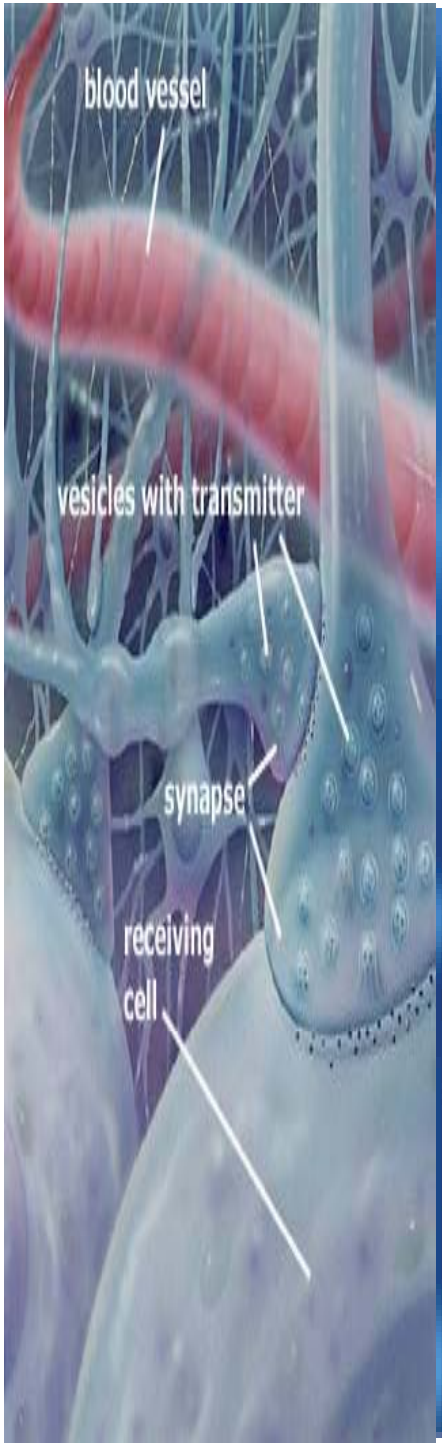
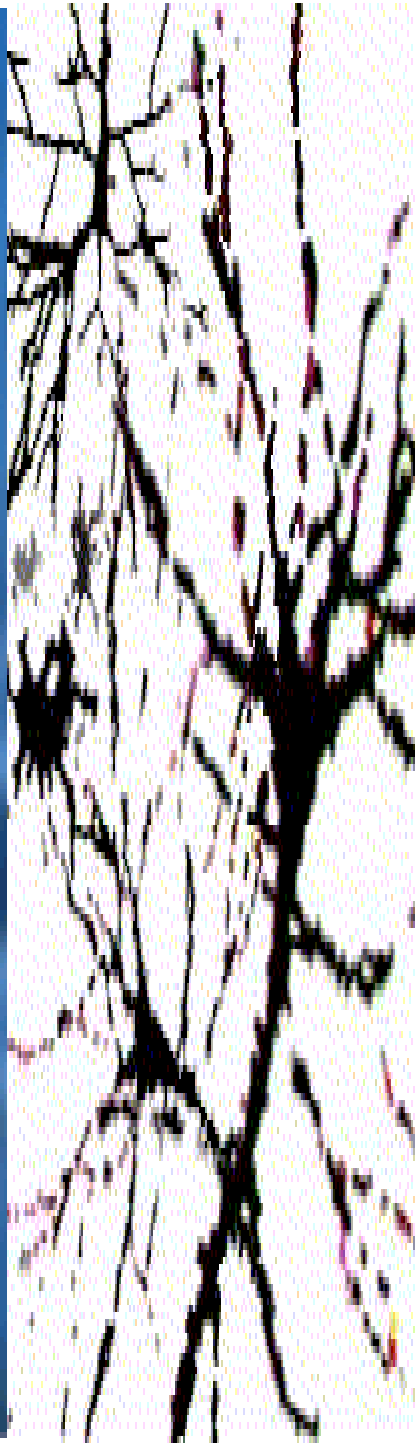
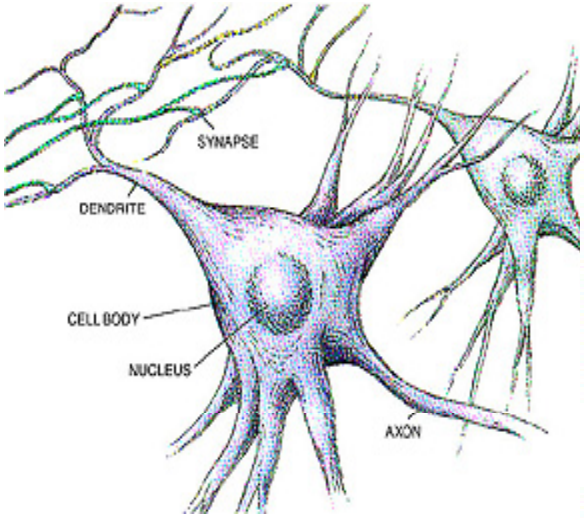
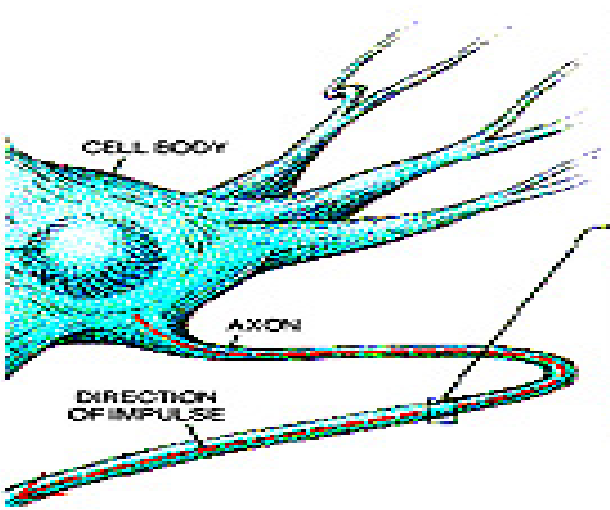


