Effect of 3-Thiadicarboxylic Acid on Lipid Metabolism in Experimental Nephrosis

Ayman AL-Shurbaji, Jon Skorve, Rolf K. Berge, Mats Rudling, Ingemar Björkhem, Lars Berglund

The effect of the sulfur-substituted fatty acid analogue 1,10 bis(carboxymethylthio)decane, also known as 3-thiadicarboxylic acid, on puromycin aminonucleoside--induced nephrotic hyperlipidemia was studied in rats. Treatment with 3-thiadicarboxylic acid (250 mg/kg) for 5 days reduced plasma levels of triglycerides from 5.8 to 2.7 mmol/L and cholesterol from 11.0 to 7.7 mmol/L. This was accounted for by decreases in very-low-density lipoprotein triglycerides, very-low-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, without any major changes in the composition of plasma lipoproteins. The activities of two enzymes involved in fatty acid synthesis (ATP:citrate lyase and fatty acid synthetase) were inhibited by 3-thiadicarboxylic acid treatment, whereas acetyl-coenzyme A carboxylase activity was unchanged. In contrast, treatment with the sulfur-substituted fatty acid analogue induced the peroxisomal β-oxidation of fatty acids ninefold and the mitochondrial β-oxidation by 54% to 73%, depending on the substrate used. This was accompanied by a 26% reduction in hepatic triglyceride secretion rate. The hepatic phosphatidate phosphohydrolase activity was unchanged. 3-Thiadicarboxylic acid treatment suppressed the activity of the rate-limiting enzyme in cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, by 58%, whereas hepatic LDL receptor expression was unaltered. The activities of lipoprotein lipase and hepatic lipase were unchanged by treatment. These results demonstrated that treatment with 3-thiadicarboxylic acid ameliorates hyperlipidemia in experimental nephrosis primarily by decreasing the overproduction of very-low-density lipoprotein present. The data also indicate that hepatic very-low-density lipoprotein synthesis and secretion is strongly influenced by the availability of the fatty acid substrate under the same hyperlipidemic conditions. (Arterioscler Thromb. 1993;13:1580-1586.)

Key Words • triacylglycerol • 3-hydroxy-3-methylglutaryl-coenzyme A reductase • hypolipidemic drugs • lipoprotein synthesis • cholesterol • β-oxidation

Hyperlipidemia is a consistent feature of the nephrotic syndrome.1,2 Patients with nephrosis usually have elevated plasma levels of both cholesterol and triglycerides and might therefore be at higher risk for developing premature atherosclerosis leading to ischemic heart disease and progressive renal failure.3-6 Because of the growing recognition of this risk, several studies have assessed the efficacy of different lipid-lowering drugs in nephrotic hyperlipidemia in humans as well as in experimental animal models.7,9 Recently, a new group of hypolipidemic agents has emerged, namely the sulfur-substituted non-β-oxidizable fatty acid analogues.10 These compounds have been shown to reduce plasma triglyceride and cholesterol levels in normolipidemic rats.10,11 We have demonstrated12 that the lipid-lowering properties of these agents in normal rats are mediated by effects on hepatic very-low-density lipoprotein (VLDL) production. Since increased lipoprotein synthesis and secretion has been suggested as a major underlying mechanism in nephrotic hyperlipidemia,13-18 we investigated the effect of the sulfur-substituted fatty acid analogue 3-thiadicarboxylic acid on lipid metabolism in the nephrotic hyperlipidemic rat.

