**Betaine in context**

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**List of abbreviations:**

BHMT Betaine-homocysteine methyltransferase

SAM *S*-adenosylmethionine

**Abstract**

Betaine, an important nutritional component for human, has been reviewed in the synopsis. Its chemical structure, synthesis, utilisation and physiological significance have been briefed. Due to its ability to donate methyl group, it plays a pivotal role in numerous pathways, including the methionine cycle. A betaine–deficient diet can disturb several cellular processes. Therefore, betaine supplementation to ameliorate certain pathological conditions has been envisaged.

Betaine, also referred as trimethyglycine, oxyneurine and glycine-betaine is a naturally occurring human nutrient which was first discovered in sugar beets and was later found in several microorganisms, marine invertebrates, plants and animals. Chemically, it is a neutral methyl derivative of glycine with a positively charged tri-methylammonium group and a negatively charged carboxyl group (Fig.1), a specific type of zwitterion that performs methylation, in addition to osmoregulation (Craig, 2004).



**Fig. 1 The structure of betaine**

**Structure of glycine-betaine, also known as trimethyglycine and oxyneurine**

Humans can obtain their daily intake of betaine (1-2.5 g) from exogenous sources such as wheat bread (201 mg/100 g), beets (114-297 mg/100 g), spinach (600-645 mg/100 g) and wheat bran (1339 mg/100 g) or it can be synthesised endogenously from its metabolic precursor choline (Craig, 2004). Dietary betaine is absorbed from the duodenal enterocytes into circulation and maintained between 20-70 μmol/L with a median plasma concentration of 27.8 μmol/L, although being slightly higher in men than in women (Awwad et al., 2014, Lever et al., 1994). It is carried to the liver and kidneys where it is catabolised by a series of enzyme-catalysed reactions, predominantly in the mitochondria, and participates in the methionine cycle. Here, betaine donates a methyl group to homocysteine to form N,N-dimethylglycine and L-methionine via the enzyme betaine-homocysteine methyltransferase (BHMT). This is a zinc thiol-enzyme expressed mainly in the liver and kidneys which also functions in glycine, serine and threonine metabolisms (Pajares and Perez-Sala, 2006). The transmethylation reaction mediated by BHMT not only helps to detoxify homocysteine but also increases serum methionine levels (Storch et al., 1991) and *S*-adenosylmethionine (SAM) (Barak et al., 1993), which itself serves as a methyl donor in DNA methylation and many anabolic pathways of phospholipids, hormones and proteins. Removal of betaine from the body is primarily by metabolism with minimal urinary excretion, even after high amounts of betaine consumption (Lever and Slow, 2010).

Un-catabolised betaine acts as an osmolyte and confers protection to the cells against environmental stresses like osmotic irregularity, adverse temperatures and dehydration. By regulating surface tension of water, it aids in water retention and thereby maintains cellular volume. Some examples of its osmoregulatory performances are the hydration of albumin where it forms a single layer of water around albumin (Courtenay et al., 2000), hydration and transport of molecules across the intestine (Kettunen et al., 2001) and sustenance of haemoglobin solvation (Hundahl et al., 2003). Additionally, while betaine can protect renal cells from high concentrations of electrolytes (Horio et al., 2001) it also protects myosin in the skeletal muscle from urea-induced structural changes (Ortiz-Costa et al., 2002)*.* Thus, betaine helps to preserve the optimal functions of several organs and cell-types. Interestingly, hepatic and renal concentrations of betaine and its availability as an osmoprotectant are controlled by the regulation of BHMT which in turn, is dependent on tonicity (Pajares and Perez-Sala, 2006).

Since betaine provides methyl groups, lack of betaine in the diet can cause hypomethylation and elevated homocysteine and reduced SAM concentrations resulting in perturbed methionine metabolism. In addition, a betaine-deficient diet can lead to liver steatosis (Craig, 2004) and increase the predisposition to stroke, cardiovascular disorders, Alzheimer’s (Finkelstein, 2000, Kittner et al., 1999, Seshadri et al., 2002) and atypical DNA methylation leading to carcinogenesis (Cooney, 1993). A betaine or choline-rich diet can increase plasma concentrations of methionine, the rate of methylation and consequently lower the risk of various neoplasms (Nitter et al., 2014, Zeng et al., 2014) and also decrease homocysteine levels in patients with inherited disorders homocysteinemia and homocystinuria (Dudman et al., 1993, Tangerman et al., 2000). Alongside, several animal studies have been conducted which present betaine as a promising therapeutic agent. Based on these studies, betaine-mediated restoration of normal DNA methylation of specific genes to ameliorate the pathogenesis of non-alcoholic fatty liver disease and alcoholic liver disease has been envisaged (Dou et al., 2014, Wang et al., 2014). In alcohol-fed animals betaine prevented and partially reversed alcoholic liver damage by increasing SAM levels and decreasing liver injury caused by endoplasmic reticulum stress (Barak et al., 1997).

**Summary**

* Betaine helps to maintain the normal physiological functions of vital organs like the heart, liver, brain and kidneys.
* It acts as an osmolyte and as a methyl donor, whereby it plays an important role in the methionine cycle.
* Lack of betaine in the diet can result in hypomethylation, elevated homocysteine and reduced SAM concentrations.
* This could cause disturbances in numerous biochemical pathways and lead to diverse physiological implications.
* Animal studies and preliminary studies with human subjects suggest that betaine supplementation can attenuate the pathogenesis of several diseases.
* Further investigation is required to elucidate the mechanism of action of betaine, along with clinical trials to determine suitable pharmaceutical dosage and the consequences of prolonged supplementation.

**Key facts of Alcoholic liver disease**

* It is caused due to excessive alcohol consumption.
* It is manifested as liver damage and can show a wide variety of symptoms.
* The disease encompasses several stages of liver damage beginning from increased deposition of fat, followed by inflammation and excessive collagen production, subsequently leading to severe liver scarring.
* Alcohol abstinence during the early stages can prevent the progression of the disease.

**Definitions and explanations of key terms (in alphabetical order)**

* DNA methylation- addition of methyl group(s) to adenine or cytosine residues on the DNA. It is one of the ways in which gene expression is regulated.
* Haemoglobin solvation- refers to the solubility of haemoglobin in an aqueous environment; here in the plasma.
* Homocystinuria and homocysteinemia- genetic disorders of methionine metabolism which elevate homocysteine levels in blood.
* Hypomethylation- Reduction in methylation.
* Liver steatosis- Deposition of high amounts of fats in the liver.
* Methylation- addition of methyl group(s).
* Osmoprotectant- a molecule which protects the cells/organisms from osmotic pressures.
* Thiol-enzyme- an enzyme that contains sulfhydryl group i.e. the -SH group
* Transmethylation- transfer of methyl group from one molecule to another.
* Zwitterion- a molecule which has both positive and negative charge(s) and is therefore electrically neutral.

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