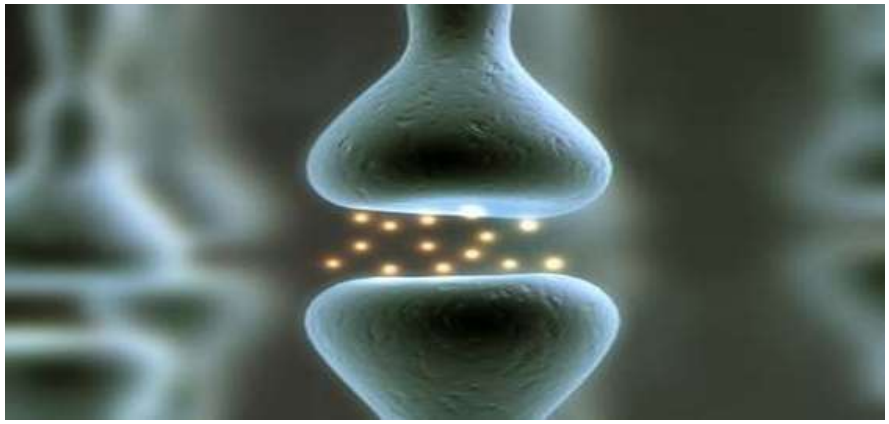
NEUROTRANSMITTERS



DR/ HEBA M. KAREEM

INTRODUCTION

Neurotransmitters are chemical messengers that transmit signals from a neuron to a target cell across a **synapse**.

Target cell may be a neuron or some other kind of cell like a muscle or gland cell.

Necessary for rapid communication in synapse.
Neurotransmitters are packaged into **synaptic vesicles** - presynaptic side of a synapse.

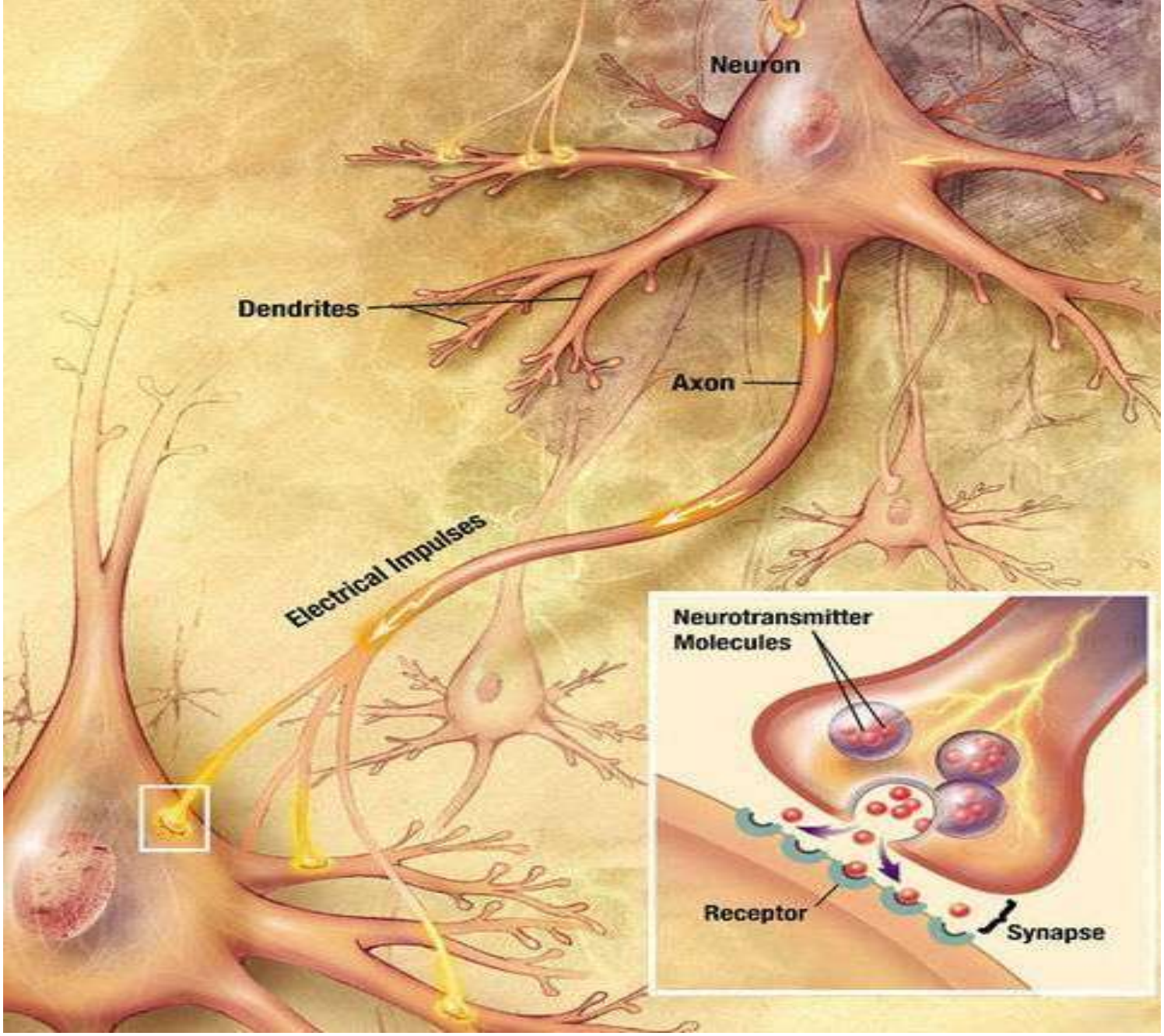
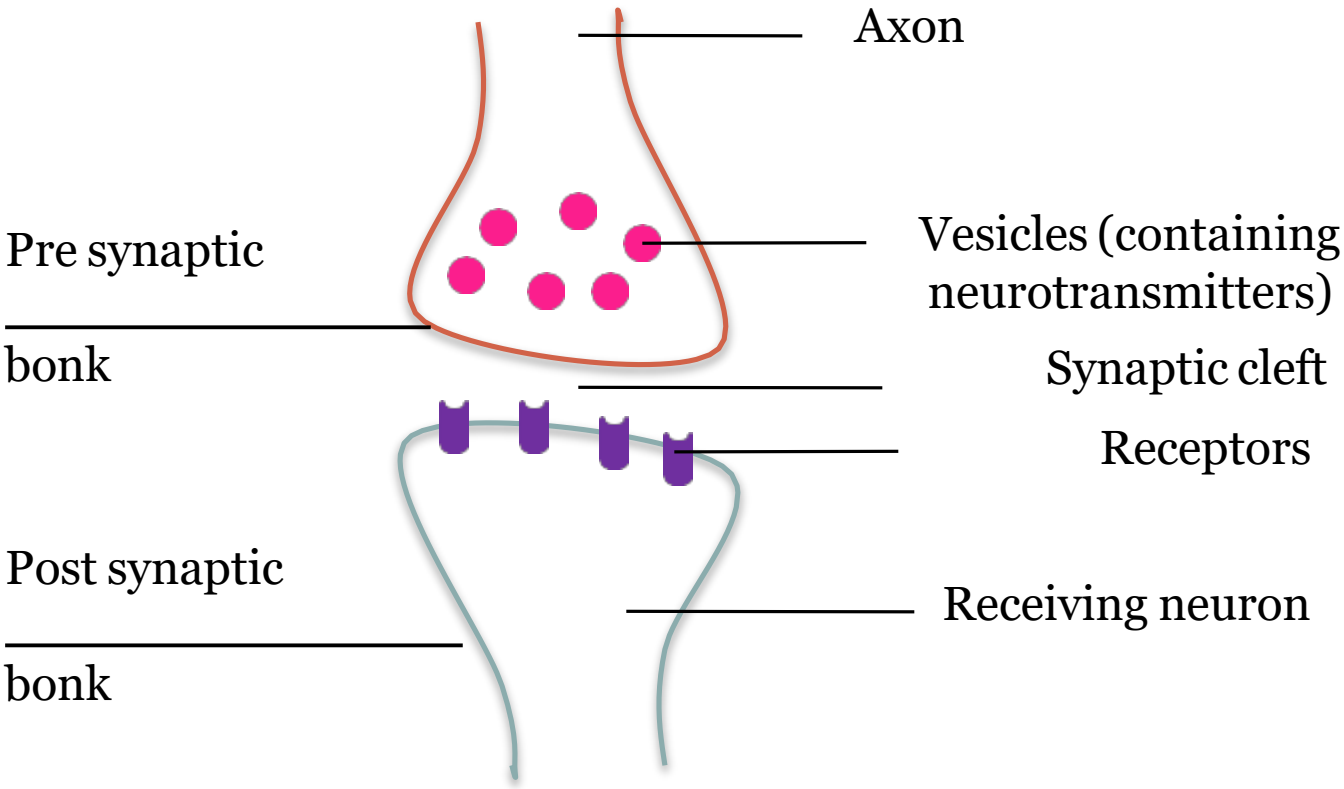


Illustration of the major elements in chemical synaptic transmission.

