BIOCHEMISTRY OF CSF AND NERVOUS SYSTEM II

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Advance Clinical Biochemistry II (MA 406)

Summer Semester

Lecture Four

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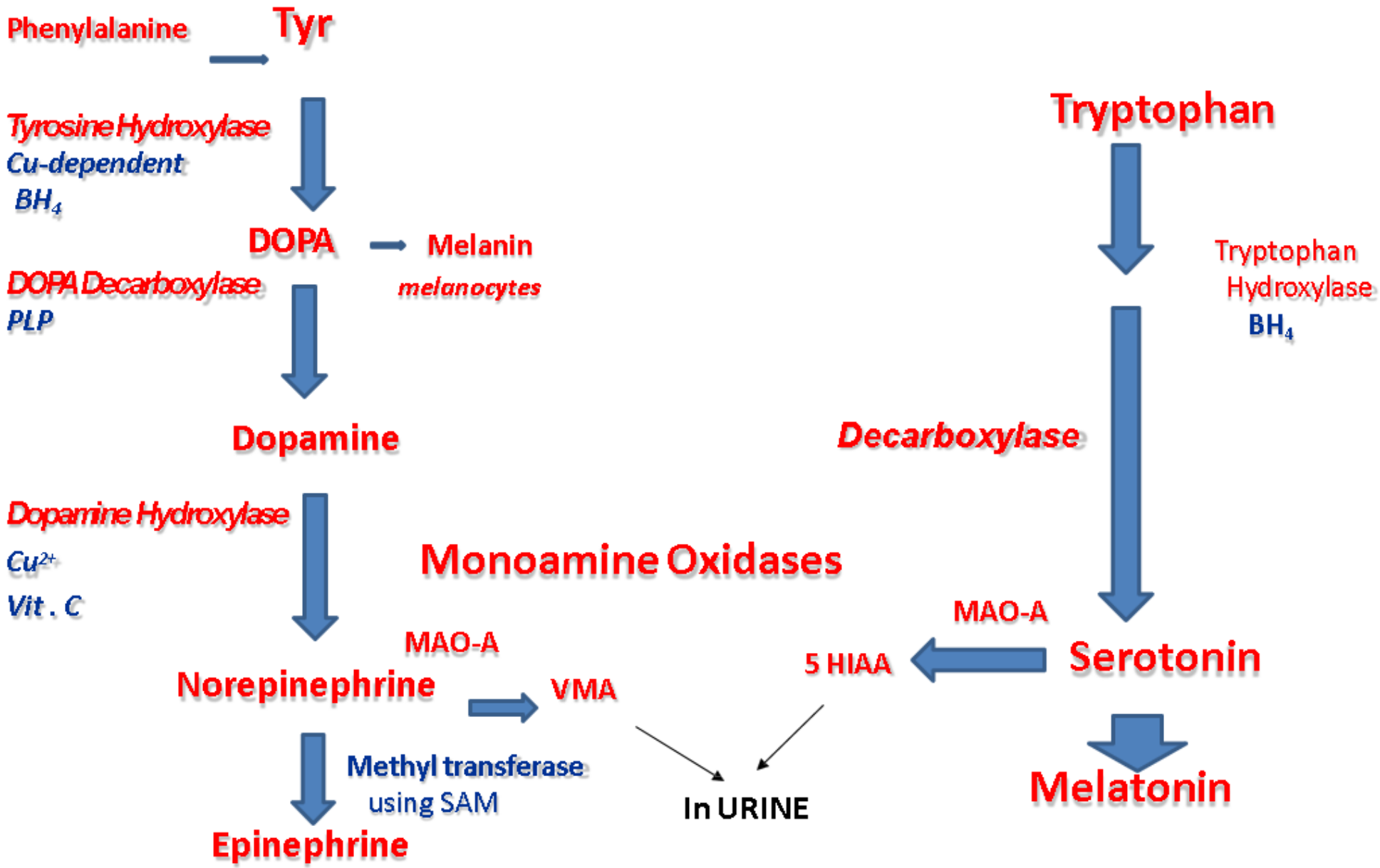
Outlines

