Biochemistry of the Nervous System

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In vertebrates **Nervous System** consists of two main parts,

- the **central nervous system** (**CNS**) and
- the **peripheral nervous system** (**PNS**).

The **CNS** consists of the brain and spinal cord.
The **PNS** consists mainly of nerves, which are enclosed bundles of the long fibers or axons, that connect the **CNS** to every other part of the body.

Nerves that transmit signals from the brain are called **motor** or **efferent nerves**, while those nerves that transmit information from the body to the **CNS** are called **sensory** or **afferent**.

The **autonomic nervous system** is the portion of the nervous system that controls most **visceral functions** of the body. This system helps to control

- arterial pressure,
- gastrointestinal motility,
- gastrointestinal secretion,
- urinary bladder emptying,
- sweating,
- body temperature,

and many other activities.

The **autonomic nervous system** is activated mainly by centers located in the **spinal cord**, **brain stem**, and **hypothalamus**.

In addition, portions of the **cerebral cortex**, especially of the **limbic cortex**, can transmit signals to the lower centers and in this way can influence autonomic control.

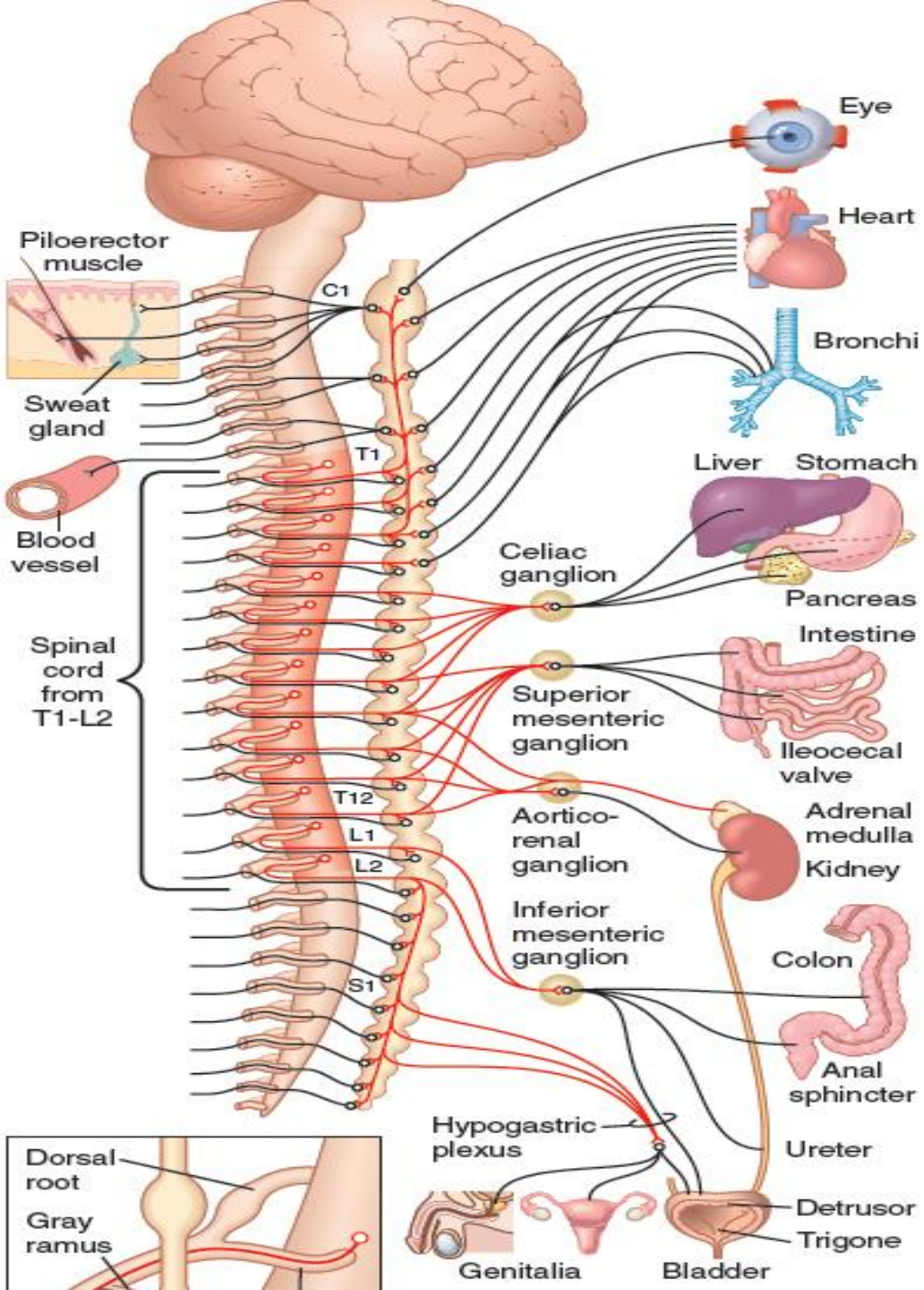
The **autonomic nervous system** also often operates through **visceral reflexes**. That is, **subconscious sensory signals** from visceral organs can enter the **autonomic ganglia**, the **brain stem**, or the **hypothalamus** and then return **subconscious reflex** responses directly back to the **visceral organs** to control their activities.

The **efferent autonomic signals** are transmitted to the various organs of the body through two major subdivisions called the

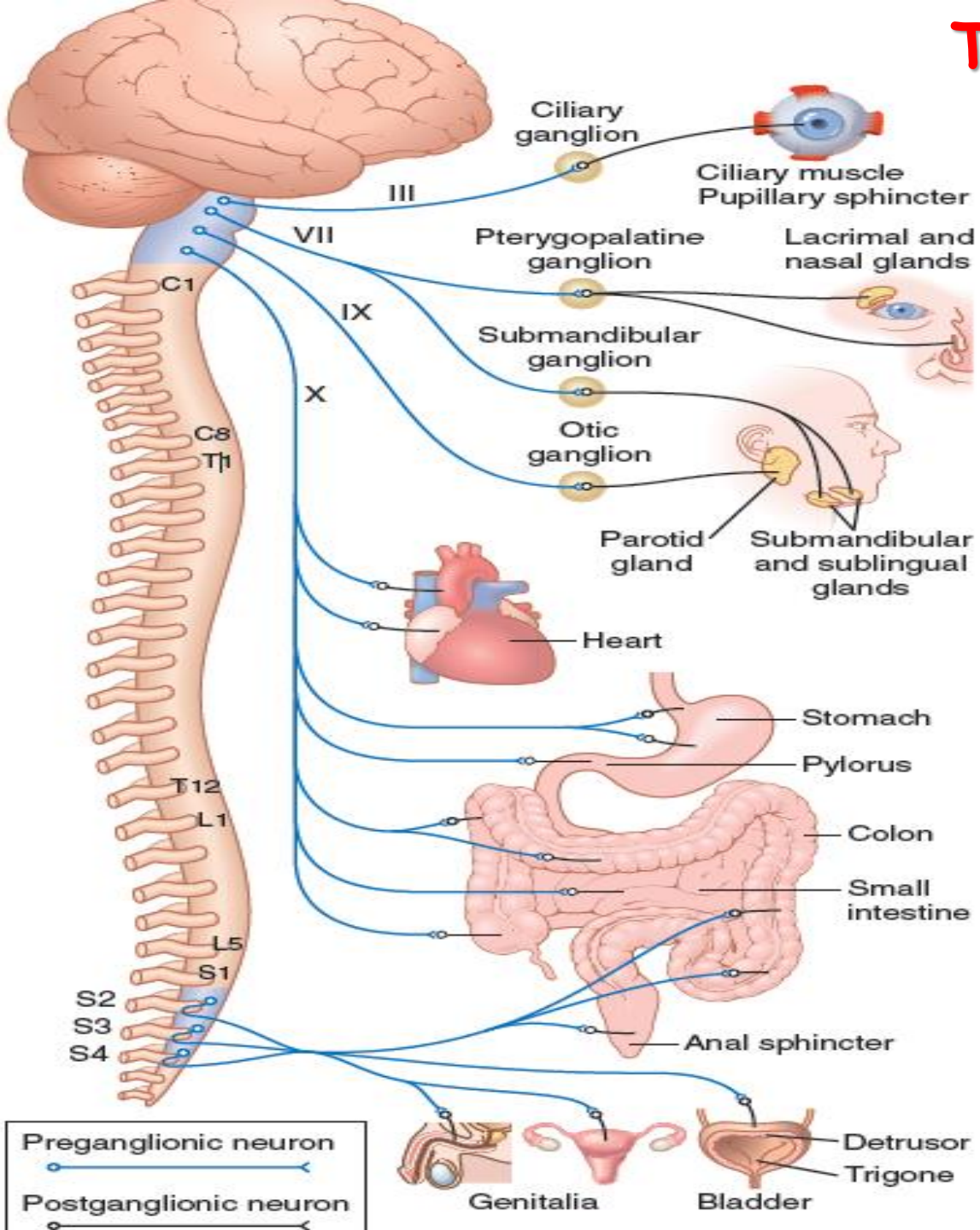
- **sympathetic nervous system**
- **parasympathetic nervous system**.

Sympathetic nervous system.

The black lines represent postganglionic fibers, and the red lines show preganglionic fibers.



The parasympathetic nervous system.

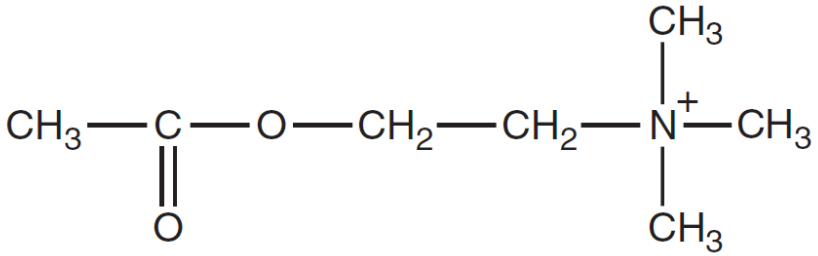


The terminal nerve endings of the **parasympathetic system** secrete **acetylcholine**.

