Homocysteine

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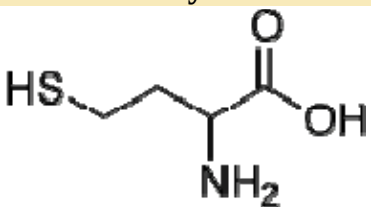
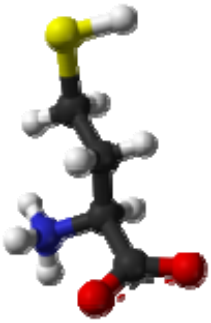




IUPAC name[hide]
2-Amino-4-sulfanylbutanoic acid

Homocysteine is an amino acid with the formula $HSCH_2CH_2CH(NH_2)CO_2H$. It is a homologue of the amino acid cysteine, differing by an additional methylene (-CH_2-) group. It is biosynthesized from methionine by the removal of its terminal C^{ε} methyl group. Homocysteine can be recycled into methionine or converted into cysteine with the aid of B-vitamins.

While detection of high levels of homocysteine has been linked to cardiovascular disease, lowering homocysteine levels may not improve outcomes.[1]

Structure

Homocysteine exists at neutral pH values as a zwitterion.

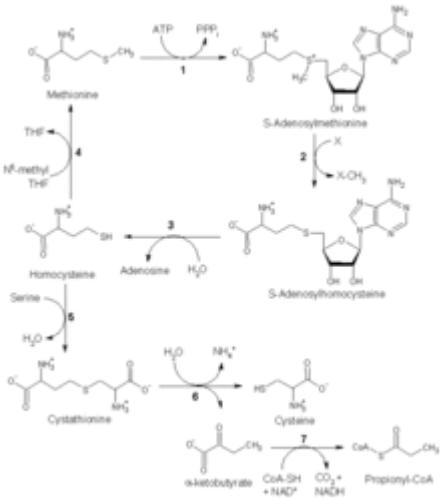
Betatine form of (*S*)-homocysteine (left) and (*R*)-homocysteine (right)

Biosynthesis and biochemical roles

Homocysteine is not obtained from the diet.[2] Instead, it is biosynthesized from methionine via a multi-step process. First, methionine receives an adenosine group from ATP, a reaction catalyzed by *S*-adenosyl-methionine synthetase, to give *S*-adenosyl methionine (SAM). SAM then transfers the methyl group to an acceptor molecule, (i.e., norepinephrine as an acceptor during epinephrine synthesis, DNA methyltransferase as an intermediate acceptor in the process of DNA methylation). The adenosine is then hydrolyzed to yield L-homocysteine. L-Homocysteine has two primary fates: conversion via tetrahydrofolate (THF) back into L-methionine or conversion to L-cysteine.[3]

Biosynthesis of cysteine

Mammals biosynthesize the amino acid cysteine via homocysteine. Cystathionine β-synthase catalyses the condensation of homocysteine and serine to give cystathionine. This reaction uses pyridoxine (vitamin B_6) as a cofactor. Cystathionine β-lyase then converts this double amino acid to cysteine, ammonia, and α-ketobutyrate. Bacteria and plants rely on a different pathway to produce cysteine, relying on *O*-acetylserine.[4]



Two of homocysteine's main biochemical roles. (Homocysteine is seen in the left middle of the image.) It can be synthesized from methionine and then converted back to methionine via the SAM cycle or used to create cysteine and alpha-ketobuterate.

Methionine salvage

Homocysteine can be recycled into methionine. This process uses N5-methyl tetrahydrofolate as the methyl donor and cobalamin (vitamin B_{12})-related enzymes. More detail on those enzymes: Tetrahydrofolate-methyltransferase

Other reactions of biochemical significance

Homocysteine can cyclize to give homocysteine thiolactone, a five-membered heterocycle. Because of this "self-looping" reaction, homocysteine-containing peptides tend to cleave themselves.[*citation needed*]

Influence, proposed and verified, of homocysteine on human health

Elevated homocysteine

Deficiencies of the vitamins folic acid (B_9), pyridoxine (B_6), or B_{12} (cyanocobalamin) can lead to high homocysteine levels.[5] Supplementation with pyridoxine, folic acid, B_{12} or trimethylglycine (betaine) reduces the concentration of homocysteine in the bloodstream.[6][7] Increased levels of homocysteine are linked to high concentrations of endothelial asymmetric dimethylarginine. Recent research suggests that intense, long duration exercise raises plasma homocysteine levels, perhaps by increasing the load on methionine metabolism.[8]

Elevations of homocysteine also occur in the rare hereditary disease homocystinuria and in the methylene-tetrahydrofolate-reductase polymorphism genetic traits. The latter is quite common (about 10% of the world population) and it is linked to an increased incidence of thrombosis and cardiovascular disease, which occurs more often in people with above minimal levels of homocysteine (about 6 μmol/L). These individuals require adequate dietary riboflavin in order for homocysteine levels to remain normal. Common levels in Western populations are 10 to 12 and levels of 20 μmol/L are found in populations with low B-vitamin intakes (e.g., New Delhi) or in the older elderly (e.g., Rotterdam, Framingham). Women have 10-15% less homocysteine during their reproductive decades than men, which may help explain the fact they suffer myocardial infarction (heart attacks) on average 10 to 15 years later than men.[*citation needed*] However, this phenomenon is more readily explained by higher levels of estrogen, which exerts a cardioprotective effect.