Methods

Animals and Animal Treatment

Male Sprague-Dawley rats weighing 200 to 250 g were housed individually in metal cages and maintained on a 12-hour light-dark cycle. After 1 week of acclimatization, nephrosis was induced by a single intraperitoneal injection of puromycin aminonucleoside (100 mg/kg body wt; Sigma Chemical Co, St Louis, Mo). Nephrosis was confirmed by measuring urinary albumin loss (>250 mg/24 h as determined by an immunonephelometric procedure; Nordic Immunology, Tilburg, The Netherlands) and plasma lipid levels 8 days after injection. The animals were treated with 3-thiadicarboxylic acid from day 9 through day 14 after the induction of nephrosis. 3-Thiadicarboxylic acid was suspended in 0.5% sodium carboxymethylcellulose (CMC) and administered by gavage in a daily dose of 250 mg/kg body wt. Control rats received only CMC. All animals had free access to food and water throughout the experiment. There was no significant difference in food consumption or weight.

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gain between the two experimental groups. On day 15 after injection, blood sampling was performed by heart puncture under neuroleptic anesthesia (Hynorm, Janssen Pharmaceutica, Beerse, Belgium), and the animals were subsequently killed. For lipoprotein lipase and hepatic lipase assays a separate group of rats was intravenously injected with heparin 1000 U/kg body wt 8 to 10 minutes before blood sampling.

**Enzyme Assays**

Liver tissue from individual rats was homogenized in 4 volumes of ice-cold sucrose buffer (0.3 mol/L) containing 50 mmol/L tris(hydroxymethyl)aminomethane-HCl, pH 7.4, 10 mmol/L EDTA, 50 mmol/L NaCl, and 10 mmol/L dithiothreitol. Cytosolic, mitochondrial, microsomal, and peroxisomal fractions were prepared by centrifugation as described elsewhere. The following microsomal enzyme activities were assayed as described previously: glycerol 3-phosphate acyltransferase; diacylglycerol acyltransferase; 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase; cholesterol 7α-hydroxylase; and acyl-CoA:cholesterol acyltransferase. ATP: citrate lyase, acetyl-CoA carboxylase, and fatty acid synthetase were assayed in the cytosolic fraction as described previously. For assay of phosphatidate phosphohydrolase activity, a cytosolic fraction was precipitated by 40% ammonium sulfate, and the enzyme activity was assayed as previously described. Mitochondrial and peroxisomal β-oxidation as well as fatty acyl-CoA oxidase activity were measured by the same procedures as detailed elsewhere. Heparin-releasable lipoprotein lipase and hepatic lipase activities were determined by the method of Nilsson-Ehle and Schotz. In this assay, one unit of enzyme activity corresponds to the release of 1 μmol fatty acid from triolein per minute at 37°C.

**Plasma and Hepatic Lipid Levels**

Lipids were extracted from 20% liver homogenates using methanol/chloroform (1:2, vol/vol). Triglycerides and cholesterol were measured in plasma and lipid extracts by using commercially available enzymatic assays (Boehringer Mannheim, Mannheim, FRG). Plasma free fatty acids (FFAs) were determined by an enzymatic colorimetric method (NEFAC, Wako Chemicals GmbH, Neuss, FRG) as described. Mitochondrial and peroxisomal β-oxidation as well as fatty acyl-CoA oxidase activity were measured by the same procedures as detailed elsewhere.

**Hepatic VLDL Triglyceride Secretion**

The VLDL triglyceride secretion rate was estimated by measuring the accumulation of triglyceride in plasma after a single intravenous injection of Triton WR 1339 as described before.

**Plasma Lipoprotein Analysis**

Lipoproteins were determined quantitatively by using a combination of ultracentrifugation and precipitation as described in detail elsewhere. Briefly, plasma samples were centrifuged at a density of 1.006 g/mL for 18 hours at 35 000 rpm in a Centrikon T-2060 ultracentrifuge (Contron Roche, Zürich, Switzerland) equipped with a 45.6 Ti rotor. Triglycerides and cholesterol were measured in both the infranatant (low-density lipoprotein [LDL]+high-density lipoprotein [HDL]) and the floating fraction (VLDL). One portion of the infranatant was treated with phosphotungstic acid to precipitate apolipoprotein B-containing lipoproteins, and the resulting supernatant was assayed for cholesterol and triglyceride content. To analyze the composition of each lipoprotein fraction, the infranatant fractions obtained after the initial centrifugation were subjected to further sequential ultracentrifugation, yielding LDL (1.025<d<1.063) and HDL (1.063<d<1.21) fractions. The isolated lipoprotein fractions were then subjected to a “wash” by a repeated ultracentrifugation at the upper density level. Before analysis, the lipoprotein fractions were dialyzed against 0.15 mol/L NaCl containing 0.3 mmol/L EDTA. Total cholesterol, free cholesterol, and triglycerides were determined enzymatically as mentioned above. Protein was measured by the Lowry procedure using bovine serum albumin as a standard.

