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Principles of Neurochemistry

Vladimir Grubisic, MD PhD
Biomedical Sciences
vladimir.grubisic@nyit.edu

Do.
Make.
Heal.
Innovate.
Reinvent the Future.

Session Objectives

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- To understand the concepts of neurotransmission and actions of key neurotransmitters
- To learn locations in the brain where key neurotransmitters are made and released
- To learn an understand the principles of chemical production, transport, and processing that are important for disorders of the nervous system

Source: Course Syllabus

Cells act as chemical compartments

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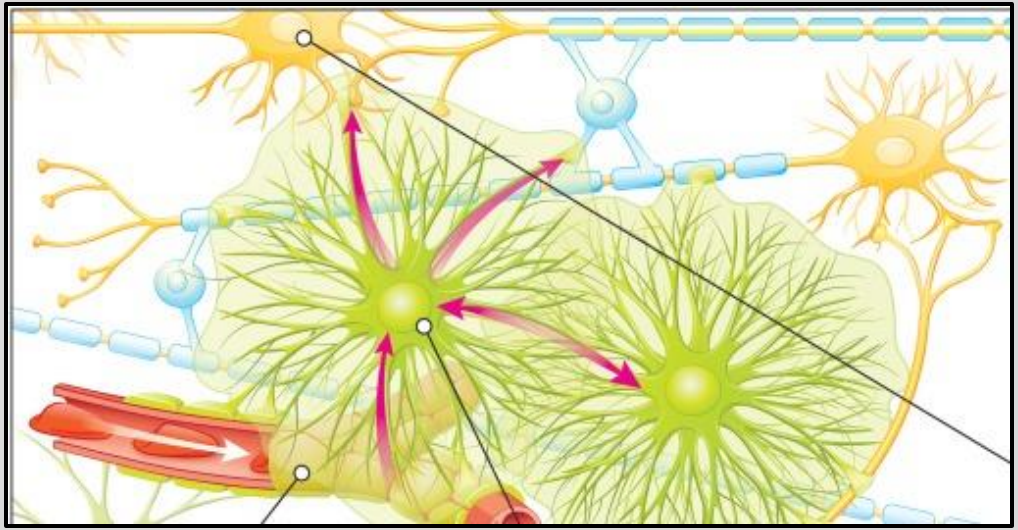
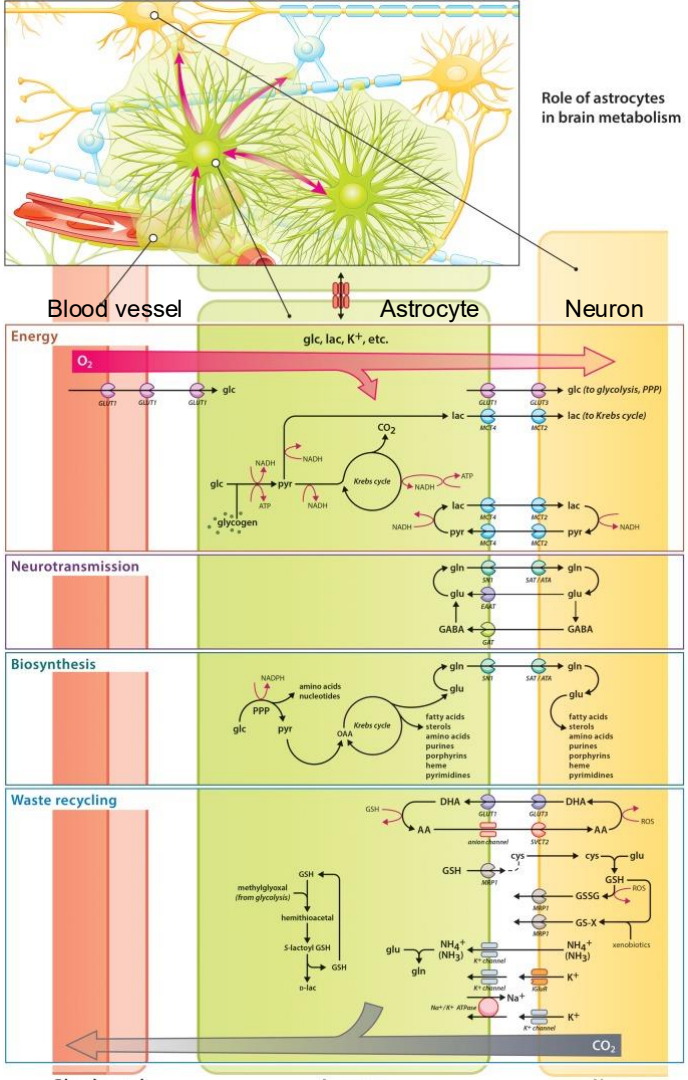
Review of brain cell types:

- Neurons
- Astrocytes
- Oligodendrocytes
- Microglia
- Endothelial cells (vasculature)
- Other cells: Pericytes, ependymal cells, NG2 glia, vascular smooth muscle cells, others

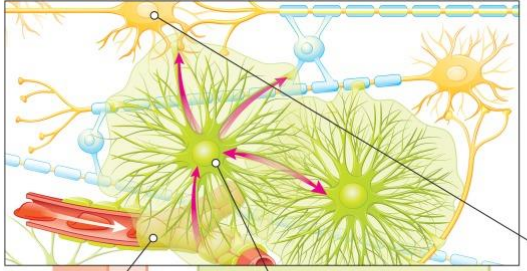


Astrocytes and neurons work as complementary compartments to achieve brain function

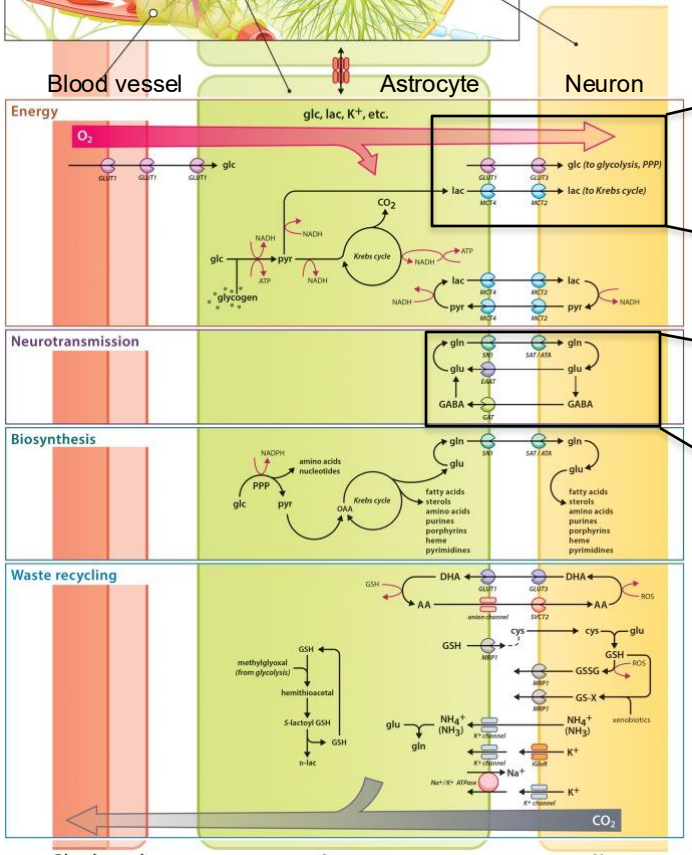


From: Weber, Bruno, and L. Felipe Barros. "The astrocyte: powerhouse and recycling center." *Cold Spring Harbor perspectives in biology* 7.12 (2015): a020396.

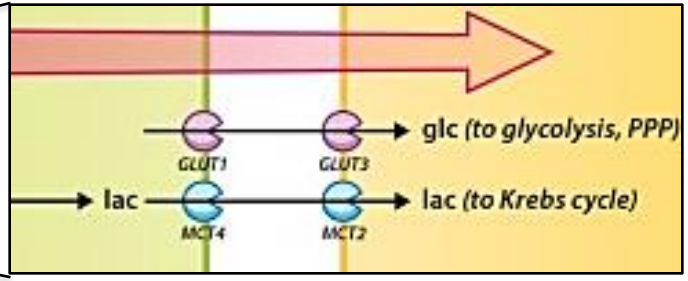
Astrocytes and neurons work as complementary compartments to achieve brain function