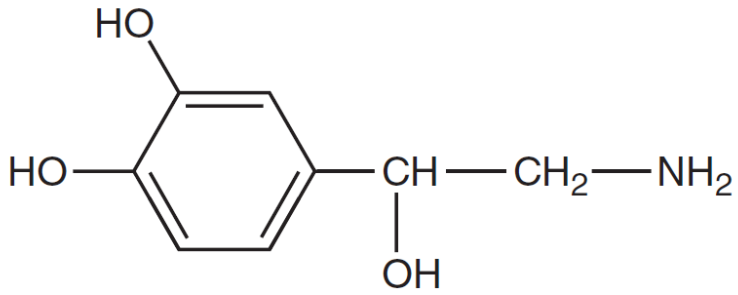
Almost all of the **sympathetic nerve endings** secrete **norepinephrine**, but a few secrete **acetylcholine**.

These neurotransmitters in turn act on the different organs to cause respective **parasympathetic** or **sympathetic** effects.

Therefore, **acetylcholine** is called a **parasympathetic** transmitter and **norepinephrine** – a **sympathetic** transmitter.



Acetylcholine



Norepinephrine

Synthesis of **norepinephrine** begins in the axoplasm of the terminal nerve endings **of adrenergic nerve fibers** but is completed inside the **secretory vesicles**. The basic steps are the following:

Tyrosine → hydroxylation → Dopa

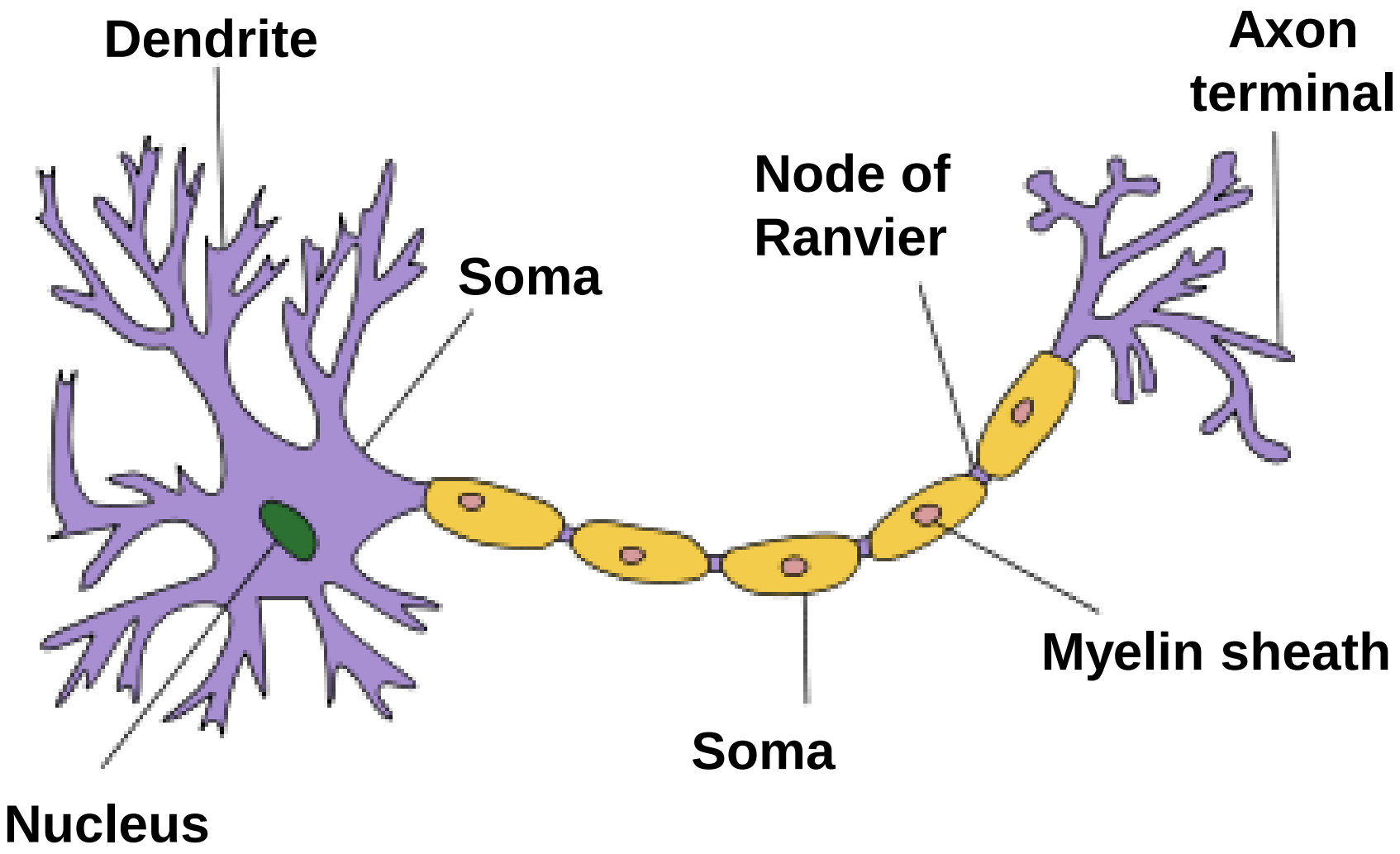
Dopa → decarboxylation → Dopamine

Transport of **dopamine** into the vesicles

Dopamine → hydroxylation → Norepinephrine

In the **adrenal medulla**, this reaction goes still one step further to transform about **80 percent** of the **norepinephrine** into **epinephrine**, as follows:

Norepinephrine → methylation → Epinephrine


Dendrite
Axon terminal
Node of Ranvier
Soma
Myelin sheath
Soma
Nucleus

Nerve tissue is composed of several cell types.

The cells of the nervous system can be divided into two broad categories:

- nerve cells (or **neurons**), and
- supporting cells called **neuroglia** (or simply **glia**).

Nerve cells are specialized for electrical signaling over long distances.

The most obvious sign of neuronal specialization for communication via electrical signaling is the extensive branching of **neurons** (**dendritic branches**).

Dendrites arise from the neuronal cell body and are the primary target for **synaptic input** from other neurons.

Metabolism of CNS

Metabolism of CNS

Sources of lipids to CNS:

- **blood-brain barrier** significantly **inhibits** entry of certain **fatty acids** & lipids into **CNS**. So, **all lipids** found in **CNS** **must be synthesized within CNS**

(***cholesterol, sphingolipids, glycosphingolipids, cerebrosides, very-long chain fatty acids*** (monounsaturated, saturated)

- ***EXCEPTION :***

Essential fatty acids (**linoleic & linolenic**) **can enter the brain**. Within **CNS**, these two FAs are **elongated** & **desaturated** to yield the **very-long chain fatty acids** required for synthesis of **myelin sheath**.

Metabolism of CNS

Very long chain fatty acids (**VLCFA**) -includes molecules containing more than **20** carbon atoms.

Nervonic acid (24:1, n-9)

- an elongation product of **oleic acid** (18:1 Δ9)

normally accounting for ~ **40%** of the total FA in **sphingolipids**.

Nervonic acid -

- has been found in **breast-milk**.
- **regulator** of the Ca^{2+} ion channel in the cell membrane of nerve tissues.
- can **regulate** the function of brain cell membranes and have a **neuroprotective** effect.

Brain Lipids Synthesis & Oxidation

Peroxisomal fatty acid oxidation is important in the brain as the brain contains **very-long-chain fatty acids** as **nervonic acid** & **branched-chain** fatty acids as **phytanic acid** (of diet)

Both are oxidized by **α–oxidation** and **β-oxidation** in the **peroxisomes**.

- **Zellweger syndrome** & **X-linked adrenoleukodystrophy** - defects in peroxisomal β-oxidation of **nervonic acids**
- **Refsumes disease** - a disorder that affects the **peroxisomes** – due to inability to metabolize **phytanic acid.**

Myelin

Myelin is a multilayered lipid (sphingolipids) & protein structure that is formed by the plasma membrane of **glial cells** to wrap around the **axon** and forming an **electrically insulating** layer.

In **PNS**, **myelin** is synthesized by **Schwan cells**

In **CNS**, **myelin** is synthesized by **oligodendrocytes**

In humans, **myelination** begins early in the **3rd** trimester.

During infancy, **myelination** occurs quickly, leading to a child's fast development.

Myelination continues through the adolescent stage of life.

Rapid rate of nerve conduction in **PNS** & **CNS** depends on the formation of **myelin.**

Myelin in biological membranes contains more than **70**% of its dry weight as lipid which is rich in **sphingolipids**:

- **cerebrosides** - **23**%;
- **sulphatides** - **4**%;
- **sphingomyelin** - **8**%.

Sphingolipids contain a high proportion of **very long chain saturated** and **monounsaturated** FA:

- **lignoceric acid (tetracosanoic acid)**, 24:0,
- **nervonic acid**, 24:1(n-9).

Lignoceric acids correlated to social interaction at one month, and **nervonic acid** to mental, psychomotor and behavioral development at 6, 10 and 18 months.

The level of **nervonic acid** in human brain **sphingolipids** increases markedly from birth to reach a maximum at about **4** years after which it remains almost constant.

Increased levels of **tetracosanoic acid** have been observed in patients with **neurodegenerative diseases.**

Cold exposure induced **brown adipose tissue** (BAT) activity.

Plasma **noradrenaline** and **dopamine** concentrations increased in response to **cold**.

