Agents of Synaptic Transmission
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Agents of Synaptic Transmission:
Small-Molecule Neurotransmitters

- **Amino acids**
  - glutamate
  - gamma-amino butyric acid (GABA)
  - aspartate
  - glycine

- **Monoamines**
  - catecholamines
    - epinephrine (adrenalin)
    - norepinephrine (noradrenalin)
  - dopamine
  - indoleamines
    - serotonin
    - melatonin
Agents of Synaptic Transmission: 
Small-Molecule Neurotransmitters

- Soluble gases
  - nitric oxide
  - carbon monoxide
- Acetylcholine

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Agents of Synaptic Transmission: 
Large-Molecule Neurotransmitters

- endogenous opioids
- substance P
- oxytocin
- antidiuretic hormone (ADH)
- cholecystokinin (CCK)
Glutamate

- Glutamate is the most common excitatory neurotransmitter in the CNS. Synapses that use glutamate are called glutamatergic. Termination of action is by reuptake.
- Implicated in Huntington’s disease. Extreme anxiety, linked to below normal GABA levels, may be treated with Valium.
- Appears to be involved with memory storage and retrieval.

GABAergic Synapse

Gamma-aminobutyric acid (GABA) is the most common inhibitory transmitter in the brain. Its synapses are called GABAergic and it is terminated by reuptake.
Monoamines: catecholamines and indoleamines

- **Catecholamines**
  - **Norepinephrine (NE)**
    - NE transmission is called *adrenergic*.
    - NE is terminated by reuptake and degradation of NE within the cytoplasm, not in synaptic vesicles, by monoamine oxidase (MAO).
    - NE is the transmitter in the sympathetic nervous system and is involved in regulating attention, concentration, arousal, sleep and depression.
  - **Dopamine (DA)**
    - A precursor to NE.
    - Found in the substantia nigra and basal ganglia
    - Involved in voluntary movements, schizophrenia, Parkinson’s disease, and addictions including nicotine, alcohol and others
Neurons using **dopamine** are called “**dopaminergic**.”

Neurons using **epinephrine** are called “**adrenergic**.”

Neurons using **norepinephrine** are called “**noradrenergic**.”

Epinephrine used to be known as adrenaline; scientists began using the current name epinephrine when the word adrenaline was used commercially by a pharmaceutical company.

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Receptors for **norepinephrine** and **epinephrine** are called **adrenergic**.

Because most receptors sensitive to norepinephrine also respond to epinephrine.
Distinguish between **epinephrine** the neurotransmitter and **epinephrine** the neurohormone.

**TH** – tyrosine hydroxylase
L-Dopa – L-dihydroxyphenylalanine

**Catecholamine synthesis** begin with the same building block - **TYROSINE**
Rhythmic tremor often occurs at first in one hand, where it resembles the motion of rolling a pill between the thumb and forefinger.

Leaning forward or backward when upright reflects impairment of balance and coordination.

Shrinkage of handwriting is a symptom in some patients. It is usually easier to write when a patient's medicine is working well and when it was not tolerated.

Difficulty dialing from a writing position is a common sign of disorientation and control over movement. Some patients report feelings of weakness and emotions that are not recognized by others but are noticeable to themselves.
NEURONAL CIRCUIT disrupted in Parkinson's disease is shown schematically. When dopamine-producing neurons die, loss of dopamine release in the striatum causes the acetylcholine producers there to overstimulate their target neurons, thereby triggering a chain reaction of abnormal signaling leading to impaired mobility.

The pars compacta region of the substantia nigra in the normal brain appears dark (left photograph) because dopamine-producing neurons are highly pigmented; as neurons die from Parkinson's disease, the color fades (right photograph).
DAMAGE TO BRAIN TISSUE can be strikingly evident in samples from people who died with Parkinson's disease.

Dopamine-producing cells (brown ovals), visible in the substantia nigra of a healthy brain (left), are virtually absent in a specimen from an afflicted individual (center).

And cells that survive often harbor a distinctive sign that the disease was at work (right): abnormal structures known as Lewy bodies (pink spheres).

SO-CALLED FROZEN ADDICTS posed together in 1991, after having received treatment. Nine years earlier all suddenly became immobile, as if they had instantly acquired Parkinson's disease, after taking an impure version of a narcotic. Studies of how an impurity in the drug led to the freezing has generated many insights into the biochemical reactions that could contribute to a more classical presentation of the disease.
DA receptors are metabotropic.

