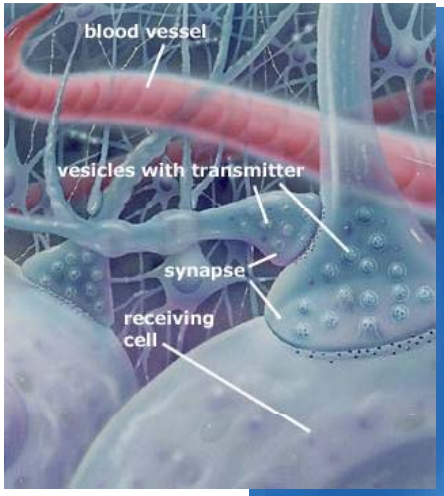
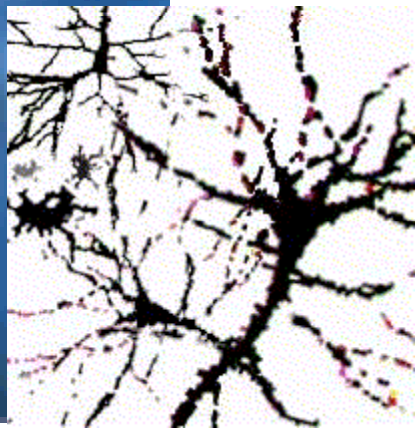
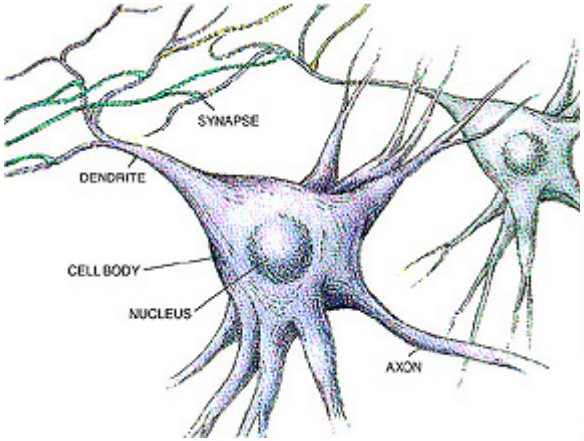
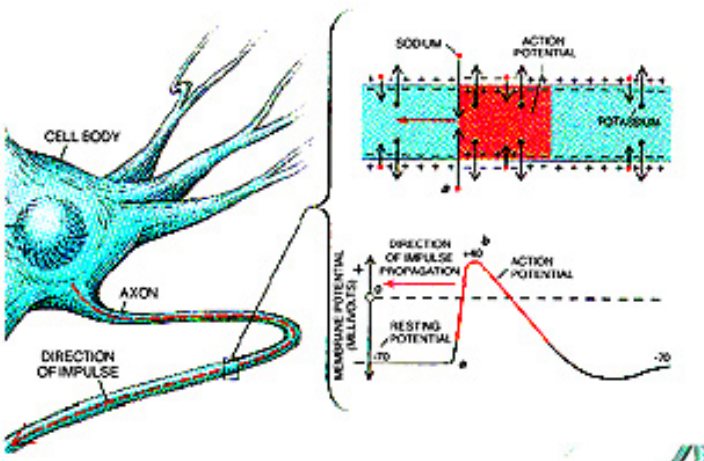
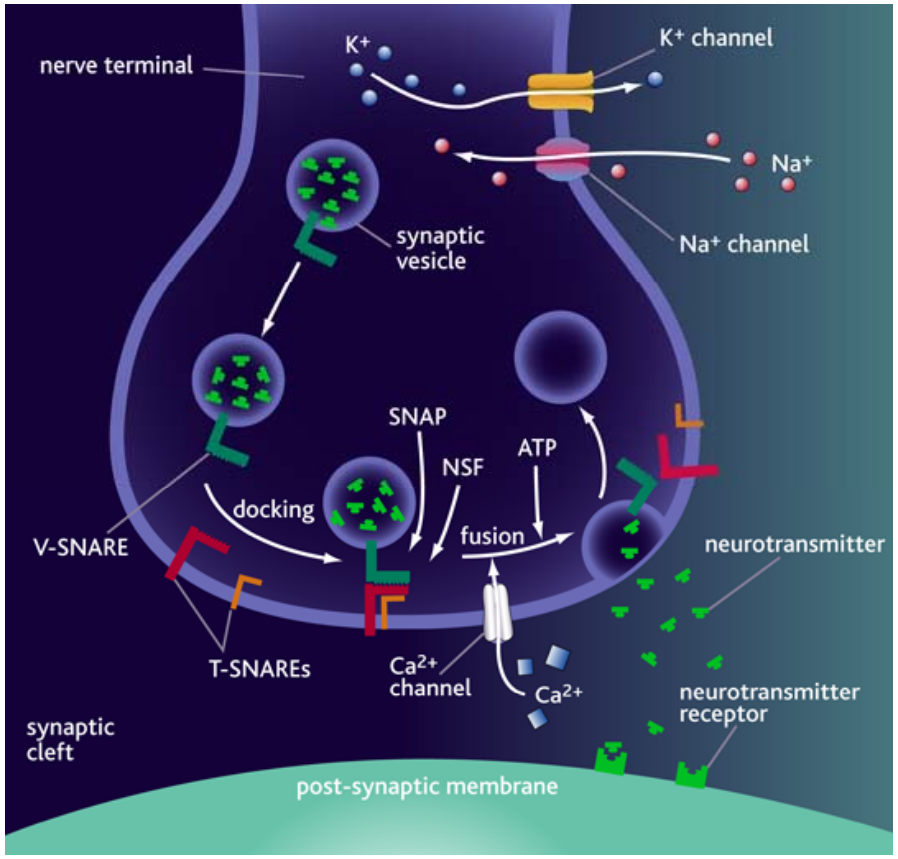