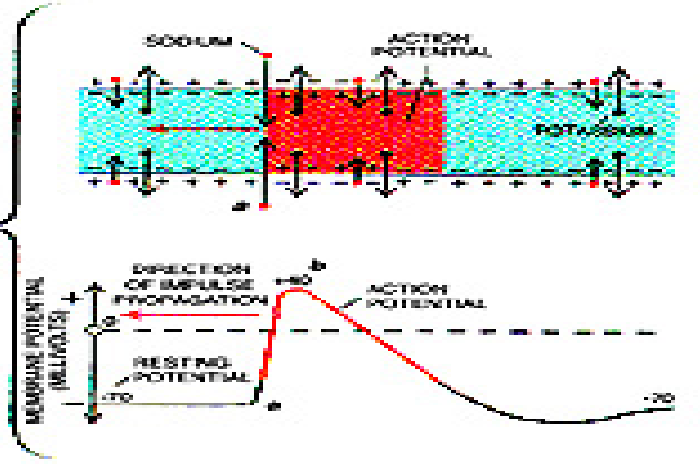
Neurotransmitters

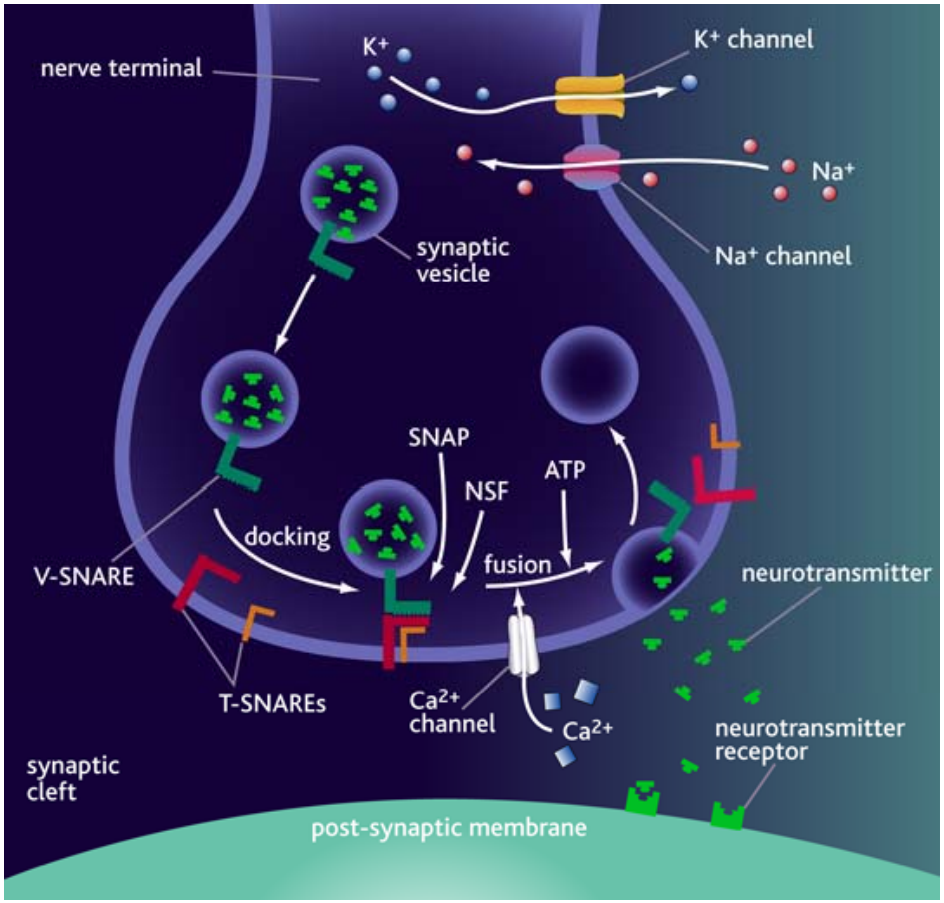
D.HAMMOUDI.MD

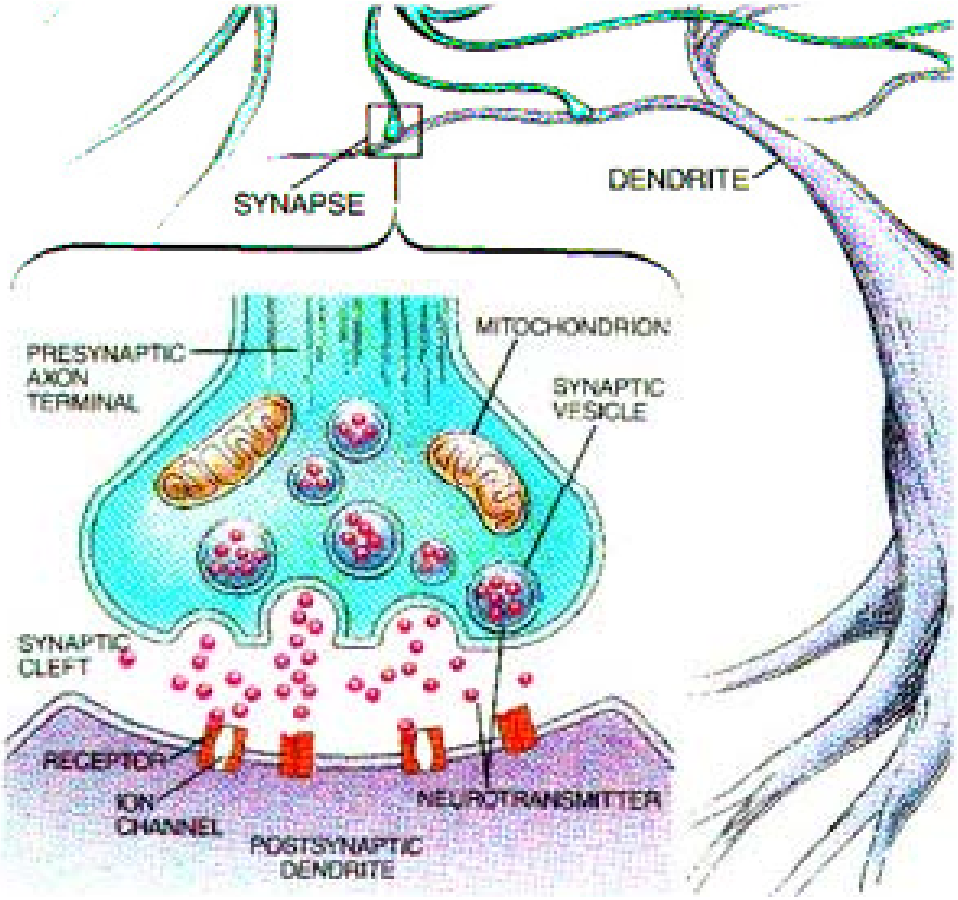


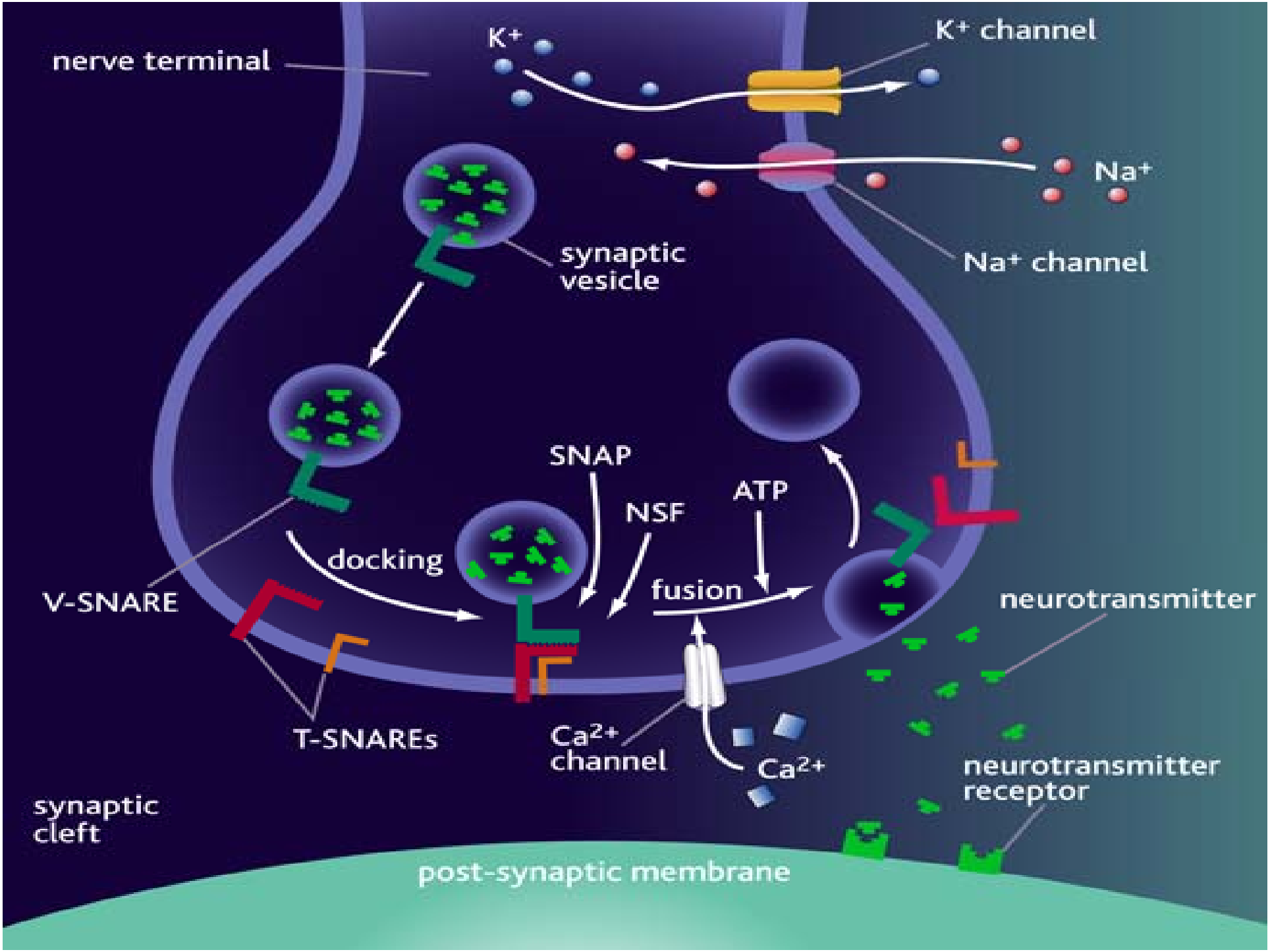

SYNAPSE
DENDRITE
CELL BODY
NUCLEUS
AXON


CELL BODY
AXON
DIRECTION OF IMPULSE


SODIUM
ACTION POTENTIAL
POTASSIUM
DIRECTION OF IMPULSE PROPAGATION
ACTION POTENTIAL
RESTING POTENTIAL
MEMBRANE POTENTIAL (MILLIVOLTS)


nerve terminal
K+
K+ channel
Na+
Na+ channel
synaptic vesicle
SNAP
NSF
ATP
docking
fusion
V-SNARE
T-SNAREs
Ca2+ channel
Ca2+
neurotransmitter
neurotransmitter receptor
synaptic cleft
post-synaptic membrane


SYNAPSE
DENDRITE
MITOCHONDRION
PRESYNAPTIC AXON TERMINAL
SYNAPTIC VESICLE
SYNAPTIC CLEFT
RECEPTOR
ION CHANNEL
NEUROTRANSMITTER
POSTSYNAPTIC DENDRITE


nerve terminal
K+
K+ channel
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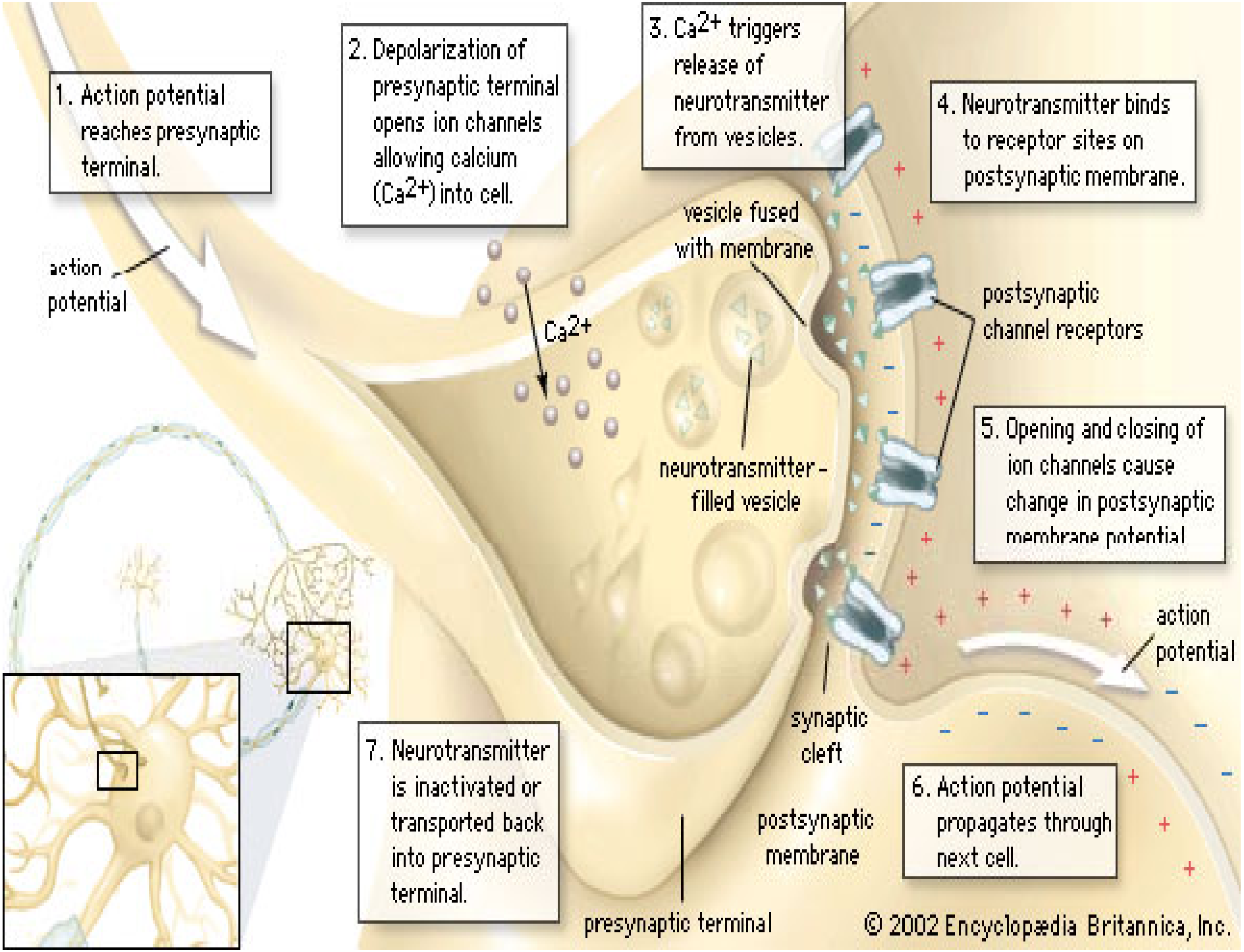
neurotransmitter receptor
synaptic cleft
post-synaptic membrane


1. Action potential reaches presynaptic terminal.
2. Depolarization of presynaptic terminal opens ion channels allowing calcium (Ca^{2+}) into cell.
3. Ca^{2+} triggers release of neurotransmitter from vesicles.
4. Neurotransmitter binds to receptor sites on postsynaptic membrane.
5. Opening and closing of ion channels cause change in postsynaptic membrane potential
6. Action potential propagates through next cell.
7. Neurotransmitter is inactivated or transported back into presynaptic terminal.
action potential
Ca^{2+}
vesicle fused with membrane
neurotransmitter-filled vesicle
postsynaptic channel receptors
synaptic cleft
action potential
postsynaptic membrane
presynaptic terminal
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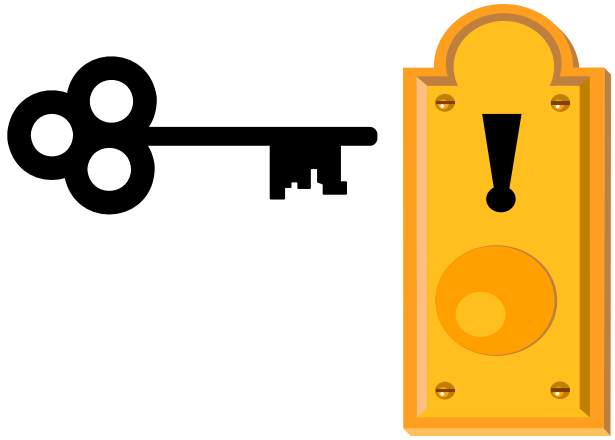
CRITERIA

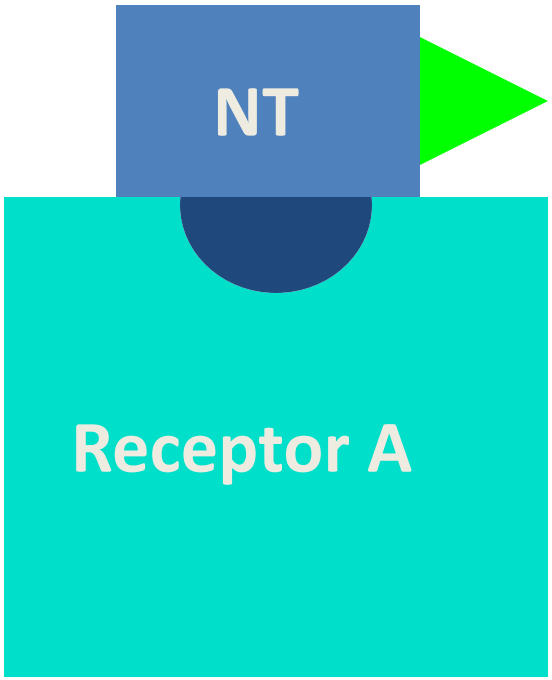
- NT found in axon terminals
- NT released by action potentials
- Synthesis identified
- External application mimic normal Response
- Pharmacology same for normal and externally applied NT ~

Lock & Key Model

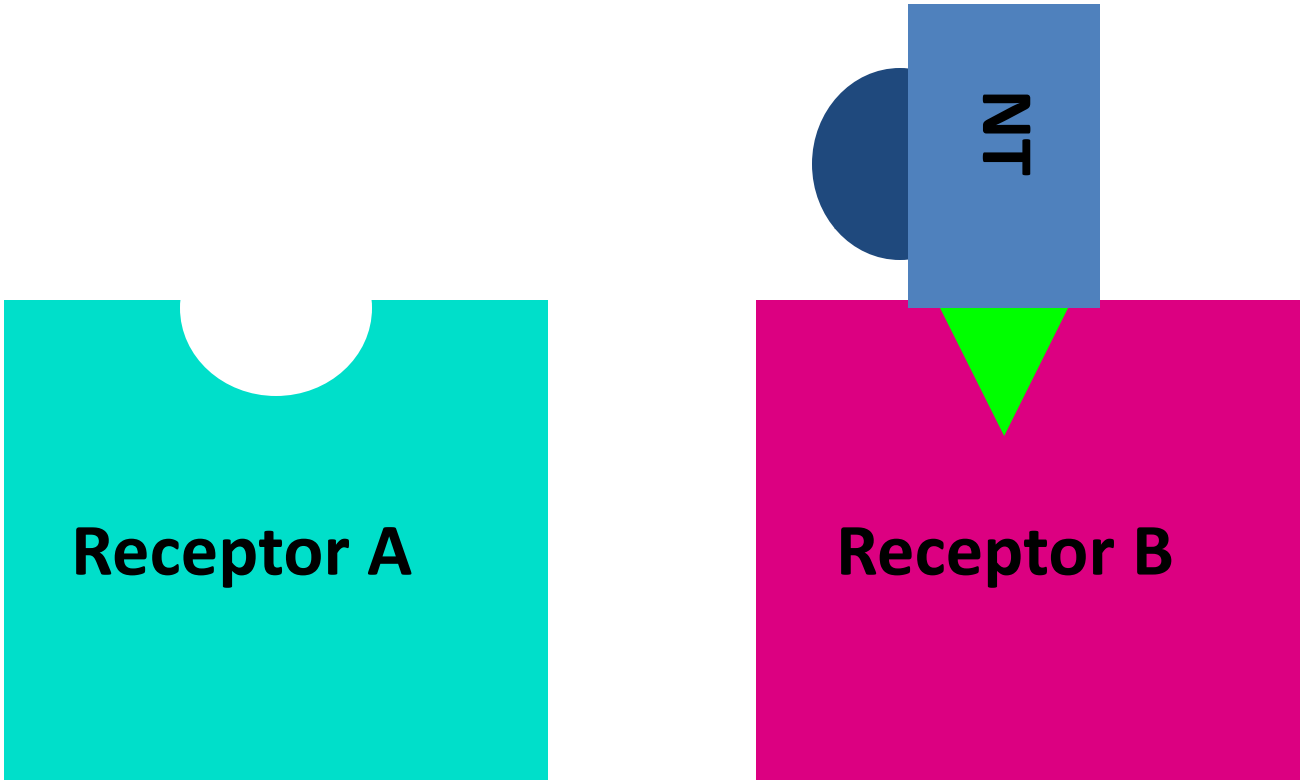
- NT binds to receptor
  - NT = key
  - Receptor = lock
- Receptor changes shape
  - determines if EPSP or IPSP
  - receptor subtypes
- NOT NT ~



