Bioavailability of Methionine Sulfoxide; supplementary effect of threonine on fatty liver induced by methionine sulfoxide

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Summary

To assess the relative bioavailability of methionine sulfoxide to methionine and the characteristics of fatty liver induced by the feeding of methionine sulfoxide, supplementary effect of threonine on hepatic triglyceride content was studied in rats fed with a low casein diet containing methionine or methionine sulfoxide at the 0.3% level.

Feeding of methionine and methionine sulfoxide caused the increase of the concentration of hepatic triglyceride. Methionine sulfoxide was less effective in hepatic triglyceride accumulation than methionine. Threonine alleviated the fatty infiltration induced by feeding of methionine and methionine sulfoxide. Threonine decreased the concentration of plasma triglyceride in animals fed with methionine, but not in those fed with methionine sulfoxide. Threonine elevated the level of plasma cholesterol in the group fed with methionine sulfoxide. Addition of threonine had no effects on the growth, food intake and liver weight in both groups.

It is suggested that methionine and methionine sulfoxide may induce fatty infiltration through a similar mechanism and the bioavailability of methionine sulfoxide is lower than that of methionine.

Introduction

In many food proteins, sulfur amino acids, in particular methionine, are often the most limiting essential amino acids. During processing of food protein, sulfur amino acids may become unavailable or be destroyed through heating or oxidation in the presence of oxidized agents. Under these conditions, methionine is readily converted to methionine sulfoxide and further to methionine sulfone. Various aspects of the biological availability of these oxidized products of sulfur amino acids have been studied utilizing such assay procedures as growth, digestibility and nitrogen balance and net protein utilization. Both methionine sulfone and cysteic acid have been reported to have no biological activity. However, bioavailability of methionine sulfoxide has been a subject
of controversy. In the previous study, a novel approach was applied to elucidate the relative bioavailability of methionine sulfoxide; the extent of fatty infiltration in the liver of rats fed a low casein diet supplemented with methionine or its sulfoxide was measured as an index. We showed that this approach may serve as a tool for evaluating the bioavailability of methionine sulfoxide.

In the present study, to elucidate the relative bioavailability of methionine sulfoxide to methionine and the characteristics of fatty liver induced by feeding of methionine sulfoxide, we compared the supplementary effect of threonine on hepatic triglyceride accumulation in rats fed a diet containing methionine or methionine sulfoxide.

**Materials and Methods**

*Animals and diets* Young male rats of the Wistar strain, weighing about 70 g, (Kyudo Co., Kumamoto) were divided into 5 groups of six rats and were housed individually in metabolic cages in a room maintained at 23–25 °C. One group was fed the 8% casein diet (basal diet) and the other groups were fed diets supplemented with 0.3% methionine, 0.3% methionine + 0.2% threonine, 0.33% methionine sulfoxide, or 0.33% methionine sulfoxide + 0.2% threonine. The amount of methionine sulfoxide added was equimolar to 0.3% level of methionine. The basal diet contained (in percent); vitamin-free casein, 8.0; corn oil, 5.0; mineral mixture, 4.0; vitamin mixture, 1.0; cellulose powder, 4.0% choline chloride, 0.15 and sucrose to 100, as used previously. Diets were also supplemented with 1,000 IU vitamin A, 200 IU vitamin D₃ and 10 mg α-tocopherol per 100 g diet. Rats were fed each diet for 7 days.

*Analytical procedures* Liver and plasma lipids were extracted and analyzed for triglyceride, phospholipids and cholesterol as described elsewhere.

*Statistical analysis* Data were analyzed by Student’s t-test.

**Results**

*Body weight gain, food intake and liver weight*

Growth, food intake and liver weight in rats fed a diet containing methionine or methionine sulfoxide at the 0.3% level were significantly higher than those of the control group fed the basal diet (Table 1 and Fig. 1). Supplementation of threonine to the both