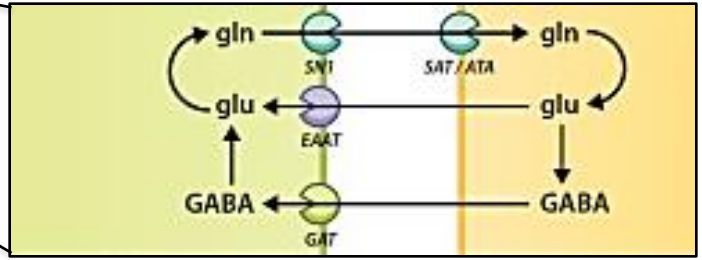
Role of astrocytes in brain metabolism



The astrocyte-neuron lactate shuttle



The glutamate/GABA-glutamine cycle



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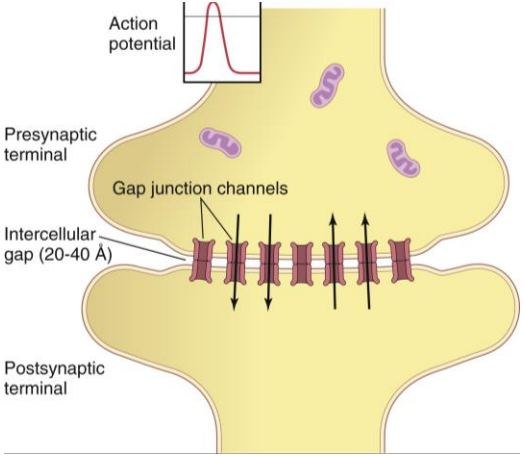
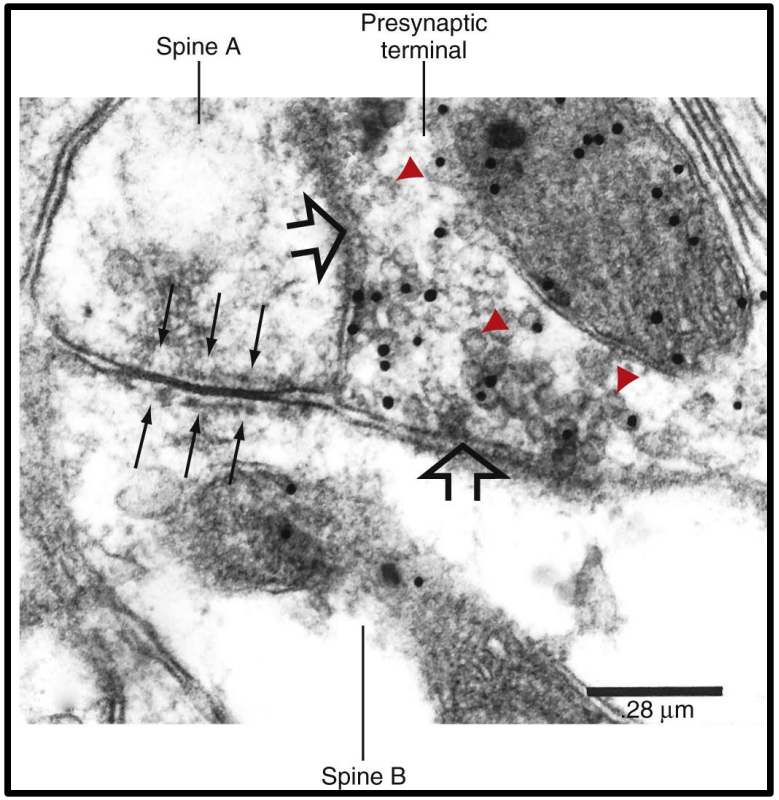
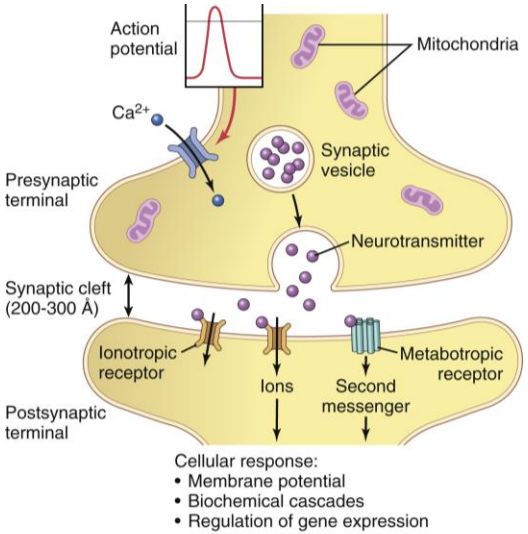
Two types of synapses







Electrical

- Gap junctions
- No synaptic delay (≈ 0.2 ms)

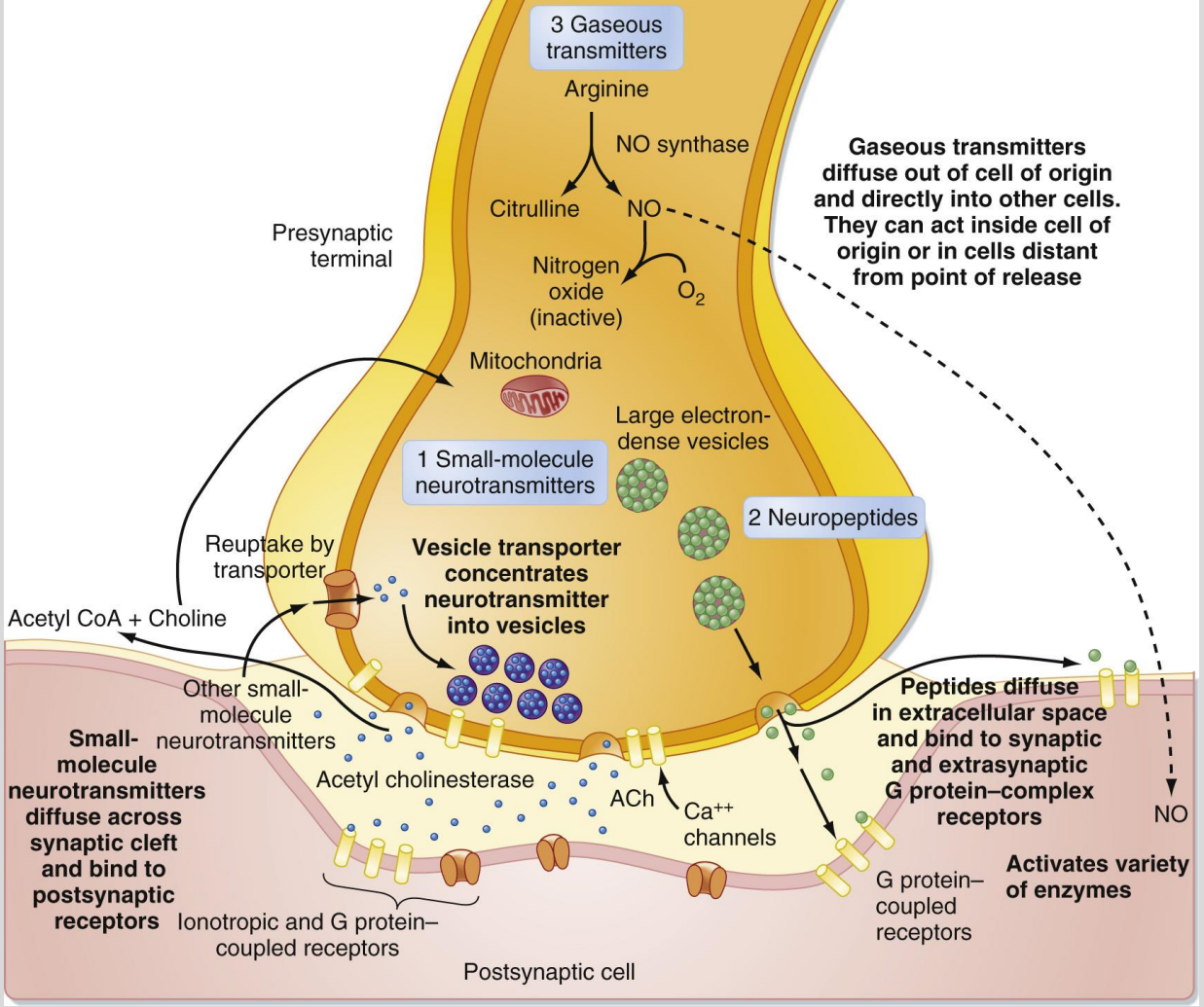
Chemical

- Neurotransmitters
- Signal amplification

Guyton and Hall Textbook of Medical Physiology. Ch 46, 569-585

Berne and Levy. Physiology, 6, 84-107

Type	Major Transmitters
Amines	Acetylcholine
	Catecholamines
	Dopamine
	Norepinephrine
	Serotonin
	Histamine
Amino acids	Glutamate
	GABA
	Glycine
Other small molecules	ATP, adenosine Gases
Neuropeptides	β-endorphin
	Cholecystokinin
	Enkephalin
	Neuropeptide Y
	Orexin
	Somatostatin
	Substance P
	Many others
Lipids, etc.	



Berne and Levy. Physiology, 6, 84-107

Small-molecule vs Peptide Neurotransmitters
(general principles)

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Nonpeptide Transmitters	Peptide Transmitters
Synthesized and packaged in the nerve terminal	Synthesized and packaged in the cell body; transported to the nerve terminal by fast axonal transport
Synthesized in active form	Active peptide formed when it is cleaved from a much larger polypeptide that contains several neuropeptides
Usually present in small clear vesicles	Usually present in large electron-dense vesicles
Released into a synaptic cleft	May be released some distance from the postsynaptic cell There may be no well-defined synaptic structure
Action of many terminated because of uptake by presynaptic terminals via Na^+-powered active transport	Action terminated by proteolysis or by the peptide diffusing away
Typically, action has short latency and short duration (msec)	Action may have long latency and may persist for many seconds

Berne and Levy Physiology, 6, 84-107

DRUGS OR TOXINS THAT ENHANCE TRANSMISSION

1. By enhancing synthesis or packaging of neurotransmitter:
L-dopa crosses the blood-brain barrier and is metabolized into dopamine, compensating for lower dopamine levels in Parkinson's disease.

2. By enhancing neurotransmitter release:
Amphetamine causes increased release of norepinephrine and dopamine, acts as a stimulant.

3. By effects on neurotransmitter-gated ion channels:
Benzodiazepine tranquilizers (e.g., diazepam, or Valium) increase the frequency of opening of GABA-gated Cl^- channels.
Barbiturate sedatives increase the duration of opening of GABA-gated Cl^- channels.

4. By effects on G protein–coupled neurotransmitter receptors:
Morphine mimics opioid peptides, binds to their receptors, causes analgesia and other effects.

5. By blocking removal of neurotransmitter:
Fluoxetine (Prozac), an antidepressant, blocks serotonin reuptake.
Cocaine blocks reuptake of norepinephrine and dopamine.

6. By blocking degradation of neurotransmitter:
Pyridostigmine (Mestinon) blocks acetylcholinesterase, is used to treat patients with myasthenia gravis.

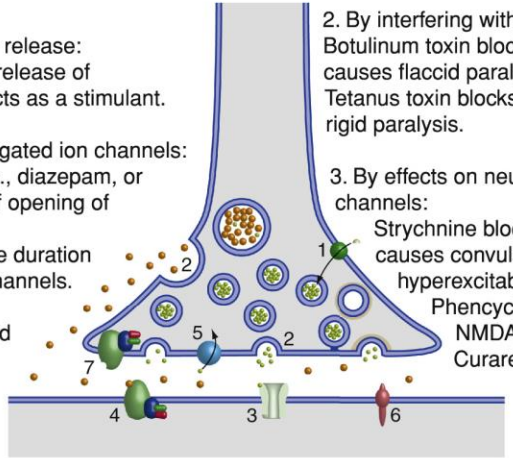
7. By blocking retrograde signaling:
Caffeine blocks presynaptic adenosine receptors, prevents suppression of transmitter release, acts as a stimulant.

DRUGS OR TOXINS THAT DEPRESS TRANSMISSION

1. By interfering with synthesis or packaging of neurotransmitter:
Vesamicol and reserpine block transport of acetylcholine and amines, respectively, into synaptic vesicles.

2. By interfering with neurotransmitter release:
Botulinum toxin blocks release of acetylcholine, causes flaccid paralysis.
Tetanus toxin blocks release of glycine, causes rigid paralysis.

3. By effects on neurotransmitter-gated ion channels:
Strychnine blocks glycine-gated Cl^- channels, causes convulsions and other signs of hyperexcitability.
Phencyclidine (PCP, "angel dust") blocks NMDA receptors.
Curare (arrow tip poison) blocks skeletal muscle nicotinic receptors, causes paralysis.
Hexamethonium blocks autonomic nicotinic receptors.



4. By effects on G protein–coupled neurotransmitter receptors:
Haloperidol (Haldol), an antipsychotic, blocks some dopamine receptors.
Atropine blocks muscarinic acetylcholine receptors, causes autonomic changes.