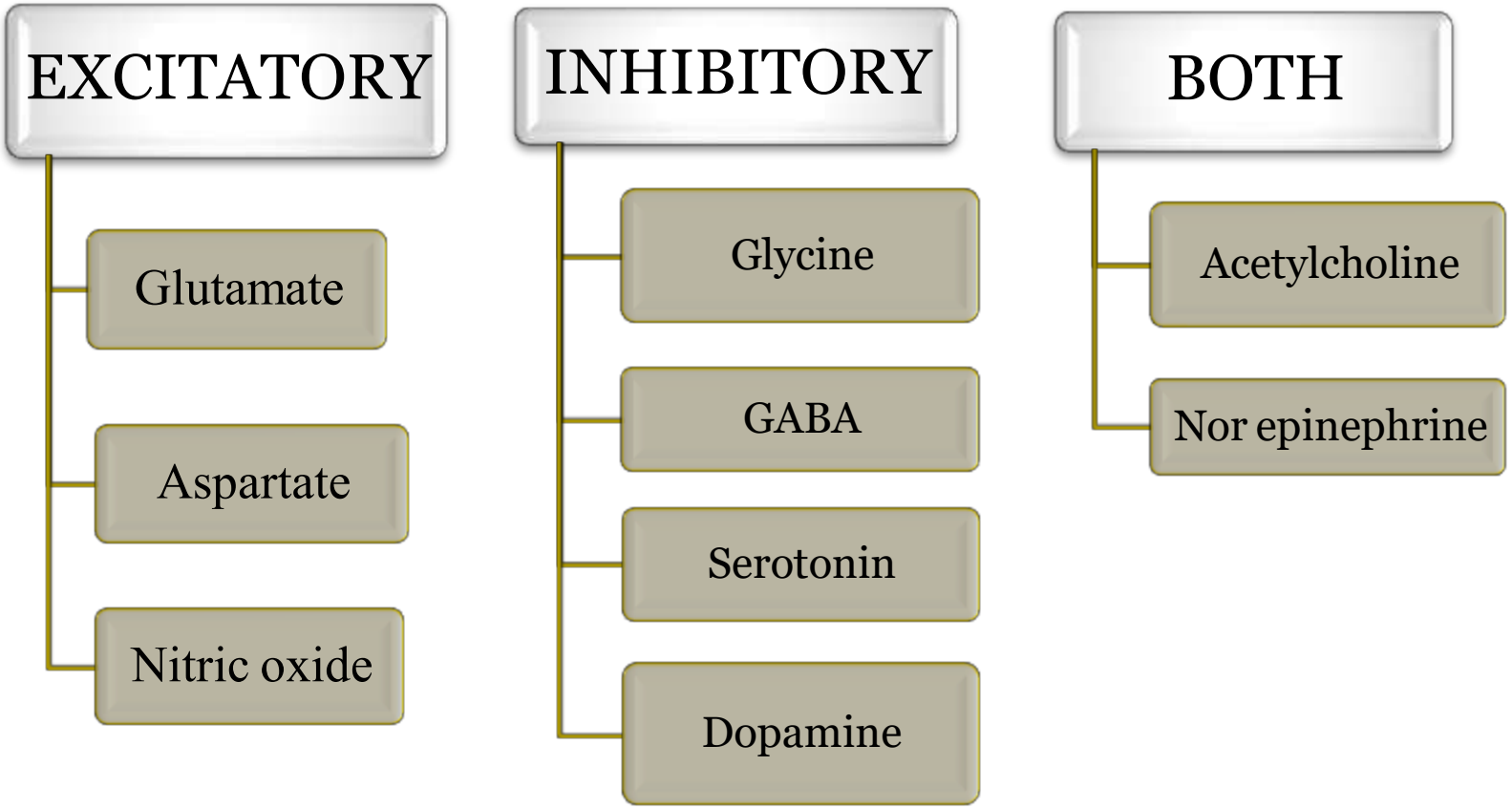
A schematic representation of a chemical synapse



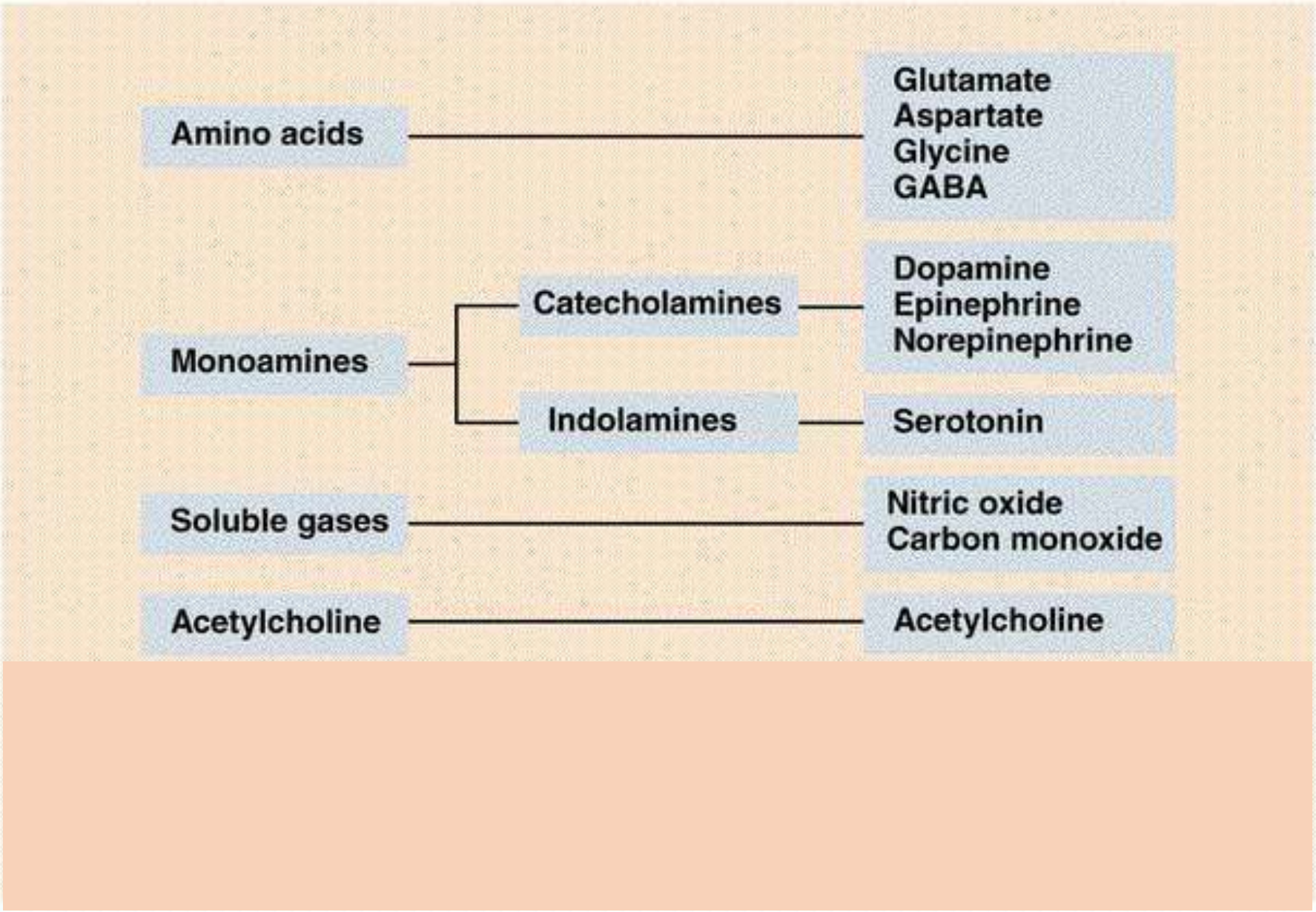
PROPERTIES OF NEUROTRANSMITTERS

1) Synthesized in the presynaptic neuron
2) Localized to vesicles in the presynaptic neuron
3) Released from the presynaptic neuron under physiological condition
4) Rapidly removed from the synaptic cleft by uptake or degradation
5) Presence of receptor on the post-synaptic neuron.
6) Binding to the receptor elicits a biological response

