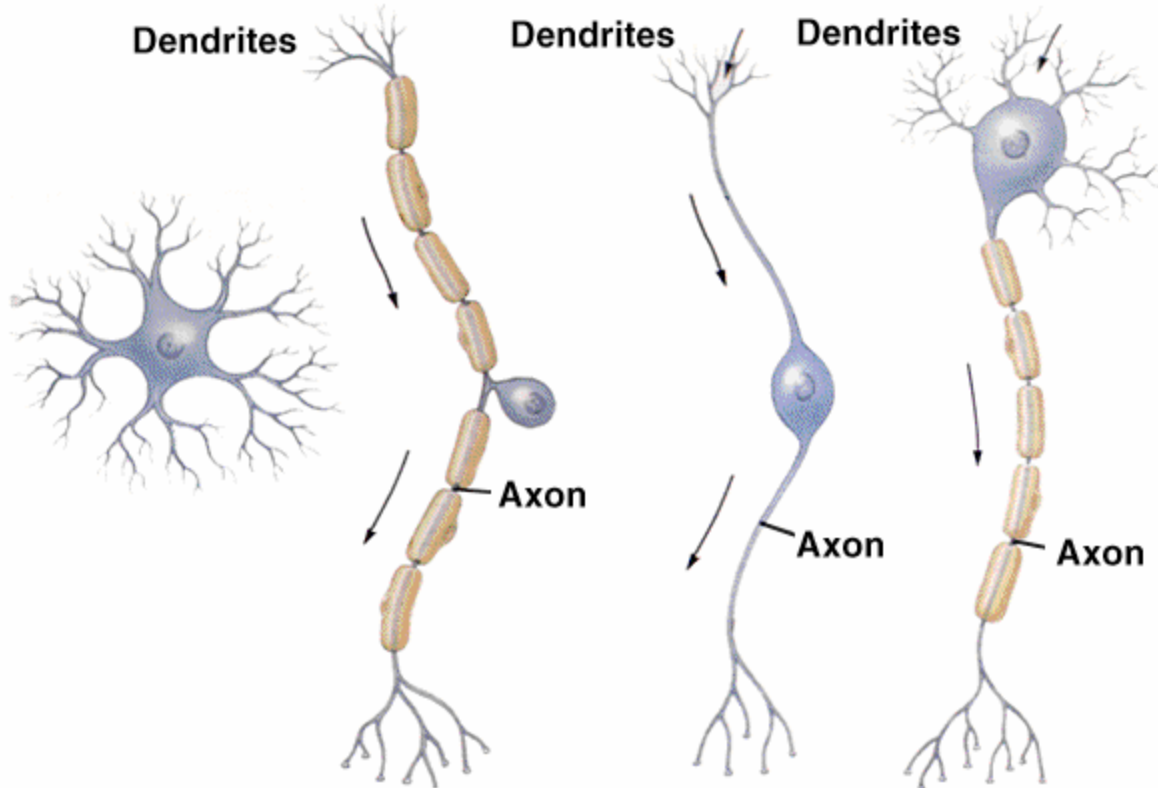


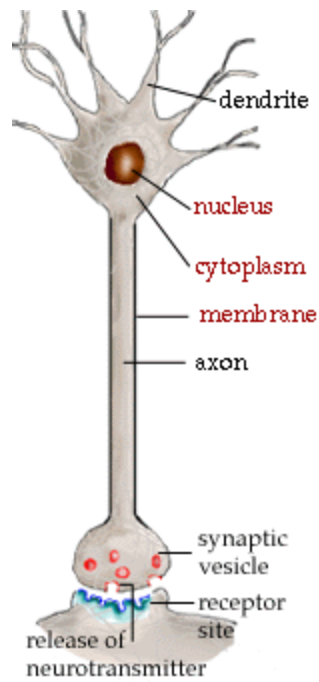
The Neuron

A. What is a **neuron**?



1. A neuron is a type of cell that receives and transmits information in the Central Nervous System (CNS – brain and spinal cord) and the Peripheral Nervous System (PNS – afferent & efferent nerves).

