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# THE ORIGIN OF PHENYLKETUNURIA AND METHODS OF ITS TREATMENT

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**Annotation:** Phenylketonuria (PKU), hereditary inability of the body to metabolize the amino acid phenylalanine. Phenylalanine is normally converted in the human body to tyrosine, another amino acid, by a specific organic catalyst, or enzyme, called phenylalanine hydroxylase. This enzyme is not active in individuals who have phenylketonuria. As a result of this metabolic block, abnormally high levels of phenylalanine accumulate in the blood, cerebrospinal fluid, and urine. Abnormal products of phenylalanine breakdown, such as highly reactive ketone compounds, can also be detected in the urine.

**Key words:** Blood, phenylketonuriya, biochemistry,skin.

Excess phenylalanine and its abnormal metabolites interfere with various metabolic processes in the central nervous system that lead to decreased production of neurotransmitters (neuronal signaling molecules) such as dopamine. The first behavioral signs of nerve cell damage are usually evident in an affected child within four to six months of birth. Older individuals with phenylketonuria often have some degree of nerve demyelination (destruction of the myelin sheath that surrounds nerve fibres) that causes progressive symptoms of cognitive dysfunction, including mental retardation, epileptic seizures, and abnormal brain activity. The retention of phenylalanine in other tissues also leads to a decrease in the formation of melanin, a product of tyrosine metabolism that produces the pigment found in the skin, hair, and eyes. This may explain why persons with phenylketonuria generally have blond hair, blue eyes, and fair skin.

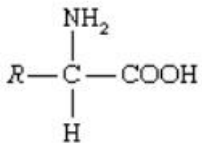
Phenylketonuria is transmitted by an autosomal recessive gene, which is present in about 1 in every 60 people. Statistically, two unaffected carriers of the gene can expect a 25 percent chance of having a child who is phenylketonuric, a 50 percent chance of having a child who is unaffected but is a carrier, and a 25 percent chance of having a completely normal child. Reliable tests are available to detect carriers of phenylketonuria, as well as infants who have the disorder. Approximately 1 in 12,000 to 15,000 newborn infants will show abnormally high plasma phenylalanine levels; out of these, about two-thirds will have the classic form of phenylketonuria.

The remainder of individuals affected by phenylketonuria have deficiencies in tetrahydrobiopterin (or BH4), a chemical cofactor required for phenylalanine hydroxylase activity. Autosomal recessive defects in enzymes that synthesize tetrahydrobiopterin or that restore its catalytic activity can lead to a general disorder called hyperphenylalaninemia, characterized by abnormally high levels of phenylalanine in the blood and urine. The symptoms of hyperphenylalaninemia include impaired cognitive function, seizures, and behavioral and developmental abnormalities that may become apparent within months of birth.

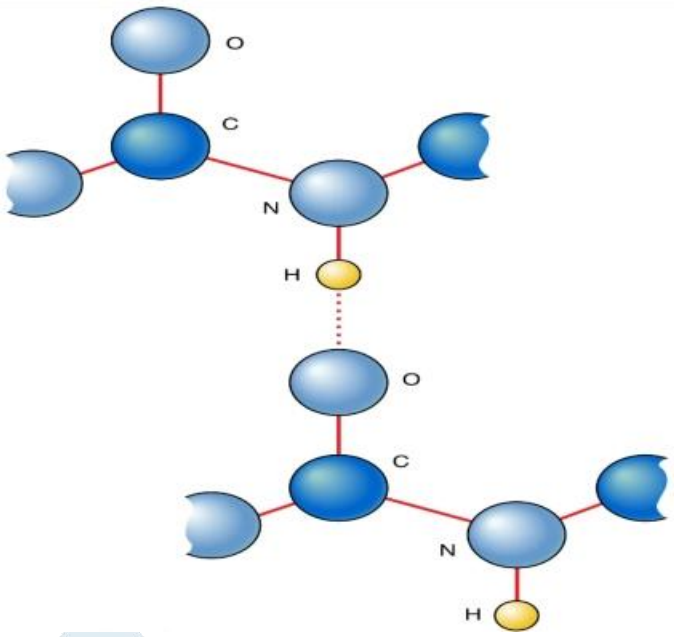
The most effective treatment of phenylketonuria is maintenance of a diet low in phenylalanine. Such a diet is achieved by avoiding meat, dairy, and other foods high in protein. Intake of nutrients normally supplied by these foods is provided instead by special phenylalanine-free amino acid drinks. In addition, a protein called glycomacropeptide (GMP), which is formed during cheese making and thus can be isolated from whey, contains only trace amounts of phenylalanine and can be purified to be phenylalanine-free. GMP can be used in solid foods, and studies have shown that individuals with phenylketonuria are better able to adhere to their strict dietary regimens when given the option to consume GMP-fortified foods in place of amino acid

drinks. These GMP foods also proved to be as safe and effective as traditional amino acid formulas. Pregnant women who have phenylketonuria must maintain a phenylalanine-restricted diet because the abnormally high levels of phenylalanine in their blood can severely damage an unborn child. While there are no drugs effective in treating classical phenylketonuria, a drug called Kuvan (sapropterin dihydrochloride), a synthetic form of tetrahydrobiopterin, is effective in treating some individuals with forms of hyperphenylalaninemia that are associated with deficiencies in tetrahydrobiopterin. Individuals taking Kuvan are instructed to remain on a phenylalanine-restricted diet.

