

Homocysteine and Its Effects in Alzheimer's and Epilepsy

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ABSTRACT: *This report covers the basis and a brief study related to homocysteine and neurological disorders caused by homocysteine. Homocysteine is basically a type of amino acid found in the human blood. An abnormal state of homocysteine in blood causes endothelial cell damage in humans, which causes several issues in the body such as irritation in veins and atherogenesis which ultimately cause ischemic diseases. Hyperhomocysteinemia is subsequently a conceivable hazard factor for coronary supply route ailment. This report also includes the information related to various neurological disorders related to homocysteine, such as Alzheimer's and epilepsy. There are various treatments and diagnosis also related to such disease caused by homocysteinemia. Stroke and Alzheimer's disease (AD) frequently occur together. Hyperhomocysteinemia was linked to both histologically proven AD and disease progression in epidemiological investigations, and dementia in AD was linked to postmortem evidence of brain infarctions. Hyperhomocysteinemia and Alzheimer's disease may thus be connected via stroke or microvascular illness. Direct causative pathways are also possible, given the established links between B-group vitamin insufficiency and both hyperhomocysteinemia and neurological impairment.*

KEYWORDS: *Alzheimer, Amino Acids, Epilepsy, Homocysteine, Hyperhomocysteinemia.*

1. INTRODUCTION

Homocysteine is a non-proteinogenic α -amino acid. It is a homologue of the amino acid cysteine, differing through a further methylene bridge (-CH₂-). It's miles biosynthesized from methionine by means of the removal of its terminal C ϵ methyl group. Homocysteine can be recycled into methionine or converted into cysteine with the useful resource of certain B-nutrients. A high level of homocysteine inside the blood (hyperhomocysteinemia) makes a person greater susceptible to endothelial cellular injury, which ends up in infection inside the blood vessels, which in flip may cause atherogenesis, that could bring about ischemic damage. Hyperhomocysteinemia is consequently a probable chance thing for coronary artery disease. Coronary artery disease takes place while an atherosclerotic plaque blocks blood go with the flow to the coronary arteries, which deliver the heart with oxygenated blood. Hyperhomocysteinemia has been correlated with the occurrence of blood clots, coronary heart attacks and strokes, although it's far doubtful whether hyperhomocysteinemia is an unbiased danger aspect for these conditions Hyperhomocysteinemia has also been associated with early being pregnant loss and with neural tube defects [1], [2].

1.1 Structure of Homocysteine:

Homocysteine exists at neutral pH values as a zwitterion of homocysteine's foremost biochemical roles. (Homocysteine is visible in the left center of the photograph.) It could be synthesized from methionine after which transformed back to methionine through the SAM cycle or used to create cysteine and alpha-ketobutyrate. Homocysteine isn't received from the food plan. As an opportunity, it is biosynthesized from methionine via a multi-step method. First, methionine receives an adenosine group from ATP, a response catalyzed by way of S-adenosyl-methionine

synthetase, to offer S-adenosyl methionine (SAM). SAM then transfers the methyl agency to an acceptor molecule, (e.g., norepinephrine as an acceptor at some point of epinephrine synthesis, DNA methyltransferase as an intermediate acceptor in the procedure of DNA methylation). The adenosine is then hydrolyzed to yield L-homocysteine. L-Homocysteine has two primary fates: conversion thru tetrahydrofolate (THF) again into L-methionine or conversion to L-cysteine. Homocysteine isn't received from the food plan. as an opportunity, it is biosynthesized from methionine via a multi-step method. First, methionine receives an adenosine group from ATP, a response catalyzed by way of S-adenosyl-methionine synthetase, to offer S-adenosyl methionine (SAM). SAM then transfers the methyl agency to an acceptor molecule, (e.g., norepinephrine as an acceptor at some point of epinephrine synthesis, DNA methyltransferase as an intermediate acceptor in the procedure of DNA methylation).

