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Research Article

The role of choline and betaine in body and therapeutic applications

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Abstract

Choline and betaine are the major sources of methyl groups in the human diet. Metabolites of these micronutrients have an essential role in forming the universal methyl donor S-adenosylmethionine (SAM). SAM donates its methyl group in biological methylation reactions. It includes the methylation of DNA, RNA, and protein. Choline is necessary for the structure and function of all cells and is crucial for sustaining life. . Humans can synthesize choline in small amounts by converting the phospholipid, phosphatidylethanolamine, to phosphatidylcholine. Humans obtain betaine from foods that contain either betaine or choline-containing compounds. Metabolism of choline and betaine occur in the liver. Phosphatidylethanolamine N-methyltransferase (PEMT), Choline dehydrogenase (CHDH), and Betaine-homocysteine methyltransferase (BHMT) are the important enzymes involved in the metabolism of choline and betaine. PEMT catalyzes the reaction for de novo synthesis of choline in the body via methylation of phosphatidylethanolamine to form phosphatidylcholine. It uses SAM as the methyl donor. CHDH catalyzes the oxidation of choline to betaine via a betaine aldehyde intermediate. BHMT catalyzes the synthesis of methionine from betaine and homocysteine. Choline and betaine have a number of therapeutic uses. These include treatment of non-alcoholic fatty liver and hyperhomocysteinemia, a risk factor for atherosclerotic disease. Choline is used in the synthesis of the phospholipids, phosphatidylcholine and sphingomyelin. Choline and Betaine helps in prevention of Cardiovascular Diseases, Cancer, alcohol toxicity of liver, cirrhosis of liver, fatty liver. They also prevent pregnancy complications like neural tube defects. Choline and betaine also helps in the improvement of cognitive functioning like memory. Choline also helps in the treatment of Alzheimer's disease, Dementia and cognitive impairments.
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Keywords: Choline, Betaine, Alzheimer's disease, Dementia, Neural tube defect

Introduction

Methyl folate, methionine, choline and betaine are the major sources of methyl groups in the human diet [1, 2]. Metabolites of these micronutrients have an essential role in forming the universal methyl donor S-adenosylmethionine (SAM). SAM donates its methyl group in biological methylation reactions. It includes the methylation of DNA, RNA, and protein.

Choline is necessary for the structure and function of all cells and is crucial for sustaining life [3]. It comes from diet or is synthesized de novo. Betaine (N,N,Ntrimethylglycine) is the substrate for betaine-homocysteine methyltransferase (BHMT). It acts as a methyl donor for methylating homocysteine. Betaine also can be obtained from food or from choline metabolism in liver and kidney. Betaine is a zwitterionic quaternary ammonium compound that is also known as trimethylglycine, glycine betaine, lycine, and oxyneurine. It is a methyl derivative of the amino acid glycine with a formula of $(CH_3)_3NCH_2COO$-and a molecular weight of 117.2. It has been characterized as a methylamine because of its 3 chemically reactive methyl groups [4].

Sources

Humans require additional choline from dietary sources besides the de novo synthesis in the body. Humans can synthesize choline in small amounts by converting the phospholipid, phosphatidylethanolamine, to phosphatidylcholine. This is referred to as de novo synthesis of choline. A diet of normal foods is estimated

to deliver 1 g choline/d. Humans obtain betaine from foods that contain either betaine or choline-containing compounds. A wide range of foods, including:

Meat (e.g., chicken and beef liver),
Dairy products (e.g., eggs),
Vegetables (e.g., spinach), and
Baking products (e.g., wheat germ).

They are sources of choline, methionine, and betaine in the human diet [5]. Choline salts, such as choline chloride and choline bitartrate are available as supplements. Phosphatidylcholine supplements also provide choline. Betaine was first discovered in the juice of sugar beets (Beta vulgaris) in the 19th century. Dietary deficiency of choline in humans results in fatty liver, liver damage, and muscle damage [6, 7]. The most recent results from the Nurses' Health Study showed that increasing choline intake was associated with an elevated risk of colorectal adenoma, whereas an inverse relationship was observed for betaine intake [8]. Total choline and betaine intake was inversely associated with total homocysteine levels in the same population [9].

Metabolism of choline and betaine in the liver

Important enzymes involved in the metabolism of choline and betaine are:

Phosphatidylethanolamine N-methyltransferase (PEMT),
Choline dehydrogenase (CHDH), and
Betaine-homocysteine methyltransferase (BHMT).

PEMT catalyzes the reaction for de novo synthesis of choline in the body via methylation of phosphatidylethanolamine to form phosphatidylcholine. It uses SAM as the methyl donor. CHDH catalyzes the oxidation of choline to betaine via a betaine aldehyde intermediate. BHMT catalyzes the synthesis of methionine from betaine and homocysteine.