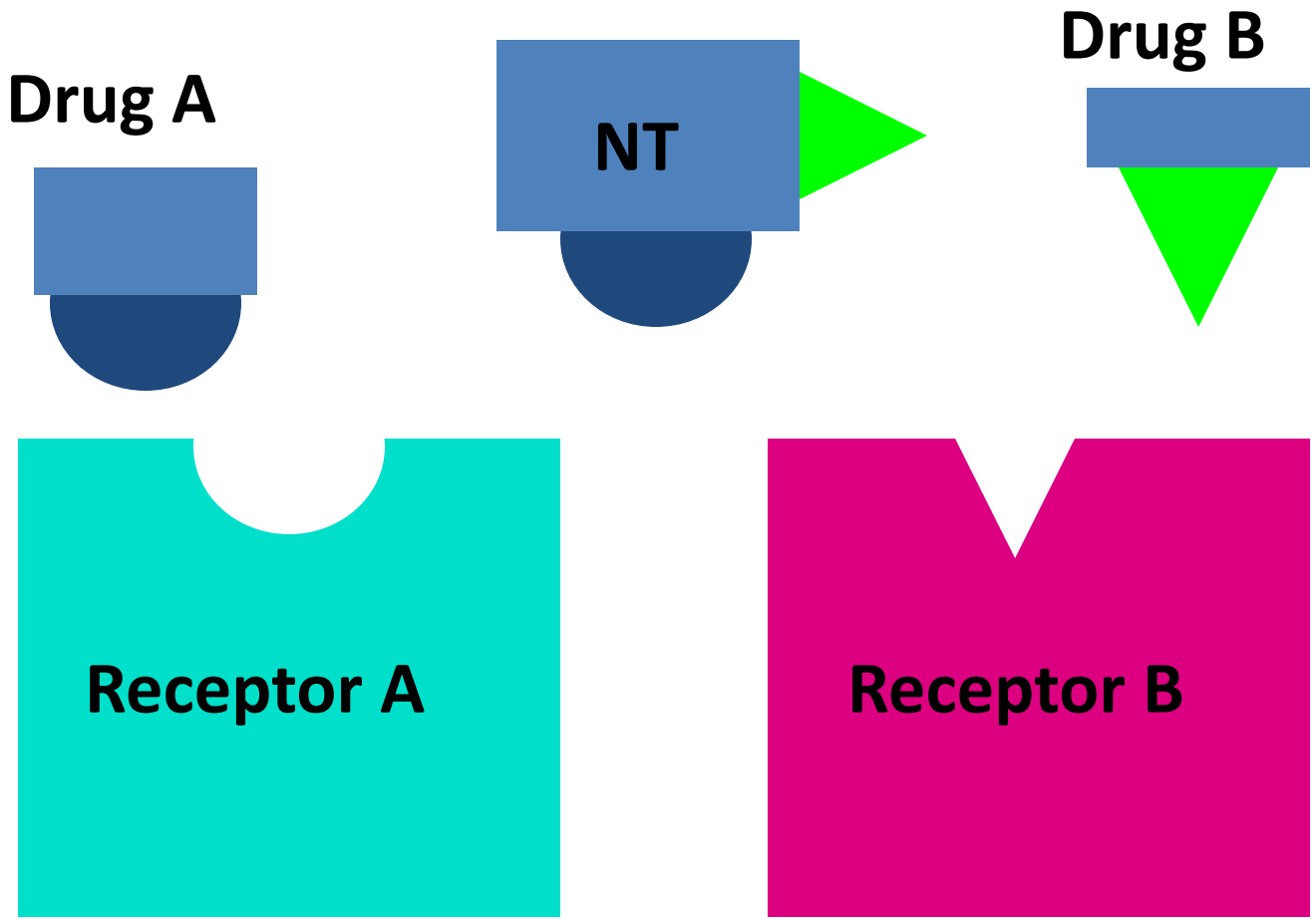
- ligand binds to receptor
- activation: + or - ~



- Same NT can bind to different -R
- different part of NT ~



Specificity of drugs



Neurotransmitter synthesis pathways:

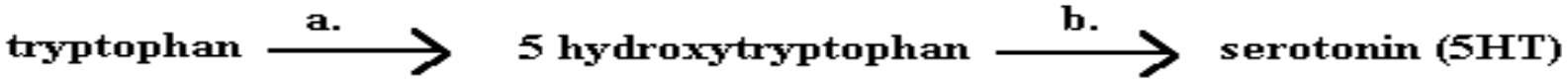
Phenylalanine --> Tyrosine --> L-Dopa --> Dopamine --> Norepinephrine

Tryptophan --> 5-Hydroxytryptophan (5-HTP) --> Serotonin (5-Hydroxytryptamine)

Choline + Acetyl-CoA --> Acetylcholine

Glutamic acid --> GABA (gamma-amino-butyric-acid)

Serotonin
Synthesis and metabolism



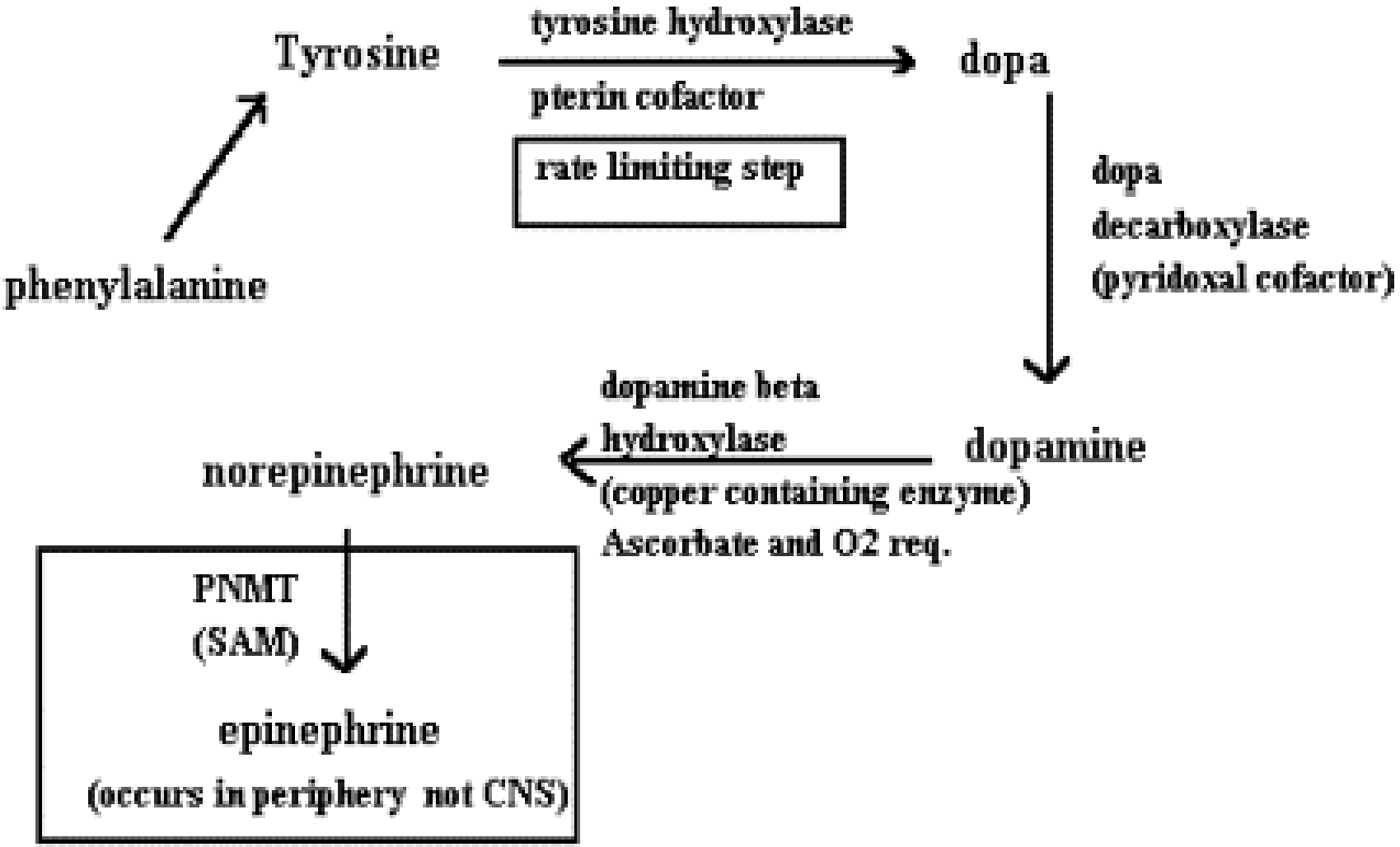
a. tryptophan hydroxylase
b. l-aromatic acid decarboxylase

substrate availability is rate limiting step
tryptophan hydroxylase is rate limiting enzyme

a. MAO
b. Aldehyde dehydroxylase

Catecholamines (dopamine and norepinephrine)

synthesis and metabolism



The genetic disorder phenylketonuria (PKU) is the inability to metabolize phenylalanine.

- Individuals with this disorder are known as "phenylketonurics" and must regulate their intake of phenylalanine.

•A (rare) "variant form" of phenylketonuria called hyperphenylalaninemia is caused by the inability to synthesize a coenzyme called **biopterin**, which can be supplemented.

•Pregnant women with hyperphenylalaninemia may show similar symptoms of the disorder (high levels of phenylalanine in blood) but these indicators will usually disappear at the end of gestation.

• Individuals who cannot metabolize phenylalanine must monitor their intake of protein to control the buildup of phenylalanine as their bodies convert protein into its component amino acids.


Medscape®
www.medscape.com
Source: Adv Neonatal Care © 2003 W. B. Saunders

Neurotransmitters

· Acetylcholine (AcH)
· Dopamine (DA)
· Histamine
· Norepinephrine (NE)
· Epinephrine
· Serotonin (5HT)

Peptides

· GammaAminobutyric Acid (GABA)
· Glutamate
· Aspartate
· Glycine

Neuropeptides

· Insulin
· Betaendorphin
· Neuropeptide Y
· Calcitonin

Neurotransmitters found in the nervous system

EXCITATORY

- **Acetylcholine**
- **Aspartate**
- **Dopamine**
- **Histamine**
- **Norepinephrine**
- **Epinephrine**
- **Glutamate**
- **Serotonin**

INHIBITORY

- **GABA**
- **Glycine**

Major Neurotransmitters in the Body

Neurotransmitter	Role in the Body
Acetylcholine	A neurotransmitter used by the spinal cord neurons to control muscles and by many neurons in the brain to regulate memory. In most instances, acetylcholine is excitatory.
Dopamine	The neurotransmitter that produces feelings of pleasure when released by the brain reward system. Dopamine has multiple functions depending on where in the brain it acts. It is usually inhibitory.
GABA (gamma-aminobutyric acid)	The major inhibitory neurotransmitter in the brain.
Glutamate	The most common excitatory neurotransmitter in the brain.
Glycine	A neurotransmitter used mainly by neurons in the spinal cord. It probably always acts as an inhibitory neurotransmitter.
Norepinephrine	Norepinephrine acts as a neurotransmitter and a hormone. In the peripheral nervous system, it is part of the flight-or-flight response. In the brain, it acts as a neurotransmitter regulating normal brain processes. Norepinephrine is usually excitatory, but is inhibitory in a few brain areas.
Serotonin	A neurotransmitter involved in many functions including mood, appetite, and sensory perception. In the spinal cord, serotonin is inhibitory in pain pathways.

NIH Publication No. 00-4871

Summary:

Neurotransmitter Molecule	Derived From	Site of Synthesis
Acetylcholine	Choline	CNS, parasympathetic nerves
Serotonin 5-Hydroxytryptamine (5-HT)	Tryptophan	CNS, chromaffin cells of the gut, enteric cells
GABA	Glutamate	CNS
Histamine	Histidine	hypothalamus
Epinephrine synthesis pathway	Tyrosine	adrenal medulla, some CNS cells
Norpinephrine synthesis pathway	Tyrosine	CNS, sympathetic nerves
Dopamine synthesis pathway	Tyrosine	CNS
Nitric oxide, NO	Arginine	CNS, gastrointestinal tract

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. 

