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Methionine transamination – metabolic function and subcellular compartmentation

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Abstract

Enzymatic activities catalysing the inter-conversion of L-methionine and its oxy analogue 4-methylthio-2-oxobutyric acid (2,4-KMB) were detected in the liver, skeletal muscle and heart of the laboratory rat and of sheep. In both species the highest activity of methionine transamination was found in the liver and was located in the cytoplasm and mitochondria. We propose that physiological and nutritional role of the cytoplasmic methionine transamination is amination of 2,4 KMB and formation of L-methionine while in mitochondria the activity is responsible for disposal of excess methionine is oxidised through oxidative decarboxylation of 2,4 KMB. (Mol Cell Biochem **129:** 39–45, 1993)

Key words: L-methionine, metabolism, transamination, mitochondria, rat, sheep

Introduction

Methionine is an essential amino acid of particular metabolic significance due to its role as a methyl donor in transmethylation processes and as an important source of sulphur containing groups. Methionine metabolism involves a variety of initial reactions in which its methyl group is transferred to methyl acceptors, followed by a catabolic pathway, the transsulfuration pathway, which leads to the formation of other sulphur containing amino acids, mainly cysteine and taurine [1]. Additionally, however, there is now evidence for the operation of an S-adenosylmethionine independent pathway, the transaminative route of methionine metabolism [2, 3]. Although this pathway has not yet been described completely, some of the metabolites of the transaminative degradation of methionine have been detected in the plasma or urine of humans and laboratory animals [4, 5].

The significant stimulation of methionine degradation through the transaminative pathway *in vitro* by thiamine pyrophosphate, coenzyme A and NAD has been suggested as a possible new therapy for patients with pyridoxine non-responsive cystathionine synthase deficiency [6]. Several nutritional studies with rats, sheep and monkeys have shown that methionine supplementation in the diet can be toxic [7]. It was suggested that these toxic effects relate to toxic metabolites generated in the transaminative pathway of methionine metabolism: 3-methylthiopropionic acid and methanethiol [8]. The characterisation of the initial step of the transaminative pathway of methionine metabolism is very sketchy. It was suggested that methionine could be a substrate for the glutamine transaminases (type L) EC 2.6.1.15. and asparagine transaminases, both isolated from rat liver [9, 10]. Methionine transamination might also be catalysed by type K glutamine transaminase, detected predominantly in rat kidney [11]. L-Leucine (Methionine) transaminase – another enzyme potential-

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ly involved in methionine transamination – was isolated from rat liver mitochondria [12]. The broad substrate specificity of the different transaminases [13] makes it difficult to identify a single enzyme responsible in practice for the transamination of methionine. We therefore decided to examine the enzymatic activity of methionine transamination with several 2-oxo acids as acceptors for the amino group of methionine. We compared the total activity detected in extracts of different tissues and determined the activity in the hepatic mitochondria and cytoplasm of rats and sheep. The main purpose of this study was to assess the nutritional and physiological significance of the enzymatic inter-conversion of methionine and 2,4 KMB in the organs and subcellular fractions of these species.

Materials and methods

L-methyl-^{3}H-methionine (sp. activity 3.11 TBq per mmol) was from Amersham Intl. (England). Sodium salts of 4-methylthio-2-oxobutyric acid, 2-oxoglutaric acid, 2-oxoisocaproic acid, oxaloacetic acid, acetylCoA lithium salt, 5,5-dithio-bis(2-nitrobenzoic acid), glyoxylic acid, pyruvic acid, L-methionine, D-methionine, L-phenylalanine; 2-amino-2-methyl-1,3 propandiol (ammediol), L-2-amino-3-ureidopropionic acid (albizziin), Triton X-100 and pyridoxal-5-phosphate were from Sigma Chemical Co. Ltd. Enzymes: glutamic dehydrogenase (beef liver) and alanine dehydrogenase (Bacillus subtilis) were from Boehringer Mannheim UK. All other chemicals (analytical grade) were from Sigma Chemical Co. Ltd.