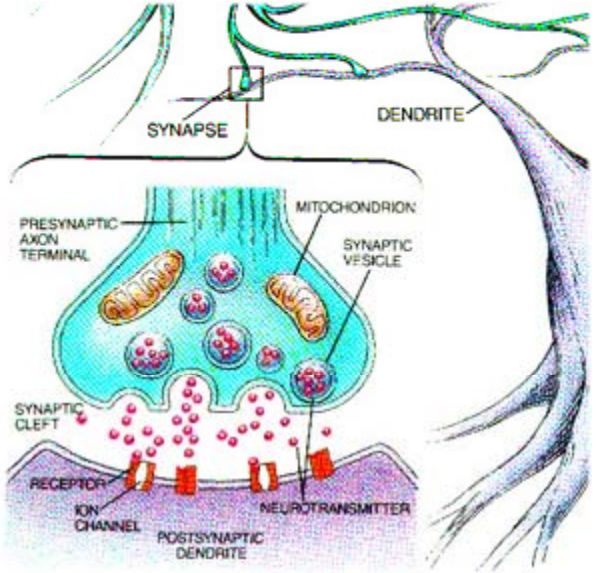
Neurotransmitters

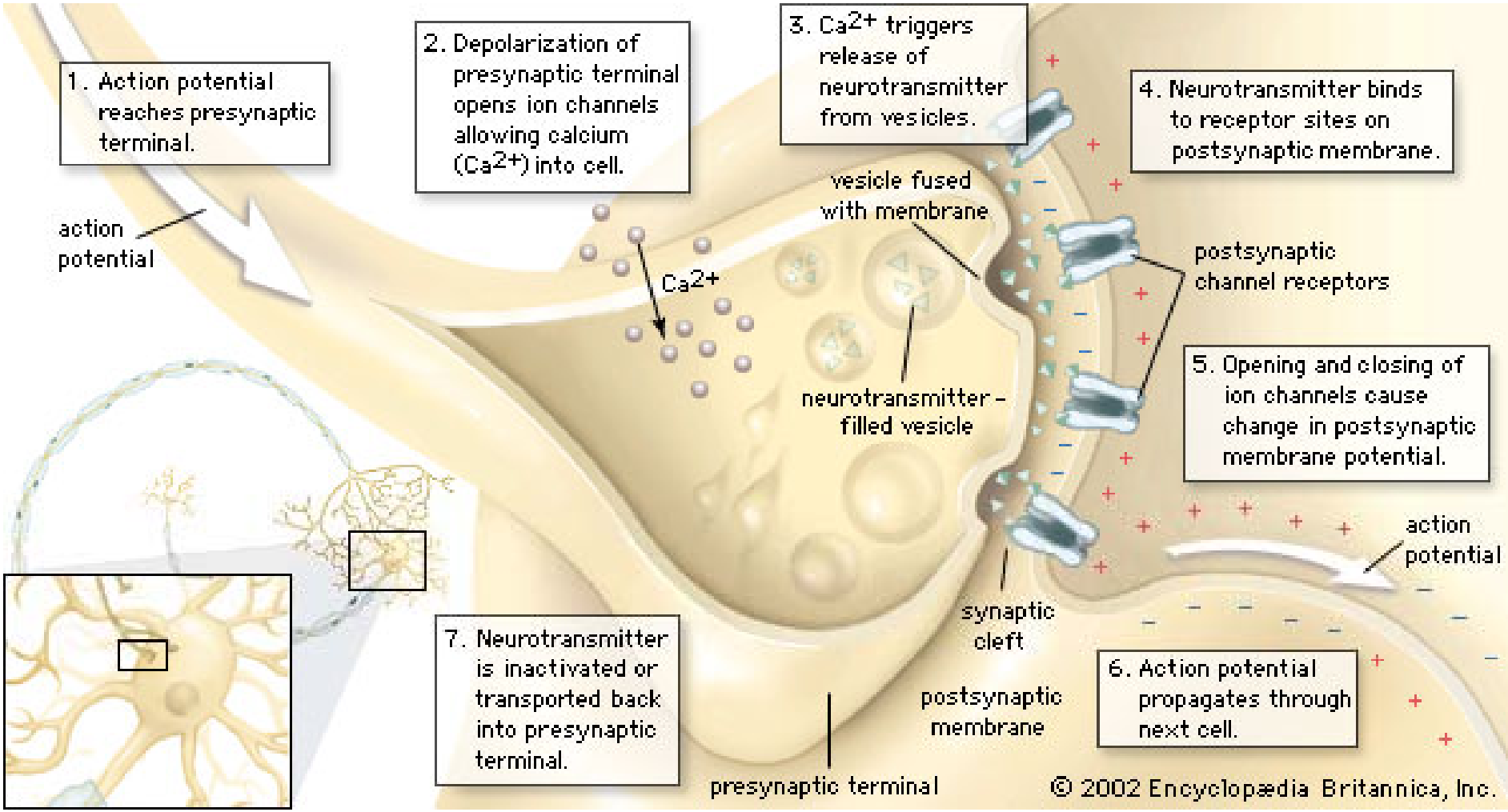



SYNAPSE
DENDRITE
CELL BODY
NUCLEUS
AXON


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


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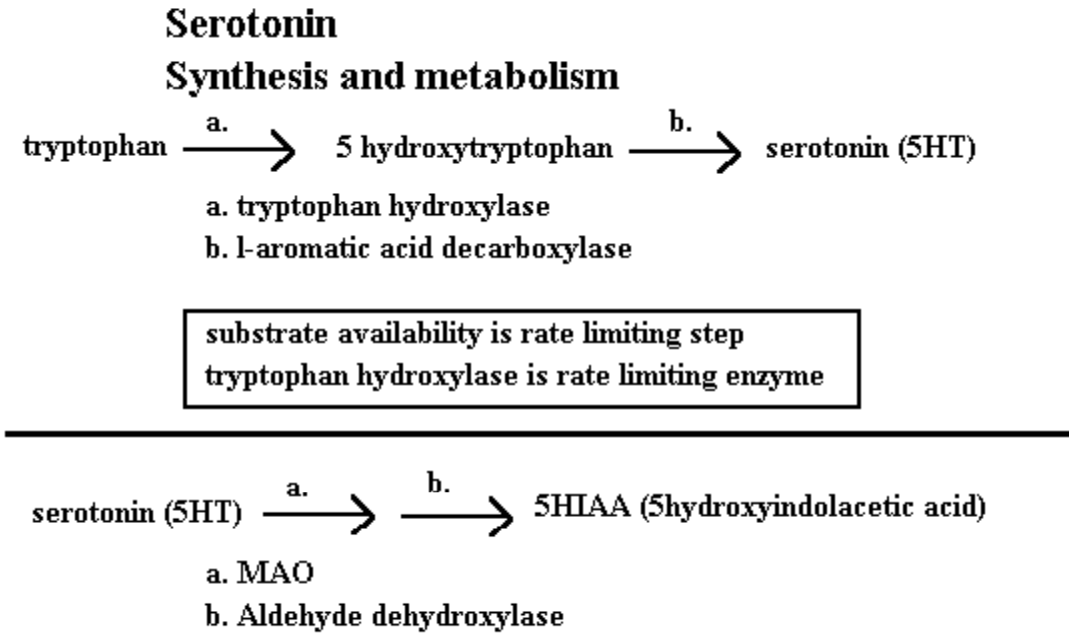
Neurotransmitter synthesis pathways:

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

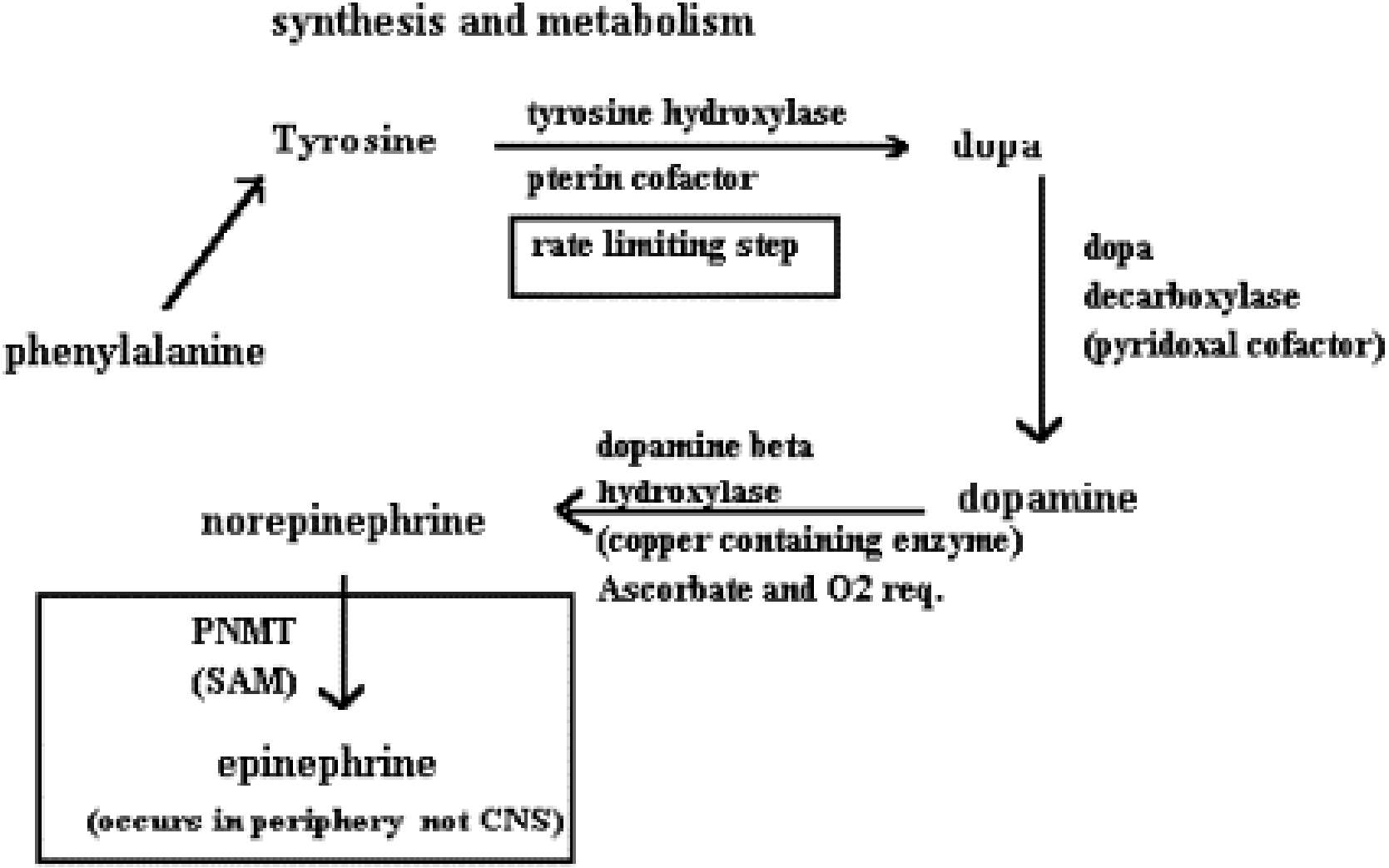
Tryptophan --> 5-Hydroxytryptophan (5-HTP) --> Serotonin (5-Hydroxytryptamine)

Choline + Acetyl-CoA --> Acetylcholine

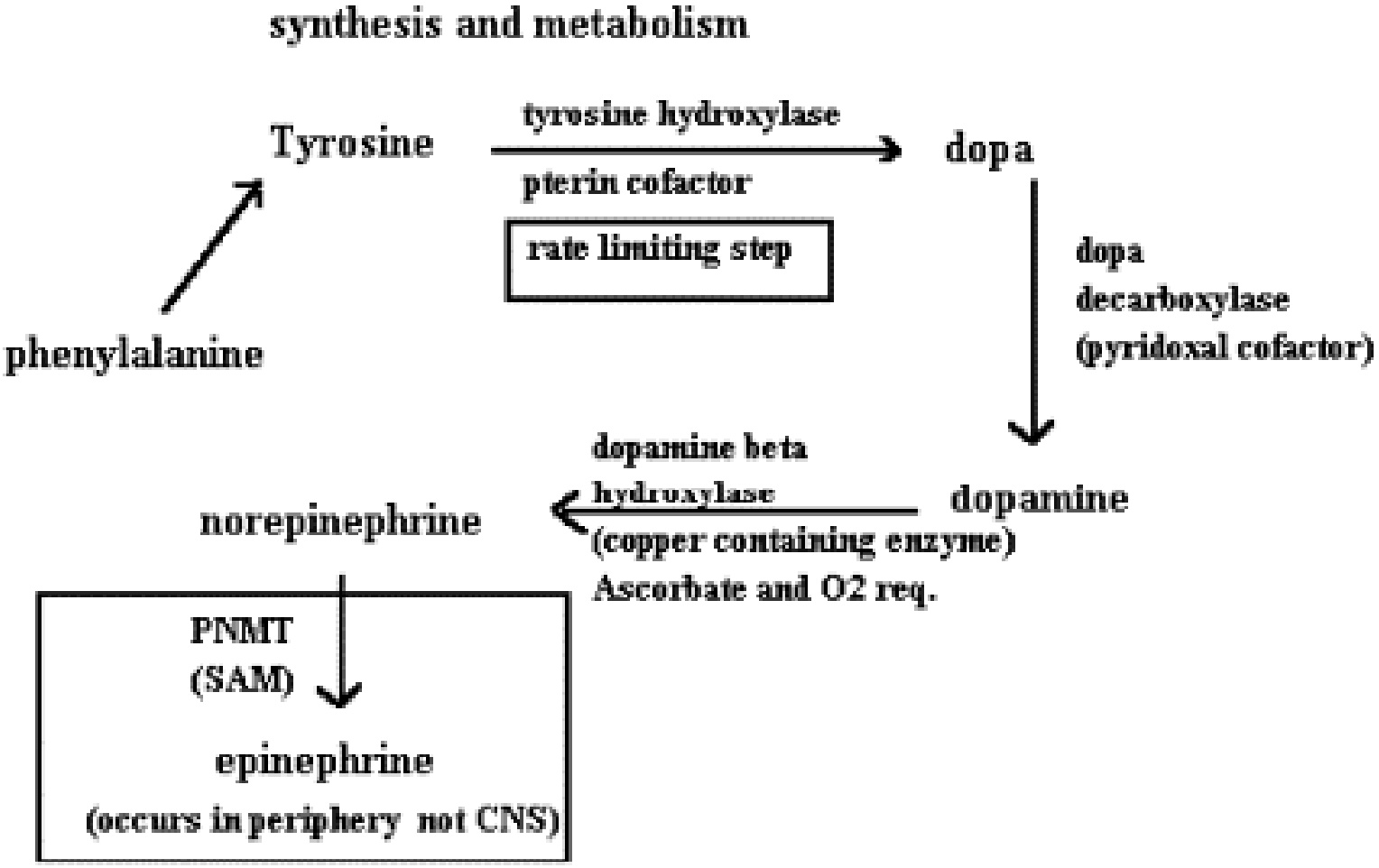
Glutamic acid --> GABA (gamma-amino-butyric-acid)



