Rapid Communication

Moderate Alcohol Consumption in Social Drinkers Raises Plasma Homocysteine Levels: A Contradiction to the ‘French Paradox’?


Department of Psychiatry and Psychotherapy, Georg-August-University of Göttingen, 1Department of Neurology, Georg-August-University of Göttingen, 2Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nürnberg and 3Department of Psychiatry and Psychotherapy, Medical School of Hannover, Germany

(Received 4 December 2000; in revised form 4 January 2001; accepted 4 January 2001)

Abstract — Evidence from observational studies suggests that elevated levels of homocysteine are associated with an increased risk of cardiovascular diseases. We assessed whether moderate alcohol intake in healthy social drinkers, suggested to be cardioprotective according to the ‘French paradox’, influences the cardiovascular risk factor homocysteine. A total of 60 normal nourished subjects who had no evidence of vascular disease or other risk factors for hyperhomocysteinaemia were assigned to receive mineral water or 30 g of alcohol per day (as beer, red wine or spirits) for a period of 6 weeks. Homocysteine levels of social drinkers, independent of which beverage was consumed, increased during the observation. We postulate that elevated levels of homocysteine in social drinkers with regular moderate alcohol intake are at risk of developing cardiovascular diseases, which contradicts the suggested cardioprotection of alcohol according to the ‘French paradox’.

Introduction

Evidence from observational studies suggests that elevated levels of homocysteine are associated with an increased risk of cardiovascular diseases, including coronary artery disease, cerebrovascular disease, peripheral vascular disease, and venous thrombosis (Nygård et al., 1997). Furthermore, it has been observed that chronic alcoholism is associated with increased homocysteine levels (Bleich et al., 2000a,b,c; Cravo and Camilo, 2000) and could therefore be responsible for the increased incidence of stroke and myocardial infarction in this group (Bleich and Degner, 2000; Bleich et al., 2000d). The ‘French paradox’ is the lower-than-expected rate of mortality from coronary heart disease (CHD) conferred by mild-to-moderate alcohol consumption in a country where traditional risk factors of CHD (hypertension, hyperlipidaemia, smoking, diabetes) are not less prevalent than in other industrialized countries and where the diet is rich in animal saturated fat. Thus, various epidemiological studies suggested that moderate alcohol intake results in a U-shaped curve in which the equivalent of two drinks (20–40 g alcohol per day) of any kind of alcohol, especially red wine consumption, is associated with a decreased incidence of CHD compared with no drinks (St. Leger et al., 1979; Renaud and de Lorgeril, 1992; Gronbaek et al., 1995). However, higher doses result in an increased risk of infarction and stroke (Numminen et al., 2000). The present study was therefore undertaken to investigate whether moderate drinking in healthy social drinkers, suggested to be cardioprotective according to the ‘French paradox’, influences the cardiovascular risk factor homocysteine.

Subjects and Methods

The study was approved by the Ethical Committee of the University of Göttingen and written, informed consent was obtained from all subjects. The present open, controlled and non-randomized study included 60 healthy males (aged 28–44 years). The groups were identified based on their alcohol consumption within the past year: abstinent individuals (n = 15) and social drinkers (n = 45) with an irregular alcohol intake in their history, but an alcohol-free phase of 3 months prior to study entry according to their own report. They were recruited by means of advertisements in a local newspaper’s health section. Clinical diagnosis and laboratory investigations were made as described recently (Bleich et al., 2000a); a brief summary follows. In this study, social drinkers were divided into three groups consuming only beer (n = 15), red wine (n = 15) or spirits (n = 15), subjects in each of which drank 30 g of their preferred source of alcohol daily with their evening meal for a period of 6 weeks. Because the subjects drank their preferred source of alcohol, the study was not randomized. The individuals did not differ in age, racial composition, education, as well as lifetime alcohol consumption patterns. The control group consisted of 15 non-drinkers consuming only mineral water during that observation period. All subjects did not have an established diagnosis of alcohol dependency or alcohol abuse according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) of the American Psychiatric Association (1994). Furthermore, in all subjects routine laboratory analysis including liver enzymes (i.e. γ-glutamyltransferase, alanine aminotransferase and aspartate aminotransferase) revealed no abnormalities. Subjects had taken neither vitamin supplements nor other drugs before being enrolled in the study. In addition, the subjects’ nutritional assessment according to Baker et al. (1982) revealed no abnormalities (data not shown). Subjects with any other commonly known risk factors for hyperhomocysteinaemia, such as an altered nutritional status, medication

*Author to whom correspondence should be addressed at: Georg-August-University, Department of Psychiatry and Psychotherapy, Von-Siebold-Str. 5, D-37075 Göttingen, Germany.

