Antiproliferative and antiangiogenic effects of 3-methylcholanthrene, an aryl-hydrocarbon receptor agonist, in human umbilical vascular endothelial cells.

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摘要

Abstract

There is increasing interest in the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin) and polycyclic aromatic hydrocarbons on cardiovascular diseases. Their chemical structures are similar, although polycyclic aromatic hydrocarbons contain no chlorine as does TCDD. The biochemical mechanism of their action is mainly mediated by the aryl hydrocarbon receptor. In addition, oxidative stress also plays a role in the biological and toxic effects of these chemicals. In this study, we used an aryl hydrocarbon receptor agonist, 3-methylcholanthrene (3-MC), to investigate its effect on the proliferation and angiogenesis of human umbilical vascular endothelial cells. 3-MC suppressed DNA synthesis of human umbilical vascular endothelial cells as determined by [(3)H]thymidine incorporation in a concentration-dependent fashion and arrested cells at the G0/G1 phase of the cell cycle. Interestingly, the inhibition of DNA synthesis by 3-MC was eliminated to a greater extent by aryl hydrocarbon receptor antagonists, alpha-NF (0.5 and 1 microM) and resveratrol (5 and 10 microM), than by the antioxidant, N-acetylcysteine (5 and 10 mM). Cell permeability, adhesion, and tube formation in human umbilical vascular endothelial cells exposed to 3-MC decreased in concentration-dependent manners. We also demonstrated that cell adhesion signaling (phosphorylated focal adhesion kinase (FAK)) decreased upon 3-MC treatment, suggesting that cell adhesion inhibited by 3-MC might be due to inhibition of cell adhesion signaling. Additionally, alpha-naphthoflavon (alpha-NF) ameliorated the effects of 3-MC on cell permeability, adhesion and tube formation, indicating the involvement of the aryl hydrocarbon receptor in angiogenesis. The results suggest that the adverse effects of 3-MC are mainly mediated by the aryl hydrocarbon receptor and not via increased oxidative stress.