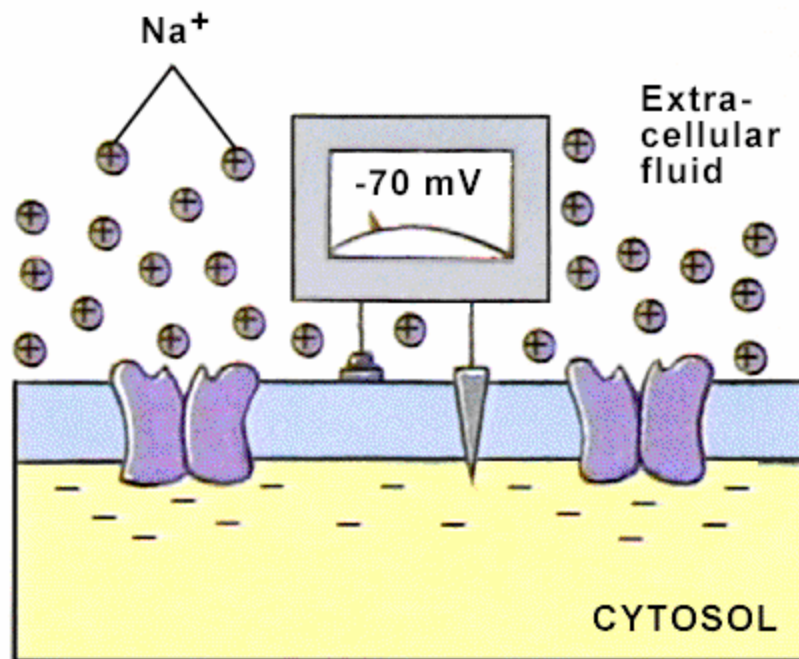
2. Parts of the neuron: **cell body** (soma), **dendrites**, **axon**, **axon hillock**, **synaptic boutons**.



The Nerve Impulse

A. The Resting Potential

1. When a neuron is at rest, the neuron maintains an electrical **polarization** (i.e., a negative electrical potential exists inside the neuron's membrane with respect to the outside). This difference in electrical potential or voltage is known as the resting potential. At rest, this potential is around -70mV .



2. **Concentration gradient** (difference in distribution of ions between the inside and the outside of the membrane): During the resting potential, a difference in the distribution of ions is established with sodium (Na⁺) 10 times more concentrated outside the membrane than inside and potassium (K⁺) 20 times more concentrated inside than outside.

Because the body has far more sodium ions than potassium ions, the concentration of sodium ions outside is greater than the potassium ions inside making the outside more positively charged than the inside.

3. The neuron membrane has **selective permeability**, which allows some molecules to pass freely (e.g., water, carbon dioxide, oxygen, etc.).

4. During the resting potential, K⁺ and (chloride) Cl⁻ gates (channels) remain open along the membrane, which allows both ions to pass through; Na⁺ gates remain closed restricting the passage of Na⁺ ions.

5. **Sodium-potassium pump**: Protein mechanism found along the neuron membrane which transports 3 Na⁺ ions outside of the cell while also drawing 2 K⁺ ions into the cell; this is an active transport mechanism (requires energy (ATP) to function).

6. **Electrical gradient** (difference in positive and negative charges across the membrane): Due to the negative charge inside the membrane, K⁺ (a positively-charged ion) is attracted into the neuron; Na⁺ is also attracted to the negative charge, but remains mostly outside of the neuron due to the sodium-potassium pump and the closing of sodium gates.

