BIOCHEMISTRY OF NERVOUS SYSTEM II

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Advanced Clinical Biochemistry II (MA 416)

Summer Semester

Lecture Four

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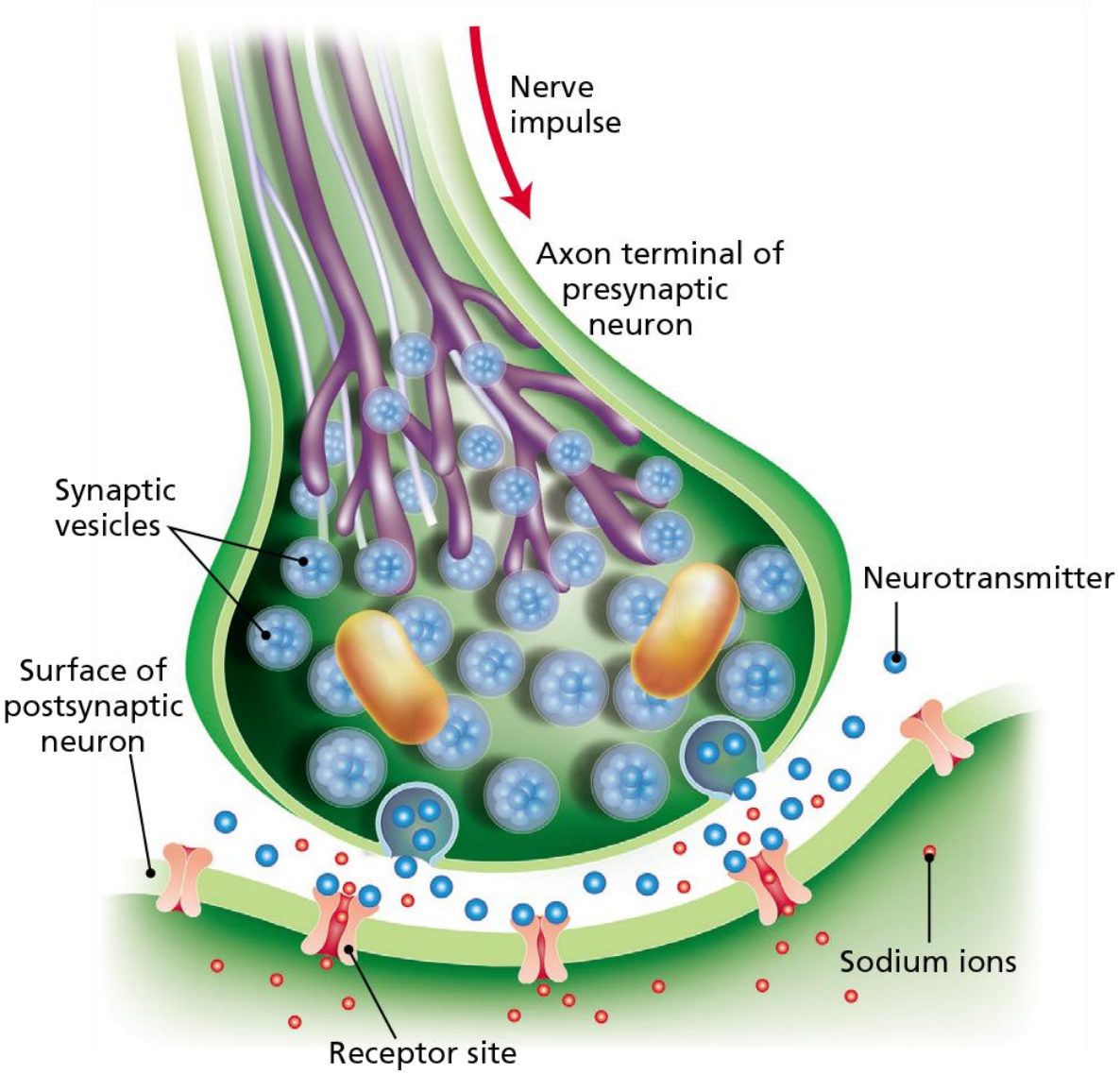
Outlines

- Neurotransmitters:
- Synthesis, release, and termination
- Energy Source of CNS
- Biochemical aspects of CNS diseases
- Hypoglycemia
- Cerebral ischemia
- Oxidative stress and Ischemia

