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Chapter

Role of Phenylalanine and Its Metabolites in Health and Neurological Disorders

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Abstract

Phenylalanine, an amino acid, is a "building block" of protein. Phenylalanine is a component of food sources and also derived through supplementation. In current treatment, phenylalanine is prescribed as anti-depressant agent. The present study reviewed the possible antidepressant potential of phenylalanine. We reviewed data using the major databases, namely, Web of Science, SciFinder, Google Scholar, and PubMed. This manuscript provides a brief overview of the role of phenylalanine in depressive disorders. Phenylalanine possesses anti-depressant potential. Significant anti-depressant activities have been studied both in-vitro and in-vivo models. Based on current data, phenylalanine could be recommended as a potential candidate for clinical anti-depressant trials. Phenylalanine hydroxylase (PAH) deficiency results in intolerance to the dietetic consumption of the phenylalanine and a variety of syndromes such as deep and permanent logical disability, impaired cognitive development.

Keywords: depression, phenylalanine, tyrosine, metabolic product of phenylalanine, diseases related to phenylalanine

1. Background

Phenylalanine is consumed either through food sources or through supplementation including wheat germ, oats, milk products, and meats. Phenylalanine is a fundamental amino corrosive and is convertible into tyrosine, however not the other way around. Transformation of phenylalanine to tyrosine is catalyzed by phenylalanine hydroxylase which is a blended capacity oxygenase [1]. Adrenaline, noradrenaline, and dopamine are subordinates of tyrosine. The transformation of tyrosine in dihydroxyphenylalanine (DOPA) is catalyzed by tyrosine hydroxylase. Decarboxylation of DOPA to dopamine is catalyzed by DOPA decarboxylase conversion of neither dopamine to nor epinephrine catalyzed by dopamine—beta-hydroxylase. Transformation of neither dopamine to nor epinephrine by transmethylation is catalyzed by phenylethanolamine-N-methyl transferase. The protein phenylethanolamine N-methyltransferase is prompted by glucocorticoids in the adrenal medulla, which acquires glucocorticoids from the adrenal cortex through entryway course in gigantic amounts. With the goal, that the adrenal medulla has

100 times a greater number of glucocorticoids than the plasma. α-Methy I—DOPA is a drug, which aggressively hinders the chemical DOPA decarboxylase, in this manner restrains the arrangement of catecholamine and is utilized as a part of the administration of hypertension. Adrenaline and noradrenaline are the hormones of the adrenal medulla and have a place with the gathering of mixes called catecholamine [2]. They are likewise discharged at postganglionic thoughtful nerve endings and go about as neurotransmitters [3]. Dopamine has imperative physiological properties, e.g., incitement of the myocardial contractility (inotropic activity). It is additionally a neurotransmitter in the focal sensory system and its inadequacy in the basal ganglia delivers additional pyramidal illness known as Parkinsonism [4]. Dopamine of the hypothalamic starting point additionally goes about as prolactin discharge restraining factor in the front pituitary organ.

1.1 Food sources

Food sources are lentils, chickpeas, pecans, soybeans, whole grains, sesame seeds, pumpkin seeds, peanuts, nuts, lima beans, cheese, cottage, corn, brewer's yeast, bananas, almonds, dairy products, and eggs [5].

1.2 Role of phenylalanine in the body

This supplement is necessary to the usual working of the central nervous system; particularly regarding manifestations like chronic pain and depression along with numerous other disorders that have been associated with the nervous system malfunction. It is involved in formation of neurotransmitters such as norepinephrine, epinephrine, and dopamine. Nervous system requires all these chemicals for proper functioning. As a nootropic, phenylalanine has numerous valuable properties improved motivation, increased concentration and focus, anxiety relief and mood enhancement [6].

1.3 Role in vitiligo

L-phenylalanine in combination with UVA exposure or application of L-phenylalanine in combination with UVA exposure to the skin appears to be useful in the treatment of vitiligo in children and adults [7].

1.4 Weight loss benefits

Phenylalanine regulates the discharge of the hormone cholecystokinin (CCK). Phenylalanine conveys signals to the brain that person is satisfied after eating. If someone is attempting to reduce some weight, incorporate supplementary diets that possess this essential amino acid into food. A person may feel more pleased after eating less.

1.5 Parkinson's disease

Restricted study recommends that administration of D-phenylalanine might reduce manifestations of Parkinson's disease [8].

