Effects of betaine supplementation on hepatic metabolism of sulfur-containing amino acids in mice

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Background/Aims: We previously reported that acute betaine treatment induced significant changes in the hepatic glutathione and cysteine levels in mice and rats. The present study was aimed to determine the effects of dietary betaine on the metabolism of sulfur-containing amino acids.

Methods/Results: Male mice were supplemented with betaine (1%) in drinking water for up to 3 weeks. Changes in hepatic levels of major sulfur amino acid metabolites and products were stabilized after 2 weeks of betaine supplementation. Betaine intake increased methionine, S-adenosylmethionine, and S-adenosylhomocysteine levels significantly, but homocysteine and cystathionine were reduced. Methionine adenosyltransferase activity was elevated to three-fold of control. Cysteine catabolism to taurine was inhibited as evidenced by a decrease in cysteine dioxygenase activity and taurine levels in liver and plasma. Despite the significant changes in the transsulfuration reactions, neither hepatic cysteine nor glutathione was altered. Betaine supplementation decreased the hepatotoxicity induced by chloroform (0.5 ml/kg, ip) significantly.

Conclusions: Betaine supplementation enhances recycling of homocysteine for the generation of methionine and S-adenosylmethionine while reducing its utilization for the synthesis of cystathionine and cysteine. However, the hepatic levels of cysteine or glutathione are not affected, most probably due to the depression of taurine generation from cysteine.

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Keywords: Methionine adenosyltransferase; S-adenosylmethionine; Transsulfuration; Glutathione; Taurine

1. Introduction

In mammals, the liver plays a central role in the metabolism of sulfur-containing amino acids because nearly one-half of the daily methionine intake is metabolized there [1]. Methionine metabolism occurs primarily via the transsulfuration pathway, which results in transfer of methionine sulfur to serine to form cysteine (Fig. 1). The first step in transsulfuration reactions is the formation of S-adenosylmethionine (SAM) that is catalyzed by methionine adenosyltransferase (MAT). SAM serves as the methyl donor for various biological methylation reactions, and the co-product, S-adenosylhomocysteine (SAH), is hydrolyzed to yield homocysteine that is either remethylated to methionine or condensed with serine into cystathionine. The transsulfuration of homocysteine to cysteine via cystathionine is mediated by the consecutive actions of cystathionine β-synthase (CBS) and cystathionine γ-lyase (CγL). Cysteine is irreversibly metabolized in liver to yield either taurine, inorganic sulfate, or glutathione (GSH). Cysteine dioxygenase (CDO) catalyzes the oxidation of this amino acid to cysteine sulfinate that is mainly converted to
taurine via hypotaurine by the activity of cysteine sulfinate decarboxylase (CDC). Synthesis of GSH is mediated by taurine via hypotaurine by the activity of cysteine sulfinate decarboxylase (CDC). Synthesis of GSH is mediated by γ-glutamylcysteine ligase (GCL) and GSH synthetase, consecutively.

Betaine, an oxidative metabolite of choline, is involved in the synthesis of methionine from homocysteine in liver. This reaction, catalyzed by betaine homocysteine methyltransferase (BHMT), has an important role in the maintenance of hepatic methionine, especially when the dietary intake of this amino acid is limited [2]. It was shown that betaine intake increased the hepatic SAM concentrations in experimental animals [3], and also reduced the homocysteine levels in human with homocystinuria [4]. Recently, it was demonstrated that the changes in hepatic GSH in animals treated with betaine may be explained by its effect on the cysteine availability in liver [8]. In that study an acute dose of betaine rapidly enhanced metabolic reactions in the methionine cycle, but inhibited cystathionine synthesis and hepatic uptake of cysteine, leading to a decrease in the cysteine availability for GSH synthesis. Reduction in GSH was reversed slowly with the induction of cysteine synthesis and GCL activity. However, the effects of repeated betaine treatment on hepatic cysteine and GSH remained unknown. Inhibition of the transsulfuration reactions from homocysteine to cysteine may lead to a decrease in the synthesis of GSH, which would produce an important impact on normal biochemistry and physiology of mammals. Therefore, it was of significance to ascertain the changes in the hepatic metabolism of sulfur amino acids in animals supplemented with betaine.