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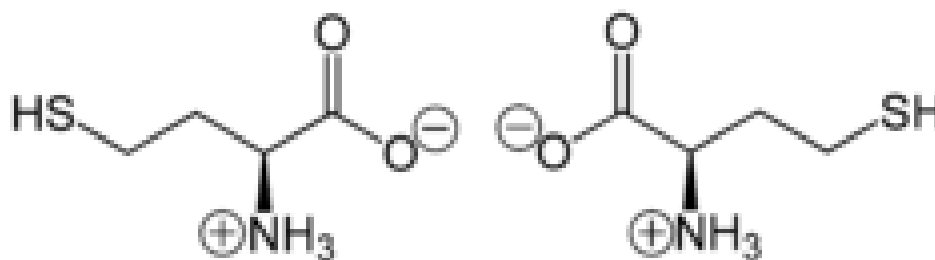


Figure 1: Zwitterionic form of (S)-homocysteine (left) and (R)-homocysteine (right)

1.2 Homocysteine ranges:

1.2.1 Factors controlling homocysteine ranges: Elevations in plasma homocysteine stages end result from a complicated interaction of received and genetic elements. Most of the obtained elements, quantitatively, the most important is the relative deficiency of folate, vitamins B6, and weight loss plan B12. Selhub alhave envisioned that thirds of the times of hyperhomocysteinemia (measured in randomly acquired samples) are because of quite low levels of these vitamins. Epidemiologically, the diet with ranges which may be most inversely correlated to hyperhomocysteinemia is folate.2Folate consumption has these days extended substantially inside the u.s.. thinking about that January 1, 1998, america food and Drug management has required that

each one enriched flour, rice, pasta, cornmeal, and one-of-a-kind grain products incorporate at the least one hundred forty μg of folate regular with a hundred g. This stage of fortification, which became chosen with the purpose of stopping neural tube defects, is predicted to growth the dietary folate intake of most adults with the useful resource of a hundred $\mu\text{g}/\text{d}$. How this low degree of fortification can have an impact on homocysteine degrees in sufferers at risk for vascular sickness isn't absolutely recounted. Malinow et al, studying patients at risk for vascular illness, located that stages of supplementation within the order of 500 $\mu\text{g}/\text{d}$ had been required to achieve sizeable discounts. However, Jacques et al found that nutrition fortification decreased homocysteine degrees thru 7% internal the trendy population and that the percentage of subjects with homocysteine stages extra than thirteen $\mu\text{mol}/\text{L}$ decreased via almost 50%. The impact of folate supplementation of food on PML homocysteine degrees has not been studied[1], [4], [5].

1.2.2 Other Obtained factors: After eating regimen concentrations, the issue maximum intently associated with extended homocysteine ranges is antique age. Homocysteine stages are specifically strong through the first 4 a few years of life after which rise sharply, mainly after age 70. Male sex is associated with better homocysteine levels at each age except in the very vintage. Pregnancy lowers homocysteine stages, and estrogen alternative therapy in postmenopausal ladies consequences in substantially decreased homocysteine levels. Renal insufficiency markedly increases homocysteine tiers, 25 both thru decreased clearance or slower metabolism of homocysteine. espresso intake of four or extra cups in line with day additionally increases homocysteine ranges,26 even as protein intake of extra than seventy five g/d lowers fasting homocysteine ranges.26 capsules including methotrexate, 6-azauridine, nicotinic acid, and bile acid sequestrants purpose elevations in homocysteine stages. Of unique importance to neurologists, intrathecal methotrexate has been related to marked elevations of homocysteine degrees in the cerebrospinal fluid, that's related to remedy-added on leukoencephalopathy. furthermore, most classic anticonvulsants beautify homocysteine ranges, as referred to in extra detail under[4]–[6].

1.2.3 Genetic factors Controlling Homocysteine levels: Intense homocysteinemia with homocystinuria turned into first diagnosed in instances of unusual inborn mistakes of metabolism characterised with the resource of marked elevations of plasma and urine homocysteine concentrations. The most not unusual of those is the deficiency of CBS, the homozygous shape of which occurs in about 1 in 2 hundred,000 live births and is associated with fasting plasma homocysteine concentrations of up to two hundred $\mu\text{mol}/\text{L}$. medical manifestations encompass mental retardation, thromboembolism, seizures, premature atherosclerosis, skeletal deformities, and ectopialentis. The heterozygote nation is expected to rise up in 1% to two% of the population, and people sufferers have moderate elevations of fasting homocysteine (commonly 20–30 $\mu\text{mol}/\text{L}$), but current epidemiologic studies recommend that they're at prolonged chance for untimely atherosclerosis. Intense homocysteinemia with homocystinuria turned into first diagnosed in instances of unusual inborn mistakes of metabolism characterised with the resource of marked elevations of plasma and urine homocysteine concentrations. The most not unusual of those is the deficiency of CBS, the homozygous shape of which occurs in about 1 in 2 hundred,000 live births and is associated with fasting plasma homocysteine concentrations of up to two hundred $\mu\text{mol}/\text{L}$. medical manifestations encompass mental retardation, thromboembolism, seizures, premature atherosclerosis, skeletal deformities, and ectopialentis. The heterozygote nation is expected to rise up in 1% to two% of the population, and people sufferers have moderate elevations of fasting

homocysteine (commonly 20-30 $\mu\text{mol/L}$), but current epidemiologic studies recommend that they're at prolonged chance for untimely atherosclerosis[4], [7], [8].

