Why Does Elevated Plasma Homocysteine Result in Severe Microvascular Injury, but Not Glomerular Damage?

To the Editors:

Chen et al. report a deleterious effect of acutely administered homocysteine (H(e), resulting in plasma H(e) levels of 14.7 [control 6.7] μmol/l) on renal function in a rat model. Furthermore, in a chronic hyperhomocysteinemic model (6 weeks, H(e) 2.5 times control level), they found marked sclerotic changes in aorta and glomeruli.

Recently, we pursued an analogous line of thinking and wondered whether hyperhomocysteinemia might lead to renal dysfunction by inducing endothelial dysfunction and glomerulosclerosis. If so, a self-perpetuating pathophysiological process would ensue, because renal dysfunction itself leads to hyperhomocysteinemia, supposedly by means of decreased activity of H(e) processing enzymes. We sought support for this hypothesis in two ways.

First, we looked for evidence in an experiment of nature: patients with homozygous homocystinuria who have strongly elevated H(e) levels (≥100 μmol/l, ie, 5 times normal, <18 μmol/l) from birth onwards. We studied the charts of 16 patients who presented at adult age (median age 35 years) and had been previously untreated for hyperhomocysteinemia. Although >50% had clinically overt macrovascular disease, all patients had normal renal function (mean creatinine clearance: males 136, females 103 mL/min) as assessed by the Cockcroft-Gault formula, 5/16 had trace albuminuria, and none had abnormalities in the urinary sediment.

Second, we hypothesized that in a group of patients with a similar degree of renal insufficiency (of various origin), the patients with the fastest rate of renal function decline would have the highest H(e) levels. We included 25 patients from a cohort longitudinally studied for prevention of renal function decline and correlated the slope of renal function decline during a median follow-up of 3.1 years with homocysteine levels. Glomerular filtration rate was measured by 125I-iothalamate clearance. We identified 12 patients with a rapid decline and 13 with a slow decline (glomerular filtration rate 59 ± 31 versus 65 ± 25 mL/min, P = 0.63, rate of decline -4.85 ± 2.5 versus -0.29 ± 1.8 mL/min/year, P < 0.001). We did not find any difference in H(e) levels in patients with rapid versus slow decline of renal function, 19.3 ± 11.9 versus 13.7 ± 3.3 μmol/l (P = 0.13).

From these analyses we conclude that there is no evidence that hyperhomocysteinemia in humans results in significant renal damage. If H(e) is noxious to the human vascular endothelium, the renal microvasculature appears to be protected from this effect.

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Response

Rensma et al argue that homocysteine (H(e)) is noxious to the human vascular endothelium and that the renal microvasculature appears to be protected from this effect. By analyzing their results, however, we found that failure to correlate changes in renal function and plasma H(e) may be related to the sensitivity of their measurements to represent renal function, the small sample sizes, and criteria for selecting patients. In the first group of patients with homocystinuria, they used creatinine clearance (CRIc) to measure glomerular filtration rate (GFR). However, CRIc overestimates GFR and cannot precisely represent renal function under certain circumstances. The Cockcroft-Gault formula usually overestimates GFR and produces an error two times larger than other methods. In addition, hyperhomocystinemic patients usually suffer from severe metabolic disorders; therefore, the creatinine metabolism may be disturbed in these patients, which would affect CRIc. In fact, a recent study reported that hyperhomocysteinemia markedly altered the activity of creatinine phosphokinases. Therefore, one should be cautious in using CRIc for evaluation of renal function during hyperhomocysteinemia. In a comparable study, McCully demonstrated the possible role of H(e) as an independent risk factor in cardiovascular diseases. He documented that renal vascular and glomerular injury in a patient with homocystinuria was similar to that in other vascular beds. Therefore, there should be no protection in the kidney from H(e)-induced sclerotic damage in homocystinuric patients.

In the second group of patients, Rensma et al used a different method to measure GFR and found that there was no significant difference in H(e) levels in patients with rapid versus slow decline of renal function. However, plasma H(e) level was 19.3 μmol/L in a group of patients with rapid decline of renal function, which in fact was higher, but not significantly higher than the 13.7 μmol/L in patients with slow decline of renal function. Perhaps the sample size of patients was too small to reach a significant difference in H(e) levels. In addition, because these patients were chosen without diet control and were suffering from different diseases and receiving different therapeutic regimens, we could not exclude the effects of these factors on the relationship of H(e) levels and renal function. Moreover, baseline GFR in these selected patients was already different at the beginning of their study (74 versus 66 mL/min by calculation), indicating that renal function in the two groups was different to begin with. It is unreasonable to compare two groups of patients with different starting status of renal function. In fact, there is considerable evidence indicating a positive relationship between GFR and plasma H(e). It should not be in question that GFR decline is associated with elevation of plasma H(e).
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