Acetylcholine

1. synthesis and metabolism

Choline + Acetyl CoA $\xrightarrow{\text{CAT}}$ acteylcholine

CAT-Choline acetyl transferase
marker enzyme for Ach neurons

acetylcholine $\xrightarrow{\text{cholinesterase}}$ Choline and actetate

terminates effect at the receptor

2. Central anatomy-interneurons of striatum

pedunculopontine nucleus-projects to thalamus

nucleus basalis-projects to cortex

Types of NT

Acetylcholine (ACh)

1. this NT has 2 types of receptors

A. nicotinic receptors:

a. agonist: is nicotine

b. antagonist: is curare

B. muscarinic receptors:

a. agonist: is muscarine

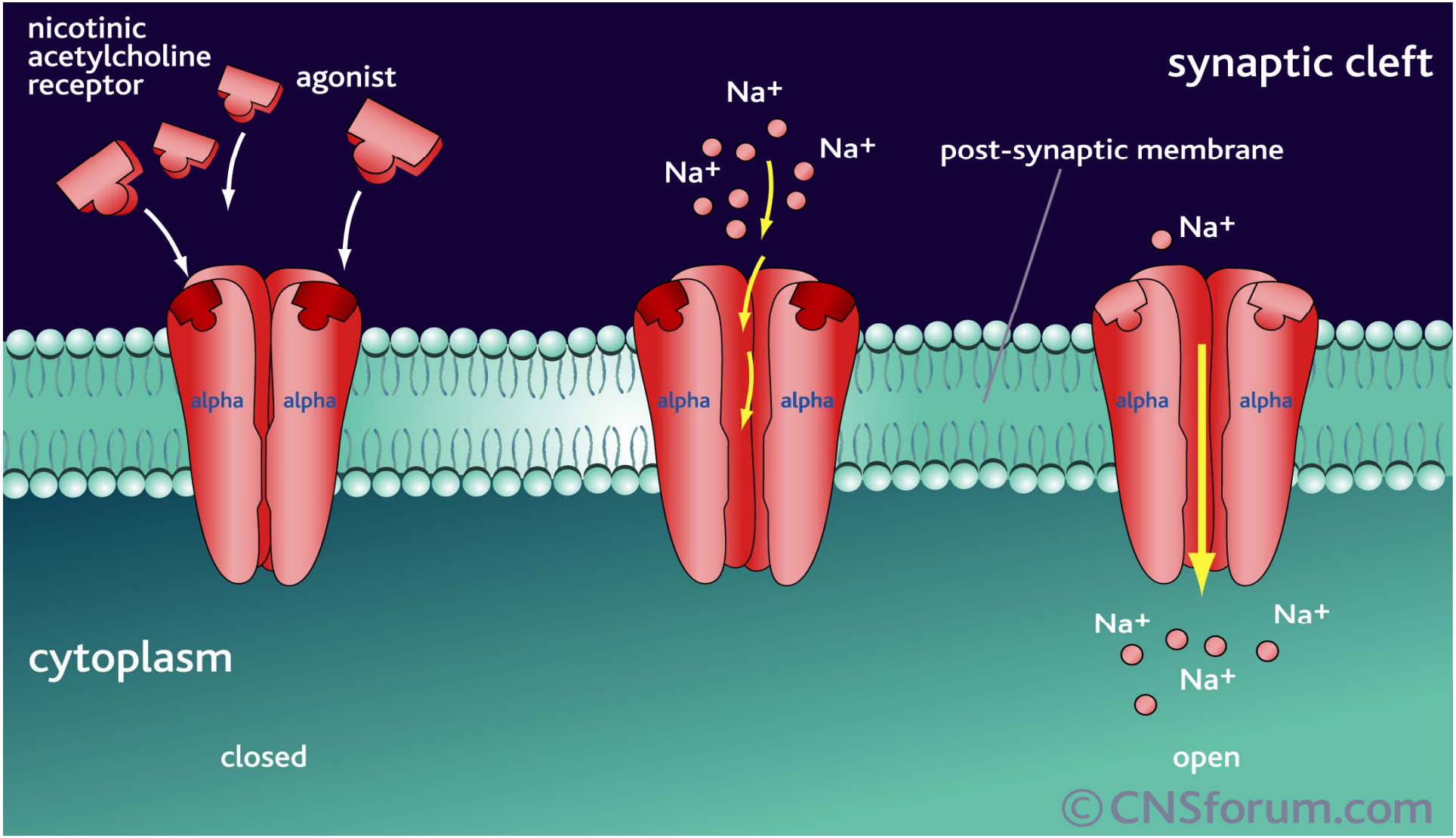
b. antagonist: in atropine (deadly nightshade

2. **deactivated** by acetylcholinesterase (AChE) & choline is reused

3. **physostigmine:** inhibits AChE (agonist) but is reversible.

4. **botulinum toxin** prevents the release of ACH from the terminal button (antagonist)

5. **black widow spider venom causes ACH terminals to release ACH (agonist**)

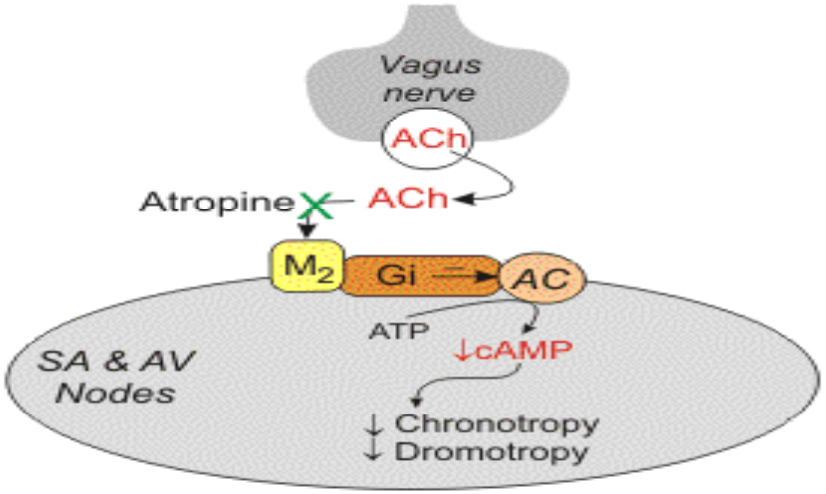


•The nicotinic acetylcholine receptor is one of the main mediators of neurotransmission.
•This receptor is activated by the binding of two acetylcholine molecules.
•As a ligand gated ion channel it permits the movement of positively charged ions from the synaptic cleft into the cytoplasm.

Amanita muscaria, the mushroom from which muscarine was isolated.

•**Muscarinic receptors**, or **mAChRs**, are acetylcholine receptors that form G protein-receptor complexes in the cell membranes of certain neurons and other cells.

•They play several roles, including acting as the main end-receptor **stimulated by acetylcholine released from postganglionic fibers in the parasympathetic nervous system.**



Abbreviations: ACh, acetylcholine; M2, muscarinic receptor; AC, adenylate cyclase; SA, sinoatrial; AV, atrioventricular

South American Indian
Preparing Curare

•Both botulinum toxin (BoTx) and black widow spider venom (b.w.s.v.) cause a presynaptic
•block of neuromuscular transmission but each has a different mode of action. BoTx impairs
•the release of acetylcholine (ACh) from motor nerve terminals and causes prolonged
•paralysis of skeletal muscle. Recovery from paralysis is slow and associated with sprouting
•of axons from nerve terminals and formation of new motor end-plates

Acetylcholine - ACh

- Most abundant NT in Peripheral N.S.
  - also found in Central N.S.
- Precursor = choline

  nutrient
- Degraded by acetylcholinesterase-
  - AChE

    Membrane bound - pre- & postsynaptic
- Nicotinic receptor - ionotropic
- Muscarinic receptor - metabotropic ~

Ach - Distrubution

- Peripheral N.S.
- Excites somatic muscle
- **Autonomic NS**
    - Ganglia
    - Parasympathetic NS
    - Neuroeffector junction

Central N.S. - widespread

Hippocampus

Hypothalamus

Cholinergic Agonists

- **Direct**
  - Muscarine
  - Nicotine
  - small doses
- **Indirect**
  - AChE Inhibitors ~

AChE inhibitors

- Physostigmine
- Organophosphates - irreversible
  - DFP
  - Soman & Sarin
  - Malathion*
- Agonist or Antagonist?

  indirect agonist

Cholinergic Antagonists

- **Direct**

  Nicotinic - Curare

  Muscarinic - Atropine

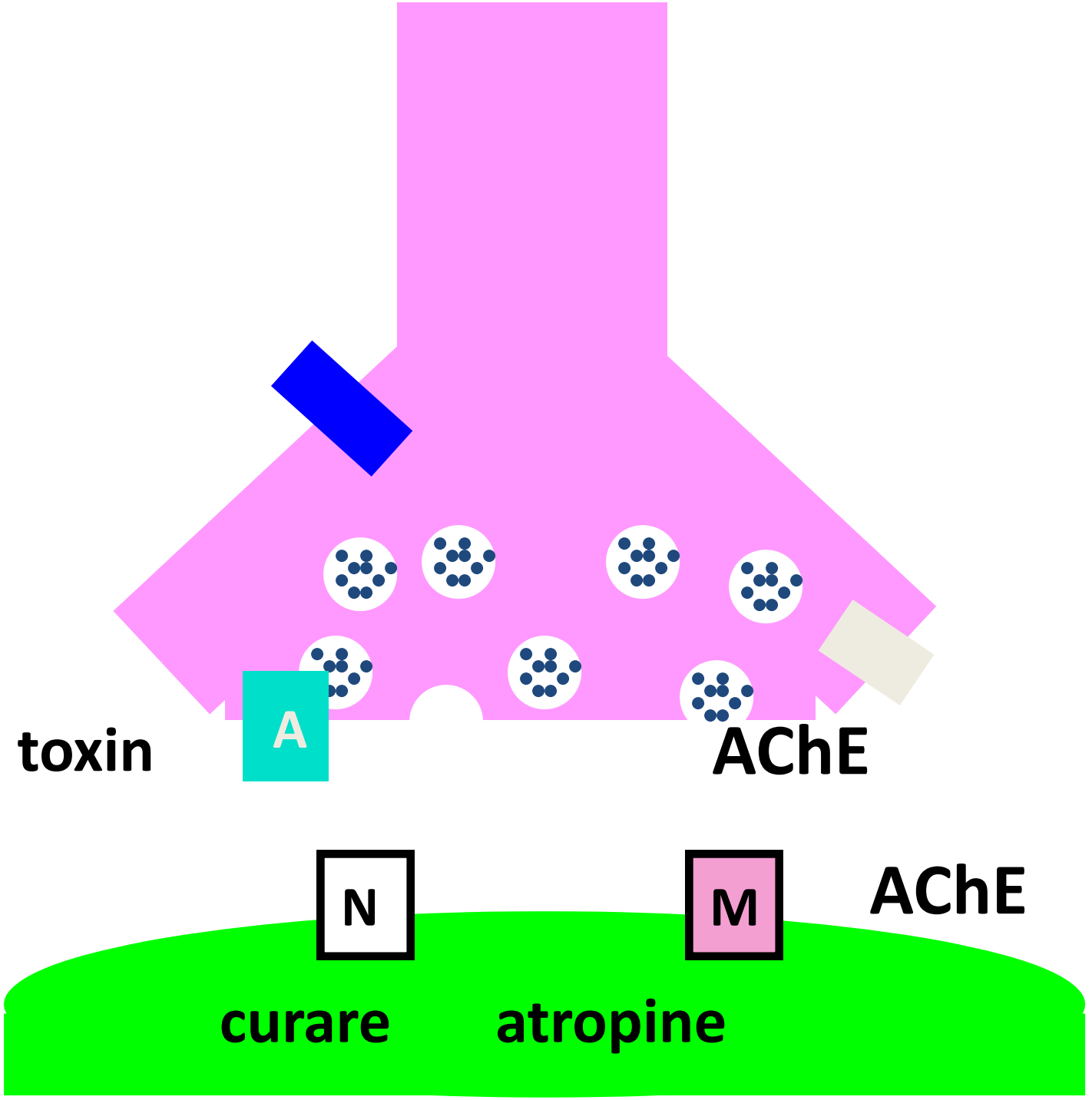
  Scopolamine

- **Indirect**

  Botulinum Toxin

  Black Widow Spider Venom ~

ACh



Monoamines

neurotransmitters and neuromodulators
All monoamines work thru metabotropic receptors
All monoaminesare derived from aromatic amino
acids like **phenylalanine, tyrosine, tryptophan, and the thyroid hormones by the action of aromatic amino acid decarboxylase enzymes**.

Monoamine oxidase (MAO) & catechol-O-methyltransferase (COMT) deactivate these.
Monoamine oxidase A (MAOA) is an enzyme involved in the metabolism of the monoamines, eg 5-HT and noradrenaline.