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight gain (g/7days)</th>
<th>Food intake (g/day)</th>
<th>Liver weight (g/100g body wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)</td>
<td>8±1.4c</td>
<td>8.7±0.3c</td>
<td>5.61±0.15c</td>
</tr>
<tr>
<td>C+ Met 0.3%</td>
<td>24±1.4c</td>
<td>11.2±0.4c</td>
<td>6.20±0.14c</td>
</tr>
<tr>
<td>C+ Met sulfoxide 0.33%</td>
<td>20±1.3c</td>
<td>11.5±0.2c</td>
<td>5.67±0.22c</td>
</tr>
<tr>
<td>C+ Met 0.3% + Thr 0.2%</td>
<td>24±1.1c</td>
<td>11.1±0.4c</td>
<td>5.73±0.26c</td>
</tr>
<tr>
<td>C+ Met sulfoxide 0.33% + Thr 0.2%</td>
<td>24±0.8c</td>
<td>11.5±0.3c</td>
<td>5.21±0.20c</td>
</tr>
</tbody>
</table>

a) Rats were fed diets ad libitum for 7 days. Met, methionine; Thr, threonine.
b) Values are the means ± SE of 6 rats.
c, d) Values not sharing a common superscript letter are significantly different at p<0.05.
imbalanced diets also caused to increase in these parameters to the same extent.

Concentration of hepatic lipid components

As shown in Table 2, there was a significant increase in the concentration of hepatic triglyceride in rats fed a diet supplemented with methionine. Feeding of diet supplemented with methionine sulfoxide also caused an increase in the hepatic triglyceride, but to a somewhat lesser degree. The addition of threonine to these diets alleviated the deposition of hepatic triglyceride. In contrast, the concentration of hepatic phospholipids increased significantly by the addition of methionine sulfoxide, methionine + threonine, or methionine sulfoxide + threonine. Decreased concentration of hepatic cholesterol was appeared by the addition of threonine to the diet containing methionine sulfoxide.

Concentration of plasma lipid components

In plasma (Table 3), the concentration of triglyceride and phospholipids was elevated by supplementation with methionine or methionine sulfoxide. Addition of threonine to these diets showed no effect on the triglyceride level. The cholesterol level of methionine sulfoxide-fed animals tended to decrease.

Discussion

Rats fed a low casein diet supplemented with small amounts of methionine (a threonine imbalanced diet) deposits triglyceride in the liver\(^{12}\). In the previous study\(^{10}\), we examined the relationship between graded supplementary levels of methionine or methionine sulfoxide and the concentration of hepatic triglyceride and found that there was an

![Fig. 1 Growth curve of rats.](image)

Male Wistar rats weighing about 70g were rained on the diets as shown in Table 1 for 7 days. Six rats in a group were individually housed with free access to food and water. \(×—×\): Basal diet, \(-○−○\): Met 0.3%, \(-●−●\): Met 0.3% + Thr 0.2%, \(-Δ−Δ\): Met sulfoxide 0.33%, \(-▲−▲\): Met sulfoxide 0.33% + Thr 0.2%.

<table>
<thead>
<tr>
<th>Group(^{a})</th>
<th>Triglyceride (mg/g liver)</th>
<th>Phospholipid (mg/g liver)</th>
<th>Cholesterol (mg/g liver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)</td>
<td>11.3 ± 0.45(^{c})</td>
<td>17.8 ± 0.92(^{c})</td>
<td>2.63 ± 0.28(^{c})</td>
</tr>
<tr>
<td>C + Met 0.3%</td>
<td>23.5 ± 1.18(^{d})</td>
<td>19.0 ± 0.41(^{d})</td>
<td>2.14 ± 0.23(^{d})</td>
</tr>
<tr>
<td>C + Met sulfoxide 0.33%</td>
<td>16.8 ± 1.53(^{e})</td>
<td>22.1 ± 0.50(^{e})</td>
<td>2.45 ± 0.23(^{e})</td>
</tr>
<tr>
<td>C + Met 0.3% + Thr 0.2%</td>
<td>13.2 ± 1.05(^{ef})</td>
<td>22.3 ± 0.84(^{ef})</td>
<td>2.21 ± 0.16(^{ef})</td>
</tr>
<tr>
<td>C + Met sulfoxide 0.33% + Thr 0.2%</td>
<td>12.1 ± 0.50(^{f})</td>
<td>22.0 ± 0.99(^{f})</td>
<td>1.66 ± 0.17(^{f})</td>
</tr>
</tbody>
</table>

\(^{a}\) See also Table 1 and Fig. 1. \(^{b}\) Values are the means ± SE of 6 rats. \(^{c − f}\) Values not sharing a common superscript letter are significantly different at \(p < 0.05\).
Table 3 Concentration of plasma lipid components

