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Principles of Neurochemistry

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

Cells act as chemical compartments

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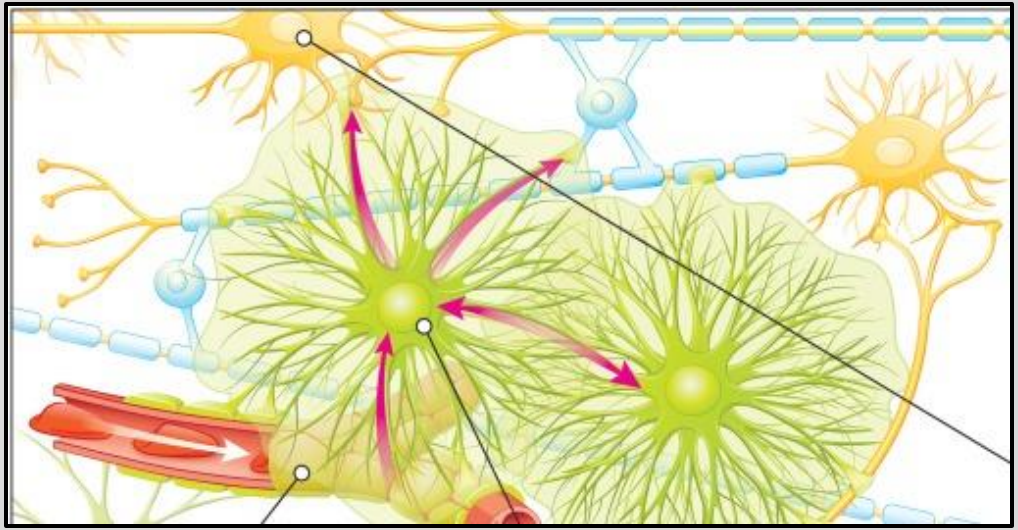
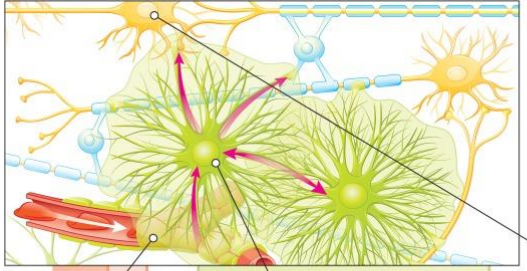
Review of brain cell types:

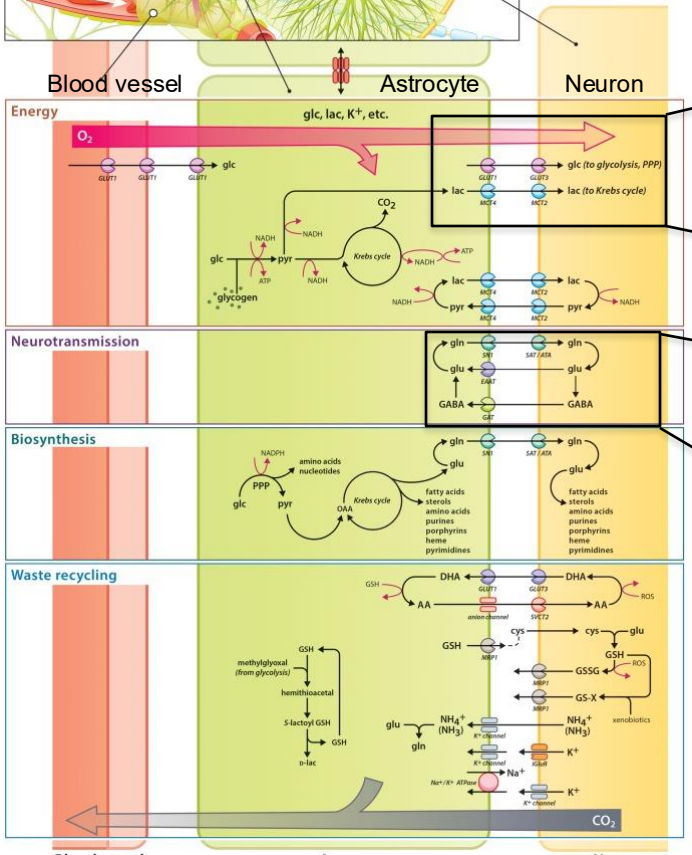
- Neurons
- Astrocytes
- Oligodendrocytes
- Microglia
- Endothelial cells (vasculature)
- Other cells: Pericytes, ependymal cells, NG2 glia, vascular smooth muscle cells, others