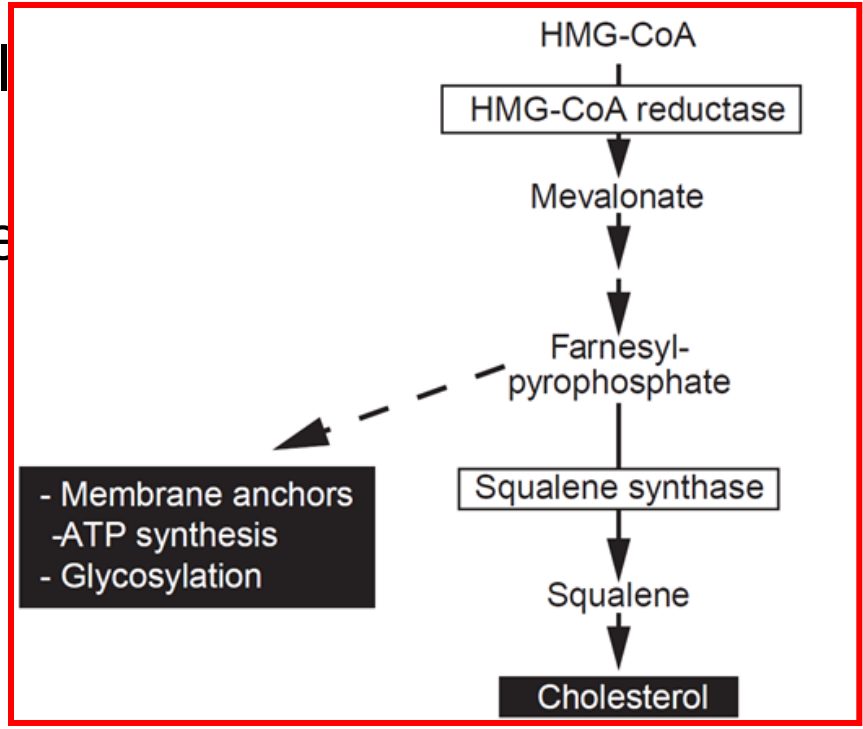
Cold-exposure induces **sympathetic nervous system** activity and BAT metabolism in humans, resulting in

- improved **glucose** metabolism without affecting pancreatic **insulin** secretion.
- altered circulating concentrations of distinct FAs – **Lignoceric acid** (C24:0) concentrations increased, whereas levels of **eicosanoic acid** (C20:1n9), **nervonic acid** (C24:1n9), and **behenic acid/docosanoic acid** (C22:0) decreased.

Iwen KA, 2017.

Cholesterol is an essential constituent of **myelin**.

Cholesterol is not imported to the brain from the circulation.



Myelin is about 40% **water**;
- the dry mass is
- about 70–85% - **lipids** (~ 25% - cholesterol);
- about 15–30% **proteins**.

Some of the **proteins** are
- **myelin basic protein** (**MBP**, which makes up ~**30**% of myelin protein),
- **myelin oligodendrocyte glycoprotein**, and
- **proteolipid protein** (**PLP**, which makes up ~**50**% of myelin protein).

Complete inactivation of ***squalene synthase***, or ***3-hydroxy-3-methylglutaryl coenzyme A reductase*** the rate-limiting enzymes in the **cholesterol** sinthesis pathway, is **lethal** during embryonic development.

Fatty acids in sphingolipids of the brain

FA	Sphingomyelin (%)	Sulphatides (%)	Cerebrosides (%)
16:O	**7.4** ± 2.1	**13.l** ± 4.3	**6.5** ± 2.5
18:O	**25.4** ± 2.4	**9.5** ± 2.8	**9.2** ± 2.0
19:o	l.l ± 0.6	0.3 ± O.l	1.7 ± 0.5
20:o	1.O ± O.l	l.0 ± o.5	0.8 ± 0.2
22.0	1.5 ± 0.1	l .6 ± 0.2	1.9 ± Q.2
23:0	l .6 ± O.2	2.4 ± o.2	2.6 ± O.4
24:0	**6.6** ± 0.9	**9.8** ± 1.7	**10.7** ± 1.6
25:0	**2.5** ± 1.2	**3.3** ± 0.2	**3.5** ± l.0
26:O	1.1 ± 0.5	0.9 ± 0.1	1 .0 ± O.1
monounsaturated FA			
16:l	0.7 ± 0.5	1.9 ± l.3	l.0 ± 0.3
18:l	**3.5** ± l.2	**3.7** ± l.l	**3.3** ± l.0
19:l	0.6 ± 0.3	0.2 ± 0.l	0.4 ± 0.l
2O:l	0.3 ± 00.2	nd	O.l ± 0.1
22:l	0.1 ± O.l	nd	0.l ± 00.l
23:l	0.8 ± 0.2	0.4 ± O.2	0.7 ± 0.2
24:l	**36.3** ± 2.5	**36.2** ± 3.1	**40.3** ± 5.7
25:l	**5.3** ± 0.6	**8.6l** ± l.3	**9.3** ± 1.6
26:l	**4.0** ± 0.7	**7.0** ± l.8	**6.6** ± 0.7

Rafts

Complexes that consist of
cholesterol,
glycosphingolipids
membrane proteins

- in a cellular membrane - **microdomains** - '**rafts**' - that serve as platforms for:

- protein sorting and
- signal transduction.

It has been suggested that **myelin** membranes may result from the accumulation of **myelin-specific rafts** in which **cholesterol** is closely associated with **myelin membrane proteins.**

Cholesterol

plays a crucial role in the regeneration of nerve after injuries both in **CNS** and **PNS**.

Local availability of **cholesterol** at nerve damage is necessary for nerve regeneration.

The **cholesterol**-rich transporter **lipoprotein Apo-E** has been reported to accumulate at the site of injury after nerve crush. The **Apo-E** is synthesized by **macrophage** and accumulated at the site of regenerating axon and it increases following an injury.

Cholesterol

The lysosomal dysfunction that occurs in **lysosomal storage diseases** may impair **mitochondrial** function and brain energy metabolism.

Intramitochondrial **cholesterol** accumulation in brain and mitochondrial dysfunction plays a role in **oxidative stress** observed in **lysosomal storage diseases** (eg. Niemann-Pick type C disease).

Accumulation of **cholesterol** within the **mitochondria** impairs **reduced glutathione** (**GSH**) **transport** into **mitochondria**, decreasing **mitochondrial GSH pool**.

Mitochondrial dysfunction leading to **caspase-9** activation and **apoptosis.**

Genetic disorders of the **cholesterol** biosynthetic pathway

- are associated with **myelination defects** but also include complex craniofacial malformations.

• lacking ***7-dehydrocholesterol reductase*** - human Smith-Lemli-Opitz-syndrome (**SLOS**):

- microcephaly;
- autistic behaviours;
- micrognathia (mandibular hypoplasia);
- heart defects and/or renal, pulmonary, liver and eye abnormalities.

• lacking ***24-dehydrocholesterol reductase*** - **desmosterolosis**:

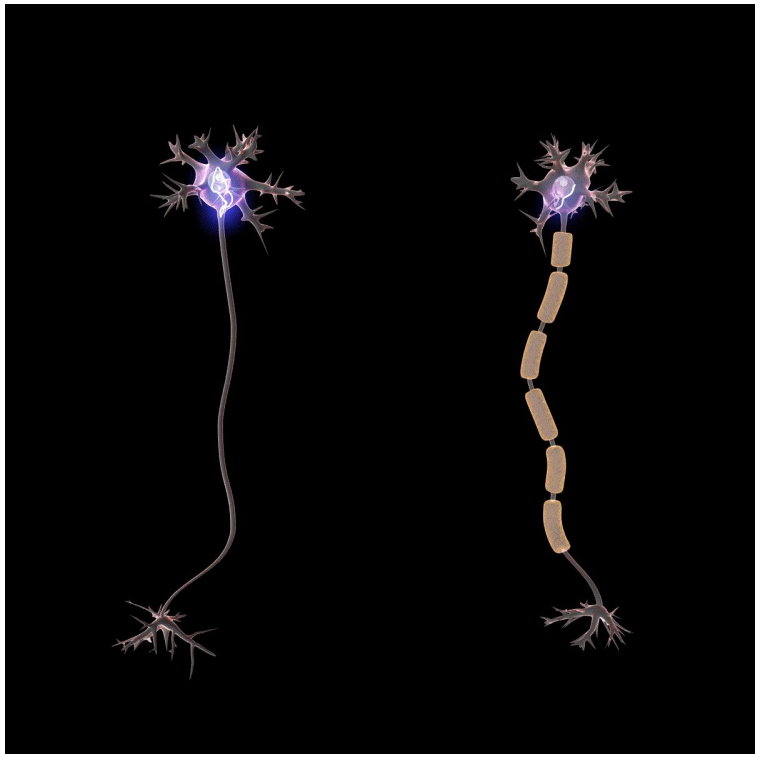
- loss of white matter;
- brain abnormalities;
- delayed speech and motor skills;
- muscle stiffness;
- heart defects.

"the brain is unusual among organs in the extent to which **the rates of its most characteristic biochemical reactions are controlled not by the amount or activity of a key enzyme**, but rather **by the extent to which that enzyme is saturated with its substrate**, which usually is both a nutrient and a precursor for a physiologically active reaction product."

[**Wurtman RJ**. 2009].

Myelin Synthesis

Rapid rate of nerve conduction in **PNS** & **CNS** depends on the formation of **myelin**.



Multiple sclerosis - progressive **demyelination** of CNS neurons

- due to an event that triggers the formation of **autoimmune antibodies** directed against components of the nervous system.

Patients with **multiple sclerosis** have decreased levels of **nervonic acid** in the brain.

Ca^{2+}

Neuronal physiology, ranging from **neurotransmitter exocytosis** to dynamic regulation of **dendritic spine morphology**, is modified by levels of **intracellular free calcium** (**$[Ca^{2+}]_i$**) that range between **10 - 50 nM** to of low **micromolar**.

Elevations of **$[Ca^{2+}]_i$** are short lived due to an elaborate network of calcium **buffers**, **pumps**, **channels**, and **exchangers** in cellular membranes & membranes of intracellular **Ca^{2+}**-storage organelles (**endoplasmic reticulum**).

Elevated [**$Ca^{2+}]_i$** binds to numerous proteins,
- **calbindin**, **calretinin** – that limit **Ca^{2+}** diffusion
- **calmodulin, troponin** - responsible for transducing multiple biochemical changes that mediate physiological responses to elevated **$[Ca^{2+}]_i$**.

Among these intracellular **Ca^{2+}**-binding proteins, **calmodulin** (**CaM**) is the most important.

Ca^{2+}

Binding of **Ca^{2+}** produces a conformational change in **CaM**, that promote interactions of the **Ca^{2+}/CaM** complex to numerous target proteins.

These **Ca^{2+}/CaM** targets modulate **cellular signaling pathways**, structural proteins, ion channels, pumps, transcription factors, and numerous rate-limiting enzymes. Among the signaling proteins is a family of

calmodulin-kinases (**CaMKs**).

CaMKs - abundant in brain, are activated via binding of **Ca^{2+}/CaM**, and phosphorylate Ser/Thr residues in their protein substrates to alter the functionality of those proteins.