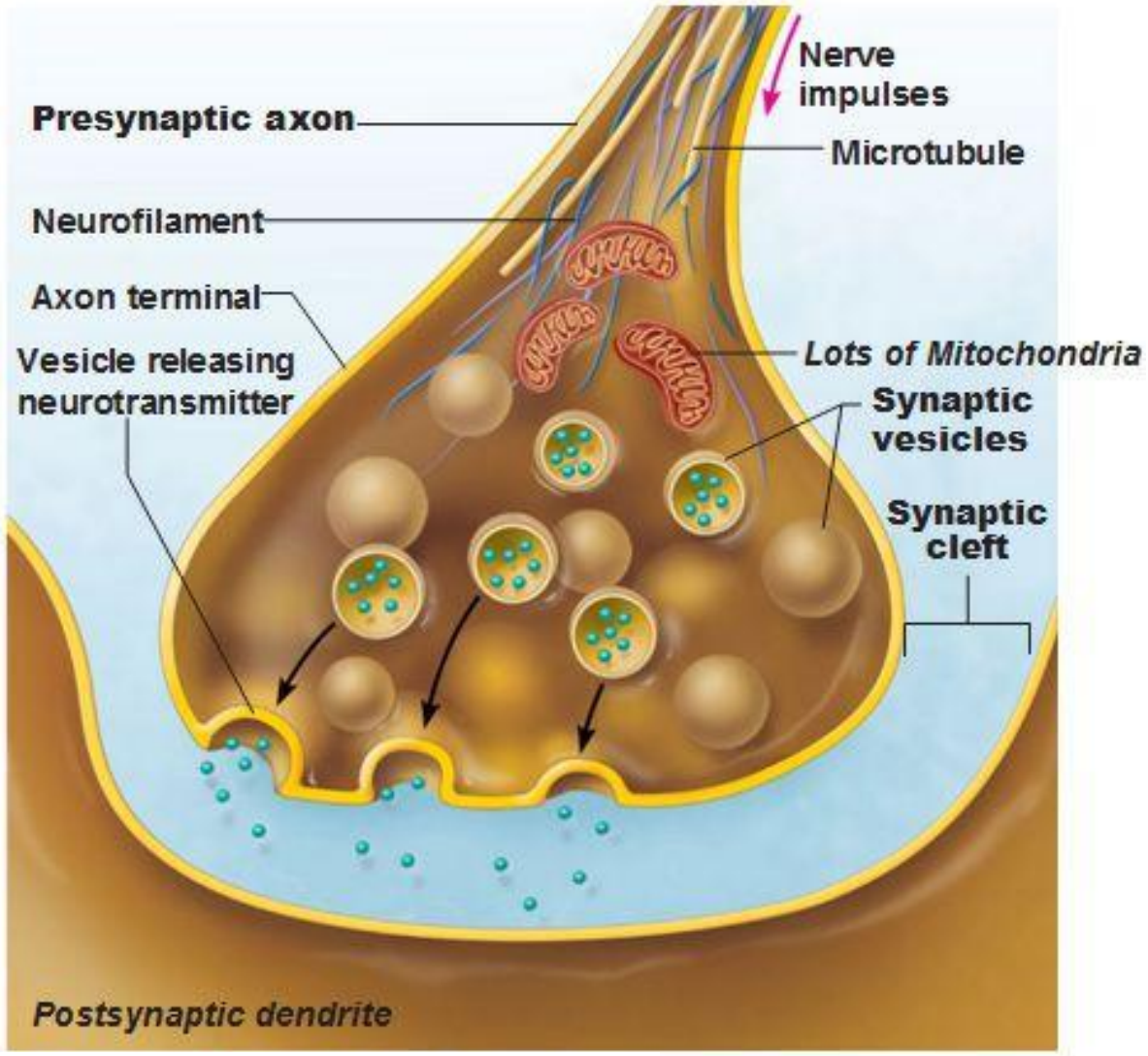
Objectives

- **At the end of this lesson, the students should be able to:**
- Understand the general concept of the nervous system.
- Understand the biochemistry behind the workings of the nervous system.
- Understand how neurotransmitters are synthesized.
- Understand the occurrence of common metabolic conditions in the brain



