

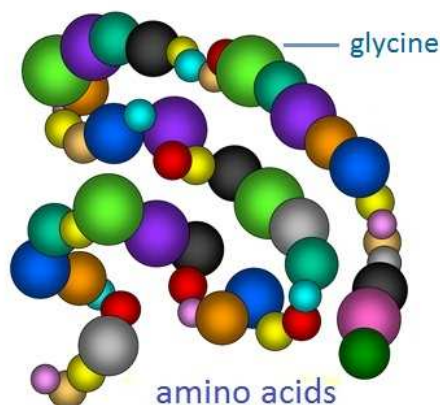
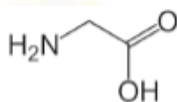
NON-KETOTIC HYPERGLYCINEMIA

WHAT IS NON-KETOTIC HYPERGLYCINEMIA?

Non-ketotic hyperglycinemia (NKH) is an **inborn error of glycine metabolism** that causes an accumulation of this amino acid in blood, urine, and brain. It is also known as **glycine encephalopathy** due to the severe disorder caused by glycine accumulation in the brain (encephalon).

WHAT IS GLYCINE?

Glycine is the simplest and most abundant amino acid which forms part of proteins (chains of amino acids). It is not essential in the human diet since we can produce it from other compounds, especially from another amino acid, **serine**.

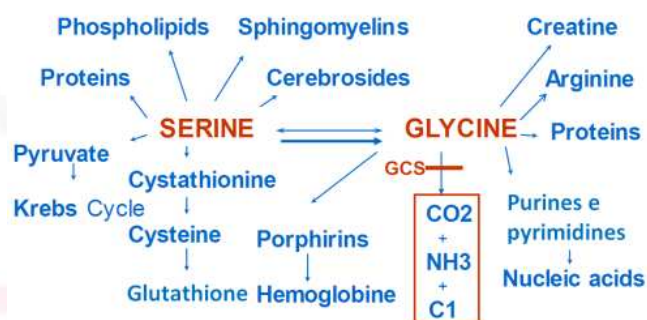


HOW IS GLYCINE METABOLIZED?

Glycine is formed from serine through an important reversible reaction.

Glycine degrades by means of a mitochondrial enzymatic complex located in the brain, liver and placenta which is composed by four proteins (P, H, T, and L) and is named the **glycine cleavage system (GCS)**. This system has a high metabolic importance since it produces methyl groups (C1) which can be given to other compounds.

Serine-glycine metabolism



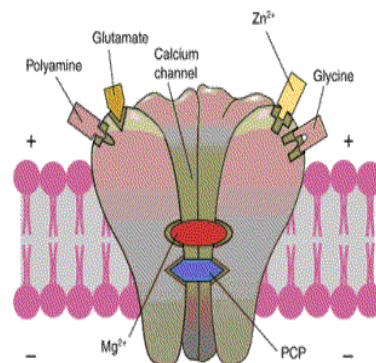
WHAT FUNCTIONS DOES GLYCINE HAVE?

Besides being a precursor of multiple compounds, glycine is a **brain neurotransmitter**.

WHAT IS A NEUROTRANSMITTER?

Neurotransmitters are chemical messengers that are released by neurons to communicate amongst each other. Some neurotransmitters cause the activation of the neurons that "receive them" (**excitatory neurotransmitters**), while others inhibit this activity (**inhibitory neurotransmitters**).

Glycine has a double function: on the one hand it is an **inhibitory neurotransmitter**, acting upon specific receptors in the brainstem and spine. On the other hand it is an **excitatory neurotransmitter, modulating the N-methyl-D-aspartate (NMDA) receptor** in the cerebral cortex. This NMDA receptor is actively involved in the development of the nervous system, brain plasticity, and also in the degenerative processes.



N-methyl-D-aspartate receptor

WHAT DOES A METABOLIC ERROR MEAN?

When an alteration (error) in the metabolism (set of enzymatic reactions that allow life) occurs, a metabolic process does not happen with the necessary efficacy and this can cause the accumulation of a toxic compound that, in this case glycine, which is a **neurotoxin**. These alterations have pathological consequences.

WHAT OCCURS IN A NON-KETOTIC HYPERGLYCINEMIA?

Non-ketotic hyperglycinemia can be caused by a **defect in one of the four enzymes of the GCS complex** involved in its cleavage.

WHY DOES A DEFICIENCY IN THE GCS COMPLEX ACTIVITY PRODUCE?

All the metabolic reactions that lead to compounds that make up our body are genetically (encoded) We all inherit from our parents the correct or altered information that will determine each of these metabolic processes.

The GCS complex deficiency can be caused by mutations (stable and heritable changes) in one of the four genes that encode the involved enzymes. NKH is inherited as an **autosomal recessive disease**, i.e. the parents carry one of the mutations in the involved genes, but they do not suffer the effects of this deficiency. If both parents transmit a mutation to their child, he/she will suffer from a **non-ketotic hyperglycinemia**.

WHAT OCCURS WHEN A BABY IS BORN WITH NON-KETOTIC HYPERGLYCINEMIA?

The first symptoms can occur at birth or in the first weeks of life, although the neurological damage could have started during gestation. The consequences of the inhibitory effect of glycine are **hypotonia, apnea, hiccup episodes, and an increase in deep tendon reflexes**. As a consequence of the excitotoxic effect of glycine, **seizures, intellectual disability, and alterations in brain development** appear. In general the development of the disease is fast, although exceptions exist.

Clinical features of NKH

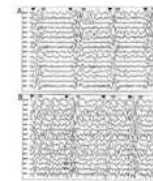


Neonatal:
hypotonia,
apnea,
hiccup,
hyperreflexia

Severe forms



Late-onset forms



seizures

WHAT ARE THE THERAPEUTIC CHANCES IN NON-KETOTIC HYPERGLYCINEMIA?

The patient needs to be diagnosed and treated as soon as possible. The diagnosis is based on an analysis of amino acids in plasma and cerebrospinal fluid in order to quantify the increase in glycine and to assess the relationship between the concentrations of this amino acid in both samples.

The treatment for non-ketotic hyperglycinemia is based on:

- a) Protein restriction.
- b) Removal of glycine excess by using oral sodium benzoate.
- c) Vitamins (folic acid and pyridoxine to stimulate the GCS complex).
- d) Dextromethorphan to limit excitotoxicity.

Non-ketotic hyperglycinemia may have serious consequences. Early diagnosis and symptomatic treatment can increase the quality of life of affected patients.

Translation

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