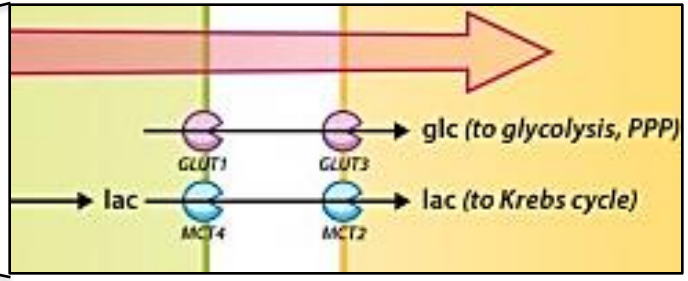
Astrocytes and neurons work as complementary compartments to achieve brain function



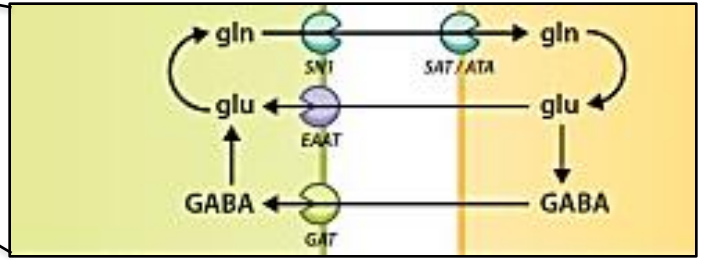
Role of astrocytes in brain metabolism



The astrocyte-neuron lactate shuttle



The glutamate/GABA-glutamine cycle



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

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

The tripartite synapse

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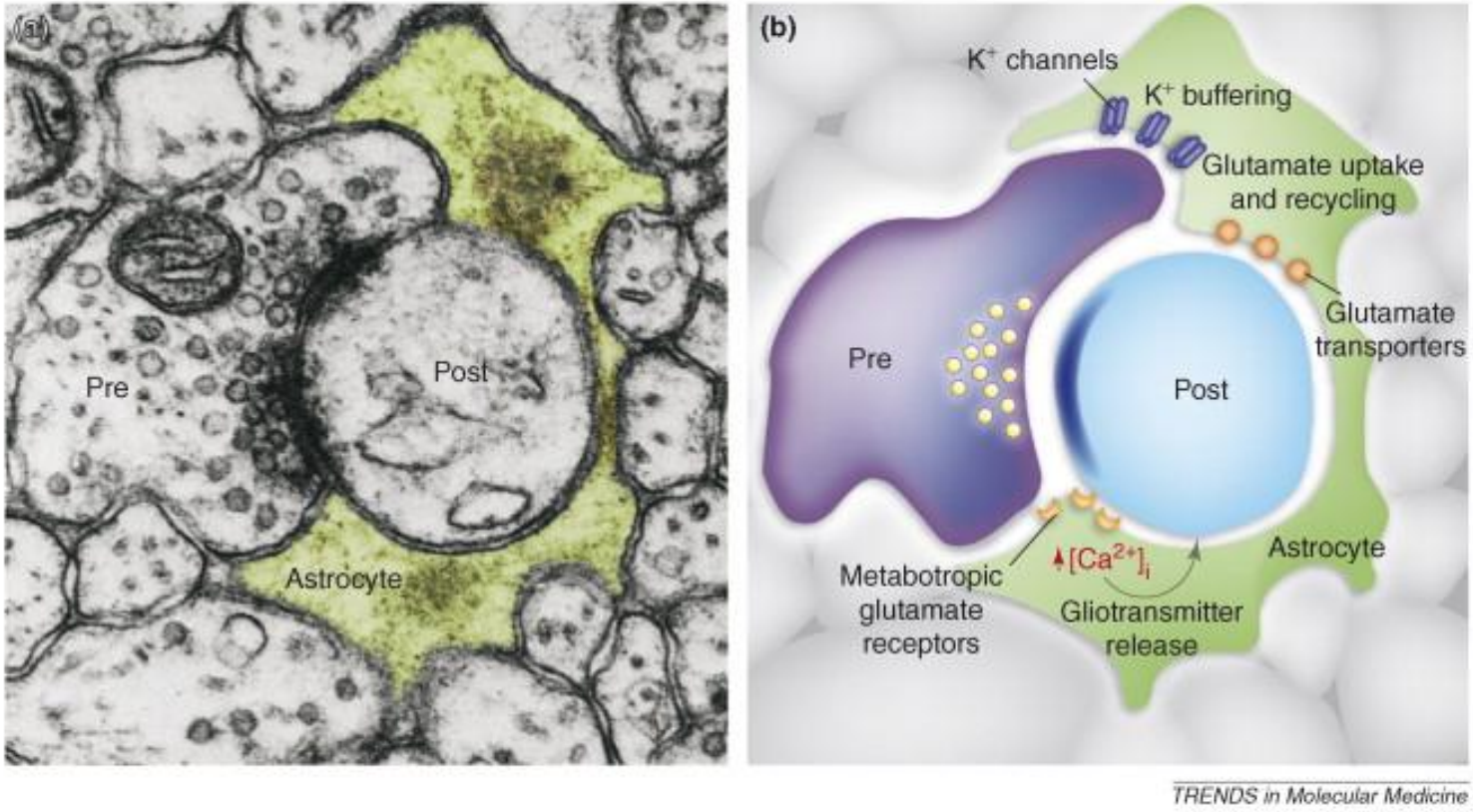