© 2001 Medical Council on Alcoholism
(e.g. methotrexate), genetic factors [i.e. methylene tetrahydrofolate reductase (MTHFR) mutation], and other diseases (i.e. thromboembolic or cardiovascular diseases) were not included in the study. Fasting blood samples were taken from each individual, first at baseline, then at the end of the study 6 weeks later. Blood samples for measurements of homocysteine and vitamins (folate, B12, B6) were collected in ethylenediaminetetra-acetic (EDTA) acid-containing tubes and were promptly centrifuged following collection. Plasma was stored at −80°C. Nutritional assessments, laboratory methods, and genotyping for the thermolabile MTHFR variant were blindly performed on the basis of a previous study (Bleich et al., 2000a).

Statistical analyses were made using the Mann–Whitney test for independent samples or the Wilcoxon test for matched samples (Statistical Analysis Software 6.12®). The results are presented as means ± SD. P < 0.05 was considered significant.

RESULTS

As shown in Table 1, plasma samples from abstinent individuals were found at baseline and after 6 weeks to have significantly lower plasma levels of endogenous homocysteine, when compared with the levels in beer, red wine, and spirit consumers (U = 28–42, P < 0.01). Furthermore, homocysteine levels did not change significantly in abstinent individuals consuming mineral water after 6 weeks (T = 54, Z = 0.34, P = 0.73) whereas homocysteine levels of social drinkers, independent of which beverage was consumed, increased during the observation period (T = 6.5–15.5, Z = 2.32–3.04, P < 0.02) (see Table 1). Additionally, at baseline, homocysteine levels among all groups were in normal ranges (5–15 μmol/l), whereas pathological raised plasma homocysteine levels were found in consumers of red wine (15.61 μmol/l ± 1.83) and spirits (16.25 μmol/l ± 2.19) at the end of the study. Significantly raised homocysteine levels were also found in consumers of beer (14.58 μmol/l ± 1.58), but were in most cases still within the normal range. Within the subgroups (social drinkers), homocysteine levels were highest in consumers of spirits than in consumers of wine or beer, respectively. However, these differences were not significant. Overall, vitamin levels (folate, B12, B6) in all subjects were within the normal ranges during the observation period (see Table 1) and we did not observe significant changes of vitamin levels, except for significantly lower folate levels (Table 1) in consumers of red wine (T = 34, P < 0.02) and spirits (T = 18, P < 0.02) at the end of the observation period. In addition, the folate concentration at baseline in the social drinkers was significantly lower than in the abstinent group (U = 30, P < 0.05).

DISCUSSION

In the present study, raised homocysteine levels in social drinkers with daily alcohol consumption of beer, red wine or spirits have been found. To our knowledge, this is the first investigation of the independent cardiovascular risk factor homocysteine in subjects with a social drinking pattern. Furthermore, we observed decreasing folate levels which may help explain the rise in total plasma homocysteine. However, this study is rather limited, taking into account the relatively small number of participants. In addition, only single measurements were taken at baseline and at the end of the trial, whereas repeated specimens may have given more precise results.

There is evidence that chronic alcoholism linked with alcohol dependency is associated with hyperhomocysteinaemia (Bleich et al., 2000a,b; Cravo and Camilo, 2000). The reasons for the significant correlation between blood alcohol concentration on the one hand, and plasma homocysteine on the other, regardless of whether beer, wine or spirits had been consumed (Bleich et al., 2000b), are most likely complex ones in alcohol-dependent patients: impairment of remethylation of homocysteine is brought about on account of a dysfunction of methionine synthase (MS), due to an alcohol-induced vitamin deficiency (folic acid and vitamin B12), as well as a direct inhibition of MS due to acetaldehyde (Kenyon et al., 1998), the product of the oxidative degradation of alcohol. In the present study, consumers of red wine and spirits had significantly lower folate levels when compared with concentrations at baseline. Taking into account that plasma homocysteine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mineral water</th>
<th>Beer</th>
<th>Red wine</th>
<th>Spirits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hcy (μmol/l)</td>
<td>9.06 ± 2.08</td>
<td>11.67 ± 2.17</td>
<td>12.69 ± 1.85</td>
<td>13.80 ± 2.22</td>
</tr>
<tr>
<td>Folate (μg/l)</td>
<td>12.3 ± 4.8</td>
<td>9.7 ± 3.3</td>
<td>9.2 ± 3.8</td>
<td>11.3 ± 5.3</td>
</tr>
<tr>
<td>B12 (ng/l)</td>
<td>512 ± 198</td>
<td>428 ± 118</td>
<td>612 ± 158</td>
<td>479 ± 87</td>
</tr>
<tr>
<td>B6 (μg/l)</td>
<td>11.3 ± 4.2</td>
<td>14.3 ± 6.2</td>
<td>9.9 ± 2.8</td>
<td>10.3 ± 4.1</td>
</tr>
<tr>
<td>Hcy (μmol/l)</td>
<td>8.47 ± 1.42</td>
<td>14.58 ± 1.58*</td>
<td>15.61 ± 1.83*</td>
<td>16.25 ± 2.19*</td>
</tr>
<tr>
<td>Folate (μg/l)</td>
<td>11.5 ± 3.9</td>
<td>8.9 ± 4.1</td>
<td>7.1 ± 3.9†</td>
<td>9.1 ± 2.3†</td>
</tr>
<tr>
<td>B12 (ng/l)</td>
<td>578 ± 112</td>
<td>479 ± 77</td>
<td>543 ± 87</td>
<td>528 ± 115</td>
</tr>
<tr>
<td>B6 (μg/l)</td>
<td>9.8 ± 3.1</td>
<td>13.8 ± 4.7</td>
<td>8.4 ± 2.8</td>
<td>9.2 ± 3.9</td>
</tr>
</tbody>
</table>