Nolte's The Human Brain, 8, 173-194

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Neurotransmitter cycling

1. Production
2. Packaging into vesicles
3. Vesicle localization to pre-synapse
4. Vesicle fusion and NT release
5. Receptor binding, Postsynaptic signaling
6. NT chemical conversion-deactivation, and/or NT uptake by transporter (astrocytes or neurons)

The tripartite synapse

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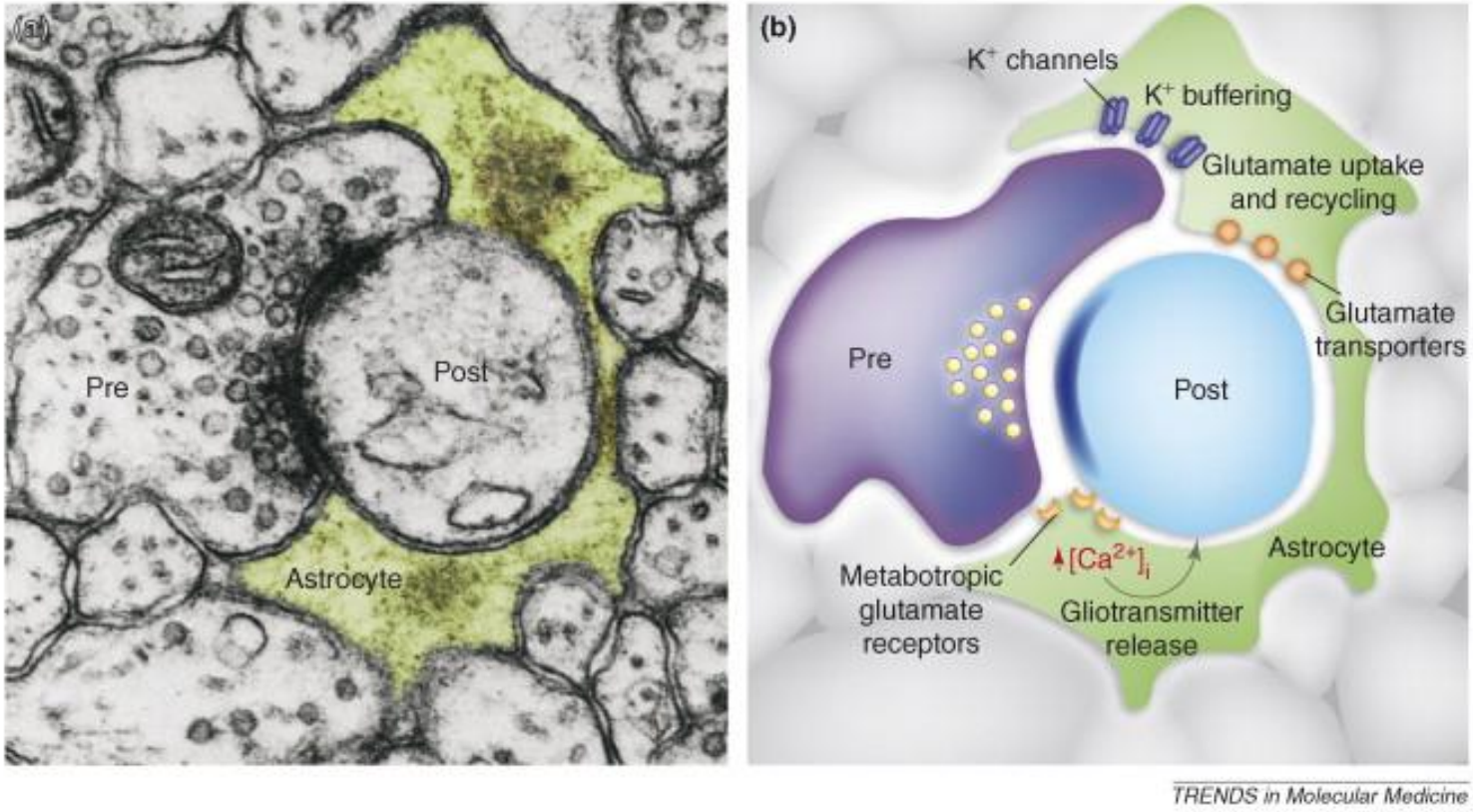

Trends in Molecular Medicine, 2007-02-01, Volume 13, Issue 2, Pages 54-63

Receptors determine neurotransmitter effects

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Effect (typical, not exclusive)	Major Transmitters
Fast excitatory	PNS: acetylcholine (nicotinic receptors)
	CNS: glutamate
	ATP (P_{2X} receptors)
Fast inhibitory	GABA ($GABA_A$ receptors, mostly in the brain)
	Glycine (mostly in the spinal cord)
Second-messenger effects	Catecholamines
	Serotonin (one type is ionotropic)
	Acetylcholine (muscarinic receptors)
	Glutamate (metabotropic receptors)
	GABA ($GABA_B$ receptors)
	ATP (P_{2Y} receptors)
	Neuropeptides

Ligand-gated **cation** channels (Depolarization)

Ligand-gated **anion** channels (Hyperpolarization)

G-coupled receptors (↑ or ↓cAMP, cGMP, DAG, IP_3, Ca^{2+}, ion channel conductance)

Neuron Cell Body Organization

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- Glutamate releasing neurons (Glutamatergic)
- GABAergic neurons

- Acetylcholine producing neurons (Cholinergic)
- Dopaminergic
- Noradrenergic
- Serotoninergic
- Histaminergic

Neuron Cell Body Organization

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- ❑ Scattered throughout the brain:
  - Glutamate releasing neurons (Glutamatergic)
  - GABAergic neurons
- ❑ Clustered cell bodies at specific locations (neuroanatomical nuclei):
  - Acetylcholine producing neurons (Cholinergic)
  - Dopaminergic
  - Noradrenergic
  - Serotoninergic
  - Histaminergic

Glutamate and GABA

Excitation - Inhibition

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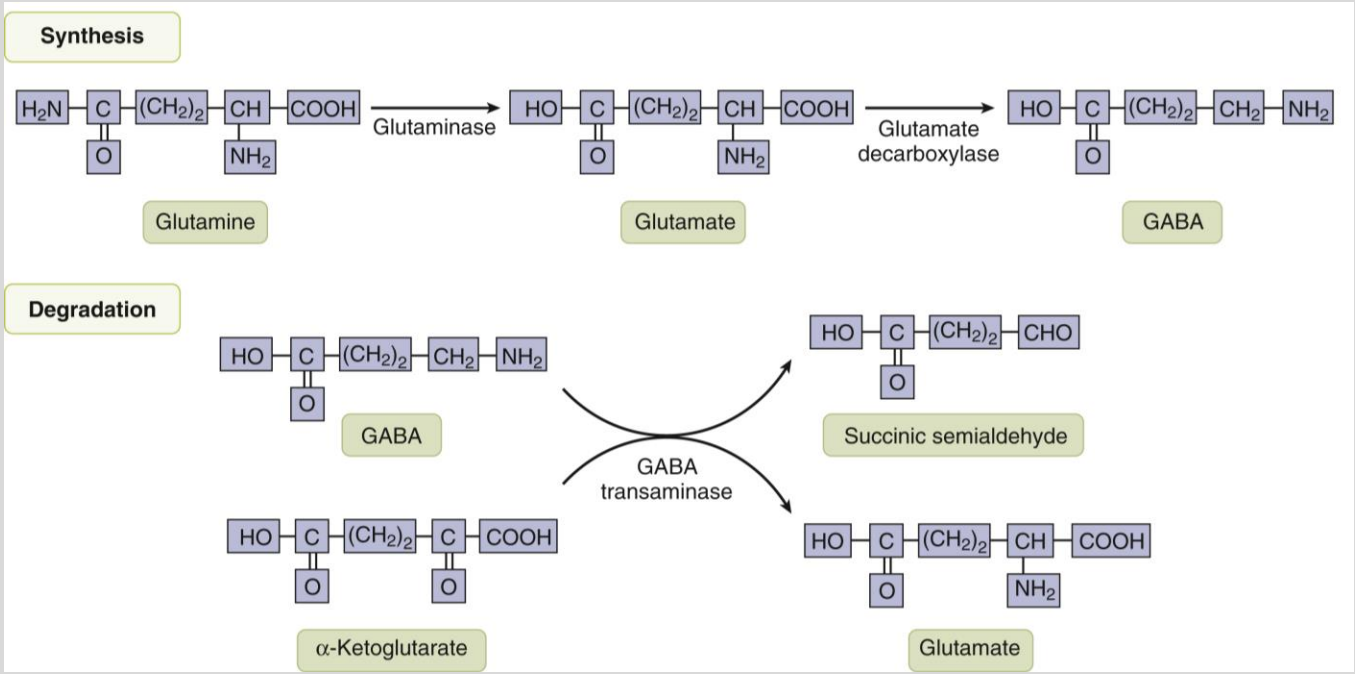

Brenner and Stevens' Pharmacology, Chapter 18, 197-207

Glutamate - Excitation

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Glutamate and aspartate act as excitatory signals

Drugs that affect the glutamate system include Ketamine (a dissociative anesthetic), Phencyclidine (PCP) and Alcohol

Three types of ionotropic receptors for the glutamate signaling pathway: NMDA, kainate and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)
Eight different metabotropic receptor (mGluR) subtypes.