1.3 Accelerated homocysteine: Extreme homocysteinemia with homocystinuria was first identified in times of uncommon inborn errors of metabolism characterized with the useful resource of marked elevations of plasma and urine homocysteine concentrations. The maximum common of these is the deficiency of CBS, the homozygous form of which occurs in approximately 1 in two hundred,000 stay births and is related to fasting plasma homocysteine concentrations of up to 2 hundred $\mu\text{mol/L}$. clinical manifestations embody mental retardation, thromboembolism, seizures, untimely atherosclerosis, skeletal deformities, and ectopialentis. The heterozygote nation is anticipated to arise in 1% to two% of the population, and people sufferers have mild elevations of fasting homocysteine (usually 20-30 $\mu\text{mol/L}$), but modern-day epidemiologic studies recommend that they may be at extended hazard for untimely atherosclerosis. Abnormally high levels of homocysteine inside the serum, above 15 $\mu\text{mol/L}$, are a medical situation known as hyperhomocysteinemia. This has been claimed to be a considerable chance element for the development of a wide variety of illnesses, along with thrombosis, neuropsychiatric illness, and fractures.

It is also discovered to be associated with microalbuminuria that is a sturdy indicator of the chance of future cardiovascular ailment and renal dysfunction. Vitamin B12 deficiency, when coupled with high serum folate degrees, has been discovered to increase typical homocysteine concentrations as well. Extreme homocysteinemia with homocystinuria was first identified in times of uncommon inborn errors of metabolism characterized with the useful resource of marked elevations of plasma and urine homocysteine concentrations. The maximum common of these is the deficiency of CBS, the homozygous form of which occurs in approximately 1 in two hundred,000 stay births and is related to fasting plasma homocysteine concentrations of up to 2 hundred $\mu\text{mol/L}$. clinical manifestations embody mental retardation, thromboembolism, seizures, untimely atherosclerosis, skeletal deformities, and ectopialentis. The heterozygote nation is anticipated to arise in 1% to two% of the population, and people sufferers have mild elevations of fasting homocysteine (usually 20-30 $\mu\text{mol/L}$), but modern-day epidemiologic studies recommend that they may be at extended hazard for untimely atherosclerosis[6]–[9].

1.4 Hyperhomocysteinemia: Hyperhomocysteinemia is a scientific circumstance characterised by way of an abnormally excessive level of homocysteine within the blood, conventionally described as above 15 $\mu\text{mol/L}$ because of the biochemical reactions in which homocysteine is involved, deficiencies of food plan B6, folic acid (weight-reduction plan B9), and diet B12 can lead to excessive homocysteine ranges. Hyperhomocysteinemia is usually managed with nutrition B6, nutrition B9 and nutrition B12 supplementation. Hyperhomocysteinemia is a danger element for cardiovascular ailment; but, dietary supplements of these vitamins do now not enhance cardiovascular disease consequences[6], [7], [10].

1.5 Homocysteine and Neurologic Illness: In 1969, McCully said the autopsy findings of a 7-week-antique little one who died because of very excessive plasma levels of homocysteine, because of an exceptional disorder within the cblCgene in the nutrients B12 (cyanocobalamin) metabolic pathway. At post-mortem, the toddler's arteries exhibited advanced atherosclerotic lesions, with pathologic functions that reminded McCullyof vascular lesions visible in youngsters with homocystinuria due to cystathionine β -synthase (CBS) deficiency. for the cause that 2 inborn

errors of metabolism had in common marked elevations in homocysteine degrees but differed within the eye of methionine (low in cblC but excessive in CBS deficiency) and cystathionine (excessive cblC however low in CBS deficiency), McCully hypothesized that "the arterial damage discovered in affiliation with each illnesses is attributed to the metabolic results of accelerated concentrations of homocysteine, homocystine, or a spinoff of homocysteine."¹ This hypothesis modified into in massive element ignored for 20 years, but over the last decade, a wealth of epidemiologic proof has made it obvious that even slight elevations in plasma homocysteine degrees, in the sort of 15 to 20 $\mu\text{mol/L}$, are a commonplace and an vital chance factor for vascular sickness.² given that extended homocysteine in principle is extra easily treatable (with nutrition supplements) than other vascular hazard factors (consisting of diabetes mellitus, excessive blood stress, hyperlipidemia, and smoking, which regularly require pharmacologic intervention), the ones observations have generated a first-rate deal pleasure in the scientific community further to in the lay press and the net.