2. Materials and methods

2.1. Animals and treatments

Male ICR mice, weighing 20–25 g, were obtained from Dae-Han Laboratory Animal (Seoul, Korea). The use of animals was in compliance with the guidelines established by the Animal Care Committee of this institute. Animals were acclimated to temperature (22 ± 2 °C) and humidity (55 ± 5%) controlled rooms with a 12-hr light/dark cycle (light: 0700–1900, dark: 1900–0700) for at least 1 week prior to use. Laboratory chow and tap water were allowed ad libitum. Betaine-dissolved tap water (1%) replaced regular tap water at the initiation of betaine supplementation. Chloroform was dissolved in corn oil.

2.2. Chemicals

Drugs and chemicals such as NADPH, betaine, amino acids standard, GSH, glutathione disulfide (GSSG), GSSG reductase, S-adenosylmethionine iodide, S-adenosylhomocysteine, and cystathionine were purchased from Sigma Chemical (St Louis, MO, USA). All other chemicals and solvents used were reagent grade or better.

2.3. Determination of sulfur amino acid metabolites in tissues and blood

Livers and kidneys were homogenized in a four-fold volume of cold 1 M perchloric acid with 2 mM EDTA. Denatured protein was removed by centrifugation at 10,000 g for 10 min. Total GSH concentration was determined using the HPLC method of Neuschwander-Tetri and Roll [9]. A HPLC system equipped with a fluorescence detector (FP-920; Jasco, Tokyo, Japan) and a 3.5 μm Symmetry C18 column (4.6 × 75 mm; Waters, Milford, MA, USA) was employed. Cysteine and cystine were quantified by the acid-ninhydrin method [10]. A HPLC method was used for determination of SAM and SAH [11]. The supernatant was directly applied to a HPLC equipped with a UV detector and a TSK-GEL ODS-80TM column (4.6 × 250 mm; Tosoh, Tokyo, Japan). Homocysteine was determined by using the method of Carducci et al. [12]. Homocysteine, after reduction by 2-mercaptoethanol, was derivatized with O-phthalaldehyde/2-mercaptoethanol before injection into a HPLC equipped with a fluorescence detector and a 3.5 μm Kromasil C18 column (4.6 × 100 mm; Eka, Bohus, Sweden).

For measurement of free amino acids, livers were homogenized in a five-fold volume of cold methanol. Serum was diluted with a three- to five-fold volume of methanol. Free amino acids, hypotaurine and taurine were all derivatized with O-phthalaldehyde/2-mercaptoethanol before injection into a HPLC equipped with a fluorescence detector and a 3.5 μm Kromasil C18 column (4.6 × 100 mm). Free amino acids were separated by using the HPLC method of Rajendra [13]. The method of Ide [14] was used to quantify hypotaurine and taurine.

Fig. 1. Metabolic pathway of sulfur-containing amino acids.

The superimposed line diagram shows the metabolic pathway of sulfur-containing amino acids. The pathway includes the synthesis of GSH from cysteine and homocysteine, the transsulfuration reactions from homocysteine and cystathionine, and the metabolism of betaine. The diagram is not to scale and is intended to provide a general overview of the metabolic pathways involved.
2.4. Enzyme assays

Livers were homogenized in a three-fold volume of a buffer consisting of 0.154 M KCl/50 mM Tris–HCl and 1 mM EDTA (pH 7.4). The homogenate was centrifuged at 10,000 g for 20 min. The supernatant fraction was further centrifuged at 104,000 g for 60 min. The 104,000 g supernatant fraction (cytosol) was used to determine the enzyme activities.

Activity of MAT was estimated by quantifying SAM and SAH production [15]. CYS activity was determined by measuring cystathionine formation [16]. CyL activity was estimated by γ-ketobutyrate production [17]. Activity of GCL was determined by generation of γ-glutamylcysteine [18]. CDO activity was quantified by cysteine sulfinate production [19]. Activity of CDC was estimated by measuring formation of hypotaurine [14].

Activity of GSH S-transferase (GST) was measured using 1-chloro-2,4-dinitrobenzene as a substrate [20]. Activity of NADPH-dependent GSSG reductase was determined employing an enzymatic recycling method [21]. GSH peroxidase activity was assayed by using hydrogen peroxide as a substrate [22]. Activity of γ-glutamyl transeptidase (GGT) was measured using whole tissue homogenates [23].