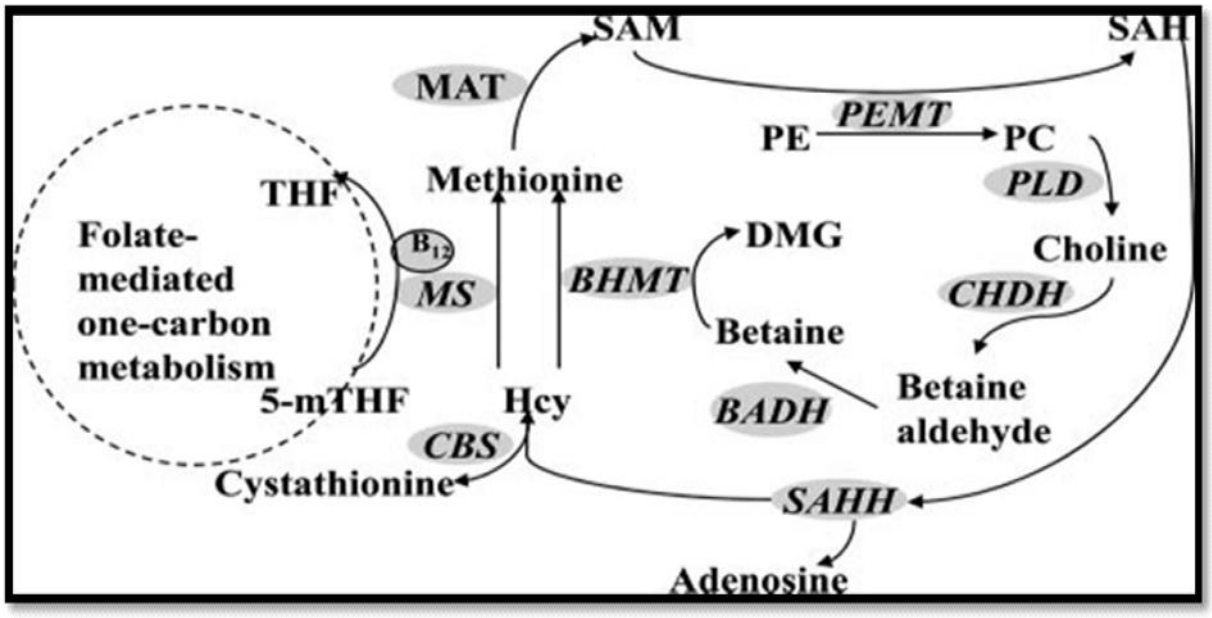

Figure 1. Schematic illustration for Choline and Betaine metabolism in the liver. Folate, choline, and methionine metabolism interact at the point at which homocysteine (Hcy) is converted to methionine. Folate mediates the generation of methionine using the methyl group, i.e., 5-methyltetrahydrofolate (5-mTHF), which is derived de novo from the one-carbon pool; alternatively, the methyl group of choline can be made available on conversion to betaine for the methylation of homocysteine. CHDH converts choline to betaine aldehyde, which can then be oxidized in the mitochondria or cytoplasm to betaine. BHMT catalyzes the methylation of homocysteine, using betaine as the methyl donor. SAM is converted following the regeneration of methionine by methionine adenosyltransferase (MAT). THF, tetrahydrofolate; MS, methionine synthase; SAH, S-adenosyl-l-homocysteine; PE, phosphatidylethanolamine; PC, phosphatidylcholine; PLD, phospholipase D; SAHH, S-adenosyl homocysteine hydrolase; BADH, betaine aldehyde dehydrogenase; DMG, N,N-dimethylglycine; CBS, cystathionine –synthase.

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Betaine-homocysteine S-methyltransferase (BHMT) is most abundant in liver compared to other tissues. This enzyme converts homocysteine to methione by transferring a methyl group from betaine and betaine gets converted to dimethylglycine (DMG). In an alternative pathway to form methionine, folate also can serve as a methyl donor and the methyl group is transferred to homocysteine by the enzyme methionine synthase with vitamin B_{12} as a cofactor. The need for two pathways may have arisen because methionine is metabolized to S-adenosylmethionine (SAM) which is produced and consumed in the liver at a rate estimated to be 6-8 g/day. About 85% of all methylation reactions occur in the liver. SAM is the universal methyl donor for methylation of diverse acceptor molecules (e.g. DNA, RNA, histones, phospholipids). During these reactions, SAM is converted to S-adenosylhomocysteine (SAH). SAH is hydrolyzed to adenosine and homocysteine. They are used to reform methionine, conserve methionine to produce more SAM, and prevent homocysteine toxicity.