Catecholamines (dopamine and norepinephrine)

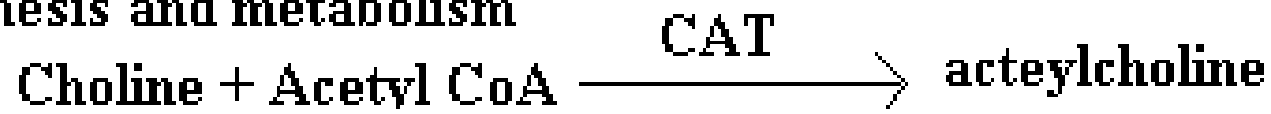


Catecholamines (dopamine and norepinephrine)



Acetylcholine

1. synthesis and metabolism



CAT-Choline acetyl transferase
marker enzyme for Ach neurons

terminates effect at the receptor

2. Central anatomy-interneurons of striatum

pedunculopontine nucleus-projects to thalamus

nucleus basalis-projects to cortex

Neurotransmitters

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

Peptides

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

Neuropeptides

· Insulin
· Betaendorphin
· Neuropeptide Y
· Calcitonin

Types of NT

1.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)

Monoamines

All monoamines work thru metabotropic receptors

Monoamine oxidase (MAO) & catechol-O-methyltransferase (COMT) deactivate these.

1. The drug reserpine prevents the storage of the monoamines

types of monoamines:

I. Indolamines:

1. Serotonin (5-HT)
   A. produced in the raphe nuclei in the midline of the pons & medulla
2. B. the drug parachlorophenylalanine (PCPA) blocks tryptophan hydroxylase & prevents the
   synthesis of 5-HT (an antagonist)
   C. iproniazid block MAO (agonists)

II. 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

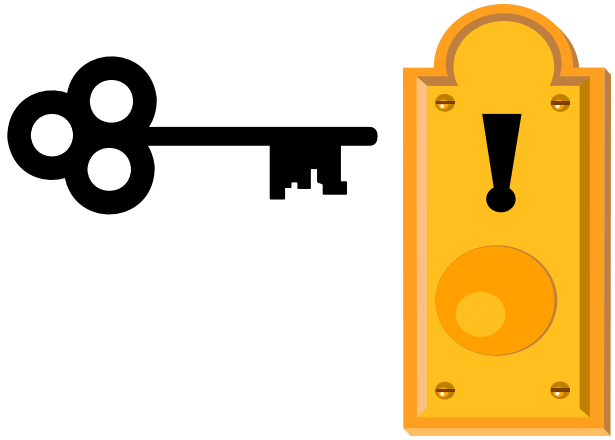
2. Epinephrine (E) adrenaline
 A. works at the same receptors as NE
 B. stimulates the sympathetic nervous system
 C. ephedrine: alpha & beta receptor agonist
 D. propranolol: beta receptor blocker has antihypertensive effects
3 Dopamine (DA)
 A. produced in substantia nigra & ventral tegmental area (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)

CRITERIA

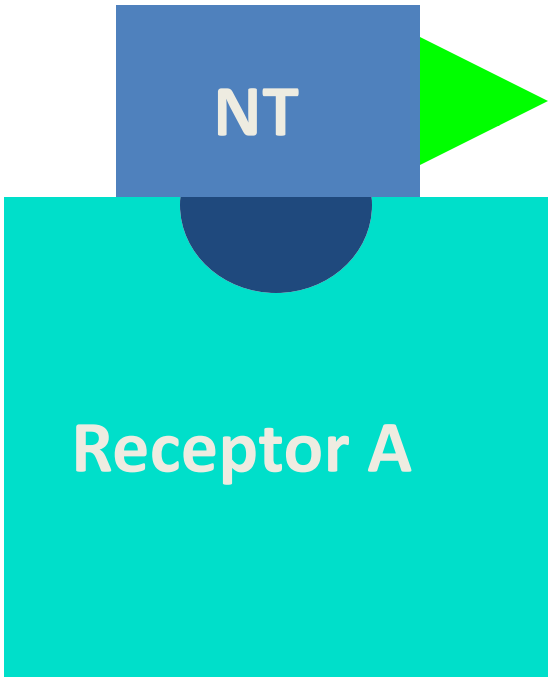
- NT found in axon terminals
- NT released by action potentials
- Synthesis identified
- External application mimic normal Response
- Pharmacology same for normal and externally applied NT ~