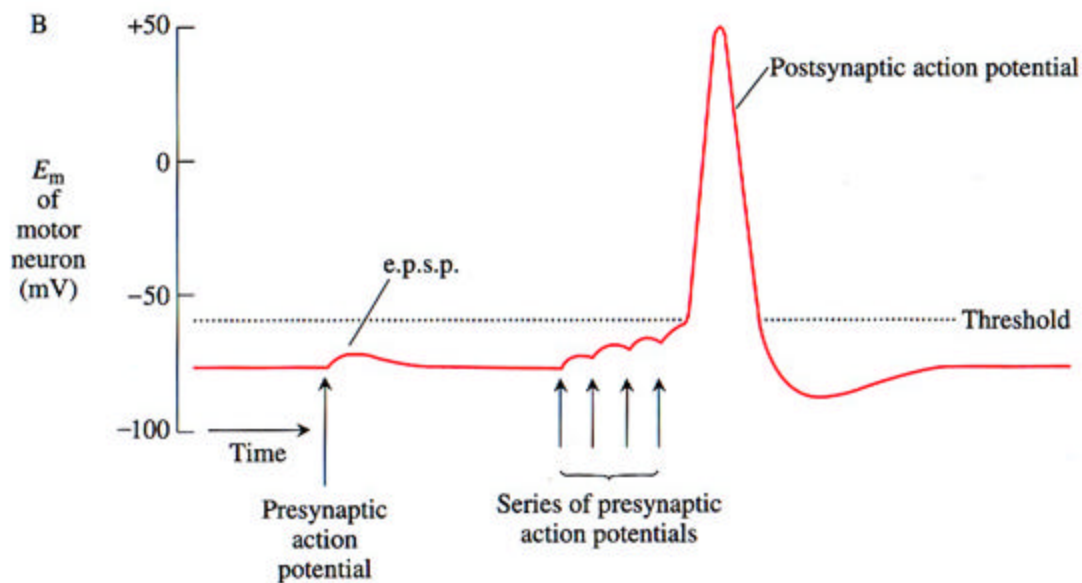
7. The advantage of the resting potential is to allow the neuron to respond quickly to a stimulus.

B. The Action Potential

1. **Hyperpolarization** (increased polarization): Occurs when the negative charge inside the axon increases (e.g., -70mV becomes -80mV).
2. **Depolarization** (decreasing polarization towards zero): Occurs when the negative charge inside the axon decreases (e.g., -70mV becomes -55mV).
3. **Threshold of excitation** (threshold): The level that a depolarization must reach for an action potential to occur. In most neurons the threshold is around -55mV to -65mV .
4. **Action potential**: A rapid depolarization and slight reversal of the usual membrane polarization. Occurs when depolarization meets or goes beyond the threshold of excitation.

Figure 8.1 (continued)

(B) Responses of the postsynaptic motor neuron to action potentials in the presynaptic sensory neuron. At the upward arrows, action potentials are triggered in the presynaptic neuron by an electrical stimulus.



5. When the potential across an axon membrane reaches threshold, **voltage-activated** (membrane channels whose permeability depends on the voltage difference across the membrane) Na^+ gates open and allow sodium ions to enter; this causes the membrane potential to depolarize past zero to a reversed polarity (e.g., -70mV becomes $+50\text{mV}$ at highest amplitude of the action potential).
6. When the action potential reaches its peak, voltage-activated Na^+ gates close, but K^+ ions flow outside of the membrane due to their high concentration inside the neuron as opposed to outside.
7. A temporary hyperpolarization occurs before the membrane returns to its normal resting potential (this is due to K^+ gates opening wider than usual, allowing K^+ to continue to exit past the resting potential).

8. After the action potential, the neuron has more Na^+ and fewer K^+ ions inside for a short period (this is soon adjusted by the sodium-potassium pumps to the neuron's original concentration gradient).

9. Local anesthetic drugs (e.g., Novocain, Xylocaine, etc.) hinder the occurrence of action potentials by blocking voltage-activated Na^+ gates (preventing Na^+ from entering a membrane).

10. General anesthetics (e.g., ether and chloroform) cause K^+ gates to open wider, allowing K^+ to flow outside of a neuron very quickly, thus preventing an action potential from occurring (no pain signal).

