Neuronal conduction

- Neurons are specifically designed to conduct nerve impulses.
- Nerve impulses are only conducted when the neuron has recovered from conducting its last nerve impulse.
  - Must also be sufficiently stimulated to conduct a new one.

Three states of a neuron

- **Resting potential**
  - The state during which no nerve impulse is being conducted although the neuron is capable of doing so.
- **Action potential**
  - The state during which the neuron is actively involved in conducting a nerve impulse.
- **Recovery/Refractory potential**
  - The state during which the neuron is unable to conduct a nerve impulse since the neuron must “recover” following the last nerve impulse.

Resting potential

- The state of the neuron when no nerve impulse is being conducted.
- During resting potential there is an ion displacement between the inside and the outside of the neuron (i.e. on either side of the neuron cell membrane) as follows:

Resting potential

- There are more Na+ ions on the outside than on the inside.
- There are more K+ ions on the inside than on the outside.
- There are many large organic anions (-ve charged ions) locked inside since they are too big to pass through the neuron’s cell membrane.

- Due to this difference in ion displacement there is a net charge difference across the cell membrane: **MEMBRANE POTENTIAL**
- This membrane potential when the neuron is at rest is called the **RESTING POTENTIAL:-70mV**
- This difference in ion displacement and thus the resting potential is largely maintained by a protein channel called the **Na+/K+ PUMP**

- This pump actively “pumps” Na+ ions out of the cell and K+ ions into the cell
- As a result of this active transport, the cytoplasm of the neuron contains more K+ ions and fewer Na+ ions than the surrounding medium.
- The sodium-potassium pump creates a concentration and electrical gradient for Na^+ and K^+, which means that K^+ tends to diffuse (‘leak’) out of the cell and Na^+ tends to diffuse in.

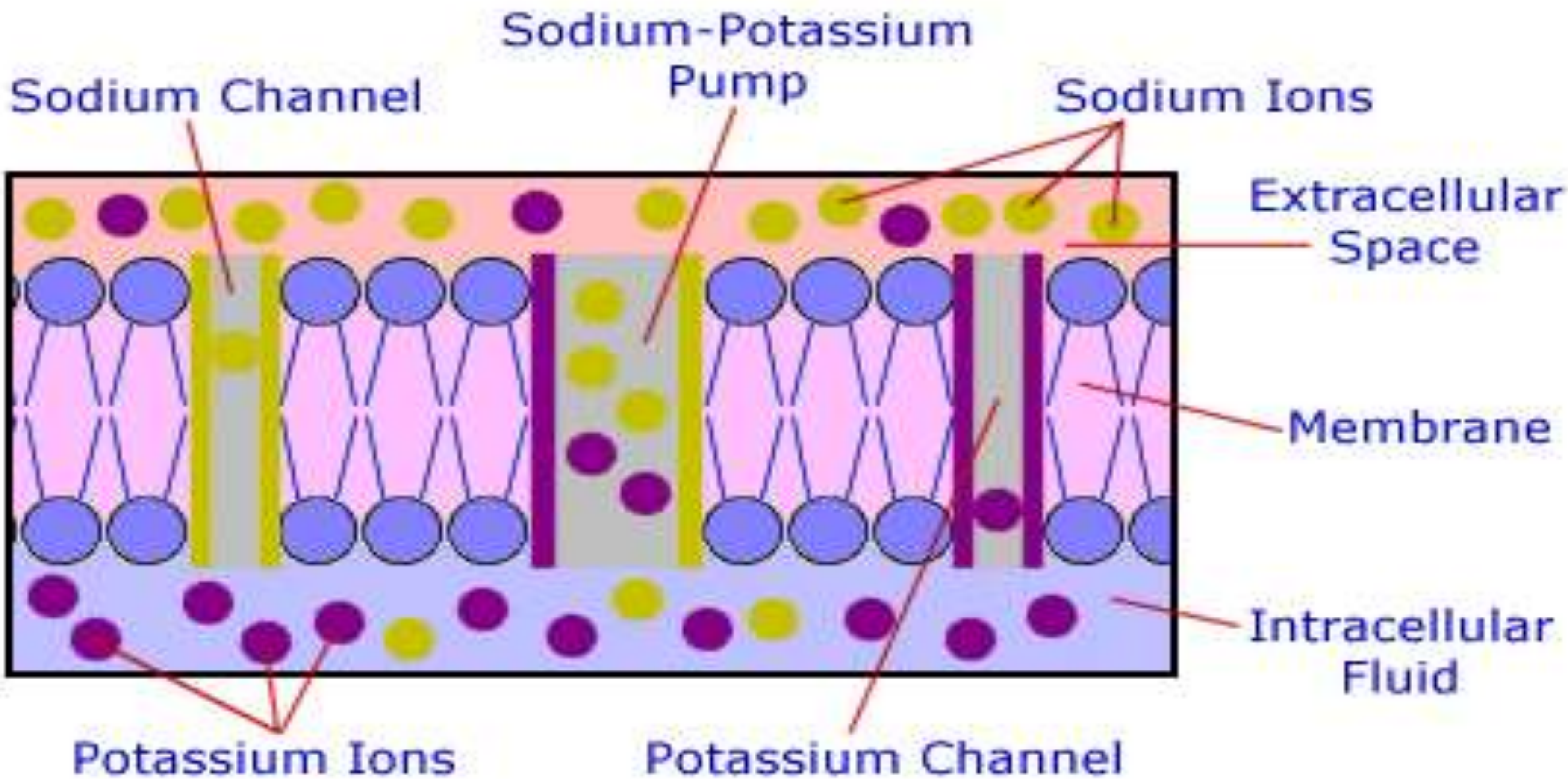
Na+/K+ PUMP

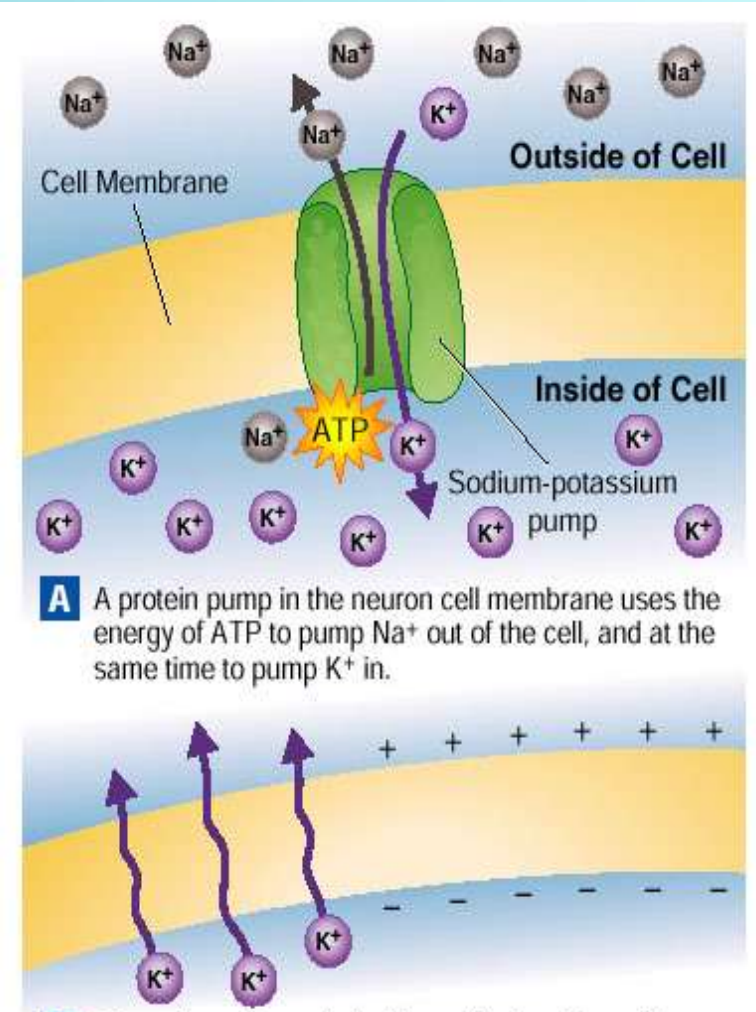
- But, the membrane is much more permeable to K^+ diffuses out along its concentration gradient more slowly.

- Results in a net positive charge outside & a net negative charge inside. Such a membrane is **POLARISED**

Na+/K+ PUMP

- There are more K+ channels than Na+ channels which means more K+ ions leak out of the cell as opposed to Na+ leaking into the cell
- As a result, K+ ions leak out of the cell to produce a negative charge on the inside of the membrane.
- This charge difference is known as the resting potential of the neuron. The neuron, of course, is not actually "resting" because it must produce a constant supply of ATP to fuel active transport.


Sodium-Potassium
Pump
Sodium Channel
Sodium Ions
Extracellular
Space
Membrane
Intracellular
Fluid
Potassium Ions
Potassium Channel



A A protein pump in the neuron cell membrane uses the energy of ATP to pump Na^+ out of the cell, and at the same time to pump K^+ in.

B The cell membrane is leakier to K^+ than it is to Na^+. Because more positive charges leak out of the cell than leak in, the inside of the cell becomes negatively charged with respect to the outside.