The principle metabolic fate of choline is via irreversible oxidation to betaine in the liver and kidney [10] via a two-step process. First, choline is oxidized to betaine aldehyde by the enzyme choline dehydrogenase. This enzyme can also convert betaine aldehyde to betaine in the presence of NAD[11]. Choline dehydrogenase activity occurs in the mitochondria, on the matrix side of the inner membrane [12]. Betaine aldehyde is then oxidized to betaine by the NAD-dependent enzyme betaine aldehyde dehydrogenase both in mitochondria and in the cytosol [13]. The remainder of dietary choline is used to make acetylcholine and phospholipids such as phosphatidylcholine.

Functions of choline and betaine

Choline and Betaine serve a number of vital biological functions.

Osmolyte

The physiologic function of betaine is either as an organic osmolyte to protect cells under stress or as a catabolic source of methyl groups via transmethylation for use in many biochemical pathways. If betaine is not catabolized, it is used as an organic osmolyte. Betaine helps in the regulation of cellular hydration state and cell volume. This is important for maintenance of cell function. Sensitive metabolic pathways include protein turnover, amino acid and ammonia metabolism, carbohydrate and fatty acid metabolism, plasma membrane transport, bile excretion, pH control, and gene expression [14].

- Betaine is the most effective osmolyte for hydration of albumin [15]. It forms a complete monolayer of water around the protein.
- Betaine can maintain hemoglobin solvation [16].
- Betaine accumulates in the kidney [17-22] from exogenous origin rather than de novo synthesis [23-25] to protect cells from high concentrations of electrolytes [26] and urea [27].
- Betaine modulates immune function in osmotically stressed liver macrophages (Kupffer cells) via tumor necrosis factor release [28], phagocytosis [29], and suppression of prostaglandin formation and cyclooxygenase-2 expression [30].
- It regulates water balance and movement across the intestinal epithelium [31].
- Betaine regulates erythrocyte (red blood cell) membrane ATPases via conformational changes, which results in cell volume control [32].
- Betaine protects skeletal muscle myosin ATPases and prevents myosin structural changes due to urea [33].
- Betaine also protects early preimplantation embryos in vitro [34] and prevents apoptosis (programmed cell death) due to hypertonic stress in porcine pulmonary arterial endothelial cells [35].
- Therefore, this osmotic adaptation to stress helps a variety of cells and organs continue to function and protects against premature apoptosis.

Structural integrity of cell membranes

Choline is used in the synthesis of the phospholipids, phosphatidylcholine and sphingomyelin. They are structural components of all human cell membranes.

Cell signalling

The choline-containing phospholipids, phosphatidylcholine and sphingomyelin are precursors for the intracellular messenger molecules like diacylglycerol and ceramide. Two other choline metabolites are platelet activating factor (PAF) and sphingophosphorylcholine. They are also known to be cell-signaling molecules.

Nerve impulse transmission

Choline is a precursor for acetylcholine. It is an important neurotransmitter involved in muscle control, memory, and many other functions.

Lipid (fat) transport and metabolism

Fat and cholesterol consumed in the diet are transported to the liver by lipoproteins called chylomicrons. In the liver, fat and cholesterol are packaged into lipoproteins called very low density lipoproteins (VLDL) for transport through the blood to tissues that require them. Phosphatidylcholine is a required component of VLDL particles. Without adequate phosphatidylcholine, fat and cholesterol accumulate in the liver.

Major source of methyl groups

Choline may be oxidized in the body to form a metabolite called betaine. Betaine is a source of methyl (CH_3) groups required for methylation reactions. Methyl groups from betaine may be used to convert homocysteine to methionine. Elevated levels of homocysteine in the blood have been associated with increased risk of cardiovascular diseases.

Therapeutic Applications

Choline and Betaine helps in prevention of Cardiovascular Diseases, Cancer, alcohol toxicity of liver, cirrhosis of liver, fatty liver.

A large number of researches indicate that even moderately elevated levels of homocysteine in the blood increase the risk of cardiovascular diseases [36]. Choline, when oxidized in the body to form betaine, provides a methyl group for the conversion of homocysteine to methionine by the enzyme, betaine-homocysteine methyltransferase (BHMT).

Dietary choline deficiency is associated with an increased incidence of liver cancer and increased sensitivity to carcinogenic chemicals. A number of mechanisms have been proposed to explain the cancer-promoting effects of choline deficiency:
(a) Choline deficiency causes liver damage and regenerating liver cells are more sensitive to the effects of carcinogenic chemicals.
(b) Choline deficiency results in decreased methylation of DNA, resulting in abnormal DNA repair.
(c) Choline deficiency results in increased oxidative stress in the liver, increasing the DNA damage.
(d) Choline deficiency may stimulate changes in the programmed cell death (apoptosis) of liver cells. It contributes to the development of liver cancer.
(e) Choline deficiency activates the potent cell-signaling molecule, protein kinase C [37,38].

