Homocysteine and oxidative stress

Review Article

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Summary. Hyperhomocysteinemia is an independent risk factor for cardiovascular disease (ischemic disease, such as stroke and myocardial infarction, and arterial and venous thrombotic events) in the general population. We can assume that the association is causal, based on the example of homocystinuria, and on the evidence put forward by several basic science and epidemiological studies; however, the results of large intervention trials, which will grant further support to this hypothesis, are not yet available. In addition, the mechanisms underlying this relationship, and also explaining the several toxic effects of homocysteine, related or not to cardiovascular disease, are unclear. Oxidation is one of the most favored postulated mechanisms; others are nitrosylation, acylation, and hypomethylation. Regarding the relative importance of these mechanisms, each of these hold pros and cons, and these are weighed in order to propose a balance of evidence.

Keywords: Homocysteine – Homocystinuria – Cardiovascular risk – Mechanisms of toxicity – Uremia – Chronic renal failure

Hyperhomocysteinemia is an independent risk factor for cardiovascular disease (ischemic disease, such as stroke and myocardial infarction, and arterial and venous thrombotic events) in the general population. Cardiovascular disease remains the major cause of morbidity and mortality, at least in the developed world. Well-studied risk factors, such as hypercholesterolemia, hypertension, smoking, obesity, etc., cannot explain in all instances the occurrence of cardiovascular disease events. Therefore, the interest of the scientific community is going towards new and potentially modifiable risk factors such as hyperhomocysteinemia. A large body of epidemiological evidence indicates the presence of an association between cardiovascular risk and hyperhomocysteinemia. In the general population, where cross-sectional and prospective studies were performed, even mild or moderate increases in blood homocysteine levels are associated with an increase in cardiovascular risk. This association is dose-related, and independent from other risk factors. However, some of the prospective large population studies were negative, so the matter is still under heated debate (Eikelboom, 1999). In a recent meta-analysis, including 30 studies and more than 6000 events, a 25% lower homocysteine level was associated with an 11% lower ischemic heart disease risk and a 19% lower stroke risk. It is concluded that homocysteine is a modest cardiovascular risk factor, in a healthy population. Nevertheless, the implications of lowering homocysteine levels could still be substantial (Homocysteine studies collaboration, 2002). In 1998, the International Task Force for Prevention of Coronary Heart Disease proposed, in a comprehensive document on cardiovascular risk factors (http://www.chd-taskforce.com), the criteria to be used to assess cause-effect relationships relevant to cardiovascular risk factors. These are: the availability of prospective studies, with the factor preceding the effect; strength and consistency of associations; independency, with a continuous effect; availability of basic science studies establishing a mechanism in the appropriate experimental models; positive intervention studies. Regarding homocysteine, several prospective studies are available, assessing independency, and the absence of a threshold. Basic science studies are available, even if conditions were not always appropriate; and several intervention trials are currently underway, both in the general population and in selected patient
population groups, such as kidney transplant recipients, with results available in the near future (Bostom, 2001).

Homocysteine (Fig. 1) is a sulfhydryl amino acid metabolized to cysteine in the transsulfuration pathway, where cystathionine-beta-synthase (CBS) is the rate-limiting enzyme. The remethylation pathway instead leads to methionine formation from homocysteine, which receives a methyl group from methyltetrahydrofolate. Methionine, contained either in the diet or originating from protein breakdown, is condensed with ATP to form S-adenosylmethionine (AdoMet). AdoMet in turn donates its methyl group in the transmethylation pathway to various methyl acceptors, and its demethylated product is S-adenosylhomocysteine (AdoHcy). AdoHcy is hydrolyzed to adenosine and homocysteine in a reversible reaction, which is inhibited by AdoHcy itself (competitive product inhibition).

The inherited enzymatic defect of CBS represents the most common form of homocystinuria, in which affected patients, who display very high homocysteine levels in blood, and a variety of clinically relevant derangements attributable to homocysteine accumulation, used to die of premature cardiovascular disease (McCully, 1969). Therefore, homocystinuria is the first described human model of hyperhomocysteinemia, in which the latter causes high mortality levels, and therapy leads to a significant increase in survival (Wilcken, 1997). Animal models are consistent with the view that homocysteine causes cardiovascular disease: knock-out mice for the methylenetetrahydrofolate gene, which display hyperhomocysteinemia, show developmental retardation and abnormal lipid deposition in the aorta (Chen, 2001). Recently, induction of hyperhomocysteinemia in ApoE-null mice, a model of genetic susceptibility to atherosclerosis, accelerates the development of atherosclerotic lesions (Hofmann, 2001).

As said above, epidemiological data are important, but in vitro molecular biology and cellular studies, in which conditions can be controlled, are of equal importance in establishing cause-effect relationships. Homocysteine may act as a toxin with respect to endothelial cells, can enhance vascular smooth muscle cell proliferation, increase platelet aggregation, and act on the coagulation cascade and fibrinolysis, thus directly inducing or acting in a synergistic manner with other factors in determining the appearance of atherosclerosis. In particular, it activates coagulation factors V, X, and XII, along with decreased activation of protein C and cell-surface thrombomodulin, and modulation of tissue plasminogen activator binding to its endothelial receptor, annexin II, thus creating a prothrombotic environment (Thambryrajah, 2000). In addition, it determines specific alterations of endothelial cells. For example, homocysteine induces alterations of the arterial endothelial barrier, but only when added in combination with copper, that is when there is generation of hydrogen peroxide (Berman, 1993). Homocysteine inhibits, through AdoHcy accumulation, methylation of protein p21ras in cultured vascular endothelial cells. P21ras hypomethylation leads to reduced membrane association of this important regulator of cell cycle, thus it may have important effects on atherosclerotic