Cigarettes and ADMA: The Smoke Hasn’t Cleared Yet

To the Editor:

The recent study by Zhang et al\(^1\) indicates that exposure to cigarette smoke extracts (CSE) increases the concentration of the endogenous NO synthase inhibitor asymmetrical dimethyl-arginine (ADMA) in human endothelial cells in vitro. They provide evidence that CSE decreases L-arginine uptake in the cells, in part because of a decreased expression of the type 1 cationic amino acid transporter. Moreover, after incubation with CSE, the intracellular ADMA concentration was significantly higher, and the L-arginine concentrations significantly lower, than in the control cells. This increase in intracellular ADMA, which also leads to a decreased endothelial NO synthase activity, could be attributable to a decrease in dimethylarginine dimethylaminohydrolase activity caused by oxidative stress. Furthermore, clinical data in a small number of men show that ADMA is doubled in smokers as compared with nonsmokers. These elevated ADMA levels in conjunction with an almost significantly decreased plasma L-arginine are thought to be the main reason for the markedly reduced NO production in the smokers examined.

Although an increase in intracellular ADMA concentrations after long-term nicotine exposure had been previously shown in rabbits,\(^2\) these new findings are intriguing in that they help to explain the deleterious effects of smoking in much more detail. As appealing as these data are, a consideration of the role of ADMA in cardiovascular disease (reviewed by Cooke\(^3\)) leads one to believe that the matter is more complex, as suggested. In contrast to this study by Zhang, Eid et al\(^4\) found decreased ADMA levels and elevated L-arginine levels resulting in higher NO\(_x\) levels, thus suggesting increased NO production, in smoking versus nonsmokers elderly men (n=563).\(^4\) The elaborate characterization of their cohort showed that body mass index, insulin levels, HOMA score, and creatinine were significantly lower in smokers as compared with nonsmokers. After correction for these variables, smokers still had higher L-arginine levels, but the difference in ADMA and NO\(_x\) levels was no longer statistically significant. These obviously important clinical variables are not provided for the very limited number of patients described by Zhang et al\(^1\) Even in the largest clinical study on ADMA (n=1874), the authors of the study found only a small, however significant, difference between median ADMA levels in current and ever smokers (0.64 \(\mu\)mol/L) versus nonsmokers (0.61 \(\mu\)mol/L), although the difference was not corrected for confounding factors. Additionally, Wang et al\(^5\) found only a modest association between smoking and increased ADMA levels in a cohort of patients with coronary artery disease (nonsmoker versus current smoker, 0.43 \(\pm\)0.07 \(\mu\)mol/L versus 0.47 \(\pm\)0.08 \(\mu\)mol/L, \(P\)=0.03).\(^5\)

Hence, the effect of smoking on the NO/ADMA pathway seems to be more complex than suggested by the described mechanisms on a cellular level. Many factors, some of them yet unknown, might lead to a multifaceted interplay resulting in the discordance between clinical and experimental data. Nevertheless, this should not keep us from relentlessly advocating smoking cessation and prevention.

Disclosures

None.

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