Hepatic microsomal drug metabolizing enzyme activities were determined using the methods described elsewhere [24]. The concentration of cytochrome P-450 was estimated from the CO difference spectrum. The microsomal p-nitrophenol hydroxylase activity was quantified by measuring formation of p-nitrocatechol.

2.5. Assessment of liver and kidney toxicity

Activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in serum were determined using the method of Reitman and Frankel [25]. The method of Gerlach [26] was used for measurement of lactate dehydrogenase (LDH) activity. Total bilirubin contents, blood urea nitrogen (BUN), creatinine, and alkaline phosphatase (ALP) activity were measured using commercially available kits (Youngdong Pharmaceutical, Seoul, Korea).

2.6. Data analysis

All results expressed as the mean ± SEM were analyzed by a two-tailed Student’s t-test or one-way analysis of variance (ANOVA) followed by Newman–Keuls multiple range test. The acceptable level of significance was established at P < 0.05 except when otherwise indicated.

3. Results

3.1. Changes in major sulfur amino acid metabolites and liver/kidney physiology

The hepatic concentrations of major metabolites and products in the transsulfuration pathway were monitored in mice supplemented with betaine for 3 weeks (Fig. 2). The methionine, SAM, and SAH levels in liver were elevated significantly, while taurine was reduced after 1 week of betaine intake. However, hepatic cysteine or its metabolic product, GSH, was not affected. The changes in methionine, SAM, SAH, and taurine were further augmented as the supplementation period was extended to 2 weeks, but no difference between the animals supplemented with betaine for 2 weeks and those for 3 weeks was observed, suggesting that most important changes in the sulfur amino acid metabolism are attained in 2 weeks of betaine supplementation.

Body weight gains, food and water consumption were measured in mice during the period of betaine administration for 2 weeks. There were no significant differences between control and betaine-fed mice in the body weight gains (7.2 ± 0.4 vs 7.1 ± 0.4 g/14 day), food (222 vs. 220 g/kg/day) or water consumption (361 vs. 377 ml/kg/day). The liver or kidney weights per 100 g body weight measured at terminal sacrifice were not changed (5.50 ± 0.4 g/14 day). The liver or kidney weights per 100 g body weight measured at terminal sacrifice were not changed (5.50 ± 0.09, 1.52 ± 0.07 in control; 5.40 ± 0.11, 1.56 ± 0.03 in betaine-fed mice, respectively). The serum ALT, AST, SDH, ALP activities, total bilirubin, creatinine, and BUN were determined to estimate the liver and kidney toxicity associated with betaine intake. Betaine supplementation for 3 weeks affected none of the parameters measured (data not shown).

3.2. Effect of betaine on transsulfuration reactions from methionine to cysteine

The effects of betaine supplementation for 2 weeks on the methionine, SAM, SAH, cystathionine, and homocysteine levels in liver and kidney are summarized in Table 1. In liver, betaine increased the hepatic methionine, SAM and SAH levels markedly, but homocysteine and cystathionine were decreased. On the other hand, neither SAM nor SAH levels were altered in kidney where the BHMT activity is negligible [27].

The enzyme activities involved in the transsulfuration reactions from methionine to cysteine were measured (Table 2). Betaine intake did not affect the protein contents in liver (control, 230 ± 6 mg/kg liver; betaine-fed mice, 244 ± 4 mg/g liver). The MAT activity was increased markedly reaching a level approximately three-fold of control. The activity of CyL, but not CβS, was increased significantly.
Mice were provided with drinking water containing 1% betaine for 2 weeks. Value given is the mean ± SEM for six mice. *, **, ***Significantly different from control at $P<0.05$, $0.01$, $0.001$, respectively.

### Table 1

**Effect of dietary betaine on methionine, SAM, SAH, cystathionine and homocysteine levels in liver and kidney**

<table>
<thead>
<tr>
<th></th>
<th>Liver</th>
<th>kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methionine</td>
<td>SAM</td>
</tr>
<tr>
<td>Control</td>
<td>39±2</td>
<td>108±4</td>
</tr>
<tr>
<td>Betaine</td>
<td>62±8*</td>
<td>152±4***</td>
</tr>
</tbody>
</table>

**Table 2**

**Effect of dietary betaine on hepatic enzyme activities involved in transsulfuration reactions from methionine to cysteine**

<table>
<thead>
<tr>
<th></th>
<th>MAT</th>
<th>CBS</th>
<th>CyL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nmol/min/mg protein</td>
<td>nmol/min/mg protein</td>
<td>nmol/min/mg protein</td>
</tr>
<tr>
<td>Control</td>
<td>0.18±0.03</td>
<td>10.2±0.2</td>
<td>5.6±0.2</td>
</tr>
<tr>
<td>Betaine</td>
<td>0.53±0.06***</td>
<td>9.9±0.2</td>
<td>7.4±0.2***</td>
</tr>
</tbody>
</table>

Mice were provided with drinking water containing 1% betaine for 2 weeks. Value given is the mean ± SEM for five mice. ***Significantly different from control at $P<0.001$.