1.6 Metabolic role of tyrosine

Metabolic products of tyrosine are tyrosine-O-sulfate, cresol, phenol, tyramine, melanin pigment, catecholamine, tri-iodotyrosine and thyroxine [9, 10].

1.7 Tyrosine becomes essential

Because the tyrosine can no longer be formed in phenylketonuria, it becomes an essential amino acid.

1.8 Development of melanin

It is the main color of the skin and is additionally present in the eye, even in the cerebrum (e.g., substantia nigra). In the skin, it is delivered by particular cells called melanocytes, which are located in the limit between the epidermis and dermis and in hair globules. Melanin is a co-polymer of dopa-quinine, indole 5, 6 quinone, and indole quinine 2—carboxylic corrosive in the proportion 3:2:1. It is delivered on the surface of intracellular granules called melanosomes, which are rich in the catalyst tyrosinase. It is exceedingly insoluble substance. Zinc particles are important for the melanin development. Arrangement of melanin is animated by light (e.g., tanning), ACTH and MSH. Nonappearance of Cu-containing protein tyrosinase (tyrosine hydroxylase) produces tyrosinase-negative oculocutaneous albinism. Human skin is presented to bright light that can harm the skin. Melanin keeps harm of skin from bright light [11].

1.9 Homogentisic acid

Homogentisic acid is a metabolite in the breakdown process of amino acids such as tyrosine and phenylalanine. In normal condition, it is not detected in urine and blood.

1.10 Homogentisic acid accumulation

In deficiency of homogentisic acid dioxygenase, homogentisic acid builds up in the blood and excretes in urine. When come in contact with air, homogentisic acid reacts with oxygen and cause the urine to become black. This is because of black pigment knows as alkapton and termed as alkaptonuria. This same black pigment in a procedure known as ochronosis causes bone and tissue to darken and degenerate. This causes disabling and painful joint disease called as osteoarthritis [12].

1.11 Alkaptonuria

It is an inborn error of metabolism, a genetic disorder caused by a deficiency of enzyme homogenetic acid dioxygenase. Without this enzyme, persons cannot break down the amino acids such as tyrosine and phenylalanine, which cause accumulation of homogentisic acid in urine, cartilage, and bone. The characteristics of Alkaptonuria are black urine, ochronosis (black cartilage and bone), and degenerative arthritis of the joint [13].

1.12 Homogentisic acid dioxygenase deficiency

The deficiency of homogentisic acid dioxygenase occurs due to the mutation in the homogentisic acid dioxygenase gene. It occurs in children when both father and mother are the carriers of mutated gene. This is known as autosomal recessive disease [14].

1.13 Hypopigmentation

Pigmentation loss is usually seen in patients with phenylketonuria due to reduction in amino acid tyrosine which is utilized by melanocytes to form melanin [15].

1.14 Catabolism of phenylalanine and tyrosine

Phenylalanine is changed over to numerous subsidiaries, which are discharged in pee. These incorporate phenyls lactic corrosive, phenyl acidic corrosive, ortho-hydroxyphenylpyruvic corrosive and ortho-hydroxyphenylacetic corrosive. In any case, this is ordinarily a minor pathway of phenylalanine and it turns out to be quantitatively more critical just when phenylalanine is not changed over to tyrosine, which is the real pathway of phenylalanine catabolism. The catabolic results of tyrosine incorporate homogentisic corrosive which is additionally separated to fumaric corrosive and acetoacetic corrosive [16].

1.15 Diseases associated with an abnormal metabolism of phenylalanine and tyrosine

1.15.1 Phenylketonuria

It is likewise called phenylpyruvic oligophrenia. It is because of absence of the chemical phenylalanine hydroxylase, which changes over phenylalanine to tyrosine. Phenylalanine is redirected to its ordinarily minor metabolic pathway framing para-hydroxy phenylpyruvic corrosive, para-hydroxy phenyl lactic corrosive, para-hydroxy phenyl acidic corrosive, and phenyl acetylglutamine all of which gather in the body alongside phenylalanine. These are discharged in pee in vast sums, which causes mental hindrance. The infection ought to be determined early because to have appropriate treatment (low phenylalanine abstains from food) the impediment of mental improvement can be halted. The best test is finding a raised blood level of phenylalanine. Nonetheless, it can likewise be analyzed prenatally (before birth) by DNA ponders as the quality for phenylalanine hydroxylase has been cloned. The name of the illness phenylketonuria is because of the discharge of parahydroxyphenyl pyruvic corrosive, which is a keto corrosive. This infection is currently gathered under the term hyperphenylalanemia of which there are numerous assortments [17].

