Homocysteine, smoking and vascular disease

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Cigarette smoking has long been recognised as a major risk factor for vascular disease, while the role of homocysteine, a relatively ‘new boy on the block’ is still unclear. Homocysteine, a sulphur-containing amino acid, was first linked to a human disorder in 1963. This was with the identification in Ireland[11] and in the U.S.A.[2] of a new inborn error of metabolism associated with the urinary excretion of homocystine, the oxidised form of homocysteine. Homocystinuria was later shown to be due to a deficiency of the enzyme cystathionine $\beta$-synthase, which mediates the conversion of homocysteine to cystathionine in the metabolism of the essential amino acid, methionine. Untreated, this defect is associated with elevated plasma methionine, very high levels of circulating total homocysteine (150–300 $\mu$mol $l^{-1}$), commonly a marfanoid bodily habitus and dislocation of the ocular lens and, importantly, with precocious vascular disease. It was McCully who first postulated that the vascular complications of the biochemical changes occurring in homocystinuria were the result of the elevated homocysteine[3]. The landmark study by Mudd and colleagues in 1985[4] documented the natural history of vascular disease in 629 patients with homocystinuria due to cystathionine $\beta$-synthase deficiency and showed that after the age of 10 years a vascular event occurred in 50% of these patients before the age of 30 years. It has been established recently that aggressive lowering of these grossly elevated homocysteine levels markedly reduces this greatly increased cardiovascular risk[5,6].

The concept that even mild elevation of circulating homocysteine might also contribute to the aetiology of vascular disease came from a recognition of the difficulty of explaining the totality of the occurrence and extent of coronary artery disease solely in terms of the recognised standard risk factors[7]. Indeed, we were only able to account for about 50% of the variance in severity of angiographically-determined coronary disease in patients aged less than 65 years, in terms of the hierarchy of circulating lipid variables and other clinical factors known to be predictive of vascular disease[8]. Many studies have now confirmed the presence of an association between modest homocysteine elevation and the occurrence of vascular disease[9], and most recently also with Alzheimer disease[10], perhaps emphasising the importance of a vascular component in its development.

The very large Hordaland total plasma homocysteine and cardiovascular risk profile study conducted in Norway identified a positive association between elevated plasma total homocysteine levels and a number of cardiovascular risk factors including, particularly, smoking[11]. The results of the study by O’Callaghan and colleagues in the present issue provide compelling support for this observation but show further that cardiovascular risk in smokers is markedly increased when plasma homocysteine is also increased[12]. In the comprehensive analysis now reported from the large European Concerted Action Project case control study, O’Callaghan and colleagues provide convincing evidence for an amplifying effect of cigarette-smoking on homocystine-associated cardiovascular risk[13]. Smokers with plasma homocysteine levels above 12 $\mu$mol $l^{-1}$ had, in this study, a 12-fold increase of cardiovascular risk when compared with the risk in non-smokers with plasma homocysteine less than 12 $\mu$mol $l^{-1}$. B vitamins, particularly folic acid, tended to be lower in the smokers, as expected, but importantly the amplification of risk persisted after controlling for the levels of B-vitamins. The mechanisms mediating this synergy between homocysteine and smoking remain unclear.

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Although a number of mechanisms have been proposed to explain the association between mild homocysteine elevation and vascular disease, and these are reviewed by O’Callaghan et al. in their paper, there is now a large literature on this subject indicating that homocysteine-associated endothelial dysfunction is a major contributor. There is also recent evidence for an association between elevated homocysteine and enhanced oxidative stress, and that this may be prevented by oral folate which also lowers elevated homocysteine\[13\]. Folic acid may also have an anti-oxidant effect as suggested by Verhaar et al.[14] and influence nitric oxide mediated vasodilatation through this mechanism.

An interesting study by Usui et al. supports this by showing that oral folate in a single large dose (10 mg) prevented the impaired flow-mediated dilatation known to occur after a standard methionine load and, importantly, without affecting the methionine-induced acute increase in plasma homocysteine concentration\[15\]. It is relevant too that Yamamoto and colleagues have recently shown that homocysteine decreases the binding to the endothelial cell of the principle enzymatic scavenger of superoxide in the extracellular space, extracellular superoxide dismutase\[16\]. Extracellular superoxide dismutase levels in the extracellular space are normally in equilibrium with glycosaminoglycans on the endothelium. The effect of an increase in homocysteine on the binding to the endothelium of endothelial extracellular superoxide dismutase would therefore result in an increased vulnerability of the endothelium to oxidative stress. Since it is now well established that cigarette smoking is also associated with an increase in markers of oxidative stress\[17\] amplification by smoking of this homocysteine-related effect may be a mechanism contributing to the finding by O’Callaghan and colleagues of synergism between the two\[14\].

In this connection the seven major homocysteine-lowering trials with folic acid currently underway in vascular patients will certainly clarify whether or not folate therapy is protective and relevant to cardiovascular risk and the results are eagerly awaited\[18\]. It is interesting to reflect, however, that if the trials are positive they will not separate the effects on cardiovascular risk of oral folate supplementation from those of lowering modestly elevated plasma homocysteine; and the issue as to whether or not a mild elevation of homocysteine is a marker of, or a mediator of, vascular disease will still remain unresolved.

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References