N-Methyl-D-Aspartate (NMDA) receptors, which have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in the developing brain

NMDA-type Glutamate Receptors

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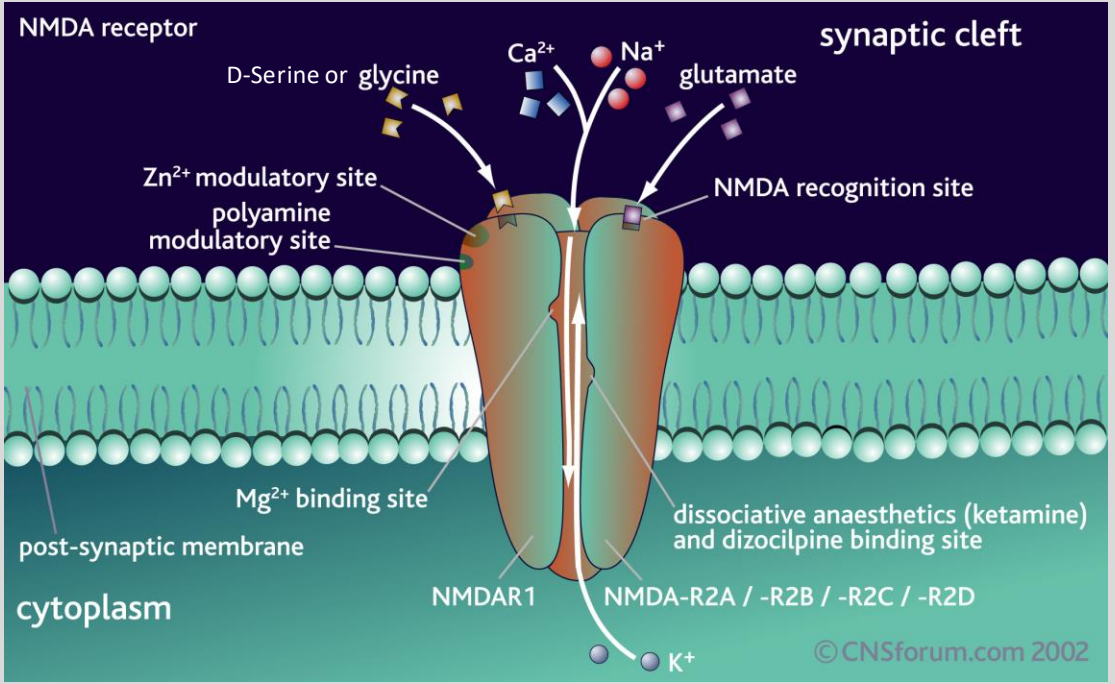
- Two ligands must bind two different protein subunits
- Also requires depolarization
- Coincidence detector
- Associated with memory formation
- Mutations associated with schizophrenia, intellectual disability, autism spectrum disorder, epilepsy and more.



GABA - Inhibition

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The neurotransmitters glycine and gamma-aminobutyric acid (GABA) **inhibit the firing of neurons**

The activity of GABA is increased by benzodiazepines (e.g., Valium) and by anticonvulsant drugs (e.g., Valproate)
Ethanol exerts many effects via GABA agonism ($GABA_A$ receptor allosteric modulator)

In Huntington's disease, the GABA-producing neurons in brain centers that coordinate movement degenerate, thereby causing uncontrollable movements

Two kinds of receptors $GABA_A$ (ionotropic) and $GABA_B$ (metabotropic).

GABA Receptors

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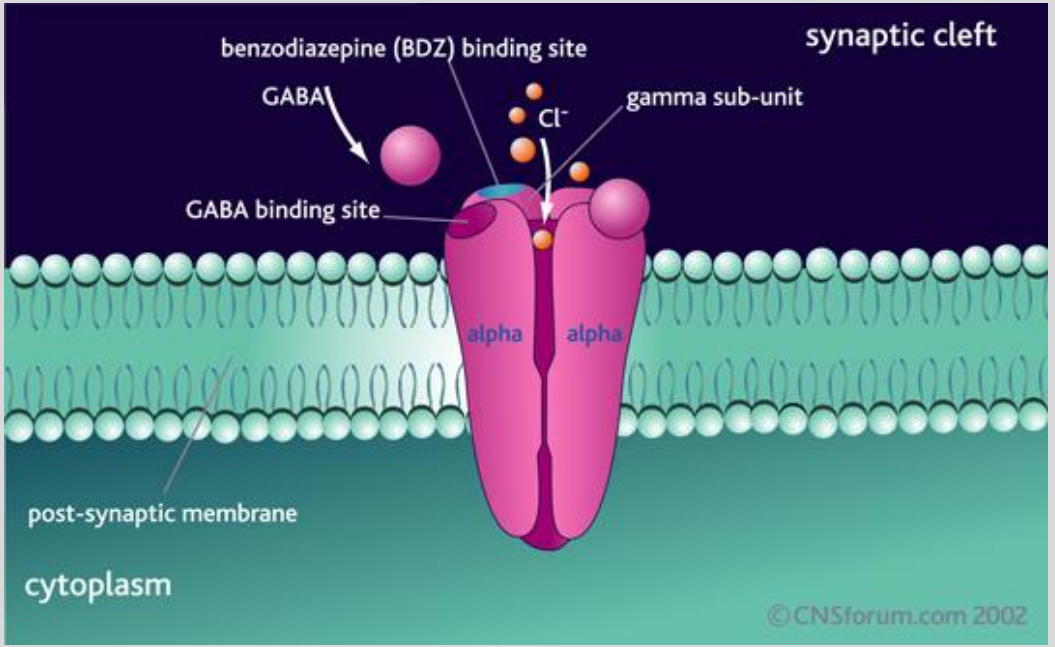
- The $GABA_A$ receptor is composed of five sub-units (two α, two β and one γ sub-unit)
- Two molecules of GABA activate the receptor by binding to the α sub-units
- Once activated, the receptor allows the passage of negatively charged ions into the cytoplasm, which results in hyperpolarization



Acetylcholine (ACh)

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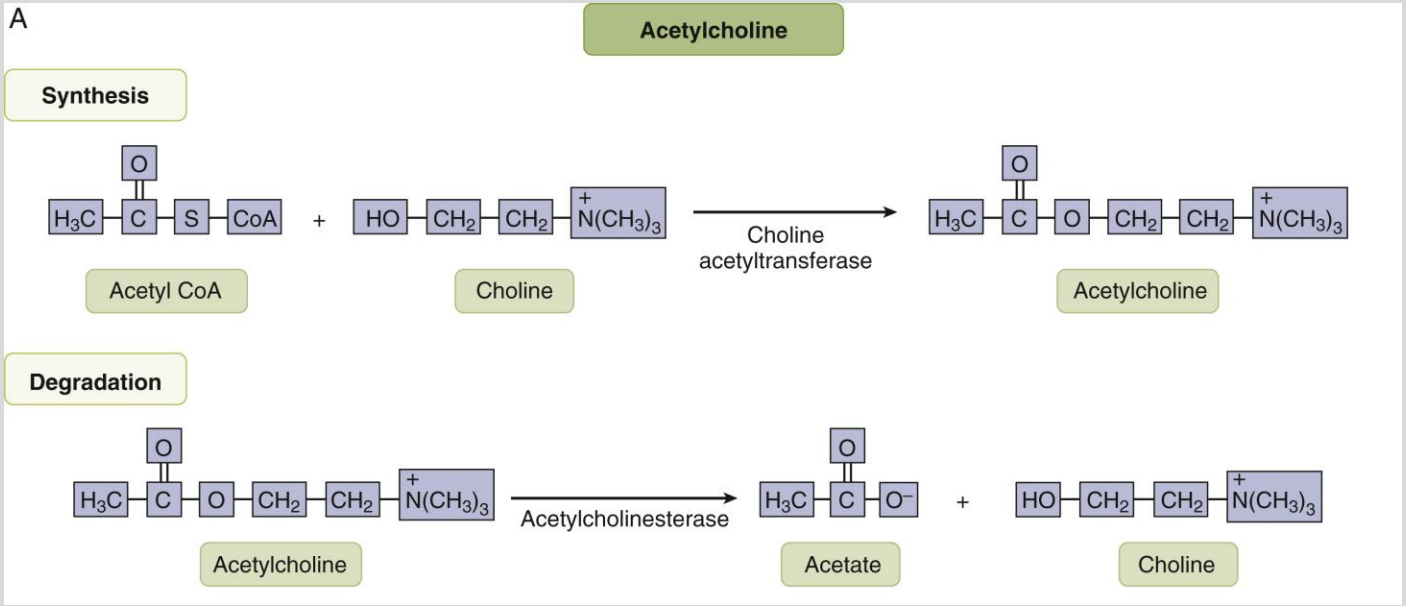

Brenner and Stevens' Pharmacology, Chapter 18, 197-207

Acetylcholine

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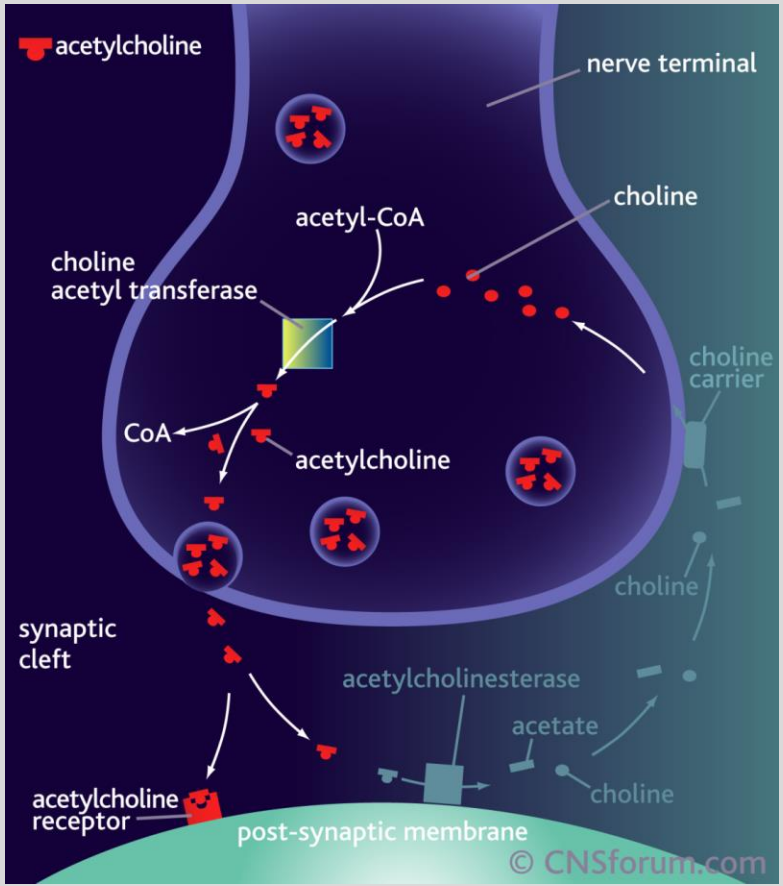

Choline acetyl transferase (ChAT) in an enzyme needed to produce acetylcholine

ChAT can be used to mark cholinergic cells

ChAT positive cells are decreased in Alzheimer's disease patient brain

Decreased cholinergic signaling may be involved with Alzheimer's disease symptoms