1.15.2 Manifestation

Manifestations include psychiatric disorders, behavioral problems, delayed development, seizures, and intellectual disability, lighter hair, skin, musty, or mouse-like odor, microcephaly. Studies propose that untreated phenylketonuria in pregnancy is linked to attention-deficit hyperactivity disorder, intellectual disability, and microcephaly.

1.15.3 Musty or mousy body odor

Aromatic amino group is present in phenylketones, which is responsible for musty or mousy odor in patients which is feature for phenylketonuria [18].

1.15.4 Maternal PKU

Maternal PKU is developed when there is increased concentration of phenylalanine in a female's blood during gestation. This goes to the developing fetus. These high levels significantly enhance the danger for a baby to be born with behavioral problems, characteristic facial features, heart defects, growth retardation, and a small head size (microcephaly). For female with phenylketonuria, it is significant that they follow a low phenylalanine diet if they plan to develop expectant or are expectant. The bad effects of high levels of phenylalanine can be stopped if this diet is followed before conception and during the pregnancy [19].

1.15.5 Adults with PKU

Adults with PKU carry on taking care throughout whole life. Older adults with phenylketonuria who may have stopped the PKU food in their teens may advantage from an appointment with their physicians. Returning to the food may increase intellectual working and performance and gentle impairment to the central nervous system in adults with increased levels of phenylalanine [20].

1.15.6 Calcium homeostasis

Calcium homeostasis is vital for brain activity and its dysregulation in phenylketonuria was recommended by numerous studies. In this background, dehydrocholecalciferol, osteocalcin and parathyroid hormone were found enhanced in blood of infants with phenylketonuria, but level of calcitonin was low. These changes were not returned by Phenylalanine restricted food. In additional work, Yu and colleagues proved that Phenylalanine modifies intracellular free calcium levels by altering plasma membrane Ca^{2+}-ATPase in cortical neurons [21].

1.15.7 Diagnosis

Phenylketonuria is analyzed by examining the amino acids in the plasma. Screening programs have been introduced in numerous countries that permit identifying the illness in neonates within the first few days of birth. The objective of these recognition programs is to manage the babies prior to the initiation of exhibiting manifestations of the illness. Once identified, the children will be referred to a reference hospital for differential diagnosis with other less frequent forms of diseases, which can cause a rise of blood phenylalanine levels and initiate the management. The analysis of the PAH gene mutations approves the diagnosis [22].

1.15.8 Tracking pH levels

Children and young kids with phenylketonuria require having consistent blood tests for measurement of phenylalanine levels. If there is too much or too little phenylalanine in the blood, the formula and diet may require to be attuned [23].

1.15.9 Molecular testing

It is usually unnecessary for a diagnosis of phenylketonuria. However, restricted genotype-phenotype association has been designated. In addition, molecular testing is necessary for prenatal diagnosis [24].

1.15.10 Screening

Blood is taken from a 2-week-old infant to test for phenylketonuria [25]. Phenylketonuria is generally incorporated into the infant screening board of various nations, with various identification systems. Most infants in created nations are screened for phenylketonuria not long after birth. Screening for phenylketonuria is finished with bacterial hindrance test (Guthrie test), immunoassays utilizing fluorometric or photometric location, or amino corrosive estimation utilizing pair mass spectrometry (MS/MS) [26]. Estimations done utilizing MS/MS decide the grouping of phenylalanine and the proportion of phenylalanine to tyrosine, the proportion will be hoisted in phenylketonuria.

1.15.11 PKU carriers

Sisters and brothers who do not have phenylketonuria still have a chance to be carriers like their parents. Except in special cases, the carrier testing should be done merely in persons older than 18. Each of the parents' sisters and brothers has a 50% chance to be a carrier. It is significant for other family members to be said that they could be carriers. There is a minor chance they are also at danger to have offspring with phenylketonuria. When both parents are carriers, newborn screening outcomes are not adequate to rule out the disorder in a neonatal baby. In this situation, special investigative testing should be done in addition to newborn screening [27].

1.15.12 Foods to be avoided in phenylketonuria

Nuts, beans, eggs, dairy, meats, chocolate, ice cream, cheese, yogurt, regular bread, birthday cake, and pizza.