Animals and feeding

Male hooded Lister (Rowett strain) rats weighing 200–250 g were fed ad libitum on a stock diet.

Young lambs up to one year old of age were given a diet based on lucerne (alfalfa). All animals had free access to food until they were killed.

Preparation of tissue extracts, mitochondria and cytoplasm

Tissues were used fresh or frozen (freeze-clamped in liquid nitrogen). Samples of 0.5–2 gm were homogenised in 5 vol. of 50 mM potassium phosphate/2 mM EDTA/0.5% Triton X-100 adjusted to pH 7.4. The homogenates were centrifuged at 4,000 × g and the supernatant was used for the enzymatic assays. Mitochondria from liver were prepared by a previously published procedure [14]. Cytoplasm was obtained by centrifugation of the postmitochondrial supernatant at 105 000 × g for 60 min.

Enzymatic assays of methionine transamination activity

Tissue extracts, isolated mitochondria or cytoplasm were incubated in the medium: 100 mM Tris-HCl pH 8.0, 0.02% v/v Triton X-100 plus 5 µM Pyridoxal phosphate and ^{3}H methyl labelled L-methionine (15×10^4 dpm) per sample and at final concentration 4 mM. The oxo acids were used at the following concentrations: 2-oxoglutaric, pyruvic, glyoxylic and 2-oxoisocaproic acids were 2 mM, 4-methylthio-2-oxobutyric acid 1 mM. Total incubation volume was 1 ml; incubation was carried out in a shaking bath at 30° C; the reaction was started by the addition of enzyme, and terminated with 100 µl 10% trichloroacetic acid. Protein was removed by centrifugation at 4,000 × g for 10 min. The aliquot (0.5 ml) of supernatant from each incubation sample was applied to a mini column, 0.3 × 2 cm of Dowex 50 W in the H^+ form. The organic acids were eluted by washing each column with 0.7 ml of H_2O. Eluate from the column was collected into scintilation vials. Radioactivity of eluted 2,4 KMB was counted after addition of 4 ml of scintillation liquid (Atomlight from Du Pont NEN). Each incubation set included two blank samples, one with the protein denatured at zero time and the second without added protein. Samples were incubated in duplicate. Under these incubation conditions the rate of the reaction was linear for up to 30 min and proportional to the amount of protein used, in the range 2–6 mg per incubation. Enzymatic activity of methionine transamination was calculated as nmoles of product formed per min per mg protein or per gm wet weight. The production of radioactive 2,4 KMB was confirmed by the counting of its 2,4 dinitrophenylhydrazone form [12] in the elute from the mini column.

Isolated mitochondria and cytoplasm from liver were similarly incubated but without radioactive methionine. The methionine dependent formation of glutamic acid and alanine from 2-oxoglutaric acid and pyruvic acid was determined enzymatically with glutamate dehydrogenase and alanine dehydrogenase respectively as described [15, 16].

Other enzymatic assays

Activity of glutamine transaminase type L and type K was assayed by spectrophotometric methods as described previously [17, 18].

Citrate synthase activity in tissue extracts and in isolated mitochondria was determined using Ellman reagent as originally described by Srere [19]. The amount of mitochondrial protein in rat and sheep liver was calculated using determined values of citrate synthase activity in the tissue extract and in isolated mitochondria as described previously [20].

Protein concentration was determined by the Biuret method [21].

