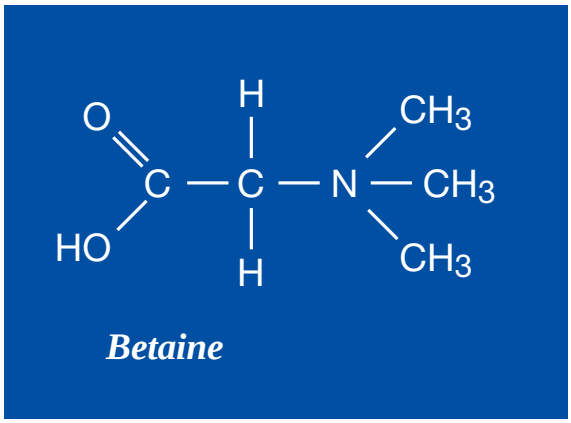


Betaine

Betaine

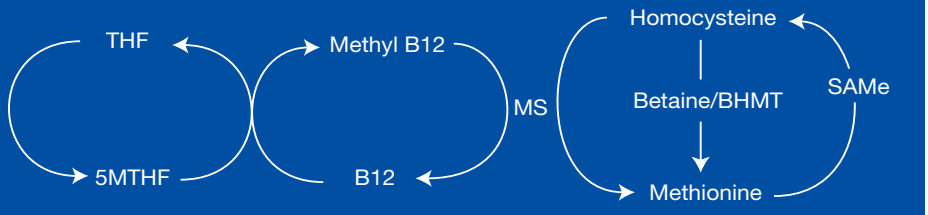
Introduction

Betaine (trimethylglycine), the trimethylated compound of the amino acid glycine, is an essential biochemical component of the methionine/homocysteine cycle. Betaine acts as a donor of methyl (CH_3) groups and, as such, is often used as a nutritional supplement to lower plasma homocysteine levels, and as a lipotropic; i.e., a substance that improves liver function. Betaine also helps maintain intercellular osmolarity and protects proteins from becoming denatured.[1] Food sources of betaine include beets, liver, eggs, fish, legumes, and whole grains. Betaine HCl is also commonly used as a nutritional supplement to increase gastric acidity. The betaine in this compound does not alter gastric acidity, but simply "delivers" the hydrochloric acid.

Biochemistry

Betaine is produced in the body by oxidation of choline, another trimethylated, methyl-donating compound. Betaine's methyl donation appears to be limited to one biochemical reaction – the conversion of homocysteine to methionine. After donating its methyl group, betaine becomes dimethylglycine (DMG). In the methionine-homocysteine cycle, the sulfur-containing essential amino acid methionine is converted to S-adenosylmethionine (SAMe), the primary methyl donor for numerous biochemical reactions in the liver and throughout human tissue. Upon losing its methyl group, SAMe becomes S-adenosylhomocysteine, which loses its adenosine, becoming homocysteine. Homocysteine is either metabolized to the amino acids cysteine and taurine (trans-sulfuration) or recycled to methionine by taking on a methyl group (methylation). This methyl group is added to homocysteine via one of two pathways. Either methylcobalamin (vitamin B12) donates a methyl group in a reaction catalyzed by the enzyme methionine synthase, or betaine donates a methyl group to homocysteine via the enzyme betaine-homocysteine methyltransferase (BHMT), a zinc-dependent metalloenzyme (Figure 1).[2-4]

Figure 1. *Involvement of Betaine in Homocysteine Recycling*



THF - tetrahydrofolate
5MTHF - 5-methyl tetrahydrofolate
MS - methionine synthase
SAMe - S-adenosylmethionine
BHMT - betaine-homocysteine methyltransferase

Pharmacokinetics

Supplemental betaine is rapidly absorbed and distributed throughout the body, with peak concentrations being reached in less than one hour. The elimination half-life in an open-label study of 12 men was 14 hours after a single dose, and increased to 41 hours after repeated dosing for five days. Plasma DMG concentrations also increased significantly after betaine dosing. Due to extensive metabolism of the compound, only four percent of the ingested dose of betaine was eliminated via the kidneys.[1]

Mechanisms of Action

Betaine transfers its methyl group to homocysteine via the enzyme BHMT. It does not appear to be involved in any other methylation reactions.