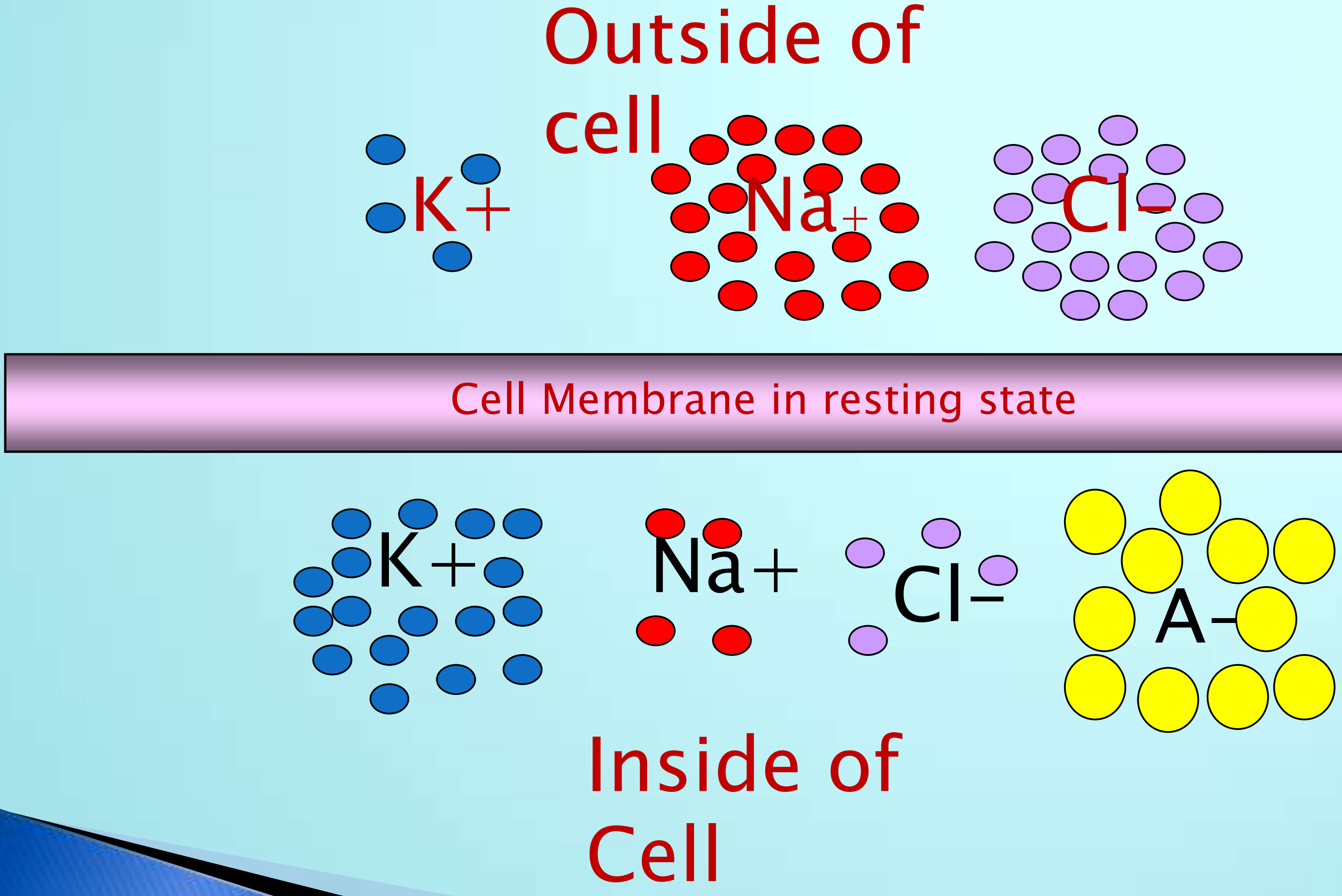
At rest, the inside of a neuron's membrane has a negative charge.

As the figure shows, a Na+ / K+ pump in the cell membran pumps sodium out of the cell and potassium into it.

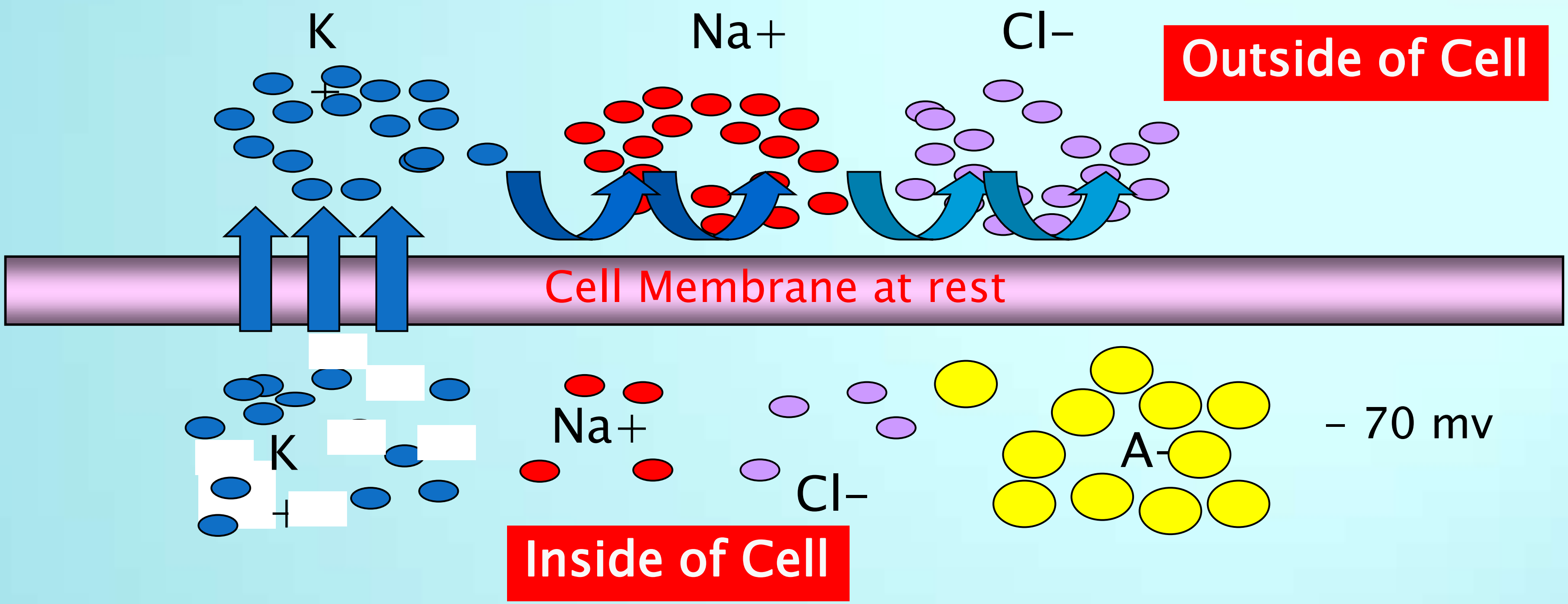
However, because the cell membrane is a bit leakier to potassium than it is to sodium, more potassium ions leak ou the cell.

As a result, the inside of the membrane builds up a net nega charge relative to the outside.

Ion concentrations



The Cell Membrane is Semi-Permeable



Potassium (K+) can pass through to equalize its concentration

Sodium and Chlorine cannot pass through

Result – inside is negative relative to outside

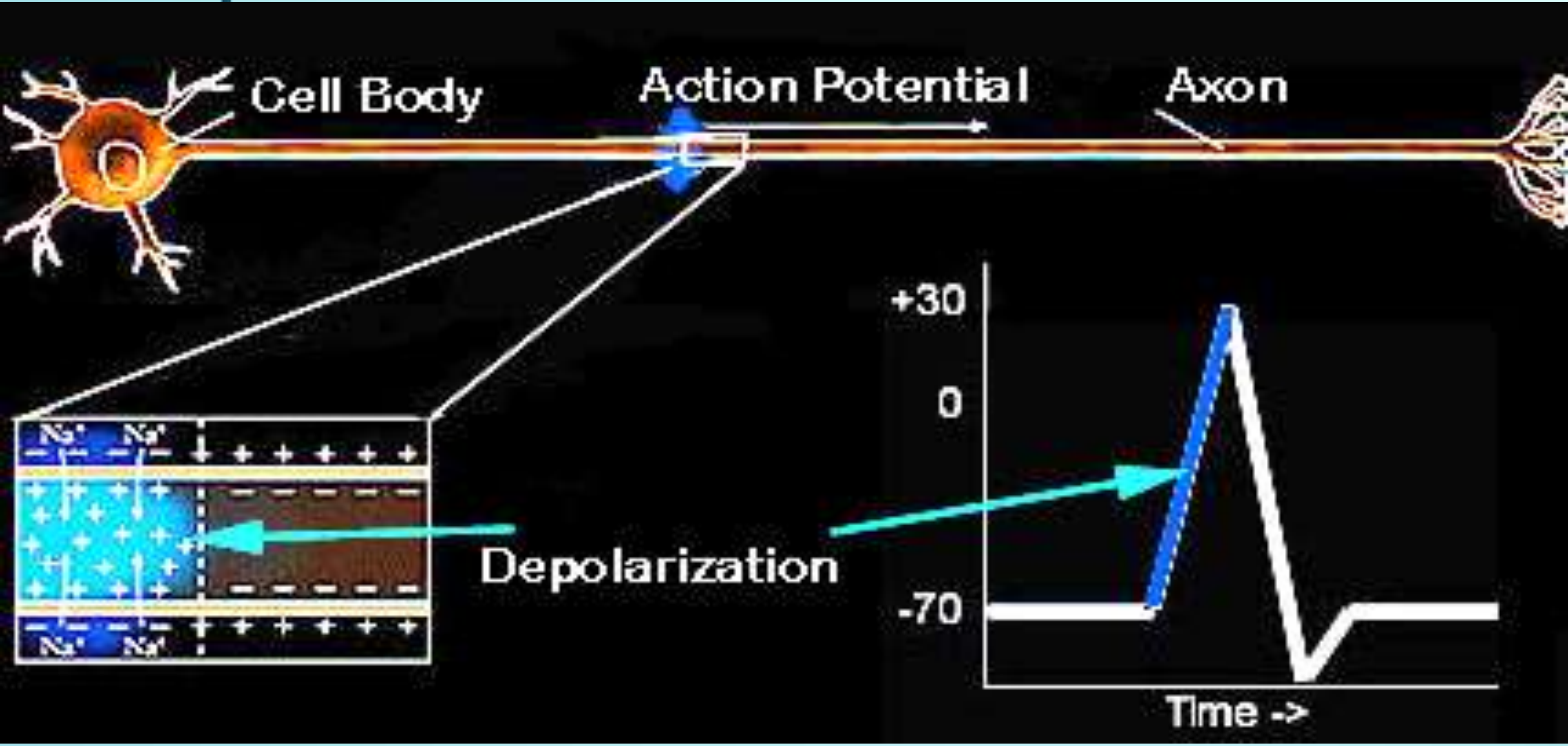
Action potential

- An action potential occurs when a neuron is conducting a nerve impulse.
- In order for an action potential to occur, the neuron must receive sufficient stimulation to open enough Na gates to reach the threshold level.
- If sufficient Na gates are opened to reach the threshold level, other Na and K gates will be stimulated to open.