Results

The total activity of L-methionine transamination was measured in the presence of methionine and its oxo analogue 2,4 KMB. The results in Table 1 show the total activity of methionine transamination in several tissue extracts from rats and sheep. The activities in liver and heart were 6 fold higher in rats then in sheep; in skeletal muscle of both species the rate of total L-methionine transamination was similar. The participation of specific transaminases in methionine transamination was examined by replacing the 2,4-KMB in the incubation mixture with 2-oxoisocaproic acid to assess the activity of leucine (methionine) transaminase (EC 2.6.1.42). To measure the activity of three aminotransferases dependent on the presence of glyoxylic acid, glutamate-glyoxylate (EC 2.6.1.4) asparagine-glyoxylate (EC 2.6.1.14) and glutamine-glyoxylate (EC 2.6.1.44) 2,4 KMB was replaced by glyoxylic acid. For the measurements of alanine aminotransferase (EC 2.6.1.2) and aspartic acid aminotransferase (EC 2.6.1.1) pyruvic acid and 2-oxoglutaric acid were used instead of 2,4 KMB. In the rat liver the most potent oxo acid for the transfer of the amino group of methionine was glyoxylic acid; however, this acounted for only one third of total methionine transaminative activity. We could not determine the transamination of methionine with 2-oxoglutaric acid in the rat liver extract but this may have been due to the of 2-oxoglutarate instability in this extract. In rat kidney the distribution of L-methionine transamination activity was similar so that in the rat liver except that leucine aminotransferase activity was higher. In heart and skeletal muscle in both species the activity of the transamination of L-methionine in the presence of 2-oxo-glutaric acid accounted for more than half of the total activity determined.

The specific activities of L-methionine transamination in liver mitochondrial and cytoplasmic fraction from the rat and sheep liver are shown in Tables 2 and 3. To estimate the contribution of mitochondrial and cytoplasmic activities of methionine transaminases we have determined the mitochondrial density in the rat and sheep livers these were 80 ± 11 and 55 ± 7 (mean ± SD, n = 5) mg of mitochondrial protein per g wet tissue, respectively. Multiplying the mitochondrial specific activity of methionine transamination by the amount of mitochondrial protein per g tissue we could estimate the contribution of mitochondrial activities. The (2,4-KMB-dependent) transamination in mitochondria represented approximately 20% and 40% of the total activity in one g of rat and sheep liver, respectively. For both subcellular fractions the sum of the transamination coupled

Table 1. Activity of amino group transfer from L-methionine to 2-oxo acid by the tissue extracts from rat and sheep

Extract	Substrates for transamination				
	2,4-KMB	2-OIC	GLYOXYL	2-OG	PYR
Rat liver	638 ± 107	10.3 ± 0.9	223 ± 33	nd	46 ± 3
Rat kidney	386 ± 40	60.0 ± 11.0	120 ± 5	90 ± 7	12 ± 2
Rat heart	130 ± 15	65.0 ± 12.0	25 ± 7	105 ± 15	3 ± 0.4
Rat muscle	25 ± 2	9.3 ± 0.6	9 ± 1	11 ± 3	3 ± 0.6
Sheep liver	98 ± 12	< 1	25 ± 6	< 1	< 1
Sheep heart	28 ± 7	10.0 ± 3.0	3 ± 0.8	< 1	< 1
Sheep muscle	21 ± 6	4.2 ± 0.6	< 1	6.1 ± 1.2	< 1

Preparation of tissue extracts and assay conditions for measurements of methionine transamination are described in the Methods section. Values are expressed in nmoles per min per g wet weight of tissue and are means ± S.D. (n = 3–5). Abbreviations: 2,4-KMB = 4-methylthio-2-oxo-butyric acid; 2-OIC = 2-oxo-isocaproic acid; Glyoxyl = Glyoxylic acid; 2-OG = 2-oxoglutaric acid; PYR = pyruvic acid; nd = not determined.

