Benfotiamine Inhibits Intracellular Formation of Advanced Glycation End Products in vivo

JIHONG LIN, ALEX ALT, JUTTA LIERSCH, REINHARD G. BRETZEL, MICHAEL BROWNLEE*, HANS-PETER HAMMES

Third Medical Department, Justus-Liebig-University Giessen, Germany

*Albert-Einstein College, New York, NY, USA

ABSTRACT

We have demonstrated previously that intracellular formation of the advanced glycation end product (AGE) Ne-ε-speronyl-carboxymethyllysine (CML) inversely correlates with diabetic vascular complications independently from glycemia (Diabetologia 42, 603, 1999). Here, we studied the effect of benfotiamine, a lipid-soluble thiamine derivative with known AGE-inhibiting properties in-vitro on the intracellular formation of (CML) and methylglyoxal-derived AGE in red blood cells. Blood was collected from 6 Type 1 diabetic patients (2 m, 4 f, age 31.8 ± 5.5 years; diabetes duration 15.3 ± 7.0 years) before and after treatment with 600 mg/day benfotiamin for 28 days. In addition to HbA1c (HPLC), CML and methylglyoxal were measured using specific antibodies and a quantitative dot blot technique.

While treatment with benfotiamin did not affect HbA1c levels, CML was shown to reduce CML and other AGE in target tissues of diabetic complications in-vivo (7). Thiamin is a potent AGE-inhibitor in-vitro on the intracellular formation of (CML) and methylglyoxal-derived AGE in red blood cells.

INTRODUCTION

Intracellular formation of the advanced glycation end product (AGE) Ne-ε-speronyl-carboxymethyllysine (CML) inversely correlates with diabetic vascular complications independently from glycemia (Figure 1) (1). Intracellular CML is generated by the oxidation of Amadori products or, alternatively, by lipid peroxidation (2,3). The dicarbonyl methylglyoxal is formed by non-oxidative fragmentation of glycolysis-derived triose phosphates (Figure 2) and is the most important intracellular AGE (4,5).

Thiamin is a potent AGE-inhibitor in-vitro, and benfotiamine, the lipid-soluble prodrug of thiamin, was shown to reduce CML and other AGE in target tissues of diabetic complications in-vivo (7). The possible mechanisms by which thiamine/ benfotiamine are thought to reduce intracellular AGE formation, are shown in Figure 3. We studied the effect of benfotiamine, a lipid-soluble thiamine derivative with known AGE-inhibiting properties in-vitro on the intracellular formation of (CML) and methylglyoxal-derived AGE in red blood cells of patients with type 1 diabetes.

Methods

Study group: six patients (2 males, 4 females), age 31.8 ± 5.5 years; diabetes duration 15.3 ± 7.0 years. Treatment with 600 mg/day benfotiamine (Milgamma, Wörwag, Böblingen, Germany) for 28 days after informed consent and approval by the local ethics committee.

Venous EDTA-blood (3 ml) drawn before and at the end of the study, samples lysed and centrifuged, adjusted to identical hemoglobin concentrations. Venous EDTA-blood (3 ml) drawn before and at the conclusion 6.88±0.88%; p not significant), Statistical analysis was performed using the alternate Welsh t test.

Conclusion

Thiamine derivatives, in particular the lipid-soluble prodrug benfotiamine, are effective inhibitor of intracellular formation of AGE and CML.

References


Fig. 1a: Correlation of retinopathy-free diabetes duration with the concentration of CML in memory T-cells. All results are given as mean ± SD. (A) Data from 10 patients before and after 4-week treatment with benfotiamine. * p<0.01

Fig. 1b: No correlation of mean glycated hemoglobin with CML levels in memory T-cells. All results are given as mean ± SD. (A) Data from 10 patients before and after 4-week treatment with benfotiamine. * p<0.01

Fig. 2: Biochemical pathways of intracellular AGE formation. (A) Data from 10 patients before and after 4-week treatment with benfotiamine. * p<0.01

Fig. 3: Thiamine as co-factor of enzyme systems possibly involved in AGE formation (red arrows: enzymes with known AGE-inhibiting properties)