Acetylcholine

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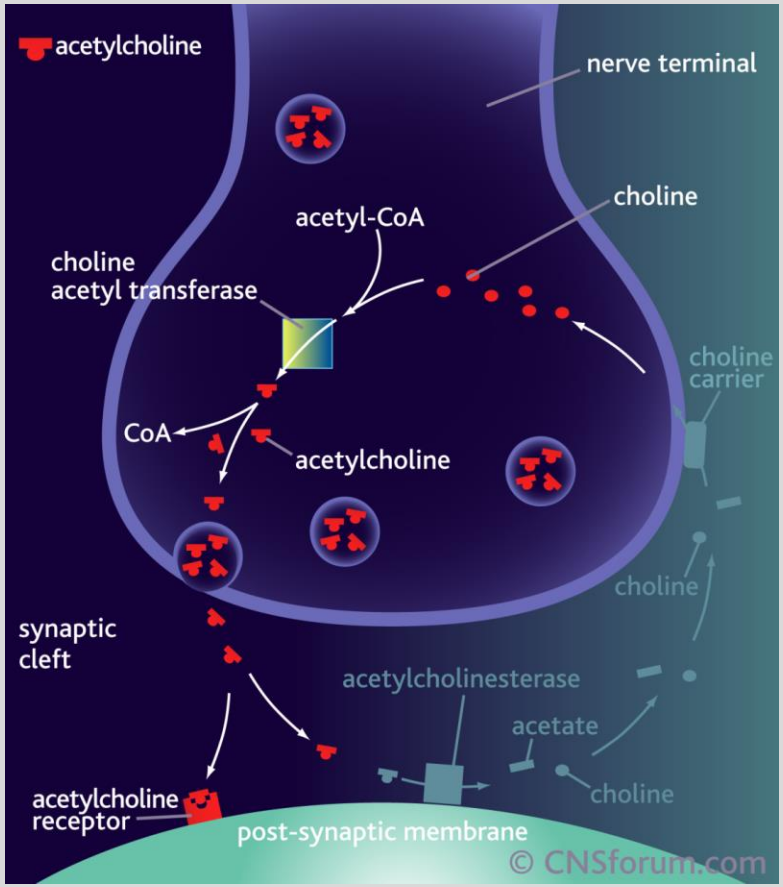

Acetylcholinesterase (AChE) attenuates cholinergic signaling to prevent runaway acetylcholine receptor activation

AChE is an enzyme that is located outside the cell within the synaptic cleft

AChE converts acetylcholine to acetate and choline

- this stops receptor activation and allows recycling of substrates

Organophosphate nerve agents and pesticides inactivate AChE

Acetylcholine

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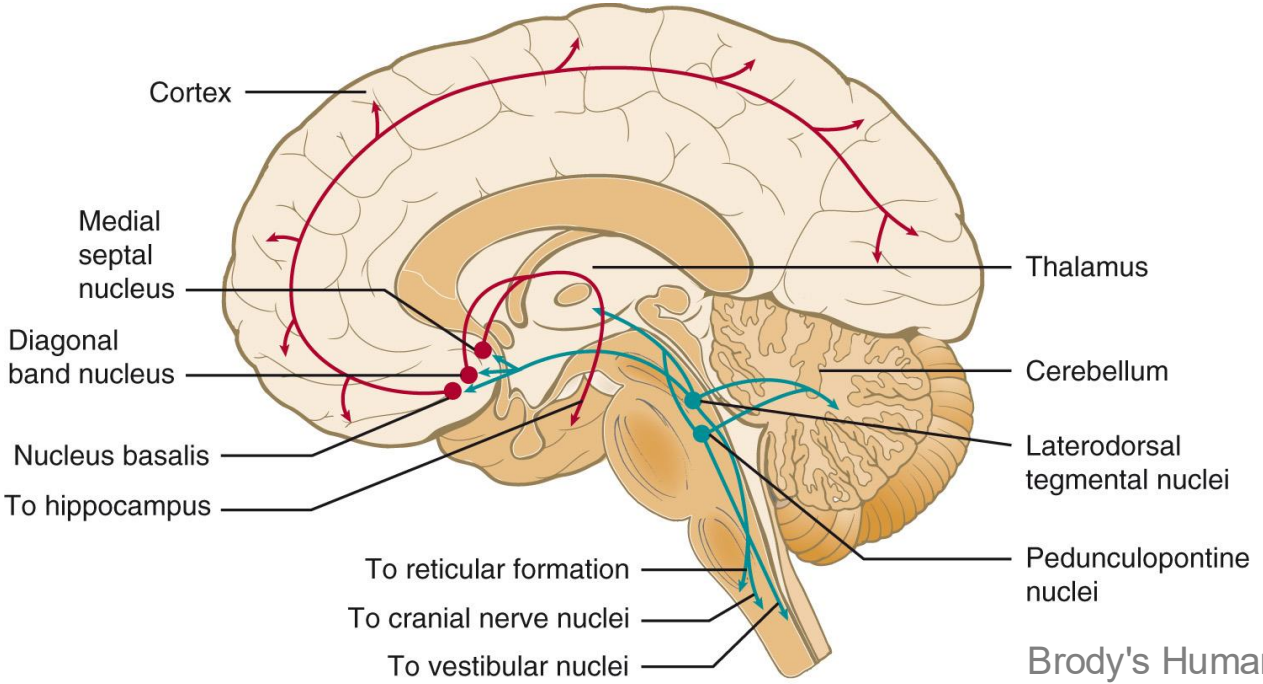

Brody's Human Pharmacology, 13, 109-120

Basal forebrain pathways	Learning and memory	Alzheimer's (↓)
Mesopontine pathways	Arousal and sleep	Sleeping disorders

Acetylcholine Receptor Distribution

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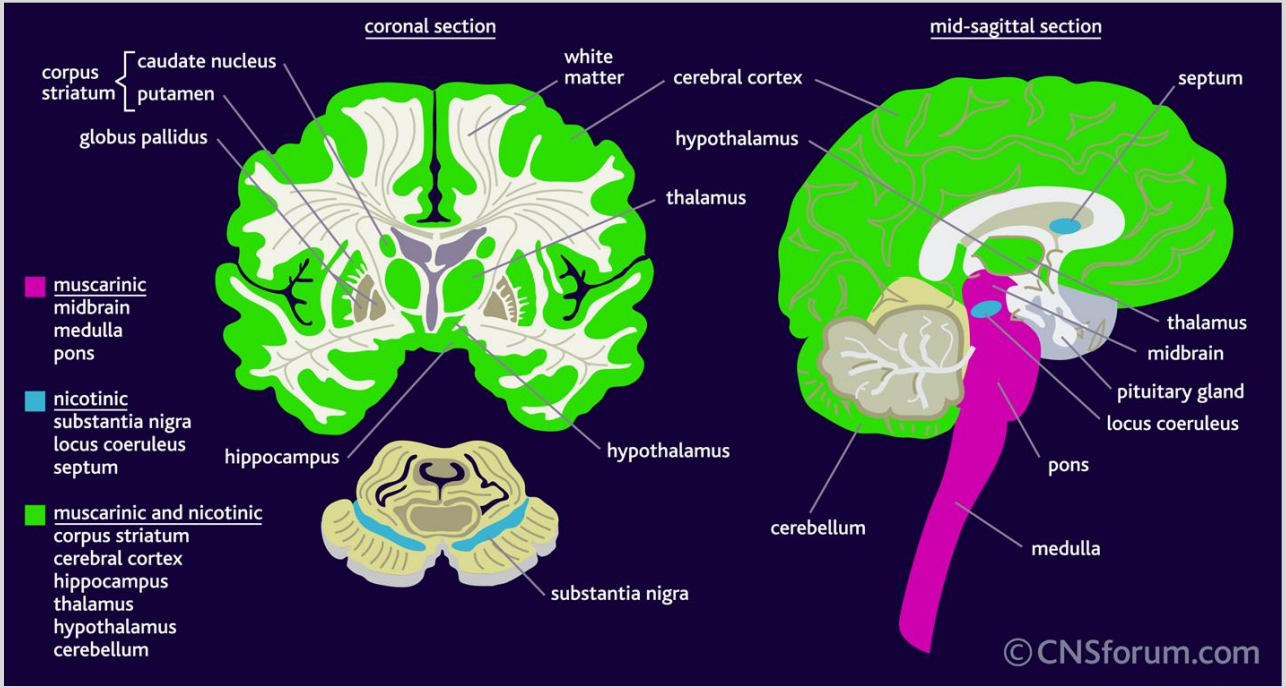

Nicotinic acetylcholine receptors (nAChR) are ligand gated ionotropic channels, positive ion conductance

Muscarinic acetylcholine receptors are metabotropic and signal through second messengers

Catecholamines

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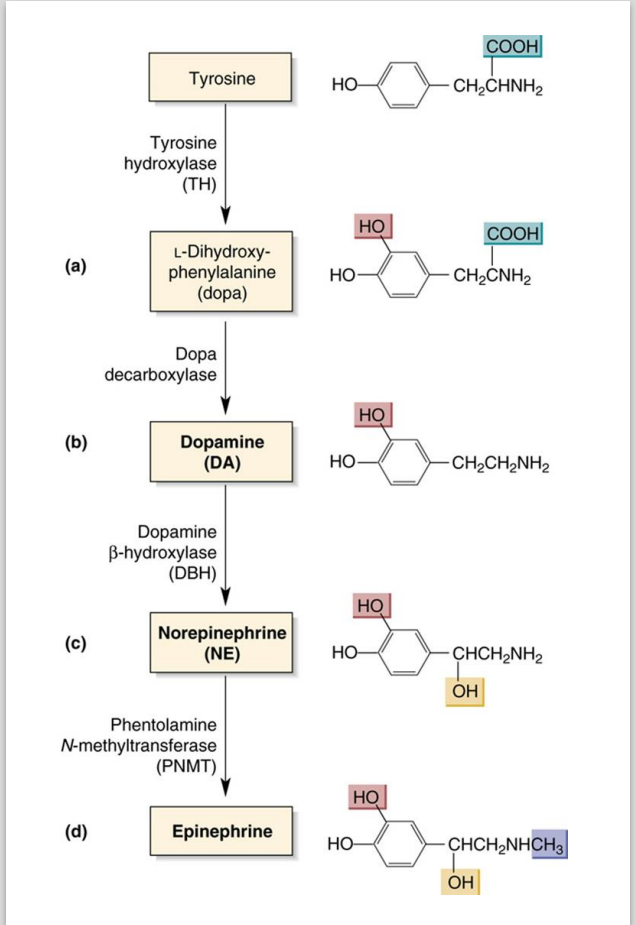
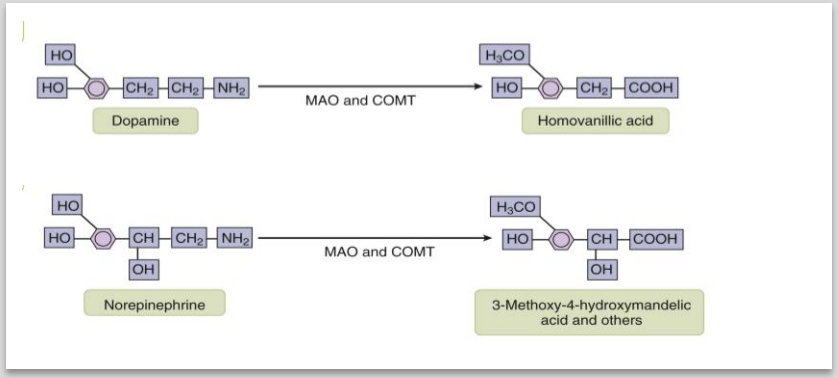
Synthesis