1. The drug **reserpine** prevents the storage of the monoamines

Types of monoamines:

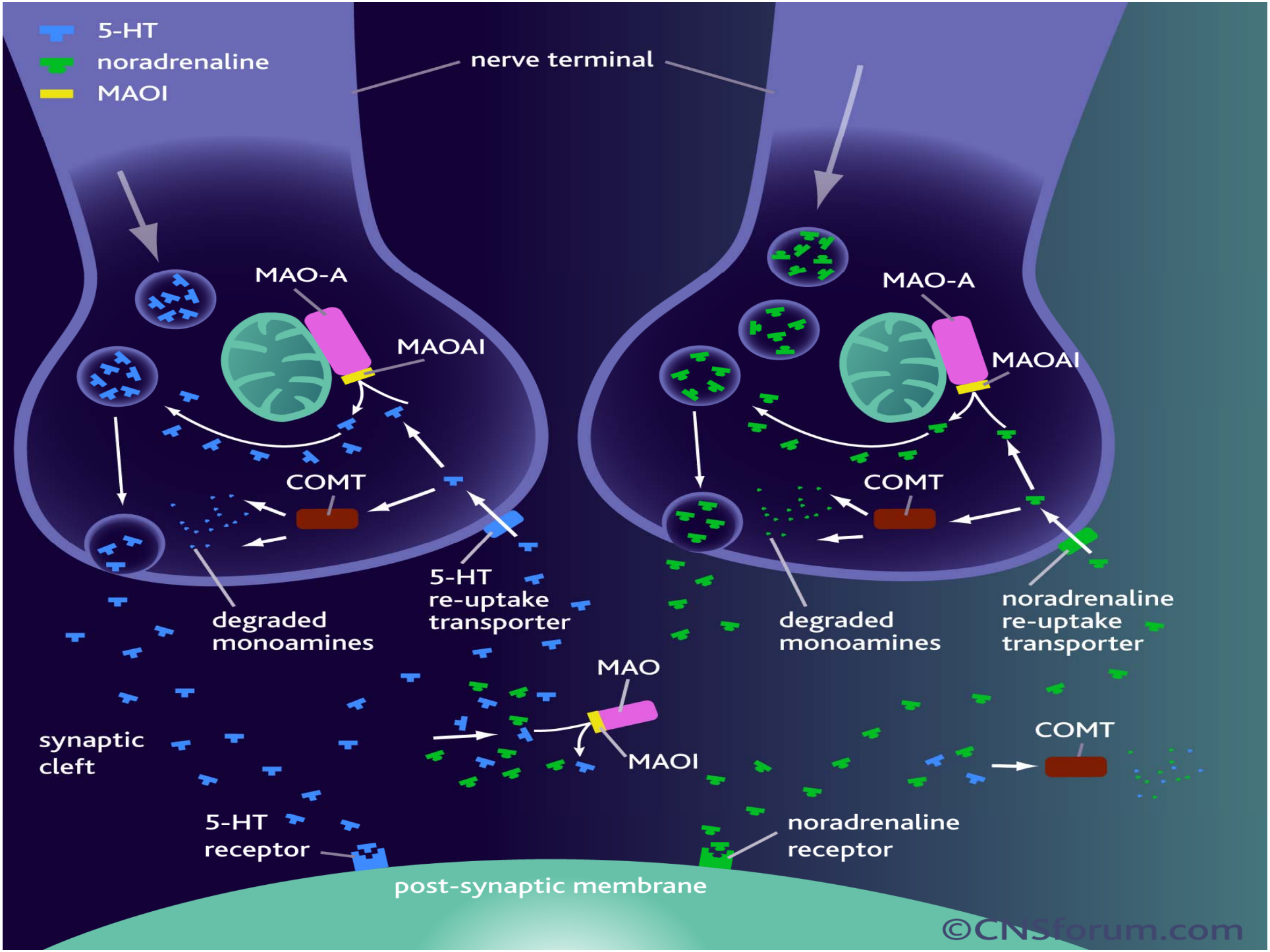
I. Indolamines:

Serotonin (5-HT)

A. produced in the raphe nuclei in the midline of the pons & medulla

B. the drug **parachlorophenylalanine** (PCPA) blocks tryptophan hydroxylase & prevents the synthesis of 5-HT (an antagonist)

C. **iproniazid** block MAO (agonists)


5-HT
noradrenaline
MAOI
nerve terminal
MAO-A
MAOAI
COMT
5-HT
re-uptake
transporter
degraded
monoamines
MAO-A
MAOAI
COMT
degraded
monoamines
noradrenaline
re-uptake
transporter
MAO
MAOI
synaptic
cleft
COMT
5-HT
receptor
noradrenaline
receptor
post-synaptic membrane
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MONOAMINES EXAMPLES

Histamine (His/H is Diamine)

Catecholamines:

- Dopamine (DA)
- Noradrenaline (NA) (Norepinephrine, NE)
- Adrenaline (Epinephrine)

Tryptamines:

- Serotonin (5-HT)
- Melatonin

Trace amines:

- β-Phenylethylamine (PEA, β-PEA)
- Tyramine
- Tryptamine

Monoamines

Catecholamines

- **Dopamine - DA**
  - Dopaminergic
- **Norepinephrine - NE**
  - Noradrenergic
- **Epinephrine - E**
  - Adrenergic ~

- **Indolamines**

Serotonin - 5-HT

  - Serotonergic

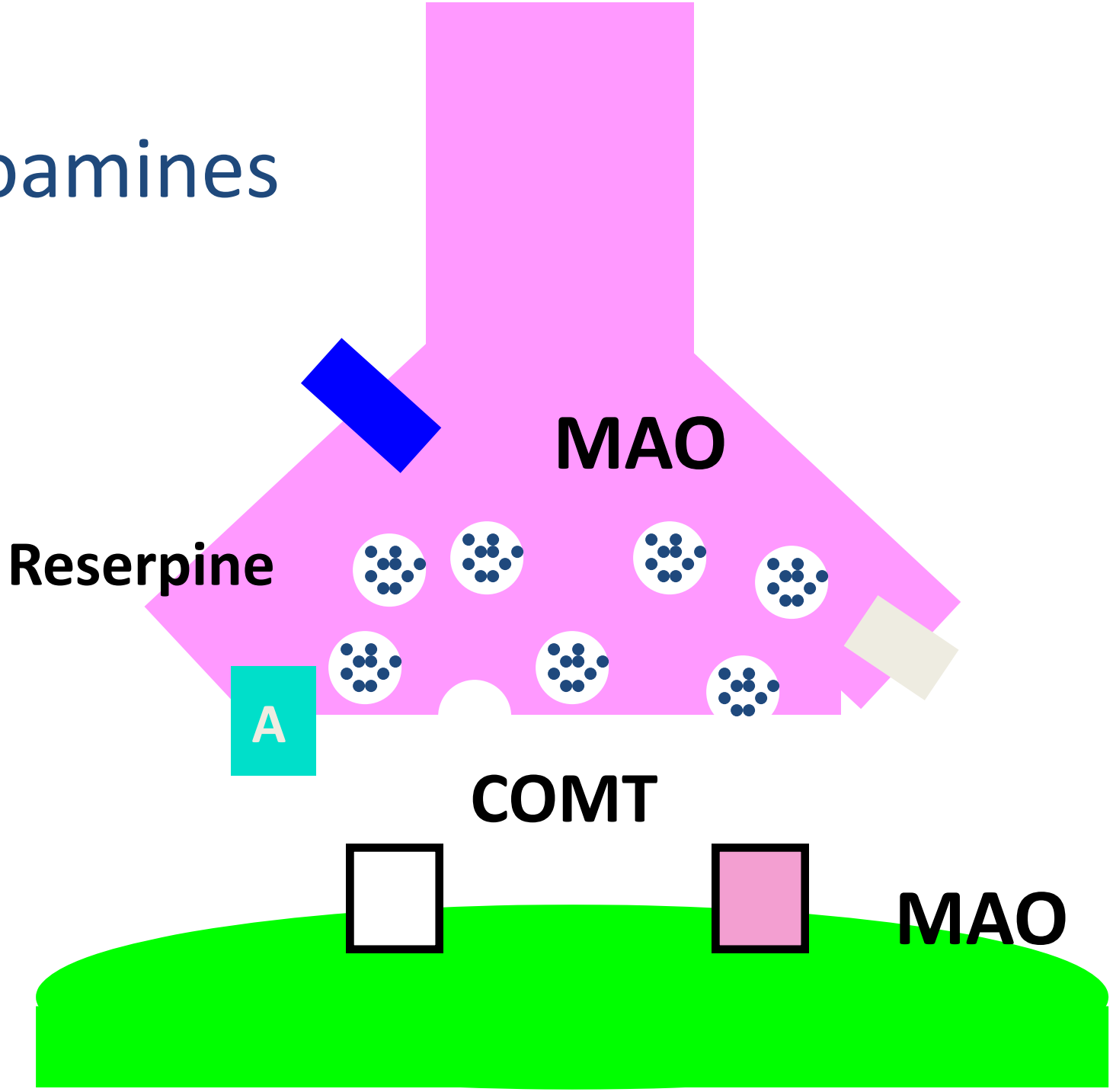
Monoamines

Terminated by...

- •reuptake
- •monoamine oxidase - MAO
- •catechol-O-methyltranferase - COMT
- •also in liver

- Reserpine ---> leaky vesicles
  depletes monoamines ~

Monoamines



Indirect Monoamine Agonists

- **MAOIs**

  Iproniazid

- **Reuptake blockers**

  – Tricyclic antidepressants

    - Imipramine
    - Desipramine

  Cocaine & Amphetamine

Catecholamines:

The amino acid tyrosine is the precursor
NT is released thru axononal varicosities: swellings on the axon

1. **Norepinephrine (NE) noradrenalin**
   A. in the CNS this is produced in the locus ceruleus (nucleus in midbrain) & is distributed though out the CNS

2. **Epinephrine (E) adrenaline**
   A. works at the same receptors as NE
   B. stimulates the sympathetic nervous system
   C. ephedrine: alpha & beta receptor agonist
   D. propranolol: beta receptor blocker has antihypertensive effects

3 Dopamine (DA)

A. produced in substantia nigra & ventral tegmental area (midbrain) & sent to the cortex, limbic system, hypothalamus, & basal ganglia
B. implicated in movement disorders e.g., in Parkinson's disease (L-DOPA)
C. cocaine and amphetamine work by preventing reuptake
D. apomorphine: stimulates only autoreceptors (an antagonist)

Dopamine

- Only in central nervous system
  mostly inhibitory systems

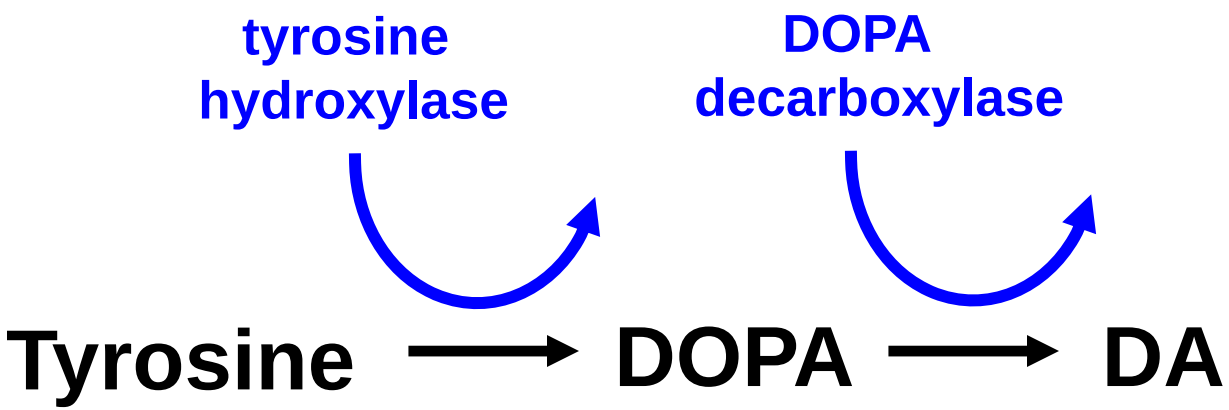
  Controls arousal levels and motor control in many parts of the brain. When levels are severely depleted in Parkinson's disease, patients are unable to move voluntarily. LSD and other hallucinogenic drugs are thought to work on the dopamine system.

- Reward
- Schizophrenia
- Movement
  - **Nigrostriatal Pathway**
- At least 5 DA-R types: D_1, D_2,D3 etc.

Dopaminergic Drugs

- Agonist
  - L-dopa
- Antagonists
  - Chlorpromazine
    - D_1
  - Haloperidol
    - D_2