Blood reference ranges for homocysteine:

Sex	Age	Lower limit	Upper limit	Unit	Elevated	Therapeutic target
Female	12–19 years	3.3 [9]	7.2[9]	μmol/L	> 10.4	< 6.3 [10] (0.85 mg/L)[10]
	>60 years	4.9 [9]	11.6 [9]	μmol/L		
Male	12–19 years	4.3 [9]	9.9 [9]	μmol/L	> 11.4	
	>60 years	5.9 [9]	15.3 [9]	μmol/L		

Cardiovascular risks and related medical studies

A high level of blood serum homocysteine "homocysteinemia" is a powerful risk factor for cardiovascular disease. Unfortunately, one study which attempted to decrease the risk by lowering homocysteine was not fruitful.[11] This study was conducted on nearly 5000 Norwegian heart attack survivors who already had severe, late-stage heart disease. No study has yet been conducted in a preventive capacity on subjects who are in a relatively good state of health.

Studies reported in 2006 have shown that giving vitamins [folic acid, B_6 and B_{12}] to reduce homocysteine levels may not quickly offer benefit, however a significant 25% reduction in stroke was found in the HOPE-2 study [12] even in patients mostly with existing serious arterial decline although the overall death rate was not significantly changed by the intervention in the trial. Clearly, reducing homocysteine does not quickly repair existing structural damage of the artery architecture. However, the science is strongly supporting the biochemistry that homocysteine degrades and inhibits the formation of the three main structural components of the artery, collagen, elastin and the proteoglycans. Homocysteine permanently degrades cysteine disulfide bridges and lysine amino acid residues in proteins, gradually affecting function and structure. Simply put, homocysteine is a 'corrosive' of long-living proteins, i.e., collagen or elastin, or life-long proteins, i.e., fibrillin. These long-term effects are difficult to establish in clinical trials focusing on groups with existing artery decline. The main role of reducing homocysteine is possibly in 'prevention' but studies in patients with pre-existing conditions found no significant benefit nor damage.[12][13][14]

Hypotheses have been offered to address the failure of homocysteine-lowering therapies to reduce cardiovascular event frequency.[15] One suggestion is that folic acid may directly cause an increased build-up of arterial plaque, independent of its homocysteine-lowering effects. Alternatively, folic acid and vitamin B_{12} may cause an overall change in gene methylation levels in vascular cells, which may also promote plaque growth. Finally, altering methlyation activity in cells might increase methylation of l-arginine to asymmetric dimethylarginine which can increase the risk of vascular disease. Thus alternative homocysteine-lowering therapies may yet be developed which show greater effects on development and progression of cardiovascular disease.

The VITATOPS trial (results presented in May 2010 by the lead investigator, Dr Graeme J Hankey of Royal Perth Hospital, Australia at the European Stroke Conference 2010, in Barcelona, Spain) has concluded that B-vitamin supplements, within 2 years, do not seem to significantly reduce subsequent stroke, MI, or vascular death in patients with a history of recent stroke and ischemic attack, despite lowering of homocysteine levels.[16]

Bone weakness and breaks

Elevated levels of homocysteine have been linked to increased fractures in elderly persons. The high level of homocysteine will auto-oxidize and react with reactive

oxygen intermediates and damage endothelial cells and has a higher risk to form a thrombus.[17][18] Homocysteine does not affect bone density. Instead, it appears that homocysteine affects collagen by interfering with the cross-linking between the collagen fibers and the tissues they reinforce. Whereas the HOPE-2 trial [12] showed a reduction in stroke incidence, in those with stroke there is a high rate of hip fractures in the affected side. A trial with 2 homocysteine-lowering vitamins (folate and B_{12}) in people with prior stroke, there was an 80% reduction in fractures, mainly hip, after 2 years. Interestingly, also here, bone density (and the number of falls) were identical in the vitamin and the placebo groups.[19]

Vitamin supplements counter the deleterious effects of homocysteine on collagen. As they inefficiently absorb B_{12} from food, elderly persons may benefit from taking higher doses orally such as 100 mcg/day (found in some multivitamins) or by intramuscular injection.