Degradation



COMT, Catechol-O-methyltransferase
MAO, Monoamine oxidase

Brenner and Stevens' Pharmacology, Chapter 18, 197-207

Dopaminergic Cell body Locations

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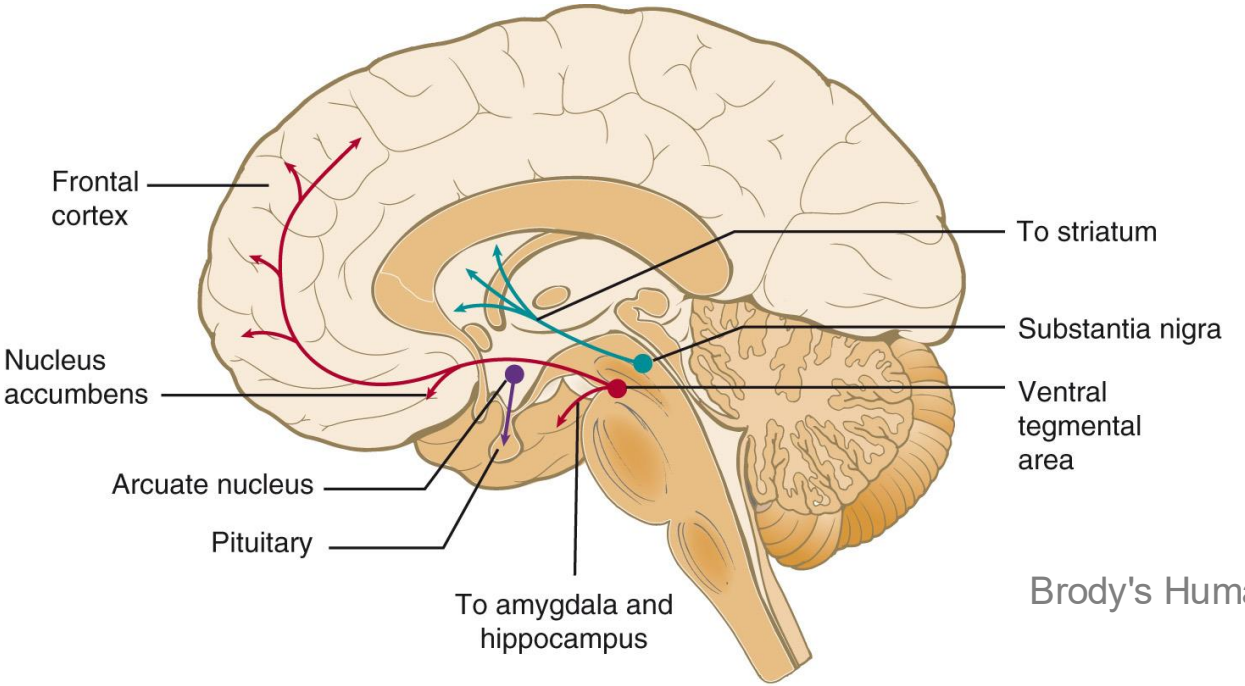

Brody's Human Pharmacology, 13, 109-120

Mesocortical/mesolimbic pathways	Cognition, pleasure, reward and emotion	Addiction and Psychotic disorders (↑)
Nigrostriatal pathway	Posture and movement	Parkinson's (↓)
Tuberoinfundibular pathway	Inhibition of prolactin secretion	Hyper- or Hypo- prolactinemia

Dopamine Receptor Locations

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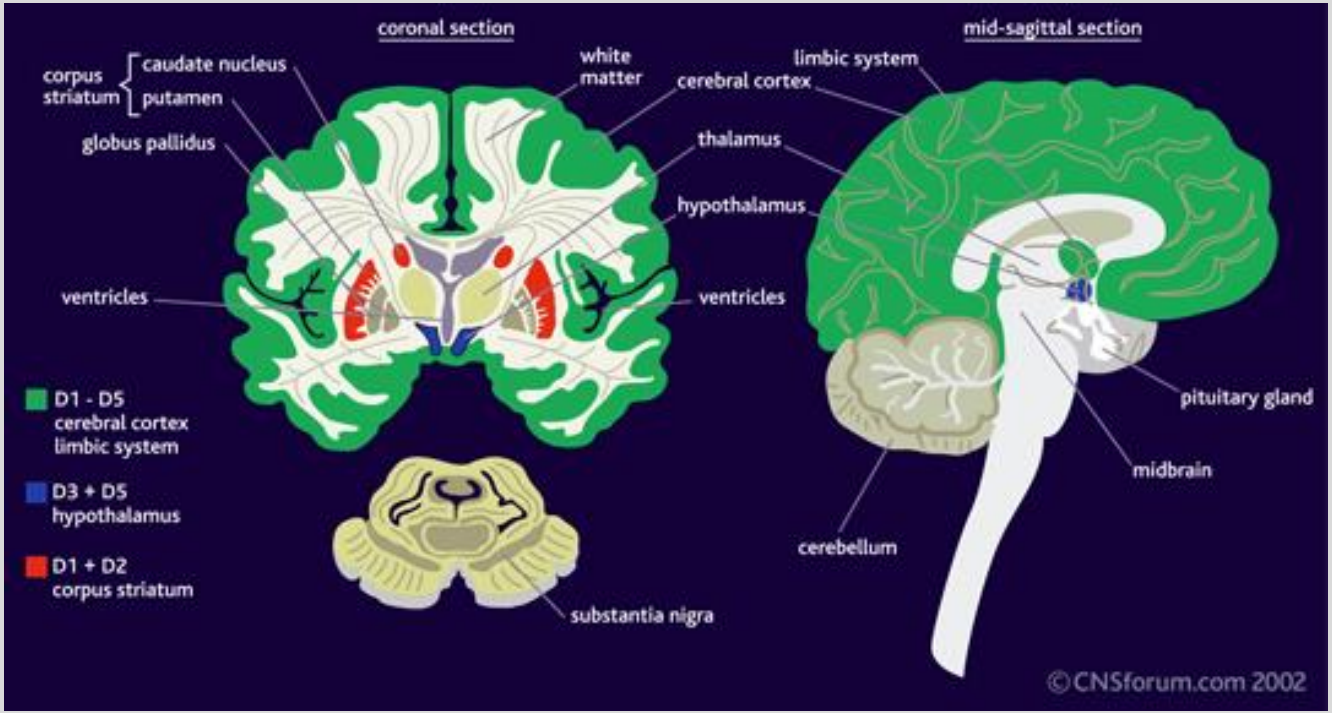

- **D_1 , D_5 Excitatory**; (↑cAMP, ↑PKA)
- **$D_{2\text{-}4}$ Inhibitory** (↓cAMP, ↑gK^+, ↓gCa^{2+})

g, ion channel conductance

Norepinephrine - Noradrenaline

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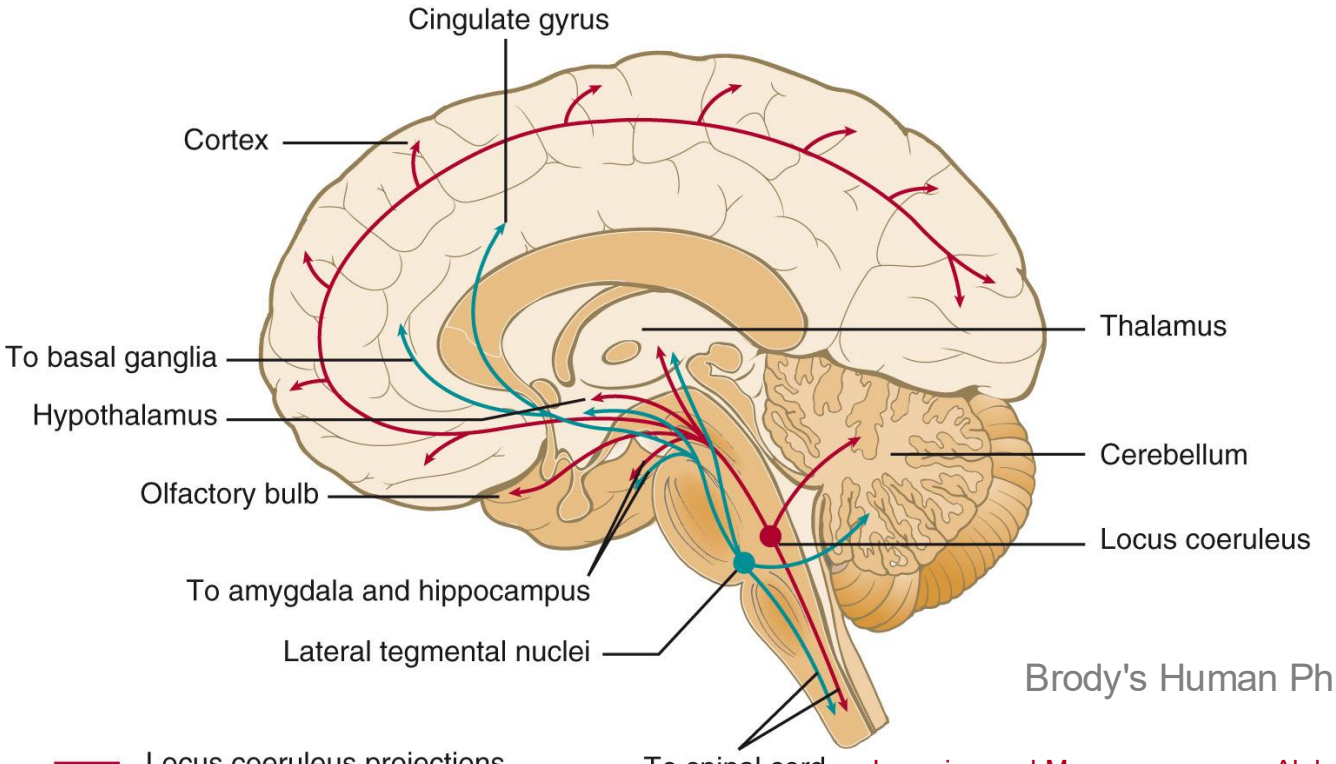

Brody's Human Pharmacology, 13, 109-120

Learning and Memory

Attention and Arousal

Alzheimer's, Parkinson's, Depression

ADHD, Narcolepsy

Norepinephrine

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The cell bodies of norepinephrine **neurons** are in the brain stem, **mainly the locus coeruleus** and lateral tegmental nuclei**.**