Table 2. Activity of methionine transamination in isolated subcellular fractions from rat and sheep liver

	2,4-KMB	2-OIC	PYR
Rat liver			
mitochondria	1.36 ± 0.21	0.11 ± 0.02	0.13 ± 0.02
cytoplasm	2.85 ± 0.38	0.04 ± 0.006	0.16 ± 0.02
Sheep liver			
mitochondria	0.77 ± 0.14	0.07 ± 0.008	0.18 ± 0.04
cytoplasm	0.49 ± 0.09	0.01 ± 0.003	0.20 ± 0.03

Results are expressed in nmoles per min per mg protein. Values are mean ± S.D. n = 3. Abbreviations are described in Table 1.

to the amination of 2-oxoglutaric, pyruvic and 2-oxoisocaproic acid accounted for no more than 50% of the total activity of L-methionine transamination. The specific activities of the L and K glutamine transaminases in cytoplasm and mitochondria of rat and sheep liver are presented in Table 4. Liver type (L) glutamine transaminase was distributed more equally between mitochondria and cytoplasm than the kidney type (K) glutamine transaminase which was mainly located in the cytoplasm in both studied species. The specific activity of type K transaminase was also approximately 50% lower than of the L-type enzyme in the rat and sheep liver.

Discussion

Activities of L-methionine transamination, specificity, and methodology

The results in this report indicate that L-methionine can be a substrate for several transaminases and it is unlikely that a single specific enzyme is responsible for the transamination of L-methionine. Current IUB classification of the transaminases is mainly based on operational criteria for their identification and it is therefore likely that some of EC numbers and names listed in our report will be changed. Our data suggest that two main groups of transaminases are involved in the transamination of L-methionine: one is a family of transaminases that react with glutamic acid or 2-oxoglutaric acid; the second is a family of glutamine and asparagine transaminases. Enzymes of this latter group operate independently of the presence of 2-oxoglutaric, oxaloacetic or pyruvic acid.

We have used labelled methionine in our assay system to determine the activity of L-methionine transamination according to the reaction:

L-methionine* + 2,4 KMB = L-methionine + 2,4 KMB*

Under such conditions the substrate concentration remained constant during the reaction. The activity of transamination in the presence of other oxo acids was also determined. We have confirmed the validity of the radioactive exchange assay by comparing the amount of 2,4 KMB and alanine generated in the presence of pyruvic acid and methionine (see results in Table 2 and 3). The concentrations of substrates used in our assay were optimum for monitoring maximum enzymatic activity and were close to physiological concentrations. We have observed that higher concentrations of 2,4 KMB (above 2 mM) inhibited the activity of transamination (data not shown). Similar effects of 2,4-KMB have been observed with purified glutamine transaminase [9]. The use of labelled L-methionine for the direct determination of the 2,4-KMB has improved the sensitivity of the assay, allowing us to confirm the earlier observation [22] that the activity of L-methionine transamination although low, is present in rat skeletal muscle.

Physiological and nutritional implications of inter organ and subcellular compartmentation of L-methionine transamination

The liver plays the central role in the metabolic distribution of amino acids and the transamination of L-methionine is most active in the liver (Table 1). The enzymatic profile of L-methionine transamination is also most complex in the liver, with potential metabolic transaminations shown in Fig. 1. Most of the transaminases are distributed between cytoplasm and mitochondria [23];

Table 3. Methionine dependent enzymatic production of glutamic acid and alanine by isolated mitochondria and cytoplasm from rat and sheep liver

	Glutamic acid	Alanine
Rat liver		
Mitochondria	0.30 ± 0.06	0.15 ± 0.02
Cytoplasm	0.42 ± 0.08	0.26 ± 0.06
Sheep liver		
Mitochondria	0.26 ± 0.05	0.15 ± 0.02
Cytoplasm	0.37 ± 0.09	0.29 ± 0.08

Incubation and assay condition are described in the Methods section. Values are expressed in nmoles per min per mg protein and are mean ± S.D. n = 4.

Table 4. Activities of glutamine transaminases type L and type K in isolated cytoplasm and mitochondria from rat and sheep

	Glutamine aminotransferase activity	
	type L	type K
Rat liver		
Mitochondria	7.2 ± 0.5	0.8 ± 0.05
Cytoplasm	11.3 ± 0.9	4.9 ± 0.35
Sheep liver		
Mitochondria	8.7 ± 0.7	1.9 ± 0.32
Cytoplasm	9.1 ± 1.2	3.9 ± 0.65

Determination of enzymatic activity is described in the Methods section. Values are mean ± S.D. n = 4 and expressed in nmoles per min per mg protein.

therefore we have considered only these two subcellular compartments in our study.

