OBJECTIVE: Reactive oxygen species have been implicated as signaling molecules modulating the activity of redox-sensitive transcription factors such as nuclear factor kappa B (NF-kappaB). Recently, the transcription factor hypoxia-inducible factor-1 (HIF-1), known to mediate gene expression by hypoxia, has been found to be also activated by nonhypoxic factors in a redox-sensitive manner. We therefore aimed to elucidate the link between these 2 important redox-sensitive transcription factors. METHODS AND RESULTS: In pulmonary artery smooth muscle cells, reactive oxygen species generated either by exogenous H2O2 or by a NOX4-containing NADPH oxidase stimulated by thrombin activated or induced NF-kappaB and HIF-1alpha. The reactive oxygen species-mediated HIF-1alpha induction occurred on the transcriptional level and was dependent on NF-kappaB. Transfection experiments with wild-type or mutant HIF-1alpha promoter constructs revealed the presence of a yet unidentified NF-kappaB binding element. Gel shift analyses and chromatin immunoprecipitation verified binding of NF-kappaB to this site. Furthermore, reactive oxygen species enhanced expression of plasminogen activator inhibitor-1, which was prevented by dominant-negative IkappaB or mutation of the HIF-1 binding site within the plasminogen activator
CONCLUSION: These findings show for the first time to our knowledge that reactive oxygen species directly link HIF-1alpha and NF-kappaB, implicating an important pathophysiological role of this novel pathway in disorders associated with elevated levels of reactive oxygen species.