Decrease of plasma taurine in Gaucher disease and its sustained correction during enzyme replacement therapy

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Summary. Gaucher disease is caused by an autosomal-recessive deficiency of glucocerebrosidase. Cells of monocytic/macrophagic origin accumulate glucosylceramide. This leads to hepatosplenomegaly, bone destruction, thrombocytopenia and anemia. Enzyme replacement therapy (ERT) with macrophage-targeted glucocerebrosidase leads to normalization of these parameters. The way of macrophage activation in Gaucher disease is not known. Recently, the osmolytes taurine, betaine and inositol were identified as important regulators of macrophage function in liver. Therefore, the role of plasma taurine in Gaucher disease as a primarily macrophage-derived disease was studied.

Fasting plasma levels were measured from blood samples of healthy control subjects (n = 29, m:f = 11:18, mean age 37 ± 3 years), from untreated Gaucher patients (n = 16, m:f = 7:9, mean age 44 ± 4 years) and those treated for 37 ± 2 months (n = 54, m:f = 19:35, mean age 47 ± 2 years). Amino acid analysis was carried out in a BioChrom amino acid analyzer.

In the untreated patients, plasma taurine was 45 ± 3 μM, as compared to the controls with a plasma taurine of 63 ± 4 μM (p < 0.01). The average increase of plasma taurine during the first year of ERT was 18 ± 8 μM (n = 10). Patients treated for an average of 37 months (range 1–9 years of ERT) had a plasma taurine of 65 ± 4 μM (n = 54), which was not different from the controls.

It is concluded that Gaucher patients show decreased plasma taurine levels and that therapy of Gaucher disease might correct this. It has to be established, whether decreased taurine availability is a cofactor of the permanent activation of glucosylceramide-storing monocytes/macrophages in this disease.

Keywords: Amino acids – Enzyme replacement therapy – Lysosomal storage disease – Macrophages – Liver disease
Introduction

Gaucher disease is the most frequent lysosomal storage disease. The molecular defect is a genetic deficiency of glucocerebrosidase. Cells of monocytic/macrophagic origin accumulate glucosylceramide, eventually leading to hepatosplenomegaly, hematologic changes and bone destruction. Since 1991, enzyme replacement therapy (ERT) by infusion of macrophage-targeted glucocerebrosidase is available and has been shown to improve the hematologic, visceral and bone changes of type I Gaucher disease (Barton et al., 1991; Pastores et al., 1993; Niederau et al., 1994; Grabowski et al., 1995; Beutler, 1997; Hollak et al., 1997; Niederau et al., 1998). The exact nature of the sustained macrophage activation in this disease is not known (reviewed in Hollak et al., 1997).

Recently, taurine has been identified as an important osmolyte in liver macrophages (Warskulat et al., 1997a,b; vom Dahl et al., 1999). Apart from the role of osmolytes in cell volume homeostasis it has been demonstrated that betaine, taurine and myo-inositol are important modulators of macrophage function at the level of gene expression, release of inflammatory mediators and phagocytotic activity (Warskulat et al., 1996, 1997b; Yancey et al., 1982; Zhang et al., 1995, 1996). Further, a hepatoprotective action of taurine has been described (Waterfield et al., 1993a,b; Wettstein and Häussinger, 1997; vom Dahl et al., 1998). Therefore, the role of plasma taurine in Gaucher disease was studied.

The results show a decrease of plasma taurine in this disease, which is effectively treated and maintained by enzyme replacement therapy.

Methods

Patients

Gaucher patients from all parts of Germany were admitted to the Dusseldorf Gaucher outpatient clinic for routine checks of blood tests, ultrasound and MR radiography every 6–12 months before and during enzyme replacement therapy (ERT). All Gaucher patients had the adult form of the disease (type I). The diagnosis had been confirmed by measurement of glucocerebrosidase activity in blood leucocytes (K. Harzer, Tübingen, Germany [Harzer, 1980]). Treatment was performed by intravenous infusion of either alglucerase (Ceredase®, Genzyme, Boston, MA) or imiglucerase (Cerezyme®, Genzyme, Boston, MA), which was performed on an outpatient basis by the patients’ respective local physicians. The dosage was 20, 40 or 60 units of i.v. alglucerase/imiglucerase every other week and was dependent on the severity of the disease. Fasting plasma levels were measured from blood samples of healthy control subjects (n = 29, m:f = 11:18, mean age 37 ± 3 years), from untreated Gaucher patients (n = 16, m:f = 7:9, mean age 44 ± 5 years) before initiation of ERT and those, who had been treated for more than a year (n = 54, m:f = 19:35, mean age 47 ± 2 years).

Amino acid analysis

Amino acid analysis was performed with a BioChrom 20 (Pharmacia, Freiburg, Germany). Plasma samples were deproteinized by mixing 100μl of plasma with 100μl of