Deficiency States

Since betaine is derived from dietary betaine, as well as via conversion from choline, a deficiency has not been documented. Certain situations, however, place an increased burden on the betaine-facilitated recycling of homocysteine, including a dietary deficiency of folic acid, alcoholism, or a genetic polymorphism involving the methylene tetrahydrofolate reductase (MTHFR) gene (which can severely decrease the activity of this enzyme).[2] In this instance, folic acid (as tetrahydrofolate) cannot be converted to 5-methyltetrahydrofolate (5-MTHF) as efficiently. As the active form of folic acid, 5-MTHF transfers its methyl group to cobalamin (vitamin B12), which in turn donates this methyl group to homocysteine in a reaction catalyzed by methionine synthase. In the case of dietary folate deficiency or MTHFR-enzyme inhibition, the betaine pathway is stressed.[2] With chronic alcohol intake, the activity of methionine synthase is inhibited; however, in this instance BHMT activity is up-regulated in an attempt to make up for the decreased activity of the other enzyme.[5] It is unknown if BHMT activity is up-regulated in the former instances. When the activity of BHMT is increased, there is a greater need for betaine, and a conditional deficiency might result if not enough is ingested in the diet or converted from choline.

Clinical Indications

Hyperhomocysteinemia/ Homocystinuria

Many disease processes have been positively correlated with high homocysteine levels, including coronary artery disease, peripheral vascular disease, osteoporosis, rheumatoid arthritis, depression, neural tube defects, spontaneous abortion, age-related cognitive decline, vascular dementia, and Alzheimer's disease.[2,3] A high level of homocysteine is believed to be a causative factor in these diseases, although the mechanism has not been completely elucidated in every disease listed. In cases where there is a dietary, metabolic, or genetic defect in homocysteine recycling involving folic acid or methionine synthase, an adequate amount of betaine is necessary to support this process.

In individuals with homocystinuria caused by a genetic defect in cystathione beta-synthase (an enzyme in the trans-sulfuration pathway of homocysteine metabolism), characterized by very high plasma levels of homocysteine (>50 µmol/L), betaine supplementation caused a drop in homocysteine levels of up to 75 percent.[6,7]

Betaine dosing of 6 g daily significantly reduced plasma homocysteine in a placebo-controlled study of obese individuals with normal levels at baseline.[8] In an open trial of 15 healthy volunteers, homocysteine levels were significantly decreased after three weeks of betaine supplementation (6 g daily).[9]

Cardiovascular Diseases

High levels of homocysteine have been linked to increased risk of coronary artery disease,[10,11] myocardial infarction,[12-14] cerebral occlusive disease,[15,16] and peripheral occlusive disease (i.e., deep vein thrombosis; intermittent claudication).[17] Homocysteine-lowering interventions using nutritional cofactors have been shown to reduce the risk of cardiovascular events.[18-20] These interventions have mainly included supplementation of folic acid, vitamin B12, and vitamin B6. In the few studies that have been conducted utilizing betaine, 6 g has been the standard dose shown to be effective in lowering homocysteine

levels and cardiovascular risk in individuals who did not respond to B6, B12, and folate.[20-22] No studies have supplemented betaine alone.