- **D₁ receptor**
  - Postsynaptic
  - Increases cAMP

- **D₂ receptors**
  - Postsynaptic
  - Presynaptic
  - Decreases cAMP
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Founded in 1998 as a search engine, this company's name is now a verb. GoogleCocaine and methylphenidate have the same action.

What is block DA reuptake?
This drug blocks DA reuptake by running the transporters in reverse.

What is amphetamine?

What is an agonist? (cocaine, Ritalin, amphetamine) A drug that blocks DA reuptake.
Dopamine is converted into Norepinephrine inside the synaptic vesicle using the enzyme dopamine β-hydroxylase.
Noradrenergic Pathways and projections

- Locus coeruleus (dorsal pons)
  - Frontal cortex
  - Thalamus
  - Hypothalamus
  - Limbic system
- Caudal Raphe Nuclei
  - Amygdala
  - Midbrain

Primary effect: an increase in **vigilance** – attentiveness to events in the environment.

**NE**

4 types of NE receptors (all are metabotropic).

- \(\alpha_1\)
- \(\alpha_2\)
- \(\beta_1\)
- \(\beta_2\)

In the brain all NE autoreceptors are of this type!

**idazoxan** – blocks \(\alpha_2\)

autoreceptors - acts as an **agonist**.
Sparse and unbundled noradrenergic fibers of different thickness (arrows) and beaded nature is shown. Scale bar is: 20 μm

When the noradrenergic neuron is stimulated with a depolarizing current, neurotransmitter is released from axonal varicosities.


Amadio et al. BMC Developmental Biology 2007 7:77

Quick Facts about monoamines

- Five monoamines - divided into two groups:
  - Catecholamines
    - (Dopamine, Norepinephrine, Epinephrine)
  - Indoleamines
    - (serotonin, melatonin)
- All monoamines are subject to reuptake from the synaptic gap following release.
- Within the axon terminal, monoamines that are not encased in vesicles may be broken down by the action of the enzyme monoamine oxidase (MAO)
• **Monoamine oxidase (MAO)**
  - An enzyme that breaks down monoamines

• **L-Dopa**
  - A substance produced during the synthesis of catecholamines that is also administered as a treatment for Parkinson’s disease.

• **Dopamine**
  - A major monoamine and catecholamine neurotransmitter implicated in motor control, reward, and psychosis

• **Tyrosine hydroxylase (TH)**
  - The enzyme that converts Tyrosine (Y) to L-Dopa
  - TH adds a hydroxyl group to tyrosine.
  - TH is the rate limiting step in all catecholamine synthesis.

• **DOPA decarboxylase**
  - The enzyme that converts L-Dopa to Dopamine (DA).
  - L-Dopa looses one carboxyl group to become DA.

• **Dopamine-Beta-hydroxylase**
  - The enzyme that converts DA to Norepinephrine (NE)
  - This enzyme is located in the vesicles.
  - DA to NE conversion occurs in the vesicles.
AMPT (\textit{alpha-methyl-p-tyrosine})
- A drug that inactivates tyrosine hydroxylase
- This drug interferes with the synthesis of the catecholamines.
- It is a catecholamine antagonist.

Reserpine
- A drug that prevents storage of monoamines in synaptic vesicles by blocking the transporters in the membrane of vesicles of monoaminergic neurons.
- Monoamine antagonist.

Major dopaminergic pathways
- Nigrostriatal system – originating in the substantia nigra and terminating in the neostriatum (caudate nucleus and putamen)
- Mesolimbic system – originating in the ventral tegmental area and terminating in the nucleus accumbens, amygdala, and hippocampus
- Mesocortical system – originating in the ventral tegmental area and terminating on the prefrontal cortex.
- **Fusaric Acid**
  - A drug that inhibits the activity of the enzyme Dopamine-Beta-Hydroxylase
  - Blocks the production of norepinephrine without affecting the production of dopamine.

- **MAO-A**
  - Excess norepinephrine in the terminal button is destroyed by monoamine oxidase A

- **Moclobemide**
  - Blocks MAO-A
  - Acts as an agonist for NE