TYPES OF NEUROTRANSMITTERS

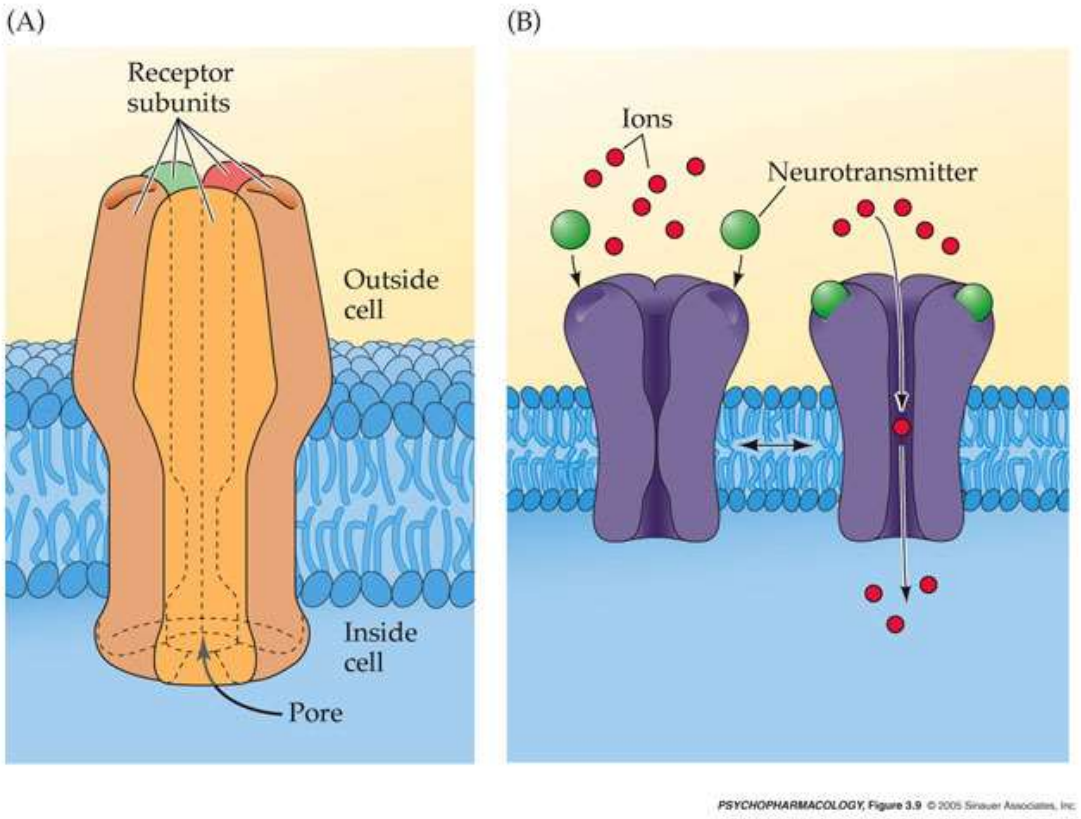


▶ Classes of Neurotransmitters



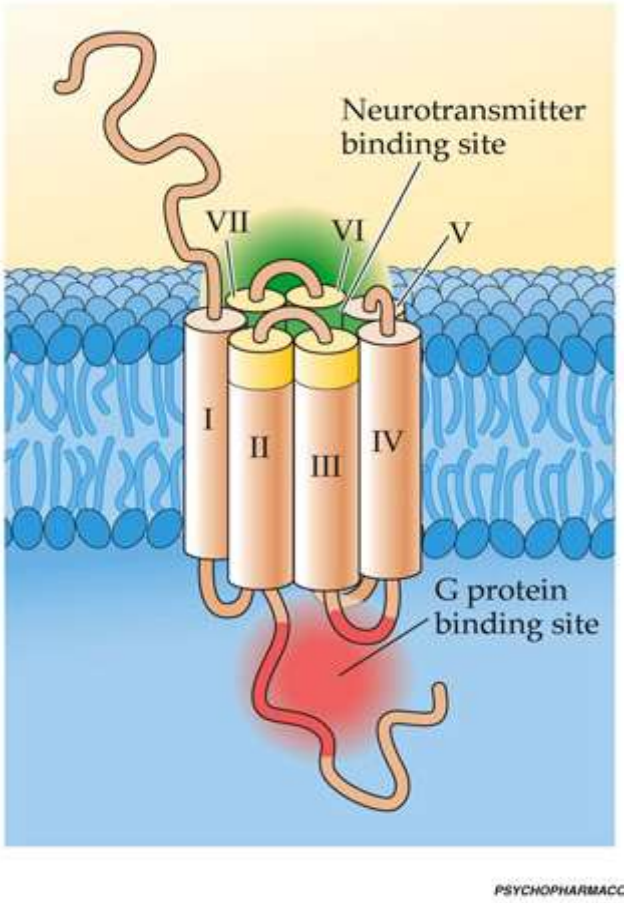
Receptors of neurotransmitters

A- Ionotropic Receptors



1. Work very fast; important role in fast neurotransmission
2. Each is made of several subunits (together form the complete receptor)
3. At center of receptors is channel or pore to allow flow of neurotransmitter
4. At rest - receptor channels is closed
5. When neurotransmitter bind -- channel immediately opens
6. When ligand leaves binding site -- channel quickly closes

B- Metabotropic Receptors



1. Work more slowly than ionotropic receptors
2. Comprise a single protein subunit, winding cell membrane seven times (**transmembrane domains**)
3. They do not possess a channel or pore

MODE OF ACTION

▶ Seven Processes in Neurotransmitter Action

1.Neurotransmitters are synthesized from precursors under the influence of enzymes

2.Stored in vesicles

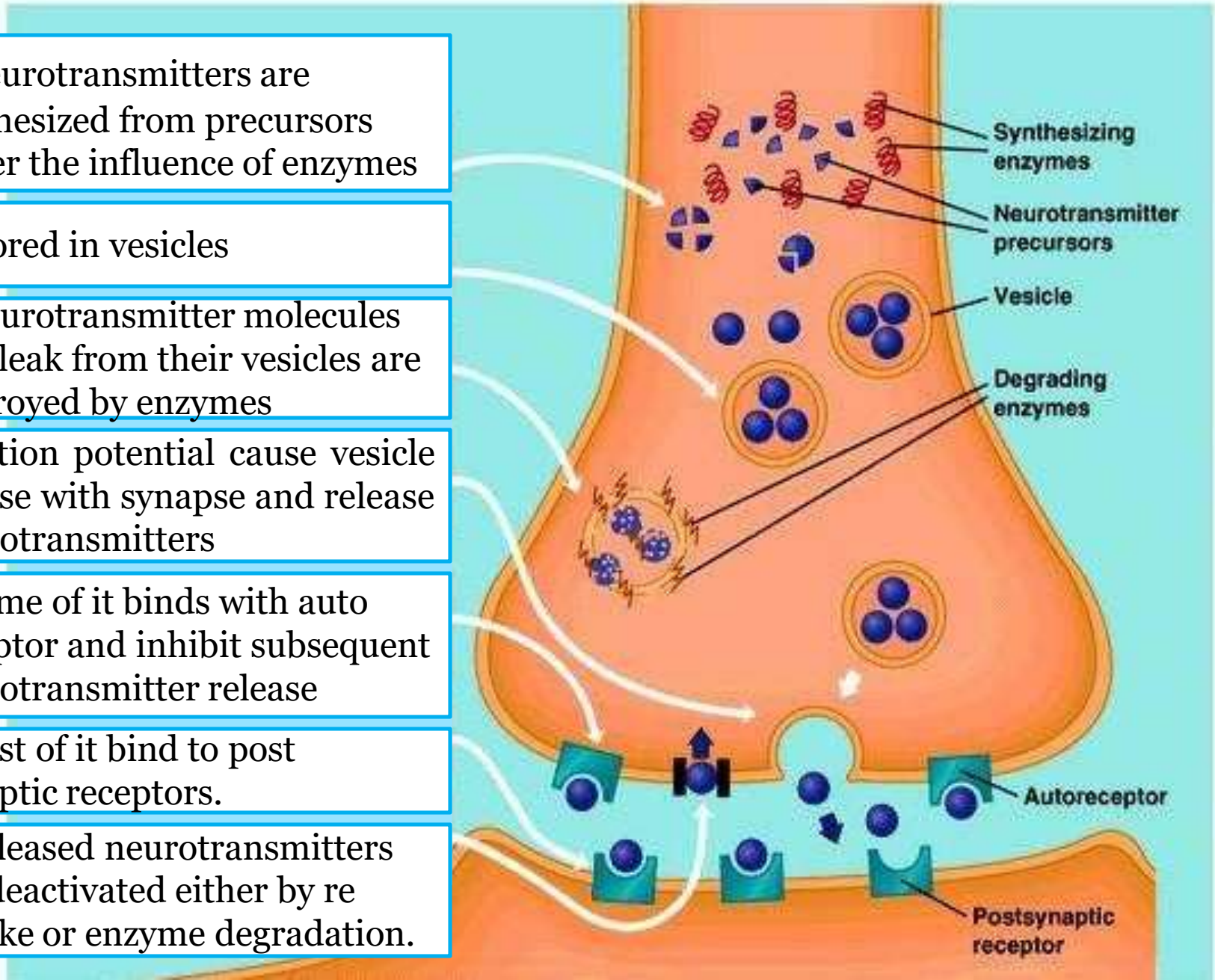
3.Neurotransmitter molecules that leak from their vesicles are destroyed by enzymes