### 3.3. Effect of betaine on hepatic metabolism of cysteine and GSH

The concentrations of cysteine and GSH in liver, kidney and plasma were determined (Table 3). Neither cysteine nor GSH levels were changed by betaine supplementation. Plasma levels of cysteine, the major form of cysteine in blood, were also unaffected (control, 44.9±1.5 nmol/ml; betaine-fed mice, 45.6±1.5 nmol/ml). The cysteine availability for GSH synthesis is maintained in a normal range despite the significant decrease in its metabolic precursor, cystathionine, in liver of betaine-fed mice (Table 1).

The effects of betaine supplementation on the activity of enzymes involved in the metabolism of GSH and cysteine are shown in Table 4. There was no difference between control and betaine-fed group in the activities of GSH peroxidase or GSSG reductase, which have important roles in the maintenance of cellular GSH redox state. The activity of GST, GCL or GGT was not changed. But betaine intake significantly decreased the hepatic CDO activity that catalyzes the first irreversible step in taurine synthesis from cysteine.

### 3.4. Changes in various amino acids in liver and plasma

Alterations in various amino acid levels in liver and plasma are summarized in Table 5. Betaine intake induced a significant decrease in the concentrations of glycine in liver and plasma, but increased the hepatic serine levels. The hepatic taurine and hypotaurine levels were reduced markedly to 67 and 43% of control, respectively. Plasma taurine levels were also decreased. The other amino acids determined in this study were not affected, indicating that the betaine-induced changes are mostly limited with sulfur amino acids.

### 3.5. Effect of betaine on hepatotoxicity induced by chloroform

The hepatotoxicity induced by a toxic dose of chloroform (0.5 ml/kg, ip) was determined in mice supplemented with betaine for 2 weeks (Fig. 3). The elevation of serum parameters measured to estimate the liver injury was decreased by betaine significantly. The hepatic microsomal enzyme activities responsible for the metabolic activation of this solvent were examined. $p$-Nitrophenol hydroxylation, a specific marker for the CYP2E1 activity [28], was not changed by betaine intake (control, 2.80±0.16 nmol product formed/min/mg protein; betaine-fed group, 2.93±0.21 nmol product formed/min/mg protein). The total cytochrome P450 and protein contents were also unaltered (data not shown).

### 4. Discussion

In the present study, dietary betaine supplementation produced significant changes in the metabolism of sulfur amino acids in liver, which were stabilized in 2 weeks after initiation of its administration to mice. The hepatic levels of methionine, SAM and SAH were increased significantly, whereas homocysteine and cystathionine were reduced. The hepatic MAT activity was markedly elevated. Betaine supplementation depressed the CDO activity resulting in reduction of taurine generation. It should be noted that, in contrast to the acute effects of betaine reported previously [7], dietary betaine intake did not alter the cysteine or GSH levels either in liver, plasma or kidney.

Betaine supplementation enhanced transsulfuration reactions in the methionine cycle as evidenced by the elevation of methionine, SAM, and SAH levels in liver, but hepatic homocysteine that is utilized both in the regeneration of methionine and the synthesis of cystathionine was reduced significantly. The distribution of homocysteine between remethylation to methionine and condensation with serine to cystathionine provides a major regulatory locus for methionine metabolism in liver. It was proposed that the two reactions are each other competitive with respect to homocysteine utilization [29]. The present results suggest
Mice were provided with drinking water containing 1% betaine for 2 weeks. Value given is the mean ± SEM for seven mice.