Lock & Key Model

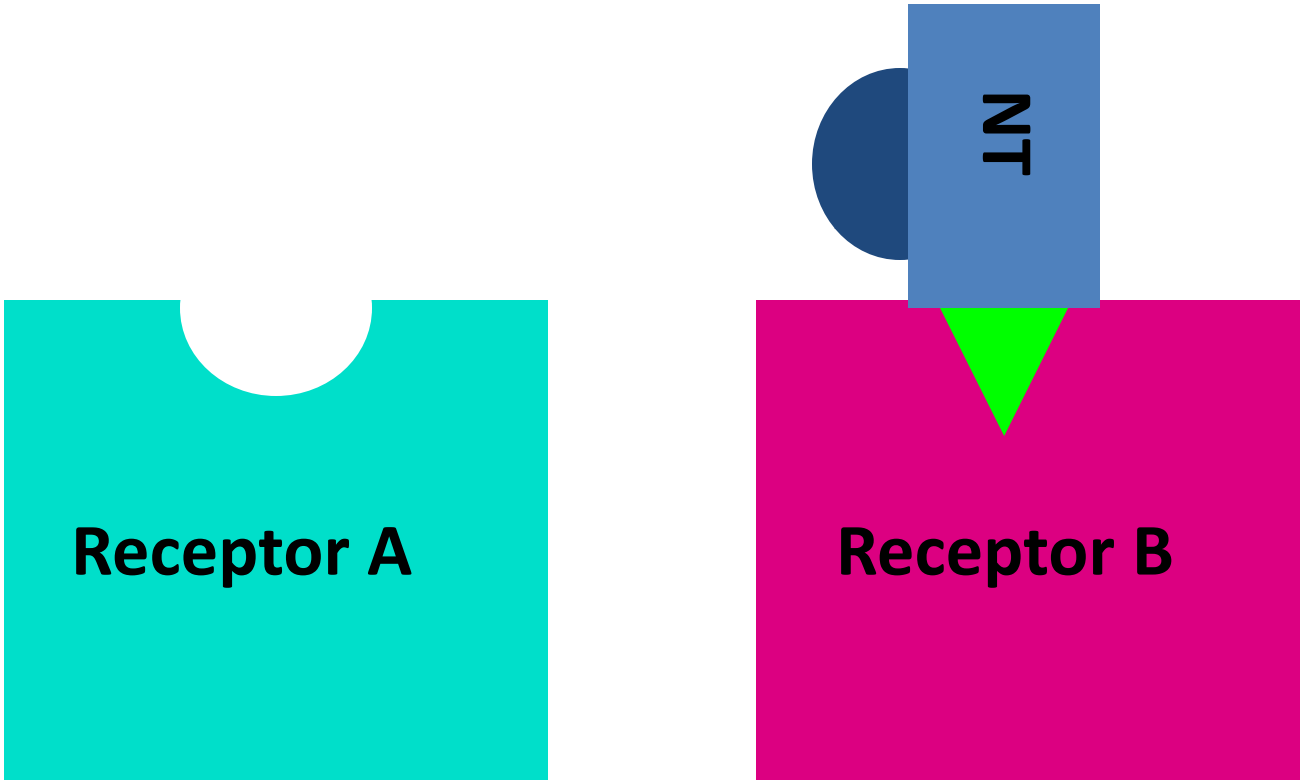
- NT binds to receptor
  - NT = key
  - Receptor = lock
- Receptor changes shape
  - determines if EPSP or IPSP
  - receptor subtypes
- NOT NT ~



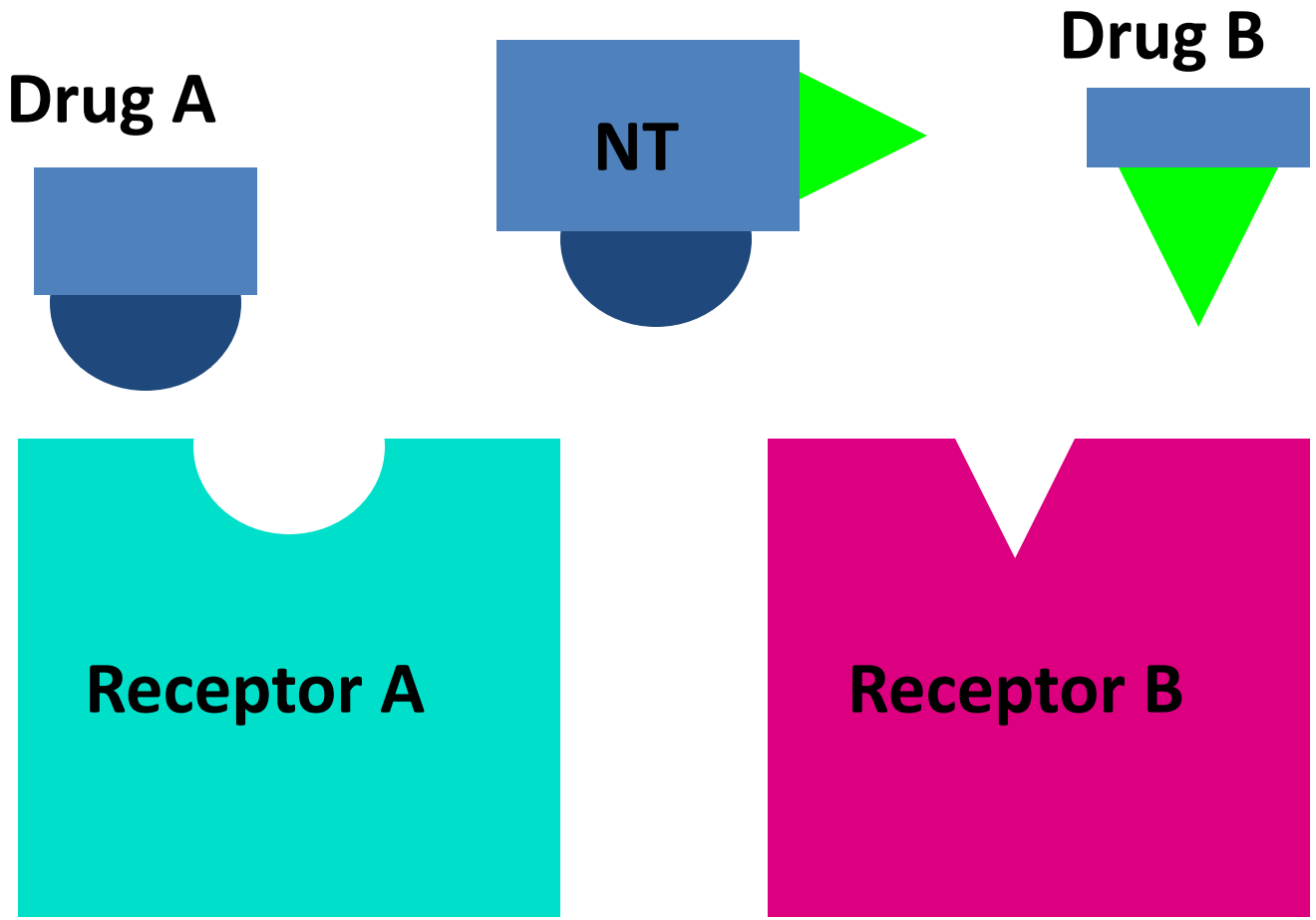
- ligand binds to receptor
- activation: + or - ~