Ligand Blotting

LDL receptor expression was measured by a ligand blot assay as described. Briefly, hepatic membranes were prepared from pooled frozen rat liver samples, and membrane proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, transferred to nitrocellulose filters, and incubated with 125I-labeled rabbit β-VLDL. After autoradiography of dried filters, LDL receptor bands were cut out, and radioactivity was measured in a gamma counter.

**Statistical Analysis**

Data were evaluated by Student’s t test with the level of statistical significance set at P<.05.

**Results**

Induction of nephrosis by puromycin aminonucleoside resulted in a marked hyperlipidemia, with increases in plasma levels of both triglycerides and cholesterol (Table 1). The increase in triglyceride levels was mainly accounted for by an increase in the VLDL fraction, whereas cholesterol levels increased in all lipoprotein fractions, albeit most notably in LDL and HDL. Treatment of nephrotic rats with 3-thiadicarboxylic acid decreased plasma triglyceride and cholesterol levels by 53% and 30%, respectively (Table 1). This was accompanied by corresponding reductions of VLDL triglycerides (59%), VLDL cholesterol (45%), and LDL cholesterol (39%) (Table 1). HDL cholesterol levels, however, were not affected. Despite its substantial effects on VLDL and LDL lipid levels, treatment with 3-thiadicarboxylic acid did not influence the composition of these particles to any large extent, apart from a relative increase in VLDL protein content (Table 2).

Nephrotic rats display an overproduction of VLDL triglycerides that is indicated by a higher entry rate of triglycerides into the circulation. Since 3-thiadicarboxylic acid decreases VLDL triglyceride production in normal rats, it was of interest to investigate whether this was also the case under the present hyperlipidemic conditions. For this purpose, rats were injected with Triton WR 1339, a detergent that inhibits the action of lipoprotein lipase on triglyceride-rich lipoproteins. As shown in Fig 1, the accumulation of triglycerides in plasma, which reflects the entry rate of newly synthesized hepatic triglycerides into the circulation, was reduced by 26% in 3-thiadicarboxylic acid–treated rats.
TABLE 1. Effect of 3-Thiadicarboxylic Acid on Plasma and Lipoprotein Lipid Levels in Nephrotic Rats

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Normal Rats</th>
<th>Non-treated</th>
<th>3-Thiadicarboxylic Acid Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.2±0.3</td>
<td>5.8±1.7*</td>
<td>2.7±1.0†</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>2.5±0.8</td>
<td>11.0±1.8*</td>
<td>7.7±1.9†</td>
</tr>
<tr>
<td>VLDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.55±0.09</td>
<td>5.46±1.08*</td>
<td>2.22±1.01†</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.21±0.06</td>
<td>1.32±0.17*</td>
<td>0.73±0.17†</td>
</tr>
<tr>
<td>LDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.18±0.03</td>
<td>0.30±0.13</td>
<td>0.27±0.14</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.87±0.21</td>
<td>5.16±0.57*</td>
<td>3.17±1.33†</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.13±0.03</td>
<td>0.18±0.12</td>
<td>0.10±0.00</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.37±0.11</td>
<td>4.72±0.73*</td>
<td>4.03±0.93</td>
</tr>
</tbody>
</table>

VLDL indicates very-low-density lipoprotein; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Values for nephrotic rats represent mean±SD for six rats in each group. Values for control rats represent mean±SD for six preparations of pooled plasma from three individual rats in each preparation.