Neurotransmitter synthesis

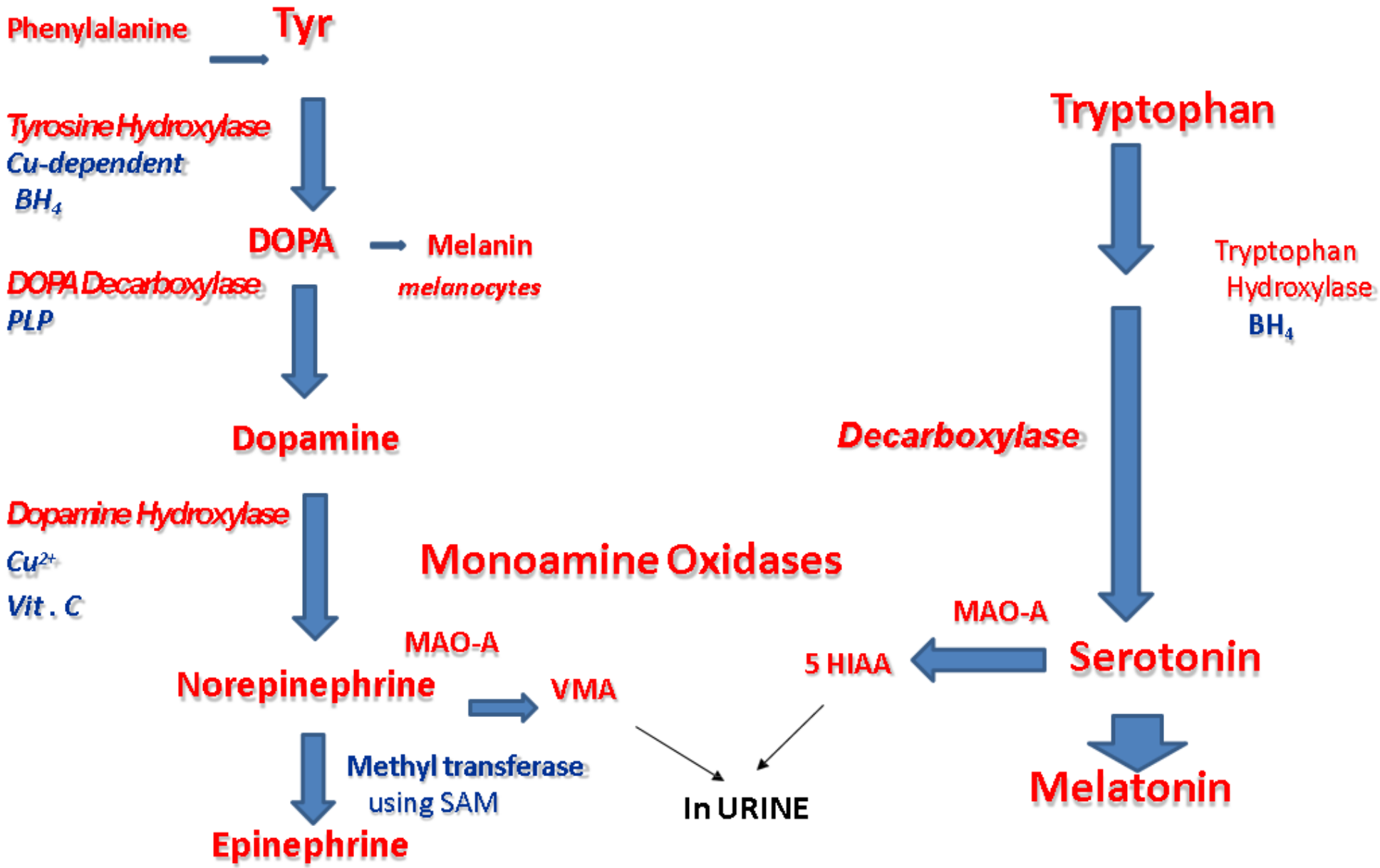
- Neurotransmitters are mostly synthesized in the presynaptic terminal.
- They are synthesized from amino acids, Intermediates of glycolysis, and Intermediates of TCA.
- Once synthesized, they are stored in vesicles (by active uptake)