In the cytoplasm the generation of 2,4 KMB occurs not only from dietary L-methionine. Another source can be 4-methylthio-2-hydroxy-butyric acid which is used as a supplement in the diet of poultry [24]; its oxidation by a specific oxidase or by lactic dehydrogenase can provide 2,4 KMB in the cell. Another precursor of 2,4 KMB of dietary origin might be D-methionine, the 2,4 KMB being formed by oxidative deamination of D-methionine. Although D-methionine is poorly utilised by humans [25] it was used by young rats with approximately 90% of the efficacy of L-methionine [26]. The third potential source of 2,4 KMB is from S-adenosylmethionine (SAM) used in the biosynthesis of polyamines. The side product of decarboxylated SAM in this pathway is methylthioadenosine; its conversion into L-methionine via 2,4 KMB has been shown *in vitro* in rat liver homogenate [27]. The generation in the cell of the 2-oxo-analogue of methionine supports the suggestion that glutamine and asparagine transaminases have a role in the production of L-methionine in the liver [28]. The nutritional significance of cytoplasmic amination of 2,4 KMB by glutamine and asparagine can be further supported by the suggestion that *in vivo* these reactions are irreversible: there is no experimental evidence that 2-oxo-glutaramic acid or 2-oxo-succinamic acid could be aminated back to glutamine and asparagine respectively. It is suggested that deamidation by ϖ-amidase generates 2-oxoglutaric acid and oxaloacetic from oxo analogues of glutamine and asparagine, respectively [28]. Moreover, the cytosolic location of the synthesis of glutamine and asparagine [29] provides further support for the proposed operation of L-methionine transamination. The transamination of L-methionine in mitochondria is very likely to be controlled by its transport through the inner membrane. The presence of a specific transporter in the inner mitochondrial membrane for the three oxo-analogues of branched chain amino acids as well as for 2,4 KMB has been reported [30]. The mitochondrial uptake of these oxo-acids was stimulated by decreasing the extramitochondrial pH [31]. Following the uptake of oxo-acids into mitochondria, their oxidative decarboxylation by the branched chain oxo-acid de-