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



Specificity of drugs



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

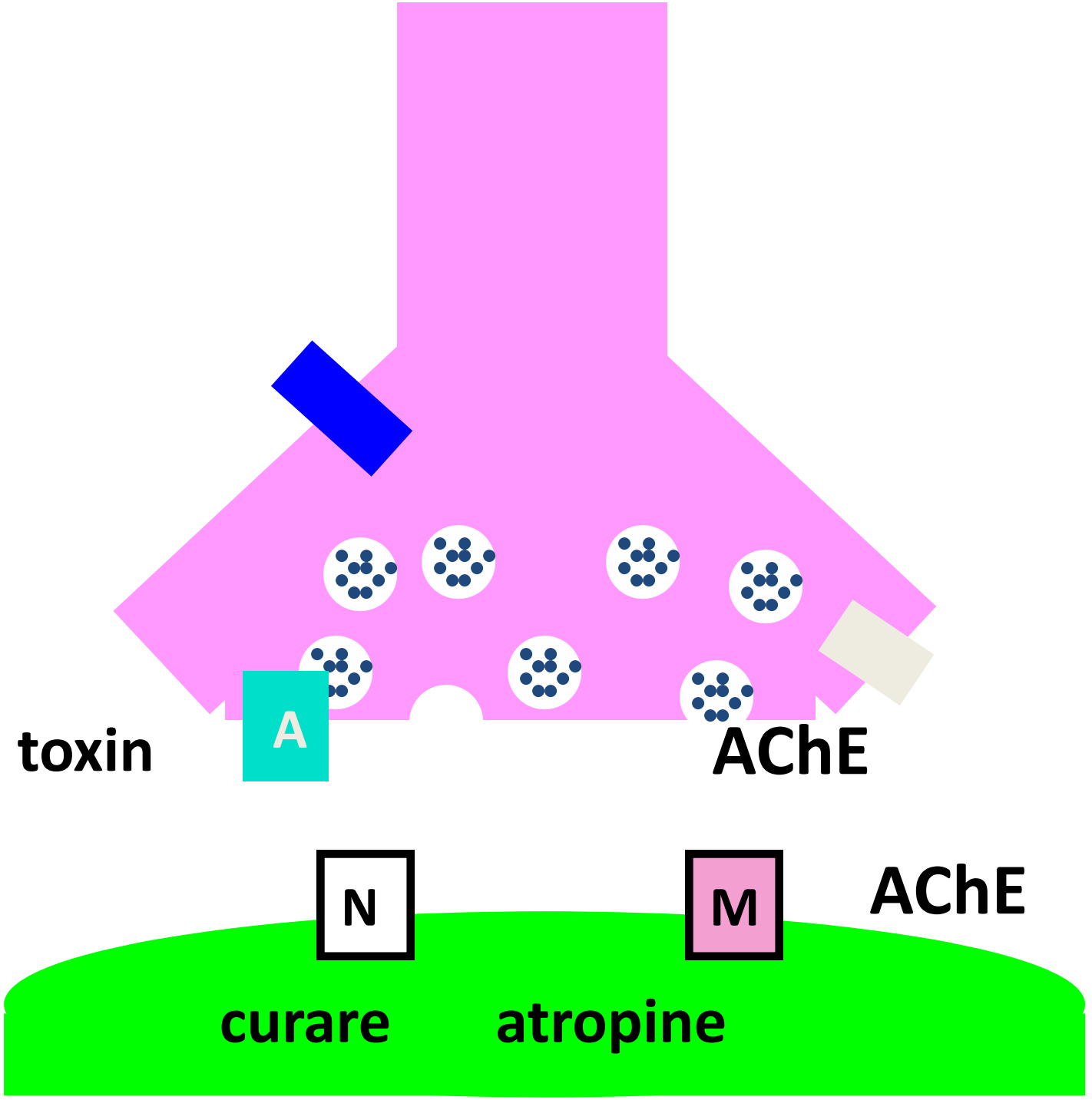
  Scopolamine

- Indirect

  Botulinum Toxin

  Black Widow Spider Venom ~

ACh



Botulinum toxin

BWSV

Monamines

- Amino acid precursors
  - single amine group
- 2 groups

  Catecholamines - catechol ring

  Indolamine - indole ring
- Affected by many of same drugs ~

Monoamines

- Catecholamines

  Dopamine - DA
  - Dopaminergic

  Norepinephrine - NE
  - Noradrenergic

  Epinephrine - E
  - Adrenergic ~

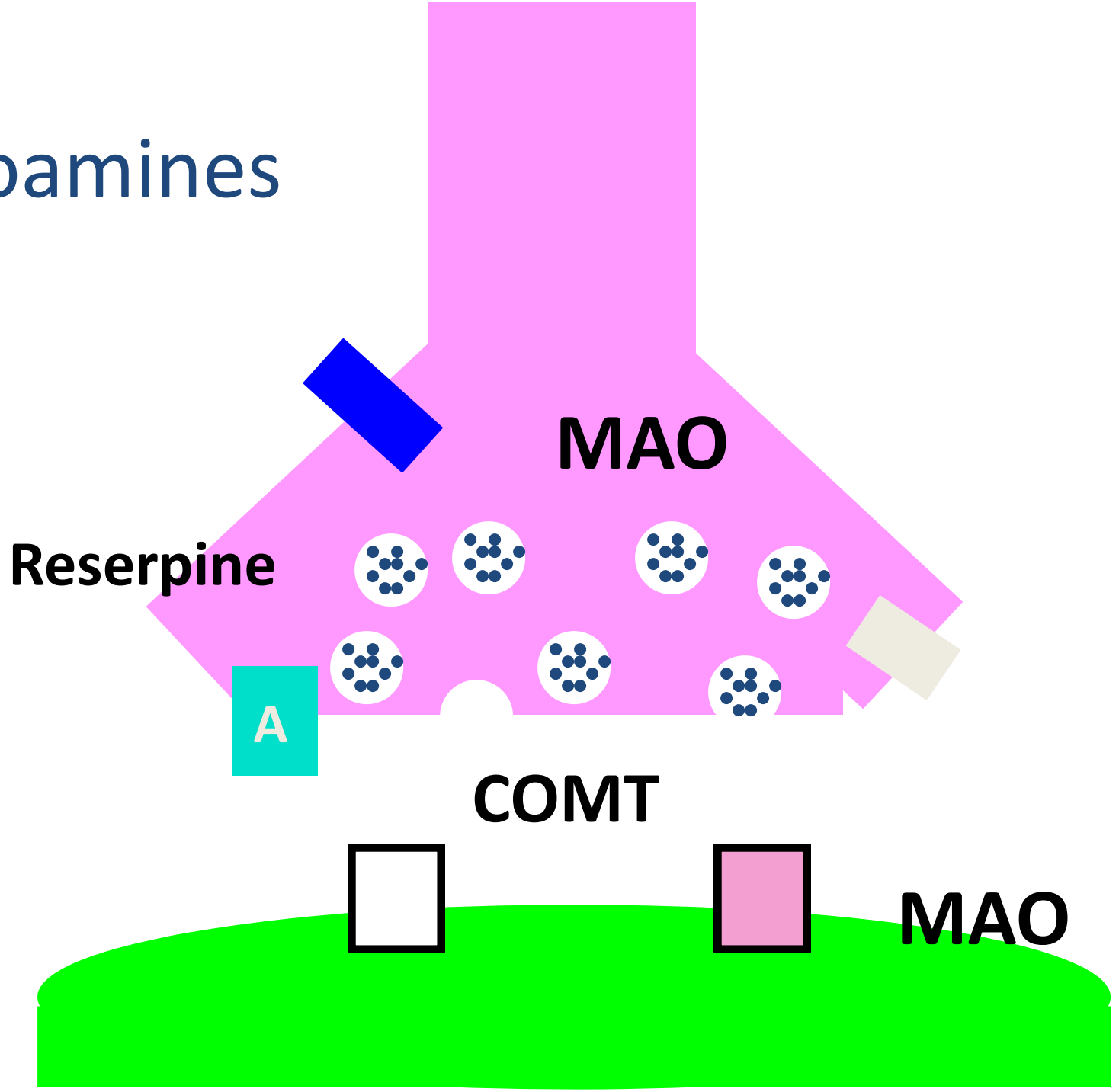
- Indolamines

  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 ~

Dopamine

- Only in central nervous system

  mostly inhibitory systems
- Reward
- Schizophrenia
- Movement
  - Nigrostriatal Pathway
- At least 5 DA-R types: D_1, D_2, etc. ~

Dopaminergic Drugs

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

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 ~

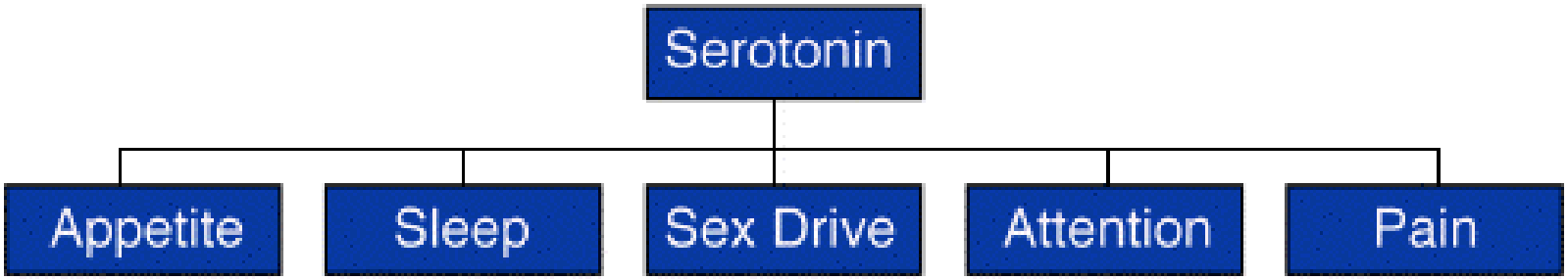
Serotonin

- 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

Sertonergic Drugs

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

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

- Opioids

  Dynorphin

  - met-enkephalin
  - leu-enkephalin
  - Beta-endorphin

Endorphins (cont.)

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

Other NTs

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