The conclusion that homocysteine is a danger element for vascular ailment coincided with observations to start with made by using Lindenbaum et al that homocysteine (alongside methylmalonic acid) changed into a touchy indicator of subtle vitamin B12 deficiency in patients presenting with dementia, psychosis, ataxia, or neuropathy. The probability that prolonged homocysteine ranges play a position in different, more typically taking vicinity dementias has obtained interest in some unspecified time in the future of the beyond decade.

The purpose of this review is to speak about the abilities of homocysteine metabolism and the epidemiologic factors which may be applicable to scientific neurologists. First, we in short assessment homocysteine metabolism and the acquired and genetic conditions resulting in hyperhomocysteinemia. 2nd, we can examine the statistics linking multiplied homocysteine degrees to cerebrovascular disorder and talk therapeutic interventions aimed closer to decreasing homocysteine ranges. 0.33, we will assessment the trendy reviews linking increased homocysteine tiers with dementia. ultimate, we are capable of in short overview the significance of homocysteine metabolism in patients with epilepsy[3], [4], [6], [7], [10].

2. DISCUSSION

2.1 Homocysteine in Epilepsy:

Systemic management of excessive doses of homocysteine in animals produce convulsive seizures, a reality that has been exploited in models of experimental epilepsy. Furthermore, as lots as 20% of sufferers with homozygous CBS deficiency have seizures, and the excessive plasma concentrations of homocysteine in those patients (typically 50-200 $\mu\text{mol/L}$) may additionally make contributions to epilepsy. Whether or not a good deal much less intense hyperhomocysteinemia (15-20 $\mu\text{mol/L}$) predisposes patients to epilepsy has not been hooked up. Homocysteine relates to two extra critical troubles within the control of sufferers with epilepsy. First, maximum anticonvulsants lower plasma folate tiers, and as a end result, nearly 1/2 of sufferers dealt with with anticonvulsants had homocysteine stages sufficiently accelerated to place them at immoderate hazard for vascular disease. Arteriosclerosis is an important problem for patients requiring lengthy-time period anticonvulsant treatment, mainly given the developing prevalence of epilepsy in older age corporations.

The effectiveness of polyvitamin treatment in lowering homocysteine tiers inside the setting of anticonvulsant use has not been at once studied. A 2nd problem relates to putative teratogenic consequences of immoderate homocysteine degrees. There may be an improved risk of most important congenital malformations in kids whose moms acquire anticonvulsants at some stage in the primary trimester. At the same time as the mechanism of teratogenicity in folate deficiency is doubtful, present day statistics implicate elevations in homocysteine. First, fasting or PML hyperhomocysteinemia is generally determined in women who have given starting to toddlers with neural tube defects. 2nd, the C677T mutation inside the MTHFR gene drastically will growth the risk of neural tube defects. Ultimately, amniotic fluid homocysteine stages were found to be significantly better in pregnancies complicated via neural tube defects. Observations consisting of those precipitated an exercise parameter recently promulgated with the useful resource of the yankee Academy of Neurology, recommending that each one girls of childbearing capability who're taking anticonvulsants eat at least 0.4 mg/d of folic acid. whether or not this or higher doses of folic acid are effective in lowering homocysteine levels or in decreasing the occurrence of neural tube defects in epileptic girls has now not been studied. It's also doubtful whether cyanocobalamin and pyridoxine hydrochloride dietary dietary supplements are necessary for this population. A 2nd problem relates to putative teratogenic consequences of immoderate homocysteine degrees. There may be an improved risk of most important congenital malformations in kids whose moms acquire anticonvulsants at some stage in the primary trimester.

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- *Epilepsy:* Epilepsy is a vast frightened gadget (neurological) sickness in which mind hobby becomes extraordinary, causing seizures or durations of unusual conduct, sensations, and once in a while loss of consciousness. Every person can develop epilepsy. Epilepsy influences every women and men of all races, ethnic backgrounds and a while. Some humans with epilepsy truly stare blankly for some seconds in some unspecified time in the future of a seizure, while others again and again twitch their palms or legs[1], [2], [7].
- *Signs and Symptoms:*
 Seizure symptoms and signs and symptoms and signs and symptoms and signs may encompass:
 - Brief confusion
 - A staring spell

