Editorial

Does Homocysteine Promote Atherosclerosis?

Steven R. Lentz

The hypothesis that homocysteine is atherogenic was proposed more than 30 years ago by Kilmer McCully, who observed vascular lesions in children with inherited disorders of methionine metabolism. Since McCully’s pioneering observations in 1969, a large number of epidemiological studies have confirmed that an elevation of total plasma homocysteine (tHcy) is prevalent in patients with stroke, myocardial infarction, peripheral vascular disease, and venous thrombosis. A significant association between hyperhomocysteinemia and clinical cardiovascular events has been observed in several large prospective studies, although a few prospective studies have failed to demonstrate this association. Nevertheless, hyperhomocysteinemia is now considered by many an independent risk factor for atherosclerotic vascular disease.

There is, however, an abundance of evidence that hyperhomocysteinemia produces functional abnormalities of blood vessels. Impairment of endothelium-dependent vasomotor responses has been observed during experimental hyperhomocysteinemia in several animal species, including nonhuman primates, rats, and mice. Abnormal endothelium-dependent vasorelaxation also occurs in human subjects with acute hyperhomocysteinemia. These observations suggest that hyperhomocysteinemia may not promote the development of atherosclerosis per se, but it instead may alter vascular function in a way that increases risk for complications of atherosclerosis. This idea is supported by a prospective study of Norwegian patients with coronary artery disease, in whom hyperhomocysteinemia was found to be a strong predictor of mortality, but it did not correlate with the extent of coronary artery atherosclerosis.

Two recent studies challenge this view, however, by demonstrating that a moderate elevation of plasma tHcy accelerates the development of atherosclerotic lesions in apoE-deficient mice. ApoE-null mice have 5 times the normal plasma concentration of total cholesterol, and they develop complex atherosclerotic lesions spontaneously. Hofmann and colleagues found that, when apoE-null mice were fed a hyperhomocysteinemic diet for 8 weeks, they developed atherosclerotic lesions in the aorta that were of greater size and complexity than those seen in apoE-null mice fed normal chow.

The findings of Hofmann and colleagues are confirmed and extended by Zhou and colleagues in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology. These investigators fed apoE-null mice a high-fat diet, and some mice received supplemental methionine or homocysteine to produce moderate hyperhomocysteinemia. After 3 months, the mice fed the hyperhomocysteinemic diets had significantly larger mean aortic lesion areas compared with apoE-null mice fed the control diet. These 2 reports are the first to demonstrate that moderate hyperhomocysteinemia influences the development of atherosclerosis in a susceptible animal model.

The similarity of the observaions by Hofmann and colleagues and Zhou and colleagues is remarkable given that the 2 studies used very different dietary approaches. Hofmann and colleagues used a low-fat diet that was enriched with methionine and deficient in folate, vitamin B₁₂, and vitamin B₉. Zhou and colleagues used a high-fat diet and produced hyperhomocysteinemia by adding homocysteine or excess methionine to the diet. The levels of plasma tHcy produced by the 2 approaches were similar (36 to 47 µmol/L). Hofmann and colleagues studied mice at a single time point (8 weeks), whereas Zhou and colleagues examined mice at 2 time points, after either 3 or 12 months of the experimental diet. Interestingly, when apoE-null mice were examined after...
12 months, no differences in aortic root lesion areas were observed between hyperhomocysteinemic and control mice. This finding is concordant with a recent study in cynomolgus monkeys, in which hyperhomocysteinemia did not alter carotid artery lesion areas in monkeys fed a high-fat diet for 17 months.23 These results suggest that the influence of hyperhomocysteinemia on atherosclerosis may be transient or that an adaptive response to the hyperhomocysteinemic diet may occur over time. Another possible explanation for the failure of these studies to demonstrate an interaction between hyperhomocysteinemia and hypercholesterolemia in older animals is that the atherosclerotic lesions produced by prolonged hypercholesterolemia may have been so advanced that the influence of a secondary risk factor such as hyperhomocysteinemia was no longer apparent.

How might hyperhomocysteinemia drive the early stages of atherogenesis? At least 3 mechanisms seem plausible. First, hyperhomocysteinemia may activate inflammatory responses that lead to the recruitment of monocytes to the arterial wall. In support of this mechanism, Hofmann and colleagues16 observed evidence of chronic inflammation in hyperhomocysteinemic mice, including an increased expression of vascular cell adhesion molecule-1 and elevated plasma levels of tumor necrosis factor-α. Second, hyperhomocysteinemia may increase the oxidative modification of LDL, thereby promoting uptake of LDL-cholesterol by macrophages.24 Third, hyperhomocysteinemia may dysregulate cholesterol and triglyceride metabolism in vascular cells through activation of the sterol regulatory element-binding factor.25 Defining the relative importance of these and other mechanisms will be an important goal of future investigations.

The studies by Hofmann and colleagues16 and Zhou and colleagues17 represent a major advance in our understanding of the pathophysiology of hyperhomocysteinemia, because they demonstrate that hyperhomocysteinemia is atherogenic, at least in the presence of another potent risk factor. These studies also raise some intriguing questions, however. Although the formation of atherosclerotic lesions was accelerated in the presence of hyperhomocysteinemia, this effect seemed to wane with time, and it remains uncertain whether hyperhomocysteinemia promotes atherosclerosis in the absence of hypercholesterolemia. It also is not apparent whether the atherogenic effects of hyperhomocysteinemia contribute to complications such as plaque rupture or thrombosis. In fact, the observations of Hofmann and colleagues16 and Zhou and colleagues17 suggest disparate effects of hyperhomocysteinemia on plaque stability. Hofmann and colleagues16 found that hyperhomocysteinemic mice had increased expression of procoagulant tissue factor and activation of metalloproteinases, findings that might be predicted to predispose to plaque rupture and thrombosis. In contrast, Zhou and colleagues17 found that hyperhomocysteinemia was associated with an increase in the collagen content of lesions, a finding that might be expected to stabilize plaques.

Answers to these questions may emerge from the continuing development of better animal models for the investigation of atherosclerosis and its complications.22 In the meantime, McCully’s6 hypothesis is being put to the test in ongoing clinical trials of tHcy-lowering vitamins.
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