Trends in Molecular Medicine, 2007-02-01, Volume 13, Issue 2, Pages 54-63

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)

Acetylcholine

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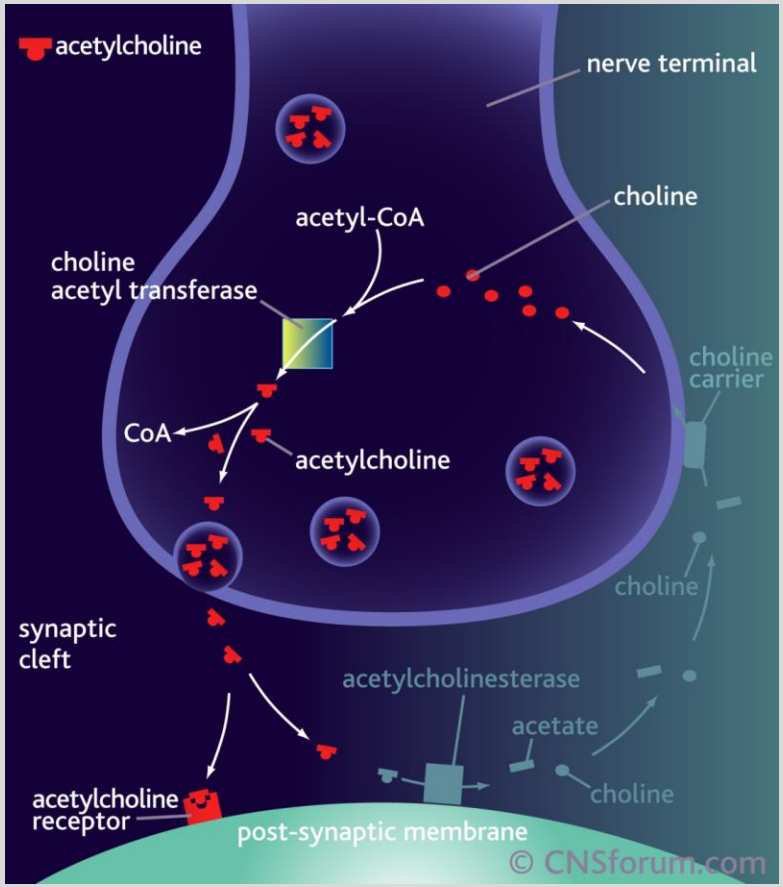