Non-Alcoholic Fatty Liver Disease (NAFLD; Fatty Liver)

NAFLD comprises a broad spectrum ranging from simple hepatic steatosis (fatty liver) to non-alcoholic steatohepatitis (NASH), which can lead to fibrosis, cirrhosis, and liver failure. The average incidence of NAFLD in the U.S. population is 20 percent, although it is usually asymptomatic. NASH is the most common form of progressive liver disease in the United States, affecting three percent of the population. Of those people with NASH, 50 percent progress to fibrosis, 15-30 percent to cirrhosis, and three percent to liver failure. It is thought that the liver damage in NASH is a consequence of insulin resistance and/or obesity, which results in increased hepatic fat synthesis, increased triglycerides in hepatocytes, and oxidative stress-induced hepatocellular damage. Aminotransferase liver enzymes are often chronically elevated by 200-300 percent.[23]

Betaine has been used as a lipotropic, and to prevent and treat NAFLD. Methyl groups are necessary for the conversion of phosphatidylethanolamine to phosphatidylcholine, and betaine may be able to act as a methyl donor in this instance. Elevated blood homocysteine is seen in NASH,[24] which may be a sign of decreased methyl group availability. In a small study of 10 NASH patients given 20 g betaine daily for one year, significant improvements in aminotransferase enzymes (ALT, AST) were noted, with normalization of these enzymes in three patients. Upon follow-up liver biopsy, decreases in steatosis and fibrosis were seen.[25]

In a double-blind, placebo-controlled study of betaine supplementation in 191 NASH patients, after eight weeks the patients given betaine had a 25-percent decrease in hepatic steatosis and significant decrease in liver enzymes.[26]

Alcohol-Induced Liver Disease

The activity of the enzyme methionine synthase is severely inhibited by chronic alcohol ingestion; however, alcohol causes BHMT activity to be up-regulated.[5] This is an occasion when betaine supplementation might be helpful, although no human clinical studies have been conducted to date. In rats dosed chronically with alcohol, then given betaine, hepatic steatosis was ameliorated.[27] Supplemental betaine has been shown to increase the production of the vital methyl donor SAMe, which is depleted in alcoholism.[28]

Obesity

Since betaine has a positive effect on fat metabolism in the liver, and decreases adipose tissue in pigs, it has been postulated that betaine might decrease fat mass in humans. Schwab et al gave 42 obese people 6 g betaine daily or placebo for 12 weeks and found no significant difference in body weight or composition in the two groups. Homocysteine concentrations decreased significantly in the betaine-supplemented group.[8]

Side Effects and Toxicity

Betaine is generally well tolerated, although nausea, loose stools, abdominal cramps, and body odor have been noted.[25]

Dosage

The standard dosage in most betaine studies has been 6 g/day in divided doses, although doses as high as 20 g have been used.

References

1. Schwahn BC, Hafner D, Hohlfeld T, et al. Pharmacokinetics of oral betaine in healthy subjects and patients with homocystinuria. *Br J Clin Pharmacol* 2003;55:6-13.
2. Miller AL, Kelly GS. Homocysteine metabolism: nutritional modulation and impact on health and disease. *Altern Med Rev* 1997;2:234-254.
3. Miller AL. The methionine-homocysteine cycle and its effects on cognitive diseases. *Altern Med Rev* 2003;8:7-19.