11. Action potentials only occur in axons as cell bodies and dendrites do not have voltage-dependent channels.

12. **All-or-none law:** The size, amplitude, and velocity of an action potential are independent of the intensity of the stimulus that initiated it. If threshold is met or exceeded an action potential of a specific magnitude will occur, if threshold is not met, an action potential will not occur.

13. **Refractory period:** A period of immediately after an action potential occurs when the neuron will resist the production of another action potential.

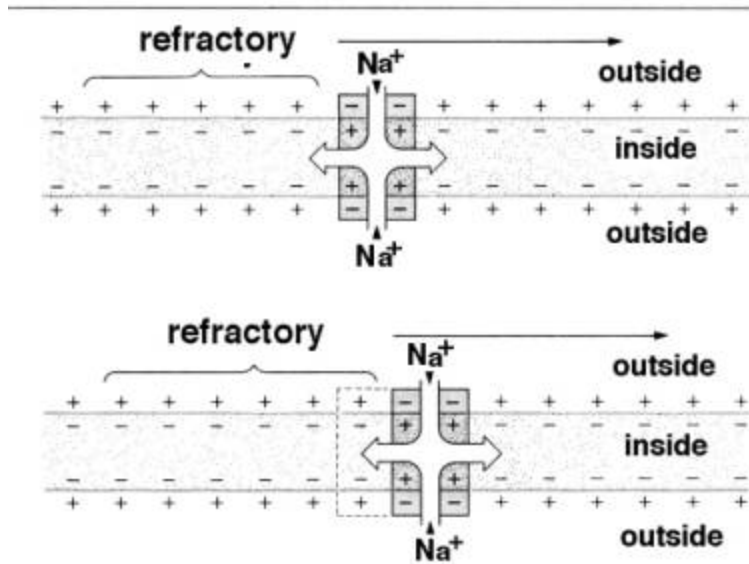
a. **Absolute refractory period:** Na^+ gates are incapable of opening; hence, an action potential cannot occur regardless of the amount of stimulation.

b. **Relative refractory period:** Na^+ gates are capable of opening, but K^+ channels remain open; a stronger than normal stimulus (i.e., exceeding threshold) will initiate an action potential.

C. **Propagation** (movement) of the Action Potential

1. The action potential begins at the **axon hillock** (a swelling located where an axon exits the cell body).

2. The action potential is regenerated due to Na^+ ions moving down the axon, depolarizing adjacent areas of the membrane.



3. **Propagation of the action potential:** Transmission (movement) of an action potential down an axon. The action potential moves down the axon by regenerating itself at successive points on the axon.

4. The refractory periods prevent the action potentials from moving in the opposite direction (i.e., back toward the axon hillock).

D. Myelin Sheath and Saltatory Conduction

1. **Myelinated axons:** Axons covered with a myelin sheath. The myelin sheath is found only in vertebrates and is composed mostly of fats.

2. **Nodes of Ranvier:** Short unmyelinated sections on a myelinated axon.

3. **Saltatory conduction:** The "jumping" of the action potential from node to node.

4. **Multiple sclerosis:** A disease characterized by the loss of myelin along axons; the loss of the myelin sheath prevents the propagation of action potentials down the axon.

The Concept Of The Synapse

A. **Synapse:** A gap between neurons where a specialized type of communication occurs.

B. C. S. Sherrington deduced the properties of the synapse from his experiments on **reflexes** (an automatic response to stimuli).

C. Sherrington discovered that:

1. Reflexes are slower than conduction along an axon; thus, there must be a delay at the synapse.

2. Synapses are capable of summing stimuli.

3. Excitation of one synapse leads to a decreased excitation or inhibition of others.

D. Temporal summation: Repeated stimulation of one **presynaptic neuron** (the neuron that delivers the synaptic potential) occurring within a brief period of time having a cumulative effect on the **postsynaptic neuron** (the neuron that receives the message).