Acetylcholinesterase (AChE) attenuates cholinergic signaling to prevent runaway acetylcholine receptor activation

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 Receptor Distribution

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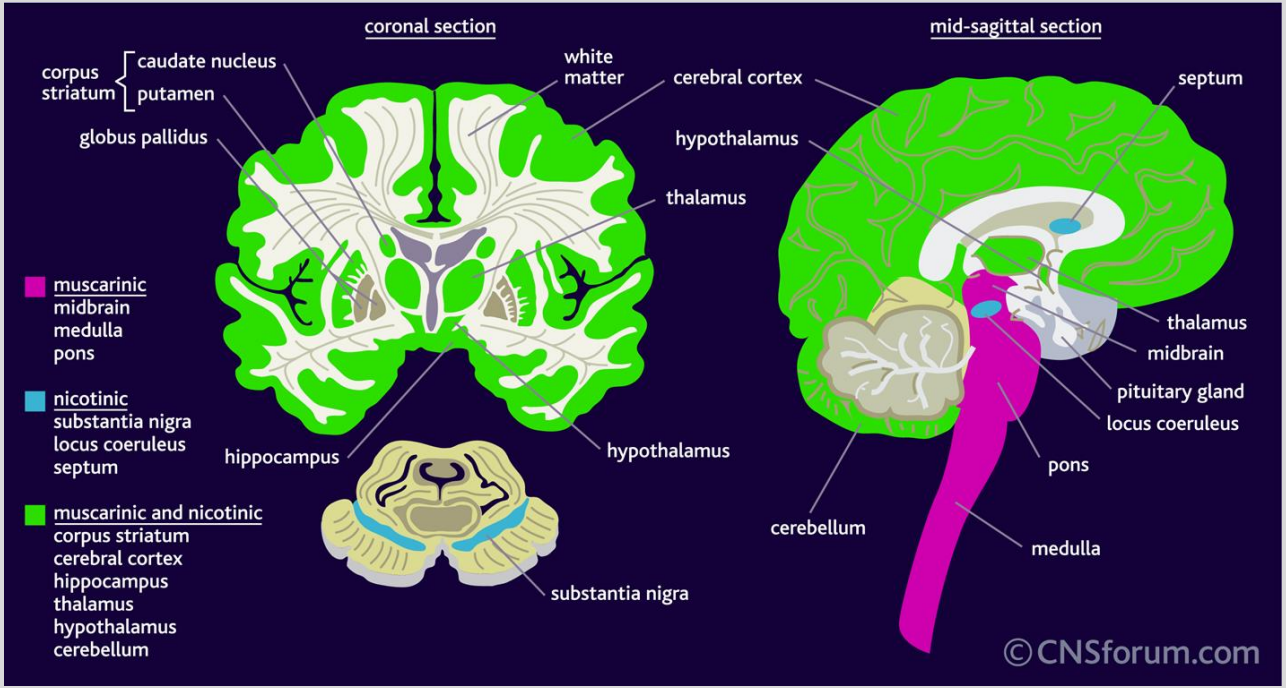

Nicotinic acetylcholine receptors (nAChR) are ligand gated ionotropic channels, positive ion conductance

Muscarinic acetylcholine receptors are metabotropic and signal through second messengers

