Dehydroepiandrosterone mimics acute actions of insulin to stimulate production of both nitric oxide and endothelin 1 via distinct phosphatidylinositol 3-kinase- and mitogen-activated protein kinase-dependent pathways in vascular endothelium.

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Dehydroepiandrosterone (DHEA) is an adrenal steroid and nutritional supplement that may improve insulin sensitivity. Although steroid hormones classically act by regulating transcription, they may also signal through cell surface receptors to mediate nongenomic actions. Because DHEA may augment insulin sensitivity, we hypothesized that DHEA mimics vascular actions of insulin to acutely activate signaling pathways in endothelium-mediating production of nitric oxide (NO) and endothelin 1 (ET-1). Treatment of bovine aortic endothelial cells with either insulin or DHEA (100 nm, 5 min) stimulated significant increases in NO production (assessed with NO-selective fluorescent dye diaminofluorescein 2). These responses were abolished by pretreatment of cells with L-NAME (nitro-L-arginine methyl ester; NO synthase inhibitor) or wortmannin [phosphatidylinositol (PI) 3-kinase inhibitor]. Under similar conditions, insulin- or DHEA-stimulated phosphorylation of Akt (Ser473) and endothelial nitric oxide synthase (Ser1179) was inhibited by pretreatment of cells with wortmannin (but not MAPK kinase inhibitor PD98059). Acute DHEA treatment also caused phosphorylation of MAPK (Thr202/Tyr204) that was inhibitable by PD98059 (but not wortmannin). DHEA treatment of bovine aortic endothelial cells (100 nM, 5 min) stimulated a 2-fold increase in ET-1 secretion that was abolished by pretreatment of cells with PD98059 (but not wortmannin). We conclude that DHEA has acute, nongenomic actions in endothelium to stimulate production of the vasodilator NO via PI 3-kinase-dependent pathways and secretion of the vasoconstrictor ET-1 via MAPK-dependent pathways. Altering the balance between PI 3-kinase- and MAPK-dependent signaling in vascular endothelium may determine whether DHEA has beneficial or harmful effects relevant to the pathophysiology of diabetes.