Table 3
Effect of dietary betaine on cysteine and GSH levels in liver, kidney and plasma

<table>
<thead>
<tr>
<th></th>
<th>GSH (μmol/g tissue or nmol/ml plasma)</th>
<th>Cysteine (nmol/g tissue or ml plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver</td>
<td>Kidney</td>
</tr>
<tr>
<td>Control</td>
<td>7.9 ± 0.3</td>
<td>4.0 ± 0.1</td>
</tr>
<tr>
<td>Betaine</td>
<td>7.5 ± 0.3</td>
<td>3.9 ± 0.1</td>
</tr>
</tbody>
</table>

Mice were provided with drinking water containing 1% betaine for 2 weeks. Value given is the mean ± SEM for six mice.

Table 4
Effect of dietary betaine on hepatic enzyme activities involved in metabolism of GSH and taurine

<table>
<thead>
<tr>
<th></th>
<th>GGT nmol/min/g liver</th>
<th>GSSG reductase unit/mg protein</th>
<th>GSH peroxidase</th>
<th>GST μmol/min/mg protein</th>
<th>GCL nmol/min/mg protein</th>
<th>CDO</th>
<th>CDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>87 ± 8</td>
<td>0.11 ± 0.01</td>
<td>0.38 ± 0.03</td>
<td>4.0 ± 0.1</td>
<td>5.9 ± 0.3</td>
<td>0.60 ± 0.03</td>
<td>25.6 ± 3.4</td>
</tr>
<tr>
<td>Betaine</td>
<td>73 ± 5</td>
<td>0.11 ± 0.01</td>
<td>0.41 ± 0.02</td>
<td>4.5 ± 0.2</td>
<td>6.3 ± 0.4</td>
<td>0.45 ± 0.04*</td>
<td>25.6 ± 4.7</td>
</tr>
</tbody>
</table>

Mice were provided with drinking water containing 1% betaine for 2 weeks. Value given is the mean ± SEM for five mice. *Significantly different from control at P<0.05.

that betaine supplementation depletes hepatic homocysteine by enhancing its utilization in the remethylation reaction to methionine, which leads to a decrease in the generation of cystathionine.

Despite the reduction in cystathionine generation, neither cysteine nor GSH levels were decreased by betaine supplementation. It seems that animals are metabolically adapted to the betaine-induced alterations in the metabolism of sulfur amino acids. The maintenance of hepatic cysteine is a dynamic process. In liver, the cysteine levels are regulated by a balance between its synthesis and hepatic uptake from blood, and conversion to GSH, inorganic sulfate and taurine [30]. In this study, betaine supplementation resulted in a significant decrease both in the generation of cystathionine, a metabolic precursor of cysteine, and the catabolism of cysteine to taurine, which would account for the relative constancy of cysteine concentrations in liver. Taurine production is largely restricted by the availability of cysteine sulfinate, a product of the CDO-mediated metabolic reaction [31]. Kohashi et al. [32] first hypothesized that CDO would play an important role in the regulation of intracellular cysteine. It has also been suggested that the inhibition of taurine production is coupled with the enhancement of GSH synthesis in liver [8,15,33]. Thus, it appears that the reduction of cysteine catabolism to taurine could salvage the cysteine supply needed for the synthesis of GSH that has numerous critical functions in cells.

Table 5
Effect of dietary betaine on levels of various amino acids in liver and plasma

<table>
<thead>
<tr>
<th></th>
<th>Liver (nmol/g)</th>
<th>Plasma (nmol/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Betaine</td>
</tr>
<tr>
<td>Taurine</td>
<td>12.280 ± 485</td>
<td>8218 ± 648**</td>
</tr>
<tr>
<td>Hypotaurine</td>
<td>274 ± 65</td>
<td>117 ± 12*</td>
</tr>
<tr>
<td>Glycine</td>
<td>1892 ± 80</td>
<td>907 ± 77***</td>
</tr>
<tr>
<td>Serine</td>
<td>461 ± 25</td>
<td>574 ± 30*</td>
</tr>
<tr>
<td>Glutamate</td>
<td>2420 ± 131</td>
<td>1982 ± 155</td>
</tr>
<tr>
<td>Glutamine</td>
<td>3249 ± 267</td>
<td>3708 ± 251</td>
</tr>
<tr>
<td>Aspartate</td>
<td>464 ± 20</td>
<td>475 ± 33</td>
</tr>
<tr>
<td>Alanine</td>
<td>2682 ± 162</td>
<td>2560 ± 83</td>
</tr>
<tr>
<td>Asparagine</td>
<td>64 ± 2</td>
<td>69 ± 6</td>
</tr>
<tr>
<td>Valine</td>
<td>335 ± 17</td>
<td>373 ± 18</td>
</tr>
<tr>
<td>Histidine</td>
<td>510 ± 24</td>
<td>502 ± 14</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>98 ± 6</td>
<td>102 ± 6</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>86 ± 5</td>
<td>76 ± 3</td>
</tr>
<tr>
<td>Threonine</td>
<td>289 ± 19</td>
<td>262 ± 23</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>124 ± 4</td>
<td>141 ± 9</td>
</tr>
<tr>
<td>Leucine</td>
<td>151 ± 6</td>
<td>172 ± 10</td>
</tr>
</tbody>
</table>