Dopamine Synthesis



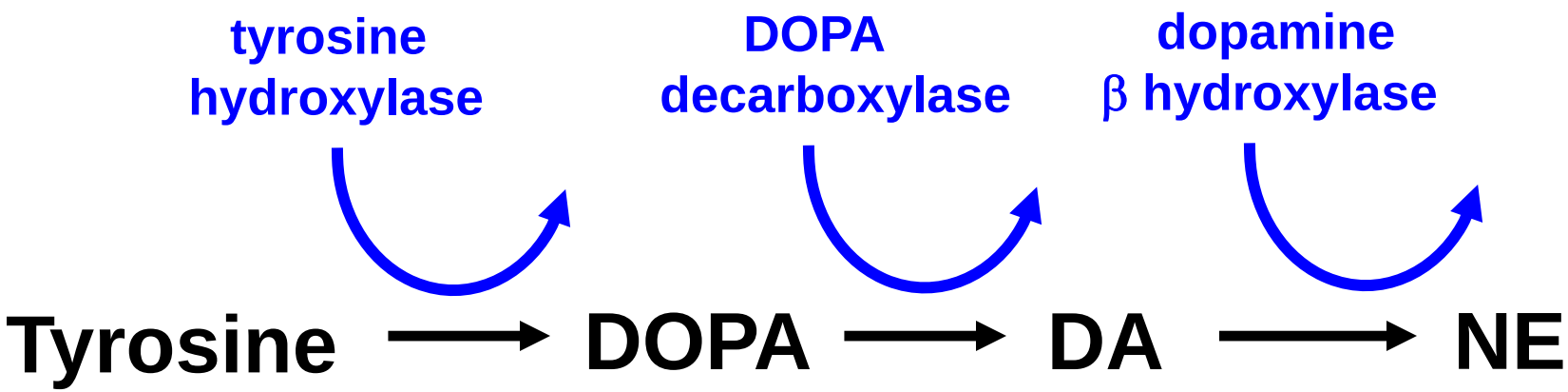
Norepinephrine

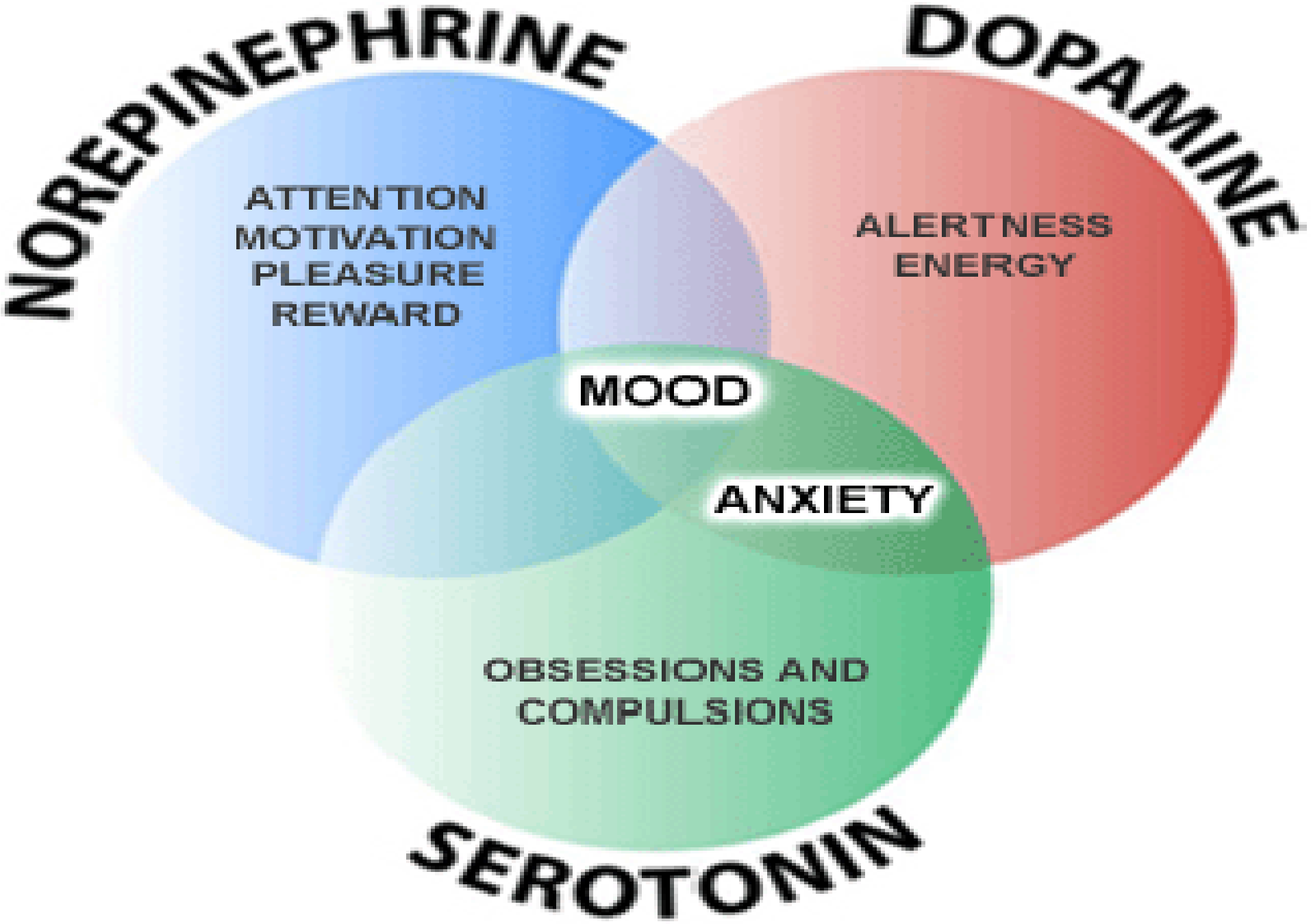
- Peripheral N.S.
  - Sympathetic neuroeffector junction
  - Adrenal glands
- Central N.S.
  - Hypothalamus
  - Locus coeruleus
- Alpha & Beta receptor subtypes
  - NE_{α} & NE_{β} ~

Noradrenergic Drugs

- Agonists
  - Mescaline
  - Ephedrine
- Antagonist
  - Propranalol -
  - beta receptors ~

Norepinephrine Synthesis




NOREPINEPHRINE
DOPAMINE
ATTENTION
MOTIVATION
PLEASURE
REWARD
ALERTNESS
ENERGY
MOOD
ANXIETY
OBSESSIONS AND
COMPULSIONS
SEROTONIN

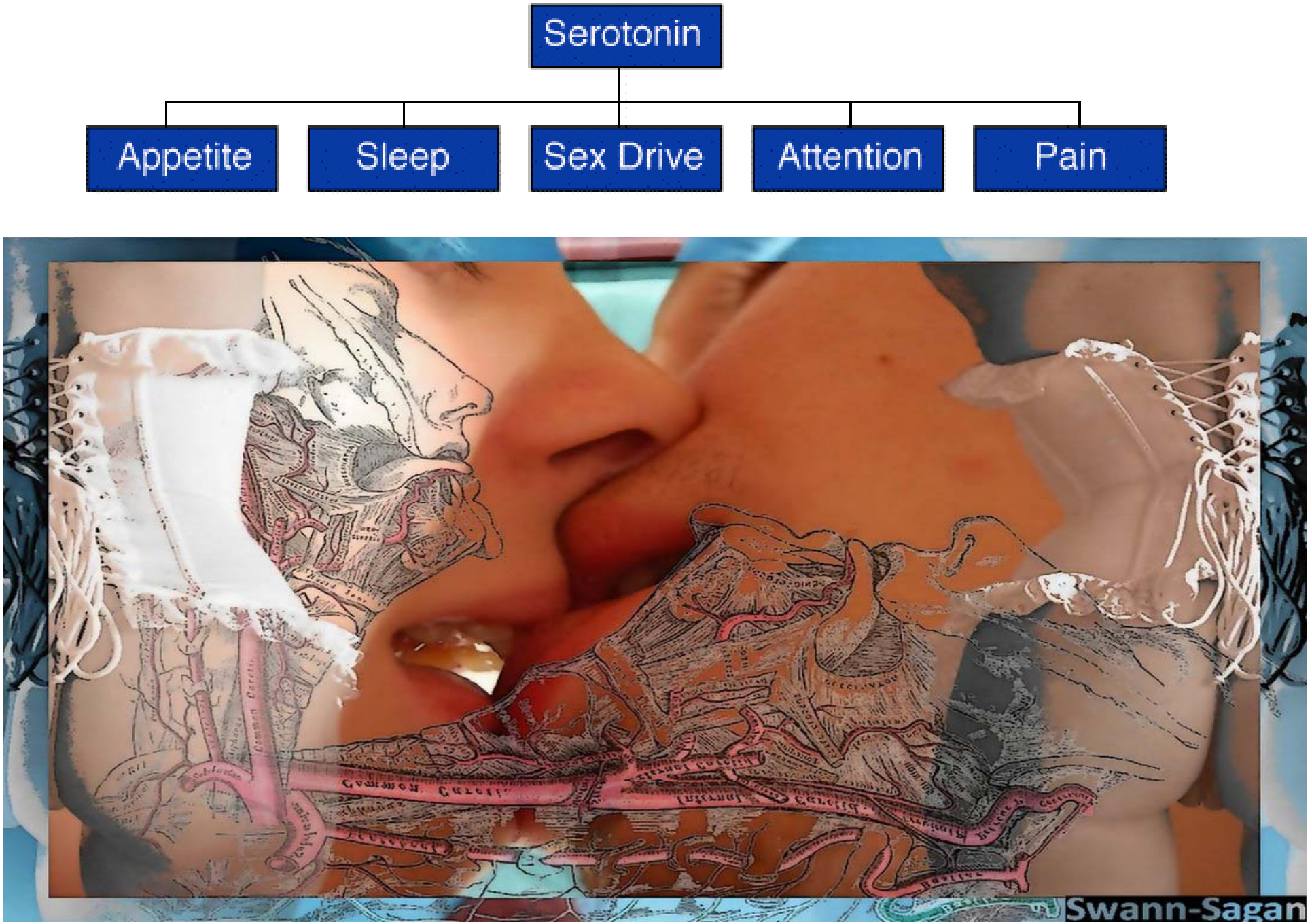
Serotonin

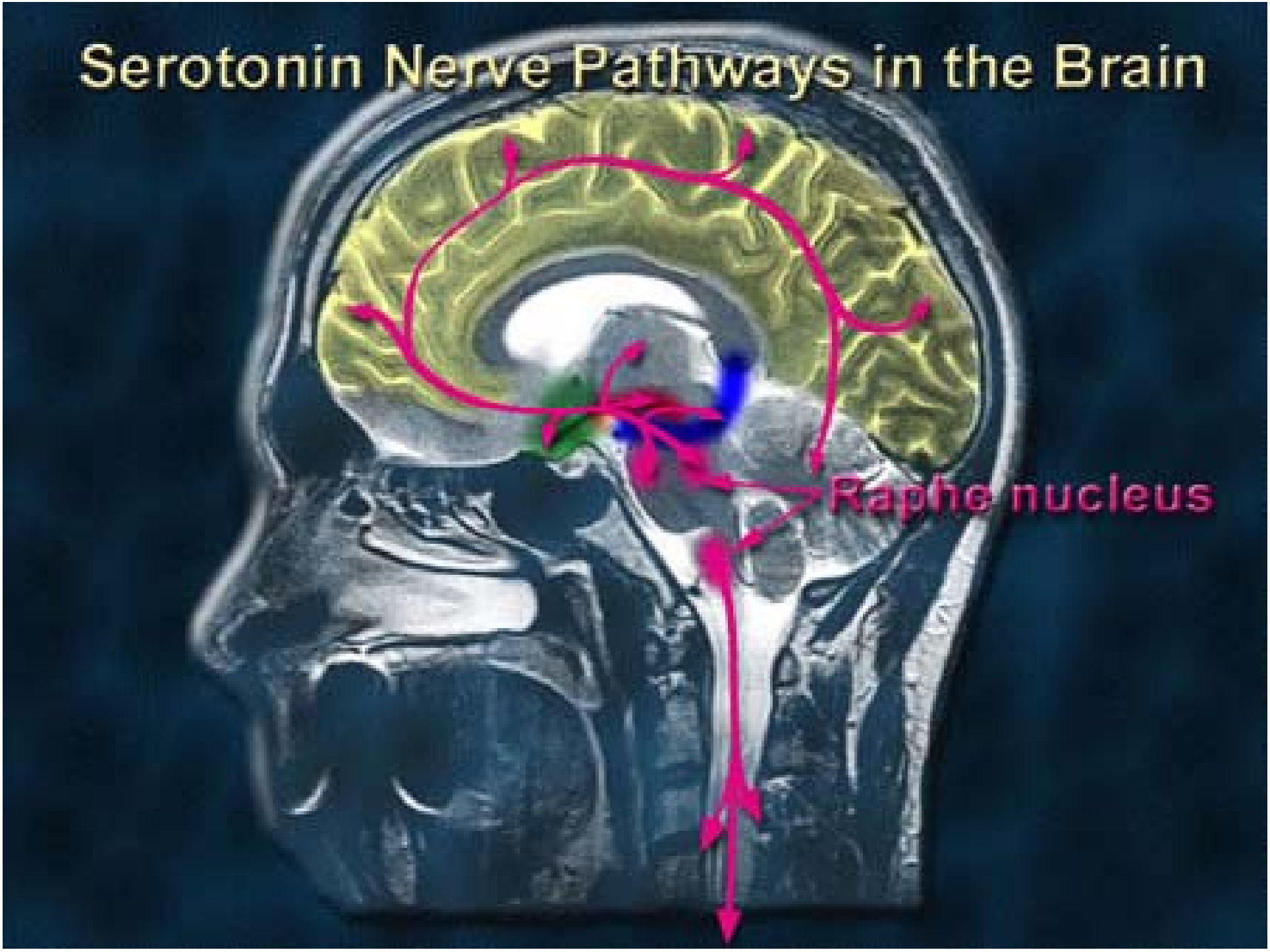
- NOT a catecholamine
- Peripheral

  98% in blood & smooth muscle
- Central N.S.