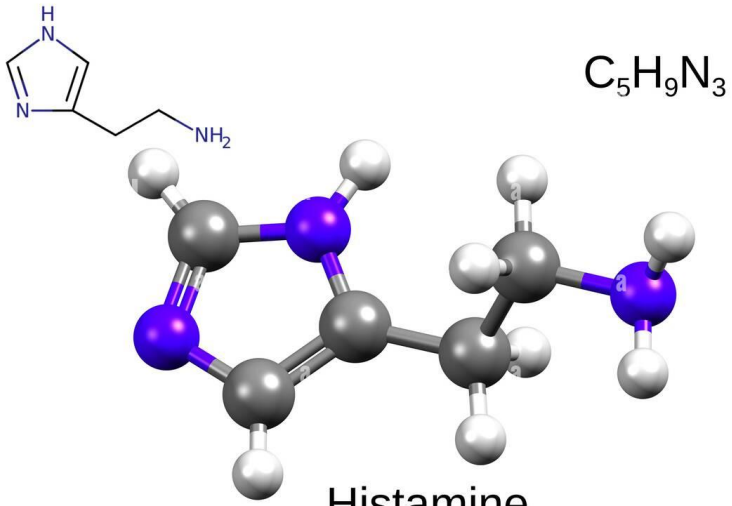
- Neurotransmitters:
- Synthesis release and termination
- Energy Source of CNS
- Biochemical aspects of CNS diseases
- Hypoglycemia
- Cerebral ischemia
- CSF chemical analysis

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

Catecholamines & Serotonin



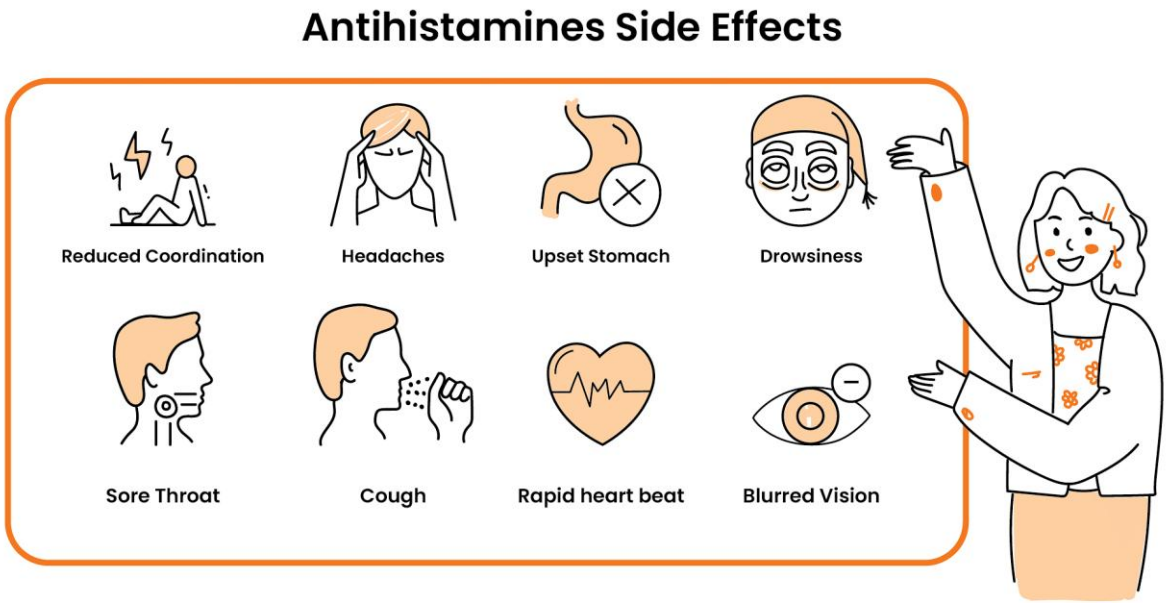


Histamine

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.

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**)

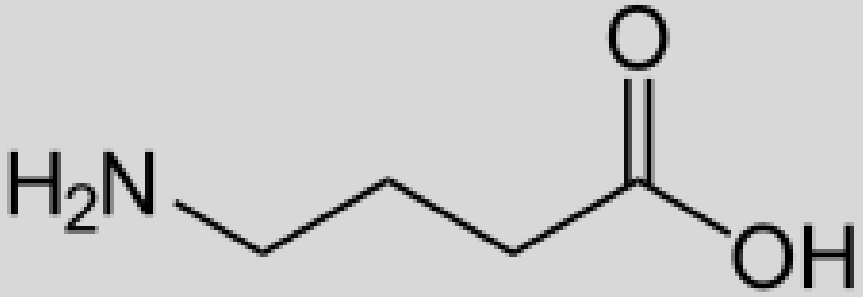
2- from **glutamine** by ***glutaminase*** (**Mn^{2+}**)

3- from **blood**

At the ***synaptic cleft*** **Glu is** reuptake by astrocytes, (**REQUIRES ATP**)