1.15.13 Management of phenylketonuria

Treatment ought to be begun as right on time as conceivable after birth. Phenylalanine is a basic amino corrosive and, in this manner, cannot be completely barred from the eating routine. Eating routine containing low phenylalanine with included tyrosine is suggested. Phenylalanine levels ought to be kept up between 6 and 9 mg%. Extremely serious limitation of phenylalanine prompts tissue breakdown. Strict limitation is suggested until eighth year of life. After this, confinement may not be so unbending [28].

1.15.14 Medical formula

Even though they require less phenylalanine, children with phenylalanine still require a definite quantity of protein. The medical formula gives children and the babies with phenylketonuria the protein and nutrients they require while keeping their phenylalanine amount within a nontoxic array. The dietician and metabolic physicians will tell you what kind of formula is greatest and how much to use. Administering a phenylketonuria formula for life is to make sure patient gets sufficient essential protein (without phenylalanine) and nutrients that are vital for general health and growth.

1.15.15 Foods that are allowed (excessive use is not allowed)

Fruits allowed include strawberries, apples, grapefruit, oranges, grapes, melons, bananas, and peaches. Vegetables allowed include tomatoes, radishes, lettuce, cucumber, celery, cauliflowers, carrots, and French beans.

1.15.16 Food not allowed

All meats including fish, fish products, chicken, bacon, pork, lamb, organ meats (liver, heart, kidney) and all dairy products including pudding, ice cream, yogurt, milk, cheese, cottage cheese, seeds, nuts, legumes, biscuits and flour cakes.

1.16 Prevention

1.16.1 Follow a low-phenylalanine diet

Female with phenylketonuria can inhibit birth defects by sticking to (or returning to) a low-phenylalanine diet prior to the becoming pregnant. Female with PKU should consult to physician prior to conception.

1.16.2 Prognosis

The consequence is predictable to be very good if the food is carefully monitored, beginning soon after the birth of child. If management is late or the disorder remains untreated, damage of brain will occur. School working may be slightly reduced. If proteins comprising phenylalanine are not evaded, phenylketonuria can lead to intellectual incapacity by the completion of the first year of life.

1.16.3 Hypertyrosinemia

It is because of the shortage of tyrosine aminotransferase [29].

1.16.4 Hereditary tyrosinemia

It occurs due to deficiency of fumarylacetoacetate hydrolase [30].

1.16.5 Alkaptonuria

This results from the lack of the enzyme homogentisate 1,2-dioxygenase. This leads to buildup in the body of homogenetisic acid, which is expelled in urine. Oxidation of homogentisic acid occurs that causes the urine to become dark. Patients with alkaptonuria are also affected with arthritis. This disease was discovered by Archibald Garrod in early 1900s. This was the major disorder in which an association between an enzyme and inheritable trait was established [31].

1.16.6 Attention deficit disorder

In the solitary double-blind, crossover study available in this part, quantities of up to DL-phenylalanine (1200 mg) were prescribed in 19 patients with attention deficit disorder. After 2 weeks, a substantial alteration in mood lability and mood was detected in the treatment cluster. After 2–4 months, however, patients who had improved with the use of DL-phenylalanine developed tolerant and did not respond to higher quantities [32].

1.16.7 Dopamine history

Dopamine was first made in 1910 by James Ewens and George Barger and at Wellcome Laboratories in London, England. In 1958, Nils-Åke Hillarp and Arvid Carlsson at the Laboratory for Chemical Pharmacology of the National Heart Institute of Sweden, found the dopamine work as a neurotransmitter. Arvid Carlsson was introduced the 2000 Nobel Prize in Medicine or Physiology for demonstrating that dopamine is not only an antecedent of epinephrine and norepinephrine however a neurotransmitter, too [33].

1.16.8 Role of dopamine in pain

Dopamine has an impact in handling of agony in various levels of the focal sensory system, for example, cingulate cortex, basal ganglia, thalamus, periaqueductal dark, and the spinal line. Diminished centralization of dopamine has been connected to excruciating signs that regularly saw in Parkinson's infection. Distortions in dopaminergic neurotransmission likewise occurs in various difficult clinical issue, for example, fretful legs disorder, fibromyalgia and consuming mouth disorder [34].

1.16.9 Drug-nutrient interactions

Phenylalanine has been revealed to contest with levodopa for passage through the blood-brain barrier [35]. Tyramine, dopamine, norepinephrine, epinephrine is derived from phenylalanine. Supposedly, attention is necessary with the concomitant use of phenylalanine and monoamine-oxidase inhibitors.