<table>
<thead>
<tr>
<th>Group</th>
<th>Triglyceride (mg/dl plasma)</th>
<th>Phospholipid (mg/dl plasma)</th>
<th>Cholesterol (mg/dl plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)</td>
<td>90.5±17.8e</td>
<td>157.7±7.9e</td>
<td>93.7±5.3e</td>
</tr>
<tr>
<td>C+Met 0.3%</td>
<td>150.7±26.3e</td>
<td>176.3±4.1e</td>
<td>97.9±7.6e</td>
</tr>
<tr>
<td>C+Met sulfoxide 0.33%</td>
<td>132.4±29.1e</td>
<td>181.3±6.2e</td>
<td>112.8±9.0e</td>
</tr>
<tr>
<td>C+Met 0.3% ± Thr 0.2%</td>
<td>120.1±23.2e</td>
<td>176.3±6.7e</td>
<td>94.5±2.2e</td>
</tr>
<tr>
<td>C+Met sulfoxide 0.33% + Thr 0.2%</td>
<td>153.8±9.9e</td>
<td>178.8±4.6e</td>
<td>115.4±0.6e</td>
</tr>
</tbody>
</table>

a) See also Table 1 and Fig. 1. b) Values are the means ± SE of three pooled plasma from 6 rats. c, d) Values not sharing a common superscript letter are significantly different at p<0.05.

apparent positive correlation between the levels of these supplements and the content of hepatic triglyceride. Rats fed methionine sulfoxide deposit hepatic triglyceride lesser extent than that in the animals fed methionine at any level above 0.2%, suggesting that the bioavailability of methionine sulfoxide is lower than that of methionine in the rat. No correlation was observed, however, between the extent of weight gain and the amount of amino acid supplemented. It is reasonable, therefore, to measure the change in the concentration of triglyceride in the liver rather than the growth, as an alternate index, for the bioavailability of oxidized methionine.

The deposition of hepatic triglyceride in rats fed a low casein diet supplemented with methionine has been reported to cause by the shortage of threonine and the supplementation of threonine has reported to reduce its deposition\textsuperscript{12}. In the present study, hepatic triglyceride accumulation in the methionine-fed rats was alleviated by the addition of 0.2% threonine, as shown in Table 1, in agreement with the results reported previously.\textsuperscript{12} Supplementary effect of threonine on hepatic triglyceride accumulation was also appeared in the methionine sulfoxide-fed rats, however, the extent of the decreased content of hepatic triglyceride was shown somewhat lesser as compared with that to the methionine-fed animals.

It is suggested that methionine and methionine sulfoxide may induce fatty infiltration through a similar mechanism and methionine sulfoxide can substitute for methionine although the bioavailability of methionine sulfoxide is somewhat inferior to that of methionine in the rat.

Acknowledgement

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References

メチオニンスルフォキシドの生物学的有効性：
メチオニンスルフォキシドによって生じる
脂肪肝に対するスレオニンの補足効果

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(食糧管理化学研究室)
昭和60年5月4日 受理

摘要
メチオニンスルフォキシドの、メチオニンに対する、相対的な生体での利用率とメチオニンスルフォキシド摂取によって惹起される脂肪肝の特徴を知るために、メチオニンまたはメチオニンスルフォキシドを0.3%レベルで含有している低カゼイン食を摂取したラットの肝臓トリグリセリド量に及ぼすスレオニンの補足効果を比較検討した。

メチオニンとメチオニンスルフォキシドの摂取により、肝臓トリグリセリド濃度は増加した。メチオニンスルフォキシドはメチオニンに比べ、肝臓トリグリセリド蓄積に対する効果は低かった。スレオニンはメチオニンおよびメチオニンスルフォキシドによって誘起される脂肪浸潤を改善した。スレオニンはメチオニン摂取動物の血中トリグリセリド濃度を低下させたが、メチオニンスルフォキシド摂取ラットでは認められなかった。スレオニンはメチオニンスルフォキシド摂取群で血中コレステロールレベルを上昇させた。スレオニンの添加は両食餌群の成長、摂食量および肝臓重量に影響しなかった。

メチオニンとメチオニンスルフォキシドは同様のメカニズムで脂肪浸潤を誘起し、メチオニンに比べて、メチオニンスルフォキシドの生体内での利用効率は低いことが示唆された。