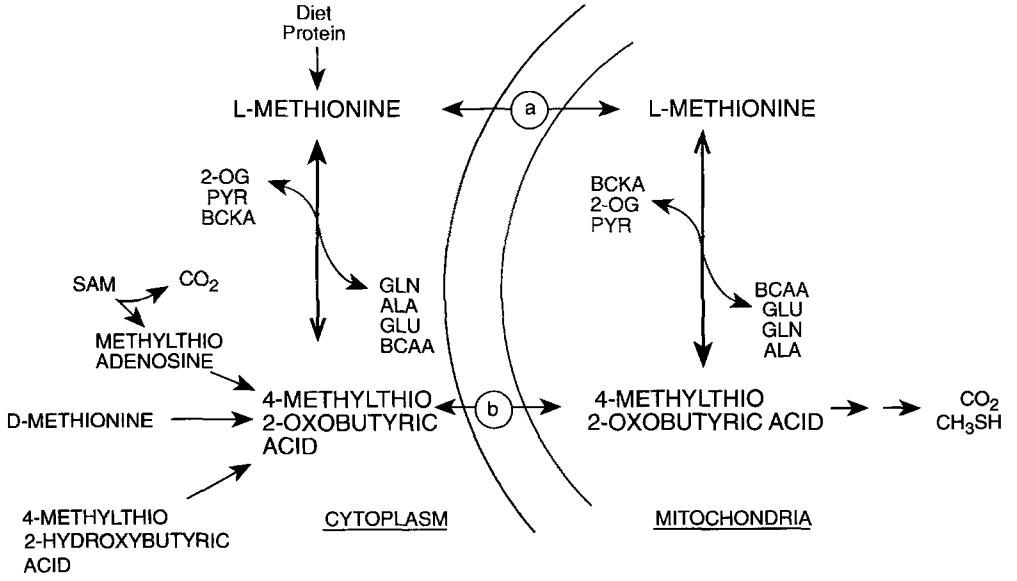

Fig. 1. Metabolic relationship of L-methionine transamination in the liver cell. Abbreviations: SAM: S-adenosylmethionine; CH_3SH: methanethiol; 2-OG: 2-oxoglutaric acid; PYR: pyruvic acid; BCKA: branched chain oxoacids; a – carrier for neutral amino acids in the inner mitochondrial membrane; b – transporter for the branched chain oxoacids.

hydrogenase was also stimulated at pH which was lower but still in the physiological range (6.8–7.8) [31]. An opposite effect of low pH has been found for the mitochondrial uptake of glutamine [32]. This, and the abundance of glutaminase activity in the liver mitochondria, strongly diminishes the physiological role of the amination of 2,4 KMB by glutamine and asparagine transaminases in the liver mitochondria. One could suggest therefore that oxo-analogues of leucine, valine, isoleucine or methionine, once taken up by the liver mitochondria, would be oxidatively decarboxylated by an active (dephosphorylated) form of the branched-chain oxo-acids dehydrogenase complex [33]. L-methionine uptake by rat liver mitochondria is mediated by the carrier for neutral amino acids present in the inner mitochondrial membrane [34]. At present we do not know the kinetic parameters of the transport of L-methionine through the inner mitochondrial membrane. It is possible that L-methionine enters the liver mitochondria and undergoes transamination mainly with pyruvic acid and 2-oxoglutaric acid, the 2,4 KMB is being further oxidised through the branched-chain oxo acid dehydrogenase complex and via the β-oxidation pathway as previously reported [35]. The activity of the mitochondrial degradation of L-methionine would therefore also be controlled by the phosphorylation state of the branched-chain 2-oxo-acid dehydrogenase. It has been shown that in normal rat heart and skeletal muscle this enzyme is phosphorylated [36] and therefore one could predict a low rate of oxidation of 2,4 KMB in these tissues. The much lower activity of total L-methionine transamination in heart and skeletal muscle supports the conclusion that transaminative degradation of L-methionine in heart and skeletal muscle is low.

As the transaminative degradation of methionine 'shares' at least two enzymatic steps (transamination and oxidative decarboxylation) with the catabolic route of branched-chain amino acids it is very likely that the oxidation of methionine as with valine and isoleucine is stimulated *in vivo* by leucine [37].

An excess of L-methionine in the diet causes toxic effects including acidosis [38] in rats, coma [39] in dogs and even death in sheep [40]. Methanethiol (CH_3SH) and H_2S generated from the transaminative degradation of L-methionine have been suggested as causing these toxic effects [7]. However, the toxicity of methionine is not fully understood. Homocysteine may also have a role in its pathological effects. In an early nutritional study on the toxic effects of the excesses of methionine it has been shown that DL-homocystine added to the diet also inhibited growth of young rats [41]; this effect could be alleviated by the additions of glycine or serine to the diet, suggesting an important role of folic acid dependent transmethylation in preventing the toxic effects of methionine and homocystine. Further clinical studies showed that a higher plasma level of homocysteine is associated with a slow flux through the transsulphuration pathway and a low rate of remethylation [42].

Very recently the transamination of L-methionine has been questioned and the pathological effects of a high methionine intake with food have been associated with the over-methylation and accumulation of S-adenosylmethionine in the rat tissues [43]. Therefore, the most important mechanism involved in the toxicity of L-methionine remains uncertain. However, in view of its potential importance in nutrition and nutritional therapy these issues warrant further study.

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