Depolarization (upswing)

- If a neuron received sufficient stimulation to reach the membrane threshold, successive Na gates along the entire neuron membrane will open
- The opening of the Na gates allows Na ions to move into the neuron
- The movement of Na ions into the neuron causes the membrane potential to change from -70mV to +40mV
- As the membrane potential becomes more positive, Na gates begin to close. At the end of depolarization, the Na gates are all closed.

Depolarization ahead of AP



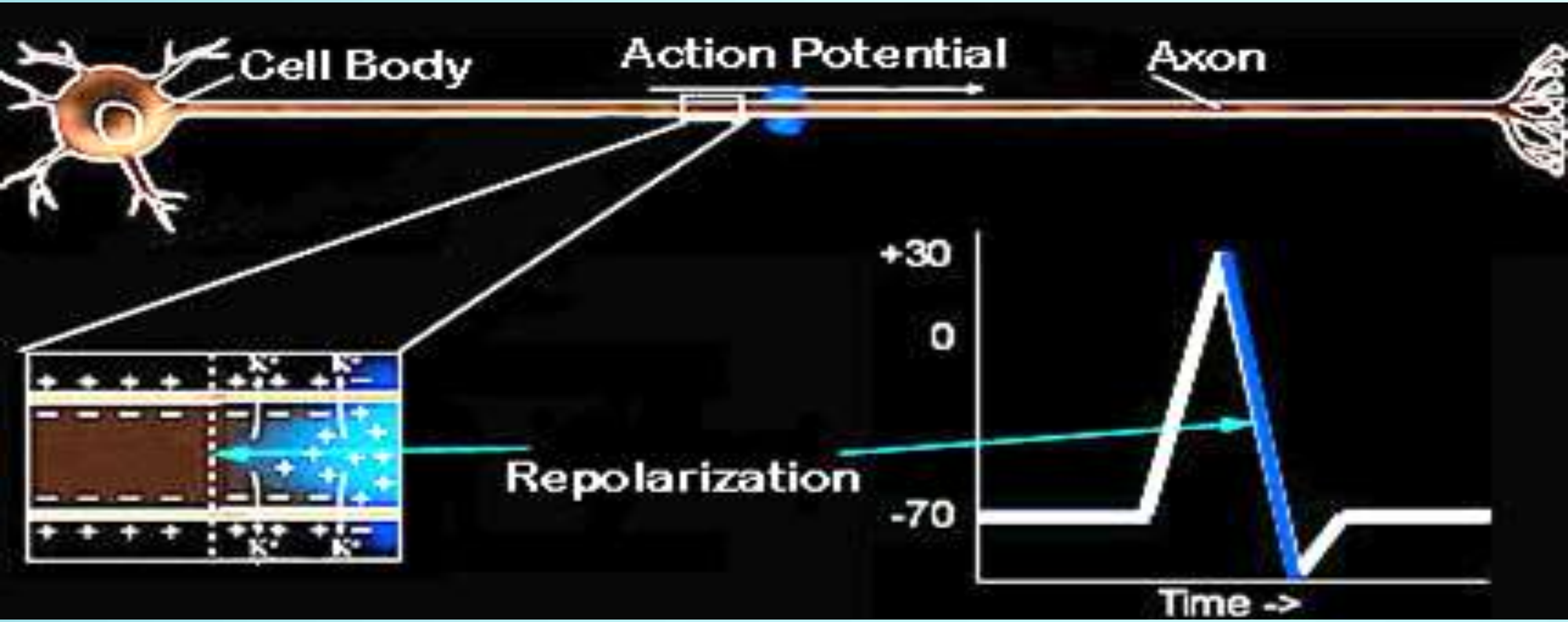
AP opens cell membrane to allow sodium (NA+) in
inside of cell rapidly becomes more positive than outside
this depolarization travels down the axon as leading edge of the AP

- During the conduction of a nerve impulse, each successive section of a neuron’s membrane will undergo an <u>action potential</u> consisting of <u>depolarization</u> followed by <u>repolarization</u>
- **Thus the nerve impulse is the movement of the action potential along the neuron cell membrane**

Repolarization (Down-swing)

- At the end of the depolarization phase, K gates begin to begin to open, allowing K to leave the neuron
- These K gates are activated at the +ve membrane potential value of about +40mV
- The movement of K ions out of the neuron produces a produces a change in membrane potential such that the that the potential becomes more –ve
- Following repolarization, the K gates close slowly

Repolarization follows

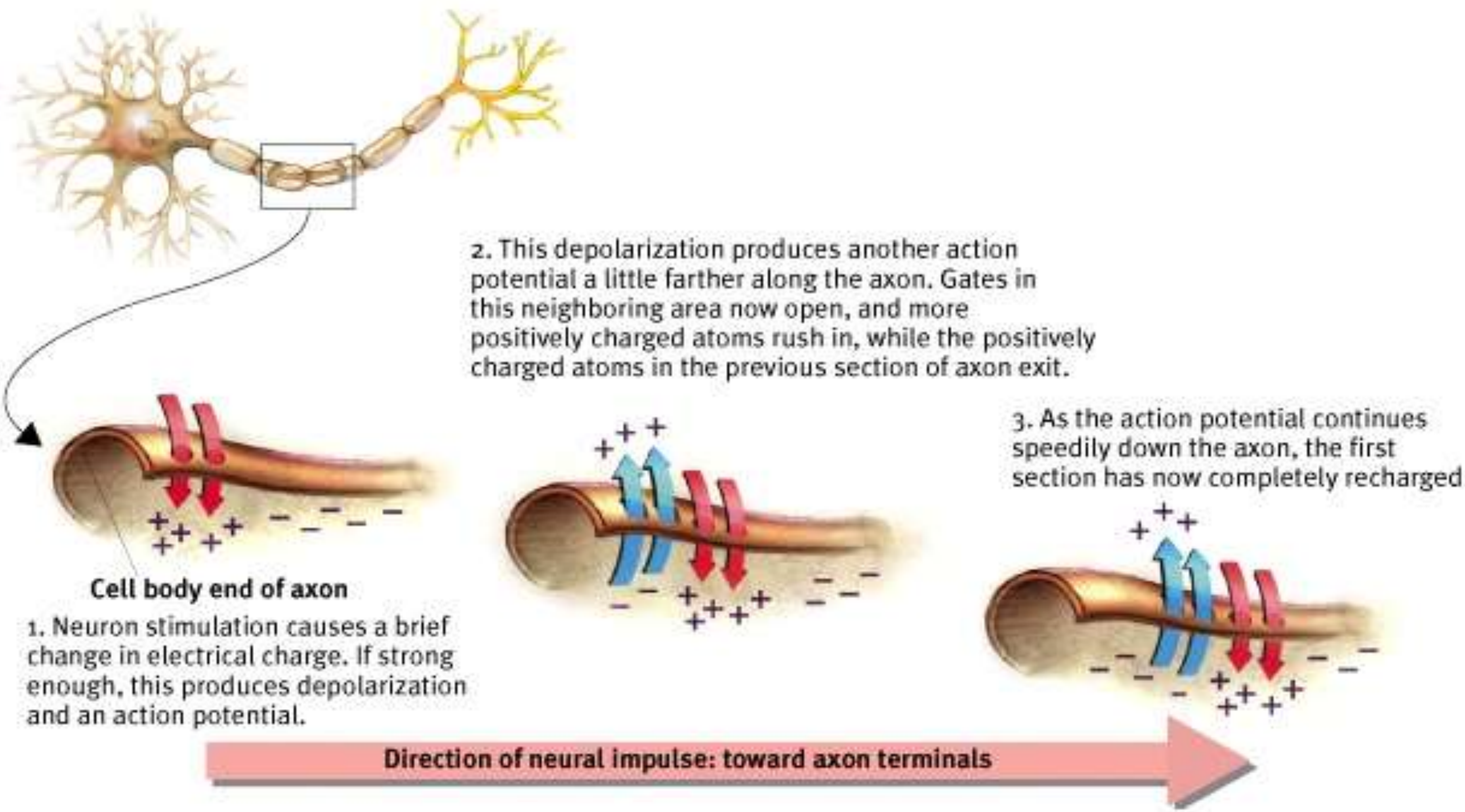


After depolarization potassium (K+) moves out restoring the inside to a negative voltage
This is called repolarization
The rapid depolarization and repolarization produce a pattern called a spike discharge

Steps of Action Potential

- Dendrites receive neurotransmitter from another neuron across the synapse.
- Reached its ***<u>threshold</u>***- then fires based on the all-or-none response.
- Opens up a portal in axon, and lets in positive ions (Sodium) which mix with negative ions ,that is already inside the axon (thus Neurons at rest have a slightly negative charge).
- The mixing of + and – ions causes an electrical charge that opens up the next portal (letting in more K) while closing the original portal.
- Process continues down axon to the axon terminal.
- Terminal buttons turns electrical charge into chemical (neurotransmitter) and shoots message to next neuron across the synapse.

Action Potential



Action Potential Conduction

- If an AP is generated at the axon hillock, it will travel all the way down to the synaptic knob.
- The manner in which it travels depends on whether the neuron is myelinated or unmyelinated.
- Unmyelinated neurons undergo the *continuous conduction* of an AP whereas myelinated neurons undergo *saltatory conduction* of an AP.