1.16.10 Side effects and toxicity

LD-50 of D-phenylalanine in rats is higher than 10 g/kg. No tissue toxicity was observed in murine studies at dose of 1 mg/kg daily for 6 months. Short time adverse effects are insomnia, aggressiveness, irritability, headache, and increase of blood pressure [32].

1.16.11 Dosage

Dosages differs with the disorder; 1–4 g daily for pain treatment and 1–14 g daily for depression.

1.16.12 Warnings and contraindications

Phenylalanine supplementation should be avoided in phenylketonuria [36]. Phenylalanine can affect efficacy and absorption of levodopa [37]. Phenylalanine use is contraindicated in patients with schizophrenia [38].

2. Research study

2.1 Impact of co-trimoxazole on phenylalanine metabolism in man

An investigation was completed to assess impact of co-trimoxazole on phenylalanine digestion. It was discovered that phenylalanine level stays high in the wake of taking co-trimoxazole. Proportion between serum-phenylalanine and tyrosine was likewise high. In a few patients, serum phenylalanine levels were marginally brought up in fasting conditions. As a conclusion, it was proposed that the trimethoprim/sulfamethoxazole blend has a synergistic activity in offending phenylalanine resistance [39].

2.2 An open study on phenylalanine in depressed patients

In a clinical trial, phenylalanine was regulated to 20 patients with gloom. Length of treatment was 20 days. Measurement of phenylalanine was 75–200 mg/day. Toward the finish of treatment, 12 patients were dealt with and there was no further need of treatment for these patients. Mellow to direct reaction was seen in 4 patients. Four patients did not react at all to phenylalanine. This examination shows that phenylalanine is significant in depressive patients [40].

2.3 Schizophrenia and blockage of dopaminergic neurotransmission

Phenylalanine is hydroxylated to tyrosine and tyrosine to dopa and dopa to dopamine. Dopamine has been embroiled for a long time in the pathophysiology of schizophrenia, and the run of the mill antipsychotics, by means of bar of dopaminergic neurotransmission, have furnished help for patients with positive

manifestations [41]. In any case, just dopamine blockage is not sufficient to ease manifestations of schizophrenia in the way it is viewed as those different neurotransmitters are additionally associated with pathophysiology of schizophrenia. Dopamine partiality for dopamine receptor is diminished by expanding adenosinergic transmission. Adenosine level might be expanded by presentation of allopurinol that is xanthine oxidase inhibitor, at last prompting antipsychotic and anxiolytic impacts. Confirmation for this treatment has been accounted for in both case reports and little clinical trials. Different investigations demonstrate that allopurinol is valuable in those patients who are ineffectively receptive to existing treatment for schizophrenia. Nevertheless, additionally study ought to be completed to discover its viability and wellbeing as a standard treatment for schizophrenia. In any case, exhibits think about demonstrate that allopurinol at 300 mg day by day is sufficient to assuage side effects of schizophrenia [42].

2.4 Impact of loading measurements of phenylalanine in unipolar discouraged patients with and without tardive dyskinesia (TD)

In a clinical trial, phenylalanine was managed to three distinct gatherings. Dosage of medication was 100 mg/kg phenylalanine. Eleven patients were in first gathering (discouraged patients with tardive dyskinesia). Ten patients were in second gathering (discouraged patient presented to neuroleptics yet without TD), 10 patients were in third gathering (patients never presented to NLs). There was no critical factual contrast among three gatherings. A relationship was found between automatic development and fasting, and phenylalanine stacking following 2 hours. Three TD patients indicated surprisingly expansive increments in phenylalanine level in plasma. This examination demonstrated that variations from the norm in digestion of phenylalanine add to the improvement and seriousness of TD in some NL-treated unipolar discouraged patients [43].

3. Conclusion

Phenylalanine hydroxylase (PAH) deficit consequences in intolerance to the dietetic consumption of the important amino acid phenylalanine and produces a variety of syndromes. The hazard of antagonistic consequence fluctuates based on the grade of PAH deficit. Deprived of effective management, maximum individuals with severe phenylalanine hydroxylase deficit, recognized as classic phenylketonuria, develop deep and permanent logical disability. Affected patients on an unrestricted food who have phenylalanine concentration above normal but below 1200 μmol/L (20 mg/dL) are at much lower hazard for impaired cognitive development in the lack of management. Phenylalanine is prescribed for alcohol withdrawal symptoms, vitiligo, weight loss, depression, rheumatoid arthritis, osteoarthritis, pain, multiple sclerosis, depression, Parkinson's disease and attention deficit-hyperactivity disorder.

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