Dopamine Receptor Locations

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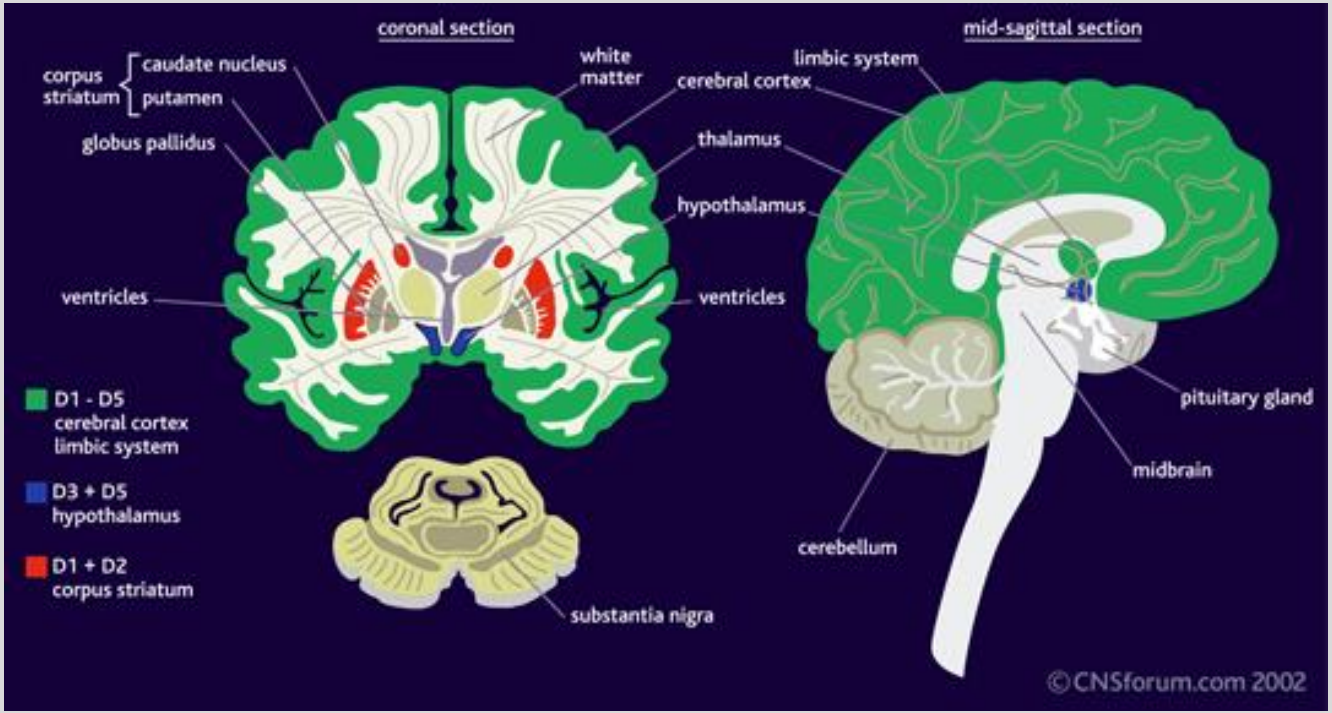

- **D_1 , D_5 Excitatory**; (↑cAMP, ↑PKA)
- **$D_{2\text{-}4}$ Inhibitory** (↓cAMP, ↑gK^+, ↓gCa^{2+})

g, ion channel conductance

Norepinephrine

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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 Synthetic Pathway