MODE OF ACTION

Postsynaptic Potentials

§ ***Neurotransmitter receptors mediate changes in membrane potential according to:***

- § The amount of neurotransmitter released
- § The amount of time the neurotransmitter is bound to receptors

§ ***The two types of postsynaptic potentials are:***

- § EPSP – excitatory postsynaptic potentials
- § IPSP – inhibitory postsynaptic potentials order

- § Spatial summation – postsynaptic neuron is stimulated by a large number of terminals at the same time
- § IPSPs can also summate with EPSPs, canceling each other out

Excitatory Postsynaptic Potentials(EPSP)

§ ***EPSPs are graded potentials that can initiate an action potential in an axon***

§ Use only chemically gated channels

§ Na + and K + flow in opposite directions at the same time

§ ***Postsynaptic membranes do not generate action potentials***

Inhibitory Synapses and IPSPs

§ ***Neurotransmitter binding to a receptor at inhibitory synapses:***

§ Causes the membrane to become more permeable to potassium and chloride ions

§ Leaves the charge on the inner surface negative

§ Reduces the postsynaptic neuron's ability to produce an action potential

Summation

§ A single EPSP cannot induce an action potential

§ EPSPs must summate temporally or spatially to induce an action potential

§ Temporal summation – presynaptic neurons transmit impulses in rapidfire order

§ Spatial summation – postsynaptic neuron is stimulated by a large number of terminals at the same time

