Enzyme Replacement Therapy in Gaucher’s and Fabry’s Disease

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ABSTRACT

Glucocerebrosidase and ceramidetrihexoside-α-galactosidase were obtained in a high degree of purity from human placental tissue. The enzymes were infused in Gaucher and Fabry patients, respectively. Following the administration of the proteins to supplement the genetically determined deficiencies, there resulted a specific reduction in the accumulated glycolipids in the circulation and liver. These results indicate that enzyme replacement may provide hope for the clinical treatment of these disorders.

A direct approach in the study of the treatment of the sphingolipidoses has been replacement of the deficient hydrolases with purified enzymes isolated from suitable human sources. Encouraging results have been obtained along this line in patients with Fabry’s disease and the adult form of Gaucher’s disease. The clinical manifestations in these two disorders are confined to peripheral organs and tissues.

Fabry’s Disease

Hopeful findings were obtained in two patients with Fabry’s disease.1 These men received ceramidetrihexoside that had been purified from human placental tissue. There was a significant decrease in the level of circulating ceramidetrihexoside. The amount of lipid cleared from the blood was proportional to the quantity of enzyme injected. Most of the ceramidetrihexoside that accumulates in the blood vessels and kidneys appears to be derived from globoside as a consequence of erythrocytosis in reticuloendothelial tissues such as the spleen and liver. Thus, reduction of the quantity of ceramidetrihexoside in the circulation might be expected to exert a beneficial effect on the vascular and renal problems in patients with Fabry’s disease.

Several other important observations were made in the course of these experiments. (1.) It appears likely that the injected enzyme exerted its catalytic effect after it was taken up by tissues such as the liver.2 (2.) Skin tests have been carried out on the recipients of placental ceramidetrihexosidase. There was no indication that they developed sensitivity to the placental enzyme. (3.) There was an augmentation of liver α-galactosidase activity similar to that observed in the
TABLE I

Catalytic Effectiveness of Glucocerebrosidase In Vivo

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Amount of Enzyme Injected</th>
<th>Glucocerebrosidase Cleared from Liver</th>
<th>Enzyme Activity, nmole/unit of Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 x 10^6</td>
<td>0.52 x 10^-6</td>
<td>0.35</td>
</tr>
<tr>
<td>2</td>
<td>3.3 x 10^6</td>
<td>1.2 x 10^-6</td>
<td>0.36</td>
</tr>
<tr>
<td>3</td>
<td>9.3 x 10^6</td>
<td>4.0 x 10^-6</td>
<td>0.43</td>
</tr>
</tbody>
</table>

*Nanomoles of glucocerebrosidase hydrolyzed per hour.
+Based on estimated liver weight of 2200 grams and average molecular weight of 770 for glucocerebrosidase.

Tay-Sachs patient who received hexosaminidase A. It was calculated that there was nearly 3.9 times more α-galactosidase activity in the liver of one of the recipients of ceramidetrihexosidase one hour after the enzyme injection than had actually been infused into the patient. Ceramidetrihexosidase is a tetramer of four polypeptide chains. It is possible that a monomer of active placental ceramidetrihexosidase combined with subunits of the inactive enzyme in the patient’s liver and conferred catalytic activity to the patient’s mutated protein.

Gaucher’s Disease

Purified human placental glucocerebrosidase has been infused into three patients with Gaucher’s disease. These injections caused a decrease in the quantity of accumulated glucocerebrosidase in the liver of each recipient (table I). Furthermore, the elevated glucocerebrosidase in the circulation which is associated with erythrocytes returned to normal by 72 hours after injection of enzyme in two of the three patients. This decrease persisted over a long period of time. It is believed by us that the lack of reduction in circulating glucocerebrosidase in the third patient was due to the extraordinarily high level of glucocerebrosidase in her liver. In this patient only an 8 percent decrease in liver glucocerebrosidase was observed after infusion of glucocerebrosidase. The level of glucocerebrosidase in the blood appears to be a function of the amount of exchangeable glucocerebrosidase in tissues such as the liver.

Several other observations made in the course of these investigations are noteworthy. (1.) None of the patients had any fever, discomfort, or other untoward reaction to the enzyme injections. (2.) The amount of glucocerebrosidase cleared from the liver of the recipients appeared to be equivalent to the quantity of lipid that had accumulated over a period of four years in the first patient, 13.3 years in the second, and 1.7 years in the third. (3.) Serum acid phosphatase activity in the third patient was 7.3 units before injection; it had decreased to 5.9 units by one month after administration of the enzyme. Five months after infusion, her acid phosphatase level was 6.8 units. (4.) There was a constant relationship between the amount of enzyme administered and the quantity of glucocerebrosidase cleared from the liver (table II).

By obtaining needle biopsy specimens of the liver, the quantity of glucocerebrosidase that has accumulated can be determined. This information can be used to estimate how much enzyme will be required for the treatment of various patients with Gaucher’s diseases. It is rea-
sonable to conclude from these studies that enzyme replacement in non-cerebral lipid storage diseases is feasible at this time and offers considerable hope for obtaining clinical improvement in Fabry's disease and Gaucher's disease.

References


