Hyperbaric oxygen induces VEGF expression through ERK, JNK and c-Jun/AP-1 activation in human umbilical vein endothelial cells

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摘要

Abstract

Hyperbaric oxygen (HBO) is increasingly used in a number of areas of medical practice, such as selected problem infections and wounds. The beneficial effects of HBO in treating ischemia-related wounds may be mediated by stimulating angiogenesis. We sought to investigate VEGF, the main angiogenic regulator, regulated by HBO in human umbilical vein endothelial cells (HUVECs). In this study, we found that VEGF was up regulated both at mRNA and protein levels in HUVECs treated with HBO dose- and time-dependently. Since there are several AP-1 sites in the VEGF promoter, and the c-Jun/AP-1 is activated through stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) and extracellular signal regulated kinase (ERK), we further examined the c-Jun, JNK and ERK that might be involved in the VEGF induced by HBO. The VEGF mRNA induced by HBO was blocked by both PD98059 and SP600125, the ERK and JNK inhibitors respectively. HBO induced phospho-ERK and phospho-JNK expressions within 15 min. We further demonstrated that c-Jun phosphorylation was induced within 60 min of HBO treatment. HBO also induced the nuclear AP-1 binding ability within 30-60 min, but the AP-1 induction was blocked by treatment with either the ERK or JNK inhibitor. To verify that the VEGF expression induced by HBO is through the AP-1 trans-activation and VEGF promoter, both the VEGF promoter and AP-1 driving luciferase activity were found increased by the cells treated with HBO. The c-Jun mRNA, which is also driven by AP-1, was also induced by HBO, and the induction of c-Jun was blocked by ERK and JNK inhibitors. We suggest that VEGF induced by HBO is through c-Jun/AP-1

activation, and through simultaneous activation of ERK and JNK pathways.