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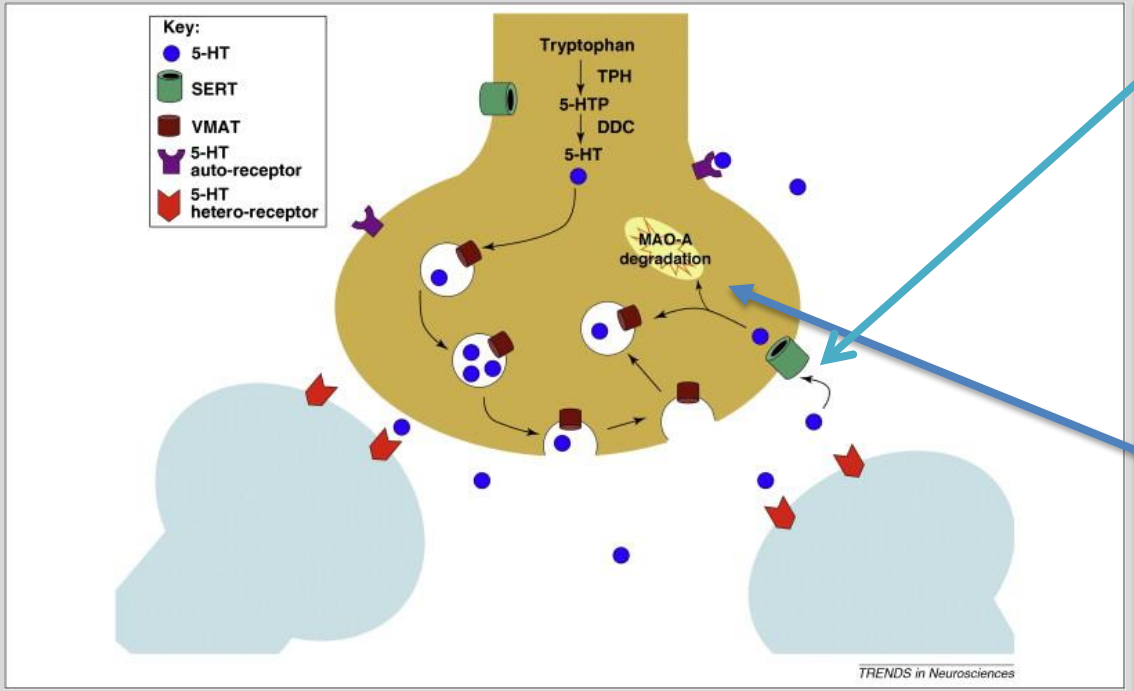

Selective serotonin reuptake inhibitors (SSRIs) such as Fluoxetine **block reuptake** transporters and thereby increasing serotonin signaling to modify depressive symptoms

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

Histaminergic Systems

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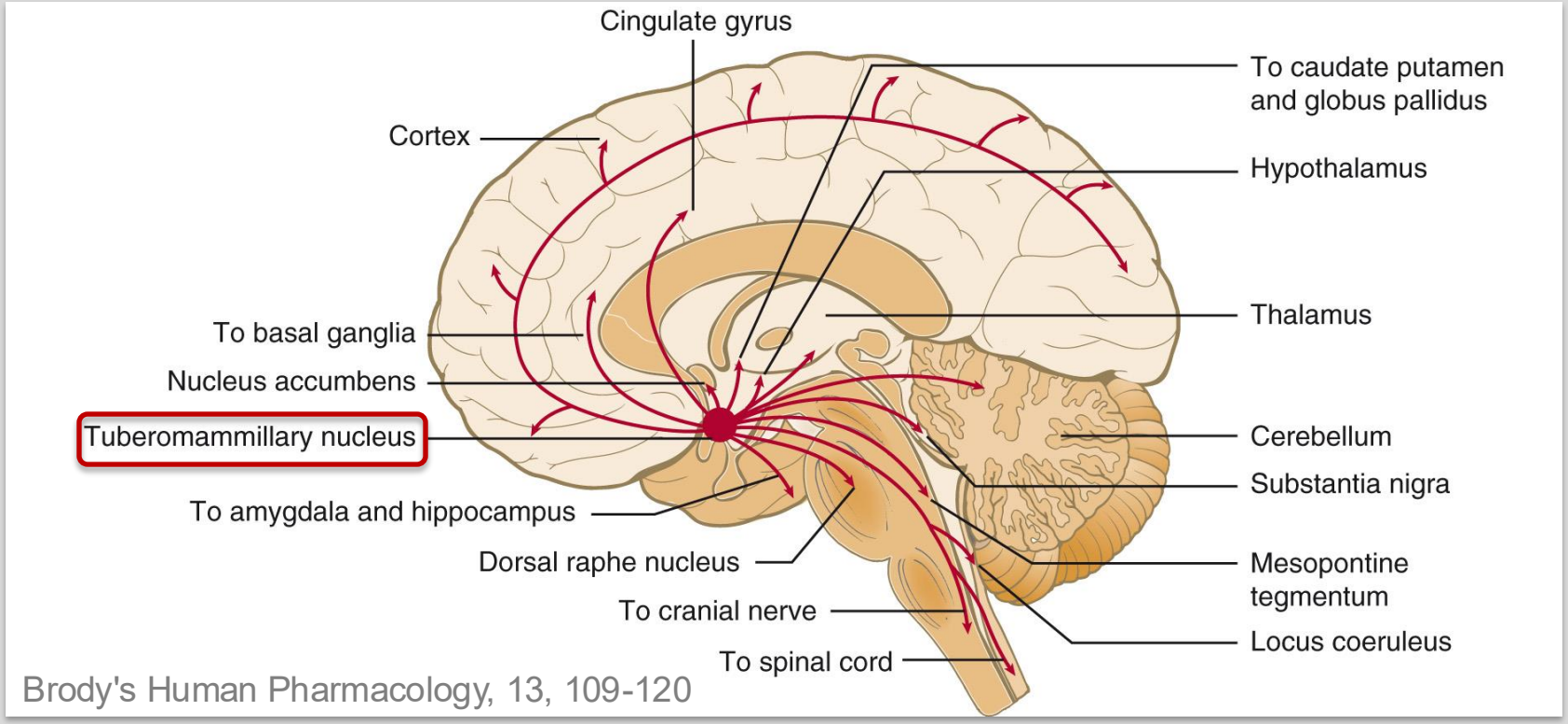