E. Graded potentials: Either depolarization (excitatory) or hyperpolarization (inhibitory) of the postsynaptic neuron. A graded depolarization is known as an excitatory **postsynaptic potential (EPSP)** and occurs when Na^+ ions enter the postsynaptic neuron. EPSP'S are not action potentials: The EPSP's magnitude decreases as it moves along the membrane.

F. Spatial summation: Several synaptic inputs originating from separate locations exerting a cumulative effect on a postsynaptic neuron.

G. Inhibitory postsynaptic potential (IPSP): A temporary hyperpolarization of a postsynaptic cell (this occurs when K^+ leaves the cell or Cl^- enters the cell after it is stimulated).

H. Spontaneous firing rate: The ability to produce action potentials without synaptic input (EPSP's and IPSP's increase or decrease the likelihood of firing action potentials).

Chemical Events At The Synapse

A. In most cases, synaptic transmission depends on chemical rather than electrical stimulation. This was demonstrated by Otto Loewi's experiments where fluid from a stimulated frog heart was transferred to another heart. The fluid caused the new heart to react as if stimulated.

B. The major events at a synapse are:

1. Neurons synthesize chemicals called neurotransmitters.

2. Neurons transport these chemicals to the axon terminal.

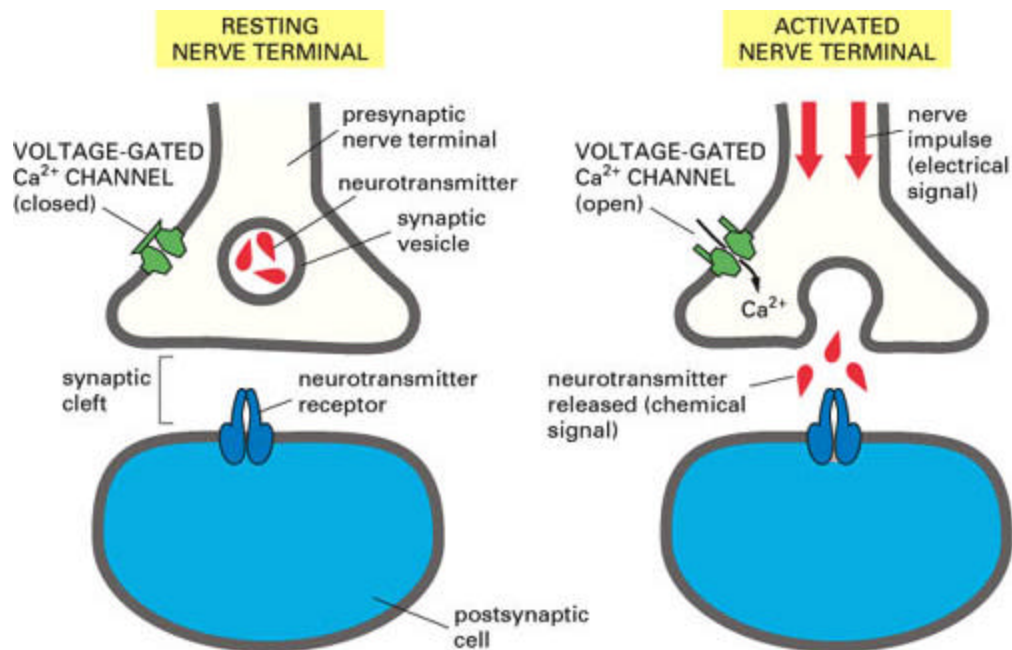
3. Action potentials travel down the axon.

4. At the axon or **presynaptic terminal**, the action potentials open voltage-gated calcium channels to open, allowing calcium to enter the cell. This leads to the release of the neurotransmitters from the terminal into the **synaptic cleft** (space between the presynaptic and postsynaptic neuron).

5. Neurotransmitters, once released into the synaptic cleft, attach to receptors and alter activity of the postsynaptic neuron.