  Raphe nucleus

  Hypothalamus
- R subtypes: $5HT_1$ & $5HT_2$ ~

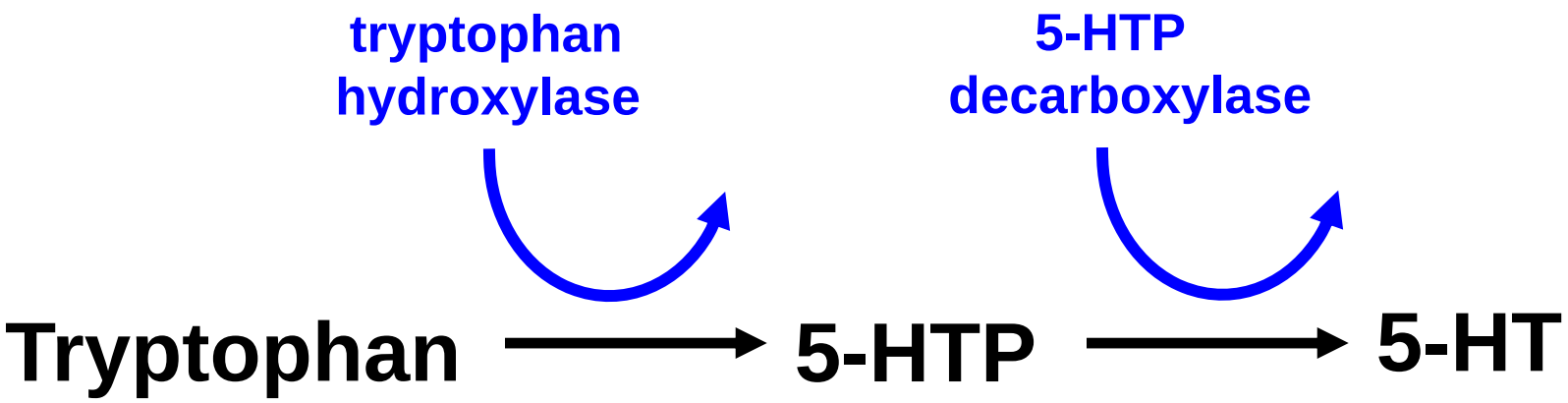

Serotonin
Appetite
Sleep
Sex Drive
Attention
Pain
Swann-Sagan


Serotonin Nerve Pathways in the Brain
Raphe nucleus

Sertonergic Drugs

- Agonists
  - **SSRIs**
    - Selective Serotonin Reuptake Inhibitors
  - **Buspirone**
  - MDMA
    - **Ecstacy**

Serotonin Synthesis



Gamma-aminobutyric acid

- GABA - GABAergic
- **Major NT in brain inhibitory system**
- Receptor subtypes

  $GABA_A$ - controls Cl- channel

  $GABA_B$ - controls K+ channel
- Precursor = glutamate ~

Neuropeptide

- Substance P - pain signaling
- Endorphins - analgesia, euphoria ~

Endorphins

Enkephalins and Endorphins

These are opioids that, like the drugs heroine and morphine, modulate pain, reduce stress etc.
They may be involved in the mechanisms of physical dependence.

- **Opioids**
  - **Dynorphin**
  - **met-enkephalin**
  - **leu-enkephalin**
  - **Beta-endorphin**

- **Agonists**
  - **morphine**
  - **heroin**
  - **codeine**
- **Antagonists**
  - **naloxone**
  - **naltrexone ~**

Other NTs

- Excitatory amino acids
  - Glutamate & Aspartate
- Histamine
  - Inflammatory Response
- Nitric Oxide - It's a gas
- Anandamide

Glutamate

- The brain's major excitatory neurotransmitter,
- vital for forging the links between neurons that are the basis of learning and long-term memory.

Neurotransmitter deficiency over 60 condition are related

- **Depression**
- **Anxiety**
- **Panic Attacks**
- **Insomnia/Sleep disorders**
- **Premenstrual Tension**
- **Fibromyalgia**
- **Obesity**
- **Anorexia**
- **Bulimia**
- **“Hypoglycemia”**
- **Chronic pain states**
- **Migraines**
- **ADD/ADHD**

Three Drugs (of many) which affect Neurotransmission

Methamphetamine

seattlepi.nwsource.com/ methamphetamines/

Nicotine

marlboro-cigarette.net

Alcohol

science.howstuffworks.com/ alcohol.htm

Methamphetamine alters **Dopamine** transmission in two ways:

1. Enters dopamine vesicles in axon terminal causing release of NT
2. Blocks dopamine transporters from pumping dopamine back into the transmitting neuron

More dopamine in the Synaptic Cleft causes neurons to fire more often than normal resulting in a euphoric feeling

seattlepi.nwsource.com/methamphetamines/

NIH Publication No. 00-4871

1. After the drug wears off, **dopamine** levels drop, and the user "crashes". The euphoric feeling will not return until the user takes more **methamphetamine**

2. **Long-term use of methamphetamine causes dopamine axons to wither and die.**

3. Note that **cocaine** also blocks **dopamine** transporters, thus it works in a similar manner.

- **Nicotine** binds to the **presynaptic** receptors exciting the neuron to fire more action potentials causing an **increase** in **dopamine** release.
- **Nicotine** also affects neurons by **increasing** the **number of synaptic vesicles released**.

NIH Publication No. 00-4871

How does alcohol affect synapses?

- Alcohol has multiple effects on neurons. It alters neuron membranes, ion channels, enzymes, and receptors.

- It **binds directly to receptors** for acetylcholine, serotonin, and gamma aminobutyric acid (GABA), and glutamate.

- We will focus on **GABA** and its receptor.

Alcohol and the GABA Receptor

- When alcohol enters the brain, it binds to **GABA** receptors and amplifies the **hyperpolarization** effect of **GABA**.
- The neuron activity is further diminished
- This accounts for some

  of the **sedative affects**

  of alcohol

science.howstuffworks.com/ alcohol.htm

The Adolescent Brain and Alcohol

From AMA pub 9416

- The brain goes through dynamic change during adolescence, and alcohol can seriously **damage long- and short-term growth processes**.
- **Frontal lobe development** and the refinement of pathways and connections continue until age 16, and a high rate of energy is used as the brain matures until age 20.
- **Damage from alcohol at this time can be long-term and irreversible.**

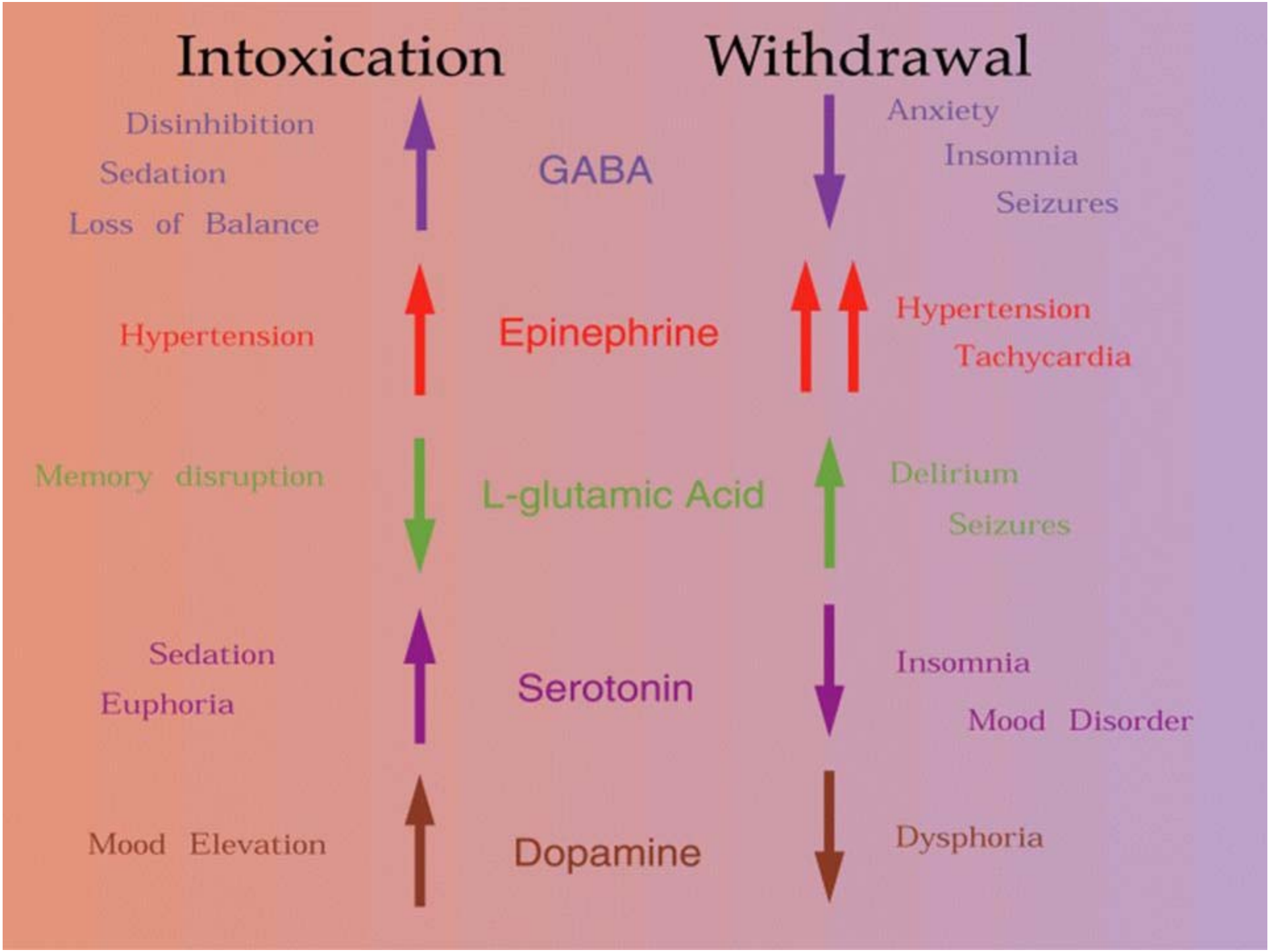
The Adolescent Brain (cont.)

- In addition, **short-term or moderate drinking impairs learning and memory** far more in youth than adults.
- **Adolescents need only drink half as much as adults to suffer the same negative effects.**
- To see an animation of GABA receptors and the influence of alcohol, http://www.thirteen.org/closetohome/animation/gaba-anim-main.html

Drugs That Influence Neurotransmitters

Change in Neurotransmission	Effect on Neurotransmitter release or availability	Drug that acts this way
increase the number of impulses	increased neurotransmitter release	nicotine, alcohol, opiates
release neurotransmitter from vesicles with or without impulses	increased neurotransmitter release	amphetamines methamphetamines
release more neurotransmitter in response to an impulse	increased neurotransmitter release	nicotine
block reuptake	more neurotransmitter present in synaptic cleft	cocaine amphetamine
produce less neurotransmitter	less neurotransmitter in synaptic cleft	probably does not work this way
prevent vesicles from releasing neurotransmitter	less neurotransmitter released	No drug example
block receptor with another molecule	no change in the amount of neurotransmitter released, or neurotransmitter cannot bind to its receptor on postsynaptic neuron	LSD caffeine

NIH Publication No. 00-4871


Intoxication
Withdrawal
Disinhibition
Sedation
Loss of Balance
GABA
Anxiety
Insomnia
Seizures
Hypertension
Epinephrine
Hypertension
Tachycardia
Memory disruption
L-glutamic Acid
Delirium
Seizures
Sedation
Euphoria
Serotonin
Insomnia
Mood Disorder
Mood Elevation
Dopamine
Dysphoria

Acetylcholine deficiency

Acetylcholine deficiency signs/symptoms:

Difficulty remembering names and faces after meeting people
Difficulty remembering peoples birthdays and numbers
Difficulty remembering lists, directions or instructions
Forgetting common facts
Trouble understanding spoken or written language
Forget where I put things (e.g. keys)
Making simple mistakes at work
Slowed and confused thinking
Difficulty finding the right words before speaking
Disorientation
Prefer to do things alone than in groups / social withdrawal
Rarely feel passionate
Feel despair and lack joy
Lost some of my creativity
Lack imagination
Dry mouth

Acetylcholine levels may be low due to a combination of genetic and acquired reasons. Acetylcholine can be raised effectively using either nutrient based therapies or medications.

Factors which reduce acetylcholine levels:

Choline (precursor) deficiency
B1 & B5 deficiency
Chronic stress
Inadequate sleep
Elevated blood sugar/insulin resistance
Mercury, lead, aluminium, PCB's, fertilizers, pesticides and EMF exposure
Over-methylation

Clinical Aspects of ACh Systems

Alzheimer's disease

loss of ACh neurons in
the basal nucleus of Meynert

Aricept—ACh agonist

Dopamine deficiency

Dopamine deficiency signs/symptoms:

Physically fatigued easily
Sleep too much and trouble getting out of bed
Reduced ability to feel pleasure
Flat, bored, apathetic
Low drive, motivation & enthusiasm
Depressed
Difficulty getting through a task even when interesting to me
Procrastinator/little urgency
Shy/introvert
Mentally fatigued easily
Difficulty paying attention and concentrating
Slow thinker and/or slow to learn new ideas
Put on weight easily
Crave uppers (e.g. caffeine/sugar/nicotine/diet soft drinks/cocaine/amphetamines)
Use these improve energy/motivation/mood
Prone to addictions (e.g. alcohol)/addictive personality
Light headedness
Reduced libido and/or impotence
Family history of depression/alcoholism/ADD

Dopamine levels may be low due to a combination of genetic and acquired reasons. Dopamine can be raised effectively using either nutrient based therapies or medications. Dopamine is synthesized form the amino acid tyrosine.

Factors which reduce dopamine levels:

Chronic stress
Inadequate sleep
Hypothyroidism
Lead, arsenic and cadmium exposure
Under-methylation
Tyrosine (precursor) deficiency
Magnesium, iron, zinc & vitamins B3/B6/C/D deficiency
Excess copper levels
Genetic dopamine receptor abnormalities
Chronic opioid, alcohol & marijuana use
Adrenal insufficiency
Glutathione deficiency
Parkinson's Disease
Influenza
Estrogen deficiency
Human growth hormone deficiency

Endorphin deficiency

Endorphin deficiency signs/symptoms:

Very emotionally sensitive
Cry easily
Emotional pain really gets to you
Find it hard to get through losses or grieving
Difficulty experiencing pleasure
Been through a lot of physical or emotional pain
Overly responsible or time urgent
Low pain tolerance
Chronic pain (e.g. back aches, neck aches)
Physical pain really gets to you
Use alcohol/chocolate/carbs for relaxation, numbing, or comfort
Use codeine, methadone, darvon, heroin
    Have had difficulty stopping one of these

Endorphin levels may be low due to a combination of genetic and acquired reasons.
Endorphins can be raised effectively using either nutrient based therapies or medications.