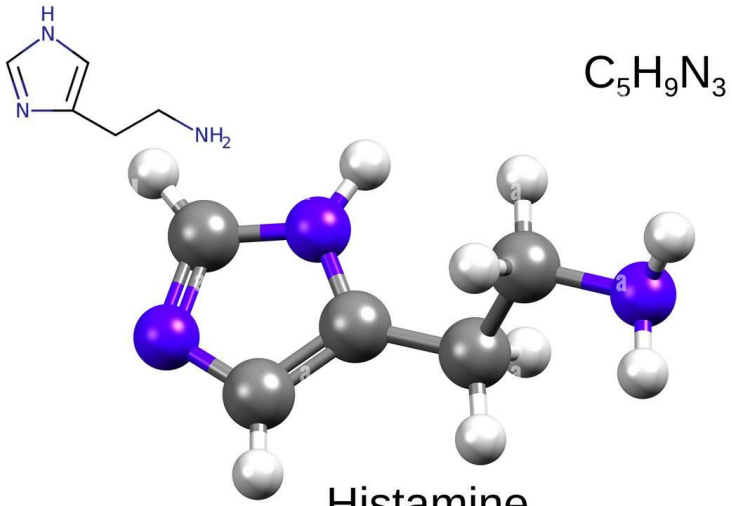


Cont.

- Neurotransmitters are released in response to nerve impulses, which causes an influx of Na^{+}/Ca^{2+} to the presynaptic terminal.
- Neurotransmitters undergo exocytosis into the synaptic cleft and bind to receptors on the postsynaptic membrane to elicit action.
- They also undergo termination through reuptake from the presynaptic terminal (or by glial cells) Or/ Enzymatic inactivation (in the pre or postsynaptic terminals)

Catecholamines & Serotonin



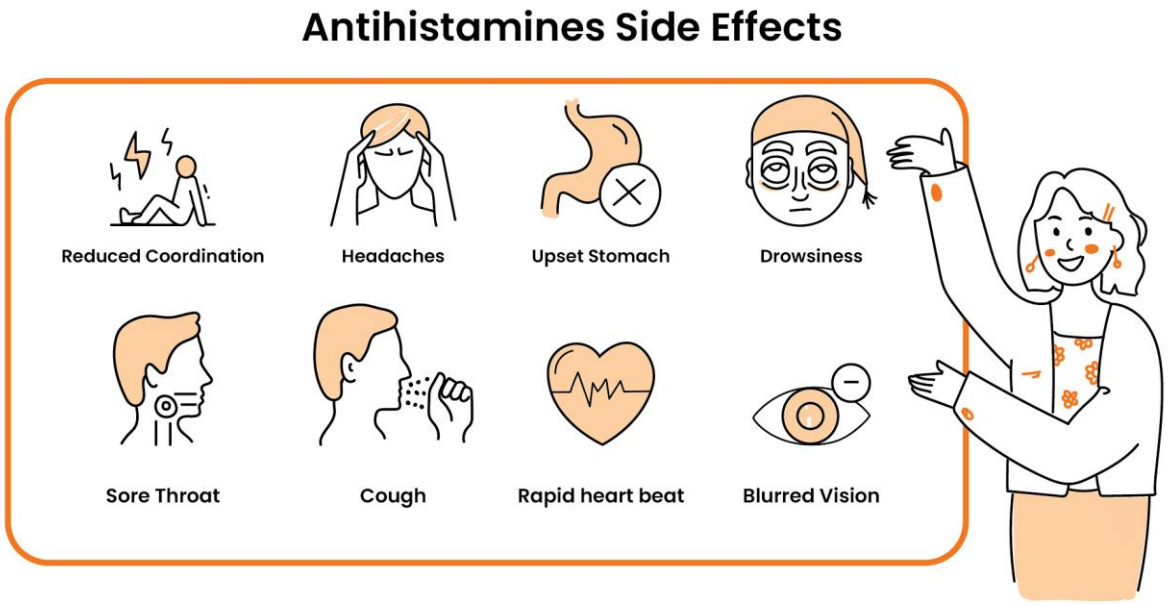


Histamine

Histamine is an excitatory neurotransmitter in the CNS.

It is synthesized in CNS from the amino acid histidine by histidine decarboxylase (requires PLP)

Antihistaminic drugs cause drowsiness, although new generations of antihistamines do not pass BBB and so do not cause CNS effects



Acetylcholine

Synthesis in CNS (in presynapses)

Choline acetyltransferase

Acetyl CoA + Choline ⟶ Acetylcholine

Acetylcholine:

- 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**

Cont.

