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The cGMP-specific Phosphodiesterase 5 Inhibitor Sildenafil Promotes Angiogenesis

Anastasia Pyriochou[1], Zongmin Zhou[2], Vasiliki Koika[1], Christos Petrou[3], Paul Cordopatis[3], Andreas Papapetropoulos[1]

[1]Laboratory of Molecular Pharmacology, Department of Pharmacy, University of Patras, Patras, Greece; [2]George P. Livanos' Laboratory, Evangelismos Hospital, Department of Pulmonary and Critical Care, University of Athens, Athens, Greece and [3]Laboratory of Pharmacognosy and Natural Products, Department of Pharmacy, University of Patras, Patras, Greece

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S u m m a r y. Endogenously produced nitric oxide (NO) has been shown to play a permissive role in neovascularization. Many of the vascular actions of NO depend on cGMP formation following activation of soluble guanylyl cyclase. However, cGMP-degrading pathways have received little attention in the context of angiogenesis. In the present study we set out to determine whether cGMP-specific phosphodiesterase 5 (PDE 5) inhibition promotes new blood vessel growth. Initially, we ascertained the ability of sildenafil to promote angiogenesis in vivo using the chicken chorioallantoic membrane (CAM) as a model system. PDE5 inhibition by sildenafil increased vascular length in the CAM in a dose-dependent manner. Moreover, incubation of EC in vitro with sildenafil promoted their proliferation, migration and organization into tube-like structures. The effects of sildenafil on the angiogenesis-related properties of EC could be blocked by co-treatment with the soluble guanylyl cyclase inhibitor (sGC) ODQ or the protein kinase G I inhibitor DT-3. In addition, overexpression of sGC in EC led to an enhanced growth and migratory response. To study the signaling pathways implicated in the sildenafil-stimulated angiogenic responses we determined the phosphorylation status of MAPK members. Incubation of cells with sildenafil increased both ERK1/2 and p38 phosphorylation in a time-dependent manner. Inhibition of MEK by PD98059 and p38 with SB203580 blocked sildenafil-induced proliferation and migration, respectively, suggesting that these MAPK members are downstream of PDE5 and mediate the angiogenic effects of sildenafil. PDE5 inhibitors could, thus, be used in disease states where neo-vessel growth is desired.