Laws and implications of action potentials

- All or none law: neurons either “fire” an action potential or they do not; there are no halfway responses
- Action potentials do not vary in intensity, either within the same neuron at different times or across different neurons
- Information is conveyed by the number and frequency of action potentials
- The information conveyed by an action potential depends on the pathway it is a part of. The image of a bee and the sound of bee are both conveyed by a chain of action potentials, but in different parts of the brain

Recovery/Refractory Potential

- Immediately following an action potential, a neuron is unable to conduct a nerve <u>impulse</u> until it has recovered because its <u>Na</u> gates won’t open
- A neuron which is undergoing recovery is said to be <u>refractory</u> since it cannot conduct a nerve <u>impulse</u>

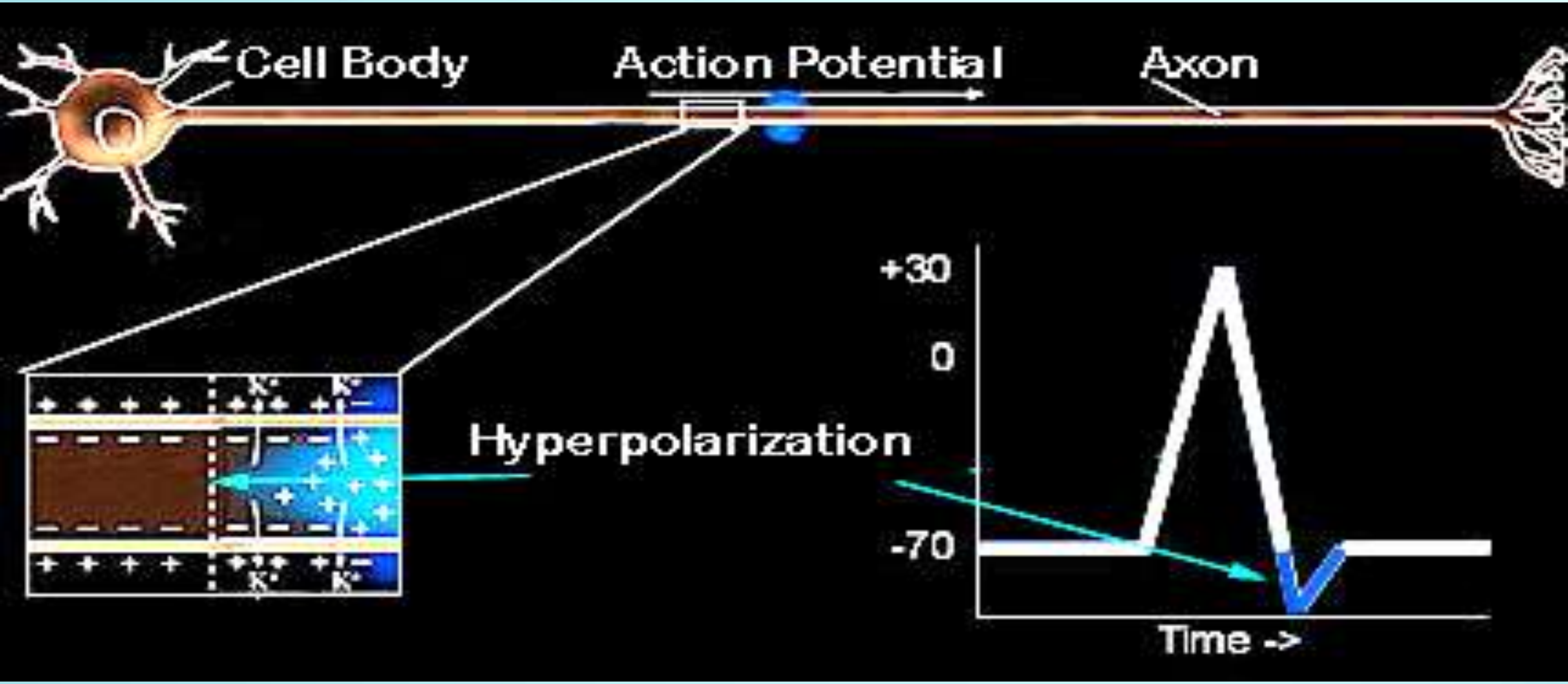
Recovery/Refractory Potential

- During the recovery phase the following events are occurring:

1. The K gates are closing
2. The Na/K pump is returning the Na ions to the outside and K ions to the inside of the neuron
3. The membrane potential is returning to its resting value of -70mV

- Once the recovery phase is complete, the neuron is no longer in its <u>refractory</u> period and is ready to conduct another nerve impulse

Finally, Hyperpolarization



- Repolarization leads to a voltage below the resting potential, called hyperpolarization
- Now neuron cannot produce a new action potential
- This is the refractory period

Absolute & Relative refractory period

- During the time interval between the opening of the Na^+ channel activation gate and the opening of the inactivation gate, a Na^+ channel cannot be stimulated.
  - This is the absolute refractory period
  - But during relative refractory period, it would take an initial stimulus that is much, much stronger than usual.

Absolute & Relative refractory period

- Imagine, if you are in, a toilet.
- When you pull the handle, water floods the bowl. This event takes a couple of seconds and you cannot stop it in the middle. Once the bowl empties, the flush is complete.
- Now the upper tank is empty. If you try pulling the handle at this point, nothing happens (*absolute refractory*). Wait for the upper tank to begin refilling. You can now flush again, but the intensity of the flushes increases as the upper tank refills *(relative refractory)*

Saltatory Conduction

- Some neurons have no myelin coating and are described as unmyelinated
- In unmyelinated neurons, an action potential must pass through each point along the neuron cell membrane which makes the conduction of the nerve impulse relatively slow

Saltatory Conduction

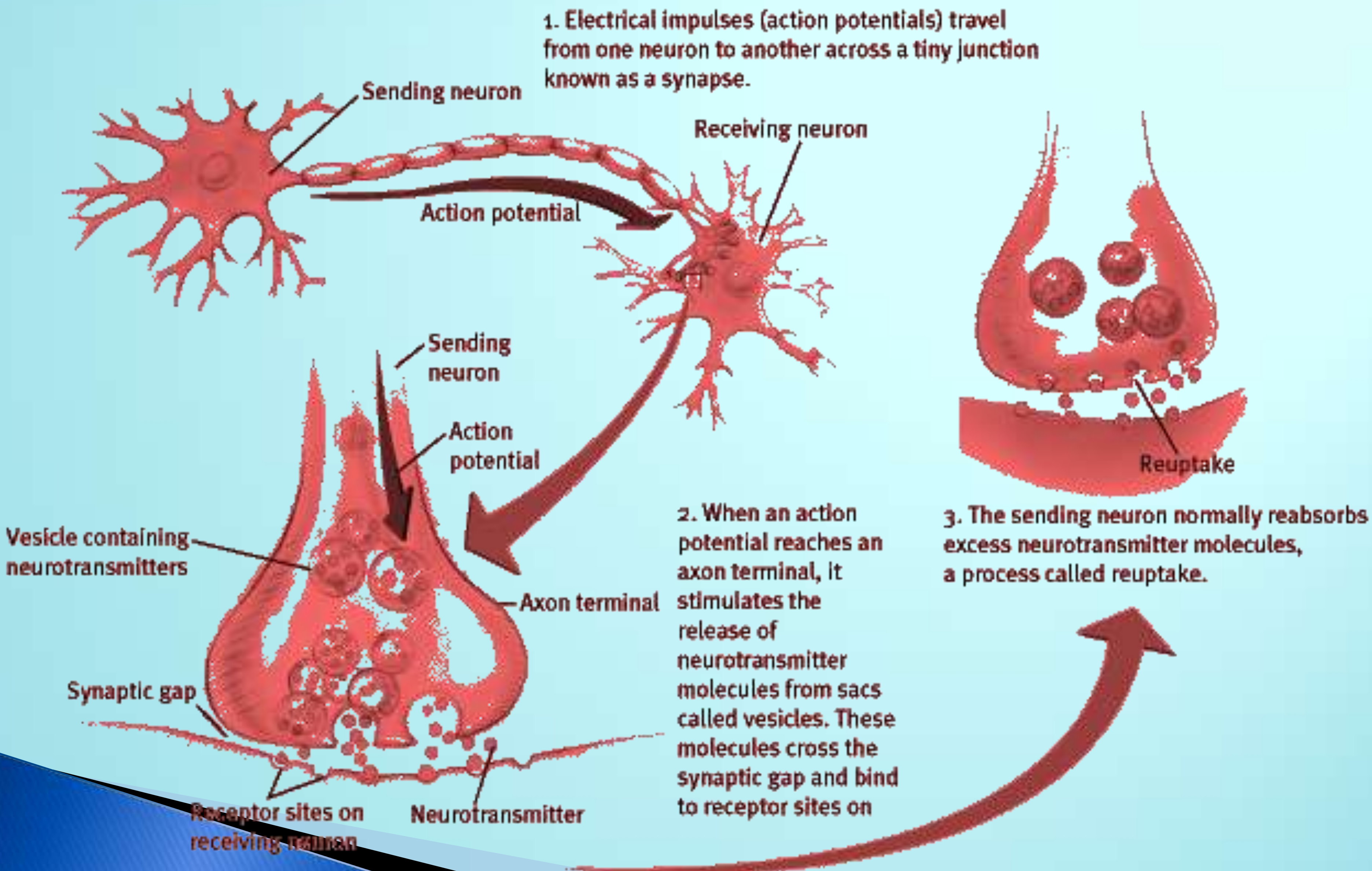
- Most neurons in humans are myelinated (since they are enclosed in a myelin coat formed by Schwann cell membranes wrapped around the neuron)
- In myelinated neurons, an action potential does not occur along sections of the neuron which are wrapped in myelin
- Ions are unable to cross the nerve cell membrane in these sections

Saltatory Conduction

- The gaps in myelin are called **Nodes of Ranvier**
- These gaps are the site of an action potential
- Thus, in myelinated neurons, the action potential jumps from one node of Ranvier to the next in a process called **saltatory conduction**

- Saltatory conduction is very rapid, allowing the nerve impulse to travel very rapidly along the neuron

How Neurons Communicate



The Nobel Prize in Physiology or Medicine 1932 *"for the discoveries regarding the functions of neurons"*

Sir Charles Scott Sherrington(1857-1952)