Deficiencies in NE occur in patients with Alzheimer's disease, Parkinson's, disease and Korsakoff's syndrome, a cognitive disorder associated with chronic alcoholism

NE is also released from **sympathetic nerves and the adrenal medulla**

Serotonin (5-HT)

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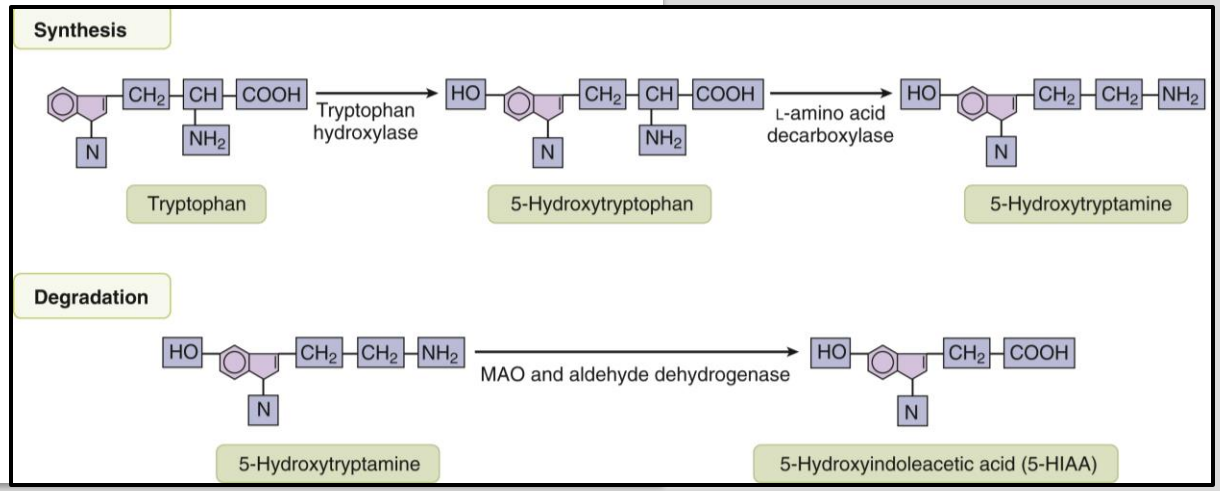
Serotonin (5-hydroxytryptamine, 5-HT) is an indoleamine present in the brain, and other tissues, particularly blood platelets and the lining of the digestive tract.

In the brain, 5-HT has been implicated in sleep, **mood, depression and anxiety**.
Drugs that alter 5-HT synaptic levels such as Fluoxetine, relieve symptoms of depression and obsessive-compulsive disorder.

Brenner and Stevens' Pharmacology, Chapter 18, 197-207



Serotonin Synthetic Pathway

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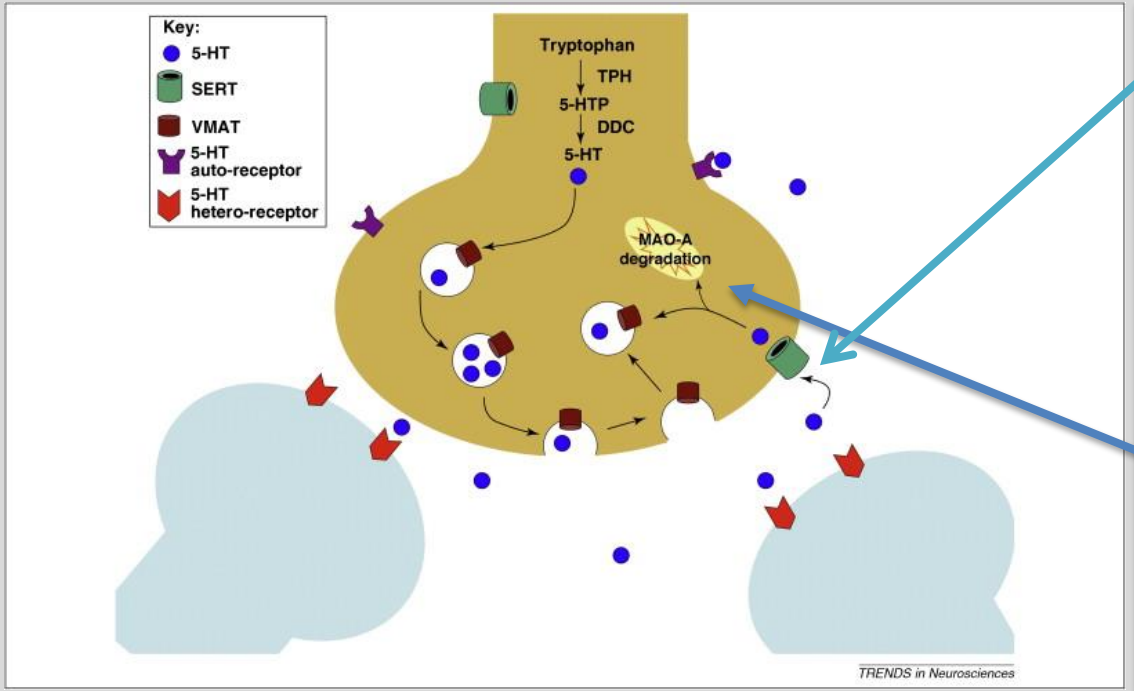

Selective serotonin reuptake inhibitors (SSRIs) such as Fluoxetine **block reuptake** transporters and thereby increasing serotonin signaling to modify depressive symptoms

Monoamine oxidase inhibitors (MAOIs) inhibit degradation of serotonin and other monoamine neurotransmitters

Serotonin (5-HT) Signaling Pathways

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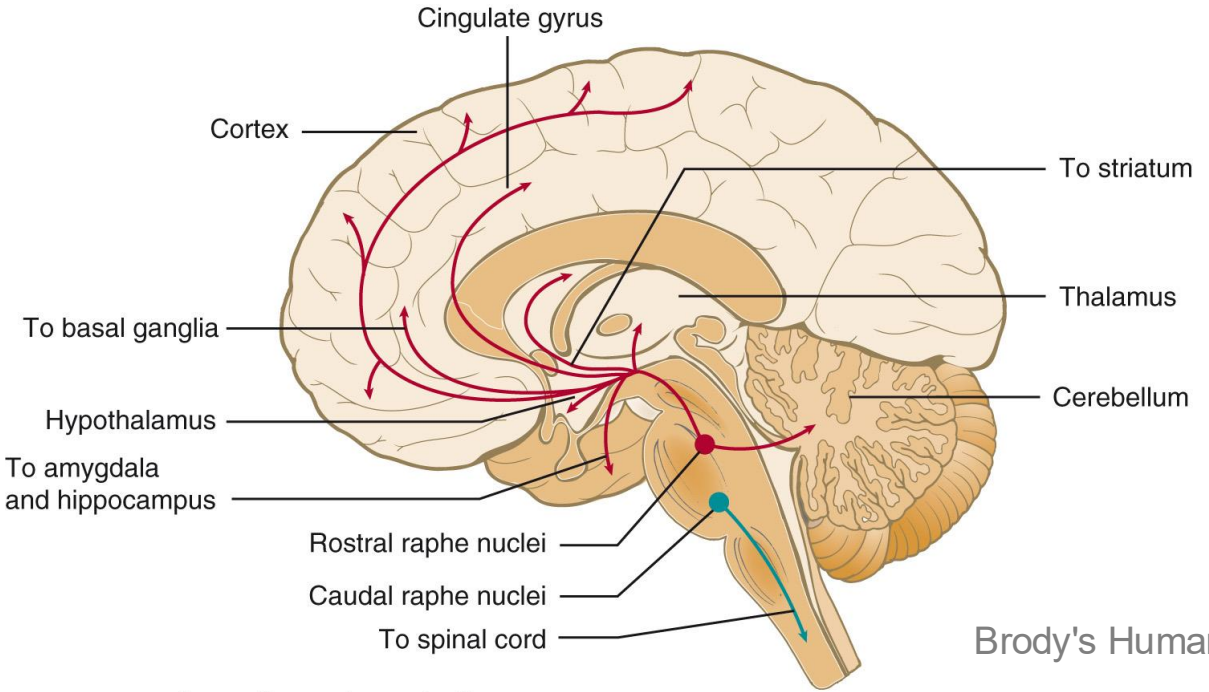

Brody's Human Pharmacology, 13, 109-120

Sensory processing and homeostasis

Depression, Psychotic behaviors, Obsessive-compulsive disorder

Histaminergic Systems

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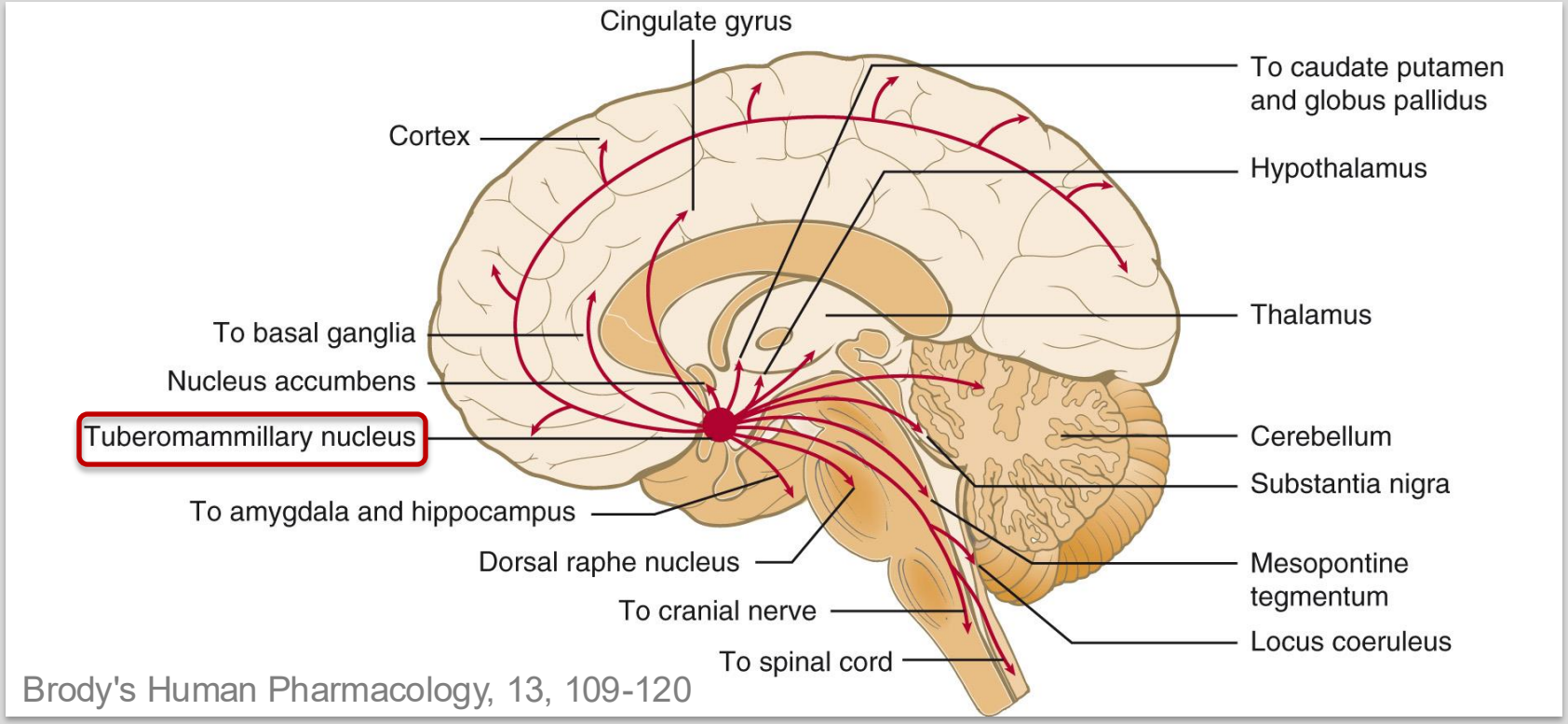