6. The neurotransmitters will separate from their receptors and (in some cases) are converted into inactive chemicals.

7. In some cells much of the released neurotransmitters are taken back into the presynaptic neuron for recycling. This is called **reuptake**.



C. Chemicals released by one neuron at the synapse and affect another neuron are **neurotransmitters**.

D. Types of neurotransmitters include

1. **Amino acids**: Acids containing an amine group (NH₂), e.g., gamma-aminobutyric acid (GABA).

2. **Neuropeptides**: A peptide is a chain of amino acids. A long chain is called a polypeptide; a still longer chain is a protein. Endorphins (endogenous opiates) are neuropeptides.

3. **Acetylcholine**: A chemical similar to an amino acid, with the NH₂ group replaced by an N(CH₃)₃ group.

4. **Monoamines**: Nonacidic neurotransmitters containing an amine group (NH₂) formed by a metabolic change of an amino acid. **Catecholamines** are a type of monoamine (see below).

5. **Purines**: Adenosine and several of its derivatives.

6. **Gases**: Specifically nitric oxide (NO) and possibly others.

E. Synthesis of neurotransmitters: Neurons synthesize neurotransmitters from precursors derived originally from food or else from old neurotransmitters recycled via reuptake.

1. Catecholamines (Dopamine (DA), Epinephrine (E) and Norepinephrine (NE)): Three closely related compounds containing a catechol and an amine group.

2. Choline is the precursor for acetylcholine. Choline is obtained from certain foods or made by the body from lecithin.

3. The amino acids phenylalanine and tyrosine are precursors for the catecholamines.

4. The amino acid tryptophan is the precursor for serotonin, another type of monoamine (indolamine).

F. Release and Diffusion of Transmitters

1. Neurotransmitters are stored in **vesicles** (tiny nearly spherical packets) in the presynaptic terminal. (Nitric oxide is an exception to this rule, as neurons do not store nitric oxide for future use). There is also a substantial amount of neurotransmitter outside the vesicles.

2. When an action potential reaches the axon terminal, the depolarization causes voltage-dependent calcium gates to open. As calcium flows into the terminal, the neuron releases neurotransmitters into the synaptic cleft for 1-2 milliseconds. This process of neurotransmitter release is called **exocytosis**.

3. After being released by the presynaptic neuron, the neurotransmitter diffuses across the synaptic cleft to the postsynaptic membrane where it will attach to receptors.

4. The brain uses dozens of neurotransmitters, but no single neuron releases them all.

H. Activation of Receptors of the Postsynaptic Cell

1. A neurotransmitter can have three types of major effects when it attaches to the active site of the receptor: ionotropic, metabotropic, and modulatory.

2. **Ionotropic effects:** Neurotransmitter attaches to the receptor causing the immediate opening of an ion gate (e.g., glutamate opens Na⁺ gates).

3. **Metabotropic effects:** Neurotransmitter attaches to a receptor and alters the configuration of the rest of the receptor protein; enabling a portion of the protein inside the neuron to react with other molecules. Activation of the receptor by the neurotransmitter leads to activation of G-proteins which are attached to the receptor.

G-proteins: A protein coupled to the energy-storing molecule, guanosine triphosphate (GTP).

Metabotropic effects are slower and longer lasting than ionotropic effects and depend on the actions of second messengers.

Second messenger: Chemicals that carry a message to different areas within a postsynaptic cell; the activation of a G-protein inside a cell increases the amount of a second messenger.

4. Neurotransmitters can interact with several different kinds of receptors. Some neurotransmitters can interact with both ionotropic and metabotropic receptors.

I. Inactivation and Reuptake of Neurotransmitters

1. Neurotransmitters become inactive shortly after binding to postsynaptic receptors.

Various neurotransmitters are inactivated in different way.