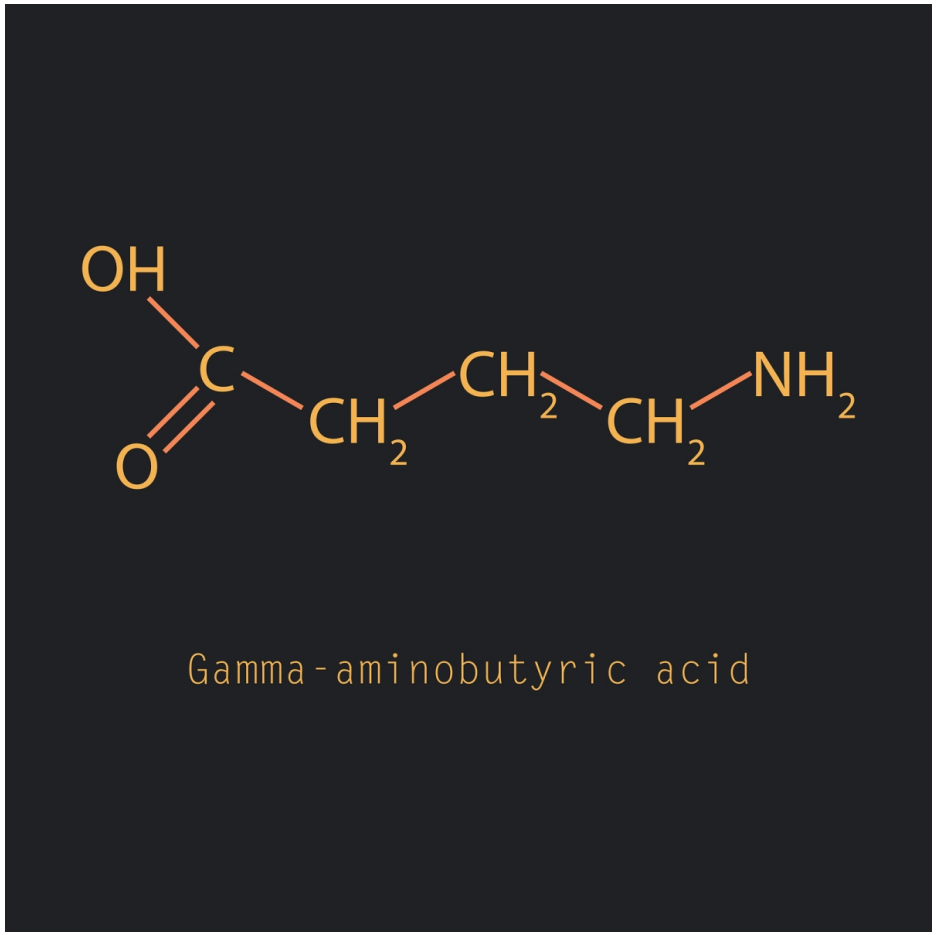
GABA

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

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

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 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 :**
  - **caprylic (octanoic acid)**
  - **heptanoic**.
- **Lactate**, **acetate**, and **amino acids**

Hypoglycemia and Hypoxia

- **Deficiencies of either glucose or oxygen affects the brain function because the 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 are rapidly removed from circulation by the **liver** and converted to **urea**.

- Only -10-20 µg/dL are normally present in peripheral **blood**.

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

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

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

Cont.

- **NH_3** can **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.
- The increased levels of **glutamine** lead to an increase in **osmotic pressure** in the astrocytes, which become swollen.
- .**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.
- Formation & secretion of **NH_3** maintains acid-base balance.

Hepatic encephalopathy

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.

What is meant by oxidative stress A condition in which cells are subjected to excessive levels of ROS (free radicals) & they are unable to counterbalance their deleterious effects with antioxidants

Cont.

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.

- The mechanism of cell death involves calcium-induced calpain-mediated proteolysis of brain tissue

- Substrates for calpain include Cytoskeletal proteins, Membrane proteins, Regulatory and signaling proteins.

Summary

- The lecture focuses on the biochemistry of the central nervous system (CNS), highlighting neurotransmitter synthesis, release, and termination, as well as the brain's unique energy requirements.

- It details key neurotransmitters such as acetylcholine, histamine, glutamate, GABA, catecholamines, and serotonin, explaining their synthesis pathways and clinical significance.

- The lecture also explores the brain's dependence on glucose and oxygen for ATP generation, with ketones and other substrates serving as alternative fuels under specific conditions.

- Clinical aspects discussed include hypoglycemia, ammonia toxicity, cerebral ischemia, and oxidative stress, emphasizing how disruptions in energy metabolism or neurotransmitter balance can lead to severe neurological impairments, including seizures, coma, and stroke-related damage through apoptosis and necrosis.

Questions for practice

- Analyze the energy metabolism of the brain, highlighting why glucose is the primary fuel source and how alternative substrates (e.g., ketones) contribute during metabolic stress.
- Examine the biochemical basis and clinical manifestations of hypoglycemia and ammonia toxicity in the brain.
- Explain the pathophysiology of cerebral ischemia, with emphasis on glutamate excitotoxicity, oxidative stress, and mechanisms of neuronal death.
- Evaluate the role of oxidative stress in CNS diseases, and discuss potential biochemical strategies to counterbalance reactive oxygen species in the brain.

Next lecture

Enzymes of clinical importance I

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Questions
Comments
Feedback