Brody's Human Pharmacology, 13, 109-120

ATP and Adenosine

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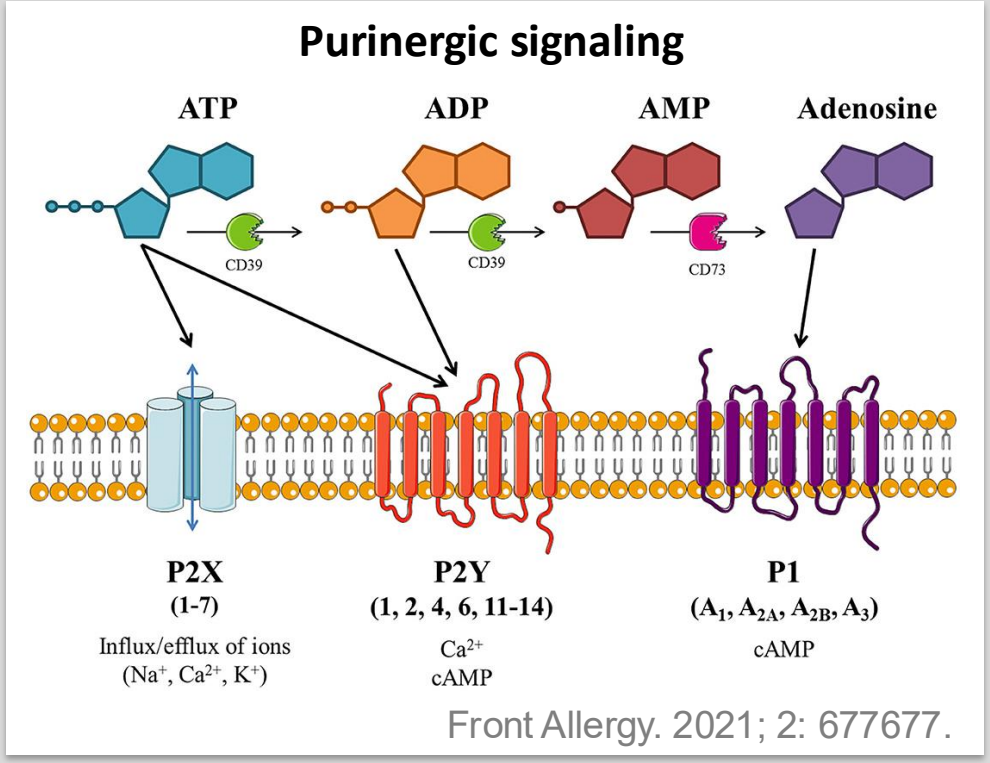
ATP is the energy currency of the cell, and it can be released via channels, vesicles and cell death.
Extracellular enzymes hydrolase ATP to Adenosine.

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.

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