*P<.05 vs normal rats.
†P<.05 vs nontreated nephrotic rats.

(3.92±0.24 mmol/L per hour versus 5.27±0.38 mmol/L per hour in controls, P<.05). In parallel, the liver content of triglyceride but not of cholesterol was reduced by 3-thiadicarboxylic acid treatment (Table 3).

Treatment with 3-thiadicarboxylic acid stimulated the mitochondrial fatty acid β-oxidation by 54% and 73% as measured with palmitoyl-CoA and palmitoyl-l-carnitine as substrates, respectively (Table 4). Also, the peroxisomal β-oxidation was markedly stimulated (by ninefold). This was reflected in a pronounced increase in the activity of peroxisomal acyl-CoA oxidase (Table 4). Of the enzymes involved in fatty acid synthesis, ATP-citrate lyase and fatty acid synthetase were significantly inhibited by 3-thiadicarboxylic acid treatment (Table 4). Acetyl-CoA carboxylase activity was not affected. Since the carboxylase is known to be the rate-limiting enzyme in fatty acid synthesis, the present findings argue against retarded fatty acid synthesis as a major underlying mechanism for the hypotriglyceridemic effect observed. Administration of 3-thiadicarboxylic acid, which decreases plasma FFA levels in normal rats, had no effect on FFA in nephrotic hyperlipidemic rats (0.45±0.06 mmol/L and 0.41±0.06 mmol/L in control and treated rats, respectively). Of the enzyme activities involved in triglyceride biosynthesis, glycerol 3-phosphate acyltransferase and diacylglycerol acyltransferase were significantly stimulated by 3-thiadicarboxylic acid treatment (Table 5). However, in con-

TABLE 2. Effect of 3-Thiadicarboxylic Acid on Lipoprotein Composition in Nephrotic Rats

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Triglycerides</th>
<th>Unesterified Cholesterol</th>
<th>Cholesterol Esters</th>
<th>Phospholipids</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontreated</td>
<td>66.2</td>
<td>6.3</td>
<td>2.5</td>
<td>15.6</td>
<td>9.4</td>
</tr>
<tr>
<td>TD treated</td>
<td>57.4</td>
<td>7.3</td>
<td>2.5</td>
<td>18.5</td>
<td>14.3</td>
</tr>
<tr>
<td>LDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontreated</td>
<td>22.8</td>
<td>6.8</td>
<td>23.9</td>
<td>24.2</td>
<td>22.3</td>
</tr>
<tr>
<td>TD treated</td>
<td>22.8</td>
<td>8.3</td>
<td>20.1</td>
<td>25.2</td>
<td>23.6</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nontreated</td>
<td>1.4</td>
<td>2.9</td>
<td>24.8</td>
<td>31.2</td>
<td>39.7</td>
</tr>
<tr>
<td>TD treated</td>
<td>1.1</td>
<td>3.3</td>
<td>24.1</td>
<td>30.7</td>
<td>40.8</td>
</tr>
</tbody>
</table>

VLDL indicates very-low-density lipoprotein; TD, 3-thiadicarboxylic acid; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.

Results represent mean values from two different experiments and are given as percent by weight. In each experiment, plasma from six rats was pooled and the respective lipoprotein fractions were isolated as described in "Methods."
The hepatic cytosolic phosphatidate phosphohydrolase activity was unaffected by treatment (Table 5). As shown in Table 1, administration of 3-thiadicarboxylic acid to nephrotic rats reduced plasma, VLDL, and LDL cholesterol levels. This was accompanied by an inhibition of HMG-CoA reductase activity (58%; Table 6). Cholesterol 7α-hydroxylase and acyl-CoA:cholesterol acyltransferase activities were depressed by 34% and 28%, respectively. Despite the inhibition of HMG-CoA reductase activity, the expression of the hepatic LDL receptor was not affected (Fig 2).