§ IPSPs can also summate with EPSPs, canceling each other out

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

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

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)**

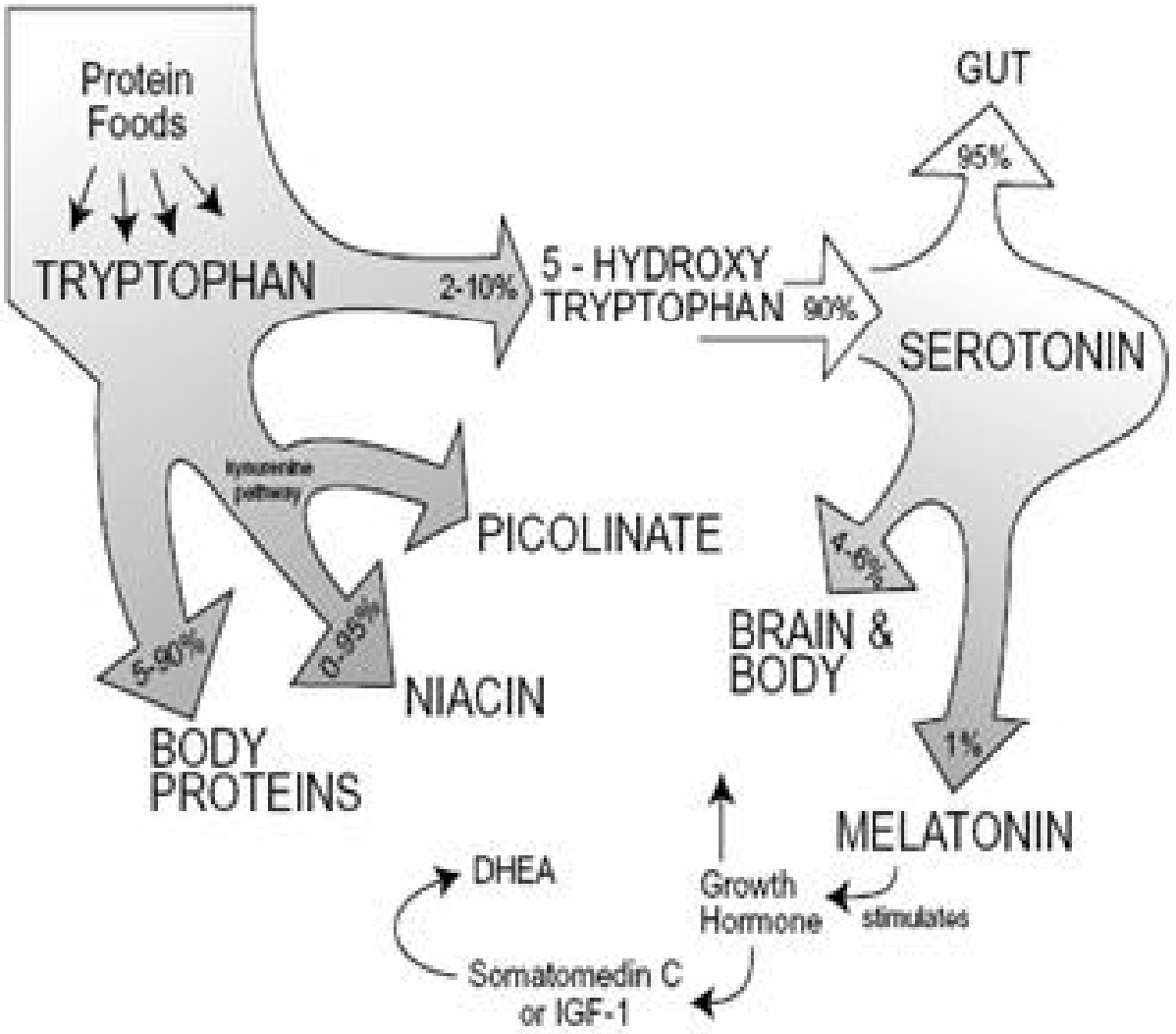
It has been suggested that several SSRI medications deplete 40-60% of the serotonin receptors in the brain. It is also reported that receptors in the liver, kidneys, and colon are also damaged by SSRIs.

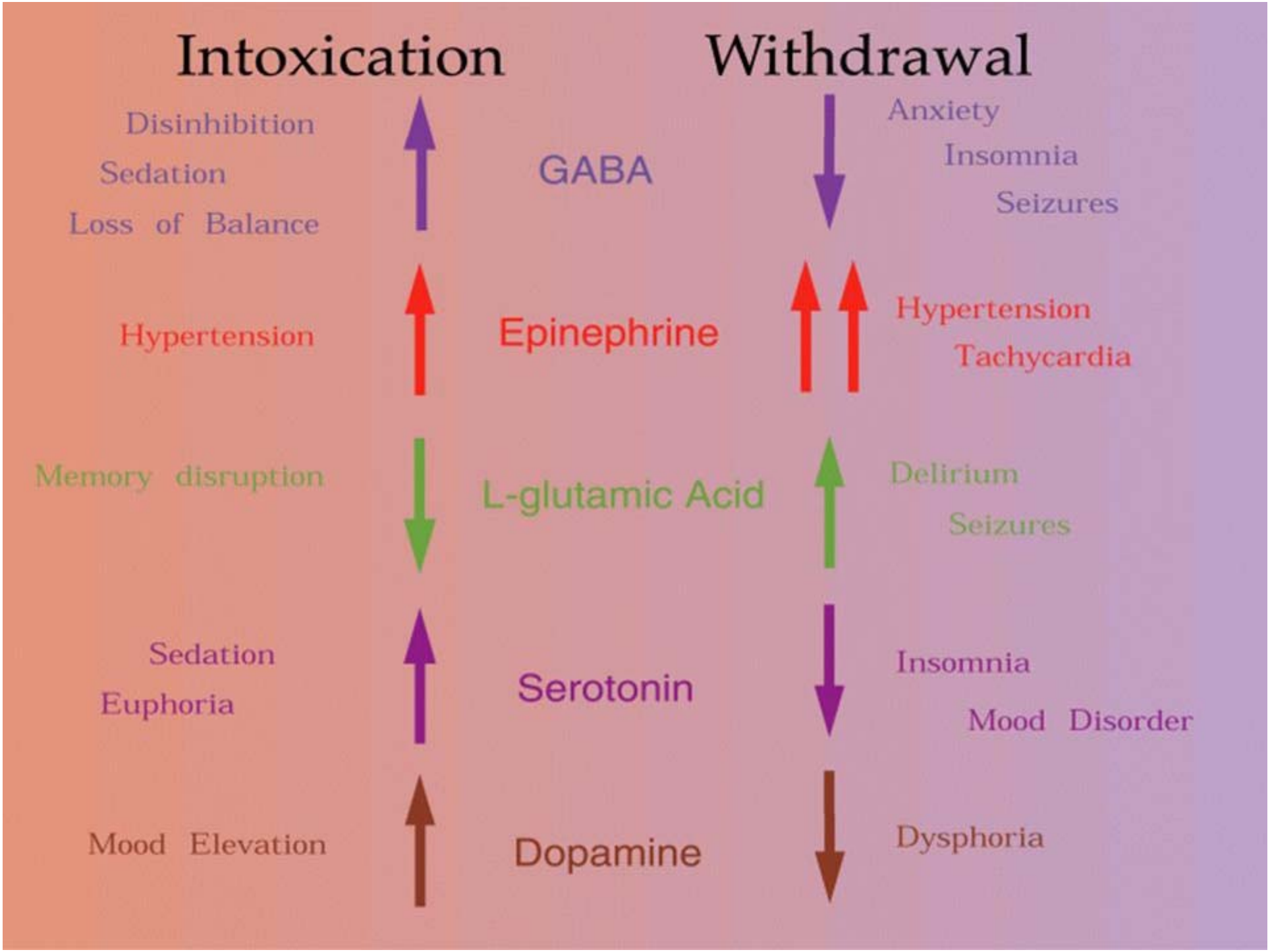
ingestion of various food allergens or sensitivities, inhalation or ingestion of various chemicals, chemical sensitivities, rapid changes in hormone levels, rapid changes in barometric pressure, head cold or sinus congestion, rapid changes in blood sugars, dehydration, inadequate exposure to sunlight (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.




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