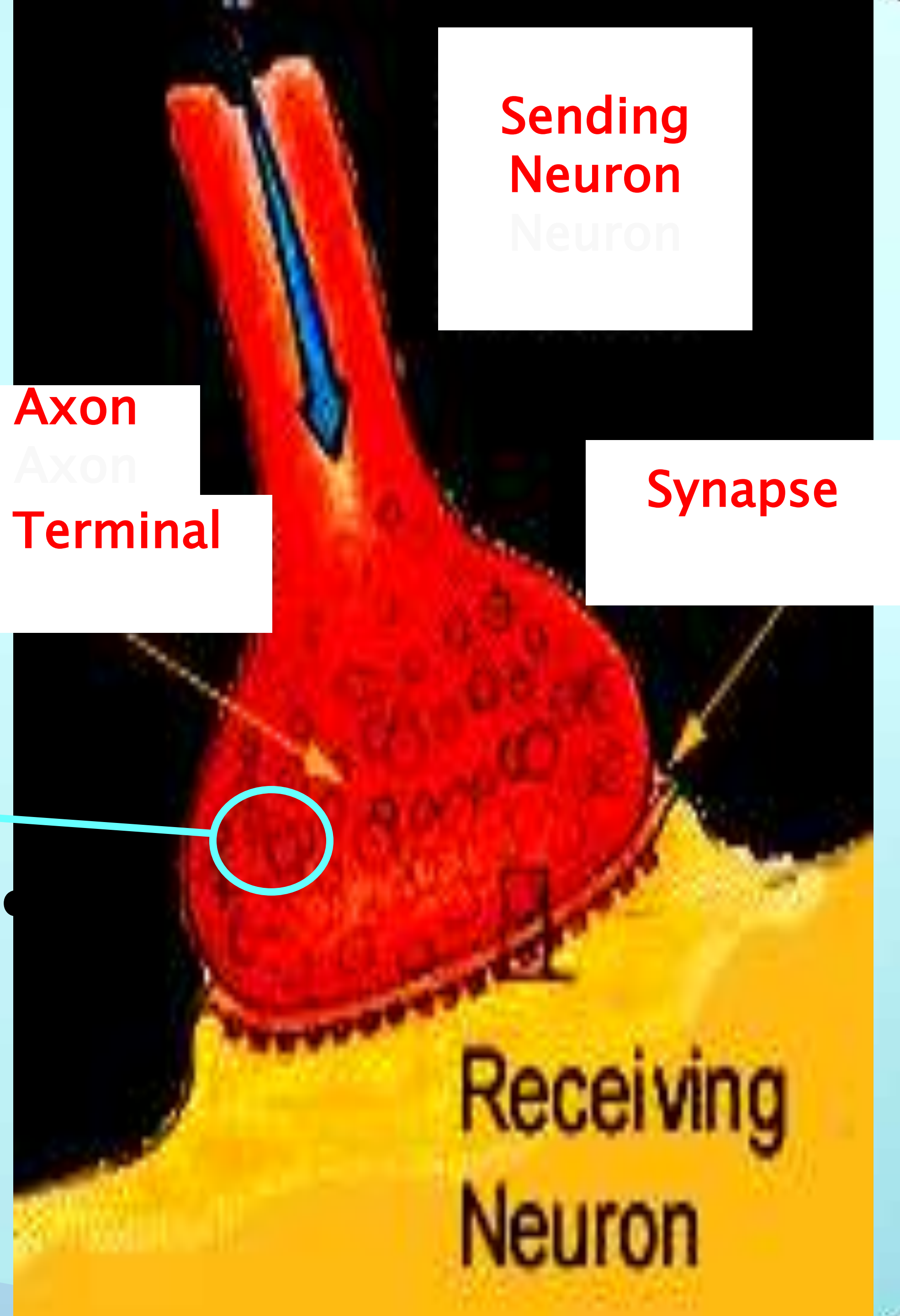
Synapses

- The term was introduced in nineteenth century by the British neurophysiologist Charles Sherrington
- A junction between the terminal buttons at the ends of the axonal branches of one neuron & the somatic or dendritic membrane of another.
- Presynaptic neuron – conducts impulses toward the synapse
- Postsynaptic neuron – transmits impulses away from the synapse

Synapse

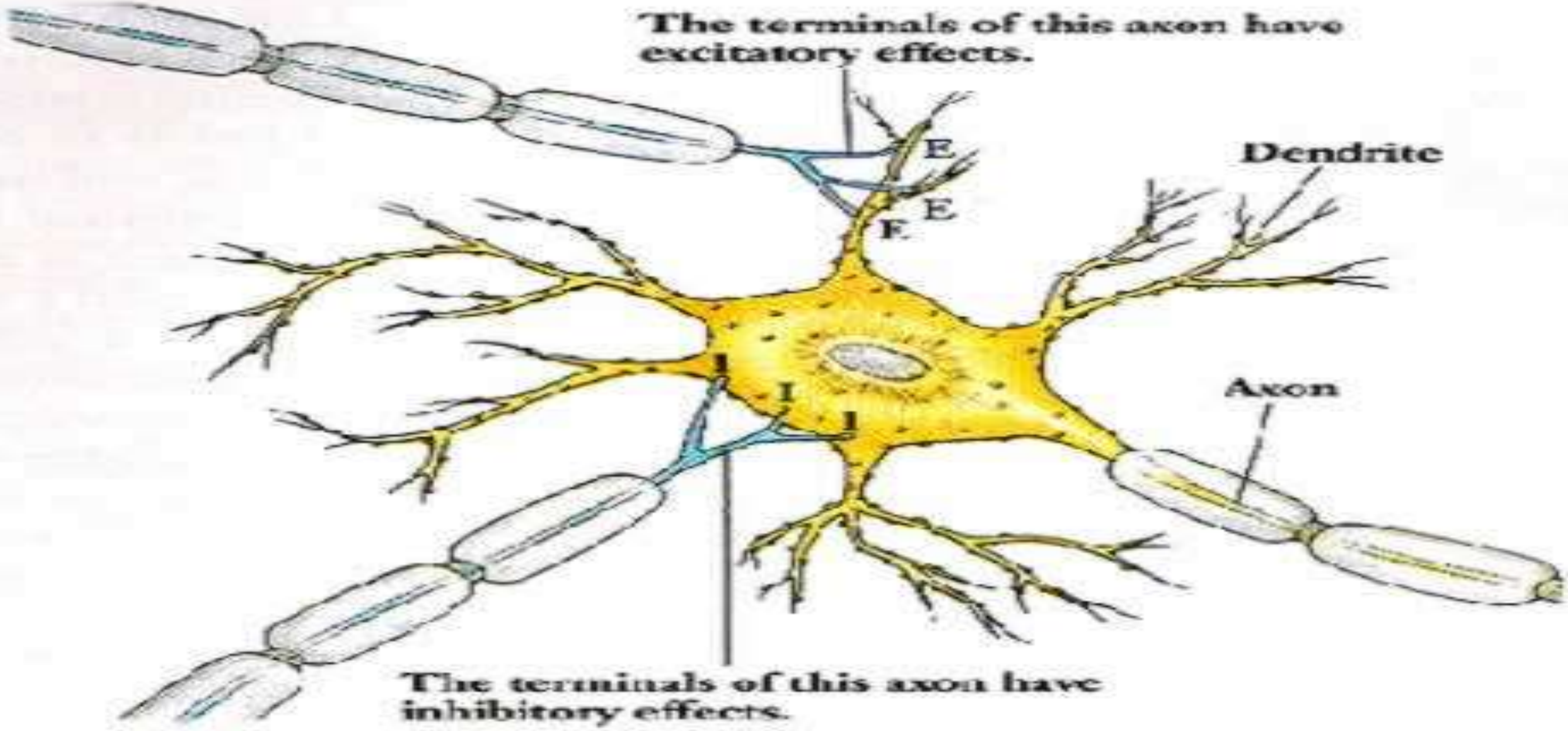
Axon terminals contain small storage
Sacs called synaptic vesicles

- **Vesicles contain neurotransmitter molecul**



Structure

- The membrane of the terminal button (transmitting neuron) is the presynaptic membrane & that of the receiving neuron is the post synaptic membrane.
- These membranes are separated by a small gap called the synaptic cleft, which contains extracellular fluid through which the transmitter substance diffuses.
- Synaptic vesicles are small, rounded objects in the shape of spheres which contain transmitter substance.



Excitatory messages

A chemical secretion that makes it more likely that a receiving neuron will fire and an action potential will travel down its axon.