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- Uncontrollable jerking moves of the legs and arms
 - loss of attention or awareness
 - Psychic signs and symptoms which includes fear, tension[5], [7], [9].
 - *Types of seizeres:*
 - Tonic seizures. Tonic seizures motive stiffening of your muscular tissues. these seizures commonly affect muscular tissues on your again, legs and arms and can motive you to fall to the floor.
 - Atonic seizures. Atonic seizures, also called drop seizures, motive a lack of muscle manage, which may additionally cause you to abruptly collapse or give way.
 - Clonic seizures. Clonic seizures are associated with repeated or rhythmic, jerking muscle moves. Those seizures commonly affect the neck, face and hands.
 - Myoclonic seizures. Myoclonic seizures generally seem as unexpected quick jerks or twitches of your arms and legs.
 - Tonic-clonic seizures. Tonic-clonic seizures, previously called grand mal seizures, are the most dramatic form of epileptic seizure and might cause an abrupt lack of focus, body stiffening and shaking, and now and again loss of bladder manage or biting your tongue[1], [5], [7], [9].

- *Treatment:*

Epilepsy medicines, on occasion known as anti-seizure or anticonvulsant medications, exchange the way your mind cells paintings and ship messages to each other. The kind of medicine your health practitioner shows relies upon on some things: The type of seizures you've got:

- How probable it is you'll have extra seizures
- Your age
- Your sex
- Different medical situations you have
- In case you need to get pregnant.

2.2 Homocysteine and Alzheimer's sickness:

Alzheimer's sickness, Dementia and Homocysteine one of the maximum thrilling factors of the component approximately the "puzzling trouble" of Alzheimer's ailment thru Chinthapalliis the truth that in a thirteen yr period, out of 101 drugs tested satisfactory 3 reached market, each with minimal therapeutic results. Many previous studies exhibit a relationship among Alzheimer's dementia and the spectrum of cardiovascular ailments, which incorporates stroke, an traditional chance element for Alzheimer's ailment. Alzheimer's illness and cardiovascular diseases percentage a common danger detail, improved blood degrees of homocysteine, an amino acid which becomes increased via insufficient nutritional intakes of vitamins B2, B6, B9 (folate) and B12. Multivitamins reliably lower homocysteine in most if not all; they're the only "remedy".

There may be epidemiological evidence for every a declining dementia / Alzheimer's disease epidemic and for advanced stroke deaths given that folate food fortification. The authors of the Framingham study concluded that homocysteine is "a robust, unbiased danger difficulty for the improvement of dementia and Alzheimer's disease", a announcement based totally at the finding

of an almost doubled fee of dementia in the maximum quartile of plasma homocysteine. Current facts display that B-nutrition supplementation surely halts gray be counted atrophy in regions of the mind related to Alzheimer's ailment even as slowing a few cognitive decline. these observations assist the idea that blood homocysteine and the B nutrients that have an impact on the extent of homocysteine are in all likelihood causal and modifiable threat factors. furthermore, the ones parameters should be decided in future research as confounding chance elements regarding Alzheimer's ailment[1], [3], [5], [7], [9].

- *Alzheimer's Disorder:* Alzheimer's disease is a modern-day illness that reasons brain cells to degenerate and die. it is the number one cause of dementia a non-forestall decline in thinking, behavioral and social abilities that disrupts a person's capacity to feature independently .there's no remedy that remedy plans Alzheimer's illness or alters the illness procedure inside the mind. In superior ranges of the ailment, headaches from intense lack of thoughts feature inclusive of dehydration, malnutrition or contamination as a result bring about lack of existence[1], [4].

3. CONCLUSION

As soon as recognized, you ought to alternate your diet to lower your homocysteine tiers. if you have a food regimen deficiency, you could growth your weight loss program B intake and folic acid by using consuming folate-wealthy meals collectively with inexperienced vegetables, orange juice, and beans. In some times, doctors can also prescribe each day vitamins dietary supplements. When you start treatment, you have to have your homocysteine tiers rechecked inside two months. If your homocysteine stages are nonetheless excessive after taking the ones dietary supplements, your medical doctor can also additionally prescribe medicines with higher levels of folic acid and weight loss plan B. When you have superior hyperhomocysteinemia as a symptom from other health conditions, remedy will cognizance on the underlying circumstance. Even as it's viable to lower high homocysteine stages, there's now not enough research to decide whether or not or now not remedy can save you associated illnesses. If identified with hyperhomocysteinemia, speak your remedy alternatives alongside your doctor. proper remedy and a few lifestyle changes can help to make sure a better wonderful of life[4], [6], [9], [10].

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