Choline and betaine also prevent pregnancy complications like neural tube defect (NTD). NTD result in either anencephaly or spina bifida. They are devastating and fatal birth defects. These defects occur between the 21st and 27th days after conception. A case-control study (424 NTD cases and 440 controls) found that women in the highest quartiles of choline and betaine intake, in combination, had a 72% lower risk of a NTD-affected pregnancy.

Choline and betaine also helps in the improvement of cognitive functioning like memory. A recent review by McCann et al. discussed the experimental evidence from rodent studies regarding the availability of choline during prenatal development and cognitive function in the offspring. So choline also helps in the treatment of Alzheimer's disease, Dementia and cognitive impairments. Alzheimer's disease has been associated with a deficit of the neurotransmitter named acetylcholine in the brain [39]. One of the cause for the acetylcholine deficit is a decrease in the expression of an enzyme that converts choline into acetylcholine in the brain. Large doses of lecithin (phosphatidylcholine) have been used to treat patients with dementia associated with Alzheimer's disease. It helps in raising the amount of acetylcholine available in the brain. Choline and betaine also have placebo effect in the treatment of patients with dementia or cognitive impairment [40].

Role in liver health: Non-alcoholic fatty liver disease (NAFLD) is a term that describes a progressive range of liver pathologies from simple steatosis (fat accumulation) to steatohepatitis (fatty inflammation), fibrosis (excessive fibrous tissue), and cirrhosis (serious liver damage) [41]. Hepatic steatosis or fatty liver is a common result of obesity, consumption of a high-fat diet, insulin resistance, diabetes, alcohol consumption, and other liver damage [42]. Betaine is a lipotrope which prevents or reduces accumulation of fat in the liver. Betaine can prevent and cure cirrhosis in rats [43,44]. It mobilizes hepatic cholesterol and phospholipids in rats fed a high-cholesterol diet [45], treat hyperlipidemia [46], and can be utilized in the synthesis of carnitine [47]. Dietary betaine increases the secretion of VLDL via methylation of phosphatidylethanolamine [48] to form phosphatidylcholine. Betaine contains an electrophilic methyl group that ameliorates pathologic states induced by reductive and oxidative stress [49] due to its lipotropic property. Betaine helps in the treatment of NAFLD, including non-alcoholic steatohepatitis (NASH) [50, 42, 51-56]. It also helps in the improvements in serum concentrations of liver enzymes like aspartate aminotransferase and alanine

aminotransferase in steatosis, in necroinflammatory grade, and in stage of fibrosis. Betaine glucuronate supplementation in combination with diethanolamine glucuronate and nicotinamide ascorbate in patients with NASH, lowers hepatic steatosis and reduces liver transaminases (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase) [57]. Betaine also helps in reducing hepatic lipidosis and necrosis. It improves morphology of mitochondria, rough endoplasmic reticulum, Golgi complexes, and nuclear DNA. It increases BHMT and SAM and decreases alanine aminotransferase. Betaine also protects against bile-induced apoptosis via inhibition of the pro-apoptotic mitochondrial pathway [58].

Ethanol consumption can decrease methionine synthetase activity [59]. This leads to increased BHMT activity to maintain hepatic SAM at normal concentrations [60-62].

Betaine supplementation of alcohol-fed animals prevents and partially reverses alcoholic fatty liver [62-64], decreases homocysteine and S-adenosylhomocysteine (SAH) concentrations, endoplasmic reticulum stress, and liver injury [65-67].

It prevents the ethanol induced accumulation ofCH3-THF (methyl-folate trap) [68].
It protects erythrocyte membranes [69].
It prevents vitamin A depletion and peroxidative damage [70].

Ethanol-induced elevations in hepatic concentrations of SAH inhibit the activity of phosphatidylethanolamine methyltransferase. It is necessary to achieve adequate concentrations of phosphatidylcholine [71]. This inhibition may reduce VLDL synthesis and transport of triacylglycerols in the liver [72] and thus it lead to the hepatic steatosis due to ethanol feeding. Elevations in the ratio of SAM to SAH by betaine may improve the altered signaling and genomic hypomethylation caused by ethanol and a high-fat diet [73]. SAM is used to treat liver disease and betaine may be an alternative therapy [74].

Toxicity

High doses (10 to 16 grams/day) of choline have been associated with
a fishy body odour,
vomiting,
salivation, and
increased sweating.
The fishy body odour results from excessive production and excretion of trimethylamine, a metabolite of choline. Taking large doses of choline in the form of phosphatidylcholine (lecithin) does not result in fishy body odour because its metabolism results in little trimethylamine. A dose of 7.5 grams of choline/day was found to have a slight blood pressure lowering (hypotensive) effect which could result in dizziness or fainting. Choline magnesium trisalicylate at doses of 3 grams/day has resulted in impaired liver function, generalized itching, and ringing of the ears (tinnitus).

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