Inhibitory Messages

A chemical secretion that prevents a receiving neuron from firing

Synaptic Cleft

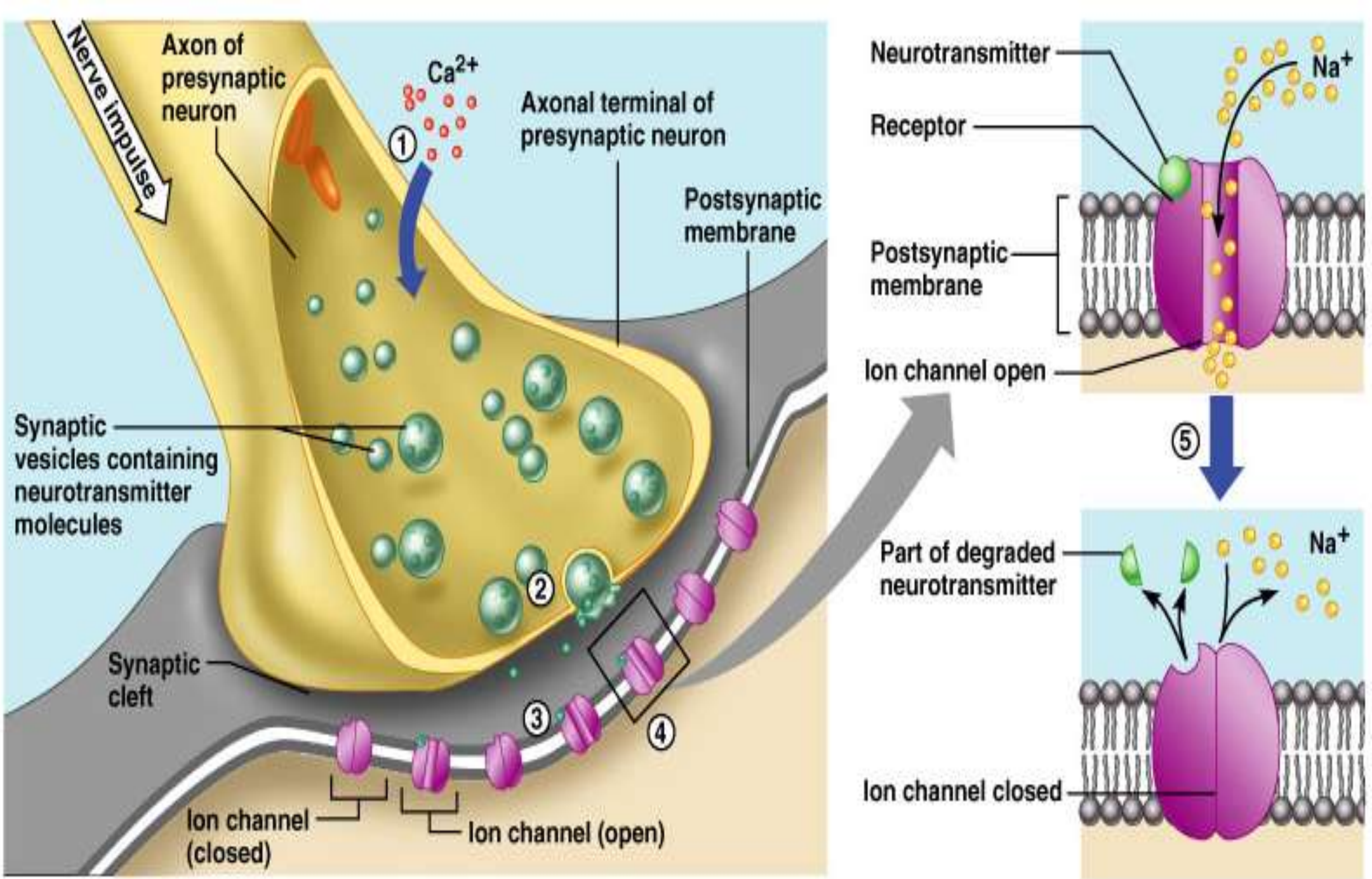
- Fluid–filled space separating the presynaptic and postsynaptic neurons
- Prevents nerve impulses from directly passing from one neuron to the next
- Transmission across the synaptic cleft:
  - Is a chemical event (as opposed to an electrical one)
  - Ensures unidirectional communication between neurons

- When an axon fires, a number of synaptic vesicles filled with a transmitter substance migrate to the presynaptic membrane, adhere to it, & then rupture, spilling their contents into the synaptic cleft.
- Transmitter substances affect the membrane potential of the postsynaptic neuron by activating the postsynaptic receptors which opens the gate of a neurotransmitter-dependent ion channel.

Synaptic Cleft: Information Transfer

- Nerve impulses reach the axonal terminal of the presynaptic neuron and open Ca^{2+} channels
- Neurotransmitter is released into the synaptic cleft.
- Neurotransmitter crosses the synaptic cleft and binds to receptors on the postsynaptic neuron
- Postsynaptic membrane permeability changes, causing an excitatory or inhibitory effect

Synaptic Cleft: Information Transfer



Post synaptic 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 change in the membrane potential can either excite or inhibit the postsynaptic neuron; they are referred to as excitatory postsynaptic potentials(EPSPs)& inhibitory postsynaptic potentials(IPSPs).

Excitatory Postsynaptic Potentials

- EPSPs are small depolarizations.
- During EPSPs Na+ enters the cell & k+ leaves it.
- As the quantity of Na that enters is much larger than the quantity of K that leaves, the net effect of the movemnet of these ions is depolarizing.
- EPSPs are graded potentials that can initiate an action potential in an axon

Excitatory Postsynaptic Potentials

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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
- IPSPs are small hyperpolarizations.
- IPSPs occur when pottasium channels permit K to leave the cell, thus hyperpolarizing it.

Inhibitory Synapses and IPSPs

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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 rapid-fire order
- **Spatial** summation – postsynaptic neuron is stimulated by a large number of terminals at the same time

The Nobel Prize in Physiology or Medicine 1936 "for the discoveries relating to chemical transmission of nerve impulses"

Otto Loewi
(1873–1961)

Discovery of neurotransmitters

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Electrical stimulation of Heart 1 caused Heart 1 to slow down. After removing the fluid in which Heart 1 had been and placing Heart 2 in the same fluid caused Heart 2 to slow down as well.

Chemical synapse

- At chemical synapses, the neurotransmitter is stored in the terminals in membrane enclosed containers called vesicles.
- When AP arrives at the terminals it opens channels that allow calcium ions to enter the terminals from the extracellular fluid.
- The ca ions cause the vesicles clustered nearest the membrane to fuse with the membrane.
- The membrane opens there and the transmitter spills out & diffuses across the cleft.
- The neurotransmitter is taken back into the terminals by a process called reuptake; it is repackaged in vesicles and used again.

The sequence of chemical events at a synapse

1. The neuron synthesizes chemicals that serve as NT.
2. The neuron transports these chemicals to the terminals of its axons.
3. An AP causes the release of the neurotransmitters from the terminals.
4. The released molecules attach to receptors & alter the activity of the post synaptic neuron.
5. The molecules separate from their receptors
6. The presynaptic neuron reabsorbs some NT molecules.

Electrical synapses:

- Are less common than chemical synapses
- characterized by direct channels that conduct electricity from one cell to the next.
- Mostly consists of small protein tubular structures(gap junctions) that allow free movements of ions from the interior of one cell to the next.
- Are important in the CNS in:
  - Arousal from sleep
  - Mental attention
  - Emotions and memory
  - Ion and water homeostasis

Dendrodenritic synapses

- Some small neurons have extremely short processes & lack axons.
- These neurons form synapses between dendrites.
- These neurons lack long axonal processes & they perform regulatory functions, helping to organize the activity of groups of neurons.

Axoaxonic synapses

- A junction between a terminal button & an axon of another cell is an axoaxonic synapse.
- It alters the amount of transmitter substance liberated by the terminal buttons of the postsynaptic neuron.
- The amount released depends on the magnitude of change in the membrane potential.
- The transition in potential must be rapid.

Axosomatic

- Synapse between axon of a neuron & soma of another neuron.
- The neuronal cell body & its dendritic tree form the receptive area of the neuron.
- Each synapse produce depolarization or hyperpolarization.
- When the summated effects produce sufficient depolarization, the axon generates an impulse at the axon hillock or initial segment of the neuron

- Sometimes, if all of the transmitter isn’t absorbed it is taken back up, this is known as reuptake
- There are 7 types of synapses
- Depends on function

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Neurotransmitters

Neurotransmitters

- The chemicals released at the synapse are neurotransmitters.
- They are used for neuronal communication with the body and the brain
- 50 different neurotransmitters have been identified
- Classified chemically and functionally
- Once they contact the postsynaptic neuron they can either:
  - a) go through *reuptake* (reabsorbtion)
  - b) be swept away through diffusion,
  - c) or leave and then *reexcite* the neuron

Properties of neurotransmitters:

1) Synthesized in the presynaptic neuron

2) Localized to vesicles in the presynaptic neuron

3) Released from the presynaptic neuron under physiological conditions

4) Rabidly removed from the synaptic cleft by uptake or degradation

5) Presence of receptor on the post-synaptic neuron.

6) Binding to the receptor elicits a biological response

The Seven Steps in Neurotransmission

- Synthesis
- Storage
- Release
- Receptor interaction
- Inactivation
- Reuptake
- Degradation

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Chemical Neurotransmitters

- Acetylcholine (ACh)
- Biogenic amines
- Amino acids
- Peptides
- Novel messengers: ATP and dissolved gases NO and CO

Neurotransmitters: Acetylcholine

- First neurotransmitter identified, and best understood
- Synthesized and enclosed in synaptic vesicles
- Degraded by the enzyme acetylcholinesterase (AChE)
- Released by:
  - All neurons that stimulate skeletal muscle
  - Some neurons in the autonomic nervous system

Neurotransmitters: Biogenic Amines

- Include:
  - Catecholamines – dopamine, norepinephrine (NE), and epinephrine
  - Indolamines – serotonin and histamine
- Broadly distributed in the brain
- Play roles in emotional behaviors and our biological clock

- Dopamine
  - Drugs ranging from marijuana to heroin increase the amount of dopamine in neural pathways responsible for experiencing pleasure
  - High levels of dopamine in some parts of the brain have been linked to schizophrenia
  - Degeneration of dopamine-producing neurons in the substantia nigra produces Parkinson’s disease

Dopamine (DA) pathways

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Parkinson's disease

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Symptoms:

- Shaking (muscle tremor)
- Stiffness (rigidity)
- Slowness
- Problems with posture and balance
- Speech changes
- Loss of facial expression
- Small handwriting
- Problems with swallowing
- Depression
- Bowel and bladder problems
- Impotence
- Sleep problems
- Tiredness (fatigue)

- Norepinephrine
  - Increases emotional arousal (fear and anxiety) and alertness
  - It is assumed to have a role in panic attacks

- Serotonin
  - Influence a great deal of our behavior, particularly the way we process information.
  - Regulates our behavior, moods & thought processes
  - Involved in many behaviors, especially important for emotional states, impulse control, and dreaming
  - Extremely low activity is associated with less inhibition & with instability, impulsivity & the tendency to overreact to situations.

- Low activity has been associated with aggression, suicide, impulsive overeating, & excessive sexual behavior.
- Low serotonin levels are impilcated in severe depression; may be responsible for sleep disturbances in depression

Neurotransmitters: Amino Acids

- Include:
  - GABA – Gamma (γ)-aminobutyric acid
  - Glycine
  - Aspartate
  - Glutamate
- Found only in the CNS

- Amino acids
  - Gamma amino butyric acid (GABA)
    - Main inhibitory neurotransmitter in the brain
    - Lowers arousal and regulates anxiety
    - Implicated in hereditary neurological disorder Huntington’s chorea.
  - Glutamate
    - Main excitatory neurotransmitter in the brain

- Glycine : inhibitory neurotransmitter in the spinal cord & lower portions of the brain.
- The bacteria that cause tetanus release a chemical that blocks the activity of glycine synapses.
- The removal of the inhibitory effect of these synapses causes muscles to contract continuously.

