No gross abnormality of plasma homocysteine after acute methionine loading in clinically stabilized patients with schizophrenia

Nurit Shlafman, Svetlana Shaldubin, Julia Applebaum, R.H. Belmaker*, Joseph Levine
Faculty of Health Sciences, Ben Gurion, University of the Negev, Beer Sheva, Israel

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ABSTRACT

Homocysteine is reported to be a risk factor for schizophrenia. The methionine loading test evaluates the summation of a multitude of enzymatic pathways associated with homocysteine metabolism. Using a challenge paradigm, we measured homocysteine levels in 10 chronic schizophrenia patients and five controls at baseline and 3 h after 100 mg/kg oral methionine. This pilot study failed to detect a gross abnormality of plasma homocysteine level after acute methionine load in patients with schizophrenia. Elevations in plasma homocysteine reported in schizophrenia do not derive from a dynamic abnormality in methionine metabolism in this challenge paradigm.

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1. Introduction

We (Applebaum et al., 2004; Levine et al., 2002) reported in two large cross-sectional studies elevated plasma and serum homocysteine levels in schizophrenia patients, especially among young males, suggesting that high serum homocysteine levels may constitute an independent risk factor for schizophrenia. A meta-analysis of eight cross-sectional case control studies suggested that a 5 μmol/L increase in homocysteine levels was associated with a 70% higher risk for schizophrenia (Muntjewerff et al., 2005). The methionine loading test may uncover latent cases of impaired homocysteine metabolism who have otherwise normal homocysteine levels. van der Griend et al. (1998) reported that about half of subjects with raised homocysteine levels after oral methionine loading test had high baseline homocysteine levels. The methionine loading test evaluates the summation of a multitude of enzymatic pathways transforming methionine to homocysteine and degrading homocysteine and is much more markedly abnormal than baseline homocysteine in heterozygote carriers of cystathionine-β-synthase deficiency (Tsai et al., 2000). den Heijer et al. (2005) found the heritability of fasting homocysteine to be 0.21, whereas the heritability of homocysteine levels after methionine loading was 0.67.

In four studies healthy controls' homocysteine levels were measured at multiple points after methionine loading (Bellamy et al., 1998; Doshi et al., 2005; Lavie and Lavie, 2004; Suliman et al., 2001). Homocysteine levels are raised about three fold after a methionine load of 100 mg/kg body weight. The rise is gradual with no clear peak and homocysteine measurements after methionine can be done at 2, 3, 4 or 6 h. Homocysteine levels vary little from lab to lab although there is some variance in mean from population to population. We hypothesized that mean homocysteine levels in schizophrenia at 3 h after methionine loading will be outside the range of the means in the studies of normals reported in literature.

The search for endophenotypes is a current major effort in the program to unravel the genetics and etiology of schizophrenia (Gould and Gottesman, 2006). We hypothesized that methionine loading may uncover a prevalent endophenotype related to schizophrenia diathesis.

L-Methionine is a naturally occurring amino acid and daily dietary intake is about 1 g per day. In many countries L-methionine is available as a food supplement, and adverse events are not reported from its use. Evidence based on the results of thousands of methionine loading tests indicates that these tests are safe (de Jong et al., 1999).

The use of methionine in schizophrenia patients is affected by reports from the 1960s and early 1970s of exacerbations of schizophrenia by methionine. We carefully examined this extensive literature (Alexander et al., 1963; Ananth et al., 1970; Antun et al., 1971; Berlet et al., 1965; Brune and Himwich, 1962; Cohen et al., 1974; Israelstam et al., 1970; Jus et al., 1970; Kakimoto et al.,...
1967; Park et al., 1965; Pollin et al., 1961). The doses used were almost always above 7 g daily and often 20 g daily. Often MAO inhibitors were given simultaneously to enhance the effect of methionine to exacerbate schizophrenia. Moreover, patients were withdrawn from antipsychotic medication. No cases were found where schizophrenia was exacerbated after one dose and usually the reported exacerbation took weeks. Only two studies (Haydu et al., 1965; Jus et al., 1970) used doses similar to those proposed here (6 g in Jus et al., 1970, 5 g in Haydu et al., 1965) and one of those used an MAO inhibitor. Neither reported exacerbation within the first few days of treatment.

We therefore felt that 100 mg/kg single dose in stable consenting outpatients on antipsychotic medication posed little risk of schizophrenia exacerbation. This statement is strengthened by the fact that there are no reports of the emergence of psychotic states in the large studies using the methionine loading test in thousands of cardiovascular, renal or Alzheimer’s patients.

2. Methods

Our study was approved by Ben Gurion University Helsinki Committee (IRB).

We recruited 10 outpatients with chronic schizophrenia (age 20–50), clinically stable for at least 3 months, all physically healthy and treated with an adequate dose of antipsychotic medication. All subjects gave written informed consent. Patients with body weight over 90 kg were excluded to avoid high doses of methionine. Patients were sent home by taxi after any symptoms of nausea or dizziness were resolved and were followed at home by telephone for 48 h. Five controls with no psychiatric illness and no chronic physical illness were recruited.

2.1. Methionine loading test

The patients were given 100 mg/kg body weight oral dose of l-methionine dissolved in 200 cc of tea or fruit juice. Blood (10 cc) for serum homocysteine levels was taken at baseline and 3 h after l-methionine loading. Eight of the 10 patients with schizophrenia smoke while three out the five controls smoke (see Table 1). None of the subjects were treated with folate or vitamin B-12 or had morbid obesity. Homocysteine was measured as previously described (Levine et al., 2002).