Non-drinking individuals (n = 15) consumed mineral water whereas social drinkers (n = 15 per group) consumed 30 g of alcohol daily in the form of beer, red wine or spirits over a period of 6 weeks. Homocysteine (Hcy) and vitamin levels (folate, B12, B6) were analysed at baseline and after 6 weeks, respectively. Normal ranges are as follows: folate (4–17 μg/l), vitamins B12 (4–20 μg/l), B6 (170–850 ng/l) and Hcy (5–15 μmol/l). Homocysteine concentrations were significantly increased in social drinkers, especially in consumers of red wine and spirits (Mann–Whitney U-test, P < 0.01). The latter alcohol consumers also had significantly lower folate levels (P < 0.02). Statistical details are summarized in the Results section. Significant (P < 0.02) changes are indicated as follows: *significant increase; †significant decrease.
concentrations are inversely correlated with the folate status, this might be consistent with the above-mentioned observation. In addition, it has been known for many years that ethanol has an effect on folate metabolism, which could not be explained by an alcohol-induced low intake of folate (Sullivan and Herbert, 1964). The aetiology of folate deficiency in alcoholism can be ascribed to several causes, such as low dietary intake, poor absorption, decreased hepatic uptake and retention, and increased urinary excretion of folate (Halsted and Keen, 1990). Furthermore, beer is a rich source of folate (about 90–120 µg/40g alcohol) and vitamin B₆ (about 0.3–0.5 mg/40 g alcohol), whereas red wine and spirits contain negligible amounts of these vitamins, which might explain that the consumers of beer had nearly consistent serum folate levels. Additionally, abstinent individuals were shown to have significantly higher levels of folate, which might be explained by the lack of an alcohol-induced folate depletion, as described above. Even though in all subjects routine laboratory analysis (i.e. liver enzymes) and nutritional assessment revealed no abnormalities, non-drinkers may have other hitherto unevaluated lifestyle habits, which possibly predispose them to lower homocysteine values.

Mildly elevated plasma homocysteine levels have been associated with an increased risk of coronary heart disease (Nygård et al., 1997; Folsom et al., 1998; Refsum et al., 1998). How can we explain the ‘French paradox’ considering the inconsistent notions discussed above, especially the observation that homocysteine levels were raised after 6 weeks of consumption of red wine and spirits by 19% and 17%, respectively? The latter increase in homocysteine coincides with an increase of CHD risk of ~20% (Verhoef et al., 1998). However, some other effects of alcohol may counteract the effect of homocysteine (Paasilta et al., 1998; Bleich et al., 2000e) and, in addition, other known risk factors for cardiovascular diseases (i.e. hypertension) must be taken into account. Furthermore, elevated plasma homocysteine levels may increase the risk for different types of vascular diseases (i.e. cerebral microangiopathy, brain infarction, peripheral vascular disease) whereby the exact mechanisms are largely unknown (Fassbender et al., 1999).

A careful interpretation must be made of even the best studies on ‘French paradox’ from the methodological point of view: it is not advisable to limit oneself to geographical studies naively comparing very different populations and attributing the differences in morbidity solely to the consumption of alcohol. For example, when analysing the ‘French paradox’, there are quite large differences between CHD death rates given by the official statistics and the MONICA data, from a project organized by the World Health Organization. For example, the north–south gradient in CHD mortality observed in France was found to be much more pronounced for case fatality than for incidence (Lang et al., 1999), which could be called an under-certification bias, at least in part. Thus, it is feasible that official statistics underestimate CHD death rate in France and overestimate the ‘French paradox’. Additionally, it has not yet been sufficiently investigated if the ‘French paradox’ might be due to the high dietary diversity in France, a low dietary diversity shown to be associated with an increased CHD mortality, rather than to be caused by a single food or beverage (i.e. red wine) (Kant et al., 1993; Criqui and Ringel, 1994).

Taking into account the present observation of elevated homocysteine levels in social drinkers, we would like to shed further light on this issue. We postulate that elevated levels of homocysteine in social drinkers with regular moderate alcohol intake are at risk of developing cardiovascular diseases, which contradicts the suggested cardioprotection of alcohol according to the ‘French paradox’. Furthermore, from a medical and ethical point of view, it must be considered alongside the significant negative effects of alcohol consumption; alcohol causes numerous health problems and immoderate intake can also lead to alcoholism, a disease with negative social and physiological effects that are likely to outweigh any benefits that accompany alcohol consumption. Nevertheless, further investigations and controlled studies are needed to clarify a possible risk assessment between social drinkers’ alcohol consumption, homocysteine and the ‘French paradox’.

REFERENCES