Factors which reduce endorphin levels:

Chronic stress
Chronic pain
Chronic GABA deficiency
Chronic opioid and alcohol use
Chronic inflammation
Genetic endorphin deficiency

GABA deficiency

GABA deficiency signs/symptoms:

Anxious/nervous/jumpy/'on edge'
Feel panicky/panic attacks
Feel stressed/pressured/overwhelmed
Have trouble relaxing/loosening up
Low stress tolerance
Body tends to be tense/stiff/uptight
Butterflies in stomach
Lump in throat
Trembling/twitching/shaking
Sweaty, clammy hands
Sleep problems
Valium/xanax/avitan/GABA relax you
Use alcohol/food/cigarettes to relax
Heart palpitations and fast pulse
History of having seizures
Family history of anxiety or panic attacks

Factors which reduce GABA levels:

Glutamaine (precursor) deficiency
B1, B6, zinc, manganese & iron deficiency
Chronic stress
Chronic pain
Inadequate sleep
Progesterone deficiency
Mercury and lead exposure
Alcohol withdrawal
Caffeine excess
Excessive electromagnetic radiation
Excessive loud noise exposure

GABA is our relaxing (anti-anxiety) neurotransmitter which is raised by valium.
GABA levels may be low due to a combination of genetic and acquired reasons.
GABA can be raised effectively using either nutrient based therapies or medications. GABA is synthesized from the amino acid glutamine.

Serotonin deficiency

Serotonin deficiency signs/symptoms:

Depressed
Nervous/anxious
Worrier
Fears/phobias
Negative/pessimistic
Irritable/impatient/edgy
Obsessive compulsive tendency
Think about the same things over & over again
Self destructive or suicidal thoughts/plans
Low self esteem/confidence
Rage/anger/explosive behavior/assaultive
Sleep problems/light sleeper
Feel worse in & dislike dark weather
Crave sugar/carbohydrates/alcohol/marijuana
    Use these substances to improve mood & relax
Chronic pain (e.g. headaches, backaches, fibromyalgia)
PMS
Antidepressants or 5-HTP improve mood
Family history of depression/anxiety/OCD/eating disorders

Serotonin levels may be low due to a combination of genetic and acquired reasons. Serotonin can be raised effectively using either nutrient based therapies or medications. Serotonin is synthesized from the amino acid tryptophan.

Factors which reduce serotonin levels:

Stress
PCB's, pesticides and plastic chemicals exposure
Under-methylation
Inadequate sunlight exposure
Tryptophan (precursor) deficiency
Iron, calcium, magnesium, zinc, B3, B6, folate & vitamin C deficiency
Inadequate sleep
Glutathione deficiency
Chronic infections
Food allergies
Genetic serotonin receptor abnormalities
Chronic opioid, alcohol, amphetamine & marijuana use
Human growth hormone deficiency
Progesterone deficiency
Impaired blood flow to brain
Insulin resistance or deficiency

"How do the levels of serotonin and catecholamine neurotransmitters get to such critically low levels?" There are several explanations.

The first is that neurotransmitter **depletion is nutritionally based**.
Neurotransmitters are made from amino acids that must be obtained in the diet.
In addition, amino acids, vitamins and minerals eaten in food are required for the creation of the neurotransmitters.
If the diet is deficient, neurotransmitter deficiency develops.
There are multiple medications that have shown to cause depletion of serotonin and/or catecholamine in the urine. as Prozac, Paxil, Zoloft
These are the medications prescribed to increase the activity of serotonin in the brain such as Prozac, Paxil, Zoloft, etc.
Apparently as a result of increasing the brain level of serotonin, the body increases the metabolism of serotonin and thus the levels slowly
decline because these medications do nothing to increase the level, they just re-circulate the already low level.
Caffeine, ephedrine, ephedra and other stimulants including Ritalin, chocolate, etc. also seem to reduce the effectiveness of
neurotransmitters thereby creating a resistance to neurotransmitters.

Phentermine (of the Phen-Fen diet) actually cause long-term damage to the receptor so that in order to get the effect of serotonin, you have to have an even higher level. This is why so many people gain even more weight after stopping Phen-Fen.

Sensory overload. The brain is bombarded by sounds, rapid visual effects from television, movies, electronic monitors flickering faster than the eye can detect, radio waves, fluorescent artificial light, etc.

All of this requires the brain to modulate this sensory bombardment so that you can stay focused on the task in front of you. Brain overload means that you have to literally calm yourself down.

Rapid lifestyle, stress, over work, etc. may also contribute.

Since the largest source of neurotransmitters is the gastrointestinal tract, dysfunction as discussed above could be a major contributory component. This would include congestive bowel toxicity, candidal/yeast overgrowth conditions, increased intestinal permeability (**leaky gut syndrome)**

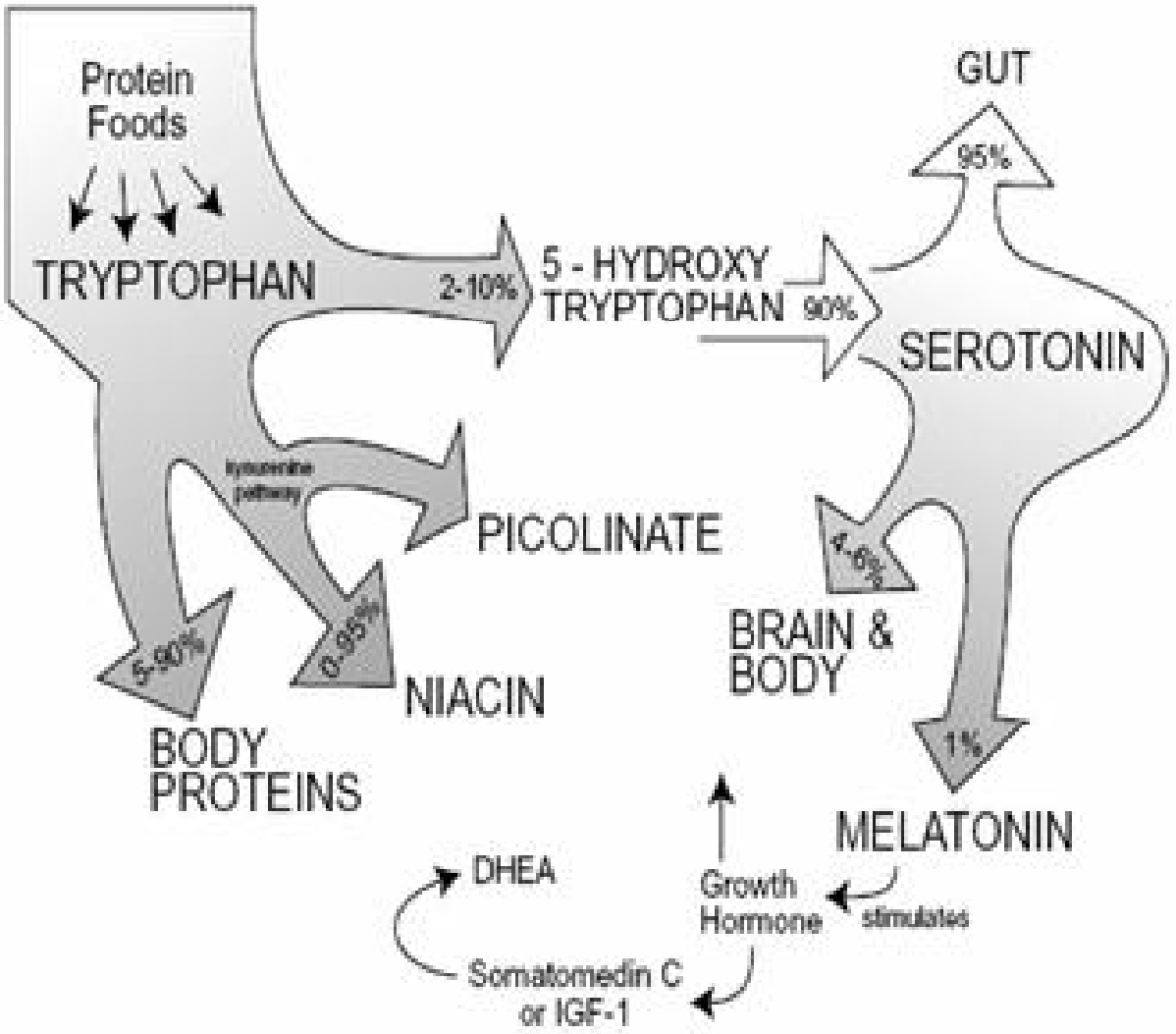
It has been suggested that several SSRI medications deplete 40-60% of the serotonin receptors in the brain. It is also reported that receptors in the liver, kidneys, and colon are also damaged by SSRIs.

ingestion of various food allergens or sensitivities, inhalation or ingestion of various chemicals, chemical sensitivities, rapid changes in hormone levels, rapid changes in barometric pressure, head cold or sinus congestion, rapid changes in blood sugars, dehydration, inadequate exposure to sunlight (hence the excessive conversion of serotonin to melatonin), and hepatobiliary dysfunction. These remarks may be based on the precipitation of migraines, to always be related to serotonin imbalance.

Symptoms seen in complex appetite (misnamed "hypoglycemia")

Tremor	Headaches	Lightheadedness
Dizziness	Sweating	Irritability
Nausea	Anxiety	Disorientation
Goose bump skin	Feeling of uneasiness	Abdominal pain

Figure 2. Tryptophan metabolism.



Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
1.Acetyl choline (Ach)	Excitatory	Acetyl co-A + Choline	Cholinergic nerve endings Cholinergic pathways of brainstem	1.Nicotinic 2.Muscarinic	Broken by acetyl cholinesterase	Cognitive functions e.g. memory Peripheral action e.g. cardiovascular system
2. Catecholamines i. Epinephrine (adrenaline)	Excitatory in some but inhibitory in other	Tyrosine produced in liver from phenylalanine	Adrenal medulla and some CNS cells	Excites both alpha α & beta β receptors	1.Catabolized to inactive product through COMT & MAO in liver 2.Reuptake into adrenergic nerve endings 3.Diffusion away from nerve endings to body fluid	For details refer ANS. e.g. fight or flight, on heart, BP, gastrointestinal activity etc. Norepinehrine controls attention & arousal.
ii.Norepinephrine	Excitatory	Tyrosine, found in pons. Reticular formation, locus coerules, thalamus, mid-brain	Begins inside axoplasm of adrenergic nerve ending is completed inside the secretary vesicles	α_1 α_2 β_1 β_2		
iii. Dopamine	Excitatory	Tyrosine	CNS, concentrated in basal ganglia and dopamine pathways e.g. nigrostriatal, mesocorticolimbic and tubero-hypophyseal pathway	D_1 to D_5 receptor	Same as above	Decreased dopamine in parkinson's disease. Increased dopamine concentration causes schizophrenia

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
3. serotonin (5HT)	Excitatory	Tryptophan	CNS, Gut (chromaffin cells) Platelets & retina	5-HT_1 to 5-HT_7 5-HT_2A receptor mediate platelet aggregation & smooth muscle contraction	Inactivated by MAO to form 5-hydroxyindoleacetic acid(5-HIAA) in pineal body it is converted to melatonin	Mood control, sleep, pain feeling, temperature, BP, & hormonal activity
4. Histamine	Excitatory	Histidine	Hypothalamus	Three types H_1, H_2, H_3 receptors found in peripheral tissues & the brain	Enzyme diamine oxidase (histaminase) cause breakdown	Arousal, pain threshold, blood pressure, blood flow control, gut secretion, allergic reaction (involved in sensation of itch)
5. Glutamate	Excitatory 75% of excitatory transmission in the brain	By reductive amination of Kreb's cycle intermediate α –ketoglutarate.	Brain & spinal cord e.g. hippocampus	Ionotropic and metabotropic receptors. Three types of ionotropic receptors e.g. NMDA, AMPA and kainate receptors.	It is cleared from the brain ECF by Na^+ dependent uptake system in neurons and neuroglia.	Long term potentiation involved in memory and learning by causing Ca^{++} influx.

Neurotransmitter	Postsynaptic effect	Derived from	Site of synthesis	Postsynaptic receptor	Fate	Functions
6. Aspartate	Excitatory	Acidic amines	Spinal cord	Spinal cord	Aspartate & Glycine form an excitatory / inhibitory pair in the ventral spinal cord	
7. Gama amino butyric acid(GABA)	Major inhibitory mediator	Decarboxylation of glutamate by glutamate decarboxylase (GAD) by GABAergic neuron.	CNS	GABA – A increases the Cl^- conductance, GABA – B is metabotropic works with G – protein GABA transaminase catalyzes. GABA – C found exclusively in the retina.	Metabolized by transamination to succinate in the citric acid cycle.	GABA – A causes hyperpolarization (inhibition) Anxiolytic drugs like benzodiazepine cause increase in Cl^- entry into the cell & cause soothing effects. GABA – B cause increase conductance of K^+ into the cell.
8. Glycine	Inhibitory	Is simple amino acid having amino group and a carboxyl group attached to a carbon atom	Spinal cord	Glycine receptor makes postsynaptic membrane more permeable to Cl^- ion.	Deactivated in the synapse by simple process of reabsorbtion by active transport back into the presynaptic membrane	Glycine is inhibitory transmitted found in the ventral spinal cord. It is inhibitory transmitter to Renshaw cells.