3. Results

Demographic data as well as baseline and 3 h post-methionine homocysteine levels are presented in Table 1. Our study showed an increase of 3 h post-methionine homocysteine levels over baseline of about two fold in schizophrenia patients. The increase from baseline at 3 h post-methionine for homocysteine level was about 20 μM.

4. Discussion

Six out 10 schizophrenia patients had baseline homocysteine levels above 15 μM and mean ± SD baseline homocysteine plasma level for the sample was 18 ± 9 μM. These results are in agreement with previous reports (Levine et al., 2002) demonstrating elevated mean homocysteine levels (>15 μM) in young male adults with schizophrenia. The control mean baseline of 10.9 μM is very similar to literature controls. The rise in homocysteine levels 3 h post-methionine in clinically stable outpatients with schizophrenia was almost identical to the controls or to literature controls (Bellamy et al., 1998; Doshi et al., 2005; Lavie and Lavie, 2004).

For all but one patient, the 3 h post-methionine test was well tolerated with no reported side effects and no exacerbation of schizophrenia. One patient however had weakness, dizziness and transient fainting following the test.

The current study used the 3 h post-methionine test. De Jonge et al. (2004) reported that there was a high correlation between plasma homocysteine measurements three and 6 h after 100 mg/kg methionine loading ($r = 0.93$). The 3 h post-methionine was used in this study to place a minimal burden of waiting and inconvenience for the schizophrenic outpatients in the study. However, one cannot completely rule out that abnormality in plasma homocysteine levels may appear after 4–6 h following methionine load and future studies may explore such a possibility.

Changes in homocysteine levels after methionine loading were suggested to reflect mainly the trans-sulfuration pathway whereas fasting homocysteine levels were suggested to mainly reflect the methylation pathway (De Jonge et al., 2004). Our results demonstrating an increase in fasting homocysteine levels in schizophrenia but not in post-methionine homocysteine levels may suggest a lack of abnormality of the trans-sulfuration pathway in schizophrenia.

### Table 1

Demographic data and baseline and post-methionine homocysteine levels in stable outpatients with schizophrenia.

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Years of illness</th>
<th>Methionine loading dose (100mg/kg)</th>
<th>Baseline homocysteine (μM)</th>
<th>Post-methionine loading homocysteine (μM)</th>
<th>Homocysteine increase (μM)</th>
<th>Side effects</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>28</td>
<td>8</td>
<td>8 g</td>
<td>17.3</td>
<td>32.5</td>
<td>15.5</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>48</td>
<td>25</td>
<td>6 g</td>
<td>12.4</td>
<td>37.4</td>
<td>25</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>40</td>
<td>16</td>
<td>8 g</td>
<td>9.2</td>
<td>26.6</td>
<td>17.4</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>44</td>
<td>20</td>
<td>6 g</td>
<td>15.5</td>
<td>26.3</td>
<td>10.8</td>
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</tr>
<tr>
<td>5</td>
<td>M</td>
<td>41</td>
<td>22</td>
<td>5.5 g</td>
<td>34.9</td>
<td>74.2</td>
<td>39.3</td>
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</tr>
<tr>
<td>6</td>
<td>M</td>
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<td>20</td>
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<td>50.6</td>
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<td>42</td>
<td>9</td>
<td>8 g</td>
<td>29.7</td>
<td>55.4</td>
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<tr>
<td>8</td>
<td>M</td>
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<td>5</td>
<td>6 g</td>
<td>9.7</td>
<td>22.2</td>
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</tr>
<tr>
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<td>M</td>
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<td>14</td>
<td>8 g</td>
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<td>35.0</td>
<td>19.2</td>
<td>Dizziness</td>
</tr>
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<td>M</td>
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<td>36.8</td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>40.1±5</td>
<td>16.1 ±7</td>
<td>7.0 ± 1</td>
<td>17.8 ± 9</td>
<td>39.7 ± 16</td>
<td>21.9 ± 9</td>
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Control subjects

<p>| | | | | | | | | |</p>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>59</td>
<td></td>
<td>9 g</td>
<td>7.9</td>
<td>22.1</td>
<td>14.2</td>
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</tr>
<tr>
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<td>M</td>
<td>53</td>
<td></td>
<td>8 g</td>
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<td>32.5</td>
<td>18.7</td>
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<td>15.4</td>
<td>37.3</td>
<td>21.9</td>
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</tr>
<tr>
<td>4</td>
<td>M</td>
<td>40</td>
<td></td>
<td>7.5 g</td>
<td>8.5</td>
<td>22.5</td>
<td>14.0</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>47</td>
<td></td>
<td>9.5 g</td>
<td>9.0</td>
<td>48.0</td>
<td>39.0</td>
<td>None</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>48.8 ±7.4</td>
<td>8.5 ±0.8</td>
<td>10.9 ±3.4</td>
<td>32.5 ±10.9</td>
<td>21.6 ±10.3</td>
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</table>
This pilot study has several limitations. The group of patients was small, and the small number of subjects did not allow a search for differential response in different subgroups of patients.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgment

This paper is dedicated to the memory of Svetlana Shaldubin who performed patient care with her usual enthusiasm, energy and warmth.

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