Alterations In Glutathione Metabolism in Individuals With Classical Homocystinuria

Brian M. Gilfix
Medical Biochemistry, Dept. of Specialized Medicine, McGill University Health Centre, Montreal Quebec, Canada

Background: Classical homocystinuria is an inborn error that results in elevated homocysteine and lowered cysteine levels. Glutathione synthesis is dependent on cysteine availability and its degradation is reflected in cysteinylglycine levels.

Aim: The relationship between glutathione and cysteine leads to the question as to whether individuals with depletion of cysteine due to classical homocystinuria show any disturbance in glutathione metabolism. As part of the measurement of aminothiols in such individuals, we examined the relationship between cysteine and cysteinylglycine.


Measurement of total plasma homocysteine, cysteine, and cysteinylglycinewas performed as Described (Gilfix BM, Blank DW, Rosenblatt DS. Clin Chem 1997;43:687-8). Each determination represented a single value performed in the years between 2010 to 2020.

Results: The cysteinylglycine concentrations were directly proportional to the cysteine concentration with $R^2$ values ranging from 0.39 to 0.85. The cysteine and cysteinylglycine concentrations generally decreased as the homocysteine concentration increased; the strength of association was poor (cysteine versus homocysteine $R^2$=0.03-0.55 and for cysteinylglycine versus homocysteine $R^2$<0.06).

Conclusions: In individuals with classical homocystinuria, it can be demonstrated that the product of glutathione degradation, cysteinylglycine, is altered in response to cysteine levels. This suggests individuals with classical homocystinuria have an alteration in glutathione metabolism.
Hypothesis.
The relationship between glutathione and cysteine leads to the question as to whether individuals with depletion of cysteine due to an inherited disorder show any disturbance in glutathione metabolism.

Study Design.
This was an observation study examining the relationship between total cysteinylglycine, homocysteine, and cysteine values in plasma samples obtained over several years from six individuals with classical homocystinuria.

Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, Sex</th>
<th>Ethnic Origin</th>
<th>Vitamin B6</th>
<th>CBS Mutation</th>
<th>Clinical Features</th>
<th>Current Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>38, F</td>
<td>French-Canadian</td>
<td>Yes</td>
<td>c.313C&gt;G (p.L105V)/c.676G&gt;A (p.A226T)</td>
<td>LC, NI, EMC</td>
<td>B12, folate, B6</td>
</tr>
<tr>
<td>F</td>
<td>40, F</td>
<td>French-Canadian</td>
<td>Yes</td>
<td>c.313C&gt;G (p.L105V)/c.676G&gt;A (p.A226T)</td>
<td>LC, NI, EMC</td>
<td>B12, folate, B6</td>
</tr>
<tr>
<td>G</td>
<td>40, M</td>
<td>French-Canadian</td>
<td>No</td>
<td>Not tested</td>
<td>LD, MI, EFH</td>
<td>B12, folate, B6, betaine</td>
</tr>
<tr>
<td>H</td>
<td>40, M</td>
<td>Armenian</td>
<td>No</td>
<td>Not tested</td>
<td>LD, MI, EFH</td>
<td>B12, folate, B6</td>
</tr>
</tbody>
</table>

LD = lens dislocation
MI= mild Intellectual impairment
NI= no Intellectual impairment
BI= Intellectual impairment
EMC = elevated homocysteine on Met challenge test

Figure 1. Relationship Between Homocysteine and Glutathione

Metabolic pathway of biological thiols. Abbreviations: Hcy, homocysteine; CBS, cystathionine β-synthase; Cys, cysteine; yGluCys, γ-glutamylcysteine; GSH, glutathione; Glu, glutamic acid; and CysGly, cysteinylglycine
Correlation coefficients ($R^2$) range from 0.39 to 0.85.

**Figure 2. Changes in Cysteinylglycine Concentration With Changes in Cysteine Concentration**

**Figure 3. Changes in Cysteinylglycine Concentration With Changes in Homocysteine Concentration**

Correlation coefficients ($R^2$) are all <0.06.
Figure 3. Changes in Cysteine Concentration With Changes in Homocysteine Concentration

Correlation coefficients ($R^2$) range from 0.03 to 0.55.

Conclusions

In individuals with classical homocystinuria, the product of glutathione degradation, cysteinylglycine, changed in a direct manner with cysteine levels. Similar observation been made previously in humans and mice (Orendac M. et al. J Inherit Metab Dis 2003; 23:761-773 and Isokawa M et al. Chromatography 2016;37:147-151). This suggests that individuals with classical homocystinuria have an alteration in glutathione metabolism.

Acknowledgements.

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