- 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.

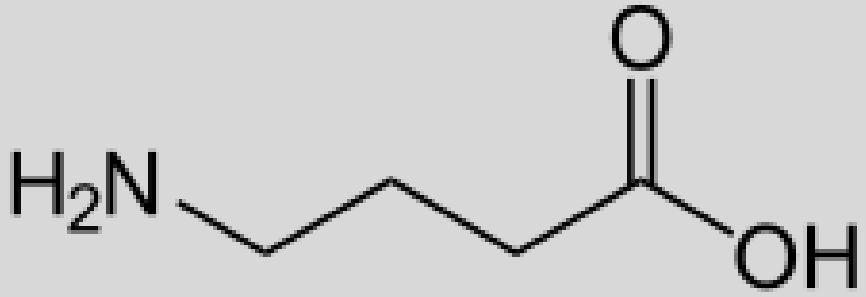
- Certain **neurotoxins** and **poisons** work by inhibiting **acetylcholinesterase**, thus leading to excess AC at the neuromuscular junction, causing **paralysis** of the muscles needed for **breathing** and stopping the **beating** of the heart.

Cont.

- Glutamate is the main excitatory neurotransmitter in the CNS
- **Sources of glutamate in nerve terminals**:
- Glucose (main source)
- Glucose $\longrightarrow$ α-Ketoglutarate $\rightleftharpoons$ Glutamate (Pyridoxal Phosphate).
- Glutamine by glutaminase (Mg^{2+}).

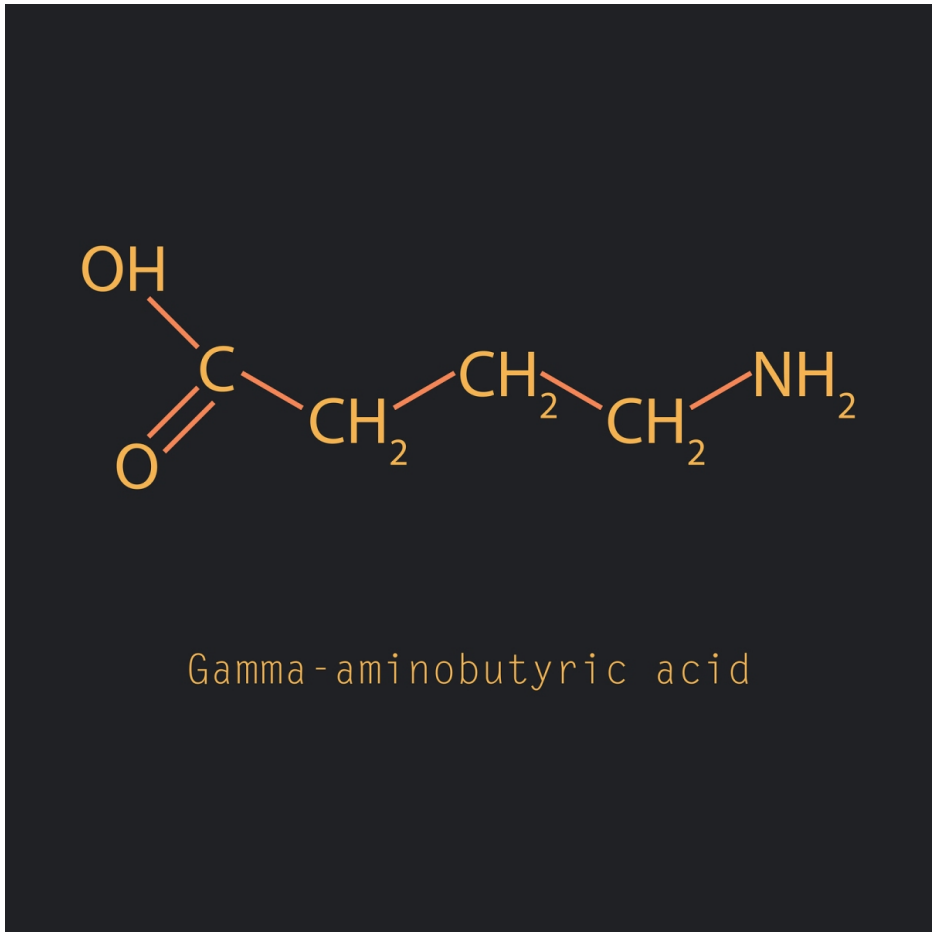
GABA

Gamma-aminobutyric acid (GABA) is an **inhibitory** neurotransmitter in the CNS.