Amino acid, any of a group of organic molecules that consist of a basic amino group (—$NH_2$), an acidic carboxyl group (—COOH), and an organic R group (or side chain) that is unique to each amino acid. The term amino acid is short for α-amino [alpha-amino] carboxylic acid. Each molecule contains a central carbon (C) atom, called the α-carbon, to which both an amino and a carboxyl group are attached. The remaining two bonds of the α-carbon atom are generally satisfied by a hydrogen (H) atom and the R group. The formula of a general amino acid is:




The amino acids differ from each other in the particular chemical structure of the R group.




Human body, the physical substance of the human organism, composed of living cells and extracellular materials and organized into tissues, organs, and systems.

Cerebrospinal fluid (CSF), clear, colourless liquid that fills and surrounds the brain and the spinal cord and provides a mechanical barrier against shock. Formed primarily in the ventricles of the brain, the cerebrospinal fluid supports the brain and provides lubrication between surrounding bones and the brain and spinal cord. When an individual suffers a head injury, the fluid acts as a cushion, dulling the force by distributing its impact. The fluid helps to maintain

pressure within the cranium at a constant level. An increase in the volume of blood or brain tissue results in a corresponding decrease in the fluid. Conversely, if there is a decrease in the volume of matter within the cranium, as occurs in atrophy of the brain, the CSF compensates with an increase in volume. The fluid also transports metabolic waste products, antibodies, chemicals, and pathological products of disease away from the brain and spinal-cord tissue into the bloodstream. CSF is slightly alkaline and is about 99 percent water. There are about 100 to 150 ml of CSF in the normal adult human body.

The exact method of the formation of the CSF is uncertain. After originating in the ventricles of the brain, it is probably filtered through the nervous-system membranes (ependyma). The CSF is continually produced, and all of it is replaced every six to eight hours. The fluid is eventually absorbed into the veins; it leaves the cerebrospinal spaces in a variety of locations, including spaces around the spinal roots and the cranial nerves. Movement of the CSF is affected by the downward pull of gravity, the continual process of secretion and absorption, blood pulsations in contingent tissue, respiration, pressure from the veins, and head and body movements.

Examination of the CSF may diagnose a number of diseases. A fluid sample is obtained by inserting a needle into the lumbar region of the lower back below the termination of the spinal cord; this procedure is called a lumbar puncture or spinal tap. If the CSF is cloudy, meningitis (inflammation of the central nervous system lining) may be present. Blood in the fluid may indicate a hemorrhage in or around the brain. Neuroglia, any of several types of cell that function primarily to support neurons. The term neuroglia means “nerve glue.” In 1907 Italian biologist Emilio Lugaro suggested that neuroglial cells exchange substances with the extracellular fluid and in this way exert control on the neuronal environment. It has since been shown that glucose, amino acids, and ions—all of which influence neuronal function—are exchanged between the extracellular space and neuroglial cells. For instance, after high levels of neuronal activity neuroglial cells can take up and spatially buffer potassium ions and thus maintain normal neuronal function. Neuroglia exceed the number of neurons in the nervous system by at least 10 to 1. Neuroglia exist in the nervous systems of invertebrates as well as vertebrates and can be distinguished from neurons by their lack of axons and by the presence of only one type of process. In addition, they do not form synapses, and they retain the ability to divide throughout their life span. While neurons and neuroglia lie in close apposition to one another, there are no direct junctional specializations, such as gap junctions, between the two types. Gap junctions do exist between neuroglial cells. Dopamine, a nitrogen-containing organic compound formed as an intermediate compound from dihydroxyphenylalanine (dopa) during the metabolism of the amino acid tyrosine. It is the precursor of the hormones epinephrine and norepinephrine. Dopamine also functions as a neurotransmitter—primarily by inhibiting the transmission of nerve impulses—in the substantia nigra, basal ganglia, and corpus striatum of the brain.

A deficiency of dopamine associated with cellular death in the substantia nigra results in Parkinson disease. Dopamine-receptor agonists, which bind to dopamine receptors on dopamine-producing neurons in the neurotransmitter’s absence, can increase dopaminergic activity in the brain, helping to lessen Parkinson symptoms.

Abnormalities in dopamine transmission, including hyperactive dopamine transmission in certain parts of the brain, have been linked to psychotic syndromes such as schizophrenia. Dopaminergic structures within the brain, such as the striatum and nucleus accumbens, have also been implicated in reward-related behaviour.

Apart from conventional histological and electron-microscopic techniques, immunologic techniques are used to identify different neuroglial cell types. By staining the cells with antibodies that bind to specific protein constituents of different neuroglia, neurologists have been able to discern four groups of neuroglia:

(1) astrocytes, subdivided into fibrous and protoplasmic types, (2) oligodendrocytes, subdivided into interfascicular and perineuronal types, (3) microglia, and (4) ependymal cells.

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