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Differential inhibition of NF- κ B subunits prevents norepinephrine dependent athero-thrombotic gene expression in experimental models of psychosocial stress

Exposure to the elevated levels of catecholamines in situations of acute and chronic psychosocial stress can be considered a daily challenge. However, excessive and repeated exposure to elevated levels of catecholamines can promote cellular damage and pathologic changes in the cardiovascular system. Activation of transcription factor NF- κ B is one of the mechanisms converting psychosocial stress into cellular activation. Inhibition of the transcription factor NF- κ B is supposed to reduce inflammation in acute and chronic disease, however, the use of drugs to systemically inhibit NF- κ B activation has not improved the outcome of disease. The latter might be due to inhibition of NF- κ B regulated protective genes, implying that a differential inhibition of NF- κ B subunits could prevent atherothrombotic gene expression, while preserving cellular defense mechanisms. In this study, we further investigated the previously shown activation of transcription factor NF- κ B upon adrenergic stimulation in order to get an insight into activation of different NF- κ B subunits. To prove the concept of a differential NF- κ B activation, we studied norepinephrine induced nuclear translocation of the NF- κ B subunits p50, p65 and cRel and the resulting subunit specific expression of three NF- κ B regulated genes: Tissue factor (TF), Intracellular Cell Adhesion Molecule 1 (ICAM-1) and Manganese Superoxide dismutase (MnSOD) in *in vitro* in cultured THP-1-cells and *in vivo* in a mouse model of transient and repeated restraint stress. Induction of THP-1 cells with 10nM norepinephrine or repeated restraint stress in ApoE^{-/-}-mice both resulted in increased binding of different NF- κ B-subunits to the binding sites on ICAM-1, TF and MnSOD genes and subsequent increase in mRNA synthesis and gene expression. While ICAM-1 was controlled by NF- κ B subunits p50, p65 and cRel, TF expression was driven by p65/cRel. In contrast, MnSOD expression was dependent on binding of p50/p65 heterodimers. *In vitro* and *in vivo* nuclear translocation of NF- κ Bp50 was dependent on PKC-activation; NF- κ Bp65 was activated via p38MAPKinase and NF- κ BcRel via the PI3/Akt pathway. Analysis of aortic tissue from ApoE^{-/-}-mice chronically stressed in the absence or presence of pathway inhibitors demonstrated that only inhibition of cRel resulted in reduction of atherosclerotic lesions. In contrast long-term inhibition of NF- κ Bp50 or NF- κ Bp65, both reducing MnSOD expression, had either no effect on vascular damage. Thus we show for the first time that norepinephrine induces differential activation of different NF- κ B subunits that control proatherogenic, atherothrombotic and cellular defence mechanisms and demonstrate that selective inhibition of NF- κ B subunits can be considered as a potential therapeutic strategy in the prevention and treatment of vascular dysfunction and atherosclerosis.