Mice were provided with drinking water containing 1% betaine for 2 weeks. Value given is the mean ± SEM for six mice. ND: not detectable. *, **, ***Significantly different from control at P<0.05, 0.01, 0.001, respectively.
In both liver and plasma glycine levels were decreased significantly by betaine supplementation. Considering that betaine is demethylated to dimethylglycine, sarcosine, and subsequently to glycine, the reduction in glycine is not easily understood. Loss of the excess labile methyl group of SAM occurs primarily via formation and degradation of sarcosine, resulting in transfer of the methyl group to tetrahydrofolate [34]. Serine hydroxymethyltransferase converts glycine to serine using the methyl group from tetrahydrofolate. In fact it was demonstrated that, in rats given an injection of [methyl-14C]methionine, up to 40% of the radioactivity was recovered in serine [35]. The present results suggest that the betaine-induced accumulation of SAM leads to an enhancement of serum generation from glycine. This view is supported by clinical findings that betaine therapy normalized the decreased plasma serine levels in patients with homocystinuria [36], and also by the results showing an elevation of plasma serine levels in heterozygous CβS mice treated with betaine [37].

Betaine supplementation for 2 weeks resulted in a greater than 40% increase in the hepatic SAM levels, which appears to be associated with the induction of MAT activity. Extensive literature survey failed to reveal the effect of betaine on this enzyme, but it was shown that in cultured rat hepatocytes methionine addition increased the transcription of MAT1A [38], mainly expressed in adult liver, which could account for the betaine-induced elevation of MAT activity and SAM generation observed in this study. Depression of MAT activity is associated with various types of hepatic disorders. It has been reported that mice deficient in MAT 1A are prone to spontaneous development of steatohepatitis and hepatocellular carcinoma [39]. Also the MAT activity was shown to be lower in cirrhotic human liver [40]. It has been demonstrated that SAM treatment is beneficial in the treatment of liver diseases including steatosis, cholestasis and cirrhosis in human and experimental animals [41–43]. The present results suggest that betaine supplementation could substitute for the direct SAM administration by elevating the MAT activity, which appears to serve as the underlying mechanism for improvement of steatosis, necroinflammation, and fibrosis in non-alcoholic hepatitis patients on betaine therapy [44]. In primates including human the remethylation of homocysteine mediated by BHMT is limited by the availability of betaine, because of a paucity of hepatic choline oxidase activity catalyzing the betaine synthesis from choline [45]. Betaine supplementation could accelerate the reaction of BHMT that has been found to be abundant in human liver [46].

The effect of betaine supplementation on the chloroform-induced hepatotoxicity was examined in this study. Elevation in the serum parameters measured to estimate the hepatotoxicity was depressed by betaine intake significantly. It has been accepted that induction of the chloroform hepatotoxicity is mostly dependent on the CYP2E1 activity, which catalyzes the metabolic activation of this solvent, and the availability of GSH, which is involved in the detoxification of the toxic metabolite, phosgene [47,48]. The present results indicate that neither the hepatic microsomal p-nitrophenol hydroxylase activity nor GSH is altered by betaine. It is suggested that the elevation of SAM levels associated with betaine supplementation plays an important role in the protection of mice from the acute liver injury.

The major finding in this study is that, although betaine supplementation inhibits the transfer of sulfur to cystathionine, the cysteine availability needed for GSH synthesis is maintained due to the decrease in generation of taurine from this sulfur amino acid. Elevation of the hepatic SAM levels by betaine intake is of particular interest in that this substance does not contain sulfur, hence, would give a minimal influence on the sulfur balance in body. Further study to elucidate the pharmacological significance of betaine-induced effects on the metabolism of sulfur amino acids is being conducted in this laboratory.

References


