ESTROGEN REGULATES ENDOTHELIAL PLASMINOGEN ACTIVATOR INHIBITOR (PAI-1) SYNTHESIS THROUGH C-FOS AND C-JUN.

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ABSTRACT
Aim: Endothelial plasminogen activator inhibitor (PAI-1) controls vascular remodeling, angiogenesis and fibrinolysis. PAI-1 blood levels in women are related to estrogen. The aim of this study is to characterize the signaling pathways through which estrogen regulates PAI-1 in endothelial cells.

Methods: Cultured human endothelial cells (HUVEC) and ovariectomized rats were used to test the effects of 17ß-estradiol (E2) on PAI-1 expression and to explore signaling mechanisms.

Results: At physiological concentrations, E2 increases expression of PAI-1 in HUVEC within 6-12 hours through activation of a signaling cascade initiated by ER? and involving G proteins, phosphatidylinositol 3-OH kinase (PI3K) and Rho-activated kinase-II (ROCK-II). ROCK-II activation turns into an over-expression of c-Jun and c-Fos that is required for E2-induced expression of PAI-1. PAI-1 protein expression decreases in the abdominal aorta of female rats after castration, and estrogen replacement counteracts this change.

Conclusions: Estradiol increases PAI-1 synthesis in human endothelial cells through a G protein-initiated signaling that targets early-immediate gene expression. These findings describe new mechanisms of action of estrogens in the vessels, which may be important for vascular function and hemostasis.

Keywords: Endothelial cells/ Estrogen/ Estrogen receptor/ ROCKII/ c-fos/c-jun/PAI-1