4. Millian NS, Garrow TA. Human betaine-homocysteine methyltransferase is a zinc metalloenzyme. *Arch Biochem Biophys* 1998;356:93-98.
5. Barak AJ, Beckenhauer HC, Tuma DJ, Donohue TM. Adaptive increase in betaine:homocysteine methyltransferase activity maintains hepatic S-adenosylmethionine levels in ethanol-treated rats. *IRCS Med Sci* 1984;12:866-867.
6. Surtees R, Bowron A, Leonard J. Cerebrospinal fluid and plasma total homocysteine and related metabolites in children with cystathionine beta-synthase deficiency: the effect of treatment. *Pediatr Res* 1997;42:577-582.
7. Wilcken DE, Wilcken B, Dudman NP, Tyrrell PA. Homocystinuria – the effects of betaine in the treatment of patients not responsive to pyridoxine. *N Engl J Med* 1983;309:448-453.
8. Schwab U, Torronen A, Toppinen L, et al. Betaine supplementation decreases plasma homocysteine concentrations but does not affect body weight, body composition, or resting energy expenditure in human subjects. *Am J Clin Nutr* 2002;76:961-967.
9. Brouwer IA, Verhoef P, Urgert R. Betaine supplementation and plasma homocysteine in healthy volunteers. *Arch Intern Med* 2000;160:2546-2547.
10. Hopkins PN, Wu LL, Wu J, et al. Higher plasma homocyst(e)ine and increased susceptibility to adverse effects of low folate in early familial coronary artery disease. *Arterioscler Thromb Vasc Biol* 1995;15:1314-1320.
11. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 1995;274:1049-1057.
12. Landgren F, Israelsson B, Lindgren A, et al. Plasma homocysteine in acute myocardial infarction: homocysteine-lowering effect of folic acid. *J Intern Med* 1995;237:381-388.
13. Chasan-Taber L, Selhub J, Rosenberg IH, et al. A prospective study of folate and vitamin B6 and risk of myocardial infarction in US physicians. *J Am Coll Nutr* 1996;15:136-143.
14. Knekt P, Alfthan G, Aromaa A, et al. Homocysteine and major coronary events: a prospective population study amongst women. *J Intern Med* 2001;249:461-465.
15. Bots ML, Launer LJ, Lindemans J, et al. Homocysteine and short-term risk of myocardial infarction and stroke in the elderly: the Rotterdam Study. *Arch Intern Med* 1999;159:38-44.
16. Brattstrom L, Lindgren A, Israelsson B, et al. Hyperhomocysteinaemia in stroke: prevalence, cause, and relationships to type of stroke and stroke risk factors. *Eur J Clin Invest* 1992;22:214-221.
17. Molgaard J, Malinow MR, Lassvik C, et al. Hyperhomocyst(e)inaemia: an independent risk factor for intermittent claudication. *J Intern Med* 1992;231:273-279.
18. No authors listed. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. *BMJ* 1998;316:894-898.
19. Schnyder G, Roffi M, Flammer Y, et al. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss Heart Study: a randomized controlled trial. *JAMA* 2002;288:973-979.
20. Yap S, Boers GH, Wilcken B, et al. Vascular outcome in patients with homocystinuria due to cystathione beta-synthase deficiency treated chronically: a multicenter observational study. *Arterioscler Thromb Vasc Biol* 2001;21:2080-2085.
21. Wilcken DE, Dudman NP, Tyrrell PA. Homocystinuria due to cystathione beta-synthase deficiency – the effects of betaine treatment in pyridoxine-responsive patients. *Metabolism* 1985;34:1115-1121.
22. Kluijtmans LA, Boers GH, Kraus JP, et al. The molecular basis of cystathionine beta-synthase deficiency in Dutch patients with homocystinuria: effect of CBS genotype on biochemical and clinical phenotype and on response to treatment. *Am J Hum Genet* 1999;65:59-67.
23. Patrick L. Nonalcoholic fatty liver disease: relationship to insulin sensitivity and oxidative stress. Treatment approaches using vitamin E, magnesium, and betaine. *Altern Med Rev* 2002;7:276-291.
24. Saeian K, Curro K, Binion DG, et al. Plasma total homocysteine levels are higher in nonalcoholic steatohepatitis. *Hepatology* 1999;30:436A.
25. Abdelmalek MF, Angulo P, Jorgensen RA, et al. Betaine, a promising new agent for patients with nonalcoholic steatohepatitis: results of a pilot study. *Am J Gastroenterol* 2001;96:2711-2717.
26. Miglio F, Rovati LC, Santoro A, Setnikar I. Efficacy and safety of oral betaine glucoronate in non-alcoholic steatohepatitis. A double-blind, randomized, parallel-group, placebo-controlled prospective clinical study. *Arzneimittelforschung* 2000;50:722-727.
27. Barak AJ, Beckenhauer HC, Tuma DJ. Dietary betaine promotes generation of hepatic S-adenosylmethionine and protects the liver from ethanol-induced fatty infiltration. *Alcohol Clin Exp Res* 1993;17:552-555.
28. Barak AJ, Beckenhauer HC, Tuma DJ. Betaine, ethanol, and the liver: a review. *Alcohol* 1996;13:395-398.