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Endothelin-1 and Smooth Muscle Cells: Induction of Jun Amino-Terminal Kinase Through an Oxygen Radical-Sensitive Mechanism

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Background: Endothelin (ET-1) has been proposed to contribute to atherogenesis and plaque rupture in coronary heart disease. Plaque progression and destabilization has been associated with the inflammatory response of vascular smooth muscle cells. Mitogen activated protein kinases (MAPK) are strong candidate signal transducers for the activation of VSMC. The present study aimed to determine if ET-1 also has direct effect on the MAPK, c-Jun amino terminal kinase (JNK) and extracellular signal regulated kinase (ERK1/2) in addition to its traditional role in vasoconstriction.

In summary, the present data demonstrated that (I): activation of both JNK and ERK were observed , with a maximum stimulation at 10^{-7} M ET-1; (II): both kinases were activated by ET-1 binding to a single receptor ($ET\text{-}1_A$). Only JNK activation was sensitive to radical scavenger N-acetylcysteine and an inhibitor of NADPH oxidase, DPI, indicating a role for reaction oxygen species (ROS); (III): both kinases, ERK and JNK, were tyrosine kinase but not PKC dependent; (IV): PI-3 kinase is involved in the SAPK/JNK signaling pathway; (V): the downstream MAPK effector and proinflammatory transcription factor, the AP-1 complex, was shown to comprise mainly the JNK substrate c-Jun. AP-1 activation was maximal at 2h after addition of ET-1 and also dependent on ROS.

Taken together, the findings suggest that activation of SAPK/JNK by ET-1 might link Gi protein-coupled receptors to the primary downstream targets of protein tyrosine kinases, which may be non-receptor protein tyrosine kinases and/or cytosolic tyrosine kinases. In addition, protein tyrosine kinases also involved in ET-1-induced MAPK/ ERK pathway in VSMCs.

Conclusion: the present data show that ET-1 may initiate and promote atherosclerosis by inflammatory activation of the vessel wall. This study also demonstrated that the generation of ROS via flavonoid oxidase, by ET-1 may be a link between hormone-receptor interaction and stimulation of JNK activity, and downstream events