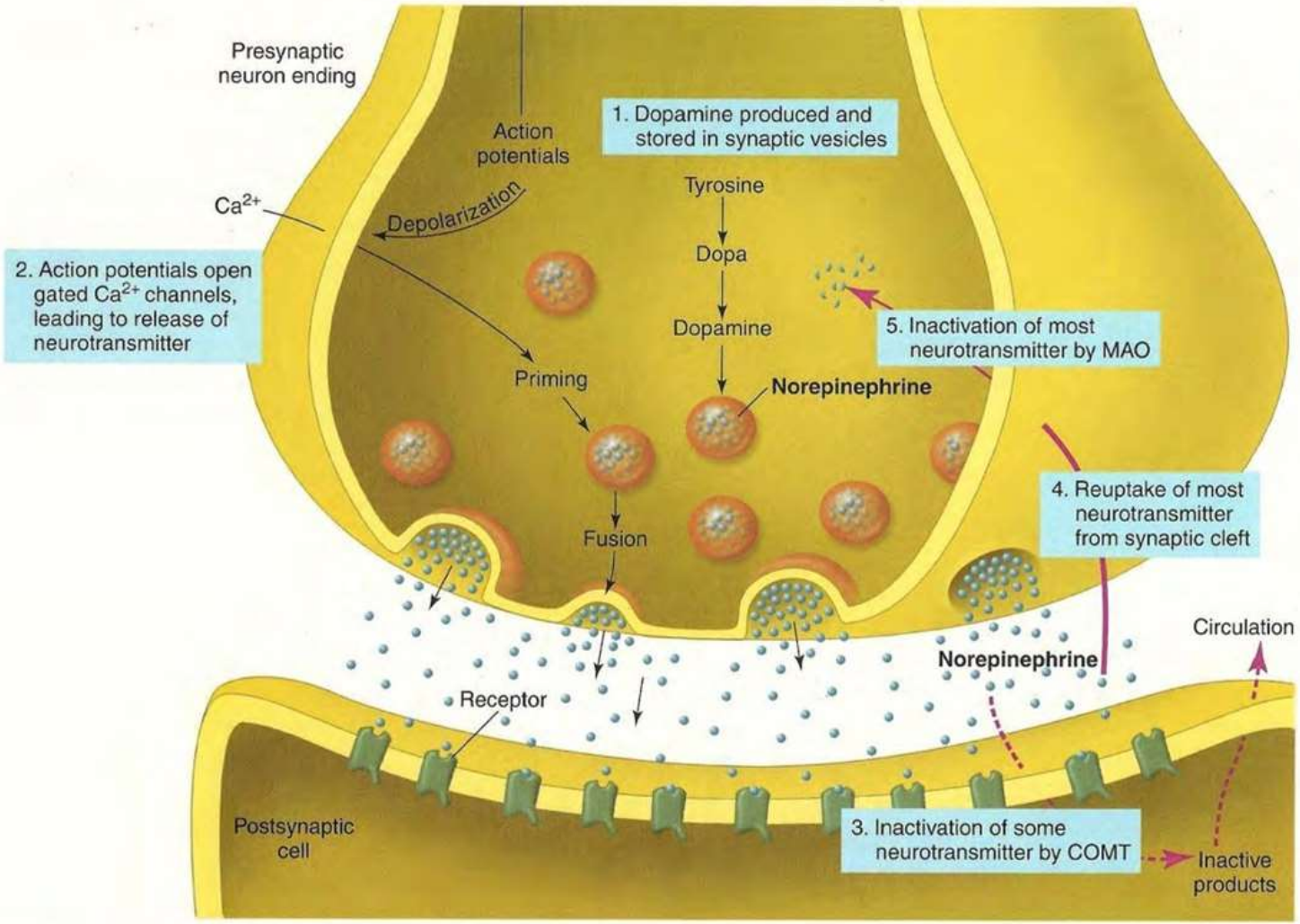
4.Action potential cause vesicle to fuse with synapse and release neurotransmitters

5.Some of it binds with auto receptor and inhibit subsequent neurotransmitter release

6.Rest of it bind to post synaptic receptors.

7.Released neurotransmitters are deactivated either by re uptake or enzyme degradation.





69 **Release and Reuptake of NE**
Figure 7.28

Steps in neurotransmitter processing are:

Synthesis: Neurotransmitters are synthesized by the enzymatic transformation of precursors.

Storage: They are packaged inside synaptic vesicles.

Release: They are released from presynaptic terminal by exocytosis when calcium enters axon terminal during an action potential

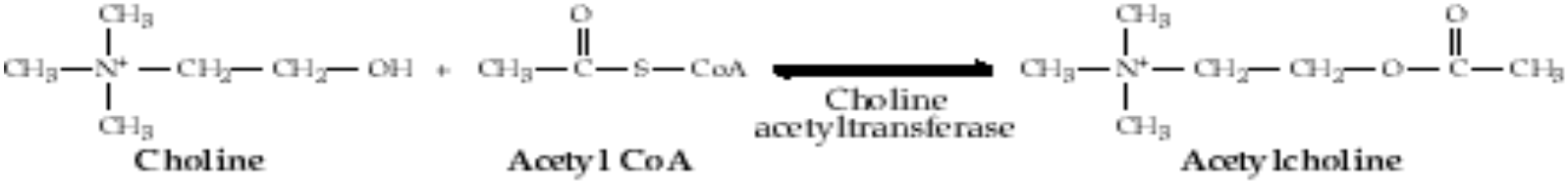
Diffuse across the synaptic cleft to the postsynaptic membrane.

Binding: They bind to receptor proteins.

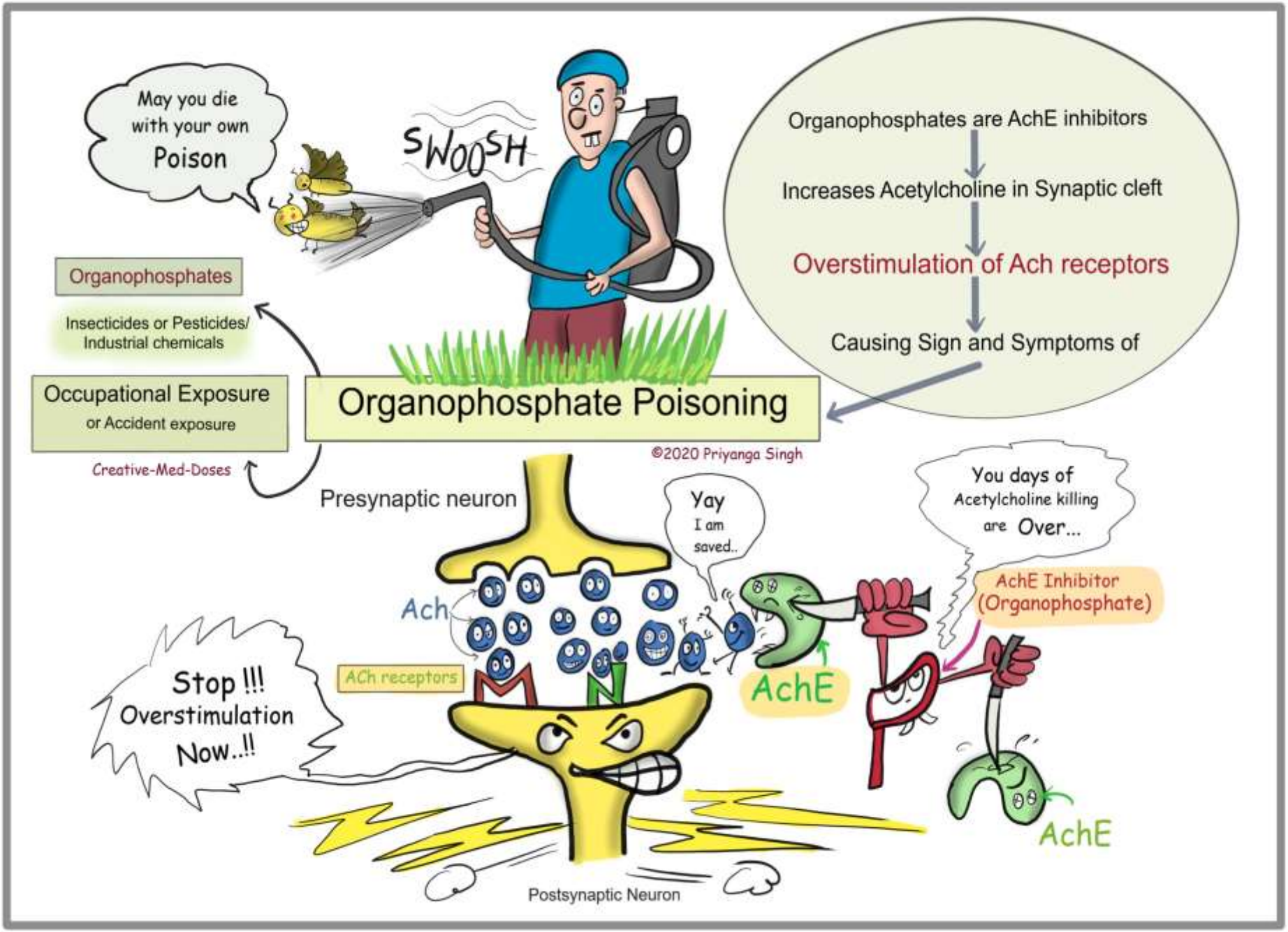
Inactivation: The neurotransmitter is degraded either by being broken down enzymatically, or reused by active reuptake.

ACETYLCHOLINE (ACH)

- Acetylcholine was the first neurotransmitter to be discovered.
- 1921 by a German biologist named **Otto Loewi**.