Brody's Human Pharmacology, 13, 109-120

Neurotransmitter Pathways and Associated Disorders

Neurotransmitter	Associated Pathways/Projections	Functions	Associated Disorders
DA	Nigrostriatal	Posture and movement	Parkinson disease
	Mesolimbic/mesocortical	Target-oriented behaviors, addiction, reinforcement	Psychoses, drug abuse
	Tuberoinfundibular	Prolactin secretion	Hyperprolactinemia/hypoprolactinemia
ACh	Intrastriatal	Motor activity	Parkinson disease
	Basal forebrain	Learning/memory	Alzheimer disease
	Mesopontine	Arousal and REM sleep	Narcolepsy (?)
5-HT	Raphe-telencephalic and diencephalic	Broad homeostatic functions, sensory processing	Depression/suicide, psychoses, obsessive compulsive disorder, anxiety
NE	Locus coeruleus	Learning/memory	Depression
	Midbrain reticular formation	Attention/arousal	Narcolepsy
Hist	Tuberomammillary projections	Arousal, cerebral metabolism	Insomnia (?)
GABA	Widespread	Anxiolytic, anticonvulsant	Anxiety, seizures
Glu	Widespread	Proconvulsant, synaptic plasticity (LTP)	Seizures, Alzheimer and Parkinson diseases (?)

Brody's Human Pharmacology, 13, 109-120

ATP and Adenosine

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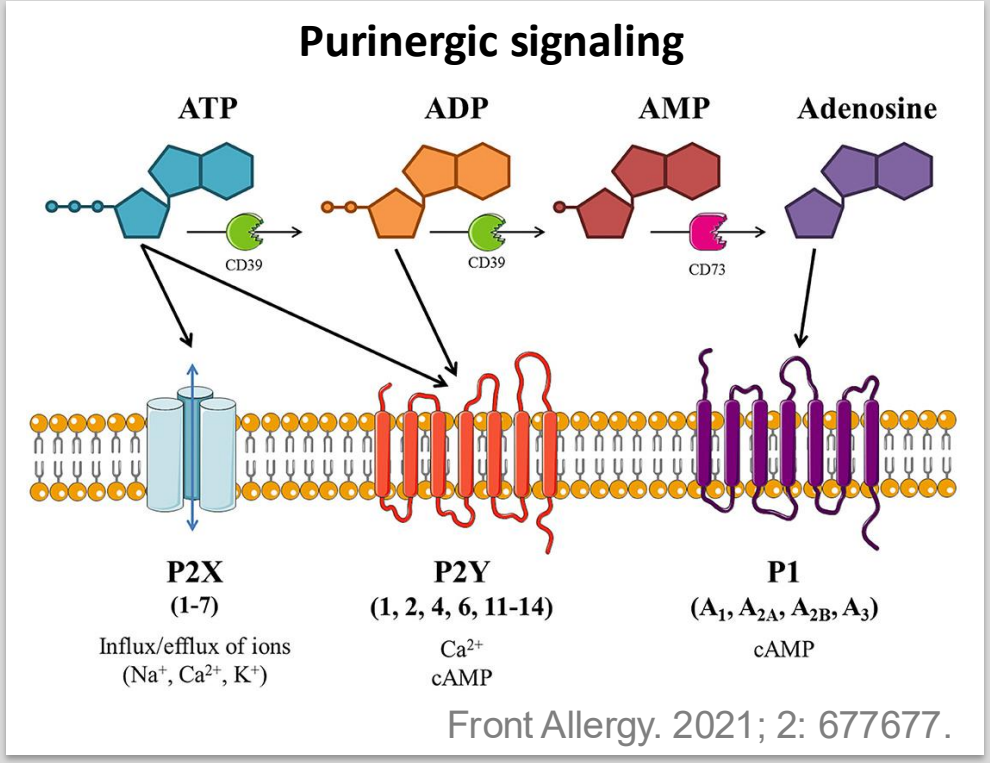
ATP is the energy currency of the cell, and it can be released via channels, vesicles and cell death.
Extracellular enzymes hydrolase ATP to Adenosine.

ATP and Adenosine are released by neurons and glia and affect both neurons and glia through purinergic receptors.

Astrocyte derived Adenosine and ATP is a driver of sleep pressure (drive to seek sleep) and circadian rhythm.

Caffeine promotes wakefulness primarily by **inhibiting adenosine receptors**.



Front Allergy. 2021; 2: 677677.

Nitric oxide

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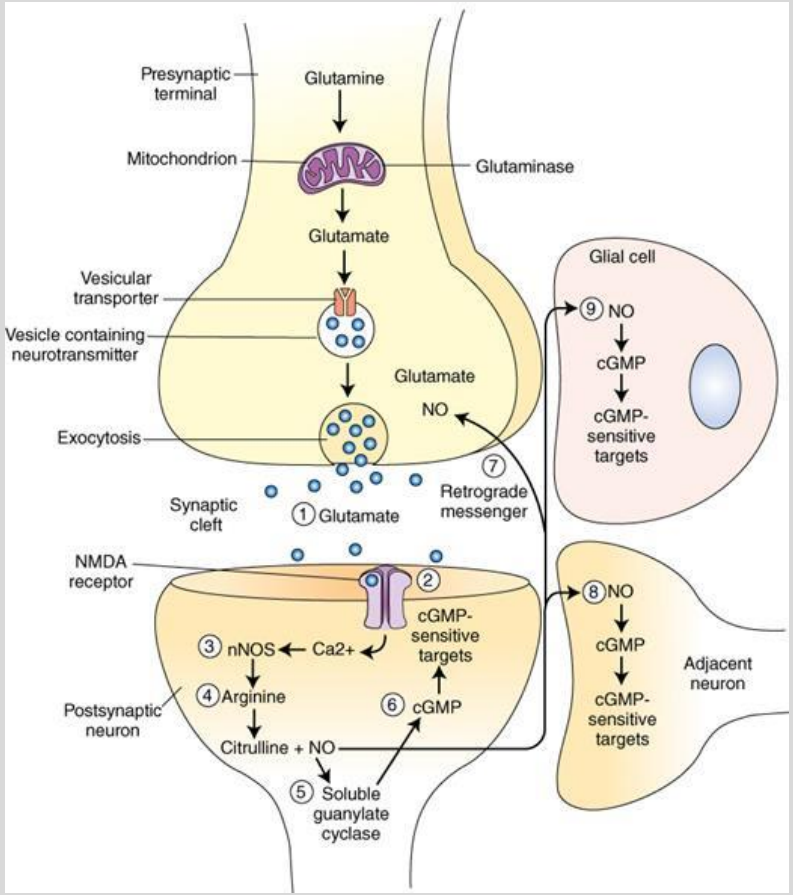

Nitric oxide and carbon monoxide are gases that also serve as neurotransmitters.

Being gases, they are not stored in any structure. Instead, they are made by enzymes (e.g., NOS) as they are needed and released from neurons by diffusion

Neuromodulator and vasodilator.

Ch 7, Essential Neuroscience, 4e.

Selected Peptide Neurotransmitters

Group	Neuropeptide	Selected CNS Function
Opioid Family	Endorphins	Analgesia (μ agonist; derived from pro-opiomelanocortin, POMC)
	Enkephalins	Analgesia (δ agonist; derived from pro-enkephalin), Feeding, Thermoregulation, Learning and memory
	Dynorphins	Analgesia (κ agonist; derived from pro-dynorphin)
Some Hypothalamic Peptides	Releasing Hormones (RH)	CRH - regulate ACTH secretion, GHRH - regulate growth hormone secretion, regulates GnRH - gonadotropin secretion, TRH – regulates thyroid-stimulating hormone secretion
	Neurotensin	Endogenous neuroleptic, Thermoregulation, Analgesia
	Neuropeptide Y	Stimulates hunger, food intake, and drinking, Locomotion, Memory
	Agouti-related protein	Stimulate hunger and food intake
Some Brain–Gastrointestinal Tract Peptides	Bombesin	Inhibition of feeding, Thermoregulation, Modulatory effect on learning and memory
	Cholecystokinin	Satiety, Modulates dopamine neuron activity, Facilitates memory processing (especially under stress)
	Secretin	Modulates motor and other functions in brain, facilitating GABA
	Galanin	Modulates release of several hormones and factors, Affects feeding, sexual behavior, and anxiety, Potent anticonvulsant effects
	Orexins (hypocretin)	Wakefulness/sleep, Regulation of energy homeostasis, Feeding behavior, Locomotion and muscle tone
	Somatostatin	Regulation of growth hormone secretion
	Tachykinins	Substance P colocalizes with serotonin and is involved in nociception
	Vasoactive intestinal polypeptide	Cerebral blood flow, Potent anti-inflammatory factor

Modified from Bradley and Daroff's Neurology in Clinical Practice, 50, 730-747.e2

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Summary:

- 3 Key Concepts
  1. Cells compartmentalize neurochemicals
  2. Cell body and release sites are different
  3. Neurotransmitter receptors produce effect

- Know sites of production and major effects of the neurotransmitters discussed
  - Glutamate
  - GABA
  - Acetylcholine
  - Dopamine
  - Norepinephrine
  - Serotonin
  - Histamine
  - Neuropeptides
  - ATP and Adenosine
  - Nitric oxide

Lecture Feedback Form:

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https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R