2. **Acetylcholinesterase** (AChE): Found in acetylcholine (ACh) synapses; AChE quickly breaks down ACh after it releases from the postsynaptic receptor.
3. Myasthenia gravis: Motor disorder caused by a deficit of acetylcholine transmission. This disease is treated with drugs which block AChE activity (thus allowing more ACh to stay in the synapse).
4. Serotonin and the catecholamines are taken up by the presynaptic neuron which released them after they separated from postsynaptic receptors. This process is called **reuptake**; it occurs through specialized proteins called **transporters**.
5. Some serotonin and catecholamine molecules are converted into inactive chemicals by enzymes such as **COMT** (converts catecholamines) and **MAO** (converts both catecholamines and serotonin).

Synapses, Abused Drugs, and Behavior

- A. Drugs can affect synapses by either blocking the effects (an **antagonist**) or increasing the effects (an **agonist**) of a neurotransmitter.
- B. Drugs can influence synaptic activity in many ways including altering synthesis of the neurotransmitter, disrupting the vesicles, increasing release, decreasing reuptake, blocking its breakdown into inactive chemical, or directly stimulating or blocking postsynaptic receptors.
- C. **Affinity**: How strongly the drug attaches to the receptor.
- D. **Efficacy**: The tendency of the drug to activate a receptor.
- E. Olds and Milner (1954) conducted the first brain reinforcement experiments by implanting electrodes in the brains of rats and allowing them to press a lever to produce **self-stimulation of the brain**.
 1. Later experiments showed that the brain stimulation is reinforcing almost exclusively in tracts of axons that release dopamine, especially in an area called the **nucleus accumbens**. Cells located in the nucleus accumbens are inhibited by increased DA activity (most abused drugs, as well as ordinary pleasures, lead to increased DA activity); some hypothesize this phenomenon occurs with drug addiction.
 2. Because of their roles in reinforcement the nucleus accumbens is regarded by many as the pleasure area and dopamine as the pleasure chemical. However, several lines of evidence conflict with this interpretation and more recent studies suggest dopamine and the nucleus accumbens play an important role in attention-getting.
- F. **Stimulant drugs** (e.g., amphetamines, cocaine, etc.) produce excitement, alertness, elevated mood, decreased fatigue, and sometimes motor activity. Each of these drugs increases activity at dopamine receptors. Stimulant drugs are often highly addictive.
 1. **Amphetamine** increases dopamine release from presynaptic terminals by reversing the flow of the dopamine transporter.

2. **Cocaine** blocks the reuptake of catecholamines and serotonin at synapses. The behavioral effects of cocaine are believed to be mediated primarily by dopamine and secondarily on serotonin.

3. The effects of amphetamine and cocaine are both short lived because of depletion of dopamine stores and tolerance.

4. **Methylphenidate** (Ritalin): Stimulant currently prescribed for Attention Deficit Disorder (ADD); works like cocaine by blocking reuptake of dopamine at presynaptic terminals. The effects of methylphenidate are much longer lasting and less intense as compared to cocaine.

G. **Nicotine** : Compound found in tobacco. Stimulates the nicotinic receptor (a type of acetylcholine receptor) both in the central nervous system and neuromuscular junction of skeletal muscles; can also increase dopamine release by attaching to receptors that release dopamine in the nucleus accumbens.

H. **Opiate Drugs** : Derived from (or similar to those derived from) the opium poppy. Common opiates include morphine, heroin, and methadone. Opiates have a net effect of increasing the release of dopamine by stimulating endorphin synapses.

I. **Marijuana** : Contains the chemical D9-tetrahydrocannabinol (D9-THC) and other **cannabinoids** (chemicals related to D9-THC); D9-THC works by attaching to cannabinoid receptors. Anandamide is a brain chemical that binds to cannabinoid receptors.

J. **Hallucinogenic drugs** : Drugs that distort perception. Many hallucinogenic drugs resemble serotonin and bind to serotonin type 2 (5-HT₂) receptors, although their exact mechanism of action remains unclear (some ligands that bind to 5-HT₂ receptors have no psychoactive effects at all).