- -Uses *choline* as a precursor - **cholinergic** neurotransmitter.
- -Used by the Autonomic Nervous System, as an inhibitory neurotransmitter.
- -Responsible for stimulation of muscles, including the muscles of the gastro-intestinal system. -Used everywhere in the brain.
- -Related to **Alzheimer's Disease.** Acetylcholine is decreased in both concentration and function in patients with Alzheimer's disease.
- Too much: muscle contractions- e.g. organophosphorus (OP) poisoning
- Too little: paralysis: curarae and botulism toxin


May you die with your own Poison
SWOOSH
Organophosphates are AchE inhibitors
Increases Acetylcholine in Synaptic cleft
Overstimulation of Ach receptors
Causing Sign and Symptoms of
Organophosphates
Insecticides or Pesticides/ Industrial chemicals
Occupational Exposure
or Accident exposure
Creative-Med-Doses
Organophosphate Poisoning
©2020 Priyanga Singh
Presynaptic neuron
Yay I am saved..
You days of Acetylcholine killing are Over...
AchE Inhibitor (Organophosphate)
Ach
ACh receptors
AchE
Stop !!! Overstimulation Now..!!
AchE
Postsynaptic Neuron

Organophosphate Poisioning

Muscarinic
Overstimulation

Musc leaks from Everywhere

Nicotinic
Overstimulation

Nics give
Tension, weakness and Paralysis

HyperTension and Muscle weakness

- Salivation
- Lacrimation
- Urination
- Defecation
- GI cramps
- Emesis

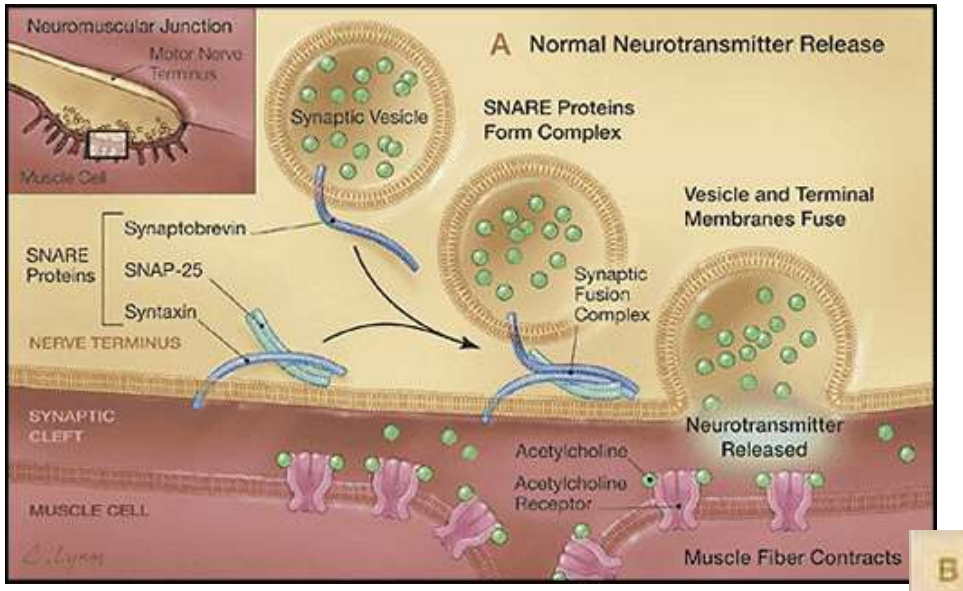
Mydriasia Tachycardia (MT)

Muscle Weakness, Twitching, Fasciculation (WTF)

High BP, Paralysis

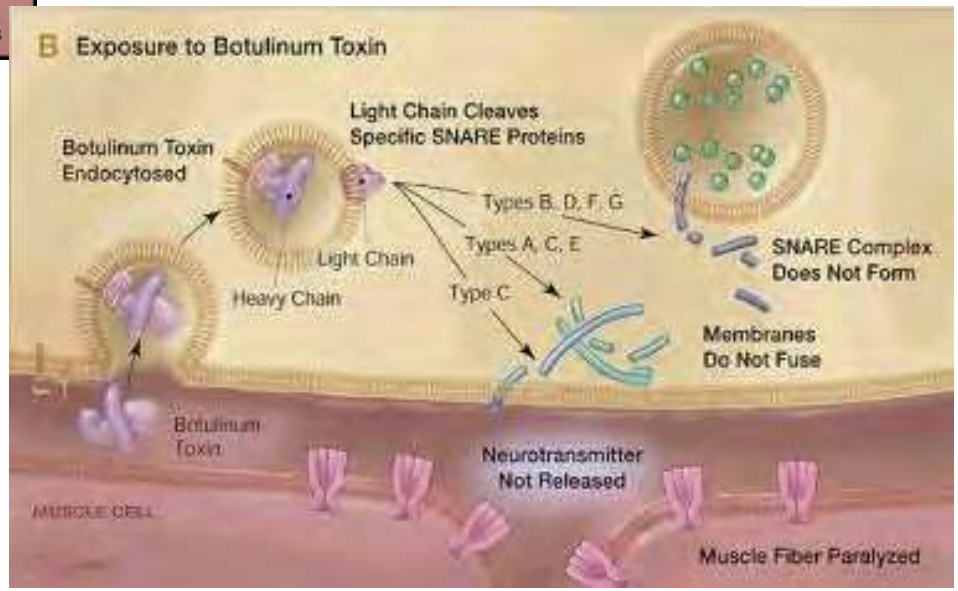
Creative-Med-Doses

Botulism: Acetylcholine vesicles can't release



http://www.247wellness.org/botulism/

Botulism causes paralysis because it prevents the release of acetylcholine (necessary for muscle contraction)



Acetylcholine

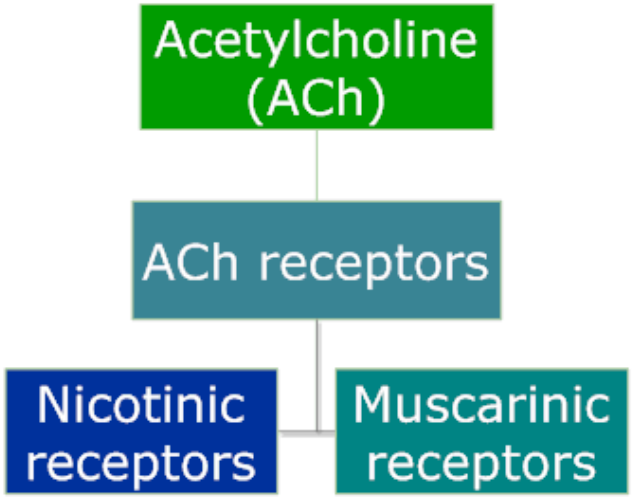
Synthesis

Acetyl CoA + Choline → (Choline Acetyltransferase (ChAT)) → CoA + ACh

Removal

Ach → (Acetylcholine Esterase (AChE)) → Acetate + Choline

- 2 receptor types
  - Nicotinic (ionotropic): Excitatory; found predominately on neuromuscular junctions
  - Muscarinic (metabotropic) :Both excitatory and Inhibitory; found predominately in brain



Monoamines

They are neurotransmitters and neuromodulators that contain one amino group connected to an aromatic ring by a two-carbon chain (such as -CH2-CH2-).