In presynaptic neurons, GABA is synthesized from Glu by glutamate decarboxylase, which requires PLP

Termination: GABA in the synaptic cleft is uptaken by glial cells



Glutamate and GABA

- Glutamate is the main excitatory neurotransmitter in the CNS.
- Neurons that synthesise or respond to glutamate are referred to as glutaminergic neurons.
- Glutamate in nerve terminals is synthesized from glucose through glucose metabolism in neurons (Glucose – αKetoglutarate).
- It can also be synthesized from glutamine (of glial cells) by glutaminase

Interaction

- What are the common electrolytes that are involved in impulse transmission?
- State the main sources of neurotransmitters' precursors?
- Mention the three main processes that NTs undergo.
- What are the specific NTs synthesized from Tryptophan and Tyrosine?
- What are the biochemical uses of the NTs?
- Name the enzyme that synthesizes histamine from Histidine.
- What are the enzymes involved in Ach metabolism?
- What are the roles of Glucose at the nerve terminal?

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 sevenfold that of the other organs.
- There is a high requirement for **glucose** and **oxygen a**t a steady rate (**~20%**).
- The main source of energy is the generation of **ATP** by the **aerobic metabolism of glucose.**

Cont.

- The **brain** typically gets most of its energy from the oxygen-dependent metabolism of **glucose**
- **Ketones** provide a major alternative source, together with contributions from
- **Medium chain fatty acids :**
  - **Octanoic acid**
  - **Heptanoic**.
- **Lactate**, **acetate**, and **amino acids**

Hypoglycemia and Hypoxia

- **Deficiencies of either glucose or oxygen affect the brain function because they influence:**

- **ATP production for CNS neurons**
- **Supply of precursors for neurotransmitter synthesis.**

Clinical Manifestations Hypoglycemia

Early clinical signs of hypoglycemia are initiated by hypothalamic sensory nuclei such as **sweating, palpitations, anxiety, and hunger**.

In **late** stages, these symptoms give way to serious manifestations of **CNS disorders such** as **confusion, lethargy, seizures & coma**

Ammonia Toxicity in Brain

- **NH_3 is** produced by enteric bacteria and absorbed into **portal venous blood,** and the ammonia produced by tissues is rapidly removed from circulation by the **liver** and converted to **urea**.

- **NH_3** is toxic to the CNS.

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

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

Cerebral Ischemia

- **Cerebral ischemia**

• It is the potentially reversible altered state of brain physiology and biochemistry that occurs when substrate delivery is cut off or substantially reduced by vascular stenosis or occlusion stroke.

• is defined as “an acute neurologic dysfunction of vascular origin with sudden (within seconds) or at least rapid (within hours) occurrence of symptoms and signs corresponding to the involvement of focal areas in the brain.”

Cont.

- **Lack of oxygen supply to ischemic neurons**

- The cell switches to anaerobic metabolism, producing lactic acid.

- ATP depletion malfunctioning of membrane ion system Induction Phase Depolarization of neurons Influx of calcium Release of neurotransmitters as glutamate (causing glutamate excitotoxicity).

- Amplification Phase Accumulation of more intracellular levels of Ca^{2+} causes additional release of glutamate (vicious cycle)

Cont.

Oxidative stress is caused by ischemia

- Reactive oxygen species (ROS) are formed from the partial reduction of molecular O_2 i.e. adding electrons to oxygen leading to the formation of superoxide, hydrogen peroxide, and hydroxyl radical. Generally, ROS causes damage to DNA, protein, and unsaturated lipids of the cells.

Apoptosis and necrosis are caused by ischemia

- Necrosis: is commonly observed early after severe ischemic insults, while apoptosis occurs with more mild insults and with longer survival periods

- Mitochondria break down, releasing toxins and apoptotic factors into the cell. The caspase-dependent apoptosis cascade is initiated, causing cells to "commit suicide.


Questions
Comments
Feedback

Next Lecture

Enzymes of clinical importance (Enzymology)

References

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