- **CaMKIII** - phosphorylates and inactivates **eukaryotic elongation factor-2** (**eEF2**) - (**eEF2-kinase**) .

CaMKI or **CaMKIV** can stimulate transcription of a **CREB** reporter gene. That is involvement of **CaMKIV** via **CREB** in dendritic development and synapse formation.

CREB (**cAMP response element-binding protein**) has a role in **neuronal plasticity** and **long-term memory** formation in the brain.

- **CREB** downregulation is implicated in the pathology of **Alzheimer's disease.**

- **CREB** has an important role in the development of **drug addiction** and in **psychological dependence**

- **CREB** is a cellular **transcription factor**. Genes whose transcription is regulated by **CREB** include:
  - brain-derived neurotrophic factor (BDNF),
  - tyrosine hydroxylase,
  - numerous neuropeptides - somatostatin, enkephalin, corticotropin-releasing hormone etc.

Excitation →
release of **glutamate** →
NMDA receptors resulting in a **Ca^{2+}** influx into the neurones →
induces the activity of **Ca^{2+}/calmodulin**-dependent protein kinases (**PKA**, **PKC**, **CK2**) →
phosphorylate **CREB** →
regulates downstream **gene expression**.

Learning and memory

Learning is the name given to the process by which new information is acquired by the nervous system and is observable through changes in **behavior**.

Memory is a complex and not yet sufficiently studied process involving phases of **capturing**, **storing** and **retrieving** the information received. All these phases are closely related.

Types of biological **memory**:

1. **Genetic**;
2. **Epigenetic**;
3. **Immunological**;
4. **Neurological** (sometimes called psychic or individual).

Neurological memory has three main stages of formation that correspond to three types of memory:

1. **Immediate memory** (duration from several milliseconds to seconds) - is the routine ability to hold ongoing experiences in mind for fractions of a second. The capacity of immediate memory is very large and each sensory modality (visual, verbal, tactile, and so on) appears to have its own memory register (**short-term memory**).
2. **Working memory** - is the ability to hold information in mind for seconds to minutes once the present moment has passed. (**short-term memory**)
3. **Long-term memory** - the retention of information in a more permanent form of storage for days, weeks, or even a lifetime.

Learning and memory

According to modern concepts, **memory traces** (***engrams***) are locked in the brain in the form of changes in the **status of the synaptic apparatus**, which results in preferential conduction of excitation in certain nerve pathways.

Learning and memory

In a **short-term memory** the changing of “fast” synapse functions occur. It is associated with the release and shift of concentration of “classical” and peptide mediators.

For the formation of a lifelong **long-term memory** persistent **synthesis of new biopolymers** is necessary. It may be done in case of stable rearrangement in some genome parts functioning. The latter can occur either as a result of **structural changes** in the **DNA**, or the formation of **stable cycles** for continuous synthesis of repressors or derepressors of transcriptons.

It is also possible that the formation of **long-term memory** embraces participation of **immunological mechanisms** due to which **antibody-like compounds** are synthesized in the brain. These compounds are able to modify the activity of synapses in certain nerve pathways for a long time.

Learning and memory

Formation of **long-term potentiation** (**LTP**) and **long-term depression** (**LTD**) by the synapse of hippocampus is a mechanisms of **learning and memory**.

LTP is divided into

- an **early stage** (**E-LTP**) lasting ~1 hr that does not require gene transcription and
- a **late-phase** (**L-LTP**, 1–4 hr) that is dependent on gene transcription, particularly mediated by the transcription factor **CREB**.

Deficits in **CREB**-dependent transcription could account for their long-term memory impairments.

The **CaMKII** gene was one of the first to be implicated in **learning** and **memory** and also appears to modulate **memory consolidation**.

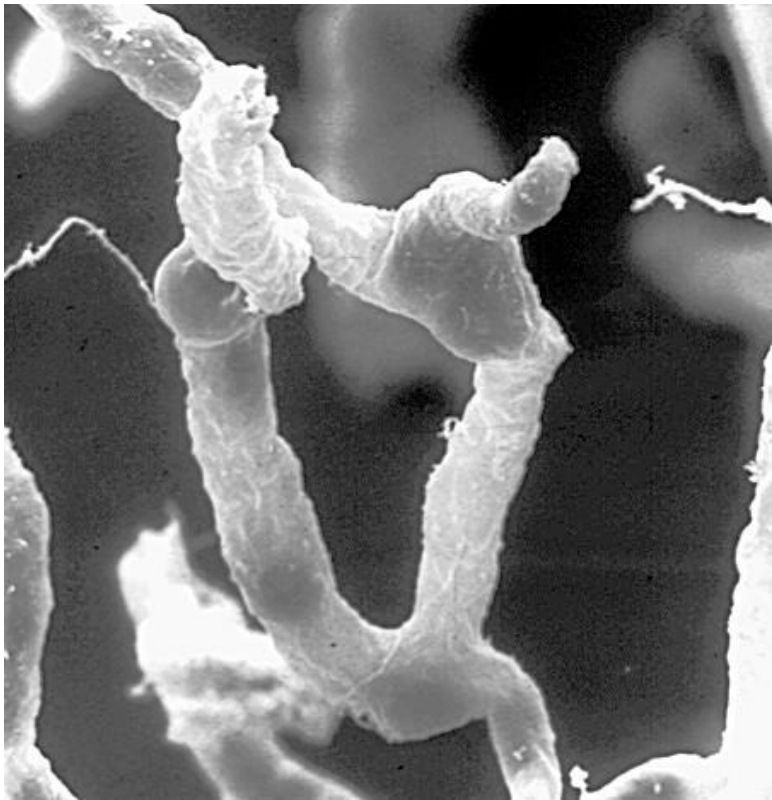
Decreases in the levels of **CaMKIV** impair **LTP** and memory, overexpression of this molecule can enhance **LTP** and memory.

The blood–brain barrier

The blood-brain barrier (BBB) is a highly selective permeability barrier that separates the **circulating blood** from the brain **extracellular fluid** in the **CNS**.

This "**barrier**" occurs along all capillaries and consists of **tight junctions** between

- **endothelial cells** around the capillaries in CNS vessels that do not exist in normal circulation,
- perivascular **base membrane** and
- the plasma membrane of **glial cells**.



The **tight junctions** and **basal lamina** of the cerebral **endothelial cells** - play the most substantial role in maintaining the barrier.

Transmembrane proteins:

- **occludin,**
- **claudins,**
- **junctional adhesion molecule.**

Specialized structures participating in sensory and secretory integration within neural circuits – the **circumventricular organs** and **choroid plexus** – do not have a **blood–brain barrier**.

Transport through Blood-Brain Barrier (BBB)

Large number of compounds are transported through endothelial capillaries by facilitated diffusion.

1- Fuels

A. Glucose – the principal fuel of the brain

Transported through membranes via GLUT-1

At blood glucose of 3,3 mmol/l, glucose is reduced to below K_m of GLUT-1 leading to appearance of symptoms of

hypoglycemia.

Transport through Blood-Brain Barrier (BBB)

B. **Essential fatty acids** (linoleic & linolenic) can pass BBB

C. **Non-essential fatty acids** - do not cross BBB

D. **ketone bodies** - can pass BBB - are important fuels for brain during prolonged **starvation.**

Transport through Blood-Brain Barrier (BBB)

2- *Amino acids* are transported by **amino acid transporters**

- **Small neutral amino acids** entry is **markedly restricted** as their influx significantly **increases** the level of **neurotransmitters**.
- High **Gly** concentration disrupts temperature and blood pressure control.
- **Glu** is in a class of chemicals known as **excitotoxins**.

3- *Vitamins*: transported by special transporters

The exchange of **free amino acids** in the **brain**:

1. Greater ability of nerve tissue to **maintain levels of amino acids** relative constancy.

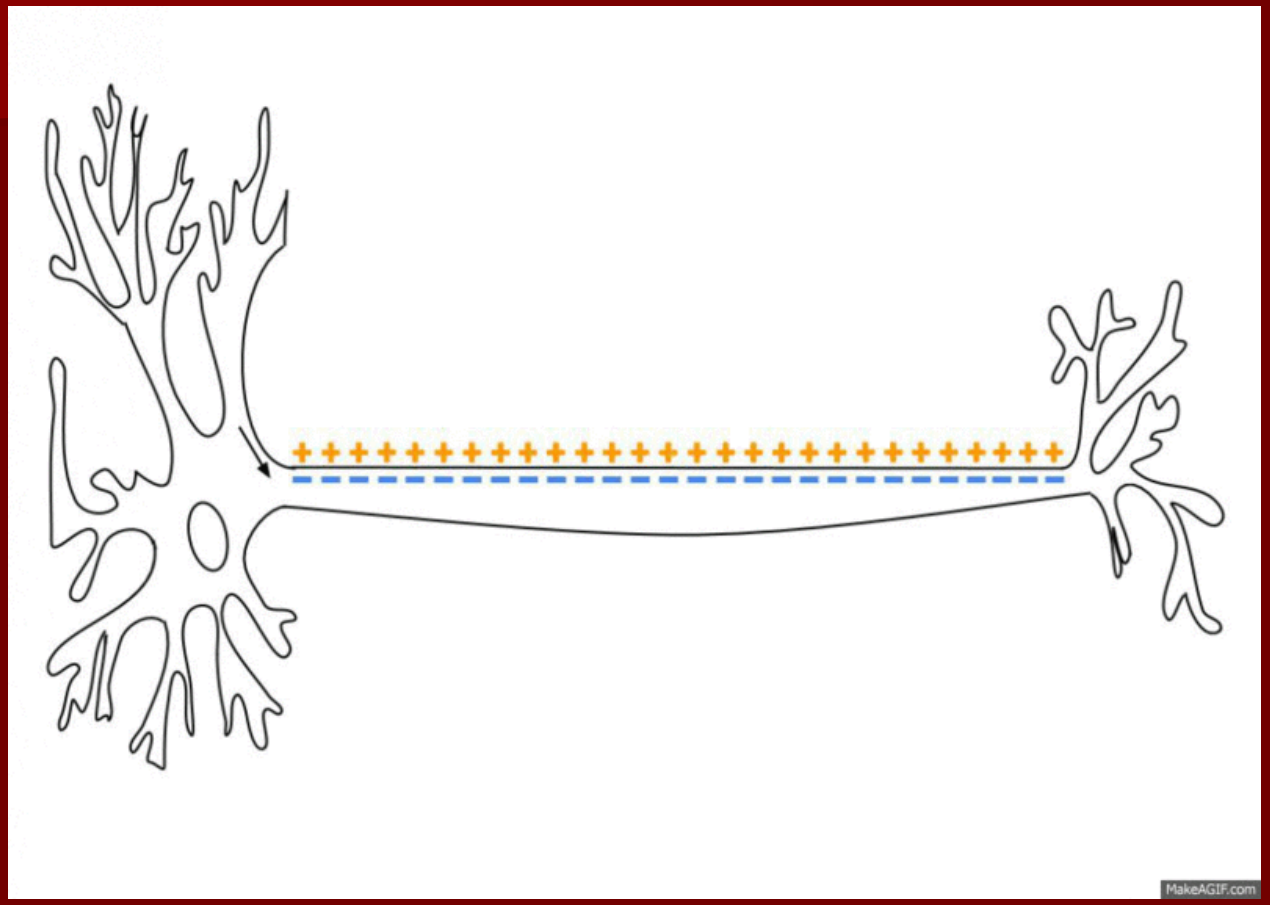
2. Content of free **amino acids** in the brain is **8-10 times higher than in plasma**.

