EPITHEORESE KLINIKES FARMAKOLOGIAS
KAI FARMAKOKINETIKES, INTERNATIONAL
EDITION 13: 77 (1999)

On the Modulation of Angiogenesis by Nitric Oxide (NO)

S. Kritikou and M.E. Maragoudakis

Dept of Pharmacology, Medical School, University of Patras, Patra, Greece

We have shown that NO is an endogenous negative regulator of angiogenesis in the chick chorioallantoic membrane (CAM) system. Both basal and stimulated angiogenesis can be suppressed by. Exogenously supplied NO by sodium nitropruside (SNP) and nitrovasodilators inhibited both angiogenesis and tumor growth and metastasis in animal models of Lung Lewis carcinoma. Furthermore upregulation of the inducible form of NO synthase (iNOS) by LPS inhibited angiogenesis in the CAM. This effect can be abolished by the iNOS inhibitor L-NAME and L-Arg, but not D-NAME. We have explored the role of NO in the control of angiogenesis at the stages of chick embryo development in the CAM. From day 8 to day 12 the rate of angiogenesis more than doubles during this period and falls off after day 12. The expression of iNOS as measured by RT-PCR increases from day 8 to day 12 and decreases at day 13. This increase and subsequent fall of mRNA of iNOS co-insides with enzyme activity as measured by citruline assay and by the release of nitrites (oxidation products of NO in solution) by Griess reaction. This presents another paradigm of an endogenous brake of a complex cascade in vivo where both promoters and inhibitors are upregulated. The cellular and molecular mechanisms of this effect of NO on angiogenesis are under investigation. NO prevents tube formation by endothelial cells (EC) in Matrigel, but does not seem to effect proliferation or migration of EC. Results will be presented on the effect of NO on the expression of the receptors of VEGF -the key angiogenic mediator-. Understanding the molecular events and the transduction mechanisms involved in the role of NO in pathological and physiological angiogenesis may provide the basis for controlling this process for therapeutic applications.