In view of earlier reports that nephrosis-induced hyperlipidemia is associated with defective clearance of VLDL, we investigated whether 3-thiadicarboxylic acid treatment affected the clearance potentiality of VLDL. As shown in Table 5, lipoprotein lipase and hepatic lipase activities were not significantly influenced by drug treatment.

**Discussion**

Treatment of nephrotic rats with the sulfur-substituted non-β-oxidizable fatty acid analogue 3-thiadicarboxylic acid resulted in a substantial reduction of markedly elevated plasma lipoprotein levels and a favorable increase in the HDL/LDL ratio. These hypolipidemic properties were mainly due to an effect on the increased hepatic VLDL synthesis and secretion, an abnormality contras to the findings in normal rats.
that has been suggested as an important causative factor in nephrotic hyperlipidemia.\cite{14,16,47,48} As shown in Fig 1, 3-thiadicarboxylic acid treatment decreased hepatic VLDL triglyceride secretion by 26%. Interestingly, this decrease was of the same magnitude as the increase in the VLDL secretion rate reported in experimental nephrosis,\cite{45} indicating that drug treatment rectified the marked stimulation of fatty acid oxidation in both peroxisomes and mitochondria (Table 4). The stimulation of fatty acid oxidation indicated that the drug interferes with the availability of the fatty acid substrate. This emphasizes the importance of this factor as a major determinant of triglyceride synthetic rate in the hyperlipidemic state. However, the role of phosphatidate phosphohydrolase as a regulatory enzyme under the present hyperlipidemic conditions is less obvious. This enzyme activity has been shown to be correlated to plasma and liver triglyceride levels and to vary in parallel with changes in plasma triglyceride levels.\cite{50,53,60,61} In normallipidemic rats, the enzyme activity decreases in parallel with the triglyceride reduction produced by 3-thiadicarboxylic acid treatment.\cite{12} However, in nephrotic rats, 3-thiadicarboxylic acid treatment did not affect this enzyme activity (Table 5). The reason for the discrepancy observed between the findings in the normolipidemic and the hyperlipidemic situations is not clear at present. It is conceivable that in the nephrotic rat, under conditions of deranged lipid metabolism and excessive plasma lipid levels, a different kind of regulation of the enzyme activity might be operative. In addition to phosphatidate phosphohydrolase, diacylglycerol acyltransferase\cite{54-57} and glycerol 3-phosphate acyltransferase\cite{48} are implicated as being of regulatory importance in hepatic triglyceride biosynthesis. The present observation that both activities were stimulated by 3-thiadicarboxylic acid treatment indicates that the triglyceride-lowering effect of this drug was not mediated through either enzyme activity. This finding would seem to argue against a rate-limiting role of glycerol 3-phosphate acyltransferase or diacylglycerol acyltransferase under the present conditions.

Hypercholesterolemia of the nephrotic syndrome might in part be due to enhanced cholesterol biosynthesis,\cite{59} which would provide a rationale for the use of drugs that inhibit cholesterogenesis to treat nephrotic hyperlipidemia.\cite{9} Indeed, HMG-CoA reductase inhibitors are effective in reducing plasma lipid levels under these conditions.\cite{7,9,60,61} In the present study, the hypocholesterolemic effect of 3-thiadicarboxylic acid was associated with a significant inhibition of HMG-CoA reductase activity (Table 6). This suggests that 3-thiadicarboxylic acid treatment might decrease cholesterol biosynthesis, thereby contributing to the decrease in VLDL secretion, as discussed above. Whether the effects on HMG-CoA reductase activity and cholesterol synthesis are secondary to retarded triglyceride production remains to be established. The finding that 3-thiadicarboxylic acid treatment also affected other enzymes in cholesterol metabolism (cholesterol 7a-hydroxylase and acyl-CoA:cholesterol acyltransferase) indicated that the drug might affect cholesterol homeostasis on different levels. It should be noted that increased cholesterol synthesis might not be the only mechanism underlying hypercholesterolemia in nephrosis. Defective LDL clearance via the receptor pathway as well as altered renal metabolism of mevalonate have also been suggested as possible mechanisms.\cite{18,62} Our finding that the hepatic LDL receptor activity was not induced by 3-thiadicarboxylic acid treatment (Fig 2) indicates that the cholesterol-lowering effect of this drug in nephrosis is probably not mediated by an effect on the LDL receptor. The hepatic mRNA levels for the LDL receptor and HMG-CoA reductase seem to be