3. The existence of **high amino acid concentration gradient between the blood and the brain** by selectively **active transport** across the BBB.

4. High concentrations of **Glu**, **Gln**, **Asn**, **GABA** and **N-acetylasparagine**. They constitute **75%** of the pool of free amino acids in the brain.

Biochemistry of "nerve impulses"

«Nerve impulses" or "spike train".



Action potentials - are discrete electrochemical impulses that travel rapidly along an axon.

Approximately **70%** of the ATP produced in the brain is spent on maintaining ionic gradients between the contents of the nerve cells and the environment.

Neurons have special structures that allow them to send signals rapidly and precisely to other cells. They send signals in the form of **electrochemical waves** traveling along axons, which cause chemicals called **neurotransmitters** to be released at junctions called **synapses**.

Malfunction of the **nervous system** can occur as a result of

- genetic **defects**,
- physical **damage** due to trauma or toxicity,
- **infection**
- simply of **ageing**.

Action potentials are generated by

voltage-gated ion channels.

These channels are **shut** when the membrane potential is near the **resting potential** of the cell.

A. they rapidly **open** if the **membrane potential** increases to a **threshold value**.

When the channels **open**, they elevate flow of Na^+ →

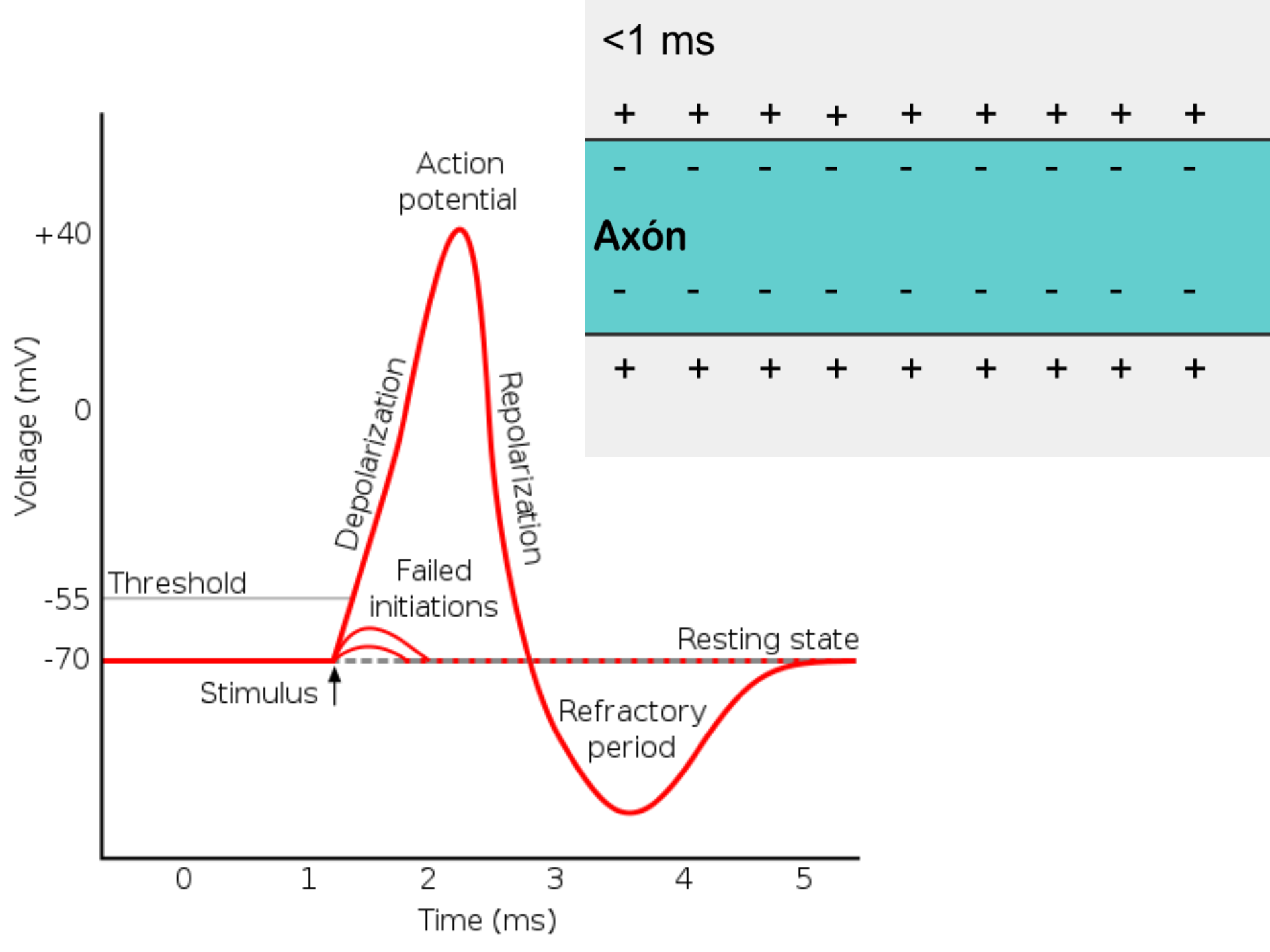
→ changes the **electrochemical gradient** →

→ **upswing the membrane potential**.

The **rapid influx** of Na^+ **reverse** the

polarity of the plasma membrane →

the ion channels then rapidly inactivate.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Axón
- - - - - - - - -
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Action potential
+40
0
-55
-70
Voltage (mV)
Depolarization
Repolarization
Threshold
Failed initiations
Resting state
Stimulus
Refractory period
0
1
2
3
4
5
Time (ms)

B. As the Na^+ channels **close**, Na^+ can no longer enter the neuron, and actively transported **back out** of the **plasma membrane**.

K^+ channels **activated** outward current of K^+ →

returning the electrochemical gradient

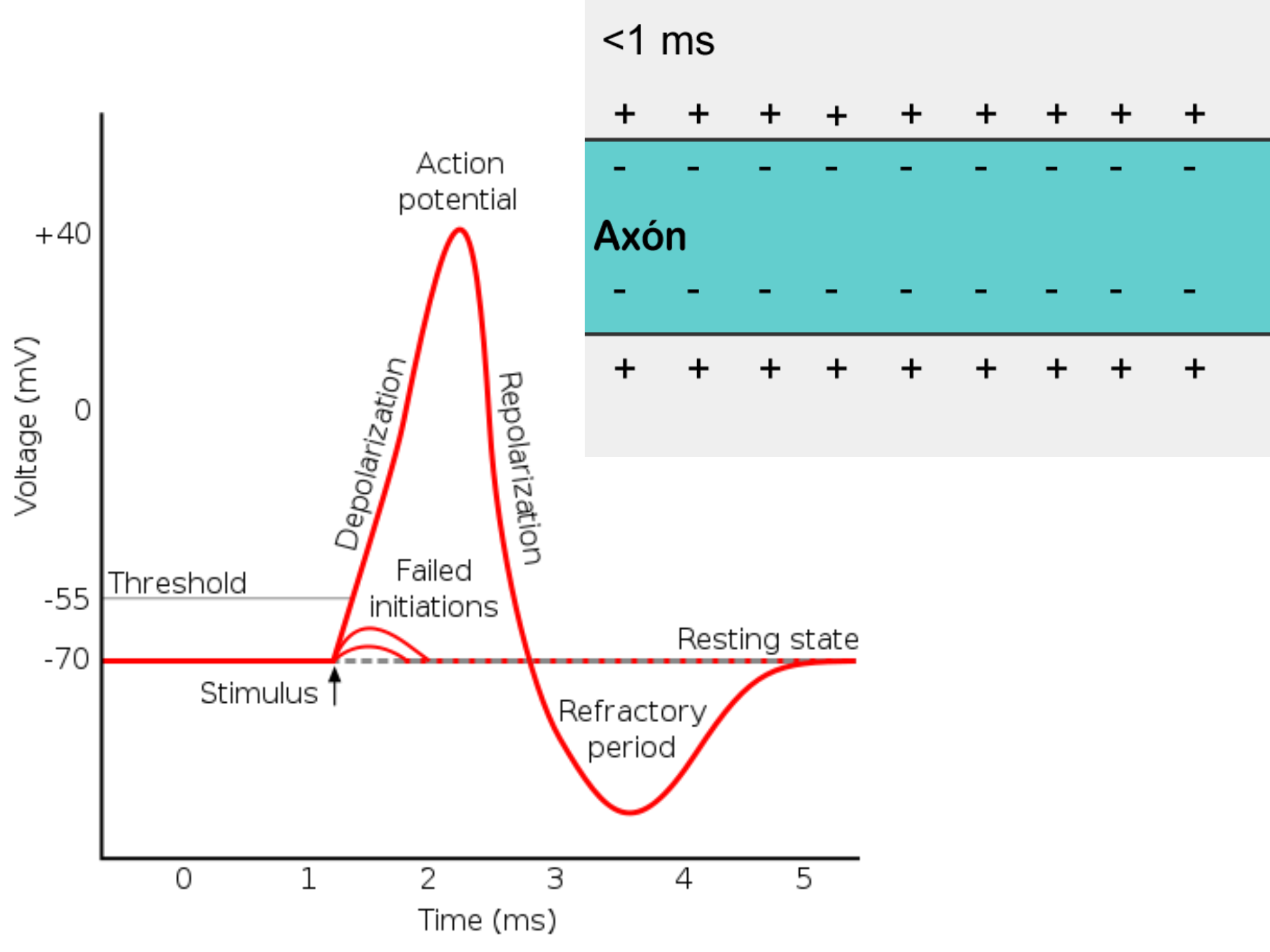
to the **resting state**.

