

Regulation of hypoxia-inducible factor-1 alpha by cyclical mechanical stretch in rat vascular smooth muscle cells

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摘要

Abstract

Vascular smooth muscle cells (VSMCs) are exposed to hormonal and mechanical stress in vivo. Hormonal factors have been shown to affect hypoxia-inducible factor-1alpha (HIF-1alpha). How mechanical stress affects the regulation of HIF-1alpha in VSMCs has not been reported previously, and therefore we sought to investigate the regulation of HIF-1alpha by cyclical mechanical stretch in cultured rat VSMCs. Rat VSMCs grown on a flexible membrane base were stretched by vacuum to 20% of the maximum elongation at 60 cycles/min. The levels of HIF-1alpha protein began to increase as early as 2 h after stretch was applied and reached a maximum of 2.8-fold over the control by 4 h. Real-time PCR showed that the levels of HIF-1alpha mRNA increased 2.1-fold after cyclical stretch for 4 h. Cyclical mechanical stretch also increased the immunohistochemical labelling of HIF-1alpha in VSMCs after cyclical stretch for 4 h. The phosphorylation of p42/p44 mitogen-activated protein kinase (MAP kinase) increased after stretch and this was inhibited by the MAP kinase kinase inhibitors PD98059 and U0126. PD98059 and U0126 also blocked HIF-1alpha gene expression induced by cyclical stretch. In conclusion, cyclical mechanical stretch activates the gene expression of HIF-1alpha in cultured VSMCs and this mechanical effect is possibly mediated by the p42/p44 MAP kinase kinase pathway.