- Catecholamines

  Dopamine - DA
  - Dopaminergic

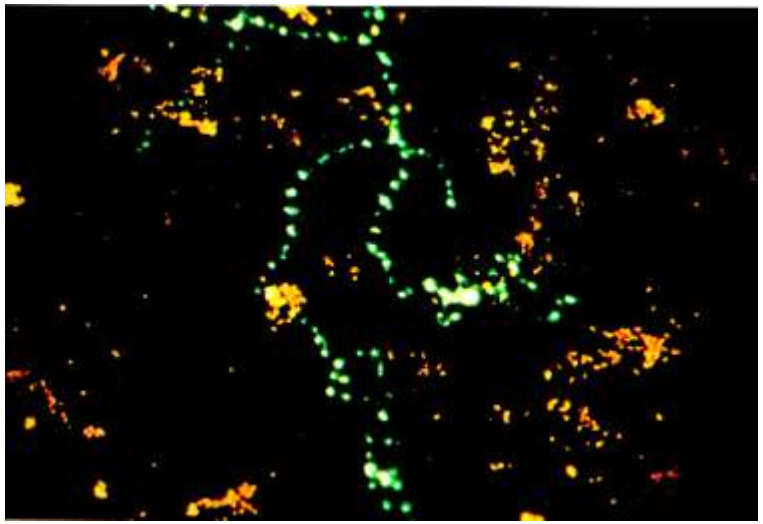
  Norepinephrine - NE
  - Noradrenergic

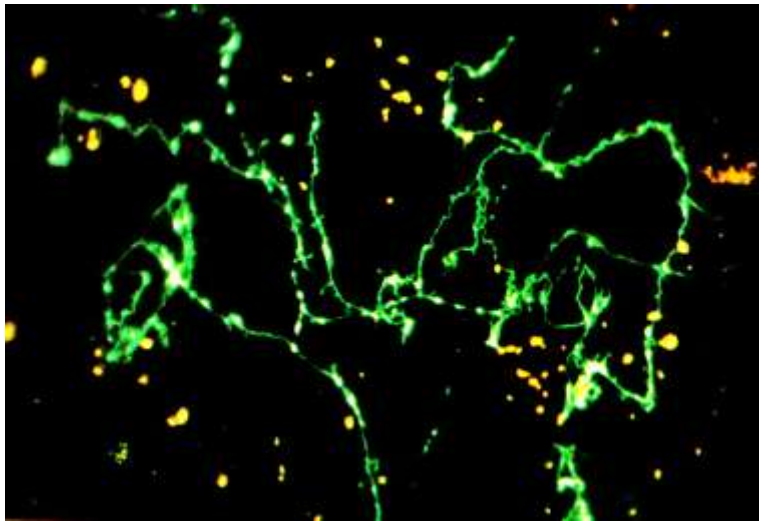
  Epinephrine - E
  - Adrenergic ~

- Indolamines

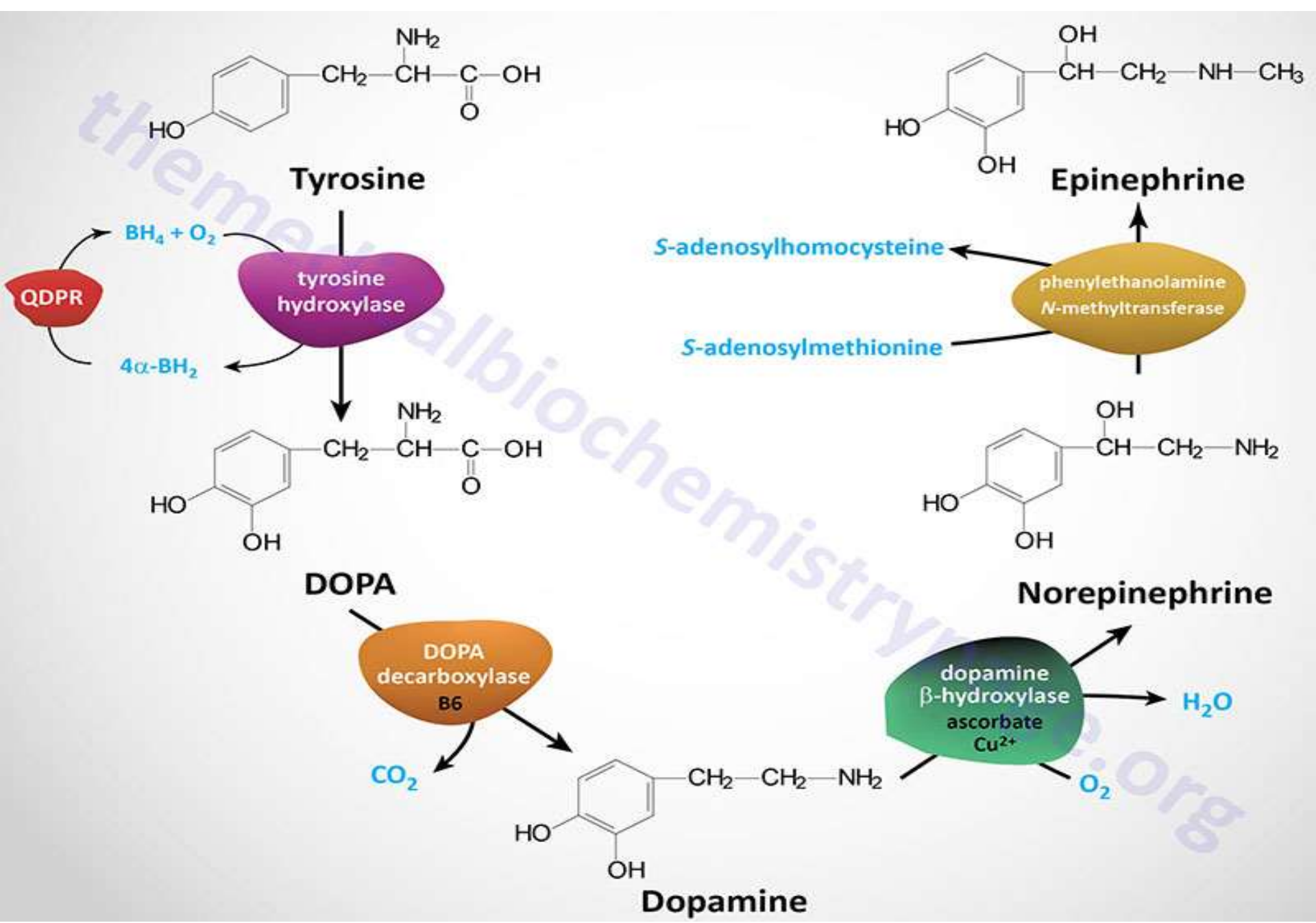
  Serotonin - 5-HT
  - Serotonergic

Monoamines (DA, NE, 5-HT)



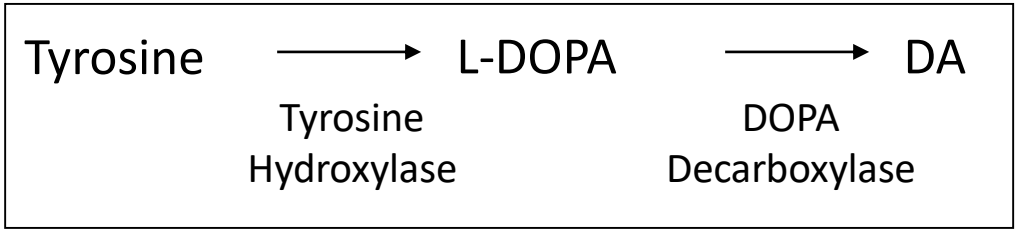


- Modulatory (can have both excitatory and inhibitory effects- varies by receptor)
- Recycled by reuptake transporter
- Excess NT in terminal broken down by
  - monoamine oxidase (MAO)
  - catechol-O-methyltranferase - COMT


Tyrosine
BH4 + O2
QDPR
tyrosine hydroxylase
4α-BH2
DOPA
DOPA decarboxylase
B6
CO2
Dopamine
dopamine β-hydroxylase
ascorbate
Cu2+
H2O
O2
Norepinephrine
S-adenosylhomocysteine
phenylethanolamine N-methyltransferase
S-adenosylmethionine
Epinephrine

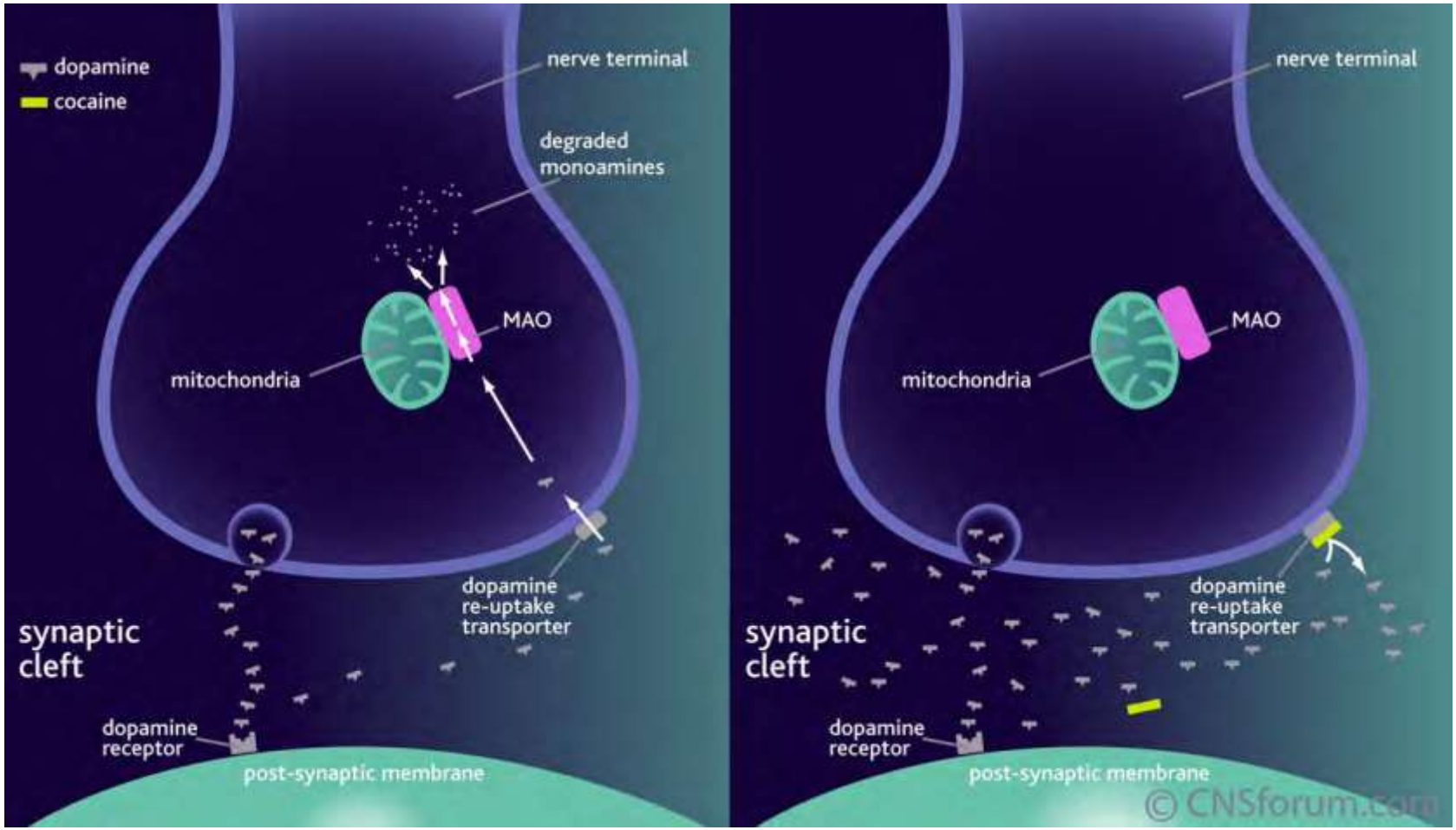
Dopamine (DA)

Biosynthesis:

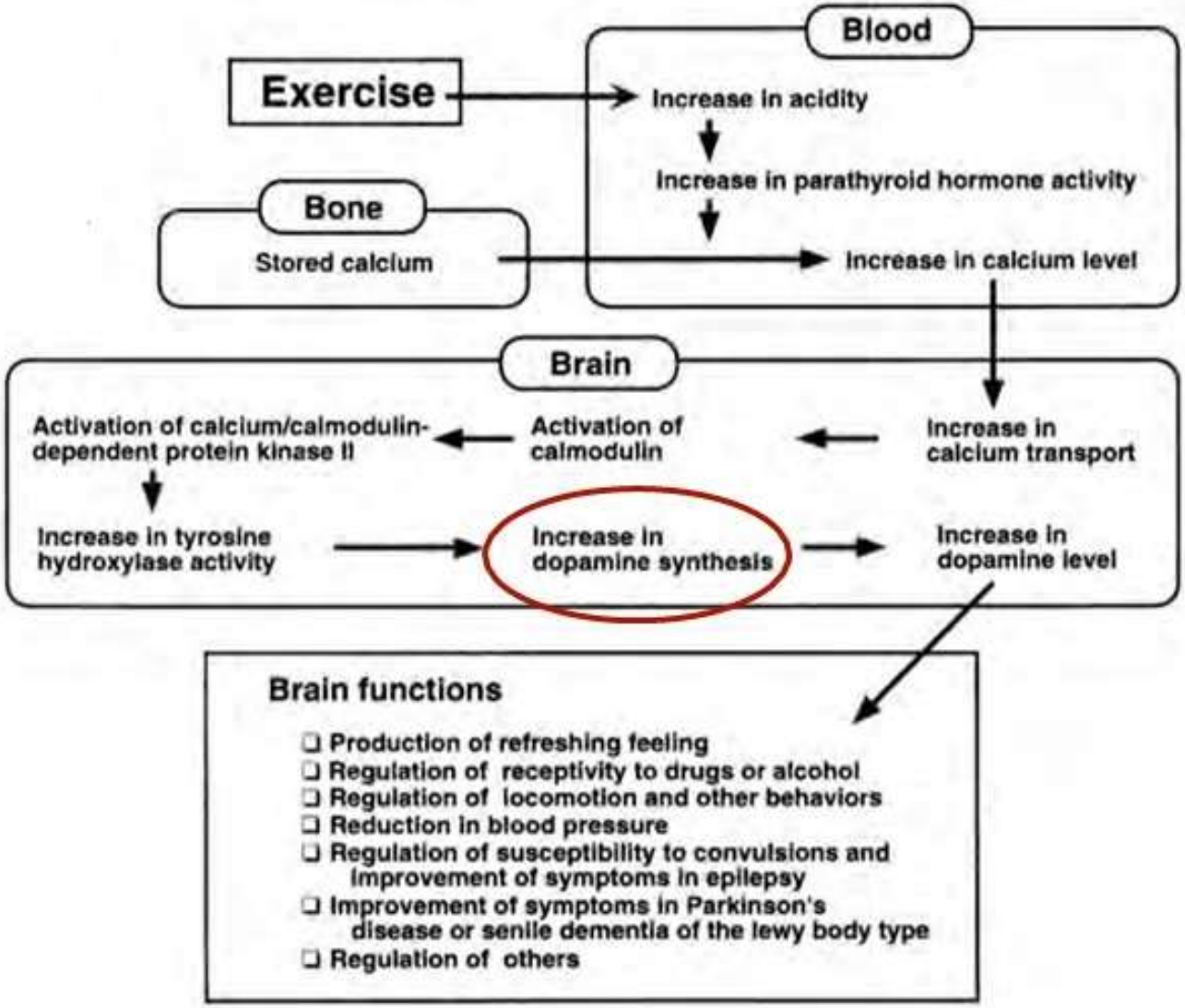


- Dopamine reuptake transporter (DAT)
- 5 receptor types (D1–D5, all metabotropic)
- Too little: Parkinson's disease:
- Treatment: Increase available DA via L-Dopa
- Too much: schizophrenia
- Treatment: Reduce available DA via antidopaminergics/antipsychotics

Cocaine increases dopamine levels

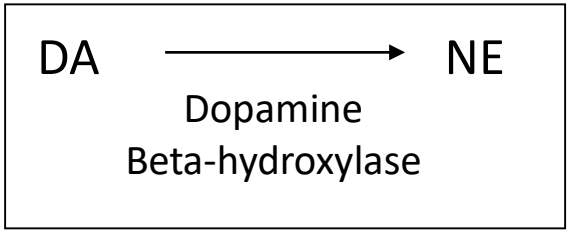


https://www.cnsforum.com/educationalresources/imagebank/substance_abuse/mao_cocaine


Exercise
Blood
Increase in acidity
Increase in parathyroid hormone activity
Bone
Stored calcium
Increase in calcium level
Brain
Activation of calcium/calmodulin-dependent protein kinase II
Activation of calmodulin
Increase in calcium transport
Increase in tyrosine hydroxylase activity
Increase in dopamine synthesis
Increase in dopamine level
Brain functions
Production of refreshing feeling
Regulation of receptivity to drugs or alcohol
Regulation of locomotion and other behaviors
Reduction in blood pressure
Regulation of susceptibility to convulsions and improvement of symptoms in epilepsy
Improvement of symptoms in Parkinson's disease or senile dementia of the lewy body type
Regulation of others

Norepinephrine

- Generally excitatory behavioral effects
- Biosynthesis:



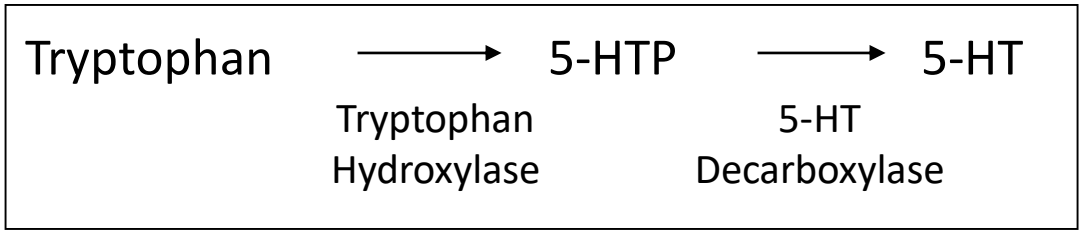
- Many receptor types (**metabotropic**)
  - α_1, $\beta_{1\text{-}2}$ (postsynaptic, excitatory) α_2 (autoreceptor, inhibitory)
  - Norepinephrine is strongly associated with bringing our nervous systems into "high alert."
  - It increases heart rate and blood pressure.
  - It is also important for forming memories.

Catabolism

- It occurs through the actions of catecholamine-O-methyltransferase, (COMT) and monoamine oxidase, (MAO). Both of these enzymes are widely distributed throughout the body. However, COMT is not found in nerve endings as is MAO.

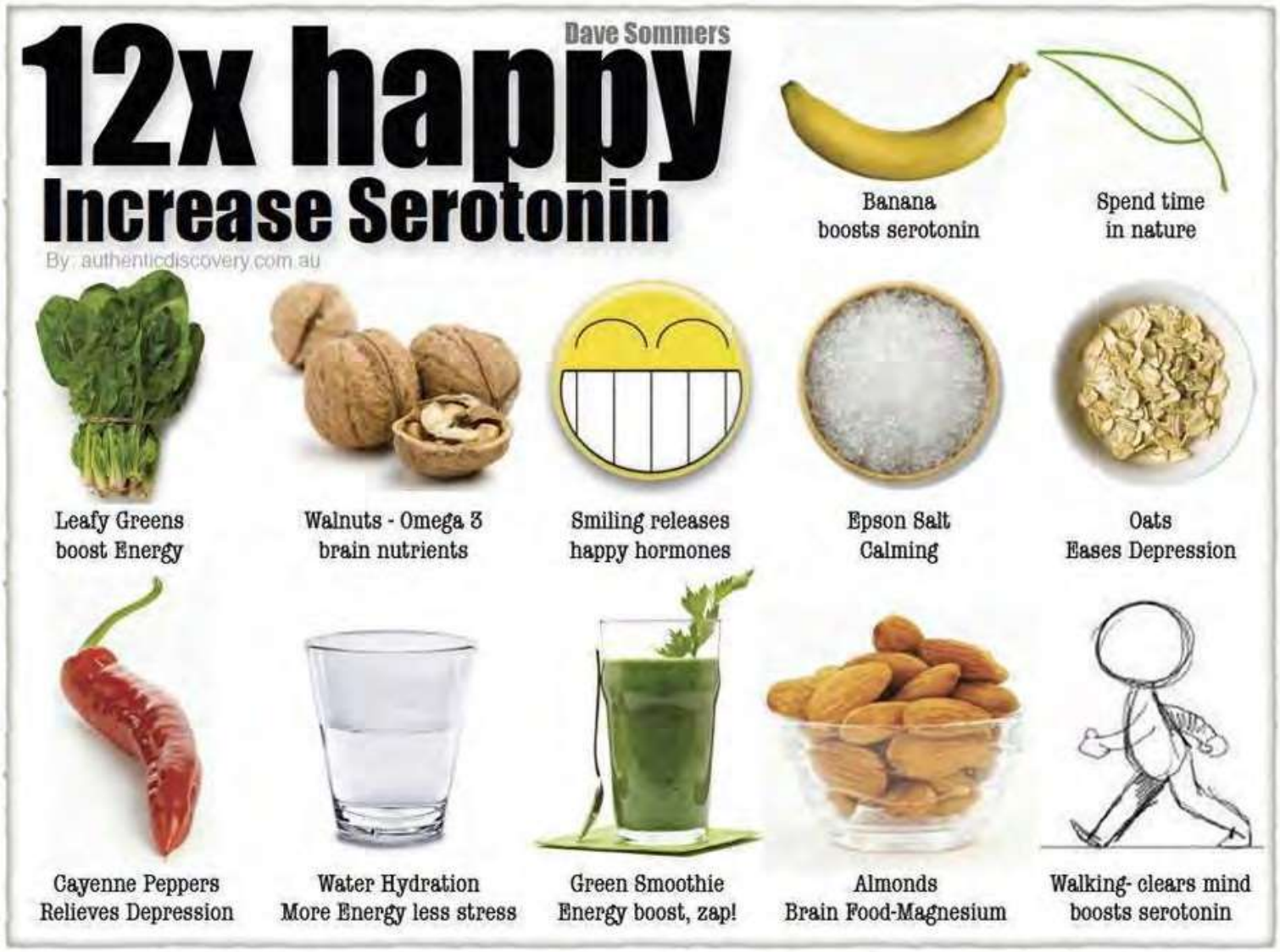
Serotonin (5-HT)