C. After an **action potential** →

afterhyperpolarization or **refractory period**,

due to additional K^+ currents. This is the mechanism that **prevents** an action potential **from traveling back**

the way it just came.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Axón
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Action potential
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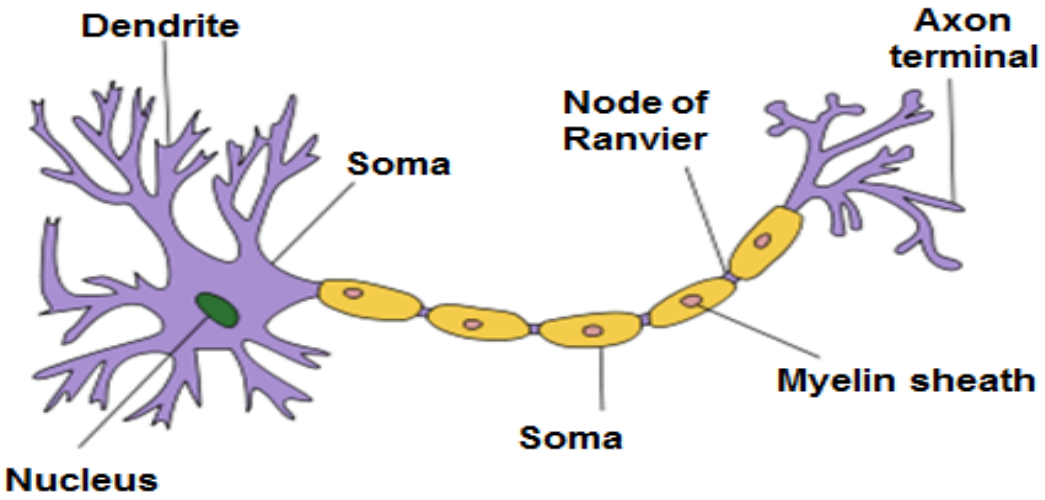
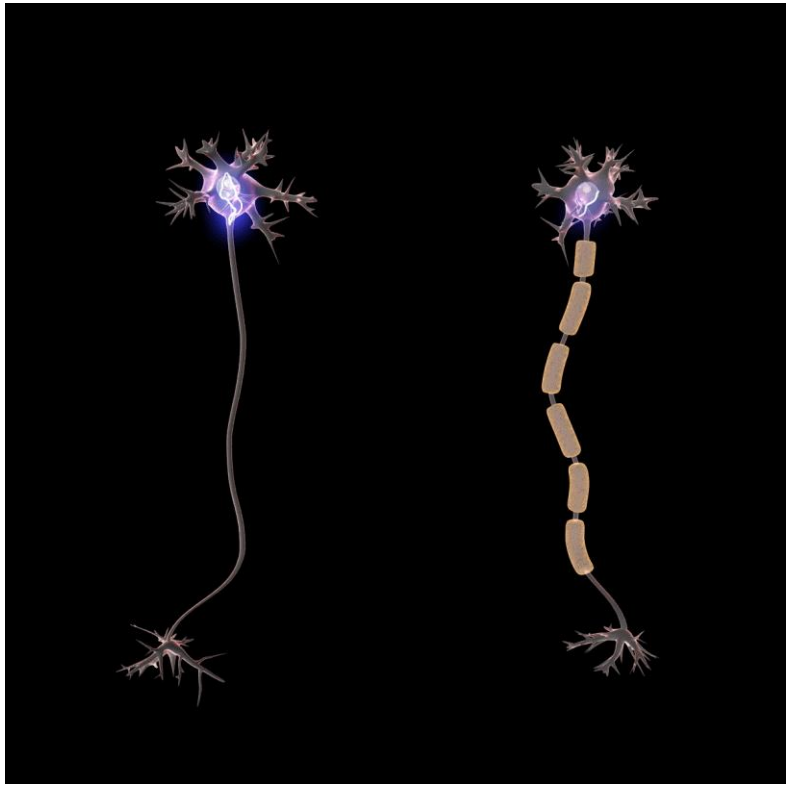
-55
-70
Voltage (mV)
Depolarization
Repolarization
Threshold
Failed initiations
Resting state
Stimulus
Refractory period
0
1
2
3
4
5
Time (ms)

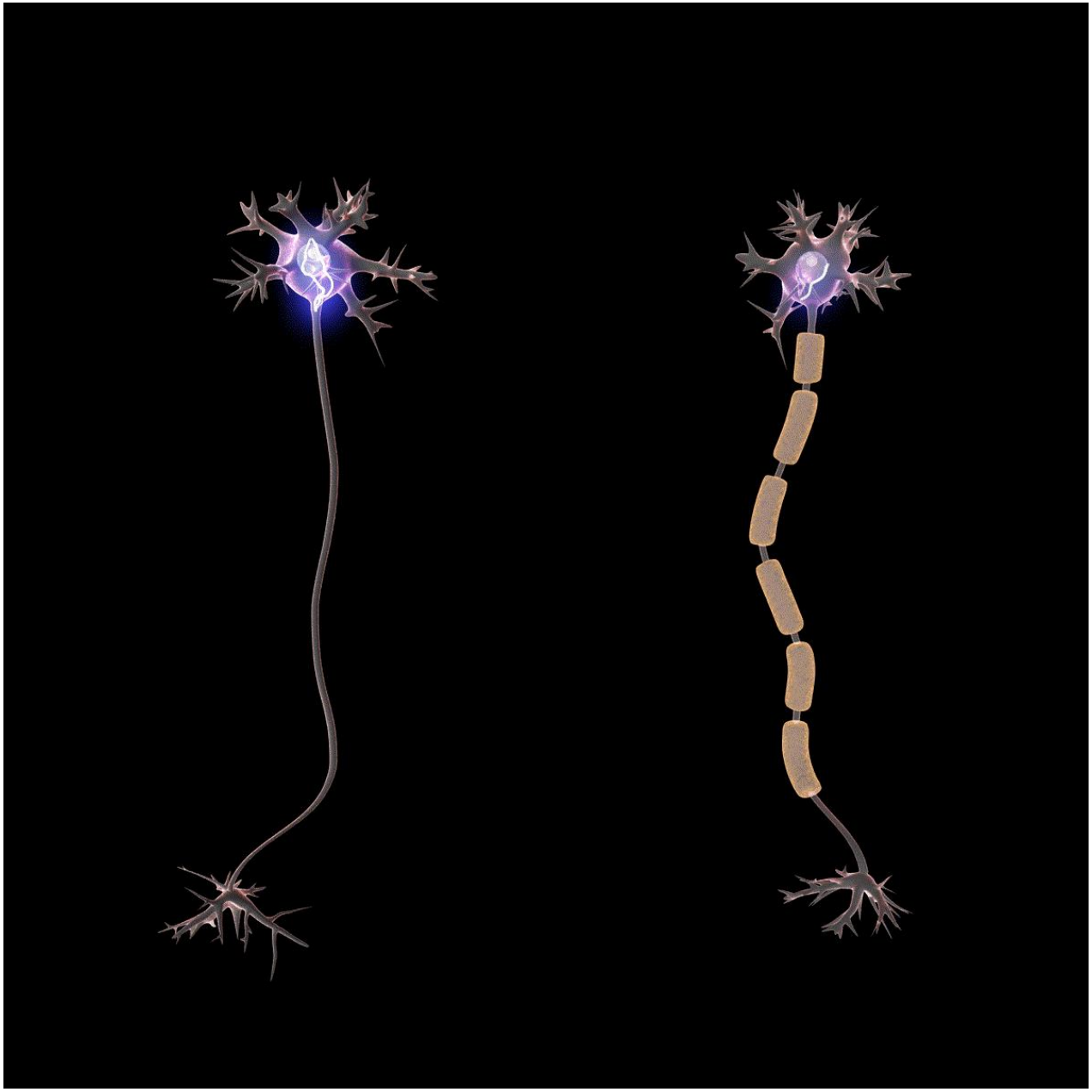
Node of Ranvier (myelin sheath gaps)

- short unmyelinated areas periodically interleaved segments of the myelin sheath of axons.



