Anti-proliferation effect of 5,5-diphenyl-2-thiohydantoin (DPTH) in human vascular endothelial cells.

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Abstract

The aim of this study was to examine the anti-proliferation effect of 5,5-diphenyl-2-thiohydantoin (DPTH), an analogue of antiepileptic drug phenytoin (5,5-diphenylhydantoin), on human umbilical vein endothelial cells (HUVEC) and its possible molecular mechanism underlying. Here we demonstrated that DPTH at a range of concentrations (12.5-50 mM) dose- and time-dependently inhibited DNA synthesis and decreased cell number in cultured HUVEC, but not human fibroblasts. DPTH was not cytotoxic at these concentrations. [3H]Thymidine incorporation and flow cytometry analyses demonstrated that treatment of HUVEC with DPTH arrested the cell at the G0/G1 phase of the cell cycle. Western blot analysis revealed that the protein level of p21 increased after DPTH treated. In contrast, the protein levels of p27, p53, cyclins A, D1, D3 and E, cyclin-dependent kinase (CDK)2, and CDK4 in HUVEC were not changed significantly after DPTH treatment. Immunoprecipitation showed that the formations of the CDK2-p21 and CDK4-p21 complex, but not the CDK2-p27 and CDK4-p27 complex, were increased in the DPTH-treated HUVEC. Kinase assay further demonstrated that both CDK2 and CDK4 kinase activities were decreased in the DPTH-treated HUVEC. Pretreatment of HUVEC with a p21 antisense oligonucleotide reversed the DPTH-induced inhibition of [3H]thymidine incorporation into HUVEC. In conclusion, these data suggest that DPTH inhibits HUVEC proliferation by increasing the level of p21 protein, which in turn inhibits CDK2 and CDK4 kinase activities, and finally interrupts the cell cycle. The findings from the present study suggest that DPTH might have the potential to inhibit the occurrence of angiogenesis. © 2003 Elsevier Inc. All rights reserved.