- Varying excitatory and inhibitory behavioral effects
- Biosynthesis:



- At least 14 receptor types, all **metabotropic** and postsynaptic except:
  - $5\text{-HT}_{1A,B,D}$ (autoreceptors) – found in CNS
  - 5-HT_{3} (inhibitory, ionotropic) – found in the intestines
  - Too little is linked to depression and sleep disorders
  - Too much: Serotonin syndrome: confusion, twitching and trembling, dilated pupils, shivering, headache, sweating and diarrhea., irregular and fast heartbeat

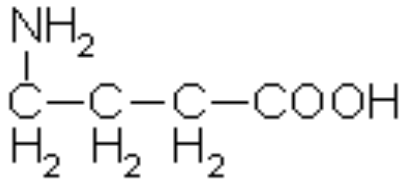
Eat nuts, be happy?



GLUTAMATE

- It is an amino acid
- It the most commonly found excitatory neurotransmitter in the brain.
- It is involved in most aspects of normal brain function including cognition, memory and learning.
- Glutamate is formed from α –ketoglutarate, an intermediate of Kreb's cycle.

GABA (Gamma Aminobutyric Acid)



- Principal Inhibitory NT
- Biosynthesis:

Glu → GABA

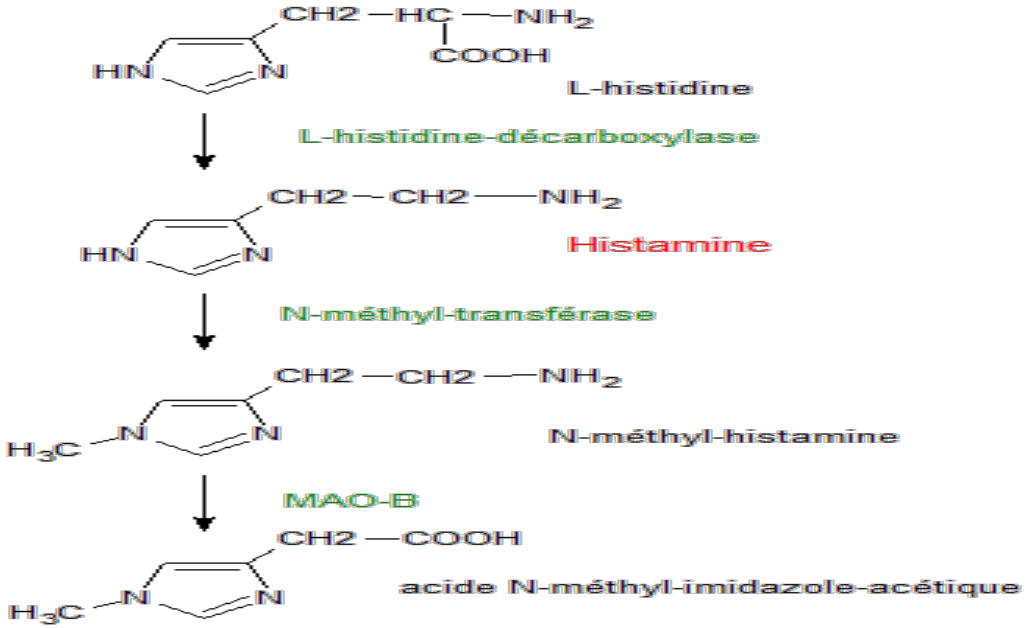
Glutamic Acid Decarboxylase (GAD) and B6

- Removed by reuptake
- 2 receptor types
  - $GABA_A$ $GABA_C$ (ionotropic; Cl^- channel)
  - $GABA_B$ (metabotropic)

If GABA is lacking in certain parts of the brain, epilepsy results.

4- Histamine

- Histamine forming cells are in posterior hypothalamus also found in gastric mucosa and in mast cells.
- Formed by histidine decarboxylation using histidine decarboxylase, while, degraded by N-methyl transferase and histaminase (MAO-B).



- Four known types of histamine receptors are found.
- Its function in brain is not very clear.
- Its main function is that it is excitatory.
- It increases during inflammation (inflammatory states causes depletion of tryptophan and serotonin)

Neuropeptides

- Low concentration in brain (picomolar)
- Large vesicles
- Co-localized with other transmitters
- Modulatory functions
- Mostly inhibitory
- Virtually all metabotropic
- Slow acting, long duration
- Examples: Enkephalins, Endorphins, Oxytocin, Vasopressin, Opioids

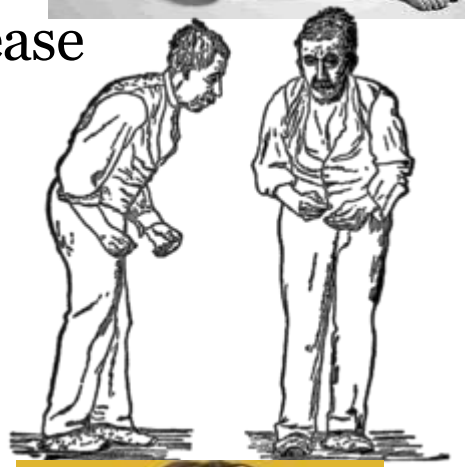
Endorphins

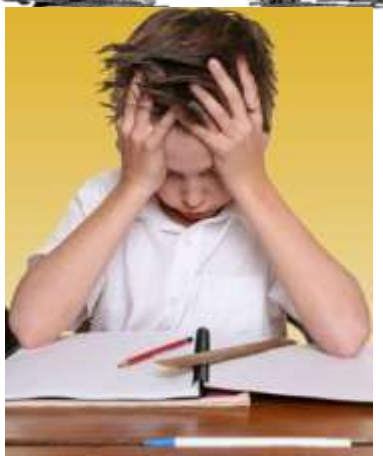
- **Morphine** and **heroin** are agonists that bind to receptor sites, thereby increasing endorphin activity

Neurotransmitter	Function
Acetylcholine	Transmitter at muscles; in brain, involved in learning, etc.
Monamines	
Serotonin	Involved in mood, sleep, and arousal, and in aggression, depression, obsessive-compulsive disorder, and alcoholism.
Dopamine	Contributes to movement control and promotes reinforcing effects of abused drugs, food, and sex; involved in schizophrenia and Parkinson's disease.
Norepinephrine	A hormone released during stress. Functions as a neurotransmitter in the brain to increase arousal and attentiveness to events in the environment; involved in depression.
Epinephrine	A stress hormone related to norepinephrine; plays a minor role as a neurotransmitter in the brain.
Amino Acids	
Glutamate	The principal excitatory neurotransmitter in the brain and spinal cord. Vitally involved in learning, and implicated in schizophrenia.
Gamma-aminobutyric acid (GABA)	The predominant inhibitory neurotransmitter. Its receptors respond to alcohol and the class of tranquilizers called benzodiazepines. Deficiency in GABA or receptors is one cause of epilepsy.
Glycine	Inhibitory transmitter in the spinal cord and lower brain. The poison strychnine causes convulsions and death by affecting glycine activity.
Peptides	
Endorphins	Neuromodulators that reduce pain and enhance reinforcement.
Substance P	Transmitter in neurons sensitive to pain.
Neuropeptide Y	Initiates eating and produces metabolic shifts.
Gas	
Nitric Oxide	One of two known gaseous transmitters, along with carbon monoxide. Can serve as a retrograde transmitter, influencing the presynaptic neuron's release of neurotransmitter. Viagra enhances male erections by increasing nitric oxide's ability to relax blood vessels and produce penile engorgement.

DISEASES ASSOCIATED WITH NEUROTRANSMITTERS

NEUROTRANSMITTER	DISEASE
Acetylcholine	Alzheimer's
Dopamine	Parkinson's disease Schizophrenia
GABA	Epilepsy
Serotonin	Migraines Depression
Glutamate	Migraine stroke





RECENT DEVELOPMENTS

- A team of scientists from **University of Barcelona** in 2011, has discovered *that* ***D-aspartic acid*** *(D-Asp)* is a novel neurotransmitter that could potentially be used in the **fight against** neurological diseases such as Parkinson's and schizophrenia.

- According to a new study by researchers at the **Ohio State University Comprehensive Cancer Center in 2011**, doses of a neurotransmitter ***dopamine*** might offer a way to boost the effectiveness of anticancer drugs and radiation therapy.

THANK U