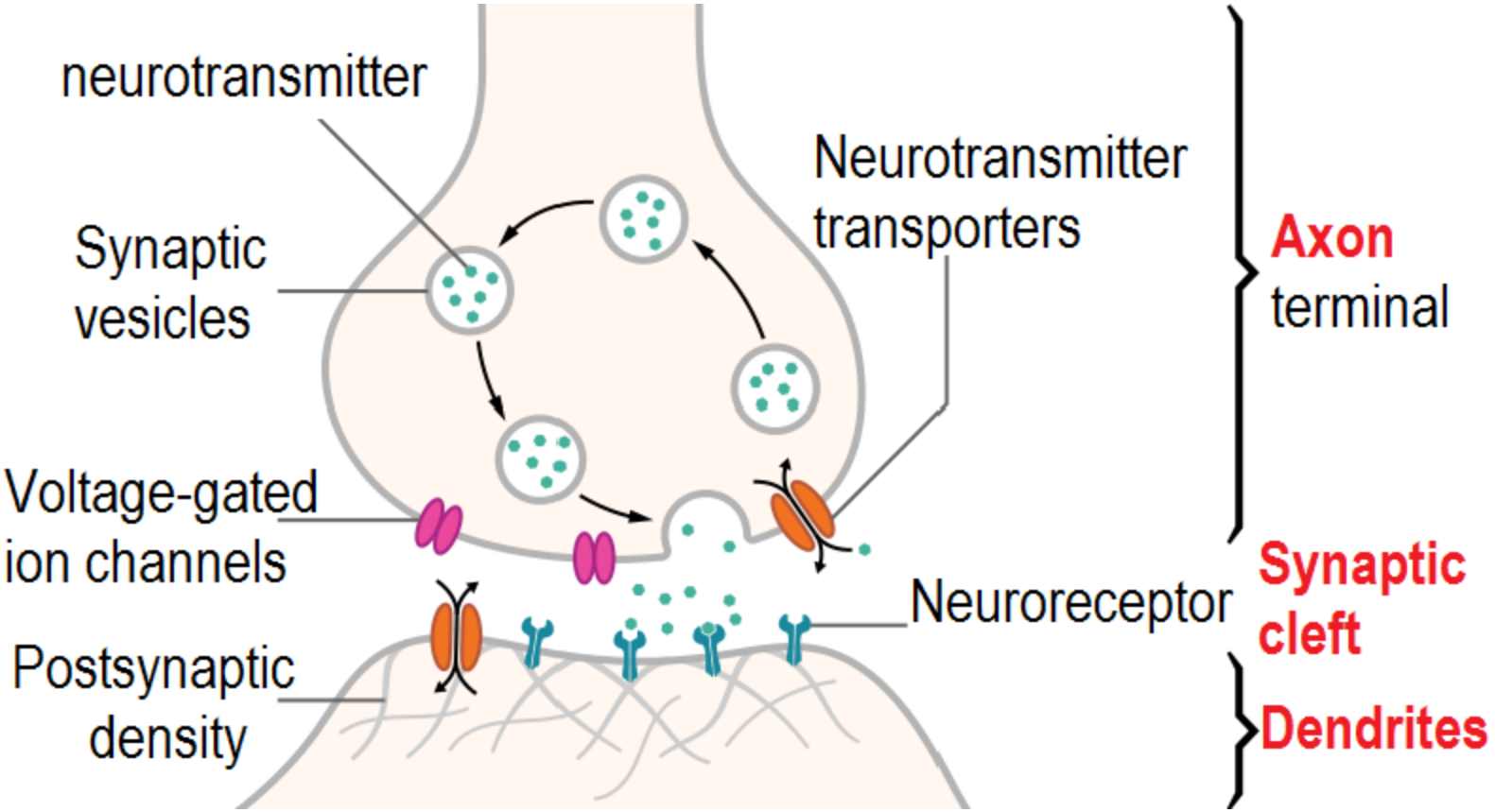


Action potentials effectively "jump" from node to node, with a very high speed of propagation.



Synapses transmission of nerve impulses

Synapses transmission



Synapses transmission

1. Wave of electrochemical excitation (**action potential**) traveling along the membrane of the **presynaptic cell**, and reaches the **synapse**.

2. The **electrical depolarization** of the membrane causes channels to open that are permeable to **calcium ions** → increasing the **Ca^{2+}** concentration in the interior.

3. The high **Ca^{2+}** concentration activates a **Ca^{2+}**-sensitive proteins attached to **synaptic vesicles** with **neurotransmitter** → causing the membranes of vesicles to **fuse** with the membrane of the **presynaptic cell**, and dumping their **neurotransmitter** contents into the **synaptic cleft**.

4. The neurotransmitter diffuses within the cleft → binds and activated **receptor** located on the membrane of **the postsynaptic cell**.

5. .**Neurotransmitter** molecules loose from the receptors and drift away → is either reabsorbed by the presynaptic cell, and then **repackaged** for future release, or **broken down** metabolically.

Neurotransmitters

Metabolism of Neurotransmitters

Neurotransmitters - chemicals released at synapses for transmission of nerve impulses

Each neuron synthesizes **only** those **neurotransmitters** that it uses for transmission through **synapses**.
The **neuronal tracts** are often identified by their neurotransmitters.

Neurotransmitters *structurally divided into two categories:*

- ***Small nitrogen-containing neurotransmitters;***

- ***Neuropeptides***: targeted in CNS as **endorphins** OR released to circulation as **GH & TSH.**

Major small nitrogen containing neurotransmitters:

- *Glutamate*
- *GABA*
- *Glycine*
- *Acetylcholine*
- *Dopamine*
- *Norepinephrine*
- *Serotonin*
- *Histamine*
- *E*pinephrine
- Aspartate
- Nitric oxide (NO*)

Metabolism of Neurotransmitters

General features of neurotransmitters

synthesis, stored, release & termination

1- Most are ***synthesized*** in presynaptic terminal from :

- amino acids
- intermediates of glycolysis
- intermediates of TCA

2 - Once synthesized, they are ***stored in vesicles*** (by active uptake);

3 - ***Released*** **in response to nerve impulse**:

a - nerve impulse causes **Ca^{2+}** influx (through ***Ca^{2+} channels***) to ***presynaptic terminal***;

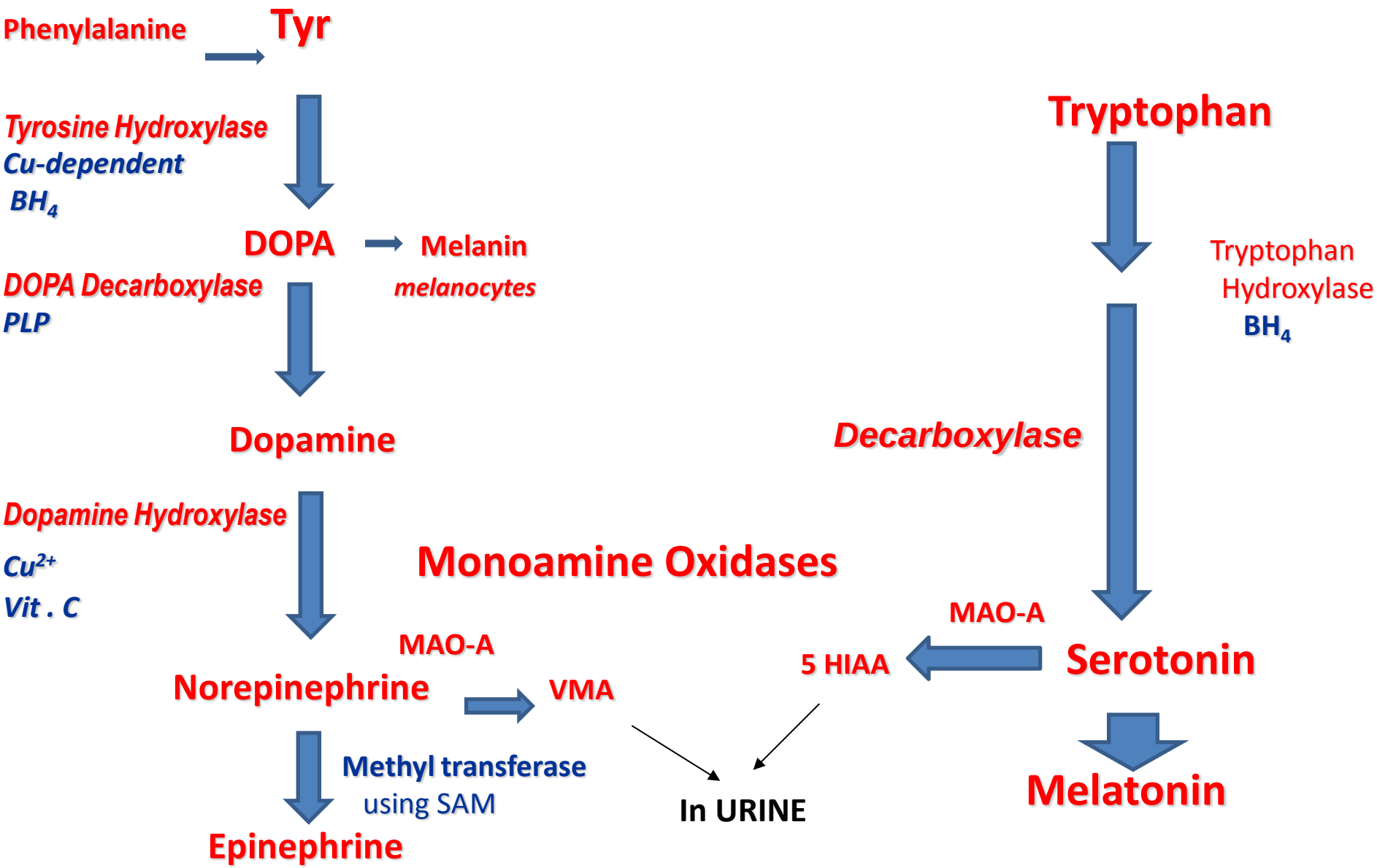
b - exocytosis of neurotransmitters into ***synaptic cleft;***

c - neurotransmitter binds to receptors on ***postsynaptic membrane*** -⟶ **EFFECT**

4 - ***Termination***:

- **Reuptake** of the neurotransmitter into ***presynaptic terminal*** (or by glial cells), **or**
- **Enzymatic inactivation** (in presynaptic terminal, postsynaptic terminal or in astrocyte)

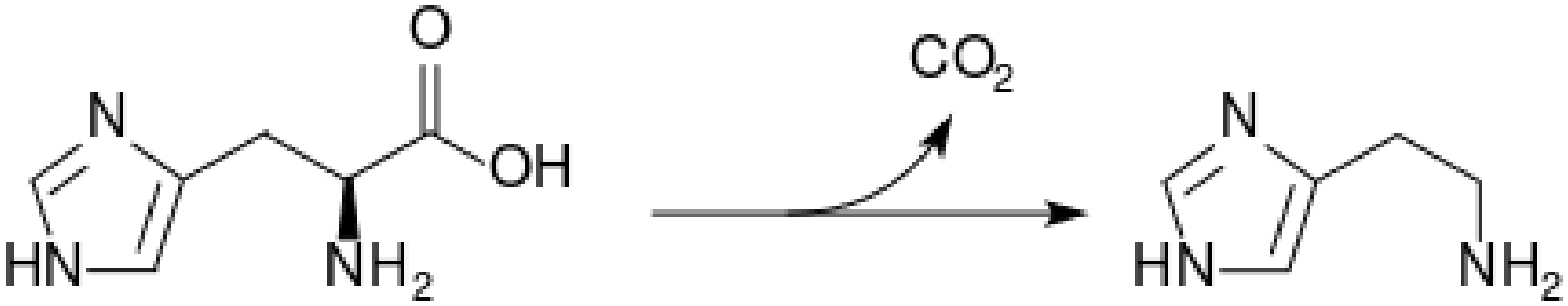
Catecholamines & Serotonin



Histamine

- **Histamine** is an **excitatory** neurotransmitter in CNS

- Synthesized in CNS from the amino acid **histidine** by ***histidine decarboxylase*** (requires **PLP**)



Acetylcholine

Synthesis in CNS (in presynapses)

Choline acetyltransferase

Acetyl CoA + Choline ⟶ **Acetylcholine**

Acetylcholine is

- the **neurotransmitter** used at the **neuromuscular junction**.

