Changes of plasma fasting carnitine ester profile in patients with ulcerative colitis

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INTRODUCTION

Ulcerative colitis (UC) is a disorder of the idiopathic and chronic inflammation of the colonic mucosa. The etiology and the pathogenesis of the disease are yet unknown; a classic study on isolated colonic epithelial cells demonstrated decreased utilization of n-butyrate. Since the major energy sources of the epithelial cells of the distal colon are the short-chain fatty acids (SCFAs), these cells are able to metabolize other fuels, such as glucose and glutamine, only at a much lower rate [1]. SCFAs are generated from carbohydrates by bacterial degradation and are readily absorbed by the colon and represent energy fuels for the colonocytes and other tissues, such as the skeletal muscle [2,3]. Patients with distal UC may have increased or moderately decreased stool SCFA concentrations, reflecting their altered absorption [4,5]. UC can, therefore, be regarded essentially as an SCFA oxidation failure-associated disease, where the energy deficiency is a primary event in the development of the disease [6].

L-carnitine plays an essential role in the energy metabolism, since it enables the transport of activated long-chain fatty acids (LCFA) as carnitine esters across the inner mitochondrial membrane. Moreover, it is able to form esters with several medium- and SCFAs of both endogenous and exogenous origins [6,7]. The impact of altered SCFA metabolism in UC prompted us to study the circulating carnitine ester profile in the UC patients.

MATERIALS AND METHODS

Patients

We examined 44 patients with UC (25 males, 19 females,
Table 1. Some major clinical and laboratory parameters in patients with ulcerative colitis and control subjects (mean ± SE)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>UC patients, n = 44</th>
<th>Controls, n = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females/males</td>
<td>19/25</td>
<td>24/20</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>12.2 ± 4.5</td>
<td>2.6 ± 0.5</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>44.6 ± 6.7</td>
<td>50.2 ± 0.8</td>
</tr>
<tr>
<td>Iron (µmol/L)</td>
<td>16.1 ± 12.2</td>
<td>23.7 ± 1.6</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>133.1 ± 25</td>
<td>139.1 ± 12</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>86.2 ± 12.2</td>
<td>94.8 ± 2.5</td>
</tr>
<tr>
<td>WBC (G/L)</td>
<td>7.6 ± 0.4</td>
<td>9.2 ± 0.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 ± 0.6</td>
<td>24.1 ± 0.5</td>
</tr>
<tr>
<td>PLT (G/L)</td>
<td>298.5 ± 13.5</td>
<td>228.3 ± 10.4</td>
</tr>
<tr>
<td>Both stool and colon localization 5/44 (11.4%)</td>
<td>8/44 (18.2%)</td>
<td>31/44 (70.4%)</td>
</tr>
</tbody>
</table>

N = 44. Statistical analysis

Statistical analysis

Student's t test for unpaired samples was used for the statistical analysis. The values were expressed as mean ± SE, in three decimals for the carnitine esters with respect to the low levels in the case of the long-chain carnitine esters. P < 0.05 was considered statistically significant.

RESULTS

The plasma circulating carnitine ester profiles are shown in Table 2. The plasma level of free carnitine and acetyl carnitine did not differ between the UC patients and the controls. By contrast, significant decreases were observed in fasting propionyl-, butyryl-, and isovalerylcaritnine ester levels in UC patients as compared with the controls. The level of total short-chain carnitine esters was markedly lower in the patients with UC (9.855 ± 0.094 µmol/L) than in the healthy controls (11.003 ± 0.100 µmol/L, P < 0.01).

The levels of octanoyl- and decanoylcaritnine were decreased in the healthy subjects. The levels of total medium-chain acylcarnitines were obviously higher in the UC patients (0.629 ± 0.007 µmol/L) than in the control subjects (0.548 ± 0.007 µmol/L, P < 0.01).

In the long-chain acylcarnitine group, the plasma levels of myristoyl-, palmitoyl-, palmitoleoyl- and oleoylcaritnine were significantly decreased in the healthy group. The levels of total long-chain carnitine esters were markedly higher in the patients with UC (0.596 ± 0.005 µmol/L) than in the controls (0.515 ± 0.009 µmol/L, P < 0.01).

In addition, the level of total carnitine esters was significantly decreased in the UC patients (11.080 ± 0.035 µmol/L) as compared with the healthy controls (12.06± 0.037 µmol/L, P < 0.01).

DISCUSSION

Carnitine [β-hydroxy-γ(trimethylamino) butyric acid]
is known as a carrier for transporting activated LCFA into the mitochondrial matrix for β-oxidation. With this function the L-carnitine plays an essential role in the energy metabolism. Moreover, the carnitine molecule is able to form esters with several medium- and short-chain fatty acids of both endogenous and exogenous origins. The circulating carnitine ester spectrum can reflect affected cellular metabolism of the short-, medium-, and long-chain fatty acids. Therefore, the monitoring of the carnitine ester composition is a widespread tool for the diagnosis of several inborn errors of metabolism. Besides the complete metabolic blockage caused by the inherited lack of enzyme activities, influences on carnitine ester spectra may be the consequence of only partially affected flux of metabolites via the carnitine acyltransferases.

In the present study, significant decrease was found in the fasting plasma levels of propionyl-, butyryl-, and isovalerylcarbaminic esters, leading to the decrease of SCFA carnitine esters. Although the pathogenesis of UC is still unknown, a widely accepted hypothesis focuses on the pivotal role of the diminished availability of SCFAs for the enteral cells. Normally, SCFAs are rapidly absorbed from the colon and have many properties, as they represent an energy source for colonocytes and if they are exported to other tissues. Moreover, they affect lipid metabolism, colonic mucosal blood flow, motility, and mucus secretion. In the normal case, the major energy source of the epithelial cells of the distal colon derives from the metabolism of the SCFAs, which is impaired in UC. In addition to the SCFA metabolism, the influenced coenzyme A esterification has been reported to be associated with UC. In the cells, the fatty acyl moieties are transferred from coenzyme A to the beta hydroxyl group of the carnitine via the short-, medium-, and long-chain carnitine acyltransferases. These events separately or in combination, can explain the decrease of the circulating SCFA carnitine esters.

The circulating plasma carnitine profile is determined by the balance of the release and uptake mechanisms. Carnitine releases into the circulation by the liver primarily as acylcarnitine. While in the hepatic vein, the ester proportion is relatively high, approximately half of the total carnitine is esterified. The actual ester pattern detected in the peripheral blood is a result of the uptake/release action of the peripheral tissues; and in a peripheral venous blood, much less (approximately 1/3-1/4 of the total carnitine) is esterified. Whereas, the decrease of the SCFA carnitine esters found in the UC patients could be explained as discussed earlier. Based on the current knowledge, it is much more difficult due to the limited nature of the data, to explain the opposite change of the medium- or long-chain carnitine esters. Only a few studies are available reporting alterations of fatty acid metabolism. However, the data are inconsistent, but suggest the involvement of LCFA metabolism in UC. Further studies are required to clarify these issues.

After the positive results on topical SCFA treatment in UC, Gabarrini et al. studied propionyl-L-carnitine administration as rectal irrigation and found that improved clinical picture and histological status of the bowel are improved. In the light of the current findings, the likely decreased tissue reserves could be corrected by administration of the drug and the positive outcome could be a consequence of the successful replacement therapy. Whether the already known beneficial therapeutic effects of special LCFA containing or supplemented with diets are due to at least in part, a similar replacement phenomenon, also remains to be elucidated.

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