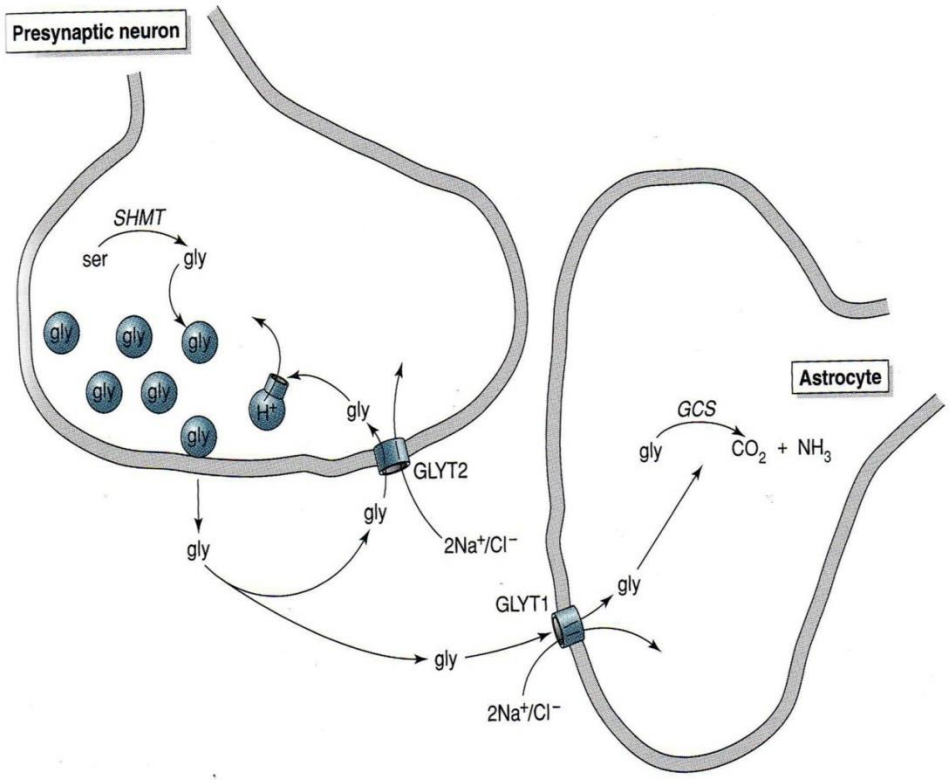


Figure 7–11. Synthesis and metabolism of the neurotransmitter pool of glycine. Serine (ser)

GCS: glycine cleavage system

Consists of 4 proteins

T protein
L protein
H protein
P protein

Transmitter Binding

- The same transmitter can bind different receptors, resulting in different actions.
- Receptor binding determines the effect, not the transmitter itself.
- In related animals, each type of transmitter binds to a family of receptors and is associated with certain functions
- Example: acetylcholine = synaptic excitation at neuromuscular junctions in vertebrates

Transmitter Binding