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Nontreated Rats</th>
<th>3-Thiadicarboxylic Acid-Treated Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol 3-phosphate acyltransferase, nmol/min per milligram protein</td>
<td>1.0±0.4</td>
<td>8.4±0.5*</td>
</tr>
<tr>
<td>Microsomal fraction</td>
<td>0.6±0.1</td>
<td>1.2±0.3*</td>
</tr>
<tr>
<td>Mitochondrial fraction</td>
<td>3.6±1.0</td>
<td>5.4±0.9*</td>
</tr>
<tr>
<td>Diacylglycerol acyltransferase, nmol/min per milligram protein</td>
<td>1.0±0.2</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>Cytosolic phosphatidate phosphohydrolase, nmol/min per milligram protein</td>
<td>1.0±0.2</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>Lipoprotein lipase, U/L</td>
<td>147±29</td>
<td>184±35</td>
</tr>
<tr>
<td>Hepatic lipase, U/L</td>
<td>100±15</td>
<td>114±13</td>
</tr>
</tbody>
</table>

*Values represent mean±SD for six rats in each group.
P<.05.
regulated in a coordinate but curvilinear pattern, implying that changes in receptor expression could be elicited only when synthesis of the reductase is severely affected. Therefore, a decrease of the reductase activity on the order of 50%, as in the present study, does not necessarily result in detectable changes in the hepatic LDL receptor expression.

The clearance defect present in nephrotic hyperlipidemia is ascribed to several mechanisms. Although possible effects of 3-thiadicarboxylic acid treatment on VLDL clearance were not specifically addressed in the present study, several observations indicated that the hypolipidemic properties of 3-thiadicarboxylic acid are probably not mediated by any major effect on VLDL catabolism. First, no effect on LDL receptor activity was seen, as discussed above. Second, treatment did not affect heparin-releasable lipoprotein lipase or hepatic lipase activities (Table 5). The lack of a substantial effect of 3-thiadicarboxylic acid on VLDL triglyceride clearance might explain why plasma lipid levels were not normalized despite the decrease in VLDL secretion. However, it cannot be ruled out that 3-thiadicarboxylic acid treatment might to some extent improve VLDL catabolism. Since plasma VLDL triglyceride levels were decreased by 3-thiadicarboxylic acid treatment, lipoprotein lipase would be less saturated, and the efficiency of lipolysis and VLDL removal would be enhanced.

In conclusion, we have for the first time demonstrated that treatment with the sulfur-substituted non-β-oxidizable fatty acid analogue 3-thiadicarboxylic acid reduces both plasma triglycerides and cholesterol in a hyperlipidemic state in the rat. The triglyceride-lowering effect in the current nephrotic model was mainly achieved by stimulating fatty acid oxidation, thereby reducing hepatic triglyceride synthesis and output. The hypocholesterolemic properties were, at least in part, mediated by an inhibition of the regulatory enzyme in cholesterol biosynthesis. In other words, similar mechanisms seem to be operative in both normolipidemic and nephrotic hyperlipidemic rats. The therapeutic potential of these so-far-experimental lipid-lowering agents in hyperlipidemia remains to be established.

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References


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