Neurotransmitters: Peptides

- Include:
  - Substance P – mediator of pain signals
  - Beta endorphin, dynorphin, and enkephalins
- Act as natural opiates; reduce pain perception
- Bind to the same receptors as opiates and morphine
- Gut-brain peptides – somatostatin, and cholecystokinin

- Peptides: modify effects of neurotransmitters
  - Endorphins
    - Endogenous [produced within the body] morphine; opiates mimic the actions of endorphins
    - Elevates mood and reduces pain

Neurotransmitters: Novel Messengers

- ATP
  - Is found in both the CNS and PNS
  - Produces excitatory or inhibitory responses depending on receptor type
  - Provokes pain sensation

Neurotransmitters: Novel Messengers

- Nitric oxide (NO)
  - Activates the intracellular receptor guanylyl cyclase
  - Is involved in learning and memory
- Carbon monoxide (CO) is a main regulator of cGMP (the secondary messenger, cyclic guanosine moonophosphate) in the brain, which plays a crucial role in the control of cardiovascular & gastrointestinal homeostasis

Functional Classification of Neurotransmitters

- Two classifications: excitatory and inhibitory
  - Excitatory neurotransmitters cause depolarizations (e.g., glutamate)
  - Inhibitory neurotransmitters cause hyperpolarizations (e.g., GABA and glycine)

- INHIBITORY
  - DOPAMINE
  - SEROTONIN
  - GABA
  - GLYCINE
- EXCITATORY
  - ACETYLCHOLINE
  - NOREPINEPHRINE
  - GLUTAMATE

Functional Classification of Neurotransmitters

- Some neurotransmitters have both excitatory and inhibitory effects
  - Determined by the receptor type of the postsynaptic neuron
  - Example: acetylcholine
    - Excitatory at neuromuscular junctions with skeletal muscle
    - Inhibitory in cardiac muscle

Major Neurotransmitter Systems

- Cholinergic, Dopaminergic, Noradrenergic, Serotonergic
- Send projections to widespread regions of the brain and spinal cord
- Are the target of many psychoactive drugs
- Ascending activating systems

Cholinergic system (Acetylcholine)

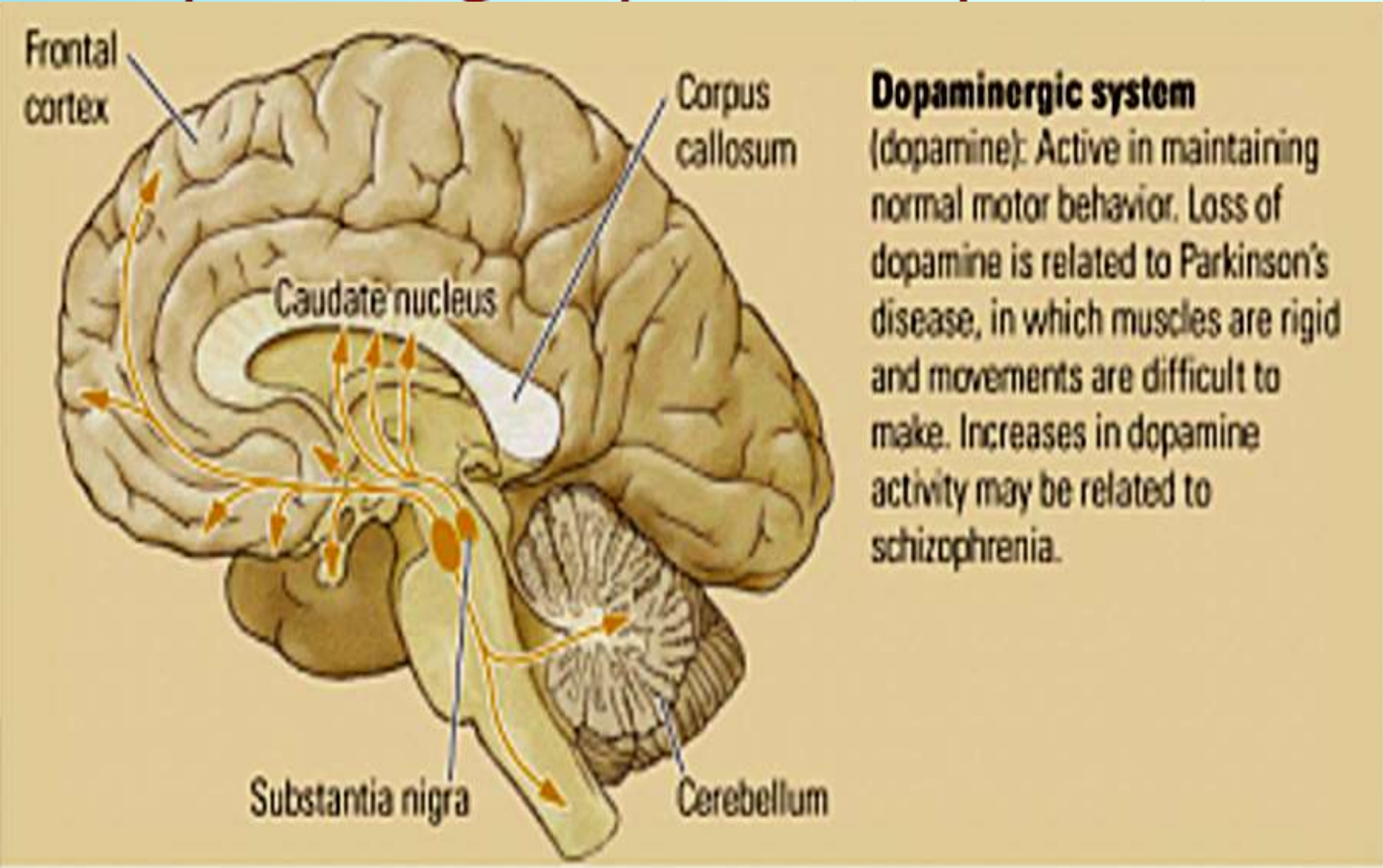
Cholinergic system (acetylcholine): Active in maintaining waking electro-encephalographic (EEG) patterns of the neocortex. Thought to play a role in memory by maintaining neuron excitability.

- **Alzheimer's disease** (AD), also known simply as Alzheimer's, is a neurodegenerative disease characterized by progressive cognitive deterioration together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes.
- The most striking early symptom is loss of short-term memory (amnesia), which usually manifests as minor forgetfulness that becomes steadily more pronounced with illness progression, with relative preservation of older memories.
- As the disorder progresses, cognitive (intellectual) impairment extends to the domains of language (aphasia), skilled movements (apraxia), recognition (agnosia), and functions such as decision-making and planning get impaired.

- **Myasthenia Gravis** is a neuromuscular disease leading to fluctuating muscle weakness and fatigability during simple activities.
- Weakness is typically caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction, inhibiting the stimulative effect of the neurotransmitter acetylcholine

- The acetylcholinergic neurons located in the pons are responsible for eliciting most of the characteristics of REM sleep.
- Those located in the basal forebrain are involved in activating the cerebral cortex & facilitating learning.
- Those located in the medial septum control the electrical rhythms of the hippocampus & modulate its functions, which include the formation of particular kinds of memories.

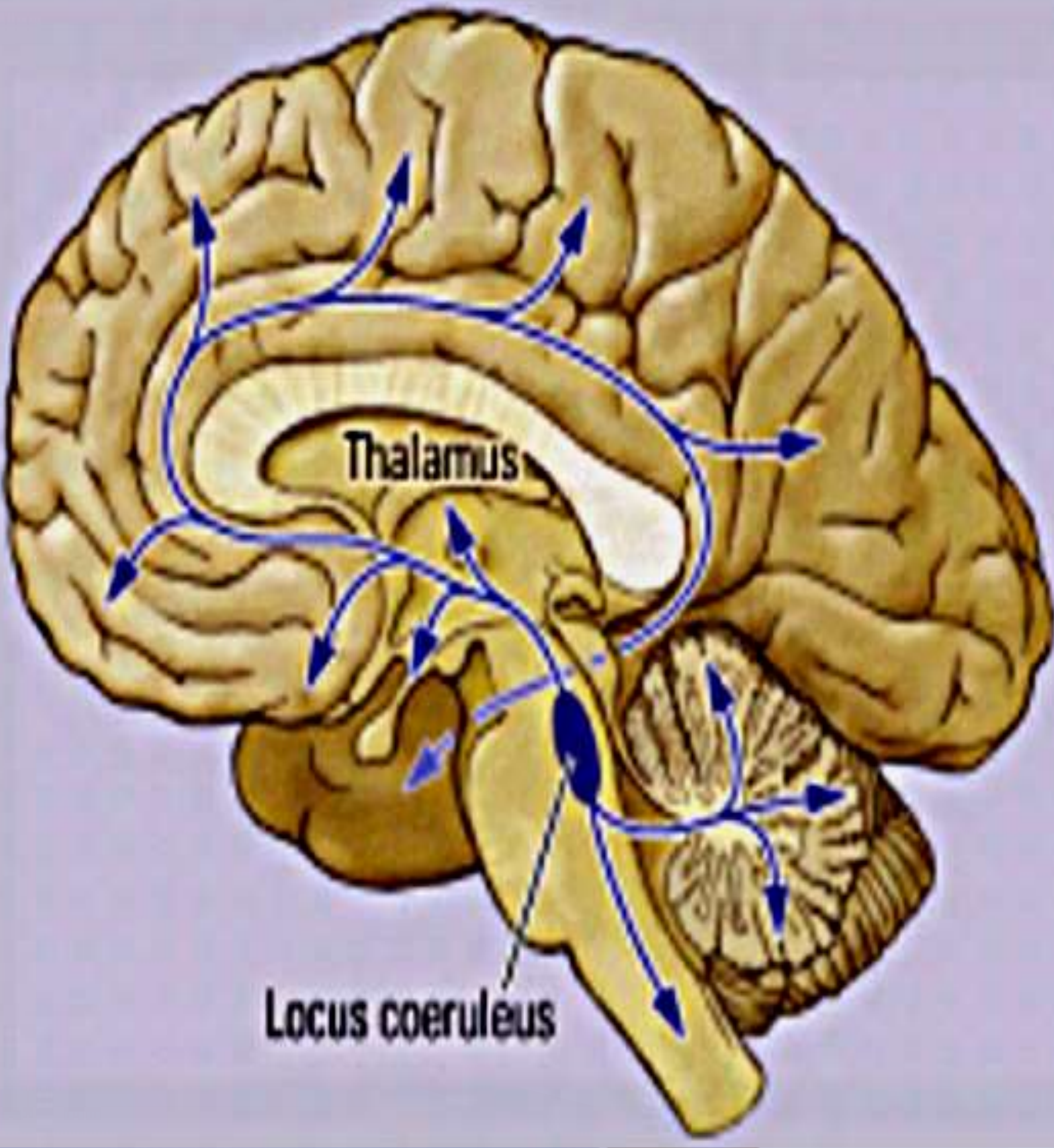
Dopaminergic system (Dopamine)



- **Parkinson's disease** (PD), is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech.
- It is characterized by muscle rigidity, tremor, a slowing of physical movement ,& in extreme cases, a loss of physical movement (akinesia).
- The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain.
- Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive.