- a **neurotransmitter** in the **autonomic nervous system**

as the internal transmitter for the **sympathetic nervous system** and as the final product released by the **parasympathetic** n.s.

Inside the brain ***acetylcholine*** functions as a **neuromodulator**

Acetylcholine

The enzyme **acetylcholinesterase** converts AC into the inactive metabolites **choline** and **acetate**.

This enzyme is abundant in the synaptic cleft, and its role in **rapidly clearing free acetylcholine** from the synapse is essential for proper muscle function.

Certain **neurotoxins** and **poisons** work by inhibiting **acetylcholinesterase**, thus leading to excess AC at the neuromuscular junction, causing **paralysis** of the muscles needed for **breathing** and stopping the **beating** of the heart.

Glutamate

Glutamate is the main excitatory neurotransmitter in the CNS

Sources of glutamate in nerve terminals:

1- synthesized from **glucose** (**main source**)

Glucose → α-Ketoglutarate ↔ Glu (**PLP**)

2- from **glutamine** by ***glutaminase*** (**Mn^{2+}**)

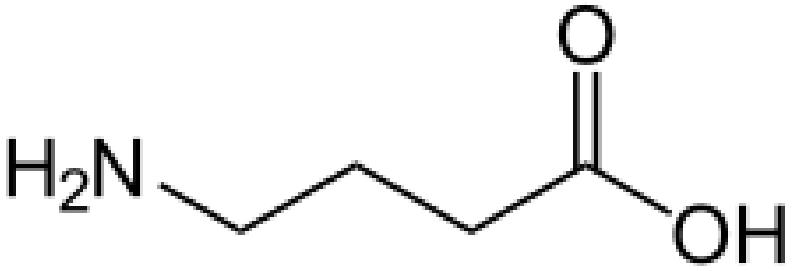
3- from **blood**

From ***synaptic cleft*** **Glu** reuptake by astrocytes.

(**REQUIRES ATP**)

GABA - gamma-aminobutyric acid

GABA is an **inhibitory** neurotransmitters in CNS.



In **presynaptic neurons**, **GABA** is synthesized from **Glu** by ***glutamate decarboxylase*** (requires **PLP**)

Termination: GABA in synaptic cleft is uptaken by glial cells (as astrocytes) & converted to **glutamate**

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Neuropeptides

In recent years has been discovered a large number of **peptides** capable even in low concentrations to affect the nervous tissue, acting as:

- **modulators** of a number of functions,
- **neurotransmitters**,
- **hormones**,
- **pharmacological agents**.

The human genome contains about **90 genes** that encode precursors of neuropeptides.

At present about **100 different peptides** are known to be released by different populations of neurons in the **mammalian brain**.

Glucose & Energy Metabolism

Energy source of the brain

- The mass of the **brain** is only ~ **2%** of the total body mass, yet its energy requirement is more than **seven times** than that of the other organs.

- there is a high requirement for **glucose** and **oxygen** at steady rate (**~20%**).

- The main source of energy is the generation of **ATP** by the **aerobic metabolism of glucose.**

The **brain** typically gets most of its energy from

- oxygen-dependent metabolism of ***glucose***
- **ketones** provide a major alternative source, together with contributions from
- **medium chain fatty acids :**
  - **caprylic (octanoic acid)**
  - **heptanoic**.
- **lactate**, **acetate**, and **amino acids**.

[Marin-Valencia I. 2013]

Hypoglycemia or hypoxia

Deficiencies of either glucose or oxygen

affect brain function because they influence:

1- ATP production for CNS neurons

2- Supply of precursors for neurotransmitter synthesis.

Clinical manifestations of hypoglycemia:

Early clinical signs in hypoglycemia initiated by hypothalamic sensory nuclei as

sweating, palpitations, anxiety & hunger.

In **late** stages, these symptoms give way to serious manifestations of **CNS disorders** as

confusion, lethargy, seizures & coma

Gluco-sensors

A population of specialized hypothalamic neurons is identified as gluco-sensors.

These neurons are classified into **two categories**:

- **excited by glucose** (glucose-excited, **GE**)
- **inhibited by glucose** (glucose-inhibited, **GI**).

Raising **plasma glucose** level after a **large meal** results in an increased brain level to **4,5 mM** and an increase in brain glucose activates **GE neurons**, while **GI** remain inactive.

During a **period of fasting**, reduction in the concentration of brain glucose inhibits **GE** neurons and activates **GI** ones.

- **Drougard A, 2015** -

The mechanism of toxicity of ammonia

The mechanism of toxicity of **ammonia**

NH3 produced by enteric bacteria and absorbed into **portal venous blood** and the ammonia produced by tissues are rapidly removed from circulation by the **liver** and converted to **urea**. Only - 10-20 μg/dL - normally are present in peripheral **blood**.

NH3 is toxic to the CNS.

Symptoms of **ammonia** **intoxication** include:

- tremor,
- slurred speech,
- blurred vision,
- coma, and ultimately death.

The mechanism of toxicity of **ammonia**

1. NH_3 is able to **inhibit the *glutaminase* in neurons**, thereby < formation of **Glu** in **presynaptic neurons.** This effect of NH_3 might contribute to the **lethargy** associated with the ***hyperammonemia*** found in patients with hepatic disease.
2. The increased levels of **glutamine** lead to an increase in **osmotic pressure** in the astrocytes, which become swollen.
3. .NH_3 reacts with α-ketoglutarate to form **Glu**. The resulting depletion of levels of α-ketoglutarate then impairs function of the TCA cycle in neurons.
4. Formation & secretion of NH_3 maintains acid-base balance.

Hepatic encephalopathy

Cerebrospinal fluid

Cerebrospinal fluid (**CSF**) - produced in the ***choroid plexus*** of the brain

~ **500 mL** of CSF per day.

This fluid is constantly **reabsorbed**,

so that only **100-160 mL** is present at any one time.

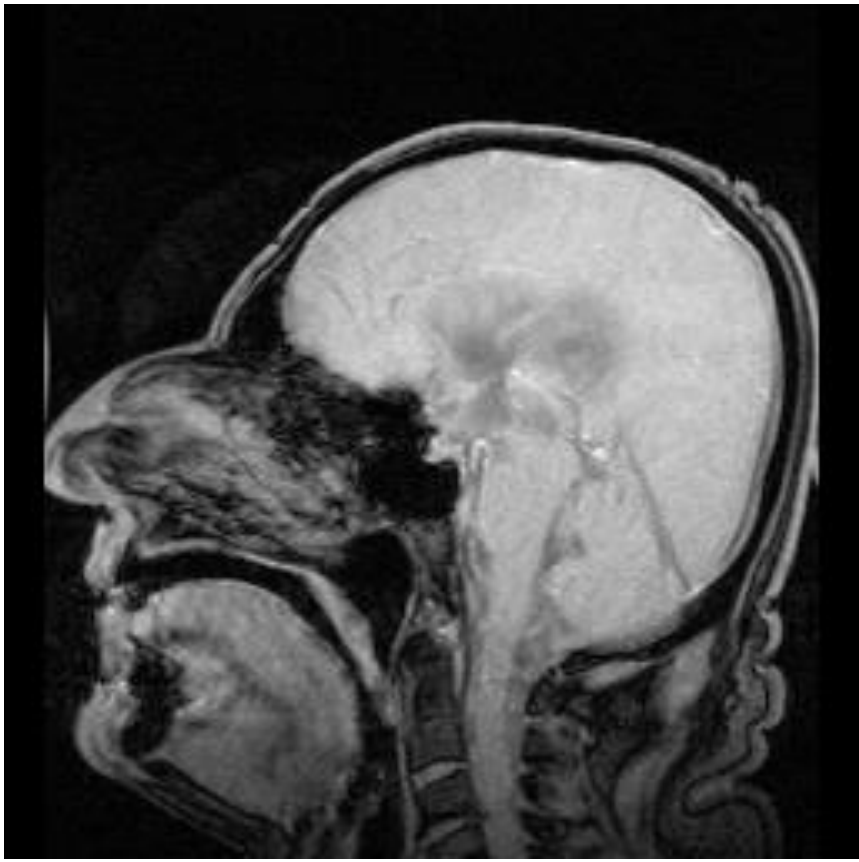
Functions of CSF

1. **Protection.** Acts as a **buffer** for the **brain's cortex**, providing basic **mechanical** and **immunological** protection to the brain inside the skull;

2. **Prevention of brain ischemia** - serves a vital function in cerebral **autoregulation** of **cerebral blood flow**.

Functions of CSF

3. Chemical stability
4. Clearing waste
5. Buoyancy (flotation)



Magnetic resonance imaging (MRI) showing pulsation of CSF

Comparison of Average Serum and CSF.

Substance	Cerebrospinal Fluid	Serum
Water Content (%)	**99**	93
Protein (g/L)	**0.2 – 0.5**	**55 - 80**
Lactic acid (mM/L)	**0.89 – 2.80 (1.54)**	0.6 – 1.7
Glucose (mM/L)	**2,2 — 3,9**	3.3 – 6.4
Sodium (mM/L)	**137 - 145**	136 - 145
Potassium (mM/L)	**2.7 – 3.9**	3.5 – 5.4
Calcium (mM/L)	**1.0 – 1.5**	2.2 – 2.6
Magnesium (mM/L)	**1.0 – 1.2**	0.8 – 1.2
Chloride (mM/L)	**116 - 122**	98 - 106
pH	**7.31 - 7.33**	7.34 - 7.41