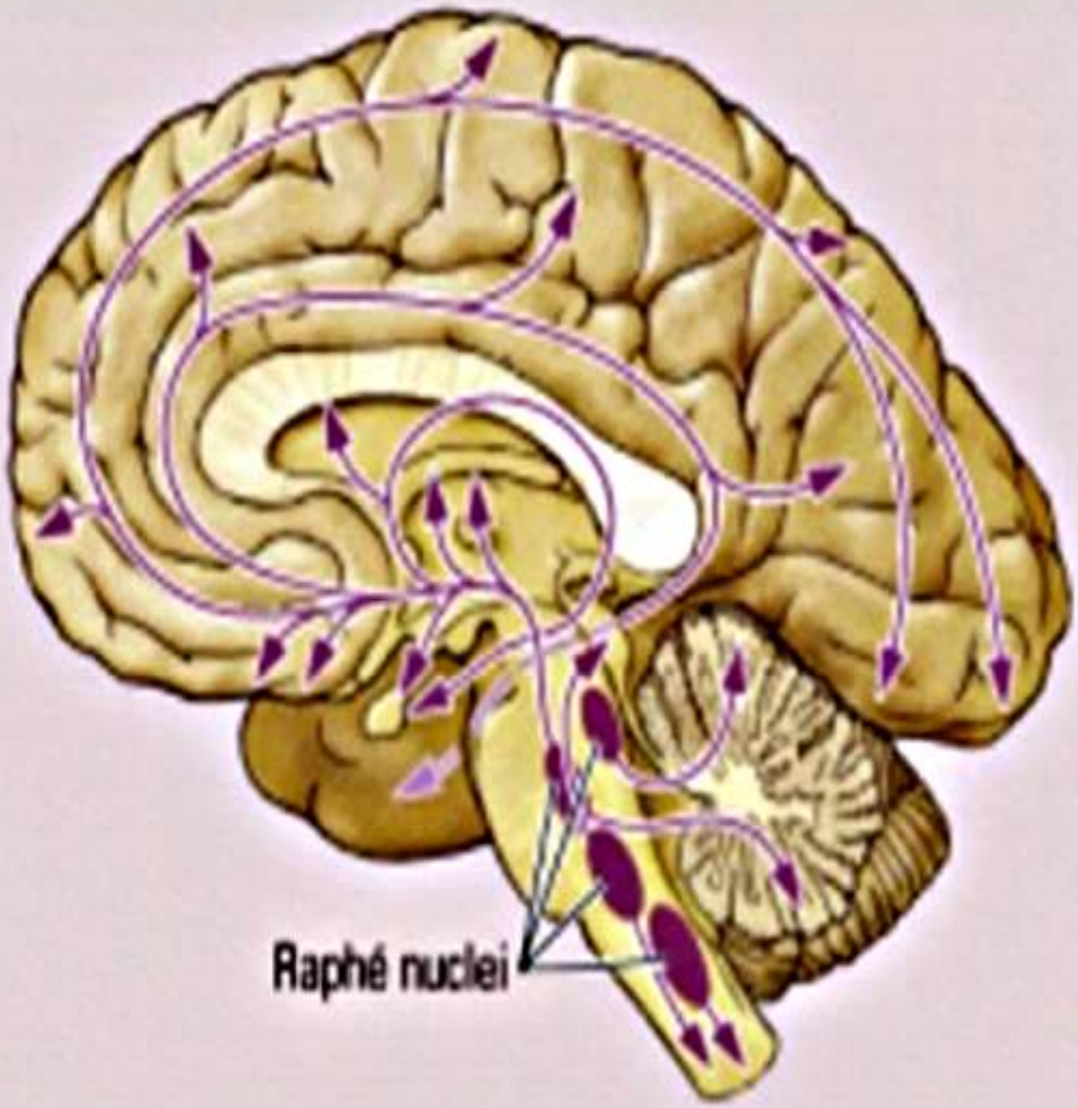
- The 3 major dopaminergic pathways are: niagrostriatal system which controls movement.
- Mesolimbic system which regulates reinforcement & effects of addictive drugs.
- Mesocortical system which plays important roles in STMs, planning, strategies for problem solving etc.

Noradrenergic system (Norepinephrine)



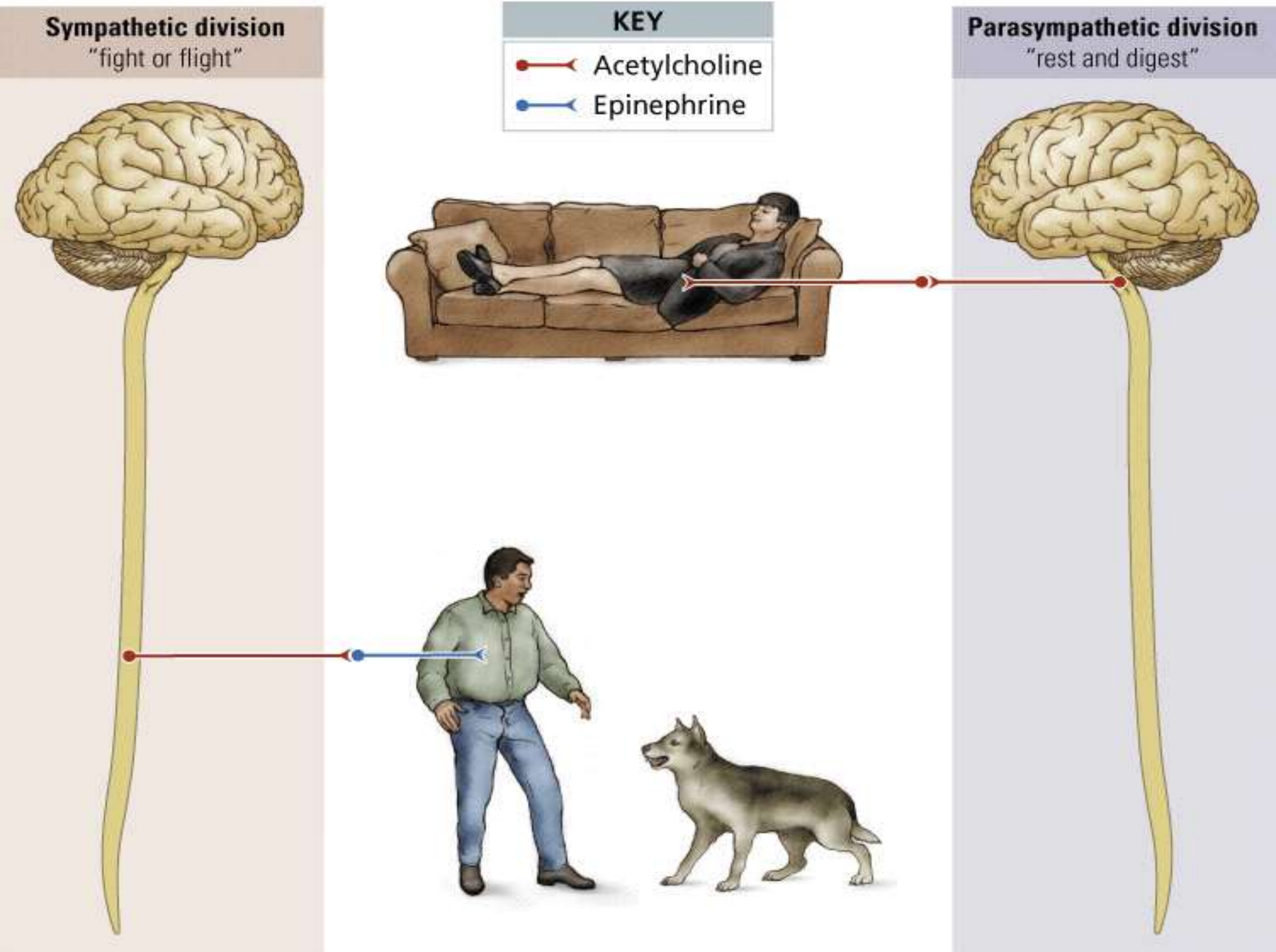
Noradrenergenic system (norepinephrine): Active in maintaining emotional tone. Decreases in norepinephrine activity are thought to be related to depression, whereas increases in it are thought to be related to mania (overexcited behavior).

Serotonergic system (Serotonin)



Serotonergic system
(serotonin): Active in maintaining waking EEG patterns. Increases in serotonin activity are related to obsessive-compulsive disorder, tics, and schizophrenia. Decreases in serotonin activity are related to depression.

- Serotonin plays a role in regulation of mood, in the control of eating, sleep & arousal & in the regulation of pain.


Sympathetic division
"fight or flight"
KEY
Acetylcholine
Epinephrine
Parasympathetic division
"rest and digest"